Two-Dimensional Shear Wave Elastography Predicts Liver Fibrosis in Jaundiced Infants with Suspected Biliary Atresia: A Prospective Study

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Objective: This study aimed to evaluate the role of preoperative two-dimensional (2D) shear wave elastography (SWE) in assessing the stages of liver fibrosis in patients with suspected biliary atresia (BA) and compared its diagnostic performance with those of serum fibrosis biomarkers.

Materials and Methods: This study was approved by the ethical committee, and written informed parental consent was obtained. Two hundred and sixteen patients were prospectively enrolled between January 2012 and October 2018. The 2D SWE measurements of 69 patients have been previously reported. 2D SWE measurements, serum fibrosis biomarkers, including fibrotic markers and biochemical test results, and liver histology parameters were obtained. 2D SWE values, serum biomarkers including, aspartate aminotransferase to platelet ratio index (APRI), and other serum fibrotic markers were correlated with the stages of liver fibrosis by METAVIR. Receiver operating characteristic (ROC) curves and area under the ROC (AUROC) curve analyses were used.

Results: The correlation coefficient of 2D SWE value in correlation with the stages of liver fibrosis was 0.789 (p < 0.001). The cut-off values of 2D SWE were calculated as 9.1 kPa for F1, 11.6 kPa for F2, 13.0 kPa for F3, and 15.7 kPa for F4. The AUROCs of 2D SWE in the determination of the stages of liver fibrosis ranged from 0.869 to 0.941. The sensitivity and negative predictive value of 2D SWE in the diagnosis of ≥ F3 was 93.4% and 96.0%, respectively. The diagnostic performance of 2D SWE was superior to that of APRI and other serum fibrotic markers in predicting severe fibrosis and cirrhosis (all p < 0.005) and other serum biomarkers. Multivariate analysis showed that the 2D SWE value was the only statistically significant parameter for predicting liver fibrosis.

Conclusion: 2D SWE is a more effective non-invasive tool for predicting the stage of liver fibrosis in patients with suspected BA, compared with serum fibrosis biomarkers.

Keywords: Hyperbilirubinemia; Biliary atresia; Liver cirrhosis; Elasticity imaging techniques; Ultrasound

INTRODUCTION

An accurate method to monitor the progression of liver fibrosis can lead to better prognosis and management of pediatric patients with chronic liver diseases [1,2]. For example, in patients with biliary atresia (BA), the stage of...
biopsy (n = 3). The remaining 48 patients were diagnosed with neonatal hepatitis syndrome (n = 38), Alagille syndrome (n = 2), intrahepatic cholestasis caused by citrin deficiency (n = 3), choledochal cyst (n = 2), and progressive familial intrahepatic cholestasis (n = 3) by liver biopsy or liver biopsy combined with intraoperative cholangiography, percutaneous ultrasound-guided cholangiography, or follow-up of the clinical and biochemical laboratory values. The 2D SWE measurements of 69 of the 216 patients have been previously reported [14]; however, the 2D SWE values were not analyzed with the histological stages of liver fibrosis in our previous study. This study was approved by the ethical committee at the First Affiliated Hospital of the Sun Yat-sen University, and written informed parental consent was obtained from all patients.

**Data Collection**

The patients’ clinical courses, documented pathological findings, and laboratory results were collected. The collected standard biochemical test results included serum levels of total bilirubin, direct bilirubin, indirect bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), albumin, bile acid, and prothrombin time-international normalized ratio (PT-INR). Platelet counts were also collected. As a non-invasive biochemical fibrosis marker, the AST to platelet ratio index (APRi) [15] was also calculated; a serum AST level of 37 IU/L was used as the upper normal limit:

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APRi = \frac{\text{AST}}{\text{upper normal limit}} \times \frac{10^9}{\text{platelet count (L)}}
\]

Direct serum fibrotic markers, including serum levels of fibronectin, hyaluronic acid (HA), laminin, procollagen type III amino-terminal peptide, and type IV collagen, were collected for 163 of the corresponding histological examinations. The remaining 53 patients were not tested for direct serum fibrotic markers since it was not a routine test in our study. The normal ranges are 180–280 mg/L for fibronectin, 0–120.0 ng/mL for HA, 0–130 ng/mL for laminin, 0–15.00 ng/mL for procollagen type III amino-terminal peptide, and 0–95.00 ng/mL for type IV collagen. The 2D SWE measurements and direct serum fibrosis marker results were obtained within 30 days of each other.

**Liver Stiffness Measurements**

An Aixplorer scanner (Supersonic Imagine) incorporating
a linear array transducer (SL15-4) was used to perform the liver stiffness measurements (Fig. 1).

The infants fasted for 1–8 hours before the liver stiffness measurements and were kept quiet by feeding while the measurements were being performed. All 2D SWE examinations were performed using an epigastric transducer positioned by a single sonographer (> 3 years of experience in elastography). We did not use the intercostal position because an infant’s intercostal position is too narrow to apply liver stiffness measurements.

2D SWE was performed in dual mode (i.e., elastograms displayed alongside grayscale sonograms in real-time) [14]. The operator chose the best static 2D SWE display images, onto which a rectangular electronic region of interest (ROI) and a circular ROI (placed within the center of the rectangular ROI with a diameter of 0.8–1.5 cm) were positioned at least 0.5 cm but not more than 1.0 cm away from the capsular surface of the liver for analysis [10,14]. Once the optimal sizes of the ROI were chosen, they were fixed for subsequent measurements in each subject. Special attention was paid to avoid any focal lesions, vessels, biliary tracts, or artifacts from nearby lung gas. A successful 2D SWE was defined as that when most of the ROI box (> 90%) could be filled with a homogeneous color and maintained for at least one respiratory cycle with the infants maintaining regular and peaceful breathing. Three independent 2D SWE measurements were performed for each patient. The average values from the three reliable measurements were used for subsequent statistical analyses.

**Evaluation of Liver Histology**

Wedge biopsy specimens (≥ 5 mm in size) were obtained during KPE. Percutaneous liver biopsies (≥ 1.5 cm in length) were performed with an 18-gauge suction needle under ultrasound guidance. The biopsy specimens were fixed in formalin, embedded in paraffin, sectioned, and stained with hematoxylin-eosin, Azan-Mallory, and Elastica van Gieson stains. Liver specimens were collected and evaluated using the METAVIR fibrosis scoring system for liver fibrosis and inflammatory activity in consensus by two pathologists who were blinded to the 2D SWE data and had > 10 years of experience in liver pathology. The METAVIR fibrosis scoring system is as follows: F0, no portal fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa or lobular distortion without cirrhosis; and F4, cirrhosis. The histological necroinflammatory activity was classified as none, mild, moderate, or severe. Disagreements were resolved by consensus.

**Statistical Analysis**

Descriptive statistics were obtained for demographic, clinical, and laboratory characteristics. The Kolmogorov-Smirnov test was used to test the normal distribution of the quantitative variables. When quantitative variables were normally distributed, the results were expressed as the mean ± SD; otherwise, the median and interquartile range (IQR) (25th–75th percentile) were reported. Qualitative variables were summarized as counts and percentages. Spearman’s rank coefficient was used to test the correlation between two study variables. A frequency distribution was obtained for choosing the optimal cut-off values of 2D SWE to maximize the sum of sensitivity and specificity for different fibrosis thresholds: F0 vs. F1–F4 (≥ F1), F0–F1 vs. F2–F4 (≥ F2), F0–F2 vs. F3–F4 (≥ F3), and F0–F3 vs. F4 (F = 4). To predict the histological stages of fibrosis, ordered logistic regression analyses were performed using the histological stages of fibrosis as ordinal data (F0, F1, F2, F3, and F4) for the dependent variable. The independent variables included the collected standard biochemical and hematological test results and age at the time of the corresponding histological examination. The diagnostic performances
of 2D SWE, APRi, and other serum markers were assessed using receiver operating characteristic (ROC) curves and area under the ROC (AUROC) curve analyses. Comparisons of AUROCs were performed for correlated data. Linear logistic regression analysis was also performed. Data analysis was performed using SPSS statistical software (SPSS, version 16; SPSS Inc.) and MedCalc Statistical Software version 15.2.2 (MedCalc Software bvba; http://www.medcalc.org; 2015). Significant differences were defined as those with a two-sided p value ≤ 0.05. For the multiple pairwise comparisons, the p value was adjusted precisely following the Bonferroni method.

RESULTS

The clinical characteristics of all patients are summarized in Table 1. We tested the correlation between the stages of liver fibrosis and other clinical characteristics (Table 2). Results showed that 2D SWE, age, bile acid, GGT, AST, APRi, total bilirubin level, and direct bilirubin level values were significantly correlated with the stages of liver fibrosis (all p < 0.05); however, the correlation coefficient of 2D SWE (r = 0.786) was the greatest (Fig. 2) compared with age (r = 0.368, p < 0.001); APRi (r = 0.178, p = 0.008), GGT (r = 0.319, p < 0.001); and serum bilirubin level (r = 0.242, p < 0.001) (Table 2). Of the five direct serum fibrosis markers, fibronectin (r = 0.251, p = 0.001); HA (r = 0.207, p < 0.008); and type IV collagen (CIV) (r = 0.241, p < 0.002) were significantly correlated with the stage of liver fibrosis.

We further included all the significantly important parameters in a multivariate analysis (direct bilirubin and indirect bilirubin were not included in the multivariate models because they correlated with total bilirubin levels). The outcome showed that 2D SWE was the only factor that influenced the stages of liver fibrosis, with a Wald of 64.871 (Table 3).

We tested the correlation between histological necroinflammatory activity and 2D SWE in the first 80 patients (including 61 patients with BA and 19 patients without BA). The results showed that histological activity was not correlated with the 2D SWE value (r = 0.096, p = 0.397 for all; r = 0.204, p = 0.402 for patients without BA; r = -0.043, p = 0.743 for patients with BA) (Fig. 3). The 2D SWE value was 9.9 (6.5–24.4) kPa (median [range]) for none, 13.1 (6.0–48.4) kPa for mild, 11.4 (8.8–24.1) kPa for moderate, and 12.7 (9.8–19.7) kPa for severe, for all patients, respectively (Fig. 3). No significant differences were detected among the activities (p = 0.493). On the other hand, the stage of liver fibrosis was significantly correlated with 2D SWE (r = 0.807, p < 0.001). Therefore, we did not analyze the histological necroinflammatory activity of the remaining patients.
Diagnostic Accuracy of the 2D SWE Value in Predicting the Stage of Liver Fibrosis

The 2D SWE value had a good diagnostic performance for predicting each stage of fibrosis (AUROCs = 0.869-0.941, all \( p < 0.001 \), Table 4, Fig. 4), and the cut-off values were calculated as 9.1 kPa for F1, 11.6 kPa for F2, 13.0 kPa for F3, and 15.7 kPa for F4. The differences in the 2D SWE value in each stage of fibrosis were statistically significant, with F0 (7.8 [7.0–8.5] kPa) (median [IQR]) vs. F1 (9.9 [8.8–11.6] kPa), \( p < 0.001 \); F1 (9.9 [8.8–11.6] kPa) vs. F2 (11.7 [10.3–13.0] kPa), \( p = 0.001 \); F2 (11.7 [10.3–13.0] kPa) vs. F3 (16.3 [14.6–23.6] kPa), \( p < 0.001 \); F3 (16.3 [14.6–23.6] kPa) vs. F4 (23.6 [16.0–37.7] kPa), \( p = 0.009 \) (Fig. 2). Notably, the sensitivity of 2D SWE in predicting \( \geq F3 \) was 93.4%. Further, the negative predictive value in determining \( \geq F3 \) and cirrhosis was 96.0–96.3% (Table 4); however, the sensitivity of 2D SWE in predicting \( \geq F4 \) was only 78.6% (Fig. 5).

Subgroup analysis showed that for patients with BA, the sensitivity and negative predictive value in determining \( \geq F3 \) could also yield 89.9% and 92.1%, respectively. Specifically, both the sensitivity and specificity of the 2D SWE value in determining \( \geq F3 \) reached 100% in patients without BA (Table 4).

Comparisons of the 2D SWE Value, Age, AST, GGT, APRI, Total Bilirubin, and Other Direct Fibrosis Biomarkers

The diagnostic performance of each parameter that was significantly correlated with the pathological stages of liver fibrosis was calculated. Comparison of AUROCs for the diagnosis of stages F2, F3, and F4 between the 2D SWE value and other biomarkers by the Delong method showed that the AUROCs of 2D SWE were significantly greater compared with the others (all \( p < 0.005 \)) (Table 5).

Correlation of 2D SWE with Clinical Characteristics

We tested the correlation between the 2D SWE value and
clinical characteristics. Results showed that age, stages of liver fibrosis, bile acid, bilirubin level, GGT level, and AST level were significantly correlated with the 2D SWE value (all \( p < 0.05 \), Table 6). Further multiple regression analysis showed that the stages of liver fibrosis yielded a coefficient of determination of 0.509. Age, AST, and GGT

Table 3. Multivariate Analysis of Important Characteristics by Ordered Logistic Regression for Liver Fibrosis Stages, F0–F4

| Variable                  | Coefficient (95% CI) | Standard Error | Wald     | \( P \) |
|---------------------------|----------------------|----------------|----------|--------|
| 2D SWE (kPa)              | 0.333 (0.252–0.414)  | 0.041          | 64.871   | < 0.001|
| \( \gamma \)-glutamyltransferase (U/L) | 0.000 (-0.000–0.001) | 0.000          | 0.169    | 0.200  |
| Total bilirubin (μmol/L)  | 0.002 (-0.003–0.007) | 0.002          | 0.480    | 0.488  |
| Age (days)                | 0.005 (-0.013–0.023) | 0.009          | 0.323    | 0.570  |
| Aspartate aminotransferase (U/L) | 0.000 (-0.003–0.002) | 0.002          | 0.288    | 0.592  |
| Bile acid (μmol/L)        | 0.002 (-0.003–0.007) | 0.003          | 0.476    | 0.735  |

CI = confidence interval, SWE = shear wave elastography, 2D = two-dimensional

Fig. 3. Box-and-whisker plot shows 2D SWE values for histological necroinflammatory activities in all 80 patients (A), in 61 patients with biliary atresia (B), and in 19 patients without biliary atresia (C).

A. The 2D SWE value was 9.9 (6.5–24.4) kPa (median [ranges]) for none, 13.1 (6.0–48.4) kPa for mild, 11.4 (8.8–24.1) kPa for moderate, and 12.7 (9.8–19.7) kPa for severe, respectively. B. The 2D SWE value was 10.7 (8.8–24.4) kPa for none, 14.1 (7.1–48.4) kPa for mild, 11.6 (9.7–24.1) kPa for moderate, and 12.7 (11.9–19.7) kPa for severe, respectively. C. The 2D SWE value was 8.6 (6.5–14.3) kPa for none, 9.0 (6.0–30.9) kPa for mild, and 9.0 (8.8–21.2) kPa for moderate, respectively. SWE = shear wave elastography, 2D = two-dimensional

Table 4. Diagnostic Accuracy of 2D SWE Score in Predicting Histological Fibrosis Stages in All Patients, Patients with BA and Patients without BA

| AUROCs (95% CI) | Cut-Off Value | Sensitivity | Specificity | NPV | PPV | Accuracy |
|-----------------|---------------|-------------|-------------|-----|-----|----------|
| All patients (n = 216) |               |             |             |     |     |          |
| \( \geq F1 \)    | 0.941 (0.901–0.968) | 9.1         | 85.2 (79.4–89.9) | 95.0 (75.1–99.9) | 32.8 (19/58) | 99.4 (157/158) | 81.5 |
| \( \geq F2 \)    | 0.869 (0.817–0.911) | 11.6        | 78.2 (70.2–84.9) | 83.1 (73.3–90.5) | 70.4 (69/98) | 88.1 (104/118) | 80.1 |
| \( \geq F3 \)    | 0.941 (0.901–0.969) | 13.0        | 93.4 (85.3–97.8) | 85.0 (78.0–90.5) | 96.0 (119/124) | 77.2 (71/92) | 88.0 |
| \( \geq F4 \)    | 0.889 (0.736–0.916) | 15.7        | 78.6 (59.0–91.7) | 81.9 (75.7–87.1) | 96.3 (154/160) | 39.3 (22/56) | 81.5 |
| BA patients (n = 168) |               |             |             |     |     |          |
| \( \geq F1 \)    | 0.935 (0.887–0.967) | 9.1         | 90.1 (84.4–94.2) | 85.7 (42.1–99.6) | 27.3 (6/22) | 99.3 (145/146) | 89.9 |
| \( \geq F2 \)    | 0.836 (0.772–0.889) | 12.1        | 77.1 (68.5–84.3) | 82.0 (68.6–91.4) | 60.3 (41/68) | 91.0 (91/100) | 78.6 |
| \( \geq F3 \)    | 0.918 (0.866–0.955) | 13.5        | 89.9 (80.2–95.8) | 83.8 (75.1–90.5) | 92.1 (82/89) | 78.5 (62/79) | 85.7 |
| \( \geq F4 \)    | 0.855 (0.793–0.905) | 15.7        | 75.0 (53.3–90.2) | 77.8 (70.1–84.) | 94.9 (112/118) | 36.0 (18/50) | 77.4 |
| Non-BA patients (n = 48) |               |             |             |     |     |          |
| \( \geq F1 \)    | 0.870 (0.742–0.950) | 9.0         | 62.9 (44.9–78.5) | 100.0 (75.3–100.0) | 50.0 (13/26) | 100.0 (22/22) | 72.9 |
| \( \geq F2 \)    | 0.896 (0.774–0.965) | 9.0         | 93.3 (68.1–99.8) | 75.8 (57.7–88.9) | 96.2 (25/26) | 63.6 (14/22) | 81.2 |
| \( \geq F3 \)    | 1.0 (0.926–1.0)   | 14.3        | 100.0 (59.0–100.0) | 100.0 (91.4–100.0) | 100.0 (41/41) | 100.0 (7/7) | 100.0 |
| \( \geq F4 \)    | 0.977 (0.886–0.999) | 14.5        | 100.0 (39.8–100.0) | 95.5 (84.5–99.4) | 100.0 (42/42) | 66.7 (4/6) | 95.8 |

AUROCs = area under receiver operating characteristic curves, BA = biliary atresia, CI = confidence interval, NPV = negative predictive value, PPV = positive predictive value, SWE = shear wave elastography, 2D = two-dimensional
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Fig. 4. Graph shows AUROC for 2D SWE values in the upper right lobe to differentiate at least the F2 stage of fibrosis from a stage of fibrosis lesser than F2, at least the F3 stage of fibrosis from a stage of fibrosis lesser than F3, and the F4 stage of fibrosis from a stage of fibrosis lesser than F4 in all 216 patients, respectively. AUROC = area under receiver operating characteristic curve, SWE = shear wave elastography, 2D = two-dimensional.

Fig. 5. Two-dimensional SWE images of a 79-day-old male infant with biliary atresia. Ultrasound images show a stiffness color map (top), which is heterogeneous, and SWE measurements in the regions of interest (bottom) of mean 29.1 kPa, which is abnormally higher than the cut-off value of F4. However, the histological stage of liver fibrosis of the infant was only F3. SWE = shear wave elastography.

also influenced the 2D SWE (all p < 0.05, Table 6).

We also correlated the stages of liver fibrosis of the patients without BA (n = 48) and the patients with BA (n = 168) with the 2D SWE values. The results showed that the correlation coefficients between the two groups of patients were similar (0.755 vs. 0.743).

DISCUSSION

In this study, we demonstrated that 2D SWE values were well correlated with the pathological stages of liver fibrosis in a large sample of jaundiced infants with suspected BA. Additionally, 2D SWE demonstrated superiority over serum fibrosis markers, including the APRI score. Our findings suggest that non-invasive determination of the stage of liver fibrosis in infants with obstructive jaundice is possible and could consequently help provide better management in clinical settings.

Several non-invasive tools for evaluating pediatric liver fibrosis exist [16-23], such as APRI and direct serum fibrosis markers. Previous studies [16,19,20] have introduced APRI to predict liver fibrosis and prognosis in BA; however, APRI was not very well correlated with liver fibrosis (20). In this study, the coefficient of APRI (r = 0.18) with the histological stage of liver fibrosis was weaker than that of 2D SWE (r = 0.79). Other serum fibrosis markers, such as fibronectin and HA, had varied values for predicting liver fibrosis in other studies as well as in this study [17,18,21,22]. Nevertheless, the diagnostic performance of these markers is insufficient for clinical practice.

Both GGT and age had a positive correlation with the histological stage of liver fibrosis, which is similar to previous studies [10,17]. Serum GGT levels have been reported to be valuable in differentiating BA from non-BA [24]. Thus, a higher GGT level potentially indicates more severe liver fibrosis; however, multiple regression analysis showed that the GGT level was not statistically significant in determining the stage of liver fibrosis.

2D SWE has been widely used for evaluating liver fibrosis in adults with chronic liver diseases [7-9,25,26]. Recently, studies have demonstrated that 2D SWE could accurately assess liver fibrosis in children with jaundice [10,11]. In the current study, 2D SWE values showed the greatest diagnostic performance in predicting the stage of liver fibrosis compared with APRI and other serum fibrosis markers. The specificity of 95.0% and the positive predictive value of 99.4% in differentiating ≥ F1 from F0 was similar to that
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might be one reason for this. On the other hand, our study showed that in predicting severe fibrosis or cirrhosis, the 2D SWE yielded a high negative predictive value (96.0–96.3%, respectively), which means that most patients with a stiffness value < 15.7 kPa would not have cirrhosis and most with a stiffness value < 13.3 kPa would not have severe fibrosis.

The correct prediction of the stage of liver fibrosis is very important for infants with obstructive jaundice because liver fibrosis is a critical predictor of disease outcomes and can affect therapy and follow-up [2,28]. For patients with BA, the progression of hepatic fibrosis is aggressive and rapid [29]. Severe fibrosis at the time of KPE is a

Table 5. Comparisons of The Diagnostic Accuracy of 2D SWE Value, Age, Total Bilirubin, AST, GGT, APRI and Other Non-Invasive Fibrosis Markers in Predicting Histological Fibrosis Stages

| Parameter                | AUROCs for ≥ F2 (P)        | AUROCs for ≥ F3 (P)        | AUROCs for F4 (P)        |
|--------------------------|---------------------------|---------------------------|--------------------------|
| 2D SWE (kPa)             | 0.868 (0.815, 0.910)     | 0.941 (0.901, 0.968)     | 0.884 (0.799, 0.917)     |
| GGT (U/L)                | 0.645 (0.577, 0.709)     | 0.701 (0.636, 0.762)     | 0.603 (0.534, 0.669)     |
| Age (days)               | 0.658 (0.590, 0.721)     | 0.659 (0.592, 0.723)     | 0.738 (0.673, 0.795)     |
| AST (U/L)                | 0.637 (0.569, 0.702)     | 0.546 (0.476, 0.614)     | 0.602 (0.533, 0.668)     |
| Total bilirubin (g/L)    | 0.629 (0.561, 0.694)     | 0.633 (0.565, 0.698)     | 0.507 (0.438, 0.575)     |
| APRI                     | 0.624 (0.555, 0.689)     | 0.540 (0.460, 0.598)     | 0.569 (0.500, 0.636)     |
| Fibronectin (mg/L)       | 0.576 (0.496, 0.653)     | 0.670 (0.592, 0.741)     | 0.673 (0.596, 0.745)     |
| Hyaluronic acid (ng/mL)  | 0.593 (0.513, 0.669)     | 0.655 (0.577, 0.728)     | 0.655 (0.577, 0.728)     |
| Type IV collagen (ng/mL) | 0.625 (0.546, 0.700)     | 0.614 (0.535, 0.689)     | 0.607 (0.528, 0.683)     |

All the p value was compared with 2D SWE. APRI = aspartate aminotransferase to platelet ratio index, AST = aspartate aminotransferase, AUROCs = area under receiver operating characteristic curves, GGT = γ-glutamyltransferase, SWE = shear wave elastography, 2D = two-dimensional

Table 6. The Correlation between 2D SWE Value and the Clinical Characteristics

| Parameter         | Spearman Correlation Test | Multiple Regression Analysis |
|-------------------|---------------------------|------------------------------|
|                   | r    | P      | β    | P      |
| Sex*              | 0.983|        |      |        |
| Age (days)        | 0.366| < 0.001| 0.285| < 0.001|
| Liver fibrosis stage | 0.786| < 0.001| 0.509| < 0.001|
| PT-INR            | 0.093| 0.185  |      |        |
| Platelet count (× 10^11) | -0.120| 0.079  |      |        |
| Bile acid (µmol/L) | 0.150| 0.034  | 0.042| 0.413  |
| Total bilirubin (µmol/L) | 0.323| < 0.001| 0.008| 0.887  |
| Direct bilirubin (µmol/L) | 0.266| < 0.001|      |        |
| Indirect bilirubin (µmol/L) | 0.244| < 0.001|      |        |
| Albumin (g/L)     | -0.076| 0.276  |      |        |
| Alanine aminotransferase (U/L) | 0.109| 0.109  |      |        |
| Aspartate aminotransferase (U/L) | 0.239| < 0.001| 0.165| 0.005  |
| γ-glutamyltransferase (U/L) | 0.358| < 0.001| 0.118| 0.022  |

*The effect of gender on 2D SWE values was assessed with the Mann-Whitney U test. PT-INR = prothrombin time-international normalized ratio, SWE = shear wave elastography, 2D = two-dimensional

reported by Franchi-Abella et al. [10]. Furthermore, the 2D SWE value could yield both good diagnostic sensitivity ranging from 93.4–94.7% and specificity of 85.0% in predicting severe fibrosis (≥ F3). However, the sensitivity and positive predictive value of 2D SWE in determining cirrhosis (F4) was only 78.6% and 39.2%, respectively. This result indicated that many patients with mild or severe fibrosis would have been incorrectly diagnosed with cirrhosis via 2D SWE. A previous study [27] reported that extrahepatic cholestasis increased liver stiffness irrespective of fibrosis due to tissue swelling, inflammation, edema, and increased intracellular pressure. The fact that all patients in the study had abnormally increased serum bilirubin levels
determinant of outcomes [3,4]. Thus, the correct detection of liver fibrosis before KPE with a non-invasive tool might help pediatric surgeons select appropriate therapy methods. For patients without BA, liver fibrosis is also an important factor in influencing the therapeutic response. Jaundiced infants without BA who have progressive liver fibrosis might not respond well to bilirubin-relieving therapy and consequently, take longer to clear jaundice.

Our study showed that 2D SWE is a useful and valuable tool for non-invasively predicting the stage of liver fibrosis. Thus, a liver biopsy might be avoided in some patients by the application of 2D SWE; however, liver stiffness can also be affected by other factors such as age, serum bilirubin level, and AST and GGT levels [8,12,14,26,27]. Importantly, stages of liver fibrosis are overestimated via 2D SWE evaluation of infants with obstructive jaundice.

In our study, the optimal cut-off value of 2D SWE in predicting significant fibrosis, severe fibrosis, and cirrhosis was 11.6 kPa, 13.0 kPa, and 15.7 kPa, respectively. These values were higher than those previously reported in studies [25,26] of adult populations. Furthermore, the 2D SWE value distribution of cirrhosis in our study was wider than that in previous adult studies; however, our findings were similar to those reported by Franchi-Abella et al. [10]. Inconsistent results may be due to the following reasons. First, studies with adult populations usually use a curved SC6-1 probe to perform liver stiffness measurements, while a linear SL15-4 probe was used in our study and the report by Franchi-Abella et al. [10]. Second, adults usually suffer from chronic hepatitis and not jaundice. All these points indicate that dramatic differences exist between jaundiced infants and adults in the evaluation of the stages of liver fibrosis via 2D SWE.

The main drawback of our study was that we did not correlate the inflammatory status of all the liver samples with the 2D SWE values. The initial analysis of 80 samples showed no correlation between METAVIR inflammatory activity and 2D SWE values. The METAVIR scores for inflammatory activity were inappropriate for evaluating the severity of liver inflammation in infants with obstructive jaundice. Therefore, a detailed histological analysis of the liver samples with new criteria is needed and might help us better understand the significance of fibrosis and inflammation reflected by the 2D SWE value.

In conclusion, the liver stiffness measurement taken by 2D SWE is a more effective non-invasive tool for predicting the stage of liver fibrosis in patients with suspected BA compared with serum fibrosis biomarkers. Specifically, 2D SWE had high sensitivity in predicting severe liver fibrosis. Thus, 2D SWE measurements might offer clinical value in directing the selection of personalized therapies.

**Conflicts of Interest**
The authors have no potential conflicts of interest to disclose.

**Author Contributions**
Conceptualization: Luyao Zhou, Huadong Chen. Data curation: Luyao Zhou, Wenying Zhou, Guotao Wang. Formal analysis: Luyao Zhou, Huadong Chen. Funding acquisition: Luyao Zhou, Xiaoyan Xie. Investigation: Luyao Zhou, Wenying Zhou, Guotao Wang. Methodology: Luyao Zhou, Bing Liao, Qinghua Cao. Project administration: Luyao Zhou, Xiaoyan Xie. Resources: Huadong Chen, Hong Jiang, Luyao Zhou. Supervision: Xiaoyan Xie. Visualization: Luyao Zhou, Bing Liao, Qinghua Cao. Writing—original draft: Luyao Zhou, Huadong Chen. Writing—review & editing: all authors.

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