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ORIGINAL ARTICLE

Hepatology

Serum bile acids early after portoenterostomy are predictive for native liver survival and portal hypertension in biliary atresia

Linda Anderson[1] | **Maria Hukkinen**[1] | **Iiris Nyholm**[1,2] | **Mikko Niemi**[3,4,5] | **Mikko P. Pakarinen**[1,2,6]

[1]Section of Pediatric Surgery, Pediatric Liver and Gut Research Group, New Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[2]Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[3]Department of Clinical Pharmacology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[4]Department of Clinical Pharmacology, HUS Diagnostic Center, Helsinki University Hospital, Helsinki, Finland

[5]Individualized Drug Therapy Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland

[6]Department of Women's and Children's Health, Karolinska Institute, Stockholm, Sweden

Correspondence

Maria Hukkinen, Section of Pediatric Surgery, Pediatric Liver and Gut Research Group, New Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland.
Email: maria.hukkinen@hus.fi

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Abstract

Objectives: To compare the predictive value of serum bile acids on native liver survival (NLS) and portal hypertension (PH) at various time points early after portoenterostomy (PE) in biliary atresia (BA).

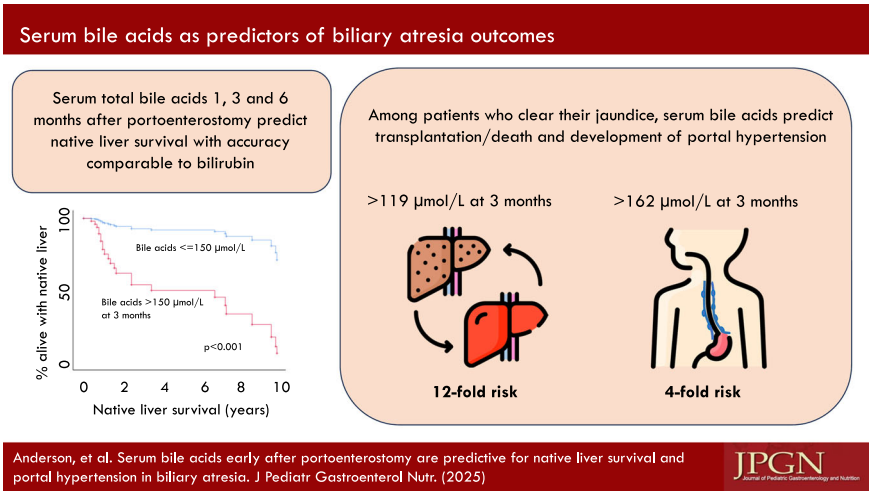
Methods: This was a retrospective observational study. Serum bilirubin and bile acid concentrations were defined by enzymatic spectrophotometry 1, 3, and 6 months after PE. After defining optimal bilirubin and bile acids cutoffs by area under the receiver operating characteristic (AUROC) curves, cutoffs were compared with other predictors of NLS and PH in Cox regression.

Results: Out of 56 patients, 42 (75%) achieved clearance of jaundice (COJ, bilirubin <20 μmol/L at 6 months). Both bilirubin and bile acids at 3 and 6 months were accurate predictors of NLS among all patients (AUROC 0.82–0.91, $p < 0.001$). In COJ patients, bile acids (AUROC 0.82, $p = 0.003$), but not bilirubin, at 1 month also predicted NLS. Among all patients, the strongest predictors of NLS were bilirubin >18.5 μmol/L and bile acids >150 μmol/L at 3 months, increasing the risk of transplantation/death seven- and eightfold, respectively ($p < 0.001$ for both). In COJ patients, the strongest predictor of NLS was bile acids >119 μmol/L at 3 months, increasing the risk of transplantation/death 12-fold ($p = 0.014$). Bile acids and bilirubin at 3 and 6 months predicted PH development in COJ patients with moderate accuracy (AUROC 0.72–0.78, $p = 0.004$–0.019). Bilirubin >8.5 μmol/L and bile acids >78 μmol/L at 6 months increased PH risk 13-fold ($p < 0.001$) and 4-fold ($p = 0.006$).

Conclusions: Serum bile acids offer a simple and useful additional tool to predict PE outcomes in BA, particularly after COJ.

Abbreviations: APRi, aspartate aminotransferase to platelet ratio index; AUROC, area under the receiving operating characteristic; BA, biliary atresia; BASM, BA splenic malformation; CI, confidence interval; COJ, clearance of jaundice; GGT, gamma-glutamyl transferase; HR, hazard ratio; LT, liver transplantation; NLS, native liver survival; PE, portoenterostomy; PH, portal hypertension; UDCA, ursodeoxycholic acid.

Linda Anderson and Maria Hukkinen shared the first authorship.



KEYWORDS

clearance of jaundice, esophageal varices, liver transplantation

1 | INTRODUCTION

Biliary atresia (BA) is a rare fibroinflammatory cholangiopathy that ultimately leads to cholestatic cirrhosis due to ascending destruction of intrahepatic bile ducts.[1] BA is diagnosed among newborns and accounts for most of childhood liver transplantations (LTs) globally.[2] Primary treatment of BA is portoenterostomy (PE), which involves the replacement of the extrahepatic bile ducts with a jejunal conduit, with the goal of preventing disease progression by restoring bile flow.[3] Over half of the patients achieve clearance of jaundice (COJ) after PE, indicated by normalization of serum bilirubin within 6 months.[4–6]

The chronic BA cholangiopathy progresses variably after PE.[7] While unsuccessful PE necessitates early LT almost uniformly, close to 20% of patients require LT within the first 2 years and around half of the patients before adulthood following successful PE.[6,8,9] Portal hypertension (PH) and esophageal varices develop in over two thirds of children by school age.[9,10] Frequent follow-ups and surveillance endoscopies are utilized to identify patients whose liver disease progresses rapidly and those who may develop life-threatening variceal bleeding.[11] Although postoperative serum bilirubin level is associated with native liver survival (NLS),[6,12–15] currently no accurate means exists to predict the development of clinical liver disease complications, especially after successful PE.

Accumulation of bile acids is considered the principal driver of liver injury in cholestatic conditions.[16] Serum bile acids measured at 6 months or thereafter following PE have been demonstrated to predict complications of liver disease as well as NLS.[17] The purpose of this study was to examine whether easily available measurement of serum total bile acids predict such outcomes even earlier after PE, and to compare their prognostic value to postoperative bilirubin levels.

What is Known

- There is a need for reliable, early markers of liver disease progression in biliary atresia.
- Serum total bile acids at 6 months after successful portoenterostomy (PE) associated with clinical outcomes.

What is New

- Serum total bile acids at 3 and 6 months after PE predicted native liver survival (NLS) with accuracy comparable to bilirubin.
- Among patients who cleared their jaundice, serum bile acids already at 1 month after PE predicted NLS, and at 3 and 6 months, both NLS and development of portal hypertension.

2 | METHODS

2.1 | Patients and study design

This was a retrospective study including all BA patients who underwent PE at Helsinki University Hospital during 2005–2022. Exclusion criteria were indeterminate COJ status in patients who deceased soon after PE due to severe associated malformations ($n = 2$) or primary LT due to late presentation ($n = 1$). In 2005, the management of BA in Finland was centralized at Helsinki University Hospital, which is also responsible for the nationwide LT

program.[18] The study protocol was approved by the research ethics committee (345/13/03/03/2008) and hospital review board (§70HUS/284/2019), and it conforms to the Declaration of Helsinki.

2.2 | Clinical management

The diagnosis of BA was confirmed by intraoperative cholangiography when possible and histopathology of the liver and biliary remnants in all cases. Ursodeoxycholic acid (UDCA, 50 mg/kg/day) was routinely started after PE as soon as enteral intake was resumed. In addition, dexamethasone was administered with decreasing doses during the first postoperative month, and antibiotic prophylaxis was continued for no less than the first year.[18] Primary prophylaxis of esophageal variceal bleeding was implemented in annual upper GI endoscopies initiating at age of 12 months or earlier after unsuccessful PE if bleeding was suspected.[18,19] Grade ≥2 esophageal varices were eradicated by using endoscopic sclerotherapy or band ligation.[18,19] Patients underwent abdominal ultrasound and serum liver biochemistry measurement at follow-up visits 3, 6, 9, and 12 months after PE and thereafter at least annually in Helsinki.[18]

2.3 | Data collection and definitions

Clinical baseline characteristics and Metavir stage at the time of PE were collected.[20] Metavir Stages 3 and 4 were considered as advanced fibrosis. COJ was defined as normalization of total bilirubin (<20 μmol/L) within 6 months of PE. PH was defined as the presence of ≥Grade 2 esophageal varices or thrombocytopenia ($<150 \times 10^9$/L) in association with splenomegaly (spleen length ≥2 *z*-scores above the age- and sex-specific reference values) as assessed by ultrasound examination.[10,21]

2.4 | Serum bilirubin and bile acids measurements

Serum total bilirubin and bile acid concentrations measured immediately before or at the time of PE as well as 1, 3, and 6 months after PE were registered. Serum bilirubin and total bile acids were measured from nonfasting serum samples using the standard methods of the accredited hospital laboratory. Enzymatic spectrophotometry (reagent by Sentinel Diagnostics®, Siemens Healthineer Atellica CH Analyzer) was used to define total bile acids concentrations.[22] The upper limit of normal for total serum bile acids was considered 6 μmol/L according to the hospital laboratory reference limits. For a subset of patients, also individual conjugated and unconjugated serum bile acids were quantified using high-performance liquid chromatography–tandem mass spectrometry.[23]

2.5 | Statistical methods

Continuous variables were expressed as medians with interquartile ranges (IQRs) unless otherwise stated. Spearman rank correlation was used to examine associations between continuous variables. Fisher exact test and Mann–Whitney *U* test were used for group comparisons, and the Wilcoxon signed-rank test was used for paired data. Receiver operating characteristic (ROC) curves and area under the ROC (AUROC) curves were used to define optimal cutoff values with the maximum sum of sensitivity and specificity for detection of LT or death and PH development. Dichotomous variables were created based on optimal cutoff values, and these variables were used as predictors of transplant- and PH-free survival in Cox proportional hazards regression models. NLS was defined from birth to last follow-up visit, date of LT or death, and PH-free survival was defined from birth until the date of PH diagnosis. Bile acids and bilirubin measurement with the best predictive value in univariable regression (1, 3, or 6 months after PE) was selected for the multivariable regression model, along with other statistically significant predictors. The level of significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Patient characteristics

Altogether 56 patients were included, of which 42 (75%) achieved COJ after PE. The median age at PE was 54 days in COJ patients as opposed to 78 days in non-COJ patients (Table 1). Most patients (95%) had Type 3 BA, and 11% had BA splenic malformation (BASM). Advanced liver fibrosis (Metavir Stages 3 and 4) was diagnosed in 38% of patients at the time of PE. At the latest follow-up, 29 (52%) patients were alive with their NL and 23 (41%) with LT, while no patient was currently listed for LT. Median NLS was 6.3 years among all patients while 7.5 years in COJ patients (Table 1). During follow-up, PH was diagnosed in 36 patients (64%) at the median age of 2.1 (1.1–6.6) years, and ≥Grade 2 esophageal varices were detected in 22 (39%) patients.

3.2 | Serum bile acids

Preoperative serum bile acid levels showed no difference between COJ and non-COJ groups. After COJ, serum bile acids decreased significantly but, unlike bilirubin, remained markedly elevated without reaching normal levels (Table 1, Figure 1). In contrast, after unsuccessful PE, bile acids showed no postoperative decline and at 3 months were significantly higher compared to preoperative values (Table 1, Figure 1).

TABLE 1 Patient characteristics.

	All patients ($n = 56$)	COJ ($n = 42$)	No COJ ($n = 14$)	p
Type of BA, *n* (%)				
1	1 (1.8)	1 (2.4)	0 (0)	
2	2 (3.6)	2 (4.8)	0 (0)	
3	53 (94.6)	39 (92.9)	14 (100)	0.57
Age at PE, d	58 (34–80)	54 (25–73)	78 (47–95)	0.038
Associated malformations, *n* (%)	19 (33.9)	14 (33)	5 (36)	1.0
BASM, n (%)	6 (10.7)	4 (9.5)	2 (14)	0.47
PH, *n* (%)	36 (64.3)	26 (61.9)	10 (71.4)	0.037
LT, *n* (%)	26 (46)	13 (31)	13 (93)	<0.001
Advanced fibrosis, *n* (%)	21 (38)	16 (38)	5 (36)	0.21
Esophageal varices, *n* (%)	22 (39.3)	18 (42.9)	4 (28.6)	0.53
Preoperative bilirubin	168 (129–203)	169 (123–206)	163 (142–200)	0.68
Bilirubin at 1 mo (μmol/L)	61 (26–102)[1]	38 (18–64)	147 (99–215)	<0.001
Bilirubin at 3 mo (μmol/L)	16 (7–30)[2]	10 (5–20)	151 (92–288)	<0.001
Bilirubin at 6 mo (μmol/L)	11 (6–37)[3]	8 (4–15)	265 (39–389)	<0.001
Preoperative bile acids	169 (130–229)	165 (125–228)	169 (140–298)	0.52
Bile acids at 1 mo	114 (81–210)[4]	106 (71–164)	220 (104–254)	0.005
Bile acids at 3 mo	122 (48–194)[5]	98 (39–162)	340 (149–417)	<0.001
Bile acids at 6 mo	82 (43–221)[6]	61 (41–138)	262 (139–490)	0.001
Follow-up time (years)[a]	6.3 (1.4-10)	7.5 (5.3-13)	0.9 (0.8-1.3)	<0.001

Note: Data missing for [1]2, [2]3, [3]4, [4]7, [5]1, and [6]9 patients. Bilirubin and bile acids are expressed as μmol/L.

Abbreviations: BA, biliary atresia; BASM, BA splenic malformation; COJ, clearance of jaundice; d, days; LT, liver transplantation; mo, months after PE; PE, portoenterostomy; PH, portal hypertension.

[a]Time to latest follow-up visit, LT, or death.

Altogether 11 patients underwent quantification of individual bile acid species median 160 (38–236) days after PE. In these measurements, total bile acid concentration was 28% (–8% to 40%) lower compared to the enzymatic routine hospital laboratory method (70 [51–114] μmol/L vs. 106 [47–205] μmol/L) and included 61% (50%–66%) of UDCA.

3.3 | Prediction of NLS

Among all patients, high AUROC values for NLS were observed for both serum bilirubin (0.84–0.91, $p < 0.001$ for all) and bile acids (0.82–0.87, $p < 0.001$ for all) at 1, 3, and 6 months after PE (Table S1). The highest AUROC values were recorded at 3 months for both serum bilirubin (0.91) and bile acids (0.87) (Table S1).

In COJ patients, the highest AUROC value was observed for bile acids at 3 months (0.85, $p = 0.001$) and bilirubin at 6 months (0.86, $p < 0.001$) (Table S1). Notably, at 1 month, bile acids predicted NLS with good accuracy (0.82, $p = 0.003$), whereas bilirubin did not (0.67, $p = 0.105$) (Table S1). Although preoperative bile acids were not associated with NLS, decreasing bile acids at 3 months predicted NLS with good accuracy in all patients (0.85, $p < 0.001$) and with moderate accuracy in COJ patients (0.77, $p = 0.005$) (Table S2).

The optimal cutoff values were determined to create dichotomous variables for regression analyses (Tables S1–S3). In univariable regression including all patients, the presence of BASM as well as bilirubin and bile acids 1, 3, and 6 months after PE predicted NLS (Table 2). Bilirubin and bile acids at 3 months after PE were associated with the highest risk of LT or death and were included in the multivariable model. Both variables remained significant predictors of NLS, with bilirubin >18.5 μmol/L increasing the risk by sevenfold and bile acids >150 μmol/L over eightfold (Table 2, Figure 1).

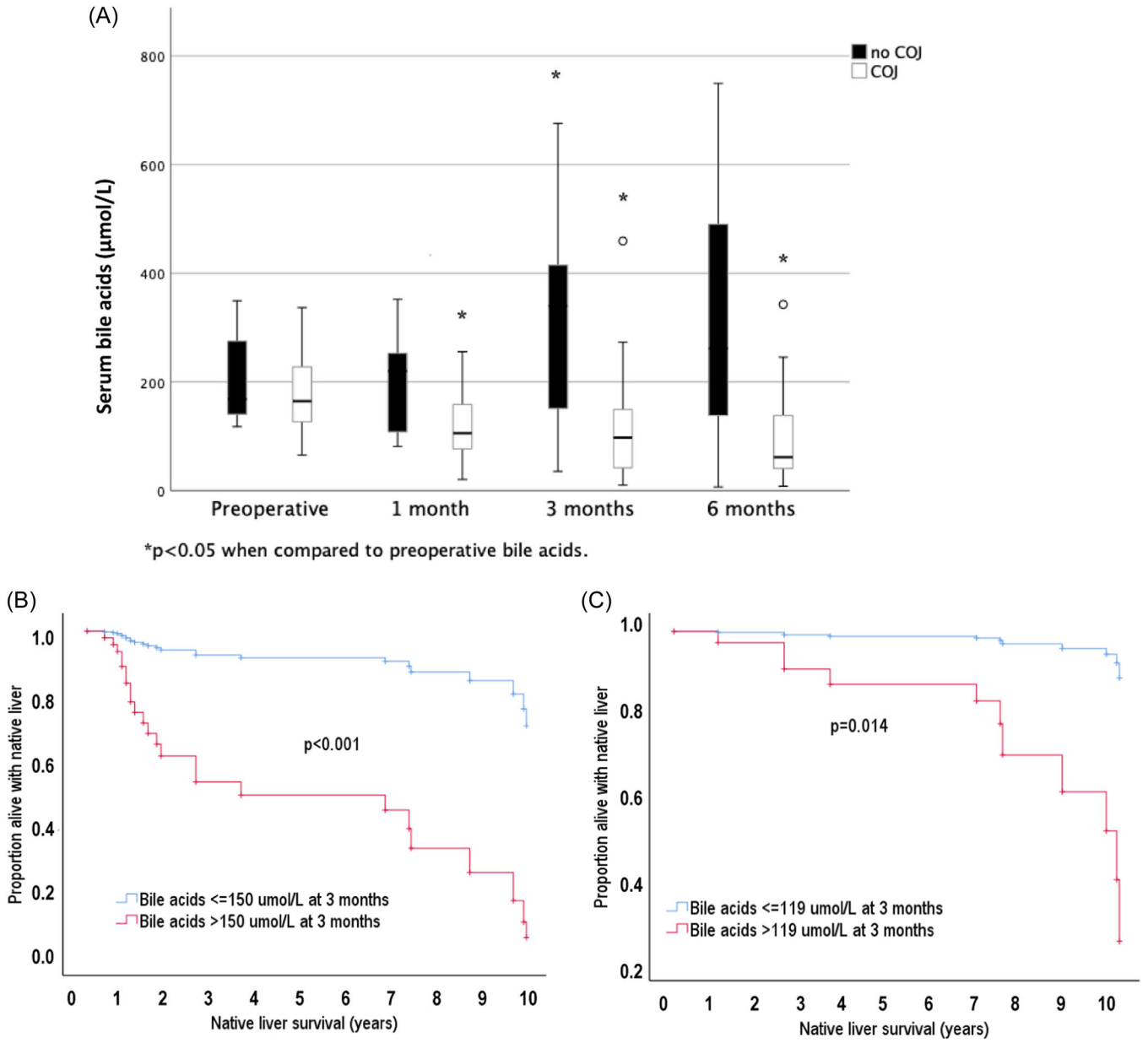


FIGURE 1 (A) Serum bile acids according to COJ. Boxplots represent median values with IQR. Dots correspond to outlier values. (B) Cumulative native liver survival in all patients according to bile acids 3 months after PE ($n = 56$). (C) Cumulative native liver survival in COJ patients according to bile acids 3 months after PE ($n = 42$). Cutoffs represent the optimal cutoffs with maximal sum of sensitivity and specificity from AUROC analyses. AUROC, area under the receiver operating characteristic; COJ, clearance of jaundice; IQR, interquartile range; PE, portoenterostomy.

In COJ patients, the strongest predictors of NLS were BASM, preoperative bilirubin, bilirubin >18.5 µmol/L at 3 months, and bile acids >119 µmol/L at 3 months after PE (Table 3). In the multivariable model, only bile acids at 3 months after PE remained a significant predictor, with values >119 µmol/L increasing the risk of LT or death 12-fold (Table 3, Figure 1).

3.4 | Prediction of PH after COJ

Prediction of PH was analyzed only after COJ as the non-COJ group included only 14 patients, 13 of whom underwent early LT at the median age of 0.5 (0.7–1.2) years. Both bile acids and bilirubin at 3 and 6 months after PE showed moderate accuracy in predicting the development of PH in COJ patients (Table S3). In univariable regression, bilirubin >8.5 µmol/L at 6 months after PE was the strongest predictor for development of PH (hazard ratio [HR]: 13, 95% confidence interval [CI]: 3.6–44, $p < 0.001$), whereas bile acids >78 µmol/L at 6 months (HR: 3.9, 95% CI: 1.5–10, $p = 0.006$) and >162 µmol/L at 3 months (HR: 3.7, 95% CI: 1.6–8.7, $p = 0.002$) as well as bilirubin >10 µmol/L at 3 months (HR: 5.1, 95% CI: 2.1–12, $p < 0.001$) were also significant. Other patient

TABLE 2 Predictors of native liver survival in all patients. Results obtained from Cox proportional hazards regression model (total $n = 56$).

	Univariable		Multivariable	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
Age at PE (continuous)	1.01 (-)	0.117		
Age >60 days at PE	1.1 (0.5–2.3)	0.819		
Associated malformations	1.8 (0.8–3.8)	0.138		
BASM	4.0 (1.6–10)	0.004	0.9 (0.3–2.8)	0.842
Type of BA (3 vs. 1/2)	24 (0.06–8900)	0.296		
Advanced fibrosis at PE	1.2 (0.5–2.9)	0.615		
Preoperative bilirubin >173 μmol/L	2.03 (0.9–4.4)	0.077		
Bilirubin >67 μmol/L at 1 mo	5.4 (2.3–12)	<0.001		
Bilirubin >18.5 μmol/L at 3 mo	8.2 (3.04–22)	<0.001	7.0 (2.2–22)	<0.001
Bilirubin >18.5 μmol/L at 6 mo	5.3 (2.3–12)	<0.001		
Bile acids >116 μmol/L at 1 mo	3.4 (1.4–8.1)	0.007		
Bile acids >150 μmol/L at 3 mo	8.6 (3.5–21)	<0.001	8.2 (2.8–24)	<0.001
Bile acids >110 μmol/L at 6 mo	5.6 (2.2–15)	<0.001		
Bile acids >40 μmol/L at 6 mo[a]	0.85 (0.35–2.0)	0.71		
Change at 3 mo <19.55 μmol/L ($n = 46$)	2.1 (0.77–5.7)	0.15		

Abbreviations: BA, biliary atresia; BASM, BA splenic malformation; Change at 3 mo, change in serum bile acids at 3 months compared to preoperative values; CI, confidence interval; HR, hazard ratio; mo, months after PE; PE, portoenterostomy.
[a]Based on reference[17].

TABLE 3 Predictors of native liver survival in COJ patients ($n = 42$). Results obtained from Cox proportional hazards regression model.

	Univariable		Multivariable	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
Age at PE (continuous)	1.00 (-)	0.816		
Age >60 days at PE	0.7 (0.2–2.1)	0.519		
Associated malformations	2.8 (0.9–8.5)	0.065		
BASM	13 (3.1–53)	<0.001	3.9 (0.7–22)	0.120
Type of BA (3 vs. 1/2)	24 (0.01–85,000)	0.403		
Advanced fibrosis at PE	1.6 (0.4–5.9)	0.505		
Preoperative bilirubin >173 μmol/L	6.6 (1.5–30)	0.014	1.0 (-)	0.308
Bilirubin >36 μmol/L at 1 mo	1.3 (0.4–4.2)	0.678		
Bilirubin >18.5 μmol/L at 3 mo	5.4 (1.6–18)	0.006	3.7 (0.8–18)	0.106
Bilirubin >10 μmol/L at 6 mo	5.1 (1.4–19)	0.014		
Bile acids >116 μmol/L at 1 mo	3.2 (0.99–11)	0.052		
Bile acids >119 μmol/L at 3 mo	6.8 (1.8–26)	0.005	12 (1.6–82)	0.014
Bile acids >138 μmol/L at 6 mo	4.5 (1.4–15)	0.013		
Bile acids >40 μmol/L at 6 mo[a]	0.86 (0.36–2.1)	0.74		
Change at 3 mo (<19.55 μmol/L)	0.49 (0.18–1.34)	0.17		

Abbreviations: BA, biliary atresia; BASM, BA splenic malformation; Change at 3 mo, change in serum bile acids at 3 months compared to preoperative values; CI, confidence interval; COJ, clearance of jaundice; HR, hazard ratio; mo, months after PE; PE, portoenterostomy.
[a]Based on reference[17].

characteristics were unrelated to the risk of PH, and none of the included variables remained significant in multivariable regression.

4 | DISCUSSION

This is the first study comparing the predictive value of bile acids and bilirubin at different postoperative time points following PE. Our findings suggest that serum total bile acid level, measured early after PE, is a valuable additional tool in predicting transplant-free survival following PE in patients with BA. In the whole sample, serum bile acid concentration >116 μmol/L at 1 month, >150 μmol/L at 3 months, and >119 μmol/L at 3 months in COJ patients strongly predicted decreased NLS.

Several studies have analyzed the value of different biomarkers in the prediction of BA outcomes.[24,25] Serum fibroblast growth factor 19 predicted NLS at time of PE, but its cutoffs await further validation in independent patient cohorts.[26] Predictive values of other biomarkers measured at time of PE, such as aspartate aminotransferase (AST) to platelet ratio index (APRi),[27,28] gamma-glutamyl transferase (GGT),[29–31] and albumin[32] have remained moderate at best. APRi, AST, alanine aminotransferase, albumin, and GGT[13,31,33] as well as matrix metalloproteinase 7[34] measured 1–3 months after PE associated to variable degree with NLS. However, none of these markers has outperformed serum bilirubin measured during the first months after PE which remains the gold standard and the mostly utilized predictor of transplant-free survival.[13–15,35] Accordingly, in our cohort, serum total bile acids measured with routine hospital laboratory methods at 1, 3, and 6 months after PE, predicted NLS with high accuracies comparable to bilirubin. However, unlike bilirubin, serum total bile acids showed a significant predictive ability for NLS already at 1 month after PE in COJ patients, demonstrating its additional prognostic value following a successful PE.

Cholestasis leads to accumulation of bile acids, which in high concentrations promotes tissue damage and activates different pro-inflammatory pathways further contributing to liver injury.[36] Inflammation-induced downregulation of bile acid transporters, on the other hand, has been shown to promote cholestasis even before obstruction of the extrahepatic biliary tree in a BA murine model.[37] Thus, bile acid accumulation plays a central role in the development of liver injury in BA, explaining its predictive ability. Considering the ability of bile acid levels to predict outcomes in various other cholestatic diseases,[38,39] it is not surprising that they are also associated with liver disease complications in BA. In addition to predicting NLS, bile acids and bilirubin are also associated with the development of PH in patients with COJ. However, optimal predictive cutoffs for bilirubin at 3 and 6 months were below the normal upper limit (<20 μmol/L), which may confuse their clinical use. Serum bile acids measured during a long-term follow-up after PE have been shown to correlate with the severity of ductular reaction, which, in turn, predicts NLS.[7]

Replacement of cytotoxic, hydrophobic bile acids from the bile acid pool is one of the numerous mechanisms of UDCA.[40] Similar to adults with chronic cholangiopathies,[40] UDCA slightly decreases serum total bile acids also in children with various cholestatic diseases.[41] Accordingly, in a previous study among BA patients, serum total bile acids were not affected by UDCA use, and COJ patients had similar bile acid levels at 6 months compared to our COJ subgroup.[17] These observations suggest that serum total bile acid concentration rather reflects the severity of liver disease than UDCA use and makes our results applicable to other COJ cohorts. In the study by Harpavat et al., a serum bile acid cutoff of 40 μmol/L was used as a predictor of poor outcomes without performing statistical analyses to justify cutoff selection.[17] We consider our higher bile acid cutoffs reliable as they were chosen according to AUROC analyses. In future studies, individual bile acid concentrations should preferably be defined and correlated to UDCA use and patient outcomes to better understand their interplay.

Among the strengths of this study were repeated measurement of bile acids at certain postoperative time points, the long follow-up period, and uniform treatment and follow-up strategies. This is also the first study to analyze serum bile acid levels longitudinally early after PE and compare their predictive value at different time points. The relatively small sample size is a limitation, and we analyzed serum UDCA fractions only in a subset of patients. However, centralized management of BA enabled comprehensive and complete collection of clinical data, including all BA patients undergoing PE nationwide.

In conclusion, the measurement of serum total bile acids offers a simple and useful additional tool to predict PE outcomes in BA. Studies in larger independent patient cohorts are needed to validate the cutoffs and evaluate further the role of bile acids in various liver disease complications in BA.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Maria Hukkinen http://orcid.org/0000-0002-2622-8391

REFERENCES

1. Bezerra JA, Wells RG, Mack CL, et al. Biliary atresia: clinical and research challenges for the twenty-first century. *Hepatology*. 2018;68:1163-1173.
2. de Ville de Goyet J, Baumann U, Karam V, et al. European Liver Transplant Registry: donor and transplant surgery aspects of 16,641 liver transplantations in children. *Hepatology*. 2022;75:634-645.
3. Hartley JL, Davenport M, Kelly DA. Biliary atresia. *Lancet*. 2009;374:1704-1713.
4. Davenport M, Makin E, Ong EG, Sharif K, Dawrant M, Alizai N. The outcome of a centralization program in biliary atresia: 20 years and beyond. *Ann Surg*. Published online March 20, 2024. doi:10.1097/SLA.0000000000006273
5. Pakarinen MP, Johansen LS, Svensson JF, et al. Outcomes of biliary atresia in the Nordic countries—a multicenter study of 158 patients during 2005-2016. *J Pediatr Surg*. 2018;53:1509-1515.
6. Witt M, van Wessel DBE, de Kleine RHJ, Bruggink JLM, Hulscher JBF, Verkade HJ. Prognosis of biliary atresia after 2-year survival with native liver: a nationwide cohort analysis. *J Pediatr Gastroenterol Nutr*. 2018;67:689-694.
7. Nyholm I, Sjöblom N, Pihlajoki M, et al. Deep learning quantification reveals a fundamental prognostic role for ductular reaction in biliary atresia. *Hepatol Commun*. 2023;7:e0333.
8. Fanna M, Masson G, Capito C, et al. Management of biliary atresia in France 1986 to 2015: long-term results. *J Pediatr Gastroenterol Nutr*. 2019;69:416-424.
9. Hukkinen M, Ruuska S, Pihlajoki M, Kyrönlahti A, Pakarinen MP. Long-term outcomes of biliary atresia patients surviving with their native livers. *Best Pract Res Clin Gastroenterol*. 2022;56-57:101764.
10. Shneider BL, Abel B, Haber B, et al. Portal hypertension in children and young adults with biliary atresia. *J Pediatr Gastroenterol Nutr*. 2012;55:567-573.
11. Duché M, Ducot B, Ackermann O, Guérin F, Jacquemin E, Bernard O. Portal hypertension in children: high-risk varices, primary prophylaxis and consequences of bleeding. *J Hepatol*. 2017;66:320-327.
12. Hukkinen M, Kerola A, Lohi J, Jahnukainen T, Heikkilä P, Pakarinen MP. Very low bilirubin after portoenterostomy improves survival of the native liver in patients with biliary atresia by deferring liver fibrogenesis. *Surgery*. 2019;165:843-850.
13. Nightingale S, Stormon MO, O'Loughlin EV, et al. Early post-hepatoportoenterostomy predictors of native liver survival in biliary atresia. *J Pediatr Gastroenterol Nutr*. 2017;64:203-209.
14. Superina R, Magee JC, Brandt ML, et al. The anatomic pattern of biliary atresia identified at time of Kasai hepatoportoenterostomy and early postoperative clearance of jaundice are significant predictors of transplant-free survival. *Ann Surg*. 2011;254:577-585.
15. Shneider BL, Magee JC, Karpen SJ, et al. Total serum bilirubin within 3 months of hepatoportoenterostomy predicts short-term outcomes in biliary atresia. *J Pediatr*. 2016;170:211-217.e2.
16. Karpen SJ, Kelly D, Mack C, Stein P. Ileal bile acid transporter inhibition as an anticholestatic therapeutic target in biliary atresia and other cholestatic disorders. *Hepatol Int*. 2020;14:677-689.
17. Harpavat S, Hawthorne K, Setchell KDR, et al. Serum bile acids as a prognostic biomarker in biliary atresia following Kasai portoenterostomy. *Hepatology*. 2023;77:862-873.
18. Hukkinen M, Kerola A, Lohi J, et al. Treatment policy and liver histopathology predict biliary atresia outcomes: results after national centralization and protocol biopsies. *J Am Coll Surg*. 2018;226:46-57.e1.
19. Lampela H, Kosola S, Koivusalo A, et al. Endoscopic surveillance and primary prophylaxis sclerotherapy of esophageal varices in biliary atresia. *J Pediatr Gastroenterol Nutr*. 2012;55:574-579.
20. Hukkinen M, Lohi J, Heikkilä P, et al. Noninvasive evaluation of liver fibrosis and portal hypertension after successful portoenterostomy for biliary atresia. *Hepatol Commun*. 2019;3:382-391.
21. Megremis SD, Vlachonikolis IG, Tsilimigaki AM. Spleen length in childhood with US: normal values based on age, sex, and somatometric parameters. *Radiology*. 2004;231:129-134.
22. Mashige F, Tanaka N, Maki A, Kamei S, Yamanaka M. Direct spectrophotometry of total bile acids in serum. *Clin Chem*. 1981;27:1352-1356.
23. Xiang X, Han Y, Neuvonen M, Laitila J, Neuvonen PJ, Niemi M. High performance liquid chromatography-tandem mass spectrometry for the determination of bile acid concentrations in human plasma. *J Chromatogr B*. 2010;878:51-60.
24. Kong F, Dong R, Chen G, et al. Progress in biomarkers related to biliary atresia. *J Clin Translat Hepatol*. 2024;12:305-315.
25. He L, Ip DKM, Tam G, Lui VCH, Tam PKH, Chung PHY. Biomarkers for the diagnosis and post-Kasai portoenterostomy prognosis of biliary atresia: a systematic review and meta-analysis. *Sci Rep*. 2021;11:11692.
26. Nyholm I, Hukkinen M, Pihlajoki M, et al. Serum FGF19 predicts outcomes of Kasai portoenterostomy in biliary atresia. *Hepatology*. 2023;77:1263-1273.
27. Muntean A, Kronfli R, Makin E, Davenport M. The AST-to-platelet ratio index (APRi) at Kasai portoenterostomy: standing the test of time. *J Pediatr Surg*. 2023;58:2347-2351.
28. Suominen JS, Lampela H, Heikkilä P, Lohi J, Jalanko H, Pakarinen MP. APRi predicts native liver survival by reflecting portal fibrogenesis and hepatic neovascularization at the time of portoenterostomy in biliary atresia. *J Pediatr Surg*. 2015;50:1528-1531.
29. Sun S, Zheng S, Shen C, et al. Low gamma-glutamyl transpeptidase levels at presentation are associated with severity of liver illness and poor outcome in biliary atresia. *Front Pediatr*. 2022;10:956732.
30. Goda T, Kawahara H, Kubota A, et al. The most reliable early predictors of outcome in patients with biliary atresia after Kasai's operation. *J Pediatr Surg*. 2013;48:2373-2377.
31. Koga H, Wada M, Nakamura H, et al. Factors influencing jaundice-free survival with the native liver in post-portoenterostomy biliary atresia patients: results from a single institution. *J Pediatr Surg*. 2013;48:2368-2372.
32. Machino K, Mimori K, Ogata S, et al. Pre-operative serum albumin predicts native liver survival in biliary atresia. *Afr J Paediatr Surg*. 2024;21:232-235. doi:10.4103/ajps.ajps_158_22
33. Ihn K, Ho IG, Chang EY, Han SJ. Correlation between gamma-glutamyl transpeptidase activity and outcomes after Kasai portoenterostomy for biliary atresia. *J Pediatr Surg*. 2018;53:461-467.
34. Chi S, Xu P, Yu P, et al. Dynamic analysis of serum MMP-7 and its relationship with disease progression in biliary atresia: a multicenter prospective study. *Hepatol Int*. 2022;16:954-963.
35. Hukkinen M, Pihlajoki M, Pakarinen MP. Predicting native liver injury and survival in biliary atresia. *Semin Pediatr Surg*. 2020;29:150943.
36. Bertolini A, Fiorotto R, Strazzabosco M. Bile acids and their receptors: modulators and therapeutic targets in liver inflammation. *Semin Immunopathol*. 2022;44:547-564.
37. Yang H, Plösch T, Lisman T, et al. Inflammation mediated down-regulation of hepatobiliary transporters contributes to intrahepatic cholestasis and liver damage in murine biliary atresia. *Pediatr Res*. 2009;66:380-385.
38. Mousa OY, Juran BD, McCauley BM, et al. Bile acid profiles in primary sclerosing cholangitis and their ability to predict hepatic decompensation. *Hepatology*. 2021;74:281-295.
39. van Wessel DBE, Thompson RJ, Gonzales E, et al. Impact of genotype, serum bile acids, and surgical biliary diversion on native liver survival in FIC1 deficiency. *Hepatology*. 2021;74:892-906.
40. Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. *Hepatology*. 2002;36:525-531.

41. Huang L, Li S, Chen J, et al. Efficacy and safety of ursodeoxycholic acid in children with cholestasis: a systematic review and meta-analysis. *PLoS One*. 2023;18:e0280691.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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