Cardiology in the Young

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Accuracy of elastography versus biopsy in assessing severity of liver fibrosis in young Fontan patients

Ozlem P. Bulut[1], Smita S. Bailey[2] and Deepti P. Bhat[3]

[1]Division of Gastroenterology, Phoenix Children's Hospital, University of Arizona Phoenix, Phoenix, AZ, USA; [2]Division of Radiology, Phoenix Children's Hospital, University of Arizona Phoenix, Phoenix, AZ, USA and [3]Division of Cardiology, Phoenix Children's Hospital, University of Arizona Phoenix, Phoenix, AZ, USA

Original Article

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Corresponding author:
Deepti P. Bhat;
Emails: dbhat@phoenixchildrens.com, dbhat@arizona.edu

Abstract

Objectives: We performed a single-centre retrospective study comparing the accuracy of non-invasive elastography with liver biopsy in accurate assessment of Fontan-associated liver disease. *Methods:* Fontan patients who underwent combined assessment with a percutaneous liver biopsy and non-invasive elastography between January 2015 and December 2023 at our Children's hospital were included. Liver biopsies were classified using the Congestive Hepatic Fibrosis Score as early Fontan-associated liver disease (scores 1, 2) and advanced Fontan-associated liver disease (score 3/bridging fibrosis and score 4/cirrhosis). Elastography values were categorised as advanced Fontan-associated liver disease for liver elasticity >2.1 m/s by ultrasound and liver stiffness >5 KPa on magnetic resonance elastography. *Results:* We included 130 patients (116 children, 89%, mean age at biopsy: 14.6 years ± 3.6) who underwent liver biopsy at a mean duration of 11.1 years (±0.3) following Fontan surgery. Advanced Fontan-associated liver disease was noted in 41 (31.5%) patients with 13 (10%) showing frank cirrhosis. Pre-biopsy ultrasound showed advanced liver fibrosis in 18/125 (14%), with low sensitivity (23%), high specificity (90%), and low accuracy (68%, $k = 0.1$) in diagnosing advanced Fontan-associated liver disease. Similarly, pre-biopsy magnetic resonance elastography showed advanced fibrosis in 23/86 (27%) of patients, with low sensitivity (30%), fair specificity (75%), and low accuracy (63%, $k = 0.1$). Interestingly, advanced Fontan-associated liver disease was missed by ultrasound in 29% and by magnetic resonance elastography in 25% of patients. Advanced Fontan-associated liver disease was associated with lower platelet count ($p = 0.02$) and higher Gamma-glutamyl Transferase levels ($p = 0.02$). *Conclusion:* Advanced hepatic fibrosis is common among paediatric Fontan patients. Non-invasive elastography may overestimate and underestimate the degree of liver fibrosis, and therefore, liver biopsy may be required for confirming disease severity.

Introduction

Patients born with single ventricle CHD undergo staged surgical palliation culminating in total cavo-pulmonary anastomosis (also known as Fontan or Kreutzer procedure).[1,2] Improved outcomes after Fontan/Kreutzer procedure have increased survival but have also resulted in increased incidence of progressive liver fibrosis also known as Fontan-associated liver disease.[1–8] Multiple factors inherent to single ventricle physiology including chronically elevated central venous pressure and hypoxic injury cause abnormalities of liver structure and function manifesting as hepatic congestion, hepatic fibrosis, portal hypertension and development of focal liver lesions, and rarely hepatocellular carcinoma.[1–2,7] Although liver fibrosis is a universal consequence of Fontan physiology, the extent and severity of hepatic involvement can vary significantly.[1–7] Management approaches may span from conservative measures to the consideration of combined heart-liver transplantation in severe cases.[6–7] The diverse range of hepatic dysfunction highlights the importance of precisely evaluating the severity of liver fibrosis for informed decision making in patients experiencing failure of Fontan physiology.[2,4,6]

There are several methods available to screen for Fontan-associated liver disease including non-invasive imaging, laboratory methods of liver function, and tissue biopsy.[1–15] However, the preferred method for evaluating liver fibrosis among these patients varies widely among treating physicians. Liver biopsy is the current gold standard to assess the degree of fibrosis.[2,6] However, many centres rely on non-invasive imaging measures of liver stiffness with elastography by ultrasound and magnetic resonance elastography, which have been shown to have some correlation with liver biopsy results in adults with non-cardiac liver cirrhosis.[16] There is, however, limited and conflicting data regarding the accuracy of these methods in detecting the stage or severity of liver fibrosis in Fontan patients.[9–15] Despite its wide availability and non-invasive nature

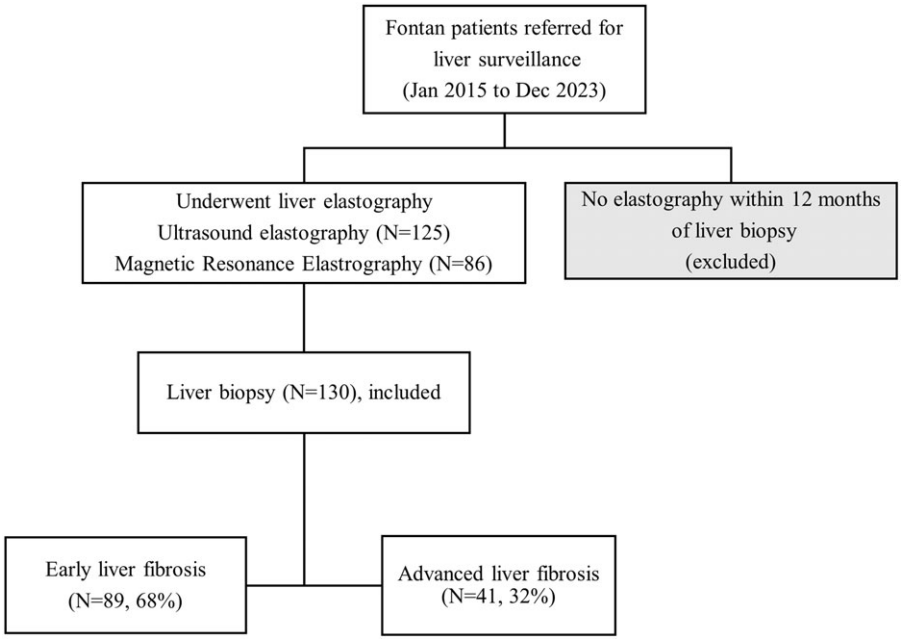

Figure 1. A total of 130 Fontan patients underwent combined liver evaluation with elastography and biopsy during the study period; and were included. Of these patients, about one-third had advanced fibrosis (bridging fibrosis/cirrhosis) on biopsy.

that make elastography an attractive alternative to biopsy, the current literature has not established if elastography can eliminate the need for a confirmatory liver biopsy.[8–13]

The objective of our study was to compare the degree of liver stiffness measured by non-invasive shear wave elastography via ultrasound and magnetic resonance with the liver fibrosis assessed on liver biopsy in young patients with Fontan physiology.

Methods

Our institute is a state-wide tertiary care referral centre for care of children and adults with single ventricle heart disease. The Fontan Program at our hospital consists of a multi-disciplinary team involving paediatric and adult congenital cardiologist, hepatologist, pulmonologist, nephrologist, nutrition, social work, and psychology. Patients referred to the Fontan program undergo routine liver surveillance with elastography (ultrasound/magnetic resonance elastography) and laboratory testing. Since 2015, the modality of elastography was routinely utilised for liver screening at our centre.

Fontan patients presenting 10 years following Fontan surgery are routinely referred for a surveillance percutaneous trans-hepatic liver biopsy and haemodynamic cardiac catheterisation as per the current surveillance recommendations by American Heart Association.[2] In patients who present within ten years of Fontan completion, liver biopsy is recommended if non-invasive elastography indicates presence of moderate to severe disease. After initial liver surveillance, our patients undergo yearly liver assessment via laboratory testing and non-invasive imaging. Liver biopsy is repeated if there are concerns for progressive liver disease or liver dysfunction. We may also repeat liver biopsy in Fontan patients who are undergoing heart transplant evaluation to assess the need for possible combined heart-liver transplantation. Our Fontan program also maintains a database of all single ventricle patients managed by our institute.

Institutional research board approved the study. We performed a retrospective analysis of our single ventricle database to identify Fontan patients who had undergone liver surveillance testing during the previous 9 years from January 2015 to December 2023. We included those patients who had undergone a combined liver assessment with elastography followed by percutaneous liver biopsy within 12 months at our institute (Fig. 1). Patients with missing data and those who had isolated imaging or biopsy were excluded.

Study procedures

Liver ultrasound elastography (USE): At our institute, shear-wave elastography of the liver was performed using an ElastPQ system (Philips Healthcare, Best, The Netherlands) using a 5 MHz broadband curved array transducer. The ultrasound exam was performed with quiet breathing or with a short breath-hold in cooperative children. Our protocol includes obtaining 10 right lobe measurements between the ribs in the right upper quadrant. A standard deviation (Std) of 30% or less of the mean value is indicative of an acquisition of good quality. Additionally, colour map images obtained with two-dimensional shear-wave elastography (EQI, Philips). The colour-coded confidence map is an evaluation of the quality of the acquired signals. The confidence threshold is set at 60%.[17–18] For the purpose of the study, we chose elasticity values <2.1 m/s as early liver fibrosis and values >2.1 m/s as advanced liver fibrosis.

Liver magnetic resonance elastography (MRE): MRI was performed on a 3.0 Ingenia (Philips Healthcare, Best, The Netherlands) unit after a minimum of 4 h of fasting. A standardised protocol was set covering the liver. A coronal and axial T2 half-Fourier single shot turbo spin-echo and a single shot spin-echo-based echoplanar imaging sequence with diffusion-weighted imaging sequences (*b* values 50–400–800) was performed pre-contrast. An axial T1-weighted 3D volumetric interpolated breath-hold examination Dixon was performed pre- and post-contrast after administration of Eovist (gadoxetate disodium) during arterial phase, portal venous phase, and hepatobiliary phase. Additionally, magnetic resonance elastography is performed using 2D Fast field echo phase contrast synchronised with an external source of mechanical vibration. Images of automated calculation of

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elastograms, reflecting tissue stiffness in kPa with statistical confidence map provided for reliability assessment.[19–20] In adult literature, liver stiffness has shown good correlation with biopsy-related fibrosis in patients with chronic liver disease, and liver stiffness values are classified as mild fibrosis (2.9–3.5 kPa), moderate fibrosis (3.5–5.0 kPa), and severe fibrosis/cirrhosis (>5.0 kPa) based on this adult literature.[16,19] For the purpose of our study, we classified patients with liver stiffness >5.0 KPa as advanced liver fibrosis.

Liver biopsy: Liver biopsy was performed under general anaesthesia, using ultrasound-guided percutaneous approach and atleast 2 right lobe core samples were obtained. The post biopsy track was embolised with Gelfoam slurry. Fresh tissue samples were analysed using H&E, reticulin, trichrome, and periodic acid Schiff stains with and without diastase. Fontan-associated liver disease was categorised based on degree and location of fibrosis, bridging necrosis, presence of nodules, and cirrhosis. While several staging scores are available for categorising liver fibrosis including Ishak score, Metavir score, etc., the current available literature on Fontan-associated liver disease supports the use of Congestive Hepatic Fibrosis Score in this patient group due to the unique pathophysiology of Fontan-associated liver disease.[6,9,21,22] We categorised our liver biopsy results using Congestive Hepatic Fibrosis Score early (scores 1 and 2) and advanced Fontan-associated liver disease (scores 3 (bridging fibrosis) and 4 (cirrhosis)).

Statistical analysis

Data were collected using the Redcap software (registered with University of Arizona). Demographic data and patient characteristics including the single ventricle type, age at Fontan surgery, age at liver biopsy, duration since Fontan surgery, and findings of the imaging studies were collected on all patients. Laboratory markers of liver function within six months of liver biopsy were also collected. Descriptive statistics using proportions for categorical data and mean with scanning electron microscopy were performed on continuous variables. Fontan-associated liver disease was categorised as early and advanced fibrosis based on the Congestive Hepatic Fibrosis Score as outlined above. As described above, for liver fibrosis classification based on elastography, ultrasound elastography derived liver lobe elasticity values >2.1 m/s (stages F3-F4), and magnetic resonance elastography derived liver stiffness values >5 kPa were considered advanced disease for correlation purpose. Results of elastography and liver biopsy were analysed for agreement using the kappa statistic with 95% confidence interval. Sensitivity and specificity analysis was performed using liver biopsy as the gold standard, and receiver operatiing characteristic curves were generated using SPSS 29.0: IBM Corp.

Results

Table 1 shows the demographic characteristics of 130 patients who met the inclusion criteria. The group was evenly divided between single right ventricle and single left ventricle physiological types. Majority were children (111, 89%) and notably underwent biopsy during their adolescent period.

Figure 1 shows the liver biopsy results of the study patients. About one-third of the patients (n = 41, 32%) showed advanced Fontan-associated liver disease on their biopsy (bridging fibrosis, n = 28, cirrhosis, n = 13). There were no major complications associated with the percutaneous liver biopsy in our series. The most common adverse effect reported was soreness at the site of the biopsy, which resolved within 24 hours. One patient (14-year-old male) reported persistent pain which resolved after a short course of analgesics. Another patient (16-year-old female) developed abdominal swelling and pain at the site of biopsy and was evaluated with an abdominal ultrasound which did not reveal any bleeding or haematoma. Her abdominal distension resolved in one week without intervention.

Table 1. Baseline characteristics of the study patients (N = 130)

Characteristic	Number (%)
Males	80 (62%)
Systemic right ventricle	62 (48%)
Heterotaxy syndrome	25 (19 %)
Age at Fontan procedure (mean)	3.4 years (SEM 0.1, 95% CI 3.3–3.7)
Time from Fontan procedure to liver biopsy (mean)	11.1 years (SEM 0.3, 95% CI 10.4–11.8)
Age at biopsy (mean) Age ≤18 years at biopsy	14.7 years (SEM 3.6, 95% CI 14.1–15.3) 116 (89%)

A total of 125 patients underwent pre-biopsy screening ultrasound elastography, and 86 patients underwent pre-biopsy magnetic resonance elastography. Table 2 compares the severity of liver fibrosis based on elastography measurements and biopsy and shows that both ultrasound elastography and magnetic resonance elastography had poor agreement and low accuracy in diagnosing advanced Fontan-associated liver disease. Using the cut-off of liver elasticity >2.1 m/s, 14% of all patients had evidence of advanced fibrosis on ultrasound elastography; however, the disease severity was downgraded to early disease on subsequent biopsy in 9 (50%). Conversely, 31/107 (29%) patients who had early disease on ultrasound elastography were subsequently found to have advanced fibrosis on biopsy. Using the cut-off value of liver stiffness (>5 KPa), 23 (27%) showed advanced fibrosis on magnetic resonance elastography, of whom disease was downgraded to mild fibrosis in 7 (30%) of cases. On the contrary, liver stiffness <5 KPa missed advanced fibrosis/cirrhosis in 16/63 (25%) of cases.

Figure 2 illustrates the receiver operating characteristic curve showing the relative performance of liver ultrasound-derived elastography versus magnetic resonance-derived elastography when compared to the liver biopsy. Both modalities performed poorly against the gold standard of biopsy. Ultrasound elastography-derived average liver lobe elasticity value >2.1 m/s had a higher sensitivity compared to magnetic resonance elastography-derived liver stiffness value >5 KPa in detecting advanced Fontan-associated liver disease on biopsy (90% versus 75%). However, both ultrasound elastography and magnetic resonance elastography had very low specificity (<30%).

Table 3 compares the presence of laboratory abnormalities in patients with Fontan-associated liver disease. Overall, there was no significant difference in the laboratory markers of liver function in the two groups except for platelet counts which were significantly lower in patients with advanced fibrosis. These markers were further compared between early Fontan-associated liver disease and those with liver cirrhosis (N = 13). Interestingly,

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Table 2. Agreement between liver biopsy and elastography on severity of FALD

Imaging modality	Total number imaged	Early FALD on biopsy	Advanced FALD on biopsy	Agreement	Accuracy
Ultrasound elastography (N = 125)					
• Early FALD (average elasticity <2.1 m/s) • Advanced FALD (average elasticity >2.1 m/s)	107 (86%) 18 (14%)	769	319	k = 0.1	68%
MR elastography (N=86)					
• Early FALD (liver stiffness <5 kPa) • Advanced FALD (liver stiffness >5 kPa)	63 (73%) 23 (27%)	4716	167	k = 0.1	63%

FALD = Fontan-associated liver disease.

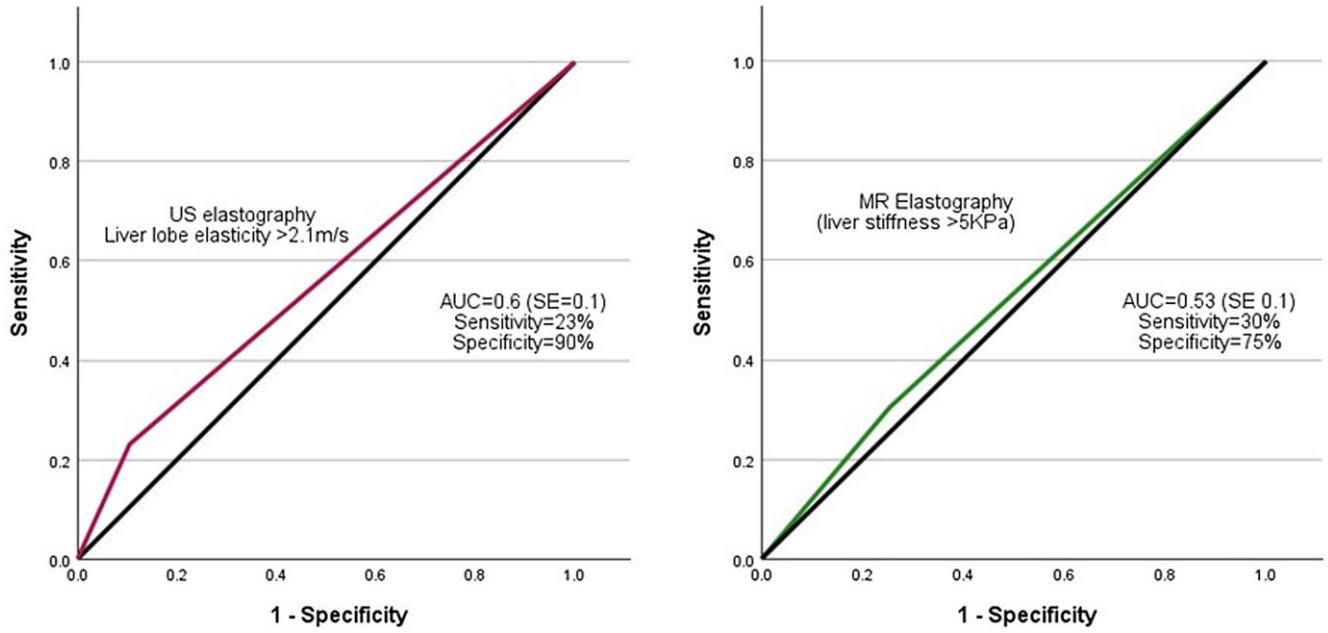

Figure 2. Comparison of ultrasound (US) vs magnetic resonance (MR) derived elastography in accurately identifying advanced liver fibrosis. The ultrasound elastography (USE) cutoff value >2.1 was more specific than magnetic resonance elastography (MRE) stiffness value >5 kPa in identifying advanced fibrosis; however, both the modalities had low sensitivity and overall poor performance on ROC curve.

those with cirrhosis had significantly higher GGT and lower albumin levels.

Discussion

Fontan-associated liver disease is universal among patients with Fontan physiology.[1–15] We studied 130 young Fontan patients (116 < 18 years of age) who underwent liver biopsy and found that a high proportion (32%) of them showed advanced liver fibrosis (including bridging fibrosis and cirrhosis). Majority of these patients were biopsied within 11 years of Fontan surgery and our findings support the current American Heart Association statement recommending early surveillance of Fontan-associated liver disease in paediatric age group.[2] We only included patients who had undergone combined surveillance with non-invasive elastography and liver biopsy and we found that liver elastography by ultrasound and magnetic resonance imaging had low accuracy and poor correlation with the degree of fibrosis by liver biopsy. To the authors' knowledge, this is one of the largest studies comparing liver biopsy with elastography in young Fontan patients.

Liver biopsy is an invasive procedure and requires the use of sedation, especially in young Fontan patients. At our centre, we coordinate the performance of liver biopsy with the cardiac catheterisation procedure, during the same anaesthesia setting. Instead of the trans-jugular approach, our paediatric interventional radiology team routinely employs the ultrasound-guided percutaneous trans-hepatic approach and post biopsy track is embolised with Gelfoam slurry to reduce the risk of haematoma. Our large series shows the safety and low complication rate of this approach, and we did not encounter any major bleeding complications in our Fontan patients. Similarly low rate of complications has been reported in previous studies on Fontan patients using the trans-jugular approach.[9,10,14,15]

Fontan-associated liver disease is known to be progressive and resultant cirrhosis can cause serious life limiting conditions such as portal hypertension and liver failure, and rarely hepatocellular carcinoma.[1–15] Therefore, surveillance for this condition is vital for guiding management decisions including need and timing for a combined heart-liver transplantation.[1,2,4,6] One of the major clinical dilemmas surrounding Fontan-associated liver disease is the choice of diagnostic modality for surveillance. The imaging modality of elastography has gained popularity as the preferred and often the sole method of Fontan-associated liver disease surveillance among several paediatric heart centres.[2,5,6] However, data are conflicting regarding association of elastography with patient outcomes in Fontan patients.[8–15] Egbe et al[11] studied serial

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Table 3. Correlation of laboratory markers of hepatic dysfunction with degree of FALD onbiopsy

Laboratory marker	Early FALD (N = 89)	Advanced FALD (N = 41)	P value #	Cirrhosis (N = 13)	P value*
Platelet count	254.6 (±10.1)	212.3 (±80.9)	0.02	202.3 (±60.3)	NS
INR	1.2 (±0.5)	1.2 (±0.2)	NS	1.2 (±0.02)	NS
Prothrombin time	14.2 (±0.5)	14.2 (±0.3)	NS	14.3 (±0.4)	NS
Albumin	4.5 (±0.1)	4.3 (±0.2)	NS	3.9 (±0.5)	0.04
Bilirubin	0.8 (±0.1)	1.0 (±0.1)	NS	1.1 (±0.3)	NS
AST	31.6 (±1.4)	28.6 (±1.4)	NS	29.4 (±3.3)	NS
ALT	29.3 (±1.6)	26.9 (±1.8)	NS	27.4 (±3.2)	NS
GGT	51.1 (±3.2)	62.9 (±8.8)	NS	79.7 (±20.1),	0.02
ALP	208.3 (±24)	194.6 (±23.5)	NS	149.9 (±31.8)	NS

FALD = Fontan-associated liver disease; INR = international normalized ratio; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase; ALP = alkaline phosphatase.
#Comparison between early FALD and advanced FALD.
*Comparison between early FALD and cirrhosis.

assessment of liver stiffness by magnetic resonance elastography in 22 adult Fontan patients. There was no statistically significant correlation between progression of liver stiffness with composite adverse endpoints. Brayer et al studied 70 adult and 58 paediatric Fontan patients and showed that while magnetic resonance elastography-derived liver stiffness was associated with portal hypertension, and poor clinical outcomes in adults, there was no association between liver stiffness and Fontan failure in children.[12] These studies raise concern if elastography can be relied upon solely to determine the need for heart-lung transplantation in this group. This often leads to the next clinical question of whether these findings have any correlation with the current gold standard test of tissue biopsy; and if so, do we really need a liver biopsy to confirm the findings.

Our study specifically aimed to assess the accuracy of the non-invasive imaging in detecting hepatic fibrosis. While adult literature shows good correlation between magnetic resonance elastography and liver fibrosis on biopsy,[16] the pathophysiology of Fontan-associated liver disease with chronic hepatic venous congestion makes it challenging to interpret the results of magnetic resonance elastography, as clear marker for fibrosis.[2,6] A study of 34 Fontan patients (mean age: 16 years) by Serai et al[11] found no statistically significant correlation between magnetic resonance elastography-derived liver stiffness and Ishak score and the authors concluded that hepatic venous congestion in Fontan-associated liver disease confounds the magnetic resonance elastography-based staging of liver fibrosis. In a large multi-centre study by Wu et al,[5] only 23 patients had both imaging and liver biopsy data available for comparison, and there was no correlation between the imaging finding and stage of sinusoidal fibrosis ($r_s = 0.05$, $p = 0.86$).[5] On the other hand, Silva-Sepulveda et al evaluated 49 adolescent Fontan patients with trans-jugular liver biopsy confirmed Fontan-associated liver disease.[9] Of these, liver magnetic resonance elastography was performed on 28 patients, and the measured liver stiffness correlated with the degree of fibrosis. The authors recommended selective use of biopsy in Fontan patients when magnetic resonance elastography score was >5 KPa. We compared the magnetic resonance elastography results of 86 patients with liver biopsy results and for the purpose of our study we used the cut-off value of >5 KPa based on the recommendation from Silva-Sepulveda et al.[9] Even with this higher cut-off value, magnetic resonance elastography overestimated the fibrosis in about 30% of patients. Additionally, we noted that among the 63 patients with the lower liver stiffness value of <5 KPa, a significant proportion (n = 16, 25%) were subsequently found to have advanced fibrosis (bridging fibrosis/cirrhosis). This finding raises the concern about using the threshold of 5 KPa for selecting patients for confirmatory liver biopsy; with the potential for underestimating severe liver fibrosis. The discrepancy between magnetic resonance elastography and biopsy in Fontan patients may be partly attributed to the heterogeneity/patchy involvement of the liver parenchyma in Fontan-associated liver disease,[1,4,6] and it is conceptually possible that liver biopsy may miss some areas of worse fibrosis noted on magnetic resonance elastography, and magnetic resonance elastography may also miss some potential areas of cirrhosis. To potentially reduce the sampling bias, percutaneous liver biopsy is preferred at our institute instead of trans-jugular approach; however, there is no uniform approach between other large paediatric centres.[9,11] Regardless, the lack of agreement between these modalities further reinforces the need for confirmatory liver biopsy prior to deciding on candidacy for heart-liver transplantation, and this is supported by the American Heart Association liver surveillance guidelines in Fontan patients which recommend liver biopsy as the current gold standard.[6] Liver magnetic resonance has additional advantages including detection of suspicious nodules as precursors of life-limiting hepatocellular carcinoma,[24] and we utilise this modality routinely at our institute to guide subsequent liver biopsy in patients.

We also evaluated the accuracy of ultrasound elastography in our study as this is one of the most used liver screening modalities in paediatric patients. Liver elasticity did not correlate with liver fibrosis in our patients and more importantly, liver elasticity value >2.1 m/s missed advanced fibrosis in 29% of patients. Previous researchers have noted similar results. Schachtler et al.[13] compared the results of shear-wave elastography with liver biopsy on 14 adult Fontan patients. Shear-wave elastography agreed with liver biopsy in 0% of cases: overestimating in 10 and underestimating in 4 cases. None of the duplex sonography indices predicted the presence or severity of liver fibrosis. Rathgeber et al reported correlation between transjugular liver biopsies in 17 children with Fontan physiology and ultrasound elastography; and found no correlation between the two modalities.[15] It is however important to note that

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while liver elasticity measured on ultrasound elastography in our study had low specificity and accuracy, liver ultrasound provides additional useful clinical information including presence of ascites, portal blood flow and is additionally used at our institute to guide performance of percutaneous biopsy. We, therefore, recommend use of ultrasoung elastography, magnetic resonance elastography, and liver biopsy as complementary modalities for the management of Fontan-associated liver disease.

Several studies on Fontan patients have shown laboratory abnormalities of liver function as unreliable markers of disease severity with mild elevation of liver enzymes including GGT, and coagulation profile noted to be common in this group, and cirrhosis has been detected with preserved liver function. Researchers have also used scores such as varices, ascites, splenomegaly, and thrombocytopenia score for assessment of cirrhosis patients.[2,5,6] Emamaullee et al. studied biomarkers of hepatic dysfunction in 106 paediatric Fontan patients and found correlation between low platelet count, higher bilirubin levels, and higher AST levels in those with advanced fibrosis (Congestive Hepatic Fibrosis Score stage 3).[22] Similarly, patients with Fontan-associated liver disease had lower platelet counts in our study. Additionally, GGT was significantly higher in our patients with cirrhosis and may be useful in trending a decline in liver function in these patients.

Our study has many limitations. This is a single centre retrospective study of a large group of young Fontan patients, and the results may not be generalizable with the other centres. Although our program attempts to standardise the imaging protocols, several patient- or procedure-related factors can potentially affect the results of elastography, and this cannot be confirmed due to the retrospective nature of the study. While our interventional radiology team follows the standard protocol and ultrasound guidance for obtaining the tissue samples, liver biopsy results can still be subject to error due to the heterogenous, and patchy nature of the Fontan-associated liver fibrosis, but the study assumes that liver biopsy is the gold standard for final diagnosis. Our study was not designed to explore the potential errors in liver biopsy findings.

In conclusion, advanced liver fibrosis appears to develop early after Fontan/Kreutzer operation in patients; therefore, routine liver surveillance should be started within the first decade of life. Our Fontan team performs early surveillance of paediatric patients using liver elastography and liver biopsy and apply these findings to implement specific targeted liver protection measures such as avoidance of hepatotoxic drugs, education about maintaining a healthy lifestyle, addressing obesity to protect from fatty liver disease and for making treatment decisions to optimise Fontan haemodynamics. Our data show that elastography may overestimate or underestimate the degree of fibrosis in patients with Fontan-associated liver disease and therefore a confirmatory liver biopsy may be required prior to making major treatment decisions such as evaluation for heart-liver transplantation.

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