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REVIEW

Accuracy of hepatobiliary scintigraphy for differentiation of neonatal hepatitis from biliary atresia: systematic review and meta-analysis of the literature

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Abstract Hepatobiliary scintigraphy is an important diagnostic modality for work-up of neonatal cholestasis. Therefore, our objective was to evaluate the literature regarding the accuracy of hepatobiliary scintigraphy in differentiating biliary atresia from non-biliary atresia causes of cholestasis (collectively called neonatal hepatitis). Our search included Medline, SCOPUS and Google Scholar. Only studies using Tc-99 m-labeled immunodiacetic acid (IDA) derivatives were included. Overall, 81 studies were included in the meta-analysis. Pooled sensitivity and specificity were 98.7% (range 98.1–99.2%) and 70.4% (range 68.5–72.2%), respectively. Factors that increased specificity included the use of radiotracers with high hepatic extraction, administration of hepatic-inducing drugs (such as phenobarbital), use of a calculated dose/kg and administration of a booster dose in cases of non-excretion of the tracer in the bowel. SPECT imaging and duodenal fluid sampling also had high specificity; however, they need further validation because of the low number of studies. Semiquantitative imaging methods do not seem to have any incremental value. We conclude that hepatobiliary scintigraphy using IDA derivatives can be very useful for diagnostic work-up of neonatal cholestasis. To improve the specificity, several measures can be followed regarding type and dose of the radiotracer and imaging protocols. Non-imaging methods seem to be promising and warrant further validation.

Keywords Biliary atresia · Neonatal hepatitis · Hepatobiliary scintigraphy · Systematic review · Meta-analysis

Introduction

Cholestasis (direct bilirubin more than 15% of total serum bilirubin) is a pathological condition that affects almost 1 in 2,500 newborns [1]. The main etiologies of cholestasis are neonatal hepatitis (which is collectively attributed to the non-biliary atresia causes of cholestasis) and biliary atresia. Early differentiation of these entities is of utmost importance because surgical treatment of biliary atresia is very successful in the early stages of the disease [2]. Several diagnostic methods including liver biopsy and ultrasonography have been used for differentiation of biliary atresia from neonatal hepatitis with variable success [3].

Hepatobiliary scintigraphy is a diagnostic method commonly used in diagnosis of biliary atresia. Despite very high sensitivity of hepatobiliary scintigraphy for this purpose, the specificity of this imaging modality is rather low, which limits its use in daily practice [4]. Several methods, such as using barbiturates or ursodeoxycholic acid or administering tracers with high extraction efficacy, have been used for increasing the specificity of hepatobiliary scintigraphy, with variable success [2].

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In this study, we systematically searched the literature regarding sensitivity and specificity of hepatobiliary scintigraphy in accurately differentiating the biliary atresia from the non-biliary atresia causes of cholestasis (collectively called neonatal hepatitis). We report the results in a review and meta-analysis format.

Search strategy, selection criteria, data abstraction

We searched Medline, SCOPUS and Google Scholar using the following terms: ("biliary atresia" or "neonatal hepatitis" or "infantile jaundice") and (scintigraphy or "nuclear medicine" or *IDA) without any language or date limits. Reference lists of the relevant studies were evaluated for any possible missed citation. Cited articles of each relevant study were also reviewed (by the "cited by" tools of the SCOPUS and Google Scholar) for any other possible relevant study. Corresponding authors were contacted if necessary.

The following criteria were set for inclusion of the studies into the systematic review:

(1) Inclusion of at least five patients.
(2) Inclusion of enough data to calculate sensitivity and specificity of hepatobiliary scintigraphy.
(3) Use of Tc-99 m-labeled immunodiacetic acid (IDA) derivatives as the radiotracer.

Retrieved articles were evaluated blindly by two of the authors and in case of any disagreement the opinion of a third author was used. Duplicated publications were discussed and only the most recent studies were included. Quality of the included studies was evaluated using the Oxford Centre for Evidence Based Medicine Checklist of diagnostic studies [5]. Data on authors, publication year, pre-scan drugs, type of the radiotracer, complementary diagnostic methods and patient characteristics, and information needed for sensitivity and specificity calculations were extracted by two authors independently.

Statistical analysis

We followed the recommendations of Devillé et al. [6] for performing meta-analyses of diagnostic studies. Because of the considerable heterogeneity of the included studies regarding methods and patients, the random effects model was used for pooling the data [7]. For heterogeneity evaluation, the Cochran Q test was used and significance level was set at P=0.05. For quantifying the heterogeneity, I^2 index was used. For threshold effect evaluation, correlation between sensitivity and specificity of included studies was used [8]. To explore the effect of radiotracer type, dosing method, dose of the tracer and premedication, we used subgroup analyses and meta-regression. To determine how much of the variance across the studies could be explained by these further analyses, we used the R^2 index. To explore the effect of varying gold standard tests on the results, sensitivity analysis was performed including only studies that used at least liver biopsy and follow-up as the gold standard. Individual tests could not be used as a gold standard and a combination of tests (ultrasonography, liver biopsy, intraoperative cholangiography, follow-up of the patients, serological and biochemistry tests, liver function tests, etc.) are the most appropriate.

Sensitivity, specificity, negative and positive likelihood ratios (LR−, LR+), and diagnostic odds ratio (DOR) were calculated for each study and overall results were calculated by pooling the data using the random effects model [8]. We used summary receiver operating characteristics curve (sROC curve) and area under the curve (AUC) calculations as well as Q* value to summarize overall performance of the test [9].

Publication bias was addressed using funnel plots. Funnel plot asymmetry was also tested statistically using the Egger linear regression method [10]. Duval and Tweedie's [11] trim and fill method was used for quantifying possible publication bias effect. Comprehensive Meta-Analysis Version 2 (Biostat, Inc. Englewood NJ, US) and Meta-DiSc version 1.4 (Madrid University, Madrid, Spain) [12] were used for statistical analyses.

Twenty studies had information regarding 389 patients for further assessment. We evaluated the effects of age, gender and serum bilirubin level on the accuracy of hepatobiliary scintigraphy by using chi-square and independent sample t-tests and the binary logistic regression method. SPSS software version 11.5 was used for these statistical analyses (SSPS, Chicago, IL).

Results

In the first search, 510 studies seemed relevant. We excluded 250 studies after screening abstracts and titles for irrelevant subjects. The full texts of the remaining 260 studies were evaluated in detail. Of those, 179 studies were excluded for being review articles, letters to editors, duplicates and case reports. Finally, 81 relevant studies were included in our meta-analysis [3, 4, 13–92]. One study had the only available data regarding duodenal fluid sampling for radioactivity determination and was included accordingly [93]. Table 1 shows a summary of these 81 studies.

Figures 1 and 2 show the forest plots of sensitivity and specificity pooling. For diagnosis of biliary atresia, the scintigraphy had an overall sensitivity of 98.7% (range 98.1–99.2%), specificity of 70.4% (range 68.5–72.2%), LR+ of 3.01 (range 2.63–3.47), LR− of 0.07 (range 0.05–0.09) and DOR of 55.8 (range 41.2–75.4). Sensitivity

Table 1 Summary of the 81 studies included in the review. *LB* liver biopsy, *IOC* intraoperative cholangiography, *FU* follow-up, *US* ultrasonography, *B* paraclinical biochemistry exams, *S* paraclinical serological exams, *LFT* liver function tests, *BA* biliary atresia, *NH* neonatal hepatitis, *P* phenobarbital, *U* ursodeoxycholic, *C* cholestyramine, *B* betamethasone

First author [ref]	Sample size	Sensitivity/ specificity (in %)	Mean age of patients	Tracer bond to Tc-99 m	Dose of the radiotracer (in mCi)	Premedication	Quality assessment according to Oxford Centre for Evidence Based Medicine					Choledochal cyst	Contribution of 24 h imaging	Semiquantitative evaluation of scintigraphy images
							Consecutive recruitment of patients	Appropriate spectrum of including patients	Blindness of reviewers to information other than scintigraphy	Gold standard	Enough explanation to ensure reproducibility			
Cox [13]	33	100/66	3–6 weeks	DISIDA	0.1 mCi/kg-IV	P	Yes	Yes	Yes	US, LB, IOC	Yes	–	3/24 patients	Visual grading (not different between BA and NH), curve of the liver clearance: incorrect in 6/11 patients
Ben Haim [14]	15	100/83	5–180 days	BrIDA	1+ Booster	No	Yes	Yes	Yes	LB in 16 patients, autopsy in some	Yes	–	3/26 visualisation	Hepatobiliary clearance curve: was not different between BA and NH
Ben Haim [14] (phenobarbital group)	21	100/100	5–180 days	BrIDA	1+Booster	P	Yes	Yes	Yes	LB in 16 patients, autopsy in some	Yes	–	3/26 visualisation	Hepatobiliary clearance curve: was not different between BA and NH
Gerhold [15]	27	100/81	17–172 days	DISIDA	1.4	No	Yes	Yes	Yes	LB, IOC, FU	No	–	2/11 NH patients	Hepatic/cardiac activity in 5 min: not different between BA and NH
Rosenthal [16]	26	83/92	67 days (mean)	DISIDA	0.1 mCi/kg (minimum of 2 mCi)	P	Yes	Yes	Yes	S,BC, US, LB, IOC, FU	Yes	–	3 out of 13	–
Tolia (PIPIDA study) [17]	28	100/41	N/A	PIPIDA	0.5	PC	N/A	Yes	N/A	LB, FU, IOC	Yes	–	N/A	–
Tolia (DISIDA study) [18]	40	100/45	2–20 weeks	DISIDA	1	PC	Yes	Yes	Yes	LB (18 patients), FU, IOC	No	–	–	–
Poddar [1]	51	100/54	2.9 months (mean)	BrIDA	1	No	Yes	Yes	N/A	US, LB, IOC	Yes	–	–	–
Poddar [1] (Urso-deoxycholic acid study)	32	100/75	2.9 months (mean)	BrIDA	1	U	Yes	Yes	N/A	US, LB, IOC	Yes	–	–	–
Yachha [20]	49	100/62	3.9±1.9 months	BrIDA	N/A	No	Yes	Yes	N/A	S, B, US, LB. Sepsis work-up, IOC, POC, FU	No		–	–
Meisheri [21]	30	88/0	7.2 weeks	N/A	N/A	No	Yes	No	N/A	POC	No	–	–	–
Anand [22]	14	100/100	41 days to 6 months	BrIDA	1	No	Yes	No	N/A	B, US, POC	Yes	–	–	–
Gupta [23] (pheno barbital group)	126	100/57	3.47 months (mean)	HIDA	2	P	No	No	N/A	IOC for those without excretion. Other tests not mentioned	Yes	–	–	–
Gupta [23] (pheno barbital and bethametasone group)	76	100/80	3.3 months (mean)	HIDA	2	PB	No	No	N/A	IOC for those without excretion. Other tests not mentioned	Yes	–	–	–
Khorasani [24] (Phenobarbital group)	30	100/64	2–8 weeks	BrIDA	1	P	Yes	Yes	N/A	LB, IOC, S, B, FU	No	–	–	–
Khorasani [24] (Ursodexoycholic acid group)	30	100/95	2–8 weeks	BrIDA	1	U	Yes	Yes	N/A	LB, IOC, S, B, FU	No	–	–	–

Table 1 (continued)

First author [ref]	Sample size	Sensitivity/ specificity (in %)	Mean age of patients	Tracer bond to Tc-99m	Dose of the radiotracer (in mCi)	Premedication	Quality assessment according to Oxford Centre for Evidence Based Medicine					Choledochal cyst	Contribution of 24h imaging	Semiquantitative evaluation of scintigraphy images
							Consecutive recruitment of patients	Appropriate spectrum of including patients	Blindness of reviewers to information other than scintigraphy	Gold standard	Enough explanation to ensure reproducibility			
Dehghani [3]	65	84/52	62±17 days	N/A	N/A	No	No	No	N/A	B, S, US, LB, sepsis work-up	Yes	–	–	–
Sadeghi [4]	20	100/50	2.41 months	BrIDA	1	P	Yes	Yes	N/A	B, S, US, IOC, LB, FU	Yes	–	–	–
Rouzrokh [25]	42	100/87	39 days	N/A	N/A	No	Yes	Yes	N/A	B, US, LB, IOC	No	–	–	–
Esmaili [26]	70	98/87	N/A	BrIDA	0.25 mCi/kg	P	Yes	Yes	N/A	IOC	No	–	–	–
Salvatori [27]	18	100/91	21–75 days	IODIDA	1	P	Yes	Yes	N/A	US, LB, IOC	Yes	–	–	Semi quantitative hepatic uptake: not different between NH and BA
Mussa [28]	54	100/75	4 days to 3 months	EHIDA	0.5 mg/kg	No	Yes	Yes	N/A	B, US, S	No	–	–	–
Stipsanelli [29]	20	100/77	4.4± 3.2 weeks	BrIDA	6 MBq/kg	P	Yes	Yes	Yes	LB	Yes	1	12/24 NH patients	Liver-to-heart (L/H) ratio lower in BA patients
Rossmüller [30]	19	100/69	40 days (median)	EHIDA	N/A	P	Yes	Yes	Yes	LB, B, S, US, FU	Yes	1	N/A	Hepatocellular extraction. (4/6 in BA and none of 4 patients with NH had good extraction)
Peters [31]	30	100/63	22.93 weeks (mean)	EHIDA	Neonates 0.2–0.5 mCi and infants 0.5–1.5 mCi	No	Yes	Yes	Yes	LB, IOC, FU, autopsy	Yes	2	N/A	Grading of the liver activity (BA 9 ++ 2−; NH 5++; 8 +; 5−)
Dressler [32]	32	92/79	BA: 7.8 weeks; NH 11.4 weeks (mean)	EHIDA	7.4 MBq/kg	P	Yes	Yes	N/A	FU, B, IOC, LB	Yes	–	N/A	Renal index, hepatobiliary transit time not different between BA and NH
Wynchank [33]	14	100/50	40 days (mean)	EHIDA	0.2	P	Yes	Yes	Yes	Cholescintigraphy	No	–	N/A	Reduced liver uptake in five patients with NH and one patient with BA
Ferretti-Cisneros [34]	51	96/56	61.4 days	DISIDA	1	P	Yes	Yes	Yes	IOC, S, FU	Yes	–	N/A	–
Eduardo Chávez [35]	25	100/53	N/A	N/A	N/A	No	Yes	Yes	N/A	LB, cholescintigraphy, FU	No	–	N/A	–
Yang [36] (2005 study)	45	100/60	18.7 days (mean)	EHIDA	3	No	Yes	Yes	Yes	LB, FU	Yes	–	N/A	–
Yang [37] (2009 study)	155	97/74	64±18 days	EHIDA	0.3	No	Yes	Yes	Yes	Liver biopsy	Yes	22	N/A	–
Yang (SPECT group) [38]	69	88/45	60±19 days	EHIDA	5	No	Yes	Yes	Yes	B, S, MRCP, US, cholescintigraphy, LB, IOC	Yes	–	N/A	–
Yang (planar group) [38]	69	94/88	60±19 days	EHIDA	5	No	Yes	Yes	Yes	B, S, MRCP, US, cholescintigraphy, LB, IOC	Yes	–	N/A	–
Wang [39]	24	100/94	25–105 days	EHIDA	4	P	Yes	Yes	N/A	FU, IOC	Yes	–	N/A	–
Chen [40]	332	100/71	18–120 days	EHIDA	3	No	Yes	Yes	Yes	FU, IOC, LB	No	6	N/A	–
Yue [41]	163	100/46	81 days (mean)	EHIDA	1	No	Yes	Yes	Yes	IOC, LB	Yes	4	N/A	–
Shao [42]	50	100/81	7–180 days	EHIDA	7.4 MBq/kg (0.2 mCi/kg)	No	Yes	Yes	Yes	LB, FU	No	–	12/43 NH in 8 h and 23/43 in 24 h	–

Table 1 (continued)

First author [ref]	Sample size	Sensitivity/ specificity (in %)	Mean age of patients	Tracer bond to Tc-99m	Dose of the radiotracer (in mCi)	Premedication	Quality assessment according to Oxford Centre for Evidence Based Medicine					Choledochal cyst	Contribution of 24h imaging	Semiquantitative evaluation of scintigraphy images
							Consecutive recruitment of patients	Appropriate spectrum of including patients	Blindness of reviewers to information other than scintigraphy	Gold standard	Enough explanation to ensure reproducibility			
Hou [43]	48	100/79	25–60 days	EHIDA	1	No	Yes	Yes	Yes	IOC, FU	Yes	–	N/A	–
Xiao [91]	119	100/76	68±34 days	EHIDA	5	P	Yes	Yes	Yes	LB, B, S, FU, IOC	Yes	–	N/A	–
Ma [90]	58	100/85	41.3 days	EHIDA	3	P	Yes	Yes	Yes	IOC, autopsy, FU	Yes	–	N/A	–
Huang [44]	212	100/100	15–90 days	EHIDA	2	No	Yes	Yes	N/A	N/A	No	–	N/A	Heart and kidney activity, liver uptake were different between NH and BA
Liu [45]	84	100/74	15–90 days	EHIDA	2	No	Yes	Yes	Yes	FU, IOC	Yes	–	N/A	–
Fischler [46]	63	100/73	N/A	IODIDA		No	Yes	Yes	Yes	Cholescintigraphy, LB, IOC	Yes	–	N/A	–
Ang [47]	110	100/73	<24 months	EHIDA	0.5–1 mCi	P	Yes	Yes	Yes	IOC, FU, LB	Yes	–	N/A	–
Tan Kendrick [48]	38	91/77	N/A	DISIDA	1	P	Yes	Yes	Yes	IOC, LB, FU	Yes	–	N/A	–
Johnson [49] (phenobarbital group)	54	100/64	6 weeks (median)	BrIDA	1	P	Yes	Yes	Yes	US, scintigraphy, LB, B, S, IOC, sepsis work-up	Yes	4	N/A	–
Johnson [49] (Ursodexoycholic acid group)	7	–/71	N/A	BrIDA	1	U	Yes	No	Yes	US, scintigraphy, LB, B, S, IOC, sepsis work-up	Yes	–	N/A	–
Manolaki [50]	63	96/33	11.4 weeks (mean)	BIDA	5	No	Yes	Yes	Yes	B, LB	No	–	N/A	–
El Tumi [51]	54	100/78	3–16 weeks	DISIDA	1	P	Yes	Yes	Yes	B, LB, FU	Yes	–	21/22 at 4 h, and 1/22 at 7 h	Hepatic to cardiac uptake (2.5–10 min after injection) was different between BA and NH
Karim [52]	58	100/100	3.5 months (mean)	BrIDA	3	P	Yes	Yes	Yes	US, scintigraphy, LB, B, S, IOC, sepsis work-up	Yes	4	N/A	–
Majd [53]	32	100/47	41.3 months (mean)	PIPIDA	1	No	Yes	Yes	Yes	Scintigraphy, IOC, LB	Yes	–	N/A	–
Majd [53] (phenobarbital group)	16	100/85	39.6 days (mean)	PIPIDA	1	P	Yes	No	No	Scintigraphy, IOC, LB	Yes	–	N/A	–
Sevilla [54] (planar group)	94	100/69	7 weeks (mean)	DISIDA	1.1	No	No	Yes	N/A	LB, IOC, S, B, US, scintigraphy	Yes	5	14 at 1 h. 35 at 4–6 h 2 at 24 h	–
Sevilla [54] (phenobarbital group)	11	100/89	7 weeks (mean)	DISIDA	1.1	P	Yes	No	N/a	LB, IOC, S, B, US, scintigraphy	Yes	–	N/A	–
Sevilla [54] (SPECT group)	80	100/77	7 weeks (mean)	DISIDA	1.1	No	Yes	Yes	N/A	LB, IOC, S, B, US, scintigraphy	Yes	–	46/80 at 4–6 h	–
Gilmour [55]	86	100/72	BA 65 days, NH 47 days (mean)	N/A	N/A	P	Yes	Yes	Yes	Scintigraphy, LB, S, B, IOC	Yes	–	–	Liver and heart activity over 60 min was not different between NH and BA
Verreault [56]	25	88/87	2 months (mean)	DISIDA	1	P	No	No	Yes	Scintigraphy, LB, IOC	Yes	1 (without excretion at 24 h)	N/A	Hepatic to heart uptake. BA 12/17 had normal hepatic uptake and NH 5/8 had normal uptake

Table 1 (continued)

First author [ref]	Sample size	Sensitivity/ specificity (in %)	Mean age of patients	Tracer bond to Tc-99m	Dose of the radiotracer (in mCi)	Premedication	Quality assessment according to Oxford Centre for Evidence Based Medicine					Choledochal cyst	Contribution of 24h imaging	Semiquantitative evaluation of scintigraphy images
							Consecutive recruitment of patients	Appropriate spectrum of including patients	Blindness of reviewers to information other than scintigraphy	Gold standard	Enough explanation to ensure reproducibility			
Donia [57]	50	100/77	83±56 days	BrIDA	N/A	P	Yes	Yes	No	US, LB, B, S	Yes	–	N/A	–
Shimono [58]	14	100/43	63 days (mean)	BIDA	2	No	Yes	Yes	Yes	Scintigraphy, IOC	Yes	–	N/A	Hepatocellular clearance was minimally higher in BA compared to NH
Ohi [59]	13	100/100	76 days (mean)	EHIDA	100 μ Ci/kg	No	Yes	Yes	Yes	Scintigraphy, IOC, LB, US	Yes	–	N/A	Liver to cardiac ratio. BA 4/5, NH 5/8 had normal clearance
Ryeom [60]	21	100/65	68.7 days (mean)	DISIDA	0.25 mCi/kg (9.25 MBq/kg)	P	Yes	Yes	Yes	MRCP, US, Scintigraphy, IOC	Yes	–	N/A	–
Kim [61]	23	100/75	59 days (mean)	DISIDA	5	P	Yes	Yes	Yes	IOC, LB	Yes	1	N/A	–
Lee [62]	95	98/60	73±29 days	N/A	N/A	No	Yes	Yes	No	B, scintigraphy, S, LB	No	–	N/A	–
Park (Seoul group) [63]	27	100/83	N/A	HIDA	2	No	No	Yes	N/A	LFT, scintigraphy	No	2	N/A	Hepatic extraction (10 min after injection). NH 11/18, BA 3/9 had decreased uptake
Park (Taego group) [63]	71	94/35	12–120 days	DISIDA	1	P	Yes	Yes	No	US, Scintigraphy, LB	Yes	–	N/A	–
Choi [65]	40	100/54	48.3 days (mean)	DISIDA	0.5	P	Yes	Yes	No	US, LB	Yes	–	N/A	–
Kirks [66]	14	100/71	7 days to 2 years	DISIDA	50 μCi (1.85 MBq)/kg minimum of 1 mCi (37 MBq)	P	Yes	Yes	N/A	IOC, LB, FU, autopsy	Yes	1 without excretion	N/A	–
Spivak [67] (phenobarbital group)	28	100/66	N/A	DISIDA	1	P	Yes	Yes	Yes	IOC, LB, FU	No	–	N/A	Cardiac blood pool 20 to 30 min after injection was different between BA and NH
Spivak [67]	10	100/62	N/A	DISIDA	1	No	Yes	No	No	IOC, LB, FU	No	–	N/A	–
Burton [68]	14	83/50	2.4 months (mean)	DISIDA	66 μ Ci/kg, 2.44 MBq/kg	No	No	No	Yes	S, B, US, scintigraphy, IOC, LB	No	1 without excretion at 22 h	N/A	–
Leonard [69]	23	100/37	0.5–4 months	EHIDA	0.09 mCi (2.2 MBq)/kg	No	No	Yes	N/A	LB	No	–	N/A	Time-activity curves could differentiate BA from NH
Ferry [70]	9	100/80	N/A	PIPIDA	N/A	No	No	Yes	No	LFT, scintigraphy, IOC, LB, autopsy	No	–	N/A	–
Karanes [71]	14	100/67	40–140 days	DISIDA	1	No	Yes	Yes	N/A	Scintigraphy, IOC, LB	Yes	–	N/A	–
Charearnrad [72] (phenobarbital group)	77	100/66	1.9± 0.2 months (mean)	DISIDA	1.85 MBq/kg	P	Yes	Yes	N/A	Scintigraphy, IOC, LB, IOC	Yes	–	N/A	–

Table 1 (continued)

First author [ref]	Sample size	Sensitivity/ specificity (in %)	Mean age of patients	Tracer bond to Tc-99m	Dose of the radiotracer (in mCi)	Premedication	Quality assessment according to Oxford Centre for Evidence Based Medicine					Choledochal cyst	Contribution of 24h imaging	Semiquantitative evaluation of scintigraphy images
							Consecutive recruitment of patients	Appropriate spectrum of including patients	Blindness of reviewers to information other than scintigraphy	Gold standard	Enough explanation to ensure reproducibility			
Charearnrad [72] (no premedication group)	18	100/100	1.9± 0.2 months (mean)	DISIDA	1.85 MBq/kg	No	Yes	Yes	N/A	Scintigraphy, IOC, LB, IOC	Yes	–	N/A	–
Wongsawasdi [73] (2003 study)	54	100/65	BA: 93.4 days, NH: 84.7 days (mean)	HIDA	N/A	P	Yes	Yes	Yes	LFT, S, US, scintigraphy, IOC	No	1	N/A	–
Wongsawasdi [74] (2008 study)	54	100/92	BA: 88.6 days, NH: 63.1 days (mean)	DISIDA	N/A	P	Yes	Yes	Yes	LFT, S, US, scintigraphy, LB, IOC	No	–	N/A	–
Kuloğlu [75]	39	100/81	2 months (mean)	N/A	N/A	N/A	Yes	Yes	Yes	LFT, S, B, LB	No	–	N/A	–
Jaw [77] (1999 study)	16	100/60	46 days (mean)	DISIDA	0.25 mCi/kg (9.25 MBq/kg)	P	Yes	Yes	Yes	LFT, MRCP, LB, FU	Yes	1 not seen on scan	N/A	–
Jaw [76] (1984 study)	23	100/63	61 days (mean)	DISIDA	1	P	Yes	Yes	N/A	IOC, LB, FU	Yes	–	N/A	–
Huang [78]	19	100/30	BA 2.2±1.1, NH 3.7± 2.9 months	DISIDA	1+Booster	P	Yes	No	No	IOC, US	No	29 (11 BA; 18 NH)	N/A	–
Lee [79]	143	100/85	55±18 days	DISIDA	1+Booster	P	Yes	No	No	IOC, LB, FU, scintigraphy	Yes	–	N/A	–
Lin [80]	63	100/87	55 days (mean)	DISIDA	0.7	PC	Yes	Yes	Yes	IOC, LB, S, B, FU	Yes	3 at 24 h	N/A	–
Wen	42	100/30	10–320 days	DISIDA	1	No	Yes	Yes	No	Imaging, IOC	No	–	N/A	–
Portnoy [82]	39	100/58	4–8 weeks	BIDA	N/A	P	Yes	Yes	No	LFT, B, LB	No	–	N/A	–
Guiscafre [83]	26	100/100	3 months	BIDA	200 μCi/kg (maximum dose 1.5 mCi)	PC	Yes	Yes	Yes	IOC, LFT, FU	Yes	–	1/10 at 6 h, 9/10 at 24 h	Flat Time Activity Curve in BA but sloping in NH
Rivera-Echegoyen [84]	30	90/25	BA 75 days, NH 49 days (mean)	HIDA	N/A	No	Yes	Yes	Yes	FU, LB, IOC	Yes	–	N/A	–
Rivera-Echegoyen [84] (phenobarbital group)	30	100/80	BA 75 days, NH 49 days (mean)	HIDA	N/A	P	Yes	Yes	Yes	FU, LB, IOC	Yes	–	N/A	–
Rendón-Macías [85]	15	100/100	BA 112 days, NH 70 days (median)	BrIDA	N/A	No	Yes	No	Yes	LFT, US, LB, IOC	No	–	N/A	–
Liberek [86]	15	100/-	2–4 weeks	EHIDA	N/A	No	Yes	No	N/A	LFT, B, S, US, IOC	No	–	N/A	–
Kaminska [87]	29	100/63	6.6 weeks (mean)	BrIDA	1.5	P	Yes	Yes	N/A	LFT, B, S, IOC	Yes	1	N/A	–

Table 1 (continued)

First author [ref]	Sample size	Sensitivity/ specificity (in %)	Mean age of patients	Tracer bond to Tc-99m	Dose of the radiotracer (in mCi)	Premedication	Quality assessment according to Oxford Centre for Evidence Based Medicine				Choledochal cyst	Contribution of 24h imaging	Semiquantitative evaluation of scintigraphy images
							Consecutive recruitment of patients	Appropriate spectrum of including patients	Blindness of reviewers to information other than scintigraphy	Gold standard	Enough explanation to ensure reproducibility		
Stepanov [88]	10	100/83	N/A	HIDA	1.5	No	Yes	Yes	Yes	Scintigraphy, IOC (in some cases suspected to BA)	No	–	N/A	–
El-Desouki [89]	44	100/50	62 days (mean)	DISIDA	1	No	Yes	Yes	Yes	US, scintigraphy, LB, IOC, S	Yes	–	N/A	–

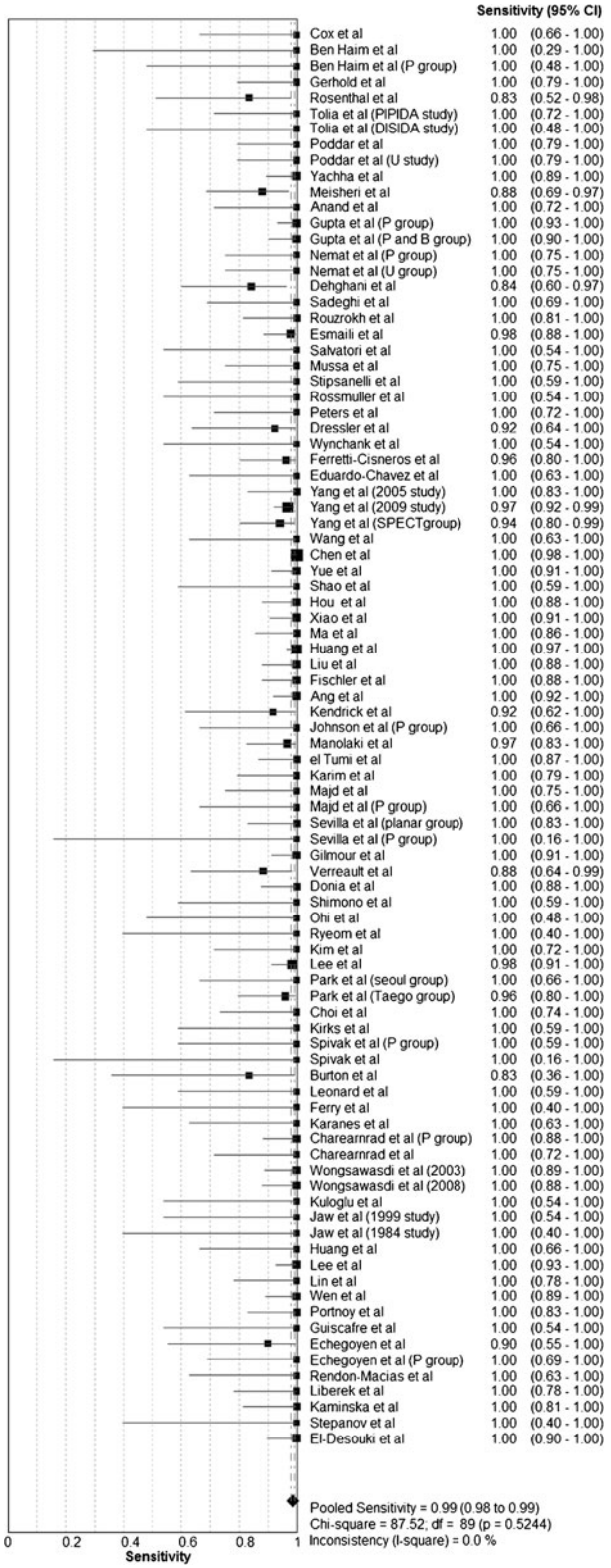

Fig. 1 Forest plot of sensitivity pooling

analysis by including only studies with at least follow-up and liver biopsy as the gold standard showed the following results:

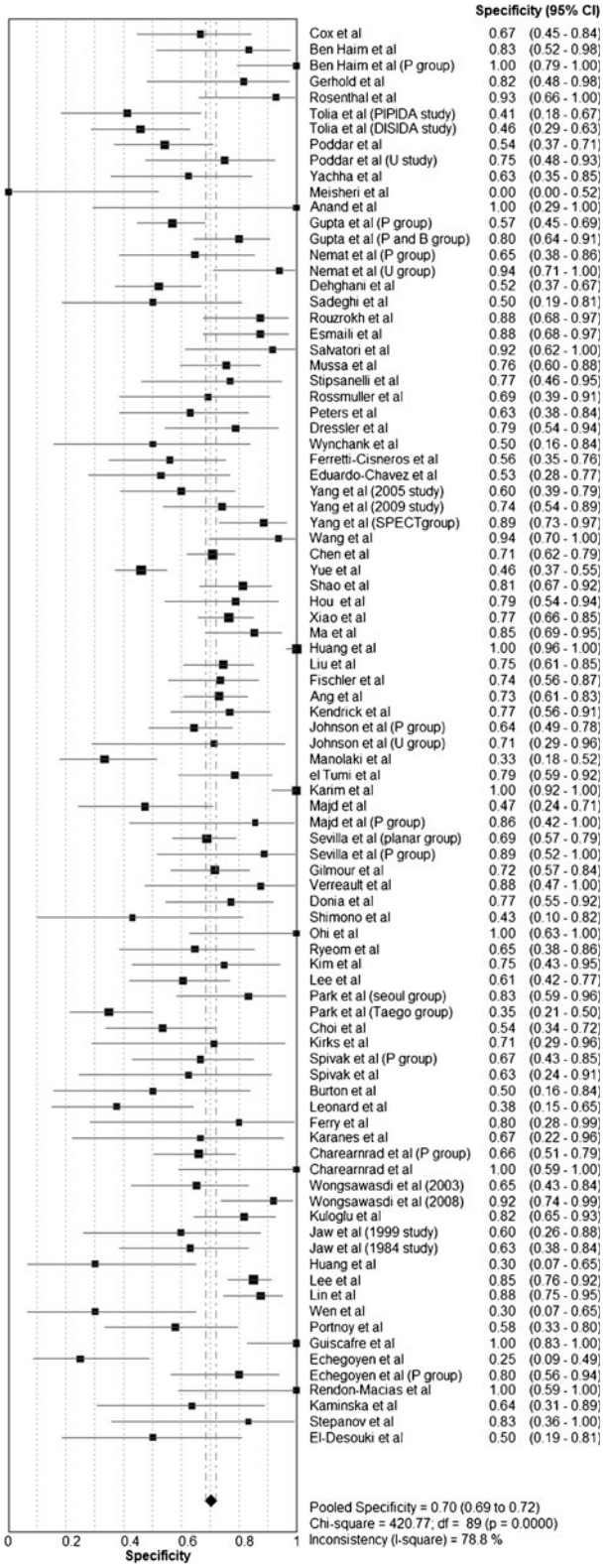

Fig. 2 Forest plot of specificity pooling

sensitivity 99.3% (range 98.3–99.8%), specificity 75.1% (range 72.2–77.9%), LR +3.19 (range 2.47–4.11), LR− 0.07 (range 0.04–0.11) and DOR 60.1 (range 31.6–114.3).

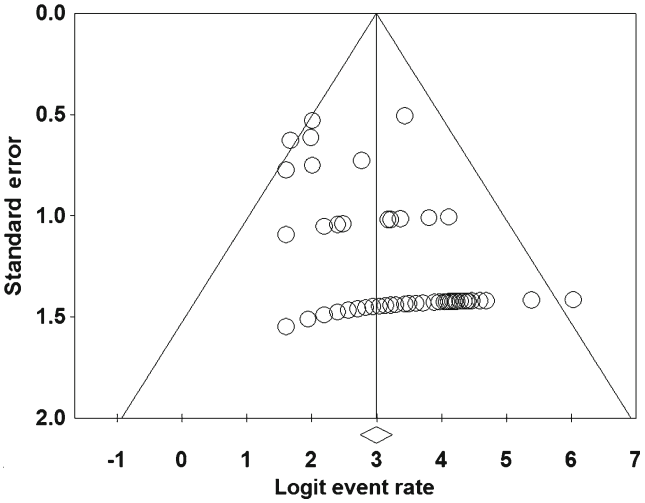

Fig. 3 Funnel plot of sensitivity pooling

Figures 3 and 4 show the funnel plots of sensitivity and specificity pooling. The Egger linear regression intercept for sensitivity and specificity pooling was 1.02 ($P<0.01$) and 1.31 ($P<0.01$) respectively. Using Duval and Tweedie's [11] trim and fill method, 31 studies for sensitivity pooling and 19 studies for specificity pooling were trimmed, and adjusted pooled sensitivity and specificity were 2% and 5% lower than the observed values. The sROC of the meta-analysis is shown in Fig. 5 with an AUC of 0.96 and Q* of 0.9.

Table 2 shows the subgroup analyses of the study regarding type of radiotracer, dosing protocol and premedications used. R^2 indices showed that 20%, 18% and 10% of the between-study variability of the specificities could be explained by the type of the radiotracer, premedication used and dosing protocol, respectively. Non-imaging methods, namely sampling of the gastrointestinal fluids, were also used in six studies and their results are shown in Table 2.

Twenty studies included information on individual patients, and overall information on 389 patients was available for further evaluation. We compared patients diagnosed

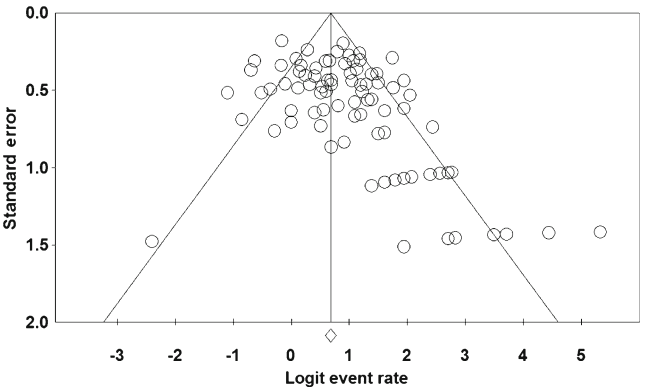

Fig. 4 Funnel plot of specificity pooling

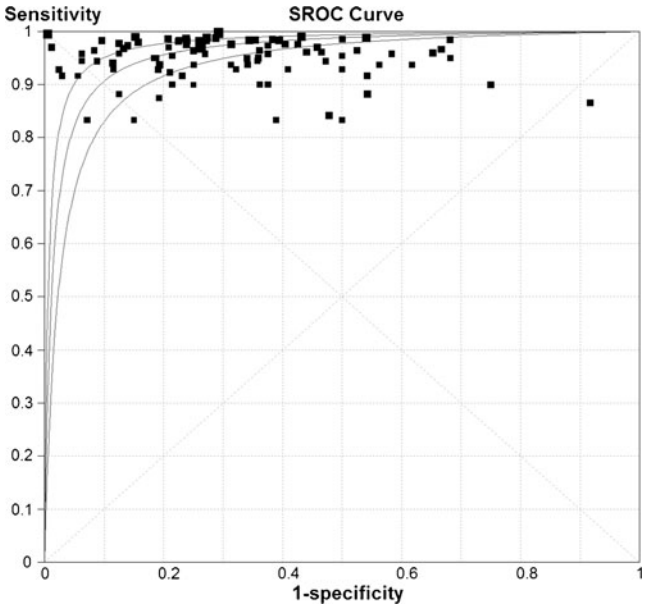

Fig. 5 Summary receiver operating characteristics (SROC) curve of the study. Area under the curve (AUC)=0.96; standard error (SE) (AUC)=0.01; Q value (Q*)=0.90; SE (Q*)=0.02

with neonatal hepatitis (NH) who had false-positive (no excretion of radioisotope tracer into the bowel) and true-negative (excretion of the tracer into the bowel) scintigraphy. There was a statistically significant difference between these groups regarding total serum bilirubin (P=0.03). However, no statistical difference was noted when comparing age at imaging (P=0.1) and gender of the patients (P=0.19). Logistic regression analysis showed that one unit increase in total or direct bilirubin would increase the odds of getting false-positive results by 0.6%.

The effect of radiotracer dosage on the accuracy of the hepatobiliary scintigraphy was also evaluated by meta-regression. The R^2 index showed that 5% of the variability in specificity across studies could be explained by the dose. In studies with a fixed dose of radiotracer, there was a correlation coefficient of 0.104 with DOR. Each unit increase in dose (in mCi) resulted in 0.14 increase in DOR.

Overall test accuracy

Hepatobiliary scintigraphy performs well in differentiating neonatal hepatitis and biliary atresia (pooled DOR 55.75, AUC 0.96 and Q* 0.9). Pooled sensitivity was very high (98.7%). This shows that false-negative results (excretion of the tracer into the bowel despite biliary atresia) are extremely rare. It is very probable that these false-negative results are misinterpretations of the scan; Verreault et al. [56] reported two false-negative results that were caused by urine contamination interpreted as bowel excretion.

On the other hand, the pooled specificity of the test was not that high (70.4%). This means that false-positive results (no excretion of tracer and bowel non-visualization in neonatal hepatitis) are the major shortcoming of hepatobiliary scintigraphy. Most of the methods used for increasing the accuracy of hepatobiliary scintigraphy aim at increasing the specificity, as shown in Table 2. The rest of the discussion is focussed on how each variable affects specificity, which is the index of more interest in hepatobiliary scintigraphy.

Specificity variables

Type of radiotracer

Radiotracers with higher hepatic excretion had better specificity. The highest pooled specificity was achieved using BrIDA and IODIDA (76.8% and 78.3%, respectively), which have high extraction efficiency compared to BIDA and HIDA (57% and 64.8% pooled specificity, respectively) [94]. Higher hepatic extraction efficiency results in more tracer excretion into the GI tract with better chance of bowel visualization in patients with neonatal hepatitis.

Premedication

Several premedications have been used for increasing the specificity of hepatobiliary scintigraphy. These drugs improve hepatic cellular function, which can increase the specificity of hepatobiliary scintigraphy. The results of our meta-analysis support this concept. Studies that used no premedication showed lower specificity (67.6%) compared to those that used phenobarbital (72.2%), phenobarbital and cholestyramine (70.8%), and ursodeoxycholic acid (84.8%). The number of studies that used the latter two is low. This is apparent in Table 2 as wide confidence intervals; however, more studies are needed for better evaluation of these pretreatments. Another pretreatment was phenobarbital and betamethasone, which was used in only one study with excellent results (sensitivity 100% and specificity 80%) [23]. Further studies are needed for better evaluation of corticosteroid effects on hepatobiliary scintigraphy.

Dosing protocol

The methods used in this meta-analysis review included fixed dosing, calculated dosing (per kilogram of body weight) and dosing in addition to a delayed booster dose. The studies with calculated dose per kilogram of body weight had higher pooled specificity compared to those using fixed dosing (74.3% vs 68.8%). Each unit increase (1 mCi) in dose of the injected tracer resulted in a 0.14 increase in DOR; however, this is not high enough to encourage high-dose scintigraphy in

Table 2 Subgroup analyses of the studies regarding type of radiotracer, dosing protocol, and premedications used. *DOR* diagnostic odds ratio, *LR−,* negative likelihood ratio, *LR* + positive likelihood ratio

		Sensitivity (%)	Specificity (%)	LR+	LR−	DOR	R^2 index for specificity pooling
Type of radiotracer	BrIDA	99.6 [97.8–100]	76.8 [71.7–81.4]	3.49 [2.51–4.86]	0.049 [0.025–0.095]	101.27 [46.21–221.92]	20%
	BIDA	98.4 [91.5–100]	57 [45.3–68.1]	1.97 [1.11–3.47]	0.084 [0.024–0.29]	29.67 [7.19–122.33]	
	PIPIDA	100 [90–100]	54.2 [39.2–68.6]	1.94 [1.33–2.81]	0.089 [0.023–0.34]	29.24 [6.011–142.28]	
	DISIDA	98.3 [96.6–99.3]	69.2 [65.8–72.5]	2.84 [2.28–3.53]	0.089 [0.058–0.13]	42.64 [25.27–71.94]	
	HIDA	99.4 [96.4–100]	64.8 [57.8–71.4]	2.92 [1.79–4.76]	0.065 [0.023–0.18]	52.67 [14.57–190.4]	
	IODIDA	100 [90–100]	78.3 [63.6–89.1]	3.96 [2.37–6.62]	0.044 [0.006–0.29]	129.87 [14.57–1157.2]	
	EHIDA	98.6 [97.6–99.3]	72.5 [69.5–75.4]	3.45 [2.57–4.62]	0.051 [0.029– 0.092]	88.23 [40.47–192.33]	
Premedication	No medication	98.2 [97.3–98.9]	67.6 [65–70.2]	2.7 [2.2–3.31]	0.077 [0.052–0.114]	45.11 [26.34–77.25]	18%
	Phenobarbital	98.8 [97.8–99.5]	72.2 [69.4–74.8]	3.18 [2.67–3.8]	0.067 [0.046–0.097]	66.09 [42.35–103.12]	
	Phenobarbital and cholestyramine	100 [90.5–100]	70.8 [61.8–78.8]	3.37 [1.26–9.03]	0.084 [0.022–0.32]	51.58 [8.26–321.8]	
	Ursodeoxycholic acid	100 [88.1–100]	84.8 [68.1–94.9]	5.46 [1.76–16.85]	0.039 [0.006–0.27]	156.97 [17.06–1443.7]	
Imaging	SPECT	96.3 [87.3–99.5]	81.1 [71.7–88.4]	5.31 [2.46–11.44]	0.057 [0.017–0.19]	126.02 [27.98–567.43]	N/A
Dosing protocol	Fixed dose	98.8 [98–99.3]	68.8 [66.4–71]	2.91 [2.45–3.44]	0.066 [0.048–0.09]	56.22 [37.77–83.68]	10%
	Calculated dose per Kg	97.9 [95.3–99.3]	74.3 [69.7–78.5]	3.19 [2.46–4.14]	0.089 [0.051–0.15]	55.33 [27.69–110.56]	
	Fixed dose with booster	100 [94.6–100]	82.6 [75–88.6]	4.53 [1.24–16.54]	0.072 [0.018–0.28]	81.56 [10.48–634.53]	
Non-imaging methods	Overall GI fluid sampling	94.2 [89.9–97.1]	73.2 [68.2–77.7]	3.006 [1.87–4.8]	0.14 [0.063–0.31]	24.3 [8.77–67.27]	N/A
	Duodenal sampling	94.6 [90.3–97.4]	77.1 [72.1–81.6]	3.48 [2.28–5.31]	0.12 [0.053–0.26]	32.26 [12.79–81.37]	N/A

fixed-dosing protocols. Use of a booster dose in non-excretory scans resulted in the highest specificity, 82.6%. This can be explained by the higher amount of radiotracer available for bowel visualization in booster dose and calculated dosing protocols.

Imaging protocol

Delayed imaging seems to be very useful to decrease false-positive results, as shown in Table 1. The contribution of 24-h imaging seems important: Stipsanelli et al. [29] and Shao et al. [42] reported that 12/24 and 23/43 cases of bowel visualization occurred on 24-h images.

The SPECT method resulted in fairly high specificity (81.1%), which was associated with better bowel visualization compared to planar images. However, only two studies evaluated the SPECT method (note wide confidence interval in Table 2) and further studies are needed [38, 54].

Semiquantitative imaging methods

The ratio of hepatic-to-cardiac (or renal) uptake 5–10 min post radiotracer injection was used in several studies to differentiate between biliary atresia and neonatal hepatitis [13, 15, 27, 29–33, 44, 51, 55, 56, 58, 59, 63, 67]. However, these studies are inconsistent regarding this approach; some reported higher hepatic-to-cardiac ratio in children with biliary atresia and others reported a lower ratio (Table 1). Overall, hepatic-to-cardiac ratio was not able to differentiate between neonatal hepatitis and biliary atresia in most studies and only two studies showed an incremental value by this method [29, 51]. Another semiquantitative method was the time activity curve (TAC) of hepatic excretion, which was evaluated in four studies [14, 32, 69, 83]. It was reported that children with biliary atresia have a flat time activity curve whereas children with neonatal hepatitis have a sloping and oscillating curve [69, 83]. However, Ben-Haim et al. [14] and Dressler et al. [32] did not report any incremental value for TAC and further studies on this concept are needed.

Non-imaging methods

Sampling of gastric and duodenal [16, 34, 44, 45, 92, 93] fluids and measurement of their activities were evaluated as a method to increase the accuracy of hepatobiliary scintigraphy. Overall, gastrointestinal (GI) sampling had fairly high specificity (73.2%); however, including only duodenal fluid sampling in the analysis resulted higher pooled specificity (77.1%). It seems that GI fluid sampling by detecting minimal activity in the bowel (which is otherwise undetectable by gamma camera) can improve the specificity.

Effect of age at imaging and total/direct serum bilirubin

The age of the patients at the time of imaging was not statistically different between children with neonatal hepatitis who had true-negative and false-positive hepatic scintigraphy. However, the total/direct serum bilirubin level could influence the result of scintigraphy (one unit increase in total or direct bilirubin would increase the odds of getting false-positive results by 0.6%). Raised total/direct bilirubin level is an indicator of hepatic dysfunction, and a higher serum bilirubin level indicates a more profound abnormality and higher chance of getting false-positive results.

Other important issues

Publication bias

We evaluated publication bias using funnel plots and several statistical methods. Funnel plots of sensitivity and specificity pooling showed considerable asymmetry, confirmed by the statistically significant Egger linear regression method. This means that publication bias could affect the results of our meta-analysis. To quantify possible publication bias, we use Duval and Tweedie's [11] trim and fill method, which showed 2% and 5% decreases in sensitivity and specificity after adjusting the observed results for possible publication bias. Overall, publication bias can be of concern, especially for specificity pooling, and this can be considered a limitation of our study.

Quality of the included studies

Not all studies in this meta-analysis were of the same quality, as shown in Table 1. Many of the studies had non-consecutive recruitment or a narrow spectrum of studied patients. However, the most important limitation is the inconsistency in gold standard tests used for diagnosis of biliary atresia or neonatal hepatitis. Although many studies used a combination of tests and follow-up for final diagnosis of biliary atresia and neonatal hepatitis, the studies we included were not consistent in this regard and not all studies used the same diagnostic tests. This can affect the accuracy of hepatobiliary scintigraphy reported by different studies and can be considered the major limitation of this meta-analysis. However, sensitivity analysis including only studies using at least follow-up and liver biopsy as the gold standard showed minimal difference in the pooled diagnostic accuracy indices and it seems that our meta-analysis was fairly robust to the variations of gold standard across studies.

Conclusion

Hepatobiliary scintigraphy using IDA derivatives can be very useful for diagnostic work-up of the neonatal cholestasis. To improve the specificity (excretion of the tracer into the bowel in children with neonatal hepatitis), several measures can be followed regarding type and dose of radiotracer and imaging protocols. Non-imaging methods seem to be promising and need further evaluation.

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