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Role of Inflammatory Markers in Early Diagnosis of Neonatal Sepsis; C-Reactive Protein or Procalcitonin or Red Cell Distribution Width; A Hospital-Based Study

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ABSTRACT

Objective: To find out the utilization of C-reactive protein (CRP), Procalcitonin (PCT) and red cell distribution width (RDW) in diagnosing neonatal sepsis considering blood culture findings as gold standard.

Study Design: Cross-sectional validation study.

Place and Duration of Study: Neonatal Intensive Care Unit (NICU) of Dr Ziauddin Medical University, Karachi Pakistan, from Feb to Jul 2022.

Methodology: A total of 42 neonates of either gender with the clinical diagnosis of neonatal sepsis were enrolled. Demographical and clinical characteristics of all neonates were noted at the time of enrollment. A blood sample of 5 ml was withdrawn for the evaluation of CRP, PCT and RDS. The association of different inflammatory markers with the outcome (neonatal sepsis) was assessed.

Results: *In* 42 neonates, the mean age was 7.24±9.24 days, and 26 (61.9%) neonates were boys. Respiratory distress, reluctance to feed and hypoglycemia were the most frequent clinical presentations observed (19,45.2%), (14,33.3%) and (8,19.0%) neonates, respectively. Mean CRP levels among blood culture positive and negative neonates were 40.02±57.84mg/dl and 7.57±13.34 mg/dl, respectively, while the difference was statistically significant (p=0.0068). RDW (p=0.6488) and procalcitonin (0.9021) levels were not statistically significant differences among positive and negative neonates of blood culture.

Conclusion: The CRP was a significant predictor of neonatal sepsis, while RDW and procalcitonin did not have a significant relationship with early prediction of neonatal sepsis.

Keywords: C-reactive protein, Neonatal sepsis, Procalcitonin, Red cell distribution width.

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INTRODUCTION

Neonatal sepsis is a systemic infection commonly occurring in the first month of life. The global incidence of neonatal sepsis is estimated to be around 2200 per 100,000 births, while it is the cause of ~3 million deaths every year globally.[1,2] Presentation of neonatal sepsis may vary according to gestational age and severity of the infection and is broadly classified as "early-onset neonatal sepsis (EOS)" or "late-onset sepsis (LOS).[3,4] The EOS is described as sepsis occurring within the first three days of life and is usually caused by vertical transmission. The LOS occurs between 4-90 days of life and could be due to vertical or horizontal transmission.[5]

In order to improve the time identification and treatment of neonatal sepsis, the fragility of the neonatal immune system needs to be understood along with its inflammatory biomarkers.[6,7] Blood culture is a gold standard diagnostic method but is time-consuming.[8] There may even be false-negative cases when less blood is collected.[9] Thus, diagnostic tests like C-reactive protein (CRP), procalcitonin (PCT) or red cell distribution width (RDW) are being explored.[10]

All these markers are universally used in different settings with various pros and cons, as mentioned earlier. All these biomarkers are not cost-effective and impose an economic burden on the population of low-middle-income countries in case of non-judicious use. This study was thought to provide objective evidence of the most appropriate inflammatory marker to identify neonatal sepsis. Our objective was to determine the utilization of CRP, PCT and RDW in diagnosing neonatal sepsis, considering blood culture findings as the gold standard.

METHODOLOGY

The cross-sectional validation study was conducted at the Neonatal Intensive Care Unit (NICU) of three campuses of Dr. Ziauddin Medical University, Karachi Pakistan, from February to July 2022, approval from the Institutional Ethical Committee was obtained (Reference No. 5280422PPPED, dated July 22nd 2022). Considering the sensitivity of PCT in detecting sepsis as 92.8%, the sample size was calculated.[11]

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Inclusion Criteria: Neonates aged 1-28 days of life, of either gender with the clinical diagnosis of neonatal sepsis were included.

Exclusion Criteria: Neonates with congenital anomalies, early preterm (from 24-33 weeks), birth asphyxia, neonates with prolonged ventilation or suspected inborn errors of metabolism were excluded.

Informed consent was acquired from parents/ caregivers of all study participants. Clinical diagnosis of neonatal sepsis was labelled as the presence of any of these: history of premature rupture of membranes (PROM) for >16 hours, fever, fits, hypoglycemia, hypothermia, jaundice, apnea, late preterm, bradycardia, respiratory distress, poor primitive reflexes, and signs of shock at birth.

Demographical and clinical characteristics of all neonates were noted at the time of enrollment in the NICU. Before initiating antibiotic therapy, a blood sample of 5 ml was withdrawn and sent to institutional laboratories to evaluate CRP, PCT and RDS, adopting full aseptic measures. A haematology analyzer calculated RDW, while CRP and PCT were determined by photometry. RDW >13%, CRP >5mg/dl & PCT >0.046 ng/ml were considered raised (above normal level).[12]

The data was analyzed using Statistical Package for Social Sciences (SPSS) version-26.0 software. Qualitative data was represented as frequency and percentages, while numeric data were highlighted using mean and standard deviation. The Chi-square and independent sample t-test were used for inferential statistics. Additionally, the receiver operating characteristics (ROC) curve was utilized to select the best cut-off value, scores and the predictive ability of different inflammatory markers and their sensitivity and specificity for the outcome (neonatal sepsis).

RESULTS

In 42 neonates, the mean age was 7.24±9.24 days and 26(61.9%) neonates were boys. The place of admission was an emergency department in 38(90.5%) neonates. The mode of delivery was caesarean section among 29(69.0%) neonates. There were 13(31.0%) neonates who were born preterm, while 13(31.0%) were also having low birth weight. Respiratory distress, reluctance to feed and hypoglycemia were the most frequent clinical presentations observed in 19(45.2%), 14(33.3%) and 8(19.0%) neonates, respectively. Figure-1 shows details of various clinical findings and complaints reported among neonates. Table-I shows laboratory parameters observed among all studied neonates.

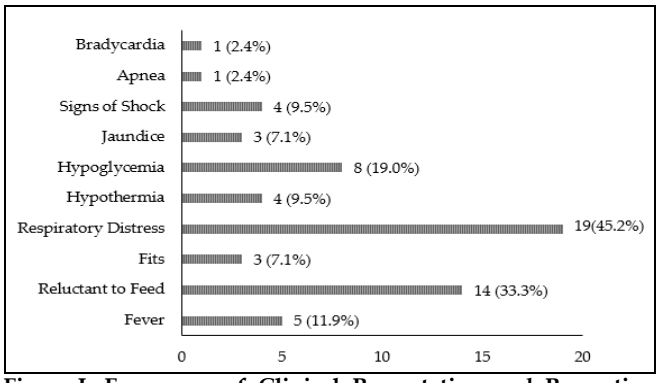

Figure-I: Frequency of Clinical Presentation and Presenting Complaints (n=42)

Table-I: Laboratory Parameters of Neonates (n=42)

Parameters	Mean±Standard Deviation	Minimum	Maximum
Hemoglobin (g/dl)	15.54±2.90	10.70	21.00
Total Leukocyte Count (x1000/mm3)	11.39±5.92	2.80	25.10
Neutrophils	53.39±18.43	11.00	82.00
Lymphocytes	37.41±17.13	11.00	76.00
Platelets (x1000)	255.02±112.50	45.00	537.00
CRP (mg/dl)	18.39±37.65	0.100	209.120
RDW (%)	18.24±3.96	13.900	39.00
Procalcitonin (ng/ml)	12.04±26.55	0.060	138.88

Table-II: Description of Area Under the Curve and Significance Level of Studied Biomarkers in Neonatal Sepsis (n=42)

Biomarkers	Area	Sensitivity (%)	Specificity (%)	*p*-Value	95% Confidence Interval	
					Upper	Lower
CRP	0.698	57.1	53.6	0.039	0.513	0.883
RDW	0.499	100	3.6	0.989	0.314	0.683
Procalcitonin	0.582	100	0	0.393	0.387	0.776

Mean CRP levels among blood culture positive and negative neonates were 40.02±57.84mg/dl and 7.57±13.34 mg/dl, respectively, while the difference was statistically significant (p=0.0068). No statistically

significant differences were observed in terms of RDW (17.84±2.43 vs. 18.44±4.56, p=0.6488) and Procalcitonin (11.32±12.40 vs. 12.40±31.27, p=0.9021) levels among blood culture positive and negative neonates. Table-II describes the biomarkers in terms of area under the curve and relevant significance levels. The CRP levels were found to be a significant predictor of neonatal sepsis (p=0.039), while the best cut-off value of CRP was noted to be 10.45 (mg/dl). The best predicting cut-off value of RDW for confirmed neonatal sepsis cases was noted to be 16.75 (%). No significant predicting relationship of procalcitonin was noted with confirmed neonatal sepsis cases, while the best cut-off procalcitonin value for confirmed neonatal sepsis was 9.78 (ng/ml). Figure-2 shows ROC curve predictions for CRP, RDW and Procalcitonin levels.

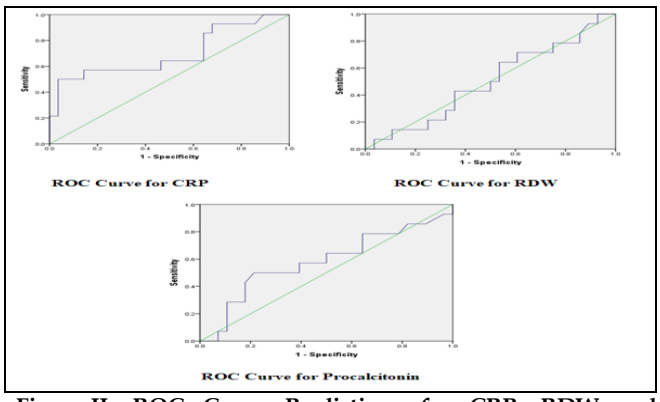

Figure-II: ROC Curve Predictions for CRP, RDW and Procalcitonin Levels

DISCUSSION

Neonatal sepsis is known to induce an inflammatory response that can further predispose the affected neonates to adverse outcomes.[12,13] Treatment mainly targeting infection is usually initiated at the earliest among cases of neonatal sepsis. However, overuse and incorrect utilization of anti-infective treatment might expose neonates to drug resistance as well as compromised outcomes.[14] Therefore, it is very important to explore relevant biomarkers pointing towards increased inclination for the presence of neonatal sepsis.

The present study noted that CRP was a significant predictor of neonatal sepsis. In contrast, other studied biomarkers like RDW and procalcitonin did not prove to have significant predictable worth in highlighting the presence of neonatal sepsis. Previous study has shown in the past that CRP is a common acute phase reaction protein among cases of neonatal sepsis that increases levels following inflammatory responses and infection, especially after bacterial infections.[15] It has been shown that CRP levels peak on the second day following infection and usually return to normal after seven days.[16] A recent study by Yang *et al*. reported that compared to the control group, neonatal sepsis cases had significantly higher levels of CRP on day one and day three following disease activity. In contrast, in most cases, CRP levels returned to normal on the seventh day.[17]

This study did not find procalcitonin to predict neonatal sepsis significantly. Our findings are contrary to what was found by Sucilathangam *et al*. who noted that procalcitonin levels were superior to serum CRP levels in detecting neonatal sepsis.[15] The difference could be that Sucilathangam *et a*l. considered cases already admitted to the NICU. At the same time, we enrolled neonates with the clinical diagnosis of neonatal sepsis from either the emergency department or outpatient department. So, procalcitonin can better predict neonatal sepsis among neonates with severe forms of the disease, but it needs further exploration.[18] Recent data have shown that increased levels of RDW are significantly linked with increased mortality among neonatal septicemia cases. RDW above 16.35% was noted to have predicted mortality with 70% sensitivity and 66.1% specificity.[19,20] In this study, we did not find RDW to be significantly different among blood culture-positive and blood culture-negative neonatal sepsis cases, so further studies are required to elaborate on the role of RDW in the early detection of neonatal sepsis.

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LIMITATION OF STUDY

We could not see outcomes in the present set of neonates, which could have further given us valuable insight into the predicting abilities of various biomarkers studied here.

CONCLUSION

The CRP was a significant predictor of neonatal sepsis, while RDW and procalcitonin did not have a significant relationship with early prediction of neonatal sepsis.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

PB & HR: Conception, study design, drafting the manuscript, approval of the final version to be published.

RA & TA: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

SK & MA: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Mersha A, Worku T, Shibiru S, Bante A, Molla A, Seifu G, et al., Neonatal sepsis and associated factors among newborns in hospitals of Wolaita Sodo Town, Southern Ethiopia. Res Reports Neonatol 2019; 2019(9): 1-8. https://doi.org/10.2147/RRN.S193074.
2. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N, et al. The global burden of paediatric and neonatal sepsis: a systematic review. Lancet Respir Med 2018; 6(3): 223-230. https://doi.org/10.1016/s2213-2600(18)30063-8.
3. Yamey G, Horvath H, Schmidt L, Myers J, Brindis CD. Reducing the global burden of Preterm Birth through knowledge transfer and exchange: a research agenda for engaging effectively with policymakers. Reprod Health 2016; 13(1): 26-28. https://doi.org/10.1186/s12978-016-0146-8.
4. Rudd KE, Johnson SC, Agesa KM. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020; 395(10219): 200-211. https://doi.org/10.1016/s0140-6736(19)32989-7.
5. Ogundare E, Akintayo A, Aladekomo T, Adeyemi L, Ogunlesi T, Oyelami O, et al. Presentation and outcomes of early and late onset neonatal sepsis in a Nigerian Hospital. Afr Health Sci 2019; 19(3): 2390-2399. https://doi.org/10.4314/ahs.v19i3.12
6. Giannoni E, Agyeman PKA, Stocker M, Klara MP, Heininger U, Spycher BD, et al. Neonatal sepsis of early onset, and hospital-acquired and community-acquired late onset: A prospective population-based cohort study. J Pediatr 2018; 201(1): 106-114.e4. https://doi.org/10.1016/j.jpeds.2018.05.048.
7. Berardi A, Sforza F, Baroni L, Spada C, Ambretti S, Biasucci G, et al. Epidemiology and complications of late-onset sepsis: an Italian area-based study. PLoS One 2019; 14(11): e0225407. https://doi.org/10.1371/journal.pone.0225407.
8. Gude SS, Peddi NC, Vuppalapati S, Venu Gopal S, Marasandra Ramesh H, Gude SS, et al. Biomarkers of Neonatal Sepsis: From Being Mere Numbers to Becoming Guiding Diagnostics. Cureus 2022; 14(3): e23215. https://doi.org/10.7759/cureus.23215.
9. Sampath S, Baby J, Krishna B, Dendukuri N, Thomas T. Blood Cultures and Molecular Diagnostics in Intensive Care Units to Diagnose Sepsis: A Bayesian Latent Class Model Analysis. Indian J Crit Care Med 2021; 25(12): 1402-1407. https://doi.org/10.5005%2Fjp-journals-10071-24051.
10. Ng S, Strunk T, Jiang P, Muk T, Sangild PT, Currie A. Precision Medicine for Neonatal Sepsis. Front Mol Biosci 2018; 5:70 https://doi.org/10.3389%2Ffmolb.2018.00070.
11. Celik IH, Hanna M, Canpolat FE, Mohan P. Diagnosis of neonatal sepsis: the past, present and future. Pediatr Res 2022; 91(2): 337-350. https://doi.org/10.1038%2Fs41390-021-01696-z.
12. 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(9): 880-883.
13. Mally P, Xu J, Hendricks-Muñoz K. Biomarkers for neonatal sepsis: recent developments. Res Reports Neonatol 2014; 4: 157-168 http://doi.org/10.2147/RRN.S48316.
14. Jandial A, Kumar S, Bhalla A, Sharma N, Varma N, Varma S, et al. Elevated Red Cell Distribution Width as a Prognostic Marker in Severe Sepsis: A Prospective Observational Study. Indian J Crit Care Med 2017; 21(9): 552-562. https://doi.org/10.4103/ijccm.ijccm_208_17.
15. Sucilathangam G, Amuthavalli K, Velvizhi G, Ashihabegum MA, Jeyamurugan T, Palaniappan N, et al. Early Diagnostic markers for neonatal sepsis: comparing procalcitonin (PCT) and C-reactive protein (CRP). J Clin Diagnostic Res 2012; 6(4): 627-631. https://doi.org/10.7860/JCDR/2012/.2150.
16. Zhang K, Xie R, Li W. The application value of inflammatory indicators and cytokine detection in the early diagnosis of neonatal sepsis. Clin Blood Transfus Test 2019; 21(4): 435-436.
17. Yang T, Wang J. Comparison of pathogenic bacteria, cytokines and immune function of sepsis between term and pre-mature infants. Chinese J Emerg Resuscit Disaster Med 2020; 15(2): 201–203.
18. Wu L, Li J, Ping L, Zhang X, Zhai L, Li Y, et al. Diagnostic Value of Inflammatory Markers and Cytokines in Neonatal Sepsis. Evid Based Complement Alternat Med 2022; 2022: 4143101. https://doi.org/10.1155%2F2022%2F4143101.
19. Xu L, Li Q, Mo Z, You P. Diagnostic value of C-reactive protein in neonatal sepsis: A meta-analysis. Europ J Inflamm 2016; 14(2): 100-108. https://doi.org/10.1177/1721727X16646787.
20. Rashwan NI, Hassan MH, Mohey El-Deen ZM, Ahmed AE. Validity of biomarkers in screening for neonatal sepsis - A single center -hospital based study. Pediatr Neonatol 2019; 60(2): 149-155.https://doi.org/10.1016/j.pedneo.2018.05.001