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Medical Status of 219 Children with Biliary Atresia Surviving Long-Term with their Native Livers: Results from a North American Multicenter Consortium

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*List of members of CHILDREN is available at www.jpeds.com (Appendix).

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Abstract

Objectives—To examine the medical status of children with biliary atresia (BA) with their native livers after hepatic portoenterostomy (HPE) surgery.

Study design—The Childhood Liver Disease Research and Education Network (ChiLDREN) database was utilized to examine subjects with BA living with their native livers 5 or more years after HPE and to describe the prevalence of subjects with BA with an “ideal” outcome, defined as no clinical evidence of chronic liver disease, normal liver biochemical indices (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, platelet count, total bilirubin, International Normalized Ratio, and albumin) and normal Health-Related Quality of Life (HRQOL) 5 or more years after HPE.

Results—Children with BA (n=219; 43% male) with median age 9.7 years were studied. Median age at HPE was 56 (range 7-125) days. Median age- and sex-adjusted height and weight Z-scores at 5 year follow-up were 0.487 (interquartile range [IQR]: -0.27 to 1.02) and 0.00 (IQR: -0.74 to 0.70), respectively. During the 12 preceding months, cholangitis and bone fractures occurred in 17% and 5.5%, respectively. HRQOL was reported normal by 53% of patients. However, only 1.8% met the study definition of “ideal” outcome. Individual tests of liver synthetic function (TB, Alb, and INR) were normal in 75%, 85% and 73% of the study cohort.

Conclusion—Cholangitis and fractures in long-term survivors underscore the importance of ongoing medical surveillance. Over 98% of this North American cohort of subjects with BA living with native livers 5 or more years after HPE have clinical or biochemical evidence of chronic liver disease.

Keywords

Outcomes; Health status; Health-related quality of life; cholangitis

Biliary atresia (BA) is a progressive fibro-obliterative cholangiopathy presenting only in infancy with a prevalence ranging from 1 in 5,000 to 18,000 newborns¹.

Hepatoportoenterostomy (HPE; the Kasai procedure) provides a means of relieving extrahepatic biliary obstruction and permitting bile flow, but is not a curative procedure^{2, 3}.

Despite HPE being performed in a timely fashion, liver transplantation (LT) is ultimately

required for the majority of patients during childhood^{4,5}. Although single center⁶⁻⁸ and multi-center⁹⁻¹¹ characterizations of the health status and medical outcomes in patients with BA who have undergone LT are available, the long-term outcomes in older children with BA living with their native livers have not been examined in detail in large patient populations, and are limited to small single-center retrospective experiences¹²⁻¹⁸. Progression to chronic liver disease was avoided in only 11% of 244 ten-year survivors of HPE performed at King's College Hospital over the 12 year period of 1979 to 1991¹⁹. Detailed information from a contemporary multi-center population of older subjects with BA surviving with their native livers currently does not exist, and would aid clinicians in providing important and generalizable information to families about school-aged children with BA.

Established in 2002, the Childhood Liver Disease Research and Education Network (ChiLDREN; originally known as the Biliary Atresia Research Consortium [BARC]) is an NIDDK/NIH-funded cooperative research consortium at 15 clinical sites in the United States and Canada with the goal of understanding the etiology, pathogenesis, course and outcomes of BA as well as other pediatric cholestatic conditions. Herein, the objectives of this cross-sectional study were to utilize enrollment data available within the ChiLDREN database to characterize the medical status of a multi-center cohort of subjects with BA who were 5 years of age or greater at time of study enrollment and still living with their native livers following HPE and to identify the percentage of subjects with BA who have no clinical findings of chronic liver disease, normal health related quality of life (HRQOL) and normal laboratory indices at least 5 years after HPE.

Methods

The Biliary Atresia Study of Infants and Children (BASIC) is one of the ongoing longitudinal studies within ChiLDREN with a specific aim to determine natural history and outcomes of older non-transplanted children with BA. Patient inclusion criteria for the BASIC protocol ([ClinicalTrials.gov](https://clinicaltrials.gov) study ID: NCT00345553) were subjects with: (1) a confirmed diagnosis of BA determined by chart review, including review of pertinent diagnostic biopsy reports, radiologic reports and surgical reports; (2) age ≥ 6 months; and (3) either native livers or post-liver transplantation; and iv) a parent/guardian willing to provide informed consent (and, when appropriate, the subject is willing to assent). For this present cross-sectional analysis, subjects were identified from the BASIC database with patient age between 5 and 17.99 years at time of BASIC enrollment, and at least one year of follow-up at a ChiLDREN study site in the year preceding BASIC enrollment. Importantly, to reduce the bias of assessing patients with BA with severe disease that were unlikely to have long-term survival with native liver, subjects were excluded from this analysis if they were already listed for LT at time of BASIC enrollment.

All of the participating ChiLDREN centers had institutional review board and/or research ethics board approval for this study²⁰. Written informed consent was obtained from parents and/or guardians and assent obtained from subjects age 7 years and older.

At BASIC entry, demographic, clinical and laboratory data were collected, physical examinations performed, and past medical histories (including medical events in the previous 12 months abstracted from the medical record) were recorded. Definitions and specific criteria for complications of chronic liver disease were standardized within the ChiLDREN protocol. Diagnosis of cholangitis required presence of fever of >38 degrees Celsius without other obvious clinical source of infection; new onset of acholic stools, right upper quadrant pain or tenderness; and both elevation of direct bilirubin by 25% and at least >1 mg/dL above previous baseline; however, positive bacterial or fungal culture (of blood or liver) was not required. Hepatopulmonary syndrome (HPS) required documentation of hypoxemia with pulse oximetry (transcutaneous saturation) levels of less than 94% and evidence of intrapulmonary shunting by contrast echocardiography with agitated saline²¹.

Data collected included sex, race, date of birth (DOB), ethnicity, date of HPE, associated congenital malformations²², and medications. Physical exam findings included weight, height, head circumference, anthropometry, liver and spleen size on examination. Laboratory indices included complete blood count (CBC) with differential, International Normalized Ratio (INR), liver biochemical results and basic metabolic panel. Growth data were expressed as Z-scores relative to published age-adjusted normative values²³.

Given the healthcare complexities involved in the care of a child with chronic medical condition, an overall framework for outcome assessment based on a hierarchy of outcome measures can provide caregivers and parents a measure of the observed versus expected health status of the individual patient²⁴. Understanding the extent to which the health of the infant with BA is restored to normal following HPE is important as a benchmark by which future interventions can be measured. For the purposes of this present analysis, “ideal” clinical outcome in BA (criteria variables provided in Table II) as derived by the ChiLDREN investigators was defined as the combination of i) normal liver biochemical test values, ii) absence of selected clinical complications of chronic liver disease (in the entire life of the subject), iii) absence of the need for additional medications specifically indicated for underlying liver disease; and iv) normal self-reported HRQOL. These criteria were dichotomized to facilitate a “yes” or “no” answer from review of the BASIC data collection forms. Normal liver laboratory values were defined as: serum total bilirubin (TB) 1.5 mg/dL, aspartate aminotransferase (AST) 45 IU/L, alanine aminotransferase (ALT) 40 IU/L, γ -glutamyltranspeptidase (GGT) 55 U/L, albumin (Alb) 3.3 g/dL, INR 1.3, and platelet count $>150 \times 10^9/L$. Absence of clinical chronic liver disease was defined as no report of ascites, hepatopulmonary syndrome, variceal bleeding and/or pathological bone fractures, in conjunction with the presence of age-adjusted growth (both weight and height) Z-scores > -2.0 , and no reported use of cholangitis prophylactic antibiotics. Normal HRQOL was defined as PedsQL™ 4.0 Generic Core Scale total score scores >69.7 for child self-report or >65.4 for parent proxy – threshold scores representing one standard deviation below the population mean^{25, 26}. Given the paucity of literature on good outcomes for patients with BA, we elected to perform a secondary analysis on our multi-center contemporaneous cohort using the criteria for good patient outcome reported by Hadzic et al. (TB <1.2 mg/dL (20 μ mol/L), AST <50 IU/L, Alb >3.5 g/dL, INR <1.2 , and platelet count $>150 \times 10^9$)¹⁹.

Statistical Analyses

This cross-sectional analysis used data collected at enrollment on subjects who were 5 years through 17.99 years at BASIC entry, and did not include longitudinal follow-up data. For dichotomous and categorical response variables, counts and percentages are reported. For continuous response variables, descriptive statistics (mean, standard deviation, minimum, median and maximum) are reported. When continuous response variables are dichotomized (e.g., when TB \leq 1.5 mg/dl is classified as “ideal” outcome, and TB $>$ 1.5 mg/dl is classified as “not ideal” outcome), counts and percentages are reported for the dichotomized version. Parallel child self-report and parent proxy-report versions of the PedsQL™ Generic Core Scales were reviewed, with higher PedsQL™ Total Scale scores (scale of 0 to 100) indicating better HRQOL. All statistical analyses were conducted using SAS v9.3 (SAS Institute, Cary, North Carolina).

Results

As of May 1, 2012, 432 subjects with BA living with their native livers were enrolled in BASIC from May 2006 to May 2012. Excluded from further evaluation were 187 subjects enrolled before age 5 years (n=163) or after age 18 years (n=24). Among the remaining 245 subjects, we further excluded those already listed for LT at time of study enrollment (n=26). The remaining 219 (43% male, 63% white) subjects with BA with their native livers (median patient age 9.7 [range 5.1-17.9] years) were included in this analysis (Table I). Median subject age at HPE was 56 (range 7-125) days, and associated malformations included polysplenia in 5 (2.3%), congenital heart disease in 23 (10.5%), and other gastrointestinal malformations in 25 (11.4%), including abdominal heterotaxia in 3 (1.4%), malrotation in 3 (1.4%), midline liver in 2 (0.9%), preduodenal portal vein in 2 (0.9%), and right-sided stomach in 1 (0.5%) subject.

Physical examination

The median weight and height Z-scores at BASIC enrollment were 0.49 (interquartile range [IQR] -0.27, 1.02) and 0.00 (IQR: -0.74 to 0.70), respectively. Only 1 (0.5%) and 7 (3.2%) children had age-adjusted weight Z-score or height Z-score less than -2.0 (Table II). Nine (4.4%) of 205 subjects had a weight Z-score greater than 2.0. Mean Z-scores for right mid-arm circumference (0.06), right triceps skinfold thickness (0.03), and right subscapular skinfold thickness (-0.18) were within the range of published norms for healthy children (Figure 1). Median spleen size measured below the left costal margin was 2 cm (IQR: 0 to 6). Ninety-seven (44%) subjects had spleen size \geq 2 cm below the costal margin.

Biochemical Outcomes

At BASIC study enrollment, median serum values included: total bilirubin 0.8 (IQR: 0.4 to 1.2) mg/dL; AST 55 (IQR: 38 to 99) IU/L; ALT 54 (IQR: 30 to 98) IU/L; albumin 4.2 (IQR: 3.8 to 4.5) g/dL; INR 1.1 (IQR: 1 to 1.2); and platelet count 138 (IQR: 85 to 209) $\times 10^9$ /L. The median GGT of this cohort was 67 (IQR: 29 to 161) U/L. Individual tests of liver synthetic function (TB, Alb, and INR) were normal in 75%, 85% and 73% of the study cohort. Platelet count was $\geq 150 \times 10^9$ /L in 78 (35.6%) subjects. Figure 2 shows the

distribution of TB, INR and platelet counts for the study cohort. Sixteen (7.3%) study subjects had normal values for the study biochemical composite of TB, AST, ALT, GGT, INR, Alb and platelet counts (Table II).

Complications

136 (62.1%) of our study cohort experienced cholangitis at least once since HPE. Multiple cholangitis episodes occurred in 11 subjects (7 patients with 2 episodes, and 4 patients with 3 episodes). Cholangitis occurred within the 12 months preceding BASIC enrollment in 36 (17%) of subjects, at a median subject age of 7.6 years. Ascites and variceal hemorrhage were seen in 17% and 9% of this study cohort. Thirty-three (15%) subjects with BA experienced a bone fracture since HPE, with fracture site available in 14 instances. Fractures affecting the upper extremity (forearm, arm, buckle wrist, hand, radial bone, arm, or thumb) were most common (8/14). Twelve (36%) fractures occurred within the 12 months preceding BASIC enrollment, of which 2 were receiving vitamin D supplementation at enrollment. There was no correlation between the presence of a bone fracture within the preceding year and serum TB levels.

Treatment and Care Interventions

Medications received by this cohort at enrollment included vitamin supplementation (132, 60.3%), ursodeoxycholic acid (122, 55.7%), non-selective beta blockers (7, 3.2%) and diuretics (1, 0.5%). Eighteen (8%) subjects were receiving antibiotics for cholangitis prophylaxis. Amongst the 36 (16%) subjects who experienced cholangitis in the preceding 12 months, 8 (22%) were receiving antibiotic prophylaxis and 17 (47%) ursodeoxycholic acid. Only 7 (21%) of the 33 subjects who reported a history of a bone fracture reported taking vitamin D supplements.

HRQOL

117 (53.4%) of our cohort of >5 year survivors with native livers had a self-reported PedsQL Total Scale Score greater than 69.7 (>-1 standard deviation below the mean score of healthy children), amongst which 41 (35%) had not experienced any clinical complications of chronic liver disease. Parent proxy-report was substituted for five subjects for whom patient self-report was not completed.

Composite profile of the subject with BA with native liver 5 years after HPE

Table II lists the clinical, biochemical, medication history and HRQOL criteria for identifying subjects who had achieved an “ideal” clinical outcome. These criteria are dichotomized to facilitate a “yes” or “no” response to the presence or absence of physical examination findings and selected laboratory data-points meeting specified target ranges. Four (1.8%) subjects fulfilled the study criteria for an “ideal clinical outcome” with “yes” to all 15 elements (Table II). Answering “no” to 1 or more variables (125 subjects) and the presence of 1 or more missing data elements (90 subjects) contributed to the remaining 215 (98.2%) subjects enrolled in BASIC who did not meet the criteria for the “ideal clinical outcome” at 5 or more years after HPE (Table III; available at www.jpeds.com).

Given our multi-center contemporaneous cohort, we analyzed our cohort utilizing the variables previously published by Hadzic et al¹⁹ in their 12 year review of patients with BA living with native liver 10 years after HPE performed at King's College Hospital in the United Kingdom. Twenty-two (10%) subjects in our cohort met this single center study's research definition of no clinical evidence of chronic liver disease and normal serum TB, AST, Alb, INR, and platelet count. This group of subjects did not have a significantly different median age at HPE when compared with our overall series (51.5 versus 57 days, $p>0.05$).

Discussion

This multi-center cross-sectional analysis of a contemporary cohort of 219 subjects with BA who were not listed for LT and living with their native livers 5 or more years after HPE, with a median age of 9.7 years, demonstrates a number of important findings. Normal growth was achievable in over 90%. Although tests of liver synthetic function were normal in 75%, other liver biochemical abnormalities and clinical complications of chronic liver disease were experienced by over 90% by 5 years following HPE. Almost half of subjects self-reported impaired HRQOL. These findings provide benchmark data that will be useful for designing interventional study protocols, for stratification estimates and sample size calculations for clinical trials, and for counseling parents about expectations following HPE in BA for those children who escape the early need for LT.

Failure to thrive in BA is one of the more common indications for LT at a younger age⁵ and is an independent risk factor for pre-transplant mortality, post-transplant mortality, and liver graft failure²⁷. Our group previously reported that early growth failure after HPE is associated with LT or death by 24 months of age²⁸. In the present study, we found mean height and weight Z-scores to be normal at > 5 years after HPE. Acknowledging organomegaly and ascites as potential confounding variables with the risk of falsely representing a normal weight-for-age, the normal growth status was corroborated by concurrent normal Z-scores for mid-arm circumference, triceps skinfolds, and subscapular skinfolds (data not shown); furthermore few subjects in our group had ascites. These findings support previous reports that growth failure in children with successful HPE is uncommon, and that improving nutritional status may slow disease progression^{29, 30}. Amongst this cohort of native liver survivors, only 4.4% of subjects were obese, in contrast to post-LT recipients, where up to 19% have been found to be obese³¹.

Cholangitis has been reported to occur in up to 60% of children with BA, and most commonly in the first 1 to 2 years after HPE³²⁻³⁴. However, over 37% of adult survivors with BA with native livers were diagnosed with cholangitis (median age at follow-up 24.7 years old)^{13, 14, 35}. In our study, utilizing strict *a priori*-determined protocol definitions, an episode of cholangitis was diagnosed in 63% of children followed at least 5 years post HPE, with over a quarter ($n=36$) of these subjects experiencing an episode in the 12 months preceding enrollment into the BASIC study. Thus, the risk of cholangitis after HPE continues throughout early childhood³², as it does in survivors with BA over the age of 15 years^{15, 17}. Wu et al³² previously reported that 50% of cholangitis episodes occurred in patients with BA not receiving prophylactic antibiotics. In our study, oral antibiotics for

cholangitis prophylaxis were used in only 8.2% of all subjects with BA, with only 8 receiving antibiotic prophylaxis among the 36 (28%) who reported cholangitis within the preceding year. Because the current variation of clinical practice among ChiLDREN investigators ranges from discontinuation of prophylactic antibiotics at 2 years post HPE to never stopping antibiotics, there may be an opportunity for more effective prevention of cholangitis episodes. Because the efficacy of antibiotic prophylaxis has not been clearly determined at this age^{32, 36, 37}, further prospective, randomized studies are indicated to provide the needed evidence upon which to establish best practices.

Pre-LT fracture prevalence rates in infants with BA have been reported to range between 8% and 35%³⁸⁻⁴¹. Patients with BA are at risk for vitamin D deficiency; contributing factors include malabsorption of fat-soluble vitamins in the setting of cholestasis, lack of sunlight exposure, and poor hepatic 25-hydroxylation^{42, 43}. We found that 14.6% of our study cohort was taking supplemental vitamin D. Although vitamin D deficiency was previously reported in 21-37% of patients with BA in the first year of life⁴⁴, suggesting that current strategies for vitamin D supplementation in patients with BA are insufficient, little is known about vitamin D status in the older survivor with BA. Thirty-three (15%) of our >5-year native livers survivors had at least one bone fracture, with average age at time of fractures of 6.5 years for female and 6.4 years for males. A population based study in Finland found an overall annual fracture incidence of 163 per 10,000 for children ages 0 to 15 years, with a peak in fracture incidence at 10 years in girls and 14 years in boys⁴⁵. Another study from northern Sweden reported an incidence of fractures of 240 per 10,000 among children and adolescents, with one-third of all children sustaining at least one fracture before the age of 17 years⁴⁶. Thus, our cohort appears to be at increased risk for bone fractures, an outcome that requires further investigation to develop evidence-based recommendations for prevention.

Portal hypertension (PHT) is a common consequence of BA and can lead to significant morbidity and mortality. Our group has previously characterized manifestations of PHT, and found definite PHT to be present in 49% of subjects enrolled in BASIC using an operational clinical definition of PHT (platelet count <150,000 and clinical splenomegaly, defined as >2 cm below the costal margin, or history of clinical complications including ascites and/or variceal hemorrhage and/or hepatopulmonary syndrome)⁴⁷. Failure to thrive and significant derangements of laboratory variables were not empirically observed in those with definite PHT. In our present study cohort, clinically detectable splenomegaly, thrombocytopenia, ascites and variceal hemorrhage were seen in 56%, 43%, 17% and 9% of patients with BA with native livers 5 or more years after HPE. Longitudinal follow-up of this group of patients will be helpful towards understanding the natural history and factors that predict progression of PHT and the development of adverse outcomes.

With reports of patients with BA entering their adult years with their native livers^{13-15, 17}, strategies started as early as possible to most fully optimize both the quality and quantity of life years will be important for families and health care provider teams. Given the complexities of chronic medical conditions, an outcome measure hierarchy may be applicable to assessing outcome in BA²⁴. In this study, we specifically targeted historical data points, physical examination findings, and biochemical tests results routinely obtained

in the ambulatory clinic surveillance of subjects with BA living with their native livers, in addition to HRQOL assessments obtained as per research protocol. Although 98% of five-year native livers survivors who were not listed for LT had clinical or biochemical evidence of chronic liver disease, it was intriguing that over half of these subjects still reported normal HRQOL, emphasizing the need to consider patient-reported subjective outcome variables in assessing clinical outcomes. Our group recently reported HRQOL in subjects with BA surviving with their native livers was similar to subjects with BA post-LT, although psychosocial and school functioning were significantly impaired in both groups compared with healthy children⁴⁸. The similarities observed between the subjects with BA with their native livers and pediatric LT recipients were mainly driven by psychosocial problems rather than issues with physical health. Indeed, the importance of psychosocial problems, increasingly identified as “hidden morbidities” across an array of pediatric conditions, will continue to significantly impact generic HRQOL.

Older patients with BA surviving with their native livers in the United Kingdom were previously reported to be underperforming on social functioning compared with normative data; however lack of power due to sample size prevented achievement of statistical significance¹⁶. Of 244 ten-year survivors of HPE at King's College Hospital, 11% had a normal physical examination and normal values for 5 liver laboratory tests. These authors concluded that progression to chronic liver disease is not inevitable in patients with BA. In our present study cohort, 10% of our subjects met these secondary analysis criteria for good outcome. However, inclusion of absence of complications of liver disease and acceptable HRQOL in our study reduced this to less than 2% of subjects with optimal outcomes. This 2% of subjects ranged in age from 6 to 17 years old, suggesting there may not necessarily be a cumulative incidence of complications. One other reason for the lower percentage with ideal outcome in our study may be that children who are doing well may have less regular clinical follow-up visits and potentially be missed for study recruitment.

Potential limitations and biases of this study relate to the retrospective nature of baseline data collection for a longitudinal clinical study. Our study relied on the analysis of historical data collected at the time of enrollment into the study. We acknowledge that this study may present an overly optimistic view of BA – those who suffered the most severe complications underwent LT at an earlier age or who were listed for LT were not included in this analysis, which may include those listed for failure to thrive. In our attempt to remove bias towards sicker patients who are being evaluated for LT, an opposite bias may have been created. However, our goal was to examine detailed information from a contemporary population of older subjects with BA with prolonged survival to provide clinicians with evidence about clinical outcomes for school-aged children with BA. Despite rigorous data quality controls, missing and incomplete data were present for variables due to differences in institutions' standard of care or the availability of the data. This is seen particularly in our analysis of the “ideal” clinical outcome, with 90 participants failing to meet “ideal” criteria simply because of missing data. In addition, baseline enrollment data did not include liver or bile duct histology or radiographic assessments, so these data could not be used as criteria for prediction of outcomes. Finally, each BASIC site was queried to ensure all available data was captured.

In conclusion, this study provides benchmarks for clinical outcomes expected in school age children with BA surviving with their native livers who are not listed for liver transplantation. Over 98% of this North American cohort of subjects with BA living with native livers 5 or more years after HPE have clinical or biochemical evidence of chronic liver disease or its consequences. Despite these findings, over half of patients rated their QOL as good. These data should prove helpful in the design of clinical interventions, stratification for clinical trials and as a baseline for longitudinal assessment of the natural history of BA. Moreover, this information will be of value in guiding expectations of families with infants and younger children with BA. Optimizing outcome is the ultimate goal for the clinician caring for children and teenagers with BA. Meticulous multidisciplinary family-focused care post-HPE is critical in order to improve outcomes beyond these benchmarks.

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Appendix

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List of Abbreviations

BA	Biliary atresia
HPE	Kasai hepatoportoenterostomy
LT	liver transplantation
AST	aspartate aminotransferase
ALT	alanine aminotransferase
GGT	gamma glutamyltranspeptidase
INR	International Normalized Ratio
HRQOL	Health-related quality of life

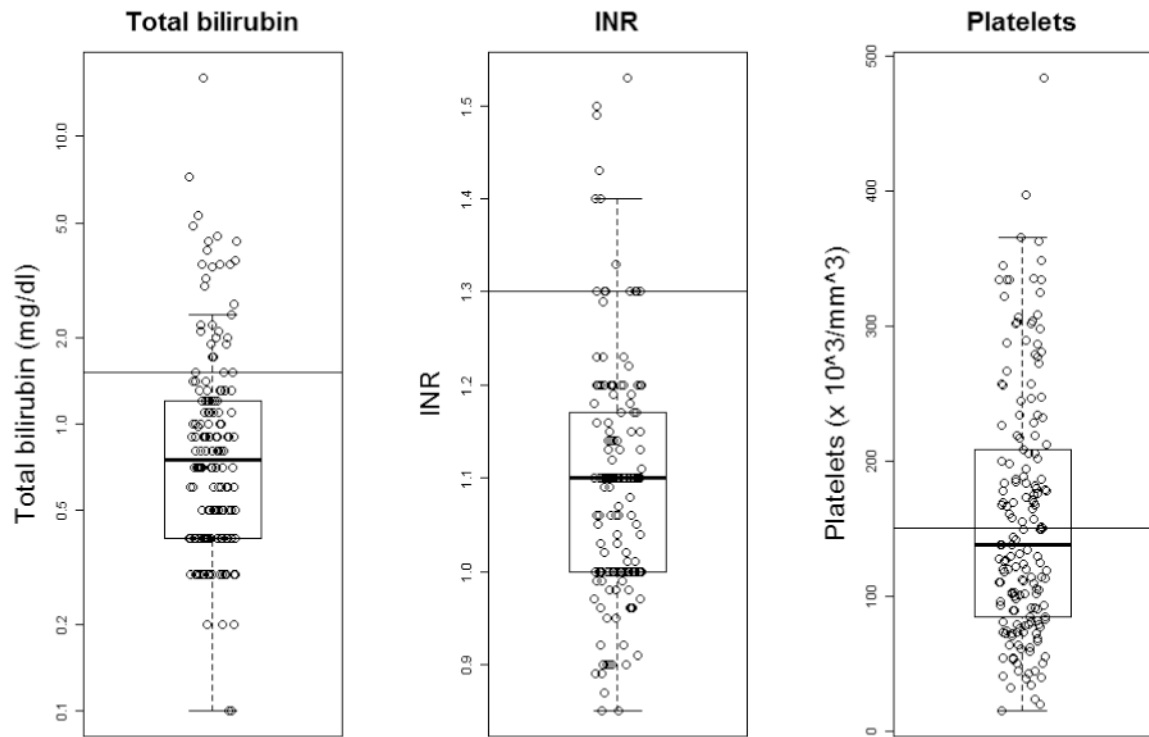


Figure 1. Boxplots of age-adjusted anthropometric Z-scores in subjects with BA. From top to bottom, the five horizontal lines represent the largest data point, which is not more than 1.5 times the interquartile range from the box, the 3rd quartile, the median, the 1st quartile, and the smallest data point which is no more than 1.5 times the interquartile range from the box, respectively.

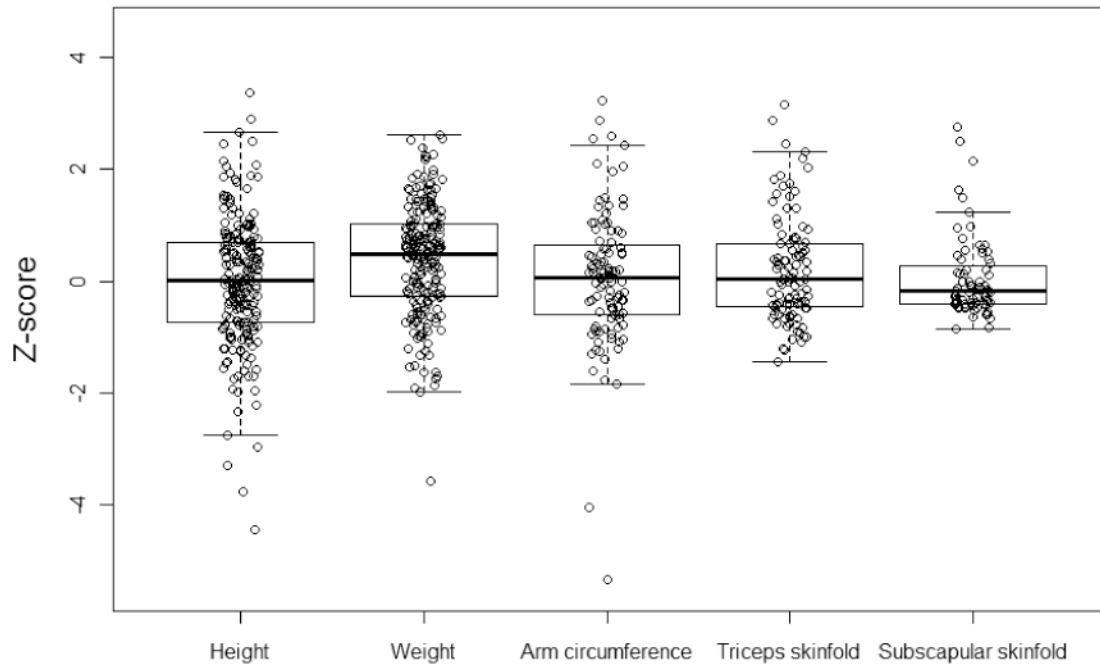


Figure 2. Boxplots of serum total bilirubin, INR, and platlet count. From top to bottom, the five horizontal lines represent the largest data point, which is not more than 1.5 times the interquartile range from the box, the 3rd quartile, the median, the 1st quartile, and the smallest data point which is no more than 1.5 times the interquartile range from the box, respectively.

Table 1
Characteristics of Study Cohort of 219 subjects with BA

Characteristic	N (%)
# patients	219
Sex	
-male	95 (43.4)
-female	124 (56.6)
Race	
-White	139 (63.5)
-Black	31 (14.1)
-Asian	23 (10.5)
-Other	26 (11.9)
Age at Kasai (days)	
- N	183
- Mean \pm SD	56.4 \pm 23.19
- Median (Range)	56 (7–125)
Current age at evaluation (years)	
- N	219
- Mean \pm SD	10.5 \pm 3.98
- Median (Range)	9.7 (5.1–17.9)
Polysplenia syndrome	5 (2.3)
Other congenital malformations present	
-Cardiac	23 (10.5%)
-Gastrointestinal	25 (11.4%)
Biochemical* characteristics at enrollment; median (IQR)	
-TB, mg/dL	0.8 (0.4–1.2)
-AST, IU/L	55 (38–99)
-ALT, IU/L	54 (30–98)
-Alb, g/dL	4.2 (3.8–4.5)
-INR	1.1 (1.0–1.2)
-platelet count, $\times 10^9/L$	138 (85–209)
-GGT, IU/L	67 (29–161)

* Normal liver laboratory values were defined as: serum total bilirubin (TB) 1.5 mg/dL, aspartate aminotransferase (AST) 45 IU/L, alanine aminotransferase (ALT) 40 IU/L, γ -glutamyltranspeptidase (GGT) 55 U/L, albumin 3.3 g/dL, INR 1.3, and platelet count $>150 \times 10^9/L$

Table 2
The “Ideal” subject with BA surviving with native livers for at least 5 years after HPE

Medical Variable: Result reported at 5 year visit	Patient data available, n	Patients who answered “yes” to variable as phrased n (%)	Patients missing data n (%)
Stability of Native livers – “Normal” Lab Indices			
1. TB level normal (< 1.5 mg/dl)	197	164 (74.9%)	22 (10%)
2. AST level normal (< 45 IU/L)	196	75 (34.2%)	23 (10.5%)
3. ALT level normal (< 40 IU/L)	199	75 (34.2%)	20 (9.1%)
4. GGT level normal (< 55 u/l)	186	82 (37.4%)	33 (15.1%)
5. INR normal (< 1.3)	167	160 (73.1%)	52 (23.7%)
6. Serum Alb level normal (> 3.3 g/dl)	196	187 (85.4%)	23 (10.5%)
7. Platelet count (> 150 × 10 ³ /mm ³)	173	78 (35.6%)	46 (21%)
TOTAL # Subjects with ALL above Lab Indices normal	186	16 (7.3%)	33 (15.1%)
Absence of known complications of chronic liver disease			
8. Ascites	209	172 (78.5%)	10 (4.6%)
9. Hepatopulmonary syndrome	201	198 (90.4%)	18 (8.2%)
10. Variceal bleeding	198	178 (81.3%)	21 (9.6%)
11. Fractures	192	159 (72.6%)	27 (12.3%)
12. Age-adjusted weight z-score > -2	205	204 (93.2%)	14 (6.4%)
13. Age-adjusted height z-score > -2	204	197 (90%)	15 (6.8%)
Absence of need for additional medications			
14. No use of cholangitis prophylaxis	219	201 (91.8%)	0
HRQOL			
15. PedsQL Total Score 69.7 (normal)	161	117 (53.4%)	58 (26.5%)
>5-year native livers survivor with “ideal” outcomes*	192	4 (1.8%)	27 (12.3%)

* “Ideal” Outcomes defined as the presence of: i) normal liver biochemical tests; ii) absence of complications of chronic liver disease; iii) not receiving medications for liver disease; and iv) normal HRQOL

Table 3
(Online): Characterization of 129 Study Participants with Complete Data Available for “Ideal” Clinical Outcome Composite Determination

All Lab Indices Normal	Absent known CLD complications	Absence of need for additional medication	Normal HRQOL	FREQ
				2
				3
				12
				31
				4
				6
				16
				46
				2
				2
				1
				4

Each shaded cell represents the presence of a post-HPE subcategory required for the study criteria of “ideal” clinical outcome in BA patients. A total of 129 subjects had information on all four categories. Achieving 4 shaded cells (normal lab indices, absence of known complications of chronic liver disease (CLD), absence of medication requirements, and normal HRQOL) are required for the composite “ideal outcome” status – and achieved in 4 patients. Patients with <4 categories (n=90) were ineligible for ideal outcome determination, and thus are not represented in this Table.