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STUDY ON HYPERBILIRUBINEMIA IN NEONATAL SEPSIS: A RETROSPECTIVE STUDY

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ABSTRACT **Background:** Neonatal sepsis is a fatal disease among neonates whose timely diagnosis is critical for the neonates. Clinical manifestations of the liver in sepsis is of paramount importance in such neonates who suffer from sepsis. Understanding the pattern of hyperbilirubinemia in such patients along with the TLC to CRP ratio is important as a biomarker for sepsis. **Methods:** data was retrospectively collected from 100 neonates. Liver function tests, serum CRP, total leukocyte count, serum urea, blood creatinine and serum electrolytes were tested on the first and third days of septicemia. Anthropometry was measured on admission. Severity was determined using a Neonatal Sepsis Severity Score. **Results:** 100 neonatal septicemic patients were involved including 23 with mild sepsis, 66 with moderate sepsis and 11 with severe sepsis. 98% of neonates had hyperbilirubinemia (serum total bilirubin > 1 mg/dl) on the first day of sepsis and 91% on the third day of sepsis. The mean (± SD) serum total bilirubin on the first day of sepsis was 8.72 ± 4.93 mg/dl and on the third day was 7.47 ± 5.03 mg/dl. The mean TLC to CRP ratio on the first day of neonatal septicemia was 0.50 ± 0.68 and on the third day was 1.38 ± 3.26. A correlation was drawn between serum total bilirubin and the severity of sepsis ($p < 0.05$) and also between the TLC to CRP ratio with the severity of sepsis ($p < 0.01$). ROC curve analysis indicated the optimal cutoff value of TLC to CRP ratio in assessing severity of sepsis in neonates to be 1.30 with 8.2% sensitivity and 91.8% specificity. **Conclusions:** hyperbilirubinemia is common among neonatal septicemic cases. The TLC to CRP ratio is reduced infections and is further lower in more severe cases of sepsis as compared to the mild cases. Hyperbilirubinemia is more severe in severe cases as compared to mild and moderate cases.

KEYWORDS : Neonatal Sepsis, Hyperbilirubinemia, TLC to CRP Ratio, Neonatal Sepsis Severity, Liver Enzymes

1. INTRODUCTION

Sepsis is defined as a systemic inflammatory response characterized by extreme reaction of one's body to an infection which can rapidly lead to tissue damage, multiple organ failure and death if left untreated. Neonatal sepsis is of 2 types: Early onset Sepsis (EOS) – presents within first 72 hours after parturition and late onset sepsis (LOS) – presents after 72 hours after delivery. Neonatal sepsis contributes 25% to neonatal mortality in developing countries [1] and accounts for about 0.52 million deaths annually in the world [2]. Sepsis is also the commonest cause of neonatal mortality in most developing countries [3]. Clinical manifestations of sepsis-associated liver dysfunction include hypoxic hepatitis, sepsis-induced cholestasis and dysfunction of protein synthesis manifesting with, e.g., coagulopathies. In critically ill patients, the liver can go into a stage of shock where hemodynamic, cellular, molecular and immunological changes can lead to severe liver hypoxia [4]. Clinical manifestations of the liver in sepsis are of utmost importance because jaundice can be observed at early stages of sepsis even in the absence of fever or leukocytosis [5].

Upon understanding the gravity of the effect that sepsis has on neonates, its mortality and outlining its relationship with the functioning of the liver, it becomes critical to understand whether liver function tests can be used as diagnostic tools for sepsis especially in cases where other parameters or clinical manifestations are not observed keeping in mind the standardization of testing serum bilirubin levels.

In sepsis, multi anti-inflammatory cytokines are released into the bloodstream inducing apoptosis of leukocytes. When the body is inflamed or infected, the liver produces a higher concentration of C - reactive protein, an acute inflammatory protein. Research has shown that CRP is a significant indicator of sepsis risk and a predictor for sepsis in neonates and adults [6]. The total leukocyte to CRP ratio is an index measured by dividing the total leukocyte count (in thousands) by the serum CRP concentration (in mg/dl). As CRP concentration increases and Total Leukocyte Count decreases, the TLC to CRP ratio should decrease in neonatal sepsis patients.

The purpose of this research project is to determine the prevalence, pattern and course of serum total bilirubin levels in neonatal sepsis, to establish a relationship between serum total bilirubin levels and neonatal sepsis and to determine if serum bilirubin levels and the TLC to CRP ratio can be used as a prognostic tool for neonatal sepsis.

2. Methodology

This study was conducted after receiving approval from the Institutional Ethics Committee of Shri Atal Bihari Vajpayee Medical College and Research Institute. Data was retrospectively collected over a period of 9 months from 19th October to 7th July in Bowring and Lady Curzon Hospital, Bengaluru, India. All of the neonates admitted in the NICU with clinical signs of sepsis like fever, respiratory distress, lethargy/irritability, convulsions, bulging fontanels, refusal to feed, jaundice, bleeding, abdominal distension, and temperature dysregulation are tested for sepsis. A positive sepsis screen includes Total Leukocyte Count < 5000 or > 22,000, Absolute Neutrophil Count < 1800, Serum C-Reactive Protein > 5 mg/dl or micro ESR > 15 mm in the first hour. The presence of any 2 of the above 4 criteria is deemed as a positive sepsis screen [7] or those who had venous blood culture positive for sepsis. Neonates were excluded from the study if they had any congenital hepatobiliary dysfunction; Rh incompatibility or ABO incompatibility or if they died during the course of infection.

2.1 Data Collection

The basic information, case history and results of relevant investigations were collected. The neonate's name, sex, gestational age (in weeks), age on development of sepsis (in days), date of development of sepsis and birth weight to the nearest 10 grams was recorded. Gestational age was calculated in weeks from the last recorded menses. In case the last menses was unknown, gestational age was calculated using the modified Ballard score. Weight was calculated with the baby in supine position on an electric weighing scale. Age was calculated by taking the day of birth as the first day.

Preliminary biochemical investigations conducted in the neonates were serum CRP, Complete Blood Count, serum total bilirubin, liver

enzymes (AST, ALP, ALT), serum electrolytes (Sodium, Potassium and Chloride) and renal function tests (urea and creatinine). The TLC to CRP ratio was calculated.

Results of the aforementioned biochemical investigations were also collected on the third day of sepsis. The data was recorded on a proforma in a Microsoft Excel 2013 sheet. TLC to CRP ratio was calculated as an inflammatory marker by dividing the total leukocyte count (*10^3) by the CRP levels (in mg/dl) on the first and third day.

2.2 Severity of Sepsis

The severity of sepsis in neonates was assessed by means of a neonatal sepsis severity score [8][9][10] which takes into account serum CRP, total leukocyte count, liver enzymes, renal function tests and serum potassium. Based on their values, a score from 0 – 2 is awarded and the total score is determined by adding the individual components

Criteria	Score		
	0	1	2
Serum CRP (mg/dl)	< 10	< 50	> 50
Total Leukocyte Count (thousands / mm3)	10 - 15	5 – 10 or 15 – 22	< 5 or > 22
Alanine Transaminase (U/L)	< 50	< 100	> 100
Alkaline Phosphatase (U/L)	< 150	< 300	> 300
Blood Urea (mg/dl)	< 20	< 50	> 50
Serum Creatinine (mg/dl)	< 0.5	< 1	> 1
Serum Potassium (mmol/L)	3.5 – 5	> 5	

Table 1: Neonatal Sepsis Severity Score

A summative score of 0 – 3 indicates mild sepsis, 4 – 7 indicates moderate sepsis and a score > 8 is severe sepsis.

2.3 Sample Size and Statistical Analysis

Prevalence of hyperbilirubinemia in neonatal sepsis was found to be 54.2% in a reference article by Sumaira Khalil et al [11]. The sample size was calculated to be 95.3 with an absolute error of 10%. Statistical analysis was done by SPSS version 25.0 (IBM). Descriptive statistics were used to calculate the frequencies and percentages. Correlation was done using Pearson correlation. Receiver operating characteristic (ROC) curve analysis was carried out for evaluation of the diagnostic significance of serum total bilirubin and TLC to CRP ratio in severity of neonatal sepsis. A comparison of the area under ROC curves (AUC) between two variables was done with the help of DeLong's test. The optimal cutoff point was calculated via Youden's index (sensitivity + specificity − 1). A two-sided p value < 0.05 was deemed statistically significant.

3. RESULTS

During the study period, data was retrospectively collected from a total of 100 neonates diagnosed with sepsis. The mean (± SD) age at development of sepsis was 5.98 ± 5.15 days. The mean (± SD) gestational age of the neonates was 36.06 ± 3.95 weeks. 51% of the neonates were born premature (gestation age < 37 weeks). The mean (± SD) birth weight of the neonates was 2.17 ± 0.69 kilograms. 62% of the neonates had low birth weights (< 2.5 kilograms).

With respect to the severity of sepsis, 23% had mild sepsis, 66% had moderate sepsis and 11% had severe sepsis. The mean (± SD) neonatal sepsis severity score was 5.11 ± 1.94 among the study cases.

3.1 Prevalence of Hyperbilirubinemia

A total of 98% of neonates had hyperbilirubinemia (serum total bilirubin > 1 mg/dl) on the first day of sepsis and 91% on the third day of sepsis. The mean (± SD) serum total bilirubin on the first day of sepsis was 8.72 ± 4.93 mg/dl and on the third day was 7.47 ± 5.03 mg/dl.

Deranged AST values (> 40 U/L) was seen in 80% of neonatal septicemic patients, elevated ALP values (>104 U/L) in 88% of neonates and elevated ALT values (>50 U/L) in 18% of patients on the first day.

On the third day, AST was elevated in 72% of the cases, elevated ALP was seen in 87% of neonatal septicemic patients and deranged ALT was seen in 19% of the total cases.

3.2 Total Leukocyte Count to C-Reactive Protein Ratio

In a control study of 20 healthy neonates (gestation age 38 to 42 weeks, birth weight > 2.5 kg, cried immediately, established immediate respiration with normal physical characteristics and absence of congenital abnormalities) the ratio of total leukocyte count (*10^3) to CRP in mg/dl was calculated to set a baseline. The mean ratio (± SD) was 38.71 ± 62.96.

The mean TLC to CRP ratio on the first day of neonatal septicemia was 0.50 ± 0.68 and on the third day was 1.38 ± 3.26.

3.3 Severity of Hyperbilirubinemia and the use of TLC to CRP Ratio in Grading Severity

In those neonates that suffered from mild sepsis showed a mean (± SD) serum total bilirubin of 8.57 ± 3.80 mg/dl on the first day and 7.71 ± 4.46 on the third day of sepsis. The TLC to CRP ratio on the first day for these neonates was 0.95 ± 1.04 and on the third day was 2.79 ± 5.74.

Neonates that suffered from moderate sepsis showed a mean (± SD) serum total bilirubin of 7.88 ± 4.48 mg/dl on the first day and 7.02 ± 5.09 mg/dl on the third. The TLC to CRP ratio on the first day for these neonates was 0.36 ± 0.44 and on the third day was 1.04 ± 1.99.

Neonates that suffered from severe sepsis showed a mean (± SD) serum total bilirubin of 14.03 ± 6.56 mg/dl on the first day and 9.69 ± 5.62 mg/dl on the third day of sepsis. The TLC to CRP ratio on the first day for these neonates was 0.38 ± 0.57 and on the third day was 0.44 ± 0.66.

A correlation was drawn between serum total bilirubin on the first day and the severity of sepsis ($p < 0.05$) and also between the TLC to CRP ratio on the first day with the severity of sepsis ($p < 0.01$).

Serum Total Bilirubin (mg/dl) (day 1)	Percentage of neonates
1 – 5	18 %
5 – 10	46 %
10 – 15	25 %
15 – 20	6 %
> 20	3 %
Serum Total Bilirubin (mg/dl) (day 3)	Percentage of Neonates
1 – 5	26 %
5 – 10	36 %
10 – 15	20 %
15 – 20	9 %
> 20	0 %

Table 2: Severity of Hyperbilirubinemia

3.4 Diagnostic significance of TLC to CRP Ratio in Assessing Severity of Sepsis

ROC curve analysis was done to assess the diagnostic significance of serum total bilirubin levels and the TLC to CRP ratio in assessing the severity of neonatal sepsis. As depicted in Figure 1, the AUC for TLC to CRP in assessing severity of sepsis was 0.95 (95% CI, 0.89 – 1.00, $p < 0.01$), indicating excellent diagnostic accuracy. The optimal cut off value for the TLC to CRP ratio in assessing the severity of sepsis was 1.30 with 8.2% sensitivity and 91.8% specificity. Based on this cutoff value, neonatal sepsis patients can be divided into 2 groups: low TLC to CRP ratio groups (TLC to CRP Ratio < 1.30) and high TLC to CRP ratio group (>1.30).

10% of the neonates had high TLC to CRP ratio on the first day and 23% of the neonates had high TLC to CRP ratio on the third day.

The breakdown of TLC to CRP ratio and mean serum total bilirubin levels in mild, moderate and severe sepsis is given in Figure 2.

In mild sepsis, 6 of the 23 cases (26.09%) had high TLC to CRP Ratio (> 1.3); in moderate sepsis, 3 of the 66 cases (4.55%) had high TLC to CRP Ratio and in severe sepsis, 1 of 11 cases (9.09%) had high ratio.

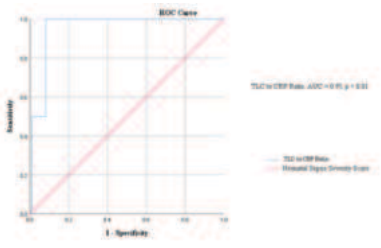

Figure 1: ROC Curve of TLC to CRP Ratio in Assessing Severity of Neonatal Sepsis

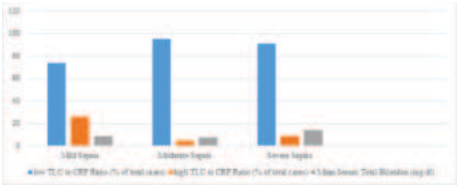

Figure 2: Variation in Patterns of TLC to CRP Ratio and Mean Serum Total Bilirubin Levels in Different Severities of Neonatal Sepsis

Parameters	Mild Sepsis (mean ± SD)	Moderate Sepsis (mean ± SD)	Severe Sepsis (mean ± SD)
	N = 23	N = 66	N = 11
Serum Total Bilirubin (mg/dl)			
Day 1	8.57 ± 3.80	7.88 ± 4.48	14.03 ± 6.56
Day 3	7.71 ± 4.46	7.02 ± 5.09	9.69 ± 5.62
Peak Value	17.80	24.90	23.90
TLC to CRP Ratio			
Day 1	0.95 ± 1.04	0.36 ± 0.44	0.38 ± 0.57
Day 3	2.79 ± 5.74	1.04 ± 1.99	0.44 ± 0.66
Lowest Value	0.07	0.01	0.04

Table 3: Variations in serum total bilirubin and TLC to CRP Ratio in different grades of sepsis

4. DISCUSSION

This retrospective observational study was conducted on 100 neonates who were diagnosed with sepsis. Hyperbilirubinemia and deranged liver enzymes (especially AST and ALP) were exceedingly common in these neonates.

The genesis of hyperbilirubinemia in neonatal sepsis is thought to be multi factorial. Neonatal sepsis results in increased hemolysis causing overload of the neonate's immature liver function and an increase in hepatocellular damage. Circulating endotoxins are associated with sepsis causing agents resulting in biliary stasis and hepatic parenchymal injury. Neonatal sepsis is also proven to hinder the binding of bilirubin to albumin, uptake of bilirubin by the hepatocytes and reduces the conjugation of bilirubin in the liver. Hyperbilirubinemia may also be associated with neonatal sepsis because of microcirculatory changes in the liver or due to endotoxin induced mediators or the direct effects of the causative agents [12]

The severity of hyperbilirubinemia is higher in more severe cases of neonatal sepsis as compared to the mild and moderate ones. One possible explanation for this is the anti-oxidant property possessed by bilirubin. It can scavenge the chain-carrying peroxyl radical by donating a hydrogen atom attached to the C-10 Bridge of the tetra pyrrole molecule to form a carbon-centered radical bilirubin. Both conjugated and unconjugated bilirubin can serve as antioxidants protecting human low-density lipoprotein from peroxidation. It is possible that elevated bilirubin is an attempt by newborn babies to cope with increased exposure to reactive oxidation stress generated as a result of sepsis [13][14].

In sepsis without direct hepatic infection, bile flow becomes markedly reduced, leading to cholestasis and conjugated hyperbilirubinemia without transaminase elevation. Also, cholestasis is considered to be a consequence of the hepatocyte response to sepsis-associated cytokines. These cytokines are responsible for the aggravated response to the normal physiologic cholestasis in neonates. It also has been theorized that mild hemolysis caused by micro-organisms also contributes to the increased serum bilirubin levels in the neonate [15].

Hyperbilirubinemia may also be related to cytokine mediated interference that impairs the bilirubin conjugation in the liver. Sepsis triggers a cascade of inflammatory cytokines, such as interleukins and tumor necrosis factor-alpha (TNF-α). These cytokines can inhibit the activity of UGT1A1 and other enzymes involved in bilirubin metabolism. This leads to an accumulation of unconjugated bilirubin in the bloodstream [16].

Gut dysbiosis is associated with neonatal sepsis [17]. Normally, conjugated bilirubin is excreted into the intestines and converted by gut bacteria into urobilinogen, which is then excreted in the stool. In cases of sepsis, delayed intestinal transit time can lead to increased reabsorption of unconjugated bilirubin from the intestines back into the bloodstream, a process known as enterohepatic recirculation. This contributes to elevated bilirubin levels.

During sepsis, systemic inflammation can lead to hepatic dysfunction. This dysfunction can manifest as impaired bilirubin uptake by hepatocytes, reduced conjugation capacity, and decreased excretion into the bile canaliculi. The liver's endothelial cells and Kupffer cells (liver macrophages) can also be affected, further contributing to impaired bilirubin processing [18].

Elevation of liver enzymes (especially AST and ALP) is also commonly associated with neonatal sepsis. Recently, this phenomenon is thought to be caused by the upregulation of guanylate-binding protein 5 (GBP-5), a component of the body's innate immune system and the decreased tissue perfusion and hepatic blood flow rate, secondary to liver hypoxia and other sepsis induced liver injuries. [19]

Sumaira Khalil et al [11] observed that any hepatobiliary dysfunction (direct bilirubin >20% of total with a minimum level of 2 mg/dL or ALT > 50 U/L) was found in 83 (54.2%) subjects. Cases of Cholestatic jaundice were 65 (42.5%), whereas those of deranged ALT were 57 (37.3%). One-fourth (25.4%) of septicemic babies had cholestatic jaundice as well as derangement of ALT.

Infections are usually characterized by increase in total leukocyte counts as more of such cells are required for the immune mediated defense against the invading pathogens. However, in neonates, as opposed to adults, have limited immunological memory and an immature immune system, which makes them vulnerable to pathogenic microorganisms and the development of infections like sepsis [20].

In sepsis, leukocytes (especially lymphocytes) undergo cytokine-mediated apoptosis. This leads to reduced leukocyte count causing an immunosuppressive state, making the neonate more susceptible to infections. CRP or C - reactive protein is an acute phase protein synthesized in the liver. Several studies have proven its increase in septic patients and its use as a reliable biomarker of sepsis [21] [22].

C - reactive protein (CRP) is noted for its elevation in inflammatory conditions such as rheumatoid arthritis, cardiovascular diseases and especially in bacterial infections. In the presence of calcium ions, it binds to polysaccharides like phosphocholine and this initiates the complement pathway involved in the body's immune response [23]. Higher CRP levels are usually associated with more severe infections.

Combining the indices of CRP and the total leukocyte count, there is potential to generate a predictive biomarker for neonatal sepsis. The ratio is calculated by dividing the total leukocyte count (in thousands per mm^3 of blood) by the serum concentration of CRP (in mg/dl). In more severe cases of sepsis or infection, the ratio is lower due to the decreased leukocyte count and increased CRP level. As the patient assumes a path to recovery and the intensity of infection decreases, or in cases of less severe sepsis, the TLC to CRP ratio is expected to increase as the TLC remains in physiological ranges (or the TLC count has increased before immunosuppression by the cytokines) and the CRP concentration is not markedly increased.

Li X et al [6] observed that the lymphocyte to CRP ratio (LCR) was significantly reduced in mild and severe cases of neonatal sepsis as compared to the control group. A greater incidence of sepsis in neonates with low LCR (LCR<3.94) was also seen as opposed to those with high LCR (77.6% vs 51.4%). The AUC for LCR in identifying neonatal sepsis was 0.70 (95% CI, 0.67–0.73, $p < 0.001$) as determined by ROC curve analysis which was higher than the use of CRP independently in the diagnosis and identification of sepsis in neonates (AUC = 0.66, 95% CI, 0.63–0.69, $p < 0.001$). The study proved that LCR was a potentially strong biomarker capable of identifying sepsis in a timely manner in neonates suspected to be septicemic.

Our study drew strong correlations between the total serum bilirubin levels on the first day of infection and with the severity of sepsis as assessed by the severity score ($r = 0.219$, $p= 0.029$) and between the TLC to CRP ratio on the first day to the severity of sepsis ($r = -0.367$, $p < 0.01$). This signifies the viability of serum total bilirubin values and the TLC to CRP ratio as a biomarker in determining the severity and prognosis of neonatal sepsis patients.

As this study only included those neonates with sepsis who survived the septic infection, this can lead to indicators that help in its prognosis. In all surviving neonates, a decrease in the serum total bilirubin and an increase in the TLC to CRP ratio was seen from the first to third day. The mean (± SD) serum total bilirubin on day 1 was 8.72 ± 4.93 and on day 3 was 7.47 ± 5.03. The mean (±SD) TLC to CRP ratio on the first day was 0.50 ± 0.68 and on the third day was recorded as 1.38 ± 3.26.

	Total Bilirubin on Day 1	Total Bilirubin on Day 3	TLC to CRP Ratio on Day 1	TLC to CRP Ratio on Day 3	Neonatal Sepsis Severity Score
Total Bilirubin on day 1		p < 0.01*	p = 0.431	p = 0.828	p = 0.029*
Total Bilirubin on day 3	p < 0.01*		p = 0.129	p = 0.740	p = 0.052
TLC to CRP Ratio on day 1	p = 0.431	p = 0.129		p = 0.161	p < 0.01*
TLC to CRP Ratio on day 3	p = 0.828	p = 0.740	p = 0.161		p = 0.054
Neonatal Sepsis Severity Score	p = 0.029*	p = 0.052	p < 0.01*	p = 0.054	
* correlation is significant at the 0.05 level (2-Tailed)					

There are some limitations associated with this study. Firstly, only serum total bilirubin values were noted and not individually as direct or indirect values. No differentiation has been made between early and late onset cases of neonatal sepsis. Severity of sepsis was calculated only on the day of admission and not during the follow up on the third day. Lastly, as this was a single center retrospective study, it may require further validation via future multicenter studies.

5. CONCLUSIONS

In conclusion, hyperbilirubinemia is highly prevalent among neonatal sepsis patients. This study elicited a strong relationship between serum total bilirubin levels, the TLC to CRP ratio and the presence of sepsis in neonates. Serum total bilirubin and the ratio of TLC to CRP are potentially helpful biomarkers that can help in the diagnosis, prognosis and management of neonates who are diagnosed with sepsis. A decrease in serum total bilirubin and an increase in TLC to CRP ratio is indicative of a path to recovery.

The findings of this study highlights that assessing serum total bilirubin levels and the TLC to CRP ratio can serve as a quick and cost-effective way in identifying neonatal sepsis that can be easily measured and calculated.

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