

ASSOCIATION OF MATERNAL AND NEONATAL RISK FACTORS WITH EARLY ONSET NEONATAL SEPSIS

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ABSTRACT

BACKGROUND

Early-onset neonatal sepsis (EONS) remains a significant cause of neonatal morbidity and mortality, particularly in low- and middle-income countries. It is primarily acquired through vertical transmission and is influenced by a combination of maternal, intrapartum, and neonatal factors. Identifying locally relevant risk factors is essential for improving early recognition, guiding preventive strategies, and optimizing neonatal care.

OBJECTIVE

To determine the association between selected maternal and neonatal risk factors and the occurrence of early-onset neonatal sepsis among neonates admitted to the neonatal unit of Combined Military Hospital (CMH) Abbottabad.

METHODS

A hospital-based unmatched case-control study was conducted over five months, from 15 August 2024 to 15 January 2025, at CMH Abbottabad. Neonates aged ≤72 hours admitted to the NICU were enrolled. A total of 240 neonates were included in the final analysis after exclusions, comprising 120 cases diagnosed with EONS and 120 controls admitted for non-infectious conditions. Data on maternal, intrapartum, and neonatal variables were collected using a structured proforma. EONS was defined based on clinical features and supportive laboratory findings, with or without a positive blood culture. Statistical analysis was performed using appropriate univariate tests, followed by multivariate logistic regression to identify independent predictors of EONS. Adjusted odds ratios (AORs) with 95% confidence intervals were reported.

RESULTS

Among the 120 EONS cases, 38 (31.7%) were culture-positive. Maternal factors significantly associated with EONS included unbooked antenatal status (40.8% vs 20.0%, $p=0.001$), maternal anemia (43.3% vs 24.2%, $p=0.002$), urinary tract infection (32.5% vs 15.0%, $p=0.002$), genital tract infection (15.8% vs 6.7%, $p=0.03$), prolonged rupture of membranes ≥18 hours (34.2% vs 10.0%, $p<0.001$), intrapartum fever ≥38°C (21.7% vs 5.8%, $p<0.001$), and suspected chorioamnionitis (15.0% vs 3.3%, $p=0.002$). Neonatal factors significantly associated with EONS included preterm birth (25.8% vs 13.3%, $p=0.01$), low birth weight (54.2% vs 30.0%, $p<0.001$), Apgar score <7 at 1 minute (24.2% vs 10.8%, $p=0.008$), and need for resuscitation at birth (19.2% vs 7.5%, $p=0.009$). On multivariate analysis, independent predictors of EONS were

prolonged rupture of membranes (AOR 3.82), maternal intrapartum fever (AOR 4.11), preterm birth (AOR 2.34), low birth weight (AOR 2.97), maternal urinary tract infection (AOR 1.96), and unbooked antenatal status (AOR 2.12). Group B Streptococcus (28.9%) and Escherichia coli (26.3%) were the most commonly isolated organisms.

CONCLUSION

Early-onset neonatal sepsis in this setting is strongly associated with preventable maternal risk factors and neonatal vulnerabilities. Prolonged rupture of membranes, maternal intrapartum fever, untreated maternal urinary tract infection, inadequate antenatal care, prematurity, and low birth weight were the most significant predictors. Strengthening antenatal screening, improving intrapartum monitoring, and ensuring early neonatal surveillance for at-risk infants may substantially reduce the burden of EONS in similar resource-limited settings.

KEY WORDS.

Early-onset neonatal sepsis; Maternal risk factors; Neonatal risk factors; Prolonged rupture of membranes; Intrapartum fever; Low birth weight; Preterm birth; Case-control study

INTRODUCTION

Early-onset neonatal sepsis (EONS) remains one of the leading causes of illness and death among newborns worldwide. Its impact is especially serious in low- and middle-income countries, where gaps in antenatal care, delays in diagnosis, and limited laboratory facilities often prevent timely treatment. EONS is usually defined as sepsis occurring within the first 72 hours of life, most often due to vertical transmission of pathogens from the mother to the baby before or during delivery. Because the disease can progress quickly—and early symptoms are often vague or easily missed—understanding the underlying risk factors is crucial for early recognition and prompt intervention.^{1–3} Maternal factors play a major role in determining a newborn's vulnerability to EONS. Well-established risks include maternal fever during labour, chorioamnionitis, prolonged rupture of membranes (PROM), urinary or genital tract infections, Group B Streptococcus (GBS) colonisation, and inadequate intrapartum antibiotic prophylaxis.^{2–4} These conditions increase the chance of ascending infection and fetal exposure to harmful organisms. Socio-demographic factors—such as young maternal age, poor nutrition, limited access to prenatal care, and overall low socioeconomic status—also influence risk by shaping the quality and timing of maternal healthcare. In many resource-limited settings, consistent antenatal screening for infections (including GBS) is lacking, which further increases vulnerability.⁵ Neonatal characteristics are equally important in shaping susceptibility to early sepsis. Preterm birth, low birth weight, intrauterine growth restriction (IUGR), perinatal asphyxia, and the need for invasive resuscitation all compromise

the already immature immune system of the newborn, making infection more likely. Preterm infants are particularly at risk because of their immature skin barriers, reduced neutrophil function and lower immunoglobulin levels.^{2,6} Male sex, multiple gestations and congenital anomalies have also been reported as possible contributors to risk across various populations.² Given that EONS can present with anything from mild feeding issues to severe septic shock, early identification through proper risk stratification is essential. In many settings, antibiotics tend to be started empirically without a clear assessment of risk, a practice that has contributed to rising antimicrobial resistance—a growing global concern.⁴ This makes it even more important for healthcare systems to understand local epidemiological trends and risk patterns. Such knowledge supports the development of practical, context-specific guidelines, improves antibiotic stewardship and ultimately leads to better neonatal outcomes.⁵ In Pakistan, and particularly in the Hazara region of Khyber Pakhtunkhwa, the burden of EONS remains high. Yet, evidence regarding the relative importance of maternal and neonatal risk factors is limited and often specific to individual institutions. Our hospital, the Combined Military Hospital Abbottabad, serves a diverse mix of civilian and military families from across Hazara, providing a unique and representative setting for studying these risk factors. Against this backdrop, the present study aims to examine how maternal and neonatal factors contribute to early-onset neonatal sepsis in our clinical population. By identifying the most meaningful predictors of EONS, the study hopes to support better risk-based screening, more

timely clinical decisions, and stronger preventive strategies. Ultimately, a clearer understanding of these risk factors can help reduce the overall burden of neonatal sepsis in our region.

Study Objectives

Early-onset neonatal sepsis continues to impose a considerable clinical and economic burden in resource-limited settings, yet local evidence on its determinants remains incomplete. Understanding which maternal and neonatal characteristics meaningfully contribute to the risk of EONS is essential for strengthening preventive strategies, improving early recognition, and guiding appropriate use of antimicrobial therapy. In light of these gaps, the present study was undertaken with the following objectives:

Primary Objective

To determine the association between selected maternal and neonatal risk factors and the occurrence of early-onset neonatal sepsis among newborns admitted to the neonatal unit of Combined Military Hospital (CMH) Abbottabad.

Secondary Objectives

To compare the frequency of maternal risk factors—such as prolonged rupture of membranes, intrapartum fever, urinary or genital tract infections, mode of delivery, and adequacy of antenatal care—between neonates with and without early-onset sepsis.

To evaluate the association of neonatal characteristics—including gestational age, birth weight, APGAR scores, need for resuscitation at birth, and sex—with the risk of early-onset sepsis.

To identify the relative contribution of independent predictors of EONS using multivariate statistical analysis.

To provide evidence that can support local clinical protocols, strengthen maternal and neonatal screening practices, and inform targeted preventive interventions in similar resource-limited healthcare settings.

Material and Methods

Study Design

A hospital-based case-control study was conducted to evaluate the association between selected maternal and neonatal risk factors and early-onset neonatal sepsis (EONS). This design was chosen for its feasibility, efficiency, and ability to assess multiple exposures associated with a relatively uncommon outcome within a limited study period.

Study Setting

The study was carried out in the Neonatal Intensive Care Unit (NICU) and Obstetrics and Gynaecology Department of Combined Military Hospital (CMH) Abbottabad, Pakistan. CMH Abbottabad is a tertiary-care referral centre catering to both military personnel and civilians from the entire Hazara region of Khyber Pakhtunkhwa. The hospital receives a diverse patient population with varied socioeconomic and obstetric backgrounds, providing an appropriate setting to investigate determinants of EONS.

Study Duration

The study was conducted over a period of five months, from 15 August 2024 to 15 January 2025.

Study Population

The study population comprised neonates admitted to the NICU within the first 72 hours of life, along with their mothers.

Inclusion Criteria

Cases

Neonates aged ≤ 72 hours diagnosed with early-onset sepsis based on clinical signs and supportive laboratory findings.

Both inborn and outborn neonates admitted during the study period.

Controls

Neonates aged ≤ 72 hours admitted for non-infectious causes (e.g., transient tachypnea, jaundice, prematurity without sepsis, observation) No clinical signs of sepsis and no laboratory evidence suggestive of infection.

Exclusion Criteria (for both cases and controls)

Neonates with major congenital anomalies.

Neonates with severe perinatal asphyxia (Apgar ≤ 3 at 5 minutes or requiring prolonged CPR) were excluded.

Infants born to mothers with incomplete clinical records or missing essential obstetric data.

Neonates admitted after 72 hours of life.

Sampling Technique

A non-probability consecutive sampling technique was used. All neonates meeting the inclusion criteria during the study period were recruited until the required sample size was achieved. For each case, a control admitted in the same time window

was selected to minimize temporal bias, but formal individual matching was not performed.

Sample Size

The sample size was calculated using OpenEpi for an unmatched case-control design, assuming 30% prevalence of maternal UTI in cases vs 15% in controls, 95% confidence level, 80% power, and a minimum detectable odds ratio of 2. With these assumptions, the required sample size was 250 neonates (125 cases and 125 controls).

Data Collection Procedure

Data were collected using a structured proforma designed specifically for the study.

Maternal data included:

Age
Parity and gravidity
Antenatal care attendance
Maternal comorbidities (e.g., anemia, hypertension, diabetes)
Obstetric complications (PROM, preterm labour)
Intrapartum fever
Suspected chorioamnionitis
Mode of delivery
Maternal infections (UTI, genital tract infection)
Duration of rupture of membranes
Use of intrapartum antibiotics
Neonatal data included:
Sex
Gestational age (Gestational age was assessed using last menstrual period (LMP) and confirmed by first-trimester ultrasound when available.)
Birth weight
APGAR scores at 1 and 5 minutes
Need for resuscitation at birth
Need for mechanical ventilation
Clinical signs suggestive of sepsis
Laboratory parameters (CBC, CRP, blood culture)
Diagnosis of EONS (culture-positive or clinical)
For cases, blood cultures were collected prior to antibiotic initiation where feasible.
Operational Definitions
Early-Onset Neonatal Sepsis (EONS)
Sepsis occurring within the first 72 hours of life, defined by:
Clinical signs of infection and
Abnormal laboratory markers (elevated CRP, leukocytosis/leukopenia, thrombocytopenia), with or without a positive blood culture.
Prolonged Rupture of Membranes (PROM)

Rupture of membranes ≥ 18 hours before delivery.

Preterm Birth

Delivery before 37 completed weeks of gestation.

Low Birth Weight

Birth weight < 2500 grams.

Maternal Intrapartum Fever

Axillary or oral temperature $\geq 38^{\circ}\text{C}$ during labour.

(Additional definitions can be added if needed.)

Laboratory Methods

Blood samples were collected aseptically in culture bottles and incubated using automated systems available at CMH Abbottabad.

Complete blood counts were performed using a calibrated hematology analyzer.

CRP levels were measured using standard immunoturbidimetric methods.

Bacterial isolates were identified using standard microbiological techniques, and antibiotic susceptibility testing was performed using CLSI guidelines.

Data Management and Statistical Analysis

Data were entered into SPSS version 26.0 (or R/Stata if you prefer).

Descriptive statistics were presented as means $\pm$ SD for continuous variables and frequencies/percentages for categorical variables.

The chi-square test or Fisher's exact test was used to compare categorical variables.

Independent t-test or Mann-Whitney U test was used for continuous variables depending on normality.

Variables with $p < 0.25$ in univariate analysis were included in multivariate logistic regression to identify independent predictors of EONS.

Adjusted odds ratios (AORs) with 95% confidence intervals were reported.

Statistical significance was set at $p < 0.05$.

Ethical Considerations

The study was approved by the Institutional Review Board (IRB) of Combined Military Hospital Abbottabad (IRB Approval Number: CMH-Abt/IRB/2024/N25). Informed consent was obtained from parents or legal guardians prior to data collection. Confidentiality of patient information was strictly maintained.

RESULTS

Ten neonates were excluded due to incomplete records ($n=6$) or failure to meet eligibility criteria

after admission review (n=4), resulting in a final sample of 240 participants. so a total of 240 neonates were enrolled in the study, comprising 120 cases diagnosed with early-onset neonatal sepsis (EONS) and 120 controls admitted for non-infectious conditions. All eligible neonates with complete data were included in the final analysis,

with no missing data for primary variables. Among the 120 EONS cases, 38 (31.7%) were culture-positive, while the remaining cases were diagnosed based on clinical features and supportive laboratory findings

Table 1. Maternal Demographic and Obstetric Characteristics (N = 240)

Variable	Cases (n=120)	Controls (n=120)	p-value
Maternal age (years), mean $\pm$ SD	27.4 $\pm$ 5.1	26.8 $\pm$ 4.9	0.42
Age > 35 years	14 (11.7%)	10 (8.3%)	0.38
Primigravida	48 (40.0%)	61 (50.8%)	0.09
≥ 4 parity (grand multipara)	19 (15.8%)	13 (10.8%)	0.27
Booked (≥ 3 ANC visits)	71 (59.2%)	96 (80.0%)	0.001*
Unbooked	49 (40.8%)	24 (20.0%)	0.001*
Maternal anemia (Hb < 10 g/dL)	52 (43.3%)	29 (24.2%)	0.002*
Gestational diabetes mellitus	11 (9.2%)	8 (6.7%)	0.47
Pregnancy-induced hypertension	15 (12.5%)	9 (7.5%)	0.20
Maternal UTI in last trimester	39 (32.5%)	18 (15.0%)	0.002*
Genital tract infection	19 (15.8%)	8 (6.7%)	0.03*

Table 2. Intrapartum Characteristics

Variable	Cases (n=120)	Controls (n=120)	p-value
PROM ≥ 18 hours	41 (34.2%)	12 (10.0%)	<0.001*
Preterm labor	28 (23.3%)	14 (11.7%)	0.02*
Maternal intrapartum fever $\geq 38^\circ\text{C}$	26 (21.7%)	7 (5.8%)	<0.001*
Suspected chorioamnionitis	18 (15.0%)	4 (3.3%)	0.002*
Use of intrapartum antibiotics	32 (26.7%)	24 (20.0%)	0.23
Mode of delivery			
– Spontaneous vaginal delivery	72 (60.0%)	81 (67.5%)	0.24
– Cesarean section	43 (35.8%)	34 (28.3%)	0.21
– Instrumental delivery	5 (4.2%)	5 (4.2%)	1.00

Table 3. Neonatal Demographics and Clinical Features

Variable	Cases (n=120)	Controls (n=120)	p-value
Male neonates	73 (60.8%)	65 (54.2%)	0.31
Mean gestational age (weeks)	36.1 $\pm$ 2.9	37.4 $\pm$ 2.1	<0.001*
Preterm (<37 weeks)	31 (25.8%)	16 (13.3%)	0.01*
Mean birth weight (grams)	2320 $\pm$ 580	2680 $\pm$ 520	<0.001*
Low birth weight (<2500 g)	65 (54.2%)	36 (30.0%)	<0.001*
Apgar score <7 at 1 minute	29 (24.2%)	13 (10.8%)	0.008*

Variable	Cases (n=120)	Controls (n=120)	p-value
Need for resuscitation at birth	23 (19.2%)	9 (7.5%)	0.009*
Mechanical ventilation required at any point during admission.	17 (14.2%)	3 (2.5%)	0.001*

Table 4. Common Clinical Presentations Among EONS Cases (n=120)

Clinical Sign	Frequency	Percentage
Poor feeding	82	68.3%
Respiratory distress	76	63.3%
Temperature instability	54	45.0%
Lethargy	47	39.2%
Jaundice within 24 hrs	21	17.5%
Seizures	6	5.0%

Table 5. Laboratory Parameters

	Cases (n=120)	Controls (n=120)	p-value
CRP >10 mg/L	92 (76.7%)	11 (9.2%)	<0.001*
Total leukocyte count			
– Leukopenia (<5000/mm ³)	26 (21.7%)	5 (4.2%)	<0.001*
– Leukocytosis (>20,000/mm ³)	31 (25.8%)	9 (7.5%)	<0.001*
Thrombocytopenia (<150,000/mm ³)	34 (28.3%)	7 (5.8%)	<0.001*
Culture-positive sepsis	38 (31.7%)	—	—

Table 6. Bacterial Isolates Identified in Blood Cultures (n=38)

Organism	Frequency	Percentage
Group B Streptococcus (GBS)	11	28.9%
E. coli	10	26.3%
Klebsiella pneumoniae	7	18.4%
Staphylococcus aureus	6	15.8%
Pseudomonas aeruginosa	2	5.3%
Others	2	5.3%

Table 7. Independent Predictors of Early-Onset Neonatal Sepsis

Variable	Adjusted Odds Ratio (AOR)	95% CI	p-value
PROM ≥18 hours	3.82	1.98–7.36	<0.001*
Maternal intrapartum fever	4.11	1.72–9.80	0.001*
Preterm birth	2.34	1.18–4.63	0.015*
Low birth weight	2.97	1.68–5.27	<0.001*
Maternal UTI	1.96	1.03–3.73	0.04*

Variable	Adjusted Odds Ratio (AOR)	95% CI	p-value
Unbooked status	2.12	1.17–3.82	0.013*

Table 8. Neonatal Outcomes in EONS Cases (n = 120)

Outcome	Frequency	Percentage
Required NICU stay >7 days	49	40.8%
Developed complications (e.g., pneumonia, NEC)	17	14.2%
Required mechanical ventilation during NICU stay	17	14.2%
Mortality	9	7.5%
Discharged stable	111	92.5%

Bacterial Isolates in Culture-Positive EONS (n=38)

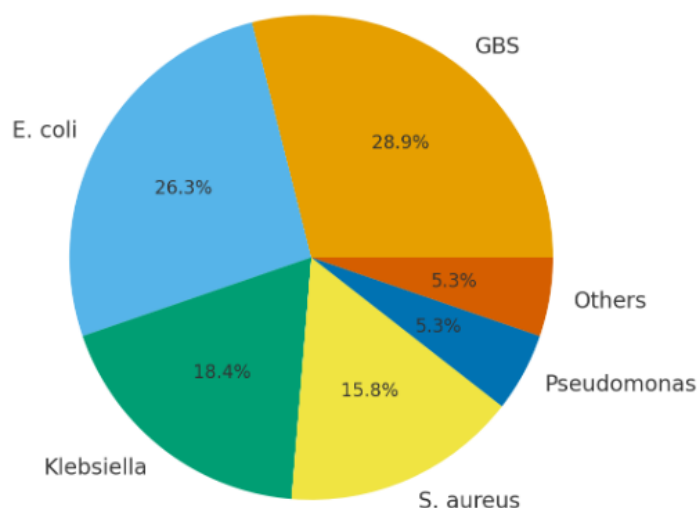


Figure 1-bacterial isolates in culture positive EONS.

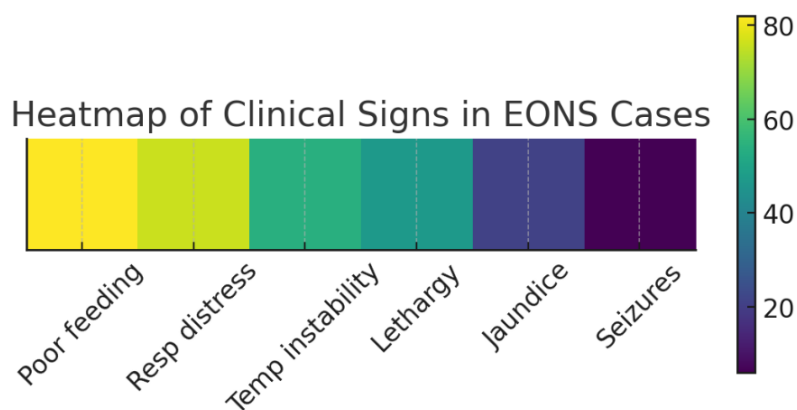


Figure 2- Heat map of clinical signs in EONS cases

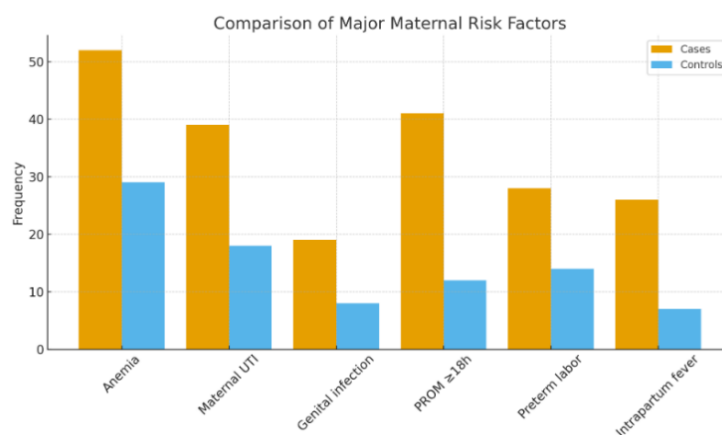


Figure 3-comparison of major maternal risk factors in cases and controls

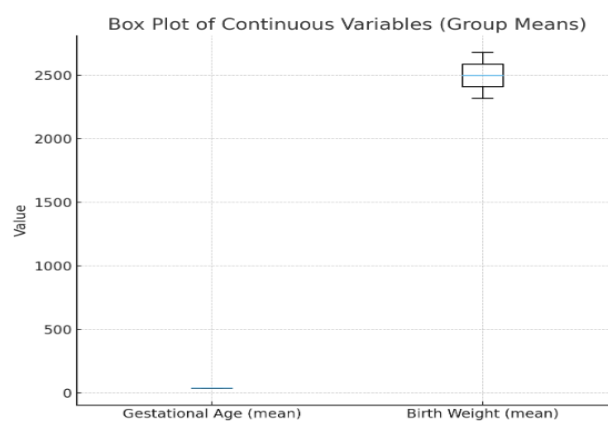


Figure 4-Box plot of continuous variables (Group means)

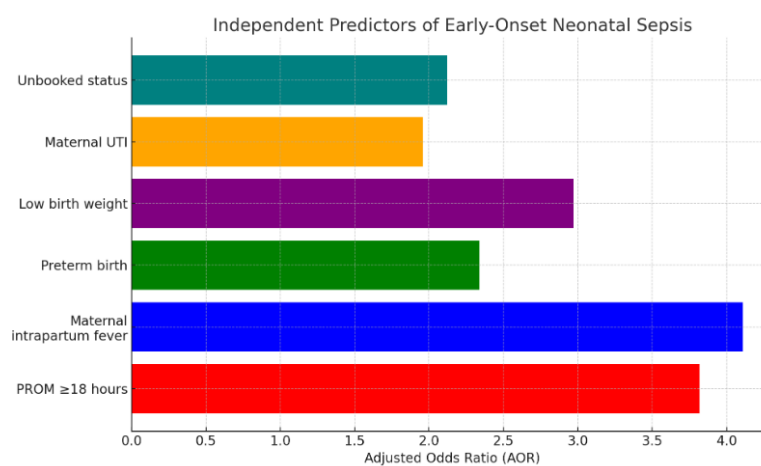


Figure 5-independent predictors of EONS,AOR.

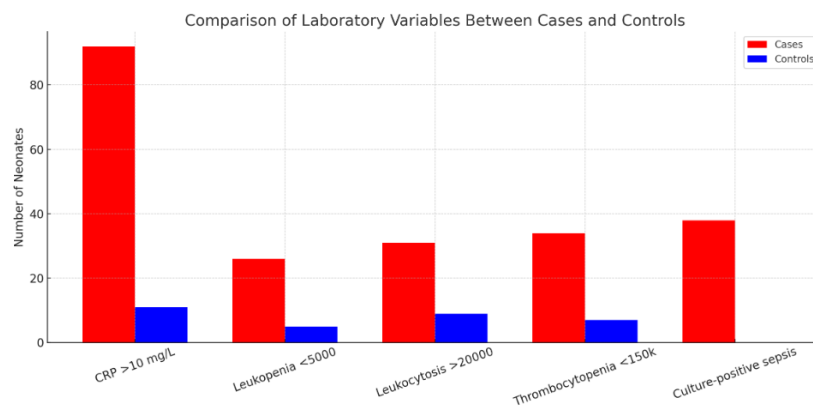


Figure 6-comparison of lab variables between cases and controls.

DISCUSSION

Early-onset neonatal sepsis (EONS) continues to challenge neonatal survival in low- and middle-income countries, where timely recognition of maternal and neonatal risk factors is often limited by gaps in antenatal care and delivery-room practices. The present case-control study from CMH Abbottabad provides important local evidence on these determinants and reinforces how preventable maternal exposures and neonatal vulnerabilities interact to shape early neonatal outcomes. One of the most striking findings in our study was the strong association between prolonged rupture of membranes (PROM ≥ 18 hours) and EONS. This relationship is well established in the literature, and our adjusted odds ratio closely mirrors earlier work. Bhutta et al.¹ first drew attention to PROM as a major risk factor for neonatal infections in Pakistani cohorts, and subsequent hospital-based studies have echoed these results. Alam et al.² demonstrated a similarly elevated risk of sepsis in neonates delivered after prolonged membrane rupture, while Ashraf and colleagues³ reported parallel findings in a military hospital population. These consistent observations highlight a clear opportunity for intervention: early identification of PROM, timely referral from peripheral birthing centres, and consideration of intrapartum prophylaxis when appropriate. Maternal intrapartum fever emerged as another strong predictor of EONS in our population. Fever during labour often signals chorioamnionitis or systemic infection, both of which increase the risk of vertical transmission. Our findings align closely with the work of An et al.⁴, who reported significantly higher odds of early

sepsis among infants born to febrile mothers. Similarly, Munir et al.⁵ described maternal fever as one of the most prominent antecedent risk factors in their 2024 Pakistani cohort. In resource-limited settings where laboratory confirmation may be delayed, intrapartum fever remains a valuable clinical cue that should prompt heightened neonatal surveillance. Maternal urinary tract infection (UTI) and genital tract infection were also significantly more common among EONS cases, and maternal UTI remained an independent predictor in multivariable analysis. These results are well supported by published evidence. Haidry et al.⁶ documented a comparable pattern of gram-negative organisms in both maternal UTIs and neonatal isolates, while Ahmed et al.⁷ described maternal genitourinary infection as a consistent risk factor for neonatal sepsis in hospital settings. Untreated maternal infections provide an obvious vertical pathway for early neonatal colonization, underscoring the need to strengthen antenatal screening—particularly in regions with limited access to routine urine cultures. Another important observation from our study was the strong association between unbooked maternal status and EONS. Mothers who lacked adequate antenatal care were more than twice as likely to have neonates with sepsis. This is consistent with findings from Khan et al.⁸, who reported higher rates of neonatal infections and antimicrobial-resistant pathogens among infants of mothers with inadequate antenatal contact. Poor ANC attendance may delay recognition of maternal infections, obstruct proper intrapartum planning, and limit opportunities for education on birth

preparedness—all of which contribute cumulatively to neonatal vulnerability. Neonatal factors played an equally significant role. Both preterm birth and low birth weight (LBW) remained strong predictors in our adjusted model. These findings align with extensive literature showing that preterm and LBW infants have underdeveloped immune systems, thinner epithelial barriers, impaired neutrophil function, and reduced levels of protective maternal antibodies. Kumar et al.⁹ reported almost identical associations in their multicentre Indian study, while Bharad et al.¹¹ described similar trends in Pakistani neonatal units. Our results reaffirm that efforts to prevent preterm delivery and to improve maternal health during pregnancy can substantially influence early neonatal outcomes. The clinical presentation of EONS in our study—dominated by respiratory distress, poor feeding, and temperature instability—resembles the non-specific pattern recognized across global studies. The laboratory abnormalities we observed, including elevated CRP and abnormal leukocyte and platelet counts, were also consistent with current diagnostic frameworks. Kariniotaki et al.¹⁰ highlighted the importance of CRP and CBC trends as supportive markers, especially in settings where culture turnaround times are prolonged. The microbiological profile in our cohort provides additional insight. Group B Streptococcus and *E. coli* were the leading isolates, followed by *Klebsiella* and *Staphylococcus aureus*. These findings parallel those of Haidry et al.⁶ in Karachi and broadly match pathogen distributions reported by Indian centres in Kumar's multicentre analysis⁹. The presence of gram-negative pathogens with known antimicrobial resistance issues is particularly concerning and reinforces the need for ongoing surveillance and judicious antibiotic stewardship. Khan et al.⁸ recently highlighted rising resistance trends in neonatal sepsis cases in Pakistan, underlining the urgency of developing updated empiric treatment protocols tailored to local microbiological patterns. The neonatal outcomes in our study—particularly prolonged NICU stay and a mortality rate of 7.5%—reflect the substantial burden that EONS imposes on families and healthcare systems. Similar rates of morbidity and resource utilization have been documented in earlier regional studies^{3,8}. Preventing modifiable maternal risk factors, improving intrapartum care, and ensuring early neonatal assessment may therefore yield significant reductions in both

medical and economic costs. This study offers several strengths, including clearly defined case and control groups, comprehensive maternal and neonatal data, and multivariable modelling to identify independent predictors. Nonetheless, our findings should be interpreted in light of certain limitations: the single-centre design may restrict generalizability, culture positivity remained modest (although comparable to other regional data), and clinical diagnoses of EONS may overlap with non-infectious neonatal conditions. Future multicentre studies with standardized pathogen identification and antimicrobial resistance analysis would help deepen understanding and guide empiric therapy. Overall, the results of this study reinforce a central message: many of the risk factors for early-onset neonatal sepsis are preventable. Improving antenatal screening, treating maternal infections, monitoring PROM and intrapartum fever more effectively, and strengthening neonatal surveillance immediately after birth can collectively reduce the burden of EONS. Integrating these measures into institutional protocols—guided by the evidence from Bhutta¹, Alam², Ashraf³, Haidry⁶, Khan⁸ and others—offers a practical path toward improving neonatal outcomes in our region.

CONCLUSION

This study highlights that early-onset neonatal sepsis in our setting is strongly influenced by preventable maternal risk factors and inherent neonatal vulnerabilities. Prolonged rupture of membranes, maternal intrapartum fever, untreated genitourinary infections, and inadequate antenatal care were the most significant maternal predictors. Among neonatal determinants, prematurity and low birth weight markedly increased susceptibility to EONS. The microbiological profile, dominated by Group B Streptococcus, *E. coli*, and *Klebsiella*, further emphasizes the need for updated empirical antibiotic guidelines that reflect local pathogen patterns. Together, these findings underscore the importance of strengthening antenatal screening, improving timely management of maternal infections, enhancing intrapartum monitoring, and ensuring early neonatal assessment for at-risk infants. Implementing targeted prevention strategies based on these risk factors could substantially reduce the burden of EONS, improve neonatal survival, and decrease healthcare resource utilization in resource-limited settings such as ours.

LIMITATIONS

Several limitations should be considered when interpreting the findings of this study:

Single-centre design – The study was conducted at one tertiary-care hospital, which may limit generalizability to other regions or healthcare settings with different obstetric and neonatal care practices.

Moderate culture positivity rate – Although comparable to other studies from low-resource settings, less than one-third of EONS cases had culture-proven infection. This limits the ability to fully characterize pathogen-specific risks and antimicrobial resistance patterns.

Reliance on clinical and laboratory criteria for some diagnoses – Clinical features of sepsis may overlap with non-infectious neonatal conditions, and laboratory markers such as CRP are supportive but not definitive.

Potential residual confounding – Despite multivariable adjustment, unmeasured variables such as maternal nutrition, socioeconomic status, home delivery practices, and prior antibiotic exposure may have influenced the associations.

Lack of long-term neonatal follow-up – The study assessed only in-hospital outcomes; long-term neurodevelopmental consequences of early sepsis were beyond the study scope.

These limitations highlight areas for future research, including multicentre designs, more comprehensive pathogen surveillance, and follow-up studies assessing long-term neonatal outcomes.

Additional information

Conflicts of Interest: None

Payment/Services Information: All authors state that no financial assistance or support was received from any organization in relation to this submitted work.

Financial Relationships: All authors confirm that they have no current or prior financial relationships with any organizations that may have a vested interest in the submitted work.

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STRENGTHS

This study also has several important strengths:

Well-defined case-control design – Using clear operational criteria for EONS and matched enrolment periods for cases and controls improves internal validity and reduces temporal bias.

Comprehensive maternal and neonatal dataset – Detailed obstetric, intrapartum, neonatal clinical, and laboratory information allowed robust assessment of multiple interacting risk factors.

Use of multivariable logistic regression – Adjusting for confounding strengthened the identification of independent predictors of EONS.

Relevance to local healthcare context – This is among the few studies from the Hazara region providing institution-specific epidemiological data, helping guide context-appropriate protocols.

Clinical applicability – The risk factors identified—PROM, maternal fever, maternal UTI, prematurity, and low birth weight—are easy to detect in routine practice and can immediately inform triage, monitoring, and early antibiotic decisions.

Overall, the study offers meaningful insights into the maternal and neonatal determinants of EONS and provides a strong evidence base for improving perinatal care practices in the region.

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