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Elastography—The New Standard in the Assessment of Fibrosis After Pediatric Liver Transplantation?

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ABSTRACT

Background: The development of graft fibrosis after pediatric liver transplantation (PLT) remains a major concern as it can lead to graft failure and ultimately graft loss. Elastography is a non-invasive method to assess liver fibrosis, but its role in the posttransplant setting is unclear. The aim of our study was to evaluate shear wave elastography (SWE) in the assessment of liver fibrosis after PLT, including split-liver recipients.

Methods: We retrospectively analyzed data from PLT recipients who underwent surveillance liver biopsy and concurrent 2D-SWE during the study period from April 2018 to July 2021. Spearman's correlation was used to compare histologic fibrosis stages with liver stiffness measurements (LSM) by 2D-SWE. AUROC analysis was performed to evaluate the performance. One sample *t*-test was used to compare results with reference values of healthy children.

Results: 62 cases were included. 29% showed histologic fibrosis. LSM by 2D-SWE were feasible in all children regardless of age or graft type. There was a significant correlation between LSM and fibrosis stage for all three scoring systems used (Ishak, $p = 0.003$; METAVIR, $p = 0.005$; LAF Score, $p = 0.003$). Patients with a history of biliary complications had increased liver stiffness ($p = 0.015$). The AUROC of 2D-SWE for predicting significant liver graft fibrosis was 0.81. Liver stiffness after PLT without graft fibrosis was higher than in healthy subjects, but comparable to that in children with chronic liver disease without fibrosis.

Conclusion: 2D-SWE can reliably detect children with significant liver graft fibrosis, even in split-liver recipients. This study demonstrates the value of a non-invasive tool for fibrosis staging after PLT. 2D-SWE has the potential to improve long-term outcomes after PLT and to reduce the number of surveillance liver biopsies. But elastography is not a substitute for liver biopsy.

1 | Introduction

Pediatric liver transplantation (PLT) is a well-established routine procedure with excellent long-term survival rates today [1–3]. Early posttransplant outcomes have improved tremendously in recent decades due to advances in organ preservation, surgical techniques, perioperative care and immunosuppressive regimens [4, 5]. As a result, the focus has shifted to long-term outcomes, with preservation of normal liver function and quality of life as primary goals [4, 6]. However, abnormal histologic findings are common in PLT recipients, even in those with normal liver function tests, and there is a high prevalence of hepatic

Abbreviations: ANOVA, analysis of variance; AR, acute rejection; AUROC, area under the receiving operator characteristic; IQR/M, interquartile range/median; LAF, liver allograft fibrosis; LBx, liver biopsy; LSM, liver stiffness measurement; PLT, pediatric liver transplantation; PTCD, percutaneous transhepatic cholangiodrainage; PTLD, posttransplant lymphoproliferative disorder; SWE, shear wave elastography; TE, transient elastography; USE, ultrasound elastography.

fibrosis, which is the most frequent pathologic finding after PLT [7–9]. Graft fibrosis remains one of the main determinants of overall morbidity and mortality after PLT [10–12]. However, hepatic fibrosis is now considered to be a dynamic and reversible process [13, 14]. The most common approach to treating patients with graft fibrosis is to intensify or adjust immunosuppression [11]. Because of the potential therapeutic consequences, detection and monitoring of fibrosis are crucial, but both are challenging.

Liver biopsy (LBx) is currently the gold standard for evaluating liver tissue and diagnosing liver fibrosis [15–17]. For these reasons, many centers perform surveillance biopsies in both adults and children [4, 7, 9, 18]. Nevertheless, the role of protocol biopsies in the posttransplant setting remains controversial [4, 19, 20]. Biopsies are invasive and stressful procedures with many disadvantages, including pain, risk of bleeding, sampling error, poor availability and, in children, the need for anesthesia [18, 19]. Consequently, there is a growing interest in non-invasive methods to assess fibrosis, the need for which has not yet been met. In principle, there are currently two categories for non-invasive assessment of liver fibrosis: serological tests and imaging techniques [21–23]. A variety of biochemical markers have been tested for this purpose, and panels combining markers have been developed to improve predictive accuracy. However, serum-based fibrosis markers lack diagnostic accuracy in the pediatric posttransplant setting and, therefore, do not play any role in the follow-up routine so far [11, 24, 25].

In contrast, ultrasound elastography (USE) has been validated as a promising, non-invasive method to detect fibrosis in different chronic liver diseases in children [26, 27]. In adults, shear wave elastography (SWE) is considered a reliable substitute for LBx in several clinical settings [17, 28, 29]. 2D-SWE is a new technique that offers high quality quantitative assessment of liver stiffness. 2D-SWE has been shown to be the most reliable method compared to point-SWE or transient elastography (TE) in children [30, 31] and showed better performance than TE in the assessment of liver fibrosis in adults [32, 33]. Advantages of 2D-SWE include visualization of the elastogram overlaid on a B-mode image in real-time, precise placement and size adjustment of the region of interest (ROI), and implementation in a conventional ultrasound machine. Therefore, 2D-SWE appears to be the ideal method for the assessment of liver stiffness after PLT. Recently, three studies have been published evaluating 2D-SWE after PLT [34–36]. These studies used different ultrasound machines. Therefore, numerical and cut-off values are not directly comparable as liver stiffness measurements (LSM) by 2D-SWE varies by manufacturer. Two showed good performance in detecting significant fibrosis. However, these included indicative LBx. Furthermore, all three studies included LSM performed under sedation or anesthesia, which is known to increase liver stiffness [37, 38].

Our study compared liver stiffness by 2D-SWE with histologic fibrosis of surveillance LBx. Furthermore, our aim was to investigate the feasibility in children after PLT, including split-liver recipients, and to interpret the results in comparison to non-transplanted children. This study is the first to evaluate 2D-SWE using the GE system after PLT.

2 | Patients and Methods

2.1 | Patients

All liver-transplanted children and adolescents at our transplant center who received surveillance LBx according to our protocol as well as LSM during the study period from April 2018 to July 2021 were included. Patient data and laboratory results at the time of LBx were obtained. The study was approved by the Ethics Committee of the University of Regensburg (sign 21-2306-104).

2.2 | Shear Wave Elastography

Liver stiffness measurements were acquired by 2D-SWE using a LOGIQ E9 (until December 2020) or E10 system (since then) with a C1-6-D convex probe and with the same software (GE Healthcare, Chalfont St Giles, United Kingdom). The recommended quality criteria for all USE methods include the number of individual measurements and the interquartile range/median (IQR/M) ratio [28, 39]. According to the manufacturer's specifications, an LSM with the E9 system was considered reliable if 12 individual measurements were made in homogeneous elastograms. The IQR/M ratio was not implemented on the E9 system. With the E10 system, an LSM was considered reliable if the IQR/M ratio for shear wave velocity (m/s) was ≤15%. According to the EFSUMB guidelines the results were reported in the unit of shear wave velocity (m/s), which is the measured quantity [28]. In patients with a whole graft, LSM were performed according to the EFSUMB guidelines [28]. In patients without right liver lobe the position of the transducer was adopted to the position of the graft, avoiding scar tissue. In addition, the EFSUMB guidelines recommend a minimum of 2 h of fasting prior to LSM. However, adherence to the fasting time frame was not possible in all cases due to age or/and clinical routine. Twelve individual measurements were obtained in each patient and the median was expressed as the result. All LSM were performed by a pediatric hepatologist with experience in ultrasound and elastography. LSM were obtained a day prior to LBx.

2.3 | Liver Biopsy and Histology

Liver biopsies were performed at 1, 2, 5, 7, 10, 15 years after PLT as surveillance biopsies according to our protocol. Liver samples were collected with a (semi-)automatic device by a pediatric hepatologist and evaluated by an experienced liver transplant pathologist. The Ishak Score was used as standard for staging fibrosis [40]. Additionally, the METAVIR fibrosis Score [41] and the liver allograft fibrosis (LAF) Score [42] were evaluated. The three different fibrosis staging systems are shown in Tables S1–S3. Significant fibrosis was defined as Ishak Score ≥ 3 or METAVIR Score ≥ F2. The Rejection Activity Index (RAI) score according to the Banff criteria was used to describe acute rejection (AR) [43, 44]. Steatosis was expressed in percent of affected hepatocytes.

2.4 | Statistical Analysis

Statistical analyses were performed using IBM Statistics SPSS 27 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). A *p*-Value

≤0.05 was considered statistically significant. Descriptive statistics were performed on the characteristics. Continuous variables are presented as median (range). Analysis of variance (ANOVA) with Bonferroni post hoc test was used to examine differences in means. The nonparametric Spearman correlation (Spearman's Rho) was used for the comparison of fibrosis stages with LSM. Receiver operating characteristic analysis, including area under the receiver operating characteristic (AUROC) curve, was used to evaluate the performance of LSM in predicting significant fibrosis. The Youden index was used to find optimal cut-off values. One-sample *t*-test was used to compare LSM of PLT recipients without fibrosis with healthy reference groups and to children with chronic liver disease without fibrosis [30, 45, 46].

3 | Results

3.1 | Patient Characteristics

Between April 2018 and July 2021, 57 patients were enrolled. Five patients had two surveillance LBx according to our protocol without retransplantation in between, resulting in a total of 62 cases. The median age at LBx was 7.5 years (range 1.25–22 years), the median age at PLT was 11 months (range 1 month-20 years), and the median time since PLT was 2 years (range 1–15 years). In general, LBx and LSM were performed during the same hospital visit within a few days. In one case, LSM was performed 6 weeks before LBx and in another case 12 weeks after LBx. LSM was performed with the E9 device in 46 cases.

82.5% of the patients received a left split organ, mainly left lateral (segments II/III, $n = 45$) and rarely full left (segments II–IV, $n = 2$). Of the split organs, 29 were from living and 18 from deceased donors. None of the included patients received a right split. The most common diagnosis leading to PLT was biliary atresia (52.6%), including the syndromal form. 27.4% had a history of AR and 48.5% had a history of biliary complication. 35.5% had completed treatment with percutaneous transhepatic cholangiodrainage (PTCD). No patient had evidence of biliary obstruction or cholestasis at the time of LBx. Three patients had a history of posttransplant lymphoproliferative disorder (PTLD). 74.2% showed an ALT below the upper limit of normal (ULN). Two patients had a significantly elevated ALT level (>2.5 ULN) at the time of the protocol LBx, both of whom had AR. Patient characteristics are shown in Table 1 and characteristics at the time of LBx are shown in Table 2.

Five patients had both 2 LBx and 2 concurrent LSM during the study period. In 4 of these, no fibrosis progression occurred with also unchanged LSM values. Only one patient had fibrosis progression, which was also associated with corresponding increase in liver stiffness.

3.2 | Liver Histology

Most LBx (71%) showed no histologic fibrosis (Ishak Score 0, METAVIR Score F0, LAF Score 0) and the majority (62.9%) had no or only minimal non-specific pathologic findings at the time of LBx. 16.1% had Ishak Score 1 (mild fibrosis) and 8.1% Ishak Score 2 (moderate fibrosis). 12.9% had METAVIR F1 (mild or not significant fibrosis). 12.9% had a LAF Score of 2 in the portal subcategory, corresponding to moderate fibrosis. Significant fibrosis, defined as Ishak score 3 or METAVIR score F2 was found in only 4.8% and 16.1%, respectively. No severe fibrosis or even cirrhosis was found in any LBx. No case of steatohepatitis was found, and only one patient had moderate steatosis, affecting 50% of hepatocytes. AR was observed in four cases,

TABLE 1 | Patient characteristics.

Patients	57 (100%)
Female	24 (42.1%)
Male	33 (57.9%)
Graft type	
Whole liver	10 (17.5%)
Split liver	47 (82.5%)
Type of donation	
Living donor	29 (50.9%)
Deceased donor	28 (49.1%)
Split liver	18 (31.6%)
Whole liver	10 (17.5%)
Number of liver transplantations	
One	52 (91.2%)
Two	2 (3.5%)
Three	3 (5.3%)
Underlying etiology leading to liver transplantation	
Biliary atresia	30 (52.6%)
Syndromal biliary atresia	3 (5.3%)
ALF (Acute liver failure) of unknown origin	6 (10.5%)
Chronic hepatopathy of unknown origin	4 (7%)
Wilson's disease (acute on chronic onset)	4 (7%)
PFIC (Progressive familiar intrahepatic cholestasis)	3 (5.3%)
Alagille syndrome	2 (3.5%)
Alpha-1 antitrypsin deficiency	1 (1.8%)
Autoimmune hepatitis	1 (1.8%)
Hepatoblastoma	1 (1.8%)
Hepatocellular carcinoma	1 (1.8%)
Liver metastasis from pancreatic tumor	1 (1.8%)
Mitochondriopathy	1 (1.8%)
Primary sclerosing cholangitis	1 (1.8%)
Tyrosinemia type 1	1 (1.8%)

TABLE 2 | Characteristics at time of liver biopsy (LBx).

Cases	62 (100%)
Age (median, range)	7.5 (1.25–22)
BMI in kg/m^2 (median, range)	16.9 (12.9–31)
BMI Z-Score (median, range)	−0.25 (−2.72 to +2.56)
Time since transplantation in years (median, range)	2 (1–15)
History of AR in present liver graft before current LBx	17/62 (27.4%)
History of biliary complication	28/62 (45.2%)
History of PTCD	22/62 (35.5%)
History of PTLD	3/62 (4.8%)
Laboratory values	
AST (U/L) (mean ± SD, range)	43.1 (±40.9, 16–315)
ALT (U/L) (mean ± SD, range)	36.0 (±52.8, 9–408)
GGT (U/L) (mean ± SD, range)	31.1 (±33.6, 7–188)
Direct Bilirubin (mg/dL) (mean ± SD, range)	0.28 (±0.15, 0.1–0.7)
ALT < ULN	46 (74.2%)
ALT > ULN < 1.5 × ULN	8 (12.9%)
ALT >1.5 ULN < 2.5 × ULN	6 (9.7%)
ALT >2.5 ULN	2 (3.2%)
Immunosuppressives taken	
Cyclosporine A	39 (62.9%)
Tacrolimus	18 (29%)
Everolimus	4 (6.5%)
Sirolimus	6 (9.7%)
Mycophenolate mofetil	25 (40.3%)
Prednisolone low dose	57 (91.9%)
Azathioprine	3 (4.8%)
Numbers of immunosuppressives taken	
One	3 (4.8%)
Two	28 (45.2%)
Three	31 (50%)

Abbreviations: ALT, alanine aminotransferase; AR, acute rejection; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; LBx, liver biopsy; PTCD, percutaneous transhepatic cholangiodrainage; PTLD, posttransplant lymphoproliferative disorder; SD, standard deviation; ULN, upper limit of normal.

which were also associated with aminotransferase elevation in 2 cases, and fibrosis in 3 cases. The latter included the patient with moderate steatosis. One patient had two AR periods with a time lapse of 2 years, with normal aminotransferases and no histological fibrosis at the time of the first LBx, but elevated aminotransferases and mild fibrosis at the time of the second one. Histological characteristics are presented in Table 3.

3.3 | Liver Stiffness Measurements

Liver stiffness measurements by 2D-SWE could be performed in all patients. Only in 1/16 (6.25%) an IQR/M of 17.9% was found, which may indicate an unreliable measurement. The median LSM was lower in the whole graft group (1.29 m/s ± 0.14) than in the split graft group (1.38 m/s ± 0.19). However, this difference did not reach significance ($p = 0.153$). In addition, in the subgroup without fibrosis, there was no significant difference ($p = 0.148$) of the LSM between whole graft (1.20 m/s ± 0.14) and split graft (1.33 m/s ± 0.15). Furthermore, there was no significant difference in the median LSM based on AR (preceding or current), history of PTLD, splenomegaly or steatosis. In contrast, patients with a history of biliary complications were found to have a significant ($p = 0.015$) higher median LSM (1.43 m/s ± 0.21) than that without (1.31 m/s ± 0.15).

ANOVA showed a significant difference of the median LSM between the different fibrosis grades for the Ishak ($p = 0.003$), METAVIR ($p = 0.006$), LAF ($p = 0.022$), Portal LAF ($p = 0.002$), Sinusoidal LAF ($p = 0.026$) and Centrilobular LAF Score ($p = 0.006$). Groupwise comparison showed also a significant difference of the median LSM between Ishak Score ≤ 1 and ≥2 ($p < 0.001$), Ishak Score 0 and ≥1 ($p = 0.003$), Ishak Score 0–2 and ≥3 ($p = 0.009$) as well as between METAVIR Score 0–1 and 2 ($p = 0.004$) and METAVIR Score 0 and 1–2 ($p = 0.003$), respectively. Bonferroni-adjusted post hoc analysis revealed significantly higher median LSM with Ishak Score 3 compared to Ishak Score 0 ($p = 0.017$, MDiff = 0.32, 95%-CI [0.04, 0.60]), for Ishak Score ≥ 2 compared to Score 0 ($p = 0.001$, MDiff = 0.25, 95%-CI [0.08, 0.41]) and for METAVIR Score F2 compared to F0 ($p = 0.006$, MDiff = 0.20, 95%-CI [0.05, 0.35]).

The median LSM showed a significant positive correlation (Spearman-Rho) of moderate effect with the stage of fibrosis for all 3 scoring systems, Ishak ($r = 0.371$, $p = 0.003$), METAVIR ($r = 0.356$, $p = 0.005$) and Total LAF ($r = 0.372$, $p = 0.003$), and with the Portal LAF Score ($r = 0.372$, $p = 0.003$). It showed also a significant positive correlation with the Sinusoidal LAF Score ($r = 0.291$, $p = 0.023$) and the Centrilobular LAF Score ($r = 0.267$, $p = 0.037$). Table 4 shows the mean of the median LSM and the associated standard deviation as well as the 95% confidence interval for the different scoring systems. The distribution of LSM by histological fibrosis score is shown in Figure 1. No correlation between stage of fibrosis and time interval since PLT was detectable and there was no correlation between aminotransferase levels and LSM. APRI (AST to Platelet Ratio Index) showed a significant positive correlation (Spearman-Rho) of moderate effect with LSM ($R = 0.389$, $p = 0.002$) and the stage of fibrosis for Ishak ($r = 0.321$, $p = 0.011$) and METAVIR ($r = 0.300$, $p = 0.018$) Score and of weak effect for Total LAF ($r = 0.275$, $p = 0.032$) and Portal LAF Score ($r = 0.282$, $p = 0.028$).

The AUROC for LSM predicting significant fibrosis (Ishak Score > 2) was 0.81. The optimum cut-off value was 1.64 m/s with a sensitivity of 67% and a specificity of 93%. The AUROC for LSM predicting significant fibrosis (METAVIR > F1) was 0.72. A cut-off value of 1.59 m/s had a sensitivity of 50% and a specificity of 92%. The AUROC for LSM predicting significant fibrosis (LAF Score in any subgroup >1) was 0.76. The optimum

TABLE 3 | Liver histology.

Fibrosis	
METAVIR score	
F0	44 (71%)
F1	8 (12.9%)
F2	10 (16.1%)
F3-4	0
Ishak score	
0	44 (71%)
1	10 (16.1%)
2	5 (8.1%)
3	3 (4.8%)
4–6	0
Liver allograft fibrosis (LAF) score	
Total LAF score	
0	44 (71%)
1	4 (6.5%)
2	6 (9.7%)
3	2 (3.2%)
4	4 (6.5%)
5	1 (1.6%)
6–9	0
Not applicable	1 (1.6%)
Portal LAF score	
0	44 (71%)
1	9 (14.5%)
2	8 (12.9%)
3	0
Sinusoidal LAF score	
0	51 (82.3%)
1	9 (14.5%)
2	1 (1.6%)
3	0
Centrilobular LAF score	
0	54 (87.1%)
1	7 (11.3%)
2–3	0
Steatosis	
None	50 (80.6%)
Mild (<33%)	10 (16.1%)
Moderate (33%–66%)	1 (1.6%)
Severe (>66%)	0
Not stated	1 (1.6%)
Rejection activity index (RAI) score	
7 = 3 + 2 + 2 (moderate AR)	1 (1.6%)
4 = 2 + 1 + 1 (mild AR)	1 (1.6%)
5 = 3 + 2 + 0 (mild AR)	1 (1.6%)
5 = 2 + 2 + 1 (mild AR)	1 (1.6%)

Abbreviations: AR, acute rejection; LAF, liver allograft fibrosis; RAI, rejection activity index.

TABLE 4 | Median LSM by 2D-SWE for the 3 different scoring systems.

Fibrosis score	Mean of median LSM (±SD) in m/s	95% Confidence interval of mean
Ishak		
0	1.32 (±0.15)	1.27–1.36
1	1.40 (±0.16)	1.29–1.51
2	1.52 (±0.28)	1.17–1.87
3	1.64 (±0.30)	0.90–2.37
METAVIR		
F0	1.32 (±0.15)	1.27–1.36
F1	1.42 (±0.19)	1.26–1.57
F2	1.52 (±0.25)	1.33–1.70
Total LAF		
0	1.32 (±0.15)	1.27–1.36
1	1.44 (±0.27)	1.00–1.87
2	1.44 (±0.14)	1.29–1.58
3	1.39 (±0.10)	0.50–2.28
4	1.60 (±0.36)	1.03–2.16
5	1.66	

Abbreviations: LSM, liver stiffness measurement; 2D-SWE, two-dimensional shear wave elastography.

cut-off value was 1.59 m/s with a sensitivity of 63% and a specificity of 93%. The AUROC for LSM predicting any degree of fibrosis (Ishak >0 and METAVIR > F0) was 0.72 with an optimum cut-off value of 1.41 m/s with a sensitivity of 61% and a specificity of 77%. The AUROC for APRI predicting significant fibrosis (Ishak Score > 2) was 0.68.

One sample t-test showed significant higher median LSM (1.32 m/s) of the PLT recipients without fibrosis compared to healthy reference groups (Farmakis [45]: 1.13 m/s, $p < 0.001$;

Mărginean [46]: age-related 1.06–1.11 m/s, $p < 0.001$, Mjelle [30]: 1.05 m/s, $p < 0.001$). On the other hand, no significant difference was found in this group compared with a group of children with liver diseases without fibrosis in the LBx (Farmakis [45]: 1.34 m/s).

4 | Discussion

Due to the excellent long-term survival rates after PLT, preservation of organ function has become a main goal [4, 6]. Fibrosis is one of the most important predictive factors for graft survival, as vascular, biliary or immune complications may ultimately lead to the development of fibrosis [4, 7, 11]. The first studies of surveillance biopsies after PLT showed a high and increasing prevalence of graft fibrosis [10, 47]. To date, fibrosis is the most common histologic alteration and a frequent finding in LBx after PLT [8, 48, 49]. Evaluation of surveillance biopsies from multiple pediatric centers has shown an increase in the prevalence and stage of fibrosis over time [4]. Prevalence of fibrosis was up to 97% after PLT [4, 50]. This has been shown in patients with normal biochemical liver function tests and is often referred to as silent graft fibrosis [7, 8, 11, 51]. Therefore, monitoring of graft fibrosis is of crucial importance due to its potential implications. In this regard, LBx is considered the reference standard for the diagnosis and staging of hepatic fibrosis, particularly in the PLT setting. However, biopsy is increasingly being questioned due to its many disadvantages. Serological tests and imaging methods are available for the non-invasive detection of fibrosis. But existing serum fibrosis markers fail in the PLT setting [25, 37, 52, 53].

USE is a non-invasive method with high reliability in the monitoring of fibrosis and good feasibility in children with chronic liver diseases [26, 27, 39]. Furthermore, USE captures a larger volume of liver tissue than LBx, and therefore, reduces the likelihood of sampling error. The first introduced SWE technique to evaluate liver fibrosis was TE [54]. Therefore, it is currently the most investigated and widely used method, especially in adults. TE is a non-imaging procedure that requires a separate device with different probes and, therefore, a separate examination procedure. As technology evolved, elastography methods with imaging were developed. 2D-SWE is the most recently introduced method and provides real-time elastography. In adults 2D-SWE performed better than TE in diagnosing liver fibrosis [32, 33]. And in children 2D-SWE shows better performance and better reliability compared to TE [30, 31]. In addition, 2D-SWE has the great advantage that it is integrated into conventional ultrasound machines and can be optimally performed during a routine ultrasound examination. The placement of the ROI under B-mode imaging, the larger ROI and the visualization of the elastograms are further advantages in comparison to TE. In adults, there are a few promising studies on the diagnostic performance of 2D-SWE after liver transplantation [55, 56]. The significance of 2D-SWE after PLT is not clarified yet. Recently, three studies have been published on the use of 2D-SWE after PLT, also showing promising results, but they were performed on machines from different manufacturers and were heterogeneous in their design [34–36]. Indicative LBx and LSM under sedation or anesthesia, which increases liver stiffness, were included. We demonstrate that LSM by 2D-SWE are feasible in children of all ages after PLT, even in those with a left lateral split-liver graft. We show that liver stiffness is higher in patients with a history of biliary complications. Other histologic findings such as AR or steatosis did not affect LSM.

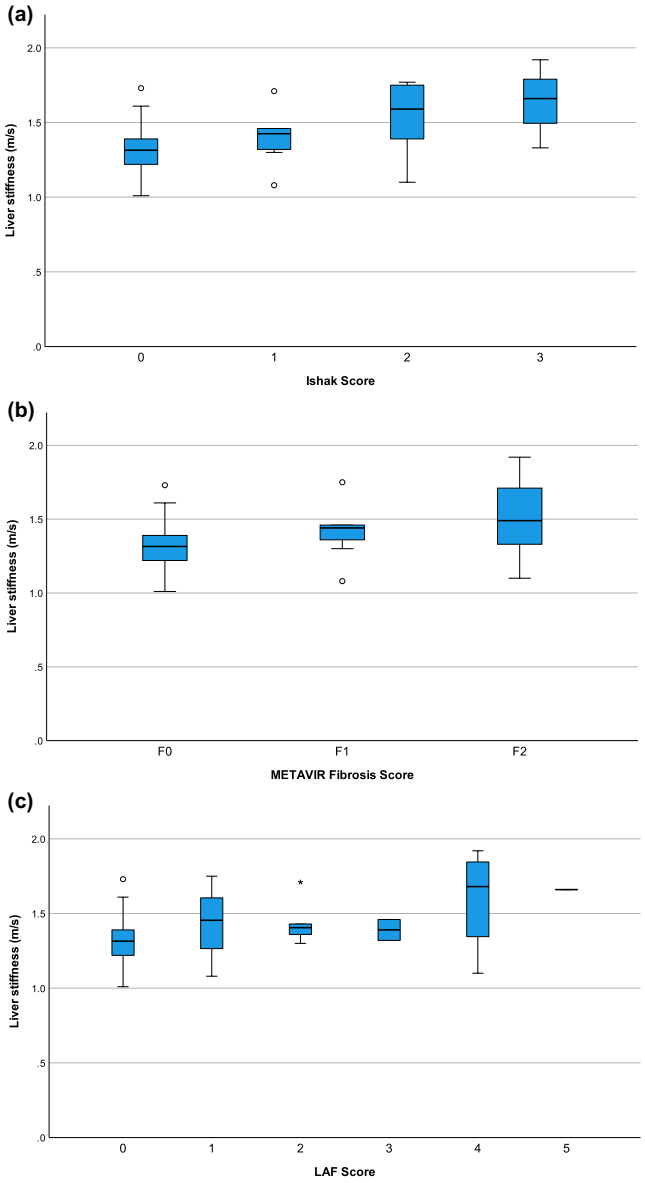

FIGURE 1 | Distributions of liver stiffness measurements (LSM) by histological fibrosis score. Box and whisker plots of the median LSM obtained by 2D-SWE versus the histological score for (a) Ishak Stage, (b) METAVIR Fibrosis Stage and (c) LAF Score. The box represents the interquartile range (IQR), the upper frame line the 3rd quartile, the lower frame line the 1st quartile and the heavy line within the box the median. The whiskers represent the maximum and minimum values (within 1.5 times the IQR). Circles represent outliers (within 3 times the IQR), asterisks extreme outliers (beyond 3 times the IQR).

The EFSUMB guidelines state, that LSM of the left liver lobe show more variability and higher results [28]. Our study showed higher LSM of the left split-liver grafts compared to those of the whole graft; however, it was not significant. Similar studies found higher LSM values for split-liver grafts, but these were also not significant [37, 52, 53, 57]. Due to the small number of

participants, it is often not possible to achieve significance in pediatric studies. In our study, histology was compared with LSM by 2D-SWE in parallel. Compared to previous studies, our cohort has a very low prevalence of fibrosis, with 71% having no histological fibrosis and none having severe fibrosis or cirrhosis. Depending on the scoring system, only 4.8%–16.1% of our patients had significant fibrosis.

We found a significant correlation between LSM and the stage of fibrosis regardless of the applied fibrosis staging systems (Ishak, METAVIR, LAF Score). Liver stiffness measured by 2D-SWE increases with the stage of fibrosis. The results are consistent with comparable USE studies after PLT, including the recent 2D-SWE studies [35, 36, 52, 57]. As in comparable studies, 2D-SWE cannot accurately discriminate between no and low-stage fibrosis [25, 26, 35]. However, 2D-SWE was able to distinguish children with significant graft fibrosis from those without.

The obtained LSM in PLT recipients without fibrosis were higher than in healthy subjects, but comparable to children with chronic liver disease without fibrosis [45]. The LSM of the different fibrosis stages after PLT are comparable to that of children with chronic liver disease [45]. Similar results have been found in comparable studies [34, 37]. In our study, most of the liver grafts came from adult donors and were split livers, which can be expected to have higher liver stiffness.

We found a cut-off value of 1.41 m/s for the prediction of any fibrosis and a value of 1.63 m/s for significant fibrosis after PLT. These values are comparable to cut-off values provided by the manufacturer for adults with chronic liver diseases with 1.35 m/s for any fibrosis and 1.66 m/s for significant fibrosis [58], but lower than in adult LT recipients [59] and higher than in children with chronic liver disease [45]. The main limitation of this study is the low number of patients with significant fibrosis. This restricts the interpretation of the AUROC curves and the cut-off values. Another limitation is that the recommended fasting time of the EFSUMB guideline was not always adhered to. On the other hand, infants may not always be able to comply with the fasting time. Ferraioli recommends performing the LSM before the next meal [39]. An LSM at a single time point cannot reliably detect low-grade fibrosis, but an increase indicates the risk of fibrosis progression. 2D-SWE does not appear to be a suitable substitute for LBx in terms of detecting early or low-grade graft fibrosis. In addition, LBx provides additional information about the status of the liver graft. However, LSM by 2D-SWE correlates well with the stage of fibrosis and 2D-SWE can reliably detect children with significant graft fibrosis. And USE can be easily integrated into a routine ultrasound examination. Therefore, 2D-SWE is a good tool to monitor the progression of fibrosis after PLT.

High or increasing LSM may indicate an LBx in centers without protocol LBx or in children in whom LBx would otherwise be rejected, and an additional LBx with long intervals between routine LBx. Elastography may help reduce the number of surveillance biopsies. As a non-invasive procedure, unlike LBx, USE can be easily repeated. The LSM must be interpreted in the context of confounding factors, clinical findings and laboratory values, such as pathological abnormalities (steatosis, hepatic congestion, biliary complications) on conventional ultrasound or elevated aminotransferase levels.

Liver biopsy serves as a reference standard, but it is imperfect. Sampling errors occur as well as segmental or focal changes that are not uncommon after PLT, and the expertise of the pathologist determines the accuracy of the histologic evaluation. In contrast, USE methods show very good interobserver compatibility and capture a larger volume. Although LBx is relatively safe, it is not without risk and requires additional resources. But the histologic assessment of the liver provides further valuable information like inflammation or steatosis. And it reveals the pattern of fibrosis. On the other hand, LBx are not suitable for frequent controls. Elastography cannot replace histologic evaluation after PLT. But it may reduce the number of biopsies.

Certainly, further studies are needed to determine the optimal timing and frequency of LSM in the posttransplant period. Nonetheless, our data suggest that SWE should be considered to complement, not replace, LBx. Only LBx can detect early or mild fibrosis. But 2D-SWE is very well suited for the monitoring of fibrosis progression over time. It is non-invasive, reliable and accurate in detecting significant fibrosis. Accordingly, we conclude that SWE has the potential to improve long-term outcomes in PLT recipients. We recommend performing protocol LBx and additional annual elastography. Increasing LSM should be controlled after 3 months. Persistently elevated liver stiffness should then lead to proof the indication for an LBx, especially in centers without surveillance biopsies.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.