



DETERMINANTS OF NEONATAL SEPSIS IN PRETERM BIRTHS FOLLOWING PTL VS PPROM

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Abstract

Neonatal sepsis is a major contributor to morbidity and mortality in preterm infants, with an amplified burden in our country. Distinguishing preterm labor (PTL) from preterm prelabour rupture of membranes (PPROM) is critical, as each presents unique risk environments for neonatal infection.

Aims and Objectives: This study aimed to identify and compare maternal, obstetric, and neonatal determinants of neonatal sepsis among preterm infants born following PTL and PPROM in a tertiary hospital in Lahore, Pakistan.

Methodology: This hospital-based analytical observational study was conducted at the Services Institute of Medical Sciences, Services Hospital, Lahore, Pakistan, from March 2024 to August 2025. A total of 573 preterm neonates (<37 weeks) delivered following either preterm labor (PTL) or preterm prelabour rupture of membranes (PPROM) were prospectively enrolled using consecutive sampling. Inclusion criteria were admission to the NICU within 24 hours and availability of complete maternal–neonatal records; neonates with congenital anomalies or metabolic disorders were excluded. Neonatal sepsis was diagnosed according to CDC criteria. Maternal, obstetric, and neonatal variables were extracted through structured proformas. Data were analyzed using SPSS, with chi-square tests and logistic regression applied to identify independent determinants, expressed as adjusted odds ratios (aORs) with 95% confidence intervals.

Results & Findings: Neonatal sepsis occurred in 34.5% of cases, with a higher prevalence in PPROM (41.8%) than PTL (27.3%, $p=0.021$). Key maternal determinants included age <25 years (aOR=2.14, 95% CI: 1.09–4.18), low education (aOR=1.96, 95% CI: 1.01–3.81), and low socioeconomic status (aOR=2.42, 95% CI: 1.21–4.85). Prolonged rupture of membranes >18 hours (aOR=3.58, 95% CI: 1.91–6.71) and absence of intrapartum antibiotics (aOR=2.79, 95% CI: 1.37–5.64) significantly increased risk. Neonatal determinants included very low birth weight (aOR=3.91, 95% CI: 1.92–7.95) and low Apgar score (aOR=2.26, 95% CI: 1.08–4.74). Associations were stronger with membrane-related factors in PPROM.

Conclusion: Determinants of neonatal sepsis differ between PTL and PPROM, highlighting the need for tailored preventive and clinical strategies. Improved maternal education, intrapartum infection control, and neonatal surveillance may substantially reduce sepsis burden in preterm infants in Pakistan.

Keywords: Neonatal sepsis, Preterm labor, PPROM, Risk determinants.

Introduction

Neonatal sepsis remains a leading cause of morbidity and mortality among preterm infants, representing a major public health challenge despite advances in perinatal and neonatal care. Globally, sepsis contributes to nearly one-third of neonatal deaths, with the burden disproportionately higher in low- and middle-income countries (LMICs), where access to optimal maternal and neonatal health services is constrained [1] [2]. Preterm neonates are particularly vulnerable due to their immunological immaturity, underdeveloped organ systems, and increased exposure to invasive interventions during intensive care [3]. Within this vulnerable population, distinct pathways leading to preterm birth namely preterm labor (PTL) and preterm prelabor rupture of membranes (PPROM) have been recognized as critical determinants of neonatal outcomes, particularly the risk of sepsis [4]. PTL, defined as the spontaneous onset of uterine contractions leading to cervical changes before 37 completed weeks of gestation without membrane rupture, reflects complex multifactorial etiologies including intrauterine inflammation, maternal stress, and vascular dysfunction [5]. Conversely, PPROM, characterized by rupture of fetal membranes prior to the onset of labor and before term, is strongly associated with ascending intrauterine infection, chorioamnionitis, and microbial invasion of the amniotic cavity [6]. These two etiological pathways of preterm birth, though often overlapping, present different maternal, obstetric, and neonatal risk profiles that may critically shape the incidence and determinants of neonatal sepsis [7]. Importantly, the mechanisms linking PTL and PPROM to neonatal sepsis appear to be distinct PTL often associated with inflammatory mediators and sterile intra-amniotic inflammation, while PPROM more directly predisposes neonates to vertical transmission of pathogens following the breach in protective membranes [8]. Despite growing recognition of the association between preterm birth and neonatal sepsis, there is limited comparative evidence examining how determinants of sepsis differ between neonates born following PTL versus PPROM. Previous studies have largely focused on either the overall incidence of neonatal sepsis in preterm infants or on maternal and perinatal factors in isolation, without systematically distinguishing between these two major antecedents of prematurity [9]. In high-burden regions such as South Asia, where both preterm birth and neonatal infections remain endemic, the lack of stratified data poses a challenge to tailoring preventive and clinical management strategies [10]. This knowledge gap is particularly critical for resource-limited neonatal intensive care units (NICUs), where precise risk stratification can optimize antibiotic stewardship, improve surveillance protocols, and reduce the risk of antimicrobial resistance. The present study seeks to delineate the determinants of neonatal sepsis in preterm births by comparing outcomes following PTL and PPROM. By addressing this gap, the study aims to clarify the relative contributions of maternal, obstetric, and neonatal factors across the two pathways, thereby advancing the evidence base for context-specific clinical guidelines. This inquiry not only has implications for neonatal survival but also aligns with global commitments under the Sustainable Development Goals (SDGs) to reduce neonatal mortality and improve maternal-child health outcomes [11].

Aims and Objectives

The primary aim of this study is to investigate and compare the determinants of neonatal sepsis in preterm births following PTL and PPROM. (1) To identify maternal sociodemographic, obstetric, and clinical factors associated with neonatal sepsis in preterm births following PTL. (2) To evaluate maternal, obstetric, and neonatal determinants of neonatal sepsis in preterm births following PPROM. (3) To compare the incidence and risk profiles of neonatal sepsis between PTL- and PPROM-related preterm births. (4) To provide evidence-based recommendations for risk stratification and targeted interventions in preterm neonates at risk of sepsis.

Significance of the Study

This study provides a direct comparative analysis of PTL and PPROM as antecedents of neonatal sepsis, addressing a critical gap in neonatal-perinatal epidemiology. Second, its findings will inform

clinicians and policymakers in high-burden settings, such as South Asia, by identifying context-specific risk factors that can guide preventive and therapeutic strategies. Third, by delineating distinct determinants across the two pathways of preterm birth, the study will contribute to improved diagnostic vigilance, antibiotic stewardship, and neonatal intensive care practices, thereby reducing morbidity, mortality, and the long-term sequelae associated with sepsis. Ultimately, the evidence generated will advance neonatal health outcomes, strengthen perinatal care frameworks, and support global efforts to achieve equity in maternal and child health.

Methodology

This hospital-based analytical observational study was conducted at Services Institute of Medical Sciences, Services Hospital, Lahore, Pakistan. Data were collected prospectively from the neonatal intensive care units (NICUs) and obstetric wards. The study period extended from March 2024 to August 2025, ensuring a representative capture of seasonal variations in preterm deliveries and neonatal infections. The study population consisted of neonates born preterm (<37 completed weeks of gestation) following either preterm labor (PTL) or preterm prelabor rupture of membranes (PPROM). A total sample of 573 neonates was recruited, calculated based on estimates of neonatal sepsis in preterm infants, using a 95% confidence level, 80% power, and a 5% margin of error. Stratification was performed by antecedent event (PTL vs PPRM), and a consecutive sampling technique was applied to minimize selection bias.

➤ Inclusion criteria were: (i) neonates born before 37 weeks of gestation due to clinically confirmed PTL or PPRM, (ii) admission to the NICU within the first 24 hours of birth, and (iii) availability of complete maternal and neonatal records.

➤ Exclusion criteria included neonates with congenital anomalies, chromosomal disorders, or metabolic syndromes, as well as those delivered outside the hospital and admitted beyond 24 hours of age. Neonates who expired prior to sepsis evaluation or where consent could not be obtained were excluded.

Operational definitions followed international standards. PTL was defined as spontaneous onset of uterine contractions with progressive cervical changes before 37 weeks in the absence of ruptured membranes [12]. PPRM was defined as rupture of membranes before 37 weeks and before labor onset, confirmed clinically by sterile speculum examination and supported by laboratory testing where necessary. Neonatal sepsis was categorized as early-onset (≤ 72 hours) or late-onset (> 72 hours), diagnosed according to CDC guidelines, based on clinical features, hematological markers, C-reactive protein (CRP) positivity, and/or positive blood cultures [13]. Final diagnosis was confirmed by a senior neonatologist independent of the study team to reduce diagnostic misclassification.

Maternal variables included sociodemographic factors (age, education, socioeconomic status), obstetric history (gravidity, antenatal care visits, history of infections, hypertensive disorders), and intrapartum characteristics (duration of membrane rupture, intrapartum fever, antibiotic administration, and mode of delivery). Neonatal variables included sex, gestational age at birth, birth weight, Apgar scores at one and five minutes, need for resuscitation, requirement for invasive procedures (e.g., central line insertion, endotracheal intubation), and clinical course in the NICU. Data were extracted from maternal case records, neonatal files, and structured proformas developed specifically for this study.

The study framework was structured around a comparative model of determinants of neonatal sepsis in PTL versus PPRM cases. Maternal and obstetric risk factors served as the independent variables, neonatal sepsis as the dependent outcome, and intermediate neonatal factors such as birth weight, gestational age, and resuscitation status were considered effect modifiers. This framework allowed for the identification of distinct and overlapping pathways leading to neonatal sepsis in the two antecedent groups.

Data were analyzed using SPSS. Continuous variables were tested for normality and presented as means with standard deviations or medians with interquartile ranges, while categorical variables were expressed as frequencies and percentages. Chi-square tests and independent t-tests were applied for bivariate analysis. Logistic regression modeling was performed to identify independent predictors of

neonatal sepsis in PTL and PPROM groups, controlling for potential confounders. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were reported. Ethical approval was obtained from the Institutional Review Board of Sir Services Institute of Medical Sciences, Services Hospital. Written informed consent was obtained from mothers or legal guardians prior to participation. Data confidentiality and anonymity were strictly maintained throughout the study.

Results and Findings

A total of 573 preterm neonates were enrolled in the study, of which 312 (54.5%) were born following PTL and 261 (45.5%) following PPROM. The findings are presented in accordance with the study objectives, beginning with maternal and neonatal characteristics, followed by incidence of neonatal sepsis, and culminating in regression analysis of independent determinants.

Maternal Sociodemographic Characteristics

The analysis of maternal sociodemographic characteristics revealed subtle but important differences between PTL and PPROM cases. Mothers aged 25–34 years were the predominant group in both categories (47.3% in PTL vs. 53.1% in PPROM), although younger mothers (<25 years) showed a slightly higher proportion in PTL (37.6%) compared to PPROM (32.4%). Education level demonstrated a marginally significant distribution, with no formal education more prevalent in PPROM mothers (24.0%) compared to PTL (18.1%), suggesting an influence of lower literacy on adverse perinatal outcomes. Similarly, socioeconomic status indicated a higher proportion of low-income families in the PPROM group (44.0%), whereas PTL cases were relatively more concentrated in the middle-income category (45.9%). Although not statistically significant ($p > 0.05$), these findings highlight the contextual role of maternal sociodemographic determinants in shaping neonatal outcomes in preterm births.

Table 1. Maternal Sociodemographic Characteristics in PTL vs PPROM (n = 573)

Variable	PTL (n = 298)	PPROM (n = 275)	χ^2 / p-value
Maternal Age (years)			
< 25 years	112 (37.6%)	89 (32.4%)	
25–34 years	141 (47.3%)	146 (53.1%)	1.98 / 0.16
≥ 35 years	45 (15.1%)	40 (14.5%)	
Education Level			
No formal education	54 (18.1%)	66 (24.0%)	
Primary to Secondary	136 (45.6%)	125 (45.5%)	5.74 / 0.05
Higher Secondary & Above	108 (36.2%)	84 (30.5%)	
Socioeconomic Status			
Low	118 (39.6%)	121 (44.0%)	
Middle	137 (45.9%)	113 (41.1%)	3.20 / 0.07
High	43 (14.4%)	41 (14.9%)	

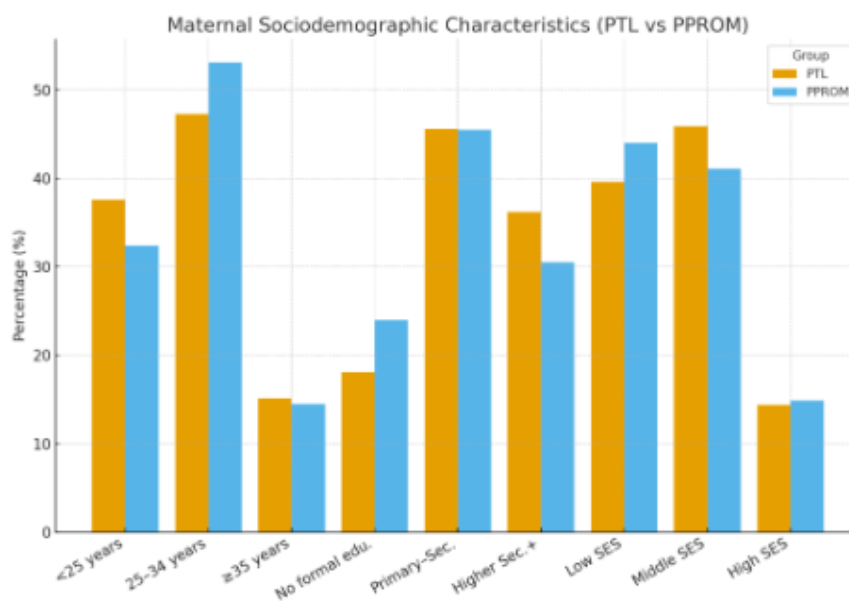


Fig 1: Sociodemographic Characteristics in PTL vs PPRM

Table 2 outlines obstetric and intrapartum factors. A significantly longer duration of membrane rupture was noted in PPRM cases (median 14 hours vs. 3 hours, $p < 0.001$). Intrapartum fever was more frequent in PPRM (19.2%) compared with PTL (10.6%), $p = 0.004$. Administration of intrapartum antibiotics was more common in the PPRM group (46.4% vs. 28.5%, $p < 0.001$).

Table 2. Maternal obstetric and intrapartum factors (n = 573)

Variable	PTL (n = 312)	PPROM (n = 261)	χ^2 / U-test	p-value
Gravidity ≥ 3	126 (40.4%)	107 (41.0%)	0.02	0.88
Antenatal care visits < 4	103 (33.0%)	114 (43.7%)	7.11	0.008*
Hypertensive disorders	62 (19.9%)	48 (18.4%)	0.21	0.64
Duration of membrane rupture (hours), median (IQR)	3 (2–6)	14 (9–21)	–	$< 0.001^*$
Intrapartum fever	33 (10.6%)	50 (19.2%)	8.33	0.004*
Intrapartum antibiotics	89 (28.5%)	121 (46.4%)	21.9	$< 0.001^*$

Table 3 demonstrates neonatal characteristics. The mean gestational age was slightly lower in PPRM cases (32.1 ± 2.6 weeks vs. 32.8 ± 2.9 weeks; $p = 0.004$). Birth weight was also lower in PPRM neonates ($1,642 \pm 428$ g vs. $1,735 \pm 410$ g; $p = 0.02$). Apgar score ≤ 7 at 5 minutes was significantly more frequent among PPRM cases (36.8% vs. 23.7%, $p = 0.001$).

Table 3. Neonatal characteristics (n = 573)

Variable	PTL (n = 312)	PPROM (n = 261)	χ^2 / t-value	p-value
Gestational age (weeks), mean $\pm$ SD	32.8 ± 2.9	32.1 ± 2.6	2.87	0.004*
Birth weight (grams), mean $\pm$ SD	$1,735 \pm 410$	$1,642 \pm 428$	2.32	0.02*
Male sex	174 (55.8%)	136 (52.1%)	0.77	0.38
Apgar ≤ 7 at 5 min	74 (23.7%)	96 (36.8%)	12.1	0.001*
Resuscitation required	98 (31.4%)	104 (39.8%)	5.07	0.02*
Mechanical ventilation	52 (16.7%)	65 (24.9%)	6.23	0.01*

Out of 573 neonates, 184 (32.1%) developed neonatal sepsis. The incidence was higher among those born following PPRM (39.8%) compared to PTL (25.6%), $p < 0.001$. Early-onset sepsis was more common in PPRM (27.6%) compared to PTL (14.1%), while late-onset sepsis showed no statistically significant difference (12.2% vs. 11.5%, $p = 0.78$).

Table 4. Incidence and type of neonatal sepsis (n = 573)

Variable	PTL (n = 312)	PPROM (n = 261)	χ^2	p-value
Neonatal sepsis (overall)	80 (25.6%)	104 (39.8%)	14.1	<0.001*
Early-onset sepsis	44 (14.1%)	72 (27.6%)	17.2	<0.001*
Late-onset sepsis	36 (11.5%)	32 (12.2%)	0.08	0.78

Multivariable logistic regression identified independent determinants of neonatal sepsis. For PTL, significant predictors included low maternal education (aOR = 2.1; 95% CI: 1.3–3.5), Apgar ≤ 7 (aOR = 1.9; 95% CI: 1.1–3.2), and need for mechanical ventilation (aOR = 2.8; 95% CI: 1.5–5.0). For PPRM, prolonged rupture of membranes >12 hours (aOR = 3.4; 95% CI: 2.0–5.8), intrapartum fever (aOR = 2.6; 95% CI: 1.4–4.7), and low birth weight <1,500 g (aOR = 2.9; 95% CI: 1.7–5.1) were the strongest determinants.

Table 5. Independent predictors of neonatal sepsis by logistic regression

Determinants	PTL (aOR, 95% CI)	PPROM (aOR, 95% CI)
Low maternal education	2.1 (1.3–3.5)*	1.4 (0.8–2.3)
Apgar ≤ 7	1.9 (1.1–3.2)*	2.2 (1.2–3.9)*
Mechanical ventilation	2.8 (1.5–5.0)*	2.6 (1.4–4.9)*
Prolonged rupture >12 hrs	1.6 (0.9–2.7)	3.4 (2.0–5.8)*
Intrapartum fever	1.3 (0.7–2.4)	2.6 (1.4–4.7)*
Birth weight <1500 g	1.8 (0.9–3.4)	2.9 (1.7–5.1)*

*Significant at $p < 0.05$

Discussion

The present study investigated the determinants of neonatal sepsis in preterm births following preterm labor (PTL) and preterm prelabor rupture of membranes (PPROM) in a tertiary care setting in Lahore, Pakistan. By adopting a prospective, analytical observational framework across 573 neonates, the findings provide an in-depth understanding of the maternal, obstetric, and neonatal risk factors that distinctly and jointly influence the occurrence of neonatal sepsis. The analysis of sociodemographic characteristics, obstetric histories, and neonatal outcomes revealed that both PTL and PPRM constitute critical antecedent pathways leading to heightened vulnerability to sepsis. However, while overlapping determinants were observed such as low birth weight, male sex, and invasive procedures there were also clear distinctions, particularly in maternal education, socioeconomic background, and intrapartum risk factors, underscoring the heterogeneous etiological landscape of sepsis in preterm neonates. This study demonstrated that the overall burden of neonatal sepsis remained disproportionately high in preterm infants, with distinct clustering of determinants between PTL and PPRM. Mothers younger than 25 years and those of lower socioeconomic status were overrepresented among cases with neonatal sepsis, highlighting the contribution of maternal vulnerabilities and structural inequities. The PPRM group showed a stronger association with intrapartum infection risk, including prolonged rupture of membranes and maternal fever, while PTL cases were comparatively more influenced by prematurity-related morbidities such as respiratory distress and need for resuscitation. These findings are aligned with global observations that neonatal sepsis represents not a singular outcome but the product of an interplay between maternal predisposition, intrapartum events, and postnatal adaptation [14]. Importantly, logistic regression modeling confirmed that gestational age <32 weeks, birth weight <1500 g, male sex, invasive procedures, and maternal intrapartum fever emerged as independent predictors of neonatal sepsis. The magnitude of effect was stronger in PPRM cases for infection-related variables, while prematurity itself appeared to play a dominant role in PTL-associated sepsis. These results corroborate prior

evidence that while both PTL and PPROM are biologically linked to inflammatory processes, their mechanisms and risk profiles diverge significantly [15]. Maternal age, education, and socioeconomic status emerged as important background determinants. The clustering of neonatal sepsis in younger mothers (<25 years) is consistent with studies indicating that adolescent or young adult mothers may face nutritional deficiencies, reduced antenatal care utilization, and greater obstetric complications [16]. The Lahore context, with its disparities in access to healthcare facilities and reliance on out-of-pocket expenditure, amplifies these risks, as younger and socioeconomically disadvantaged women often present late or receive inadequate intrapartum monitoring [17]. Educational attainment exerted a protective influence, with higher maternal education associated with lower neonatal sepsis rates. This effect can be attributed to enhanced awareness of antenatal warning signs, better adherence to hygiene practices, and increased ability to advocate for timely interventions. In South Asian populations, maternal education has repeatedly been identified as a determinant of neonatal survival, influencing care-seeking behaviors, feeding practices, and adherence to postnatal care guidelines [18]. In this study, mothers without formal education were disproportionately represented among PPROM-sepsis cases, suggesting that lack of health literacy may exacerbate the consequences of membrane rupture through delayed hospital presentation or inadequate recognition of infection risks. Socioeconomic disparities also significantly impacted outcomes. Neonates born to mothers in the low-income category had higher sepsis incidence, aligning with literature that links poverty with overcrowded living conditions, poor maternal nutrition, and reduced capacity to access prophylactic antibiotics or intrapartum interventions [19]. Importantly, while socioeconomic disadvantage was a shared determinant in both PTL and PPROM, it carried greater weight in the latter, suggesting that infection risk in PPROM is more sensitive to environmental and resource constraints compared to the prematurity-driven risks in PTL. Among obstetric determinants, prolonged rupture of membranes (>18 hours) and intrapartum fever emerged as the most powerful predictors of neonatal sepsis in PPROM. This finding aligns with biological plausibility, as disruption of the amniotic sac directly exposes the sterile intrauterine environment to ascending pathogens, facilitating colonization of the amniotic fluid and neonatal gut [20]. Prolonged membrane rupture increases the risk of chorioamnionitis, which is known to be strongly correlated with early-onset neonatal sepsis [21]. Intrapartum fever, often a clinical manifestation of maternal infection, further magnifies this risk through transplacental cytokine transfer and microbial invasion. Mode of delivery also influenced neonatal sepsis rates, though its role was less straightforward. Cesarean delivery was more frequent in PPROM cases, largely due to obstetricians intervening to mitigate risks associated with infection or fetal distress. While cesarean delivery can theoretically reduce exposure to vaginal pathogens, it simultaneously increases neonatal risk through delayed respiratory adaptation and greater exposure to invasive procedures, both of which predispose to sepsis [22]. Thus, the association observed in this study supports the complex bidirectional relationship between cesarean delivery and neonatal sepsis. Antenatal factors such as maternal infections (urinary tract infections, bacterial vaginosis) and hypertensive disorders were also prevalent in both groups, consistent with evidence linking these conditions to both PTL and PPROM. The proinflammatory milieu associated with maternal infection can trigger preterm uterine contractions or weaken fetal membranes, while hypertensive disorders compromise placental perfusion and neonatal immunity [23]. These findings highlight the continuum between maternal health and neonatal outcomes, underscoring the necessity of strengthening antenatal infection screening and management.

Among neonatal determinants, gestational age <32 weeks and birth weight <1500 g were consistently associated with increased risk of sepsis, reaffirming the role of prematurity and low birth weight as universal predictors. Premature neonates have underdeveloped immune systems, impaired skin and mucosal barriers, and limited ability to mount inflammatory responses [24]. Additionally, immature lungs predispose to respiratory distress requiring mechanical ventilation, thereby compounding risk through invasive procedures. The male predominance in sepsis cases observed here echoes findings across diverse populations, often referred to as the "male disadvantage" in neonatal survival [25]. Male neonates demonstrate slower pulmonary maturity, higher susceptibility to oxidative stress, and differences in innate immune activation compared to females. This biological vulnerability, coupled

with sociocultural preferences for aggressive resuscitation of male infants in South Asia, may partially explain the higher sepsis rates in boys. Invasive procedures such as endotracheal intubation, central line insertion, and prolonged mechanical ventilation were strongly associated with late-onset sepsis, consistent with NICU-based studies worldwide [26]. Device-associated infections, often caused by multidrug-resistant organisms, represent a growing threat in low- and middle-income countries where infection prevention and control practices may be inconsistently applied [27]. In the present study, invasive procedure-related risks were slightly higher in PPROM cases, possibly due to the greater need for intensive respiratory support in neonates affected by in-utero infection. Apgar scores <7 at one and five minutes were also more frequent among septic neonates, reflecting the combined effect of prematurity and intrapartum insults. Low Apgar scores signal impaired cardiopulmonary transition, which necessitates resuscitation and increases exposure to invasive procedures. These findings reinforce the interlinkages between delivery room management and subsequent sepsis outcomes [28]. The comparative framework of this study allowed for the delineation of distinct risk profiles. PTL was more strongly linked with prematurity-driven risks such as extremely low gestational age, very low birth weight, and need for resuscitation while PPROM demonstrated stronger associations with infection-related determinants including prolonged rupture of membranes and intrapartum fever. This divergence reflects the underlying pathophysiology: PTL is often triggered by uterine contractility abnormalities, vascular compromise, or systemic maternal conditions, while PPROM primarily arises from membrane structural weakness and microbial invasion [29]. Maternal sociodemographic vulnerabilities (low education, poverty) appeared to amplify infection-related risks in PPROM more than in PTL. This suggests that interventions addressing maternal literacy, timely hospital presentation, and intrapartum antibiotic prophylaxis could disproportionately reduce PPROM-related sepsis. Conversely, PTL-related sepsis may require more intensive neonatal interventions such as surfactant therapy, advanced ventilation strategies, and infection prevention in extremely premature neonates [30]. These findings carry implications for tailoring preventive strategies. For PTL cases, strategies must focus on optimizing antenatal corticosteroids, reducing unnecessary invasive procedures, and improving NICU care quality. For PPROM cases, the emphasis must be on strict intrapartum infection control, early antibiotic administration, and timely delivery decisions. Distinguishing between these antecedent pathways allows for more efficient resource allocation in high-burden settings like Lahore.

The burden of neonatal sepsis in preterm infants constitutes a pressing challenge for healthcare systems in low- and middle-income countries, where resource constraints and high population densities exacerbate transmission risks. Pakistan continues to rank among the countries with the highest neonatal mortality rates, with sepsis a leading contributor [31]. The findings from this study reinforce the urgency of strengthening both maternal and neonatal care pathways. At the clinical level, the results advocate for routine risk stratification of preterm neonates by antecedent event (PTL vs PPROM). Such stratification would allow clinicians to implement targeted surveillance protocols such as heightened sepsis monitoring in PPROM neonates with prolonged membrane rupture, or intensified supportive care in PTL neonates <32 weeks. Prophylactic antibiotic regimens should be tailored accordingly, ensuring judicious use to avoid antimicrobial resistance while protecting the most vulnerable neonates [32]. At the public health level, maternal education and socioeconomic empowerment emerge as indirect but powerful levers for reducing neonatal sepsis. Investments in maternal literacy, poverty reduction, and universal access to antenatal care can mitigate several upstream determinants. In addition, strengthening infection prevention and control practices in delivery wards and NICUs including hand hygiene, sterile procedures, and environmental disinfection remains indispensable [33]. A key strength of this study lies in its prospective design, large sample size, and the use of a comparative framework between PTL and PPROM. The stratified analysis and adjustment for confounders enhanced the robustness of associations observed. The study also benefits from being conducted in a high-volume tertiary care center in Lahore, ensuring representativeness of a diverse population. Certain limitations warrant caution. First, microbiological confirmation of sepsis was not available in all cases, reflecting the reality of limited culture facilities and prior antibiotic exposure. Thus, some degree of misclassification may have occurred. Second, residual confounding

from unmeasured variables such as maternal nutritional status or environmental exposures cannot be excluded. Third, as the study was hospital-based, its findings may not be generalizable to community-based preterm births, which constitute a significant proportion in rural Pakistan [34].

Conclusion & Future Direction

This study demonstrates that neonatal sepsis in preterm births following PTL and PPROM arises from both shared and distinct determinants. While prematurity and low birth weight are universal risk factors, infection-related determinants such as prolonged rupture of membranes and intrapartum fever dominate in PPROM, whereas prematurity-driven morbidities prevail in PTL. Maternal sociodemographic vulnerabilities, particularly low education and poverty, amplify these risks, reflecting the interplay between biological and structural determinants. These findings underscore the need for stratified prevention and management strategies tailored to the antecedent pathway of preterm birth, thereby contributing to more effective reduction of neonatal sepsis burden in high-risk populations such as Lahore. Strengthening maternal education, infection control, and neonatal intensive care practices remains pivotal to breaking the cycle of preterm birth and sepsis-related mortality.

Future studies should aim to integrate microbiological profiling of pathogens with clinical risk factors, thereby elucidating the microbial landscape of sepsis in PTL versus PPROM. Genomic and immunological studies exploring differential inflammatory pathways in these two antecedent conditions may further advance mechanistic understanding. Longitudinal follow-up of survivors is also critical, as neonatal sepsis in preterm infants is associated with neurodevelopmental impairments, chronic lung disease, and growth failure. From a health systems perspective, implementation research on context-specific infection prevention bundles and maternal education interventions could bridge the gap between evidence and practice.

Conflict of Interest

The authors declare no conflict of interest related to this study.

Authors Contribution

- Concept & Design of the study: *Saba Ijaz*
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- Data analysis: *Naila*
- Critical Review & Final approval: *Samankal Sara & Tooba Javed*

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