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# Outcome of Neonatal Sepsis in Preterm Neonates in Relation to Gestational Age

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Author`s Contribution

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**ABSTRACT**

**Objective:** To determine the outcome of neonatal sepsis in preterm neonates in relations to gestational age among preterm neonates presenting with sepsis at tertiary care hospital.

**Methodology:** A descriptive study was conducted at Department of Pediatrics, LUMHS, Jamshoro, from December 2021 to June 2022, on preterm neonates with sepsis presenting to the emergency department were included. After a detailed medical history and physical examination, patients were treated according to clinical indications and hospital protocols, and subsequently followed until discharge to assess outcomes. All the information was entered and analyzed using SPSS version 26.

**Results:** Overall mean age of the neonates was 5.7 ± 6.05 days, and out of them 32.8% were boys and 67.2%) were girls. Based on outcomes, feed intolerance was in 22.4% neonates, weight gain in 7.7%, respiratory distress in 70.7%, hypoglycemia in 4.3%, hypothermia in 9.5%, necrotizing enterocolitis in 16.4%w, and intra-ventricular hemorrhage in 21.5% neonates. Gestational age showed no significant effect on neonatal outcomes (p = 0.991). Birth weight was significantly associated (p = 0.010), with neonates 1.5–2.5 kg showing higher adverse outcomes. Mode of delivery was not significant (p = 0.538), while male neonates had higher rates of complications.

**Conclusion:** Respiratory distress observed to be a most common complication followed by feed intolerance, necrotizing enterocolitis and intra-ventricular hemorrhage while the outcomes were insignificantly related to the gestational age. Further large-scale work is recommended for validation of current findings.

**Keywords:** Preterm birth, Sepsis, Gestational Age.

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## Introduction

Neonatal sepsis, a bloodstream infection caused by either bacterium, fungus, or virus, continues to be a global concern in terms of significant morbidity and high mortality among neonates aged below 28, particularly among the residents of low- and middle-income countries (LMICs).[1] Annual global estimates for neonatal sepsis reflect around 3,000,000 million neonates suffering from sepsis, where 203,000 deaths are solely attributed to sepsis and nearly 570000 deaths occur among neonates of LMICs, with mortality rates ranging between 10% and 29%.[2,3] Preterm neonates, born before gestational age of 37 weeks, are more likely to develop neonatal sepsis due to underdeveloped immune systems and weak organ function, increasing the susceptibility to serious infections.[4] This life-threatening condition is traditionally categorized into early-onset that occurs during first 72

hours of life and late-onset that occurs after 3 to 27 days of life.[5,6]

Preterm birth complicated by serious infection like neonatal sepsis contributes to almost 90% of all cause neonatal mortality; while 99% of these neonatal deaths are reported from LIMCs.[7] Sustainable Development Goal 3 of neonatal mortality reduction to 12/1000 live births by the year 2030 cannot be accomplished without achieving significant reduction in infection-related mortality among neonates in LIMCs.[8] Despite advances in neonatal intensive care, neonatal sepsis still continues to result in life-threatening complications such as respiratory distress, hypoglycemia, hypothermia, necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH). [9,10]

Pakistan is a resourced limited country, where around 29.25% of neonates are projected to struggle with sepsis, and neonatal sepsis-associated mortality remains a major public health concern, with reported mortality rate of 7%, mostly attributed to low birth weight. [11,12] Moreover, preterm birth is also a serious concern in this country due to high burden of maternal conditions (gestational diabetes, hypertension, infections), which negatively affect the neonatal outcomes.[13]

Several studies have focused on neonatal sepsis in terms of incidence, risk factors, and mortality, while studies on intermediate outcomes including feed tolerance, weight gain, or specific morbidities like necrotizing enterocolitis (NEC) or intraventricular hemorrhage (IVH) are limited, mainly in preterm neonates.[14,15] The outcomes of neonatal sepsis may vary with gestational age, as early preterm neonates often demonstrate higher rates of complications and poorer prognosis compared to late preterm infants.[16] However, there is insufficient evidence addressing the relationship between gestational age and specific outcomes in preterm neonates with sepsis in the local context. Hence this study was conducted to determine the outcomes of neonatal sepsis in preterm neonates in relation to gestational age. Exploration of outcomes across different gestational age groups may help in risk stratification and optimized clinical management.

# Methodology

This descriptive study was conducted in the Department of Pediatrics, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, over a six-month period from December 15, 2021, to June 14, 2022, after obtaining approval from the Institutional Review Board (IRB) of the institute and the College of Physicians and Surgeons Pakistan (CPSP) Ref no CPSP/REU/PED-2019-164-5458. Using a reported incidence of respiratory distress in neonates with sepsis of 78.4%, with a 95% confidence interval and a 7.5% margin of error, the sample size was calculated to be 116. A non-probability consecutive sampling technique was employed. Preterm neonates with sepsis whose parents/guardians provided informed consent for hospitalization were included. Neonates with congenital malformations detected on clinical examination, a history of birth asphyxia, or early preterm neonates were excluded. Eligible neonates presenting to the emergency department or referred from other care units were enrolled. The purpose of the study was explained to parents/guardians, and written informed consent was obtained, with assurance that participation was voluntary and withdrawal could occur at any stage without consequence. A detailed history and physical examination were performed, and blood cultures were obtained before initiating antibiotics. Patients were followed until discharge to assess outcomes, including feed tolerance, weight gain, respiratory distress, hypothermia, hypoglycemia, necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH). Data on study variables such as age, gender, weight, gestational age, mode of delivery, and duration of symptoms were recorded on a predesigned proforma. All research procedures were carried out by the principal investigator. Data analysis was performed using SPSS version 26.

# Results

In this study, 116 patients were included, with an overall mean age of 5.7 ± 6.05 days, mean weight of 2.4 ± 0.6 kg, and mean gestational age of 31.2 ± 2.6 weeks. The mean duration of symptoms was 7.2 ± 1.9 days. Based on neonatal gender, 38 (32.8%) were boys and 78 (67.2%) were girls. Regarding the mode of delivery, 92 (79.3%) neonates were delivered by cesarean section, while 24 (20.7%) were delivered vaginally. (Table 1)

**Table I: Descriptive statistics of demographic and clinical variables. (n=116)**

| VARIABLE | | STATISTICS |
|---|---|---|
| Age (days) | | 5.7±6.05 |
| Weight (kg) | | 2.4±0.6 |
| Gestational Age (weeks) | | 31.2±2.6 |
| Duration of Symptoms (days) | | 7.2±1.9 |
| Gender | Male | 38(32.8%) |
| | Female | 78(67.2%) |
| Mode of delivery | C-section | 24(20.7%) |
| | NVD | 92(79.3%) |

According to the neonatal outcomes, feed intolerance was observed in 26 (22.4%) neonates, weight gain in 9 (7.7%), respiratory distress in 82 (70.7%), hypoglycemia in 5 (4.3%), hypothermia in 11 (9.5%), necrotizing enterocolitis in 19 (16.4%), and intra-ventricular hemorrhage in 25 (21.5%) neonates as shown in figure 1.

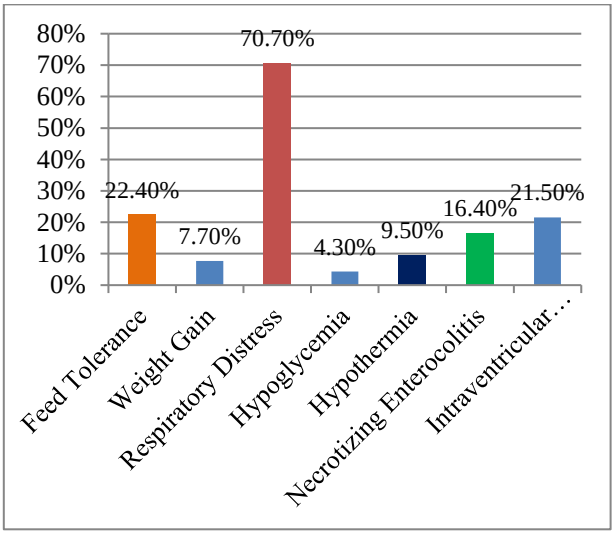


**Figure 1. Outcomes of neonatal sepsis. (n=116)**

Based on stratification gestational age did not significantly influence feed tolerance, weight gain, respiratory distress, hypoglycemia, hypothermia, necrotizing enterocolitis, or intraventricular hemorrhage (p = 0.991). Most adverse outcomes occurred in neonates aged 0–6 days, (p = 0.573). Boys neonates having higher rates of respiratory distress (78.0%), hypoglycemia (100%), and intraventricular hemorrhage (64.0%) compared to females. Birth weight was also significantly associated with outcomes (p = 0.010), as neonates weighing 1.5–2.5 kg had higher frequencies of respiratory distress (86.6%), necrotizing enterocolitis (63.2%), and intraventricular hemorrhage (56.0%) compared to those >2.5 kg. MOD showed no statistically significant association (p = 0.538), although C-section deliveries were more frequent among those with adverse outcomes as shown in table II.

# Discussion

Neonatal sepsis, though presenting with broad-spectrum of signs, can progress to septic shock and multi-organ failure, causing significant long-term morbidity and even deaths in premature neonates, which makes it a serious global health concern.[17,18] The relevant research in neonatal sepsis is heterogeneous. This study assessed the outcome of neonatal sepsis in relations to gestational age among preterm neonates presenting with sepsis among 116 patients with an overall mean age of 5.7 ± 6.05 days, mean weight of 2.4 ± 0.6 kg, and mean gestational age of 31.2 ± 2.6 weeks. The mean duration of symptoms was 7.2 ± 1.9 days. Based on neonatal gender, girls were in majority (67.2%) boys (32.8%). Regarding the mode of delivery, most neonates were delivered by cesarean section (79.3%), while 20.7% were delivered vaginally. In line with these findings, study conducted by Kaffe et al[19] caesarian section was the most frequent mode of delivery in 72%, while mean gestational age 29.7±2.7 weeks was slightly lower and the mean Body weight (1299 ± 350 gr) was 2-fold lower than our study. Consistently, in the study of Salama et al[20] mean gestational age was 31 ± 2 weeks, the most common mode of delivery was Cesarean-section (69.9%), while mean weight 1490±411g was lower than our study cohort.

In this study, respiratory distress (70.7%) emerged as the most frequent neonatal outcome, consistent with Salama et al[20] who also reported respiratory distress (78.4%) as the leading complication, suggesting its strong association with neonatal morbidity across populations. In contrast, Demisse et al[21] identified hypothermia (71%)

**Table II: Stratification of neonatal outcomes. (n=116)**

| Variables | | FT | WG | RD | HG | HT | NE | IH | p-value |
|---|---|---|---|---|---|---|---|---|---|
| **Gestational Age (weeks)** | 28 –32 | 16 (61.5) | 5 (55.6) | 56 (68.3) | 3 (60.0) | 7 (63.6) | 16 (84.2) | 17 (68.0) | 0.991 |
| | >32.5 | 10 (38.5) | 4 (44.4) | 26 (31.7) | 2 (40.0) | 4 (36.4) | 3 (15.8) | 8 (32.0) | |
| **Age (days)** | 0 – 6 | 20 (76.9) | 7 (77.8) | 63 (76.8) | 5 (100.0) | 1 (33.3) | 15 (78.9) | 19 (76.0) | 0.573 |
| | >6 | 6 (23.1) | 2 (22.2) | 19 (23.2) | 0 (0.0) | 2 (66.7) | 4 (21.1) | 6 (24.0) | |
| **Gender** | Male | 13 (50.0) | 5 (55.6) | 64 (78.0) | 5 (100.0) | 1 (33.3) | 9 (47.4) | 16 (64.0) | 0.015 |
| | Female | 13 (50.0) | 4 (44.4) | 18 (22.0) | 0 (0.0) | 2 (66.7) | 10 (52.6) | 9 (36.0) | |
| **Fetal wright (kg)** | 1.5 – 2.5 | 19 (73.1) | 8 (88.9) | 71 (86.6) | 2 (40.0) | 2 (66.7) | 12 (63.2) | 14 (56.0) | 0.010 |
| | >2.5 | 7 (26.9) | 1 (11.1) | 11 (13.4) | 3 (60.0) | 1 (33.3) | 7 (36.8) | 11 (44.0) | |
| **Mode of delivery** | C-Section | 16 (61.5) | 7 (77.8) | 66 (80.5) | 4 (80.0) | 2 (66.7) | 16 (84.2) | 18 (72.0) | 0.538 |
| | NVD | 10 (38.5) | 2 (22.2) | 16 (19.5) | 1 (20.0) | 1 (33.3) | 3 (15.8) | 7 (28.0) | |

FT= **Feed Tolerance,** WG=**Weight Gain,** RD= **Respiratory Distress,** HG= **Hypoglycemia,** HT= **Hypothermia,** NE= **Necrotizing Enterocolitis,** IH= **Intraventricular Hemorrhage**

and hypoglycemia (18.5%) as the major outcomes, while respiratory distress was less common (10.9%), likely reflecting differences in environmental conditions, neonatal care standards, and the sample selection criteria.

Additionally, in this study, gestational age did not significantly influence neonatal outcomes in terms of feed tolerance, weight gain, respiratory distress, hypoglycemia, hypothermia, necrotizing enterocolitis, or intra-ventricular hemorrhage p-0.991. Consistently, Başerdem et al[22] reported no significant difference in feeding intolerance across gestational weeks p-0.82. Though, in contrast to our results, they found significant associations of gestational age with respiratory complications, hypoglycemia, and intra-ventricular hemorrhage p =< 0.05, with respiratory complications highest at 34 weeks and lowest at 36 weeks, while hypoglycemia was more common at 35 weeks. In aligns to this study, Wang et al[23] and Shapiro-Mendoza et al[24] observed that preterm neonates are at higher risk of respiratory distress, intra-ventricular hemorrhage, temperature instability, hypoglycemia, and feeding difficulties compared to term neonates. In another study by Sheikh et al[13] reported the neonatal jaundice, respiratory distress syndrome, and probable sepsis in 58.5%, 57.1%, and 55.3% of patients respectively. The study further noted significant association survival outcomes and birth weight, gestational age, cesarean section, feeding initiation, APGAR scores, and hypothermia ($p < 0.05$).

In this study, male neonates demonstrated higher rates of respiratory distress (78.0%), hypoglycemia (100%), and intra-ventricular hemorrhage (64.0%) compared to females. In aligns to this series Elsmén et al[25] who reported significantly higher respiratory morbidity among males (60.8%) than females (46.2%) during the first 6 days of life ($p = 0.026$), attributed to delayed lung maturation and hormonal influences. Consistently, Anadkat et al[26] found that respiratory distress morbidity was significantly more common among preterm males compared to preterm females (p- 0.001). In supporting our findings, Tioseco et al[27] reported a significantly higher prevalence of intra-ventricular hemorrhage in males (19.8%) than in females (3.9%) (p-0.0001). Boys neonates show higher rates of complications, may due to delayed lung maturation an hormonal influences. Furthermore, in this study, the mode of delivery was not significantly associated with neonatal outcomes. This finding is supported by Alfirevic et al[31], who also reported no significant association between mode of delivery and neonatal complications, including respiratory distress (RR = 0.55), neonatal birth injury (RR = 0.56), and birth asphyxia (RR = 1.63). Generally, available evidence of the study indicates that the preterm birth is strongly associated with neonatal complications, particularly respiratory distress, with a notable predominance among male infants, but due to several limitations of this study, further large-scale research is recommended to validate these findings and to which may helpful to develop the preventive strategies and management protocols aimed at reducing complications among patients with preterm births.

# Conclusion

Based on study conclusion the respiratory distress observed as the most common neonatal complications, followed by feed intolerance, necrotizing enterocolitis and intra-ventricular hemorrhage, without significant association with gestational age. However, based on few significant limitations there is further need for larger, multicenter studies to validate the findings and to inform evidence-based strategies for improving neonatal care in preterm populations.

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