The accuracy of magnetic resonance cholangiopancreatography in the diagnosis of biliary atresia in preterm infants with cholestasis

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Background: Magnetic resonance cholangiopancreatography (MRCP) is a useful and non-invasive method to diagnose biliary atresia (BA) in term infants, however few studies have investigated its use in preterm infants. This study aimed to evaluate the accuracy of MRCP in the diagnosis of BA in preterm infants with cholestasis.

Methods: Infants aged less than 6 months who received MRCP for cholestasis at a tertiary medical center were enrolled from 2011 to 2020. Demographic and laboratory data were retrospectively obtained. One pediatric radiologist reviewed the MRCP images. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of MRCP to diagnose BA based on surgical proof or at least 6 months of follow-up were assessed.

Results: A total of 80 infants (36 preterm and 44 term) were analyzed. The mean post-chronological age was 1.8 months, and the female-to-male ratio was 0.78. Six (16.7%) preterm and 16 (36.4%) term infants were confirmed to have BA. BA was obscured by a choledochal cyst preoperatively in two term infants. In the preterm infants, the sensitivity, specificity, PPV, NPV, and accuracy of MRCP to diagnose BA were 100%, 77%, 46%, 100%, and 81%, respectively, compared to 81%, 86%, 76%, 89%, and 84% in the term infants. Using MRCP to differentiate BA from other cholestasis in the preterm infants had superior sensitivity (100% vs. 81%) and NPV (100% vs. 89%), and lower specificity (77% vs. 86%) and PPV (46% vs. 76%) than in the term infants.

Key Words
biliary atresia; magnetic resonance cholangiopancreatography; preterm
Biliary atresia (BA) is a serious hepatobiliary disease during infancy characterized by progressive inflammation and fibrosis of the extrahepatic biliary ductal system. With inadequate or no treatment it can result in bile flow obstruction, persistent cholestasis, and secondary biliary cirrhosis.1 The early diagnosis of BA is of great clinical importance, because a timely surgical intervention can restore bile flow and prevent progression to end-stage liver disease.2 Early recognition and prompt management can improve the native liver survival rate in infants with BA. In Taiwan, the government introduced a universal infant stool color card in 2004 for the early diagnosis of BA.3 This policy increased the rate of infants with BA receiving the Kasai operation before 60 days of age, and the 5-year jaundice-free survival rate with a native liver increased from 27.3% before screening to 64.3% after screening.4 These results highlight the importance of the early and prompt diagnosis of BA in infants with cholestasis. Therefore, it is essential to develop a highly accurate diagnostic method to avoid unnecessary surgery in infants with non-BA cholestasis.5,6

Of the current diagnostic methods to differentiate BA from other infantile cholestasis diseases, liver biopsy with histological examination is the main tool with the highest sensitivity, specificity, and accuracy.7–9 However, liver biopsy has the potential risks of bleeding and infection, and it can even be life-threatening. Therefore, several non-invasive methods such as serology, ultrasonography, and hepatobiliary scintigraphy have been studied as alternatives to biopsy. However, these methods have been shown to have either low sensitivity (ultrasonography) or inadequate specificity (scintigraphy).10–12 Magnetic resonance cholangiopancreatography (MRCP) is a very reliable non-invasive imaging modality to diagnose BA, with a reported sensitivity of 87%–100% and specificity of 75%–96%.13–15 Moreover, a combination of MRCP and ultrasonography has been shown to improve the diagnostic accuracy of BA.16 Therefore, MRCP is now widely used to differentiate BA from other cholestasis in infants.

The incidence of BA in preterm infants is significantly higher than in term infants in both western (1.06 vs. 0.54 per 10,000 live births) and eastern (2.37 vs. 1.43 per 10,000 live births) countries.1,17 Preterm infants with BA usually have a delayed diagnosis and worse outcome than term infants due to the high rate of total parenteral nutrition-related cholestasis (TPN-C).18 However, the use of liver biopsy in preterm infants with cholestasis is limited because of their extremely low weight and the similar histopathology between TPN-C and BA. MRCP could be an effective non-invasive tool to overcome this issue. Therefore, the aim of this comparative study was to investigate the diagnostic accuracy of MRCP in preterm infants with BA at a tertiary referral center compared to term infants.

1. Introduction

2. Methods

2.1. Patient population

Infants aged less than 6 months who underwent MRCP due to cholestasis and clinically suspected BA at National Cheng Kung University Hospital from 2011 to 2020 were enrolled. Preterm infants were defined as those born alive before 37 weeks of gestational age. Preterm infants receiving intermittent mandatory ventilation support were excluded due to the difficulty in performing MRCP. Critical patients with cholestasis caused by sepsis, multi-organ failure, and congenital genetic or organic anomalies were also excluded. This study was evaluated and approved by the Ethical Committee of our hospital (B-ER-110-546).

2.2. Etiology survey

The etiology of cholestasis was evaluated according to the protocol for infants at our department, with laboratory biochemistry studies including aspartate transaminase (AST), alanine aminotransferase (ALT), direct bilirubin, alkaline phosphatase, γ-glutamyl transferase (GGT), thyroxine, and thyroid-stimulating hormone, and viral antibodies including cytomegalovirus IgG and IgM. Information of the patients’ gestational age, age, sex, body weight, laboratory data, drug and TPN history were obtained retrospectively. Each patient received abdominal ultrasonography after an 8-h fasting period prior to MRCP. Ultrasonographic findings of triangular cord (thickness of more than 4 mm, gallbladder length of less than 15 mm, abnormal gallbladder shape, and sub-capsular flow on color Doppler ultrasonography) were used as the diagnostic criteria of BA.13

2.3. MRCP techniques and analysis

MRCP examinations were performed using a Philips Achieva 1.5T A series magnetic resonance imaging (MRI) system (Philips Medical Systems, Andover, MA, USA) after an 8-h fasting period. The MRI sequences included axial free-breathing T1-weighted images, axial and coronal turbo spin-echo (TSE) T2-weighted images, 3D MRCP TSE with fat suppression, coronal single-shot thick-slab T2-weighted MRCP, and axial, sagittal and coronal T2-weighted 3D volume isotropic turbo spin-echo acquisition (VISTA) images. No contrast agents were given. Sedation was achieved with oral or rectal chlorate hydrate at a dose of 50 mg/kg of body weight or an intravenous injection of propofol at a dose of 2 mg/kg of body weight. The vital signs of the patients were carefully monitored during and after the examination. One pediatric radiologist reviewed the MRCP images. A non-BA diagnosis was made if the extrahepatic central biliary duct and common bile duct were visualized.

Conclusions: Negative MRCP findings can be used to exclude BA in preterm infants with cholestasis based on a favorable NPV.

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BA was diagnosed if any portion of the extrahepatic central biliary duct or common bile duct could not be delineated, regardless of whether or not the gallbladder was present (Fig. 1B).\(^{18}\)

### 2.4. Diagnostic criteria of probable BA

Patients who met two of the three diagnostic criteria of BA (GGT, ultrasonography, and MRCP) were diagnosed with probable BA. Intra-operative cholangiography and/or Kasai portoenterostomy was performed in these patients. Histologic analysis of surgical remnants was also performed after the operation.

### 2.5. Statistical analysis

Statistical analyses were performed using SPSS software (SPSS, version 17.0; SPSS, Chicago, Ill). Results were considered significant if the \(P\) value was less than 0.05. Descriptive data were expressed as the mean ± standard deviation (SD) or frequency. Statistical differences were tested using the independent \(t\)-test, Mann–Whitney test, or Fisher’s exact test, as appropriate. We compared the positive predictive value (PPV) and negative predictive value (NPV) between the two groups (preterm and term infants) using inferential statistics with Bonferroni adjustment.\(^{19}\) A significance level of \(p < 0.025\) was thus used.

### 3. Results

#### 3.1. Demographic data of the enrolled patients

A total of 80 patients including 36 preterm and 44 term infants were enrolled. The mean age was 54 days (range 3–142 days), and the male-to-female ratio was 1.29 (45/35). The mean corrected age of these patients at MRCP was 21.9 days (standard deviation: 31.5 days, 95% confidence interval: 14.9–28.9 days). Twenty patients (6 preterm and 14 term infants) were diagnosed with BA as confirmed by intra-operative cholangiography or histologic analysis of surgical remnants, seven patients had a choledochal cyst, one patient had a cystic duct tortuous with gallbladder fibrosis due to a shortened cystic artery, and two patients had both BA and a choledochal cyst. The other 50 children were diagnosed with neonatal hepatitis based on histology and intra-operative cholangiography combined with clinical and laboratory improvements after 6 months of follow-up.

Two term infants with the initial impression of a choledochal cyst on ultrasonography and MRCP were finally diagnosed with cystic biliary atresia (CBA) after intra-operative cholangiography (Fig. 2). These two infants were diagnosed very early (at 3 days old and 7 days old, respectively) due to a relatively high bilirubin level (8.3 mg/dL and 18 mg/dL, respectively). The first infant had a poor outcome and finally died of complications because the infant’s parents hesitated to consent to surgery, which was finally performed at 42 days of age (39 days after the diagnosis). The second infant had a good outcome with a bilirubin level <2 mg/dL 3 months after surgery.

#### 3.2. Comparisons of clinical and laboratory data between the preterm and term infants

Table 1 shows comparisons of the clinical and laboratory data between the preterm and term infants. The preterm infants were significantly older (2.1 vs. 1.6 months, \(p = 0.03\)) at the initial evaluation for cholestasis, and significantly more were male (75% vs. 41%, \(p < 0.01\)) than the term infants. In addition, body weight (2707 vs. 4101 g, \(p < 0.01\)) was significantly lower in the preterm infants than in the term infants. There were no significant differences in AST, ALT, direct/total bilirubin, or...
GGT level between the preterm and term infants (all \( p > 0.05 \)).

3.3. The sensitivity and specificity of ultrasonography and GGT in the diagnosis of BA

Abdominal ultrasonography was performed in all of the patients, and the sensitivity and specificity were 87.5% and 53.6% in the term infants, respectively, compared to 83.3% and 23.3% in the preterm infants. Receiver operating characteristic curve analysis showed that for a serum GGT level of >250 IU/L, the sensitivity and specificity were 50% and 81.5% in the term infants and 66.7% and 82.8% in the preterm infants, respectively. The total accuracy of ultrasonography and serum GGT >250 IU/L to diagnose BA were 65.9% and 69.8% in the term infants and 33.3% and 80% in the preterm infants, respectively.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The demographic and laboratory data of the preterm and term infants receiving MRCP for cholestasis.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Demographic and laboratory data</td>
</tr>
<tr>
<td>Age (months)</td>
<td>2.1 ± 1.0</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>27 (75%)</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>2707 ± 1139 4101 ± 1131 &lt;0.001</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>154 ± 135</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>78 ± 79</td>
</tr>
<tr>
<td>Bil-T (mg/dL)</td>
<td>7.8 ± 4.6</td>
</tr>
<tr>
<td>Bil-D (mg/dL)</td>
<td>5.3 ± 4.3</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>193 ± 125</td>
</tr>
</tbody>
</table>

AST: aspartate transaminase, ALT: alanine aminotransferase, Bil-T: total bilirubin, Bil-D: direct bilirubin, GGT: \( \gamma \)-glutamyl transferase.

3.3. The sensitivity and specificity of ultrasonography and GGT in the diagnosis of BA

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![Figure 2](image1.png) Two term infants were diagnosed with choledochal cyst on MRCP due to cystic dilatation of the extrahepatic biliary tract (arrow), but they were finally diagnosed with CBA at surgery.

![Figure 3](image2.png) The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of magnetic resonance cholangiopancreatography (MRCP) in preterm (A) and term (B) infants with cholestasis.
3.4. The diagnostic accuracy of MRCP to diagnose BA in the preterm and term infants

There were no equivocal cases of MRCP using the diagnostic criteria in this study. The diagnostic accuracy of MRCP to diagnose BA among the 80 infants was 82.5%, with sensitivity, specificity, PPV, and NPV of 86.4%, 81%, 63.3%, and 94%, respectively. With regards to the effectiveness of MRCP to diagnose BA in the preterm (Fig. 3A) and term (Fig. 3B) infants, the preterm infants had superior sensitivity (100% vs. 81%, difference = 19%; p = 0.0060) and NPV (100% vs. 89%, difference = 11%; p = 0.0413), but lower specificity (77% vs. 86%, difference = 9%; p = 0.3008) and PPV (46% vs. 76%, difference = 30%; p = 0.0061) than the term infants. The accuracy of MRCP to diagnose BA was similar between the preterm (81%) and term (84%) infants with cholestasis.

3.5. Combining ultrasonography and GGT to improve the PPV of MRCP in the diagnosis of BA in the preterm infants with cholestasis

In spite of the high sensitivity and NPV of MRCP to diagnose BA in the preterm infants with cholestasis, the low PPV (46%) may have resulted in a high rate of unnecessary surgeries. Because ultrasonography (87.5%) and serum GGT >250 IU/L (92.3%) also yielded a high NPV, we combined ultrasonography and GGT to improve the false positive rate of MRCP in the preterm infants. Ultrasonography was positive in 12 of the 13 infants with cholestasis. Compatible with our results, the reported accuracy of ultrasonography for BA is around 65%–69% in term infants. In addition, using the triangular cord sign on ultrasonography to differentiate BA from other cholestasis has been reported to increase the sensitivity and specificity to 67%–86%. Moreover, studies using different cut-off values of serum GGT to diagnose BA have reported accuracy, sensitivity, and specificity values of 65.6%–85%, 39.7%–73.7%, and 67%–98.1%, respectively. Wang et al. reported that combining ultrasound characteristics and GGT level resulted in a sensitivity and NPV of 100%. However, the specificity, PPV, and accuracy were only 63.5%, 64.8%, and 78.2%, respectively. Therefore, a more accurate non-invasive diagnostic method for BA to determine the optimal surgical time and prevent unnecessary surgery is still needed.

MRCP has been validated as a useful tool for the diagnostic work-up of neonatal cholestasis. He et al. conducted a meta-analysis study to analyze the accuracy of diagnostic methods in differentiating BA in neonates with jaundice. Consistent with our term infants, the pooled sensitivity and specificity of MRCP to diagnose BA were 89.7% (range: 84.8%–93.4%) and 64.7% (range: 58.0%–71.0%), respectively. Nevertheless, the accuracy of MRCP in differentiating BA from cholestasis in preterm infants is unknown. Due to the higher incidence of BA and also higher rate of unsatisfactory outcomes in preterm infants compared to term infants with BA, a non-invasive and accurate diagnostic method to improve the long-term outcomes of preterm infants with BA is urgently needed. This study is the first to report that the accuracy of MRCP to diagnose BA in preterm infants (81%) was similar to that in term infants (84%). Moreover, in the preterm infants, MRCP showed a high NPV (100%) but low PPV (46%) to diagnose BA. These results indicate that non-invasive MRCP is a reliable tool to rule out BA in preterm infants with cholestasis.

4. Discussion

This study is the first to compare the accuracy of MRCP in the diagnosis of BA between preterm and term infants with cholestasis. The results showed that MRCP had high diagnostic accuracy in both the term and preterm infants with cholestasis. Moreover, MRCP had better sensitivity and NPV to diagnose BA in the preterm infants than in the term infants. These findings imply that MRCP is a good tool to rule out BA in preterm infants with cholestasis.

To avoid unnecessary laparotomy, pre-operative diagnosis with a highly accurate non-invasive method is critical. Ultrasonography is an easy and rapid tool to screen infants with cholestasis. Compatible with our results, the reported accuracy of ultrasonography for BA is around 65%–69% in term infants. In addition, using the triangular cord sign on ultrasonography to differentiate BA from other cholestasis has been reported to increase the sensitivity and specificity to 67%–86%. Moreover, studies using different cut-off values of serum GGT to diagnose BA have reported accuracy, sensitivity, and specificity values of 65.6%–85%, 39.7%–73.7%, and 67%–98.1%, respectively. Wang et al. reported that combining ultrasound characteristics and GGT level resulted in a sensitivity and NPV of 100%. However, the specificity, PPV, and accuracy were only 63.5%, 64.8%, and 78.2%, respectively. Therefore, a more accurate non-invasive diagnostic method for BA to determine the optimal surgical time and prevent unnecessary surgery is still needed.
Although CBA is radiographically similar to a choledochal cyst, it clinically behaves in a similar manner to isolated BA.\textsuperscript{25} In our series, two term infants were initially suspected of having a choledochal cyst by ultrasonography and MRCP, but a final diagnosis of BA with extrahepatic cyst was made via intra-operative cholangiography. In a similar case, Kunwar et al. reported that it was quite difficult to differentiate CBA from choledochal cyst using ultrasonography and MRCP.\textsuperscript{26} This highlights the diagnostic dilemma of using MRCP for CBA in infants with cholestasis.

Previous studies have suggested that combining MRCP with other modalities such as ultrasonography could improve the diagnostic accuracy of BA in infants with cholestasis.\textsuperscript{16,18} In an attempt to improve the low PPV of MRCP in differentiating BA from other cholestasis in our infants, we used ultrasonography and serum GGT combined with positive MRCP, however the results were unsatisfactory. Most of the MRCP-positive preterm (92%) and term (94%) infants had positive ultrasonography findings, and therefore the combination of ultrasonography and MRCP was not superior to MRCP alone in the diagnosis of BA in the preterm infants with cholestasis.

Although using a serum GGT cut-off value of 250 IU/L to diagnose BA in the preterm infants had a high NPV, GGT $\leq 250$ IU/L could only identity five (71%) of the seven preterm infants with positive MRCP findings, and the other two (29%) cases were true positive for BA and were missed preoperatively. However, in the term infants with cholestasis, using GGT $> 250$ IU/L combined with positive MRCP strongly suggested a diagnosis of BA. Nevertheless, GGT $\leq 250$ IU/L only excluded four (36.4%) of the 11 term infants with positive MRCP findings for BA. Taken together, the accuracy of MRCP alone or in combination with serum GGT to diagnose BA was quite different between the preterm and term infants with cholestasis.

In conclusion, our results showed that the accuracy of MRCP to diagnose BA in the preterm infants was similar to that in the term infants. MRCP appears to be a good tool to exclude BA in preterm infants with cholestasis based on a 100% NPV. Combining ultrasonography or serum GGT with MRCP did not improve the low PPV of MRCP alone in the diagnosis of BA in the infants with cholestasis.

Author contributions

Wei-Che Chen—involved in the study design, study conduct, collection of clinical data, and in drafting the manuscript. Hsiao-Yu Lo—involved in the follow-up of patients and data interpretation. Yi-Shan Tsai—in involved in the interpretation of MRCP and editing the manuscript. Yao-Jong Yang—in involved in the setting of the study design and conduct, interpretation of data, editing and final approval of the manuscript.

Declaration of competing interest

No potential conflicts of interest relevant to this article were reported.

References


