

Clinical presentation and outcomes of neonatal cholestasis: Experience from a tertiary care hospital

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Conflict of Interest: None

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ABSTRACT:

Background: Neonatal cholestasis is a disorder that develops in the first few months of life and is characterised by an increase in direct (conjugated) bilirubin and jaundice due to defective bile synthesis or excretion.

Objective: To observe the clinical manifestation and outcome of neonatal cholestasis.

Methods: This was a hospital-based cross-sectional study carried out among 50 children attending the Department of Pediatrics, Bangladesh Shishu Hospital & Institute (BSH&I), between January 2023 and December 2023. Cholestasis was considered to be conjugated bilirubin levels above 1 mg/dL when serum total bilirubin levels were below 5 mg/dL, or conjugated bilirubin was more than 20% of total when total bilirubin levels were above 5 mg/dL. Children with Jaundice due to other reasons than cholestasis were excluded from the study

Results: Among the neonatal cholestasis cases majority (72%) were intrahepatic and 28% were extrahepatic cholestasis. Regarding etiology 13(26%) were idiopathic neonatal hepatitis, 12(24%) biliary atresia, 10(20%) were infection. Mean age of onset for extrahepatic cholestasis was 6.7 ± 1.4 days, while for intrahepatic cholestasis it was 8.2 ± 2.8 days. Mean age of admission for extrahepatic cholestasis was 78.9 ± 21.8 days, while for intrahepatic cholestasis it was 75.4 ± 16.9 days ($p > 0.05$). Male 42.9% had extrahepatic cholestasis, whereas 21 (58.3%) had intrahepatic cholestasis ($p > 0.05$). Twelve cases (85.7%) of persistent pale stool were found in extra-hepatic cholestasis, while eleven cases (30.6%) were detected in intra-hepatic cholestasis, which was substantially higher in terms of clinical presentation ($p < 0.05$). Significantly higher improvement were found in intra hepatic cholestasis then Extra hepatic cholestasis [24(66.7%) vs 1(7.1%), $p < 0.01$]. Regarding mortality 7(50%) cases died in extra hepatic cholestasis and 7(19.4%) died in Intra hepatic cholestasis ($p < 0.001$).

Conclusion: Common etiological factors of neonatal cholestasis include idiopathic newborn hepatitis, biliary atresia, infection, metabolic abnormalities, and hereditary cholestatic diseases. Extra-hepatic cholestasis was associated with persistent pale stool. Treatment seeking in tertiary care hospital was delayed. Intrahepatic cholestasis showed significantly better results than extrahepatic cholestasis.

Key Words:

Extra-hepatic cholestasis, Intra hepatic cholestasis, Clinical presentation, outcomes.

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Introduction

Neonatal cholestasis is defined as accumulation of bile substances in blood due to impaired excretion.¹ The most common causes of cholestatic jaundice in the first months of life are biliary atresia, idiopathic neonatal hepatitis, infections (Cytomegalovirus, herpes simplex toxoplasma, rubella, urinary tract infection, sepsis), endocrine (hypothyroidism), metabolic (Galactosemia, tyrosinemia, neonatal hemochromatosis), genetic (progressive familial intrahepatic cholestasis, Down syndrome, Alagille syndrome) along with many unknown or multifactorial (eg, parenteral nutrition-related) one. Conjugated hyperbilirubinemia, pale stools and dark urine are the cardinal features of neonatal cholestasis.¹ Neonatal cholestasis (NC) is a major cause of morbidity and mortality in young infants. Neonatal cholestasis (NC) is a reduced bile formation or flow with retention of biliary substances inside the liver, which can be presented as conjugated hyperbilirubinemia in the first 90 days of extra-uterine life.²

Neonatal cholestasis is a condition that starts in the first months of life and progresses with direct (conjugated) bilirubin increase and jaundice as a result of impaired bile production or excretion.³ The reasons of this are because of the irregularity in canalicular structure and function, the increase in hypomotility and paracellular permeability, and the decrease in hepatic immaturity and bile flow. Hepatic maturation is complete around the end of the first year. Therefore, there is no consensus regarding the age range of neonatal cholestasis. In most studies, it was considered to be about the first six months.⁴ Predicting the outcome of neonatal cholestasis could be useful. By discriminating unfavourable outcomes such as in-hospital mortality among patients with neonatal cholestasis, clinicians are able to identify high-risk neonatal cholestasis cases and to prepare focused and multidisciplinary strategies for them. There are several mortality prediction models for liver diseases in paediatric hepatology, including the Pediatric End-Stage Liver Disease (PELD) score for chronic liver disease, the King's College Hospital criteria (KCHC) score, and the Liver Injury Units (LIU) for acute liver failure.^{5,6} The training dataset of these models originated from end-stage liver disease and fulminant hepatitis in paediatric groups with wide age ranges, mostly more than 6 months. In addition, the primary goal of these predictions is to estimate the risk-benefit of liver transplantation in affected infants and children. Currently,

there is no prediction model for mortality in neonatal cholestasis using a bigenough dataset of neonatal cholestasis cases.⁷ In this study, we investigated the aetiologic characteristics of neonatal cholestasis and its outcome in a tertiary hospital.

Materials and Methods

This was a hospital-based cross-sectional study carried out among 50 children attending the Department of Pediatrics, Bangladesh Shishu Hospital & Institute (BSH&I), between January 2023 and December 2023. Cholestasis was considered to be conjugated bilirubin levels above 1 mg/dL when serum total bilirubin levels were below 5 mg/dL, or conjugated bilirubin was more than 20% of total when total bilirubin levels were above 5 mg/dL. Children with Jaundice due to other reasons than cholestasis were excluded from the study. Clinical history, physical examination, investigation results, and treatments given were recorded. The outcome was recognized by identifying improvement, deterioration with morbidity, or mortality based on various clinical and biochemical parameters. Demographic characteristics, etiological factors, clinical signs, treatment and final status of patients were examined and etiological factors were determined in the liver transplant cases. Statistical analysis was performed using SPSS for Windows version 25.0. Armonk, NY, USA). Descriptive statistics of evaluation results; number and percentage for categorical variables, mean $\pm$ standard deviation for continuous variables were given as minimum, maximum, and median. Chi-square test was used to analyze the differences between the ratios of categorical variables in independent groups. Statistical significance level of alpha was accepted as $p < 0.05$.

Results

Among the neonatal cholestasis cases majority (72%) were intrahepatic and 28% were extrahepatic cholestasis (Fig 1).

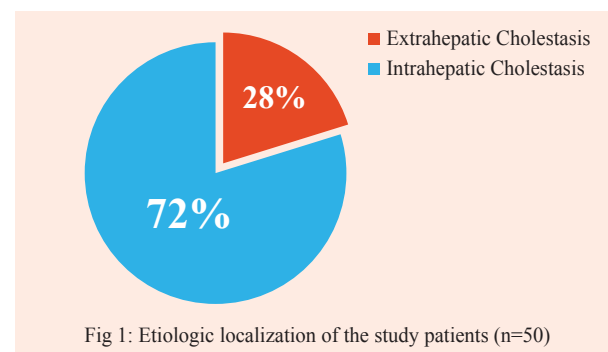


Fig 1: Etiologic localization of the study patients (n=50)

Table I**Baseline characteristics of the study patients (n=50)**

Variable	Extra hepatic cholestasis (n=14)		Intra hepatic cholestasis (n=36)		p value
	Mean	±SD	Mean	±SD	
Age of onset (days)	6.7	±1.4	8.2	±2.8	0.063
Age of admission (days)	78.9	±21.8	75.4	±16.9	0.548
Sex					
Male	6	42.9	21	58.3	0.324
Female	8	57.1	15	41.7	
Gestational age (weeks)					
Term (37-40)	11	78.6	20	55.6	0.132
Preterm (<37)	3	21.4	16	44.4	

The average age of onset for extrahepatic cholestasis was 6.7±1.4, while for intrahepatic cholestasis it was 8.2±2.8. Mean age of admission for extrahepatic cholestasis was 78.9±21.8 days, while for intrahepatic cholestasis it was 75.4±16.9 days ($p>0.05$). Male 42.9% had extrahepatic cholestasis, whereas 21 (58.3%) had intrahepatic cholestasis ($p>0.05$). There were 11 (78.6%) term pregnancies in extrahepatic cholestasis and 20 (55.6%) in intrahepatic cholestasis ($p>0.05$) (Table I).

Table II**Etiologic factor of the study patients (n=50)**

Etiologic factor	Frequency	Percentage
Idiopathic neonatal hepatitis	13	26.0
Biliary atresia	12	24.0
Infections	10	20.0
Metabolic	6	12.0
Hereditary cholestatic diseases	5	10.0
Choledochal cyst	2	4.0
Ductal paucity	1	2.0
UTI with sepsis	1	2.0

Regarding etiology 13(26%) were idiopathic neonatal hepatitis, 12(24%) biliary atresia, 10(20%) were infection, 6(12%) were metabolic disorders, 5(10%) were genetic cholestatic illnesses, and 2(4%) were choledochal cysts (Table II).

Table III**Clinical presentation of the study patients (n=50)**

Clinical presentation	Extra hepatic cholestasis (n=14)		Intra hepatic cholestasis (n=36)		p value
	n	%	n	%	
Jaundice	14	100.0	36	100.0	-
Dark urine	11	78.6	21	58.3	0.181
Persistent pale stool	12	85.7	11	30.6	0.001
Hepatomegaly	11	78.6	31	86.1	0.396
Splenomegaly	8	57.1	27	75.0	0.185
Ascites	1	7.1	4	11.1	0.567

Twelve cases (85.7%) of persistent pale stool were discovered in extra-hepatic cholestasis, while eleven cases (30.6%) were detected in intra-hepatic cholestasis, which was substantially higher in terms of clinical presentation ($p<0.05$). Jaundice, dark urine, hepatomegaly, splenomegaly, and ascites were among the additional presentations; nevertheless, there was no statistically significant difference between intrahepatic and extrahepatic cholestasis ($p>0.05$) (Table III).

Table IV**Liver function tests of the study patients (n=50)**

Liver function tests	Extra hepatic cholestasis (n=14)	Intra hepatic cholestasis (n=36)	p value
	Mean±SD	Mean±SD	
S. total bilirubin (mg/dl)	8.2 ±2.1	9.7 ±2.6	0.060
Direct bilirubin (mg/dl)	4.3 ±1.5	3.9 ±1.0	0.278
ALT (U/L)	146.7±62.4	462.1 ±47.3	0.001
Alkaline phosphatase (U/L)	749.5±107.6	346.7 ±72.9	0.001
GGT (U/L)	594.9±231.6	377.4 ±207.1	0.001
INR	1.21 ±0.11	1.48 ±0.26	0.001

Table IV shows significant Liver function tests were found ALT (U/L), Alkaline phosphatase (U/L), GGT (U/L) and INR between extra hepatic cholestasis and Intra hepatic cholestasis ($p<0.05$).

Table V**Outcome of the study patients (n=50)**

Outcome	Extra hepatic cholestasis (n=14)		Intra hepatic cholestasis (n=36)		p value
	n	%	n	%	
Improved	1	7.1	24	66.7	0.001
Deteriorating	6	42.9	5	13.9	
Died	7	50.0	7	19.4	

Significantly higher improvement were found in intra hepatic cholestasis then Extra hepatic cholestasis [24(66.7%) vs 1(7.1%), $p<0.01$]. Regarding mortality 7(50%) cases died in extra hepatic cholestasis and 7(19.4%) died in Intra hepatic cholestasis ($p<0.001$) (Table V).

Table VI**Cause of death of the study patients**

Outcome	Extra hepatic cholestasis (n=7)		Intra hepatic cholestasis (n=7)		p value
	n	%	n	%	
Liver cirrhosis with failure	7	100.0	6	85.7	0.500
Liver cirrhosis with failure with sepsis	0	0.0	1	14.3	

In terms of the cause of death, six patients had intrahepatic cholestasis and seven patients with extrahepatic cholestasis died from liver cirrhosis with failure. Liver cirrhosis with failure of sepsis in intrahepatic cholestasis was the cause of death in one case (Table VI).

Discussion

In this study, it was observed that among neonatal cholestasis cases 28% were extrahepatic cholestasis and 72% were intrahepatic. Nahid et al.⁸ in an earlier study on Bangladesh, also observed similar finding. Sag et al.⁴ reported extrahepatic cholestasis was detected in 24.4% patients and intrahepatic cholestasis was detected in 75.6% patients. Rani et al.⁹ found 45.1% extra hepatic biliary atresia and 36.5% intrahepatic cholestasis.

Current study showed that average age of onset for extra-hepatic cholestasis was 6.7 ± 1.4 days, while for intrahepatic cholestasis it was 8.2 ± 2.8 days. Mean age of admission for extrahepatic cholestasis was 78.9 ± 21.8 days,

while for intrahepatic cholestasis it was 75.4 ± 16.9 days ($p>0.05$). Male 42.9% had extrahepatic cholestasis, whereas 21 (58.3%) had intrahepatic cholestasis ($p>0.05$). There were 11 (78.6%) term pregnancies in extrahepatic cholestasis and 20 (55.6%) in intrahepatic cholestasis ($p>0.05$). Mahmud et al.² revealed the mean age of onset of the overall cohort was 10.23 days and ranging from 3 to 17 days. Although the mean age of onset of intra and extrahepatic cases were significantly different (p value <0.001), there was no significant difference between the mean age of admission of the two groups (p value 0.09). Significant difference (p value=0.002) was observed between the male to female ratio of the intrahepatic group (male to female=1.6:1) and the extrahepatic group (male to female=1:2.2). Intra-hepatic cholestatic cases were more frequently observed among pre-term (66.6%) children and extra-hepatic cholestasis was more frequent among full-term children (p value <0.001). Sag et al study also reported 61.1% male.⁴

Present study showed 26% and 24% respectively had idiopathic newborn hepatitis and biliary atresia; 12% had metabolic disorders; 10% had hereditary cholestatic diseases and 4% choledochal cysts. Mahmud et al.² reported among extrahepatic cases, BA was the most common cause followed by CC. For intrahepatic cases, most common causes were INH and TORCH infections. Hypothyroidism, galactosemia, and PIBD were found in 4.1% cases. Down syndrome with hypothyroidism, UTI with sepsis and PFIC were found in 2.0% cases. Down syndrome are common in intrahepatic cases and some endocrine, metabolic, and genetic disorders might be present with intrahepatic cholestasis^{8,10,11} and our study observed similar findings. Other causes of extrahepatic cholestasis were biliary cyst, biliary hypoplasia, and cholelithiasis. Cystectomy was performed in five patients with biliary cyst, external drainage was performed on a patient with biliary hypoplasia, cholecystectomy was performed on a patient with cholelithiasis. The most common and most important cause of extrahepatic cholestasis is BA and 16.8% of all cholestasis cases constitute extrahepatic cholestasis, while 75% of extrahepatic cholestasis is BA.^{12,13}

Present study showed 85.7% of persistent pale stool were discovered in extra-hepatic cholestasis, while 30.6% were detected in intra-hepatic cholestasis, which was substan-

tially higher in terms of clinical presentation ($p < 0.05$). Jaundice, dark urine, hepatomegaly, splenomegaly, and ascites were among the additional presentations; nevertheless, there was no statistically significant difference between intrahepatic and extrahepatic cholestasis ($p > 0.05$). Mahmud et al.² reported persistent pale stool was more in extra-hepatic cases, and intermittent pale stool was predominant in intrahepatic cases (p value < 0.001 for both). No significant difference was observed among the two groups for the other clinical characteristics. Sag et al.⁴ findings other than jaundice were hepatomegaly (77.9%), splenomegaly (36.6%), acholic stool (35.1%), umbilical hernia (6.9%), limb anomaly (5.3%) and atypical facial appearance (5.3%).

Present study showed significant difference in liver function tests were found [ALT (U/L), Alkaline phosphatase (U/L), GGT (U/L) and INR] between extra hepatic cholestasis and Intra hepatic cholestasis ($p < 0.05$). Mahmud et al.² reported Serum total, direct bilirubin, ALT, alkaline phosphatase, and GGT were higher than the normal range for both the cholestatic groups. There was no significant difference between the serum total of the two groups as well as the direct bilirubin. ALT was significantly greater in intra-hepatic cases. Alkaline phosphatase and GGT were significantly higher in extra-hepatic cases (p value < 0.001). INR was normal in extra-hepatic cases but slightly raised in intra-hepatic cases (p value < 0.001). Sag et al.⁴ Neonatal cholestasis accounts for more than half of the causes of liver transplantation in children, and the most common cause is known as BA (40%-50%). Rani et al.⁹ observed direct serum bilirubin level showed 6.62 ± 3 mg/dl in BA Vs 6.44 ± 3.1 mg/dl in NH with a p value = 0.824. ALP showed no statistical significance with mean value 702.4 ± 312.3 in BA Vs 522.3 ± 451.9 (p value = 0.488). Mean value for SGOT were 323.6 ± 377 in BA and 432 ± 506 in NH babies showed no statistical significance.

In current study showed significantly higher improved were found in Intra hepatic cholestasis then Extra hepatic cholestasis ($p < 0.01$) and 50% cases died in extra hepatic cholestasis and 19.4% died in Intra hepatic cholestasis ($p < 0.001$). Similar observation was found Mahmud et al.² they showed more than half of the extrahepatic cases died, and only around 6% cases improved. But among the intrahepatic cases, 72.9% improved, 12.5% deteriorated and 14.6% died.

Conclusion

Common etiological factors of neonatal cholestasis include idiopathic newborn hepatitis, biliary atresia, infection, metabolic abnormalities, and hereditary cholestatic diseases. Extra-hepatic cholestasis was associated with persistent pale stool. Treatment seeking in tertiary care hospital was delayed. Intrahepatic cholestasis showed significantly better results than extrahepatic cholestasis.

Conflict of Interest: None

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