



Enlarged hepatic hilar lymph node: an additional ultrasonographic feature that may be helpful in the diagnosis of biliary atresia

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Abstract

Objectives To prospectively assess whether the detection of hepatic hilar lymph nodes (LNs) contributes to the diagnosis of biliary atresia (BA).

Methods A total of 80 jaundiced infants were enrolled in this study and had abdominal ultrasound (US). The hepatic hilar LNs, the gallbladder classification, and the triangular cord (TC) thickness of all infants were evaluated. The area under the receiver operating characteristic curve (AUROC) analysis, *t* tests, and chi-squared tests were used to compare US signs between infants with BA and those without BA.

Results BA was found in 45 patients and excluded in 35 patients. The length of the hepatic hilar LNs in infants with BA (median with interquartile range, 11 mm (8, 13.5)) was significantly greater than that in infants without BA (0 mm (0, 0)) ($p < 0.001$). The AUROCs of the enlarged hepatic hilar LNs, gallbladder classification, and TC thickness were 0.867, 0.894, and 0.832, respectively. The accuracy of LNs (87.5%) in the diagnosis of BA was close to that of the gallbladder classification scheme (88.8%) ($p = 0.049$) and was higher than that of the TC thickness (82.5%) ($p = 0.031$). The enlarged LNs had the highest sensitivity (93.3%) in distinguishing BA from non-BA.

Conclusions The presence of enlarged hepatic hilar LNs is an additional highly sensitive sign for the noninvasive diagnosis of BA. Through the combination of enlarged LNs, gallbladder classification, and TC thickness, most BA could be identified.

Key Points

- An enlarged hepatic hilar LN is an additional US sign for the noninvasive diagnosis of biliary atresia.
- Combining enlarged hepatic hilar LNs, gallbladder classification, and TC thickness, BA could be diagnosed in most infants.

Keywords Biliary atresia · Lymph nodes · Ultrasonography · Gallbladder

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Abbreviations

BA	Biliary atresia
TC	Triangular cord
US	Ultrasonography
LNs	Lymph nodes
HPE	Hepatic portoenterostomy
AUROCs	Area under receiver operating characteristic curves

Introduction

Biliary atresia (BA) is an obliterative fibrosing cholangiopathy of unknown origin that leads to liver cirrhosis and portal hypertension [1]. Early diagnosis of biliary atresia is of great clinical importance because timely surgery can restore bile flow and prevent liver disease worsening [1–3].

In a previous study, we showed that gallbladder abnormalities and triangular cord (TC) thickness were the two most significant features on ultrasonography (US) for the diagnosis of BA [4, 5]. However, these two features were not always present in every BA patient, and the identification of TC signs was considered to be operator-dependent [4]. Elastography is useful for the diagnosis of BA [6, 7], but its diagnostic performance did not exceed that of grayscale US in our previous study [8]. It is still necessary to find new useful US features for the diagnosis of BA to reduce or even preclude the need for hepatobiliary scintigraphy or biopsy.

Pediatric surgeons often observe swelling of the hepatic hilar lymph nodes (hepatic hilar LNs) during the Kasai procedure. Naoya et al revealed that the ratio of both total Treg cells and activate Treg cells were higher in the hepatic hilar LNs of BA patients than those in patients without BA due to the sequestration of Treg cells within the liver or liver draining hilar LNs in BA patients [9]. Bove et al reported that the hepatic hilar LNs removed from infants with BA during hepatic portoenterostomy (HPE) procedures were significantly larger than those obtained at autopsy from non-septic infants [10]. In clinical practice, we occasionally observed enlarged hepatic hilar LNs in infants with BA at US. However, the diagnostic value of enlarged hepatic hilar LNs on US for the diagnosis of BA has not yet been discussed.

The purpose of this study was to prospectively assess whether the presence of hepatic hilar LNs contributes to the diagnosis of BA and to compare and/or combine this sign with previously described US features.

Materials and methods

Patients

This study was approved by the institutional Clinical Research Ethics Committee of Fujian Provincial Maternity and Children's Hospital, and written informed parental consent was obtained from all participants.

Between January 2016 and December 2018, a total of 178 consecutive infants with conjugated hyperbilirubinemia of unknown causes were prospectively evaluated in Fujian Provincial Maternity and Children's Hospital. A total of 98 patients were excluded due to the following reasons: (1) the infant was older than 5 months in age ($n = 3$) and (2) the final diagnosis was unclear ($n = 95$). Finally, 80 patients were included in the study.

US techniques

All patients underwent abdominal ultrasound scanning performed by one operator (Z.J.W.) with more than 7 years of experience with pediatric US. The US equipment used was a

Voluson E8 scanner (GE Medical Systems) that incorporated a 4–8-MHz curvilinear transducer and an 11-MHz linear array transducer.

First, high-frequency transducers (> 10 MHz) were used to detect the hepatic hilar LNs. The hepatic hilar LN was located at the porta hepatis, in front of the main portal vein, around the hepatoduodenal ligament (Fig. 1). The maximal length of the hepatic hilar LN long axis was measured. Those with undetectable hepatic hilar LNs were arbitrarily assigned a length of zero. If the patient had two or more detectable hepatic hilar LNs, only the length of the largest one was used for data analysis.

We also evaluated the following other US signs: the type of gallbladder and the TC thickness.

According to the gallbladder classification scheme, gallbladders were classified into four types by two radiologists (L.Y.Z., with over 7 years of experience; and W.Y.Z., with 1 year of experience): type I, gallbladder not detected; type II, gallbladder detected with the lumen being unfilled or incompletely filled; type III, gallbladder detected with a fully filled lumen and the lumen had a length of up to 1.5 cm; or type IV, gallbladder detected with a fully filled lumen and the lumen had a length of more than 1.5 cm without wall thickening. For type IV, the length and width of the gallbladder were measured on the maximal longitudinal image. The gallbladders of types I, III, and IV with length-to-width ratios of more than 5.2 were used to predict BA. The gallbladders of types II and IV with length-to-width ratios of up to 5.2 were used to predict non-BA [5]. Both radiologists were blinded to all data other than the maximum-length and maximum-width sections of the US gallbladder image.

The TC thickness feature was defined as the thickness of the echogenic anterior wall of the anterior branch of the right

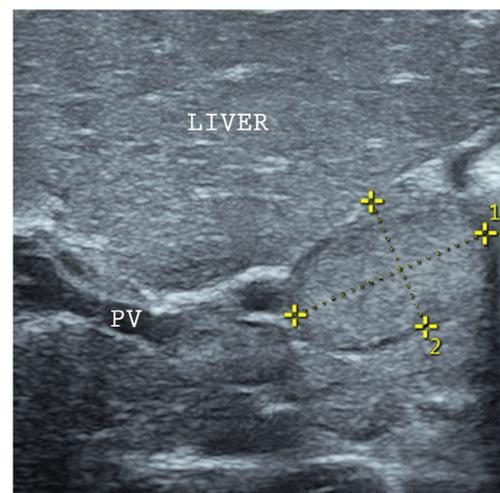


Fig. 1 Longitudinal US images of the enlarged hilar lymph nodes

portal vein that was immediately distal to the right portal vein on a longitudinal image; without including the branch of the hepatic artery; the optimal cutoff value for TC was determined as being more than 2 mm.

The maximum length of LNs, the length and width of gallbladder, and TC thickness were measured at least twice, and the largest measurement was used for data analysis.

Histology

Hall staining was performed on 65 hepatic hilar LNs removed at the time of the Kasai portoenterostomy. We mainly observed whether there were bile-stained macrophages in the hepatic hilar LNs.

Statistical analysis

The continuous variables were first tested for normality by using a Kolmogorov-Smirnov test. The chi-squared test was used to assess categorical data (presence or absence of triangular cord sign and gallbladder classifications). An unpaired *t* test was used to compare the normally distributed continuous variables. A Mann-Whitney *U* test was used to compare the non-normally distributed continuous variables. Isolated variables (enlarged hepatic hilar LN, TC signs, gallbladder classifications) and a combination of ultrasound signs were studied. The diagnostic value of US signs was presented using

sensitivity, specificity, and positive and negative predictive values expressed as percentages.

The areas under the receiver operating characteristic curves (AUROCs) were compared by DeLong's test to evaluate the accuracies of each US parameter in regard to discriminating between BA and non-BA diagnoses. The diagnostic performance was expressed as AUROC.

Statistically significant differences were defined as those with *p* values less than 0.05, and analyses were performed with statistical software (SPSS, version 21).

Results

Clinical characteristics

Eighty patients were included in the study (Fig. 2). The patients were comprised of 45 boys and 35 girls with a mean age of 56.1 days (range, 8–121 days). Of the 80 patients, 45 patients were diagnosed with BA and 35 patients were not diagnosed with BA. Among the 45 infants with BA, the diagnoses were confirmed by means of Kasai surgery and subsequent histological examination. The 35 infants without BA were diagnosed by using intraoperative cholangiography (*n* = 5) or clinical follow-up (*n* = 30). There were no significant differences between BA group and non-BA group in terms of age, alanine aminotransferase, or aspartate aminotransferase level (all *p* > 0.05), but there were differences in the sex (*p* = 0.016), total bilirubin (*p* = 0.001),

Fig. 2 Flow diagram of the inclusion criteria for the patients

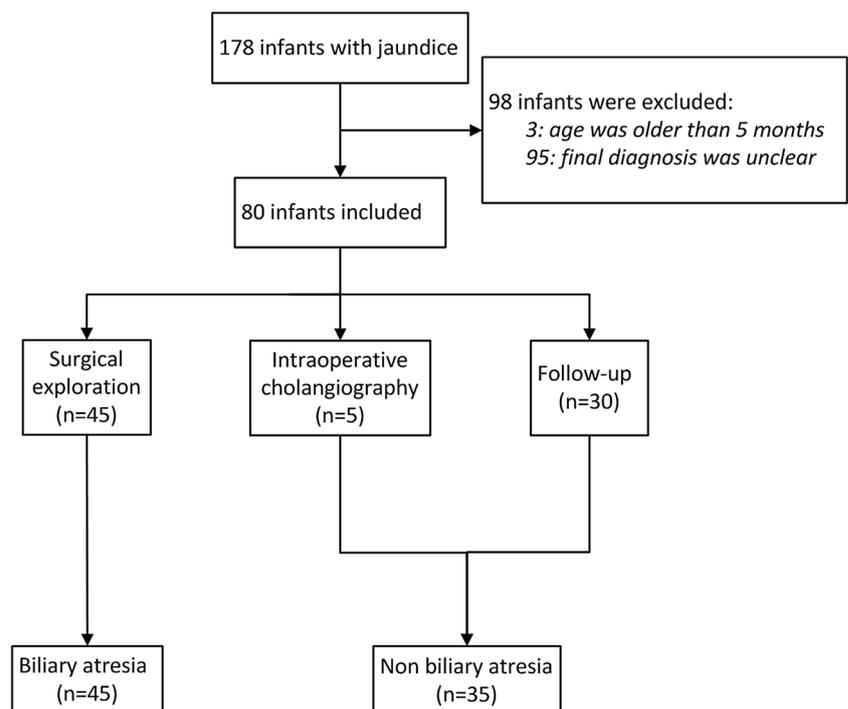


Table 1 Patient characteristics at the time of US examination

Characteristic	Infants with BA (n = 45)	Infants without BA (n = 35)	p value
Patient age (days)*	53.7 ± 23.9 (8–121)	59.1 ± 23.1 (8–121)	0.314
Male-to-female ratio ^{&}	20:25	25:10	0.016
TB (μmol/L)*	188.7 ± 63.0 (77.3–381.8)	135.2 ± 61.4 (12.4–320)	0.001
DB (μmol/L)*	122.9 ± 55.8 (18.2–290.1)	76.8 ± 40.4 (6.1–163.9)	<0.001
ALT (U/L)*	173.7 ± 226.1 (7.1–1313.9)	160.9 ± 178.4 (8.3–911)	0.794
AST (U/L)*	216.3 ± 137.3 (20–616)	201.2 ± 158.2 (35–691)	0.668
GGT (U/L)*	483.7 ± 349.5 (71–1835)	197.7 ± 134.5 (68–666)	<0.001

TB, total bilirubin; DB, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase

*Data are means ± standard deviations, with ranges in parentheses. An unpaired *t* test was used to compare the variables between two groups

[&]Data are numbers of patients. The chi-square test was used to test the sex distribution between two groups

direct bilirubin ($p < 0.001$), and γ-glutamyltransferase levels ($p < 0.001$) (Table 1).

Hepatic hilar LNs

Among the 45 infants with BA, hepatic hilar LNs were detected in 93.3% (42 of 45 patients with a total 65 hepatic hilar LNs). Of the 65 detected hepatic hilar LNs, the median number of specimens obtained from individual patients was 1 (range, 0–3). Among the 35 infants without BA, hepatic hilar LNs were detected in 20% of the patients (7 of 35 patients with a total of 9 hepatic hilar LNs). The optimal cutoff value for hepatic hilar LN long axis was 6.0 mm in the identification of BA, with an AUROC of 0.889. This criteria yielded an accuracy, sensitivity, and specificity of 87.5% (70 of 80), 91.1% (41 of 45), and 82.9% (29 of 35), respectively. On the other hand, the presence of hepatic hilar LN, whatever the long axis length, yielded an AUROC of 0.867 and had an accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 87.5% (70 of 80 patients), 93.3% (42 of 45 patients), 80% (28 of 35 patients), 85.7% (42 of 49 patients), and 90.3% (28 of 31 patients), respectively. There was a statistically significant difference in the detection rate of hepatic hilar LNs between the BA group

and the non-BA group ($p < 0.001$). The length of hepatic hilar LNs in infants with BA (median with interquartile range, 11 mm (8, 13.5)) was significantly higher than that in infants without BA (median with interquartile range, 0 mm (0, 0)) ($p < 0.001$) (Table 2). The length of the hepatic hilar LNs was positively correlated with the infants' bilirubin levels ($p = 0.021$), and the correlation coefficient was 0.271. However, the length of the hepatic hilar LNs was not correlated with the infants' age ($p = 0.056$).

Bile-stained macrophages could be observed in the hepatic hilar LNs of 38 patients with BA (Fig. 3).

Gallbladder classification and TC thickness

Among the 35 infants without BA, 21 had type II gallbladders, 2 had type III gallbladders, and 12 had type IV gallbladders with length-to-width ratios ≤ 5.2 . Among the 45 infants with BA, 5 had type I gallbladders, 4 had type II gallbladders, 18 had type III gallbladders, 15 had type IV gallbladders with length-to-width ratios > 5.2 , and 3 had type IV gallbladders with length-to-width ratios ≤ 5.2 . Based on the gallbladder classification scheme, the accuracy in the identification of BA was 88.8% (71 of 80 patients).

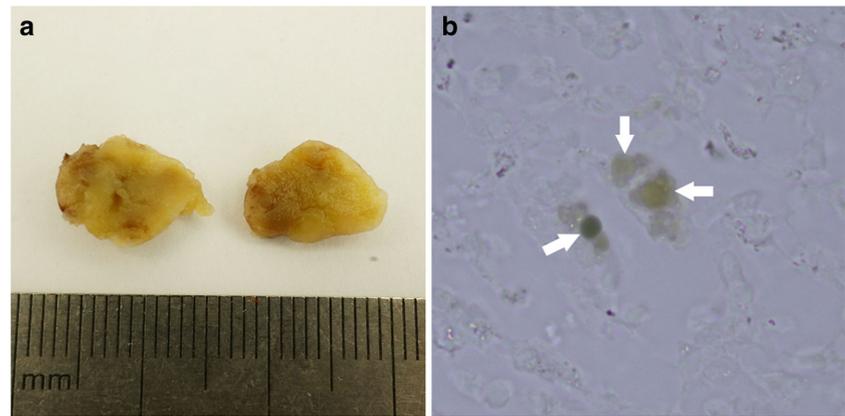
Table 2 Comparison of hepatic hilar lymph nodes between infants with BA and infants without BA

US parameter	Infants with BA (n = 45)	Infants without BA (n = 35)	p value
Hepatic hilar lymph node*	42 (93.3)	7 (20)	<0.001
Hepatic hilar lymph node length (mm) [#]	11 (8, 13.5)	0 (0, 0)	<0.001

*Data are the numbers of patients, with percentages in parentheses. The chi-squared test was used to compare the variable between two groups

[#]Data are medians, with interquartile ranges in parentheses. A Mann-Whitney U test was used to compare the variable between two groups

Fig. 3 Examples of the enlarged hepatic hilar lymph nodes in infants with biliary atresia. **a** A hepatic hilar lymph node removed at the time of the Kasai portoenterostomy. The lymph node was determined to be 11 mm × 8 mm. **b** Bile granules (arrow) in a 67-day-old male infant with biliary atresia. Bile granules appear yellow or green. Hall stain, × 1000



The TC thickness in infants with BA (mean ± standard deviation, 3.0 mm ± 1.1) was significantly higher than that in infants without BA (1.5 mm ± 0.4) ($p < 0.001$). According to the previous study, the optimal cutoff value of the TC thickness was defined as 2.0 mm. This criterion showed that the accuracy in BA diagnosis was 82.5% (66 of 80 patients).

Diagnostic performance of US features

AUROC for each measurable feature in the identification of biliary atresia are listed in Table 3 and Fig. 4. There was no statistical difference between inclusion of a LN > 6 mm threshold (AUROC, 0.889) and the presence of hepatic hilar LN without any threshold (AUROC, 0.867) in the diagnosis of BA ($p = 0.347$). For this reason, only the presence/absence of hepatic hilar LN, more sensitive, was used for the comparison with the other two US features. The AUROC of the gallbladder classification and TC thickness were 0.894 and 0.832, respectively. The combinations of the presence of hepatic hilar LN, gallbladder classification, and TC thickness yielded an AUROC of 0.843 and had an accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 86.3% (69 of 80 patients), 100% (45 of 45 patients), 68.6% (24 of 35 patients), 80.4% (45 of 56 patients), and 100% (24 of 24 patients), respectively. No significant differences in AUROC were found among the three US features or in the combinations of the features (all $p > 0.05$).

Discordance between enlarged hepatic hilar LNs, the gallbladder classification, and TC thickness

Discordance between enlarged LNs and gallbladder classification was found in 20% (16 of 80 patients) (Fig. 5). Among 12 infants with LNs and negative gallbladder classification, 6 infants had BA and 6 patients did not have BA. In contrast, among 4 infants without LNs and positive gallbladder classifications, biliary atresia was diagnosed in 2 and excluded in 2.

Discordance between enlarged LNs and TC thickness was found in 22.5% (18 of 80 patients) of the infants (Fig. 5). Among 14 infants with LNs and TC thicknesses of up to 2 mm, 8 infants had BA and 6 infants did not have BA. In contrast, among 4 infants without LNs and TC thicknesses greater than 2 mm, biliary atresia was diagnosed in 1 and excluded in 3.

Discussion

In this study, we demonstrated that the presence of enlarged hepatic hilar LN is a sign of great value for the identification of BA. For distinguishing BA from non-BA in neonates with jaundice, the accuracy of enlarged LNs (87.5%) was close to that of the gallbladder classification scheme (88.8%) ($p = 0.049$) and was higher than that of TC thickness (82.5%) ($p = 0.031$). Of these three US features, enlarged LNs had the highest sensitivity (93.3%). When the three parameters were combined, the sensitivity could even reach 100%. Since BA is a rare disorder [11–13] with poor outcome, a highly sensitive method for detection is beneficial. Combining enlarged LNs, gallbladder classification scheme, and TC thickness, most infants with BA could be identified with US, potentially without the need for further nuclear scintigraphy. This is why our results are clinically relevant.

Although the cause of biliary atresia is largely unknown, inflammatory infection bile duct damage is generally accepted as the main etiopathogenesis [2, 14–16]. We assume that the swelling of the hepatic hilar LNs might be a secondary change due to prolonged hepatic inflammation and jaundice. In this study, the level of total bilirubin in the BA group was significantly higher than that in the non-BA group. Bilirubin, as a toxin, is not excreted and may lead to inflammatory changes in the liver. Consequently, the hepatic hilar LNs, as liver draining, will phagocytize the bile and enlarge. In the vast majority (38 of 45) of infants with BA, we observed bile-stained macrophages within the LNs and the size of LNs

Table 3 Diagnostic performance of different US parameters in 80 infants with conjugated hyperbilirubinemia

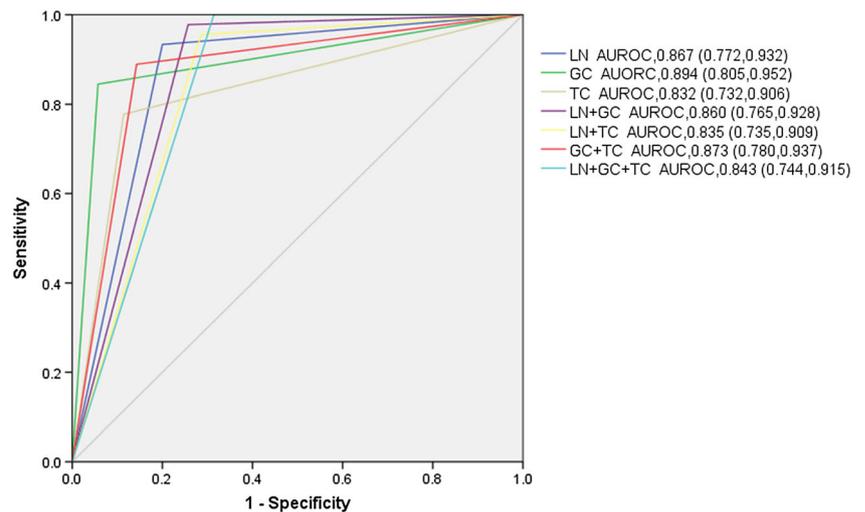
US parameters	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)	AUROC	<i>p</i> value _{1*}	<i>p</i> value _{2*}	<i>p</i> value _{3*}
Enlarged hepatic hilar LN	93.3 (81.7, 98.6)	80 (63.1, 91.6)	85.7 (72.1, 93.6)	90.3 (73.1, 97.5)	87.5 (78.3, 93.3)	0.867 (0.772, 0.932)	NA	0.6039	0.5120
Gallbladder classification	84.4 (70.5, 93.5)	94.3 (80.8, 99.3)	95 (81.8, 99.1)	82.5 (66.6, 92.1)	88.8 (79.8, 94.2)	0.894 (0.805, 0.952)	0.6039	NA	0.1304
TC thickness	77.8 (62.9, 88.8)	88.6 (73.3, 96.8)	89.7 (74.8, 96.7)	75.6 (59.3, 87.1)	82.5 (72.6, 89.4)	0.832 (0.732, 0.906)	0.5120	0.1304	NA
Enlarged hepatic hilar LN and gallbladder classification	97.8 (88.2, 99.9)	74.3 (56.7, 87.5)	83 (69.7, 91.5)	96.3 (79.1, 99.8)	87.5 (78.3, 93.3)	0.860 (0.765, 0.928)	0.8014	0.4362	0.5959
Enlarged hepatic hilar LN and TC thickness	95.6 (84.9, 99.5)	71.4 (53.7, 85.4)	81.1 (67.6, 90.1)	92.6 (74.2, 98.7)	85 (75.4, 91.4)	0.835 (0.735, 0.909)	0.2301	0.2656	0.9416
Gallbladder classification and TC thickness	88.9 (75.9, 96.3)	85.7 (69.7, 95.2)	88.9 (75.1, 95.8)	85.7 (69.0, 94.6)	87.5 (78.3, 93.3)	0.873 (0.780, 0.937)	0.9089	0.4705	0.1357
Enlarged hepatic hilar LN, gallbladder classification and TC thickness	100 (92.1, 100)	68.6 (50.7, 83.1)	80.4 (67.2, 89.3)	100 (82.8, 100)	86.3 (76.9, 92.3)	0.843 (0.744, 0.915)	0.4724	0.2734	0.8110

Data in parentheses are 95% confidence intervals

LN, lymph node; TC, triangular cord

*Only AUROCs were compared by the DeLong test. The first column of *p* value was the result of the AUROC of enlarged hepatic hilar lymph node compared with the AUROCs of the other US parameters. The second column of *p* value was the result of the AUROC of the gallbladder classification compared with the AUROCs of the other US parameters. The third column of *p* value was the result of the AUROC of the triangular cord thickness compared with the AUROCs of the other US parameters

Fig. 4 Comparison of ROC curves for different parameters alone or combined in the determination of biliary atresia. Data in parentheses are 95% confidence intervals. LN, enlarged hepatic hilar lymph node; GC, gallbladder classification; TC, triangular cord

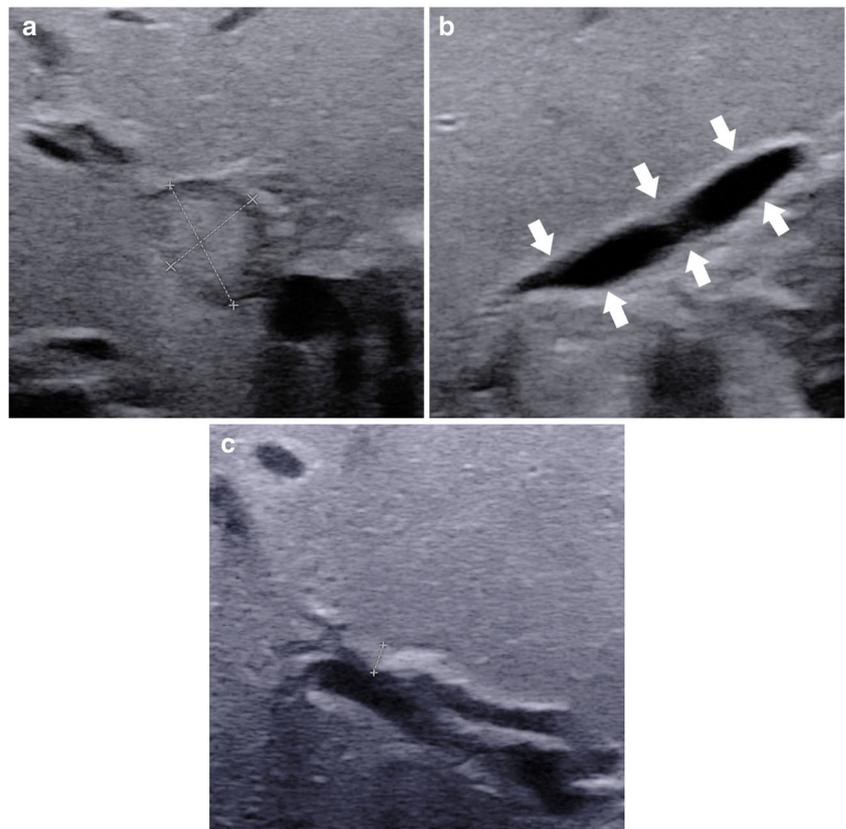


increased altogether with total bilirubin levels. Bove et al suggested that the main factor contributing to hepatic hilar LN size was the variable expansion of the interfollicular cortical lymphoid tissue plus reactive sinusoidal histiocytosis with a mixture of hematopoietic precursors and bile-stained macrophages [9]. They also suggested that the reactivity of the hepatic hilar LNs was correlated with the time of liver transplantation after HPE [9]. The size of the hepatic hilar LN may reflect the degree of obstruction of the BA and the activity

of the macrophages and also be related to the outcome after the Kasai portoenterostomy.

The TC sign had the lowest performance in the diagnosis of BA in this study, with an accuracy of 82.5% and a rather low sensitivity of 77.8%. Identifying the TC sign still remains a subjective task. The gallbladder classification scheme showed the highest accuracy (88.8%) and AUROCs (0.894). However, in this study, 5 patients with BA and detectable hepatic hilar LNs were false-negatives of gallbladder

Fig. 5 A 53-day-old male infant with biliary atresia. **a** A hepatic hilar lymph node (calipers) in the infant with biliary atresia. The size of the lymph node was determined to be 10 mm × 8 mm. **b** A type II gallbladder (arrows) with hyperechogenic mucosa. **c** A triangular cord (calipers) thickness of 1.5 mm in the same infant



classifications as well as false-negative of TC signs. This indicates that the combination of enlarged hepatic hilar LNs, gallbladder classification, and TC thickness helps to diagnose more BA cases with US. Other two US features, hepatic artery enlargement and the presence of hepatic subcapsular flow, have been reported in the diagnosis of BA in some studies [4, 17–19]. They were not routinely assessed in our institution.

In this study, the hepatic hilar LNs of 35 infants without BA were assessed by only US examination. No further examination was used to verify the status of the hepatic hilar LNs, such as magnetic resonance imaging or surgery exploration, because these patients had no indications for further examinations. For undetectable hepatic hilar LNs, we defined their length as zero, which may cause errors in comparing the length of hepatic hilar LNs between the BA group and the non-BA group. With the improvements of US devices, we can detect the slightly enlarged lymph nodes more than ever, so that there would be risk of false-positive when using the presence/absence of hilar LN as diagnostic criterion. In a prospective view, it would be better to work up a cutoff value of hilar LN length, which is less valuable in the current study, to more accurately differentiate BA from non-BA with a large sample of jaundice infants. Besides, other nonspecific causes, such as TORCH (toxoplasmosis, rubella, CMV, hepatitis) infections, can also cause hepatic hilar LN enlargement. However, the inflammation caused by BA is usually more severe, which may lead to LNs to be larger than in other liver infections or inflammations.

There were some limitations in our study. First, this is a single-institution study, which may introduce biases like US interpretation. Second, the number of patients was small with a potential impact on statistical validity.

In conclusion, the presence of enlarged hepatic hilar LNs is an additional US sign with high sensitivity for the noninvasive diagnosis of biliary atresia, and through the combination of enlarged hepatic hilar LNs, gallbladder classification scheme, and TC thickness, most infants with biliary atresia could be identified with US only.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Min Liu.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology

- Prospective
- Diagnostic study or prognostic study
- Performed at one institution

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