**Name of Journal: World Journal of Gastroenterology**

**Manuscript NO: 34992**

**Manuscript Type: ORIGINAL ARTICLE**

***Observational Study***

**Chronic liver disease is universal in children with biliary atresia living with native liver**

Lee WS *et al*. CLD in biliary atresia living with native livers

Way Seah Lee, Sik Yong Ong, Hee Wei Foo, Shin Yee Wong, Chen Xi Kong, Ru Bin Seah, Ruey Terng Ng

**Way Seah Lee, Sik Yong Ong, Hee Wei Foo, Shin Yee Wong, Chen Xi Kong, Ru Bin Seah, Ruey Terng Ng**, Department of Paediatrics, University Malaya Medical Centre, Kuala Lumpur 59100, Malaysia

**Way Seah Lee,** Paediatrics and Child Health Research Group,University Malaya, Kuala Lumpur 50603, Malaysia

**Author contributions:** Lee WS and Ong SY conceived the concept of the present research; Ong SY, Foo HW, CX Kong, RB Seah and Ng RT collected the clinical data; Wong SY provided statistical analysis; Lee WS and Ong SY wrote the first draft; Lee WS provided critical analysis to the draft; Lee WS revised the final draft; All authors approved the final draft.

**Supported by** University Malaya High Impact Research (UM.C/625/HIR/MOHE/CHAN/13/1) from Ministry of Higher Education, Malaysia.

**Institutional review board statement:** The study was reviewed and approved by the University Malaya Medical Center, Kuala Lumpur Medical Ethical Committee (MEC 902.15).

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrolment.

**Conflict-of-interest statement:** None of the authors has any potential conflict of interest to declare.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Correspondence to: Way Seah Lee, MBBS, MD, FRCPCH, Professor,** Department of Paediatrics, University Malaya Medical Centre, Kuala Lumpur 50603, Malaysia. leews@um.edu.my

**Telephone:** +603-79492065

**Fax:** +603-79494704

**Received:** June 9, 2017

**Peer-review started:** June 10, 2017

**First decision:** July 13, 2017

**Revised:** August 3, 2017

**Accepted:**

**Article in press:**

**Published online:**

**Abstract**

***aim***

to examine the medical status of children with biliary atresia (BA) surviving with native livers.

***Methods***

In this cross-sectional review, data collected included complications of chronic liver disease (CLD) (cholangitis in preceding twelve months, portal hypertension, variceal bleeding, fractures, hepatopulmonary syndrome, portopulmonary hypertension), and laboratory indices (white cell and platelet counts, total bilirubin, albumin, international normalized ratio, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase). Ideal medical outcome was defined as absence of clinical evidence of CLD or abnormal laboratory indices.

***ResultS***

Fifty-two children ]females = 32; 62%; median age 7.4 years; *n* = 35 (67%) older than 5 years] with BA (median age at surgery 60 d, ranged 30 to 148 d) survived with native liver. Common complications of CLD noted were portal hypertension (40%; *n =* 21; two younger than five years), cholangitis (36%) and bleeding varices (25%; *n =* 13, one younger than five years). Fifteen (29%) had no clinical complications of CLD and three (6%) had normal laboratory indices. Ideal medical outcome was only seen in one patient (2%).

***Conclusion***

Clinical or laboratory evidence of CLD are present in 98% of children with BA living with native livers after hepatoportoenterostomy. Portal hypertension and variceal bleeding maybe seen in children younger than five years of age, underscoring the importance of medical surveillance for complications of BA starting at a young age.

**Key words:** biliary atresia; medical status; Chronic liver disease

**© The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Previous study showed that more than 90% of children with biliary atresia (BA) surviving with native livers have clinical and laboratory evidences of chronic liver disease (CLD). In the present cohort, we found that 71% of patients with BA living with native livers had no clinical complications of CLD and 90% had normal liver synthetic function, only 2% had ideal medical outcome. Common medical complications encountered were cholangitis, portal hypertension and bleeding esophageal varices. Portal hypertension and bleeding esophageal varices were seen in 12% and 6% of children younger than five years of age. Medical surveillance in children with BA after Kasai surgery for medical complications should start even before five years of age.

Lee WS, Ong SY, Foo HW, Wong SY, Kong CX, Seah RB, Ng RT. Chronic liver disease is universal in children with biliary atresia living with native liver. *World J Gastroenterol* 2017; In press

**Introduction**

Biliary atresia (BA) is a progressive fibro-obliterative cholangiopathy presenting only in the first three months of life[[1](#_ENREF_1),[2](#_ENREF_2)]. Without surgery, BA is a fatal disease with children rarely survive beyond three years of age[[3](#_ENREF_3)]. Worldwide, the reported prevalence of BA ranged from 1 in 5000 to 18000 newborns[[4](#_ENREF_4)]. Since the introduction of Kasai hepatoportoenterostomy (HPE), long term survival of children with BA has been possible [[1](#_ENREF_1), [2](#_ENREF_2)]. However, the surgery can only provide temporary relief to the biliary obstruction and has been considered as a bridge to eventual liver transplantation (LT)[[3](#_ENREF_3),[5](#_ENREF_5),[6](#_ENREF_6)].

In individuals surviving with native livers after HPE, long term follow up is necessary to ascertain the health status and to detect complications of biliary cirrhosis[[7-9](#_ENREF_7)].Malnutrition[[10](#_ENREF_10),[11](#_ENREF_11)], cholangitis[[12](#_ENREF_12),[13](#_ENREF_13)], and fractures are common medical complications[[14](#_ENREF_14),[15](#_ENREF_15)].Ng *et al*[[7](#_ENREF_7)] reported that cholangitis and bone fractures are the two major complications in long-term survivors of children with BA living with native livers.More importantly, majority of these children have clinical or biochemical evidence of chronic liver disease (CLD)[[7](#_ENREF_7)].Most of the studies addressing the medical complications of children with BA surviving with native livers were in setting where LT is readily available[[7-9](#_ENREF_7)]. Children who needed LT were transplanted when indicated. Those children who survived with native livers were probably still in “optimal health”[[7](#_ENREF_7)].

We have previously reported that the short-to-medium term outcome of Malaysian children with BA were favourable[[16](#_ENREF_16)]. However, like in other developing countries, LT is not widely available in Malaysia[[16](#_ENREF_16)]. Many children with BA who had unsuccessful surgery died within the first few years of life due to a lack of timely LT[[4](#_ENREF_4),[16](#_ENREF_16)]. Nevertheless, in those who survived with their native livers after initial successful surgery, the quality of life was comparable to healthy children[[17](#_ENREF_17)].However, the prevalence and types of medical complications were not addressed[[16](#_ENREF_16),[17](#_ENREF_17)].

The aim of the present study was to describe the medical status of children with BA living with their native livers in a setting where LT is not common. The present study is unique as most of the current studies on the long-term outcome and medical status of BA were conducted in countries where LT is readily available.

**MATERIALS AND METHODS**

This was a cross sectional study conducted among children with BA attending the Paediatric Gastroenterology Unit of University Malaya Medical Centre (UMMC), Malaysia. Patients with BA diagnosed between January 1993 and December 2015 were identified. The medical record, latest clinic review and laboratory data were reviewed. The present study was approved by the institutional ethic review committee (MEC reference: 902.15).

***Inclusion criteria***

Only children who had surgery performed at UMMC were included. The diagnosis of BA was confirmed via an operative cholangiogram and a histology compatible with BA. The following children were excluded: (1) patients who had surgery performed at other centres but subsequently followed up at UMMC; (2) patients younger than 6 mo of age at the last clinic review; (3) inadequate data; and (4) who had LT.

***Post-operative care***

After HPE, prophylactic oral antibiotics were given for three months. All episodes of cholangitis were treated with 10-14 d of intravenous antibiotics. Children with persistent abnormal liver indices were given ursodeoxycholic acid. All children received fat-soluble vitamins, including vitamin D supplementation.

***Data collection***

Demographic, clinical and laboratory data were collected from chart review. Data collected included age, gender, ethnicity, date of birth, age at surgery, latest age at review, physical examination, growth status, size of liver and spleen, and signs of chronic liver disease. Laboratory data obtained were part of routine laboratory assessment performed on patients, and included the following: indices of hypersplenism [white cell (WBC) and platelet counts], synthetic [international normalized ratio (INR), albumin] and excretory (total bilirubin) functions of liver, and indices of hepatic inflammation [aspartate aminotransaminase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γGT)].

***Age at surgery***

Age at Kasai surgery was considered as early if the surgery was performed ≤ 60 d of age, and late if > 60 d of life.

***Growth parameters***

For children aged ≤ 5 years old, the World Health Organization (WHO) age- and sex-specific growth charts were used[[18](#_ENREF_18)]. For children aged > 5 years of age, the Centers for Disease Control and Prevention (CDC) age- and sex-specific growth charts were used [[19](#_ENREF_19)].Failure to thrive (FTT) was characterized as the weight-for-age z-score < -2.0 while short stature was defined as height-for-age z-score of < -2.0.

***Medical complications***

Medical ccomplications of CLD included portal hypertension (PHT) and bleeding esophageal varices, cholangitis in the preceding twelve months, hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPT), and fracture.

Criteria for the diagnosis of PHT were the presence of one of the following: (1)complication of PHT (such as ascites); (2) splenomegaly (≥ 2 cm palpable below the costal margin) and thrombocytopenia (platelet count ≤ 150 x109/L); or (3) endoscopic evidence of esophageal varies, esophageal variceal bleeding, or hypertensive gastropathy[[7](#_ENREF_7)].

As the yield of a positive blood culture in cholangitis is low, a positive blood culture was not required. Its diagnosis was based on the presence of fever of > 38 ℃ without other obvious source of infection, abdominal pain and new onset of acholic stools, and an elevation of conjugated bilirubin and/or (γGT) from the previous baseline[[7](#_ENREF_7)].

The presence of HPS required the evidence of reduced partial pressure of oxygen < 80 mmHg under room air and evidence of intrapulmonary shunting by contrast echocardiography with agitated saline[20]. POPH was defined as the presence of echocardiographic evidence of raised pulmonary arterial pressure (≥ 25 mmHg)[[20](#_ENREF_20), [21](#_ENREF_21)].

***CLD***

Laboratory evidence of hypersplenism included the presence of WBC < 4.0 x 109/L and/or platelet count < 150 x 109/L in the absence of other identifiable causes such as virus infection. Indices of CLD included: (1) impaired excretory function [total serum bilirubin ≥ 17 μmol/L]; (2) impaired synthetic function [albumin level < 35 g/L or INR ≥ 1.3]; and (3) presence of hepatitis (ALT ≥ 40 IU/L, or AST ≥ 40 IU/L, or γGT ≥ 55 IU/L).

***Definition of an ideal medical outcome***

The definition of an ideal medical status in survivors of BA with native livers was modified from that of Ng *et al*[[7](#_ENREF_7)]: (1) absence of clinical complications of CLD; (2) absence of cholangitis in the preceding 12 mo; and (3) normal liver laboratory indices.

***Statistical analysis***

Data were entered by using SPSS 21.0 (SPSS Inc., Chicago, IL, United States) for Windows XP (Microsoft, Seattle, Washington, United States). Data are quoted as medians and range. **2 tests were used for categorical data, while one sample *t*-test was used for comparison of numerical data. Independent samples *t* test was used when two different groups of continuous variables were compared.

**Results**

During the study period between 1993 and 2015, 140 children were diagnosed to have BA at UMMC, Kuala Lumpur (Figure 1). Of these, 112 (80%) had Kasai surgery. Twenty of these 112 patients developed liver cirrhosis and had LT. Seven of these 20 patients died after LT. Forty of the remaining 92 patients who had Kasai surgery died of liver cirrhosis without LT. Six of the 28 children who did not have Kasai surgery had LT as primary treatment, while the remaining 22 patients died without LT. Fifty two patients (37% of the original cohort) survive with their native livers and were included in the present analysis. The overall survival rate (native livers and LT) was 51%.

***Patients characteristics and associated congenital anomalies***

The median age of the 52 patients [females = 32, (62%); Table 1] at review was 7.4 years (ranged 10 mo to 22 years). Two-thirds (*n =* 35, 67%) were aged five years or older. The median age at Kasai surgery was 60 d (ranged 30 d to 148 d) days. Twenty nine (59%) of the patients had HPE performed before 60 d of age. Three (6%) patients had associated congenital anomalies: one each for aortic stenosis, atrial septal defect, craniosynostosis. Another three patients developed unrelated medical conditions: asthma, Sjogren’s syndrome and polycystic ovarian syndrome. None of the patients in the present cohort had BA splenic malformation (BASM) syndrome.

***Growth parameters***

Presence of FTT and short stature are shown in Table 1, while the distribution of weight and height-adjusted z-score are shown in Figure 1. Overall, approximately one quarter (*n =* 14; 27%) had a weight-for-age *z*-score < - 2.0 while ten children (20%) had a height-for-age *z*-score < -2.0. Data on parental height were not available for comparison. FTT was present in 17.6% of children younger than five years of age, and in 31.4% of children older than five years (*P =* 0.29). There was no difference between the proportion of children with short stature in those younger (6.3%) and older than 5 years of age (27%; < 5 years old *vs* ≥ 5 years old; *P =* 0.089).

***Medical complications***

PHT (*n =* 21, 40%), the commonest complications encountered, was seen in four out every 10 patients, but bleeding esophageal varices was only occurred in one quarter of the patients (*n =* 13, 25%). Another indicator of PHT, *i.e.,* ascites was uncommon (*n =* 3; 6%). Cholangitis was common and was diagnosed in approximately one-third (*n =* 19, 36%) of the patients in the preceding 12 months. No patients with bone fracture was noted in the present cohort. No patients were found to have HPS. However, two patients (aged 19 and 20 years, respectively) were diagnosed to have POPH. One was asymptomatic and the hepatopulmonary hypertension was diagnosed during pre-LT assessment while the second patients presented with chest symptoms. Both patients are receiving appropriate therapy while being assessed for LT (Table 2).

***Laboratory indices***

The distribution of various laboratory indices is shown in Figure 2. Leukopenia and thrombocytopenia were noted in 25% and 54% of the patients, respectively. Half (*n =* 26, 50%) of the patients had raised total bilirubin level. Elevated liver enzymes were also common (ALT 67%, AST 73%, ɣGT 69%; Figure 2). A great majority of patients (*n =* 46, 90%) had normal serum albumin level, while more than half (*n =* 27 of 39; 59.2%) had a normal INR value.

***Influence of age on the presence of chronic liver disease***

Generally, as compared to patients younger than 5 years of age, patients older than 5 years of age were more likely to develop complications of liver cirrhosis, *i.e.,* portal hypertension (*P =* 0.034), bleeding esophageal varices (*P =* 0.026), and leukopenia (*P =* 0.017; Table 3).

***Ideal medical outcome***

Fifteen patients (29%) had no complications associated with CLD noted (Table 2). These included six of the 17 (36%) patients younger than 5 years old and nine of the 35 (26%) older than 5 years of age. Three patients had normal laboratory indices. Of these, only one patient (2% of the entire cohort) had an ideal outcome, *i.e.,* absence of any clinical complications and normal laboratory indices. The remaining two patients who had normal laboratory indices had an episode of cholangitis in the preceding 12 months. 98% of the patients in the present study had either presence of medical complications or abnormal laboratory indices.

**Discussion**

The present study confirmed that the vast majority of patients with BA surviving with native livers after HPE had either clinical or laboratory evidence of CLD[[7](#_ENREF_7)]. Although 71% of the patients had no clinical complications of CLD and 90% had normal liver synthetic function, only one of the 49 patients (2%) in the present study fulfilled had an ‘ideal’ outcome after HPE. This is consistent with the finding from Childhood Liver Disease Research and Education Network (CHiLDREN) where 98% of children with BA either had clinical complications of CLD or biochemical abnormalities[[7](#_ENREF_7)].Hadzic *et al*[[22](#_ENREF_22)] using slightly different criteria, also noted that only 11% of children with BA living with native livers had absence of surgical complications and normal laboratory indices.

In the present study, although clinical complications of CLD were absent in 30% of the children living with native livers after HPE, most had raised liver enzymes indicating persistent hepatitis. Normal liver biochemistry were only seen in three children in the present cohort, two of whom had cholangitis in the preceding twelve months. This underscores the importance of continuing surveillance in children with BA after HPE as well as regular laboratory assessment even in the absence of clinical complications of CLD.

There are major similarities and differences in the findings between the present study and the CHiLDREN study[[7](#_ENREF_7)].In both studies, PHT and cholangitis were the two most common complications noted. Bleeding esophageal varices and cholangitis were noted in 19% and 17%, respectively in the CHiLDREN cohort and 13% and 19%, respectively, in the present cohort[[7](#_ENREF_7)].

However, fractures of the long bone which was common in the CHiLDREN cohort (27%) was not seen in the present study. Hepatic osteodystrophy is a well-known complication in children with cholestatic CLD[[23](#_ENREF_23)]. Radiological changes of long bone has been reported to be as high as 76% in children with BA[[23](#_ENREF_23)]. The reported incidence of bone fractures in children with BA before LT was between 8% and 35%[[24](#_ENREF_24),[25](#_ENREF_25)].The reason for the discrepancies in the incidence of fractures observed in the CHiLDREN as well as other studies and present cohort is unknown. We have previously reported that 28% of children with CLD had vitamin D non-sufficiency despite being on vitamin D supplementation in a tropical climate setting[[26](#_ENREF_26)].Thus, it is unlikely that adequate exposure to sunlight in the tropical climate among the patients in the present study is a satisfactory reason.

Malnutrition in patients with BA after HPE, a well-known complication [[10](#_ENREF_10)], is associated with LT or death by 24 mo of age[[10](#_ENREF_10)]. It is also an independent risk factor for pre- and post-LT mortality, and even graft failure[[4](#_ENREF_4)]*.* Careful monitoring of the nutritional intake, early nutritional supplementation, regular monitoring of growth parameters including tricep skinfold thickness and mid-upper arm circumference, are important[[27](#_ENREF_27)]. When adequate nutrition has been provided and malnutrition persisted, LT should be considered[[28](#_ENREF_28)].

In the present study, the prevalence of weight and height *z*-score of less than -2.0 were 28% and 20%, respectively. This is much higher as compared to the findings in the CHiLDREN cohort where only 0.5% and 3.2% of the patients had a weight and height z-score of less than -2.0[[7](#_ENREF_7)]. These discrepancies can be partly explained by a much higher prevalence of both underweight (13.0%, 95%CI: 11.7, 14.5) and stunting (13.4%, 95%CI: 15.1, 21.5) in Malaysian children under 18 years of age[[29](#_ENREF_29)]. Nevertheless, underweight and stunting in children with BA post HPE in the present cohort is common. Intensive efforts in improving the nutritional status of these children is important. In the present study, we did not include growth parameters in the analysis of ideal medical status. Besides the high prevalence of underweight and stunting in Malaysian children, the growth status of the parents of these children were not available. Thus, we were unable to exclude familial short stature.

PHT is a common occurrence in BA, commonly presenting as splenomegaly and thrombocytopenia[[30](#_ENREF_30)]. In the present study, 40% of the patients had PHT while 25% had bleeding varices. This is consistent with another study on PHT from the CHiLDREN cohort, where 49% and 15% of the 211 patients had PHT and bleeding varices, respectively[[30](#_ENREF_30)]. Ascites, another complication of PHT, was uncommon, being only observed in 6% of the patients. More importantly, 12% and 6% of the patients in the present study who were younger than five years old had PHT and bleeding esophageal varices. This underscores the importance of monitoring of PHT and its complications even in younger patient with BA[[30](#_ENREF_30)].

In the present study, 36% of the patients experienced at least one episode of cholangitis. This included 31% of the patients older than five years of age. A total of eight children aged older than 10 years experienced cholangitis. Thus, the risk of cholangitis after HPE continues throughout early childhood to adolescent period and even into early adulthood[[7](#_ENREF_7)].

POPH and HPS were uncommon complications of BA[[21](#_ENREF_21)]. In the present study, POPH was diagnosed in two young adults (3.8%).

As compared to the CHiLDREN cohort, the strength of the current study was that it was conducted in a single unit where a consistent post-surgical clinical care was practiced throughout the study period. The variability in clinical care as seen in the CHiLDREN cohort was not seen in our study[[7](#_ENREF_7)].Other practice such as routine administration of fat-soluble vitamins in BA after HPE could also explained the low incidence of bone fracture seen in the present study.

However, there are several weaknesses in the present study. Firstly, it was a single-centre study and the number of patients studied was relatively small. Thus, children younger than five years of age were included in this review. Nevertheless, even in young children, PHT and bleeding esophageal varices were seen in 12% and 6% of patients, respectively.

Health-related quality of life survey was not included in the present study but was studied separately[[17](#_ENREF_17)].The health-related quality of life in children with BA was similar to that of healthy children, and was not adversely affected by the presence of complications of CLD such as PHT, cholangitis or impaired synthetic function of the liver[[17](#_ENREF_17)].

The most important factor adversely affecting the overall outcome of children with BA in Malaysia was a lack of timely LT in those with unsuccessful surgery[[16](#_ENREF_16)].The median age for HPE in the present study was 60 d, which was comparable to figures from other centres[[31](#_ENREF_31)], ranging from 54 days in England and Wales[[32](#_ENREF_32)] to 68 d in Switzerland[[33](#_ENREF_33)].

The survival rate of patients with BA living with native livers in the present study was 37%. This was comparable to the survival rates in the review by Verkade *et al*[[31](#_ENREF_31)], where the survival rates with native livers ranged from as low as 20% in Germany[[34](#_ENREF_34)] to 60% in Japan[[6](#_ENREF_6)].The overall survival rate of the present study at 51%, however, is much lower that similar figures of 73% in the Netherlands [[35](#_ENREF_35)] to 92% in Switzerland[[33](#_ENREF_33)].

Thus, the lack of timely LT in those with unsuccessful surgery is the biggest unmet medical need in children with BA in Malaysia. Factors contributing to a lack of LT included a low deceased organ donation rate and the relative high cost of LT surgery[[36](#_ENREF_36)]. It is unlikely that the lack of deceased organ donation in Malaysia will be overcome in the near future.

We have previously shown that early referral for surgery significantly affected the outcome of surgery[16]. Children with BA who were operated before 60 d of age had a 65% chance of surviving with native liver at two years of age as compared to those who had surgery at or after 60 d of age. The median age of survival for those with unsuccessful surgery was 14 mo (range 3 to 25 mo)[16]. Thus in a country such as Malaysia where LT remains limited, early referral for successful surgery remains the most important opportunity to avoid early LT.

Thus, clinicians in Malaysia caring for children need to familiarize themselves with signs of an unsuccessful surgery to facilitate early referral for assessment of LT. We have shown that children with unsuccessful surgery were more likely to have a significantly bigger liver and spleen size, a more deranged coagulation profile, a significantly lower serum albumin level, and a significantly higher serum GGT level as compared to children who had successful surgery. Thus monitoring of children with BA after surgery should include regular measurement of liver and spleen size, assessment of liver synthetic function such as coagulation and albumin level, and liver enzymes.

As stated earlier, opportunity to improve the overall survival rate of BA in Malaysia include strategies to enhance early referral and surgery[[31](#_ENREF_31)].The provision of stool color cards to parents of new-born for identification of acholic stools, has been practiced in Taiwan and Switzerland[[37](#_ENREF_37),[38](#_ENREF_38)]. In Taiwan, five years after starting the stool color card screening, the rate of HPE performed at < 60 d increased from 49% to 66% while the 5-year survival rate with native liver improved from 27% to 64%[[37](#_ENREF_37)].This strategy should be adopted in countries where LT is limited, such as Malaysia.

In conclusion, about 98% of children with BA living with native livers after HPE had clinical or laboratory evidence of CLD, underscoring the importance of continuing medical surveillance. PHT and variceal bleeding maybe seen in children younger than five years of age. We recommend that surveillance for the complications of CLD in children with BA living with native livers should be started before five years of age. The major unmet medical need for children with BA living with their native livers is a lack of timely LT in those with unsuccessful surgery. Opportunities to improve the overall survival rate include universal new-born screening in all infants to improve early referral ate and the surgical outcome of HPE.

**COMMENTS**

***Background***

In individuals with biliary atresia (BA) surviving with native livers after hepatoportoenterostomy, biliary cirrhosis is an inevitable long term sequelae. Malnutrition, cholangitis, and fractures are common medical complications encountered in these children, arising as a result of biliary cirrhosis. Previous study has shown that cholangitis and bone fractures are the two major complications in long-term survivors of children with BA living with native livers.

***Research frontiers***

It is important to determine the prevalence of medical complications in children with BA surviving with their native livers, particularly in a setting where liver transplantation (LT) is limited.

***Innovation and breakthrough***

The present study shows that clinical or laboratory evidence of chronic liver disease are present in 98% of children with BA living with native livers after surgery. Portal hypertension and variceal bleeding maybe seen in children younger than five years of age, underscoring the importance of medical surveillance for complications of BA starting at a young age.

***Applications***

The authors recommend that in all children with BA who survive with their native livers, systemic surveillance to ascertain medical complications to be started at an age younger than five years. Ascending cholangitis, portal hypertension and variceal bleeding are important medical complications encountered.

***Peer-review***

This manuscript describes current situation of treatment of BA in Malaysia. In Malaysia, lt is not common. Therefore, most patients with BA must live with their native livers after Kasai’s hepatic portoenterostomy. This manuscript reemphasized devastating nature of BA and essentialness of LT for patients with BA.

**References**

1 **Chardot C**. Biliary atresia. *Orphanet J Rare Dis* 2006; **1**: 28 [PMID: 16872500 DOI: 10.1186/1750-1172-1-28]

2 **Schreiber RA**, Kleinman RE. Biliary atresia. *J Pediatr Gastroenterol Nutr* 2002; **35** Suppl 1: S11-S16 [PMID: 12151815]

3 **Liu MB**, Huong TB, Hoang X, Doan L, Trinh S, Anh Nguyen HP, Thanh Le H, Holterman AX. Biliary atresia in Vietnam: Management and the burden of disease. *Surgery* 2017; **161**: 533-537 [PMID: 27743713 DOI: 10.1016/j.surg.2016.08.012]

4 **Utterson EC**, Shepherd RW, Sokol RJ, Bucuvalas J, Magee JC, McDiarmid SV, Anand R; Split Research Group. Biliary atresia: clinical profiles, risk factors, and outcomes of 755 patients listed for liver transplantation. *J Pediatr* 2005; **147**: 180-185 [PMID: 16126046 DOI: 10.1016/j.jpeds.2005.04.073]

5 **Shneider BL**, Mazariegos GV. Biliary atresia: a transplant perspective. *Liver Transpl* 2007; **13**: 1482-1495 [PMID: 17969203 DOI: 10.1002/lt.21303]

6 **Nio M**, Ohi R, Miyano T, Saeki M, Shiraki K, Tanaka K; Japanese Biliary Atresia Registry. Five- and 10-year survival rates after surgery for biliary atresia: a report from the Japanese Biliary Atresia Registry. *J Pediatr Surg* 2003; **38**: 997-1000 [PMID: 12861525]

7 **Ng VL**, Haber BH, Magee JC, Miethke A, Murray KF, Michail S, Karpen SJ, Kerkar N, Molleston JP, Romero R, Rosenthal P, Schwarz KB, Shneider BL, Turmelle YP, Alonso EM, Sherker AH, Sokol RJ; Childhood Liver Disease Research and Education Network (CHiLDREN). Medical status of 219 children with biliary atresia surviving long-term with their native livers: results from a North American multicenter consortium. *J Pediatr* 2014; **165**: 539-546.e2 [PMID: 25015575 DOI: 10.1016/j.jpeds.2014.05.038]

8 **Kumagi T**, Drenth JP, Guttman O, Ng V, Lilly L, Therapondos G, Hiasa Y, Michitaka K, Onji M, Watanabe Y, Sen S, Griffiths W, Roberts E, Heathcote J, Hirschfield GM. Biliary atresia and survival into adulthood without transplantation: a collaborative multicentre clinic review. *Liver Int* 2012; **32**: 510-518 [PMID: 22098694 DOI: 10.1111/j.1478-3231.2011.02668.x]

9 **Shinkai M**, Ohhama Y, Take H, Kitagawa N, Kudo H, Mochizuki K, Hatata T. Long-term outcome of children with biliary atresia who were not transplanted after the Kasai operation: &gt;20-year experience at a children's hospital. *J Pediatr Gastroenterol Nutr* 2009; **48**: 443-450 [PMID: 19330933]

10 **DeRusso PA**, Ye W, Shepherd R, Haber BA, Shneider BL, Whitington PF, Schwarz KB, Bezerra JA, Rosenthal P, Karpen S, Squires RH, Magee JC, Robuck PR, Sokol RJ; Biliary Atresia Research Consortium. Growth failure and outcomes in infants with biliary atresia: a report from the Biliary Atresia Research Consortium. *Hepatology* 2007; **46**: 1632-1638 [PMID: 17929308 DOI: 10.1002/hep.21923]

11 **Shepherd RW**, Chin SE, Cleghorn GJ, Patrick M, Ong TH, Lynch SV, Balderson G, Strong R. Malnutrition in children with chronic liver disease accepted for liver transplantation: clinical profile and effect on outcome. *J Paediatr Child Health* 1991; **27**: 295-299 [PMID: 1931221]

12 **Lünzmann K**, Schweizer P. The influence of cholangitis on the prognosis of extrahepatic biliary atresia. *Eur J Pediatr Surg* 1999; **9**: 19-23 [PMID: 10207698 DOI: 10.1055/s-2008-1072206]

13 **Wu ET**, Chen HL, Ni YH, Lee PI, Hsu HY, Lai HS, Chang MH. Bacterial cholangitis in patients with biliary atresia: impact on short-term outcome. *Pediatr Surg Int* 2001; **17**: 390-395 [PMID: 11527173]

14 **Okada T**, Honda S, Miyagi H, Minato M, Taketomi A. Hepatic osteodystrophy complicated with bone fracture in early infants with biliary atresia. *World J Hepatol* 2012; **4**: 284-287 [PMID: 23293713 DOI: 10.4254/wjh.v4.i10.284]

15 **Högler W**, Baumann U, Kelly D. Endocrine and bone metabolic complications in chronic liver disease and after liver transplantation in children. *J Pediatr Gastroenterol Nutr* 2012; **54**: 313-321 [PMID: 22064631 DOI: 10.1097/MPG.0b013e31823e9412]

16 **Lee WS**, Chai PF, Lim KS, Lim LH, Looi LM, Ramanujam TM. Outcome of biliary atresia in Malaysia: a single-centre study. *J Paediatr Child Health* 2009; **45**: 279-285 [PMID: 19493120 DOI: 10.1111/j.1440-1754.2009.01490.x]

17 **Lee WS**, Ong SY. Health-Related Quality of Life in Children with Biliary Atresia Living with Native Livers. *Ann Acad Med Singapore* 2016; **45**: 61-68 [PMID: 27125347]

18 Physical status: The use of and interpretation of anthropometry, Report of a WHO Expert Committee. World Health Organization, 1995

19 Growth Charts. Atlanta: Centers for Disease Control and Prevention, 2010

20 **Machicao VI**, Balakrishnan M, Fallon MB. Pulmonary complications in chronic liver disease. *Hepatology* 2014; **59**: 1627-1637 [PMID: 24089295 DOI: 10.1002/hep.26745]

21 **Ecochard-Dugelay E**, Lambert V, Schleich JM, Duché M, Jacquemin E, Bernard O. Portopulmonary Hypertension in Liver Disease Presenting in Childhood. *J Pediatr Gastroenterol Nutr* 2015; **61**: 346-354 [PMID: 25885880 DOI: 10.1097/mpg.0000000000000821]

22 **Hadzić N**, Davenport M, Tizzard S, Singer J, Howard ER, Mieli-Vergani G. Long-term survival following Kasai portoenterostomy: is chronic liver disease inevitable? *J Pediatr Gastroenterol Nutr* 2003; **37**: 430-433 [PMID: 14508212]

23 **Hirano A**, Katayama H, Shirakata A. [Bone changes in congenital biliary atresia--review of 42 cases after surgery]. *Nihon Igaku Hoshasen Gakkai Zasshi* 1990; **50**: 29-39 [PMID: 2330287]

24 **DeRusso PA**, Spevak MR, Schwarz KB. Fractures in biliary atresia misinterpreted as child abuse. *Pediatrics* 2003; **112**: 185-188 [PMID: 12837886]

25 **Guichelaar MM**, Schmoll J, Malinchoc M, Hay JE. Fractures and avascular necrosis before and after orthotopic liver transplantation: long-term follow-up and predictive factors. *Hepatology* 2007; **46**: 1198-1207 [PMID: 17654700 DOI: 10.1002/hep.21805]

26 **Lee WS,** Siow YY, Wong SY, Ong SY, Foo HW, Ng RT, et al.. Vitamin D insufficiency is common in children with chronic inflammatory bowel disease and chronic liver disease in a tropical country. World Congress of Paediatric Gastroenterology, Hepatology and Nutrition; October 5-8, 2016; Montreal.

27 **Squires RH**, Ng V, Romero R, Ekong U, Hardikar W, Emre S, Mazariegos GV. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *Hepatology* 2014; **60**: 362-398 [PMID: 24782219 DOI: 10.1002/hep.27191]

28 **Sundaram SS**, Mack CL, Feldman AG, Sokol RJ. Biliary atresia: Indications and timing of liver transplantation and optimization of pretransplant care. *Liver Transpl* 2017; **23**: 96-109 [PMID: 27650268 DOI: 10.1002/lt.24640]

29 National Health and Morbidity Survey. Institute of Public Health, Ministry of Health Malaysia, 2015

30 **Shneider BL**, Abel B, Haber B, Karpen SJ, Magee JC, Romero R, Schwarz K, Bass LM, Kerkar N, Miethke AG, Rosenthal P, Turmelle Y, Robuck PR, Sokol RJ; Childhood Liver Disease Research and Education Network. Portal hypertension in children and young adults with biliary atresia. *J Pediatr Gastroenterol Nutr* 2012; **55**: 567-573 [PMID: 22903006 DOI: 10.1097/MPG.0b013e31826eb0cf]

31 **Verkade HJ**, Bezerra JA, Davenport M, Schreiber RA, Mieli-Vergani G, Hulscher JB, Sokol RJ, Kelly DA, Ure B, Whitington PF, Samyn M, Petersen C. Biliary atresia and other cholestatic childhood diseases: Advances and future challenges. *J Hepatol* 2016; **65**: 631-642 [PMID: 27164551 DOI: 10.1016/j.jhep.2016.04.032]

32 **Davenport M**, Ong E, Sharif K, Alizai N, McClean P, Hadzic N, Kelly DA. Biliary atresia in England and Wales: results of centralization and new benchmark. *J Pediatr Surg* 2011; **46**: 1689-1694 [PMID: 21929975 DOI: 10.1016/j.jpedsurg.2011.04.013]

33 **Wildhaber BE**, Majno P, Mayr J, Zachariou Z, Hohlfeld J, Schwoebel M, Kistler W, Meuli M, Le Coultre C, Mentha G, Belli D, Chardot C. Biliary atresia: Swiss national study, 1994-2004. *J Pediatr Gastroenterol Nutr* 2008; **46**: 299-307 [PMID: 18376248 DOI: 10.1097/MPG.0b013e3181633562]

34 **Leonhardt J**, Kuebler JF, Leute PJ, Turowski C, Becker T, Pfister ED, Ure B, Petersen C. Biliary atresia: lessons learned from the voluntary German registry. *Eur J Pediatr Surg* 2011; **21**: 82-87 [PMID: 21157692 DOI: 10.1055/s-0030-1268476]

35 **de Vries W**, de Langen ZJ, Groen H, Scheenstra R, Peeters PM, Hulscher JB, Verkade HJ; Netherlands Study Group of Biliary Atresia and Registry (NeSBAR). Biliary atresia in the Netherlands: outcome of patients diagnosed between 1987 and 2008. *J Pediatr* 2012; **160**: 638-644.e2 [PMID: 22082947 DOI: 10.1016/j.jpeds.2011.09.061]

36 **Ghods AJ**. Current status of organ transplant in Islamic countries. *Exp Clin Transplant* 2015; **13** Suppl 1: 13-17 [PMID: 25894121]

37 **Lien TH**, Chang MH, Wu JF, Chen HL, Lee HC, Chen AC, Tiao MM, Wu TC, Yang YJ, Lin CC, Lai MW, Hsu HY, Ni YH; Taiwan Infant Stool Color Card Study Group. Effects of the infant stool color card screening program on 5-year outcome of biliary atresia in Taiwan. *Hepatology* 2011; **53**: 202-208 [PMID: 21140377 DOI: 10.1002/hep.24023]

38 **Wildhaber BE**. Screening for biliary atresia: Swiss stool color card. *Hepatology* 2011; **54**: 367-8; author reply 369 [PMID: 21488071 DOI: 10.1002/hep.24346]

**P-Reviewer:** hashimoto T, Neri v **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** Malaysia

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B, b

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**Table 1 Clinical and laboratory characteristics of the 52 patients with biliary atresia surviving with native livers after Kasai surgery**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics**  |  | ***n* (%)** | **%** |
| Gender | MaleFemale | 20 32  | 38.461.6 |
|  |  |  |  |
| Ethnicity | ChineseMalaysIndians | 32 15 5  | 61.528.89.6 |
|  |  |  |  |
| Age at Kasai surgery (d) | Mean ± SDMedianRange  | 65.5 ± 26.36030–148  |  |
|  |  |  |  |
| Kasai surgery ≤ 60 d | YesNo | 30 22  | 57.742.3 |
|  |  |  |  |
| Age at latest follow up (in years) | Mean ± SDMedian | 8.3 ± 6.17.4 |  |
|  |  |  |  |
| Medical conditions present | No  | 46 | 88.5 |
|  | Yes  | 6 | 11.5 |
|  | Congenital anomalies  | 3 | 5.7 |
|  |  |  |  |
| Presence of failure to thrive |  |  |  |
|  All (*n =* 52) | Yes No  | 1438 | 26.973.1 |
|  < 5 years old (*n =* 17) | Yes  | 3 | 17.6 |
|   | No  | 14 | 82.4 |
|  ≥ 5 years old (*n =* 35) | Yes  | 11 | 31.4 |
|  | No  | 24 | 68.6 |
|  |  |  |  |
| Short stature |  |  |  |
|  All (*n =* 51) | Yes  | 10 | 19.6 |
|  | No  | 41 | 80.4 |
|  < 5 years old (*n =* 16) | Yes  | 1 | 5.9 |
|  | No  | 16 | 94.1 |
|  ≥ 5 years old (*n =* 32) | Yes  | 9 | 26.5 |
|  | No  | 25 | 73.5 |
|  |  |  |  |
| Laboratory indices at review | White cell count (x109/L) | 6.2 | (4.8) |
|  Median (IQR) | Platelet count (x109/L) | 131 | (169) |
|  | Total bilirubin (μmol/L) | 18 | (39) |
|  | Serum albumin (g/L) | 41 | (8) |
|  | International normalised ratio | 1.1 | (0.1) |
|  | Alanine transferase (IU/L) | 54 | (64) |
|  | Aspartate transferase (IU/L) | 70 | (80) |
|  | Gamma glutamyl-transpeptidase (IU/L) | 109 | (174) |

Congenital anomalies present: one each for aortic anomalies, atrial septal defect, and craniosynostosis. IQR: inter-quartile range.

**Table 2 Medical status of the 52** **patients with biliary atresia surviving with native livers after Kasai surgery *n* (%)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Medical variables** | **Data available, n** | **All (*n =* 52)** | **< 5 years old (*n =* 17)** | **≥ 5 years old (*n =* 35)** | ***P*-value****(< 5 years old *vs* ≥ 5 years old)** |
| Failure to thrive (weight-for-age z-score < 2 SD) | 52 | 14 (26.9) | 3 (17.6) | 11 (31.4) | 0.29 |
| Short stature (height-for-age z-score < 2 SD) | 51 | 10 (19.6) | 1 (5.9) | 9 (26.5) | 0.089 |
|   |  |  |  |  |  |
| Medical complications |  |  |  |  |  |
|  Portal hypertension | 52 | 21 (40.4) | 2 (11.8) | 19 (54.3) | 0.034 |
|  Variceal bleeding | 52 | 13 (25.0) | 1 (5.8) | 12 (34.3) | 0.026 |
|  Ascites  | 52 | 3 (5.8) | 2 (11.8) | 1 (2.9) | 0.20 |
|  Cholangitis  | 52 | 19 (36.3) | 8 (47.1) | 11 (31.4) | 0.27 |
|  Portopulmonary hypertension | 52 | 2 (3.8) | 0 (0) | 2 (5.7) | 0.31 |
|  Hepatopulmonary syndrome | 52 | 0 (0) | 0 (0) | 0 (0) | - |
|  Bone fracture | 52 | 0 (0) | 0 (0) | 0 (0) | - |
|  |  |  |  |  |  |
| Laboratory indices |  |  |  |  |  |
|  White cell count (< 4 x 109/L) | 49 A | 13 (25.0) | 1 (5.9) | 13 (40.6)  | 0.017 |
|  Platelet count (< 150 x 109/L) | 50 A | 28 (53.8) | 8 (47.1) | 22 (66.7)  | 0.28 |
|  Total bilirubin (≥ 17 µmol/L) | 52 | 26 (50.0) | 6 (35.3) | 21 (60.0) | 0.09 |
|  Albumin (< 35 g/L) | 52 | 6 (11.5) | 1 (5.8) | 5 (14.3) | 0.37 |
|  International normalized ratio (≥ 1.3) | 52 | 12 (23.1) | 5 (29.4) | 7 (20.0) | 0.70 |
|  Alanine transferase (≥ 40 IU/L) | 52 | 35 (67.3) | 13 (76.5) | 24 (68.6) | 0.56 |
|  Aspartate transferase (≥ 40 IU/L) | 52 | 38 (73.1) | 15 (88.2) | 25 (71.4) | 0.18 |
|  Gamma glutamyl-transpeptidase (≥ 55 IU/L) | 52 | 36 (69.2) | 11 (64.7) | 27 (77.1) | 0.34 |
|  |  |  |  |  |  |
| Absence of any medical complications | 52 | 15 (28.8) | 6 (35.3) | 9 (25.7) | 0.98 |
| Absence of abnormal laboratory indices | 49 | 3 (6.1) | 1 (5.9) | 2 (6.3) | 0.47 |
|  |  |  |  |  |  |
| Ideal medical outcome  | 49 | 1 (2.0) | 0 (0) | 1 (2.9) |  |
|  |  |  |  |  |  |

A: data for white cell count for three patients and platelet count for two patients were not available for review. Ideal medical outcome was defined as an absence of any medical complications and presence of normal laboratory indices.



**Figure 1 Boxplot showing distribution of weight-for-age and height-for-age z-score in 52 children with biliary atresia surviving with native livers.** From top to bottom, the 5 horizontal lines represent the largest data point, which is not more than 1.5 times from the box, the third quartile, the median, the first quartile and the smallest data point which is not more than 1.5 times the IQR from the box, respectively.



**Figure 2 Boxplot showing distribution of white cell count, platelet count, total serum bilirubin, and liver enzymes in 52 children with biliary atresia surviving with native livers.** From top to bottom, the 5 horizontal lines represent the largest data point, which is not more than 1.5 times from the box, the third quartile, the median, the first quartile and the smallest data point which is not more than 1.5 times the IQR from the box, respectively.