Original Article

Reliability of C-Reactive Protein in the Diagnosis of Neonatal Sepsis in Combined Military Hospital, Malir

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Abstract

Objective: To determine the reliability of C-reactive protein (CRP) as an early diagnostic biomarker for neonatal sepsis by assessing its correlation with clinical features, and potential perinatal risk factors, in order to support its use as a rapid and accessible tool for early diagnosis and management.

Methodology: A descriptive cross-sectional study was conducted at the Neonatology Unit of Combined Military Hospital (CMH), Malir, from July 2021 to November 2021. All neonates aged ≤28 days, of either gender, presenting with signs and symptoms suggestive of sepsis such as lethargy, poor feeding, temperature instability, respiratory distress, or convulsions were included. A total of 2 to 3 mL of venous blood was drawn aseptically from each neonate for CRP testing. A CRP level greater than 10 mg/L was considered positive and indicative of infection, serving as a key marker in assessing the likelihood of neonatal sepsis. All data were entered and analyzed using SPSS version 25.

Results: A total of 101 neonates were assessed, with 51.5% being male and 48.5% female. Among them, 96% had a positive CRP level. The most common clinical features observed were lethargy (72.3%), reluctance to feed (51.5%), and persistent vomiting (46.5%). CRP levels were predominantly in the range of 6–30 mg/L (51.5%) and 31–50 mg/L (40.6%). There was a statistically significant association between CRP status and both mode of delivery (p = 0.020) and type of feeding (p = 0.042), while no significant association was found with age, gender, PROM, meconium-stained liquor, or maternal fever (p=>0.05).

Conclusion: C-reactive protein observed to be a reliable and accessible biomarker for the early diagnosis of neonatal sepsis, with its positivity rate of 96% among clinically suspected cases and strong alignment with key clinical features such as lethargy and feeding difficulties, CRP proves to be a valuable diagnostic aid in neonatal care.

Keywords: Neonatal sepsis, CRP, Reliability, Effective, Diagnostic tool.

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Introduction

Neonatal sepsis raises global concerns regarding morbid condition and mortality among infants of age below 1 month, particularly in resource-constrained nations. It accounts for approximately 3 million cases annually worldwide and nearly 600,000 deaths each year. In low- and middle-income countries (LMICs), neonatal sepsis contributes to 10%–29% of neonatal deaths.[1] Early diagnosis and timely intervention are essential to reduce mortality and improve survival outcomes. Neonatal sepsis is diagnosed through clinical symptoms and laboratory biomarkers. However, clinical symptoms are often nonspecific in presentation, which makes the diagnosis more complicated.[2] Although, blood culture is valued as gold standard biomarker in sepsis diagnosis, but has several limitations including delayed diagnosis and limited accessibility in resource-constrained settings. On the other hand, C-reactive protein (CRP) is relatively rapid, economical, and widely

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accepted supportive biomarker.[3,4] CRP is an acute phase reactant protein, synthesized primarily by hepatocytes and to some extent by other extrahepatic cells. Its production increases by 1000-times due to inflammatory response or infection, but returns to normal level once underlying condition is improved, making it a valuable marker for monitoring the infection status.[5] CRP levels in neonates can fluctuate based on different factors including maternal complications, gestational age (such as, preterm versus term neonates), neonate's clinical aspects (i.e., disease severity, inflammatory conditions, or non-infectious causes), and blood sampling time corresponding to sepsis onset.[6]

Emerging scientific research revealed that CRP has 67%-92.3% sensitivity and 58.3%-79% specificity, making it a reliable indicator of sepsis.[7,8] Sepsis positive cases have generally been noted with significantly higher levels of CRP. However, in case of sepsis at early stages in neonates, CRP elevation remains insensitive, but constant monitoring following 12 to 24 hours of infection can assist in diagnosing neonatal sepsis, while facilitating the treatment with antibiotics.[9] Some studies suggest that in some of the late onset sepsis (LOS) cases, a high negative predictive value (NPV) of CRP indicates its potential to exclude sepsis,[10,11] while others concluded a statistically non-significant difference of CRP status between LOS and control groups of neonatal sepsis.[12] Despite widespread use of CRP, studies are largely inconsistent regarding its reliability as a supportive biomarker for diagnosing neonatal sepsis.[13]

In Pakistan, variability in maternal infection rates, delivery practices, and neonatal microbiology necessitate the local empirical evidence regarding the performance of CRP in sepsis, which would help guide clinical protocols, support its use as a rapid and accessible tool for early diagnosis and management, reduce unnecessary treatment, and ultimately improving neonatal outcomes. Therefore, this study was conducted to determine the reliability of C-reactive protein (CRP) as an early diagnostic biomarker for neonatal sepsis by assessing its correlation with clinical features, and potential perinatal risk factors.

Methodology

The present descriptive cross-sectional study was conducted at the Neonatology Unit of Combined Military Hospital (CMH), Malir, over a period of six months, from July 2021 to November 2021. All neonates aged ≤28 days, of either gender, who presented with signs and symptoms suggestive of sepsis (including lethargy, poor feeding, temperature instability, respiratory distress, or convulsions) were included in the study. Neonates with congenital anomalies, birth asphyxia, or those who had already received antibiotics prior to admission were excluded.

A total of 101 neonates admitted with clinical suspicion of sepsis were enrolled after obtaining ethical approval from the Ethics Committee of Combined Military Hospital (CMH), Malir (Ref No: 57/2021/Trg/ERC). Before enrollment, the purpose and procedures of the study were clearly explained to the parents or legal guardians in a language they understood. Confidentiality and anonymity of patient data were strictly maintained throughout the study.

Detailed demographic and clinical information was recorded, including age (in days), gender, gestational age, mode of delivery, history of maternal fever, presence of meconium-stained amniotic fluid, premature rupture of membranes (PROM), type of feeding, and whether resuscitation was required at birth. Each neonate also underwent a thorough clinical assessment for signs of sepsis, such as difficulty breathing, lethargy, poor feeding, vomiting, fever with seizures, hypothermia, and loose stools.

A 2–3 mL sample of venous blood was drawn aseptically from each neonate by trained medical staff under sterile conditions and immediately sent to the diagnostic laboratory for C-reactive protein (CRP) testing and other relevant investigations as required. CRP was measured quantitatively using a latex-enhanced turbidimetric immunoassay. CRP levels greater than 10 mg/L were considered positive and indicative of infection, serving as an important marker in the assessment of neonatal sepsis.

All data were entered and analyzed using SPSS version 25. Descriptive statistics were presented as frequencies and percentages. Post-stratification analysis was performed to assess the association between CRP status and potential effect modifiers. The chi-square test was applied, and a p-value ≤0.05 was considered statistically significant.

Results

Out of all 101 neonates included in the study, 51.5% were male and 48.5% were female. The majority of babies were aged between 3–7 days (43.6%), followed by 30.7% at 3 days and 25.7% older than 7 days. Majority were born at a gestational age of over 37 weeks (41.6%), with smaller proportions born between 28–32

weeks (12.9%). According to MOD, 47.5% were delivered via normal vaginal delivery and 44.6% by cesarean section. Premature rupture of membranes (PROM) and meconium-stained liquor were each present in 33.7% of cases. Around half of the neonates required resuscitation at their birth. A history of maternal fever was reported in 37.6% of cases. In terms of feeding, combination feeding was most common (33.7%), followed by top feeding (32.7%), expressed breast milk (19.8%), and exclusive breastfeeding (13.9%). Table I.

Table I: Demographic and clinical characteristics of the patients. (n=101)

Variables		N	%
Gender of baby	Male	52	51.5
	Female	49	48.5
Day of life (age)	<3 days	31	30.7
	3-7 days	44	43.6
	>7 days	26	25.7
	Total	101	100.0
Gestational age	28-32 weeks	13	12.9
	33-35 weeks	23	22.8
	36-37 weeks	23	22.8
	>37 weeks	42	41.6
Mode of delivery	NVD	48	47.5
	Instrumental	5	5.0
	Episiotomy	3	3.0
	C-section	45	44.6
PROM	Yes	34	33.7
	No	67	66.3
Meconium stain liquor	yes	34	33.7
	No	67	66.3
Need of resuscitation	Yes	46	45.5
	No	55	54.5
History of maternal fever	Yes	38	37.6
	No	63	62.4
Types of feeding	Breast feeding	14	13.9
	Expressed Breast milk	20	19.8
	Combination feed	34	33.7
	Only Top feed	33	32.7

The most commonly observed symptom was lethargy, among 72.3% of cases, followed by difficulty in breathing was 40.6%, 51.5% were reluctant to feed, 46.5% had persistent vomiting, fever with fits and hypothermia were each found in 28.7% of the babies and loose stools were reported in (15.8%) babies, while blood culture results showed that 50.5% of the neonates had a positive culture. Table II.

Based on post-stratification analysis CRP status showed a significant association with mode of delivery (p = 0.020) and type of feeding (p = 0.042), while no significant links were found with age, gender, PROM, meconium-stained liquor, or maternal fever. CRP positivity was more frequent among neonates delivered via NVD and C-section, and CRP-negative cases were mainly observed in those on combination feeds as shown in table III

Table II: C-reactive protein status among septic neonates. (n=101)

Variables		N	%
CRP level	Positive	97	96.0
	Negative	04	04.0
	Total	101	100.0
CRP range	6-30	52	51.5
	31-50	41	40.6
	>50	08	07.9

Table III: Post stratification with respect to the effect modifiers (n=101)

Variables		CRP status		Total	p-value
		Positive	Negative		
Age of neonates	3 days	29	2	31	0.195
		28.7%	2.0%	30.7%	
	3-7 days	44	0	44	
		43.6%	0.0%	43.6%	
	>7 days	24	2	26	
		23.8%	2.0%	25.7%	
Gender	Male	50	2	52	0.952
		49.5%	2.0%	51.5%	
	Female	47	2	49	
		46.5%	2.0%	48.5%	
PROM	Yes	33	1	34	0.708
		32.7%	1.0%	33.7%	
	No	64	3	67	
		63.4%	3.0%	66.3%	
Mode of delivery	NVD	48	0	48	0.020
		47.5%	0.0%	47.5%	
	Instrumental	5	0	5	
		5.0%	0.0%	5.0%	
	Episiotomy	2	1	3	
		2.0%	1.0%	3.0%	
	C-section	42	3	45	
		41.6%	3.0%	44.6%	
Meconium stain liquor	Yes	34	0	34	0.146
		33.7%	0.0%	33.7%	
	No	63	4	67	
		62.4%	4.0%	66.3%	
Maternal fever history	Yes	38	0	38	0.113
		37.6%	0.0%	37.6%	
	No	59	4	63	
		58.4%	4.0%	62.4%	
Types of feeding	Breast feeding	14	0	14	0.042
		13.9%	0.0%	13.9%	
	Expressed Breast milk	20	0	20	
		19.8%	0.0%	19.8%	
	Combination feed	30	4	34	
		29.7%	4.0%	33.7%	
	Only Top feed	33	0	33	
		32.7%	0.0%	32.7%	

Discussion

Neonatal sepsis is a significant cause of neonatal mortality in developing world, with estimates suggesting

30% to 50% of deaths in neonatal community of low- and middle-income countries.[8,14] Therefore early identification of sepsis is very important for proper treatment and improved survival rates in neonatal population at risk. However present study assessed the reliability of CRP as an early diagnostic biomarker for neonatal sepsis, its correlation with clinical features, and potential perinatal risk factors. The study enrolled 101 neonates with clinical suspicion of sepsis where demographically most of the babies were aged 3–7 days (43.6%), baby boys were 51.5% and baby girls were 48.5%. Additionally, most of the babies were born at term, delivered by normal vaginal delivery (47.5%), with common risk factors including PROM and meconium-stained liquor (33.7% each), and combination feeding as the most common feeding practice. Comparable demographic characteristics and clinical characteristics of patients were observed in the studies conducted by Berhane et al,[15] and Mahallei et al.[16] Though, some variations were noted across studies in demographic variables, which may be due to differences in sample size, sample selection criteria, and slight variations in the purpose of the studies.

Current study, the most commonly observed symptom of neonatal sepsis was lethargy (72.3%), followed by reluctant to feed (51.5%), persistent vomiting (46.5%), difficulty in breathing (40.6%), fever with fits (28.7%), hypothermia (28.7%), and the least common symptom was loose stools (15.8%). In aligns to this study Chakravarthi et al[17] reported that the lethargy was the most frequently observed symptom in 61.66% of the patients, followed by refusal of feeds (55.0%), apnoea (34.17%), respiratory distress (21.67%), vomiting (16.67%), and hypothermia (6.66%). Similarly, in the study of Verma et al.,[18] most common clinical feature was refusal to feed (45%), followed by lethargy (38%), respiratory distress (36%), vomiting (25%), hypothermia (22%), fever (22%), and diarrhea (9%)

In this study, blood culture results showed that 50.5% of the neonates were positive for sepsis. On the other hand, C-reactive protein (CRP) was positive in 96% of cases, indicating a strong association with neonatal sepsis. Regarding CRP levels, the majority (51.5%) had values in the range of 6–30 mg/L, followed by 31–50 mg/L (40.6%), and >50 mg/L (7.9%). In line with these findings, in the study of Kumar et al,[19] neonatal sepsis was diagnosed in 48.5% of cases through both the CRP and blood culture, where CRP was positive in 51.2% and blood culture was positive in 22.4% of cases. In another study by Lamicchane et al,[20] neonatal sepsis was confirmed by blood culture in 42.5% of cases and out of these positive blood cultures, CRP was positive in 88.5% of cases. Some disparities in findings across the studies may because of inconsistencies in sample size, severity of disease and laboratory protocol pattern of CRP levels as well as blood culture evaluation.

In this study, based on post-stratification analysis, CRP status showed a significant association with mode of delivery ($p = 0.020$), type of feeding ($p = 0.042$), and PROM, while no significant associations were found with age, gender, meconium-stained liquor, or maternal fever. CRP positivity was more frequent among neonates delivered via normal vaginal delivery (NVD) and cesarean section, whereas CRP-negative cases were mainly observed in neonates receiving combination feeding.

A consistent finding was reported in the study by Mogollón CA et al.21, which revealed that gestational age and the occurrence of maternal urinary tract infection during the third trimester were significantly associated with neonatal sepsis. On the other hand, a systematic review and meta-analysis by Andini N et al.22 showed that neonatal sepsis was significantly more frequent among neonates born to mothers with a history of PROM compared with those without PROM ($p < 0.05$). Additionally, evidence from 17 eligible case-control studies demonstrated a higher risk of sepsis among preterm neonates compared to term neonates ($p < 0.05$).

In comparison with our findings, the study conducted by Cao et al.23 reported that gestational age, PROM, and mode of delivery were associated with higher CRP values. Similarly, in the study by Wasim and Naseem et al.24, gender, PROM, meconium-stained liquor, and mode of delivery were all significantly associated with CRP levels in neonatal sepsis. Some variations in findings across the studies may be due to differences in study design, blood sampling timing, and local practices; notably, the feeding methods observed in our study represent unique findings that may vary due to differing NICU protocols and sociocultural factors in other settings.

Conclusion

Study revealed that the CRP is a reliable and accessible biomarker for the early diagnosis of neonatal sepsis, with its positivity rate of 96% among clinically suspected cases and strong alignment with key clinical features such as lethargy and feeding difficulties, CRP proves to be a valuable diagnostic aid in neonatal care. CRP

diagnosis into routine neonatal sepsis screening protocols can enhance timely diagnosis, reduce morbidity, and may support targeted therapeutic interventions particularly in resource-limited settings where rapid and cost-effective tools are essential. However due to few significant limitations, further studies are recommended to validate the findings.

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