



Two-Dimensional Shear Wave Elastography Evaluation of Post-transplantation Complications in Pediatric Receipt: A Retrospective Cohort

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Background: The 20-year survival rate in pediatric patients after liver transplantation (LT) was no more than 70%. Hepatic fibrosis is one of the principal factors affecting the long-term prognosis. Imaging evaluation was the first-line examination for pediatric liver graft assessment. However, the sensitivity and specificity were insufficient. Thus, two-dimensional shear wave elastography (2D-SWE) was performed to evaluate liver graft stiffness and complication in post-transplant pediatric receipt.

Materials and Methods: In this retrospective cohort, 343 pediatric recipients who underwent liver graft biopsy in our tertiary LT center were recruited between June 2018 and December 2020. The 2D-SWE evaluation, laboratory examination, routine post-transplant biopsy, and hepatic pathological assessment were performed.

Results: Ninety-eight of the 343 pediatric patients were included according to the protocol. The Liver Stiffness Measurements (LSM) value of 2D-SWE was significantly elevated in post-transplant fibrosis ($p < 0.0001$). The LSM value of patients with post-transplant biliary complications ($p < 0.0001$) and biopsy-proven rejection (BPR, $p = 0.0016$) also rose compared to regular recovery patients. Concerning the sensitivity and specificity of 2D-SWE in diagnosing liver graft fibrosis, the area under the ROC curve (AUC) was 88%, and the optimal cutoff value was 10.3 kPa.

Conclusion: Pediatric LSM by 2D-SWE was efficient. Routine 2D-SWE evaluation could be optimal to predict significant liver graft fibrosis.

Keywords: transplantation, two-dimensional shear wave elastography, ultrasound, pediatric, complications (COMP)

HIGHLIGHTS

- This article provides insight into the effects of Two-dimensional shear wave elastography (2D-SWE) and the Liver Stiffness Measurements (LSM) on pediatric liver graft assessment.
- Liver Stiffness Measurements value of 2D-SWE was elevated in post-transplant fibrosis, post-transplant biliary complication, and biopsy-proven rejection.

INTRODUCTION

Liver transplantation (LT) is the most effective treatment of end-stage liver disease in pediatric patients. However, the 5 and 10-year survival rates in pediatric patients after LT were 83 and 80%, respectively, and the 20-year survival rate was no more than 70% (1–3). The principal factors affecting the long-term prognosis in pediatric recipient contained viral infection (Epstein-Barr virus, cytomegalovirus), liver graft rejection, hepatic fibrosis, biliary tract complications, and drug-induced injury (4–7). Though liver biopsy is the golden standard for assessing liver disease and abnormal liver function, it required sedation for pediatric patients and induced approximately 20% post-biopsy discomfort and pain (8, 9). Therefore, a liver biopsy might not be the optimal approach for monitoring the post-transplant chronic rejection and liver injury in pediatric patients.

Imaging evaluation, including ultrasound, was the first-line examination for liver graft assessment, which was considered non-invasive and non-radiation, especially for children. However, the sensitivity and specificity were insufficient (10). By contrast, pediatric patients may not be able to hold their breath long enough to complete the computed tomography (CT) and magnetic resonance imaging (MRI) scan; infantile patients usually require sedation to maintain high-quality CT/MRI imaging. Routine ultrasound examination is requisite in post-transplant pediatric patients to evaluate the morphology of the allograft and macrovascular patency. However, conventional ultrasound is not diagnostic, especially for the earlier stages of fibrosis (11). Two-dimensional shear wave elastography (2D SWE) is a non-invasive technique for measuring liver stiffness (12, 13). Distinguished from transient elastography (TE), 2D-SWE was equipped with conventional ultrasound equipment, displaying both real-time gray scale ultrasound images for assessing morphologic changes and real-time quantitative map without stress concentration artifacts for assessing liver stiffness. Though some literature had reported the utility of 2D-SWE in evaluating liver fibrosis in hepatitis B, hepatitis C, or non-alcoholic fatty liver disease (NAFLD) (14, 15), little is known about the assessment of 2D-SWE in liver graft after pediatric LT.

In this study, 2D-SWE was performed to evaluate liver graft stiffness in post-transplant pediatric patients. The results were compared with pathologic findings of liver graft biopsy to clarify the value of 2D-SWE for pediatric patients.

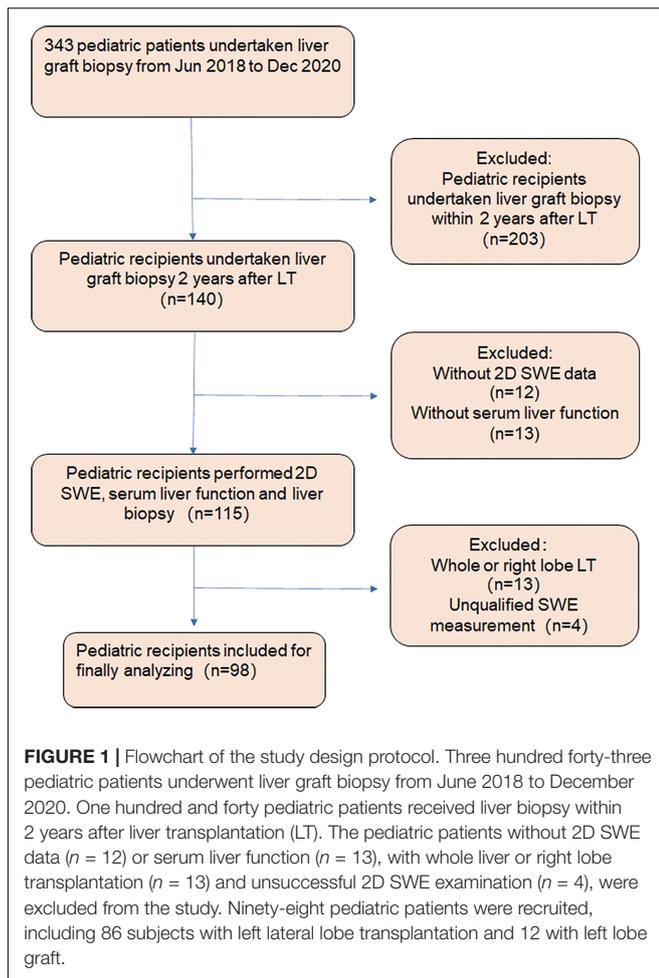
MATERIALS AND METHODS

Study Participants

In this retrospective cohort study, 343 pediatric patients underwent liver graft biopsy in our tertiary liver transplantation department from June 2018 to December 2020. The studies involving human participants were reviewed and approved by the Ethical Committee of Renji Hospital. The participants provided their written informed consent by their parents to participate in this study. One hundred and forty pediatric patients received liver biopsies within 2 years after LT. The pediatric patients without 2D SWE data ($n = 12$) or serum liver function ($n = 13$), or unsuccessful 2D SWE examination ($n = 4$) were excluded from the study. Additionally, in a normal situation, measurement of LSM in the left lobe is inappropriate because it is affected by cardiac pulsation. However, in pediatric recipients, as the majority of the pediatric recipients have a body weight of <25 kg, donation of the left lateral lobe (segments II + III) is sufficient in most cases. Considering the potential differences in the shape and texture of different liver segments, for comparability of data, the pediatric patients with whole liver or right lobe transplantation ($n = 13$) were also excluded from the study (Figure 1). A total of 98 pediatric patients were recruited, including 86 subjects with left lateral lobe transplantation and 12 subjects with left lobe graft. The underlying disease included biliary atresia, cholestatic cirrhosis, cryptogenic cirrhosis, tyrosinemia, and glycogen storage disease. All 98 patients underwent serum liver function tests, conventional ultrasound examinations, and 2D SWE measurement. Serum liver function tests included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), direct total bilirubin (DB), alkaline phosphatase (ALP), and gamma-glutamyl transferase (γ GT) levels. The time interval between serum liver function examination and liver biopsy was less than 1 week. The time interval between 2D SWE measurements and liver biopsy was no more than 2 days.

Two-Dimensional Shear Wave Elastography Measurement

An Aixplorer scanner (Aixplorer; SuperSonic Imagine SA, Aix-en-Provence, France) was used with a curvilinear transducer (1–6 MHz) and a linear array transducer (4–15 MHz). Ultrasound examination was performed by one radiologist (G.L.H. with 10 years of experience in liver transplantation ultrasound and 4 years of experience in 2D SWE measurement). The time interval between 2D SWE measurement and liver biopsy was less than 2 days. The pediatric patients were fed with milk during the examination or sedated with oral chloral hydrate (0.5–1 mg/kg body weight) before the test to keep quiet if necessary. A high-frequency linear transducer SL15-4 (4–15 MHz) was used. The pediatric patient was maintained in the supine position, and the left lateral (or left) lobe of the graft liver was scanned. The SWE sampling frame was 2 cm \times 2 cm and was put at 0.5 cm below the liver capsule to avoid the influence. A 10-mm-diameter region of interest was positioned in the center of the sample frame with a complete and homogeneous



filling color map. The examination was considered successful when most of the area of the interest box ($>90\%$) could be filled with homogeneous color and maintained at least one calm breath. When taking the measurement, major blood vessels and biliary ducts in the liver graft should be avoided. Five qualified data were obtained from each patient, and the median values (with their range) were calculated (expressed in kilopascals). The 2D SWE value was 3.5–4 kPa for healthy children and 7.5–8.5 kPa for post-transplant pediatric patients with normal liver function.

Histological Examination

Ultrasound-guided liver biopsy was performed with an 18-gauge needle automatic biopsy gun, and the pediatric patient was in the supine position. The length of the liver specimen was at least 15 mm with six portal spaces. The liver tissue strips were routinely fixed in formalin and embedded in paraffin. Hematoxylin-eosin (HE) staining was used to find the histologic change. Two hepatopathologists blinded to clinical data and 2D SWE results made the pathological diagnosis. Masson staining was used to stage liver graft fibrosis based on the Scheuer score system. Substantial was defined as S2 or more significant.

Statistical Analysis

All data were first analyzed for normality of distribution using the Kolmogorov-Smirnov test of normality. Continuous normal distribution variables were expressed as mean \pm standard deviation (SD). Non-normally distributed variables are represented by median (P25, P75) and range. Categorical variables are represented by counts and percentages. A receiver operating characteristic (ROC) curve was performed to determine the liver fibrosis stage. A frequency distribution was obtained for choosing the optimal cutoff values of 2D SWE to maximize the sum of sensitivity and specificity for different fibrosis thresholds. Optimal cutoff values to predict fibrosis stages were identified. Sensitivity, specificity, positive predictive values, negative predictive values, and accuracy were calculated. Statistical analysis was performed using software (SPSS, version 22.0; IBM, Armonk, NY, United States). The graph was performed by GraphPad Prism (Version 8.0, GraphPad Software, La Jolla, CA, United States). A P -value of < 0.05 was considered statistically significant.

RESULTS

Participants' Clinical Characteristics

Ninety-eight pediatric patients underwent liver graft biopsy 2 years after LT (Table 1). The median age at LT was 8 months (6–14 months); liver graft biopsy was 4-year-old (43–65.5 months). The median interval between liver graft biopsy and LT was 41 months. The pediatric patients were divided into six groups according to pathological diagnosis; these were normal (steady recovery), DILI (drug-induced liver injury), fibrosis, BPR (biopsy-proven rejection), BC (biliary complication), and VI [virus infection, including Epstein-Barr-Virus (EBV)/Cytomegalovirus (CMV) and HBV], respectively. The Liver Stiffness Measurements (LSM) by 2D-SWE increased in pediatric patients with liver graft cirrhosis, liver graft rejection, biliary complications, and EBV/CMV/HBV infection. Also, the median value was 17, 12.2, 18.7, and 10.3 kPa, respectively.

Correlation of Liver Stiffness Measurements and Liver Complication in Pediatric Receipt

The LSM value of 2D-SWE was significantly elevated in post-transplant fibrosis ($p < 0.0001$, Figure 2A), the difference between means was 8.824 ± 1.397 kPa (Figure 2B). The LSM value of patients with post-transplant biliary complication ($p < 0.0001$) and biopsy-proven rejection (BPR, $p = 0.0016$) also rose compared to regular recovery patients, with the difference between means at 9.025 ± 1.530 kPa (Figure 2C) and 3.283 ± 0.9918 kPa (Figure 2D), respectively. Additionally, the LSM ascended when the grade of fibrosis grew, despite there being no significant difference among each group ($p = 0.166$, Figure 2E). This trend was not detected in acute rejection (Figure 2F).

TABLE 1 | Baseline characteristics of the pediatric recipients.

Feature	Case (%) or median [range]
Gender (male/female)	42/43 (49.4/50.6)
Underlying disease (Biliary atresia/cholestatic cirrhosis/cryptogenic cirrhosis/tyrosinemia/glycogen storage disease)	75/4/3/2/1 (88.2/4.7/3.5/2.4/1.2)
Age at LT (month)	8 (6,14) [5, 120]
Age at liver biopsy (month)	51 (43, 65.5) [30, 192]
The time interval between LT and biopsy (month)	40 (32.5, 48.5) [24, 123]
2D SWE measurement (kPa)	8.1 (7.4, 12) [6, 31.8]
Alanine aminotransferase (IU/L)	28 (16, 162) [10, 776]
Aspartate aminotransferase (IU/L)	51 (28, 160.5) [20, 1,339]
Gamma-glutamyl transpeptidase (IU/L)	31 (12, 184.5) [6, 811]
Alkaline phosphatase (IU/L)	284 (217.5, 436) [19, 1,293]
Total bilirubin ($\mu\text{mol/L}$)	7.3 (5.75, 14.2) [2.5, 308.4]
Direct bilirubin ($\mu\text{mol/L}$)	3.2 (2.2, 6.35) [0.5, 214.1]

Categorical variables are represented as number (percentages), and non-normally distributed variables are represented as median (P25, P75) [range].

TABLE 2 | Two-dimensional shear wave elastography (2D-SWE) values in the pediatric patients with normal serum ALT level ($\text{ALT} \leq 1\text{ULN}$) after liver transplantation (LT) according to liver fibrosis stage.

Fibrosis stage	Number of patients	%	2D SWE value (kPa)
S0	10	34.48%	7.3 (6.6, 7.8) [6, 10.2]
S1	9	31.03%	7.4 (7.1, 7.6) [6.8, 8.5]
S2	7	24.14%	7.9 (7.4, 8.3) [7.1, 8.5]
S3	3	10.34%	14.5 (11.0, -) [11, 15.6]

Results are expressed as median (P25, P75) [range].

TABLE 3 | Accuracy of two-dimensional shear wave elastography (2D-SWE) in predicting liver fibrosis in pediatric recipients with stable serum alanine aminotransferase (ALT) level ($\text{ALT} \leq 1\text{ULN}$) after liver transplantation (LT).

Fibrosis stage	AUC	Cut-off (kPa)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
2D SWE							
$\geq\text{S1}$	0.68 (0.47-0.90)	7.35	73.68	60	77.78	54.55	68.97
$\geq\text{S2}$	0.80 (0.63-0.97)	7.80	70.0	84.21	70.0	84.21	79.31
$\geq\text{S3}$	1.00 (1.00-1.00)	10.60	100	100	100	100	100

2D SWE, two dimensional shear wave elastography; LT, liver transplantation; AUC, the area under the ROC curve; PPV, positive prediction value; NPV, negative predictive value.

Two-Dimensional Shear Wave Elastography and Pathologic Findings in Liver Graft Fibrosis

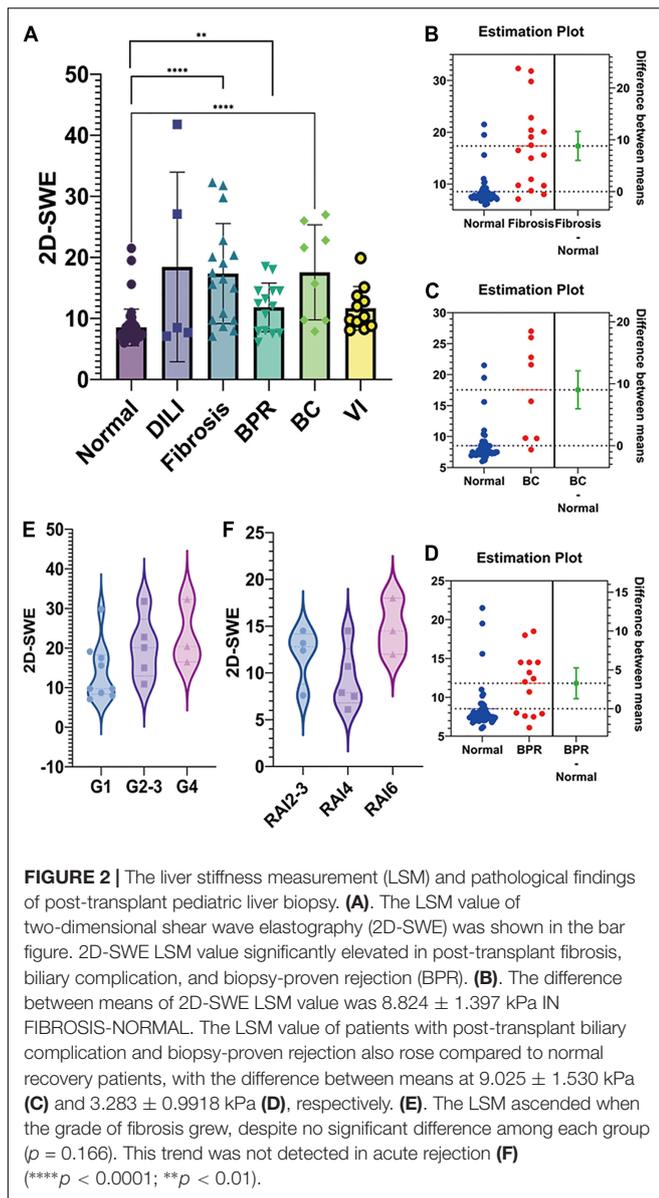
The 2D SWE value had a good diagnostic performance for predicting liver graft fibrosis, the AUC was 88% (95% CI 0.78–0.99%), the optimal cutoff value was 10.3 kPa, and the optimal cutoff value was 18.3 and 21.6 kPa for Grades 2–3 and Grade 4, respectively (Figure 3A). However, no correlation was detected between LSM and C4D staining, which is a biomarker for antibody-mediated rejection (ABMR)-induced tissue damage (Figure 3B).

Although LSM also increased with elevated serum ALT levels ($\text{ALT} \leq 1\text{ULN}$, $1\text{ULN} < \text{ALT} \leq 2\text{ULN}$, $\text{ALT} > 2\text{ULN}$), the sensitivity and specificity of 2D SWE were still reassuring. For instance, in 44 pediatric patients with $\text{ALT} \leq 1\text{ULN}$ who had routine liver graft biopsy, Masson-staining was performed on 29 subjects. Scheuer's score was graded as S0

in 10 subjects, S1 in nine recipients, S2 in seven recipients, and S3 in three recipients (Table 2). SWE could distinguish mild liver fibrosis (S1), liver fibrosis-S2, and significant liver fibrosis (S3) even in this situation. The AUCs were 0.68 (95% CI, 0.47–0.90) for $\geq\text{S1}$, 0.80 (95% CI, 0.63–0.97) for $\geq\text{S2}$, and 1 (95% CI, 1–1) for $\geq\text{S3}$, respectively (Table 3). The Masson staining of the biopsy was consistent with the LSM (Figure 4).

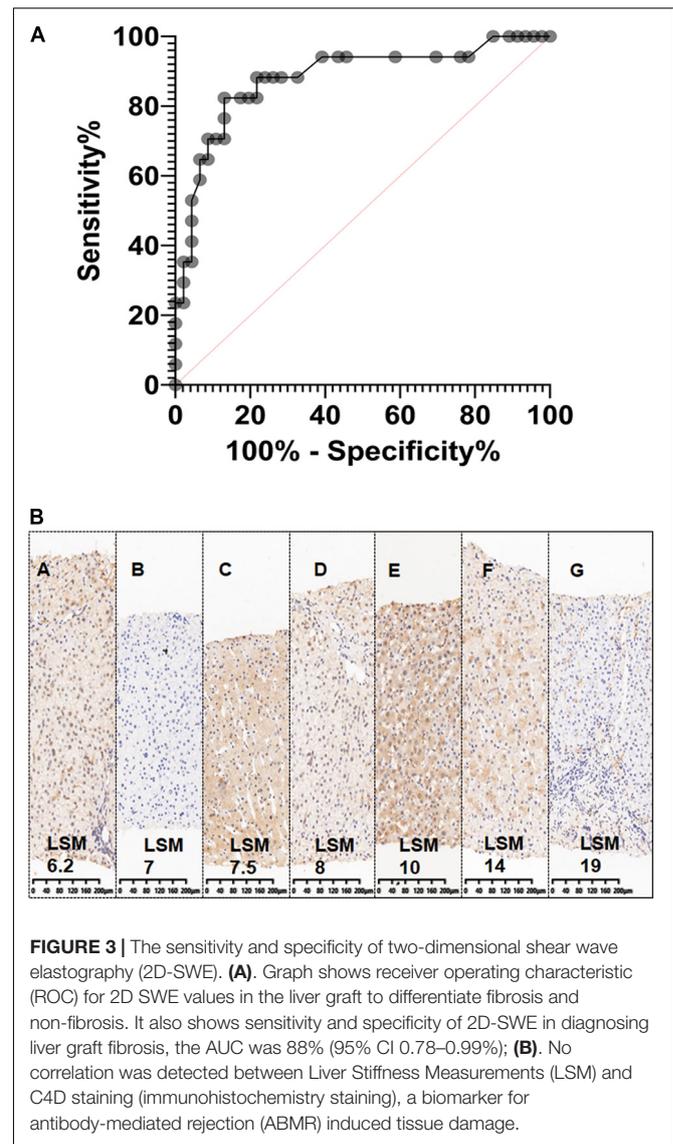
DISCUSSIONS

Two-dimensional shear wave elastography is a newer elastography method using several lines of acoustic radiation force impulse to generate shear waves over a large region of interest within the liver in real-time to obtain quantitative images of the elasticity. 2D SWE can detect the propagation of the shear wave, obtain elastic images based on conventional



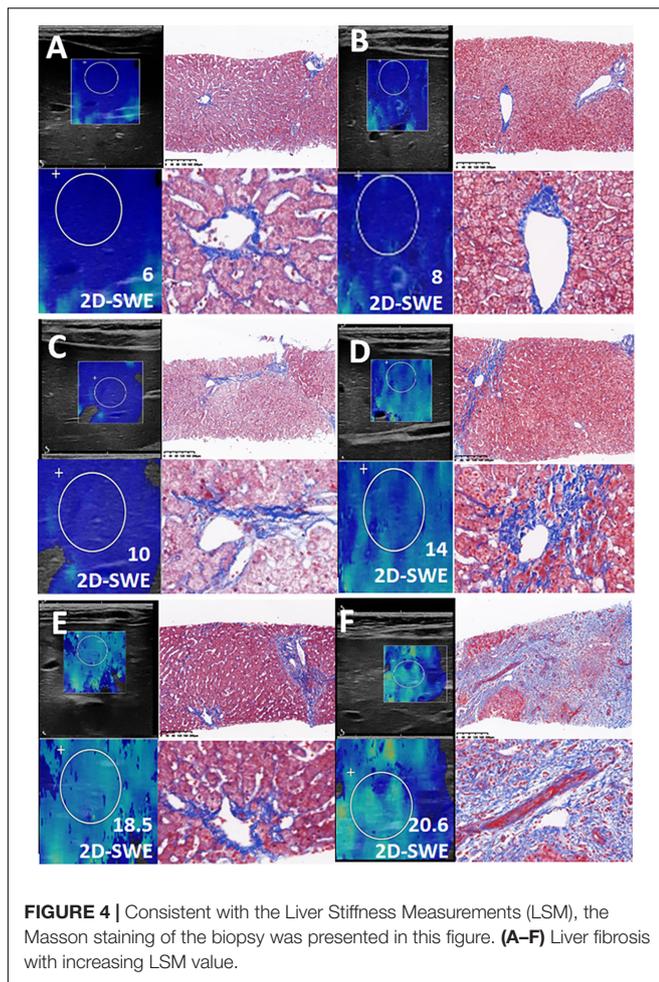
ultrasonic images, and quantitatively measure liver stiffness (16). The successful rate of LSM by 2D SWE was above 98% in children (17, 18). The main factor affecting pediatric patient measurement was poor image quality caused by crying and movement, which can be solved by feeding and sedation. It has been reported that the LSM of the left lobe is higher than the right lobe, and the stability of the left lobe is less than the right due to the influence of cardiac pulse and abdominal vessel pulse (19, 20). In our study, LSM were all performed in left lobe liver graft, and most pediatric patients acquired successful value.

Liver stiffness measurements increased in pediatric patients with liver graft cirrhosis, liver graft rejection, drug-induced liver injury, EBV/CMV infection, bile duct complication, hepatic venous-occlusive disease, and hepatitis. Due to the liver capsule



around the liver, the size of the liver is relatively fixed; when inflammation, edema, congestion, and cholestasis make the liver volume increase, the intrahepatic pressure rises. In addition, literature reported that patients with liver cholestasis, acute inflammation, bile duct complication, and hepatic vein obstruction lead to an elevated LSM, which is consistent with our findings (21, 22).

Recently, the pilot study reported by Vo et al. (23) has indicated that the LSM value of 2D-SWE was significantly elevated in pediatric LT recipients with liver graft fibrosis. However, 81.8% of patients' graft type was whole liver, and the graft should be from Donation after Cardiac Death (DCD) or Donation after Brain Death (DBD). In this study, living donor liver transplantation (LDLT) with the left lateral segment (LLS) is the majority. Given the small sample size, Vo et al. could not reliably examine the impact of concurrent acute liver rejection and/or hepatic inflammation. The present study further



demonstrated the role of LSM in the assessment of pediatric liver graft fibrosis based on a larger sample size from a more homogenous LT protocol. Considering abnormal ALT levels will affect LSM, in this study, pediatric patients were divided into three groups: $ALT \leq 1$ ULN, 1 ULN < $ALT \leq 2$ ULN, and $ALT > 2$ ULN group. Zeng et al. (24) reported that remarkably elevated ALT levels (five times greater than normal liver function level) would elevate liver stiffness. Zeng et al. (25) distinguished double diagnostic thresholds in diagnosing liver fibrosis according to ALT level ($ALT \leq 2$ ULN and $ALT > 2$ ULN), thus, reducing the influence of ALT level on the evaluation of liver fibrosis.

In our study, the pathologic findings in thirteen patients were liver graft rejection, LSM was 7.8, 10.7, and 12.6 kPa in $ALT \leq 1$ ULN, 1 ULN < $ALT \leq 2$ ULN, and $ALT > 2$ ULN groups, respectively. LSM increased with the elevated serum ALT level. In the patients with liver graft rejection but with normal serum ALT levels, LSM was not significantly increased. Yoon et al. (26) performed 2D SWE to monitor graft liver stiffness during the early postoperative period in adult LT; 2D SWE measurement could suggest graft liver rejection 4 weeks after LT in adult patients.

Scheenstra et al. (27) found that the incidence of fibrosis in pediatric patients after LT was extremely high, 34, 48, 65, and 69% at 1, 3, 5, and 10 years after LT, respectively. Evans et al. (28) found in 158 pediatric patients, with stable serum liver function levels after LT, that the incidence of liver fibrosis was as high as 17.7, 45.9, and 65.6% at 1, 5, and 10 years after LT, respectively. Venturi et al. (29) reported that graft fibrosis in pediatric patients was up to 74% 10 years after LT, 70% of which showed the liver function level was stable. Acute and chronic rejection, drug injury, viral infection, and vascular or biliary tract complications could cause liver damage and inflammatory response after LT. When the repair was excessive or out of control, abnormal hyperplasia and the deposition of the extracellular matrix formed liver fibrosis and gradually developed into cirrhosis (30). Thus, even in the pediatric recipients with stable liver function levels, the damage to the graft liver potentially happened.

In this study, we analyzed the pediatric recipients who received liver graft biopsy with normal ALT levels after LT; the pathological results showed liver fibrosis stages $\geq S1$, $\geq S2$, and $\geq S3$ were accounted for 65.5% (19/29), 34.5% (10/29), and 10.3% (3/29), respectively. LSM was satisfactory in diagnosing significant liver graft fibrosis with a sensitivity and specificity of 100%. However, the sensitivity and specificity for diagnosing mild liver graft fibrosis and significant liver graft fibrosis were 73.7 and 60%, 70 and 84.2%, respectively. Zhuang et al. (22) performed 2D SWE to assess liver fibrosis caused by chronic hepatitis B in an adult patient, and the sensitivity and specificity for significant liver fibrosis, severe liver fibrosis, and cirrhosis reached 92, 91.6, and 94.6% and 90, 96.7, and 94.9% respectively. The 2D SWE could also be performed by another platform, such as the LOGIQ E9 system (GE Medical Systems, Wisconsin, United States) (31).

Limitations

Firstly, the enrolled children may not widely represent the pediatric recipients. In recent years, a routine liver biopsy was performed in our center, and the parents were not preferred for the invasive and possible complications after liver graft biopsy. Secondly, the pediatric recipient was not strictly fasting when taking the SWE examination, and the measuring was started while feeding (32, 33). Thirdly, we enrolled the pediatric recipients 2 years after LT to reduce liver function fluctuation. However, elevated liver function levels might still affect the cutoff value of liver fibrosis staging (34). Fourth, LSM by 2D SWE was performed in the left liver graft; literature reported that the stability and accuracy of LSM in the right lobe is higher than left lobe; in this study, pediatric patients have received a left lobe liver graft. Thus, we acquired satisfactory LSM in the left lobe.

CONCLUSION

The LSM by 2D-SWE in the left liver graft was efficient. Besides liver graft fibrosis, elevated post-transplant pediatric LSM could also be present by liver graft rejection and biliary duct complications. Routine 2D-SWE evaluation could be optimal to predict significant liver graft fibrosis.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of Renji Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HFe, L-HG, and Z-FX: substantial contributions to conception and design, acquisition of data, analysis and interpretation of the data, and drafting of the manuscript. Y-CH, Z-CL, R-LG,

HFa, and L-XJ: revising for critically important intellectual content. HFe and QX: final approval of the versions to be published. All authors contributed to the article and approved the submitted version.

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