Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Bilirubin level 1 week after hepatoportoenterostomy predicts native liver survival in biliary atresia

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BACKGROUND: To determine a very early predictive biomarker after hepatoportoenterostomy (HPE) for the prediction of native liver survival in biliary atresia (BA) patients.

METHODS: A retrospective chart review was conducted of BA patients in our hospital between August 2000 and April 2019. The serum total bilirubin (T-bil), direct bilirubin, and gamma-glutamyl transferase level 1 week after HPE were analyzed. The clinical outcome predictors were investigated.

RESULTS: A total of 90 BA patients were recruited. Receiver operating characteristic curve analysis showed that a post-HPE 1-week T-bil level ≤4.85 mg/dL predicted jaundice-free after HPE ($P = 0.02$). BA patients with a post-HPE 1-week T-bil ≤4.85 mg/dL were more likely to be jaundice-free within 3 months of HPE (odds ratio = 3.53; $P = 0.006$). Kaplan–Meier plot analysis showed that the likelihood of native liver survival and jaundice-free native liver survival were significantly higher in BA subjects with a post-HPE 1-week T-bil ≤4.85 mg/dL than in other subjects ($P = 0.01$ and 0.01, respectively).

CONCLUSIONS: The serum post-HPE 1-week T-bil level may predict the long-term outcome in BA patients. A post-HPE 1-week T-bil ≤4.85 mg/dL correlated with better native liver survival and jaundice-free native liver survival in BA patients.

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INTRODUCTION

Biliary atresia (BA) is the leading cause of pediatric liver transplantation.[1] However, it is a relatively rare disorder, occurring in 1 in 5000–20,000 live births.[2–7] Hepatoportoenterostomy (HPE), aimed at restoring biliary drainage to the intestine, is the standard surgical intervention for BA and has been shown to improve survival with native liver.[8] The underlying mechanisms of progressive obstructive cholangiopathy are unclear in large, and the long-term prognosis remains difficult to predict.

Several factors have been reported to determine the ultimate success of HPE, including age at the time of HPE,[9–11] presence of cirrhosis,[12] case load of the hospital,[13] occurrence of postoperative cholangitis,[14,15] and a decrease in serum bilirubin in the first few months after HPE.[16–24] Among all variables, serum bilirubin after HPE appears to be the most predictive biomarker of clinical outcomes.[21] The timing of the evaluation of the total bilirubin (T-bil) level has ranged from 7 days to 6 months in previous publications,[16–19,21,23] while the serum T-bil level at 3 months after HPE is regarded as the most important outcome predictor.[20,21,25]

Earlier prediction of outcome after HPE may assist the family and physician in arranging a long-term treatment plan, such as liver transplantation. Nevertheless, a 3-month wait places a huge emotional burden on the parents, who would like to know as soon as possible whether their baby could survive with native liver. Besides, unfavorable outcome prediction allows the family to prepare for further liver transplantation earlier. This study aimed to investigate earlier clinical predictors of native liver survival in BA patients.

METHODS

Subjects and clinical data

BA patient who underwent HPE at the National Taiwan University Hospital between August 2000 and April 2019, with complete clinical data 1 week after HPE, were recruited consecutively to this retrospective study. The inclusion criteria are the BA patients who received HPE at our hospital, with available laboratory data 1 week after the surgery. The exclusion criteria are receiving HPE at other hospitals or no available laboratory data 1 week after the surgery. The diagnosis of BA was confirmed by intra-operative cholangiography in all study subjects. The medical charts of these patients were reviewed retrospectively. A serum T-bil level <2 mg/dL was defined as jaundice-free in this analysis.

Data on age at HPE, gender, types of BA, other associated comorbidities, serum levels of T-bil, direct bilirubin (D-bil), gamma-glutamyl transferase (GGT), and bile acid measured 1 week after HPE, and the use of ancillary medical treatment including ursodeoxycholic acid (UDCA) and steroids were collected for analysis. The study protocol was approved by the Institutional Review Board of the National Taiwan University Hospital.

Statistical analysis

The STATA (ver. 14.0; StataCorp LP, College Station, TX) and MedCalc (ver. 18.6; MedCalc Software, Ostend, Belgium) software were used for statistical analyses. The primary outcome was jaundice-free survival after HPE, and the secondary outcome was native liver survival. Overall native liver survival was defined as the period from the date of birth until liver transplantation, death, or the end of this study, whichever occurred first, while jaundice-free native liver survival was defined as the period from the date of

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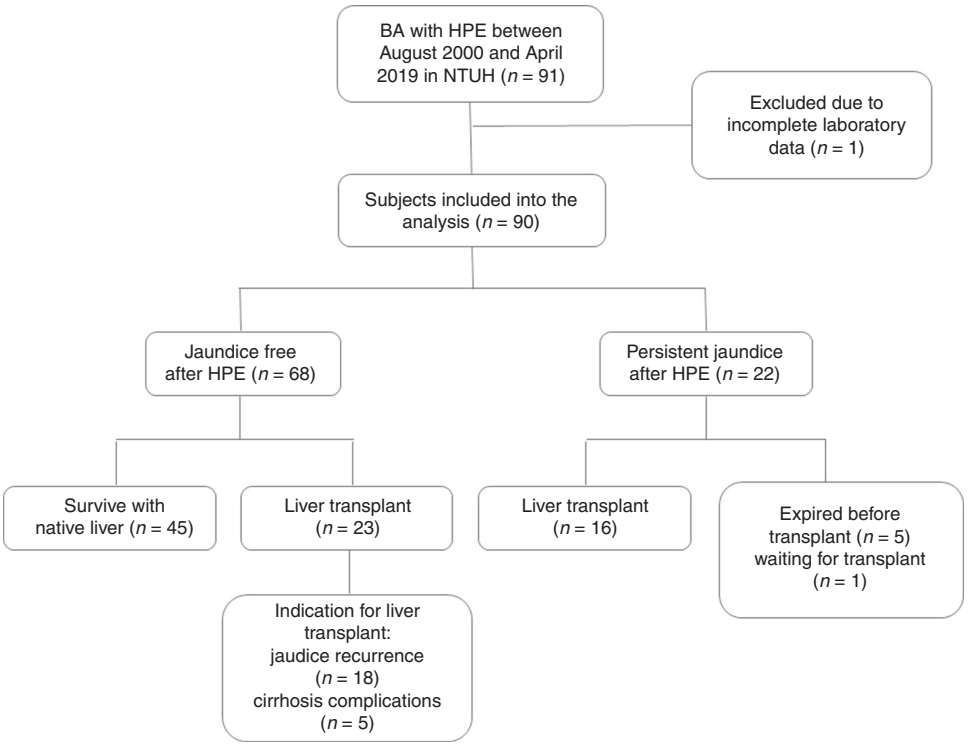

Fig. 1 The flow diagram summarized the general characteristics and clinical outcomes of the study cohort

becoming jaundice-free after HPE until the recurrence of jaundice, liver transplantation, death, or the end of the analysis.

Receiver operating characteristic (ROC) curve analyses were performed to determine cutoff values and area under curve. The positive predictive value and negative predictive value (NPV) of each cutoff value were calculated. Logistic regression was used to assess the odds ratio (OR) and 95% confidence interval (CI) for predicting jaundice-free within 3 months of HPE. Cox's proportional hazard analysis, Kaplan–Meier plot, and log-rank test were applied to the survival analysis for the prediction of native and jaundice-free native liver survival in this study. A P value < 0.05 was regarded as statistically significant.

RESULTS

General characteristics

A total of 91 children underwent HPE at the National Taiwan University Hospital between August 2000 and April 2019 (Fig. 1). One of them was excluded owing to incomplete laboratory data 1 week after HPE. The other 90 children (38 males and 52 females) were included in this retrospective analysis. The median patient age at HPE was 50 days of age in this cohort. Sixty-eight children (75.55%) achieved jaundice-free after a median time of 37.5 days after HPE, while the other 22 children had persistent jaundice after HPE. There are 39 subjects (43.33%) who received liver transplant after a median time of 11 months. The median overall follow-up time, including post-liver transplantation follow-up, was 62.5 months. The numbers and general characteristics of the study population are summarized in Table 1 and Fig. 1.

Table 1. General characteristics of 90 biliary atresia patients who received hepatoportoenterostomy (HPE)

	$N = 90$
Male sex, *n* (%)	38 (42.22%)
HPE age, median (IQR), days	50 (36–64)
Post-HPE 1-week T-bil, median (IQR), mg/dL	5.47 (4.27–6.96)
Post-HPE 1-week D-bil, median (IQR), mg/dL	3.52 (2.76-4.56)
Post-HPE 1-week GGT, median (IQR), U/L	432 (280–705)
Jaundice-free after HPE, *n* (%)	68 (75.56)
Time to jaundice-free, median (IQR), days	37.5 (21–94)
Liver transplantation, *n* (%)	39 (43.33)
Time to liver transplant, median (IQR), months	11 (8.25–16.75)
Overall follow-up time, median (IQR), months	62.5 (23.5–110.25)
Biliary atresia type, *n* (%)	
Type 1	14 (15.56%)
Type 2	21 (23.33%)
Type 3	55 (61.11%)
Biliary atresia polysplenia syndrome, *n* (%)	1 (1.11%)

Cutoff for the prediction of jaundice-free survival after HPE

ROC analyses were performed to determine the best cutoffs for predicting jaundice-free at 1 week after HPE. The serum T-bil level ≤4.85 mg/dL at 1 week after HPE significantly predicted jaundice-free after HPE in BA subjects ($P = 0.02$) (Fig. 2). The D-bil cutoff ≤3.30 mg/dL demonstrated a borderline significance in predicting jaundice-free after HPE in BA subjects ($P = 0.06$). The GGT level failed to achieve statistical significance in ROC analysis ($P = 0.40$). Therefore, we applied the post-HPE 1-week T-bil level ≤4.85 mg/dL as the marker in our statistic model.

A serum post-HPE 1-week T-bil level ≤4.85 mg/dL was also predictive of jaundice-free within 3 months of HPE in univariate logistic regression analyses after application of the Bonferroni correction (OR = 3.53, $P = 0.006$; Table 2). In the multivariate logistic regression model that included an age at HPE ≤60 days and a post-HPE 1-week T-bil ≤4.85 mg/dL, only the post-HPE 1-week T-bil ≤4.85 mg/dL reached statistical significance (OR = 3.73, $P = 0.006$) while the HPE age did not (OR = 2.48, $P = 0.07$; Table 2). The general characters between BA children with T-bil ≤4.85 vs.

>4.85 mg/dL are summarized in Table 3. The prevalence of liver transplant is higher in subjects with post-HPE 1-week T-bil level >4.85 mg/dL than in others ≤4.85 mg/dL (53.85% vs. 28.95%, $P = 0.019$).

Predictors of native liver survival

Cox's proportional hazard analysis showed that serum T-bil ≤4.85 mg/dL at 1 week after HPE was predictive of a higher chance of native liver survival (hazard ratio = 2.33, 95% CI = 1.17–4.64, $P = 0.02$). Kaplan–Meier plot analysis with log-rank test (Fig. 3a) further demonstrated that the possibility of native liver survival was significantly higher in BA subjects with a post-HPE 1-week T-bil level ≤4.85 mg/dL vs. those with a T-bil level >4.85 mg/dL (log-rank test, $P = 0.01$). The possibility of jaundice-free native liver survival was also higher in BA subjects with a post-HPE 1-week T-bil level ≤4.85 mg/dL vs. those with a T-bil level >4.85 mg/dL (Fig. 3b, log-rank test, $P = 0.01$).

All of the BA subjects received HPE from four well-experienced pediatric surgeons in our hospital. Neither native liver survival ($P = 0.15$) nor jaundice-free native liver survival ($P = 0.11$) had significant difference between different surgeons. In this cohort, 66 BA children (73.33%) received steroid therapy, and all 90 BA children received UDCA and prophylactic antibiotics after HPE. However, the combination of UDCA and steroid failed to predict jaundice-free ($P = 0.63$), jaundice-free within 3 months ($P = 0.25$), liver transplantation ($P = 0.44$), native liver survival ($P = 0.37$), or jaundice-free native liver survival ($P = 0.19$) in our cohort.

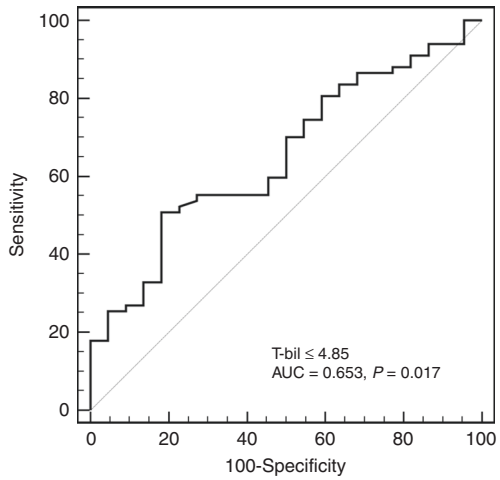

Fig. 2 Receiver operating characteristic curve analysis showed that a total bilirubin (T-bil) cutoff value ≤4.85 mg/dL was optimal for predicting jaundice-free survival after hepatoportoenterostomy (HPE) (positive predictive value = 89.5%, negative predictive value = 34.6%, $P = 0.017$)

Table 2. Predictors of jaundice-free within 3 months of hepatoportoenterostomy (HPE)

	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Male ($n = 38$) vs. female ($n = 52$)	0.625 (0.27–1.46)	0.276	—	—
HPE age ≤60 days ($n = 64$) vs. >60 days ($n = 26$)	2.27 (0.90–5.75)	0.083	2.48 (0.93–6.63)	0.07
Post-HPE 1-week T-bil ≤4.85 mg/dL ($n = 38$) vs. >4.85 mg/dL ($n = 52$)	3.53 (1.43–8.74)	0.006	3.73 (1.47–9.45)	0.006

DISCUSSION

BA remains the leading cause of liver transplantation in children in the world.[1] The severity of liver fibrosis progresses in the majority of BA patients even after HPE.[12] Early predictors of prognosis after HPE for BA may allow risk stratification, precise planning and monitoring of potential complications related to progressive liver disease, implementation of intensified nutritional support, and early preparation for liver transplantation, especially for area shortage of cadaveric liver donor, such as Taiwan.

Prior investigations have delved into the role of different laboratory data in prediction of the outcome after HPE.[16–19,23,26–30] We summarized these articles in Table 4. Among them, discussions regarding a T-bil level <2 mg/dL within 3 months after HPE as a good short-term outcome predictor has dominated research in recent years.[22,26–29] In a prospective multicenter cohort study, Shneider et al. found a 2-year native liver survival of 86% among patients with a T-bil <2 mg/dL within 3 months after HPE, while the 2-year survival rate without transplantation was only 20% in those with a T-bil ≥2 mg/dL at 3 months post-HPE.[21] On the other hand, Chusilp et al. proposed a >20% decrease in serum T-bil at seventh day post-HPE, the earliest timing in the literature, to predict jaundice-free within 6 months and 5-year survival with native liver.[16] Our previous studies demonstrated the serum matrix metallopeptide 7 (MMP-7) levels and the liver stiffness measurement assessed after HPE is predictive of the risk of liver transplantation in BA, but the assessment of MMP-7 level and liver stiffness measurement by transient elastography are not

Table 3. The general characters between biliary children with total bilirubin 1 week after hepatoportoenterostomy (post-HPE 1-week T-bil) ≤4.85 vs. >4.85 mg/dL

	Post-HPE 1-week T-bil >4.85 ($n = 52$)	Post-HPE 1-week T-bil ≤4.85 ($n = 38$)	*P*
Male gender, *n* (%)	21 (40.38%)	17 (44.74%)	0.68
HPE age, median (IQR), days	50 (36–64)	50 (29.25–67.75)	0.60
BA type, *n* (%)			
Type 1	8 (15.38%)	6 (15.79%)	
Type 2	11 (21.15%)	10 (26.32%)	
Type 3	33 (63.46%)	22 (57.89%)	0.93
Biliary atresia polysplenia syndrome, *n* (%)	1 (1.92%)	0 (0%)	1.00
Bile acid level before HPE, median (IQR)	119 (86–153) ($n = 25$)	131 (100–149) ($n = 19$)	0.73
Jaundice-free 3 m within HPE, *n* (%)	23 (44.23%)	28 (73.68%)	0.005
Jaundice-free after HPE, *n* (%)	34 (65.38%)	34 (89.47%)	0.009
Liver transplantation, *n* (%)	28 (53.85%)	11 (28.95%)	0.019

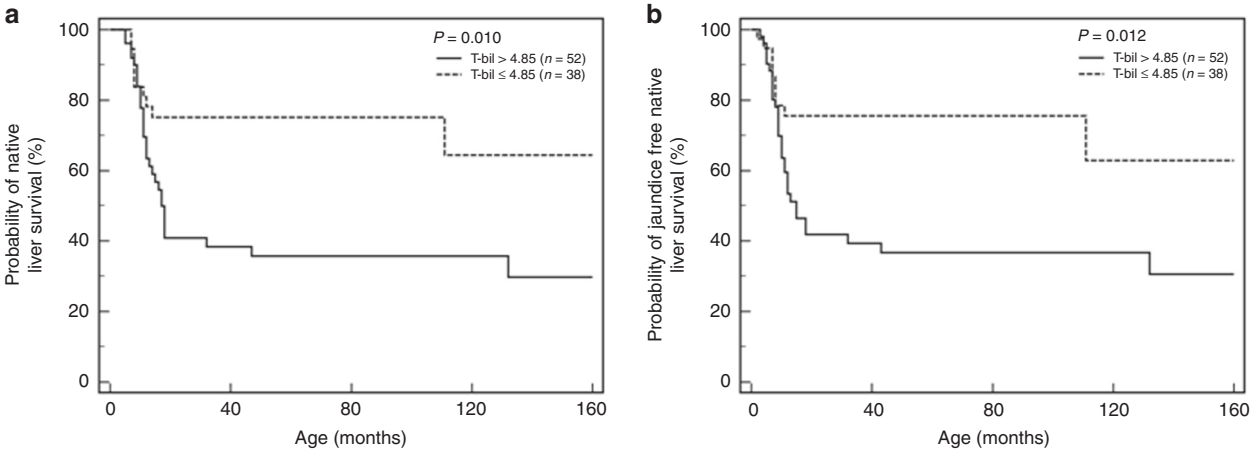

Fig. 3 **a** Kaplan–Meier plot showing that the probability of native liver survival was significantly higher in biliary atresia (BA) patients with a T-bil level ≤4.85 mg/dL at 1 week after HPE than a T-bil level >4.85 mg/dL (log-rank test, $P = 0.010$). **b** Kaplan–Meier plot further showed that the probability of jaundice-free native liver survival was significantly higher in BA patients with a T-bil level ≤4.85 mg/dL at 1 week after HPE than a T-bil level >4.85 mg/dL (log-rank test, $P = 0.012$)

Table 4. Summary of previous studies regarding the outcome predictors of BA subjects after hepatoportoenterostomy

Study	*N*	Time after HPE	Predictor cutoff value	Clinical outcomes
Our study	90	1 week	T-bil <4.85 mg/dL	Jaundice-free within 3 months, native liver survival, jaundice- free native liver survival
Chusilp et al.[16]	133	1 week	$T\text{-bil}_7/T\text{-bil}_0$ <0.8	Jaundice-free within 6 months, 5-year native liver survival
Wu et al.[30]	32	6 months	MMP-7 >10.3 ng/mL	Liver transplant
Rodeck et al.[17]	67	6 weeks	T-bil <3.33 mg/dL	5-year event-free survival rate
Nakajima et al.[18]	66	60 days	T-bil <1.2 mg/dL	Native liver survival, liver transplant
Goda et al.[19]	54	2 months	D-bil <0.7 mg/dL AST <94 U/L	15-year survival rate
Ohhma et al. [20]	142	3 months	T-bil <1 mg/dL	12-year survival rate
Shneider et al.[21]	137	3 months	T-bil <2 mg/dL	2-year native liver survival, ascites, hypoalbuminemia, coagulopathy
van Heurn et al.[22]	77	3 months	T-bil <3 mg/dL	Transplant-free survival rate (15–20 years)
Chiang et al.[23]	58	6 months	T-bil <1.17 mg/dL	Native liver survival
de Vries et al.[24]	214	6 months	T-bil <1.2 mg/dL	Native liver survival
Alkozai et al.[27]	522	Early elevation	GGT	5-year native liver survival

routine test to date.[12,30] In this study, we featured that the T-bil level alone at 1 week after HPE was a very early predictor of long-term native liver survival in BA patients. The rapid improvement of the T-bil level after HPE indicated satisfactory bile flow and prevented rapid progression of biliary cirrhosis by eliminating cholestasis and peri-portal inflammation.[13,31–33] A cutoff serum T-bil level of ≤4.85 mg/dL at 1 week after HPE was a good predictor of jaundice-free within 3 months, native liver survival, and jaundice-free native liver survival in this BA cohort.

The use of ancillary medical treatments, such as prophylactic antibiotics, UDCA, or steroids, to improve the outcome of HPE remains in debate.[28,29,31–34] A recent meta-analysis done by Qiu et al. presented that combined UDCA and steroid intervention was superior in accelerating the clearance of serum bilirubin in BA patients after HPE.[34] Since all BA subjects in this study cohort received UDCA and prophylactic antibiotics after HPE, we are not able to compare the difference in clinical outcomes between subjects with and without UDCA and/or prophylactic antibiotics after HPE. The use of steroids after HPE failed to predict jaundice-free, jaundice-free within 3 months, liver transplantation, native liver survival, or jaundice-free native liver survival in our cohort. A large-scale clinical trial demonstrated that steroid therapy following HPE did not result in statistically significant treatment differences in bile drainage at 6 months in BA infants is also supporting our observation.[29]

A major limitation of this framework is the unsatisfactory NPV, which may result from the nature of retrospective designed and relatively small sample size. Since BA is a rare disease in Taiwan, it is difficult to have a very large sample in a single center.[5] Our current study has proven that the serum T-bil ≤4.85 mg/dL 1 week after HPE is already predictable of clinical outcomes after HPE in BA children. Further larger cohort may be needed in the future to elucidate which marker is better in the outcome prediction. In addition, we did not assess the size of small ductules communicating with the bile ducts of these surgical specimens in this study,[35] because some pathology specimens were unable to be retrieved.

In conclusion, we report that a T-bil level ≤4.85 mg/dL at 1 week after HPE, a very early timing, was correlated with jaundice-free at 3 months after HPE and also with long-term native and jaundice-free native liver survival in BA children.

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AUTHOR CONTRIBUTIONS

C.-Y.H. and J.-F.W. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. C.-Y.H. wrote the manuscript. C.-Y.H., M.-H.C., and J.-F.W.: study concept, design and contribution to study design. C.-Y.H. and J.-F.W.: acquisition of data, analysis and interpretation of data, statistical analysis. C.-Y.H.: drafting of the manuscript. M.-H.C., H.-L.C., Y.-H.N., H.-Y.H., and J.-F.W.: critical revision of the manuscript for important intellectual content. M.-H.C., H.-L.C., Y.-H.N., and H.-Y.H.: administrative, technical support. J.-F.W.: obtained funding, study supervision. All authors have seen and approved the submission of this version of the manuscript and take full responsibility for the manuscript.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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