



Practical approach to imaging diagnosis of biliary atresia, Part 1: prenatal ultrasound and magnetic resonance imaging, and postnatal ultrasound

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Abstract

We present a practical approach to imaging in suspected biliary atresia, an inflammatory cholangiopathy of infancy resulting in progressive fibrosis and obliteration of extrahepatic and intrahepatic bile ducts. Left untreated or with failure of the Kasai procedure, biliary atresia progresses towards biliary cirrhosis, end-stage liver failure and death by age 3. Differentiation of biliary atresia from other nonsurgical causes of neonatal cholestasis is challenging because there is no single method for diagnosing biliary atresia, and clinical, laboratory and imaging features of this disease overlap with those of other causes of neonatal cholestasis. Concerning imaging, our systematic literature review shows that ultrasonography is the main tool for pre- and neonatal diagnosis. Key prenatal features, when present, are non-visualisation of the gallbladder, cyst in the liver hilum, heterotaxy syndrome and irregular gallbladder walls. Postnatal imaging features have a very high specificity when present, but a variable sensitivity. Triangular cord sign and abnormal gallbladder have the highest sensitivity and specificity. The presence of macro- or microcyst or polysplenia syndrome is highly specific but less sensitive. The diameter of the hepatic artery and hepatic subcapsular flow are less reliable. When present in the context of acholic stools, dilated intrahepatic bile ducts rule out biliary atresia. Importantly, a normal US exam does not rule out biliary atresia. Signs of chronic hepatopathy and portal hypertension (portosystemic derivations such as patent ductus venosus, recanalised umbilical vein, splenomegaly and ascites) should be actively identified for — but are not specific for — biliary atresia.

Keywords Biliary atresia · Imaging · Infant · Magnetic resonance imaging · Recommendations · Review · Ultrasound

Introduction

Biliary atresia is an important cause of obstructive jaundice in infants, causing progressive fibrosis and obliteration of extrahepatic and intrahepatic bile ducts, resulting in biliary cirrhosis in the absence of early surgery. Jaundice with pale stools and dark urine are present within the first days or weeks after birth. The prevalence of biliary atresia ranges from 1 in 5,000 to 1 in 20,000 depending on the geographic area, with the highest prevalence reported in Taiwan [1–3]. Biliary atresia

aetiology is unknown and different causes were proposed including viral infections, genetic factors or toxins [4]. There are two forms of biliary atresia: the non-syndromic form, accounting for about 80% of cases; and the syndromic form, also called biliary atresia splenic malformation syndrome, accounting for about 20% of cases. The syndromic form is associated with polysplenia, intestinal malrotation, preduodenal portal vein, absent inferior vena cava, aberrant hepatic artery and abdominal heterotaxia [5]. Whatever the form, there are different subtypes of biliary atresia according to the extent of fibrosis on extrahepatic bile ducts and the presence of a cyst of the extrahepatic bile duct. In all cases intrahepatic bile ducts are fibrotic, explaining the absence of bile duct dilatation despite complete obstruction [6] (Fig. 1). The histology is characterised by bile duct proliferation, bile plugs, portal or

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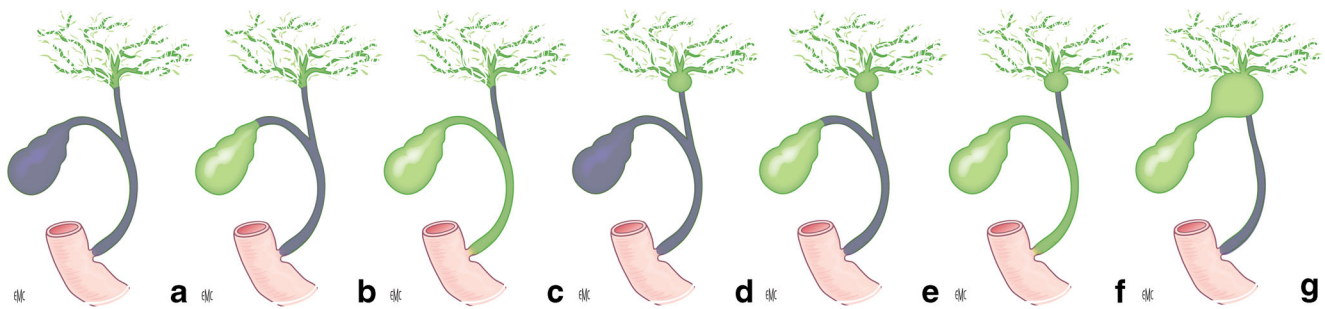


Fig. 1 Different types of biliary atresia — in grey the obstructed bile ducts or gallbladder, in green the patent parts. **a** Complete atresia of the extrahepatic bile duct and the gallbladder. This is the most frequent type, accounting for about 2/3 of patients. **b** Patent gallbladder with atretic cystic duct and extrahepatic bile duct. **c** Patent gallbladder, cystic duct

and choledochus with atretic main common bile duct. **d–g** Cystic forms with macrocyst at the liver hilum and variable atresia of the gallbladder and the extrahepatic bile ducts. Note that intrahepatic bile ducts are always pathological; hence, they do not display dilation. With permission from Pariente et al. [6]

perilobular fibrosis, edema and preservation of the basic hepatic lobular architecture [7, 8]. Histology is not specific, and disorders such as parenteral-nutrition-associated cholestasis, cystic fibrosis and α -1-antitrypsin deficiency can mimic biliary atresia. Liver biopsy specimens obtained before 6 weeks of age might be indistinguishable from neonatal hepatitis [8–10]. If left untreated, children with biliary atresia die within the first years of life by complications of biliary cirrhosis and end-stage liver disease. The primary treatment is surgery, the Kasai hepatportoenterostomy, which consists of resection of the choledochal remnants, gallbladder and portal plate and construction of a jejunal Roux-en-Y anastomosis or cholecystostomy to restore biliary drainage. If children with biliary atresia are operated within the first 60 days of age, bile flow can be established in 70% of cases; in those operated after 90 days of age, sufficient bile flow is achieved in only 20% of cases [11]. Liver transplantation is performed if Kasai hepatportoenterostomy fails or for advanced cirrhosis. Prompt diagnosis is the main goal of imaging, considering the paramount importance of early surgical treatment, ideally between 30 days and 60 days of age. Yet, differentiation of biliary atresia from other nonsurgical causes of neonatal cholestasis is challenging. Gamma glutamyl transpeptidase is an important biomarker in the differential diagnosis of neonatal cholestasis, showing higher levels in children with biliary atresia than those without biliary atresia [12]. Ultrasound (US), MR cholangiopancreatography, hepatobiliary scintigraphy, liver percutaneous biopsy, percutaneous cholecysto-cholangiography and endoscopic retrograde cholangiopancreatography are used for biliary atresia diagnosis, but surgery with intraoperative cholangiography and biopsy is the reference standard for diagnosis. In this study, we systematically reviewed the relevant literature regarding the use of US in the diagnosis of biliary atresia and provide an accurate pooled estimate of the US diagnostic performance. We also reviewed the literature to analyze the accuracy of other imaging methods of biliary atresia. Based on this literature review and after discussions within the European Society

of Paediatric Radiology (ESPR) abdominal task force, we propose a diagnostic pathway for children with suspected biliary atresia.

Literature search

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. In December 2018 two independent authors (M.N. and M.B.D.) searched on PubMed all articles published from January 1999 to December 2018. Keywords included (triangular cord or gallbladder or ultrasound or US) AND (biliary atresia). The first selection was based on the title and abstract. Eligible articles were those reporting in the abstract, or likely in the text, true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN). Eligible articles were read in full and references were hand-searched for further eligibility. Disagreement was settled by discussion and consensus. Only English articles with at least 10 biliary atresia patients using surgery as the reference standard for biliary atresia diagnosis were considered. We matched author names and affiliations to avoid data duplication, and we included only the most recent or complete study. No papers were dismissed because of children's age.

In December 2019 two independent reviewers (M.N. and M.B.D.) searched on PubMed all articles published from January 1999 to December 2019. Keywords included (prenatal diagnosis) AND (biliary atresia). All relevant English-language papers were included.

Data were extracted by the same two readers, while discrepancies were discussed by consensus. A 2×2 contingency Table (TP, TN, FP and FN) was obtained independently for each of the US characteristics reported, and if more than one type of gallbladder abnormality was included, only the most frequent in the study was adopted for calculating data. Forest plot, summary receiver operating characteristic (sROC) curve, sensitivity, specificity, positive likelihood ratio (LR+),

negative likelihood ratio (LR⁻) and diagnostic odds ratio (DOR) for each US sign were calculated if at least four studies were eligible. Statistical analysis was performed using R software (version 3.3.3, package metaphor in R; R Foundation for Statistical Computing, Vienna, Austria).

Review of reported findings

Prenatal diagnosis

Seventy-seven studies regarding prenatal diagnosis were identified for initial review. On the basis of title or abstract, 66 papers were excluded and 11 papers [13–23] were identified as relevant.

Prenatal diagnosis of biliary atresia is quite rare. Reported prenatal signs in foetuses with biliary atresia are non-visualisation of the gallbladder, cyst in the liver hilum, heterotaxy syndrome and irregular gallbladder walls [13–20, 22, 23]. Persistent non-visualisation of foetal gallbladder is rare, and 15–43% of cases with this condition have isolated gallbladder agenesis, a benign condition [22]. Persistent non-visualisation of foetal gallbladder could be associated with other abnormalities (such as renal agenesis, hydronephrosis, cerebral ventricular dilatation, chromosomal anomalies [particularly Trisomy 21], cystic fibrosis, biliary atresia and multiple malformations) [15, 22, 23]. Prenatal hepatic cysts have been reported in the context of biliary atresia. The main differential diagnosis is a choledochal cyst. Morel et al. [19] reported a case of prenatal biliary atresia characterised by irregular gallbladder wall associated with a cyst of the extrahepatic biliary tract. Prenatal differentiation between cystic biliary atresia and choledochal cyst is most often impossible

because of the difficulty of showing intrahepatic bile duct dilatation (Fig. 2), which is either not yet present or not visible because of poor spatial resolution. Postnatal diagnosis is based on intrahepatic bile duct dilatation associated with choledochal cyst. US markers of left heterotaxy, especially in the presence of polysplenia, should raise the possibility of biliary atresia splenic malformation syndrome (Fig. 3). MRI is not specific but could help in visualising the gallbladder, characterising a heterotaxia syndrome and searching for bile duct dilatation in the context of cyst at the liver hilum [21].

Neonatal ultrasound evaluation

We identified 599 studies for initial review. On the basis of title or abstract we excluded 553 papers and considered 46 papers to be relevant. After full review of the 46 articles, we found that 20 papers [24–43] fulfilled all the inclusion criteria; these papers comprised 1,906 infants with an age range of 3–360 days (Table 1) [24–43]. The following US signs were evaluated: the triangular cord sign, gallbladder abnormalities, cysts, common bile duct visibility, hepatic subcapsular flow, hepatic artery enlargement, and polysplenia syndrome. Table 2 presents a summary of diagnostic performances of several US features in our meta-analysis [24–43].

Triangular cord sign

Triangular cord sign consists of the obliterated fibrous ductal remnant and was first described by Choi [44] and further by Lee [29] and colleagues as the thickness of the echogenic anterior wall of the anterior branch of the right portal vein just distal to the right portal vein on a longitudinal image without including the right hepatic artery. Other authors evaluated for

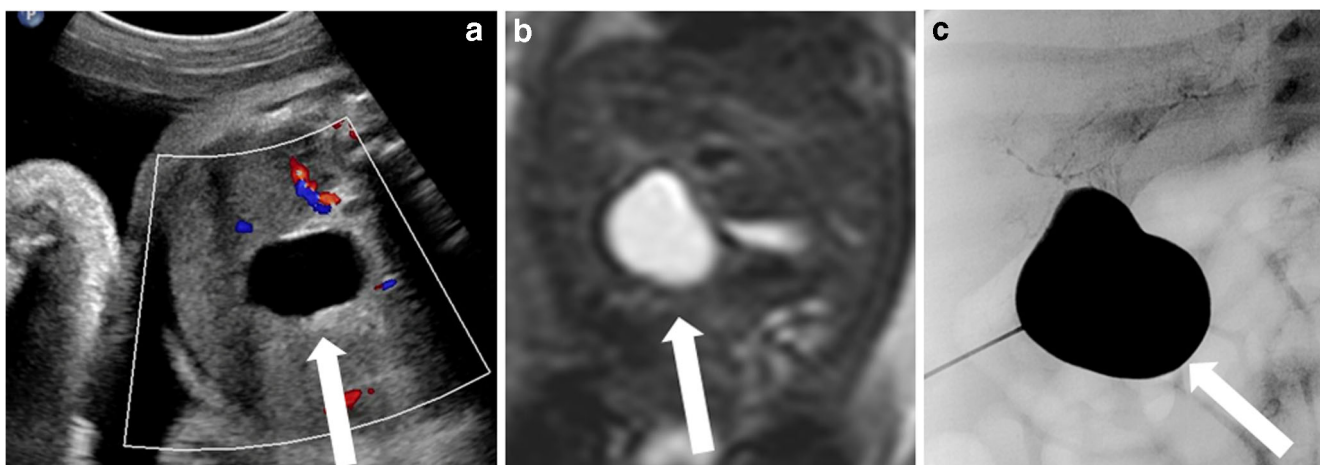
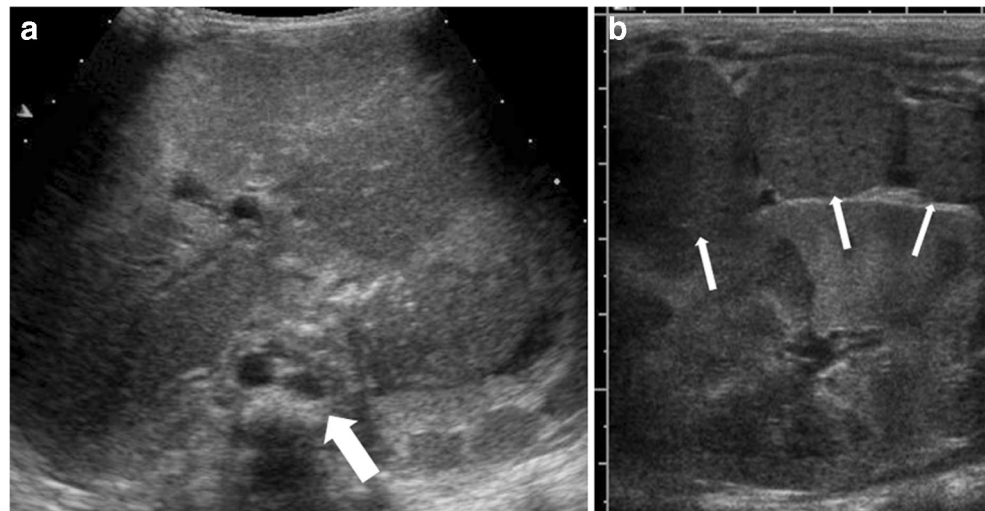


Fig. 2 A female foetus with a cystic form of biliary atresia at 33 weeks of gestation and at 12 days old. **a**, **b** Foetal axial US with color Doppler (**a**) and coronal T2-weighted MR image (**b**; repetition time/echo time [TR/TE] 5,000/100 ms) show a macrocyst at the liver hilum (arrows) and non-visualisation of gallbladder. **c** Postnatal percutaneous transhepatic cysto-

cholangiography shows the macrocyst (arrow) communicating with very abnormal atretic intrahepatic bile ducts, with no opacification of the extrahepatic bile duct and the duodenum, confirming the diagnosis of cystic biliary atresia

Fig. 3 Syndromic biliary atresia in a 5-month-old girl. **a** Axial US image shows interrupted inferior vena cava with azygos continuation (*arrow*). **b** Sagittal US image shows polysplenia (*arrows*)



the triangular cord sign anterior to or near the bifurcation of the portal vein measured both in transverse and longitudinal scans. Triangular cord sign is usually reported positive if >3 – 4 mm, and the variability of its measurements is caused by the positioning of the measurement (Fig. 4). There is no consensus in the literature on how or where to measure, or on whether to include the hepatic artery. Biliary atresia is a progressive disease, as supported by Hwang et al. [45], who showed that triangular cord sign was present in 17% of infants younger than 30 days and 56% in the older group. Figure 5 shows the forest plots and sROC curve of the 19 papers using triangular cord sign for biliary atresia diagnosis included in our meta-analysis [24–41, 43]. Table 2 presents the diagnostic performance of triangular cord sign, which shows the highest diagnostic odds ratio (40.2) among the signs in biliary atresia, with intermediate sensitivity (0.68) and high specificity (0.95). Only two papers included infants younger than 90 days: Tan Kendrick et al. [26] reported a triangular cord sign sensitivity of 84% and specificity of 100% (31/217 cholestatic infants with biliary atresia); Mittal et al. [37] reported that triangular cord sign has a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 23.3%, 97.1%, 77.8% and 74.4%, respectively (30/99 cholestatic infants with biliary atresia).

Gallbladder abnormalities

Several gallbladder abnormalities associated with biliary atresia have been reported (Fig. 6):

- absence of visibility of the gallbladder lumen (which is different from gallbladder agenesis because at surgery the fibrotic remnant of the gallbladder is found);
- small gallbladder with a cut-off length <15 – 19 mm, according to different authors;
- abnormal shape and wall of the gallbladder; and

- no emptying of the gallbladder after feeding.

Figure 7 shows the forest plots and the sROC curve of the 17 papers using gallbladder abnormalities for biliary atresia diagnosis included in our meta-analysis [24–28, 30, 32, 33, 35–43]. Table 2 summarises the diagnostic performances of gallbladder abnormalities, which showed a good diagnostic odds ratio (16.5) among the signs in biliary atresia, with high sensitivity (0.79) and specificity (0.81). Figure 8 shows the forest plots and the sROC curve of the four papers included in our meta-analysis that used absence of the gallbladder for biliary atresia diagnosis [30, 36, 37, 43]. Table 2 summarises the diagnostic performance of gallbladder absence, which showed a good diagnostic odds ratio (17.5) among the signs in biliary atresia, with very low sensitivity (0.20) and very high specificity (0.98). Figure 9 shows the forest plots and the sROC curve of the four papers included in our meta-analysis that used gallbladder length abnormality for biliary atresia diagnosis [30, 33, 38, 39]. Table 2 summarises the diagnostic performances of gallbladder length, with a low diagnostic odds ratio (10.1) among the signs in biliary atresia, and with intermediate sensitivity (0.72) and good specificity (0.79).

Gallbladder abnormalities were common in infants in both biliary atresia age groups — younger and older than 30 days — without a statistically significant difference among the various abnormalities [45]. It is crucial to remember that a normal gallbladder does not rule out biliary atresia (Fig. 10). Irregular and thickened gallbladder wall might be a helpful sign for biliary atresia in infants with normal gallbladder length. Only three series [27, 30, 36] evaluated the diagnostic performance of irregular gallbladder wall as an isolated sign and reported sensitivity ranging from 0.50 to 0.91 and specificity ranging from 0.91 to 0.95. Tan Kendrick et al. [26] defined the “gallbladder ghost triad” as atretic gallbladder length (outer-to-outer wall) <1.9 cm; thinned or lack of smooth/complete

Table 1 Characteristics of included US postnatal series

Authors	Year	Country	First author's department	Prospective design	Total Patients	Patients with BA	Mean patient age or range, in days	US features	Reference standard
Park [24]	1999	Korea	Pediatric surgery	Yes	79	25	16–150	TC GBA	Surgery
Kotb [25]	2001	Egypt	Pediatrics and radiology	Yes	65	25	32–161	TC GBA	Percutaneous liver biopsy + surgery
Tan Kendrick [26]	2003	Singapore	Diagnostic imaging	Yes	217	31	14–84	TC GBA ghost triad HA	Surgery
Visutaratna [27]	2003	Thailand	Radiology	No	46	22	19–139	TC GBA TC+GBA	Surgery or liver biopsy
Kanegawa [28]	2003	Japan	Radiology	Yes	55	29	53.6, 8–144	TC GBA	Surgery
Lee [29]	2003	Korea	Diagnostic imaging	No	86	20	66, 5–210	TC	Surgery
Humphrey [30]	2007	UK	Radiology	Yes	90	30	48.5, 18–143	TC GBA CBD absence	Surgery
Kim [31]	2007	Korea	Radiology	Yes	85	38	61, 13–138	TC CBD absence HA>1.5 mm HA:PV ratio >0.45	Surgery
Takamizawa [32]	2007	Japan	Surgery	No	85	48	47, 4–144	TC GBA	Surgery
Lee [33]	2009	Korea	Radiology	No	64	29	51, 3–91	TC GBA HSF	Surgery
Imanieh [34]	2010	Iran	Pediatric gastroenterology	No	58	10	46, 30–120	TC	Surgery
Sun [35]	2011	China	Ultrasound	No	204	151	16–360	TC GBA TC+GBA	Surgery
Aziz [36]	2011	USA	Radiology and biomedical imaging	No	35	15	3–139	TC GBA	Surgery
Mittal [37]	2011	India	Radiologic diagnosis and imaging	Yes	99	30	13–89	TC GBA CBD absence HA>1.5 mm HA:PV ratio >0.45 TC+GBA	Surgery
El-Guindi [38]	2013	Egypt	Pediatric hepatology	Yes	76	27	69.5	TC, GBA, HA>2.1 mm, HSF	Surgery
El-Guindi [39]	2014	Egypt	Pediatric hepatology	Yes	60	30	64	TC GBA HA>2.1 mm HSF HA:PV ratio >0.45	Surgery
Hanquinet [40]	2015	Switzerland	Pediatric radiology	No	20	10	52.1	TC, GBA	Surgery
Lee [41]	2015	Korea	Radiology	No	100	46	60, 3–129	TC, GBA, CBD visualization, HA and PV diameter	Surgery
Ağm [42]	2016	Turkey	Pediatric gastroenterology	No	61	34	59	GB not visualized or <1.9 cm	Surgery
Koob [43]	2017	France	Pediatric radiology	No	321	193	55.1, 1 day–8 months	GBA, TC, polysplenia syndrome, cysts at the porta hepatis or in the hepatic pedicle, portal hypertension	Surgery or percutaneous transhepatic or endoscopic retrograde cholangiography

BA biliary atresia, CBD common bile duct, GBA gallbladder abnormality, HA hepatic artery, HSF hepatic subcapsular flow, PV portal vein, TC triangular cord sign

Table 2 Meta-analysis of US features for the diagnosing biliary atresia

US feature	Number of studies [ref]	Sensitivity ^a	Specificity ^a	Diagnostic odds ratio ^a	Positive likelihood ratio (LR+) ^a	Negative likelihood ratio (LR-) ^a
Triangular cord sign (TCS)	19 [24–41, 43]	0.68 (0.57–0.78)	0.95 (0.92–0.97)	40.2 (20.8–70.8)	13.0 (8.3–19.7)	0.34 (0.23–0.46)
Gallbladder abnormality (GBA)	17 [24–28, 30, 32, 33, 35–43]	0.79 (0.70–0.86)	0.81 (0.73–0.86)	16.5 (8.1–30.1)	4.2 (2.9–5.9)	0.27 (0.17–0.38)
Gallbladder absence	4 [30, 36, 37, 43]	0.20 (0.13–0.29)	0.98 (0.93–1.00)	17.5 (4.0–50.1)	14.2 (3.4–40.5)	0.81 (0.73–0.88)
Gallbladder length	4 [30, 33, 38, 39]	0.72 (0.59–0.81)	0.79 (0.70–0.86)	10.1 (5.5–16.9)	3.5 (2.5–5.0)	0.36 (0.24–0.50)
TCS+GBA	5 [24, 27, 32, 35, 37]	0.87 (0.51–0.97)	0.90 (0.68–0.86)	99.0 (7.8–441.0)	10.0 (2.7–28.8)	0.19 (0.03–0.54)
Hepatic artery enlargement	4 [31, 37–39]	0.82 (0.71–0.89)	0.70 (0.51–0.84)	12.8 (3.1–36.1)	2.9 (1.5–5.3)	0.28 (0.14–0.51)

ref reference numbers

^a Values in parentheses are 95% confidence intervals

echogenic mucosal lining and indistinct wall; and knobby, irregular or lobular gallbladder contour. The authors, using the search “gallbladder ghost triad” in a population younger than 90 days, found a sensitivity of 97% and a specificity of 100%. Mittal et al. [37] found in a population younger than 90 days that sensitivity, specificity, PPV and NPV of an abnormal gallbladder were 83%, 83%, 68% and 92%, respectively; for non-contractility of the gallbladder, these percentages were 87%, 73%, 51% and 94%, respectively.

Combined triangular cord sign and gallbladder abnormalities

Figure 11 shows the forest plots and the sROC curve of the five studies included in our meta-analysis that used a combination of triangular cord sign and gallbladder abnormalities for biliary atresia diagnosis [24, 27, 32, 35, 37]. Table 2 summarises diagnostic performance of the combination of triangular cord sign and gallbladder abnormalities, which showed

the best diagnostic odds ratio (99.0), with very high sensitivity (0.87) and specificity (0.90).

Cysts

Two types of cysts associated with biliary atresia were reported in the literature:

- macrocysts along the hilar pediculum with a diameter ranging 0.5–4.0 cm [46]; and
- microcysts located at the confluence of the intrahepatic bile ducts, at the porta hepatis, in the same area of the triangular cord sign, and a lot smaller in size (less than 0.5 cm) [47].

Macrocysts are reported in the cystic form of biliary atresia and can also be seen on prenatal diagnosis [43]. The differential diagnosis of cystic biliary atresia is a choledochal cyst; the latter is often associated with intrahepatic bile duct dilatation

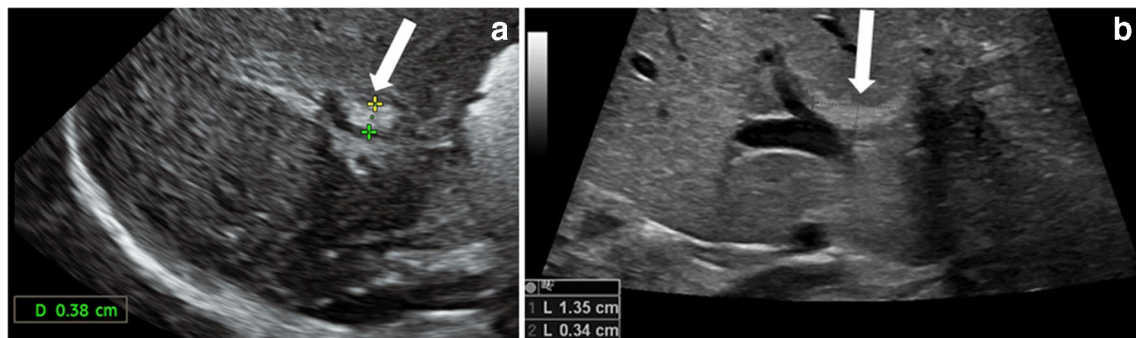


Fig. 4 Triangular cord sign corresponding to the fibrotic transformation of the bile ducts at the site of the ductal plate in two infants. **a** Longitudinal US image in a 35-day-old girl shows triangular cord sign (arrow) as a hyperechoic area measured against the anterior wall of the

anterior branch of the right portal vein just distal to the right portal vein without including the right hepatic artery. **b** Axial US image in a 59-day-old boy shows triangular cord sign (arrow) measured anterior to the bifurcation of the portal vein

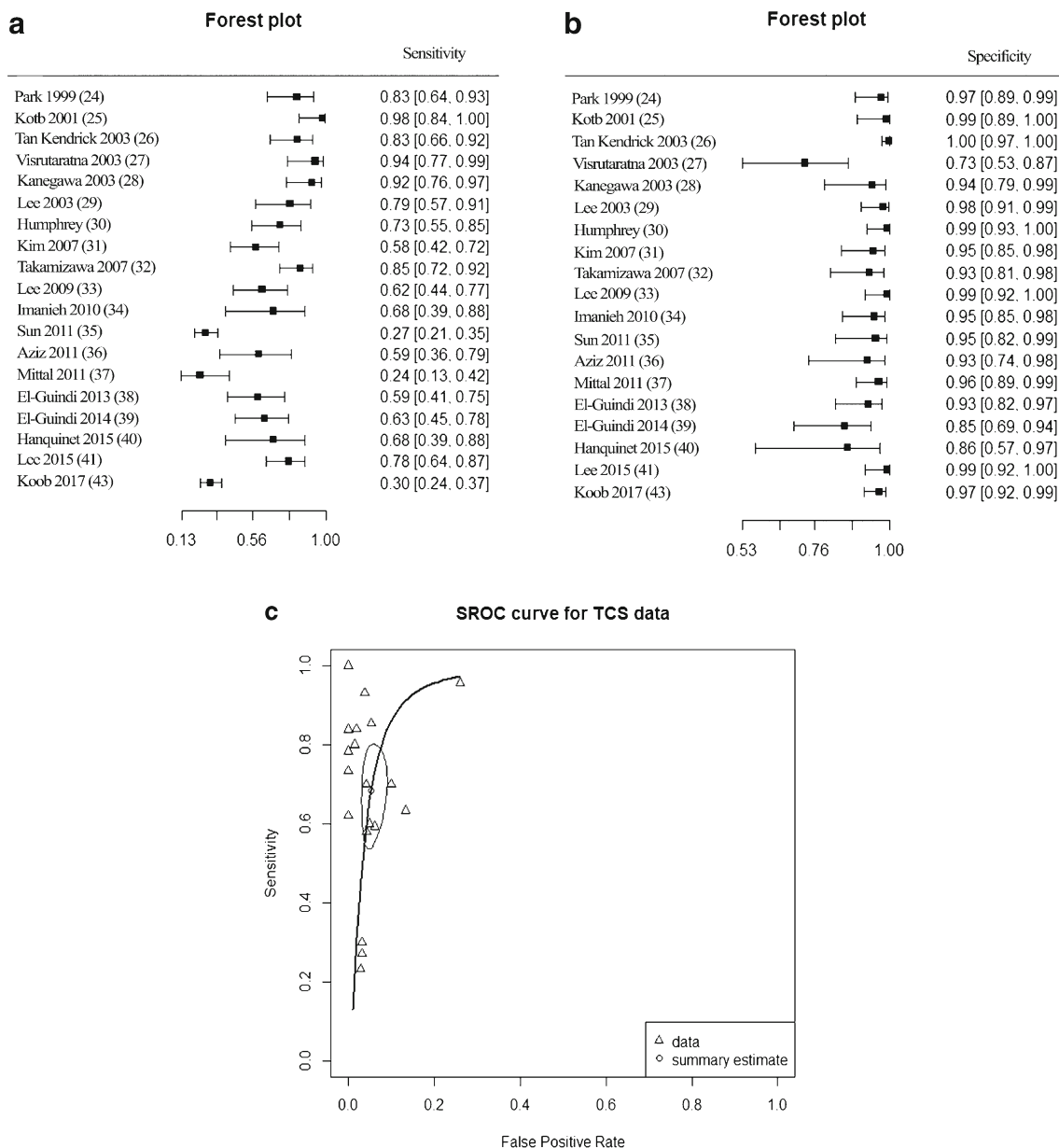


Fig. 5 Diagnostic efficacy of the triangular cord sign. **a–c** Forest plots for sensitivity (**a**), specificity (**b**) and summary receiver operating characteristic (SROC) curve (**c**) for triangular cord sign (TCS) data in our meta-analysis

(Fig. 12). In an infant with acholic stools, a macrocyst at the hilar pediculum without intrahepatic bile duct dilation is almost pathognomonic of biliary atresia, according to the experience of ESPR abdominal task force members.

Microcysts are located at the porta hepatis and have a small diameter ranging 2–4 mm. Because of their small size they are not visible on prenatal imaging. They can disappear during follow-up before surgery. Color Doppler is useful to differentiate microcysts from curving vessels (Fig. 13). Koob et al. [43] reported sensitivity and specificity for biliary atresia, respectively, for macrocysts (10% and 99%) and microcysts (20% and 98%) and a combination of macro- or microcysts

(25% and 97%). Thus, the presence of macro- or microcysts is a sign with very high specificity and low sensitivity.

Common bile duct visibility

Absent visibility of the extrahepatic bile duct has been proposed as a criterion for the diagnosis of biliary atresia, especially in MR studies. Only three series used absent extrahepatic bile duct visibility for biliary atresia diagnosis [30, 31, 37] and reported a sensitivity ranging from 0.93 to 0.95 and a large specificity range from 0.48 to 0.92. The visibility of part of the extrahepatic bile duct, whatever its diameter, does not rule out biliary atresia. The difficulty is to see the whole

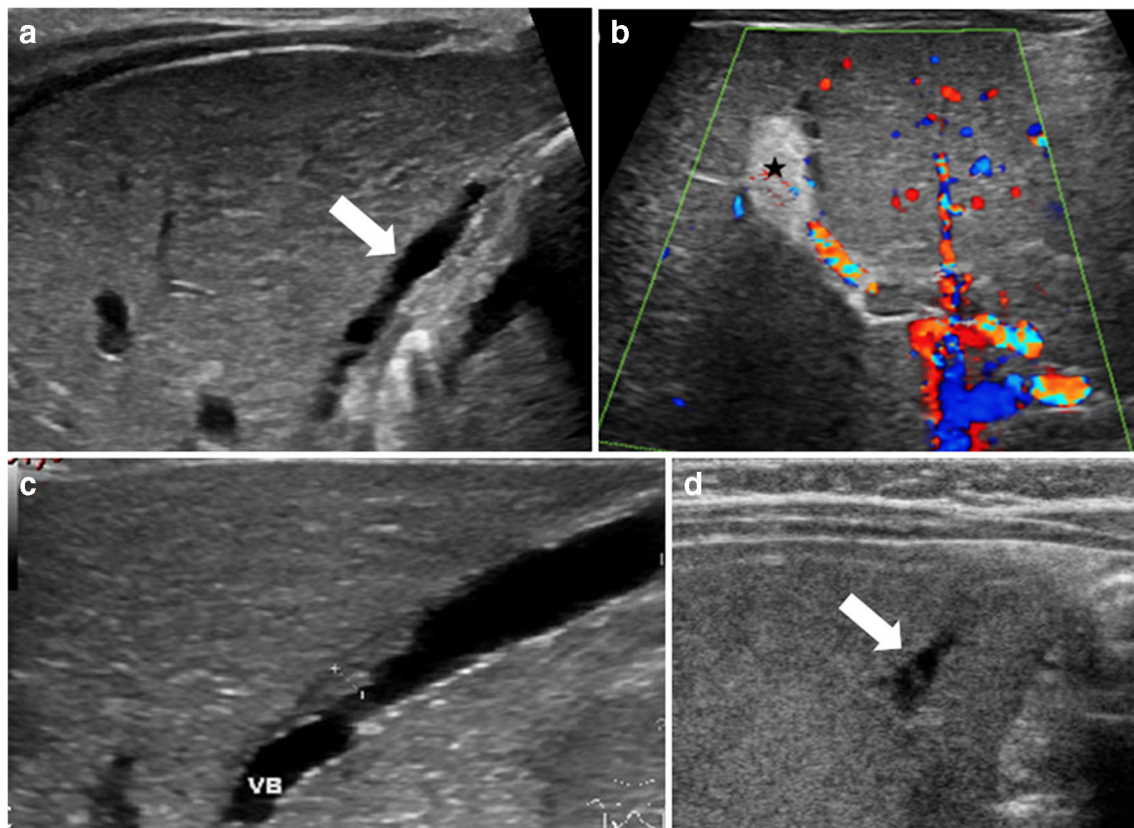


Fig. 6 Oblique US imaging in infants with abnormal gallbladder related to biliary atresia. **a** Gallbladder is small with irregular margins (*arrow*) in a 50-day-old boy. **b** Hyperechoic fibrotic gallbladder with no lumen visible (*star*) in a 72-day-old girl. **c** Gallbladder (*VB*) has a normal size

but irregular, thickened walls in a 35-day-old boy. **d** Gallbladder is very small, with interruption of the lumen and no wall clearly visible in a 60-day-old girl (*arrow*)

extrahepatic biliary tree from the right and left branches to the distal common bile duct.

Hepatic subcapsular flow

Analysis of hepatic subcapsular flow in infants with biliary atresia using color Doppler sonography can detect hyperplastic and hypertrophic changes in branches of the hepatic artery (Fig. 14) and this phenomenon has been proposed as a diagnostic criterion for biliary atresia. Only three papers using hepatic subcapsular flow for biliary atresia diagnosis were included in this review [33, 38, 39], and they reported sensitivities and specificities ranging from 0.96 to 1.00 and from 0.86 to 0.97, respectively. Reproducibility is a limiting factor because different US vendors, probes, Doppler settings and presets were used. There is no clear quantification available to allow for comparison of patients and objective follow-up.

Hepatic artery diameter

The hepatic artery diameter is larger in children with biliary atresia compared to normal controls or children with hepatitis [31] from decreased portal flow secondary to developing cirrhosis. Biliary atresia is a progressive disease and hepatic artery diameter was significantly smaller in the biliary atresia group younger than 30 days [45]. Kim et al. [31] reported a range of diameters of the normal hepatic artery to be 1.0–1.4 mm. We have to underline the difficulty of correctly measuring these small vessels at this age, and the necessity for assuring a proper and not an oblique section and for using high-frequency probes with high resolution. Figure 15 shows the forest plots and the sROC curve of the four studies included in our meta-analysis that used hepatic artery diameter for biliary atresia diagnosis [31, 37–39]. Table 2 summarises the diagnostic performances of hepatic artery enlargement, including a low diagnostic odds ratio (12.8), with good sensitivity (0.82) and low specificity (0.70) for biliary atresia.

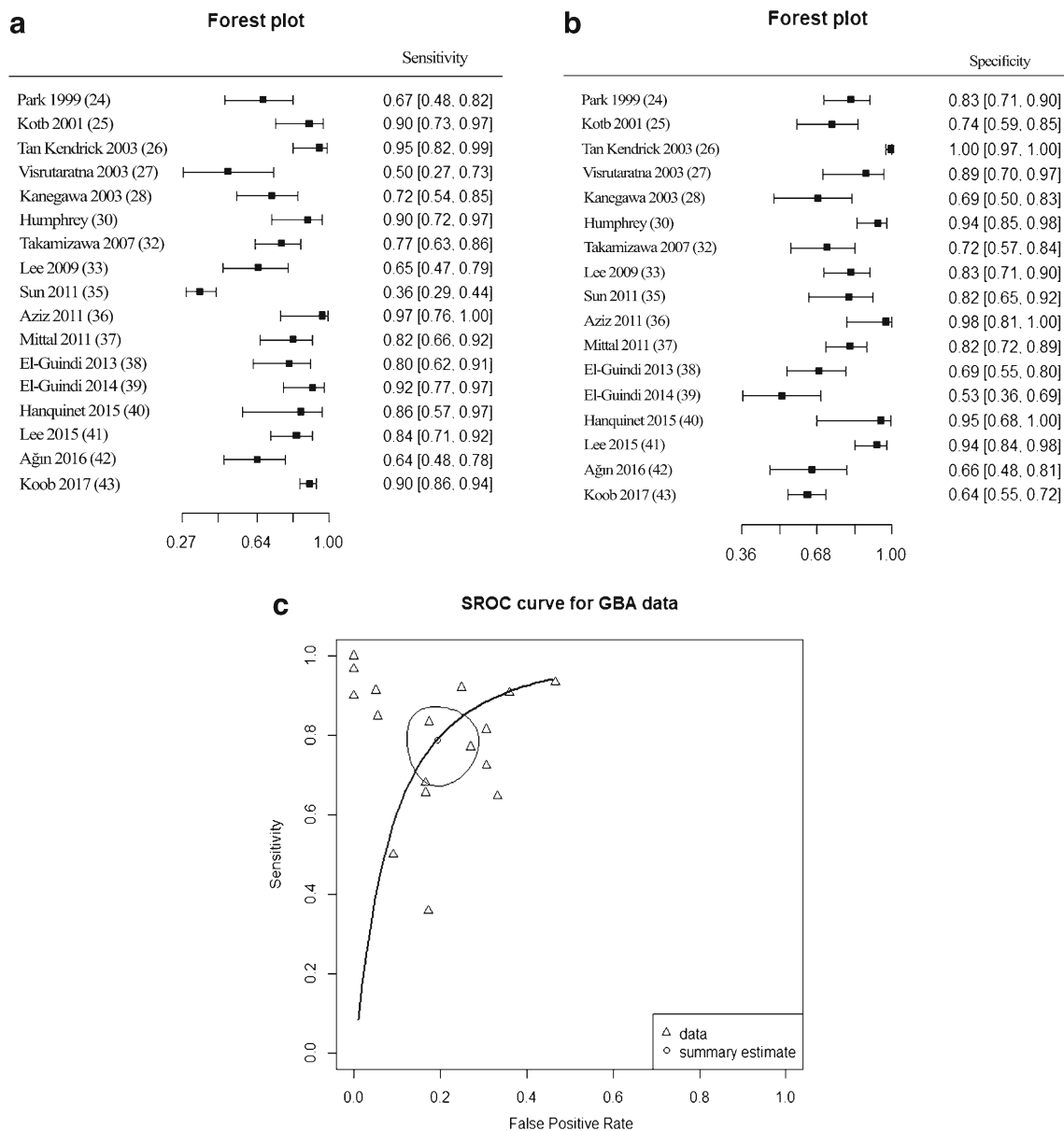


Fig. 7 Diagnostic efficacy of gallbladder abnormalities (GBA). **a–c** Forest plots for sensitivity (**a**), specificity (**b**) and summary receiver operating characteristic (SROC) curve (**c**)

Three series used hepatic artery diameter-to-portal vein diameter ratio >0.45 for biliary atresia diagnosis [25, 31, 33] and reported a sensitivity ranging from 0.67 to 0.77 and a large specificity range from 0.46 to 0.79.

Polysplenia syndrome

The syndromic form of biliary atresia is associated with polysplenia, intestinal malrotation, preduodenal portal vein,

absent or interrupted inferior vena cava, aberrant hepatic artery and abdominal heterotaxia. Humphrey and Stringer [30] and Koob et al. [43] reported that elements of the polysplenia syndrome in the setting of cholestasis had a low sensitivity but a high specificity for biliary atresia diagnosis. Humphrey and Stringer [30] reported a sensitivity of 10% and a specificity of 100% for polysplenia and a sensitivity of 17% and a specificity of 100% for associated interrupted inferior vena cava. Koob et al. [43] reported a specificity of 99–100% for

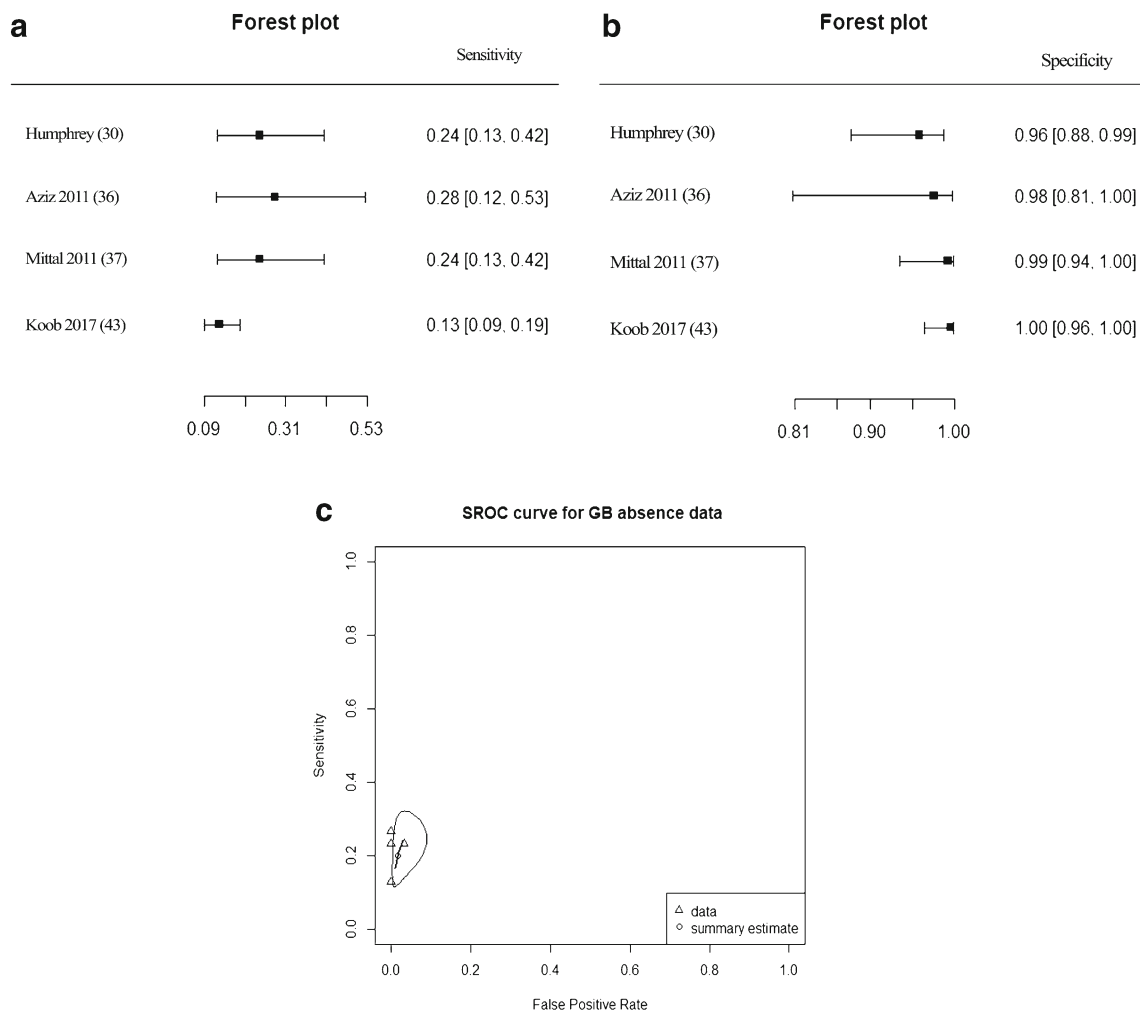


Fig. 8 Diagnostic efficacy of absent gallbladder (GB). **a–c** Forest plots for sensitivity (**a**), specificity (**b**) and summary receiver operating characteristic (SROC) curve (**c**)

polysplenia syndrome elements and a sensitivity of 11% for polysplenia, 5% for abnormal situs, 7% for azygos continuation and 5% for preduodenal portal vein.

Liver stiffness

Liver US elastography allows for quantitative assessments of liver stiffness using, depending to the technique, either shear wave speed measurement in metres per second (m/s) or stiffness in kilopascals (kPa). We included four papers that used elastography for biliary atresia diagnosis [48–51] with sensitivity ranging from 0.81 to 0.97 and specificity ranging from 0.67 to 1.00. In these reports, liver shear wave speed measurements or liver stiffness measurements were significantly higher in infants with biliary atresia when compared to infants with other causes of cholestatic jaundice. However, there was a large overlap of the values in the two groups. In one study,

grey-scale US was reported to have better diagnostic performance for biliary atresia than elastography [48]. In another paper [50], shear wave elastography not only helped differentiate biliary atresia from cholestatic hepatic diseases but also increased the diagnostic specificity when combined with grey-scale US. Elastography improved the diagnostic performance on prognosis assessment, especially in infants >30 days (Fig. 16) (Dabadie expert presentation ESPR 2018). Still there was no cut-off value to differentiate cirrhosis caused by biliary atresia from other causes of cirrhosis. A normal elastography does not rule out biliary atresia.

Discussion

Based on our systematic review, we confirm that US signs are very useful for biliary atresia diagnosis. When assessing

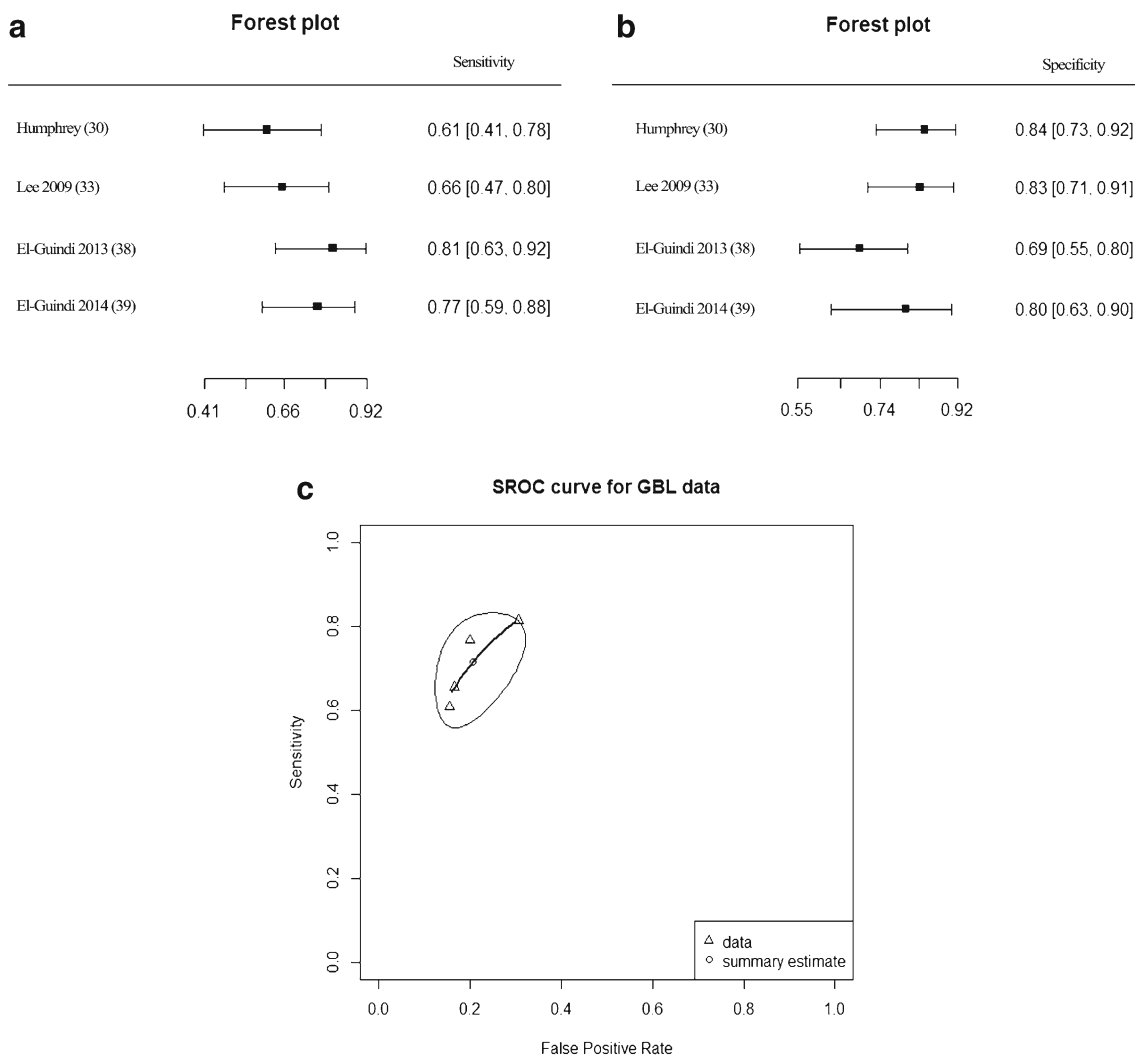


Fig. 9 Diagnostic efficacy of gallbladder length (GBL). **a–c** Forest plots for sensitivity (**a**), specificity (**b**) and summary receiver operating characteristic (SROC) curve (**c**)

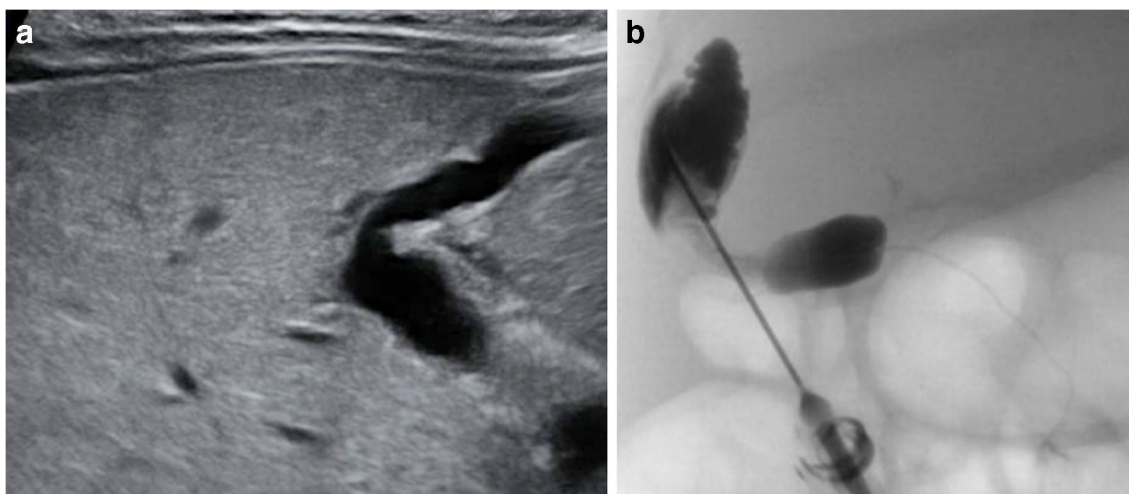


Fig. 10 Biliary atresia in a 19-day-old boy with normal-appearing gallbladder. **a** Oblique US shows normal aspect of the gallbladder. **b** Posteroanterior percutaneous cholecysto-cholangiography shows the

communication of the gallbladder with the extrahepatic duct and no reflux in the intrahepatic ducts, confirming the diagnosis of biliary atresia

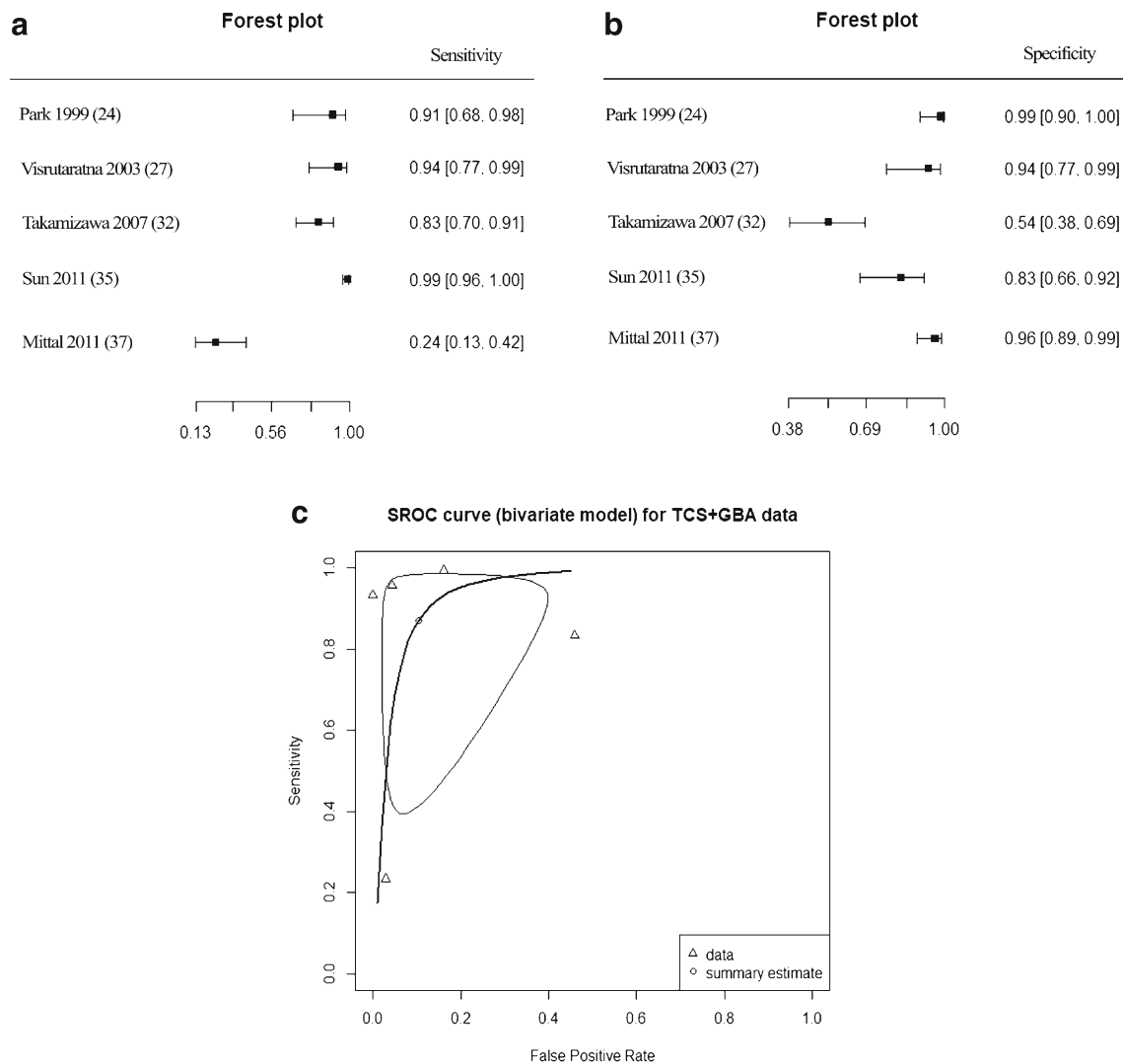


Fig. 11 Diagnostic efficacy of triangular cord sign combined with gallbladder abnormalities (TSC+GBA). **a–c** Forest plots for sensitivity (**a**), specificity (**b**) and summary receiver operating characteristic (SROC) curve (**c**)

infants for biliary atresia we suggest using microconvex and linear US probes with the highest frequency applicable to achieve the best spatial resolution.

Among the potential US signs, triangular cord sign showed the highest diagnostic odds ratio (40.2) among the signs in biliary atresia, with intermediate sensitivity (0.68) and high specificity (0.95). Gallbladder abnormalities showed a good diagnostic odds ratio (16.5), with high sensitivity (0.79) and specificity (0.81). Absence of the gallbladder showed a good diagnostic odds ratio (17.5) with very low sensitivity (0.20) and the highest specificity (0.98), so this sign is not frequent but is highly suggestive of biliary atresia. Gallbladder length showed a low diagnostic odds ratio (10.1) with

intermediate sensitivity (0.72) and good specificity (0.79). A combination of triangular cord sign and gallbladder abnormalities had the best diagnostic odds ratio (99.0), with the highest sensitivity (0.87) and very high specificity (0.90), and is very suggestive of biliary atresia. Hepatic artery enlargement had a low diagnostic odds ratio (12.8) with low specificity (0.70) and a sensitivity of 0.82. Macro- or microcysts or a combination was a very specific sign but had a low sensitivity. Polysplenia syndrome elements had very high specificity but low sensitivity.

Zhou [52] and Yoon [53] and colleagues’ meta-analyses also included papers that used surgery or liver biopsy as a reference standard for biliary atresia. Our

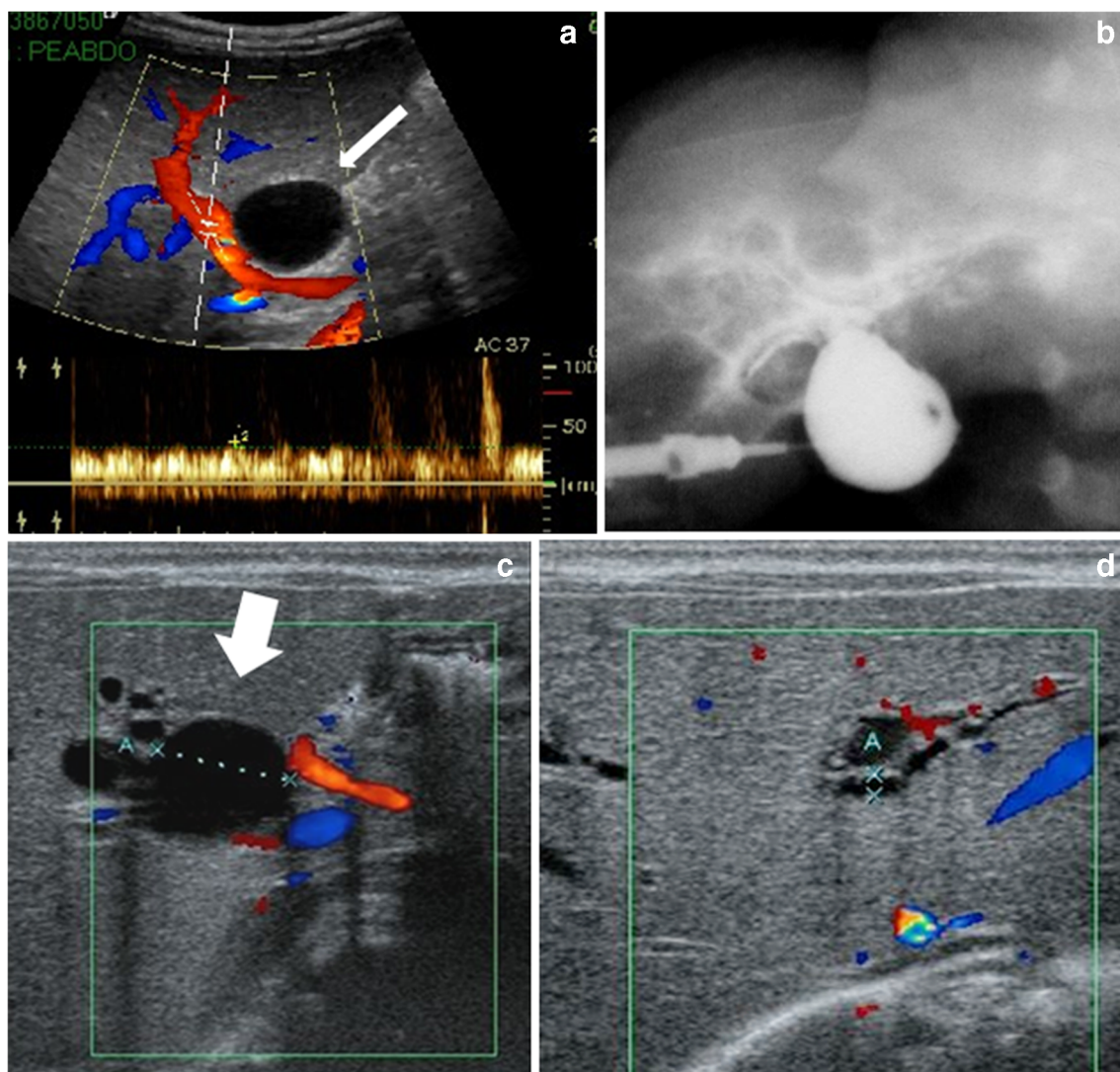


Fig. 12 Cholestasis and prenatal diagnosis of cyst at the liver hilum. **a, b** A 54-day-old girl presents with macrocyst at the liver hilum (*arrow*) with no intrahepatic bile duct dilatation on oblique US Doppler (**a**). Posteroanterior perioperative cystography (**b**) confirms cystic biliary atresia with reflux of the iodine in very irregular and thin atretic intrahepatic bile ducts and no

opacification of the choledochus and the duodenum. **c, d** A 4-day-old girl with choledochal cyst. Oblique color Doppler US shows a cyst at the liver hilum (*arrow* in **c**) communicating with dilated intrahepatic bile ducts visible in the more cranial image (**d**). *A distance between calipers*

results are not so different from Zhou et al.'s [52] regarding triangular cord sign, gallbladder abnormalities, triangular cord sign + gallbladder abnormalities, and hepatic artery enlargement. Yoon et al.'s [53] meta-analysis evaluated only triangular cord sign and reported higher values for sensitivity and specificity. Table 3 compares the results of our meta-analysis with those of Yoon and Zhou and colleagues.

The results of our meta-analysis are in accordance with the European Society for Paediatric Gastroenterology, Hepatology & Nutrition (ESPGHAN) and the North

American Society for Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN) guidelines [54]:

- Postnatal US is useful to exclude choledochal cyst, intrahepatic bile duct dilatation and gallstones.
- Postnatal US is useful to demonstrate features suggestive but not diagnostic of biliary atresia and a normal US does not rule out biliary atresia.
- The US features suggestive of biliary atresia are: (1) triangular cord sign, (2) gallbladder abnormalities and (3) micro- or macrocysts and malformations related to polysplenia syndrome.

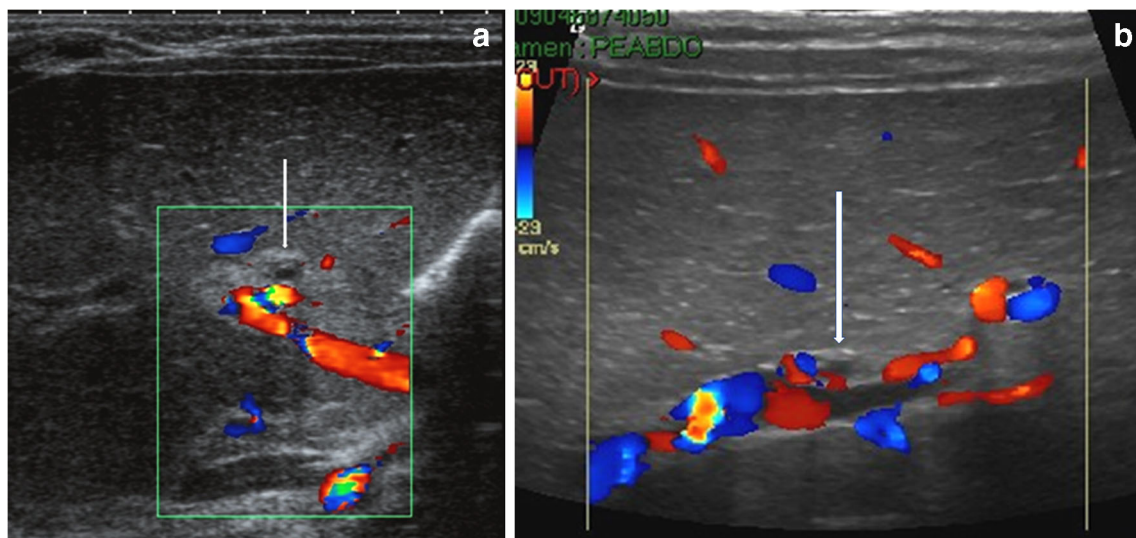


Fig. 13 Biliary atresia with microcyst. **a** Oblique color Doppler US shows a microcyst within a triangular cord sign (*arrow*) and no bile duct dilatation in a 30-day-old girl. **b** Oblique color Doppler US shows

a microcyst (*arrow*) with no triangular cord sign and intrahepatic bile duct dilation in a 37-day-old boy

- The US features that do not seem reliable for suggesting biliary atresia are: (4) hepatic subcapsular flow, (5) hepatic artery enlargement and (6) non-visualisation of common bile duct.

Signs of portal hypertension (portosystemic derivations such as patent ductus venosus, recanalised umbilical vein, splenomegaly and ascites) should be actively searched for but are not specific for biliary atresia.

According to the limited number of papers available, further evaluation is necessary to assess the role of liver

elastography for biliary atresia diagnosis and prognosis [48–51].

In Table 4, we propose a standardised US report in infants evaluated for cholestasis.

Our study has several limitations. The papers included showed a patient age range of 3–360 days, which is very large for an evolutive pathology that must be diagnosed as early as possible, and it creates a bias because some US signs (triangular cord sign and hilar cysts) are age-dependent. Only two papers [26, 37] included infants younger than 90 days and four papers [38–40, 42] did not report the age range of patients. The criteria used to define a positive triangular cord sign or gallbladder abnormalities differed across studies. Patient characteristics among studies were different; for example, some included cystic biliary atresia and some excluded cystic biliary atresia. There was a heterogeneity of study design: nine papers were prospective [24–26, 28, 30, 31, 37–39] and the remainder were retrospective [27, 29, 32–36, 40–43]. We included only English-language papers with surgery used as a reference standard for biliary atresia and with at least 10 patients, which excluded some types of publications.

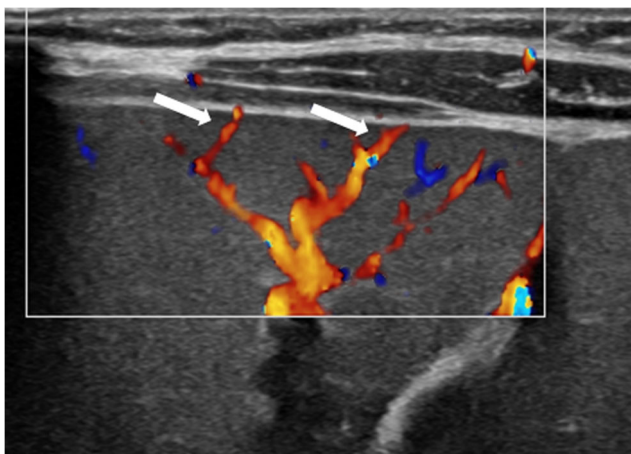


Fig. 14 Subcapsular flow in a 61-day-old boy with biliary atresia. Oblique color Doppler US shows hepatic arterial flow (*arrows*) extending to the hepatic surface

Conclusion

Early diagnosis is challenging but is the main goal of imaging in suspected biliary atresia and is of paramount importance for a favourable outcome. Biliary atresia is a progressive disease;

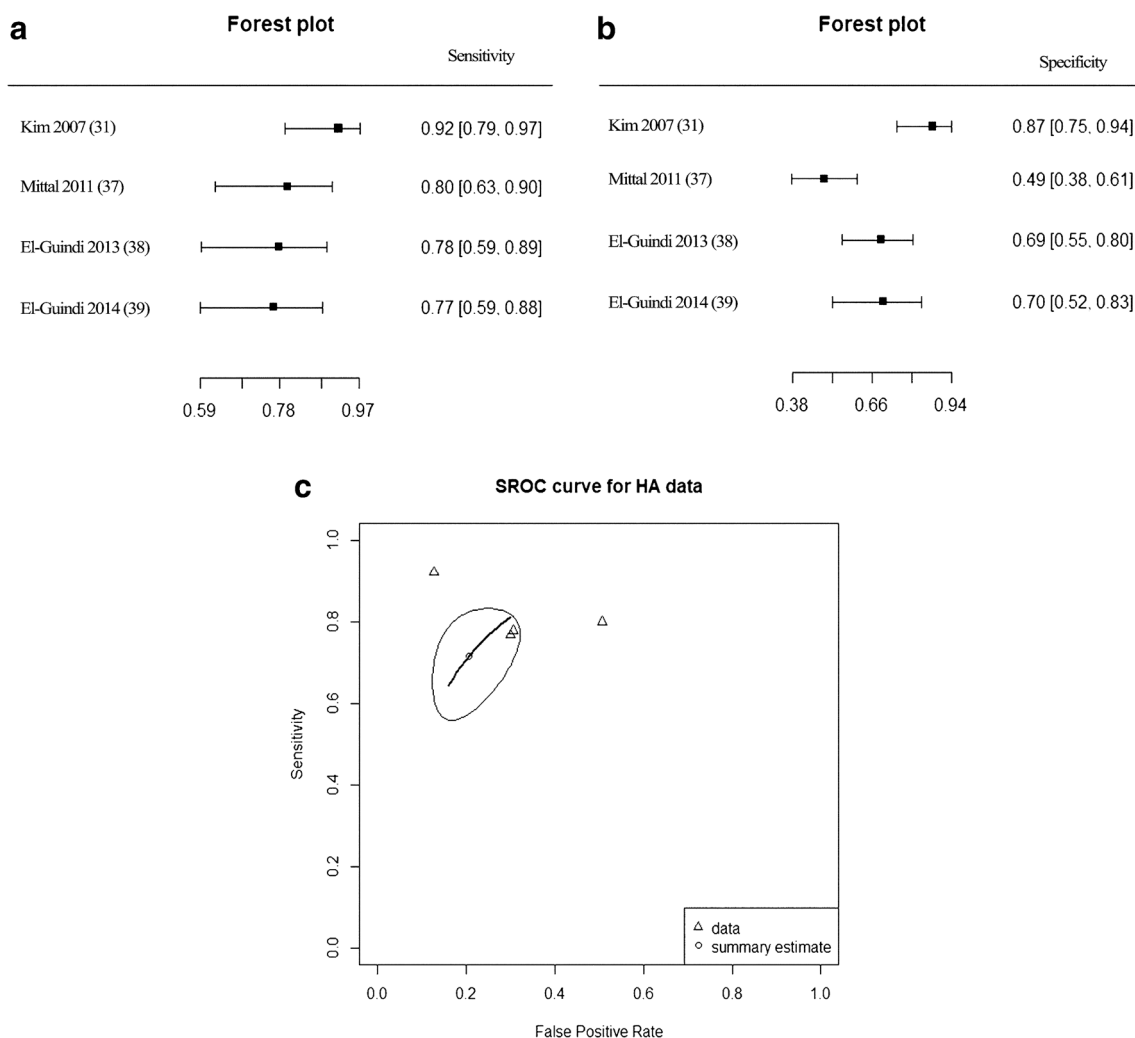


Fig. 15 Diagnostic efficacy of hepatic artery (HA) enlargement. **a–c** Forest plots for sensitivity (**a**), specificity (**b**) and summary receiver operating characteristic (SROC) curve (**c**)

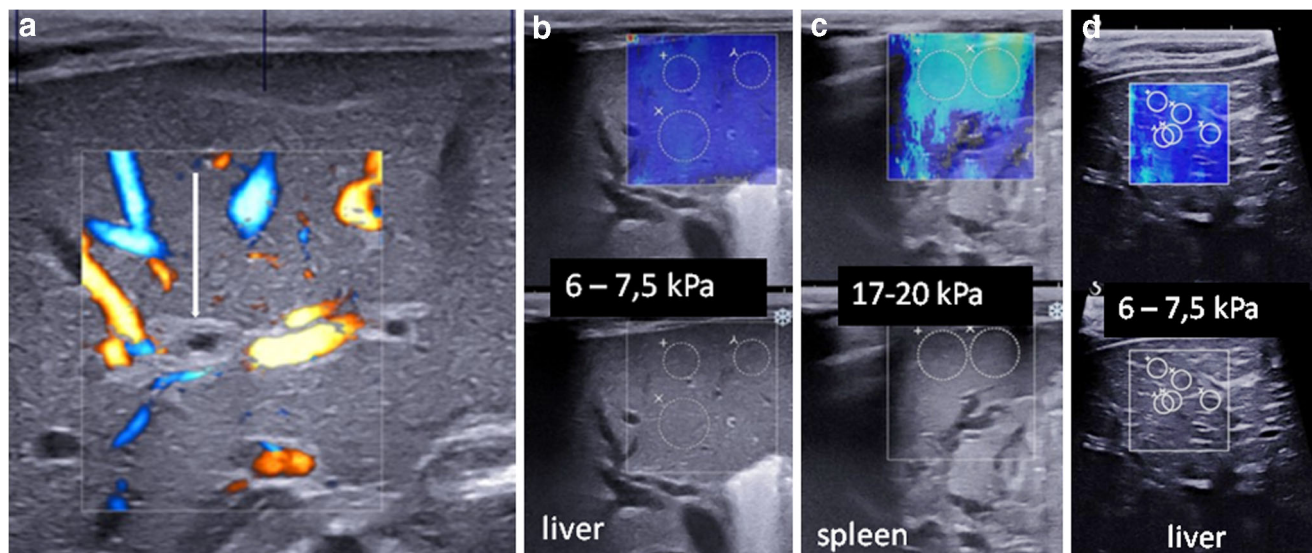


Fig. 16 A 12-day-old girl born preterm with pale stools with biliary atresia. **a** Oblique color Doppler US shows triangular cord sign and microcyst (*arrow*). **b** Oblique hepatic shear wave elastography measurements at diagnosis are in the normal range. **c** Oblique splenic shear wave elastography measurements

at diagnosis are in the normal range. **d** Two years later in the same girl, after a successful Kasai hepatopuertoenterostomy, oblique shear wave elastography liver measurements show normal values in relation with an exceptional excellent outcome with the absence of liver fibrosis

Table 3 Summary sensitivity, specificity and diagnostic odds ratio of US features comparing the results of our meta-analysis with those of Yoon et al. [53] and Zhou et al. [52]

Triangular cord sign (TCS)				
	Sensitivity	Specificity	Diagnostic odds ratio	
Present study ^a	0.68 (0.57–0.78)	0.95 (0.92–0.97)	40 (21–71)	
Yoon [53] ^a	0.85 (0.77–0.90)	0.97 (0.94–0.99)	175 (75–405)	
Zhou [52] ^a	0.74 (0.61–0.84)	0.97 (0.95–0.99)	101 (41–246)	
Gallbladder abnormality (GBA)				
	Sensitivity	Specificity	Diagnostic odds ratio	
Present study ^a	0.79 (0.70–0.86)	0.81 (0.73–0.86)	16 (8–30)	
Zhou [52] ^a	0.85 (0.76–0.91)	0.92 (0.81–0.97)	61 (18–204)	
TCS+GBA				
	Sensitivity	Specificity	Diagnostic odds ratio	
Present study ^a	0.87 (0.51–0.97)	0.90 (0.68–0.97)	99 (8–441)	
Zhou [52] ^a	0.95 (0.70–0.99)	0.89 (0.79–0.94)	140 (31–637)	
Hepatic artery enlargement				
	Sensitivity	Specificity	Diagnostic odds ratio	
Present study ^a	0.82 (0.71–0.89)	0.70 (0.51–0.84)	12 (3–36)	
Zhou [52] ^a	0.79 (0.71–0.86)	0.75 (0.60–0.86)	11 (5–26)	

^a Values in parentheses are 95% confidence intervals

Table 4 Proposal for a standardized US report in cholestatic infants

US sign	Present	Absent
Gallbladder	Visible	Not visible
Gallbladder length	>1.5 cm	<1.5 cm
Gallbladder shape	Normal	Abnormal
Gallbladder wall	Regular	Irregular
Triangular cord sign	Present	Absent
Macrocyst	Present	Absent
Microcyst	Present	Absent
Polysplenia syndrome	Present	Absent
Detailed signs: polysplenia, intestinal malrotation, preduodenal portal vein, absent or interrupted inferior vena cava, aberrant hepatic artery, and abdominal heterotaxia		
Splenomegaly	Present	Absent
Portal hypertension	Present	Absent
Detailed signs: umbilical vein, ductus venosus, other portosystemic shunt, ascites		

hence, our presented numbers are not absolute but rather an indication of the sensitivity and specificity of the various signs because the literature is inhomogeneous, both in terms of age-span and of definitions of the different pathological signs. US is a major imaging tool for biliary atresia and US signs have a high specificity, especially when associated with one another. They include triangular cord sign, gallbladder abnormalities, and macro- and microcysts and malformations related to polysplenia syndrome. However, a normal US examination does not rule out biliary atresia diagnosis.

Compliance with ethical standards

Conflicts of interest None

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