Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/tskvtk14

SERUM NT-PRO BNP AND ITS ROLE IN THE DIAGNOSIS OF NEONATAL SEPSIS. A TERTIARY CARE HOSPITAL BASED STUDY

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Abstract: The present study aimed to evaluate the effectiveness of NT-proBNP levels in diagnosing and prognosticating neonatal sepsis within a cohort of Kashmiri neonates.
The study was conducted over two years at the Department of Pediatrics and Neonatology at SKIMS Soura Srinagar, employing a hospital-based prospective design. A total of 100 neonates were included, equally divided into cases (suspected sepsis) and controls (healthy neonates). The primary objective was to assess whether NTproBNP, a biomarker traditionally used in diagnosing heart failure, could serve as a reliable marker for neonatal sepsis.The methodology involved selecting neonates with a Töllner sepsis score of 5 or higher, who were subsequently subjected to a range of diagnostic tests including NT-proBNP measurement, blood cultures, and routine biochemical assessments. The study meticulously excluded preterm neonates under 35 weeks of gestation, those with congenital heart diseases, and those who died within 72 hours of hospitalization. NT-proBNP levels were measured at the time of hospitalization and compared between the case and control groups.The results of this study highlighted significant disparities between neonates diagnosed with sepsis and the control group across various parameters. NT-proBNP levels were markedly elevated in the sepsis group, with 40% of the neonates exhibiting levels above 30,000 ng/L compared to just 4% in the control group. This substantial difference suggests a strong correlation between high NT-proBNP levels and the presence of neonatal sepsis, reinforcing the potential of NT-proBNP as a diagnostic biomarker.In terms of clinical presentation, neonates in the sepsis group showed a higher incidence of respiratory distress (60%), fever (40%), hypothermia (30%), and seizures (20%) compared to the control group. These symptoms were significantly more frequent in the sepsis group, indicating the severe systemic involvement typically seen in septic neonates. Additionally, the general examination revealed that neonates with sepsis had higher pulse rates and respiratory rates, along with lower systolic and diastolic blood pressures, which are indicative of cardiovascular stress and dysfunction. Laboratory findings further supported the clinical diagnosis of sepsis. The sepsis group demonstrated significantly lower total leukocyte counts, hemoglobin levels, and platelet counts, along with higher levels of urea, creatinine, and total bilirubin. These abnormalities are consistent with the systemic inflammatory response and multi-organ involvement characteristic of severe sepsis. The liver function tests indicated significant hepatic involvement, with elevated levels of ALT, ALP, and

prolonged PT and INR, reflecting coagulopathy in septic neonates. Arterial blood gas analysis revealed acidosis, hypoxemia, and hypercapnia in the sepsis group, further indicating severe respiratory and metabolic derangements. Additionally, positive blood and cerebrospinal fluid cultures were found in 40% and 10% of the sepsis group, respectively, underscoring the bacterial etiology of sepsis in these neonates.

Study Design

Study was designed as a hospital-based prospective study conducted in the Department of Pediatrics and Neonatology at SKIMS, Soura Srinagar, over a period of two years. The inclusion criteria comprised patients hospitalized in the Neonatal Unit with suspected neonatal sepsis without any cardiac or surgical problems, and patients with hospital acquired sepsis. The exclusion criteria included pre-term neonates under 35 weeks, neonates with congenital heart disease, and neonates who expired before 72 hours. Sample size was obtained using Cochran's Formula.

Objective: To determine the role of NT-pro BNP as a novel marker of neonatal sepsis.

Methodology: The patients included in the study were divided equally into cases (n=50) and controls (n=50). Infants scoring 5 or above neonatal sepsis, possible sepsis, and confirmed sepsis within the first 28 days were included. Before initiating empirical antibiotic therapy in neonates with a Töllner score of 5 or higher, 1 cc of blood was collected in an EDTA tube for NT-ProBNP analysis and routine examinations, which were conducted in the biochemistry laboratory. Blood culture, urine culture, CSF culture, and other cultures such as umbilical swab, rectal swab, and tracheal aspirate were obtained as needed, based on the clinical presentation. Lumbar punctures were performed in patients showing signs of meningitis, and chest radiographs on the Töllner sepsis scoring system and diagnosed with suspected were taken in those suspected of neonatal sepsis and presenting with respiratory symptoms. Hemogram, peripheral smear, and blood gas analysis required for the Töllner sepsis scoring were also evaluated in each patient. Clinical sepsis diagnosis was made in patients who exhibited at least two criteria, including a Töllner score of ≥ 5, hematological findings such as leukocytosis, leukopenia, thrombocytopenia, an I/M ratio of ≥ 0.2, or increased CRP levels. Neonates meeting these criteria were included in the case group. NT-ProBNP levels were assessed at the time of hospitalization for the case group, while the control group consisted of age and weight-matched healthy babies. (Töllner score: The Tollner score is a clinical tool for evaluating the severity of neonatal sepsis, incorporating parameters such as clinical signs (e.g., temperature instability, tachycardia, hypotonia), laboratory findings (elevated C-reactive protein, abnormal white blood cell count), and inflammatory markers. This scoring system aids in early detection, risk stratification, and management of sepsis, thereby enhancing clinical decision-making and improving neonatal outcomes.)Symptoms such as poor feeding, fever, toxic appearance, lethargy, irritability, cyanosis, tachypnea, dyspnea, convulsions, vomiting, abdominal distention, and hypotonia were evaluated as indicators of infection, with clinical findings monitored during hospitalization. The case group was further divided into subgroups of recovered and deceased patients. Investigations conducted for all neonates included CBC using Beckman Coulter CBC Analyzer, blood culture with the BACTEC method, urine analysis and culture by supra-pubic tap, chest x-ray, CRP measurement by fluorescence immunoassay, abdominal ultrasound, and lumbar puncture for those with signs of meningitis. NT-ProBNP levels were measured byimmunoassay using the QDX Instacheck Pro-BNP kit. The study focused on NT-ProBNP levels in neonatal sepsis, correlating these levels with clinical features and laboratory parameters such as CBC, platelet count, KFT, LFT, CSF, cultures (urine/blood), and chest x-rays. By comparing clinical features and laboratory parameters, the study aimed to determine the NTProBNP level with maximum sensitivity and specificity for predicting neonatal sepsis.

Ethical consideration:

The Institutional Ethics Committee of the SKIMS, Soura reviewed and approved the project before it was carried out vide order number. SIMS 131/IEC-SKIMS/2024-93. All of the participants were informed in their own language about the study and their rights for participation before providing

data for the researcher administered questionnaire. They were informed about the participant's role and rights, to clarify that their participation was voluntary, the information was treated confidentially, and they could withdraw from the study at any time. After the collection of data, the data was cleaned, anonymized an stored in a password protected spreadsheet for data analysis. Observations and Results:

Observations and Results:

Table 1. Distribution of patients according to age (days) (n=100)

Age (days)	Neonatal sepsis (n=50)	Control (n=50)	p-value
Mean	7.5	7.8	0.451
SD	2.1	2.3	

Figure 1: Distribution of patients according to age (days) (n=100)

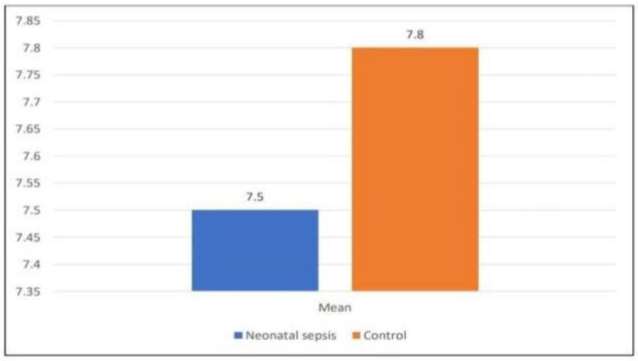

Table 2: Distribution of patients according to gender (n=100)

Sex	Neonatal sepsis (n=50)	Control (n=50)	p-value
Male	28 (56%)	26 (52%)	0.678
Female	22 (44%)	24 (48%)	
Total	50 (100%)	50 (100%)	

Figure 2: Distribution of patients according to gender (n=100)

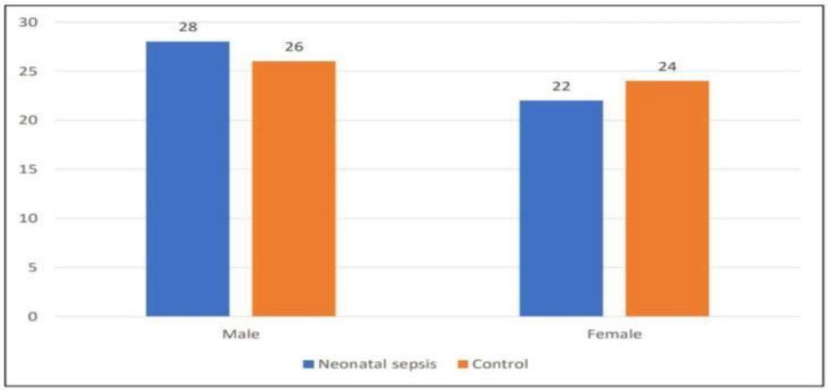

Table 3: Distribution of patients according to family history of consanguinity (n=100)

Consanguinity	Neonatal sepsis (n=50)	Control (n=50)	p-value
No	32 (64%)	35 (70%)	0.521
Yes	18 (36%)	15 (30%)	
Total	50 (100%)	50 (100%)	

Figure 3: Distribution of patients according to family history of consanguinity (n=100)

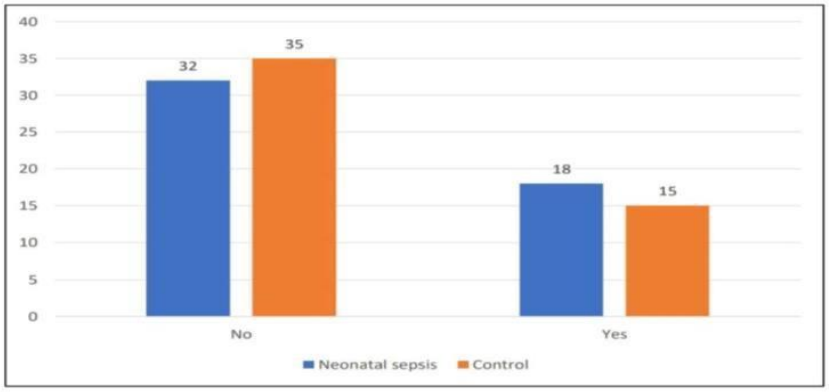

Table 4: Distribution of patients according to residence (n=100)

Residence	Neonatal sepsis (n=50)	Control (n=50)	p-value
Rural	38 (76%)	30 (60%)	0.088
Urban	12 (24%)	20 (40%)	
Total	50 (100%)	50 (100%)	

Figure 4: Distribution of patients according to residence (n=100)

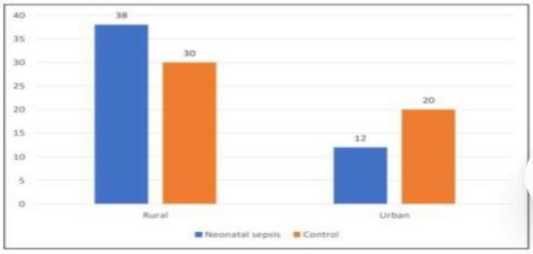

Table 5: Distribution of patients according to presenting complaints (n=100)

Complaints*	Neonatal sepsis (n=50)	Control (n=50)	p-value
Respiratory distress	30 (60%)	10 (20%)	<0.001
Fever	20 (40%)	8 (16%)	0.022
Hypothermia	15 (30%)	5 (10%)	0.011
Seizure	10 (20%)	2 (4%)	0.033
Abdominal distension	8 (16%)	3 (6%)	0.078

**Multiple complaints possible in a single patient*

Figure 5: Distribution of patients according to presenting complaints (n=100)

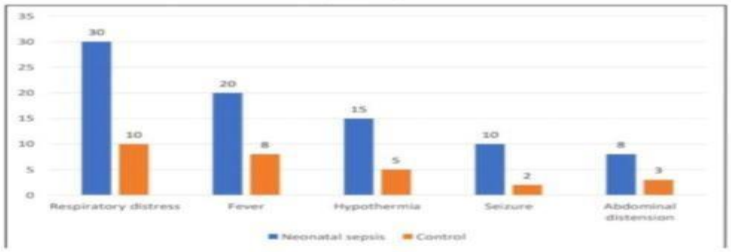

Table 6: Distribution of patients according to general examination findings (n=100)

Findings (mean ± SD)	Neonatal sepsis (n=50)	Control (n=50)	p-value
Pulse rate (/min)	160.2±20.1	144.8±18.3	<0.001
SBP (mmHg)	65.9±10.1	70.8±9.2	0.033
DBP (mmHg)	40.4±8.4	45.0±7.1	0.021
Respiratory rate	60.1±15.8	55.6±12.2	0.010

Figure 6: Distribution of patients according to general examination findings (n=100)

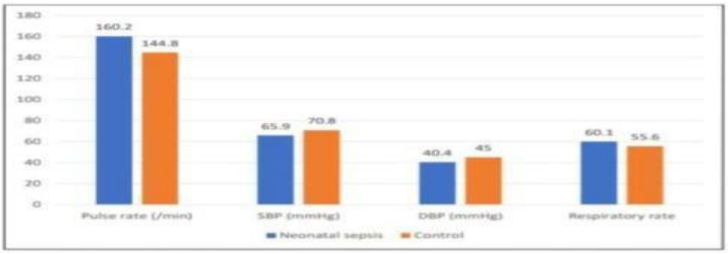

Table 7: Distribution of patients according to laboratory examination findings (n=100)

Findings (mean ± SD)	Neonatal sepsis (n=50)	Control (n=50)	p-value
TLC (cells/cc)	1.8±5.1	10.1±3.3	<0.001
Hemoglobin (gm/dl)	14.2±2.8	16.7±1.5	<0.001
Platelet (*lakh/cc)	1.2±0.6	2.5±0.7	<0.001
Urea (mg/dl)	45.2±10.6	35.5±8.3	<0.001
Creatinine (mg/dl)	1.2±0.3	0.7±0.2	<0.001
Calcium (mg/dl)	8.2±1.1	9.4±1.2	0.003

Figure 7: Distribution of patients according to laboratory examination findings (n=100)

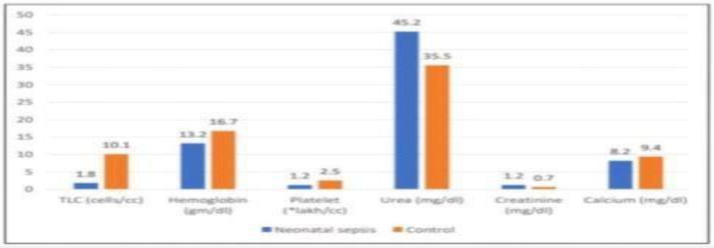

Table 8: Distribution of patients according to liver function test findings (n=100)

Findings (mean ± SD)	Neonatal sepsis (n=50)	Control (n=50)	p-value
Total bilirubin (mg/dl)	5.4±2.2	2.1±1.8	<0.001
ALT (U/L)	52.1±15.4	25.6±10.8	<0.001
ALP (U/L)	200.6±54.2	158.3±32.1	<0.001
PT (sec)	18.6±3.7	14.2±2.4	<0.001
INR	1.5±0.2	1.2±0.1	<0.001

Figure 8: Distribution of patients according to liver function test findings (n=100)

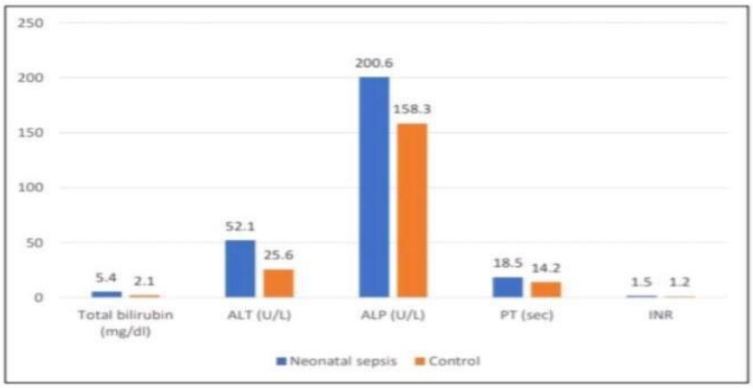

Table 9: Distribution of patients according to arterial blood gas findings (n=100)

Findings (mean ± SD)	Neonatal sepsis (n=50)	Control (n=50)	p-value
pH	7.2±0.1	7.4±0.1	<0.001
PaO2 (mmHg)	62.1±11.3	85 ±12.4	<0.001
PaCO2 (mmHg)	52.4±8.5	44.3±6.2	<0.001
HCO3 (mmol/L)	18.1±2.1	22.3±3.3	<0.001
Lactate (mmol/L)	4.2±1.4	2.1±0.8	<0.001

Figure 9: Distribution of patients according to arterial blood gas findings (n=100)

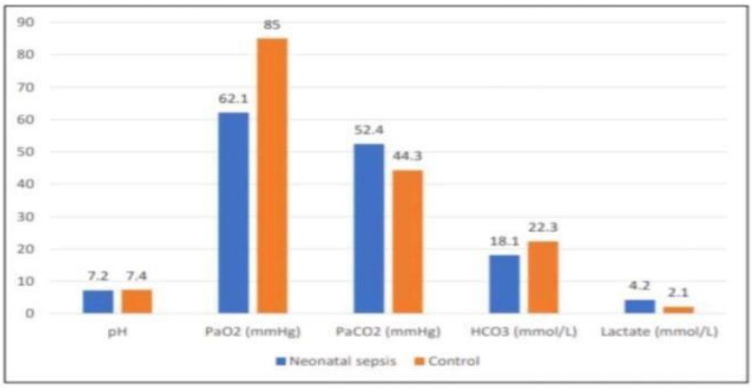

Figure 10: Distribution of patients according to culture and sensitivity findings (n=100)

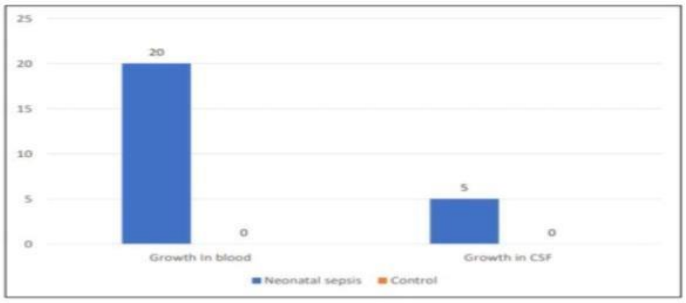

Table 11: Distribution of patients according to chest X-ray findings (n=100)

Findings	Neonatal sepsis (n=50)	Control (n=50)	p-value
Normal	15 (30%)	50 (100%)	<0.001
Infiltrates	20 (40%)	0 (0%)	
Consolidation	15 (30%)	0 (0%)	
Total	50 (100)	50 (100)	

**Multiple findings possible in a single patient*

Figure 11: Distribution of patients according to chest X-ray findings (n=100)

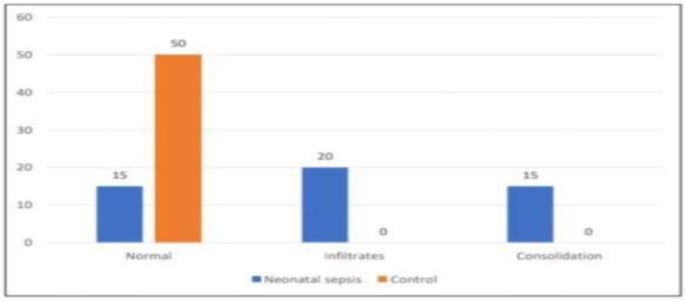

Table 12: Distribution of patients according to abdominal ultrasound findings (n=100)

Findings	Neonatal sepsis (n=50)	Control (n=50)	p-value
Normal	27 (54%)	45 (90%)	<0.001
Ascites	10 (20%)	0 (0%)	
Dilated bowel loops	8 (16%)	5 (10%)	
Necrotic features	5 (10%)	0 (0%)	
Total	50 (100)	50 (100)	

**Multiple findings possible in a single patient*

Figure 12: Distribution of patients according to abdominal ultrasound findings (n =100)

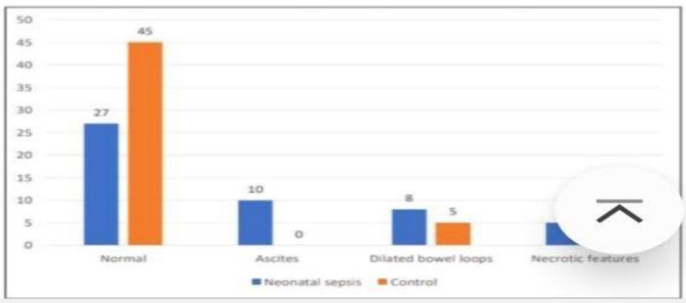

Table 13: Distribution of patients according to NT-ProBNP levels (ng/L) (n=100)

NT-ProBNP (ng/L)	Neonatal sepsis (n=50)	Control (n=50)	p-value
10-30000	30 (60%)	48 (96%)	<0.001
>30000	20 (40%)	2 (4%)	
Total	50 (100%)	50 (100%)	

Discussion:

The findings regarding the sociodemographic factors of the patients in the study, including age, gender, family history of consanguinity, and residence, revealed that there were no statistically significant differences between the neonatal sepsis group and the control group. The mean age of neonates in the sepsis group was 7.5 days compared to 7.8 days in the control group, which aligns with findings from Samransamruajkit et al., where early-onset sepsis (EOS) typically presents within the first week of life. Gender distribution was nearly equal in both groups, with 56% of males in the sepsis group and 52% in the control group, which is consistent with the findings reported by Lin et al., who noted no significant gender disparity in the incidence of neonatal sepsis.Regarding family history of consanguinity, the study found that 36% of the sepsis group had a positive family history, compared to 30% in the control group, though this was not statistically significant. This observation is in line with the study by Mousavy et al., which highlighted the role of genetic predispositions in the context of neonatal sepsis in specific populations, such as the Kashmiri population. Furthermore, the study indicated a higher percentage of neonates with sepsis from rural areas (76%) compared to the control group (60%), although this difference was not statistically significant. This rural predominance is supported by findings from Liu et al., who reported similar trends in rural settings, where limited healthcare resources and delayed access to medical care could contribute to higher rates of neonatal sepsis.When assessing the presenting complaints of neonates with sepsis, the study highlighted significant differences between the sepsis group and the control group. Respiratory distress was the most common presenting complaint, reported in 60% of neonates with sepsis, compared to only 20% in the control group. This aligns with findings from Yang et al., who observed that septic neonates with cardiac dysfunction exhibited earlieronset of respiratory symptoms, which were significantly more pronounced compared to those without sepsis. Similarly, Melendez et al. Found that respiratory distress was a key symptom correlating with higher NT-proBNP levels, which are indicative of greater illness severity in septic neonates. Fever was another prominent symptom, reported in 40% of neonates with sepsis, compared to 16% in the control group. This observation is consistent with the findings of Mousavy et al., who reported fever as a primary symptom in their study cohort, noting that septic neonates with elevated NT-proBNP levels presented more frequently with fever compared to controls. Additionally, hypothermia was significantly more common in the sepsis group (30%) than in the control group (10%), reflecting findings from Yang et al., who noted that hypothermia, alongside fever, was a common manifestation in septic neonates with cardiovascular dysfunction. Seizures were reported in 20% of neonates with sepsis, compared to 4% in the control group. This finding is supported by Lin et al., who reported that neonatal sepsis is often accompanied by neurological symptoms, including seizures, particularly in cases of severe sepsis or septic shock. The increased incidence of seizures in septic neonates suggests a potential correlation with the severity of the condition, as highlighted in studies by Yang et al. And Mousavy et al., where

higher NT-proBNP levels were associated with more severe clinical presentations, including neurological symptoms. The analysis of general examination findings in neonates with sepsis, revealed significant differences in vital signs between the sepsis and control groups. Neonates with sepsis had a significantly higher mean pulse rate (160.2±20.1/min) compared to the control group (144.8±18.3/min), reflecting findings from studies such as Lin et al., who reported that septic neonates with heart failure had elevated NT-proBNP levels, correlating with tachycardia and other signs of cardiovascular stress. Blood pressure parameters also differed significantly between the two groups. The mean systolic blood pressure (SBP) was lower in the sepsis group (65.9±10.1 mmHg) compared to the control group (70.8±9.2 mmHg), and the diastolic blood pressure (DBP) was similarly lower in the sepsis group (40.4±8.4 mmHg) compared to controls (45.0±7.1 mmHg). These findings are consistent with the results of studies by Samransamruajkit et al, who observed that hypotension is a common finding in neonates with sepsis, particularly in severe cases where cardiovascular dysfunction is prevalent. In their study, neonates with lower blood pressure readings had higher NT-proBNP levels, indicating greater cardiovascular compromise. Respiratory rates were also significantly higher in the sepsis group (60.1±15.8/min) compared to the control group (55.6±12.2/min), which aligns with findings by Melendez et al., who reported that increased respiratory rates were associated with higher NT-proBNP levels in septic neonates. This finding underscores the impact of sepsis on respiratory function, often leading to tachypnea as the body attempts to compensate for the systemic effects of infection. Laboratory parameters of neonates with sepsis when compared to controls showed significant disparities between the two groups. The total leukocyte count (TLC) was notably lower in the sepsis group, with a mean of 1.8±5.1 cells/cc, compared to 10.1±3.3 cells/cc in the control group. This marked leukopenia aligns with findings from Lin et al., who observed that septic neonates, particularly those with severe sepsis, often presented with depressed leukocyte counts, which correlated with higher NT-proBNP levels and a more severe systemic inflammatory response. Hemoglobin levels were also significantly lower in the sepsis group (14.2±2.8 gm/dl) compared to controls (16.7±1.5 gm/dl). This finding is consistent with the study by Samransamruajkit et al., where hemoglobin levels were lower in septic neonates, reflecting t systemic effects of sepsis on hematopoiesis and red blood cell turnover. The study noted that anemia is a common finding in sepsis and can exacerbate the overall clinical condition, contributing to poorer outcomes. Platelet counts were significantly reduced in the sepsis group, with a mean of 1.2±0.6 lakh/cc compared to 2.5±0.7 lakh/cc in the control group. This thrombocytopenia is in line with the findings of Melendez et al., who reported that septic neonates often exhibit decreased platelet counts, which are associated with increased NT-proBNP levels and a higher risk of bleeding complications. The reduction in platelet counts is a critical marker of the severity of sepsis, reflecting the consumption of platelets in the inflammatory and coagulatory responses. Additionally, the study found significantly higher levels of urea (45.2±10.6 mg/dl) and creatinine (1.2±0.3 mg/dl) in the sepsis group compared to controls, which had mean values of 35.5±8.3 mg/dl and 0.7±0.2 mg/dl, respectively. These findings are consistent with those of Samransamruajkit ,who noted that elevated urea and creatinine levels are indicative of renal impairment in septic neonates. The study highlighted that renal dysfunction is a common findings in neonates with sepsis and observed significant abnormalities in several parameters when compared to controls. The mean total bilirubin levels were significantly higher in the sepsis group (5.4±2.2 mg/dl) compared to the control group (2.1±1.8 mg/dl). This finding complication of sepsis, often correlating with higher NT-proBNP levels, which indicate systemic cardiovascular stress. Furthermore, calcium levels were lower in the sepsis group (8.2±1.1 mg/dl) compared to the control group (9.4±1.2 mg/dl), reflecting findings from Mousavy et al., who reported that hypocalcemia is frequently observed in neonates with sepsis, particularly in those with severe cases. The study suggested that hypocalcemia, along with other electrolyte imbalances, could exacerbate the clinical condition of septic neonates, contributing to the overall morbidity and mortality associated with the condition.The present study assessed the liver function test (LFT) aligns with the study by Resende et al., which observed that elevated bilirubin levels are a common finding in neonatal sepsis, indicating hepatic dysfunction as a result of systemic inflammation. Elevated bilirubin in septic neonates often reflects the liver's response to both infection

and the increased breakdown of red blood cells, a phenomenon also highlighted in the study by Ozdemir et al., which noted similar patterns of hyperbilirubinemia in their cohort.

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