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Clinical Outcomes, Biochemical Markers and Risk Factors Associated with Neonatal Sepsis in Hospitalized Neonates: A Cross-Sectional Study

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ABSTRACT

Objective: To evaluate the clinical outcomes, biochemical markers, and associated risk factors among neonates with culture-confirmed sepsis admitted to a tertiary care hospital. **Study Design:** Cross-sectional study. **Settings:** Neonatal Nursery Unit, Department of Pediatrics, CMH Kharian Medical College, in collaboration with CMH Kharian Hospital, Pakistan. **Duration:** Six months from January to June 2024. **Methods:** A total of 164 neonates with culture-confirmed sepsis were enrolled through consecutive sampling. Demographic characteristics, maternal and neonatal risk factors, clinical manifestations, and biochemical parameters, including C-reactive protein (CRP), serum lactate, and random blood glucose, were recorded using a structured pro forma. Clinical outcomes were categorized as clinical recovery, prolonged ICU stay (>7 days), and in-hospital mortality. Data were analyzed using IBM SPSS Statistics version 25.0. Multivariable binary logistic regression was performed to identify independent predictors of adverse clinical outcomes. **Results:** Male neonates accounted for 67.7% of the study population, while prematurity and low birth weight were observed in 45.1% and 42.1% of cases, respectively. Prolonged rupture of membranes was the most frequent maternal risk factor (31.1%). Respiratory distress (56.1%) and poor feeding (51.2%) were the predominant clinical manifestations. Elevated CRP (>10 mg/L), serum lactate (>2 mmol/L), and hypoglycemia were significantly associated with prolonged ICU stay and in-hospital mortality. Multivariable logistic regression identified elevated CRP, serum lactate, and hypoglycemia as independent predictors of adverse clinical outcomes. **Conclusion:** Prematurity, low birth weight, and maternal risk factors were commonly observed among neonates with sepsis. Elevated CRP, serum lactate, and hypoglycemia were independently associated with unfavorable clinical outcomes, highlighting the importance of early biochemical assessment and prompt risk stratification to improve neonatal management.

Keywords: Neonatal sepsis, C-reactive proteins, Intensive care unit, Hypoglycemia, Hyperlactatemia.

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INTRODUCTION

Neonatal sepsis is a life-threatening systemic infection affecting newborns within the first 28 days of life and is a significant contributor to neonatal illness and death globally. Even in developed countries such as the United Kingdom and the United States the prevalence of neonatal sepsis is approximately 1-8/1000 live births. However, the burden is considerably higher in developing and underdeveloped countries. According to the 2016's report, the rate of neonatal deaths due to sepsis was about 250000, highlighting its major contribution to worldwide neonatal mortality.¹ One of the most common etiological factors is the microbial invasion in blood stream with positive clinical signs of infection. Multiple factors contribute to the development of neonatal sepsis and out of

them the commonest are the immature immune system of neonates, especially in preterm and low birth weight. Neonatal sepsis can lead to serious complications including septic shock, meningitis, respiratory distress, multiorgan failure, neurodevelopmental disorders and even death. All are related mostly to delayed diagnosis and treatment.^{2,3} According to the data of WHO, about 2.4 million neonatal deaths occur annually throughout the world and neonatal sepsis contribute significantly to these deaths.⁴ Out of them 1/3rd neonatal mortality rate is in developing and underdeveloped countries where healthcare resources, infection control measures and neonatal intensive care facilities are limited or inaccessible. This burden of neonatal sepsis is continuously increasing due

to antimicrobial resistance, nosocomial infections, prematurity, prolonged hospitalization and invasive neonatal procedures.⁵

Both early and late-onset sepsis are related to the timing of symptoms. Early-onset neonatal sepsis occurs during the initial 72 hours of life and is primarily related to maternal and perinatal determinants, i.e. prolonged rupture of membranes, maternal fever, prematurity, birth asphyxia, and intrauterine infections. Late-onset neonatal sepsis occurs beyond 72 hours after birth and is commonly linked to environmental or nosocomial infections.⁶ Neonates admitted to neonatal intensive care units are at more risk due to frequent exposure to invasive procedures, prolonged intravenous cannulation, endotracheal intubation and broad-spectrum antibiotic therapy.⁷ The clinical presentation of neonatal sepsis is sometimes very confusing, making early diagnosis very difficult. Common features include respiratory distress, poor feeding, lethargy, hypothermia, fever, irritability, seizures, cyanosis, apnea and circulatory instability. As the reference standard for diagnosing neonatal sepsis, blood culture facilitates accurate identification of infecting microorganisms and guides appropriate antibiotic selection through susceptibility testing. Early identification of microorganisms is integral for timely administration of effective antimicrobial therapy and reduction of neonatal complications.^{4,8} Other than culture, biochemical and inflammatory markers are used to diagnose neonatal sepsis. Parameters such as C-reactive protein (CRP), serum lactate and blood glucose abnormalities are commonly used to assess the severity of infection and to predict the clinical outcomes and to get guidance on treatment line.⁹

In the world of neonatal intensive care unit, the antimicrobial resistance among neonatal pathogens has become a major challenge. Due to excessive use of broad-spectrum antibiotics, now the increased resistance among gram-positive and gram-negative organisms is very common. So, present study was conducted to evaluate the clinical outcomes, biochemical markers and related risk factors among neonates diagnosed with sepsis in a tertiary care hospital. The study also aimed to identify the common clinical presentations and to assess the association of biochemical abnormalities with neonatal outcomes.

METHODS

This cross-sectional study was held in Neonatal Nursery Unit, Pediatrics department, in CMH Kharian Medical College in collaboration with CMH Kharian Hospital over six consecutive months from January 2024 to June 2024 after obtaining approval from the Institutional Review Committee (IRC) with number IERB/AC-0253. This study aimed to evaluate the clinical outcomes, biochemical markers and associated risk factors among neonates diagnosed with culture-positive sepsis. Using the WHO sample size calculator, a sample of 164 neonates was determined at a 95% confidence interval and 5% margin of error, taking an anticipated *Pseudomonas* isolation rate of 12.1% from earlier studies.¹⁰ A non-probability consecutive sampling technique was used. Neonates of both genders aged <28 days with clinical features of sepsis and having culture-confirmed infection were eligible for inclusion in the study. Neonates already receiving antibiotic therapy prior

to admission, with major congenital anomalies and those whose guardians declined to provide informed consent were not included in study. After enrollment, detailed demographic, clinical, microbiological and biochemical information was recorded on a structured pro forma. Variables including age, gender, birth weight, gestational age, sepsis types, maternal determinants, delivery method and neonatal clinical presentation were documented. Maternal and neonatal risk factors i.e. prematurity, prolonged rupture of membranes, maternal fever, birth asphyxia and meconium aspiration were also assessed. Clinical features such as respiratory distress, poor feeding, lethargy, hypothermia, fever and seizures were recorded during hospital admission.

A venous blood sample of approximately 2 mL was obtained and immediately transported to the microbiology laboratory for incubation and culture. Microbiological identification and culture sensitivity testing were performed using standard laboratory protocols. Biochemical parameters including C-reactive protein (CRP), serum lactate level and random blood glucose were recorded from laboratory investigations performed at the time of admission. Clinical outcomes including recovery status, duration of ICU stay and mortality were also documented during hospitalization. Neonates requiring ICU stay of more than seven days were categorized as prolonged hospital stay cases. A CRP level >10 mg/L was considered indicative of a significant inflammatory response based on established diagnostic criteria for neonatal sepsis.^{19,20} Similarly, a serum lactate level >2 mmol/L was considered elevated, reflecting impaired tissue perfusion and increased disease severity in accordance with published recommendations and standard neonatal laboratory reference ranges.²¹ Clinical outcomes defined as complete resolution of the clinical signs and symptoms of sepsis with survival to hospital discharge without major complications,^{1,3} including recovery status, lengthy ICU stay (defined as admission to the neonatal intensive care unit for more than seven days¹³ and mortality (defined as in-hospital death occurring during the same admission as a consequence of neonatal sepsis or its complications,^{3,16} were also documented during hospitalization.

Data were analyzed using SPSS version 25.0. Quantitative variables were summarized as mean $\pm$ standard deviation, whereas categorical variables were expressed as frequencies and percentages. A multivariable binary logistic regression model was constructed to identify independent predictors of adverse clinical outcomes after adjustment for potential confounding variables. Adjusted odds ratios (AORs) with 95% confidence intervals (95% CIs) were calculated. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 164 neonates with culture-confirmed sepsis were enrolled in the study. Male neonates and prematurity along with low birth weight were frequently seen. Respiratory distress and poor feeding were the most common clinical manifestations. Elevated biochemical markers were associated with prolonged ICU stay and poor clinical outcomes. Detailed findings are presented in the following tables.

Table 1: Demographic and risk factor profile of neonates with sepsis (n=164)

Variable	Frequency (n)	Percentage (%)
Male	111	67.7
Female	53	32.3
Prematurity	74	45.1
Low birth weight	69	42.1
PROM >18 hours	51	31.1
Maternal fever	33	20.1
Birth asphyxia	28	17.1
Meconium aspiration	19	11.6

Table 2: Clinical presentations among neonates with sepsis (n=164)

Clinical Feature	Frequency (n)	Percentage (%)
Respiratory distress	92	56.1
Poor feeding	84	51.2
Fever	71	43.3
Lethargy	65	39.6
Hypothermia	31	18.9
Seizures	17	10.4

Table 3: Association of biochemical markers with clinical outcome in neonatal sepsis

Biochemical markers	Improved outcome n (%)	ICU stay >7 days n (%)	Mortality n (%)
CRP <10 mg/L	41 (87.2)	5 (10.6)	1 (2.1)
CRP >10 mg/L	82 (70.1)	24 (20.5)	11 (9.4)
Serum Lactate >2 mmol/L	37 (57.8)	18 (28.1)	9 (14.1)
Hypoglycemia Present	19 (61.3)	7 (22.6)	5 (16.1)

Table 4: Multivariable binary logistic regression analysis of factors associated with mortality among neonates with sepsis

Variable	Adjusted OR	95% CI	p-value
Prematurity	2.18	1.10–4.32	0.025
Low birth weight	1.74	0.96–3.15	0.067
PROM >18 hours	1.29	0.62–2.69	0.492
Maternal fever	1.83	0.81–4.13	0.145
Birth asphyxia	2.61	1.18–5.77	0.018
CRP >10 mg/L	3.46	1.64–7.30	0.001
Serum lactate >2 mmol/L	4.18	2.02–8.65	<0.001
Hypoglycemia	2.39	1.09–5.23	0.030

DISCUSSION

Worldwide, neonatal sepsis contributes substantially to neonatal illness and death, especially among premature and low

birth weight neonates. Our results have evaluated maternal and neonatal risk factors, clinical presentation, biochemical markers and clinical outcomes within septic neonates admitted to a tertiary care hospital. Early identification of these risk factors and biochemical changes are essential for timely diagnosis and improvement in neonatal treatment. In our study, out of the calculated sample size 67.7% cases were male neonates while females accounted for 32.3% as shown in Table 1. The higher proportion of male neonates observed in the present study may also reflect the greater number of male admissions to neonatal intensive care units and their increased susceptibility to severe infections requiring hospitalization. In addition, biological differences in immune maturation during the neonatal period may contribute to this pattern, resulting in a greater burden of sepsis among male infants. Similar male predominance has been mentioned in several studies. Kelly *et al.* reported that female neonates generally exhibit a stronger immune and inflammatory response to infections, whereas male newborns are particularly vulnerable to sepsis and other infectious diseases during the neonatal period. Differences in endotoxin-mediated inflammatory pathways and hormonal influences are believed to contribute to altered immune regulation in male neonates, increasing their vulnerability to community-acquired and hospital-acquired infections.¹¹

Prematurity was identified in 45.1% of neonates while low birth weight was in 42.1% of cases (Table 1). The high frequency of prematurity and low birth weight may be explained by the fact that these neonates often require prolonged hospitalization, respiratory support, intravenous access and other invasive procedures. These interventions increase exposure to hospital pathogens and reduce the ability of the immature immune system to effectively control infection. Similar observations have been reported in earlier studies showing that prematurity and low birth weight as major contributing factors for neonatal sepsis. Nurrosyida *et al.* reported that preterm neonates are at more risk for bloodborne infections due to poor immune response, immature skin barrier protection and increased exposure to invasive procedures.¹² Similarly, studies from Pakistan have also shown that premature neonates frequently require prolonged NICU stay, mechanical ventilation and intravenous catheterization, increasing chances of hospital-acquired infections.¹³ Prolonged rupture of membranes (PROM) >18 hours was observed in 31.1% of cases while maternal fever was in 20.1% of neonates' mothers (Table 1). Maternal infections and prolonged rupture of membranes are well known risk factors for early-onset neonatal sepsis. Previous studies by Iqbal *et al.* have shown that ascending bacterial infection from the maternal genital tract increases neonatal exposure to pathogenic microorganisms during delivery.¹⁴ In our study, birth asphyxia and meconium aspiration were identified in 17.1% and 11.6% of neonates respectively (Table 1). Comparable results are in study of Osman *et al.* where birth asphyxia and meconium aspiration were found to damage the neonatal defense mechanisms and increase chances of severe systemic infections.¹⁵

The most frequently reported clinical feature in current study was respiratory distress, present in 56.1% of neonates, poor feeding in 51.2%, fever in 43.3%, lethargy in 39.6%, hypothermia in 18.9% and seizures in 10.4% as demonstrated

in Table 2. Similar observations were documented by Damatopoulou *et al.*, who found respiratory distress and feeding intolerance as the most frequent complication of neonatal sepsis. The nonspecific presentation of neonatal sepsis mostly delays the diagnosis because symptoms overlap with various neonatal metabolic and respiratory conditions.¹⁶ Respiratory distress can result from systemic inflammatory response, congenital pneumonia or septic shock leading to pulmonary dysfunction.¹⁷ Similarly, lethargy and poor feeding represent the systemic metabolic compromise and reduced neonatal activity due to infection.¹ Fever and hypothermia were also observed in our study. These are important indicators of neonatal infection and systemic inflammatory response. Neonates can develop temperature instability because of immature thermoregulatory mechanisms and cytokine-mediated inflammatory processes.¹⁸ Seizures observed in 10.4% of cases (Table 2), indicating severe sepsis, meningitis, metabolic derangements and cerebral hypoperfusion.

Biochemical markers showed a strong association with clinical outcomes in current study as shown in Table 3. Neonates with CRP levels greater than 10 mg/L showed increased ICU stay and mortality as compared to those with lower CRP levels. Elevated CRP is considered as an important acute-phase inflammatory marker released in response to infection and tissue injury.¹⁹ Similar findings have been reported in previous study on neonatal sepsis where raised CRP levels were associated with severe infection and poor prognosis. Eichberger *et al.* reported that inflammatory markers including CRP can assist in early diagnosis of septic neonates and disease severity.²⁰ Serum lactate levels above 2 mmol/L were associated with prolonged ICU stay and mortality in our results (Table 3). Elevated serum lactate reflects tissue hypoxia and impaired perfusion during systemic infection. Studies conducted in critically ill neonates have shown that hyperlactatemia is associated with septic shock, multiorgan dysfunction and increased mortality.²¹ Our findings support the clinical significance of serum lactate as an important prognostic marker in neonatal sepsis. Hypoglycemia was also associated with poor clinical outcomes and increased mortality in our study (Table 3). Neonates with sepsis often develop hypoglycemia because of increased metabolic demand, insufficient glycogen storage and impaired glucose regulation during systemic inflammatory response. Similar observations have been reported in study of Kumar *et al.* where hypoglycemia was considered an indicator of severe neonatal illness and adverse prognosis. The association between hypoglycemia and poor clinical outcomes emphasizes the importance of routine metabolic monitoring in neonatal intensive care units. Early correction of glucose abnormalities can reduce complications and contribute to improved clinical outcomes in critically ill neonates.²²

To confirm that whether the observed associations were independent of established maternal and neonatal factors, multivariable binary logistic regression analysis was performed (Table 4). After adjustment for potential confounders including prematurity, low birth weight, prolonged rupture of membranes, maternal fever, birth asphyxia and type of sepsis, elevated CRP, increased serum lactate and hypoglycemia remained significant independent predictors of adverse clinical

outcomes. These findings suggest that CRP, serum lactate and hypoglycemia are useful indicators of poor clinical outcomes in neonates with sepsis. Similar study by Eichberger *et al.* have also discussed those inflammatory and metabolic biomarkers independently predict the severity of disease and mortality in neonatal sepsis. The addition of these readily available laboratory parameters into routine neonatal assessment can help a lot in early identification of high-risk patients and can improve the treatment outcomes.²⁰

CONCLUSION

Preterm and low birth weight neonates are disproportionately affected by neonatal sepsis, which continues to be a major cause of adverse neonatal outcomes. Prematurity, prolonged rupture of membranes, maternal fever and birth asphyxia were important risk factors identified in our study. Respiratory distress and poor feeding were common complications among septic neonates. Elevated biochemical markers including CRP, serum lactate and hypoglycemia were associated with prolonged ICU stay and poor clinical outcomes. Early identification of high-risk neonates along with timely clinical and biochemical assessment can improve neonatal management, reduce complications and enhance survival chances in neonatal intensive care units.

LIMITATIONS

- 1- It was a single center study with a relatively limited sample size. Multicenter studies with larger sample sizes should be conducted for broader representation.
- 2- Advanced inflammatory markers and long-term neurodevelopmental outcomes were not evaluated because of limited resources and follow-up difficulties.

SUGGESTIONS / RECOMMENDATIONS

Advanced biochemical and molecular markers should be included in future studies for better diagnostic accuracy and long-term follow-up studies should be performed to assess neurodevelopmental outcomes in septic neonates.

CONFLICT OF INTEREST / DISCLOSURE

None.

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