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Original Article

Post-hepatoportoenterostomy Acoustic Radiation Force Impulse Elastography to Predict Two-year Outcome of Biliary Atresia

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Abstract

Background and Aims: Early identification of prognostic factors to predict transplant/death outcome of biliary atresia (BA) is challenging. We aimed to investigate the longitudinal changes and predictive value of dynamic changes in acoustic radiation force impulse elastography with shear wave speed (SWS) quantification and other parameters within three months after hepatoportoenterostomy (HPE) for 2-year BA outcomes. ***Methods:*** Seventy-four patients who underwent HPE between July 2016 and June 2019 were prospectively enrolled. Outcomes were classified into native liver survival and transplant/death groups. Acoustic radiation force impulse elastography was performed sequentially at 3 months intervals post-HPE. Cox regression analysis was used to determine the superior SWS values and other predictors of liver transplantation or death. ***Results:*** Among patients 2 years of age, 36 survived with a native liver, nine died, and 29 underwent liver transplantation. The trend in SWS levels in the transplant/death group was significantly different from that in the native liver survival group. ΔSWS at 1–3 months post-HPE and total bilirubin at 1 month post-HPE were selected as superior predictors of liver transplantation or death using multivariate Cox regression models: hazard ratio (HR)=1.927; 95% confidence interval (CI): 1.475–2.661; $p<0.001$ and HR=1.010; 95% CI: 1.003–1.017; $p=0.007$, respectively. The combination of the selected ΔSWS and total bilirubin had good predictive power, with an area under the receiver operating characteristics curve of 0.89, specificity 94.44% and sensitivity 73.68%. ***Conclusions:*** Our results suggest that early postoperative bilirubin levels and SWS changes were reliable predictors of 2-year BA outcomes.

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Keywords: Biliary atresia; Hepatoportoenterostomy; Acoustic radiation force impulse elastography; Native liver survival; Liver transplantation.

Abbreviations: ARFI, acoustic radiation force impulse; AUC, area under receiver operating characteristic curve; BA, biliary atresia; DBIL, direct bilirubin; GEE, generalized estimating equation; HPE, hepatoportoenterostomy; HR, hazard ratio; NLS, native liver survival; ROC, receiver operating characteristic; TBIL, total bilirubin; TC, triangular cord; US, ultrasonography.

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Introduction

Biliary atresia (BA) is a progressive fibroinflammatory disease of the intra- and extra-hepatic biliary tree that can lead to cirrhosis, end-stage liver disease, and death by 2 years of age if untreated.[1,2] Surgical procedures, such as Kasai hepatoportoenterostomy (HPE) and liver transplantation (LT), are the only curative treatments. HPE is the first-line treatment for BA worldwide.[3] Although effective HPE treatment can re-establish bile drainage and greatly improve prognosis, most patients still have continuous inflammation and fibrosis post-operatively and require LT for long-term survival, which accounts for nearly 50% of all pediatric transplants.[4,5] However, hepatic fibrosis progression and complications of portal hypertension after HPE lead to a need for LT, which is heterogeneous and unpredictable. An early prognostic indicator for post-HPE disease dynamics is crucial to the management of BA patients because late referral for LT could cause pediatric mortality due to the scarcity of donor organs, especially for infants.[5,6]

Although many investigators have examined prognostic factors to identify short- or long-term outcomes of HPE for infants with BA in the early stages, only a few markers may be indicative of the ultimate success of HPE, such as patient age and initial aspartate aminotransferase to platelet ratio index (APRI) at the time of surgery.[1,7–10] Recent reports indicate that postoperative bilirubin levels are markedly associated with native liver survival (NLS) in children.[11,12] Nevertheless, there is a lack of identified reliable and accurate biomarkers to predict postoperative liver deterioration.

Currently, novel ultrasonography (US)-based elasticity tools using acoustic radiation force impulse (ARFI) technology are available and have been proposed for predicting BA outcome.[7] ARFI imaging is a noninvasive, reliable, and consistent tool for grading liver fibrosis. Advancing liver fibrosis

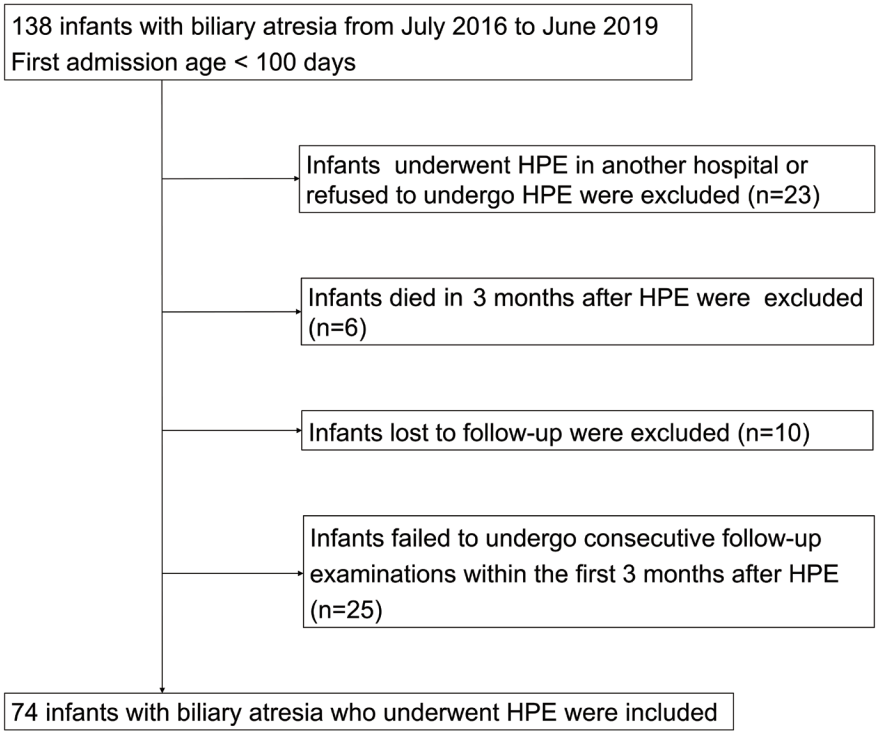

Fig. 1. Flow chart of the study population. HPE, hepatoportoenterostomy

has been shown to predict significantly worse survival.[13,14] Shima *et al*.[15] demonstrated the potential of ARFI to detect fibrosis in eight post-Kasai patients. Hahn *et al*.[16] found that liver stiffness measurement using transient elastography predicted the progression of decompensated hepatic failure with cirrhosis after operation. However, the value in patients after HPE monitoring for poor outcome such as death or transplantation remains unknown, which may also ignore the value of dynamic change. Therefore, it is necessary to explore the predictive value of the postoperative and dynamic changes in patients with BA after HPE. In the current study, we explored the potential practical value of pre- and post-HPE ARFI values, as well as hepatocyte serum biomarkers and their dynamic changes for predicting the 2-year outcomes in a prospective cohort of patients with BA undergoing HPE treatment. Additionally, we built a combination of these significant variables to shed light on the predictive power of this tool for prognosis assessment.

Methods

Study participants

In this prospective observational longitudinal study, 138 infants <100 days of age were consecutively enrolled between July 2016 and June 2019. BA was diagnosed on the basis of intraoperative cholangiography findings that failed to show a patent biliary tree or intraoperative liver biopsy. All infants with BA who received HPE at our hospital were included, while those who underwent HPE at another hospital or refused to undergo HPE were excluded (n=23). All parents or legal guardians were fully informed of the research protocol and they provided written consent. The study was carried out by following the guidelines of Standards for Reporting of Diagnostic Accuracy Studies 2015.[17]

Follow-up and outcomes

The patients were routinely followed-up monthly for the first 3 months after the surgery and then every 3 months until 2 years of age or until an endpoint, i.e. LT or death. Follow-up assessments included serum liver function tests, routine blood tests, and ultrasound examinations. All the children were evaluated using a standardized protocol after the HPE. Low-dose corticosteroids were routinely administered to the patients at one week after the surgery and then gradually tapered until 6 weeks. Antibiotics were administered to patients with cholangitis during the follow-up period. During follow-up visit, surgeon would consider whether to perform LT based on the available clinical information. Indications for LT include recurrent cholestasis, severe portal hypertension, intractable cholangitis, refractory ascites, upper gastrointestinal bleeding, and liver failure.[18,19]

To analyze factors associated with outcomes at 2 years of age, we classified outcomes after the HPE into LT/death and NLS groups. To obtain preoperative and postoperative trajectories for predicting the 2 years outcomes, liver function tests and US were conducted sequentially before and at 1, 2, and 3 months after the HPE. Patients who died in the 3 months after the HPE operation (n=6), were lost to follow-up (n=10), or failed to undergo consecutive follow-up examinations within the first 3 months after the HPE (n=25) were excluded from the analysis. The remaining 74 patients with BA who underwent HPE were finally included in this study (Fig. 1).

Candidate predictors and definitions

The following clinical variables were studied: sex, age, weight at HPE, clayey stool, and hepatomegaly at admission. Liver function variables included gamma-glutamyl transferase (U/L), total bile acid (μmol/L), alanine transaminase (U/L), aspartate transaminase (AST, U/L), alkaline phosphatase

(U/L), total bilirubin (TBIL, μmol/L), direct bilirubin (DBIL, μmol/L), APRI score. The APRI was calculated as AST (IU/L) / AST upper normal limit (IU/L) (38) / platelet count (10^9/L) × 100.[20]

US was conducted with an ACUSON S2000 ultrasound system (Siemens Medical Solutions, Mountain View, CA, USA) equipped with a 4 to 9 MHz linear transducer.[21] All infants were fasted for at least 4 h and then were soothed, and placed in the supine position. First, a standard conventional US examination was performed to assess the size, shape, and consistency of the liver and spleen, as well as the flow in native liver vessels and the presence of ascites. In addition, the size of the gallbladder and triangular cord (TC) sign were detected before HPE. Gallbladder abnormalities were defined as absent or small (<1.5 cm).[22] The TC sign was defined as an abnormal triangular or tubular echogenic area located in the porta hepatis with a thickness of 3 mm or more.[22]

After the conventional examination was completed, the same operator, with more than 10 years of experience in pediatric ultrasound, switched to the virtual touch tissue quantification mode for ARFI elastography to determine liver stiffness by measuring the shear wave speed (SWS) in m/s. The methods were similar to those of our previous study.[21] The region of interest was the right liver lobe, approximately 2 cm under the liver capsule, which is devoid of any vessels and bile ducts. The SWS was measured within the user-placed region of the box of interest. Numerical measurements were performed using US tracking beams.[23] Ten ARFI measurements were obtained to calculate the average SWS values. To find the predictive values of dynamic change of liver function or SWS values, changes in the monitoring parameters (Δ) were determined as: Δ pre–post HPE 1 = variables at one month post-HPE – variables of pre-HPE; Δ pre–post HPE 2 = variables at 2 months post-HPE – variables of pre-HPE; Δ pre–post HPE 3 = variables at 3 months post-HPE – variables of pre-HPE; Δ post-HPE 1–2 = variables at 2 months post-HPE – variables at 1 month post-HPE; Δ post-HPE 1–3 = variables at 3 months post-HPE – variables at 1 month post-HPE; Δ post-HPE 2–3 = variables at 3 months post-HPE – variables at 2 months post-HPE.

Statistical analysis

Descriptive results were analyzed using the Student's t-test, Wilcoxon's rank-sum test, or chi-square test, as appropriate. Quantitative variables are expressed as mean and standard deviation or median and interquartile range. Qualitative variables are summarized as counts and percentages. A generalized estimating equation (GEE) model with an exchangeable correlation structure was used to perioperatively investigate the changing trend differences between outcomes and repeated measures of SWS and other parameters. The cumulative probabilities of LT or death were calculated using the Kaplan-Meier method and log-rank test. Variables with a *p*-values <0.05 in the univariate analyses were selected for the Cox regression analyses. Univariate Cox regression analysis was used to identify superior SWS values and other predictors. A correlation matrix was used to display the correlation coefficients of the different variables. Multicollinearity may be present if the correlation was >0.7. Factors with no multicollinearity and significant differences with high hazard ratios (HRs) identified in the univariate Cox regression were then used to construct a multivariate model. Significant cutoff values for the factors of interest and their corresponding sensitivities, specificities, and accuracies were determined using the receiver operating characteristic (ROC) curve. Statistical analyses were conducted using IBM SPSS Statistics (version 20.0; IBM Corp., Armonk, NY, USA) and R software (Version 4.0.2). Illustrations were plotted using Origin 9 (OriginLab Corp., Northampton, MA, USA) and MedCalc 15 (MedCalc Software, Ostend, Belgium).

Results

Baseline and early postoperative characteristics

A total of 34 boys and 40 girls were included. The median perioperative age was 56 (range, 12–86) days, and the median weight was 4,457.5 (range, 2,720.0–6,200.0) g. All patients were from the Han Chinese population. Among the participants, 38 (51.4%) had poor BA outcomes, 9 (12.2%) died within 2 years after HPE, and 29 (39.2%) required LT. The median death or transplant age was 9.7 (range, 5–24) months, and 36 patients (48.6%) were alive with a native liver at 2 years of age.

There were no significant differences between the NLS and transplant/death groups in all preoperative data, including age and weight at HPE, clayey stools, hepatomegaly, gallbladder abnormalities, positive TC sign, SWS value, and liver functional variables ($p>0.05$). In the follow-up period for patients with NLS at 2 years of age, the median SWS values were 1.6, 1.8, and 1.9 m/s at 1, 2, and 3 months, respectively. Patients who died or received LT, presented with higher median SWS values at the corresponding follow-up intervals of 1.7, 2.0, and 2.9 m/s. There were significant differences in postoperative 2- and 3 months SWS values between the NLS transplant/death and control groups ($p<0.05$). Monthly serum TBIL and DBIL levels after surgery were significantly lower in the NLS group than in the transplant/death group ($p<0.05$). Serum APRI values were significantly higher in the transplant/death group than in the NLS group three months postoperatively ($p=0.006$, Table 1).

Dynamic changing patterns of those significant parameters between different outcome groups

As TBIL, DBIL, APRI, and SWS levels were significantly different between the NLS and transplant/death groups within 3 months after HPE, we determined their dynamic trends before and after the HPE. Longitudinal changes in the indices with data points and spline curve fitting are shown separately (Fig. 2). For TBIL and DBIL trajectories, the value of the transplant or death group showed a lower decrease rate within two months after the HPE and a sharply increased rate at 2–3 months after the HPE, while for SWS trajectories, the value of the transplant or death group showed a steady increase after the HPE.

The GEE results showed that there were significant differences between the trajectories of the NLS group and transplant or death group in the TBIL, DBIL, and SWS variables ($p<0.01$). For the TBIL and DBIL levels, a tendency toward the significance of time factor was observed for all data points. For the SWS value, there was no significant change between pre- and one month post-HPE, whereas the SWS significantly increased at two and three months after the operation (Supplementary Table 1).

To further explore the predictive value of dynamic changes in the SWS and other parameters, we compared the different periods of these variables (Fig. 3). The changes in SWS from pre-HPE to 3 months post-HPE, 1–3 months post-HPE, 2–3 months post-HPE, change in TBIL from pre-HPE to 3 months post-HPE, 2–3 months post-HPE, and change in DBIL from pre-HPE to 3 months post HPE showed extremely significant differences between the NLS and transplant or death groups (all $p<0.001$). Changes in the APRI at all the follow-up periods were not significant.

Table 1. Perioperative characteristics of patients with biliary atresia who underwent HPE (*n*=74)

	Native liver survival, *n*=36	Transplant or death, *n*=38	*P*-value
Age at HPE (days)	53.3±21.5	54.1±16.2	0.856
Sex, male, *n* (%)	18 (50.0%)	16 (42.1%)	0.496
Weight at HPE (days)	4,515.1±992.8	4,442.2±574.6	0.703
Pre-HPE clayey stool, *n* (%)	19 (52.8%)	15 (39.5%)	0.251
Pre-HPE hepatomegaly, *n* (%)	13 (36.1%)	16 (42.1%)	0.598
Pre-HPE abnormal gallbladder, *n* (%)	18 (50.0%)	27 (71.1%)	0.064
Pre-HPE triangular cord sign positive, *n* (%)	31 (86.1%)	31 (81.6%)	0.597
GGT (U/L)			
Pre-HPE	502.1 (320.4, 853.0)	433.0 (210.8, 656.3)	0.165
Post-HPE 1 month	992.0 (664.5, 1,352.8)	1,133.5 (623.8, 1,744.0)	0.336
Post-HPE 2 months	958.0 (460.6, 1,277.8)	1,115.0 (605.9, 1,422.0)	0.272
Post-HPE 3 months	390.0 (168.0, 883.0)	536.5 (202.8, 931.0)	0.350
ALT (U/L)			
Pre-HPE	105.0 (68.0, 209.8)	128.0 (72.7, 254.3)	0.272
Post-HPE 1 month	177.0 (100.0, 254.0)	241.5 (164.0, 327.5)	0.062
Post-HPE 2 months	138.0 (63.0, 229.0)	148.3 (97.4, 220.3)	0.434
Post-HPE 3 months	91.0 (44.0, 113.0)	119.0 (58.3, 186.5)	0.053
AST (U/L)			
Pre-HPE	160.0 (115.0, 236.0)	197.5 (148.5, 308.0)	0.059
Post-HPE 1 month	155.0 (102.8, 221.3)	178.5 (118.5, 253.0)	0.192
Post-HPE 2 months	128.0 (75.3, 172.0)	131.3 (93.4, 164.3)	0.737
Post-HPE 3 months	82.0 (59.8, 176.3)	126.0 (84.5, 192.8)	0.051
ALP (U/L)			
Pre-HPE	465.5 (358.5, 631.0)	482.5 (364.8, 620.3)	0.867
Post-HPE 1 month	334.5 (287.0, 420.5)	334.3 (247.0, 426.3)	0.693
Post-HPE 2 months	450.0 (356.0, 535.0)	400.8 (330.4, 512.5)	0.307
Post-HPE 3 months	456.5 (331.8, 614.0)	512.0 (424.0, 726.0)	0.112
TBIL (μmol/L)			
Pre-HPE	153.7 (117.7, 176.2)	146.5 (115.0, 178.2)	0.713
Post-HPE 1 month	36.6 (22.5, 64.2)	64.2 (34.9, 99.0)	0.004
Post-HPE 2 months	29.5 (16.1, 65.9)	81.2 (35.1, 99.8)	0.003
Post-HPE 3 months	21.8 (9.45, 67.8)	102.6 (43.6, 169.1)	<0.001
DBIL (μmol/L)			
Pre-HPE	96.8 (77.4, 120.3)	94.6 (74.0, 126.1)	0.846
Post-HPE 1 month	27.6 (15.5, 51.6)	48.6 (23.1, 70.9)	0.019
Post-HPE 2 months	18.0 (10.9, 12.9)	49.5 (24.5, 76.6)	0.002
Post-HPE 3 months	16.0 (4.5, 36.4)	78.4 (30.5, 132.0)	<0.001
APRI			
Pre-HPE	1.0 (0.6, 1.9)	1.6 (0.8, 2.9)	0.232
Post-HPE 1 month	0.9 (0.6, 1.5)	1.1 (0.7, 1.6)	0.405
Post-HPE 2 months	0.9 (0.5, 1.5)	1.0 (0.6, 2.3)	0.175
Post-HPE 3 months	0.8 (0.6, 1.3)	1.4 (0.9, 3.9)	0.006
SWS (m/s)			
Pre-HPE	1.7 (1.5, 1.9)	1.8 (1.5, 2.0)	0.417
Post-HPE 1 month	1.6 (1.5, 2.0)	1.7 (1.6, 2.0)	0.284
Post-HPE 2 months	1.8 (1.6, 2.1)	2.0 (1.7, 2.5)	0.049
Post-HPE 3 months	1.9 (1.5, 2.3)	2.9 (2.1, 3.6)	<0.001

ALP, alkaline phosphatase; ALT, alanine transaminase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate transaminase; DBIL, direct bilirubin; GGT, γ-glutamyl transferase; HPE, hepatoportoenterostomy; SWS, shear wave speed; TBIL, total bilirubin.

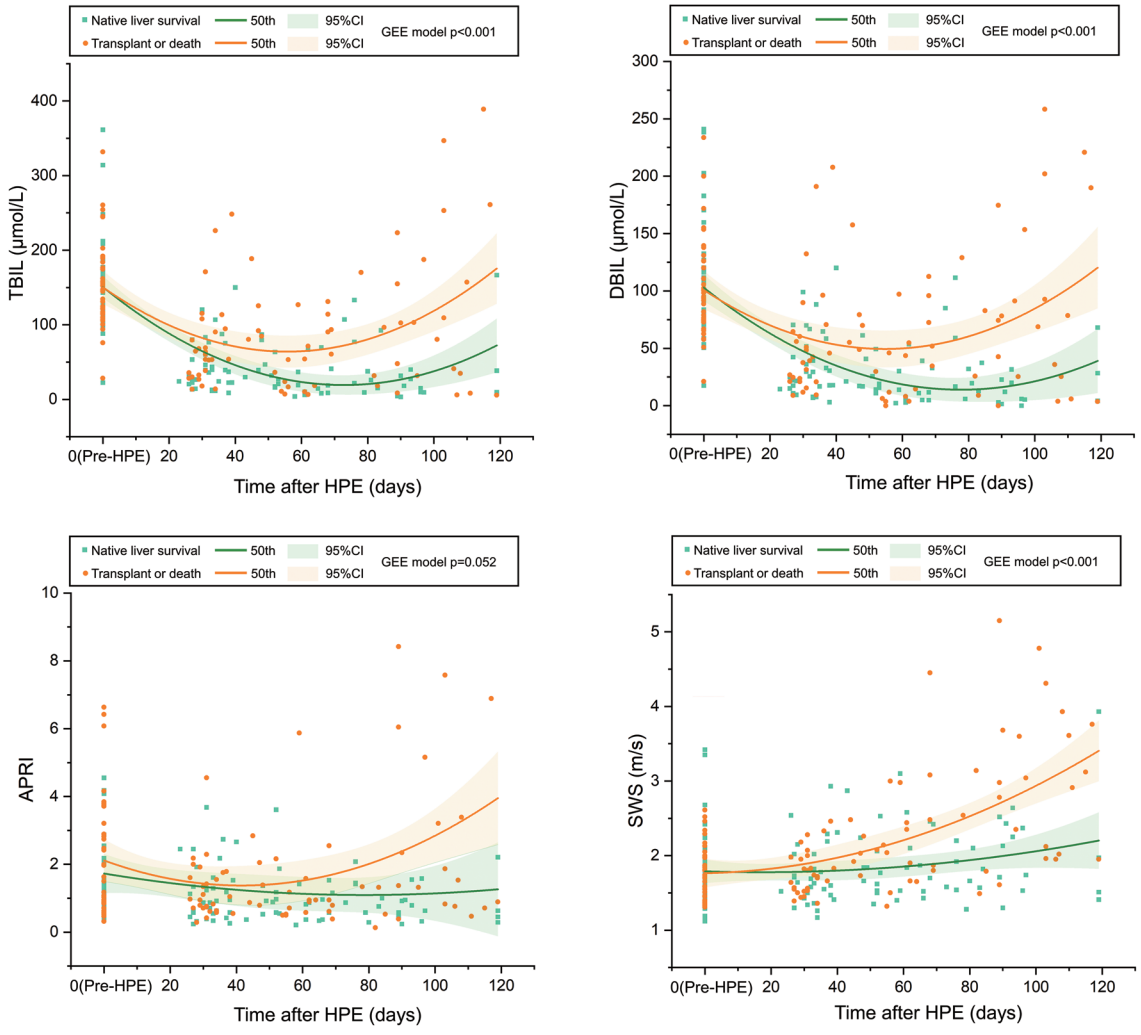

Fig. 2. Preoperative and postoperative trends of TBIL, DBIL, APRI, and SWS in patients with biliary atresia. Spline curve fitting for bilirubin level, APRI, and SWS values of two outcomes in patients with biliary atresia. Generalized estimating equation (GEE) analysis showed significant between-group differences between the trajectories TBIL, DBIL, and SWS (all $p<0.001$). APRI, aspartate aminotransferase to platelet ratio index; DBIL, direct bilirubin; SWS, shear wave speed; TBIL, total bilirubin.

Predictors of 2-year outcomes of BA

The Kaplan-Meier analysis of all the patients divided by different levels of SWS-related parameters whose *p*-value was <0.05 above is shown in Figure 4. The cutoff values of SWS at 2 and 3 months after the HPE and change in SWS from pre-HPE to three months post-HPE, 1–3 months post-HPE, and 2–3 months post-HPE determined by the ROC analysis were 1.84, 2.64, 0.97, 0.50, and 0.16, respectively (Supplementary Fig. 1). Higher values of SWS at 3 months after the HPE and higher changes in SWS from pre-HPE to 3 months post-HPE, 1–3 months post-HPE, and 2–3 months post-HPE indicated poor prognosis than lower values of the same parameters (all log-rank $p<0.001$).

Univariate Cox regression analysis showed that SWS at 3 months after the HPE [HR=2.074; 95% confidence interval (CI): 1.556–2.763; $p<0.001$], ΔSWS of pre-HPE to 3 months post-HPE [HR=1.006; 95% CI: 1.003–1.009; $p<0.001$], 1–3 months post-HPE [HR=2.832; 95% CI: 1.924–4.169; $p<0.001$], 2–3 months post-HPE [HR=2.162; 95% CI: 1.615–2.892; $p<0.001$], and TBIL or DBIL-related parameters were significantly associated with the development of LT or death (all $p<0.05$). Age at HPE, sex, and APRI value at 3 months post-HPE were not significantly associated with the two-year outcomes of BA (Table 2).

The correlation matrix of the predictors, as mentioned above, indicated the presence of multicollinearity (Supplementary Fig. 2). There was collinearity between TBIL and DBIL values. According to the HR value, the predictors with no multicollinearity and highest HR value, including ΔSWS of post-HPE 1–3 and TBIL at 1 month post-HPE were included in the multivariate Cox regression. Multivariable analysis revealed that ΔSWS of post-HPE 1–3 [HR=1.927; 95% CI: 1.475–2.661; $p<0.001$] and TBIL at 1 month post-HPE [HR=1.010; 95% CI: 1.003–1.017, $p=0.007$] were found to be significant independent risk factors for predicting transplant/death outcome.

Predictive accuracy of ΔSWS and TBIL for the two-year outcomes

The ROC curve analysis was applied to estimate the clini-

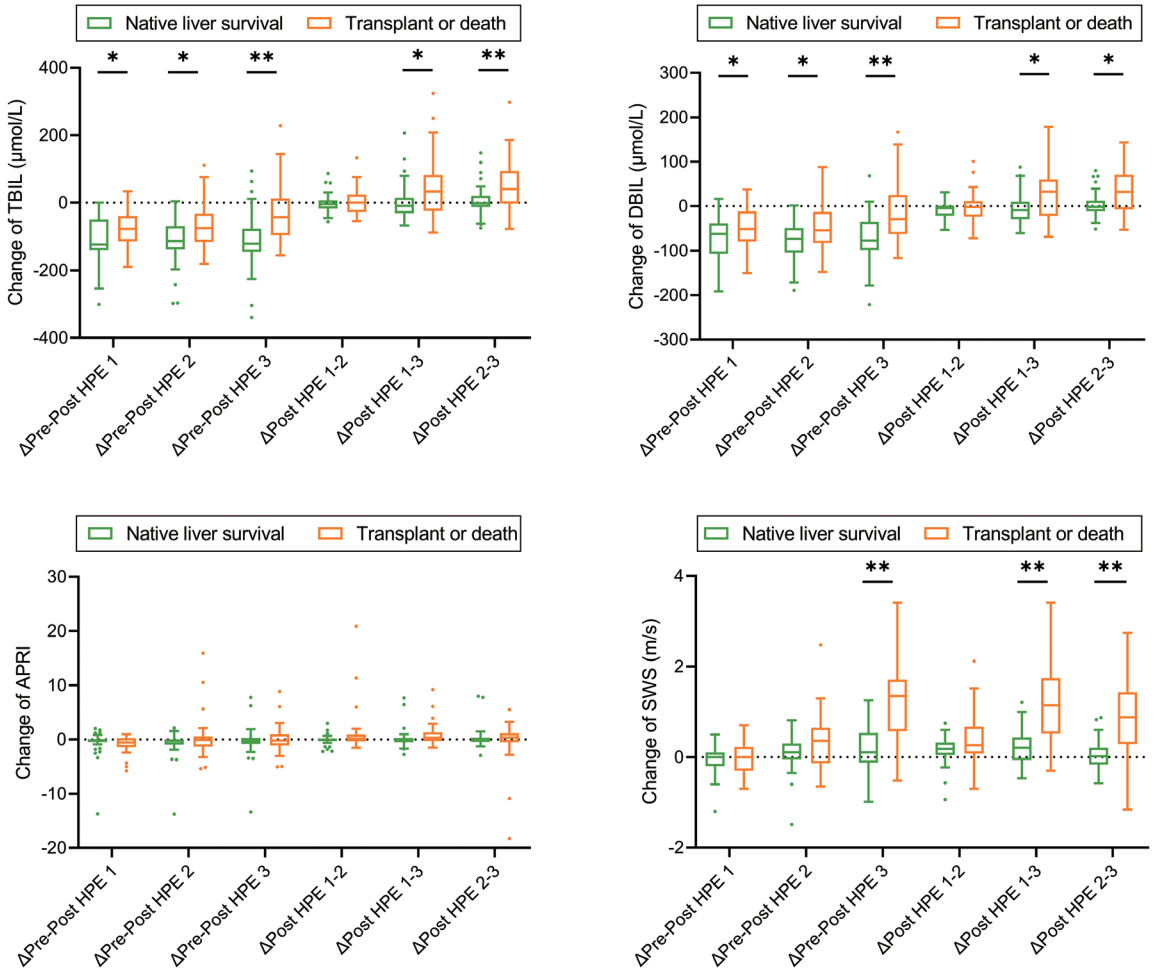

Fig. 3. Dynamic changes in TBIL, DBIL, APRI, and SWS in patients with biliary atresia who received HPE. Box- and whisker-plots showing different outcome groups in six time intervals before and after the HPE specified on the x-axis. The box shows 25–75% interquartile range (boxes) around the median (line in a box) and the whisker shows data range (minimum to maximum values) except for outliers (circles). *p<0.05, **p<0.001. APRI, aspartate aminotransferase to platelet ratio index; DBIL, direct bilirubin; HPE, hepatoportoenterostomy; SWS, shear wave speed; TBIL, total bilirubin.

cal value of selected predictors, including ΔSWS of post-HPE 1–3, TBIL at 1 month post-HPE, and their combination (Fig. 5). The ΔSWS of post-HPE 1–3 had a higher accuracy, with an area under the receiver operating characteristic curve (AUC) of 0.85 (0.76–0.94), which was significantly superior to the AUCs of TBIL at 1 month post-HPE [AUC=0.69 (0.57, 0.81); p=0.045]. The optimal cutoff values of the selected ΔSWS and TBIL were 0.5 and 43.5, respectively. When the selected ΔSWS and TBIL values were combined, the formula for predicting the 2-year transplant or death of patients with BA (P) was: P = 1 / (1 + exp [−(−2.8288 + 0.0215 × TBIL at 1 month post-HPE + 2.6734 × ΔSWS of post-HPE 1–3)].

The combined models had the highest AUC (0.89) for predicting liver transplant or death, with a specificity of 94.44 (81.3–99.3)% and sensitivity of 73.68 (56.9–86.6)%. A calculated value of >0.66 indicated greater likelihood of transplant or death at the age of 2 years. This formula can be used as a predictive tool for BA outcomes. (Supplementary Table 2).

Discussion

In this prospective study, we investigated the prognostic effects of ARFI with SWS value and other preoperative and early postoperative parameters for two-year outcomes in 74 patients with BA who underwent HPE in our hospital. SWS at 3 months post-HPE, ΔSWS of pre–post HPE at 3 months, 1–3 months post-HPE, and 2–3 months post-PE were characterized by similar prognostic abilities, as high levels of these parameters predicting transplant/death outcome. A combination of ΔSWS at 1–3 months and TBIL at 1 month post-HPE had good predictive accuracy, with an AUC of 0.89, 94.44% specificity, and 73.68% sensitivity.

HPE is considered an effective treatment for BA. Two years post-HPE is a critical period that affects the survival of children with BA, with almost 90% of patients with a 2-year NLS to reach adulthood.[24] The reported 2-year NLS rate of patients after HPE for BA varies greatly, ranging from 46–65%.[25] Our results showed a similar rate of 48.6%. As approximately half of the patients with BA after HPE requires LT, early identification could help the patient to receive a graft in a more optimal time frame and help the patient, parents, and family to prepare psychologically for the operation.

Recently, ARFI elastography has been proposed as an alternative noninvasive method to assess liver fibrosis, rather than liver biopsy, which is an invasive procedure with some unavoidable risks and complications.[15] Several studies have

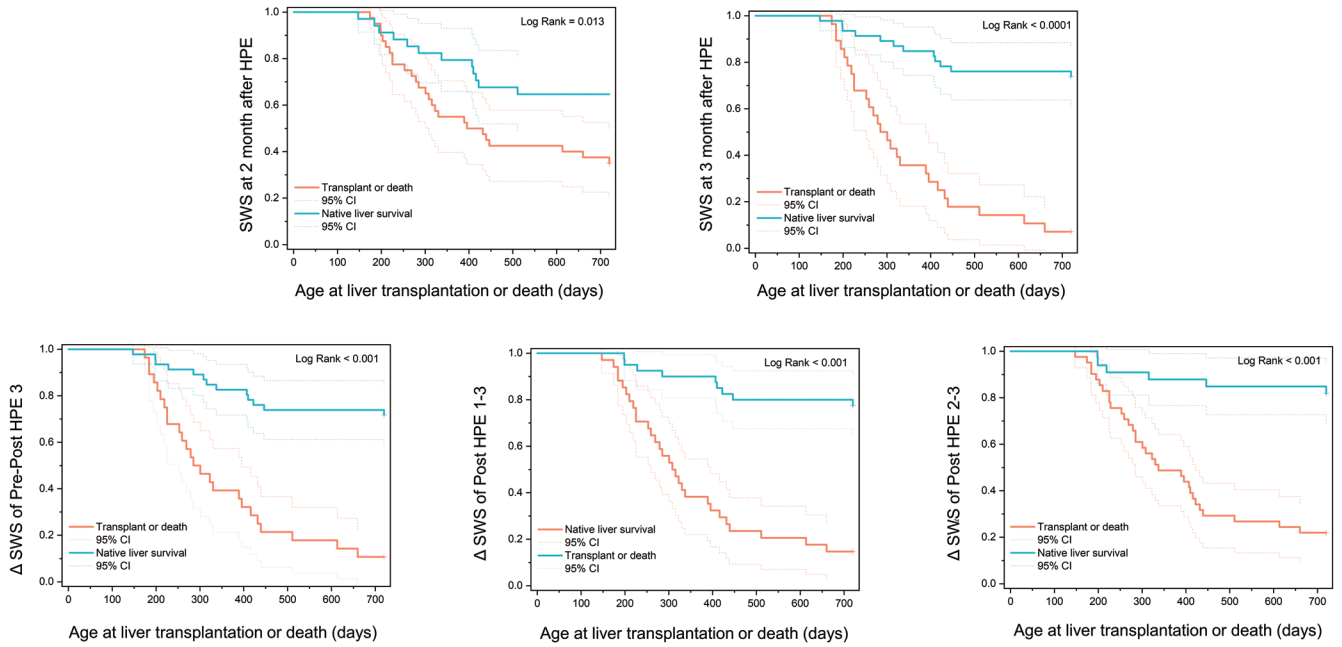

Fig. 4. Kaplan-Meier analysis of developing LT or death based on SWS monitoring. The Kaplan-Meier estimate and its 95% confidence interval for developing transplant/death outcome relative to age in days after HPE, which is derived by dividing the patients on the basis of the optimal SWS cutoff value generated by ROC curve analysis at different time points and intervals. Significant differences were observed for SWS at 3 months post-HPE, Δ SWS from pre-HPE to three3 month post-HPE, 1–3 months post-HPE, 2–3 months post-HPE of pre–post (all log-rank $p<0.001$). HPE, hepatoportoenterostomy; LT, liver transplantation; SWS, shear wave speed.

demonstrated the effective role of ARFI in hepatic fibrosis severity,[26] and severe fibrosis was reported to have worse overall survival compared to mild and moderate fibrosis in children with BA.[27] In our previous study, we demonstrated that SWS >1.35 m/s and the presence of the TC sign had high accuracy for diagnosing BA.[21] In this study, we found that a dynamic change in SWS between 1–3 months post-HPE had an AUC of 0.85, with a cutoff of 0.5 in predicting death/transplantation outcomes. Other studies have reported the use of elastography to monitor children with BA. Wang *et al*.[7] found that pre-HPE shear wave elastography plays a potentially important role in predicting the NLS of BA. In contrast, we did not find a significant difference in the SWS value in either group before or at one month after the HPE. Several studies have reported that an ARFI value ≥2 m/s was correlated with liver fibrosis or cirrhosis, and that patients with two consecutive ARFI values ≥2 m/s in the 6 months follow-up after HPE were likely to need LT.[16,28] Similarly, we found that the median SWS values at 2 or 3 months after HPE were more likely to be above 2 m/s in the death and transplantation groups than in the NLS group. In another study by Liu *et al*.,[19] liver stiffness measured by ultrasound elastography at 3 months after surgery itself was not useful for predicting the prognosis within 2 years post-HPE. However, our SWS trajectory showed a gradual increase in the transplant/death outcomes, which sharply increased at 3 months after the HPE. Dynamic changes in SWS between 1 and 3 months after the HPE appeared to be a superior predictor of the 2-year outcome in our study. Our results revealed that liver stiffness might not be apparent at the initial time after HPE, but when it becomes progressive for 1–3 months after HPE, patients should prepare for possible poor outcomes.

Other than ultrasound imaging, other prognostic indicators have also been presented with the NLS or transplantation outcome for BA after the operation, with perioperative age and jaundice clearance being the most frequently studied.[7,9,24,25,29] Generally, early surgery achieves a better prognosis.[9,29] In our study, we did not find out whether age at HPE had significant impact on the prognosis of BA. Not surprisingly, our data confirm that bilirubin levels after HPE were strongly related to 2-year outcome. Biliary drainage after HPE, which was estimated based on serum TBIL levels, has been reported as an independent factor for higher NLS rates.[27] Shneider *et al*.[12] found that a total serum bilirubin level of <34 μmol/L at 3 months after HPE correlated strongly with good 2-year outcomes. Our results showed that TBIL at 1 month after HPE was an effective predictor of BA outcome, with a cutoff of 43.5 μmol/L. However, the predictive performance evaluated by ROC analysis showed that TBIL at one month post-HPE had a significantly lower accuracy than ΔSWS, indicating that ΔSWS might be a superior predictor of BA outcome.

In addition to bilirubin, other liver function parameters have been proposed as potential predictors for BA outcomes, such as AST/ALT ratio index, aspartate aminotransferase, and gamma-glutamyl transpeptidase.[30,31] In this study, univariate analysis of liver function tests showed that there were no significant differences in ALT, AST, and GGT values between the NLS and death/transplant groups during the perioperative period. Furthermore, APRI, a noninvasive biochemical marker reflecting fibrosis progression, was also used to predict the prognosis of BA.[9,19,32] Our results did not show that APRI at HPE had significance in predicting NLS, which is inconsistent with data from previous studies.[19,32] Though APRI at 3 months after the HPE was significantly higher in the transplant/death group than in the NLS group in the current study, this variable was not selected as an independent risk factor for BA prognosis in later analysis. We assumed that monitoring the change in APRI within 3 months after HPE might not be more valuable than other biomarkers, such as TBIL and SWS values, in predicting BA outcome.

A novel finding of our study was that a combination of ΔSWS at 1–3 months and TBIL at 1 month had the best

Table 2. Univariate Cox regression analysis for identifying the superior predictors of liver transplantation or death

Variables	HR	95% CI	*P*-value
Age at HPE	1.002	0.986–1.019	0.805
Sex	0.747	0.392–1.422	0.374
SWS (m/s)			
Post-HPE 2 months	1.516	0.929–2.476	0.096
Post-HPE 3 months	2.074	1.556–2.763	<0.001
ΔPre-Post HPE 3	1.006	1.003–1.009	<0.001
ΔPost HPE 1–3	2.832	1.924–4.169	<0.001
ΔPost HPE 2–3	2.162	1.615–2.892	<0.001
TBIL (μmol/L)			
Post-HPE 1 month	1.015	1.008–1.023	<0.001
Post-HPE 2 months	1.013	1.005–1.020	0.001
Post-HPE 3 months	1.011	1.006–1.015	<0.001
ΔPre-Post HPE 1	1.009	1.002–1.017	0.014
ΔPre-Post HPE 2	1.010	1.003–1.016	0.003
ΔPre-Post HPE 3	1.009	1.005–1.014	<0.001
ΔPost HPE 1–3	1.010	1.004–1.016	<0.001
ΔPost HPE 2–3	1.011	1.005–1.017	<0.001
DBIL (μmol/L)			
Post-HPE 1 month	1.012	1.005–1.018	<0.001
Post-HPE 2 months	1.011	1.005–1.018	<0.001
Post-HPE 3 months	1.006	1.003–1.009	<0.001
ΔPre-Post HPE 1	1.006	1.001–1.012	0.024
ΔPre-Post HPE 2	1.005	1.001–1.010	0.019
ΔPre-Post HPE 3	1.006	1.003–1.009	<0.001
ΔPost HPE 1–3	1.005	1.002–1.009	0.003
ΔPost HPE 2–3	1.006	1.003–1.010	0.001
APRI			
Post-HPE 3 months	1.076	0.961–1.206	0.205

APRI, aspartate aminotransferase to platelet ratio index; DBIL, direct bilirubin; HPE, hepatoportoenterostomy; SWS, shear wave speed; TBIL: total bilirubin.

predictive performance, with an AUC of 0.89. In addition, the combined model showed that, when probability >0.66, patients should be prepared for a poor outcome. Several non-invasive serological tests have been suggested to evaluate liver fibrosis in postoperative patients with BA, and determine the optimal timing of LT.[33,34] Serum matrix metalloproteinase-7 has been reported as a novel biomarker for diagnosing BA. However, it has a moderate accuracy of 78.1% for predicting LT.[1] Gunadi *et al*.[33] and Zhen *et al*.[34] developed a liver transplant score, including eight or nine parameters, some of which should be evaluated clinically. Our predictive model contains dynamic change of SWS and one bilirubin level, which are easy to obtain.

This study has some limitations. First, it was a single-center study, and the ARFI requires trained and experienced radiologists. Second, the 2-year follow-up period was too short to assess the overall effectiveness of clinical care. A longer follow-up period may have affected the accuracy of the results. Finally, we compared the SWS and TBIL values after HPE in infants with BA. However, we did not include infants without BA, such as those with infantile hepatitis, as control patients for comparative analyses. Further comparisons of this predictive tool in other pediatric hepatic patients should be conducted to verify its effectiveness in patients with BA.

Conclusion

We developed a novel prognostic combination of BA in children who had transplant or death outcomes at 2 years of age. A high dynamic change in SWS levels at 1–3 months and serum TBIL levels at 1 month after HPE were associated with poor BA outcomes. The combination also supported continued routine monitoring of ARFI, and bilirubin levels to optimize pretransplant management and guide clinicians for further prognostic estimation after HPE.

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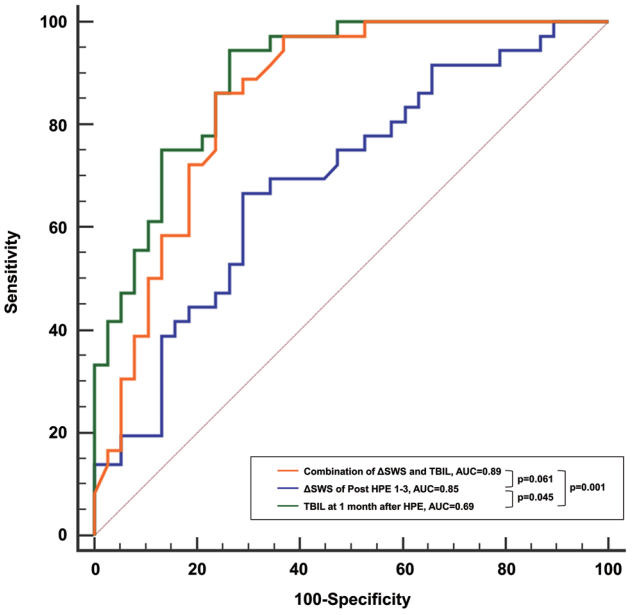

Fig. 5. Predictive performance of single and combined predictors. The AUC indicating predictive performances for 2 years biliary atresia outcomes. The ΔSWS at 1–3 months and TBIL at 1 month post-HPE were 0.85 and 0.69, respectively. Combination of the two parameters had an AUC of 0.89, 94.44% specificity, and 73.68% sensitivity. The p-values show that both the AUC for the combination and ΔSWS 1–3 months post-HPE were significantly higher versus the AUC of TBIL 1 month post-HPE ($p<0.05$). AUC, area under the receiver operating characteristic curve; HPE, hepatoportoenterostomy; SWS, shear wave speed; TBIL, total bilirubin.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis (YZ), concept and design (YZ), data collection (YL, WX, WW), drafting of the manuscript (DZ, YC), critical revision of the manuscript for important intellectual content (YZ), statistical analysis (DZ, YC), made a significant contribution to this study and approved the final manuscript (DZ, YL, WX, WW, YC, YZ).

Ethical statement

The study was conducted in accordance with the principles of the Declaration of Helsinki, and was approved by the Ethical Committee of Xinhua Hospital, Shanghai Jiaotong University School of Medicine (ethical approval No. XHEC-C-2019-073). All parents or legal guardians were fully informed of the research protocol and provided written consent.

Data sharing statement

No additional data are available.

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