



Ultrasound elastography in the diagnosis of biliary atresia in pediatric surgery: a systematic review and meta-analysis of diagnostic test

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Background: Biliary atresia (BA) is one of the most fatal hepatobiliary diseases in infants and young children, and is easy to cause obstructive jaundice in infants and children, and liver transplantation in children. BA and infantile hepatitis syndrome are the main causes of cholestatic jaundice. The early clinical manifestations are extremely similar, and timely identification is difficult. Therefore, early and differential diagnosis of BA is crucial. At present, there are many imaging diagnosis methods for BA, such as ultrasound examination and nuclear magnetic resonance. Ultrasound elastography (USE) is the most popular method. However, the application of USE in BA is still in the exploratory stage.

Methods: PubMed, Web of Science, Embase, Cochrane Library, and other databases were searched for articles on USE diagnosis of pediatric surgical BA. Later, the articles were screened, and the included articles should meet the following requirements: the research objects were children with BA; the intervention measures were USE diagnosis; the control group was diagnosed by other methods than USE. RevMan5.3 was adopted for quality assessment, and forest maps and summary receiver operating characteristic (SROC) curves were constructed.

Results: Finally, seven articles covering 490 patients were included. There were 120 patients in the control group. The included articles showed good quality and there was no obvious bias. The area under the SROC curve (AUC) for USE diagnosis of BA was 0.93, the sensitivity was 0.93 (95% CI: 0.72–1.00), and the specificity was 0.95 (95% CI: 0.74–1.00).

Discussion: USE showed high diagnostic value for pediatric surgical biliary tract closure.

Keywords: Ultrasound elastography (USE); pediatric surgery; biliary atresia (BA); diagnosis; meta-analysis

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Introduction

Biliary atresia (BA) is a common and serious hepatobiliary disease in neonates. It is generally caused by intrahepatic BA, resulting in intrahepatic cholestasis, which further leads to liver injury and fibrosis progression from the frontal day (1). Untreated treatment often leads to liver failure and

ultimately death. The clinical symptoms of BA are often similar to those of some cholestasis disorders (2-4). This brings great challenges to the clinical diagnosis of BA. Early and effective treatment of BA can significantly improve the prognosis of patients (5). Clinical study shows that the jaundice clearance rate of children with BA is 52.5% at

1 month after birth, 42.2% at 2 months after surgery, and only 10.2% at 73 days after surgery (6). Other studies have shown that for children with BA, open surgery can provide the optimal survival time of their own liver within 55 days after birth (7-9). If the child was older than 62 days, each 9-day delay reduced the surgical success rate by 48.0% and the risk of liver failure obviously increased. As the liver fibrosis process of BA is earlier and faster than other biliary diseases, the early differential diagnosis of BA is very important. However, due to the clinical characteristics of BA similar to other biliary diseases, the early diagnosis of BA is a major clinical challenge (10-12).

In recent years, ultrasound elastography (USE) has been widely used in adult liver, breast, thyroid, prostate, and other organs, and has shown broad application prospects in non-invasive evaluation of tissue stiffness. USE is a newly developed elastography technology based on two-dimensional ultrasound imaging (13,14). By measuring the propagation velocity of shear wave in tissue, the hardness of tissue can be measured indirectly and quantitatively. Compared with 1d elastography, USE is less affected by tissues and patients, and shows faster and more accurate measurements and great advantages in the diagnosis and treatment of childhood diseases (15-17). Compared with other ultrasound techniques, USE has the following advantages. First, it is based on traditional ultrasound diagnostic equipment and makes full use of real-time grayscale imaging mode to evaluate tissue morphological changes or avoid large vessels, which is superior to transient elastography (TE) (18,19). Second, the use of larger and wider s-waves enhances the ability to identify the extent of liver fibrosis, making it more effective in the diagnosis of liver fibrosis. Finally, USE allows real-time analysis and mapping of elastograms in this area, which exceeds the capabilities of TE and acoustic radiation force impulse (ARFI) (20). However, its test results are susceptible to exercise, diet, liver congestion, transaminase, inflammation, and other factors. Therefore, its diagnostic efficiency in child missile lock-in is still controversial. For example, some scholars compared the effectiveness of USE and magnetic resonance cholangiopancreatography (MRCP) in the diagnosis of neonatal BA. The results show that diagnostic accuracy of USE is lower than that of MRCP. Therefore, the diagnostic efficacy of USE in pediatric BA needs further study and unification (21,22). This work intended to conduct a meta-analysis of the related literature on USE in diagnosing BA in recent years, and preliminatively evaluate

its diagnostic value. We provide the following articles based on the PRISMA-DTA reporting checklist (available at <https://tp.amegroups.com/article/view/10.21037/tp-22-159/rc>).

Methods

Literature retrieval

Articles published from establishment date till now were searched from PubMed, Medline, Embase, Chinese BioMedical Literature Database (CBM), WanFang, and other databases. The subject terms included “Ultrasonic elastography” and “biliary atresia” when searching. The above phrases were combined for search to obtain more documents. The search terms appeared in the title, keywords, abstract, etc. Some references cited by the articles could be traced back.

How to include and exclude the literature

According to the principles of PICOS, the literature retrieval standards were defined. Articles meeting following criteria could be included in this study: (I) articles that were diagnostic study designs; (II) studies involving research subjects who were obstructive jaundice patients and met the obstructive jaundice diagnostic criteria; (III) articles whose test standard was USE; (IV) studies that applied the gold standard for the diagnosis of BA (i.e., clear fibrosis of the gallbladder cord by surgical exploration, intraoperative cholangiography suggesting that the intra- and extra-hepatic bile ducts were not developed, and postoperative pathological examination confirmation of BA); (V) studies that applied the gold standard for diagnosis of non-BA (i.e., intraoperative cholangiography indicating patency of the bile ducts inside and outside the liver, pathological examination of liver biopsy indicating other cholestatic diseases, and clinical conservative treatment and follow-up of jaundice resolution); (VI) articles involving observation indicators such as sensitivity and specificity, and those in which the data required by the four-grid table could be extracted. Articles meeting the following criteria were excluded: (I) reviews, conference papers, dissertations, newsletters, case reports, etc.; (II) replications or duplicates of published data; and (III) articles that did not include the data required by the four-grid table.

Quality assessment

Two researchers were required to use RevMan5.3 software (Cochrane Collaboration, UK) and the quality assessment of diagnostic accuracy studies (QUADAS) for quality assessment of the searched articles. If there was any disagreement between the two researchers, a third researcher was invited to conduct an intervention evaluation, and a consensus could be reached through discussion. The evaluation criteria covered the cases selection, assessment method, gold standard, assessment process, and progress.

A total of 16 items were included in the QUADAS tool to evaluate the included articles, and the quality assessment results were displayed as “Yes”, “No”, and “Unclear”. “Yes” signified that the standard was met and “No” meant that the standard was not satisfied. When the information was incomprehensive or only partially met the standard, it was defined as “Unclear”.

Data extraction

Two researchers were required to independently read the titles and abstracts of the retrieved literature, complete the literature selection process, and obtain the full texts, and extract required information. The two researchers could discuss to solve the disagreement, and a third researcher was required to arbitrate in cases where a unanimous opinion could not be reached.

The data to be extracted included first author, year of publication, research country, detection method, gold standard, numbers of true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN), and other information. The researchers were required to verify the data and then conduct a systematic analysis.

Statistical analysis

RevMan5.3 software was adopted for risk bias analysis. The SROC curve was adopted for diagnostic analysis; a shoulder-like shape of SROC curve meant the consistency was found, or the sensitivity was negatively correlated with specificity ($P < 0.05$). After SROC curve was obtained, the area under SROC curve (AUC) should be calculated, and the value of the diagnostic test based on the AUC was calculated. An AUC of 0.5–0.7, 0.7–0.9, and 0.9–1.0 signified a low, medium, and high diagnosis rate, respectively.

Results

Literature retrieval and basic characteristics of the included articles

A total of 864 records were initially retrieved, and 837 abstracts related to this study were obtained after deleting duplicates. After the titles and abstracts of these articles were read, they initially screened and retrieved 48 articles were qualified. After further reading the full texts of these studies and excluding non-random, duplicate publications, and unavailable articles, seven qualified articles were finally included (23–29). The literature retrieval process was displayed in *Figure 1*, and related basic information was given in *Table 1*.

Quality assessment

Firstly, the tool recommended by the Cochrane System Review Manual was adopted for quality assessment. The results were illustrated in *Figures 2, 3*. The evaluation revealed that Dillman *et al.*'s equivalence (29) was not clear about the risk, and Duan *et al.* (23) was high-risk. Taken together, the seven included articles exhibited a large proportion of “low risk” and “low concerns”, which suggested that the included studies met the analysis requirements.

Subsequently, the QUADAS was employed for quality assessment each article (*Table 2*). This evaluation showed that all seven articles showed a low risk of bias, satisfying the requirements.

Meta-analysis of BA diagnosed with USE

We evaluated the diagnostic value of USE in BA in pediatric surgery, and the results are shown in *Figure 4*. Our findings indicated that the estimated sensitivity range of USE for the diagnosis of BA in pediatric surgery was 0.72–1.00, and the specificity of diagnosis was 0.74–1.00.

SROC of BA diagnosed by USE

A bivariate model was used to analyze the diagnostic value of USE in BA in pediatric surgery (as illustrated in *Figure 5*). Our findings suggested that aggregate estimated value of sensitivity and specificity for different studies were 0.93 (95% CI: 0.70–1.00) and 0.95 (95% CI: 0.35–1.00), respectively, and the AUC was 0.93.

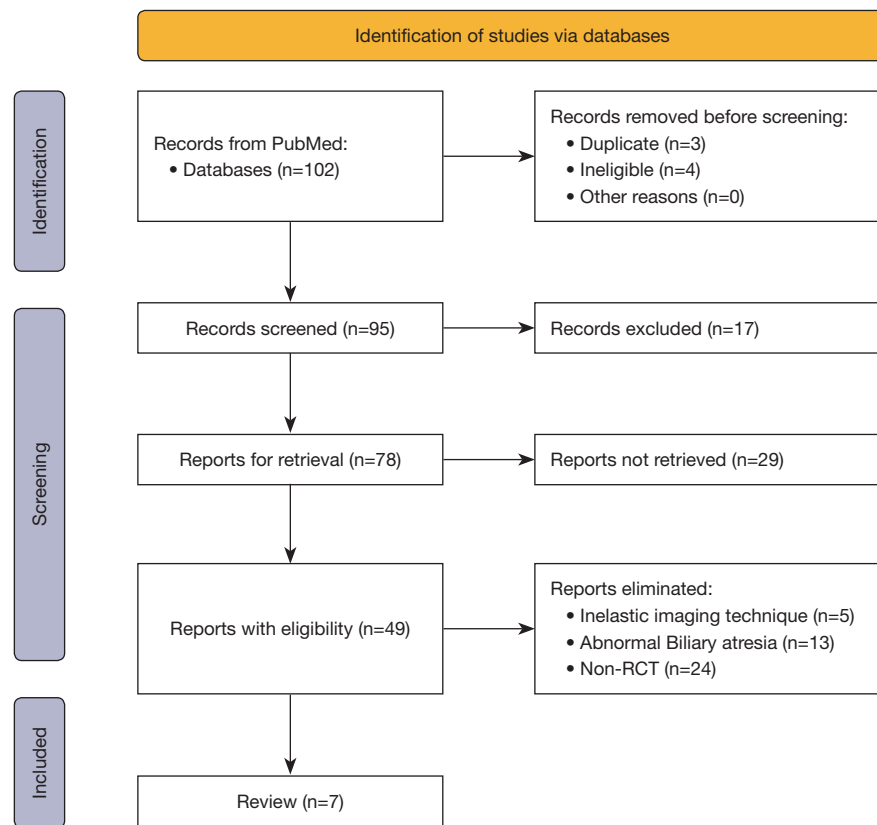


Figure 1 Literature retrieval process.

Table 1 Basic characteristics of articles

First author	Year of publication	TP	FP	FN	TN	Gold standard
Duan	2019	37	0	14	87	Cholangiography
Wu	2018	15	0	0	33	Cholangiography
Hanquinet	2015	7	1	3	9	Cholangiography
Shima	2012	7	0	0	1	Cholangiography
Wang	2016	37	1	0	31	Cholangiography
Zhou	2017	109	12	11	40	Cholangiography
Dillman	2019	13	0	0	28	Cholangiography

TP, true positives; FP, false positives; TN, true negatives; FN, false negatives.

Discussion

Elastography technology is a new ultrasound imaging technology that has been gradually developed over the past 20 years. It can detect the propagation velocity of shear waves in tissues and quantitatively measure tissue hardness, and is commonly used in liver hardness determination in

clinical practice (30). Its earliest clinical application is the one-dimensional TE, namely Fibroscan, but this is subject to the interference of the tissue itself. In addition, even slight movement by the patient during the detection process will interfere with the final detection result. Moreover, there are particular disadvantages in children with greater cooperation difficulties (especially newborns) (31).

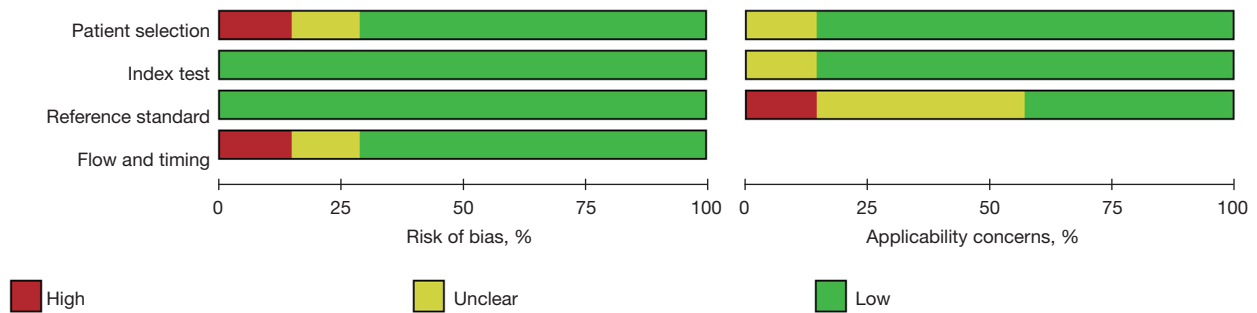


Figure 2 Risk bias assessment of articles.

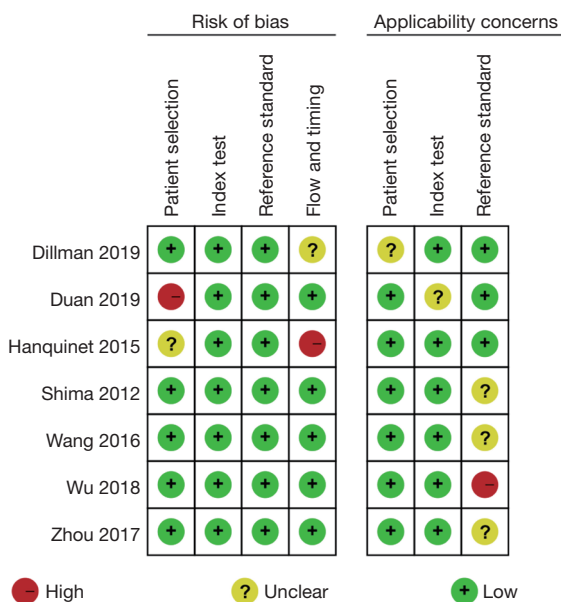


Figure 3 Multiple risk bias evaluation results.

In recent years, with the advancement of elastography technology, two-dimensional real-time shear wave elastography has slowly been adopted in clinical practice. It can select the region of interest (ROI) based on conventional two-dimensional ultrasound imaging. ARFI technology is used to generate shear waves inside the tissue, which are then received by the same ultrasonic probe to measure the wave and velocity of the shear wave (32,33). This is the most advanced elastography technology in the world. Numerous studies have shown that TE test results exhibit a good correlation with the pathological gold standard liver fibrosis classification (34,35). It is an accurate and non-invasive method for assessing the degree of liver cirrhosis; its diagnostic sensitivity can reach 80% in children and adolescents (95% CI: 70–87%), and its specificity can

reach 90% (95% CI: 84–96%) (36).

In addition, multiple studies have shown that the elastic stiffness of patients with BA is also strongly correlated with the classification of pathological liver fibrosis (37,38). Due to intrahepatic and extrahepatic bile duct obstruction caused by intrahepatic cholestasis, the liver fibrosis of BA progresses faster, and the liver stiffness value is markedly different to that of infant hepatitis syndrome and other diseases (39). Therefore, the preoperative measurement of liver stiffness may be helpful for diagnosis and treatment (40).

USE technology in the diagnosis of BA is in its infancy. Most case-control studies have small sample sizes and generally of low quality. Therefore, comprehensive analysis is required according to specific rules. All BA studies that the gold standard for diagnosing BA is not uniform, and the final diagnosis of BA mostly depends on clinical follow-up (41). At the same time, with the exception of a few studies, most research does not explain the time interval between the examination to be tested and the implementation of the gold standard, which is a major flaw of previous studies.

According to the results of various studies and the combined results of meta-analysis, USE has a certain value in the diagnosis of BA, and its sensitivity and specificity are around 90%. Ultrasound is a highly subjective examination that is closely related to the experience of the examiner, while USE is a quantitative measurement of tissue stiffness based on two-dimensional ultrasound. In the future, the addition of elasticity measurement technology to ultrasound examination will provide new insights in the diagnosis of BA.

USE is the latest reliable, non-invasive method to assess the degree of liver fibrosis. There are a limited number of studies on BA, and further research is needed to evaluate the prognosis of BA. Seven articles were included according to

Table 2 Bias risk assessment

First author	Year of publication	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Duan	2019	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	Y	Y
Wu	2018	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	Y	Y
Hanquinet	2015	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	Y	Y
Shima	2012	Y	Y	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	Y
Wang	2016	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	Y	Y
Zhou	2017	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	Y	Y
Dillman	2019	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	Y	Y

1–14 were the criteria of the QUADAS items. Y, Yes; U, Unclear.

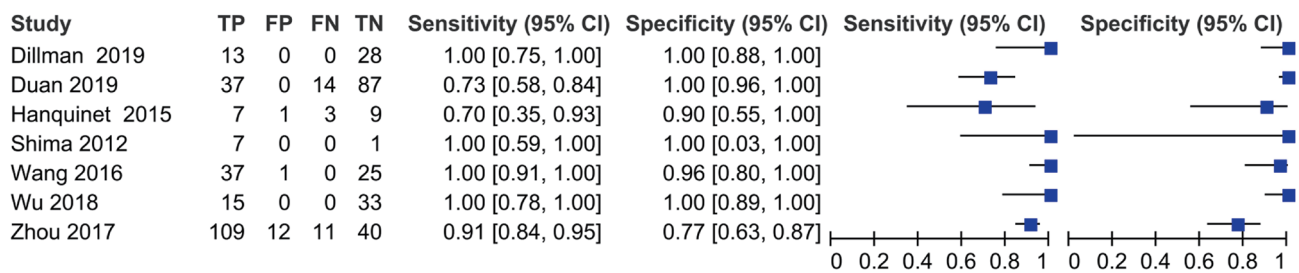


Figure 4 Diagnostic efficiency of USE in BA. TP, number of true positives; FP, number of false positives; TN, number of true negatives; FN, number of false negatives; USE, ultrasound elastography; BA, biliary atresia.

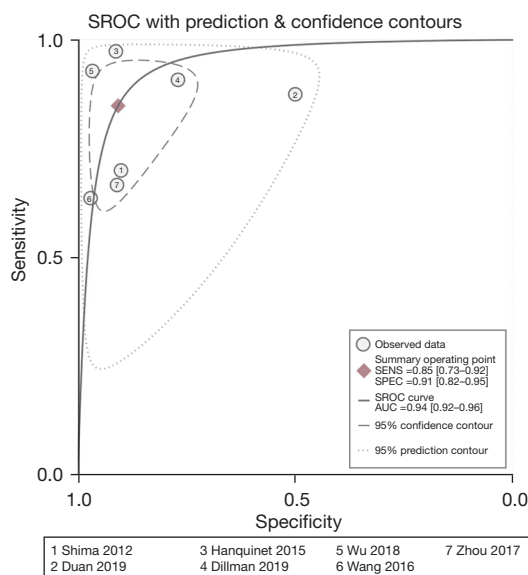


Figure 5 SROC curve for diagnostic efficiency of USE in BA. SROC, summary receiver operating characteristic; USE, ultrasound elastography; BA, biliary atresia.

the inclusion and exclusion criteria. The results suggested that the fitting AUC of USE for diagnosis of BA was 0.93, the sensitivity was 0.93 (95% CI: 0.72–1.00), and the specificity was 0.95 (95% CI: 0.74–1.00). The diagnostic efficiency fluctuates greatly, which may be affected by manipulation and image interpretation experience of doctors.

Conclusions

It aimed to evaluate systematically the clinical application value of USE in diagnosing BA. Seven related articles were included, and meta-analysis results of diagnostic accuracy rate showed that the sensitivity and specificity of USE in the diagnosis of BA were 0.93 (95% CI: 0.72–1.00) and 0.95 (95% CI: 0.74–1.00), respectively, and the AUC was 0.93. These results indicate that this method has moderate efficiency for the diagnosis of ischemic cerebrovascular disease.

However, we only used computer retrieval methods to search for relevant articles, and did not consider evaluating

the effect of combining USE and other imaging techniques in the diagnosis of BA. This would have resulted in a larger number of documents, and the article quality could have been controlled according to standards outlined in this paper.

In summary, the results could offer a theoretical basis for promoting and applying clinical diagnosis of BA via USE. We found that USE provided a certain value in BA diagnosis. However, there was a lack of high-quality prospective clinical diagnostic tests included in this analysis; hence, a prospective study with more samples was needed to confirm the accuracy of USE in the diagnosis of BA, and to further unify and improve the detection methods of USE in children.

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Footnote

Reporting Checklist: The authors have completed the PRISMA-DTA reporting checklist. Available at <https://tp.amegroups.com/article/view/10.21037/tp-22-159/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tp.amegroups.com/article/view/10.21037/tp-22-159/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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