P-ISSN: 2664-3685
E-ISSN: 2664-3693
www.paediatricjournal.com
IJPG 2025; 8(1): 19-23
Received: 10-01-2025
Accepted: 14-02-2025

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Biliary atresia vs. non-biliary atresia: An assessment of the ultrasonography and scintigraphy findings with liver biopsy

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DOI: https://doi.org/10.33545/26643685.2025.v8.i1a.256

Abstract
Introduction: Children with biliary atresia referred for surgery before 60 days of age do dramatically better than those older than 90 days at the time of operation in regard to re-establishment of bile flow which is more than 80% versus less than 20% respectively. There are a lot of investigations available for diagnosing BA but it takes more time to conclude the diagnosis. Ultimately there is delay in surgery which increases the mortality of the patient.
Aim of the study: To assess the ultrasonographic and scintigraphic findings with liver biopsy and evaluate the comparison between biliary atresia and non-biliary atresia.
Materials and Methods: A cross-sectional study was conducted in Department of Pediatric Gastroenterology, Hematology & Nutrition, Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh from March 2018 to August 2019. Results were expressed as mean ± standard deviation (SD) or number or percentage as appropriate and were presented in the form of table and diagram. Ultrasonography & Hepatobiliary scintigraphy findings were analyzed. The accuracy of the abdominal ultrasonography and hepatobiliary scintigraphy was evaluated for diagnosis of BA and differentiation from non-BA cases. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of ultrasonography and hepatobiliary scintigraphy was calculated with liver biopsy as gold standard. Statistical analyses were carried out using the SPSS statistical package, version 23 (SPSS Inc., Chicago, IL, USA) for Windows XP. Data were expressed as numbers and percentages for qualitative variables or as mean± SD and median range (minimum and maximum) for quantitative variables.
Results: Ultrasonography & scintigraphic findings with liver biopsy was assessed in this study. On comparing the ultrasonographic findings between biliary atresia and non-BA, the frequency of a non-contractile gallbladder was significantly higher in BA than that in non-BA infants. Contracted gallbladder was found in 13 (61.9%) cases with BA and 8 (27.5%) in non-BA cases and difference is significant (p 0.001). No pre and postprandial change of size of gallbladder were 17 (81%) in BA vs 10 (34.5%) in non BA cases. The difference was statistically significant (p 0.001). An ultrasonographic diagnosis of BA was made in 27 (54.0%) infants and that of non-BA in 23 (46%) infants. Scintigraphy was significantly negative (n=19, 90.5%) among BA than non BA (n=16, 55.2%) subjects (p 0.001). An scintigraphic diagnosis of BA was made in 35 (70.0%) infants and that of non-BA in 15 (30.0%) infants. Diagnostic accuracy of USG and hepatobiliary scintigraphy for diagnosis of BA was 72.0% and 64.0% respectively.
Conclusion: Ultrasonography & hepatobiliary scintigraphy are two important investigations for diagnosing biliary atresia Numerous ultrasonographic & hepatobiliary scintigraphy findings have been described as useful pointers for the diagnosis of BA in this study. Diagnostic accuracy of ultrasonography is more than hepatobiliary scintigraphy for diagnosing biliary atresia.

Keywords: Liver biopsy, atresia, non-biliary atresia

Introduction
Cholestasis is a clinical condition characterized by a decreased flow of canalicular bile and direct hyperbilirubinemia. Decreased bile flow leads to the accumulation of substances, such as bile acids, that would normally be expelled in the bile. Cholestasis developing in early life can arise from a hepatic response to exogenous agents or because of a specific congenital pathology [1]. The evaluation of patients with cholestasis is difficult because of the variety of cholestasis syndromes, the fact that the pathogeneses are not fully understood, and that the clinical findings are not specific to the disease.

Because of the severity of conditions leading to neonatal cholestasis, it is essential to diagnose cholestasis and its underlying cause early. Differential diagnosis helps clinicians identify diseases that do not respond to specific treatments and provide appropriate general supportive therapy. The most common causes of cholestasis jaundice in the first month of life are biliary atresia (BA) and neonatal hepatitis. Diagnostic evaluation must be performed within 45–60 days in the early period of life, and BA must be excluded [2]. Biliary atresia is one of the most common causes of cholestasis in newborns and infants, being responsible for approximately one in three of all cases of neonatal cholestasis and for at least 90% of all cases of obstructive cholestasis [3]. It is a destructive, inflammatory cholangiopathy affecting both the intra and extra hepatic bile ducts [4]. Time is of great importance in BA: if the Kasai procedure is not performed early in life, death can occur within 2 years from biliary cirrhosis and liver failure [5]. However, it is difficult to differentiate the causes of BA and other causes of neonatal cholestasis (non-BA) based on histopathology, biochemistry, clinical examination, or imaging alone, with no single test known to provide a definitive diagnosis of BA [6]. Clinicians must, therefore, make their differential diagnosis by combining several parameters. The purpose of this study was to determine the sensitivity and specificity of the tests used in the differential diagnosis of BA, assessed both separately and in combination; to better explain the requirement for intraoperative cholangiography; and to facilitate earlier diagnosis. Therefore, a multidisciplinary approach to the evaluation of neonatal jaundice is needed to determine the cause of the condition. This study was conducted to assess the usefulness and roles of abdominal ultrasonography and hepatobiliary scintigraphy in differentiating the biliary atresia from other form of neonatal cholestasis and to propose the best diagnostic approach.

Methodology and Materials

A supervised cross-sectional study was conducted on Department of Pediatric Gastroenterology, Hematology & Nutrition, Dhaka Shishu (Children) Hospital from March 2018 to August 2019 in Dhaka, Bangladesh. Ultrasonography of abdomen specially the hepatobiliary system is an important tool in the diagnostic work-up of neonatal cholestasis. It is a useful test to identify for instance a choledochal cyst, gall stones, sludge in the biliary tree or gallbladder. A small or absent gallbladder is suggestive but not diagnostic for biliary atresia and the presence of a normal gallbladder, on the other hand does not exclude biliary atresia either. The finding of the triangular cord sign (An echogenic area at the portal hepatics) is believed to be a specific finding of biliary atresia [7]. Ultrasonography was performed in all the cases before liver biopsy. Percutaneous liver biopsy is the investigation with the highest diagnostic usefulness in neonatal cholestasis. The diagnostic accuracy for biliary atresia in several studies was more than 90%. Liver biopsy was used as the gold standard for diagnosis of BA and comparison of ultrasonography and hepatobiliary scintigraphy. The typical histological findings in extra hepatic biliary atresia include bile duct proliferation, bile plugs in small bile ducts, portal tract edema and fibrosis. Biliary atresia is an inflammatory, progressive, fibrosclerosing cholangiopathy of infancy, affecting both extra hepatic and intrahepatic bile ducts to a variable extentthat results in destruction and obstruction of the biliary tract [8]. Neonatal cholestasis other than biliary atresia was considered as non-biliary atresia. Statistical analyses were carried out using the SPSS statistical package, version 23, for Windows XP.

Results

In Figure-1 showed, total 50 cases were diagnosed by liver biopsy, among them 21(42.0%) were biliary atresia (BA) and 29(58.0%) were non biliary atresia. Table-1 showed, the studied subjects most of the cases 11(52.4%) and 15(51.7%) were ≤2 month age in BA and non-BA group respectively but there was no significant difference between two groups. Table-2 is Comparison of sex distribution of the studied subjects in BA group female (81.0%) were predominant & non-BA group males (58.6%) were predominant and that was statistically significant (p<0.05). Table-3 is Comparison of clinical symptoms of the studied subjects presenting history and clinical characteristics were compared between BA and non-BA cases. Most of the infants (19, 90.5%) of BA were term while pre-term babies (28, 96.6%) in case of non-BA cases were statistically significant (p 0.023). The presence of persistently pale colored stool was more commonly seen in patients with BA (BA vs. non- BA: 90.5% vs. 13.8%). The difference was statistically significant (p 0.001). Table-4 is Comparison of USG findings of the studied subjects on comparing the ultrasonography findings between biliary atresia and non-BA, the frequency of a non-contractile gallbladder was significantly higher in BA than that in non-BA infants. Contracted gallbladder was found in 13 (61.9%) cases with BA and 8 (27.5%) in non-BA cases and difference is significant (p 0.001). No pre and postprandial change of size of gallbladder were 17 (81%) in BA vs. 10 (34.5%) in non BA cases. The difference was statistically significant (p 0.001). There is no statistically significant difference between BA and non BA cases in other sonographer parameters such as hepatomegaly and splenomegaly. Table-5 is Ultrasonography diagnosis of the studied subjects of BA was made in 27 (54.0%) infants and that of non-BA in 23 (46%) infants. Table-6 showed the comparison of scintigraphy findings between subjects with biliary atresia and subjects with non-BA. Scintigraphy was significantly negative (n=19, 90.5%) among BA than non BA (n=16, 55.2%) subjects (p 0.001).A scintigraphy diagnosis of BA was made in 35 (70.0%) infants and that of non-BA in 15 (30.0%) infants. Table 7 showed that, diagnostic usefulness of USG and hepatobiliary scintigraphy in the order of accuracy for diagnosis of BA. Hepatobiliary scintigraphy had highest sensitivity of 90.5% but low specificity of 44.8%. Sensitivity and specificity of USG for the diagnosis of BA was found to be 81.0% and 65.5% respectively in this study. Diagnostic accuracy of USG and hepatobiliary scintigraphy for diagnosis of BA was 72.0% and 64.0% respectively.

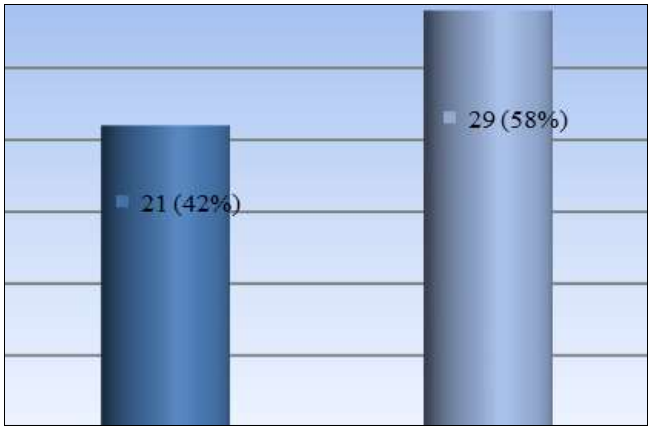

Fig 1: Bar diagram shows distribution of the studied subjects (n=50)

Table 1: Comparison of age distribution of the studied subjects (n=50)

Age (months)	Liver biopsy				P value
	BA group (n=21)		Non-BA group (n=29)		
	n	%	n	%	
≤2	11	52.4	15	51.7	
3-4	10	47.6	14	48.3	
Mean±SD	2.14	±1.11	2.51	±1.02	0.223[ns]
Range (min-max)	1.0	-4.0	1.0	-4.0	

ns = not significant and P value reached from unpaired t-test

Table 2: Comparison of sex distribution of the studied subjects (n=50)

Sex	Liver biopsy				P value
	BA group (n=21)		Non-BA group (n=29)		
	n	%	n	%	
Male	4	19.0	17	58.6	0.005[s]
Female	17	81.0	12	41.4	

s = significant and P value reached from fisher exact test

Table 3: Comparison of clinical symptoms of the studied subjects (n=50)

Clinical variables	Liver biopsy				P value
	BA group (n=21)		Non BA group (n=29)		
	n	%	n	%	
History of consanguinity	0	0.0	2	6.7	0.331[ns]
Gestational age (weeks)					
≤36 (Preterm)	2	9.5	28	96.6	0.001[s]
37-40 (Term)	19	90.5	1	3.4	
Birth weight (kg)					
<2.5 (LBW)	2	9.5	28	96.6	0.001[s]
≥2.5 (Normal)	19	90.5	1	3.4	
Pale color stool					
Persistent	19	90.5	4	13.8	0.001[s]
Intermittent	2	9.5	25	86.2	

s= significant, ns= not significant and P value reached from fisher exact test

Table 4: Comparison of USG findings of the studied subjects (n=50)

Clinical variables	Liver biopsy				P value
	BA group (n=21)		Non BA group (n=29)		
	n	%	n	%	
Gallbladder					
Normal	4	19.0	19	65.5	
Non-visualized	4	19.0	2	6.9	[a]0.001[s]
Contracted	13	61.9	8	27.5	
Gallbladder contractility					
Normal	4	19	19	65.5	[b]0.001[s]
[c]Non contractile	17	81	10	34.5	
Hepatomegaly	21	100.0	29	100.0	-
Splenomegaly	14	66.7	22	75.9	[a]0.475[ns]

s= significant, ns= not significant, [a]P value reached from chi square test, [b]P value reached from fisher exact test and [c]Non contractile gallbladder means no pre and postprandial change of size of gallbladder

Table 5: Ultrasonography diagnosis of the studied subjects (n=50)

Usg Diagnosis	Liver biopsy			
	Ba group (n=21)		Non-BA Group (n=29)	
	n	%	n	%
BA	17	81.0	10	34.5
Non-BA	4	19.0	19	65.5

Table 6: Comparison of scintigraphy findings of the studied subjects (n=50)

Scintigraphy findings	Liver biopsy				P value
	BA group (n=21)		Non BA group (n=29)		
	N	%	n	%	
Uptake of the radiotracer					
Good[a]	17	81.0	12	41.4	0.003[s]
Poor	4	19.0	17	58.6	
Excretion of the radiotracer into the intestine					
Positive[b]	2	9.5	13	44.8	0.001[s]
Negative	19	90.5	16	55.2	
Scintigraphy diagnosis					
BA	19	90.5	16	55.2	
Non-BA	2	9.5	13	44.8	

s= significant, P value reached from fisher exact test, [a]Good uptake means perfusion of the radiotracer to the liver within 30 min of scan and [b]A positive scan means excretion of the radiotracer into the intestine within 24 hour.

Table 7: Sensitivity, specificity, positive and negative predictive values of the USG and hepatobiliary scintigraphy diagnosis evaluation for diagnosis of BA

Validity test	USG	Hepatobiliary scintigraphy
Sensitivity	81.0	90.5
Specificity	65.5	44.8
Positive predictive value	63.0	54.3
Negative predictive value	82.6	86.7
Diagnostic accuracy	72.0	64.0

Discussion

In this study observed on comparing the ultrasonography findings between biliary atresia and non-BA; the frequency of a non-contractile gallbladder was significantly higher in BA than that in non BA infants. Contracted gallbladder was found in 13 (61.9%) with BA and 8 (27.5%) in non-BA cases and difference is significant (p 0.001). No pre and postprandial change of size of gallbladder were 17 (81%) in BA vs. 10 (34.5%) in non BA cases. The difference was statistically significant (p 0.001)[9] reported abdominal US revealed no visualization of gall bladder in 25(69%) cases and visualization of gall bladder in 11(30%) cases. There were 25/36 (61%) abnormal studies, which included cases with small gallbladder (n = 8) and non-visualized gallbladder (n=17), but not perioral fibrosis [10] reported the features with the greatest individual sensitivity and specificity, respectively, in the diagnosis of BA were triangular cord sign (73% and 100%), abnormal gallbladder wall (91% and 95%) and shape (70% and 100%), and an absent common bile duct (93% and 92%) [11] also concluded that a small or non-visualized gall bladder is more suggestive of biliary atresia than infantile intrahepatic cholestasis and have used this finding together with the 'triangular cord' (TC) sign. The present study found ultrasonography sensitivity and specificity 81.0% and 65.5% respectively and diagnostic accuracy 72.0% which are higher than [12] diagnostic accuracy 53% and findings of [13] sensitivity and specificity 52.6% and 76.1% for BA, respectively and accuracy 69.2%. Accuracy of US for differentiation between BA and non-BA in the present study was lower than [14] (sensitivity, specificity, and accuracy were 86.7%, 77.1%, and 79.4%, respectively) and [15] (85%, 100%, and 95%, respectively). This lower accuracy may be due to the usability of our sonographer for detection of triangular cord sign.Tc-99m-IDA hepatobiliary scintigraphy can be used to evaluate the degree of hepatocyte dysfunction using hepatocyte clearance and bile duct patency using excretion of tracer into the small bowel. The majority of the infants who have BA are expected to have no excretion of tracer into the small bowel. The diagnosis of infantile cholestasis is mostly dependent on the presence or absence of tracer excretion rather than degree of hepatocyte clearance [15]. The majority of the literature report that the sensitivity of the Tc-99m-IDA hepatobiliary scintigraphy for the diagnosis of BA is as high as 97% to 100%, whereas the specificity varied from the reports, ranging from 33% to 91% [15]. The causes of false-positive cases (i.e. absence of drainage due to causes other than biliary atresia) may include severe neonatal hepatitis, total parenteral nutrition cholestasis, Alagille syndrome, cystic fibrosis, bile plug syndrome, choledochal cyst, hypothyroidism and alpha-1 antitrypsin deficiency [16]. Thus, excretion of tracer can exclude BA but no excretion of tracer requires further investigation such as percutaneous needle biopsy because of its low specificity.

Limitations of the study

The study population was selected from one selected hospital in Dhaka city, so that the results of the study may not reflect the exact picture of the entire country. The present study was conducted at a very short period of time. Small sample size was also a limitation of the present study.

Conclusion and Recommendations

There are a lot of investigations available for diagnosing biliary atresia. Ultrasonography & hepatobiliary scintigraphy are two important investigations for diagnosing biliary atresia. Numerous ultrasonographic & hepatobiliary scintigraphy findings have been described as useful pointers for the diagnosis of BA in this study. Diagnostic accuracy of

ultrasonography is more than hepatobiliary scintigraphy for diagnosing biliary atresia. Our recommendation is to do abdominal ultrasonography for all cases with neonatal cholestasis and training and orientation of the sonologist on identifying the important findings of gallbladder abnormality that will help early diagnosis of BA.

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