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## ORIGINAL ARTICLE

# Diagnostic Accuracy of Scintigraphy and Sonography for Biliary Atresia

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## ABSTRACT

***Objectives:*** *To determine the diagnostic accuracy and predictive values of hepatobiliary scintigraphy and sonography in the evaluation of clinically suspected biliary atresia.*

***Methods:*** *All infants who underwent hepatobiliary scintigraphies for suspected biliary atresia within a 3-year period (2006–2008) in the New Territories East Cluster of Hong Kong were retrospectively analysed. All scintigraphies and peri-scintigraphic ultrasound images were reviewed for signs suggestive of biliary atresia. The accuracy of imaging studies was determined by surgical findings and clinical follow-up.*

***Results:*** *Forty-two cases were retrieved with two excluded due to incomplete clinical records. Seven (18%) of 40 patients had surgically confirmed biliary atresia; all of these had positive scintigraphies and 6/7 (86%) had positive sonographic findings. Among the 40 scintigraphies, there were 7 true-positive, 28 true-negative, and 5 false-positive studies. The scintigraphic sensitivity, specificity, and positive and negative predictive values were 100%, 85%, 58% and 100%, respectively. Among the 5 false-positive scintigraphies caused by hepatic dysfunction, 3 had normal sonography; 2 became negative on repeated scintigraphy, 2 had spontaneous clinical improvement, and 1 had normal intra-operative cholangiography. Thirty-eight of the 40 patients had performed peri-scintigraphic sonography. There were 23/38 (61%) abnormal studies which included cases with small gallbladder (n = 15) and non-visualised gallbladder (n = 8), but not periportal fibrosis. The sensitivity, specificity, positive and negative predictive values of these sonograms were 86%, 45%, 27% and 93%, respectively.*

***Conclusions:*** *Both hepatobiliary scintigraphy and sonography are currently the standard imaging investigations for suspected biliary atresia. This study revealed relatively low positive predictive value for biliary atresia by either investigation. We therefore consider their complementary role in which a correlation between scintigraphy and sonography is important, and recommend follow-up imaging reassessment before making definitive surgical decisions. This will serve to decrease the frequency of false-positive imaging diagnoses of biliary atresia, and hence, avoid unnecessary surgeries.*

***Key Words:*** *Biliary atresia; Jaundice, neonatal; Radionuclide imaging; Technetium Tc 99m Lidofenin; Ultrasonography*

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# 中文摘要

## 膽道閉鎖核素顯像和超聲診斷的準確性

譚家盈、呂沛欣、李嘉樂、郭永剛、蔡柏達、朱昭穎

**目的：**探討肝膽核素顯像和超聲對臨床疑診為膽道閉鎖病例的診斷準確性和預測值。

**方法：**回顧分析香港新界東聯網於2006至2008年的三年期間，懷疑患有膽道閉鎖而須接受肝膽核素顯像的所有嬰兒。審視病人的核素顯像和核素顯像期間的超聲檢查以找出膽道閉鎖的跡象，然後以手術結果和臨床隨訪來確定影像學的準確性。

**結果：**42例中有兩例因臨床記錄不完整而不被列入研究範圍。餘下的40例中，7例（18%）以手術證實膽道閉鎖，這些患者核素顯像均呈陽性結果，6例（86%）的超聲呈陽性結果。40例核素顯像中，7例呈真陽性、28例呈真陰性、5例呈假陽性的顯像結果。核素顯像的敏感性、特異性、陽性和陰性預測值分別為100%、85%、58%和100%。5個因肝功能障礙而引致的假陽性顯像結果中，3例出現正常的超聲結果；2例在重複進行顯像時出現陰性結果，2例自發性有臨床症狀改善，1例術中膽管造影正常。40例中有38例進行了核素顯像期間的超聲檢查，其中23例（61%）出現異常結果，包括小膽囊（n = 15）和膽囊未見（n = 8），但無肝門區纖維化的病例。超聲的敏感性、特異性、陽性和陰性預測值分別為86%、45%、27%和93%。

**結論：**肝膽核素顯像和超聲是目前對臨床疑診為膽道閉鎖的標準成像。本研究發現這兩種工具對於膽道閉鎖的陽性預測值相對較低。因此我們認為核素顯像和超聲之間的互補性非常重要，並建議重覆進行成像以作重新評估，才作出最終的手術決定。這將有助減少膽道閉鎖的假陽性結果，從而避免不必要的手術。

## INTRODUCTION

Biliary atresia is characterised by progressive fibrosing obliteration of intrahepatic and extrahepatic bile ducts. It affects 1 in 5000 to 19,000 live births as reported from different parts of the world.[1] It is the leading cause of end-stage liver disease if left untreated, and is the most common indication for liver transplantation in paediatric patients.[1,2] The Kasai procedure of hepatoportoenterostomy and various modified procedures aim at re-establishing a communication between the biliary system and gastrointestinal tract.[3,4] Early surgery was associated with 90% success rate if performed within 60 days of birth. The success rate of surgery dropped significantly to 17% when performed after 90 days of birth.[3] A French national study by Serinet et al[5] estimated that if every patient with biliary atresia underwent the Kasai operation before 46 days of age, 5.7% of paediatric liver transplantations could be saved per year. Prompt accurate diagnosis and timely surgical intervention are, therefore, important. Imaging plays an important role in decision making, with hepatobiliary sonography and scintigraphy being the two most commonly used investigations.[6,7]

We retrospectively determined the diagnostic accuracy and predictive values of hepatobiliary scintigraphy and sonography in the evaluation of infants with clinically suspected biliary atresia in two regional hospitals in Hong Kong.

## METHODS

All infant patients who had hepatobiliary scintigraphies performed during a 3-year period (from 2006 to 2008) in the New Territories East Cluster of Hong Kong were retrospectively analysed. Clinical and imaging findings were retrieved from electronic medical records. Scintigraphies had been performed using a standardised protocol, comprising pre-medication with oral phenobarbital (5 mg/kg/day in two divided doses) for a minimum of 3 to 5 days, intravenous administration of $^{99m}$Tc-mebrofenin as the radiotracer followed by dynamic imaging for 60 minutes, and sequential static planar imaging of hepatobiliary system at intervals up to 24 hours. A positive scintigraphy study was defined by the absence of drainage of radiotracer into the intestine throughout the study for up to 24 hours; if otherwise, it was considered a negative study. Peri-

scintigraphic sonography was performed using high-frequency transducers (9-12 MHz) to look for specific signs suggestive of biliary atresia: periportal fibrosis or triangular cord sign (echogenicity anterior to the bifurcation of the portal vein representing remnant of the extra-hepatic bile duct), small gallbladder (defined as longitudinal axis <15 mm) or non-visualised gallbladder.[8,9] The gold standard for the diagnosis of biliary atresia was intra-operative cholangiogram. In cases without surgical confirmation, clinical resolution of jaundice and normalisation of liver function tests on follow-up were considered as criteria for excluding the diagnosis of biliary atresia.

## RESULTS

Forty-two scintigraphies were retrieved; two cases had to be excluded because of incomplete clinical records. The remaining 40 patients had a mean age of 2.1 months (range, 16 days to 6 months 25 days) and a male-to-female ratio of 1:1. Seven (18%) of them were surgically confirmed with biliary atresia; all these cases had positive scintigraphies (absence of drainage of radiotracer into the intestine) while 6/7 (86%) had positive sonographies (small gall bladder in 4 cases; non-visualised gallbladder in 2 cases).

Qualitative assessment of the scintigraphies showed that hepatic parenchymal uptake of $^{99m}$Tc-mebrofenin was visually impaired with persistent background blood pool activity in 14% (1/7) of cases with biliary atresia and 21% (7/33) of cases with cholestasis due to other causes. This difference was not statistically significant ($p = 0.57$), and we did not perform further quantitative assessment or deconvolution analyses.

Among the 40 scintigraphies, 7 were true-positive, 28 true-negative, and 5 false-positive, but no false-negative studies for biliary atresia. The sensitivity, specificity, positive and negative predictive values of scintigraphy were 100%, 85%, 58% and 100%, respectively. The overall diagnostic accuracy was 88%. All five false-positive scintigraphies were attributed to hepatic dysfunction. Two of them showed negative results on repeated scintigraphies performed after 3 to 4 weeks, two showed spontaneous clinical improvement on follow-up, and one had normal intra-operative cholangiogram. The results are summarised and illustrated in Figures 1 to 2.

Peri-scintigraphic sonography had been performed in 38/40 patients. Overall, there were 23 (61%) abnormal studies of which 15 (39%) had small gallbladder (Figure 3) and 8 (21%) non-visualised gallbladder. However, no definite periportal fibrosis was identified in this group of patients. Among these 38 sonographies, there were 6 true-positive, 14 true-negative, 17 false-positive,

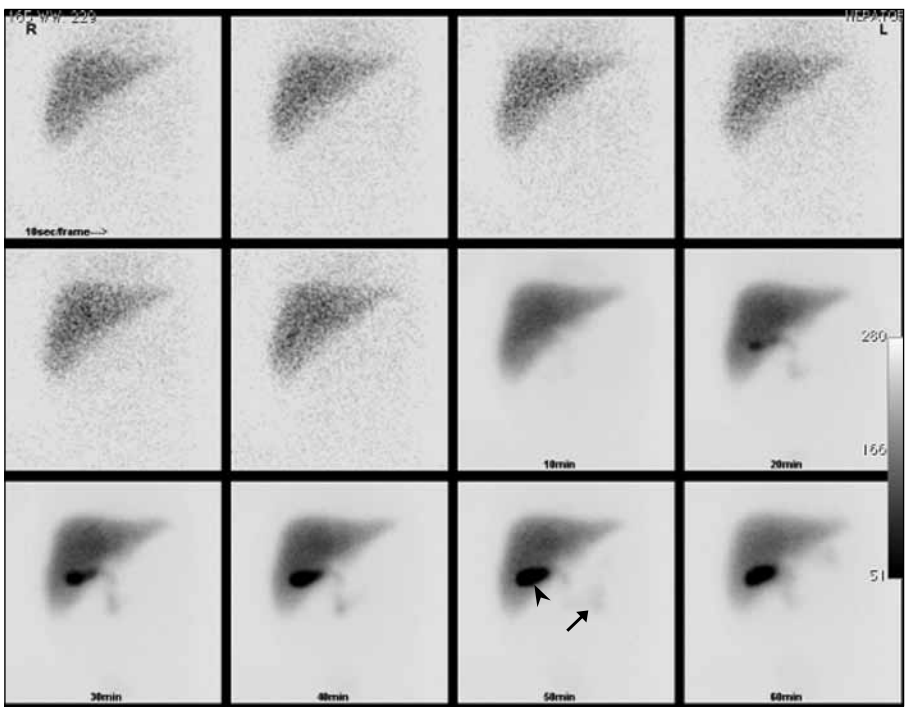


**Figure 1.** Hepatobiliary scintigraphy with radiotracer visualised in gallbladder (arrowhead) and duodenum (arrow) within 60 minutes, hence a negative study for biliary atresia. The displayed images were formatted as 10 seconds per frame from 0 to 60 seconds, and then 10 minutes per frame up to 60 minutes.

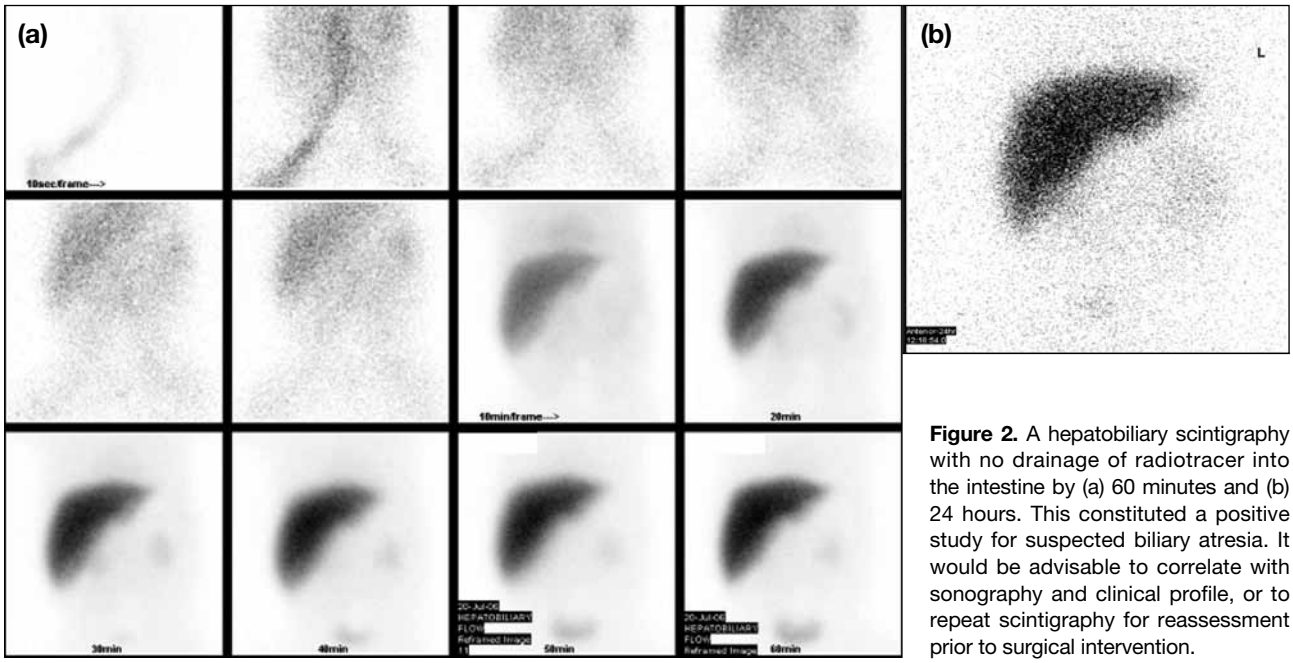


**Figure 2.** A hepatobiliary scintigraphy with no drainage of radiotracer into the intestine by (a) 60 minutes and (b) 24 hours. This constituted a positive study for suspected biliary atresia. It would be advisable to correlate with sonography and clinical profile, or to repeat scintigraphy for reassessment prior to surgical intervention.

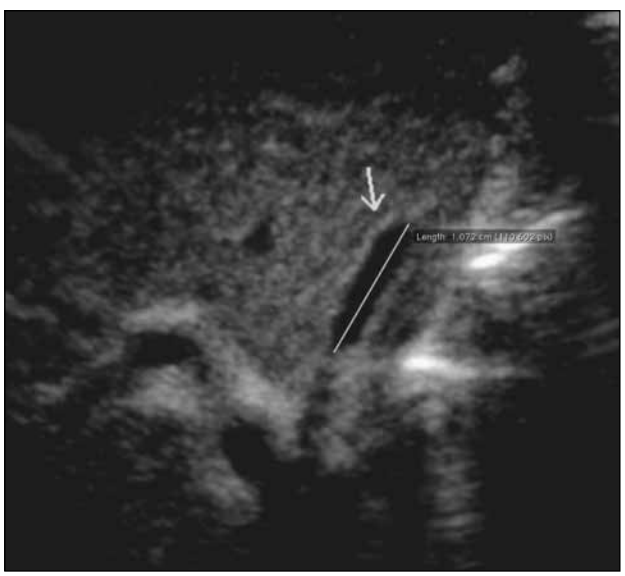

**Figure 3.** Ultrasonography showing a small gallbladder (arrow) measuring less than 1.5 cm in length.

and 1 false-negative studies. Hence, their sensitivity, specificity, positive and negative predictive values for biliary atresia were 86%, 45%, 27% and 93%, respectively. Among the 5 patients with false-positive scintigraphy, 3 had normal sonography. The overall diagnostic accuracy was 53%.

## DISCUSSION

Hepatobiliary scintigraphy and sonography are the two most common imaging investigations for infantile cholestasis or suspected biliary atresia. This study found that scintigraphy was superior to sonography in diagnosing biliary atresia (diagnostic accuracy, 88% and 53%, respectively). The outperformance of scintigraphy over sonography was also established in prior reports in medical literature[10-14]; however, several studies also report the reverse.[9,15,16] It is likely that the discrepant results across these studies may have arisen due to the variations in radiotracer used, premedication practices, imaging protocol, interpretative criteria, study timing (patient age), and operator experience. Regardless of which technique bears a higher accuracy, both scintigraphy and sonography had relatively low positive predictive values for biliary atresia in this study (58% and 27%, respectively). This underscores the importance of recourse to other investigations or follow-up reassessment before making definitive surgical decisions.

Hepatobiliary scintigraphy using technetium-labelled iminodiacetic acid derivatives as the radiotracer can objectively assess hepatic parenchymal function and biliary drainage. $^{99m}$Tc-mebrofenin is always the preferred radiopharmaceutical in neonates with hyperbilirubinaemia because of its high hepatic

extraction efficiency.[7,17] Mebrofenin scintigraphy has very high sensitivity (100% in this study) for biliary atresia. This suggests that any false-negatives (i.e. apparent drainage despite biliary atresia) should be rarely encountered; a common cause of false-negative results is misinterpretation of renal excretion or urinary contamination, especially in a diaper. However, the specificity of mebrofenin scintigraphy was not particularly high (85% in this study), varying from 54% to 93% in the literature.[11,12,16,18] The causes of false-positive cases (i.e. absence of drainage due to causes other than biliary atresia) may include severe neonatal hepatitis, total parenteral nutrition cholestasis, Alagille syndrome, cystic fibrosis, bile plug syndrome, choledochal cyst, hypothyroidism and alpha-1 antitrypsin deficiency.[7] In this study, there were five false-positive cases. The first scintigraphy was suggestive of biliary obstruction in two of these cases; however, their clinical condition improved spontaneously with decreasing hepatic biochemical markers. Despite the recommendation to validate the diagnosis of biliary atresia with repeat scintigraphy, they were discharged and remained well without further imaging. The interpretation of scintigraphy results should, therefore, always be in conjunction with clinical progress and biochemical findings. Two other cases underwent repeat scintigraphies within a short interval (3 to 4 weeks), which confirmed biliary-to-enteric drainage and excluded biliary atresia (Figures 4 to 5). The fifth case showed scintigraphic findings compatible with biliary atresia. No repeat study was performed. The patient subsequently underwent surgery

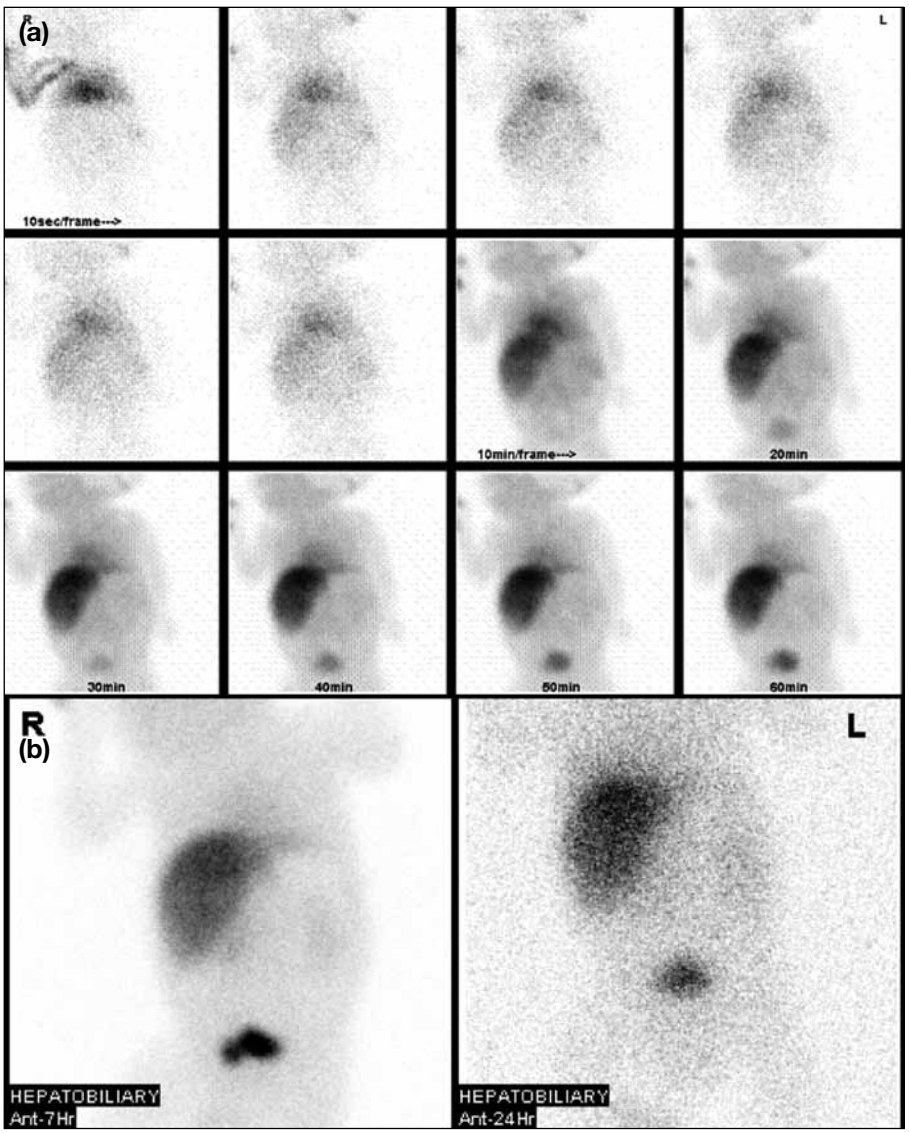


**Figure 4.** A hepatobiliary scintigraphy with absence of radiotracer in gallbladder or small bowel by (a) 60 minutes, and (b) 7 and 24 hours. This was a false-positive study as proven with repeat scintigraphy shown in Figure 5.

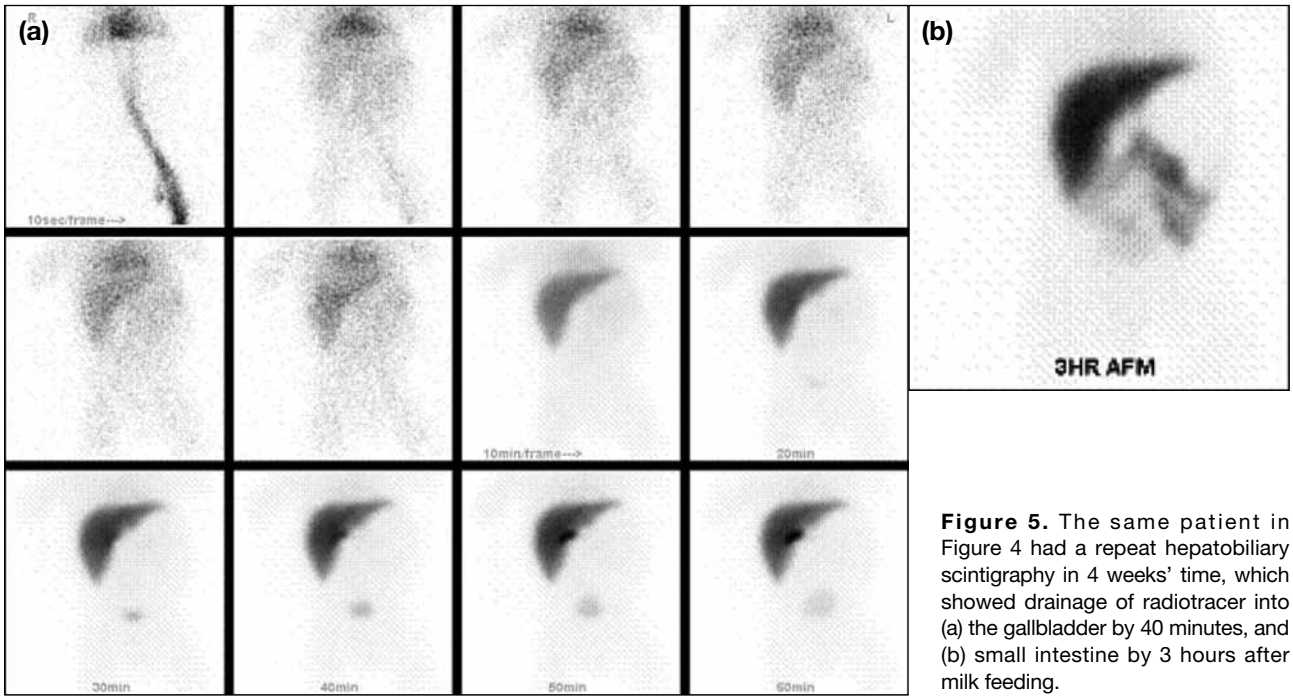


**Figure 5.** The same patient in Figure 4 had a repeat hepatobiliary scintigraphy in 4 weeks' time, which showed drainage of radiotracer into (a) the gallbladder by 40 minutes, and (b) small intestine by 3 hours after milk feeding.

with intra-operative cholangiogram showing a patent biliary system. This patient had undergone a previous sonography which showed the presence of a normal-sized gallbladder. These cases illustrate the importance of repeating scintigraphy and making correlation with sonography when in doubt.

Ultrasonography is simple, readily available, non-invasive, in affordable cost, and is free of radiation. It is useful for visualising biliary tract anatomy and excluding other causes of prolonged jaundice such as choledochal cyst, and hence recommended as an initial investigation for the evaluation of infants with cholestasis of unknown aetiology.[19] Choi et al[20,21] first described the sonographic 'triangular cord' sign, representing obliterated fibrous ductal remnant in biliary atresia, and concluded that if this sign was visualised, no further studies were necessary, and exploratory laparotomy could be performed. This sign was reconfirmed in subsequent studies to have high specificity between 95% and 100%.[6,8,9,15,22-28] However, its sensitivity varied widely from 23%[28] to 93%.[8] One speculated reason was that this sign may evolve with patient age; it may be absent or undetectable in infants younger than 90 days, but become detectable on follow-up sonography.[28-30] In this study, the triangular cord sign was not identified in seven cases with biliary atresia aged 29 to 61 days (mean age, 45 days). This supported the notion of a lower sensitivity of this sign in the early course of disease. Besides, biliary atresia was associated with either small, non-visualised or absent gallbladder.[22,31] Tan Kendrick et al[9] remarked that the triangular cord sign and gallbladder length together are very useful markers for biliary atresia. Takamizawa et al[25] further showed that biliary atresia could be accurately diagnosed with ultrasonography using the findings of the triangular cord sign along with gallbladder length and gallbladder contractility. However, in the absence of the triangular cord sign (as in this study), gallbladder findings alone can be influenced by factors such as inadequate fasting, which is difficult to control in infants, and thus lead to false-positive results. Nevertheless, a normal ultrasonography has high negative predictive value so that it can alert clinicians to the possibility of a false-positive scintigraphy. In our study, there were five cases with false-positive scintigraphy, three of whom showed normal sonographic findings. The overall accuracy of ultrasonography is deemed to improve in the future, based upon operator experience and careful evaluation of a multitude of primary and secondary features, as demonstrated in recent studies. These features may include abnormal gallbladder shape, irregular gallbladder wall, absent common bile duct, enlarged

liver, abnormal spleen size, polysplenia, interrupted inferior vena cava, enlarged hepatic artery diameter, and presence of hepatic subcapsular flow.[6,24,27,28]

Percutaneous liver biopsy is generally regarded as the most reliable investigation for biliary atresia with sensitivity reported from 90% to 100%, specificity from 76% to 100%, and accuracy from 88% to 100%.[11-16,26,32] The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends liver biopsy in most infants with undiagnosed cholestasis, to be interpreted by experienced histopathologists before performing a surgical procedure to diagnose biliary atresia.[19] Although liver biopsy could be safely and expeditiously performed in young infants,[33] it is not a common practice in our locality owing to its invasiveness. Thus, none of the infants included in this study had undergone liver biopsy. Cases with high index of suspicion proceeded to exploratory laparotomy and intra-operative cholangiography, procedures which have hitherto remained the gold standard for making a diagnosis of biliary atresia.

To avoid unnecessary invasive procedures, magnetic resonance cholangiography is another imaging modality worth consideration. With procedural variations, its sensitivity for biliary atresia was reported from 82% to 100%, specificity from 57% to 100%, and accuracy from 65% to 100%.[14,34-38] Of particular interest, Ryeom et al[37] studied the feasibility of using mangafodipir trisodium, a non-radioactive liver-specific contrast medium excreted through the biliary system, in 23 infants (four of whom had biliary atresia), and showed a promising result of 100% accuracy in diagnosing biliary atresia. Thus, magnetic resonance cholangiography with specific contrast medium may potentially offer a combined anatomical and functional assessment, comparable with respective merits of ultrasonographic and scintigraphic assessments. However, there are limited data on magnetic resonance cholangiography, and the procedure is associated with several drawbacks such as technical difficulties, motion artefacts and mandatory sedation of infants. Therefore, this imaging modality has not yet been included in the standard routine investigation algorithms for biliary atresia.

There were inherent limitations in this retrospective study on scintigraphy and sonography for clinically suspected biliary atresia. Firstly, the results were based on those cases with high or adequate suspicion to warrant scintigraphic evaluations prior to surgical intervention at our hospitals, among which 5% had no accompanying sonographies. The results, by no means, reflect the whole spectrum of neonatal jaundice cases and sonographies performed during the study period. Secondly, the results were unblinded, with the scintigraphic findings accessible to the operators of sonography, or vice versa. Thirdly, the results of sonography were based on the prevailing interpretative criteria of the triangular cord sign and gallbladder findings at the material time of imaging; they do not reflect the diagnostic value of other features described more recently. We would recommend further research in a prospective blinded design, with sampling by predefined criteria of infants with prolonged cholestasis, to compare the accuracy of different imaging modalities in making a timely diagnosis of biliary atresia at an early age.

## CONCLUSION

Conventionally, ultrasonography visualises biliary tract anatomy whereas scintigraphy emphasises a functional assessment of biliary excretion and, hence, patency. Both are currently the standard imaging investigations for infantile cholestasis or suspected biliary atresia. This study found that scintigraphy was associated with higher diagnostic accuracy than sonography in a cohort of cases with clinically suspected biliary atresia. However, both investigations had low positive predictive value for biliary atresia. We, therefore, consider their complementary role in which a correlation between scintigraphy and sonography is important, and also recommend follow-up imaging reassessment before making definitive surgical decisions. This will serve to decrease the frequency of false-positive imaging diagnosis of biliary atresia, and, hence, avoid unnecessary surgeries.

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