Supersonic shearwave elastography in the assessment of liver fibrosis for postoperative patients with biliary atresia

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To explore an effective noninvasive tool for monitoring liver fibrosis of children with biliary atresia (BA) is important but evidences are limited. This study is to investigate the predictive accuracy of supersonic shearwave elastography (SSWE) in liver fibrosis for postoperative patients with BA and to compare it with aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 (FIB-4). 24 patients with BA received SSWE and laboratory tests before scheduled for liver biopsy. Spearman rank coefficient and receiver operating characteristic (ROC) were used to analyze data. Metavir scores were F0 in 3, F1 in 2, F2 in 4, F3 in 7 and F4 in 8 patients. FIB-4 failed to correlate with fibrosis stage. The areas under the ROC curves of SSWE, APRI and their combination were 0.79, 0.65 and 0.78 for significant fibrosis, 0.81, 0.64 and 0.76 for advanced fibrosis, 0.82, 0.56 and 0.84 for cirrhosis. SSWE values at biopsy was correlated with platelet count (r = −0.426, P = 0.038), serum albumin (r = −0.670, P < 0.001), total bilirubin (r = 0.419, P = 0.041) and direct bilirubin levels (r = 0.518, P = 0.010) measured at 6 months after liver biopsy. Our results indicate that SSWE is a more promising tool to assess liver fibrosis than APRI and FIB-4 in children with BA.

Biliary atresia (BA), characterized by progressive fibro-obliteration of the bile ducts, is a common infantile cholestatic disease with high morbidity and mortality1. Kasai portoenterostomy (KPE) remains the initial strategy to restore bile flow2. However, despite of timely KPE, the progressive fibrosis develops in almost all patients3, which results in liver cirrhosis and requires subsequent liver transplantation (LT)4. The degree of liver fibrosis after KPE contributes to be the main prognostic factors for the survival of patients5. Therefore, close monitoring of fibrosis is critical for identifying high-risk patients and referring them to LT.

Liver biopsy is the criterion standard for evaluating liver fibrosis. However, as an invasive procedure, it has many limitations including complications, discomfort, inter-observer variations and sampling errors6,7. Given this situation, various non-invasive methods have rapidly emerged as alternatives to liver biopsy, such as quantitative elastography and serum fibrosis biomarkers.

Several quantitative elastography technologies such as transient elastography (TE), acoustic radiation force impulse (ARFI), and supersonic shearwave elastography (SSWE), have been used to evaluate liver fibrosis in pediatric patients and showed good correlation (ρ = 0.53–0.63) between liver fibrosis and elastographic value8–11. However, TE has many pitfalls such as the inability to choose different locations for the region of interest (ROI) and to avoid other structures such as liver vessels and bile ducts12, and has also been reported to have more technical failures in young children13,14. APRI, also named as point shear wave elastography, has the limitation in being unable to provide a real-time quantitative map of liver tissue stiffness15. SSWE, a newly developed elastography technology, has three advantages over TE. First, SSWE is integrated into a conventional diagnostic ultrasound (US) system and therefore can make use of real-time gray scale mode imaging for the assessment of morphologic

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SWE examination. An Aixplorer scanner (Supersonic, Paris, France) incorporating a SC6-1 curvilinear transducer (1–6 MHz) was used to perform the SWE examinations. The infants were remained still by sedation or by holding their breath. Segments V or VI were selected as the target areas for measurement. All SWE examinations were performed by a single sonographer (Luyao Zhou, 6 years of experience for US and 3 years of experience for elastography, respectively) with an intercostal or a subcostal transducer position. If possible, SWE was performed while the infants were holding their breath. Segments V or VI were selected as the target areas for measurement. All SSWE examinations were collected venously as part of routine clinical care throughout the follow-up. Data including AST, ALT, serum albumin (ALB), serum total bilirubin (TBIL), serum direct bilirubin (DBIL), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), and PLT count were obtained. Laboratory data obtained within 1 week of liver biopsy and at 6 months after liver biopsy were used for analysis in this study. The diagnosis of gastrointestinal bleeding was confirmed by endoscopic finding that bleeding developed from the variceous veins in the distal esophagus or gastric fundus. Ascites was diagnosed when fluid was found in peritoneal cavity by imaging tests such as ultrasonography or computed tomography. Jaundice (serum bilirubin ≥ 5 mg/dl [85 mmol/l]) was defined based on the guidelines of Asian Pacific Association for the study of liver. In addition, to biochemical parameters of liver function at 6 months after liver biopsy.

Liver Histopathology. Under the guidance of US, liver biopsy was performed percutaneously in the right liver lobe using an inter-costal approach with an 18-gauge needle (Bard, USA). A minimum length of 20 mm for biopsy specimens must be guaranteed. Then, all specimens were fixed in formalin and embedded in paraffin. Following staining with haematoxylin-eosin (H&E) and Masson trichrome, each specimen was evaluated by two independent and blinded pathologists with more than 10 years of experience in liver pathology. Only the adequate samples defined by showing at least six portal tracts were included for further analysis. Disagreement was resolved by the consultation of a third pathologist. Liver fibrosis and necroinflammatory activity was assessed using the Metavir classification as follows: F0, no fibrosis; F1, portal expansion; F2, intra- and perisaccular fibrosis; F3, bridging fibrosis; F4, cirrhosis.
follows: F0, no fibrosis; F1, portal fibrosis with no septa; F2, portal fibrosis with rare fibrous septa; F3, bridging fibrosis with many fibrous septa; F4, cirrhosis. Activity was staged as follows: A0, none; A1, mild; A2, moderate; A3, severe.

Statistical Analysis. The normal distribution test was conducted in the variables using Shapiro-Wilk test. Normally distributed variables were represented as mean ± SD while non-normally distributed variables such as skew variables were represented as median and inter-quartile range (IQR). Differences between two groups were compared by the t test for normally distributed variables, Wilcoxon rank test for skewed variables and χ² test for categorical variables. Spearman’s rank coefficient test was performed to evaluate the correlation between variables. The Kruskal–Wallis test was used to detect the variation of SSWE values and APRI among different fibrosis stages. The diagnostic performance of SSWE, APRI and their combination to predict liver fibrosis severity (F0–1 vs. F2–4: F ≥ 2; F0–2 vs. F3–4: F ≥ 3; F0–3 vs. F4: F = 4) was estimated by the area under the receiver operating characteristic (ROC) curve. The optimal cut-off values were determined based on the largest Youden index. The differences of AUROCs between different parameters were presented as P values estimated by Z tests. Statistical significance was considered as a two-sided P value of less than 0.05. All the analyses was performed by the SPSS 20.0 (SPSS Inc., Chicago, IL, USA), SAS 9.2 (SAS Institute, Inc, Cary, NC) and Sigmaplot 10.0. Ink (Systat Software, Inc.).

Results

Subject Characteristics. A total of 24 patients met the inclusion criteria for our study. Biochemical tests, SSWE examinations and liver biopsy were performed within one week of each other. In terms of fibrosis stage, there were 3 (12.5%) patients for F0, 2 (8.3%) for F1, 4 (16.7%) for F2, 7 (29.2%) for F3, 8 (33.3%) for F4. The demographics, biochemical results, ultrasonic findings, histological features and follow-up data of patients by fibrosis level are summarized in Table 1. The mean age at liver biopsy was 6.6 years with 13 (54.2%) male patients. Patients with more advanced fibrosis stage were found to have significantly higher serum AST levels, GGT, DBIL levels and lower serum ALB level (P = 0.046; P = 0.049; P = 0.025; P = 0.044). SSWE values ranged from 6.2 to 60.6 (median, 13.2 kPa). On serum fibrosis biomarkers, the median value of APRI and FIB-4 was 1.3 (0.34–12.5) and 0.31 (0.03–3.5) with the corresponding wide ranges. During the follow up from liver biopsy, no liver-related death or gastrointestinal bleeding was detected. There were two patients in need of liver transplantation (one with F4 has underwent surgery and one with F2 is on the waiting list). Three patients showed with ascites (1 with F4, 1 with F3 and 1 with F2).

Performance of APRI, FIB-4 and SSWE in Predicting Liver Fibrosis Severity. APRI scores had a positive correlation with fibrosis stage (r = 0.583, P < 0.001) (Supplementary Figure A) whereas FIB-4 scores had a very weak correlation (r = 0.075, P = 0.001). APRI scores showed a significant difference between different fibrosis stages (P = 0.035; Fig. 2A) whereas FIB-4 scores did not. Thus, we moved to further explore the performance of APRI in predicting fibrosis severity. A significant difference was detected between consecutive fibrosis stages except F3 and F4 (F0 vs. F1: P < 0.001; F1 vs. F2: P < 0.001; F2 vs. F3: P = 0.009; F3 vs. F4: P = 0.323). Moreover, the AUROCs of APRI were 0.65 (95% CI: 0.35–0.96), 0.64 (95% CI: 0.41–0.88), and 0.56 (95% CI: 0.31–0.80) respectively for predicting significant (≥F2), advanced fibrosis stage (≥F3), and cirrhosis (F4) (Table 2, Fig. 3). With the corresponding cut-off values of 0.70, 0.93 and 1.00 in the above three situations, the performance of APRI in predicting fibrosis severity was estimated (Table 2). SSWE values showed a positive correlation with
Table 1. Patient demographics and clinical characteristics. KPE, Kasai portoenterostomy; SD, standard deviation; IQR, inter-quartile range; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; ALB, albumin; TBIL, total bilirubin; DBIL, direct bilirubin; PLT, platelet; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4; SSWE, supersonic shearwave elastography.

| Variable                        | Total   | F0-2   | F3-4   | P value |
|---------------------------------|---------|--------|--------|---------|
| Sex, n (%)                      | 24      | 9      | 15     | 0.341   |
| Men                             | 13      | 6      | 7      |         |
| Female                          | 11      | 3      | 8      |         |
| Age at KPE, months (SD; range)  | 2.1 (1.1; 0.50–6.0) | 2.5 (1.5; 1.0–6.0) | 1.8 (0.6; 0.50–3.0) | 0.124 |
| Follow-up time, months (SD; range) | 32.8 (7.6; 6.0–39.0) | 35.9 (4.8; 27.0–39.0) | 31.0 (8.5; 6.0–39.0) | 0.131 |

During the liver biopsy period

| Age, years (SD; range) | 6.6 (5.7; 0.67–20.0) | 8.4 (5.1; 1.5–16.0) | 5.5 (5.9; 0.67–20.0) | 0.089 |
|------------------------|----------------------|---------------------|----------------------|-------|
| AST, IU/L (IQR; range) | 62.0 (40.0–120.0; 27.0–533.0) | 40.0 (33.5–82.5; 27.0–136.0) | 83.0 (48.0–128.0; 27.0–533.0) | 0.046 |
| ALT, IU/L (IQR; range) | 53.5 (27.3–80.8; 14.0–558.0) | 42.0 (21.0–73.5; 14.0–136.0) | 68.0 (31.0–91.0; 14.0–558.0) | 0.340 |
| ALP, IU/L (IQR; range)  | 274.0 (145.0–309.0; 83.0–335.0) | 253.0 (145.0–309.0; 83.0–335.0) | 240.0 (91.0–325.0; 83.0–308.0) | 0.049 |
| GGT, IU/L (IQR; range)    | 167.5 (66.3–250.8; 14.0–468.0) | 89.0 (39.0–177.5; 14.0–251.0) | 240.0 (91.0–325.0; 83.0–468.0) | 0.049 |
| DBIL, μM/L (IQR; range)   | 43.3 (4.3; 35.9–51.8) | 45.5 (3.5; 38.6–51.8) | 42.0 (4.7; 35.9–47.8) | 0.044 |
| FIB-4 (IQR; range)        | 13.2 (7.4–33.4; 6.2–60.6) | 7.5 (6.2–11.3; 4.1–13.2) | 13.3 (7.0–20.8; 3.9–138.2) | 0.107 |
| APRI (IQR; range)         | 3.2 (2.1–8.7; 0.7–69.8) | 2.7 (1.2–3.4; 0.7–4.1) | 7.2 (2.4–11.6; 0.90–69.8) | 0.025 |
| SSWE, kPa (IQR; range)     | 148.5 (107.5–181.0; 40.0–308.0) | 151.0 (115.5–204.5; 91.0–234.0) | 146.0 (82.0–182.0; 40.0–308.0) | 0.676 |

Follow-up

| Ascites             | 2       | 1       | 1       | 0.703   |
| Gastrointestinal bleeding | 3   | 1       | 2       | 0.692   |
| Hepatic encephalopathy | 0      | 0       | 0       | 1.000   |
| Liver transplantation | 2      | 1       | 1       | 0.703   |
| Liver related death  | 0       | 0       | 0       | 1.000   |

Discordance between SSWE, APRI and Fibrosis Stage. Based on the above cut-off values, the predicted fibrosis stage by SSWE and APRI and the actual fibrosis level was compared. APRI was in agreement with fibrosis staging 50% (12/24) of the time. Overall, APRI overestimated fibrosis stage 29.2% of the time and underestimated fibrosis 20.8% of the time. For SSWE, more patients (15, 62.5%) were diagnosed with agreement to actual fibrosis stage than APRI. SSWE overestimated fibrosis stage in 20.8% of the time. However, the combination of SSWE and APRI could slightly improve the diagnostic accuracy for cirrhosis, with the AUROC being 0.84 (95% CI: 0.63–1.00) (Table 2). However, the difference between combination and SSWE was not statistically significant (P = 0.33).
Correlation between SSWE and Liver Function Biomarkers after 6 months from biopsy. In order to preliminarily investigate the role of SSWE in predicting patients’ liver function in future, we analyzed the correlation between our SSWE results and liver function biomarkers after 6 months from liver biopsy. It showed that SSWE had significant negative correlation with PLT count ($r = -0.426$, $P = 0.038$) and serum ALB level ($r = -0.670$, $P < 0.001$). Besides, SSWE values appeared to be positively correlated with serum TBIL ($r = 0.419$, $P = 0.041$) and DBIL levels ($r = 0.518$, $P = 0.010$) at 6 months after liver biopsy.

Discussion

Our study revealed that SSWE examination had a promising diagnostic accuracy to predict liver fibrosis stage, which is better than APRI. SSWE values had significant positive correlations with liver fibrosis severity in patients after kaisai surgery. Moreover, SSWE values were correlated with biological parameters of liver function at 6 months after liver biopsy.

Liver stiffness measurement has become a reliable tool to assess liver fibrosis in adult patients with chronic liver diseases, however, the evaluation of its use in children is limited. Until now, there are a few studies on assessing the predictive power of Fibroscan, TE, ARFI in fibrosis stage for children with various liver diseases.

To the best of our knowledge, this is the first study to investigate the performance of SSWE in predicting liver fibrosis for postoperative children with BA and to compare with those of APRI and FIB-4. The reported cutoff values of TE for predicting advanced fibrosis and cirrhosis in previous literatures varied, ranging from 7.9 to 11 and 11.0 to 25.8 kPa, respectively. Besides, a study on the performance of SSWE in the evaluation of liver fibrosis for children reported a cut-off value of 10.4 kPa for predicting significant fibrosis. In our study, the cut-off values for diagnosis of significant fibrosis, advanced fibrosis and cirrhosis were 9.4, 10.8 and 24.4 kPa, which were within the ranges presented in the previous studies. However, we should note that the cutoff values for diagnosing liver fibrosis differ depending on the method we used. Compared to the results of Fibroscan in previous pediatric BA studies, SSWE yielded similar performance characteristics with AUROC of 0.80 in our study. Shin NY et al. reported the AUROCs of 0.86 and 0.96 respectively in predicting severe fibrosis and cirrhosis for TE in 47 infants with BA, which was slightly better than those of our study. This might be probably due to the relatively poorer discriminative power of our small sample size. For ARFI, Shima H et al. only suggested a correlation between ARFI and fibrosis stage in 8 patients with BA and there was no data regarding AUROC of ARFI in predicting fibrosis in BA patients.

Since there was limited data on the efficacy of SSWE in liver fibrosis for pediatric patients, we tried to compare them with those of adult studies. Two
data from U.S.A also demonstrated that APRI had poor diagnostic accuracy for significant (AUROC

not be completely reduced by sedation for pediatric patients. Second, the serum levels of bilirubin especially the

influence the SSWE results to a dominant level. Fourth, it remained uncertain whether there existed differences

there was no significant difference in SSWE values among different age groups which meant that age might not

adult studies reported the AUROCs of 0.88 to 0.90 and 0.90 to 0.93 for SSWE in predicting significant fibrosis and

severe fibrosis, respectively. Compared to these, the diagnostic accuracy of SSWE was slightly poorer in our

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study. The underlying explanations might be as follows. First, adults could corporate better than children with

readily available and non-expensive technique, has shown encouraging predictive accuracy in liver fibrosis, which

fibrosis, SSWE has technical and operating advantages over TE and ARFI. Unlike TE, SSWE can be performed

predicting fibrosis. This required further studies to elucidate. In addition to its promising efficacy in predicting

inflammation, edema, and increased intracellular pressure. Therefore, the threshold values of SSWE for differ-

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complete breath holding during the SSWE examination and the influence of respiration to SSWE results could

not be completely reduced by sedation for pediatric patients. Second, the serum levels of bilirubin especially the

DBIL could affect the SSWE values, and they were relatively not high for patients in adult studies but might be

abnormally high for some children in our study. It was reported that bile duct obstruction with increased level of

bilirubin could influence the evaluation of liver stiffness by over-diagnosis of liver cirrhosis. The mechanisms

behind the high stiffness in cholestasis remained unclear but might be probably associated with tissue swelling,

increase in various adult liver diseases with AUROCs of more than 0.80. Previous studies were consistent in reporting

that APRI was superior to FIB-4 in predicting fibrosis stage for pediatric liver diseases. As in our study, FIB-4

completely failed to be the reliable fibrosis biomarker (AUROC < 0.50). However, controversy remained regard-

ing the diagnostic accuracy of APRI in liver fibrosis for children. On one hand, Leung DH et al. reported that

APRI exhibited a high AUROC (0.81) in predicting advanced liver fibrosis in children with cystic liver fibrosis liver

disease. Kim SY et al. also suggested that APRI was a promising surrogate of advanced fibrosis (AUROC = 0.92)

cirrhosis (AUROC = 0.91) in children with BA. On the other hand, a study from China reported a sub-

optimal performance of APRI in predicting cirrhosis (AUROC = 0.54) for children with BA. A multicenter
data from U.S.A also demonstrated that APRI had poor diagnostic accuracy for significant (AUROC = 0.67)
or advanced fibrosis (AUROC = 0.63) in children with nonalcoholic fatty liver disease. In our study, APRI
proved to be a poor predictor for liver fibrosis in children with BA (AUROC = 0.65, 0.64, 0.56 for F ≥ 2, F ≥ 3,
F = 4, respectively), which was consistent with the above two studies. Therefore, although APRI show extremely

Table 2. Diagnostic accuracy of APRI and SSWE for liver fibrosis based on optimal cut-off values in
children with BA. APRI, aspartate aminotransferase to platelet ratio index; SSWE, supersonic shear wave
elastography; BA, biliary atresia; AUROC, area under the receiver operating characteristic curve; CI, confidence
interval; PPV, positive predictive value; NPV, negative predictive value.

|                | F2-4 vs. F0-1 | F3-4 vs. F0-2 | F4 vs. F0-3 |
|----------------|---------------|---------------|-------------|
| **APRI**       |               |               |             |
| Cut-off        | 0.70          | 0.93          | 1.00        |
| AUROC (95% CI) | 0.65 (0.35–0.96) | 0.64 (0.41–0.88) | 0.56 (0.31–0.80) |
| Sensitivity, % (95% CI) | 60.0 (17.0–92.7) | 66.7 (30.9–91.0) | 56.3 (30.6–79.2) |
| Specificity, % (95% CI) | 84.2 (59.5–95.8) | 80.0 (51.4–94.7) | 87.5 (46.7–99.3) |
| PPV, % (95% CI) | 50.0 (13.9–86.1) | 66.7 (30.9–91.0) | 90.0 (54.1–99.5) |
| NPV, % (95% CI) | 88.9 (63.9–98.1) | 80.0 (51.4–94.7) | 50.0 (24.0–76.0) |
| **SSWE**       |               |               |             |
| Cut-off        | 9.4           | 10.8          | 24.4        |
| AUROC (95% CI) | 0.79 (0.54–1.00) | 0.81 (0.63–0.99) | 0.82 (0.58–1.00) |
| Sensitivity, % (95% CI) | 80.0 (29.9–98.9) | 77.8 (40.2–96.1) | 93.8 (67.7–99.7) |
| Specificity, % (95% CI) | 73.7 (48.6–89.9) | 80.0 (51.4–94.7) | 87.5 (46.7–99.3) |
| PPV, % (95% CI) | 44.4 (15.3–77.5) | 70.0 (35.4–91.9) | 93.8 (67.7–99.7) |
| NPV, % (95% CI) | 93.3 (66.0–99.7) | 85.7 (56.2–97.5) | 87.5 (46.7–99.3) |
| **APRI + SSWE**|               |               |             |
| AUROC (95% CI) | 0.78 (0.55–1.00) | 0.76 (0.55–0.97) | 0.84 (0.63–1.00) |
| Sensitivity, % (95% CI) | 60.0 (17.0–92.7) | 44.4 (15.3–77.3) | 50.0 (25.5–74.5) |
| Specificity, % (95% CI) | 73.7 (48.6–89.9) | 86.7 (58.4–97.7) | 87.5 (46.7–99.3) |
| PPV, % (95% CI) | 37.5 (10.2–74.1) | 66.7 (24.1–94.0) | 88.9 (59.1–99.4) |
| NPV, % (95% CI) | 87.5 (60.4–97.8) | 72.2 (46.4–88.3) | 46.7 (22.3–72.6) |
promising results in adult studies, the results could not be confirmed in BA children after KPE based on the data in this and previous studies. Besides, SSWE outperformed APRI in predicting liver fibrosis in our study. APRI did not seem to improve the diagnostic accuracy and reliability of SSWE in evaluating fibrosis stages. This might be explained by the fact that SSWE could reflect fibrosis severity with application of local mechanical compression on liver tissue using focused ultrasonography and acquiring strain images whereas the parameters used in the APRI such as AST and ALT are increased because of cholestasis itself or liver disease, in which their power in evaluating fibrosis stages is very limited. Since SSWE could reflect a patient's liver fibrosis stage to some extent whereas laboratory tests could not, SSWE has the advantage over them as the tool to predict prognosis and to assist with designing future treatment plan. Moreover, SSWE is cheaper than laboratory tests. In such a limited resource world, SSWE may be cost-effective.

Furthermore, the effective measurement of liver fibrosis may help predict the liver function during follow-up. Thus, we turned to investigate the correlation of SSWE with the biochemical parameters of liver function at 6 months after SSWE. Results showed that SSWE were negatively correlated with PLT and ALB which reflected the extent of portal hypertension and synthesis function of liver. SSWE appeared to be moderately correlated with bilirubin (TBIL or DBIL) which was the recognized factor associated with prognosis of patients with BA. Thus, these results showed that SSWE might probably serve as the predictor of the prognosis of liver fibrosis during follow-up, which was consistent with the previous study suggesting that liver stiffness measurement values of 3 months after KPE can be used to predict the development of liver related events46. However, future studies with large sample size are needed to validate the above results.

In our study, there was two patients' fibrosis stages over-diagnosed by SSWE. However, careful analysis of these cases suggested that they both had laboratory features suggestive of portal hypertension or actual cirrhosis. This indicates that the gold standard of liver biopsy is not always reliable due to the sampling error and the subjective nature of the reading. We should evaluate a patient's fibrosis stage based on pathologic results together with clinical, laboratory and ultrasonic features.

There are a number of limitations to our study. First, the sample size is small without even distribution of patients in different fibrosis stage. The cut-off value chosen here is a relatively limited result based on the data of 24 patients. These factors make the statistical power of this study low. Second, it is a retrospective study with all its inherent defects. Third, our study excluded the patients with failure in performing SSWE examinations, in which we could not investigate the applicability of SSWE examinations in children with BA. In conclusion, SSWE might be a reliable and noninvasive tool for assessing liver fibrosis in postoperative children with BA whereas APRI showed poor predictability for fibrosis stage. However, due to the relatively low statistical power of this study, the findings here need to be validated in large prospective studies with long follow-up time in the future.

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Author Contributions
L.Z. and S.C. designed and conceived the study; S.C., B.L., Z.Z., Y.Z., B.L. and Q.S. collected data, performed the statistical analysis and interpreted the data; S.C., B.L. and L.Z. drafted the manuscript; L.Z., X.X. and S.C. revised and recheck the articles; all the authors approved the final version of the manuscript.

Additional Information
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