A MULTICENTER STUDY OF THE OUTCOME OF BILIARY ATRESIA IN THE UNITED STATES, 1997 TO 2000

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Objective To determine the prognostic factors and optimal approaches to the diagnosis and management of biliary atresia, the leading indication for liver transplantation in children.

Study design A retrospective study was performed of all children who underwent hepatoportoenterostomy (HPE) for biliary atresia between 1997 and 2000 at 9 centers in the United States. Outcome at age 24 months was correlated with demographic and clinical parameters.

Results A total of 104 children underwent HPE; 25% had congenital anomalies, and outcome was worse in those with biliary atresia splenic malformation syndrome. Diagnostic and clinical approaches varied, although specific approaches did not appear to correlate with outcome. The average age at referral was 53 days, and the average age at HPE was 61 days. At age 24 months, 58 children were alive with their native liver, 42 had undergone liver transplantation (37 alive, 5 dead), and 4 had died without undergoing transplantation. Kaplan-Meier analysis of survival without liver transplantation revealed markedly improved survival in children with total bilirubin level < 2 mg/dL at 3 months after HPE (84% vs 16%; $P < .0001$).

Conclusions Outcome in the study centers was equivalent to that reported in other countries. Total bilirubin in early follow-up after HPE was highly predictive of outcome. Efforts to improve bile flow after HPE may lead to improved outcome in children with biliary atresia. *(J Pediatr 2006;148:467-74)*

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Biliary atresia is a disease of unknown etiology characterized by progressive fibro-obliteration and obstruction of the extrahepatic biliary tree. The disease affects 1:8,000 to 1:18,000 live births and presents in the neonatal period with jaundice, acholic stools, and hepatomegaly in an otherwise apparently healthy infant.[1] If biliary atresia is diagnosed within the first 3 months of life, then surgical therapy with hepatoportoenterostomy (HPE) can successfully restore bile flow from the liver into the intestinal tract in 30% to 80% of patients.[1-3]

Several factors have been reported to determine the ultimate success of HPE, including the patient's age at the time of surgery, presence of cirrhosis, surgeon's experience with performing HPE, occurrence of postoperative cholangitis, and perhaps unknown genetic factors.[1-7] However, even with successful HPE, progressive inflammation and fibrosis of the intrahepatic bile ducts develops to varying degrees, leading to biliary cirrhosis and the need for liver transplantation in 70% to 80% of patients.[5,6] The major research challenges include increased understanding of the pathogenesis and etiology of biliary atresia, improved biomarkers to reliably predict outcome and help guide therapy, and more effective means of diagnosis, prevention, and treatment. These considerations led to the formation of the Biliary Atresia Research Consortium (BARC) in 2002. BARC

BARC	Biliary Atresia Research Consortium	HPE	Hepatoportoenterostomy
BASM	Biliary atresia splenic malformation		

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is a National Institutes of Health–supported cooperative network of 9 clinical centers and a data-coordinating center focused on conducting clinical and basic research of the etiology, pathogenesis, diagnosis, and therapy of biliary atresia.[8]

METHODS

A retrospective study was undertaken to analyze the results of a large cohort of patients with biliary atresia from a diverse group of US institutions with expertise in management of children with liver disease. As a first step, BARC embarked on a retrospective study of the clinical presentation and current management of biliary atresia and the surgical results after HPE. This analysis was particularly important because most of the literature on outcome of HPE from the United States are reports from single centers,[6,9] as opposed to nationwide biliary atresia registry data reported for other countries, including France[5] and Japan.[10] To establish a benchmark representing a contemporary national experience with biliary atresia in the United States, BARC conducted a retrospective chart review of clinical data and outcomes for all patients with biliary atresia undergoing HPE between January 1, 1997 and December 31, 2000 at the 9 BARC clinical centers.

All children (n = 104) who underwent HPE for biliary atresia between January 1, 1997 and December 31, 2000 were followed for 2 years or until loss of the native liver as a result of transplantation or death. Among these 104 children, 65 were white, 17 were black, 10 were Hispanic, and 9 were Asian. As in most series of biliary atresia patients, there was a slight preponderance of females (60%). Children with biliary atresia who did not undergo HPE were not included in this study. The study consisted of a comprehensive review of medical records available at each BARC site. Information was extracted from records by trained clinical research coordinators at the following time points: (1) initial evaluation at the BARC center; (2) performance of HPE; (3) discharge from the hospital after HPE; (4) the first postoperative outpatient visit after HPE; the visits closest to (5) 3 months postoperatively, (6) 6 months postoperatively, (7) age 12 months, (8) age 18 months, (9) age 24 months; and (10) the final visit before death or first liver transplantation. Data collected included demographic information, presenting signs and symptoms, diagnostic studies at the time of evaluation for cholestasis, and clinical course after HPE. Growth parameters, laboratory values, medication use, nutritional support, and sentinel events (eg, cholangitis, ascites, variceal hemorrhage) were recorded from chart review at each time point. Definitions of sentinel events and the case report form used in this study are available at the BARC website (http://www.barcnetwork.org/). Biliary atresia splenic malformation (BASM) syndrome was defined as a splenic malformation occurring together with another major malformation in infants diagnosed with biliary atresia. For the purpose of this study, good outcome was defined as alive with native liver and total serum bilirubin level < 6.0 mg/dL at age 24 months; poor outcome was defined as either death or liver transplantation before age 24 months; and indeterminate outcome was defined as alive with native liver but with serum total bilirubin level > 6.0 mg/dL. The study was approved by the Institutional Review Board at each BARC center with a waiver of consent.

Data are presented as percents or as means and standard deviations. Rates are compared using Fisher's exact test. Means are compared using 2-tailed, 2-sample *t*-tests with unequal variances (Behrens-Fisher test).

RESULTS

Associated Congenital Anomalies

Among the 104 patients, 78 (75%) had no congenital anomalies identified, 13 (12.5%) had 1 anomaly, and the remaining 13 (12.5%) had more than 1 anomaly. The most common anomaly was splenic malformation (12 subjects); the second most common was interrupted inferior vena cava (11 subjects). Eleven of the 13 infants with more than 1 anomaly had BASM (1 asplenia, 10 polysplenia). Nine subjects had a cardiac malformation, and 9 had intestinal malrotation. The most common grouping included 7 subjects with an interrupted inferior vena cava, a cardiac anomaly, and either polysplenia (6 subjects) or asplenia (1 subject).

Age at Evaluation and Surgery

The average age at initial evaluation at a BARC center was 53 days, and average age at HPE was 61 days (Table I); 44% of the patients underwent HPE after age 60 days, and 12% underwent HPE after age 90 days (Table II). There were no differences in age at HPE by sex, but there were differences by race and ethnicity (Table I). Non-Hispanic whites were more likely to have undergone HPE by age 60 days compared with other racial/ethnic groups (44 out of 65 non-Hispanic whites underwent HPE at age $\leq$ 60 days vs 15 out of 39 others; $P = .0044$). Infants with more than 1 anomaly were evaluated and underwent HPE earlier than those without anomalies and those with only 1 anomaly (Table I; $P = .04$ and .06, respectively, compared with those without anomalies).

Laboratory Values at Presentation and Diagnostic Testing

Table III reports initial laboratory values for routine liver biochemistry studies. Characteristic elevations in bilirubin (total and direct), alkaline phosphatase, gamma glutamyl transpeptidase, and alanine aminotransferase levels were observed.

The typical steps in diagnostic evaluation varied considerably among the 9 BARC clinical centers. Most commonly, an ultrasound was obtained (87%). The triangular cord sign[11] was not visualized by ultrasound in any subject, and 10% of subjects had a normal gallbladder. Fewer than half of the subjects (43%) underwent hepatobiliary scintigraphy (3 centers used scintigraphy in $< 25\%$ of cases, and 3 centers did so in $> 75\%$ of cases), and only small numbers underwent either endoscopic retrograde cholangiopancreatography (1%)

Table I. Demographic and clinical characteristics and age at evaluation and HPE of 104 children with biliary atresia

Characteristic	Age at evaluation		Age at time of HPE	
	n	Mean ± standard deviation [range]	n	Mean ± standard deviation [range]
All	101	53 ± 28 [0–155]	104	61 ± 26 [11–153]
Sex				
Male	41	58 ± 29	42	64 ± 29
Female	60	49 ± 26	62	59 ± 24
Race/ethnicity				
Non-Hispanic white	63	48 ± 28	65	55 ± 26
African-American	17	61 ± 27	17	72 ± 29
Hispanic	10	65 ± 26	10	76 ± 19
Asian	8	52 ± 31	9	62 ± 21
Other	3	68 ± 22	3	78 ± 32
Congenital anomaly				
None	75	55 ± 27	78	63 ± 26
One	13	54 ± 35	13	60 ± 33
More than 1	13	40 ± 23	13	50 ± 22

Age at evaluation at the BARC center and at the time of hepatoportoenterostomy are shown for the entire cohort of 104 children with biliary atresia and for specific subdivisions of the cohort.

or magnetic resonance cholangiopancreatography (3%). Two-thirds of the subjects underwent percutaneous liver biopsy before surgery (2 centers obtained liver biopsies in < 25% of cases, and 5 centers did so in > 75% of cases).

Medication Use

Table II shows the percentage of patients receiving each of 3 categories of medications at 4 time points: during hospitalization after HPE, at the time of hospital discharge, on the first postoperative outpatient visit, and at 3 months after HPE. Ursodeoxycholic acid was the most frequently used medication (80% at 3 months after HPE). Antibiotics were used in 69% of children and corticosteroids were used in 16% of children at 3 months after HPE.

Overall Outcome

At age 24 months, 58 children were alive with their native liver, 42 had undergone liver transplantation (37 alive and 5 dead) and 4 had died without undergoing liver transplantation (Figure 1). All 4 deaths without liver transplantation were directly attributable to congenital heart disease. Thus no child died of end-stage liver disease while awaiting liver transplantation during the first 2 years of life.

Cholangitis was common and occurred more frequently in the first year of life (31% of the subjects within 3 months of HPE, 24% at 3 to 6 months after HPE, 10% at age 6 to 12 months, 9% at age 12 to 18 months, and 15% at age 18 to 24 months); 47% of patients did not experience an episode of cholangitis, 30% had a single episode, and 23% had 2 or more episodes.

Ascites, as documented by clinical examination or the need for diuretic therapy, developed in 24% of children at a mean age of 185 days (range, 84 to 393 days). Esophageal varices were found on endoscopy in 8 children; in 3 of these cases, variceal bleeding was noted. Bacterial peritonitis was reported in 3 children.

Correlation of Demographic Features and Clinical Practice With Outcome at Age 24 Months

The 24-month outcome after HPE was assessed based on survival with native liver. Serum bilirubin levels were assessed as another marker of outcome after HPE. Three strata of serum bilirubin levels were established a priori as surrogate markers to reflect bile flow: < 2.0 mg/dL (good), 2.0 to 6.0 mg/dL (intermediate), and > 6.0 mg/dL (poor). Figure 2 illustrates the distribution of patients in these categories over the first 18 months of life.

For the purpose of analyzing factors associated with outcome at age 24 months, good outcome was defined as survival without liver transplantation and with total serum bilirubin level < 6.0 mg/dL. Poor outcome was defined as death or liver transplantation before age 24 months. Indeterminate outcome was defined as survival without liver transplantation but with serum bilirubin level > 6.0 mg/dL, reflecting poor bile flow; these children were not included in the analysis. At age 24 months, 54 children (52%) had a good outcome, 46 (44%) had a poor outcome, and 4 had an indeterminate outcome.

The relationships among various demographic features and clinical practices were examined relative to good versus poor outcome (see Table II). The presence of BASM was associated with poor outcome ($P = .021$). There was a trend (not statistically significant) suggesting that children with poor outcome were older at evaluation and at HPE compared with those with good outcome (age at evaluation [days, mean ± standard deviation]: poor outcome, 55 ± 30, vs good

Table II. Association of outcome at age 24 months with demographic and clinical parameters (100 subjects with good or poor outcome)

Characteristic	n	% with good outcome	*P* value
Overall cohort	100	54%	
Sex			
Male	41	56%	
Female	59	52%	.84
Race/ethnicity			
Non-Hispanic white	63	52%	
African-American	15	60%	
Hispanic white	10	60%	
Asian	9	33%	.61
Age at HPE			
<30 days	10	70%	
<60 days	56	57%	
60–90 days	32	50%	
90–120 days	9	67%	.25
> 90 days	12	50%	
>120 days	3	0%	
Congenital anomalies			
None	76	55%	
One	12	75%	
More than 1	12	25%	.046
BASM	11	18%	
No BASM	89	58%	.021
Antibiotic use			
At time of HPE			
Yes	62	53%	
No	30	50%	.77
At hospital discharge			
Yes	69	54%	
No	28	50%	.75
At first postoperative visit			
Yes	60	53%	
No	21	62%	.50
At 3-month postoperative visit			
Yes	58	59%	
No	25	40%	.12
Corticosteroid use			
At time of HPE			
Yes	41	56%	
No	59	53%	.84
At hospital discharge			
Yes	35	54%	
No	61	51%	.83
At 3-month postoperative visit			
Yes	14	43%	
No	69	55%	.56
Ursodeoxycholic Acid Use			
At hospital discharge			
Yes	66	50%	
No	31	58%	.52
At 3-month postoperative visit			
Yes	68	56%	
No	17	41%	.29
Cholangitis after HPE			
Yes	52	63%	
No	48	44%	.070
Ascites after HPE			
Yes	25	8%	
No	75	69%	<.0001

The percentage of patients with good outcome as defined in the methods is shown relative to the presence or absence of the specified demographic or clinical feature.
The *P* value compares percentages.
UDCA, ursodeoxycholic acid.

outcome, 49 ± 25, $P = .28$; age at HPE: poor outcome, 64 ± 27, vs good outcome, 57 ± 24; $P = .14$). No other demographic or laboratory parameters or clinical interventions, except the presence of BASM or more than 1 congenital anomaly, were identified as being significantly related to outcome (Table II).

Correlation of Sentinel Events and Biomarkers With Outcome at Age 24 Months

The most common sentinel events in this cohort were cholangitis, growth failure, and ascites. Nutritional and growth issues will be analyzed in a separate study and are excluded from further analysis here. Only 8% of the 25 subjects who developed ascites had good outcome, whereas 67% of the 75 subjects who never had ascites had good outcome ($P < .0001$). Forty-eight children had no episodes of cholangitis, 30 had a single episode, and 22 had 2 or more episodes. The percentage of children with good outcome was greater ($P = .07$) in those with episodes of cholangitis (62%) than in those who did not develop cholangitis (42%). Fifty-five children received antibiotics at both hospital discharge and the first postoperative visit. Subsequent development of cholangitis in these 55 patients (55%) was similar to that in the 49 infants (51%) who did not receive antibiotics at both of these time points.

Bile flow was previously shown to be an important factor affecting outcome after HPE and was estimated based on serum total bilirubin level in these analyses. By 3 months after HPE, a clear difference in total bilirubin levels could be seen between those children with good outcome and those with poor outcome at age 24 months (Figure 3). Kaplan-Meier analysis of survival without transplantation in the 3 strata of serum bilirubin, measured 3 months after HPE, revealed markedly improved survival in children with total bilirubin < 2 mg/dL at 3 months after HPE compared with those with total bilirubin > 6 mg/dL (84% vs 16%; $P < .0001$); the survival rate for the intermediate bilirubin group was 40% (Figure 4).

Table III. Laboratory values at evaluation for biliary atresia

Test	n	Mean ± standard deviation	Median [interquartile range]
Total bilirubin (mg/dL)	93	9.5 ± 3.3	7.5–11.2
Direct bilirubin (mg/dL)	61	6.5 ± 2.6	4.8–7.7
Alkaline phosphatase (IU/L)	88	535 ± 303	361–676
γGTP (IU/L)	74	558 ± 397	266–737
ALT (IU/L)	87	168 ± 163	81–198

Standard serum biochemistry values measured at the time of presentation to the BARC center are shown.
γGTP, gamma glutamyltranspeptidase; ALT, alanine aminotransferase.

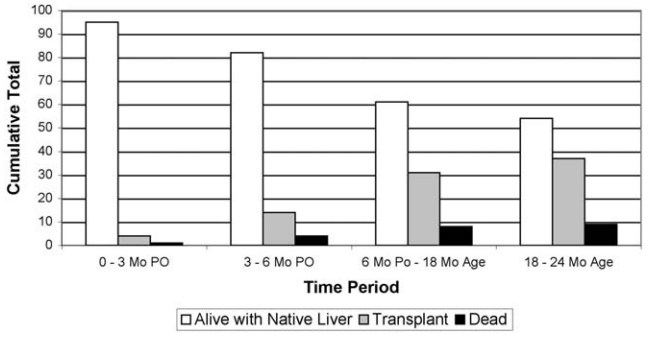

Figure 1. Overall outcome in the first 24 months of life in children with biliary atresia. The absolute numbers of children who were alive with their native liver, who were alive after liver transplantation, and who had died either with or without undergoing liver transplantation are shown at the specific time intervals indicated on the *x*-axis. MO, month; PO, postoperative relative to HPE.

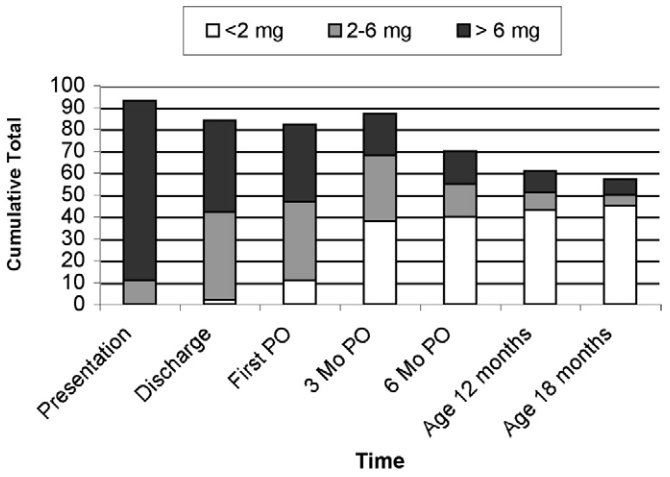

Figure 2. Total bilirubin levels for subjects with biliary atresia from the time of evaluation until age 18 months. The numbers of children with total bilirubin levels in the specified ranges at the noted time points are shown. These numbers reflect the children who underwent measurements, not the entire cohort of 104 children. Some children did not have measurements at the specified time intervals, and children who died or underwent liver transplantation were not included. TB, total bilirubin; PO, postoperative relative to HPE; MO, month of life.

One defining feature of outcome in these studies was liver transplantation. Because inadequate bile drainage can be an indication for transplantation, the development of ascites was used as an additional marker of advancing liver disease. Poor bile flow (as reflected by total serum bilirubin > 6 mg/dL) at 3 and 6 months after HPE was associated with the development of ascites ($P < .001$ and .015, respectively; Table IV).

DISCUSSION

This study describes a population of 104 infants with biliary atresia diagnosed and treated between 1997 and 2000 at 9 centers participating in the BARC. Thus, the patient population and outcomes are likely to reflect the current standard practice against which future changes in management and clinical trials can be measured. At present, HPE is the only effective therapy for biliary atresia short of liver transplantation. Thus, the findings of most interest were the rate of success of HPE and the factors that correlated with successful HPE. The data from this retrospective study show that there was no standard approach to the diagnosis of biliary atresia and that postsurgical management varied considerably among the BARC centers. Nevertheless, the outcomes at age 2 years for the 9 centers were comparable to the best outcome data published from other countries and in large single-center reports.[5,6,10,12,13] The small differences in total numbers of patients among the BARC centers and the relatively limited absolute numbers of patients did not permit an analysis of potential center effects on outcome.

An unexpected finding was the variation in perioperative care among the centers. There was fairly consistent use of ursodeoxycholic acid across the centers, with 75% to 80% of the patients receiving this treatment at 1 to 3 months after HPE. Less consistent was the use of oral prophylactic antibiotics; 60% to 70% of patients received antibiotics within 1 to 3 months after HPE. Corticosteroid use was infrequent; only 22% of patients received them at 1 month post-HPE and 16% did so at 3 months post-HPE. These findings indicate that there is little consensus as to standard postoperative treatment of biliary atresia. Furthermore, the findings do not reveal an obvious effect of these clinical practices on outcome, although the limited size and retrospective nature of the study preclude reliable analysis of the independent effects of these medications on outcome.

An important finding from this study is the predictive

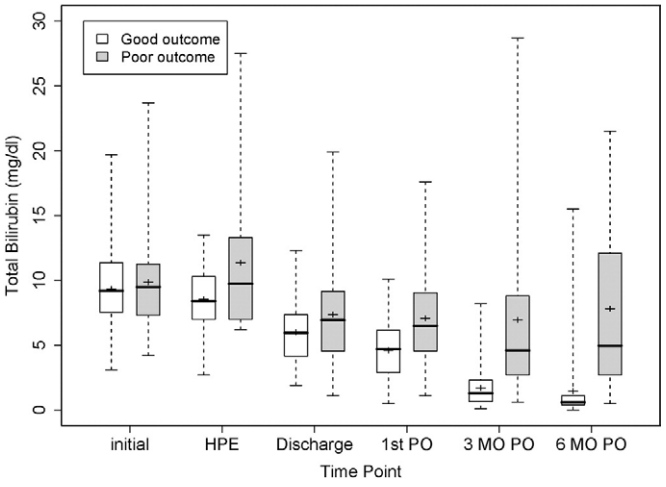

Figure 3. Total bilirubin levels over time in children with good outcome and children with poor outcome at age 24 months. This box-and-whiskers plot gives total serum bilirubin levels in children with good or poor outcome at the time points specified on the *x*-axis. The box represents the interquartile range (25^{th} and 75^{th} percentiles), and the whiskers represent the range (the minimum and maximum). The cross represents the mean; the line, the median. At 3 and 6 months after HPE ($P < .0001$ and .0015, respectively), total serum bilirubin levels were significantly greater in children with poor outcome compared with those with good outcome. HPE, time of hepatoportoenterostomy; PO, postoperative relative to hepatoportoenterostomy; MO, month.

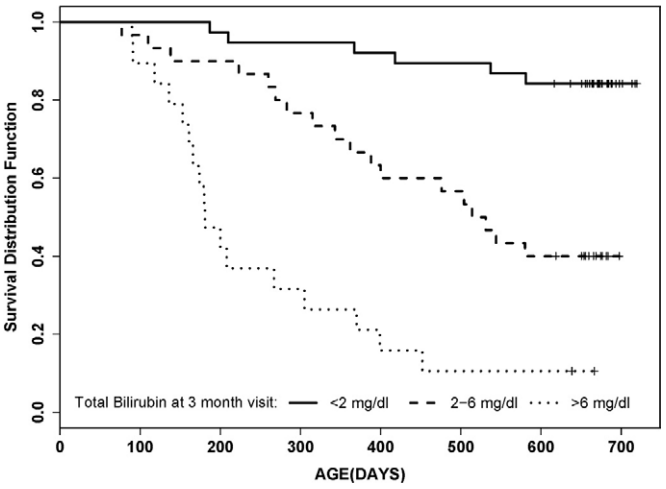

Figure 4. Kaplan-Meier analysis of outcome based on total bilirubin level 3 months after HPE. Survival with native liver relative to age in days after HPE is shown in the 3 Kaplan-Meier curves, derived by dividing the cohort of patients on the basis of their total serum bilirubin level 3 months after HPE. At 3 months after HPE, total bilirubin level was < 2 mg/dL in 38 children, between 2 and 6 mg/dL in 30 children, and > 6 mg/dL in 19 children.

value of postoperative serum bilirubin level for outcome. A total serum bilirubin level < 2 mg/dL at 3 months post-HPE correlated strongly with good outcome at 2 years, whereas serum bilirubin > 6 mg/dL at 3 months post-HPE predicted poor outcome. Intermediate serum bilirubin values (2 to 6 mg/dL) at 3 months post-HPE were associated with an intermediate risk.

A shortcoming of these findings is that the 2-year follow-up affords too limited a period of follow-up to assess the overall effectiveness of clinical care. However, even after 2 years, only 58 children were alive with their native liver, and 54 of these children had good bile flow as estimated by serum bilirubin concentration. In a recent report from France, 63 of 271 patients (23%) with biliary atresia diagnosed and treated between 1968 and 1983 were found to be alive with their native liver 20 years after surgery.[7] Examination of the survival curves in that report revealed 2 phases: a rapid decline (failure of HPE) in the first 2 years of life, resulting in about 40% survival, and a slower decline over the next 18 years, leaving 23% survival at 20 years. Thus survival at 2 years is likely to reflect successful diagnosis and surgical treatment, as was shown in previous studies.[14,15] In the current series, the 3-month post-HPE serum total bilirubin level was a useful early biomarker reflecting the early-phase success. Furthermore, 2-year outcome appears to be a reasonable endpoint for studies examining changes in operative and perioperative management in regard to improving outcome.

A potential problem associated with using bilirubin level as a marker for good outcome is the fact that some centers may equate a high postoperative bilirubin level with poor bile flow and the finding thus becomes an indication to proceed with transplantation. Thus bilirubin level may affect the outcome by guiding clinical decisions rather than reflecting worsening liver function. For this reason, another endpoint of poor liver function and outcome was also analyzed. Additional analysis of 3- and 6-month post-HPE serum total bilirubin level showed that they also correlated with the development of ascites, an independent marker of advancing liver disease.

Another important finding from this retrospective study is the differences in outcome of the 2 clinical forms of biliary atresia. Children with BASM were more likely to be evaluated and to undergo HPE at an earlier age than those with no or only 1 anomaly. One explanation for the earlier diagnosis and surgery in children with BASM is that they had an earlier onset of biliary obliteration and consequent jaundice, as would be expected in congenital as opposed to acquired biliary atresia. However, the reasons for earlier presentation could not be analyzed in this retrospective study, and the earlier clinical referral may have been triggered by the presence of the associated congenital anomalies (eg, complex congenital heart disease) rather than by earlier onset of jaundice. The interval between evaluation and performance of HPE did not vary according to the presence of anomalies, suggesting that the presence of anomalies neither accelerated diagnosis nor delayed surgical intervention. Despite this earlier diagnosis and surgical treatment, subjects with multiple associated anomalies had poor outcome from HPE; only 2 of the 11 subjects with BASM (18%) had good outcome. Furthermore, all 4 disease-related deaths occurring before liver transplantation were attributable to complex congenital heart disease. These data emphasize that BASM should be considered separately

Table IV. Relationship of total bilirubin level and development of ascites

	TB < 2 mg/dL		TB 2 to 6 mg/dL		TB > 6 mg/dL		
	% ever develop ascites	n	% ever develop ascites	n	% ever develop ascites	n	*P* value
Discharge	0%	2	20%	40	31%	42	.41
First PO Visit	9%	11	25%	36	31%	35	.37
3 MO PO	16%	38	20%	30	63%	19	<.001
6 MO PO	8%	40	20%	15	40%	15	.015
Age 12 MO	7%	43	25%	8	30%	10	.054

The percentage and absolute number of patients who ever developed ascites relative to the specific range of total serum bilirubin at the specified time are shown. The *P* values reflect a comparison of the low and high TB groups. TB, total bilirubin; PO, postoperative relative to the hepatoportoenterostomy; MO, month of life.

from other types of biliary atresia when considering clinical care paradigms and evaluating outcomes.

Two factors reported to be determinants of survival after HPE are age at surgery (with older age associated with poorer outcome) and development of ascending cholangitis after surgery. The age at HPE is affected by many factors, including local custom in regard to scheduling postnatal care, access to medical care, efficiency of diagnosis, and scheduling of surgery. The standard schedule for postnatal care in the United States is for routine evaluation at age 2 and 8 weeks, which may be at least partly responsible for the delay in diagnosis and referral of children with biliary atresia, the peak presentation of which occurs at approximately age 6 weeks. We also found that non-Hispanic white children were referred at a significantly younger age than other infants. This disparity may be related to better access to medical care and the easier identification of mild jaundice in light-skinned infants. This retrospective study did not permit evaluation of access to health care. Early presentation and surgery has been demonstrated by some to be a risk factor for poor outcome.[16] In this study, this was observed with respect to patients with BASM who tended to have early diagnosis and worse prognosis; however, it was not confirmed among the other subjects.

Cholangitis after HPE is often cited as a risk factor for poor outcome but was not associated with decreased survival in this study. Whereas slightly more than half of the subjects experienced an episode of cholangitis after HPE, there was no evidence that experiencing 1 or more episodes of cholangitis negatively affected outcome. Indeed, patients with multiple episodes of cholangitis appeared to have better outcome. This discrepancy was possibly related to the fact that infants with better biliary drainage post-HPE may be at greater risk for ascending infection, or that current therapies for cholangitis are more effective than older therapies. These issues merit prospective examination to determine the optimum approaches to facilitate early diagnosis and treatment, which would have a positive effect on outcome.

The overall outcomes of infants with biliary atresia treated at the 9 BARC centers were similar, if not identical, to those reported from Europe and Japan as well as from single-center studies that report expertise in the management of infants with biliary atresia.[5,6,10,12,13] The most recent data from the United Kingdom, after institution of health administration regulations requiring referral of all infants with suspected biliary atresia to 3 centers of expertise, show 50% 2-year survival with the native liver,[12] similar to the outcomes recorded in our cohort. The BARC center 2-year survival data are equivalent to those reported from Germany (extrapolated from reported data to be approximately 48%)[13] and somewhat better than those recorded in the French national study, in which average 2-year survival with the native liver approximated 30%.[5] A recent report of a national survey in Japan, in which 208 of 222 patients received postoperative corticosteroids, recorded 57% anicteric survival with the native liver, 59% in the group treated with corticosteroids and 36% in the nontreated group.[17] Although these data suggest that corticosteroid therapy improved outcome after HPE, this was not supported by data from the Japanese biliary atresia registry, which showed that 5-year survival with the native liver was approximately 60% in patients undergoing HPE between 1989 and 1994.[10]

In summary, our data demonstrate that contemporary management of biliary atresia in the 9 US BARC centers results in outcomes equivalent to those reported from Western Europe and Japan despite significant variability in the approaches to diagnosis and management among the BARC centers and differences in approach with respect to other countries. Total serum bilirubin level measured at 3 months post-HPE appears to be a biomarker that is predictive of subsequent outcome and can be useful in planning alternative treatment, including liver transplantation. Finally, the coexistence of splenic malformations with biliary atresia (BASM syndrome) has negative implications with regard to outcome.

REFERENCES

1. Sokol RJ, Mack C, Narkewicz MR, Karrer FM. Pathogenesis and outcome of biliary atresia: current concepts. J Pediatr Gastroenterol Nutr 2003;37:4-21.
2. Ohi R. Biliary atresia: a surgical perspective. Clin Liver Dis 2000;4:779-804.
3. Schweizer P. Treatment of extrahepatic biliary atresia: results and long-term prognosis after hepatic portoenterostomy. Pediatr Surg 1986;1:30-36.

4. Karrer FM, Bensard DD. Neonatal cholestasis. Semin Pediatr Surg 2000;9:166-9.
5. Chardot C, Carton M, Spire-Bendelac N, Le Pommelet C, Golmard JL, Auvert B. Prognosis of biliary atresia in the era of liver transplantation: French national study from 1986 to 1996. Hepatology 1999;30:606-11.
6. Karrer FM, Price MR, Bensard DD, Sokol RJ, Narkewicz MR, Smith DJ, et al. Long-term results with the Kasai operation for biliary atresia. Arch Surg 1996;131:493-6.
7. Lykavieris P, Chardot C, Sokhn M, Gauthier F, Valayer J, Bernard O. Outcome in adulthood of biliary atresia: a study of 63 patients who survived for over 20 years with their native liver. Hepatology 2005;41:366-371.
8. Hoofnagle JH. Biliary Atresia Research Consortium (BARC). Hepatology 2004;39:891.
9. Wildhaber BE, Coran AG, Drongowski RA, Hirschl RB, Geiger JD, Lelli JL, et al. The Kasai portoenterostomy for biliary atresia: a review of a 27-year experience with 81 patients. J Pediatr Surg 2003;38:1480-5.
10. Nio M, Ohi R, Miyano T, Saeki M, Shiraki K, Tanaka K. 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.
11. Choi SO, Park WH, Lee HJ, Woo SK. "Triangular cord": a sonographic finding applicable in the diagnosis of biliary atresia. J Pediatr Surg 1996;31:363-6.
12. Davenport M, De Ville de Goyet J, Stringer MD, Mieli-Vergani G, Kelly DA, McClean P, et al. Seamless management of biliary atresia in England and Wales, 1999–2002. Lancet 2004;363:1354-7.
13. Schweizer P, Schweizer M, Schellinger K, Kirschner HJ, Schittenhelm C. Prognosis of extrahepatic bile duct atresia after hepatoportoenterostomy. Pediatr Surg Int 2000;16:351-5.
14. Grosfeld JL, Fitzgerald JF, Predaina R, West KW, Vane DW, Rescorla FJ. The efficacy of hepatoportoenterostomy in biliary atresia. Surgery 1989;106:692-701.
15. Lilly JR, Karrer FM, Hall RJ, Stellin GP, Vasquez-Estevez JJ, Greenholz SK, et al. The surgery of biliary atresia. Ann Surg 1989;210:289-94.
16. Volpert D, White F, Finegold MJ, Molleston J, Debaun M, Perlmutter DH. Outcome of early hepatic portoenterostomy for biliary atresia. J Pediatr Gastroenterol Nutr 2001;32:265-9.
17. Muraji T, Nio M, Ohhama Y, Hashimoto T, Iwanaka T, Takamatsu H, et al. Postoperative corticosteroid therapy for bile drainage in biliary atresia: a nationwide survey. J Pediatr Surg 2004;39:1803-5.

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