http:// ijp.mums.ac.ir
Original Article (Pages: 9265-9275)

Non-Invasive Diagnostic Methods for Differentiation of Biliary Atresia from Neonatal Hepatitis in Upper Egypt

*Ashraf Abou-Taleb[1], Wafaa Abdelhameed[2], Ahmed RH Ahmed[3], Ahmed El-Hennawy[4]

[1]Department of Pediatrics, Faculty of Medicine, Sohag University, Egypt.
[2]Nuclear Medicine Department, Faculty of Medicine, Sohag University, Egypt.
[3]Department of Pathology, Faculty of Medicine, Sohag University, Egypt.
[4]Department of Pathology, Faculty of Medicine, Cairo University, Egypt.

Abstract

Background

Cholestatic jaundice in infancy is always pathologic and mainly caused by biliary atresia (BA), and neonatal hepatitis (NH). The early discrimination of both conditions is critical for the outcome of BA. We aimed to assess different non-invasive diagnostic tools in differentiating BA from NH.

Materials and Methods

Forty infants (25 boys, 15 girls) with cholestatic jaundice and final diagnosis of BA (n=17), and NH (n=23) were studied retrospectively from January 2015 to December 2017. All patients were subjected to thorough history and complete physical examination. Liver function tests, abdominal ultrasonography, hepatobiliary scintigraphy using (hepatobiliary iminodiacetic acid [HIDA]), and percutaneous liver biopsy were performed for all patients. Finally the accuracy of HIDA scan and liver function tests for differentiating BA from NH, in comparison with histopathological diagnosis, was evaluated.

Results

Acholic stool, absence of gall bladder visualization by ultrasonography and high level of serum gamma-glutamyl transpeptidase (GGT), and positive HIDA scan findings were strong indicators of BA. The accuracy of GGT > 250 IU/L for diagnosis of BA was 92.7 % and that of positive HIDA scan findings was 82.7 %. The diagnostic accuracy for using both parameters was 98.1% (95% CI: 94.9 - 100.0%, p<0.001).

Conclusion

According to the results, BA can be differentiated from NH by non-invasive methods as presence of acholic stool, absent gall bladder by ultrasonography, elevated GGT, positive HIDA scan findings. GGT > 250 IU/L and positive HIDA scan had high accuracy to differentiate BA from NH and combination of both parameters has increased the accuracy to 98.1%.

Key Words: Biliary atresia, Egypt, Hepatobiliary Scintigraphy, Neonatal hepatitis.

*Please cite this article as: Abou-Taleb A, Abdelhameed W, Ahmed ARH, El-Hennawy A. Non-Invasive Diagnostic Methods for Differentiation of Biliary Atresia from Neonatal Hepatitis in Upper Egypt. Int J Pediatr 2019; 7(4): 9265-75.DOI: **10.22038/ijp.2018.36960.3219**

Corresponding Author:

Ashraf Abou-Taleb (M.D), Pediatric Department, Faculty of Medicine, Sohag University, Sohag, PO 82524, Egypt. Fax: +20 934602963.

Email: ashmaabu@yahoo.com AND ashraf_radwan@med.sohag.edu.eg

Received date: Jun.19, 2018; Accepted date: Dec.22, 2018

1- INTRODUCTION

Jaundice is a common presentation in neonates, usually secondary to indirect (unconjugated) hyperbilirubinemia, and mostly not risky to the infant. On the other hand, cholestatic jaundice (conjugated hyperbilirubinemia) is always pathologic and denotes hepatobiliary disorder. Conjugated hyperbilirubinemia warrants proper evaluation as the outcome of some cases is directly affected by timing of intervention(1). Cholestatic jaundice in infancy approximately affects 1 in every 2,500 term infants (2). The recent guidelines (2017) for the evaluation of infants presented with cholestatic Jaundice recommend that, any jaundiced infant after the age of two weeks should be investigated for cholestasis with measurement of total and fractionated serum bilirubin and that an elevated direct serum bilirubin more than 1.0 mg/dl necessitates expedient evaluation by a pediatric gastroenterologist or hepatologist (3). Differential diagnoses of cholestatic jaundice in early infancy include hepatocellular causes as neonatal hepatitis (NH), metabolic diseases (galactosemia, alpha one antitrypsin deficiency, cholestasis associated with parenteral nutrition, and tyrosinemia), paucity of interlobular bile duct, and obstructive causes as biliary atresia (BA), and choledochal cyst. BA and NH together comprise approximately 70% of neonatal cholestasis syndrome (4).

Preoperative differentiation of BA from NH is of crucial importance, as while BA is a surgical emergency, conservative treatment is very effective in the management of almost all NH cases. Nevertheless, there is no single preoperative diagnostic method that can provide a final diagnosis of BA. Although there are a number of diagnostic methods used together to reach a preoperative definitive diagnosis of BA, there is a general lack of agreement about what methods should be used for the diagnosis (5). The diagnostic algorithm used to discriminate BA from medical causes of cholestatic jaundice includes a comprehensive history and physical examination, inspection of stool color, fasting abdominal ultrasonography, liver function tests including gamma-glutamyl transpeptidase (GGT), percutaneous liver biopsy (PLB), and hepatobiliary scintigraphy (HBS) (4). In a systematic review, Lee et al., demonstrated that preoperative liver biopsy, being the most invasive of the different diagnostic methods, is highly specific and sensitive in preoperative diagnosis of BA (5). The aim of this study was to assess the diagnostic accuracy of non-invasive diagnostic tools as liver function test, abdominal ultrasonography, and hepatobiliary scintigraphy to differentiate biliary atresia from NH in comparison with histopathological diagnosis.

2- MATERIALS AND METHODS

2-1. Patients

This was a retrospective study conducted in Pediatric Department, Sohag University Hospital, Upper Egypt in the period from January 2015 to December 2017. Forty consecutive infants (25 boys and 15 girls) with cholestatic jaundice, were included in this study. Cholestasis is defined as a conjugated bilirubin> 1mg/dl, if Total Bilirubin < 5mg/dl or a conjugated bilirubin >20% of Total Bilirubin, if Total Bilirubin > 5mg/dl (3). Infants with cholestatic jaundice and final diagnosis of BA and NH were included in the study. Infants with cholestatic jaundice due to other causes were excluded from the study.

2-2. Ethical Consideration

The protocol of the study was approved by our institution's Ethics Committee in accordance with international agreements. Written informed consent was obtained from the parents of all participants.

2-3. Methods

All patients were subjected to thorough clinical history and complete physical examination with observation of stools color by one of the authors to detect acholic stools. Laboratory studies done for all patients included serum level of bilirubin (total and fractionated), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, GGT, complete blood count, prothrombin (PT) time, partial thromboplastin time (PTT), International Randomization Ratio (INR), urine analysis, reducing substance in urine, and thyroid function tests. After fasting for 4 hours, abdominal ultrasonography was performed for all patients to detect abnormalities of gall bladder or presence of choledochal cyst. HBS using (hepatobiliary iminodiacetic acid [HIDA]), was done for all patients. After assurance of normal coagulation profile, percutaneous liver biopsy was performed for all patients for histopathological diagnosis. Finally, the accuracy of hepatobiliary iminodiacetic acid (HIDA) scan and liver function tests for differentiation of BA from NH, in comparison with histopathological diagnosis, was evaluated.

2-4. HIDA Scan

Before HBS, patients received phenobarbital (5 mg/kg/day) for 5 days to maximize sensitivity of views. After intravenous administration of T Tc 99m - HIDA (200uci\kg) into a peripheral vein, images have been acquired in a rate of one image every second for a total 60 s, then one image every minute for a total of 60 minutes. This is followed by serial static images acquired at 2 h, 4 h and 24 h after radiotracer administration. The HIDA scans were evaluated by an experienced nuclear physician and considered positive for BA if the scans showed absence of radiotracer excretion into the intestine after 24 h.

2-5. Histopathological tissue sections of liver biopsy

Tissue sections of liver biopsies were de-parafinized, rehydrated and stained with either Haematoxylin and Eosin (H&E), or Masson`s trichrome stains. Before Masson`s trichrome staining; the sections were re-fixed in Bouin's solution followed by washing in running water. After incubation in Weigert's iron hematoxylin for 10 min, the sections were incubated in Biebrich acid fuchsin for 10 min, then the color was differentiated by incubation for 15 min in phosphotungstic and phosphomolybdic acids solution. The tissue was stained by aniline blue solution for 10 min; rinsed thoroughly in running water and incubated in acetic acid (1%) for 5 min. The tissue sections were then dehydrated in upgraded alcohol and mounted.

2-6. Statistical analysis

The results were analyzed using IBM-SPSS version 22.0 for Windows; IBM Inc. Mann-Whitney U test was used to compare continuous variables and relationships of categorical groups were measured by Chi-square test. The validity of different parameters for diagnosis of BA was determined by Receiver operating characteristic (ROC) curve. Significant relationships were considered when P-value was <0.05.

3-RESULTS

This study included 40 infants with jaundice presented to pediatric department, Sohag University Hospital, Upper Egypt between January 2015 and December 2017; including 25 boys and 15 girls. The age at presentation ranged from 6 to 115 days with mean (±SD), and median values of 57.03 (± 28.3), and 52.5 days, respectively. One quarter (n= 10) of the investigated infants were neonates (≤ 28 days), and the vast majority (n=37) had a full term gestational age. Consanguinity

among parents was reported in 10 infants. Jaundice was the main leading symptom in all patients; while associated acholic stool, abdominal distention, and itching were recorded in 24, 16, and 2 infants, respectively. On clinical evaluation, the patient's weight ranged between 2.3 and 9 kg with mean (±SD) of 5.1 (±1.7) kg and a median value of 5.0 kg. Evaluation by ultrasonography showed hepatomegaly, splenomegaly and ascites in 19, 9, and 1 children, respectively. The liver has coarse echo pattern in 2 (5%) infants and gall bladder was not visualized in 8 (10%) infants. Laboratory investigations showed that all children had direct hyperbilirubinemia. Considerable rise of serum total bilirubin above 10mg/dl was recorded in 12 (30.0%) of the cases. Liver enzymes were raised in all cases, of which 12 (30 %) and 11 (27.5 %) patients had ALT and AST values above 300 IU, respectively. The mean (±SD) of GGT was 221.5 U/L (±161.2) and the median was 144.5 U/L. Serological screening for hepatitis B and C viruses was negative in all cases. According to histopathological evaluation of liver biopsies, the final diagnosis of NH was established in 23 (57.5%) infants, while BA was recorded in the remaining 17 (42.5%) cases. The main histopathological changes of both conditions are summarized in **Table.1**. Generally, hepatic fibrosis, distortion of liver architecture, mixed inflammatory cell infiltration and moderate to marked cholestasis are significantly more frequent in cases of BA (**Figure.1**). Hepatic necrosis, ballooning, steatosis and giant cells changes were recorded in few cases.

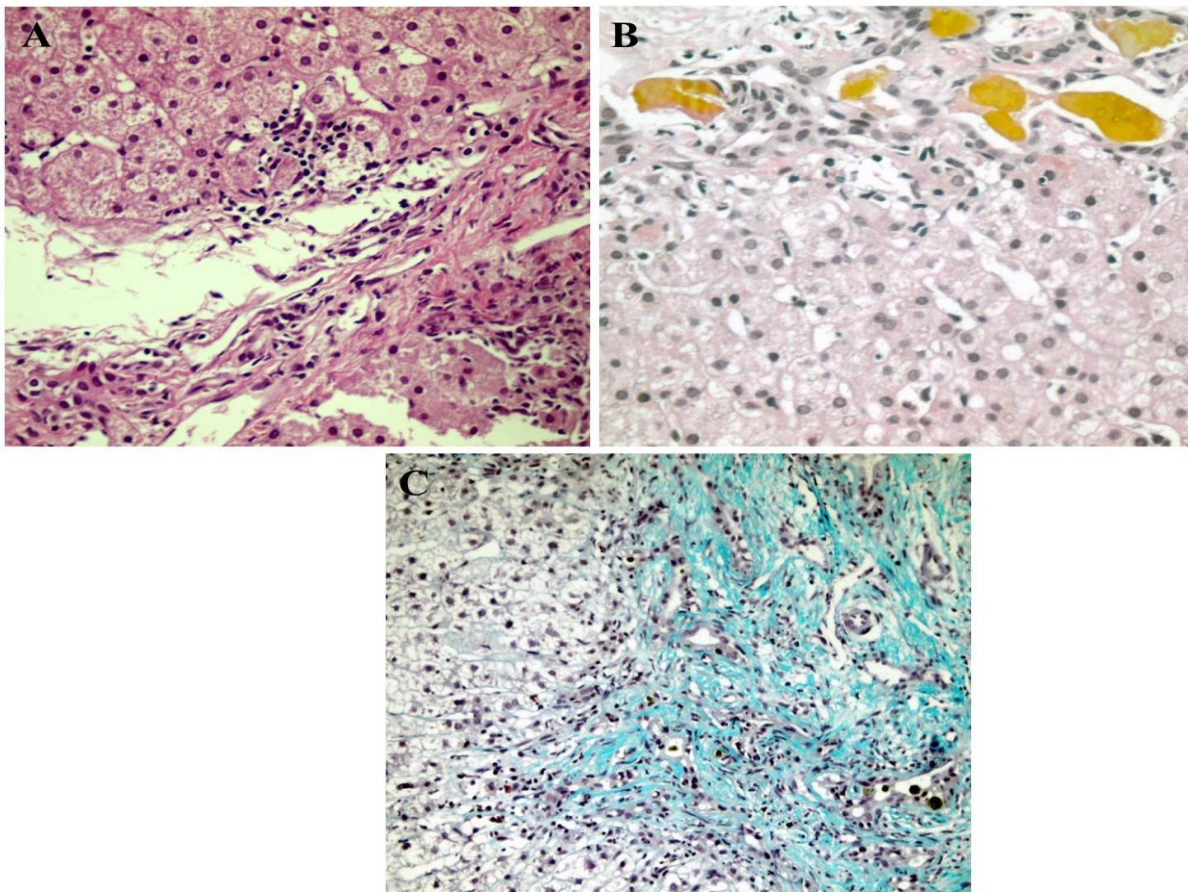

Fig.1: Hematoxylin and Eosin stained sections for portal inflammation (A) in cases of neonatal hepatitis (A) and cholestasis (B) in cases of biliary atresia. Masson trichrome stain (C) for portal fibrosis in cases of biliary atresia. Magnification: x400 for A and B and x200 for C.

Table-1: Histopathological characteristics of the investigated cases.

Parameter	Pathological condition		P- value*
	Biliary atresia Number (%)	Neonatal hepatitis Number (%)	
Liver architecture:			
- Preserved	9 (52.90)	22 (95.65)	0.002
- Distorted	8 (47.05)	1 (4.34)	
Hepatic fibrosis:			
- No	0	15 (65.21)	
- Mild	6 (35.29)	7 (30.43)	0.0001
- Moderate	9 (52.9)	1 (4.34)	
- Marked	2 (11.76)	0	
Intrahepatic cholestasis:			
- Mild	0	4 (17.39)	
- Moderate	4 (23.52)	10 (43.47)	0.038
- Marked	13 (76.47)	9 (39.13)	
Hepatic cell necrosis:			
- Absent	17 (100)	21 (91.30)	0.212
- Mild	0	2 (8.69)	
Inflammatory reaction:			
- Minimal	2 (11.76)	2 (8.69)	
- Mild	7 (41.17)	17 (73.91)	0.19*
- Moderate	6 (35.29)	6 (26.08)	
Inflammatory cells:			
- Lymphocytes	4 (23.52)	20 (86.95)	0.0001
- Mixed	13 (76.47)	3 (13.04)	
Ballooning of hepatocytes:			
- Absent	1 (5.88)	0	0.23
- Present	16 (94.11)	23(100)	
Steatosis of hepatocytes:			
- Absent	16 (94.11)	22(95.65)	0.82
- Present	1 (5.88%)	1(4.34)	
Giant cell change of hepatocytes:			
- Absent	16 (94.11)	18 (78.26)	0.165
- Present	1 (5.88)	5 (21.73)	

Statistical relationships were evaluated by Chi-square test*.

None of these parameters, gender, serum ALT, serum AST, serum total bilirubin level, and serum direct bilirubin level had a predictive diagnostic validity of biliary atresia .On the other hand, acholic stool, absence of gall bladder visualization by ultrasonography, and high serum level of GGT were strong indicators of BA (**Table.2**). Moreover, BA tends to present at a relatively younger age compared to NH, and it is more frequently associated with hepatomegaly. Pre-biopsy assessment by HIDA scan strongly suggested diagnosis of BA in 16 infants, and non-obstructive hepatic disease in the remaining 24 infants (**Figure.2**).

Table-2: Clinical, ultrasonography and laboratory characteristics of the investigated cases

Parameter	Histopathological diagnosis		P-value
	Biliary atresia	Neonatal hepatitis	
Gender: - Females - Males	 -7 -10	 -8 -15	0.68*
Age - Mean (±SD) - Median	 -47.5 (±20.3) -50.0	 -64.1 (±31.6) -60.0	0.09**
Weight - Mean (±SD) - Median	 -4.8 (±134) -4.7	 -5.3 (±2.1) -6.0	0.56**
Stool color - Pigmented - Alcoholic	 0 17	 16 7	0.0001*
Liver size - Normal - Hepatomegaly	 6 11	 15 8	0.06*
Gall bladder by Ultrasonography - Visualized - Not visualized	 9 8	 23 0	0.0001*
ALT (IU) - Mean (±SD) - Median	 -1941 (±118.5) -166	 -228.0 (±103.1) -230.0	0.32**
AST (IU) - Mean (±SD) - Median	 -190.4 (±118.5) -153.0	 -230.9 (±123.5) -213.0	0.25**
Total bilirubin (mg/dl) - Mean (±SD) - Median	 -9.01 (±2.4) -8.7	 -8.2 (±3.1) -7.8	0.29**
Direct bilirubin (mg/dl) - Mean (±SD) - Median	 -7.7 (±2.3) -8	 -6.8 (±2.6) -6.9	0.27**
GGT - Mean (±SD) - Median	 -396.4 (±76.2) -390.0	 -82.19 (±28.6) -80.0	0.0001**

Statistical relationships were evaluated by Chi-square test* or Mann-Whitney test**. SD: Standard deviation; GGT: gamma-glutamyl transpeptidase.

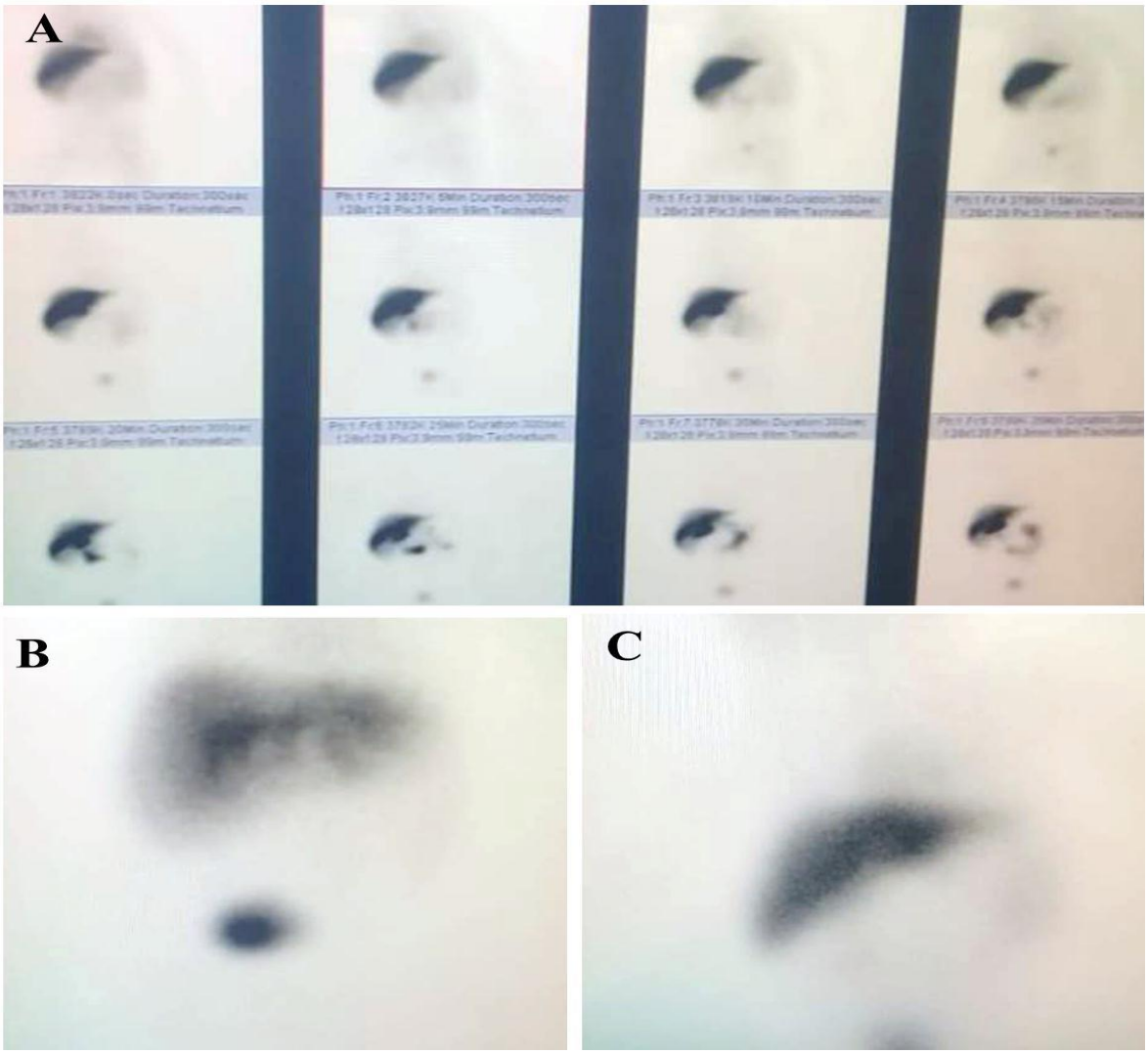

Fig.2: Passage of radiotracer to intestine in cases of neonatal hepatitis (A) while there is no bowel activity after 18 (B) and 24 (C) hours of radiotracer injection in cases of biliary atresia with only renal clearance to urinary bladder could be visualized.

Positive HIDA scan findings were strongly associated with BA compared to standard histopathological diagnosis (Chi-square 16.3, p<0.001). The validity of HIDA scan and serum level of GGT for diagnosis of BA was measured both separately and in combination. Serum level of GGT > 250 IU/L showed a strong diagnostic accuracy of BA (area under the curve [AUC]: 0.927; standard error [SE]: 0.048; 95% confidence interval [CI]: 0.833 – 1.00, p<0.001; **Figure. 3A**). In the same context, receiver operating characteristic [ROC] curve analyses showed a significant validity of HIDA scan positivity for diagnosis of BA (AUC: 0.817; SE: 0.073; 95% CI: 0.673 - 0.961, p=0.001; **Figure. 3B**). There was a strong augmenting validity for the model using both serum GGT level and HIDA scan evaluation for diagnosis of BA (**Figure. 3C**). The diagnostic accuracy for using these two parameters was 98.1% (95% CI: 94.9 - 100.0%, p<0.001).

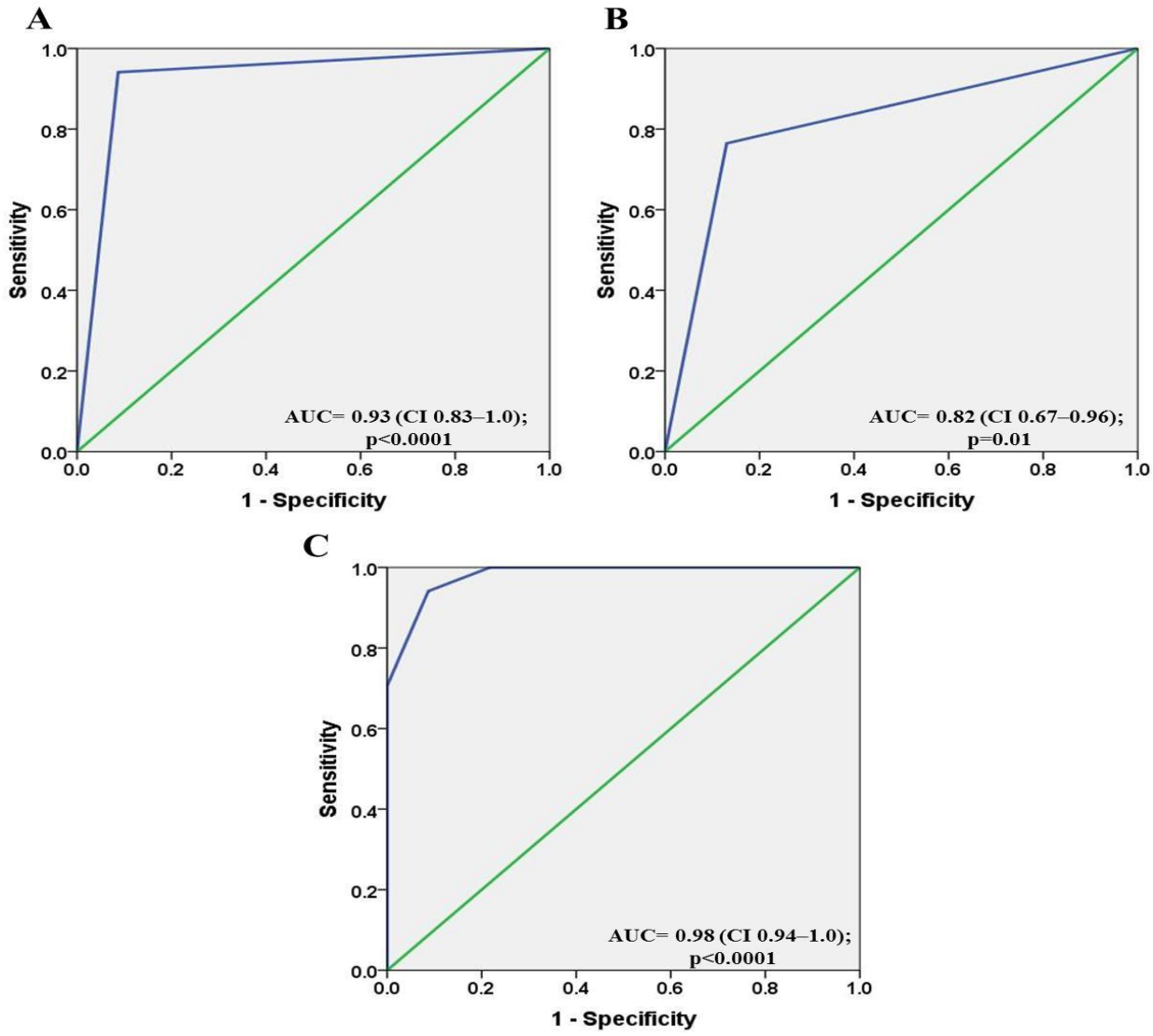

Fig.3: ROC curve for diagnosis of BA using serum gamma glutamyle transpeptidase level (A), HIDA scan positivity (B) and combined serum gamma glutamyle transpeptidase level and HIDA scan findings (C).

4- DISCUSSION

Cholestasis in neonates and infants can be attributed to BA and non- BA etiologies (6). The early diagnosis of BA is mandatory as prognosis is related to timely surgical correction by Kasi portoenterostomy (ideally in the first 6o days of life). So, the main goal of all diagnostic algorithms for cholestatic jaundice is to differentiate BA from medical causes, especially NH. However, no preoperative diagnostic test has 100% diagnostic accuracy (4). The objective of this study was to assess the diagnostic accuracy of different non-invasive diagnostic methods to differentiate BA from NH. The gold standard for diagnosis was liver biopsy and histopathological examination. The study included 40 infants (25 boys and 15 girls) presented with cholestatic jaundice. Twenty-three of them (15 boys, 8 girls) were diagnosed with NH, and 17(10 boys, 7 girls) were diagnosed with BA. The mean age at presentation of all patients was 57.03 (± 28.3) days. BA tends to present at a relatively younger age

compared to NH (mean age at presentation was 47.5±20.3 days for BA versus 64.1±31.6 days for NH). This is in agreement with the results of a study done by Yang et al., whereas age at onset of BA cases was younger than that of NH cases (7). Jaundice is clinically evident when serum bilirubin is 2.5-3 mg /dl, and it is highly recommended to observe the stool color for detection of pale stool in cholestatic jaundice. Screening for BA using stool color cards is currently used in Japan and Taiwan with sensitivity of 95.2% (8). In the present study acholic stool was detected in 24 patients. Of them, 17 had BA (100%), and 7 had NH (30%).

These findings agree with the study done by Dehghani et al., wherein acholic stool was recorded in about 95% of BA cases, and in 56,5% of NH cases (9). Many studies have demonstrated that elevated serum GGT level have high accuracy for differentiation of BA cases from non-BA cases of neonatal cholestasis (10-12). In the current study, high serum level of GGT was a strong indicator of biliary atresia. The mean GGT in BA cases was 396.4 ±76.2 IU/L, while in NH cases it was 82.19±28.6 IU/L (p=0.001).

On the other hand, ALT, AST, serum total bilirubin level, and serum direct bilirubin level had no predictive diagnostic validity of biliary atresia. In the present study, serum level of GGT >250 IU/L showed a strong diagnostic accuracy of biliary atresia (p<0.0001). This was in consistent with the previous study which reported that GGT >300 U/L or a daily increase of 6 U/L can be used to differentiate BA from NH with an accuracy of 85% and 88%, respectively (11).

Abdominal ultrasonographic examination is useful in diagnosis of extrahepatic bile duct obstruction caused by choledochal cyst or gall stones. In addition, it can suggest diagnosis of BA by demonstration of "an absent gall bladder", or the presence of "triangular cord" sign. Many studies have reported high sensitivity and specificity of "triangular cord", and low sensitivity of "absent gall bladder" sign. Despite being operator dependent, abdominal ultrasonography is recommended in evaluation of cholestasis (3, 13). In the current study, the "absent gall bladder" finding by ultrasonography was a strong indicator of BA (p=0.001). There was no detection of "triangular cord" sign, perhaps due to the low experience of our sonographers for detection of this sign. This was in agreement with the results reported by Yang et al. (7). Although no statistically significant difference (p=0.06) was reached, hepatomegaly tends to be detected more in BA cases than NH cases. This finding was consistent with Robie et al., whereas hepatomegaly was recorded in 80% of BA cases and 30% of non-BA (p = 0.07) (14). HBS has been used since the late 1970s to assess patency of biliary tract. It is useful for differentiating BA from non-obstructive causes of cholestasis.

Excretion of the radiotracer into the intestine excludes BA, but absence of excretion of the radiotracer into the intestine does not confirm the diagnosis and further evaluation required (15). In this study, absence of excretion of the radioactive radiotracer into the intestines at 24 hours (positive HIDA scan findings), was highly suggestive of biliary atresia compared to standard histopathological diagnosis (Chi-square 16.3, p<0.001).

This finding was in agreement with Anand et al. who reported that HBS is a simple, noninvasive and accurate diagnostic tool for suspected BA(16). Using ROC curve, the results of this study demonstrated that the overall accuracy of positive HIDA scan findings in diagnosis of BA was 81.7 % (p=0.001). This was in agreement with Dong et al. who reported that the accuracy of HBS in detecting BA was 85.3% (17). Furthermore, Kianifar et al., in a meta-analysis, demonstrated that the overall

accuracy of HBS in differentiating BA and NH was 96% (pooled diagnostic odd ratio: 55.75, AUC: 0.96) (18). Preoperative liver biopsy is the most accurate method for diagnosis of BA, but it is invasive, leading to many complications. So, noninvasive methods are preferred for the early diagnosis. However, they are not as accurate as liver biopsy, so a combination of noninvasive diagnostic methods is a good idea for early differential diagnosis of BA from other causes of neonatal cholestasis (19). In the present study, the combination of serum gamma-glutamyl transferase level and HIDA scan in diagnosis of BA has increased the diagnostic accuracy of these two parameters to 98.1% ($p<0.001$). This was in agreement with the results of a Chinese study which found that serum GGT, combined with other factors, is superior to serum GGT alone in the preoperative diagnosis of BA (10).

4-1. Limitations of the study

This study is limited by being a retrospective single center study. The small number of patients is another weak point in our study.

5- CONCLUSION

In conclusion, the early differentiation of biliary atresia from medical causes of cholestatic jaundice is paramount to prevent adverse consequences. Preoperative liver biopsy is the most accurate method for diagnosis of BA, but it is invasive and leads to many complications. This study demonstrates that BA can be differentiated from NH by the presence of acholic stool, absent gall bladder by ultrasonography, elevated serum GGT, positive HIDA scan findings. Also, BA tends to present at a relatively younger age compared to NH and it is more frequently associated with hepatomegaly. In addition, the results show that the accuracy of GGT > 250 IU/L and positive HIDA scan, to differentiate BA and NH, were 92.7%, 81.7%, respectively. Furthermore, the combination of GGT level and HIDA scan in diagnosis of BA has increased the diagnostic accuracy of these two parameters to 98.1% (95% CI: 94.9 - 100.0%, $p<0.001$).

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Lane E, Murray KF. Neonatal Cholestasis. Pediatr Clin North Am 2017;64(3):621–39.

2. Fischler B, Lamireau T. Cholestasis in the newborn and infant. Clin Res Hepatol Gastroenterol 2014;38(3):263–7.

3. Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, et al. Guideline for the evaluation of cholestatic jaundice in infants: Joint recommendations of the North American society for pediatric gastroenterology, hepatology, and nutrition and the European society for pediatric gastroenterology, hepatology, and nutriti. J Pediatr Gastroenterol Nutr 2017;64(1):154–68.

4. Mandelia A, Lal R, Mutt N. Role of Hepatobiliary Scintigraphy and Preoperative Liver Biopsy for Exclusion of Biliary Atresia in Neonatal Cholestasis Syndrome. Indian J Pediatr 2017;84(9):685–90.

5. Lee JYJ, Sullivan K, El Demellawy D, Nasr A. The value of preoperative liver biopsy in the diagnosis of extrahepatic biliary atresia: A systematic review and meta-analysis. J Pediatr Surg 2016;51:753–61.

6. Verkade HJ, Bezerra JA, Davenport M, Schreiber RA, Mieli-Vergani G, Hulscher JB, et al. Biliary atresia and other cholestatic childhood diseases: Advances and future challenges. J Hepatol 2016;65(3):631–42.

7. Yang JG, Ma DQ, Peng Y, Song L, Li CL. Comparison of different diagnostic methods for differentiating biliary atresia from idiopathic neonatal hepatitis. Clin Imaging 2009;33(6):439–46.

8. Chen, S.-MChen SM, Chang MH, Du JC et al. Screening for Biliary Atresia by

Infant Stool Color Card in Taiwan. Pediatrics 2006;117:1147–54.

9. Dehghani SM, Haghighat M, Imanieh MH, Geramizadeh B. Comparison of different diagnostic methods in infants with Cholestasis. World J Gastroenterol 2006;12(36):5893–6.

10. Dong R, Jiang J, Zhang S, Shen Z, Chen G, Huang Y, et al. Development and Validation of Novel Diagnostic Models for Biliary Atresia in a Large Cohort of Chinese Patients. EBioMedicine 2018;34:223–30.

11. Chen X, Dong R, Shen Z, Yan W, Zheng S. Value of gamma-glutamyl transpeptidase for diagnosis of biliary atresia by correlation with age. J Pediatr Gastroenterol Nutr 2016;63(3):370–3.

12. Lu FT, Wu JF, Hsu HY, Ni YH, Chang MH, Chao CI, et al. Gama Glutamyl Transpeptidase Level As a Screening Marker Among Diverse Etiologies of Infantile Intrahepatic Cholestasis. J Pediatr Gastroenterol Nutr 2014;59(6):695–701.

13. Moyer V, Freese DK, Whitington PF, Olson AD, Brewer F, Colletti RB at al. Guideline for the Evaluation of Cholestatic Jaundice in Infants : Recommendations of the North American Society for Pediatric Gastroenterology , Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2004;39(August):115–28.

14. Robie DK, Overfelt SR, Xie LI. Differentiating biliary atresia from other causes of cholestatic jaundice. Am Surg 2014;80(9):827–31.

15. Malik D, Khan SH, Ali SW, Rather TA, Pakala R, Hassan MU, et al. Comparison of phenobarbitone and ursodeoxycholic acid in drug-augmented hepatobiliary scintigraphy for excluding the diagnosis of obstructive cholestasis in neonatal cholestasis syndrome. Nucl Med Commun 2015;36(8):827–32.

16. Anand SS, Handa RK, Singh J, Sinha I. Hepato-biliary scintigraphy in diagnosis of biliary atresia. Med J Armed Forces India 2006;62:20–1.

17. Dong C, Zhu H yun, Chen Y chao, Luo X ping, Huang Z hua. Clinical Assessment of Differential Diagnostic Methods in Infants with Cholestasis due to Biliary Atresia or Non-Biliary Atresia. Curr Med Sci 2018;38(1):137–43.

18. Kianifar HR, Tehranian S, Shojaei P, Adinehpoor Z, Sadeghi R, Kakhki VRD, et al. Accuracy of hepatobiliary scintigraphy for differentiation of neonatal hepatitis from biliary atresia: Systematic review and meta-analysis of the literature. Pediatr Radiol 2013;43(8):905–19.

19. Wang L, Yang Y, Chen Y, Zhan J. Early differential diagnosis methods of biliary atresia: a meta-analysis. Pediatr Surg Int 2018;34(4):363–80.