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Evaluation of Fontan liver disease: Correlation of transjugular liver biopsy with magnetic resonance and hemodynamics

Jose A. Silva-Sepulveda MD[1] | Yudy Fonseca MD[2] | Irine Vodkin MD[3] | Gabrielle Vaughn MD[1] | Robert Newbury MD[4] | Vera Vavinskaya MD[5] | Jerry Dwek MD[6] | James C. Perry MD[1] | Preeti Reshamwala MD[7] | Cynthia Baehling MD[8] | James Lyon MD[9] | Christopher Davis MD, PhD[1] | Jesse W. Lee MD[1] | Hannah El-Sabrout BS[10] | Doaa Shahbah MD[11] | Laith Alshawabkeh MD[12] | John W Moore MD[1] | Howaida El-Said MD[1]

[1]Division of Pediatric Cardiology, University of California San Diego and Rady Children's Hospital, USA

[2]Division of Pediatric ICU, University of California San Diego and Rady Children's Hospital, USA

[3]Division of Gastroenterology, University of California San Diego, USA

[4]Division of Pediatric Pathology, University of California San Diego and Rady Children's Hospital, USA

[5]Division of Pathology, University of California San Diego, USA

[6]Department of Radiology, Rady Children's Hospital, USA

[7]Department of medicine, Division of digestive diseases & transplant, University of Emory, USA

[8]Department of Pathology, Sharp Memorial hospital, USA

[9]Department of Interventional Radiology, Sharp Memorial hospital, USA

[10]University of California, Los Angeles, USA

[11]University of Zagazig, Faculty of Medicine, Egypt

[12]Division of Cardiology, University of California San Diego, USA

Correspondence
Howaida El-Said, Rady Children's Hospital, 3020 Children's Way, San Diego, CA 92123.
Email: helsaid@rchsd.org

Abstract

Introduction: Liver fibrosis and cirrhosis are late complications in Fontan palliation. Liver biopsy is the gold standard. The goal of this study is to correlate transjugular liver biopsy (TJLB) in the setting of Fontan palliation with noninvasive testing and hemodynamics.

Methods: Between August 2014 and July 2017, 49 Fontan patients underwent TJLB. All the patients had hemodynamic evaluation, 28 patients had MRE (magnetic resonance elastography) and 40 patients had cardiopulmonary exercise test. Histologic liver fibrosis was quantitated using traditional histologic scoring systems and a modified Ishak congestive hepatic fibrosis score.

Results: Median age 17.8 years, median time since Fontan 15.2 years. Primary diagnosis and Fontan type were variables, but predominantly LV morphology (30/49), lateral tunnel Fontan (29/49), originally fenestrated (37/49), and 11/49 had a pacemaker. Histologic fibrosis correlated with MRE ($R = 0.62$, $P \leq .001$). Histologic fibrosis and MRE correlated with Fontan pressure ($R = 0.38$, $P = .008$ & $R = 0.59$, $P \leq .001$). Morphology of the single ventricle did not correlate with liver fibrosis. The presence of a fenestration resulted in a higher cardiac index ($P = .026$) but did not resulted in lower liver fibrosis ($P = .64$).

Conclusion: Noninvasive tests, such as MRE, may be suitable for longitudinal follow-up in patients with single ventricle physiology. Our data suggest that there is reasonable correlation of MRE liver stiffness with biopsy scoring systems and Fontan pressures. We demonstrated the feasibility of TJLB in the setting of Fontan palliation and demonstrated its correlation with noninvasive measures particularly MRE. We recommend selective use of TJLB when MRE score is >5 KPa or when there are other clinical signs of cirrhosis.

KEYWORDS

cirrhosis, exercise stress test, fontan, liver biopsy, magnetic resonance elastography, transient elastography

Work was done at University of California San Diego and Rady Children's Hospital, California, USA

1 | INTRODUCTION

The Fontan operation is the current procedure of choice for patients with single ventricle physiology.[1] It consists of directing the superior and the inferior vena cava flow into the pulmonary arterial confluence, which results in passive venous blood flow into the pulmonary arteries. This nonpulsatile venous filling results in increased central venous pressure and decreased cardiac output, which lead to multiple negative effects on extracardiac organs. The liver is particularly affected, with pathologic changes occurring both before and after the Fontan operation.[2,3] The etiology of hepatic fibrosis and cirrhosis in patients with the Fontan circulation is multifactorial. Prior to the creation of the Fontan, the liver experiences episodes of hypoxia, ischemia and elevated right atrial pressures. Establishing the Fontan circuit results in elevated hepatic venous pressure and low cardiac output causing hepatic congestion, hypoxia, and decreased portal blood flow.[3,4] These factors lead to a unique pattern of injury characterized by both sinusoidal and portal fibrosis which is distinctly different when compared to injury related to standard causes of chronic liver disease and other forms of congestive hepatopathy.[2,5-10] Liver disease is associated with long-term morbidity and mortality in this population and development of hepatocellular carcinoma has been reported as a consequence.[11-14] Fibrosis in Fontan patients often progresses without associated symptoms or biochemical abnormalities.[14]

Liver biopsy is the gold standard for the diagnosis of hepatic fibrosis and cirrhosis. However, it is an invasive procedure which carries the risk of bleeding, infection, and even death.[15] Transjugular liver biopsy in many scenarios is safer, but still has risks. Biopsy interpretation is limited by current scoring systems which are designed for use in chronic liver disease and other forms of congestive hepatopathy. These scoring systems either focus on sinusoidal or on portal fibrosis, thus often fail to adequately describe the unique pattern of fibrosis seen in the Fontan liver that involves both sinusoidal and portal fibrosis. There is not a clear consensus in determining the most appropriate scoring system for the Fontan liver.[3,5,6,16-18] Most studies examining liver biopsies have relied on reporting various scoring systems at different institutions and even adding fibrosis scores without taking into account the unique characters of the Fontan liver.[5,7,18]

Magnetic resonance elastography (MRE) and ultrasound transient elastography (FibroScan), have emerged as noninvasive methods for evaluation of liver stiffness, hepatic fibrosis, and cirrhosis in nonFontan patients.[14,19-22] The data examining the role of these new modalities in the Fontan population is limited due to small sample sizes and lack of robust histologic correlation.[17,18] The presence of hepatic congestion can lead to overestimation of stiffness by both FibroScan and MRE. More data are needed on how these noninvasive markers correlate with histologic and hemodynamic parameters in Fontan patients.

As part of our post-Fontan surveillance program, TJLB has been routinely performed during cardiac catheterization to assist in the assessment of liver pathology. In addition, we have often performed liver assessments using MRE. Clearly, it is desirable to assess liver pathology using noninvasive techniques for routine liver assessment. Our specific aim is to correlate histopathologic results obtained by TJLB in Fontan palliation with noninvasive testing including MRE as well as laboratory, and hemodynamic. We also aim to establish a cutoff using MRE liver stiffness values, below which a TJLB is not needed.

2 | METHODS

This is a retrospective study of all Fontan patients who underwent cardiac catheterization with TJLB liver biopsy between August 2014 and July 2017 at Rady Children's Hospital San Diego (RCHSD) who had additional noninvasive testing. Our practice at RCHSD and the University of California, San Diego (UCSD) is routine screening 5-10 years post-Fontan, with a cardiac catheterization, TJLB and imaging of the liver by MRE. Forty-nine Fontan patients had surveillance cardiac catheterization with TJLB during the study period and also had comprehensive evaluation. All the patients had hemodynamic evaluation, 28 patients had MRE and 40 patients had cardiopulmonary exercise test (CPET).

The institutional review boards at both institutions (RCHSD and UCSD) approved the study. The data were collected by reviewing medical records for patient demographics, cardiac diagnosis, surgical procedures, echocardiograms, hemodynamic catheterization, liver biopsy, cardiac MRI, CPET, and MRE. Ventricular function and AV valve regurgitation were evaluated by echocardiogram and cardiac MRI when available. Continuous data were summarized as mean with standard deviation when normally distributed, as median with range for data with skewed distribution, or as numbers with percentages for discrete data. Linear regression was used to estimate the relationship between continuous data where we reported Pearson correlation coefficient. Two-sample t-test was used for continuous data and a Fishers exact test for categorical data as appropriate. A P value of less than .05 was considered statistically significant.

2.1 | Cardiac catheterization with TJLB

Cardiac catheterization and TJLB were performed by two operators using the same technique. The hemodynamic portion of the catheterization was done with conscious sedation whenever possible (to simulate realistic hemodynamics), but in younger patients the entire procedure was done under general anesthesia. Blood pressure was manipulated by medications or fluid bolus, when under general anesthesia, to match a physiologic blood pressure whenever necessary. The patient was always placed under general anesthesia for the TJLB portion. The TJLB was performed via the jugular approach using the TLAB transjugular liver biopsy system (ARGON Medical Devices, Frisco, TX). The biopsies were obtained from hepatic segments 5 and 8 whenever possible. Two

to three cores of liver tissue were obtained. Ideally the samples would be long and worm-like to assure that adequate number of portal tracts are collected for better pathologic interpretation. Hemodynamic measurements at room air were obtained before angiography and included Fontan pressure, pulmonary capillary wedge pressure, and transpulmonary pressure gradient. Angiography was performed with each case to identify Fontan pathway stenosis, veno-venous collaterals, pulmonary arteries stenosis, or arterial pulmonary collaterals.

2.2 | Histopathological examination

Two pathologists were blinded to patient data and independently reviewed the liver biopsy specimens. The fibrosis was graded using standard scoring systems such as the Ishak fibrosis stage (stages 0-6)[5,6] and congestive hepatic fibrosis score (CHS) (stage 0-4).[9] Additionally, we evaluated liver biopsy specimens by combining the congestive hepatic fibrosis score (CHS) and the Ishak score characteristics into a modified score. In this article, we referred to this modified score as the modified Ishak congestive hepatic fibrosis (ICHF) score (see Figure 1): 0 = no fibrosis (similar to CHS score 0); 1 = central fibrosis (similar to CHS score 1); 2A = central zone and portal fibrosis, with accentuation of fibrosis in the central zone (similar to CHS score 2A); 2B = portal fibrosis and central zone fibrosis, with accentuation of fibrosis in the portal zone (similar to CHS score 2B); 3 = fibrous expansion of most portal areas with occasional portal to portal bridging (similar to Ishak score 3); 4 = fibrous expansion of portal areas with marked bridging (portal to portal as well as portal to central) (similar to Ishak score 4); 5 = marked bridging with occasional nodules (incomplete cirrhosis) (similar to Ishak score 5); and 6 = cirrhosis (similar to CHS score 4 and Ishak score 6).

2.3 | Magnetic resonance elastography (MRE)

MRE of the liver was performed after the cardiac MRI study or during a separate visit. MRE was performed using a passive MRE driver (Resoundant, Rochester, NY) placed on the abdomen. Four axial slices through the liver were obtained using the GE MR Touch sequence. Measurements were performed on a dedicated workstation by an independent reader who was blinded to the results of the liver biopsy. Measurements were performed by delimiting each of the slices through a freehand trace along the liver excluding cross-hatched areas where measurements of liver stiffness were unreliable. The average stiffness of the four slices was then reported.

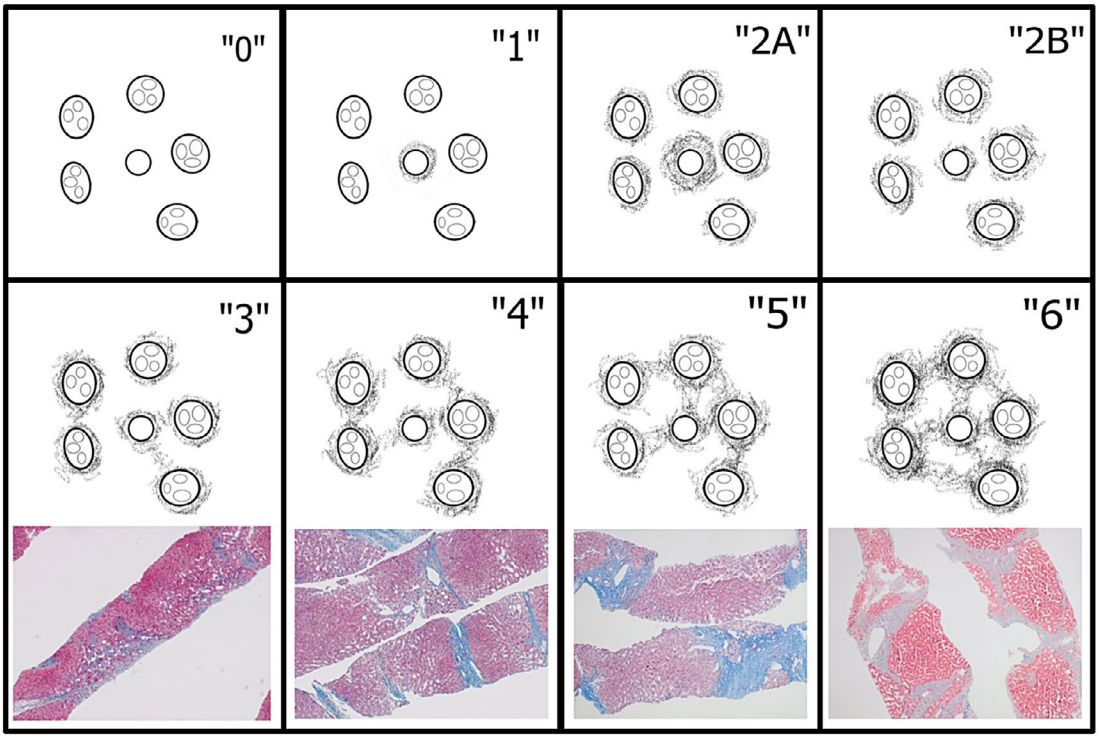

FIGURE 1 Proposed modified Ishak congestive hepatic fibrosis (ICHF) score was derived using the combination of the congestive hepatic fibrosis score (CHS) and the Ishak score. Score "0" indicates no fibrosis (similar to CHS score 0); score "1," central fibrosis only (similar to CHS score 1); score "2A," central zone and portal fibrosis, with accentuation of fibrosis in the central zone (similar to CHS score 2A); score "2B," portal fibrosis and central zone fibrosis, with accentuation of fibrosis in the portal zone (similar to CHS score 2B); score "3," fibrous expansion of most portal areas with occasional portal to portal bridging (similar to CHS score 3); score "4," fibrous expansion of portal areas with marked bridging (portal to portal as well as portal to central) (similar to Ishak score 4); score "5," marked bridging with occasional nodules (incomplete cirrhosis) (similar to Ishak score 5); and score "6," cirrhosis (similar to CHS score 4 and Ishak score 6). Masson trichrome stain examples of the modified Ishak congestive hepatic fibrosis (ICHF) (scores 3-6)

2.4 | Cardiac MRI

Cardiac magnetic resonance imaging was obtained using a 1.5 T 450 GE Healthcare (GE Waukesha, WI). Cardiac MRI was performed using the following sequences: three-plane localizer; Axial, sagittal, and coronal nongated FIESTA; Axial and sagittal oblique T1-weight DIR; Sagittal oblique, left ventricular outflow tract, two-chamber, four-chamber, and short axis-gated cine SSFP with breath-holding; PC flow imaging of ascending aorta and pulmonary arteries; Coronal Gd-enhanced MRA with postprocessing 3-D reconstructions on a dedicated workstation; Delayed enhancement imaging post-Gd; 3-D SSFP coronary artery sequence; eight-channel cardiac coil, with and without ASSET. Cardiac MRI data was only used to evaluate ventricular function.

2.5 | Cardiopulmonary exercise testing

CPET was performed on either a treadmill (Trackmaster, Newton, KS) using the Bruce Protocol or a bicycle ergometer (Ergoline, Bitz, Germany) using a ramp protocol appropriate to each patient's size, age, and predicted exercise capacity. Pulmonary function testing was performed pre-exercise and postexercise and gas exchange data were obtained continuously during exercise and recovery using a metabolic cart (Vyaire, Mettawa, IL). Subjects exercised to volitional fatigue and a test was considered adequate to have achieved maximal effort if the respiratory exchange ratio was ≥ 1.1. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were recorded continuously. Ventilatory efficiency was calculated as VE/VCO_2. Continuous pulse oximetry and electrocardiographic monitoring occurred throughout each test.

2.6 | Laboratory testing

All patients had the following laboratory studies: ϒ-glutamyl transferase (GGT) level, aspartate aminotransferase (AST) level, alanine aminotransferase level (ALT), alkaline phosphatase level, total protein level, albumin level, total bilirubin level, direct bilirubin level, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), B-type natriuretic peptide (BNP) level, platelet count, and hemoglobin level. The Fibrosis-4 (FIB-4) and AST to Platelet Ratio Index (APRI), noninvasive methods for fibrosis, were calculated for every patient. The APRI combines AST and platelet count to estimate fibrosis.[23] The FIB-4 score combines standard biochemical values (platelets, ALT, AST) and age.[24] Hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and hepatitis C antibody were checked for all patients who had any of their surgeries prior to 1992 (25/49 patients).[25] There was no laboratory evidence of hepatitis for any of the patients that were tested.

3 | RESULTS

The median age at the time of the TJLB was 17.8 years (range 5-39 years) and the median interval between the Fontan operation and the liver biopsy was 15.2 years (range 2-33 years). Fifty-nine percent (29/49) were males. The underlying anatomy consisted of tricuspid atresia in 9/49 (18%), heterotaxy syndrome (single ventricle) in 8/49 (16%), hypoplastic left heart syndrome in 7/49 (14%), pulmonary atresia with intact ventricular septum in 6/49 (12%), double inlet left ventricle in 6/49 (12%), double outlet right ventricle in 5/49 (10%), unbalanced atrioventricular canal defect in 5/49 (10%), complex single ventricle in 2/49 (4%), and Ebstein's anomaly in 1/49 (2%). The systemic ventricle was the morphological left ventricle in 30/49 (61%) and the morphological right ventricle in 19/49 (39%). The initial Fontan procedures before any revisions consisted of a lateral tunnel in 29/49 (59%), an extracardiac conduit in 18/49 (37%) and an atrio-pulmonary Fontan in 2/49 (4%). Six patients underwent Fontan revision to an extracardiac Fontan (two with an original atriopulmonary Fontan, three with an original lateral tunnel, and one with an original extracardiac conduit). Eleven patients had a permanent pacemaker. See Table 1 for summary of patient data. Seventy-five percent (37/49) had a fenestration at the time of their Fontan. At the time of their last cardiac catheterization, 51% (20/49) had a patent fenestration at the time of their cardiac catheterization. Eleven patients had spontaneous closure of their fenestration and six patients had the fenestration closed in a previous catheterization procedure. Fontan pathway stenosis was discovered in 26% (13/39) of patients, 61% (8/13) of those patients had veno-venous collaterals present at the time of the cardiac catheterization, and 42% (15/36) of those without stenosis had veno-venous collaterals.

All testing data and cardiac catheterization data used in this study were data after the Fontan procedure or after the Fontan revision when applicable. Eighty percent (39/49) of patients had normal ventricular function, 14% (7/49) had mildly decreased ventricular function, and 6% (3/49) had moderately to severely decreased ventricular function. Sixty-one percent of patients (30/49) had minimal AV valve regurgitation, 25% (12/49) had mild AV valve regurgitation, and 14% (7/25) had moderate to severe AV valve regurgitation. The mean Fontan pressure was 13 mm Hg (2.4 mm Hg), the mean pulmonary wedge pressure was 7.8 mm Hg (2.1), transpulmonary gradient was 4.2 mm Hg (1.5), the mean resting cardiac index was 3.5 L/min/m^2 (1.2), and the mean pulmonary vascular resistance index was 1.6 Wood units·m^2 (0.7). See Table 2 for laboratory, echo, and cardiac MRI, and hemodynamics summary. Fifty-seven percent (28/49) had an MRE and abdominal MRI performed. The mean value for MRE liver stiffness was 4.5 kPa (0.9). MRI liver findings are all summarized as follow: Fifty percent (14/28) had hepatomegaly, 25% (7/28) had splenomegaly, 7% (2/28) had asplenia, 32% (9/28) had ascites, 32% (9/28) had a nodular/lobular liver, 14% (4/28) had varices, and 7% (2/28) of patients had image-based cirrhosis.

Liver biopsy results (including several histologic scoring systems) were compared with MRE. MRE liver stiffness correlated with previous utilized scoring systems, such as the Ishak scoring system and congestive hepatic fibrosis (CHF) score. MRE also correlated against the modified Ishak congestive hepatic fibrosis (ICHF) score (Table 3). The ICHF score, the Ishak scoring system, and the congestive hepatic fibrosis scoring system were evaluated against other variables

TABLE 1 Summary of patient data (N = 49)

Characteristics	Total number
Male sex: *n* (%)	29 (59%)
Age of patient: years (median and range)	17.8 (5-39)
Time since Fontan operation: years (median and range)	15.2 (2-33)
Primary congenital diagnosis: *n* (%)	
Tricuspid atresia	9 (18.4%)
Heterotaxy syndrome (single ventricle)	8 (16.3%)
Hypoplastic left heart syndrome	7 (14.3%)
Pulmonary atresia with intact ventricular septum	6 (12.2%)
Double inlet left ventricle	6 (12.2%)
Double outlet right ventricle	5 (10.2%)
Unbalanced atrioventricular canal defect	5 (10.2%)
Complex single ventricle	2 (4.1%)
Ebstein's anomaly	1 (2%)
Systemic Ventricle: *n* (%)	
Morphologically left ventricle	30 (61%)
Morphologically right ventricle	19 (39%)
Type of Fontan Surgery: *n* (%)	
Lateral Tunnel	29 (59%)
Extracardiac Fontan	18 (37%)
RA-PA	2 (4%)
Fontan revisions	6 (12%)
Originally fenestrated: *n* (%)	37 (75%)
Patent fenestration	20 (41 %)
Spontaneous closure of fenestration	11 (29 %)
Fenestration closed in the catheterization lab	6 (13.3 %)
Pacemaker: *n* (%)	11 (22%)
Medical treatment: *n* (%)	
B-blocker	9 (18%)
ACE inhibitor	31 (63%)
Diuretics	18 (37%)
Phosphodiesterase 5 inhibitors	9 (18%)

(Table 3). Fontan pressures and time since the Fontan correlated with the ICHF score, the Ishak fibrosis score, and congestive hepatic fibrosis score (see Table 3). MRE liver stiffness values underwent regression analysis against other variables (Figure 2, Table 3). MRE liver stiffness correlated with time since Fontan operation (R = 0.53; P = .004), Fontan pressure (R = 0.59, P < .001), transpulmonary gradient (R = 0.39, P = .043), and exercise VO2 max (R = −0.51, P = .025). The data for FIB-4 and APRI values in this study was limited. Our data show that all our patients with cirrhosis have FIB-4 values of less than 1.45 and APRI values of less than 0.5. None of our patients in this study have FIB-4 values of more than 3.25 or APRI values of more than 1.5.

Further analysis was performed to determine any difference between Fontan anatomic variables. Histologic fibrosis (P = .099) was not different between a systemic left ventricle and right ventricle. MRE liver stiffness values (P = .026) and Fontan pressures (P = .042) were higher for patients with a left systemic ventricle. The presence of a fenestration did not create any difference in Fontan pressures (P = .484), MRE liver stiffness (P = .587), or histologic fibrosis (P = .644). The Fontan pressures (P = .656), MRE liver stiffness (P = .245), and histologic fibrosis (P = .452) were not significantly different between patients that had spontaneous closure of their Fenestration and those patients with a patent fenestration. In this group, the presence of a patent fenestration was associated with a higher cardiac index (L/min/m^2) (P = .037). Further analysis was performed to determine how the presence of Fontan stenosis and veno-venous collaterals affected liver fibrosis. The Fontan pressures (P = .248), MRE liver stiffness (P = .500), and histologic fibrosis (P = .149) were not different for those patients who had a patent Fontan pathway versus those with stenosis versus those without stenosis. Transpulmonary gradient was more elevated for patients who had Fontan pathway stenosis (P = .032). The Fontan pressures (P = .680), MRE liver stiffness (P = .341), and histologic fibrosis (P = .149) were not different for those patients who had a V-V collaterals versus those without collaterals. Further analysis showed no difference in the amount of fibrosis (P = .652) seen in the biopsy results between patients with a pacemaker and those without a pacemaker.

4 | DISCUSSION

Liver disease is universal in the Fontan population and is associated with long-term morbidity and mortality in this population.[11-14] Liver biopsy is the gold standard for the diagnosis of hepatic fibrosis and cirrhosis. Currently used methods of assessing liver fibrosis do not adequately describe liver histopathology in Fontan physiology. Traditional scoring systems, such as the METAVIR, Ishak, or Scheuer scoring systems, have been used primarily to assess liver damage in chronic hepatitis.[3] Hepatic fibrosis in two ventricle physiology caused by cardiac dysfunction is predominantly sinusoidal with portal areas affected later in the disease process.[26] The congestive hepatic fibrosis score (CHS) developed by Dai et al. highlights the need for a separate scoring system to describe fibrosis associated with congestive hepatopathy. However, liver architecture in the Fontan patient has unique histologic features. Hypoxic and ischemic insults which occur from birth result in variable degrees of both sinusoidal and portal fibrosis that start even before the creation of the Fontan circuit.[6,27] Post-Fontan biopsies show a global disease involving portal and centrilobular areas. Swartz et al[5] reported 100% sinusoidal and 92% portal based fibrosis in biopsies of only 13 patients. A multicenter study by Wu et al. examined 68 biopsies and found 97% with sinusoidal fibrosis and 90% with portal fibrosis.[7] The congestive hepatic fibrosis score (CHS) does not address the clinically relevant range of portal fibrosis between central fibrosis (CHS 2B) and cirrhosis (CHS 4). At the same time, early central fibrosis is not evaluated in traditional scoring systems,

TABLE 2 Hemodynamic, imaging, and laboratory data

Variable (*n* = 49)	Mean (SD)
Laboratory	
Gamma-glutamyl transferase (U/L)	74.5 (53.6)
Aspartate aminotransferase (U/L)	41.3 (13.4)
Alanine aminotransferase (U/L)	33.7 (11.0)
Total bilirubin (mg/dL)	1.3 (0.3)
Albumin (g/dL)	4.4 (0.4)
International normalized ratio	1.2 (0.1)
Creatinine (mg/dL)	0.6 (0.2)
Hemoglobin (g/dL)	15.6 (1.9)
Platelets (1000/dL)	170.0 (53.2)
BNP	36.1 (33)
Cardiac Cath	
Aortic oxygen saturation (%)	91.8 (3.8)
Mix-venous oxygen saturation (%)	70.4 (5.7)
Fontan pressure (mm Hg)	13.1 (2.4)
Pulmonary capillary wedge pressure (mm Hg)	7.8 (2.1)
Transpulmonary gradient (mm Hg)	4.2 (1.5)
Pulmonary vascular resistance index (WU × m^2)	1.6 (0.7)
Cardiac index (Fick) (L/min/m^2)	3.5 (1.2)
Fontan pathway stenosis: *n* (%)	13 (26%)
Veno-venous collaterals: *n* (%)	23 (47%)
Exercise stress test	
Peak VO2 (mL/kg/min)	27.4 (8.7)
VE/VCO2 slope	33.1 (6.4)
TTE/MRI data: *n* (%)	
Decreased ventricular function (mild)	7 (14%)
Decreased ventricular function (moderate or severe)	3 (6%)
AV valve regurgitation (mild)	12 (25%)
AV valve regurgitation (moderate or severe)	7 (14%)
Fibrosis scores	
AST to Platelet Ratio Index (APRI)	0.58 (0.23)
Fibrosis-4 (FIB-4)	0.85 (0.54)
MRE	
Mean liver stiffness (kPa)	4.5 (0.9)

such as the Ishak score and METAVIR, which ignore specific characteristic of the Fontan liver. Due to the limitations of applying existing histologic scoring systems to Fontan associated liver disease, most studies examining liver biopsies have relied on reporting multiple scoring systems and even adding fibrosis scores when evaluating Fontan liver fibrosis.[5,7,18,27] These studies highlight the importance of creating a common histologic scoring system for the Fontan population that considers the specific characteristics of the Fontan liver and also the use of noninvasive imaging to evaluate the Fontan liver disease.

In the present study, we report the correlation between histopathologic data obtained by TJLB in Fontan palliation and noninvasive liver testing such as MRE and hemodynamics. We utilized traditional histopathologic score systems (such as the CHS score and the Ishak scoring system) to assess Fontan associated liver disease in a population of 49 patients. We also combined the Ishak scores and the congestive hepatic fibrosis scores into a modified Ishak congestive hepatic fibrosis (ICHF) score to evaluate specific characteristic of the liver fibrosis in the Fontan population not evaluated by each method independently. We found a correlation between histopathologic score system and hemodynamics. To our knowledge, this study reports the largest number of liver biopsies and MRE studies in a single study and thus provides a strong correlation. The previously reported data examining the role of the MRE in

TABLE 3 Correlation between various histology fibrosis scores, liver stiffness, and hemodynamic parameters and labs (Pearson correlation and *P* value (<.05**))

Variable	Ishak fibrosis	Congestive hepatic fibrosis score	Modified Ishak congestive hepatic fibrosis (ICHF) score	MRE liver stiffness (kPa)
Time since Fontan (years)	0.38 (0.008)**	0.29 (0.040)**	0.36 (0.013)**	0.53 (0.004)**
Fontan pressure (mm Hg)	0.38 (0.008)**	0.36 (0.011)**	0.38 (0.008)**	0.59 (<0.001)**
Pulmonary wedge pressure (mm Hg)	0.41 (0.004)**	0.21 (0.160)	0.37 (0.012)**	0.16 (0.442)
Trans-pulmonary gradient (mm Hg)	−0.06 (0.702)	0.04 (0.770)	−0.06 (0.691)	0.39 (0.043)**
PVR index (WU × m^2)	−0.257 (0.082)	−0.152 (0.301)	−0.211 (0.155)	0.21 (0.312)
End-diastolic pressure (mm Hg)	0.40 (0.009)**	0.33 (0.031)**	0.37 (0.015)**	0.150 (0.473)
Cardiac index (Fick) (L/min/m^2)	0.304 (0.038)*	0.221 (0.131)	0.271 (0.066)	0.09 (0.647)
Peak VO2 (mL/kg/min)	0.02 (0.894)	0.08 (0.616)	−0.001 (0.996)	−0.51 (0.025)**
VE/VCO2 slope	0.35 (0.027)**	0.25 (0.116)	0.33(0.039)**	0.04 (0.884)
Gamma-glutamyl transferase (U/L)	0.27 (0.062)	0.144 (0.325)	0.28 (0.050)	0.21 (0.283)

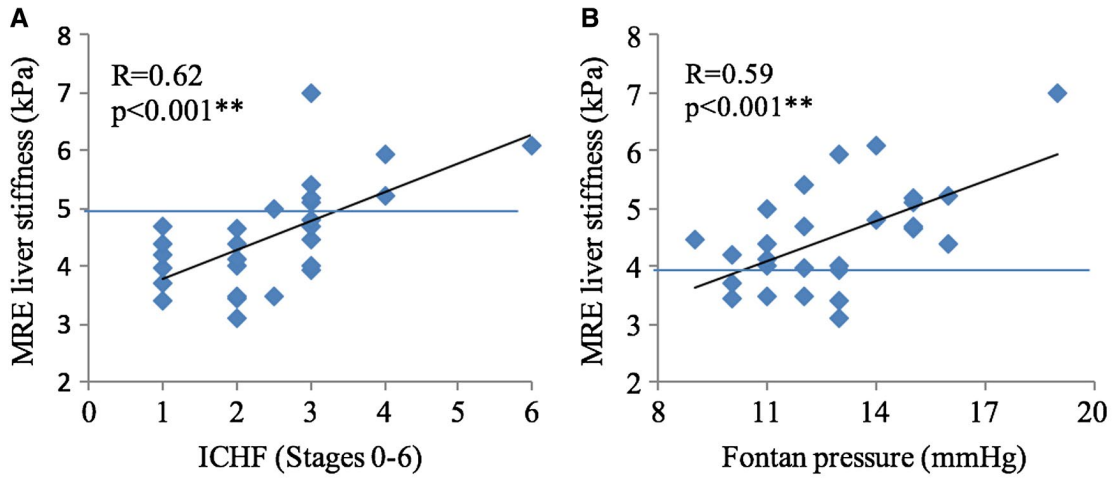

FIGURE 2 Correlation of modified Ishak congestive hepatic fibrosis (ICHF) score with MRE liver stiffness (A). Correlation of MRE liver stiffness with Fontan pressure (B)

the Fontan population is promising, but is limited due to small sample sizes and lack of robust histologic correlation.[17,18]

We suspect that noninvasive modalities, such as MRE are becoming promising in the evaluation of Fontan liver disease. MRE has emerged as a noninvasive method for evaluation of liver stiffness, hepatic fibrosis, and cirrhosis in non-Fontan patients.[14,19,21] Although liver biopsy is still considered the gold standard for the diagnosis of fibrosis, noninvasive testing such as MRE would be preferable for long-term follow-up.[14] We observed a significant correlation between the MRE liver stiffness and liver fibrosis using the Ishak and the congestive hepatopathy scores. We also found a positive correlation between ICHF score (liver fibrosis) and MRE liver. We observed that higher Fontan pressures were associated with higher liver biopsy scores (more fibrosis) and higher MRE liver stiffness values. We also found a correlation between the histologic fibrosis scores and the time since the Fontan operation as reported in previous publications.[8,11] MRE liver stiffness values also correlated with the time since the Fontan.

The current study data suggest that MRE values are influenced by both liver fibrosis and Fontan pressures, as noninvasive modalities cannot distinguish between fibrosis and venous congestion.

We found a strong association between MRE and the Fontan pressure as well as the transpulmonary gradient. Previous studies in adults with biventricular physiology have established an MRE liver stiffness value of more than 4.9 kPa that is associated with liver cirrhosis.[28,29] For the Fontan population, Poterucha et al[18] suggested a cutoff of 5 kPa as part of their criteria to evaluate patients that may need a liver biopsy. However, MRE values have not been validated in the Fontan population the same way as other populations because of confounding liver congestion and higher Fontan pressures increasing

stiffness scores. Our data show that MRE values of more than 4 kPa are associated with Fontan pressures of more than 14 mm Hg, and MRE values of more than 5 kPa are associated with significant bridging fibrosis and cirrhosis. This suggests two potential cutoffs to prompt hemodynamic or histologic evaluation, while potentially eliminating the need for invasive procedures in the low risk group. MRE may help obviate the need for liver biopsy for patients with values <4.5-5 kPa if enough data suggest this is adequate to rule out advanced fibrosis.[18] However, given the nature of the Fontan circulation, it is not possible at this time to use MRE to distinguish whether or not a measure of >4.5-5 correlates with an increased pressure in the Fontan, the liver or both. Liver biopsy and cardiac catheterization may still be needed if it is clinically necessary to ascertain the etiology of increased liver stiffness. MRE may also be a useful modality for following response to treatment (ie, afterload reduction, pulmonary vasodilation, Fontan revision) over time. Trending MRE values can serve as a marker for treatment response for some patients. Combining liver MRE and abdominal MRI can also offer important information that we cannot obtain from biopsy, by allowing evaluation of the entire liver parenchyma. This allows us to look for abnormal venous drainage, veno-venous collaterals, and liver nodules, all of which are important information if considering future cardiac or cardiac-liver transplantation. Regardless of biopsy or MRE results, evidence of portal hypertension (varices, ascites, and splenomegaly) on imaging may be concerning for increased risk for a major adverse event as previously reported in the VAST study.[30]

5 | CONCLUSION

We demonstrated the feasibility of TJLB in the setting of Fontan palliation and demonstrated a correlation of liver fibrosis with noninvasive measures such as MRE and Fontan pressures. We were able to demonstrate that Fontan liver disease can be evaluated with traditional scoring systems, such as the Ishak and the congestive hepatopathy fibrosis score. We also were able to demonstrate an equivalent correlation with MRE and Fontan hemodynamics using a modified Ishak congestive hepatic fibrosis (ICHF) score. Noninvasive tests, such as the MRE, can provide longitudinal follow up date in patients with single ventricle physiology. Our data suggest that there is reasonable correlation of MRE liver stiffness with biopsy scoring systems and Fontan pressures. This study shows liver cirrhosis for MRE values >5 kPa. MRE values >4kPA are associated with higher Fontan pressures, thus allowing more targeted use of TJLB in the setting of Fontan. We now recommend selective use of TJLB when MRE score is >5 kPa or when there are other clinical signs of cirrhosis.

5.1 | Study limitations

Our data is limited to relatively younger patient population and shorter time from Fontan, compared to other studies.[5,6,17,18] The association of liver stiffness, fibrosis scores, and suboptimal hemodynamics may become more apparent in patients with advanced liver fibrosis. Alcohol evaluation was not performed in all our patients in this study. Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, and Hepatitis C antibody were only checked for 24 patients, however according to the screening guidelines[25] all the patients that were operated before 1992 were screened for hepatitis C. There was no laboratory evidence or any history of hepatitis for any of the patients.

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AUTHOR CONTRIBUTIONS

First author did data analysis and wrote the paper: Silva-Sepulveda
Data collection and data analysis: Fonseca
Hepatologist prospective on data analysis and wrote section related to liver biopsy: Vodkin
Data analysis and wrote paper from heart failure standpoint: Vaughn
Pathologist, read the liver biopsy slides blindly. Also helped write section on pathology: Newbury
Pathologist, read the liver biopsy slides blindly. Wrote section on liver biopsy and came up with the scoring system: Vavinskaya
Radiologist who read all the MREs blindly and wrote the section on MRE: Dwek
Adult congenital heart disease specialist and director of EP. Helped with paper writing and EP prospective: Perry
Hepatologist prospective on data analysis and wrote section related to liver biopsy: Reshamwala
Pathologist, read the slides blindly. Also helped write section on pathology: Baehling
Interventional radiologists, performed trans-jugular liver biopsies and mentored interventionists and helped write section on biopsy: Lyon
Did stress tests and helped analyze data related to stress test: Davis
Cardiology fellow, helped with doing the transjugular liver biopsies and helped analysis the data and write paper: Lee
Data collection and data analysis and helped with paper writing: El-Sabrout
Data collection and helped with paper writing: Shahbah
Adult congenital specialist helped with data analysis and writing the paper from ACHD prospective: AlShawabkeh
Performed trans jugular liver biopsies. Helped with writing the paper: Moore
Senior author who formatted the idea of the project, performed trans jugular liver biopsies, worked with all members to coordinate work. Also did data analysis and wrote the paper: El-Said

ORCID

Jesse W. Lee https://orcid.org/0000-0001-8335-5357

Howaida El-Said https://orcid.org/0000-0002-3447-7398

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