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# Evaluation of Hepatic Shear Wave Elastography to Assess Liver Fibrosis in Biliary Atresia Patients and Its Correlation with Liver Histology and Surgical Outcomes: A Prospective Observational Study

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## Abstract

**Introduction** The native liver survival in biliary atresia (BA) depends on various factors, and one of the crucial factors is the rate of progression of liver fibrosis after portoenterostomy, but there is no reliable investigation to assess it. This study evaluated shear wave elastography (SWE) to detect liver fibrosis in BA patients and assess its utility during follow-up.

**Materials and Methods** This was an observational study; SWE was done preoperatively and postoperatively at 3 and 6 months. The SWE values were analyzed to determine their correlations with preoperative liver histology as well as with postoperative SWE variation between different postoperative outcomes.

**Results** Twenty-one patients were included in the study; the preoperative SWE values were strongly correlated with liver biopsy grading ($p < 0.001$). At the 3 months postoperatively, SWE was done for 18 children: 12 in group A (patent bilioenteric drainage on hepatobiliary iminodiacetic acid scan) and 6 (nonpatent) in group B; mean SWE value was 12.8 and 17.3 kPa, respectively ($p < 0.001$). Ten children from group A underwent SWE 6 months postoperatively, and the mean value was 13.23 kPa.

**Conclusion** The SWE values correlate with liver histology grading, suggesting a reliable alternative to biopsy. Additionally, the baseline SWE values and their trend during follow-up can provide information on the disease's progression.

**Keywords**
- biliary atresia
- shear wave elastography
- liver biopsy
- Kasai portoenterostomy
- liver fibrosis

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## Introduction

Extrahepatic biliary atresia (BA) is a progressive obstructive cholangiopathy, and Kasai portoenterostomy (KPE) is the initial surgical intervention that can be offered to restore bilioenteric drainage.[1,2] The prognosis of BA depends on multiple factors: age at the time of surgery, syndromic or nonsyndromic variety, and cytomegalovirus (CMV) infectivity.[3,4] The native liver survival after KPE mainly depends on the status of liver fibrosis/cirrhosis at the time of surgery, the appropriate surgical technique (KPE), and the incidence of postoperative cholangitis.[5] One of the crucial prognostic factors is the "extent of liver damage at the time of surgery and progression of liver fibrosis with time." There is still no standard investigation that can suggest the progression of pathology during follow-up and is reproducible. Previously, liver biopsy was considered a "gold standard" to assess liver cirrhosis/fibrosis; currently, it is regarded as a "best available" option.[6] Furthermore, liver biopsy is an invasive investigation with its inherent risk of complications.

There are various serum markers (hyaluronate, laminin, alanine transaminase, aspartate transaminase, and gamma-glutamyl transferase [GGT]), serum panels (fibroindex, fibrotest, hepa score), and radiological investigations (ultrasonography [USG], computed tomography [CT], magnetic resonance imaging) to assess liver status by noninvasive methods. However, none has proven its reliability.[7] There is an imminent need for a reliable and noninvasive method that can be repeated during follow-up to assess liver fibrosis so that it can predict prognosis and aid in further management.

Sonoelastography is a reliable and noninvasive tool for assessing hepatic stiffness to detect adult liver fibrosis.[8] There are various forms of ultrasound-based elastography, including transient elastography (TE), acoustic radiation force impulse imaging, and two-dimensional shear wave elastography (SWE). The SWE provides color maps for the degree of stiffness, thus allowing tissue homogeneity assessment.[9] In this study, we assessed the role of SWE in evaluating liver fibrosis in patients with BA and correlated its parameters with liver histology and subsequent surgical outcomes.

## Materials and Methods

This prospective observational cohort study was conducted at a tertiary care center from January 2020 to July 2021. The institutional ethics board approved the study (approval no.: NK/6086/MCH/109). As per the inclusion criteria, all patients of neonatal cholestasis with suspicion of BA who underwent standard preoperative investigation protocol, including biochemical liver function tests (LFT), USG, hepatobiliary iminodiacetic acid (HIDA) scan, and SWE, were included. The children who had not undergone KPE due to advanced stage of cirrhosis lost to follow-up had not survived 3 months postoperatively, and had syndromic BA were excluded from the study. Once investigated, an intraoperative cholangiogram (IOC) was done to confirm the diagnosis. All diagnosed patients were treated by standard extended KPE. A liver wedge biopsy was taken during KPE and examined for various histopathological parameters as adopted previously.[10] The study design and workflow are illustrated in ►**Fig. 1**.

Postoperatively, all children received 1 week of intravenous antibiotics (piperacillin–tazobactam, amikacin, and metronidazole) and were kept nil by mouth for 4 days. All children were followed up weekly for the initial 3 weeks, then once a month for 3 months, and then 3 months for a year. During follow-up at 3 months, all patients underwent a repeat HIDA scan, LFT, and SWE; furthermore, a repeat SWE along with LFT was done at 6 months. According to the HIDA scan result, patients were divided into HIDA patent (established bilioenteric drainage) and nonpatent (absent bilioenteric drainage); subsequently, SWE was compared between both groups. The liver biopsy was not performed at 3 and 6 months postoperatively as it was not feasible.

### Two-Dimensional Shear Wave Elastography

The two-dimensional SWE was performed by a single experienced radiologist performing SWE for 6 years, using the Aixplorer multiwave, SIG2320, Radio-1410 system (Hologic SuperSonic Imagine, France). Patients were supine with their right arm extended above their head to increase intercostal space. The free-breathing SWE was performed for cooperative children.[11] Temporary bottle feeding was employed to calm patients during SWE acquisition. Occasionally, sedation was used when the child was not cooperative. Two different transducers were used: a high-frequency linear transducer (4–15 MHz) and a low-frequency convex abdominal transducer (1–6 MHz). The probe was placed in the intercostal space overlying the liver. The transducer was positioned to assess the right and left lobes of the liver with a large liver

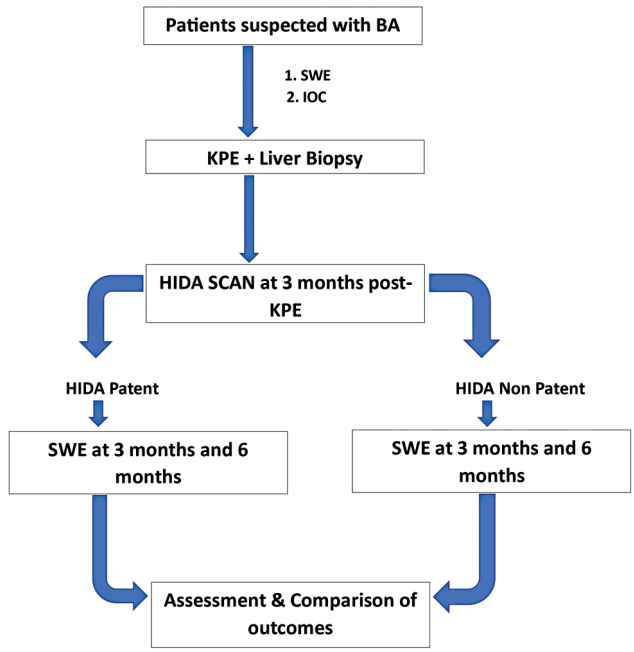


**Fig. 1** Study design. BA, biliary atresia; HIDA, hepatobiliary iminodiacetic acid scan; IOC, intraoperative cholangiogram; KPE, Kasai portoenterostomy; SWE, shear wave elastography.

 

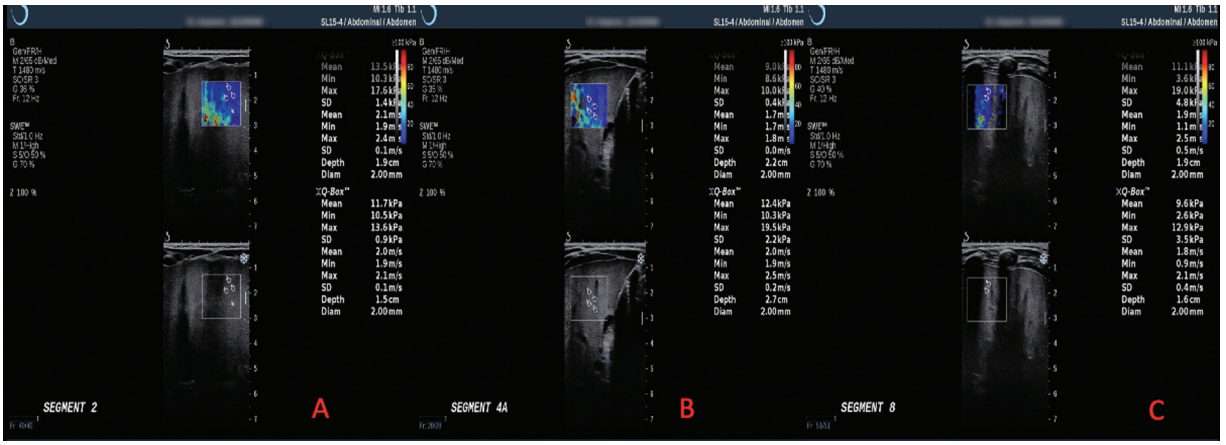


**Fig. 2** Shear wave elastography images of the liver in an 88-day-old boy with biliary atresia. Colored maps (upper panels) of segment VIII (**A**), segment IV (**B**), and segment II (**C**) with region of interests within the box show elasticity values ranging from 9 to 13.5 kPa. The corresponding grayscale images are shown in the lower panels with an irregular outline of the liver and heterogenous echotexture.

area selected with B-mode imaging, avoiding rib attenuation and vessels. Care was taken not to include biliary structures or large vessels in the area of interest. The SWE was done at 2 cm deep from the anterior surface of the liver in segments II, IVA, and VIII through subcostal and intercostal approaches (►**Fig. 2**). Three SWE readings were noted for each segment (II, IVA, and VIII), and then the mean of each segment was calculated separately. Subsequently, the mean value of all three segments was calculated, which was considered the SWE value in kilopascals (kPa) for the subject. The mean normal liver elasticity value in neonates and infants is 4.63 (±0.6) kPa.[12] The higher values of SWE suggest more liver stiffness/fibrosis.

### Liver Biopsy and Histopathology

A liver biopsy was obtained during KPE. The biopsy sample was fixed in formalin and embedded in paraffin. A single histopathologist examined all liver biopsies, and fibrosis grading was done. The liver fibrosis stage was determined according to the METAVIR five-point (F0–F4) scoring system as follows: stage F0—no fibrosis, F1—mild fibrosis (portal fibrosis without septa), F2—substantial fibrosis (portal fibrosis and a few septa), F3—severe fibrosis (numerous septa without cirrhosis), and F4—cirrhosis.[13] Liver histological grading was based on five parameters (►**Table 1**): cholestasis, hepatocellular damage, bile duct proliferation, portal edema, and portal inflammation.[10]

**Table 1** Histopathological grading and scoring system

| Liver biopsy scoring | | |
|---|---|---|
| Cholestasis | Canalicular | 1 |
| | Hepatocytes | 2 |
| | Centrilobular | 3 |
| Hepatocellular damage | Ballooning | 1 |
| | Feathery degeneration | 2 |
| | Necrosis | 3 |
| Bile duct proliferation | Mild | 1 |
| | Moderate | 2 |
| | Severe | 3 |
| Portal edema | Mild | 1 |
| | Moderate | 2 |
| | Severe | 3 |
| Portal inflammation | Mild | 1 |
| | Moderate | 2 |
| | Severe | 3 |
| Minimum score—5 and maximum score—15 | | |

### Statistical Analysis

All quantitative variables were estimated using measures of central location (mean and median) and measures of dispersion (standard deviation [SD] and standard error). For normally distributed data, means were compared using Student's *t*-tests for groups, and the Mann–Whitney's *U* test was applied for skewed data. Repeated measure analysis of variance (ANOVA) was applied for time-related variables, followed by one-way ANOVA for normally distributed data or the Wilcoxon's signed rank test for skewed data. The correlation between median and mean SWE measurements was compared against the liver fibrosis scores and liver biopsy grading using Spearman's rho (rs) correlation. The correlation was graded as negligible (rs = 0–0.09), weak (rs = 0.10–0.39), moderate (rs = 0.40–0.59), strong (rs = 0.60–0.79), and very strong correlation (rs = 0.80–1.00). All statistical tests were conducted at a 5% significance level using SPSS software (version 23; SPSS, Inc., Chicago, IL, United States).

## Results

Out of 29 patients screened with suspected BA, 8 were excluded (unproven diagnosis in 2 syndromic patients, distal patency on IOC in 4, and advanced stage of liver cirrhosis for 1 where KPE was abandoned and 1 was lost to follow-up). Twenty-one patients (nine females) who fulfilled the inclusion criteria were enrolled in the study. The baseline

 

**Table 2** Preoperative demographics and clinical characteristics of children

| Sl. no. | Parameter | Value |
|---|---|---|
| 1 | Age (d), mean ± SD | 71.86 ± 28.13 |
| 2 | Weight (kg), mean | 3.82 |
| 3 | M:F, *N* (%) | 12:9 |
| 4 | Bilirubin (mg/dL), mean | 10.25 ± 2.95 |
| 5 | AST (IU/L), mean ± SD | 241.15 ± 94.95 |
| 6 | ALT (IU/L), mean ± SD | 178 ± 132.2 |
| 7 | GGT (IU/L), mean ± SD | 604.86 ± 385.74 |
| 8 | ALP (IU/L), mean ± SD | 619.90 ± 215.15 |
| 9 | Preoperative SWE (kPa), mean ± SD | 12.49 ± 2.81 |
| 10 | Portal fibrosis grading: F2/F3 | 10/11 |
| 11 | Liver biopsy scoring, mean ± SD | 9.52 ± 1.5 |

Abbreviations: Age, age at surgery; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; M:F, male:female; SD, standard deviation; SWE, shear wave elastography.

demographic characteristics are illustrated in ►**Table 2**. The median age at the time of surgery was 72 days, while the mean value of preoperative elastography was 12.49 ± 2.81 kPa.

The mean liver biopsy scoring was 9.52 ± 1.50 out of 15; applying the Spearman' correlation test showed a strong positive correlation (►**Fig. 3A**) between preoperative elastography and liver biopsy scoring (rho = 0.61, $p = 0.003$). Similarly, 10 patients (47.6%) had F2 portal fibrosis with a mean SWE of 10.28 kPa. In contrast, 11 (52.4%) had F3 portal fibrosis with a mean SWE of 14.49 kPa (►**Fig. 3B**), and this difference between the groups (using the Wilcoxon and Mann–Whitney's *U* test) was found to be significant ($W = 2.000$, $p = < 0.001$).

The treatment success was assessed at 3 months with a HIDA scan as patency of bilioenteric drainage. Of 21 patients, 12 were HIDA patent 3 months after surgery, and 6 were nonpatent. Unfortunately, we lost three patients after surgery as they succumbed before the 3-month postoperative mark. One patient died at the hospital due to sepsis and severe cholangitis with liver failure, and the other two died at home for unclear reasons that could be related to their underlying disease, the coronavirus disease 2019 (COVID-19) pandemic, or both.

The mean age (days) at the time of surgery in the patent group was 70 ± 14.76 and 79.5 ± 10.13 in the nonpatent group. The mean preoperative SWE in the patent group was 11.97 ± 2.12 kPa; among the nonpatent group, it was 14.92 ± 2.94 kPa (►**Fig. 4**); the difference was statistically significant ($W = 14.500$, $p = 0.049$). Similarly, the mean preoperative liver biopsy score for the patent group ($n = 12$) was 9.0 ± 1.54 out of 15, while for the nonpatent group ($n = 6$), it was 10.83 ± 0.98. The mean SWE at 3 months in the patent group was 12.8 ± 2.28 kPa, and among the nonpatent group, it was 17.3 ± 2.28 kPa (►**Fig. 4**); the difference was statistically significant ($p = 0.001$).

The mean preoperative total bilirubin was 10.25 mg/dL (±2.95); among the patent group, it was 10.65 mg/dL (±-2.77), while in the nonpatent group, it was 10.70 mg/dL (±3.50) with a *p*-value of 0.892. The mean total bilirubin at 3 months post-KPE in the patent group was 3.92 mg/dL

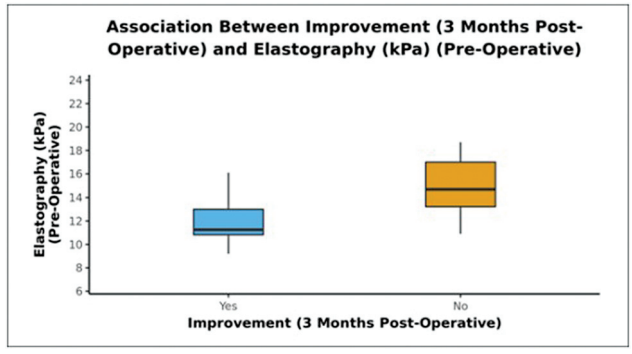


**Fig. 4** Association between preoperative elastography and postoperative outcome. Improvement = patent bilioenteric drainage on hepatobiliary iminodiacetic acid scan.

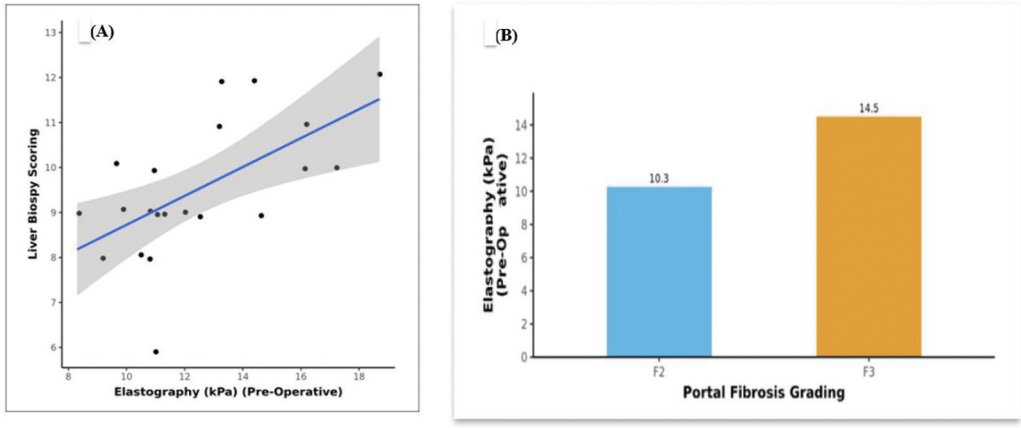


**Fig. 3** (**A**) Correlation of preoperative shear wave elastography value with liver biopsy scoring. (**B**) Association between portal fibrosis grading and preoperative elastography.

 

(±1.61), and in the nonpatent group, it was 12.08 mg/dL (±2.08) with a *p*-value of 0.001. At 3 months, the GGT value in the patent group ($n = 12$) was 417.25 ± 105.15 IU/L, whereas in the nonpatent group ($n = 6$), it was 841.50 ± 263.86 with a *p*-value of 0.002. At 6 months, the GGT value in the patent group ($n = 10$) was 233.3 IU/L.

Out of 12 patients in the HIDA patent group at 3 months, 10 underwent elastography 6 months postsurgery. The other two patients were lost to follow-up. The mean ± SD elastography in these patients was 11.97 ± 2.12 kPa preoperatively, 12.80 ± 2.28 kPa at 3 months postoperatively, and 13.23 ± 2.25 kPa at 6 months postoperatively (►**Fig. 5**). It showed a slow but continuous rise in elastography values over time in the HIDA patent group.

On the other hand, in the HIDA nonpatent group (►**Fig. 5**), the mean elastography score was 14.92 kPa preoperatively and 17.3 at 3 months; this rise was significantly higher and sharp compared with the patent group. None of the patients in the nonpatent group underwent elastography at 6 months, either because of mortality, lost to follow-up, or referred for a liver transplant (►**Fig. 5**).

## Discussion

This study was performed to determine the accuracy of SWE in evaluating various stages of liver fibrosis in pediatric patients with BA. In this study, we demonstrated that SWE values were well correlated with pathological stages of liver fibrosis in children. Although the study showed that fibrosis progressed over time even after KPE, the progression rate differed for patent and nonpatent KPEs. Therefore, SWE can serve as a prognostic marker for predicting the outcome of KPE by assessing liver fibrosis and monitoring its rate of progression at regular intervals during the postoperative period.

The result of our study is consistent with previous elastography studies proving that SWE of the liver can reliably identify fibrosis compared with normal livers.[14–16] Various

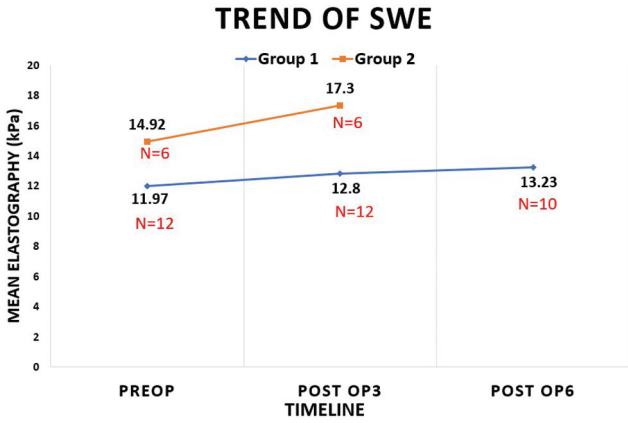


**Fig. 5** Trend of pre- and postoperative elastography in hepatobiliary iminodiacetic acid patent and nonpatent groups. Group 1—patent bilioenteric drainage group. Group 2—nonpatent bilioenteric drainage group. N, number of patients; PREOP, preoperatively; POSTOP3, postoperatively at 3 months; POSTOP6, postoperatively at 6 months.

studies have found that SWE has greater utility in identifying severe fibrosis from mild fibrosis but cannot reliably distinguish different fibrosis stages.[17] Similarly, Farmakis et al found that children with mild fibrosis have the lowest median SWE values compared with those with advanced fibrosis but could not differentiate between various fibrosis stages.[18] A recent meta-analysis demonstrated that elastography can differentiate between higher fibrosis scores (F3–F4) and lower fibrosis (F0–F2) with a sensitivity of 85% and specificity of 81%.[19] Yoon et al found that advanced liver fibrosis (F3–F4) was associated with older age, elevated preoperative direct bilirubin levels, and higher preoperative SWE values. The mean preoperative SWE values for F0–F2 and F3–F4 were 11.6 and 18.4 kPa, respectively.[20] In our cohort, patients were either F2 or F3 fibrosis, and SWE value correlated well with the stages, 10.28 kPa in the F2 group and 14.49 kPa in the F3 group. None of the patients had mild fibrosis or cirrhosis, so we could not define cutoffs for various fibrosis stages. Chen et al also mentioned that SWE values correlated with the stages of liver fibrosis, with cutoff values for different stages as 9.1, 11.6, 13.0, and 15.7 kPa for F1, F2, F3, and F4, respectively.[21]

Diagnosing BA early is crucial, as a higher degree of fibrosis interferes with biliary drainage after KPE.[3] A similar observation was also found in our cohort of patients; patients who were HIDA patent 3 months after surgery had lower values of preoperative SWE than nonpatent. So, SWE can help predict the outcomes of KPE. Caruso et al retrospectively analyzed the role of SWE in BA patients according to treatment outcome. The preoperative SWE value significantly predicts the patient outcome (receiver operating characteristic analysis identified a cutoff value of 9.6 kPa, sensitivity = 55.6%, specificity = 100%).[22] Yoon et al conducted postoperative SWE assessments in BA patients on the 3rd, 5th, 7th, and 180th postoperative days, and they found that in patients with poor outcomes, the SWE values were 18.0, 15.3, 17.0, and 25.6 kPa, respectively. To predict poor liver outcomes, they established various cutoff values for SWE at different durations of follow-up.[20] We followed SWE in patients at 3 and 6 months following KPE. Ten patients were followed up out of 21 at the end of 6 months. All 10 patients had HIDA patency at 3 months postoperatively. There was a gradual rise in SWE values in these patients over time, thus suggesting that the disease was gradually progressing even after a patent KPE. Therefore, its utility is identifying patients with fibrosis with this noninvasive method and following them over time.

Multiple studies have assessed the role of elastography in predicting the risk of esophageal varices after KPE.[23–26] However, in these studies, TE was used, which has many pitfalls, like the inability to choose different locations for the region of interest and to avoid liver vessels/bile ducts. Also, TE causes more technical failure in young children.[27,28] In the index study, children did not undergo endoscopic screening for esophageal varices. For children with long-term follow-ups, SWE can be used to determine the appropriate timing of screening endoscopy. Chen et al studied SWE to assess liver fibrosis after surgery.[26] They compared SWE with liver

 

biopsy in postoperative patients and found a significant correlation.

Due to ethical and feasibility constraints, it was not possible to repeat liver biopsy postoperatively, so, in our study, the surgical outcomes were taken under consideration at 3-month and 6-month follow-ups. We believe that liver fibrosis would be less in patients with patent bilioenteric drainage. In contrast, in the nonpatent group, the progression of liver fibrosis would be rapid, so the rate of alteration in SWE values would be different in both groups. This approach allows the evaluation of liver fibrosis progression and treatment outcomes without requiring invasive procedures. In our study, BA patients were evaluated by SWE from preoperative phases to 6 months postoperatively, and all were within the same cohort. This longitudinal approach offers more profound insights into disease progression and the efficacy of interventions over time.

The main limitation of this study is the small sample size, primarily because of the COVID-19 pandemic during the study period. In addition, multiple factors that can affect liver fibrosis progressions, such as CMV positivity and postoperative cholangitis, were not considered separately in the result. Furthermore, the follow-up period after surgery was only 6 months. All the patients had either F2 or F3 fibrosis on histopathology; a more extensive dataset is needed to identify cutoff values on SWE for different stages of fibrosis.

## Conclusion

SWE is a reliable and noninvasive investigation for evaluating and monitoring the progression of liver fibrosis in BA patients. It can potentially minimize the need for percutaneous liver biopsy and thus provide a noninvasive method for assessing fibrosis progression. In addition, SWE can predict the outcomes of KPE and might help in better prognostication.

### Authors' Contributions

S.S. and M.F.A. conceptualized the study and contributed to writing—original draft preparation; S.S., R.P.K, and S.B.L. did the methodological analysis; S.S. and S.B.L. validated the study; A.B., A.K.S., and K.G. performed the formal analysis; S.S. and R.P. K. contributed to writing—review and editing, and supervised the study. All authors have read and agreed to the published version of the manuscript.

### Funding

None.

### Conflict of Interest

None declared.

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