Original Research Article

ASSOCIATION OF RISK FACTORS AND OUTCOMES OF EARLY ONSET NEONATAL SEPSIS AMONG PRETERM NEONATES

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ABSTRACT

Background: *Early-onset neonatal sepsis (EONS) is a major cause of morbidity and mortality among preterm neonates, particularly in resource-limited settings. Identification of maternal and neonatal risk factors is essential for early diagnosis, timely intervention, and improved clinical outcomes.* **Objective:** *To determine the risk factors of early-onset neonatal sepsis, assess early outcomes, and evaluate the association between identified risk factors and outcomes among preterm neonates.* **Study Design:** *Case–control study.* **Setting:** *The Department of Pediatrics, Khyber Teaching Hospital, Peshawar, Pakistan.* **Duration of Study:** *From 16 February 2025 to 16 May 2025.* **Methods:** *A total of 176 preterm neonates were included, comprising 88 cases with early-onset neonatal sepsis and 88 age-matched controls without sepsis. Cases were defined as neonates aged birth to seven days presenting with clinical features of sepsis confirmed by hematological criteria, while controls were healthy preterm neonates without sepsis. Data were collected on potential risk factors, including mode of delivery, premature rupture of membranes (PROM), prolonged rupture of membranes (>18 hours), maternal urinary tract infection, low birth weight, meconium-stained amniotic fluid, and low Apgar score at five minutes. Clinical outcomes, including recovery, mortality, and length of hospital stay, were also recorded. Statistical analysis was performed using SPSS, and comparisons between groups were made using appropriate significance tests, with p ≤ 0.05 considered statistically significant.* **Results:** *Premature rupture of membranes occurred in 63.6% of cases compared with 44.3% of controls (p = 0.01). Maternal urinary tract infection was observed in 34.1% of cases versus 18.2% of controls (p = 0.01), while prolonged rupture of membranes occurred in 29.5% of cases compared with 13.6% of controls (p = 0.01). Low birth weight was present in 81.8% of cases versus 63.6% of controls (p = 0.007). Meconium-stained amniotic fluid was noted in 31.8% of cases compared with 13.6% of controls (p = 0.004), and a low Apgar score at five minutes occurred in 42.0% of cases compared with 26.1% of controls (p = 0.02). Among septic neonates, 73.9% recovered, mortality was observed in 5.7%, and 67.0% required a hospital stay of seven days or longer.* **Conclusion:** *Premature rupture of membranes, maternal urinary tract infection, prolonged rupture of membranes, low birth weight, meconium-stained amniotic fluid, and low Apgar score were significant risk factors for early-onset neonatal sepsis among preterm neonates. Early identification and management of these factors may improve neonatal outcomes and reduce sepsis-related morbidity and mortality.*

Keywords: Neonatal Sepsis, Preterm Infants, Risk Factors, Outcomes, Mortality, Hospital Stay

INTRODUCTION

Early-onset neonatal sepsis is a life-threatening condition that occurs within the first 72 hours of birth, mainly caused by bacterial invasion immediately after birth or during labour. It is considered one of the major causes of morbidity and mortality across the world, with peak burden observed in the low-income countries in which resources are constrained (1-3). Preterm neonates are vulnerable to early-onset neonatal sepsis because of their immature immune systems and exposure to invasive procedures in NICUs. Sepsis contributes considerably to neonatal mortality, emphasizing the need for early recognition as well as effective management strategies (4, 5).

Lower gestational age is shown to be linked with increased vulnerability to infection, extended NICU admission, and greater mortality rates (4, 6). Preterm neonates, in comparison to term infants, are more likely to face sepsis, hemodynamic instability, and multi-organ dysfunction, which muddle the clinical management (6, 7). Maternal risk factors, including the PROM and chorioamnionitis, further intensify the probability of pathogens' vertical transmission, thus increasing the occurrence of neonatal sepsis within the preterm infants. PROM has been recognized as a major maternal risk factor linked to early neonatal infection (8, 9).

The non-specificity of clinical signs emphasises the importance of maternal risk stratification and neonatal evaluation for improving early detection. Over time, identification of risk factors and implementation of antibiotic therapy remain central to reducing sepsis-related mortality (10). Inconsistent practices in identifying and

responding to such risk factors in resource-scarce contexts may delay diagnosis and exacerbate outcomes. Surviving preterm neonates with early-onset sepsis usually experience complications, including necrotising enterocolitis and developmental delays, which may have strong effects on long-term QoL. Preterm neonates are vulnerable to complications arising from the prolonged antibiotic exposure, raising concerns regarding antimicrobial resistance (10-12).

Preterm infants are predisposed to infection due to immunological immaturity and the frequent need for invasive supportive interventions, making them vulnerable during the first 72 hours of life. Understanding the association between risk determinants and clinical outcomes in preterm neonates with early-onset neonatal sepsis is essential for improving risk stratification and optimising NICU practices. Generating context-explicit evidence will also support the Development of targeted preventive strategies and contribute to reducing the sepsis-associated mortalities among such high-risk populations.

METHODOLOGY

This case-control study was conducted in the Department of Pediatrics at Khyber Teaching Hospital, Peshawar, from 16 February 2025 to 16 May 2025. Ethical approval was obtained from the hospital's ethics review board. The sample size was 176, with 88 cases and 88 controls. Inclusion criteria for cases were for neonates born in this hospital who were preterm with early neonatal sepsis; the age of the neonates was from birth to 7 days of life. Early onset neonatal sepsis referred to an

infection involving bloodstream in newborn infants from birth to 7th day of life, characterized by fever (>37.5"C) or hypothermia (> 60 breaths per minute), severe chest indrawing, not feeding well and was confirmed by the presence of two of the hematological criteria (total leukocyte count < 4000 or > 12000 cells/mm³, absolute neutrophil count < 1500 cell/mm³ or > 7500 cells/mm³, erythrocyte sedimentation rate (ESR) > 15 in the first hour and positive microbiological cultures from blood or cerebrospinal fluid. It was labelled if two hematological criteria and any one clinical criterion were met.

The inclusion criteria for controls included both genders, all preterm neonates born in this hospital presenting without early neonatal sepsis, and age from birth to seven days of life. The exclusion criteria for both cases and controls included neonates with perinatal asphyxia, neonates whose mothers were not available for interview, neonates who were born outside of the hospital, neonates who were clinically suspected of sepsis but not confirmed by hematological tests, and neonates who expired without receiving any treatment on arrival.

All neonates presenting to the Department of Pediatrics with clinical features of early neonatal sepsis and diagnosed as such were included in the study, according to the inclusion and exclusion criteria, as cases in group A. The cases were managed in accordance with the unit's neonatal sepsis treatment protocol. An equal number of age-matched neonates were included in group B as controls, according to the inclusion and exclusion criteria. Informed consent was taken from the parents for their inclusion in this study. All cases were admitted to the pediatrics ward to obtain a proper history, conduct an investigation, and thoroughly examine the patients. The controls were sent home and called for weekly follow-up until one month of age to ensure their health status. Risk factors were recorded, such as premature rupture of the membrane, defined as the rupture of the amniotic sac and leakage of amniotic fluid before the onset of labor in a pregnant woman. Prolonged rupture of membrane was defined as the time from membrane rupture to the onset of delivery > 18 hours. Meconium-stained amniotic fluid, low birth weight (< 2500 grams). Maternal UTI was defined as the presence of at least 100,000 organisms per milliliter of urine in an asymptomatic patient or as more than 100 organisms/mL of urine with accompanying pyuria (> 7 white blood cells/mL) in a symptomatic patient. A low APGAR score was defined as less than 7 at 5 minutes after delivery.

SPSS 23 was used for data analysis. Mean and standard deviation were used for numerical variables such as age, gestational age, APGAR score, and birth weight. Frequencies and percentages were used for categorical variables, such as neonatal gender, risk factors, and sepsis outcomes. Risk factors were assessed between cases and controls using the chi-square test, with a P-value significant at ≤ 0.05.

RESULTS

This study included 176 preterm neonates with 88 cases diagnosed with early-onset sepsis and 88 controls without sepsis. The mean age of neonates in the case group was 4.30±2.01 days, while in the control

group it was 4.11±1.94 days. Male neonates were the majority in both groups, with 59 (67.0%) in the case group and 52 (59.1%) in the control group.

Table 4 presents the analysis of risk factors of new onset of neonatal sepsis in both groups. Regarding mode of delivery, normal vaginal delivery occurred in 49 (55.7%) of cases and 57 (64.8%) of controls, while Caesarean section was performed in 39 (44.3%) of cases and 31 (35.2%) of controls (p=0.21). Premature rupture of membranes was observed in 56 (63.6%) neonates in cases compared to 39 (44.3%) in the control group (p=0.01). Maternal urinary tract infection was present in 30 (34.1%) of cases and 16 (18.2%) of controls (p=0.01). Prolonged rupture of membranes occurred in 26 (29.5%) cases, while 12 (13.6%) controls, which was statistically significant (p=0.01). Low birth weight was observed in 72 (81.8%) of cases, while 56 (63.6%) in the control group (p=0.007). Meconium-stained amniotic fluid was observed in 28 (31.8%) of cases and only 12 (13.6%) of controls (p=0.004). A low APGAR score of less than seven at five minutes was observed in 37 (42.0%) of cases and 23 (26.1%) of controls (p=0.02). Among the 88 neonates with early-onset sepsis, 65 (73.9%) recovered from sepsis. Mortality was observed in 5 (5.7%) cases. Regarding duration of hospitalization, 29 (33.0%) of sepsis neonates had a hospital stay of less than 7 days, while 59 (67.0%) had a hospital stay of> 7 days.

Table 1: Descriptive statistics

Groups		Age (days)	Gestational age (weeks)	APGAR score	Birth weight (grams)
Group A (Cases)	Mean	4.30	33.22	5.75	2197.9318
	N	88	88	88	88
	Std. Deviation	2.007	1.745	2.780	309.29567
Group B (Controls)	Mean	4.11	33.52	7.16	2372.3864
	N	88	88	88	88
	Std. Deviation	1.938	1.755	1.492	246.66760

Table 2: Gender distribution

		Groups			
		Group A (Cases)		Group B (Controls)	
		n	%	n	%
Gender	Male	59	67.0%	52	59.1%
	Female	29	33.0%	36	40.9%

Table 3: Outcomes of early-onset neonatal sepsis

Outcomes		n	%
Recovery from sepsis	Yes	65	73.9%
	No	23	26.1%
Mortality	Yes	5	5.7%
	No	83	94.3%
Hospital stay	< 7 days	29	33.0%
	> = 7 days	59	67.0%

Table 4: Risk factors of sepsis

Risk factors of sepsis		Groups				P value
		Group A (Cases)		Group B (Controls)		
		n	%	n	%	
Mode of delivery	Normal vaginal	49	55.7%	57	64.8%	0.21
	C-section	39	44.3%	31	35.2%	
PROM	Yes	56	63.6%	39	44.3%	0.01
	No	32	36.4%	49	55.7%	
Maternal UTI	Yes	30	34.1%	16	18.2%	0.01
	No	58	65.9%	72	81.8%	
Prolonged rupture of membranes	Yes	26	29.5%	12	13.6%	0.01

	No	62	70.5%	76	86.4%	
Low birth weight	Yes	72	81.8%	56	63.6%	0.007
	No	16	18.2%	32	36.4%	
Meconium-stained amniotic fluid	Yes	28	31.8%	12	13.6%	0.004
	No	60	68.2%	76	86.4%	
Low APGAR < 7 at 5 mins	Yes	37	42.0%	23	26.1%	0.02
	No	51	58.0%	65	73.9%	

DISCUSSION

The present study examined the risk factors and outcomes associated with early-onset neonatal sepsis among preterm infants. The mean age of neonates in the case group was 4.30±2.01 days, which aligns with findings from Munir et al., who reported a mean age of 4.13±0.85 days in neonates with sepsis (14). This similarity suggests that early-onset sepsis typically manifests within the first few days of life across different geographical settings. The mean gestational age in the present study was 33.22±1.75 weeks for cases, which is again comparable to the gestational age of 32.56±0.25 weeks reported by Munir et al. in their preterm group.[14] Birgisdottir et al. also reported similar gestational ages in their cohort (15).

The mean birth weight in the present study was lower among cases at 2197.93 ± 309.30 grams, consistent with the work of Wilar et al., who reported that nearly half of their neonatal sepsis subjects weighed less than 2500 grams at birth.[16] Munir et al. documented that 82% of their early onset sepsis cases had low birth weight, with rates of 75.8% in preterm and 92.1% in full term neonates (14). Another study by Guo et al. confirmed very low birth weight as a significant risk factor with a pooled odds ratio of 3.79 (4).

Regarding mode of delivery, the present study found no statistically significant difference between cases and controls, with C-section rates of 44.3% and 35.2%, respectively. This aligns with Hussain et al., who reported similar C-section rates of 40.8% in early-onset sepsis and 41.4% in late-onset sepsis, with no significant association (17). Lemma et al. also reported that while C-section showed an initial association on crude analysis, it lost significance after multivariable adjustment (18). These findings suggest that the mode of delivery may not independently influence sepsis risk when other factors are accounted for.

Premature rupture of membranes was a significant risk factor for sepsis in the present study, affecting 63.6% of cases compared to 44.3% of controls. This finding is consistent with Guo et al., who reported a pooled odds ratio of 2.63 for this factor (4). The present study further observed that rupture > 18 occurred in 29.5% of cases compared to 13.6% of controls. At the same time, Lemma et al. similarly reported that the risk of neonatal sepsis was higher in neonates born to mothers who had premature rupture of membranes greater than eighteen hours (18). Maternal urinary tract infection was observed in 34.1% of cases, compared with 18.2% of controls; this finding is supported by several studies (4, 16).

Meconium-stained amniotic fluid was observed in the majority of cases in this study, compared with controls; this finding is supported by Guo et al., who reported a pooled odds ratio of 4.51, making it one of the strongest risk factors identified (4).

A low APGAR score at five minutes was significantly more common among cases; this finding aligns with Wilar and Lestari, who noted that low APGAR scores were present in a substantial proportion of cases (16).

The findings of this study reinforce the importance of maternal factors such as urinary tract infection, premature rupture of membranes, and meconium-stained amniotic fluid in the pathogenesis of early-onset sepsis. The study also adds to the limited data on clinical outcomes among preterm neonates with sepsis in the local context, providing recovery and mortality rates that can inform clinical expectations and resource planning.

CONCLUSION

In conclusion, the present study identified premature rupture of membranes, maternal urinary tract infection, meconium-stained amniotic fluid, low birth weight, and low APGAR score as significant risk factors for early-onset neonatal sepsis in preterm neonates. The recovery rate was 73.9%, the mortality rate was 5.7%, and 67% of neonates needed a prolonged hospital stay. These findings emphasize the need for enhanced antenatal monitoring, strict intrapartum monitoring, and prompt identification of neonates at risk to improve clinical outcomes.

DECLARATIONS

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

***MUHAMMAD ZAID HAMID** (Postgraduate Resident)*
Data collection, data entry, data analysis, and drafting an article, Review of Literature.
***ZIA MUHAMMAD** (Associate Professor)*
Conception of Study, Development of Research Methodology Design, Study Design, Review of manuscript, and final approval of manuscript and critical input.

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