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ORIGINAL ARTICLE

Does liver biopsy accurately measure fibrosis in Fontan-associated liver disease? A comparison of liver biopsy pre–combined heart and liver transplant and liver explant post-transplant

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Abstract

The accuracy of liver biopsy to stage fibrosis due to Fontan-associated liver disease (FALD) remains unclear. We compared the results of biopsy pre–combined heart and liver transplantation (CHLT) to the results of whole liver explant. Liver biopsy and explants from 15 Fontan patients (ages 16-49, median 28 years) were retrospectively reviewed. Staging was as follows: stage 0: no fibrosis, stage 1: pericellular fibrosis, stage 2: bridging fibrosis, and stage 3: regenerative nodules. There is no stage 4. Clinical characteristics including Model of End-stage Liver Disease eXcluding INR and Varices, Ascites, Splenomegaly, and Thrombocytopenia (VAST) scores were collected, and descriptive statistics and Mann-Whitney *U* tests were used to analyze the data. All patients had biopsies with at least bridging fibrosis, and all had nodularity on explant; transjugular biopsy never overestimated fibrosis. Explant showed higher-grade fibrosis (stage 3) than pre-CHLT biopsy (stage 2) in 6 of 15 patients and equal grade of fibrosis (stage 3) in 9 of 15 patients. Though clinical characteristics varied significantly, VAST score was ≥2 in all but two patients. Transjugular liver biopsy does not overestimate and can underestimate fibrosis in Fontan patients undergoing CHLT, likely due to the patchy nature of fibrosis in FALD.

KEYWORDS
biopsy, Fontan, Fontan-associated liver disease, liver fibrosis

1 | INTRODUCTION

Fontan-associated liver disease (FALD) encompasses abnormalities in liver structure and function that result from Fontan circulation unrelated to other disease processes.[1] FALD induces liver fibrosis, which is universal in all Fontan patients.[2,3] Fibrosis does not start just with Fontan circulation but begins at some point before Fontan along the patient's single ventricle palliation pathway.[4] FALD can lead to cirrhosis and portal hypertension and complicate the management of patients with "Fontan failure."[5] In some centers, heart transplantation is not offered to patients with Fontan failure and liver fibrosis due to the high morbidity and mortality risk.[6] Combined heart and liver transplantation (CHLT) may be appropriate in certain cases. Liver biopsy in FALD may help to characterize and stage liver fibrosis as part of a comprehensive evaluation of patients considered for heart and/or CHLT.[7-9] However, liver biopsy may not accurately

identify the degree of fibrosis.[2] We thus sought to perform a retrospective descriptive analysis of our Fontan CHLT cohort to compare fibrosis on liver biopsy pre-CHLT to fibrosis found on whole liver explant.

2 | PATIENTS AND METHODS

All patients, unless there is a contraindication, being evaluated for CHLT undergo liver biopsy as part of a comprehensive evaluation for CHLT. Since 2008, 18 adolescents and adults >14 years of age with failing Fontan physiology have undergone CHLT at our center and thus met inclusion criteria. Three patients who did not undergo liver biopsy due to concern for bleeding were excluded. Liver biopsy was performed via transjugular technique (except in two patients), and whole explants from the remaining 15 patients (ages 16-49, median 28 years) were reviewed. All biopsies were comprised of at a minimum three cores with lengths ranging from 0.2 to 1.5 cm. All biopsies and explants were reviewed at the time of biopsy and transplant by at least two members of the pathology faculty and re-reviewed by three authors (SV, JH, and TD) for the purposes of this study. Hematoxylin and eosin–stained slides from formalin-fixed, paraffin-embedded material were examined. Additional special stains, including trichrome, reticulin, and elastin van Gieson, were examined on representative sections for each liver explant. Immunohistochemical stains for cytokeratin 7, cytokeratin 19, and CD61 were also performed in each case. The staging system of liver biopsy at our center is as follows: stage 0: no fibrosis, stage 1: pericellular fibrosis, stage 2: bridging fibrosis, and stage 3: regenerative nodules. There is no stage 4. This staging system was designed to prevent "overstaging" of biopsies, as biopsies only reflect a small sample of the liver, and for its simplicity and reproducibility.[10] In addition to biopsy results, clinical characteristics including time from Fontan, results of echocardiography and cardiac catheterization, advanced liver imaging, and Model of End-stage Liver Disease eXcluding INR (MELD-XI) and Varices, Ascites, Splenomegaly, and Thrombocytopenia (VAST) scores were collected for each patient.[11,12] Descriptive statistics were calculated, and Mann-Whitney *U* tests were used to assess these characteristics for association with biopsy results. The study protocol was approved by the Stanford University Institutional Review Board.

3 | RESULTS

All patients had evidence of sinusoidal dilation, pericellular fibrosis, and at least bridging fibrosis on pre-CHLT liver biopsy; all patients had sinusoidal dilation, pericellular fibrosis, bridging fibrosis, and nodularity on whole liver explant. Liver explant showed higher-grade fibrosis (stage 3, nodularity) than biopsy (stage 2, bridging fibrosis) in 6 of 15 patients and the same grade of fibrosis (stage 3, nodularity) in 9 of 15 patients. No patient had less fibrosis on explant than biopsy. Results of echocardiography, cardiac catheterization, advanced liver imaging, and MELD-XI scores varied significantly (Tables 1 and 2). Time from biopsy to transplant, Fontan duration, Fontan or end-diastolic pressures nor MELD-XI scores were associated with fibrosis stage on biopsy. All but two patients (one with asplenia) had a VAST score ≥2. One patient was diagnosed with hepatocellular carcinoma (HCC) by advanced imaging post-biopsy but pre-transplantation; explant confirmed this diagnosis.

4 | DISCUSSION

Our aim was to evaluate the degree of liver fibrosis in our cohort of CHLT patients comparing pre-CHLT biopsy and post-CHLT explant specimen. We found the majority of biopsies and explant specimens to be concordant in fibrosis grade, while a substantial minority of biopsies underestimated the degree of fibrosis found on explant. One potential explanation for why some biopsies underestimated fibrosis could be that there was a lag in time between date of biopsy and date of transplant, and thus, there was progression of FALD that led to higher-grade fibrosis on explant. However, there was no difference in the median time from biopsy to transplant for those with bridging fibrosis (stage 2) versus those with stage 3 (nodularity) (1.1 versus 1.2 years, respectively). More likely, the discordance of some biopsies showing less fibrosis than explant was due to potential sampling error from the patchy nature of fibrosis in FALD. No biopsy overestimated fibrosis despite the use of transjugular approach in all but two patients.

Liver biopsy is the gold standard for assessment of FALD, as many of the typical laboratory values used to monitor liver inflammation and synthetic function in other types of liver disease, such as liver enzymes, albumin, and coagulation factors do not consistently correlate with the severity of FALD. That no patient showed higher-grade fibrosis on the pre-CHLT biopsy when compared to liver explant is significant in that all but two of these biopsies were done by transjugular technique. Due to the obligatory central venous congestion, some have argued that transjugular biopsy may overestimate liver disease in the Fontan population since it samples the area around the central vein. Percutaneous transhepatic biopsy has thus been advocated to give a more accurate fibrosis assessment.[13] The only other study with data comparing pre-CHLT biopsy (all by percutaneous technique) and liver explant, however, showed only four of seven patients with a concordant degree of fibrosis. The other three patients had disparate results on biopsy versus explant—one had biopsy overestimate fibrosis and two had biopsy still underestimate fibrosis.[7] Thus, transjugular biopsy should not be viewed as inferior to percutaneous technique regarding accurate assessment of liver fibrosis and may be more appropriate in patients with significant coagulopathy or ascites (Book's type III Fontan failure) and obviate the need for hospitalization for overnight observation.[5,13]

It is important to note the assessment of FALD is complicated by the various center-specific pathologic scoring systems used to classify liver disease overall and specifically, congestive hepatopathy due to cardiac disease. Since the original pathologic scoring systems

TABLE 1 Individual cardiac characteristics of patients undergoing pre-CHLT liver biopsy and CHLT from 2012 to 2020

	20-yo F DORV	28-yo F AVSD	31-yo M AVSD	19-yo F TA	16-yo M TA	31-yo M HLHS	41-yo F DORV	21-yo M HLHS	43-yo M DILV	28-yo F DILV	26-yo M AVSD	18-yo M AVSD	44-yo F AVSD	49-yo F TA	22-yo M TGA
Transplant date	5/4/12	2/5/15	7/9/16	8/16/17	11/7/17	1/18/18	2/23/18	10/22/18	1/28/19	3/15/19	3/18/19	5/11/19	12/13/19	1/31/20	3/1/20
Sternotomies	3	3[a]	3	3	5	6	3	5	6	6	5	5	2	2	6
Fontan to transplant (years)	17.2	23.1	26.3	13.2	11	17	26.2	17.7	35.9	22	19.5	15.8	22	42.3	18.6
Fontan Type	LT	LT	LT	EC	EC	EC	EC	EC	AP->LT	LT	EC	LT	LT	AP	EC
Single ventricle dysfunction	Moderate	None	Severe	Severe	Moderate	Mild	None	None	None	Severe	Severe	Moderate	None	None	None
Atrioventricular valve regurgitation	Moderate	Moderate	Moderate	None	Moderate	Mild	None	Mild	Mild	None	Moderate	Mild	Severe	Mild	None
Arrhythmia	Heart block PM	IART	IART	IART PM	SND PM	Heart block PM	SND IART PM	None	SND PM IART	SND IART PM	Heart block NSVT PM LifeVest	SND PM	IART	IART	None
Cardiac Index (L/min/m^2)	3.8	7.8	2.2	3.9	4.7	2.6	2.1	2.4	3.0	3.0	1.4	3.0	4.0	1.8	2.6
PVRi (indexed Wood units)	1.8	1	1	2	1	1.7	2.7	4.6	1.8	1.1	2.8	1.8	1.6	2	2.2
EDP (mm Hg)	6	14	14	12	22	23	10	16	6	16	13	6	8	9	21
Fontan pressure (mm Hg)	15	16	18	17	24	27	16	N/A	11	22	17	12	13	13	20

Abbreviations: AP, atriopulmonary; AVSD, atrioventricular septal defect; CHLT, combined heart and liver transplantation; DILV, double inlet left ventricle; DORV, double outlet right ventricle; EC, extracardiac; EDP, end-diastolic pressure; HLHS, hypoplastic left heart syndrome; IART, intraatrial reentrant tachycardia; LT, lateral tunnel; NSVT, non-sustained ventricular tachycardia; PM, pacemaker; PVRi, pulmonary vascular resistance indexed; SND, sinus node dysfunction; TA, tricuspid atresia; TGA, transposition of the great arteries.

[a]Complex heterotaxy anatomy due to left-sided Kawashima, separate hepatic vein grafts, or bilateral SVC.

TABLE 2 Individual gastrointestinal/liver characteristics of patients undergoing pre-CHLT liver biopsy and CHLT from 2012 to 2020

	20-yo F DORV	28-yo F AVSD	31-yo M AVSD	19-yo F TA	16-yo M TA	31-yo M HLHS	41-yo F DORV
Biopsy to explant (years)	0.87	1.35	1.18	3.84	0.36	0.45	6
Hepatic vein/wedge	N/A	N/A	15/15	18/19	27/29	N/A	16/17
GFR (ml/min/1.73 m^2)	130	35	110	87[c]	83[c]	110	108
PLE	No	No	No	Yes	Yes	No	No
Child-Pugh	8 (B)	12 (C)	7 (B)	9 (B)	6 (B)	7 (B)	8 (B)
MELD-XI	10	25	9	11	8	10	11
VAST	4 (VAST)	2 (VA)[d]	2(AT)[d]	3 (VAS)	3 (VAS)	3 (VAS)	1(V)[d]
Liver imaging	CT Hepatomegaly Nodular surface Regenerative nodules Splenomegaly Splenorenal shunt Ascites	MR Shrunken Liver Nodular surface Ascites Esophageal varices	MR Nodular surface	CT Nodular surface Regenerative nodules Esophageal varices	MR Hepatomegaly Nodular surface Splenomegaly Ascites Esophageal varices Splenorenal shunt	CT Hepatomegaly Nodular surface Splenomegaly Esophageal varices Ascites	CT Hepatomegaly Nodular surface Esophageal varices
Liver biopsy	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis[a]	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis[a] Hepatitis C	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis[a]
Liver explant	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging Fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity

Abbreviations: AVSD, atrioventricular septal defect; CHLT, combined heart and liver transplantation; CT, computed tomography; DILV, double inlet left ventricle; DORV, double outlet right ventricle; GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; HLHS, hypoplastic left heart syndrome; MELD-XI, Model for End-Stage Liver Disease eXcluding INR; MR, magnetic resonance; PLE, protein-losing enteropathy; TA, tricuspid atresia; TGA, transposition of the great arteries; VAST, Varices, Ascites, Splenomegaly, and Thrombocytopenia.

[a]Outside biopsy.

[b]Percutaneous biopsy.

[c]GFR estimated by cystatin c, rather than creatinine.

[d]Heterotaxy with asplenia or polysplenia so maximum VAST score is 3.

(Ishak and METAVIR) were based on the portal fibrosis that predominates in inflammatory hepatitis, Dai et al[14] developed the "congestive hepatic fibrosis score" to assess the central fibrosis specific to congestive hepatopathy from right heart failure. Our group similarly has devised a system of pathological classification of degree of liver fibrosis stemming from right heart failure (see Section 2 above for stages) which we apply to FALD. Though FALD-induced fibrosis was thought to be solely centrilobular rather than portal in nature, it is now known that both centrilobular and portal fibrosis occur, and some centers have implemented scoring systems with both central and portal fibrosis components such as the "modified Ishak congestive hepatic fibrosis" (ICHF) score.[15-17] The unique nature of fibrosis in FALD is likely due to the combination of insults to the liver—ischemia and hypoxia from cyanotic heart disease, and perioperative insults from staged surgical palliation culminating in total cavopulmonary anastomosis and its elevated central venous pressure and low cardiac output. This combination of insults and their interplay, rather than solely elevated central venous pressure, may account for why we did not see the theoretical overestimation of fibrosis with transjugular biopsy.

Some have questioned liver biopsy as the gold standard for assessing FALD due to its patchy nature.[2] Ongoing studies have tried to correlate biopsy with clinical, laboratory, and imaging data with mixed results. The most consistent association has been seen with time from Fontan operation (regardless of type of Fontan).[3,18-20] Our study with its limited sample size did not show this association, but our pathological scoring system does not include a quantitative scale (eg, Sirius Red staining) which may allow for a better method

21-yo M HLHS	43-yo M DILV	28-yo F DILV	26-yo M AVSD	18-yo M AVSD	44-yo F AVSD	49-yo F TA	22-yo M TGA
1.16	1.22	3.7	5.58	0.64	0.16	0.78	2.2
N/A	11/13	24/26	18/19	12/13	N/A	15/16	19/21
85[c]	109	46[c]	112[c]	130[c]	76[c]	46	85[c]
No	No	No	No	No	No	No	Yes
6 (A)	8 (B)	8 (B)	6 (A)	5 (A)	8 (B)	9 (B)	8 (B)
9	13	19	13	9	9	13	10
2(VS)	2 (ST)	4 (VAST)	3 (VST)	3 (VST)	1 (A)	2 (AS)	2 (AT)
CT Nodular surface Splenomegaly Esophageal varices	CT HCC Nodular surface Splenomegaly	CT Hepatomegaly Nodular surface Splenomegaly Esophageal varices Ascites Splenorenal shunt	CT Nodular surface Splenomegaly Esophageal varices	CT Hepatomegaly Nodular surface Splenomegaly Esophageal varices	MR Nodular surface Steatosis	MR Nodular surface Splenomegaly	MR Hepatomegaly Nodular surface
Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity[a]	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity Steatosis	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Steatosis[b]	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity[a]	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity[a]
Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity HCC	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity Steatosis	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity Steatosis	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity	Sinusoidal dilation Pericellular fibrosis Bridging fibrosis Nodularity

of demonstrating the correlation of time from Fontan and degree of fibrosis. Interestingly, we did note that our oldest patient (with an atriopulmonary Fontan for 42 years) showed patchy fibrosis and nodularity on explant, while one of our younger patients (with an extracardiac Fontan for 18 years) showed a much more diffusely fibrotic liver (see Figure 1). This observation again points to a unique pathophysiological interplay of ischemic insults, decreased cardiac output and hypoxia along with elevated central venous pressure and length of time in a Fontan circulation as the driver of FALD progression. Finally, a recent study did find correlation among results of liver magnetic resonance elastography (MRE), invasive hemodynamics, and the ICHF score and suggested liver biopsy can be reserved for use only in patients whose MRE values are >5 kPa.[17] Though clinical data including imaging findings are provided for each patient (see Tables 1 and 2), the correlation of biopsy with imaging was outside the scope of this small descriptive study. Further research is necessary to elucidate which diagnostic modalities, including liver biopsy, can best assess the mechanism, progression, and impact of FALD. As our techniques for advanced imaging continue to expand, the role of liver biopsy may diminish.

5 | LIMITATIONS

This study pertains only to FALD and should be not extrapolated to other cardiac or liver diseases. FALD leads to patchy fibrosis, and liver biopsy may lead to sampling error. There is a unique pattern of both central and portal fibrosis in FALD, and there is no standardized

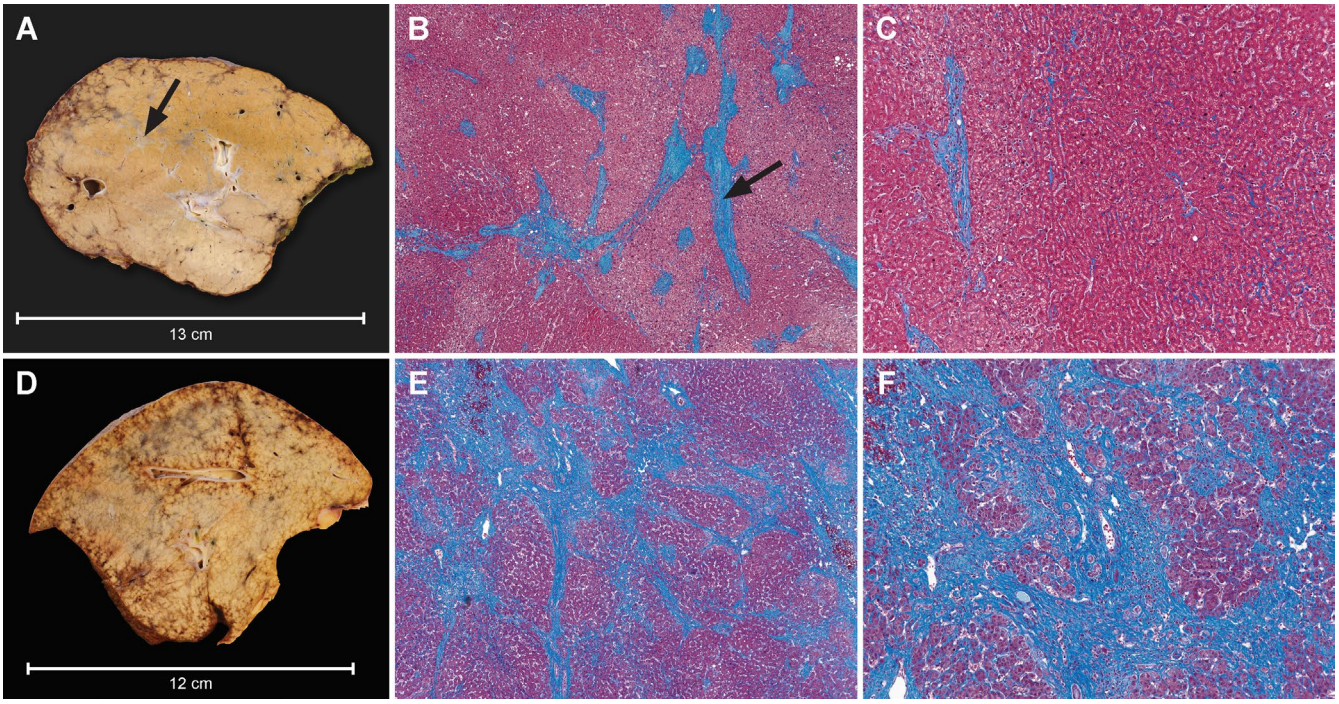

FIGURE 1 Representative liver explant specimens. A, Liver explant gross specimen from a 49-year-old female with atriopulmonary Fontan for 42 years showing variable fibrosis but minimal nodularity (arrow) on the capsular surface with some areas that appear normal. B, At low magnification (40×) with trichrome staining, there are areas with broad fibrous bands (arrow) and areas that lack fibrosis altogether. C, At higher magnification (100×) with trichrome staining, there is mild pericellular fibrosis, characteristic of congestive hepatopathy. D, Liver explant gross specimen from a 22-year-old male with extracardiac Fontan for past 18 years showing diffuse nodularity and brown discoloration suggestive of chronic congestion. E, At low magnification (40×) with trichrome staining, there is diffuse fibrosis with bridging and regenerative nodules. F, At higher magnification (100×) with trichrome staining, the fibrous septa contain residual portal tract structures, with thick fibrous bands surrounding residual lobules that lack central veins. The hepatocyte nodules show more pronounced pericellular fibrosis

pathologic staging system; we use a scoring system as detailed above. Future studies will be important to elucidate a uniform staging system for Fontan-associated liver disease. Finally, many of our Fontan patients had pacemakers which precluded abdominal MRI, and even of those who had MRI (six patients), only two patients had elastography data. Thus, the comparison of elastography and biopsy was not done, and a more general comparison of imaging and biopsy was outside of the scope of our study, as the mix of CT and MRI imaging precluded an adequate sample size for appropriate analysis of imaging results.

6 | CONCLUSIONS

Pre-CHLT transjugular liver biopsy does not overestimate the degree of fibrosis in FALD. However, the patchy nature of fibrosis can lead to underestimation of fibrosis in some patients. Further studies on the role of liver biopsy and pathologic classification in the evaluation of FALD are needed.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Vaikunth involved in the design concept. Vaikunth and Higgins collected data. Vaikunth, Higgins, and Daugherty analyzed the data and interpreted the data. Vaikunth drafted the manuscript. Vaikunth, Higgins, Concepcion, Chen, Haeffele, Lui, and Daugherty critically revised the article and approved the article.

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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REFERENCES

1. Daniels CJ, Bradley EA, Landzberg MJ, et al. Fontan-associated liver disease: proceedings from the American College of Cardiology Stakeholders Meeting, October 1 to 2, 2015, Washington DC. *J Am Coll Cardiol*. 2017;70(25):3173-3194.
2. Wu FM, Jonas MM, Opotowsky AR, et al. Portal and centrilobular hepatic fibrosis in Fontan circulation and clinical outcomes. *J Heart Lung Transplant*. 2015;34(7):883-891.
3. Goldberg DJ, Surrey LF, Glatz AC, et al. Hepatic fibrosis is universal following Fontan operation, and severity is associated with time

from surgery: a liver biopsy and hemodynamic study. *J Am Heart Assoc*. 2017;6(5):e004809.
4. Schwartz MC, Sullivan L, Cohen MS, et al. Hepatic pathology may develop before the Fontan operation in children with functional single ventricle: an autopsy study. *J Thorac Cardiovasc Surg*. 2012;143(4):904-909.
5. Book WM, Gerardin J, Saraf A, Marie Valente A, Rodriguez F. Clinical phenotypes of Fontan failure: implications for management. *Congenit Heart Dis*. 2016;11(4):296-308.
6. Jacob KA, Hjortnaes J, Kranenburg G, de Heer F, Kluin J. Mortality after cardiac surgery in patients with liver cirrhosis classified by the Child-Pugh score. *Interact Cardiovasc Thorac Surg*. 2015;20(4):520-530.
7. D'Souza BA, Fuller S, Gleason LP, et al. Single-center outcomes of combined heart and liver transplantation in the failing Fontan. *Clin Transplant*. 2017;31(3):e12892.
8. Reardon LC, DePasquale EC, Tarabay J, et al. Heart and heart-liver transplantation in adults with failing Fontan physiology. *Clin Transplant*. 2018;32(8):e13329.
9. Vaikunth SS, Concepcion W, Daugherty T, et al. Short-term outcomes of en bloc combined heart and liver transplantation in the failing Fontan. *Clin Transplant*. 2019;33(6):e13540.
10. Louie CY, Pham MX, Daugherty TJ, Kambham N, Higgins JP. The liver in heart failure: a biopsy and explant series of the histopathologic and laboratory findings with a particular focus on pre-cardiac transplant evaluation. *Mod Pathol*. 2015;28(7):932-943.
11. Heuman DM, Mihas AA, Habib A, et al. MELD-XI: a rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc*. 2007;13(1):30-37.
12. Elder RW, McCabe NM, Hebson C, et al. Features of portal hypertension are associated with major adverse events in Fontan patients: the VAST study. *Int J Cardiol*. 2013;168(4):3764-3769.
13. Srinivasan A, Guzman AK, Rand EB, et al. Percutaneous liver biopsy in Fontan patients. *Pediatr Radiol*. 2019;49(3):342-350.
14. Dai D-F, Swanson PE, Krieger EV, Liou IW, Carithers RL, Yeh MM. Congestive hepatic fibrosis score: a novel histologic assessment of clinical severity. *Mod Pathol*. 2014;27(12):1552-1558.
15. Kendall TJ, Stedman B, Hacking N, et al. Hepatic fibrosis and cirrhosis in the Fontan circulation: a detailed morphological study. *J Clin Pathol*. 2008;61(4):504-508.
16. Schwartz MC, Sullivan LM, Glatz AC, et al. Portal and sinusoidal fibrosis are common on liver biopsy after Fontan surgery. *Pediatr Cardiol*. 2013;34(1):135-142.
17. Silva-Sepulveda JA, Fonseca Y, Vodkin I, et al. Evaluation of Fontan liver disease: Correlation of transjugular liver biopsy with magnetic resonance and hemodynamics. *Congenit Heart Dis*. 2019;14(4):600-608.
18. Evans WN, Winn BJ, Yumiaco NS, et al. Transvenous hepatic biopsy in stable Fontan patients undergoing cardiac catheterization. *Pediatr Cardiol*. 2014;35(7):1273-1278.
19. Surrey LF, Russo P, Rychik J, et al. Prevalence and characterization of fibrosis in surveillance liver biopsies of patients with Fontan circulation. *Hum Pathol*. 2016;57:106-115.
20. Johnson JA, Cetta F, Graham RP, et al. Identifying predictors of hepatic disease in patients after the Fontan operation: a postmortem analysis. *J Thorac Cardiovasc Surg*. 2013;146(1):140-145.

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