

# Fontan-Associated Liver Disease: Monitoring Progression of Liver Fibrosis

*Tamir Diamond, M.D,\* and Nadia Ovchinsky, M.D, M.B.A<sup>†</sup>*

Since its introduction more than 40 years ago, the Fontan procedure, which redirects venous blood flow directly to pulmonary circulation to palliate single-ventricle physiology, has enabled many children to survive to adulthood. Their improved prognosis has unveiled a multitude of complications related to the unique Fontan physiology. Fontan-associated liver disease (FALD) is a process universal to the post-Fontan population and includes a spectrum of pathology that ranges from mild liver fibrosis (LF) to liver cirrhosis (LC) and hepatocellular carcinoma (HCC).<sup>1,2</sup> We will review advances in the field and their implications for patient management.

## AREAS OF FOCUS IN FONTAN-ASSOCIATED LIVER DISEASE CLINICAL PRACTICE AND RESEARCH

Clinical manifestations of liver disease in the post-Fontan population are variable. Some patients with FALD may be

entirely asymptomatic, or have only mild nonspecific symptoms of compensated cirrhosis (Table 1). Others may present with common signs and symptoms of severe decompensated disease. Several clinical, laboratory, and imaging modalities to assess LC are summarized in Table 1; however, liver biopsy remains the gold standard for diagnosis.<sup>3</sup>

The two main areas of focus in clinical practice and research are the standardization of histological grading of fibrosis and the identification of noninvasive modalities to assess LF and LC.<sup>1,4,5</sup> Their common goal is to help risk-stratify this population and identify opportunity for early intervention in those at risk for the severe sequelae, LC, and HCC.<sup>6</sup>

### Novel Histological Grading

Recent publications have attempted to tailor a histological grading system, evaluating the unique disease

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; CT, computed tomography; FALD, Fontan-associated liver disease; GGT, gamma-glutamyltranspeptidase; HCC, hepatocellular carcinoma; HT, heart transplant; INR, international normalized ratio; LC, liver cirrhosis; LF, liver fibrosis; LHT, liver-heart transplant; LS, liver stiffness; MELD, Model of End-stage Liver Disease; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; PELD, Pediatric End-Stage Liver Disease; PT, prothrombin time.

From the \*Department of Pediatrics; and <sup>†</sup>Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital at Montefiore, Bronx, NY.

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**TABLE 1. MODALITIES TO DIAGNOSE LIVER CIRRHOSIS**

Category	Modality	Findings
Physician preliminary evaluation	Symptoms assessment	<ul style="list-style-type: none"> <li>• Anorexia</li> <li>• Fatigue</li> <li>• Weight loss</li> </ul>
	Physical examination	<ul style="list-style-type: none"> <li>• Jaundice</li> <li>• Palmar erythema</li> <li>• Splenomegaly</li> <li>• Asterixis</li> <li>• Ascites (may appear secondary to heart failure without cirrhosis)</li> <li>• Spider nevi</li> <li>• Clubbing</li> <li>• Gynecomastia</li> <li>• Caput medusa</li> </ul>
Laboratory evaluation	(1) APRI score*	APRI < 1.0: cirrhosis is unlikely APRI > 2.0: suggests presence of cirrhosis
	(2) FIB-4 score†	FIB-4 < 1.45: cirrhosis is unlikely FIB-4 < 3.25: suggests presence of cirrhosis
Radiology	Ultrasonography	<ul style="list-style-type: none"> <li>• Nodular liver surface</li> <li>• Irregular borders</li> <li>• Increased echogenicity</li> <li>• Splenomegaly</li> </ul>
	CT	Reticular hepatic enhancement during portal venous phase
	MRE	Score >4.9 diagnostic for cirrhosis in other populations; not validated in FALD because of confounding hepatic congestion increasing stiffness scores
	Shear wave elastography	Measures liver stiffness as surrogate for fibrosis
Pathology	Liver biopsy	Gold standard for diagnosis; generally not required if other tests described earlier are confirmatory of cirrhosis

\*Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) score = (AST [IU/L]/AST upper limit of normal [IU/L] × 100)/platelet count (×10<sup>9</sup>/L).

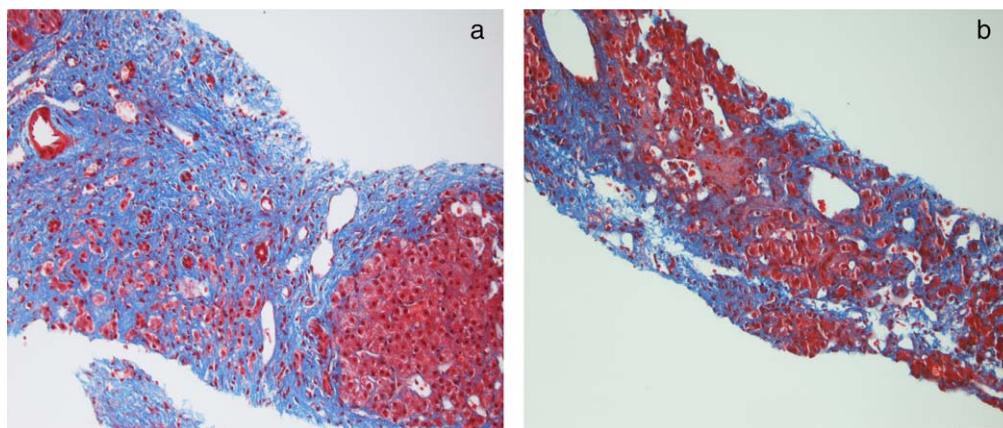
†Fibrosis-4 (FIB-4) score = age (years) × (AST [IU/L]/AST upper limit of normal [IU/L])<sup>1/2</sup>/platelet count (×10<sup>9</sup>/L).

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progression of both portal and sinusoidal fibrosis in FALD. Hypoxia both pre- and post-Fontan secondary to low cardiac output, continuous nonpulsatile hepatic congestion, and increased mesenteric vascular resistance all contribute to the FALD pattern of fibrosis (Fig. 1).<sup>3</sup> A fibrosis score using multiple grading systems and a quantitative percent collagen deposition score have been suggested to create a common language between the pathologist and hepatologist.<sup>1,5</sup> Use of sirius red staining, with digital analysis to calculate a quantitative fibrosis score, described by Surrey et al.,<sup>5</sup> is an example of a novel approach to histological analysis in FALD (Table 2).<sup>4</sup> This may facilitate timely identification of changes in liver architecture, which could have implications for treatment.

### Serum Markers

Several studies over the past decade tried to correlate certain serum markers with disease progression, but they had inconsistent results and small cohorts.<sup>7</sup> Aminotransferases may be normal or only mildly elevated in FALD. Gamma-glutamyltranspeptidase (GGT) was mildly elevated (median 69 U/L) in 75% of patients in a study by Wu et al.,<sup>1</sup> but was not correlated to histological progression of disease. Elevated prothrombin time (PT/international normalized ratio [INR]) may be a marker for disease progression, as shown by Surrey et al.<sup>5</sup> to be correlated with high-grade fibrosis scores. A recent series evaluating a validated tool for fibrosis in adult populations from other etiologies, FibroSure (LabCorp,



**FIG 1** FALD histology. Trichrome stains from a patient 14 years post-Fontan demonstrating (A) portal area replaced by expanded band of fibrosis resulting in nodule and (B) fibrosis extending from portal tracts with pericellular fibrosis in the areas of dilated sinusoids. (Images courtesy of Michelle R. Ewart, M.D.)

Burlington, NC), did not show significant correlation to progression of disease.<sup>8</sup> There are no official guidelines, and evaluation is institution dependent (Fig. 2).

### Radiological Monitoring

Most patients with FALD will have some abnormal finding on routine imaging. Heterogeneous enhancement of liver parenchyma and irregular liver contour are seen in up to 98% and 50% of patients, respectively, across all imaging including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI).<sup>1,7-10</sup> Correlations between radiological findings and progression of LF on histology have inconsistent results among various studies.<sup>1,5,7</sup> The use of diffusion-weighted imaging has recently been described as a research tool to evaluate liver microperfusion in FALD. Results have shown its utility in differentiating the unique histopathological changes in the portal circulation of FALD causing cirrhosis (Fig. 1) from those caused by congestive hepatopathy from other

cardiac etiologies.<sup>11</sup> However, this modality has yet to be clinically validated.

There is inconsistency between institutional practices of radiological monitoring.<sup>1,6,7,10,12</sup> Annual ultrasound imaging appears to be the consensus in the studies detailed earlier and is also the common practice in our institution. MRI is the preferred modality to monitor patients with confirmed cirrhosis who are at risk for development of HCC.<sup>6,7</sup>

### Elastography

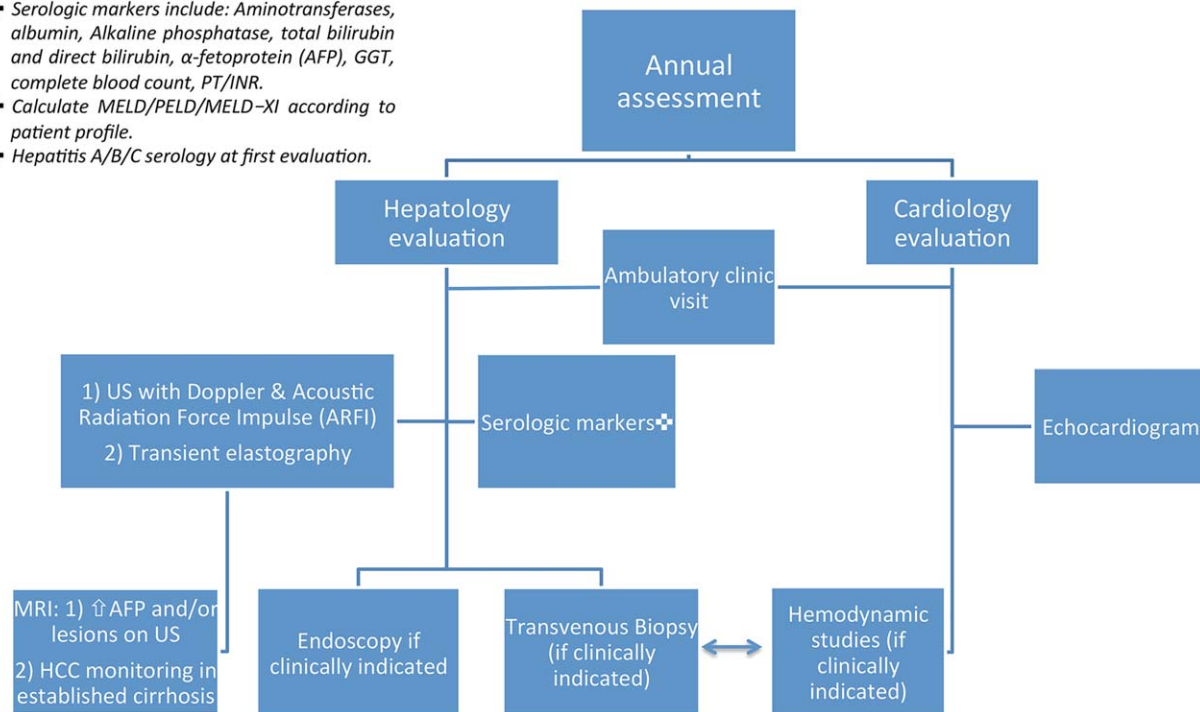
Elastography is a tool validated in the adult population for monitoring chronic LF in various noncardiac causative factors.<sup>7,10,12</sup> Liver stiffness (LS) scores are described in kilopascals. Hepatic congestion may increase LS scores unrelated to progression of fibrosis. This may be a confounding variable while trying to standardize LS scores, which are based on other etiologies of fibrosis such as

**TABLE 2. SUGGESTED HISTOLOGICAL GRADING SYSTEM FOR FONTAN-ASSOCIATED LIVER DISEASE**

Scoring System	Range of Scoring	Use
Metavir	F0-F4	Is used to evaluate fibrosis originating in the portal system, which differentiates FALD fibrosis from congestive hepatopathy
Congestive hepatic fibrosis score	0-4	A scoring system commonly used for congestive hepatopathy; used to evaluate congestive component of FALD
Sinusoidal dilation score	0-3	Scores the percent of sinusoidal dilation present on histology
Sinusoidal fibrosis score	0-3	Scores the percent of sinusoidal fibrosis present on histology

Describes the use of multiple conjoined fibrosis scores to address the unique natural history of fibrosis. Adapted from *Human Pathology*.<sup>5</sup> Copyright 2016, Elsevier.

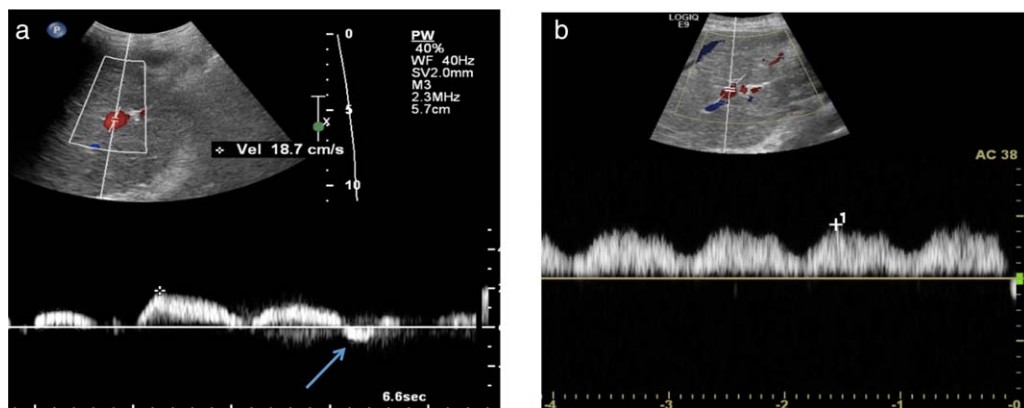
- ❖ Serologic markers include: Aminotransferases, albumin, Alkaline phosphatase, total bilirubin and direct bilirubin,  $\alpha$ -fetoprotein (AFP), GGT, complete blood count, PT/INR.
- ❖ Calculate MELD/PELD/MELD-XI according to patient profile.
- ❖ Hepatitis A/B/C serology at first evaluation.



**FIG 2** Authors’ institutional algorithm for FALD patient evaluation. Abbreviations: MRI, magnetic resonance imaging; PELD, Pediatric End-Stage Liver Disease.

hepatitis. However, LS scores are elevated at baseline in FALD in both transient elastography and magnetic resonance elastography (MRE), even compared with other causes of congestive hepatopathy. MRE has shown promising results from a single-center study as a screening tool for HCC.<sup>12</sup> The main limitation of studies to

date is lack of data correlating LS scores to histology and cardiac hemodynamics prospectively over time. Our group is trying to bridge this knowledge gap, as are other institutions around the world, to help assess whether these exciting new modalities may be useful as monitoring tools.



**FIG 3** Restoration of portal vein flow after cardiac catheterization intervention. (A) Portal flow reversal seen (arrow) in a 17-year-old male with severe portal hypertension and esophageal variceal bleeding found to have a compromised Fontan circulation secondary to constriction of baffle. (B) Normalization of flow in portal vein on Doppler, 2 weeks after stenting of baffle restoring Fontan circulation.

## IMPLICATIONS FOR TREATMENT

The main hepatology consideration when assessing a patient for either heart transplant (HT) or combined liver-heart transplant (LHT) is the ability of the liver to sustain such complex procedures. In a review by Greenway et al.,<sup>6</sup> the authors recommended that patients suffering from failing Fontan physiology, with low Child-Pugh class A score (<7) and Model of End-stage Liver Disease (MELD) score (<12), be listed for HT (1-year posttransplant survival rate of 80%). Pharmacological treatments being considered are phosphodiesterase-5 inhibitors, such as sildenafil, which improve pulmonary vasodilation and reduce afterload in hepatic vein, or renin-angiotensin system inhibitors, which have demonstrated antifibrotic properties in addition to their reduction of systemic afterload.<sup>5</sup> The hepatologist's role is to recognize liver findings suggestive of compromised Fontan circulation and decrease in cardiac output in patients who may benefit from interventional or surgical revision of Fontan, possible HT, or combined LHT (Fig. 3).

## SUMMARY

FALD continues to attract much research interest as complications affecting patient morbidity and mortality become increasingly apparent. Currently, there are still no official guidelines for monitoring this population, and multicenter cohort studies have only been published within the past year.<sup>1</sup> Guidelines are institution dependent (Fig. 2, Table 1).<sup>1,3,7,10,12</sup> Future research will continue to focus on risk stratification of patients for severe sequelae of liver disease and on understanding the role of elastography and noninvasive markers in this population while trying to learn more about the pathophysiological etiology of FALD.

## CORRESPONDENCE

Tamir Diamond, M.D., PGY-3, Department of Pediatrics, Children's Hospital at Montefiore, Bronx, NY. E-mail: tamdiamo@montefiore.org

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