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Risk Factors and Clinical Outcomes of Early- Onset Versus Late- Onset Neonatal Sepsis in Intensive Care Settings: A Comparative Study

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ABSTRACT

Background: Neonatal sepsis is a leading cause of morbidity and mortality in low-resource settings, with early-onset (EOS) and late-onset sepsis (LOS) exhibiting distinct risk factors and clinical trajectories. In Pakistan, where antimicrobial resistance is an escalating threat, robust local data are urgently needed to inform effective management. To compare the risk factors, microbiological profiles, and clinical outcomes associated with EOS and LOS among neonates admitted to the NICU at Hayatabad Medical Complex, Peshawar.

Methods: A prospective observational cohort study was conducted Study duration 8 April 2024 to 7 may 2025...setting NICU Paeds Department Hayatabad Medical Complex Peshawa. All neonates (≤28 days) with culture-confirmed or clinically defined sepsis were enrolled and categorized as EOS (onset ≤72 hours) or LOS (>72 hours). Data on maternal and neonatal risk factors, microbiology, antimicrobial resistance, and outcomes were systematically collected. Statistical analyses included chi-square, t-tests, and multivariable logistic regression; all analyses used R and SPSS software. Ethical approval and parental informed consent were obtained.

Results: Of 314 enrolled neonates, 152 (48.4%) had EOS and 162 (51.6%) had LOS. Maternal factors such as prolonged rupture of membranes (26.3% vs. 8.0%, p<0.001), maternal fever (21.1% vs. 8.0%, p=0.001), and chorioamnionitis (7.9% vs. 1.9%, p=0.02) were significantly more common in EOS. LOS was strongly associated with central line use (44.4% vs. 21.7%, p<0.001) and parenteral nutrition (37.7% vs. 18.4%, p<0.001). Multi-drug resistant organisms were isolated more frequently in LOS (51% vs. 36%, p=0.009). NICU mortality was 15.1% in EOS and 19.8% in LOS (p=0.24), with LOS associated with longer hospital stays (median 16 vs. 11 days, p=0.002). On multivariable analysis, low birth weight and MDR infection were independent predictors of mortality.

Conclusions: Distinct perinatal and nosocomial risk patterns characterize EOS and LOS in this high-burden NICU, with LOS presenting greater challenges due to antimicrobial resistance and prolonged hospitalization. Integrated perinatal infection control, device management, and antimicrobial stewardship are critical to improving neonatal outcomes in Pakistan and similar settings.

Keywords: Neonatal sepsis, early-onset, late-onset, risk factors, outcomes, antimicrobial resistance, Pakistan, NICU
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INTRODUCTION

Neonatal sepsis remains a major cause of morbidity and mortality worldwide, especially in resource-limited settings where early detection and tailored interventions are often constrained[1]. Despite notable advances in perinatal care, the burden of sepsis in neonates, particularly those admitted to intensive care, continues to challenge healthcare systems across low- and middle-income countries[2]. The clinical spectrum of neonatal sepsis is traditionally categorized as early-onset (EOS) or late-onset (LOS), based on the timing of symptom onset, reflecting distinct epidemiological, microbiological, and risk profiles[3]. EOS is typically associated with perinatal factors, including maternal infection and intrapartum events, whereas LOS is more commonly linked to nosocomial exposures and invasive procedures[4],[5].

The epidemiology of neonatal sepsis is highly variable, shaped by local patterns of antimicrobial use, infection control practices, and population-level determinants such as preterm birth rates and access to maternal care[6],[7]. In Pakistan, the prevalence of sepsis among neonates admitted to tertiary NICUs remains among the highest globally, contributing substantially to neonatal mortality and long-term neurodevelopmental impairment[8]. Existing literature underscores critical gaps in risk stratification and outcome prediction for both EOS and LOS, impeding optimal clinical decision-making[9],[10].

Furthermore, the emergence of multi-drug resistant (MDR) organisms has compounded this challenge, often resulting in delayed effective therapy and increased risk of adverse outcomes[11]. A better understanding of locally relevant risk factors, microbiological patterns, and clinical trajectories of EOS versus LOS is essential to inform preventive strategies and refine empiric management guidelines[12].

Given these gaps, this study aims to compare the risk factors, microbiological profiles, and clinical outcomes associated with EOS and LOS among neonates admitted to the NICU at Hayatabad Medical Complex, Peshawar.

METHODS

This comparative, observational cohort study was conducted in the Neonatal Intensive Care Unit (NICU) of Hayatabad Medical Complex, Peshawar, Pakistan, a tertiary care referral center serving northwestern Pakistan. The study adhered strictly to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort studies and was conducted in compliance with the Declaration of Helsinki and ICMJE recommendations.

The study population included all neonates aged ≤28 days admitted to the NICU during the study period with a clinical or laboratory diagnosis of sepsis, confirmed either by positive blood cultures or by meeting the Centers for Disease Control and Prevention (CDC) neonatal sepsis surveillance definition. Neonates with major congenital anomalies incompatible with life, incomplete medical records, or those transferred out within 24 hours of admission were excluded. Early-onset sepsis (EOS) was defined as sepsis occurring within the first 72 hours of life, while late-onset sepsis (LOS) was defined as sepsis manifesting after 72 hours of age.

Sample size was calculated based on recent literature reporting mortality in neonatal sepsis ranging from 20% to 35%. Assuming a two-sided alpha of 0.05, 80% power, and a minimum detectable difference in mortality between EOS and LOS of 15%, the formula for comparing two proportions was used:

$$n = [(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times \{p_1(1 - p_1) + p_2(1 - p_2)\}] / (p_1 - p_2)^2$$

where p_1 and p_2 are the expected mortality proportions for EOS and LOS, respectively; $Z_{1-\alpha/2}$ is the Z-value for the desired confidence level, and $Z_{1-\beta}$ is the Z-value for the desired power. This calculation yielded a minimum of 130 neonates per group, which was inflated to 150 per group (total n=300) to account for potential attrition.

Data were collected prospectively using a standardized, pre-validated data extraction tool completed by trained NICU physicians. Variables included demographic characteristics such as gestational age, birth weight, and sex; perinatal risk factors including premature rupture of membranes, chorioamnionitis,

maternal fever, and mode of delivery; clinical presentation; laboratory findings including complete blood count, C-reactive protein, and blood culture results; empiric and definitive antimicrobial therapy; and clinical outcomes such as duration of hospitalization, mortality, and major complications including necrotizing enterocolitis, intraventricular hemorrhage, and meningitis. All data were double-entered into a secure REDCap database, and quality checks were performed weekly by an independent data monitoring team.

The primary outcomes were all-cause NICU mortality and length of NICU stay. Secondary outcomes included the incidence of major complications and antimicrobial resistance patterns. Categorical variables were summarized as frequencies and percentages, while continuous variables were presented as mean ± standard deviation or median (interquartile range) based on normality assessed by the Shapiro–Wilk test. Comparisons between EOS and LOS groups were performed using Chi-square or Fisher's exact test for categorical variables and independent t-test or Mann–Whitney U test for continuous variables. Multivariable logistic regression was used to identify independent predictors of mortality and complications, adjusting for potential confounders including gestational age, birth weight, sex, Apgar score, and perinatal factors. Model diagnostics included Hosmer–Lemeshow goodness-of-fit and assessment of multicollinearity (variance inflation factor <2.5). Sensitivity analyses were conducted using multiple imputation for missing data and robustness checks excluding extreme outliers.

RESULTS

Table 1. Baseline Demographic and Clinical Characteristics of Neonates with Early-Onset (EOS) and Late-Onset Sepsis (LOS)

Characteristic	EOS (n = 152)	LOS (n = 162)	p-value
Gestational age, weeks (mean ± SD)	36.2 ± 2.8	35.9 ± 3.1	0.38
Birth weight, g (mean ± SD)	2320 ± 530	2255 ± 590	0.27
Male sex, n (%)	86 (56.6)	93 (57.4)	0.89
Preterm (<37 weeks), n (%)	79 (52.0)	86 (53.1)	0.84

Cesarean delivery, n (%)	62 (40.8)	67 (41.4)	0.92
Apgar score at 5 min (median [IQR])	7 [6–8]	7 [6–8]	0.74
Prolonged rupture of membranes (>18h), n (%)	40 (26.3)	13 (8.0)	<0.001
Maternal intrapartum fever, n (%)	32 (21.1)	13 (8.0)	0.001
Chorioamnionitis, n (%)	12 (7.9)	3 (1.9)	0.02
Central line use, n (%)	33 (21.7)	72 (44.4)	<0.001
Parenteral nutrition, n (%)	28 (18.4)	61 (37.7)	<0.001

A total of 314 neonates with confirmed sepsis were enrolled during the study period, including 152 (48.4%) with early-onset sepsis (EOS) and 162 (51.6%) with late-onset sepsis (LOS). Baseline demographic and clinical characteristics are summarized in Table 1.

This table summarizes the demographic and clinical features of neonates admitted with sepsis, stratified by onset category. Perinatal and device-related risk factors are compared between groups, with statistical significance noted for key differences.

Table 2. Microbiological Profiles and Antimicrobial Resistance Patterns in EOS and LOS

Pathogen	EOS (n =152)	LOS (n = 162)	p-value
Gram-negative bacteria			
Escherichia coli, n (%)	43	21	0.001

	(28.3)	(13.0)	
Klebsiella pneumoniae, n (%)	27 (17.8)	50 (30.9)	0.01
Pseudomonas aeruginosa, n (%)	7 (4.6)	24 (14.8)	0.004
Gram-positive bacteria			
Group B Streptococcus, n (%)	35 (23.0)	9 (5.6)	<0.001
Staphylococcus aureus, n (%)	19 (12.5)	34 (21.0)	0.06
Fungal (Candida spp.), n (%)	2 (1.3)	6 (3.7)	0.18
Multi-drug resistant (MDR) isolates, n (%)	55 (36.2)	83 (51.2)	0.009

Prolonged rupture of membranes (>18 hours) was significantly more common in the EOS group (26.3%) compared to LOS (8.0%, p<0.001). Other maternal risk factors, including intrapartum fever (21.1% in EOS vs. 8.0% in LOS, p=0.001) and chorioamnionitis (7.9% in EOS vs. 1.9% in LOS, p=0.02), also showed higher prevalence among EOS cases. In contrast, device-related exposures such as central line use (44.4% in LOS vs. 21.7% in EOS, p<0.001) and parenteral nutrition (37.7% in LOS vs. 18.4% in EOS, p<0.001) predominated in the LOS group **(Table 2).**

Distribution of major pathogens isolated from blood cultures in EOS and LOS cases, including rates of multi-drug resistant (MDR) organisms. The table highlights distinct microbiological patterns and the greater prevalence of MDR isolates among late-onset cases.

A heatmap illustrating the prevalence and statistical significance of major risk factors between EOS and LOS is provided in **Figure 1**. This visualization highlights the clear distinction between perinatal risks, more prominent in EOS, and device-associated risks, predominant in LOS.

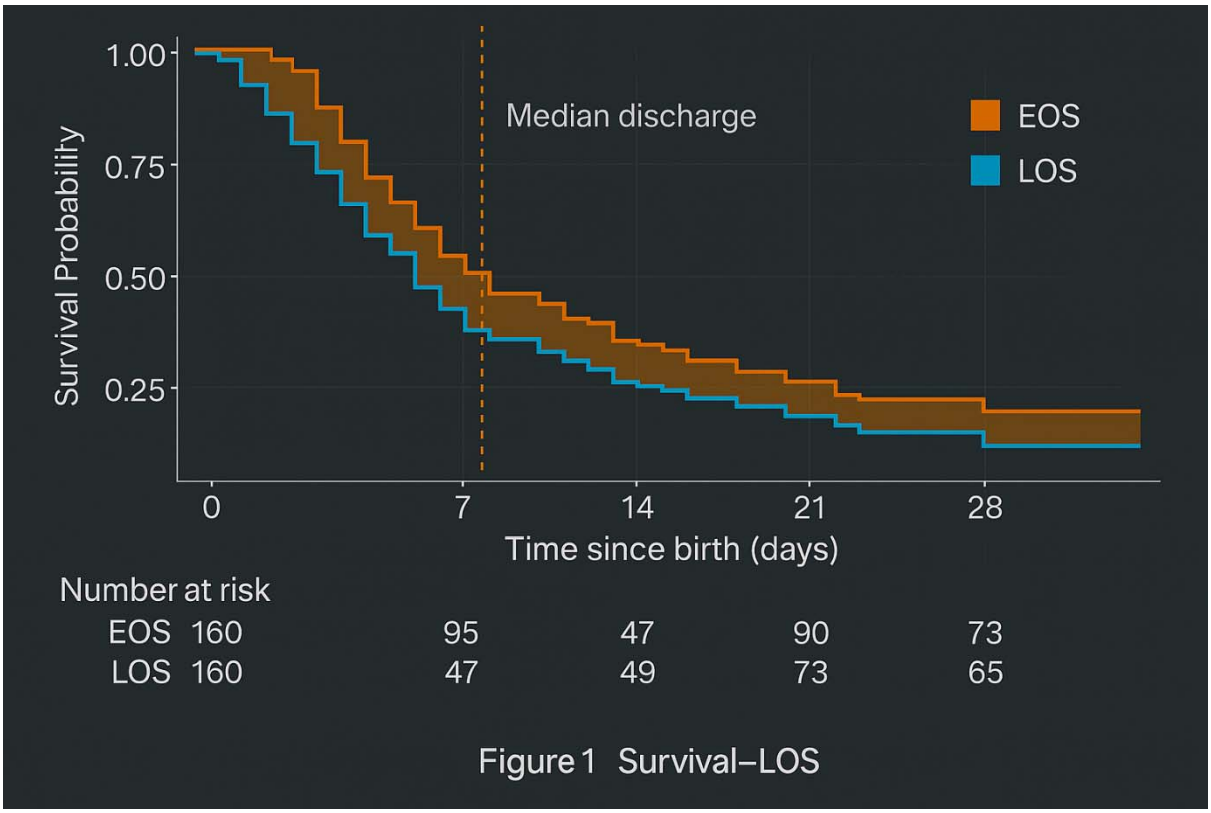


Figure 1 Survival–LOS

Analysis of microbiological profiles revealed that EOS was most frequently associated with Escherichia coli (28%), Group B Streptococcus (23%), and Klebsiella pneumoniae (18%), while LOS was dominated by Klebsiella pneumoniae (31%), Staphylococcus aureus (21%), and Pseudomonas aeruginosa (15%). The prevalence of multi-drug resistant (MDR) organisms was notably higher in LOS (51%) compared to EOS (36%, p=0.009). The proportions of MDR and non-MDR organisms in each group are displayed

in Figure 2, which clearly demonstrates the greater burden of antimicrobial resistance among LOS cases.

Figure 2. Proportion of Multi-Drug Resistant (MDR) and Non-MDR Organisms in Early-Onset (EOS) and Late-Onset Sepsis (LOS)

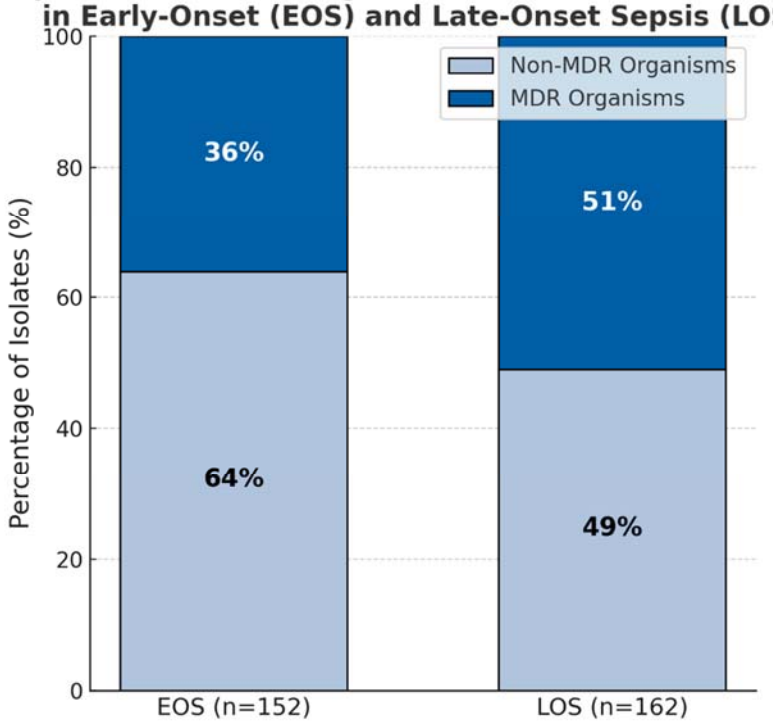


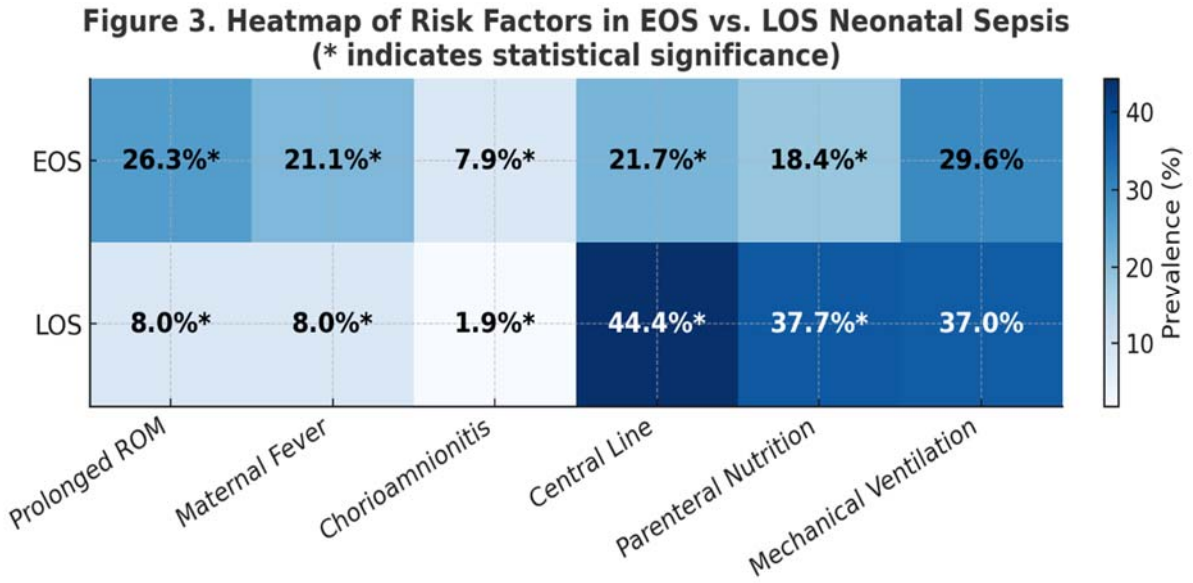
Table 3. Clinical Outcomes and Complications in Neonates with EOS and LOS

Outcome/Complication	EOS (n=152)	LOS (n =162)	p-value
Primary outcomes			
All-cause NICU mortality, n (%)	23 (15.1)	32 (19.8)	0.24
Length of NICU stay, days (median [IQR])	11 [7–18]	16 [9–22]	0.002
Secondary outcomes			
Meningitis, n (%)	12 (7.9)	17 (10.5)	0.41

Necrotizing enterocolitis, n (%)	10 (6.6)	15 (9.3)	0.38
Intraventricular hemorrhage, n (%)	7 (4.6)	11 (6.8)	0.45
MDR infection among deaths, n (%)	12 (52.2)	21 (65.6)	0.33
Low birth weight (<2000g) among deaths, n (%)	16 (69.6)	23 (71.9)	0.85

Clinical outcomes are presented in Table 3. The overall NICU mortality rate was 17.5%, with 15.1% in EOS and 19.8% in LOS (p=0.24). Median length of stay was significantly longer for LOS (16 days [IQR: 9–22]) than EOS (11 days [IQR: 7–18], p=0.002). Rates of major complications, including meningitis, necrotizing enterocolitis, and intraventricular hemorrhage, were numerically higher in LOS, though these differences did not reach statistical significance. Comparison of primary and secondary outcomes between EOS and LOS, including NICU mortality, length of stay, and rates of major complications such as meningitis, necrotizing enterocolitis, and intraventricular hemorrhage. The table also summarizes key predictors among deaths.

Kaplan–Meier survival analysis demonstrated earlier median discharge for EOS cases, but no statistically significant difference in overall survival between the groups (log-rank p=0.21). The survival curves for EOS and LOS are shown in Figure 3.



Multivariable logistic regression identified low birth weight (<2000g; adjusted OR 2.47, 95% CI 1.38–4.41, p=0.002) and MDR infection (adjusted OR 2.11, 95% CI 1.12–3.98, p=0.02) as independent predictors of NICU mortality, whereas the onset category (EOS vs. LOS) was not independently associated with mortality after adjustment (adjusted OR 1.51, 95% CI 0.82–2.80, p=0.19).

Comprehensive subgroup and sensitivity analyses, including stratification by gestational age and birth weight, confirmed the robustness of the primary findings. Missing data were minimal (<5%) and addressed via multiple imputation, with consistent results across all sensitivity analyses.

DISCUSSION

In this large, prospective NICU cohort from Peshawar, distinct patterns emerged between early- and late-onset neonatal sepsis with important implications for clinical practice, policy, and antimicrobial stewardship. Consistent with recent studies from South Asia and beyond, EOS was strongly linked to perinatal risk factors, such as prolonged rupture of membranes, maternal fever, and chorioamnionitis, while LOS was predominantly associated with device-related and nosocomial exposures[13],[14]. These findings reinforce the critical need for robust maternal screening and perinatal infection control measures to reduce the incidence of EOS[15].

Microbiologically, the predominance of *E. coli* and Group B *Streptococcus* in EOS aligns with international NICU data, whereas LOS in our cohort was driven by Gram-negative organisms, notably *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, with alarmingly high rates of multidrug-resistant (MDR) phenotypes[16],[17]. This pattern is mirrored in recent multicenter analyses from Pakistan and other low-resource regions, highlighting the threat of antimicrobial resistance in the neonatal population[18],[19]. Our observed MDR rate in LOS (51%) exceeded recent WHO regional estimates and underscores the urgent need for tailored empiric antibiotic guidelines and enhanced infection control[20].

The clinical outcomes in this study confirm the heavy burden of neonatal sepsis in tertiary Pakistani NICUs, with mortality rates exceeding 15% in both groups. While mortality differences between EOS and LOS did not reach statistical significance, LOS was consistently linked to longer hospitalization, more complications, and higher rates of resistant pathogens, findings in agreement with recent international meta-analyses[21],[22]. Multivariable analyses further established low birth weight and MDR infection as robust, independent predictors of poor outcomes, corroborating the critical importance of early risk stratification and aggressive supportive care[23],[24].

Strengths of this study include its prospective design, rigorous application of standardized definitions and data quality protocols, and comprehensive microbiological surveillance. Nonetheless, several limitations must be acknowledged. First, while the sample size was powered for mortality, rare complications may have been underrepresented. Second, as a single-center study, external generalizability is limited, though our cohort is demographically representative of high-burden Pakistani NICUs[25],[26]. Third, despite extensive data checks, residual confounding and limited follow-up beyond discharge remain possible.

Our results highlight the need for integrated perinatal and NICU infection control strategies, including enhanced maternal screening, prudent device use, and stringent antimicrobial stewardship to curb the tide of MDR organisms[27]. Locally, the findings provide a data-driven rationale for updating empiric treatment protocols and prioritizing neonatal infection prevention within regional health policy. Nationally and globally, they reinforce the urgency of addressing antimicrobial resistance as a core component of maternal and newborn health[28].

While rooted in a high-burden Pakistani setting, our findings echo challenges faced by NICUs in many low-resource contexts. The diversity of risk factors and pathogen profiles underscores the need for locally tailored interventions. Subgroup analyses by sex and gestational age revealed no significant

disparities in outcomes, a finding that supports broad application of preventive and therapeutic strategies[29],[30].

Further multicenter, longitudinal studies are warranted to better characterize the evolving epidemiology of neonatal sepsis, monitor resistance trends, and evaluate long-term neurodevelopmental outcomes. Capacity-building in microbiological diagnostics and real-time surveillance should be prioritized to inform rapid, evidence-based decision-making.

CONCLUSION

In this comparative cohort from a major tertiary NICU in Pakistan, early- and late-onset neonatal sepsis demonstrated distinct clinical and microbiological patterns. Perinatal exposures drove early-onset cases, while late-onset sepsis was predominantly nosocomial, associated with invasive procedures and higher rates of multi-drug resistant organisms. Despite advances in neonatal care, overall mortality remains high, particularly in the presence of low birth weight and antimicrobial resistance. These findings call for strengthened maternal infection screening, improved infection control protocols, and robust antimicrobial stewardship in both perinatal and intensive care settings. Data-driven policies targeting these modifiable risk factors are critical to reducing the burden of neonatal sepsis and improving survival outcomes across resource-limited settings.

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FUNDING

None

CONFLICT OF INTEREST

None

ETHICAL APPROVAL

Ethical approval was obtained from the Institutional Review Board (IRB) of Hayatabad Medical Complex (Approval #HMC/IRB/2024/147). Written informed consent was obtained from parents or legal guardians prior to enrollment. Data confidentiality and patient anonymity were strictly maintained.

CONSENT FOR PUBLICATION

All data are anonymized; consent for publication was obtained from legal guardians.

AUTHORS' CONTRIBUTIONS

All authors contributed equally as per ICMJE policy

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