

Correlation of NT-proBNP with Procalcitonin and C-Reactive Protein in Neonatal Sepsis: A Retrospective Observational Study

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ABSTRACT

Introduction: Neonatal Sepsis (NS) is a life-threatening condition characterised by high morbidity and mortality rates, necessitating prompt diagnosis and treatment. To ensure the early, specific, and reliable identification of NS, selecting optimal biomarkers is crucial due to the limitations of traditional haematological and microbiological techniques. Procalcitonin (PCT) and C-Reactive Protein (CRP) are most frequently used in hospitals for diagnosis and follow-up. Another biomarker N terminal Brain Natriuretic Peptide (NT-proBNP) can be used in correlation with CRP and PCT to aid in diagnosis and prognosis of NS.

Aim: To study the role of NT-ProBNP in NS and its correlation with PCT and CRP.

Materials and Methods: The present retrospective observational study was conducted at a Tertiary Care Hospital in North India Action Balaji Hospital, for a period of six months. Study included 50 neonates diagnosed with NS admitted for treatment. Blood

samples reports were collected for blood culture, PCT, CRP, NT-proBNP. Correlation between NT-proBNP and CRP, PCT was determined by Spearman's correlation and linear regression.

Results: Out of total 40 neonates, 70% were females and 30% males. The mean birth weight was 2.01 ± 0.28 Kg. An 80% of neonates were with early onset and 20% with late onset sepsis. The mean $\pm$ SD of PCT and CRP were 2.677 ± 3.67 ng/mL and $39.7 \pm 19.82.6$ mg/L and NT-proBNP 3595 ± 4472 pg/mL, respectively. NT-proBNP had significant correlation with CRP ($r=0.692$, $p<0.001$) and PCT ($r=0.609$, $p<0.001$).

Conclusion: In the present study, NT-proBNP was elevated and had significant correlation with CRP and PCT. Larger prospective studies are required to confirm utility of NT-proBNP in combination with other sepsis markers like PCT and CRP to detect early sepsis leading to timely and appropriate treatment.

Keywords: Inflammatory markers, Laboratory biomarkers, N terminal brain natriuretic peptide, Neonatal mortality, Septic shock

INTRODUCTION

One of the main causes of neonatal mortality, NS accounts for over 42% of infant fatalities in the first week of life [1]. NS is typically divided into two groups: early onset (within first 72 hours of life) and late onset (beyond 72 hours). Early NS is associated with a significant mortality rate with preterm and low Birthweight (BW) babies are at higher risk despite modern treatment strategies [1]. *E coli*, *Klebsiella*, and *Staphylococcus Aureus*, which are often acquired in hospitals or the community from the maternal flora intrauterinally, are among the main pathogens that cause sickness. Sepsis in newborns commonly presents with a range of clinical signs [2].

In addition to the blood culture, other tests that are usually used for the diagnosis of NS include estimations of the White Blood Cell count (WBC), the Absolute Neutrophil Count (ANC), micro ESR, CRP. But lack of high sensitivity, specificity and significant variability with day of life, gestational age and low sensitivities leads to difficulty in interpretation and diagnosis of NS [3,4]. CRP is an acute-phase reactant which is synthesised by the liver, which does not reliably differentiate between the systemic inflammatory response and sepsis [5].

Due to the absence of precise diagnostic markers and its modest appearance, newborn sepsis management and therapy continue to be difficult. Despite being the gold standard, bacteriologic results are time-consuming and in neonates they have low positive rates necessitating development of laboratory biomarkers for early disease

diagnosis and prognosis of NS [3]. PCT, a precursor of the hormone calcitonin which is normally secreted by the C cells of the thyroid and usually negligible under normal conditions [6]. A meta-analysis of 12 studies has confirmed significantly higher sensitivity (88% vs. 75%) and specificity (81% vs. 67%) of Serum PCT in detecting bacterial infections compared to CRP [7]. Bacterial infections in the context of sepsis causes elevated PCT levels, which can aid in distinguishing between infectious and non-infectious causes of systemic inflammation minimising unnecessary use of antibiotics [5,8]. Studies have shown that PCT works better in comparison to CRP levels as PCT levels rise earlier and return to normal levels more quickly [9-11].

The use of PCT for prognosis is controversial. PCT values should be used as a complementary tool in conjunction with available clinical and diagnostic parameters [12,13]. BNP is a neurohormone with diuretic, natriuretic and vasodilator effects, and it converts to BNP as the active peptide and to the biologically inactive NT-proBNP. Sepsis mortality is correlated with elevated levels of NT-proBNP [14].

Distinguishing between sepsis-induced myocardial dysfunction and primary cardiac disease can be done by looking at elevated NT-proBNP levels in the absence of a cardiac history [15]. NT-ProBNP can be a useful biomarker to predict survival in patients with severe NS. Studies have shown its utility as an early predictor of myocardial dysfunction in patients with sepsis [16-18]. Both NT-proBNP and PCT can offer useful data for the assessment and treatment of sepsis. PCT can direct antibiotic therapy and aid in

the differentiation of bacterial sepsis from other sources of systemic inflammation, while NT-proBNP can reveal the existence and degree of myocardial dysfunction brought on by sepsis.

To determine the best course of action, these biomarkers should be interpreted in light of the clinical picture and results from additional diagnostic procedures. The study was aimed to study the role of NT-ProBNP in NS and its correlation with PCT and CRP.

MATERIALS AND METHODS

The present retrospective observational study was conducted at Tertiary care hospital, Action Balaji Hospital in North India for a period of six months from March 2011 to August 2011 and data was analysed. The study was approved by the hospital review board Committee. Informed consent was obtained from the parents or caretakers at the time of admission. The data were collected from medical clinical record data and laboratory data.

Inclusion criteria: The neonate (up to age 28 days) and infants who were admitted to the Neonatal Intensive Care Unit (NICU) with sign and symptoms suggestive of sepsis (breathing problems, respiratory distress, apnea, tachycardia, bradycardia, hypotension, feeding intolerance, abdominal distension, Gastrointestinal (GI) bleed, diarrhoea, vomiting, jaundice, reduced movements, reduced sucking, seizures, hypothermia, hyperthermia, hypoglycaemia, petechial rash, purpura, mottling) were included.

- Any neonate born with maternal risk factors for sepsis, Prolonged Preterm Rupture of Membrane (PROM) >18 hours, maternal intrapartum pyrexia, urinary tract infection, prolonged labour, or chorioamnionitis were included [19,20].

Fifty neonates with Confirmed sepsis (Total Leucocyte Count (TLC) >24000/cubic mm, C-reactive protein (CRP) 6 mg/L and Procalcitonin (PCT) >=0.5 ng/mL [20]) were included.

Exclusion criteria: Any neonate with apparent major congenital anomalies, Apgar score less than 7, or on antibiotics therapy before the start of the study was excluded.

Study Procedure

Study size: The study population consisted of 50 patients with confirmed sepsis admitted during the period of six months whose detailed data could be retrieved from medical record data.

Data collection: The specimens of blood (2 mL for haematological and 2 mL for inflammatory parameters) were obtained from each neonate prior to the commencement of the antibiotics for the sepsis work up, which included haematological parameter like total leukocyte count, PCT and CRP, NT-proBNP estimation. The reference range for the parameters was as per kit inserts.

- Procalcitonin (PCT):** Card test PCT was measured semi quantitatively by a rapid immunochromatographic kit as per the manufacturer's recommendations (BRAHMS PCT-Q test). The level of >0.5 ng/mL for PCT was taken as significant, suspicion of sepsis.
- Serum CRP:** The serum CRP level was measured by using the A-15 CRP Kit. (Bio-system, Costa Brava, Barcelona, Spain). The quantitative measurement of CRP from the serum was done by an immunoturbidimetric method in the laboratory according to the manufacturer's instructions. The value greater than 6 mg/L was considered pathological.
- NT ProBNP:** Immunoassay run on Cobas e411 by two-site sandwich immunoassay method. For NT-proBNP, normal

levels are less than 125 pg/mL for people under 75-year-old and less than 450 pg/mL for people over age 75. NT-proBNP levels over 900 pg/mL may be a sign of heart failure [18].

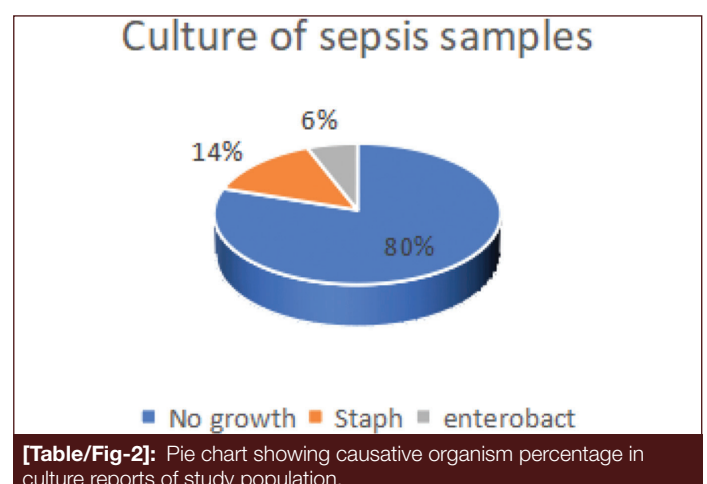
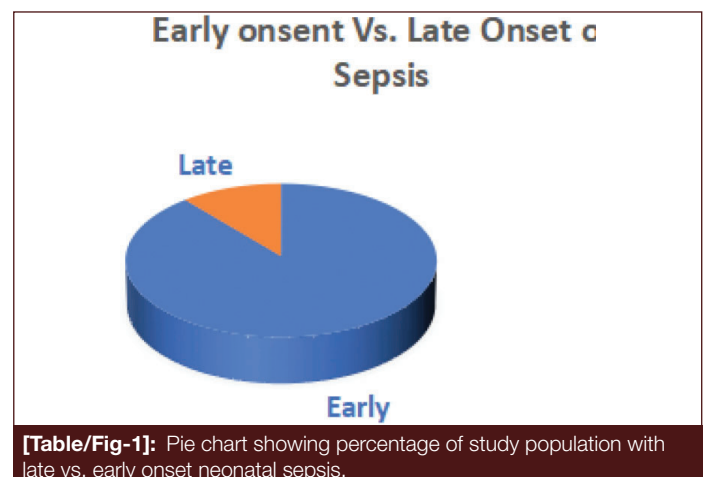
- Blood culture growth blood culture:** Blood culture was taken from before starting antibiotic therapy. A 0.5-1 mL of venous blood was inoculated into the paediatric BACTEC culture media. The media were placed in the oven of BACTEC 9120 (Becton Dickinson, USA) haemoculture device. The samples were daily checked for reproduction.

STATISTICAL ANALYSIS

Data were analysed by using Statistical Package for Social Sciences (SPSS) (version 16 software). All the data were entered in Microsoft excel. All parameters underwent Sapiro wilkis test of normality testing after which it was categorised into parametric and non-parametric. The non-parametric data was entered in median and interquartile range. The culture reports based on early and late NS were presented in pie chart in percentage non-parametric Spearman's 2 tail correlation was applied between PCT and Pro BNP and CRP and Pro BNP. Linear regression was applied to see sensitivity of Pro BNP as a possible marker of NS alongside PCT and CRP.

RESULTS

A total of 40 (80%) of the neonates in the present study were classified as early onset sepsis compared to 10 (20%) with late onset sepsis [Table/Fig-1]. When samples were cultured to identify causative organism, 7 (14%) showed staphylococcus, 3 (6%) Enterobacteria and 40 (80%) did not show any growth on culture [Table/Fig-2]. A 35 (70%) of neonates were female as compared to 15 (30%) males. The median Period of Gestation (POG) was 35.82 weeks with mean BW of 2.01 Kg. The mean PCT and CRP were

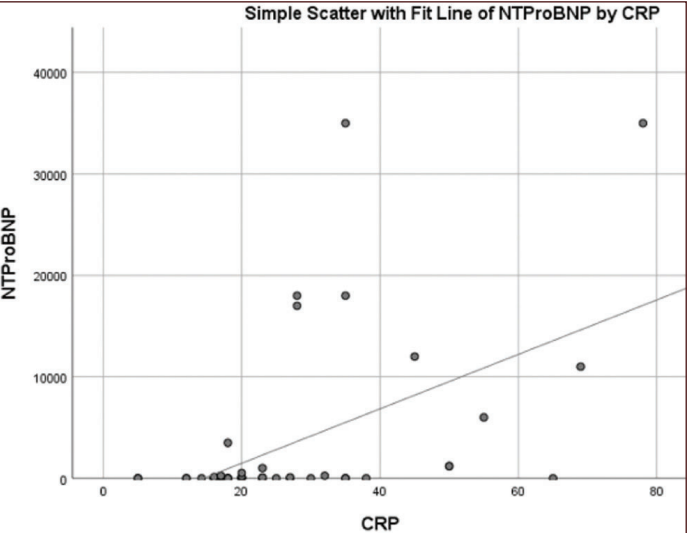


Gender	Period of gestation (weeks) (mean±SD)	Birthweight (Kg) (mean±SD)	PCT (Mean±SD)	CRP (Mean±SD)	NT-proBNP (Mean±SD)
35 (F) 70% 15 (M) 30%	35.82±2.01	2.01±0.28	2.677±3.67	39.7±19.82	3595±4472

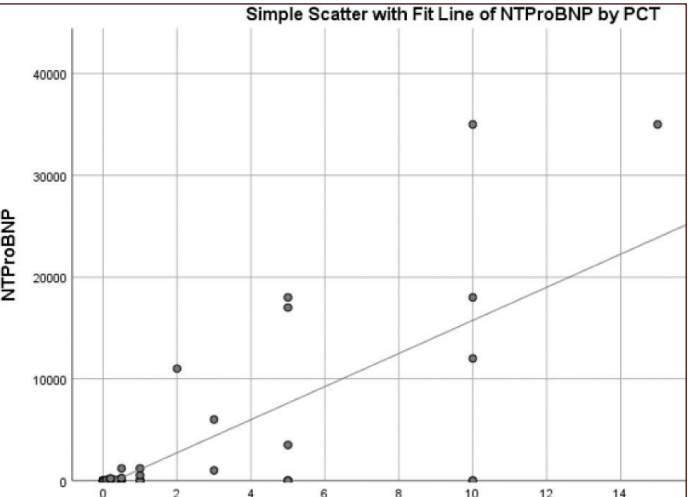
[Table/Fig-3]: Biochemical characteristics of the neonatal study population.
N: Number of study population; PCT: procalcitonin; CRP: C-reactive protein; NT ProBNP: N terminal Pro Brain Natriuretic peptide

2.677±3.67 ng/mL and 39.7±19.82.6 mg/L respectively while NT-proBNP was 3595±4472 pg/mL [Table/Fig-3]. The raised level of ProBNP in a lot of patients could be due to the involvement of the heart which is common in neonates with sepsis.

There was significant correlation ($p<0.05$) between CRP and ProBNP (Correlation coefficient 0.692, p -value <0.001) and PCT and ProBNP (Correlation coefficient 0.609, p -value <0.001) [Table/Fig-4-6].



[Table/Fig-4]: Scatter plot showing correlation between NT ProBNP and CRP.
($r=0.692$, $p<0.001$)



[Table/Fig-5]: Scatter plot showing correlation between NT ProBNP and PCT.
($r=0.609$, $p<0.001$)

In order to assess the role of ProBNP as another possible marker of NS alongside PCT and CRP, we applied linear regression with defining cases based on raised PCT levels and CRP levels while adjusting the parameters to CRP, PCT values Their regression coefficient of NT-proBNP with PCT was 0.622 ($p<0.001$) and 0.268 (p 0.17) with CRP taking BNP as a dependent variable [Table/Fig-7].

The equation in linear regression ($\text{NT-proBNP}=1387.06\times\text{PCT}+139.01\times\text{CRP}$) indicates that for every 1 pg/mL increase in NT-Pro BNP, there is an associated increment of 1387.06 ng/mL in PCT

		NTProBNP	PCT	CRP
Spearman's rho	Correlation coefficient (r)	1.000	0.609**	0.692**
	Sig. (2-tailed)	.	$p<0.001$	$p<0.001$
	N	50	50	50

[Table/Fig-6]: Correlation coefficient (r) showing correlation between NT-proBNP and CRP and PCT.
**Correlation is significant at the 0.01 level (2-tailed)

Predictor	B (Unstan- dardised coefficient)	SE (Standard error)	β (Stan- dardised coefficient)	t	p- value
PCT (ng/ mL)	1387.06	226.38	0.622	6.13	<0.001
CRP (mg/L)	139.01	52.66	0.268	2.64	0.011

[Table/Fig-7]: Linear regression to assess NT-proBNP possible role as a marker of Neonatal Sepsis (NS).
PCT: Procalcitonin; CRP: C-reactive protein; NT ProBNP: N terminal pro brain natriuretic peptide

levels and 139.01 mg/L in CRP levels. ProBNP should be further studied for use as marker of NS in correlation with CRP and PCT.

DISCUSSION

The NS is a life-threatening condition characterised by high morbidity and mortality rates, necessitating prompt diagnosis and treatment. The gold standard for diagnosing NS remains blood culture, but this method has limitations such as low sensitivity, false negative results that make it less reliable for early and accurate detection [21]. To ensure the early, specific, and reliable identification of newborns at high risk of infection, especially for NS, selecting optimal biomarkers is crucial due to the limitations of traditional haematological and microbiological techniques.

The PCT and CRP are most frequently used in hospitals for diagnosis and follow-up. While CRP levels are easily, quickly measured and sensitive but low specificity makes it challenging to diagnose sepsis. In contrast to other markers, PCT exhibits greater specificity and can be detected more quickly than CRP [22]. On the other hand, PCT is considered a more specific marker for bacterial infections and can be detected earlier, but its role as a stand-alone diagnostic tool for NS remains controversial. Therefore, in the present study the authors tried to correlate another biomarker NT-proBNP with that of PCT and CRP. Therefore, in the present study we tried to correlate another biomarker NT-proBNP with that of PCT and CRP.

The mean CRP level in present study was 39.7±19.82 mg/L. CRP is a frequently used test in the diagnosis of NS. CRP, is the most commonly used laboratory test in NS [23]. Benitz WE et al., showed that the incidence of proven sepsis is 10% when CRP is >5 mg/dL [24]. Most of the studies revealed that CRP levels were of importance in the diagnosis and follow-up of NS [23-25]. However, CRP is an acute-phase reactant which is synthesised by the liver, which does not reliably differentiate between the systemic inflammatory response and sepsis. It has limited specificity, as it can be elevated in various non-infectious conditions such as fetal distress, stress delivery and maternal fever, restricts its reliability as

a sole indicator of sepsis. Therefore, it is best used in conjunction with other biomarkers and should be interpreted alongside clinical findings to improve diagnostic accuracy and guide treatment decisions effectively [26].

Another biomarker used was PCT. The mean PCT was 2.677 ± 3.67 ng/mL in present study. PCT, a calcitonin precursor has been linked to severity of bacterial infection. Elevated PCT levels are indicative of bacterial infection, predicting septicemia in neonates. Conversely, low PCT levels can effectively help rule out septicemia, reducing the need for unnecessary antibiotic treatments. A study by Sucilathangam G demonstrated that serum PCT levels are superior to serum CRP levels for the early diagnosis, prognosis and evaluating the response to antibiotic treatment [27]. Similarly, a cross-sectional study conducted by Yadav S et al., found that PCT is a more effective sepsis marker than CRP in terms of sensitivity, specificity, and accuracy, and it showed a strong positive correlation with blood culture results [20]. These findings suggest that PCT may be a more reliable biomarker for early diagnosis and management of NS compared to CRP.

The CRP correlates with late onset and PCT early onset sepsis. A multi-modal approach that combines various biomarkers with clinical evaluation is necessary to ensure sensitivity, reliability for timely diagnosis of NS, ultimately improving outcomes and reducing mortality rates [28]. PCT and CRP together with other clinical and lab data improved accuracy of diagnosis of NS. Metanalysis study reports CRP of ≥ 60 mg/L among 1339 neonates and PCT of ≥ 0.5 ng/mL among 617 neonates demonstrated the greatest discriminatory value for the diagnosis of NS [29].

PCT has the benefit of rising more quickly than CRP. However, its clinical use is limited compared to CRP due to rapid fluctuations in baseline levels immediately after birth and the need for different cut-off values depending on the neonate's age. Therefore, therapeutic utility of employing NS biomarkers may be a topic of ongoing debate and research [30].

Children are more prone to cardiac dysfunction than adults in cases of severe sepsis or septic shock. Notably, 58% of paediatric patients present with low cardiac output coupled with high systemic vascular resistance, while 22% experience both low cardiac output and low systemic vascular resistance [31,32]. Consequently, a biomarker linked to cardiac dysfunction in children with septic shock would be eminent. One potential biomarker is NT-proBNP, which is synthesised and secreted by myocytes and fibroblasts in the atria and ventricles [33,34]. This biomarker has been shown to correlate with cardiac dysfunction, making it a promising candidate for monitoring and managing paediatric septic shock. Present study revealed significant correlation between initial PCT level and plasma NT-proBNP levels which is in congruence with other studies.

The mean NT-proBNP was 3595 ± 4472 pg/mL in present study and had significant correlation with CRP and PCT. Brain natriuretic peptide, plays an important role in the regulation of blood pressure during fetal development and natriuretic and diuretic changes during transition to postpartum life. There is a dramatic increase in NT-ProBNP levels in the early postnatal period [34]. Similar studies by Okur N et al., reported median NT-proBNP levels were higher in septic patients, showing a significant correlation with CRP levels [35]. Samransamruajkit R et al., reported a significant difference in initial NT-proBNP levels between survivors and deceased among infants and children with severe sepsis [36]. Survivors had NT-proBNP levels averaging 6280.3 ± 9597 ng/L, while no

significant difference was found for PCT levels between these groups (12.7 ± 24.8 µg/L in survivors and 29.3 ± 46 µg/L in non-survivors). An initial NT-proBNP level of more than 11,200 pg/mL was a strong predictor of Paediatric Intensive Care Unit (PICU) mortality, with high sensitivity and specificity. Elevated NT-proBNP levels were thus associated with increased mortality risk. In another study, Deger İ et al., observed significant differences in NT-proBNP, CRP, and leukocyte counts between neonates with sepsis and healthy controls [34]. The NT-proBNP level in the case group was $19,624.1 \pm 15,027.6$ pg/mL, compared to $3,203.8 \pm 4,506.8$ pg/mL in the control group. NT-proBNP levels were statistically significantly higher in deceased patients, indicating its strong correlation with poor outcomes [37]. Similarly, another study found that BNP levels at ICU admission were correlated with mortality and suggested that NT-proBNP could guide fluid therapy in septic patients [38]. Han YY et al., also emphasised the importance of early and aggressive haemodynamic resuscitation in children with septic shock, showing that early treatment is associated with improved outcomes [39].

Based on the findings of the present study and supporting evidence from other research, NT-proBNP may serve as a valuable marker for the early detection and prognostic assessment of NS. Given its strong correlation with mortality, more aggressive treatment should be prioritised in patients with elevated NT-proBNP levels to improve outcomes.

Limitation(s)

It was a retrospective study and patient follow-up was not done. No Recover Operating Character (ROC) analysis was done to evaluate sensitivity, specificity, positive and negative predictive values of PCT and CRP levels as diagnostic test performance. Sample size was small.

CONCLUSION(S)

The PCT and CRP are commonly used sepsis markers. NT-proBNP was elevated and had weak but significant correlation with CRP and PCT. Elevated BNP levels are known to be associated with cardiovascular dysfunction and systemic inflammation. In the present study, NT-proBNP was elevated and had significant correlation with CRP and PCT. Larger prospective studies are required to confirm utility of NT-proBNP in combination with other sepsis markers like PCT and CRP to detect early sepsis leading to timely and appropriate treatment.

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