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Study Of Clinical Profile And Outcome Of Sepsis In Neonatal Intensive Care Unit In A Tertiary Care Hospital - A Prospective Observational Study

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ABSTRACT

BACKGROUND: Neonatal sepsis (NS) is defined as a clinical syndrome of bacteraemia with systemic signs and symptoms of infection in the first 4 weeks of life. Sepsis is the commonest cause of neonatal morbidity and mortality.[1] Neonatologists managing NICUs constantly encounter the ongoing challenge of addressing newborn infections due to evolving microbial flora patterns. Understanding the microbiological profile and antimicrobial susceptibility patterns is crucial for paediatricians when selecting the most effective antibiotics for treating neonates with sepsis.[2]

OBJECTIVES: To determine the clinical profile of neonatal sepsis in neonates admitted to NICU and Sick Neonatal Intensive Care Unit(SNICU).

METHODOLOGY: This prospective study was done in neonatal intensive care unit at R.L.JALAPPA HOSPITAL. All neonates who were admitted in NICU or SNICU fulfilling the inclusion criteria were included in the study and evaluated for clinical profile of sepsis and outcome.
RESULTS: In the present study, among the 80 neonates, tachypnea was the most prevalent symptom, noted in 57.5% of cases. Blood culture results showed that 25 neonates (31.3%) were tested positive, while 55 neonates (68.8%) tested negative. The most frequently identified organism was Klebsiella species, found in 11 neonates (13.8%). Additionally, Candida was detected in 5.0% of cases, E. coli in 3.8%, Acinetobacter in 2.5%, and Enterococci in 2.5%.It was observed that 31.25% of neonates had Culture Positive Sepsis (Definitive) while 68.75% had Probable (Clinical) Sepsis.
CONCLUSION: This study focuses on the clinical profile and outcome of neonatal sepsis in a NICU setting, highlighting its substantial burden on neonatal health. Clinical manifestations varied widely, with tachypnea being the most common symptom. Blood culture results highlighted Klebsiella species as the most prevalent pathogen. Despite advances, the high mortality rate underscores the ongoing need for better early detection, prompt intervention, and overall care practices to improve outcomes for newborns affected by sepsis.

INTRODUCTION

"Neonatal sepsis (NS) is defined as a clinical syndrome of bacteraemia with systemic signs and symptoms of infection in the first 4 weeks of life." It covers a range of systemic infections

affecting newborns, including septicemia, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections. Sepsis is the commonest cause of neonatal morbidity and mortality.[1]

The clinical presentations of NS are nonspecific. This includes symptoms like fever, respiratory distress, lethargy/irritability, convulsions, bulging fontanelles, refusal to feed, jaundice, bleeding, abdominal distension, and temperature dysregulation.[2]

Early-onset sepsis (EOS) presents within 72 hrs of life, and late-onset sepsis (LOS) presents beyond 72 hours of life.[2] In EOS maternal genital tract is the source of the infection. Maternal risk factors like premature rupture of membranes (PROM), chorioamnionitis, peripartum fever, urinary tract infection within 2 weeks prior to delivery and prolonged rupture of membranes > 18 hours, multiple gestations, and caesarean sections are associated with increased risk of EOS.[2]

LOS occurs because of postnatal nosocomial infections or community-acquired infections. The risk factors associated with LOS are prematurity, prolonged invasive interventions like mechanical ventilation and intravascular catheterization, failure of early enteral feeding with breast milk, long duration of parenteral nutrition, hospitalization, surgery, and underlying respiratory and cardiovascular diseases. [2]

The spectrum of bacteria which cause NS varies in different parts of the world. Bacterial infections are the most common cause of morbidity and mortality during the neonatal period. Fulminant and fatal course of infection may result in complications such as shock, disseminated intravascular coagulation (DIC) and multi-system organ failure.[3] This mandates the need for early diagnosis of these life-threatening conditions for timely treatment and a favourable outcome. [2,3]

Multidrug antibiotic resistance is an emerging problem in Neonatal Intensive Care Unit (NICU) particularly in developing countries. Neonatologists who supervise NICU always face a continuous challenge in managing neonatal infections due to the changing patterns of the microbial flora. The knowledge of the bacteriological profile and its antibiotic sensitivity pattern is of great use to paediatricians in choosing antibiotics optimally to treat neonates with septicaemia. [2]

AIM & OBJECTIVES

- To determine the clinical profile of neonatal sepsis in neonates admitted to NICU and Sick Neonatal Intensive Care Unit (SNICU).
- To determine the complications and outcome associated with neonatal sepsis in neonates admitted to NICU and SNICU.

MATERIAL AND METHODS

Source of Data: All neonates admitted to NICU and SNICU with sepsis or later who develop sepsis in NICU and SNICU at R.L. Jalappa Hospital & Research Centre.

Study Design: A Prospective observational study.

Study Period: 1 year 4 months from September 2022 to December 2023.

Method of Collection of Data:

Inclusion Criteria:

All neonates admitted to NICU and SNICU having 1 or more established clinical features suggestive of sepsis such as fever (temperature >38°C), hypothermia, poor suck, lethargy, irritability, seizure, apneic spells, respiratory distress, abdominal distention, poor moro reflex,

with or without maternal risk factors (PROM of >12 hours, maternal fever during delivery, prolonged labour, urinary tract infection, chorioamnionitis and meconium- stained amniotic fluid).

Exclusion Criteria:

- Birth asphyxia
- Congenital anomalies
- Suspected metabolic disease.
- Refusal of parental consent.

Sample Size:

The sample size was estimated by using the proportion of death in subjects who had sepsis (9.7%) from the study by Melkamu Berhane et al. by using the formula

$$\text{Sample Size} = \frac{Z_{1-\alpha/2}^2 P (1-P)}{d^2}$$

$Z_{1-\alpha/2}$ = is standard normal variate(at 5% type 1 error ($P<0.05$) it is 1.96 and at 1% type1 error($P<0.01$) it is 2.58).As in majority of studies P values are considered significant below 0.05 hence 1.96 is used in formula.

P= Expected proportion in population based on previous studies or pilot studies

d= Absolute error or precision

P = 9.7% or 0.097

q = 90.3 or 0.903

d = 7.5% or 0.075

Using the above values at 95% Confidence level a sample size of 60 subjects were included in the study. Considering 10% Non response a sample size of 60 + 6 ≈ **66 minimum subjects** were included in the study.

Methodology:

- This study was started after obtaining approval from the institutional ethical committee and taking informed consent from parents. All neonates fulfilling the inclusion criteria were included in the study.
- Complete physical examination of neonates was performed.
- After taking informed consent, the following investigations were done for all subjects: Complete blood count (CBC), CRP and blood culture.
- The following investigations were done as and when required: Chest X- ray; Neurosonogram; Cerebrospinal fluid (CSF) analysis; Liver function tests; Renal function tests; CT; MRI.

- Based on the results of the investigations, the subjects were divided into 2 groups namely Probable (Clinical) Sepsis and Culture Positive Sepsis (Definitive).
- Neonates were treated as per the institutional protocol and followed up till discharge from the NICU.

For the study purpose following definitions were used:

EOS: Sepsis which manifests within first 72 hours of life and **LOS** is one which manifests beyond 72 hours of life. [4]

Probable (Clinical) Sepsis: In a neonate having clinical picture suggestive of septicemia, if there was presence of **any one** of the following criteria:

- Positive septic screen
- Presence of predisposing factors (maternal fever or foul-smelling liquor or PROM or gastric polymorphs (>5 hpf)
- Radiological evidence of pneumonia.[5]

Culture Positive Sepsis (Definitive): In a neonate having clinical picture suggestive of septicemia, pneumonia or meningitis with isolation of pathogens from blood or CSF or urine or abscess.[5]

Septic screen was considered positive **when 2 or more** of the following parameters were present:[5]

1. Total leukocyte count: < 5000/mm^3 or > 24,000/mm^3.

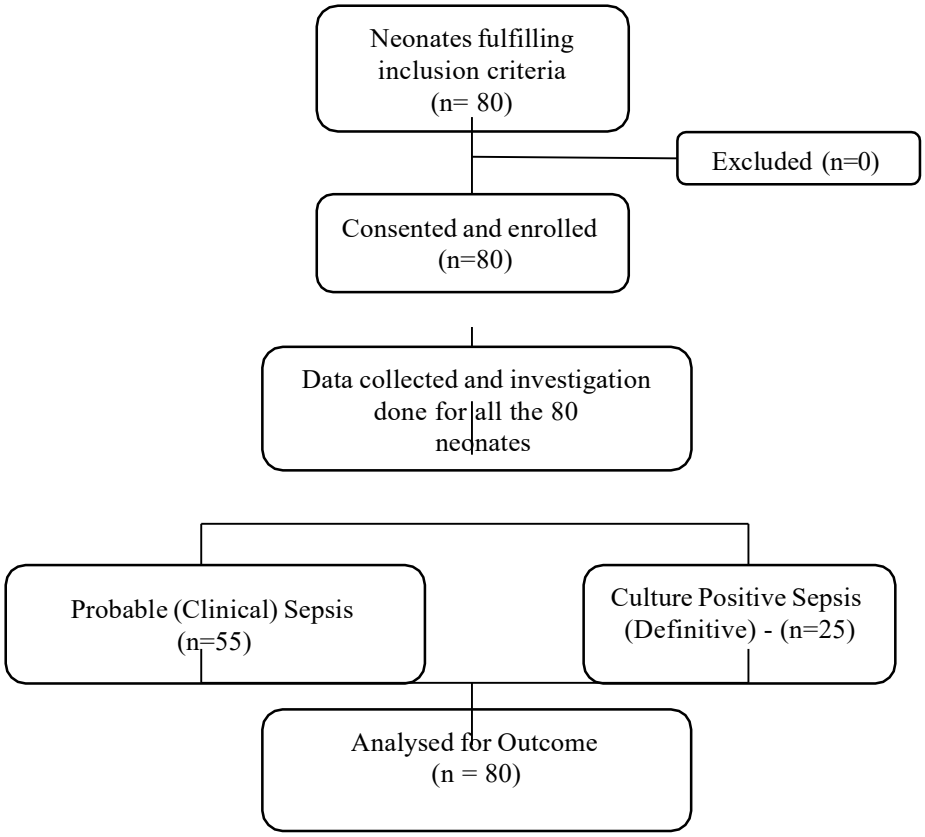
2. Absolute neutrophil count: low count as per Monroe chart for term infant and Mouzinho chart for VLBW infants.

3. Immature or band cells to total neutrophil ratio: >0.2

4. Micro ESR: >15 mm 1st hour

5. CRP: >1mg/dL.

Figure 1: Flow diagram for collection and analysis of data



RESULTS & OBSERVATIONS

Table 1: Distribution of neonates based on gender (n=80)

		Frequency	Percentage
Gender	Male	45	56.3
	Female	35	43.8
	Total	80	100

Figure 2: Distribution of neonates based on gender

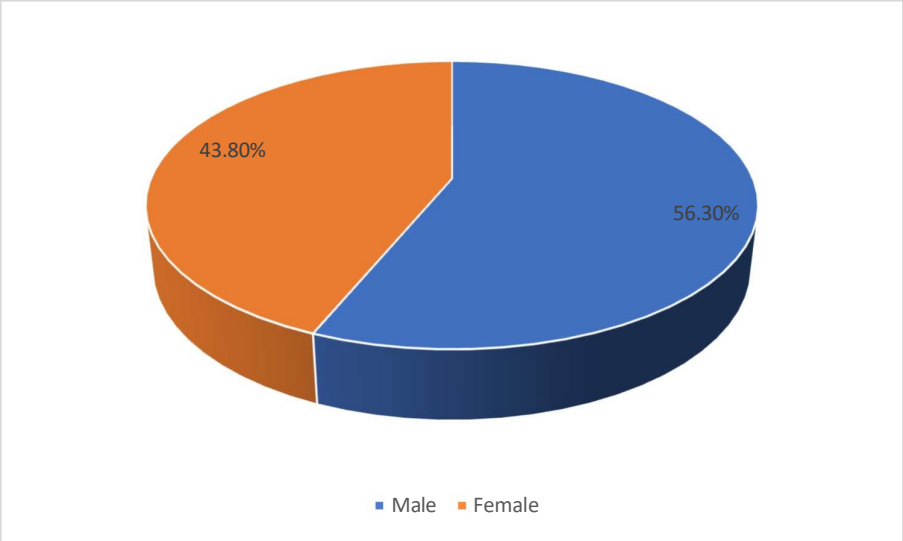


Table 1 & Figure 2 depict the distribution of cases based on gender. It was observed that out of 80 neonates diagnosed with NS, 45 (56.3%) were males while 35 (43.8%) were females.

Table 2: Distribution of neonates based on birth weight (n=80)

		Frequency	Percentage
Birth Weight	<1 kg	4	5.0
	1- <1.5 kg	23	28.8
	1.5 - < 2 kg	36	45.0
	2.0 - <2.5 kg	11	13.8
	>2.5 kg	6	7.5
	Total	80	100

Figure 3 : Distribution of neonates based on birth weight (n=80)

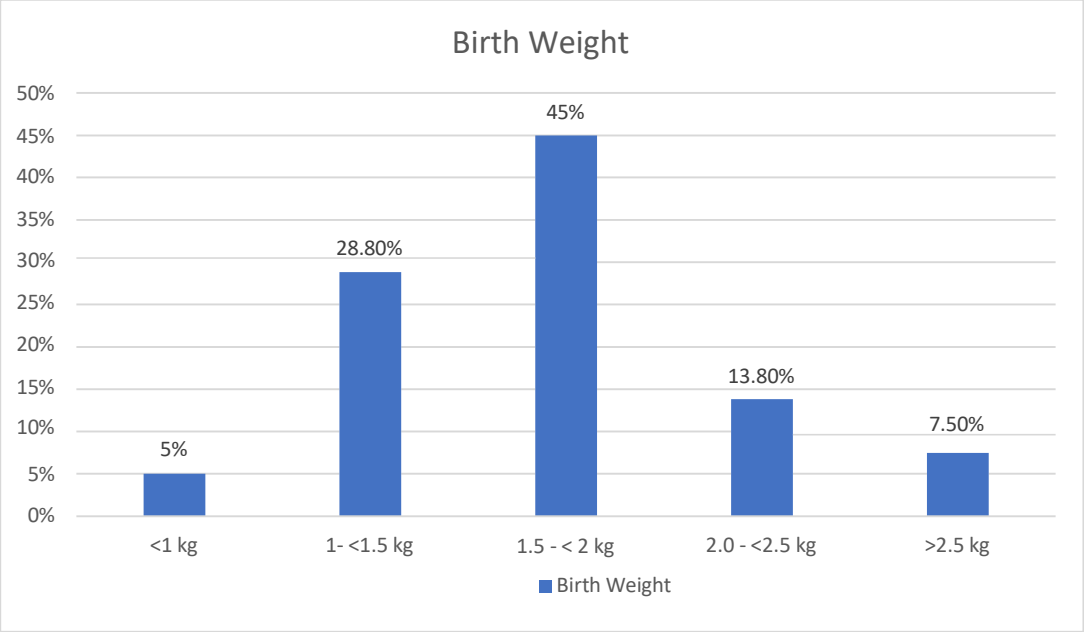


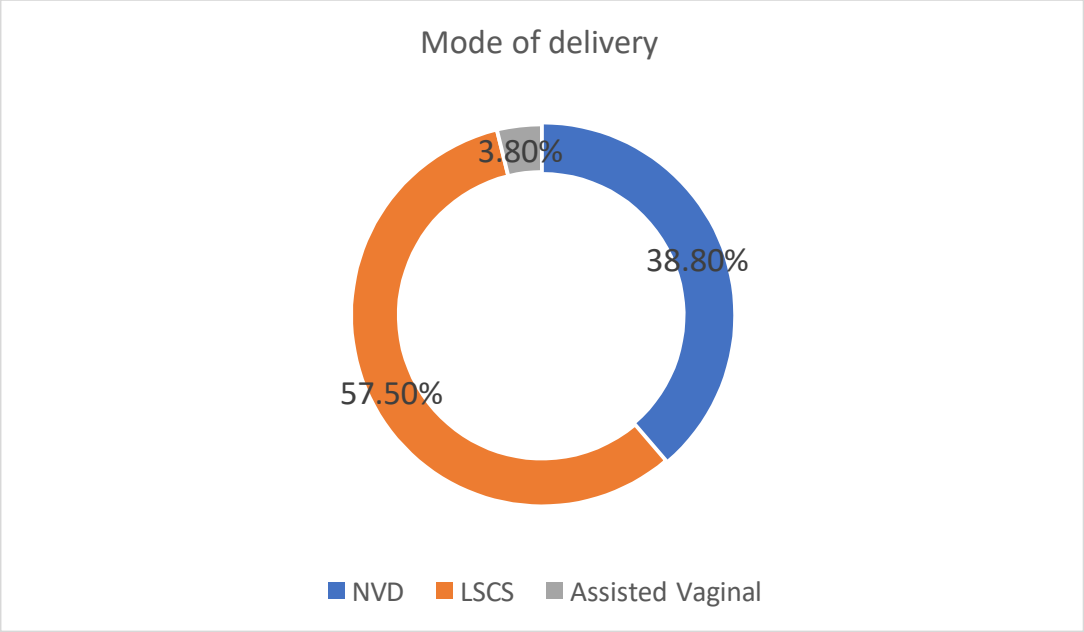
Table 2 & Figure 3 depict the distribution of cases based on birth weight. Majority (45%) of neonates were in the birth weight category of 1.5 Kg to <2 Kg. In the birth weight category of 1 Kg to < 1.5 Kg, 23 (28.8%) neonates were present. There were 11(13.8%) neonates in the birth weight category of 2 Kg to < 2.5 Kg. Four (5%) and 6 (7.5%) neonates were in the birth weight categories of < 1 Kg and > 2.5 Kg respectively.

Table 3: Distribution of neonates based on mode of delivery (n=80)

		Frequency	**Percentage**
Mode of Delivery	*NVD	31	38.8
	#LSCS	46	57.5
	Assisted Vaginal	3	3.8
	Total	80	100

*Normal vaginal delivery; #Lower segment caesarean section

Figure 4: Distribution of neonates based on mode of delivery (n=80)



It was observed that majority (57.5%) of neonates were delivered by LSCS while 31 neonates (38.8%) were delivered through NVD, and 3 neonates (3.8%) were delivered through assisted vaginal methods. (Table 6 & Figure 5)

Table 4: Distribution of neonates based on time of onset of sepsis (n=80)

Time of onset of sepsis	Frequency	Percentage
*EOS	32	40
#LOS	48	60
Total	80	100

*Early onset sepsis; #Late onset sepsis

Table 4 depicts distribution of neonates based on time of onset of sepsis. It was observed that 60% of neonates had LOS while 40% had EOS.

Table 5: Distribution of neonates based on risk factors (n=80)

Risk Factors	Frequency	Percentage
Central Line	44	55.0
*PROM	34	42.5
#IUGR	17	21.3
^MAS	12	15.0
Intrapartum Fever	6	7.5

* Premature rupture of membranes; # Intrauterine growth restriction; ^ meconium aspiration syndrome

Table 5 depicts distribution of cases based on risk factors. More than half (55%) of the neonates with sepsis had central lines. History of PROM was noted in 34 cases (42.5%), IUGR was seen in 17 (21.3%) and MAS was present in 12 (15.0%) neonates. Maternal history of intrapartum fever was present in 6 (7.5%) cases.

Table 6: Distribution of cases based on clinical features

Clinical features	Frequency	Percentage
Tachypnea	46	57.5
Lethargy	36	45.0
Refusal of feeds	32	40.0
Temperature instability	32	40.0
Abdominal distension	29	36.3
Conjunctivitis	29	36.3
Vomiting	27	33.8
Grunting	25	31.3
Bleeding	24	30.0
Apnea	22	27.5
Sclerema	21	26.3
Seizures	19	23.8
Weak cry	18	22.5
Umbilical sepsis	7	8.8

Table 6 depicts the distribution of neonates based on clinical features. It was observed that tachypnea was the most common symptom observed in 46 neonates (57.5%). The other clinical features noted were lethargy in 36 neonates (45.0%), refusal of feeds and temperature instability in 32 neonates each (40.0%), abdominal distension and conjunctivitis in 29 (36.3%) neonates each, vomiting in 27 (33.8%), grunting in 25 (31.3%), bleeding in 24 (30.0%), and apnea in 22 cases (27.5%). Sclerema was present in 21 neonates (26.3%), seizures in 19 (23.8%), weak cry in 18 (22.5%) and umbilical sepsis in 7 cases (8.8%).

Table 7: Distribution of neonates based on complications

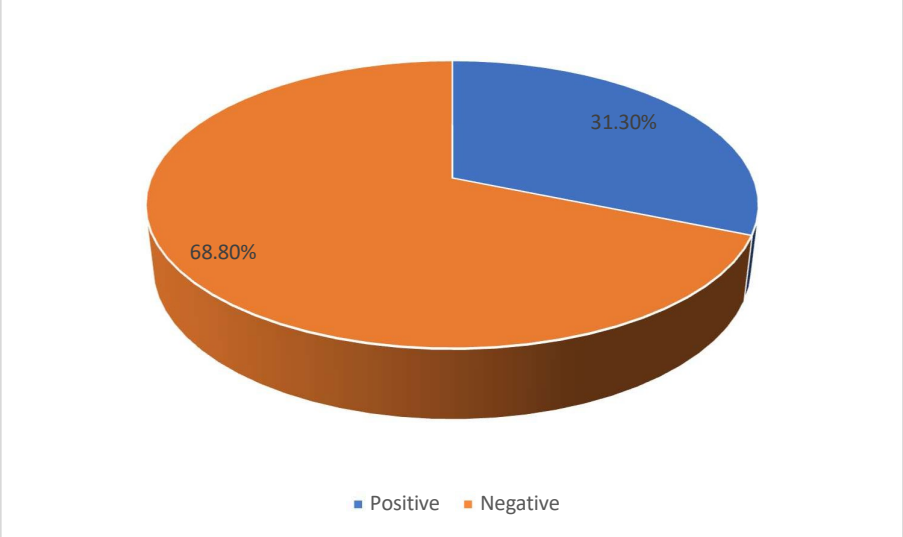
Complications	Frequency	Percentage
Hypoglycemia	34	42.5
Thrombocytopenia	32	40.0
AKI	26	32.5
MODS	21	26.3
Meningitis	4	5.0

Hypoglycaemia was present in 34 neonates (42.5%) and thrombocytopenia in 32 neonates (40.0%). Acute kidney injury (AKI) was seen in 26 cases (32.5%), multiple organ dysfunction syndrome (MODS) in 21 neonates (26.3%) and meningitis in 4 cases (5.0%) – Table 10.

Table 8: Distribution of neonates based on the blood culture report (n=80)

		Frequency	Percentage
Blood culture	Positive	25	31.3
	Negative	55	68.8
	Total	80	100

Figure 5: Distribution of neonates based on the blood culture report (n=80)



Out of 80 neonates, blood culture was positive in 25 neonates (31.3%) – Table 8 & Figure 5.

Table 9: Spectrum of organisms isolated from blood culture (n=25)

		Frequency	Percentage
Organism			
	Gram Negative organisms		
	Klebsiella pneumoniae	11	44
	E coli	3	12
	Acinetobacter	2	8
	Enterobacter	1	4
	Kleb oxytoca	1	4
	Gram positive organisms		
	Enterococci	2	8
	CONS	1	4
	Fungus		
	Candida	4	16
	Total	25	100

Klebsiella species was the most isolated organisms (44%) followed by Candida (16%) and E. coli (12%). Other organisms identified were Acinetobacter and Enterococci in 2 (8%) neonates each. Coagulase-negative Staphylococci (CONS), Enterobacter, and Klebsiella oxytoca were identified in 1 (4%) neonate each – Table 9.

Table 10: Distribution of cases based on type of sepsis (n=80)

Type of sepsis	**Frequency**	**Percentage**
Probable (Clinical) Sepsis	55	68.75
Culture Positive Sepsis (Definitive)	25	31.25
Total	80	100

Tabe 10 depicts type of sepsis based on investigations. It was observed that 31.25% of neonates had Culture Positive Sepsis (Definitive) while 68.75% had Probable (Clinical) Sepsis.

Table 11: Distribution of neonates based on duration of NICU stay (n=80)

		Frequency	Percentage
NICU Stay (Days)	≤7 days	18	22.5
	8-14 days	30	37.5
	15-21 days	25	31.3
	>21 days	7	8.8
	Total	80	100

Eighteen neonates (22.5%) were in NICU for a duration of ≤7 days, while 30 neonates (37.5%) stayed for 8 to 14 days. Twenty-five neonates (31.3%), and 7 neonates (8.8%) were in NICU for 15-21 days and >21 days respectively.

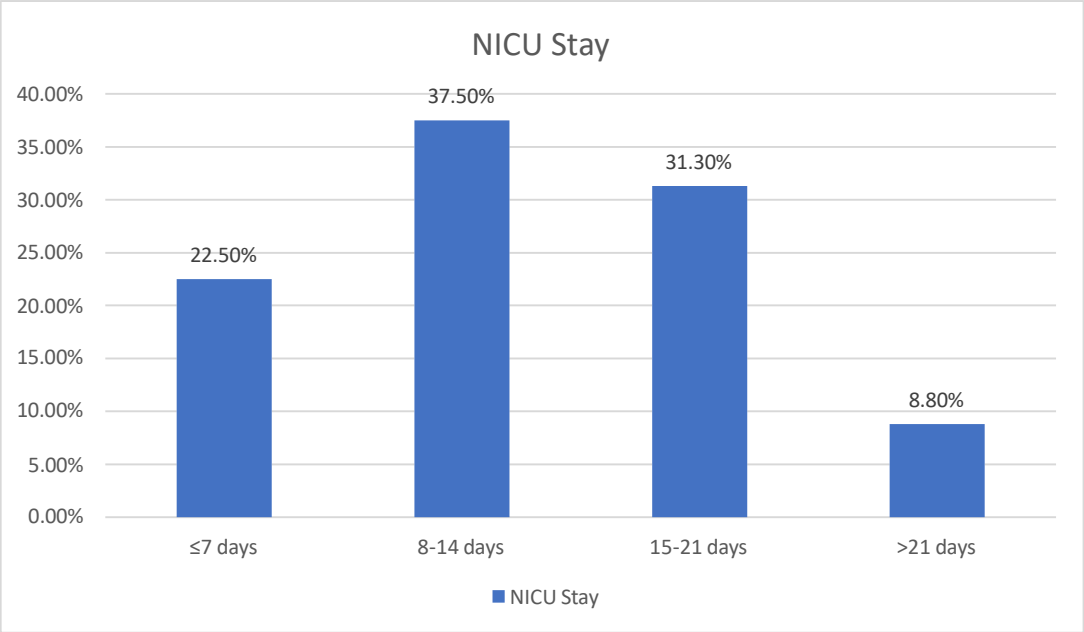


Figure 6: Distribution of neonates based on the NICU stay duration

Table 12: Distribution of neonates based on their outcome (n=80)

		Frequency	Percent
Outcome	Death	7	8.75
	Recovered	67	83.75
	*DAMA	6	7.5

	Total	80	100

* Discharged against medical advice

Out of 80 neonates with sepsis, 67 (83.75%) recovered while 7 neonates (8.75%) died due to sepsis-related complications. Six neonates (7.5%) were discharged against medical advice for various reasons – Table 12.

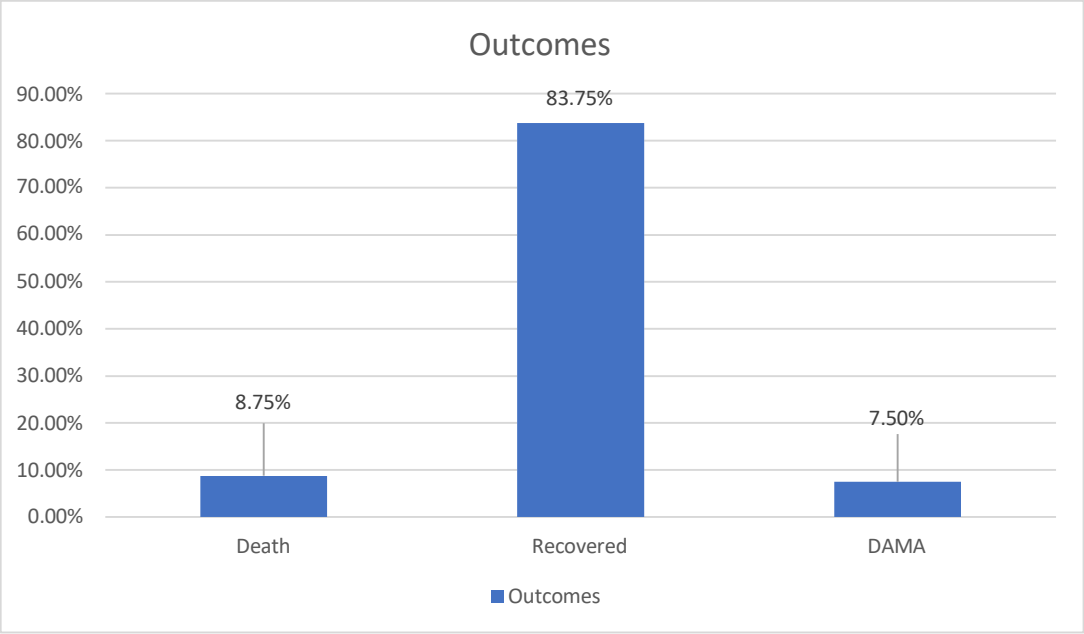


Figure 7: Distribution of neonates based on the outcome (n=80)

DISCUSSION

NS is considered the leading cause of infant mortality and morbidity in the NICU. Early diagnosis and therapy are essential for the prevention of morbidity and mortality of NS. The incidence and the causative organisms of sepsis vary from place to place. Knowledge of the bacterial profile and the antibiotic susceptibility pattern of the isolates play an important role in the management of sepsis. The present study was conducted to determine the clinical profile of NS in neonates admitted to NICU and SNICU.

Sepsis and Gender

In this study, a total of 80 neonates diagnosed with sepsis were included. Among these patients, 45 were male, accounting for 56.3% of the sample, while 35 were female, representing 43.8%. This distribution indicates a slight predominance of male neonates. Similar findings were reported by Thapa S et al., [7], Pokhrel B et al.,[8], Ghosh S et al.,[9], Ekwochi U et al., [10], Yadav SK et al., [11] , Panda PK et al., [12]. Shrivastava AK et al., [13] Devkota K et al., [14] . However, no explanation can be offered for this male preponderance.

Sepsis and Birth weight

In the present study, majority (45%) of neonates were in the birth weight category of 1.5 Kg to <2 Kg. In the birth weight category of 1 Kg to < 1.5 Kg, 23 (28.8%) neonates were present. There were 11(13.8%) neonates in the birth weight category of 2 Kg to < 2.5 Kg. Four (5%) and 6 (7.5%) neonates were in the birth weight categories of < 1 Kg and > 2.5 Kg respectively.

In Budhiarta KDL et al., [15] found that lower birth weight was associated with higher mortality, particularly in neonates with birth weights less than 2500 grams. Yadav SK et al., [11] reported that 45% of the neonates had a birth weight of less than 2.5 kg. Panda PK et al., [12]highlighted that preterm and low birth weight neonates had lower discharge rates and higher mortality.Shrivastava AK et al., [13] highlighted that preterm (41.46%) and low birth weight (22.73%) were the most common associated factors in early-onset neonatal septicemia. Devkota K et al., [14] reported that 25.36% of neonates with sepsis had low birth weight, and 18.12% had very low birth weight. These studies consistently demonstrate that neonates with birth weights below 2500 grams are at increased risk of mortality and sepsis. This highlights the increased vulnerability of preterm and low birth weight infants to serious health complications, particularly early-onset neonatal septicemia.

Sepsis and Mode of delivery

In the present study it was observed that majority (57.5%) of neonates were delivered by LSCS while 31 neonates (38.8%) were delivered through NVD, and 3 neonates (3.8%) were delivered through assisted vaginal methods. Ghosh S et al.,[9] reported that 52.18% of neonates were delivered normally, while 47.82% were delivered by caesarean section. Devkota K et al.,[14] reported that 62.32% of neonates with sepsis were delivered via spontaneous vaginal delivery and while 37.68% were delivered via caesarean section. However, no significant interpretations or conclusions were drawn regarding these differences in delivery methods across the studies.

Time of onset of sepsis

In present study it was observed that 60% of neonates had LOS while 40% had EOS.

Devkota K et al., [14] Rawat et al.[16],reported that 71.01% of neonates had early-onset NS, while 28.99% had late-onset NS. In a study conducted by Gurung B et al.,[3] among neonates with sepsis, 30.2% had early onset and 69.8% had late onset neonatal sepsis. Berhane M et al.,[17] reported that out of 304 neonates, 195 (64.1%) had clinical evidence for sepsis, majority (84.1%) of them having early onset neonatal sepsis.

Sepsis and risk factors

In the present study more than half (55%) of the neonates with sepsis had central lines. History of PROM was noted in 34 cases (42.5%), IUGR was seen in 17 (21.3%) and MAS was present in 12 (15.0%) neonates. Maternal history of intrapartum fever was present in 6 (7.5%) cases. Rawat et al.,[16] reported various maternal risk factors affecting neonatal septicaemia; rupture of membranes for more than 18 hours was the commonest factor with 63.64% cases followed by foul smelling liquor in 27.27%. febrile illness in mother 18.18% and maternal urinary tract infection (UTI) in 9.09%. Studies conducted by Rawat et al.,[16] Devkota K et al., [14] concluded that factors such as low birth weight, prematurity, mechanical ventilation, invasive procedures were the predisposing factors for sepsis in neonates.

Sepsis and Blood culture

In the present study Klebsiella species was the most isolated organisms (44%) followed by Candida (16%) and E. coli (12%). Other organisms identified were Acinetobacter and Enterococci in 2 (8%) neonates each. Coagulase-negative Staphylococci (CONS), Enterobacter, and Klebsiella oxytoca were identified in 1 (4%) neonate each.

Thapa S et al.[7], reported that the majority (69.6%) of neonatal septicemia cases were caused by gram-negative isolates. Acinetobacter species were the most frequently isolated pathogens (32.1%), followed by Staphylococcus aureus (19.6%). In early-onset septicemia, Acinetobacter species (32.1%) and Staphylococcus aureus (16%) predominated, while in late-onset septicemia, Staphylococcus aureus (19.6%) and Acinetobacter species (8.9%) were most prevalent.

According to Pokhrel et al.,[8] the majority (77%) of bacterial isolates were gram-negative. Klebsiella species, Coagulase-negative Staphylococci (CONS), and Enterobacter were identified as the most common pathogens. However, the blood culture positivity rate in our study is low compared to the results reported by Rawat et al.,[16]Thapa et al.,[7] and Pokhrel et al..[8]

Sepsis and clinical profile

In the present study it was observed that tachypnea was the most common symptom observed in 46 neonates (57.5%). The other clinical features noted were lethargy in 36 neonates (45.0%), refusal of feeds and temperature instability in 32 neonates each (40.0%), abdominal distension and conjunctivitis in 29 (36.3%) neonates each, vomiting in 27 (33.8%), grunting in 25 (31.3%), bleeding in 24 (30.0%), and apnea in 22 cases (27.5%). Sclerema was present in 21 neonates (26.3%), seizures in 19 (23.8%), weak cry in 18 (22.5%) and umbilical sepsis in 7 cases (8.8%).

Rawat D et al., [16] reported respiratory distress (65.30%) as the commonest presentation among culture positive cases followed by encephalopathy (22.44%) and seizures (14.28%). Common clinical findings observed by Pokhrel B et al.,[8] were respiratory distress (79.7%), tachycardia (60.9%), cyanosis (59.4%) and hypothermia (53.6%). Ekwochi U et al., [10] reported fever as the most common symptom, with 84.2% of the presentations manifesting as such. Poor suckling (39.3%), fast breathing (43.6%), jaundice (39.3%), lethargy (31.6%), and poor cry (30.4%) were other common symptoms, while vomiting (17.5%), diarrhea (1.8%), abdominal distention (15.8%), excessive cry (12.5%), and bleeding from the cord (3.5%) were not very common. Budhiarta KDL et al., [15] included common symptoms such as respiratory distress, jaundice, and signs of infection in the clinical profiles of neonates with sepsis. Yadav SK et al., [11] emphasized clinical signs like tachypnea, respiratory distress, and abdominal distension as key indicators of sepsis.

The study observed tachypnea as the most prevalent symptom among neonates (57.5%), with additional common features including lethargy, refusal of feeds, and temperature instability. Other symptoms such as abdominal distension, conjunctivitis, vomiting, grunting, and bleeding were also noted. Comparisons with other studies underscored variations in clinical presentations of neonatal sepsis, highlighting respiratory distress, fever, jaundice, and feeding difficulties as frequent symptoms across different research findings.

Sepsis and Outcome

In the present study, 7 (8.75%) neonates died due to sepsis-related complications. Majority (83.75%) of neonates recovered and were discharged from the NICU. Six neonates (7.5%) were discharged against medical advice (DAMA) due to various reasons. Rawat D et al., [16] observed a mortality of

10.2% among neonates with sepsis which was almost similar to the findings of our study. Panda PK et al., [12] reported a slightly higher mortality rate of 11%. Higher mortality rates of 15.94% and 28.2% were reported by Pokhrel B et al.,[51] and Budhiarta KDL et al., [15] respectively. NS is a major cause of death in low- and middle-income countries. Various characteristics have been reported to be associated with mortality in NS such as sclerema, ELBW, thrombocytopenia, leukopenia and hyperglycemia.[18]

CONCLUSION

This study focuses on the clinical profile and outcome of neonatal sepsis in a NICU setting, highlighting its substantial burden on neonatal health. The findings emphasize the vulnerability of neonates with lower birth weight and stresses the need for careful monitoring and targeted treatments. Clinical manifestations varied widely, with tachypnea being the most common symptom. Blood culture results highlighted Klebsiella species as the most prevalent pathogen. Effective treatment depends on understanding local bacterial types and which antibiotics are effective against them. Despite advances, the high mortality rate underscores the ongoing need for better early detection, prompt intervention, and overall care practices to improve outcomes for newborns affected by sepsis.

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