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ORIGINAL ARTICLE

Long-term clinical and socioeconomic outcomes of children with biliary atresia

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Abstract

Background: Biliary atresia (BA) is rare liver disease of unknown etiology, and is a major indication for liver transplant (LT). Previous data indicate improved outcomes with early referral for Kasai portoenterostomy (KPE).
Objective: Evaluate the long-term outcomes in BA, with particular focus on those transitioned to adult care with native livers.
Subjects and Methods: Patients with BA treated between1980 and 2012 were identified. Data were collected from the time of referral, transition to adult care, and the most recent clinic notes, from which patient and native liver survival were calculated.
Results: Four hundred and fifty-four patients with BA were identified, who were followed up for median of 16.4 years from birth; 74 died (41 of whom had a LT), giving a 20-year survival rate of 83.6%. Two hundred and seventy-two patients received an LT, with the median native liver survival being 35 months. Of patients who transitioned to adult care, 54 of 180 (30.0%) retained their native liver. Of these, 72% (39 of 54) had evidence of chronic liver disease at transition, of whom 8 were subsequently lost to follow-up, 9 were transplanted, and 22 remained stable with compensated liver disease. Of the 15 of 54 patients (28%) with no evidence of chronic disease in their native liver disease at transition, 3 were subsequently lost to follow-up; none received transplants, although 3 patients developed new-onset liver disease. All patients transitioned to adult care completed secondary school education ($N = 180$), with 49% having attended college/university and 87% being in employment or education at the last follow-up. Of female patients, 34% had at least one pregnancy (27 children in 21 women), while 22% of males had fathered a child.
Conclusion: Long-term outcomes in BA are good, with patients surviving into adult life. Progression of chronic liver disease and associated morbidity is common in those who retained their native livers, suggesting that these patients require monitoring of liver disease throughout adult life, and early recognition of the need for LT.

Introduction

Biliary atresia (BA) is an inflammatory fibrosing process affecting the extrahepatic and intrahepatic biliary tree, resulting in fibrous obliteration of the extrahepatic biliary tract, ductopenia of intrahepatic bile ducts, and biliary cirrhosis. BA is the most frequent surgical cause of cholestatic jaundice in neonates.[1] BA is commonly isolated (~90%) without the presence of other malformations, but may also be part of a syndrome.[2–4] Syndromic BA can be associated with various congenital anomalies, such as polysplenia or asplenia, malrotation, intestinal atresia, situs inversus, preduodenal portal vein, absence of the retrohepatic inferior vena cava, or cardiac anomalies. BA is a rare disease, with the reported incidence ranging from 5 to 32 cases per 100 000 live births in different parts of the world.[5–10]

While the exact etiology of the disease remains unknown, various viruses including cytomegalovirus, reovirus, and rotavirus have been implicated to be the causative agents, inducing inflammatory damage of the bile ducts, resulting in progressive ductal injury and obstruction.[11–13]

The natural history of the disease is to rapidly progress to increasing jaundice, failure to thrive, portal hypertension, decompensated liver disease and, ultimately, death if surgical treatment is not instituted. The Kasai portoenterostomy (KPE) remains the preferred initial surgical treatment.[14] The results of KPE have improved over last few decades, due to better

understanding of the disease and patient care in specialist liver units, with provision of better pharmacological agents and endoscopy treatment.[15]

Survival with native liver has been reported to be up to 40–57% at 10 years, with some BA patients now surviving with their native livers up to 30–40 years of age, although a significant proportion of these patients continue to have ongoing problems with recurrent cholangitis, portal hypertension, variceal bleeding, progression of cirrhosis, and chronic liver disease.[16,17] In some cases, patients with BA can develop hepatocellular carcinoma, requiring liver transplantation (LT), although this is relatively rare.[18–21]

Although BA is a neonatal disease, its implications are not confined to childhood. Since most young people born with BA will now survive into adulthood, ongoing requirements for health care will necessitate their transition from a family-centered pediatric service to a patient-centered adult service. As such, adult hepatologists should be aware of the clinical management and complications of BA and the long-term consequences of LT in childhood.[22]

This study encompasses the management of BA patients in a single center over four decades. This is a unique cohort of large numbers of BA patients, given that the numbers of babies born with BA in the United Kingdom are less than 50 per year.[23]

Aim. The aim of this study was to evaluate the long-term outcomes of the patients managed in our center, with particular emphasis on those transitioned to adult services with their native liver, and on socioeconomic outcomes, including education and employment.

Subjects and Methods

Setting. This is retrospective review of patients referred to Birmingham Children's Hospital (BCH), a national pediatric center in the United Kingdom, for assessment and treatment of BA. The treatment pathway commenced with KPE, where possible, with LT being the alternative approach in patients referred too late for KPE. After initial treatment, patients were followed up in pediatric outpatient clinics, although some patients were subsequently transferred to their local or regional pediatric centers for ongoing follow-up. Patients were then transitioned from pediatric to adult care when both the patient and clinicians deemed this appropriate. The majority of BA patients from BCH are transitioned to the adult liver unit at the Queen Elizabeth Hospital Birmingham (QEHB; 69.4% [125/180] of the study cohort), which has strong ties with BCH.

Data collection. All patients with BA referred to BCH between October 1980 and December 2012 were identified from the unit's clinical database. Patients were entered on the database following consent for the use of anonymized data for audit. Medical records were reviewed to identify the date of initial treatment for BA (KPE or LT), as well as the dates of any LT or death occurring during follow-up at our center. After transfer to regional pediatric centers, or transition to adult care, attempts were made to ascertain whether any LT or deaths had occurred at the new center. Where this was possible, the end of follow-up for a patient was classified as the final appointment at their current center, with the final appointment at our center used otherwise.

Native liver survival was defined as the time from birth to LT or death, with patients being censored at the date of their last known follow-up. Four patients treated early in the study period were known to have died in childhood while being followed up at an external pediatric center, but did not have a date of death recorded. For these, the survival time was imputed using the median time to death for the remainder of the subgroup of patients who died during follow-up.

In patients who retained their native liver at the time of transition, native liver survival from the time of transition was additionally calculated. The most recent clinical notes for these patients were also reviewed, to identify whether there was evidence of symptoms of chronic liver disease, either at the time of transition, or at the most recent follow-up.

In addition to disease-related outcomes, data were collected for socioeconomic outcomes for patients who had transitioned to adult care, where available. This primarily used clinical records at BCH and QEHB, along with clinical letters, to extract details of patient's highest level of education and current employment status, as well as the numbers of pregnancies in females, and children fathered in males. Patients for whom contact details were still available were also sent questionnaires requesting details of their socioeconomic status, in an attempt to maximize data completeness.

Statistical analysis. Continuous variables were reported as mean ± standard deviation (SD) where approximately normally distributed, or as medians and interquartile ranges (IQRs) otherwise. Survival outcomes were assessed using Kaplan–Meier curves, which were used to estimate the survival rates at different follow-up intervals, as well as the median survival times, where applicable. Associations between liver disease at transition and subsequent LT rates were assessed using log-rank tests, in order to account for the follow-up time. For those patients who transitioned to adult care, comparisons between those who retained their native liver, and those who had received an LT were performed using Fisher's exact tests for nominal variables, and Mann–Whitney U tests for ordinal or continuous variables.

Cases with missing data were excluded from the analysis of the affected variables, and the numbers of cases included in each analysis are stated throughout. All analyses were performed using IBM SPSS 24 (IBM Corp. Armonk, NY), with $P < 0.05$ deemed to be indicative of statistical significance throughout.

Results

Cohort characteristics. Data were available for a total of 454 patients (53.5% female), of whom 90.3% had isolated BA and 9.7% had BA-polysplenia malformation syndrome. KPE was performed in 94.7% ($N = 430$), at a mean age of 57 ± 25 days. The remaining 24 were referred too late for a KPE, with the majority (21/24) undergoing LT, at a median age of 9 months (IQR: 7–11).

The cohort as a whole had a median follow-up of 16.4 years (IQR: 9.7–21.9) from birth, during which time there were 74 deaths, giving 1-, 5-, 10-, and 20-year survival rates of 93.3%, 88.4%, 86.6%, and 83.6%, respectively (Fig. 1). A total

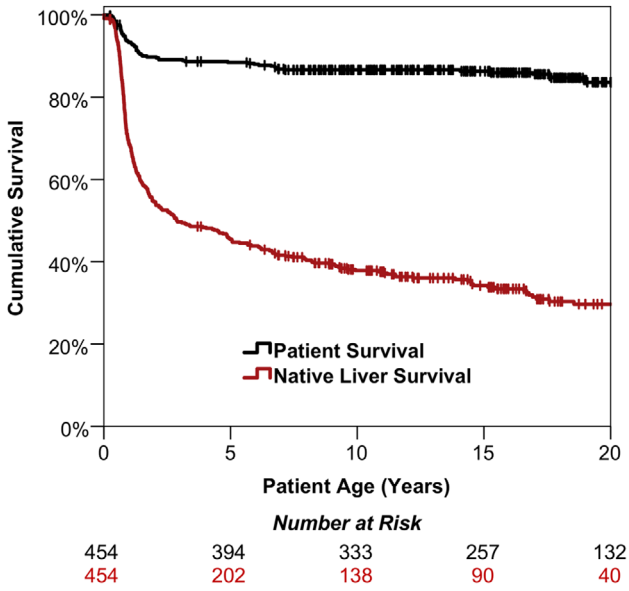

Figure 1 Kaplan–Meier curves of overall and native liver survival.

of 272 patients underwent LT, giving a median native liver survival of 35 months, and native liver survival rates of 68.4%, 45.4%, 37.9%, and 29.7% at 1, 5, 10, and 20 years, respectively. The longest observed native liver survival was for a patient who was 38 years old at the end of follow-up.

Transition to adult care. A total of 66 patients died during pediatric follow-up at our center, of whom 33 had previously undergone LT. A further 23 patients were transferred to a regional centers for ongoing pediatric care, and were lost to follow-up at this point. At the time of data collection, 185 patients were still under pediatric care at our center, with a mean age of 13.4 ± 3.8 years. The remaining 180 patients were transitioned to adult care during the follow-up period, at a mean age of 18.7 ± 2.4 years (Fig. 2).

Outcomes in patients transitioning to adult care with a native liver. Of those transitioning to adult care, the majority ($N = 126$; 70.0%) had undergone LT prior to transition, with the remaining 54 (30.0%) patients retaining their native liver into adulthood. At the time of transition, the majority of patients with native livers had symptoms of chronic liver disease (39 of 54; 72%) (Table 1). The most common were portal hypertension (69%) and varices (64%), with almost half of the cohort having cirrhosis/fibrosis (49%) or splenomegaly (50%).

Of those transitioning with a native liver, no further follow-up data were available for 11 patients, with the remaining 43 subsequently being followed up for a median of 7.3 (IQR: 4.0–9.6) years post-transition, to a mean age of 27.1 ± 5.4 years. Of these, 9 of 43 subsequently received an LT, giving a native liver survival at 5 and 10 years after transition of 89% and 78%, respectively (Fig. 3). The nine patients undergoing LT were aged between 19 and 35 years at the time of LT, and all had both portal hypertension and varices prior to transition, with the majority also having cirrhosis or fibrosis. The primary reason for transplant was BA-associated portal hypertension in four patients (one patient additionally had hepatocellular carcinoma), with the remaining five transplanted due to biliary cirrhosis; all nine patients were still alive at the end of the follow-up period. Of those not receiving an LT during post-transition follow-up ($N = 34$), 22 had chronic liver disease prior to transition, all of whom remained stable with compensated liver disease at the end of follow-up. The remainder($N = 12$) had no evidence of chronic liver disease at the time of transition, of whom three patients subsequently developed new-onset chronic liver disease and nine patients had no evidence of chronic liver disease at the end of follow-up.

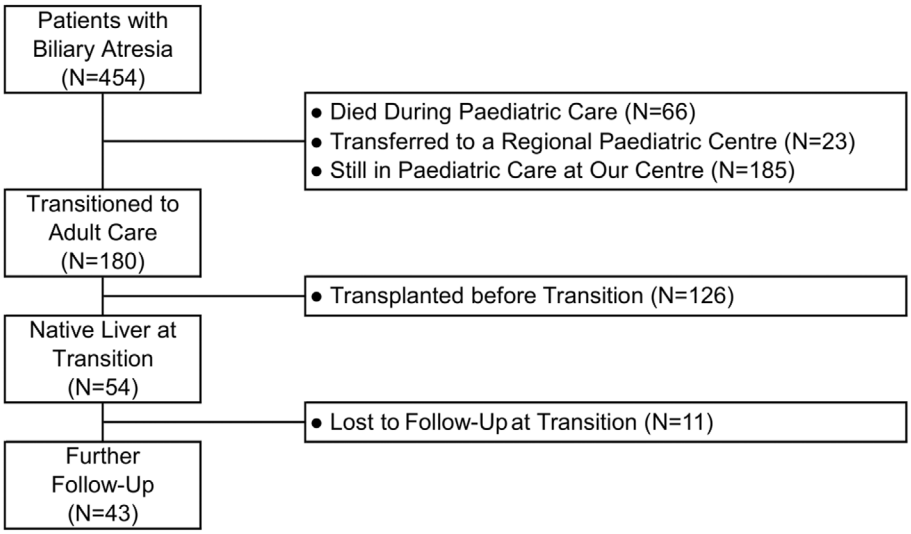

Figure 2 Study flowchart.

Table 1 Chronic liver disease in patients transitioning to adult care with a native liver

	Disease at transition	Onset after transition
Cirrhosis/Fibrosis	22/45 (49%)	4/18 (22%)
Portal Hypertension	37/54 (69%)	3/13 (23%)
Varices	34/53 (64%)	1/15 (7%)
Bleeding	6/28 (21%)	0/17 (0%)
Splenomegaly	18/36 (50%)	0/16 (0%)
Ascites	1/18 (6%)	1/13 (8%)
Any of the above*	39/54 (72%)	3/12 (25%)**

*The proportion of patients identified as having any of stated symptoms; those with missing data were treated as not having the associated symptom when calculating these percentages.
**The proportion of those with no symptoms of liver disease that developed symptoms after transition.
Analysis of disease history at transition includes those patients with native livers at the time of transition ($N = 54$), and excludes those for whom data relating to the stated symptom was not available. Analysis of onset after transition additionally excludes those patients who were lost to follow-up at transition ($N = 11$), as well as those patients who had the stated symptom at the time of transition.

Associations between chronic liver disease symptoms and post-transition transplant rates were then assessed. This found a tendency for an increased LT rate in those with portal hypertension (30% *vs* 0%, $P = 0.084$) or varices (33% *vs* 0%, p = 0.069) at transition, although neither reached statistical significance. Similar trends were also observed for bleeding and splenomegaly (Table 2).

Socioeconomic outcomes. In addition to disease-related outcomes, attempts were made to collect data on socioeconomic outcomes at the most recent follow-up. However, as this information was not routinely recorded in the medical notes, the availability of data was sporadic, with the majority of outcomes being unavailable in over half of the cohort. Of the 187 patients in whom data were available, 9% ($N = 16$) attended special schools, or required special needs provision in a normal school. Of those transitioned to adult care ($N = 180$), all had completed primary and secondary school education, with 49% (49/100) having a college or university-level qualification; 87% were in employment or education at the last follow-up (Table 3). Of female patients who had transitioned to adult care, 34% (21 of 62) had at least one pregnancy. There were 3 miscarriages and 27 babies born to 21 mothers; no cases of BA were reported in these babies. Of male patients who transitioned to adult care, 22% (6 of 27) reported having fathered a child. Socioeconomic outcomes were also compared between patients with native livers and those who had received an LT at the time of transition to adult care. This found no significant differences, with the exception of the employment status ($P = 0.043$), for which there was a tendency for a lower rate of unemployment in patients with native livers at transition.

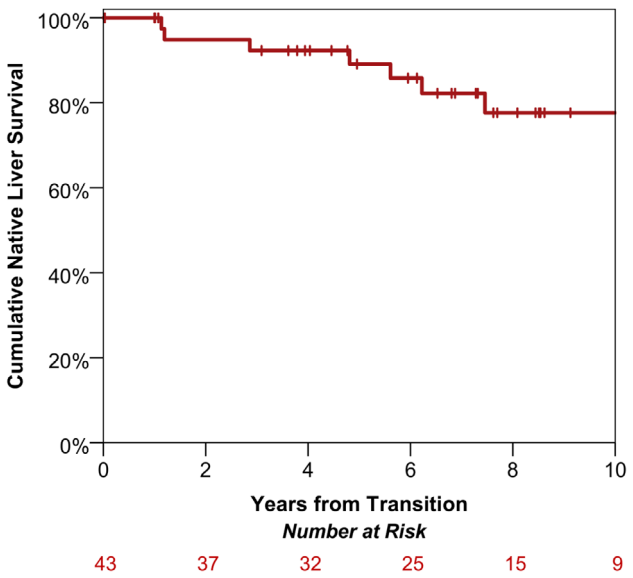

Figure 3 Kaplan-Meier curve of native liver survival after transition to adult care. Only those patients who transitioned with a native liver, and had follow-up after transition were included ($N = 43$).

Table 2 Post-transition transplant rates by chronic liver disease status at transition to adult care

Evidence of disease at transition	Crude transplant rate	*P*-value
Cirrhosis/Fibrosis		0.307
No	2/18 (11%)	
Yes	6/19 (32%)	
Portal hypertension		0.084
No	0/13 (0%)	
Yes	9/30 (30%)	
Varices		0.069
No	0/15 (0%)	
Yes	9/27 (33%)	
Bleeding		0.222
No	2/17 (12%)	
Yes	2/4 (50%)	
Splenomegaly		0.107
No	1/16 (6%)	
Yes	5/13 (38%)	
Ascites		0.763
No	3/13 (23%)	
Yes	1/1 (100%)	

Analyses include those patients with native liver at the time of transition, for whom subsequent follow-up was available ($N = 43$). Evidence of disease is assessed at the time of transition; hence those developing symptoms after transition are classified as "no". Crude transplant rates represent the total number of patients undergoing transplants after transition, and do not account for the follow-up time. *P*-values are from log-rank tests on Kaplan–Meier curves, to account for follow-up time.

Discussion

BA is a rare disease, with an incidence of 1 case per 15 000 live births in United Kingdom, but is the main indication for LT in children.[2,7] Without medical and surgical intervention, disease progression leads to hepatic fibrosis, cirrhosis with portal

Table 3 Socioeconomic outcomes by status at transition to adult care

	N	Patients transitioned to adult care ($N = 180$)	Status at transition		*P*-Value
			Native Liver ($N = 54$)	*Transplanted ($N = 126$)*	
Age at transition (Years)	167	18.7 ± 2.4	19.1 ± 1.6	18.6 ± 2.6	0.193
Age at last follow-up (Years)	180	24.1 ± 5.9	25.1 ± 6.1	23.7 ± 5.7	0.120
Gender (% Female)	180	99/180 (55%)	30/54 (56%)	69/126 (55%)	1.000
Attended special school	97	1/97 (1%)	0/39 (0%)	1/58 (2%)	1.000
Highest level of education	100				0.064
School (GCSE)		29/100 (29%)	16/42 (38%)	13/58 (22%)	
Vocational qualification		22/100 (22%)	5/42 (12%)	17/58 (29%)	
College/University		49/100 (49%)	21/42 (50%)	28/58 (48%)	
Employment	89				**0.043**
Full-time		52/89 (58%)	20/34 (59%)	32/55 (58%)	
Part-time		21/89 (24%)	10/34 (29%)	11/55 (20%)	
Unemployed		12/89 (13%)	1/34 (3%)	11/55 (20%)	
Still in education		4/89 (4%)	3/34 (9%)	1/55 (2%)	
Relationship status	80				0.160
Single		42/80 (53%)	18/28 (64%)	24/52 (46%)	
Partner		38/80 (48%)	10/28 (36%)	28/52 (54%)	
Fathered children (males)**	27	6/27 (22%)	2/11 (18%)	4/16 (25%)	1.000
Number of pregnancies (females)**	62				0.614*
None		41/62 (66%)	14/22 (64%)	27/40 (68%)	
1		12/62 (19%)	3/22 (14%)	9/40 (23%)	
2		7/62 (11%)	5/22 (23%)	2/20 (5%)	
3		2/62 (3%)	0/22 (0%)	2/20 (5%)	
Miscarriage (pregnant females)***	21	3/21 (14%)	1/8 (13%)	2/13 (15%)	1.000

**P*-value from Mann–Whitney *U* test, as the factor is ordinal.

**Within the subgroup of male ($N = 81$) or female ($N = 99$) patients.

***Within the subgroup of females with at least one pregnancy ($N = 21$).

The "*N*" column represents the number of patients for whom data were available for the stated variable. Data are reported as *n*/*N* (%), with *P*-values from Fisher's exact tests, or as mean ± standard deviation, with *P*-values from Mann–Whitney *U* tests, unless stated otherwise. Bold *P*-values are significant at $P < 0.05$.

hypertension, liver failure, and death in the first few years of life. Early diagnosis and timely surgical intervention with KPE to restore the bile flow remains the primary management. Due to improvements in surgical and medical care of these patients, native liver survival has considerably improved. The purpose of this study was to evaluate the long-term outcomes of BA patients, with emphasis on socioeconomic outcomes.

This study reviews 454 BA patients who were referred to BCH for treatment and had dedicated meticulous follow-up from the time of diagnosis to their transition to adult services. The clinical presentation of this cohort is similar to other published series, with 90.3% of cases of isolated BA, although there have been reports of incidence of congenital anomalies ranging from 4.9%[12] to 29.2%.[4,24]

The mean age at KPE was 57 ± 25 days, which is consistent with several published series from different centers in the world.[7,15,25] However, the average age at KPE from the Far-East and Asian subcontinent tends to be higher, due to delayed referrals and shortfalls in the health system, with a median of 69 days (range: 50–73 days) reported by Holdar et al.[26]

Many studies have shown improved outcomes in terms of clearance of jaundice and native liver survival if KPE is performed early, with most published series reporting better results of KPE if performed before 30 days of age, and significantly worse outcomes if surgery is performed later than 90 days.[7,15,27–29] A better outcome at late age KPE has been reported from an Indian series.[30]

In our series, the median native liver survival was 35 months, with the longest observed native liver survival being in a patient who was 38 years old at the end of follow-up. According to the literature, the oldest survivors from the KPE are from Sendai, Japan, and are approaching their 60th birthday, with the oldest reported survivor from United Kingdom being 40 years old.[16]

The native liver survival rate in our series was 45.4% at 5 years, which is comparable to other series in the literature. A five-year survival rate for BA patients with native liver was reported to be 41.9% in a series of 185 children over 25 years follow-up in Taiwan.[31] Survival with native liver (SNL) after Kasai operation was 40%, at 5 years in a French series of 1107 BA children.[32] However, superior outcomes have been reported, with 5-year native liver survival rates of 63% from Japan[33] and 55.2% from Australia.[34]

Native liver survival at 10 and 20 years was 37.9% and 29.7%, respectively, in our series. This is again comparable to other international series. SNL after KPE was 35%, 26%, and 22% at 10, 20, and 30 years, stable in the four cohorts in a series of 1428 patients born with BA between 1986 and 2015 in

France[35] and was 32% at 10 years, 17.8% at 20 years, and 14.9% at 40 years in a single Italian center.[36] However, the Japanese Biliary Atresia Registry reported 49% 20-year native liver survival among 3160 patients operated during 1989–2015.[33]

In our series, of the 180 patients who transitioned to adult services during the follow-up period, 54 (30.0%) retained their native livers into adult life. This is comparable to most of other series, especially as it includes those who presented in the early 1990s before there was adequate professional awareness of the need for early referral. Native liver survival differs worldwide, with some centers from Asia reporting better outcomes than European centers. In general, 20–44% children survived to their adulthood with their native livers.[8,15,16,31,32,37]

Of those with native livers at transition for whom data were available, 49% had cirrhosis/fibrosis, 69% had portal hypertension, and 64% had varices. Nine patients with native livers at transition to adult services subsequently received LT during adulthood, aged between 19 and 35 years. These findings are consistent with a multicenter study from the United States, which reported that clinically definable portal hypertension (evidence of thrombocytopenia or splenomegaly, with or without complications of portal hypertension) was present in two-thirds of long-term BA native liver survivors.[38] In a publication by North American multicenter consortium of 219 BA patients surviving with their native liver with a follow-up of more than 5 years, 98% had clinical or biochemical evidence of chronic liver disease or its consequences.[39] Nevertheless, a small proportion of our cohort never developed liver disease, even in adult life.

There is limited published literature about the long-term educational outcomes of BA patients surviving with their native livers, or after undergoing LT. Ng et al. assessed neurodevelopmental outcomes of BA patients with their native livers, and concluded that children with unsuccessful Kasai were four times more likely to have neurodevelopment impairment, compared with those with a successful procedure.[39,40]

In a systemic review, BA patients had lower school functioning scores than controls, with between 2% and 48% of children requiring additional educational support.[41] However, this systematic review found no evidence of a difference in educational outcomes between those that maintained their native liver and those requiring LT. This is consistent with our finding that all patients transitioning to adult care completed primary and secondary school education, with 49% subsequently entering college or university, with no significant difference detected between those with native livers versus LT at transition. This systematic review additionally reported employment rates of 60–100% in adults with BA, which was consistent with the 87% in employment or education in our cohort.

As more females with BA are surviving to adulthood with their native livers or after LT, they may present as difficult challenges to gynecologists and obstetricians, due to portal hypertension and underlying liver disease. While normal pregnancies have been reported in these women, symptoms of bleeding from esophageal varices, hypersplenism, and portal hypertension are common. There have been reports of problems associated with pregnancies requiring an individualized approach to each patient, depending upon their symptoms and complications.[42–44] Shimaoka et al[45] reported two abortions due to hemorrhagic shock after massive bleeding from esophageal varices, abruptio placenta, ascending cholangitis, and severe liver dysfunction requiring LT[45]. In our series, normal pregnancies were reported in 21 patients (8 with native liver and 13 after LT). There were 3 miscarriages and 27 babies were born; none of these babies had BA.

We report on a large cohort of BA patients managed in a single center, some of whom transitioned to adult services with their native liver. These patients are at increased risk of cholangitis, worsening liver disease, and development of hepatic malignancies. These young patients merit a meticulous follow-up by adult services in order to have a favorable outcome, as their issues differ from adult onset diseases.

The primary limitation of this study was the difficulty in obtaining current follow-up data in those patients who had transferred to regional centers before or after transition. This may have introduced selection bias, which may have led to post-transition outcome rates being overestimated. This was a particular issue for the socioeconomic outcomes, for which data were unavailable for over half of the included cases.

In conclusion, our long-term follow-up study has shown that many patients with BA survive with their native liver into their adult life, with the majority being able to complete their education, start families, and make good socioeconomic contribution to society. However, BA patients who retain their native livers into adulthood may develop cholangitis, portal hypertension, and progressive liver disease. As such, lifelong follow-up by adult hepatology services with early recognition of the need for liver transplantation is the key to a better outcome for these patients.

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