Circulation

WHITE PAPER

Fontan-Associated Liver Disease

Screening, Management, and Transplant Considerations

ABSTRACT: Surgical innovation and multidisciplinary management have allowed children born with univentricular physiology congenital heart disease to survive into adulthood. An estimated global population of 70 000 patients have undergone the Fontan procedure and are alive today, most of whom are <25 years of age. Several unexpected consequences of the Fontan circulation include Fontan-associated liver disease. Surveillance biopsies have demonstrated that virtually 100% of these patients develop clinically silent fibrosis by adolescence. As they mature, there are increasing reports of combined heart-liver transplantation resulting from advanced liver disease, including bridging fibrosis, cirrhosis, and hepatocellular carcinoma, in this population. In the absence of a transplantation option, these young patients face a poor quality of life and overall survival. Acknowledging that there are no consensus guidelines for diagnosing and monitoring Fontan-associated liver disease or when to consider heart transplantation versus combined heart-liver transplantation in these patients, a multidisciplinary working group reviewed the literature surrounding Fontan-associated liver disease, with a specific focus on considerations for transplantation.

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The Fontan operation was first described in 1971 for patients with tricuspid atresia but has increasingly been applied as final-stage surgical palliation for pediatric patients with univentricular physiology heart disease.[1] As this procedure has gained acceptance and achieved excellent short-term outcomes, it has become evident that most post-Fontan patients develop hepatic fibrosis and even cirrhosis over time, referred to as Fontan-associated liver disease (FALD). FALD is in the spectrum of congestive hepatopathy, related at least in part to chronically elevated central venous pressures (CVPs) and a lack of pulsatility, resulting in passive venous congestion and impaired hepatic blood flow (Figure 1).[2] Although it is generally accepted that all patients after Fontan have some degree of FALD, it is unclear what proportion of patients after Fontan will develop clinically significant advanced liver disease. Similarly, the prevalence of and preferred algorithm to provide surveillance for FALD-related hepatocellular carcinoma (HCC) are yet to be determined.

Recognizing the challenges of managing patients with FALD and the paucity of guidelines for selection and management of patients for heart transplantation alone versus combined heart-liver transplantation (CHLT), a multidisciplinary group of American Society of Transplantation members collaborated to review FALD

Key Words: Fontan procedure ■ heart transplantation ■ liver diseases ■ liver transplantation

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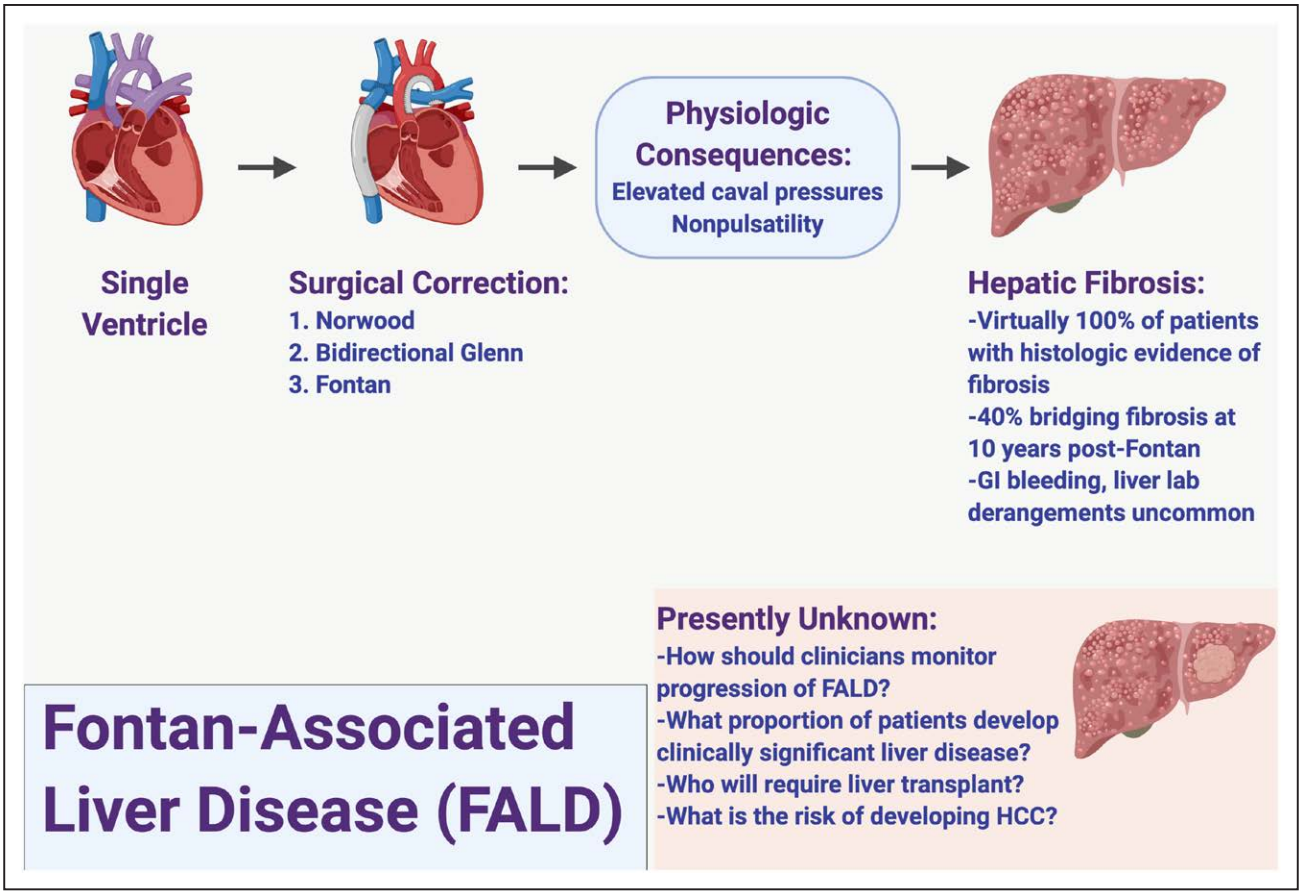

Figure 1. Fontan-associated liver disease.
GI indicates gastrointestinal; and HCC, hepatocellular carcinoma.

specifically from the perspective of the transplantation professional. In this article, we provide the epidemiology, clinical diagnosis, and options for monitoring progression of FALD. We also explain the challenges and considerations for patients after Fontan who may benefit from liver transplantation. The projected mean age of post-Fontan patients is 23 years by 2025, with an estimated global population of 70 000 post-Fontan patients that could double over the next decade. It is therefore imperative that the transplantation community proactively develops algorithms for managing post-Fontan patients with FALD.[3,4]

BRIEF REVIEW OF THE FONTAN PHYSIOLOGY

Most children born with unrepaired univentricular physiology face an early death during infancy. As a result of advancements in surgical technique and perioperative care, these patients can now expect to survive into adulthood. A single, functional ventricle can be found in patients with tricuspid or mitral atresia, hypoplastic left or right heart syndrome, and other rare complex congenital heart disorders for which biventricular repair is not possible. Following the Norwood and Glenn procedures, which create a superior cavopulmonary connection, the Fontan procedure involves implantation of a surgical shunt to divert blood from the inferior vena cava and superior vena cava to the pulmonary arteries without passing through the subpulmonic ventricle: a total cavopulmonary connection.[1] In essence, the systemic and pulmonary circulations are placed in series with the functional single ventricle. The consequence of this total cavopulmonary connection is chronic hepatic venous congestion secondary to high-pressure nonpulsatile flow in the inferior vena cava.

The primary characteristic of Fontan hemodynamics is a lack of a subpulmonary ventricle, which automatically leads to high CVP. This creates additional driving pressure for the pulmonary circulation and diminished cardiac preload for the systemic ventricle, resulting in chronically low cardiac output.[1,5] Mild but significant low arterial blood oxygen saturation is also a major hemodynamic feature, which likely results from intrapulmonary ventilation-perfusion mismatch and the development of veno-venous collaterals.[6] Thus, it is postulated that the pathophysiological complications after the Fontan operation are driven by the following conditions: multi–end-organ congestion caused

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by high CVP, chronic heart failure resulting from low cardiac output, and mild but significant hypoxia that over time may contribute to multiorgan dysfunction.[7] Possible causes of elevated CVP include (but are not limited to) precapillary factors such as stenosis of the Fontan conduit and high pulmonary vascular resistance or postcapillary factors, for example, systolic or diastolic systemic ventricle dysfunction and atrioventricular valve regurgitation or stenosis.

In the United States, >900 Fontan operations are performed each year, with 97% early survival.[3] To put that into perspective, an estimated 500 to 600 children are born with biliary atresia each year in the United States, and approximately half will undergo primary liver transplantation, which makes up the majority of pediatric liver transplantations performed each year.[8,9] The Fontan operation is usually performed in children 2 to 5 years of age, but the effects of the post-Fontan physiology continue to affect these patients through adulthood.[10] Only one-third of adult patients after Fontan are in optimal condition, defined as acceptable cardiac function with no clinically evident end-organ disease.[11] Although these results have been encouraging and represent a dramatic survival effect on what was previously considered a terminal patient population, these patients may develop clinically silent liver, kidney, and pulmonary disease and chronic systemic inflammation.

WHICH PATIENTS AFTER FONTAN ARE AT RISK FOR FALD?

FALD, including the development of cardiac cirrhosis and liver neoplasms, is recognized to be highly prevalent in post-Fontan patients.[12–16] Chronic passive congestion of the liver as a result of the absence of a functional subpulmonic ventricle is likely the chief driver of the hepatic fibrosis and hepatomegaly observed in FALD. Systemic venous pressure elevation caused by passive pulmonary blood flow results in elevated systemic venous pressure, causing liver congestion.[17] In addition, cardiac output and cardiac index are diminished, and as a result, zone 3 hepatocytes may be compromised by decreased oxygen delivery to centrilobar cells.[18] Over the long term, systolic performance diminishes.[19] Shear stress on the hepatic vasculature caused by chronic congestion results in reactive fibrogenesis caused by centrilobular hepatocyte atrophy, sinusoidal fibrosis, and eventual bridging fibrosis and then cardiac cirrhosis.[20,21]

In a retrospective study at a single center, 13 of 32 post-Fontan patients evaluated for heart transplantation had imaging studies suggestive of cirrhosis (irregular and nodular liver contour), but liver tests did not distinguish among those with and without cirrhosis.[16] In a prospective assessment of adult post-Fontan patients, most had advanced liver disease. Histological evidence of fibrosis was present in all biopsies and was classified as severe on the basis of a gross architectural distortion score (modified from METAVIR staging) of 3 to 4 in 68% of the patients.[12,22] Complications of portal hypertension, including varices and ascites, were present in more than half of the patients, and the presence of varices correlated with the severity of fibrosis. Liver nodules were detected in more than half of these patients. Although the majority of studies describing FALD involve young adult patients, it is important to note that adolescents, particularly those with refractory intrapulmonary shunting and a failing Fontan, may develop evidence of end-stage liver disease much earlier. It is also important to note that both radiographic and histological findings are incompletely evaluated in FALD and may not accurately represent all aspects of the disease.

Over the past decade, several studies have attempted to identify relationships between hemodynamics and the extent of liver fibrosis in post-Fontan patients. A recent study involving 33 post-Fontan patients who were undergoing routine surveillance liver biopsy and had no clinical signs of chronic liver disease determined that the degree of liver fibrosis on biopsy was independent of total cavopulmonary connection hemodynamics.[23] This has also been observed in a larger single-center cohort of ≈100 adolescent patients undergoing surveillance cardiac catheterization and liver biopsy ≥10 years after Fontan.[24,25] Another surveillance cardiac catheterization and liver biopsy cohort involving 49 patients 15.2 years after Fontan reported that all patients had histological evidence of liver fibrosis, and Fontan pressure ≥14 mm Hg and magnetic resonance elastography liver stiffness >4 kPa were associated with more advanced fibrosis.[26] In a study involving 46 adult patients with late post-Fontan follow-up (mean, 17.8 years), a weak positive correlation between liver stiffness and Fontan pressures was observed.[27] A retrospective review of invasive hemodynamic right-sided heart cardiac catheterization in 60 adult patients with failing Fontans was recently published.[28] In the univariate analysis of associations between liver dysfunction and hemodynamic variables, an increase in CVP was associated with the presence of liver disease (as measured by Child-Pugh and Model of End Stage Liver Disease [MELD] scores). It is notable that except for CVP, none of the hemodynamic measurements were remarkably abnormal in this group, even according to the reference values for subjects with normal biventricular hearts.

There is a lack of robust literature describing a direct relationship between invasive cardiac hemodynamics in post-Fontan patients and confirmed FALD. Multiple surveillance biopsy studies in adolescent patients with no overt evidence of failing Fontan or decompensated chronic liver disease have shown that all post-Fontan patients exhibit some degree of liver fibrosis.[23,24,26,29] Thus, it should not be assumed that

acceptable Fontan hemodynamics implies that liver fibrosis will not occur. That being said, several smaller single-center studies have suggested that there may be a relationship between hemodynamic cardiac catheterization values and the progression of fibrosis; that is, high Fontan pressures or increased liver stiffness measurements are associated with more advanced fibrosis.[23,26–28]

The best methods for surveillance of Fontan hemodynamic status and associated liver health are still being investigated and debated. In many centers, the routine use of right-sided heart catheterization in the management of patients with Fontan remains "for cause," that is, limited to the evaluation of anatomic or structural issues such as stenosis in the Fontan conduit that may be amenable to catheter-based directed intervention and to make adjustment to medication regimens as deemed appropriate by clinicians. In parallel, some centers have begun surveillance cardiac catheterization combined with transjugular liver biopsy in all patients 10 to 15 years after Fontan with minimal procedural complications, and these studies have shown that the prevalence and severity of FALD-related liver histopathology most strongly correlate with overall time since Fontan.[13,15,24–26,29]

DIAGNOSIS AND MONITORING PROGRESSION OF FALD

Serum Biomarkers

Although FALD is highly prevalent in the Fontan population, it can be a clinical challenge to diagnose and monitor. The value of history or physical examination in identifying progressive, clinically significant liver disease is limited because the majority of patients will have no detectable abnormalities. In 74 patients 15 years after Fontan, physical examination identified hepatomegaly in 30%, splenomegaly in 9%, and ascites in 4%.[30] Liver enzyme evaluation is inadequate in identifying FALD or determining its severity (summarized in Table 1). In a single-center series, the only biomarker associated with a high-grade stage of fibrosis (F3–F4) and sinusoidal fibrosis was an elevated international normalized ratio (P=0.046 and P=0.018, respectively).[30] The MELD score is generally not elevated in patients after Fontan. The MELD excluding international normalized ratio (MELD-XI) score has been explored to eliminate the effect of therapeutically elevated international normalized ratio among patients who are being pharmacologically anticoagulated. In a cohort of 70 post-Fontan patients, the MELD-XI score was reported to have a statistically significant correlation with biopsy-proven fibrosis, although a specific MELD-XI threshold was not identified that could indicate advanced fibrosis with high sensitivity and specificity.[31]

Liver Imaging Approaches for FALD

Several imaging methodologies have been evaluated for their ability to diagnose advanced FALD (summarized in Table 1). In patients with congestive hepatopathy, ultrasound, computed tomography, and magnetic resonance imaging (MRI) have traditionally been used to detect findings suggestive of cirrhosis and its complications. A study of 55 post-Fontan patients screened with ultrasound imaging found heterogeneous hepatic echotexture or surface or liver surface nodularity in 67% of patients, and this correlated with time since Fontan.[32] A specific consideration when reviewing cross-sectional imaging in FALD is that the presence of nodularity does not necessary imply underlying cirrhosis. The imaging changes of contrast-enhanced computed tomography or MRI in post-Fontan patients include signs of portal hypertension: altered portal venous phase enhancement of the liver periphery compared with the hilar region, heterogeneous reticular enhancement of the liver parenchyma in the portal venous phase, and ascites, venous collaterals, or dilated hepatic veins with contrast reflux and intrahepatic venous-venous collaterals.[33,34]

The Role of Elastography

Elastography, a noninvasive approach to measure liver stiffness, may be useful for patient evaluation and management in the Fontan population. Although elastography is not specific for hepatic fibrosis—it also detects congestive hepatopathy from hepatic venous outflow obstruction—liver stiffness increases as fibrosis progresses.[35] At present, 3 major modalities are used to assess liver stiffness: MRI elastography, shear wave elastography, and transient elastography. It is important to note that elastography using any of these techniques can be hampered by the presence of ascites.

Only small case series have evaluated the performance of imaging and elastography to determine the degree of fibrosis in FALD. A recent study of 38 post-Fontan patients who underwent multiple modalities of hepatic surveillance detected biopsy-confirmed cirrhosis in 29%.[12] However, neither transient elastography nor MRI elastography was able to discriminate between mild and severe fibrosis. In a separate study of 50 post-Fontan patients who underwent transient elastography plus hemodynamic testing through cardiac catheterization, transient elastography measurements were associated with higher Fontan pressures.[36] Serial measurements of liver stiffness have been shown to correlate with clinical deterioration and may be useful in monitoring patients over time.[37] Thus, elastography may be a more useful marker of failing Fontan physiology than severe fibrosis in FALD. Standardizing liver stiffness ranges to account for a combination of congestion and fibrosis may be useful in the Fontan population.

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Table 1. Considerations for Diagnostic Testing in Patients With Suspected FALD

Investigation	Utility	Problems
Liver biopsy	Gold standard for histological assessment of fibrosis and cirrhosis	Risk for procedural complications (low)
	Transvenous approach allows simultaneous hemodynamic pressure measurements	No universally accepted scoring criteria for screening for FALD
Blood tests		
Liver enzymes (ALT, AST)	Assess for hepatocyte injury/dysfunction	Rarely elevated in stable FALD
		Do not correlate with degree of fibrosis in FALD
ALP, bilirubin, GGT	Evaluate biliary injury or stasis	Rarely elevated in stable FALD
		Elevated GGT across all post-Fontan patients in 1 case series
		Do not correlate with degree of fibrosis in FALD
INR	Marker of hepatic synthetic dysfunction	Elevated INR correlated with degree of fibrosis in FALD in 1 case series
AFP	Serum tumor marker that may be raised in some patients with HCC	Does not correlate with disease severity in FALD
		No data on proportion of patients with FALD and HCC who have elevated AFP
MELD-Na	Determines mortality risk in patients with end-stage liver disease	Does not correlate with disease severity and is rarely elevated in patients with FALD
	Calculated with INR, creatinine, bilirubin, Na, and presence/absence of renal replacement therapy	Can be confounded by systemic anticoagulation in post-Fontan patients
	Used for liver transplantation waiting list prioritization	
MELD-XI	Modified MELD without INR to risk stratify patients with cirrhosis on anticoagulation	Correlated with degree of fibrosis in FALD in 1 case series
Imaging modalities		
MR elastography	Assesses global liver stiffness	Does not distinguish between passive congestion and fibrosis
	Can perform serial studies to evaluate for progression	For high-quality liver imaging, patient must be in scanner for at least 30 min and participate in examination with breath holding, etc, which may be challenging in pediatric patients or those with a failing Fontan
MRI abdomen (with contrast)	Evaluates for and characterizes liver nodules vs HCC (with contrast phase)	Liver nodules in FALD being evaluated for HCC may be difficult to categorize with OPTN criteria
	Evaluates portal hypertension, identifies complex anatomic variations for surgical planning for liver transplantation (with contrast phase)	
Shear wave ultrasound elastography	Assesses global liver stiffness	Does not distinguish between passive congestion and fibrosis
	Can perform serial studies to evaluate for progression	Limited application in patients with ascites
Transient elastography	Assesses liver stiffness	Does not distinguish between passive congestion and fibrosis
	Can perform serial studies to evaluate for progression	Limited utility in patients with ascites
Ultrasound	Assesses liver morphology	Difficult to detect small lesions due heterogeneous parenchyma
	Evaluates for liver nodules and vascular patency	Limited utility in patients with ascites
	Evaluates for ascites	
Contrast computed tomography	Assesses liver morphology and vascular patency	Radiation exposure
	Evaluates for and characterize liver nodules vs HCC	Nephrotoxic contrast
	Evaluates complex anatomic variations for surgical planning for liver transplantation	Liver nodules in FALD being evaluated for HCC may be difficult to categorize according to OPTN criteria

AFP indicates α-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FALD, Fontan-associated liver disease; GGT, γ-glutamyl transferase; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, Model of End-Stage Liver Disease; and OPTN, Organ Procurement and Transplantation Network.

Other Liver-Related Invasive Approaches to Monitor FALD

Endoscopy allows the assessment of esophageal varices and other gastrointestinal pathologies in cirrhosis and may have a role in post-Fontan patients with evidence of liver disease. However, few reports have detailed the use of screening endoscopy to detect varices in FALD. Chang and colleagues[37a] reported that 27% of adult patients at ≈15 years after Fontan had esophageal varices on upper endoscopy. Most studies have relied on noninvasive imaging to determine the presence of varices. Cross-sectional imaging helped identify of varices in 19 of 38 adult patients (50%) at a mean of 21 years after Fontan.[12] Similarly, a study examining MRI, computed tomography, or ultrasound data illustrated that 19.2% of adult and pediatric patients had radiographic evidence of varices at an average age of 24 years and an average of 16 years after Fontan.[38] The necessity of surveillance endoscopy (versus imaging) for the detection of varices—and the appropriate intervention if varices are noted—remains to be clarified, but surveillance endoscopy may be useful in patients with evidence of liver fibrosis.

Utility of Hepatic Venous Pressure Gradients

Hepatic venous pressure gradients are measured as a surrogate measurement of portal hypertension, comparing the wedged hepatic sinusoidal pressure with the unwedged free hepatic venous pressure (normal hepatic venous pressure gradient, 1–5 mm Hg). The value of the hepatic venous pressure gradients in FALD is unclear; small studies have shown an absence of a significant gradient even in patients with confirmed cirrhosis.[33] Catheter-measured hemodynamic variables more often associated with the outcomes of death or heart transplantation in post-Fontan patients include CVP and cardiac index.[28] It is unknown whether further efforts to associate these measures with FALD will provide additional insight.

Liver Biopsy

Liver biopsy remains the gold standard for the detection of advanced fibrosis in FALD.[12] However, the potential for procedural complications, including bleeding, may discourage its routine use. It is notable that a report of 67 post-Fontan patients who underwent 68 liver biopsies identified hemorrhage in 7.4% as the sole complication; 1 patient required blood transfusions because of hemobilia.[39] That being said, in a single-center experience with >100 surveillance biopsies performed during cardiac catheterization ≈10 years after Fontan, only 1 patient had a postbiopsy bleed, which did not require transfusion.[24,25] Single-center experience at a mature adult congenital and transplantation center also suggests, as noted, that transjugular liver biopsy in the post-Fontan patient is safe with limited periprocedural complications.[40] Traditional staging of portal fibrosis such as METAVIR can identify the development of cirrhosis. However, intermediate METAVIR stages of portal fibrosis may not sufficiently describe the overall disease severity of FALD. Because of hepatic venous outflow obstruction in FALD, the degree of centrilobular and sinusoidal fibrosis should also be taken into consideration. Studies have calculated the overall percent collagen deposition using quantitative Sirius red staining, which provides a global interpretation of portal, sinusoidal, and centrilobular fibrosis.[30] In a group of 67 patients 15 years after Fontan, 56% demonstrated ≥20% collagen deposition on Sirius red staining of liver biopsy specimens.[29] The Congestive Hepatic Fibrosis Score is increasingly being reported in FALD studies, which may be a more appropriate approach to grade severity of fibrosis in this patient population.[26,30,39,41] However, unless cirrhosis is confirmed, a biopsy should always be interpreted with caution because of the risk of sampling bias, such that focal areas may be more or less representative of the overall true degree of fibrosis of the patient. Many programs are performing 2 distinct passes during the biopsy procedure to reduce the effect of sampling bias.[24,26,29,30,42]

Evaluation of Liver Lesions

Elevated CVPs after Fontan are associated with the growth of hypervascular nodules in the liver.[33,43,44] Large regenerative nodules and focal nodular hyperplasia are common and may occur in as many as 20% to 30% of patients after Fontan.[32,43,45,46] Nodules in patients with cirrhosis from any cause, including after Fontan, should be vigorously evaluated as potential HCC.[44,47] Two recent retrospective, single-center studies have reported rates of 3% to 15% for the development of HCC in FALD up to 22 years after Fontan.[48,49] The American Association for the Study of Liver Diseases guidelines for HCC surveillance in general recommend ultrasound and α-fetoprotein determination every 6 months.[50] For post-Fontan patients, the optimal imaging modality remains unclear because of unique liver morphology and vascular characteristics, but American Association for the Study of Liver Diseases guidelines may be reasonable until a FALD-specific approach is validated. Reports of MRI elastography evaluation have demonstrated an association between elevated liver stiffness and the development of malignant lesions, although it is unclear whether increased fibrosis alone or in combination with the failing Fontan physiology contributes to this finding.[51] MRI may be helpful in characterizing these tumors, although a liver biopsy is usually necessary

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because the typical HCC pattern of contrast washout in the delayed venous phase may not be appreciable with a background of congestive hepatopathy.[52] In particular, distinguishing dysplastic lesions caused by underlying FALD from true HCC within the Liver Imaging Reporting and Data System criteria (which has not been validated in FALD) or the Organ Procurement and Transplantation Network (OPTN) guidelines can be extremely challenging.[53]

The literature makes clear that time since Fontan is the most important predictor of advanced FALD.[25,26,28,30] Thus, any hepatic surveillance strategy can likely be infrequent and noninvasive in the first 10 years after Fontan. However, patients 10 to 15 years after Fontan may benefit from a systematic approach to testing. As described here, few tests are associated with advanced FALD, and severe fibrosis on a liver biopsy may not in and of itself indicate the need for liver transplantation or an increased risk of liver-related mortality. However, it would be prudent to provide surveillance for liver dysfunction with liver biochemistry, international normalized ratio testing, and MELD-XI calculation, as well as for malignancy with ultrasonography or MRI. Elastography may be helpful to alert the multidisciplinary team to increased congestive hepatopathy from a failing Fontan and the need to reduce pulmonary pressures. Ideally, these patients should be followed up by an integrated multidisciplinary team that includes congenital cardiologists, heart failure cardiologists, cardiac interventionalists, cardiac surgeons, radiologists, and hepatologists to monitor and manage FALD.

Summary and Recommendations for FALD Surveillance

Although there have been no comprehensive studies to clearly define the best practice for monitoring development and progression of FALD, we have proposed an algorithm that should capture most patients with FALD based on biopsy findings (Figure 2). Patients without clinical signs and symptoms of chronic liver disease should undergo surveillance biopsy at ≈10 years after Fontan because virtually all patients have been reported to have some evidence of fibrosis at this point, and these data will direct further clinical management.[24,26,29] According to the severity of the fibrosis on biopsy, these patients should also undergo baseline magnetic resonance elastography with continued surveillance to determine liver stiffness, establish initial anatomic features, identify concerning nodules, and evaluate for signs of portal hypertension and splenomegaly. Although liver laboratory values alone do not correlate with severity of fibrosis, monitoring these values over time will provide additional perspective for a liver specialist. For patients with evidence of bridging fibrosis or cirrhosis, upper endoscopy may be useful to assess for the presence of varices. Interventions for modifiable risk factors for chronic liver disease, including fatty liver (steatosis on biopsy), obesity, hepatotoxic medications, and alcohol use, should be considered in all patients with bridging fibrosis and cirrhosis. Screening for HCC is particularly challenging, but serial ultrasound and α-fetoprotein measurements to assess changes over time according to American Association for the Study of Liver Diseases guidelines are reasonable until FALD-specific approaches can be proven. For patients with concern for decompensating chronic liver disease, including the presence of ascites, splenomegaly, thrombocytopenia <100 000/μL, gastrointestinal bleeding, jaundice, or failure to thrive/sarcopenia, collaboration with hepatology will be important to fully assess the severity of liver disease and consider referral for liver transplantation evaluation.

WHEN DOES FALD REQUIRE LIVER TRANSPLANTATION?

Once high-grade fibrosis is observed in a post-Fontan patient, strategies can be implemented to lower right-sided heart pressures and improve hepatic venous outflow. What remains unclear is how to correlate degree of fibrosis with the risk of progression to decompensated cirrhosis and need for liver transplantation (Figure 3). Furthermore, it is uncertain how to predict which patients can stabilize or even regress their hepatic fibrosis after heart transplantation alone versus those who may unexpectedly decompensate their liver disease after heart transplantation alone, which represents the most feared early postoperative outcome in these patients. Even with a "perfect" Fontan, liver transplantation alone in this population is not advisable because of the inability to manage or control elevated right-sided pressures, particularly during the anhepatic and reperfusion phases of the procedure. However, several centers have reported excellent outcomes for CHLT in post-Fontan patients[40,54–58] (summarized in Table 2).

The effect of FALD on graft and patient survival after heart transplantation alone is limited. Because histological evidence of fibrosis in FALD is typically observed at least 10 years after Fontan, the discussion concerning proceeding with heart transplantation alone in the setting of underlying FALD generally refers to late adolescent or adult transplantation candidates, as opposed to pediatric patients who proceed to heart transplantation alone within a few years of the Fontan. These children can achieve acceptable long-term outcomes, presumably with minimal risk for progression of FALD after heart transplantation, although there are very few data on chronic liver disease as an exclusion criterion for proceeding with heart transplantation alone (Table 2).[18,64] A retrospective review of a single-institution experience

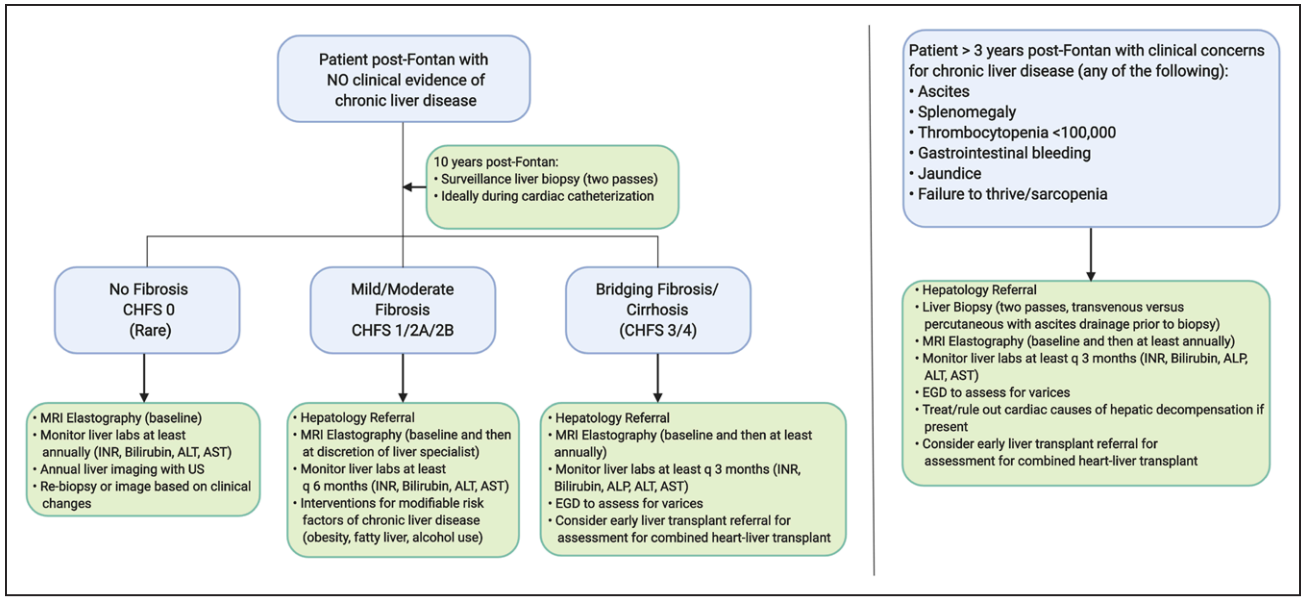

Figure 2. Approach to surveillance of FALD.
Magnetic resonance may be challenging in patients with pacemaker devices, and shear wave elastography for liver stiffness and computed tomography of the abdomen/pelvis with contrast to assess for stigmata of portal hypertension can be considered in these patients. Transvenous biopsy may be safer than the percutaneous approach for patients at higher risk of bleeding (blood thinners, thrombocytopenia, etc). There are no validated modalities or criteria for diagnosing HCC in the setting of FALD. Current HCC screening guidelines from the American Association for the Study of Liver Diseases recommend α-fetoprotein and US every 6 months in patients with cirrhosis. ALP indicates alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHFS, Congestive Hepatic *Fibrosis* Score; EGD, esophagogastroduodenoscopy; FALD, Fontan-associated liver disease; HCC, hepatocellular carcinoma; INR, international normalized ratio; MRI, magnetic resonance imaging; q, every; and US, ultrasound.

with heart transplantation alone in 30 pediatric patients after Fontan demonstrated an overall 30% mortality at 4.8 years after transplantation with no mortalities related to liver pathogenesis.[72] Unfortunately, in the United States, there are no diagnostic codes in the OPTN heart data set that specifically capture post-Fontan patients. Similarly, there are no diagnostic codes to capture FALD in the OPTN liver data set. Instead, a code for congenital heart disease with surgery has been used as a surrogate marker to study these patients from the heart data set.[57] In this study, ≈900 patients in the congenital heart disease with surgery category underwent heart transplantation alone, and 27 underwent CHLT. In both circumstances, patients with congenital heart disease had a higher early mortality with superior long-term survival compared with patients with noncongenital heart disease who received heart transplantation alone. In a recent analysis of the OPTN data, 10 patients with a history of heart transplantation for congenital heart disease with surgery were subsequently placed on the liver transplantation wait list. Only 1 pediatric patient ultimately received a liver transplantation, and 4 of 6 (67%) of the adult patients died while on the liver transplantation wait list.[73]

There is some evidence that FALD can stabilize after heart transplantation alone. In a retrospective histological study of 74 patients after Fontan, with 5 who underwent heart transplantation alone, the degree of pretransplantation hepatic fibrosis was not predictive of heart transplantation–free survival or overall survival.[74] In another series of 20 post-Fontan patients who received a heart transplantation alone, 1-year survival was not affected by the presence of preexisting cirrhosis, although the average time interval between Fontan and heart transplantation was only 8.5 years in this study.[16] A recent case report from Switzerland described a 24-year-old patient with Child-Pugh A cirrhosis who underwent heart transplantation alone 14 years after Fontan. These investigators reported histological evidence of regression of bridging fibrosis 18 months after transplantation, suggesting that this phenomenon is possible, although this may represent sampling bias.[69] This team proceeded with heart transplantation alone with a mechanism in place to list the patient for urgent liver transplantation should the patient experience hepatic decompensation postoperatively. It remains to be determined what the long-term risk of developing HCC will be in post-Fontan patients who receive heart transplantation alone because it is well recognized that HCC can still occur in the absence of frank cirrhosis and even after regression of other chronic liver diseases.[75]

CHLT is one of the rarest multivisceral transplantations reported in the OPTN data set, and as stated, there is no way to know with certainty the proportion of patients who had a history of Fontan.[76] However, several recent single-institution series of CHLT, including post-Fontan patients, provide intriguing results. Stanford has reported its experience with en bloc CHLT in 9 adolescent and adult post-Fontan patients since 2006, with 100% 1-year patient survival and no rejection episodes at 30 days and

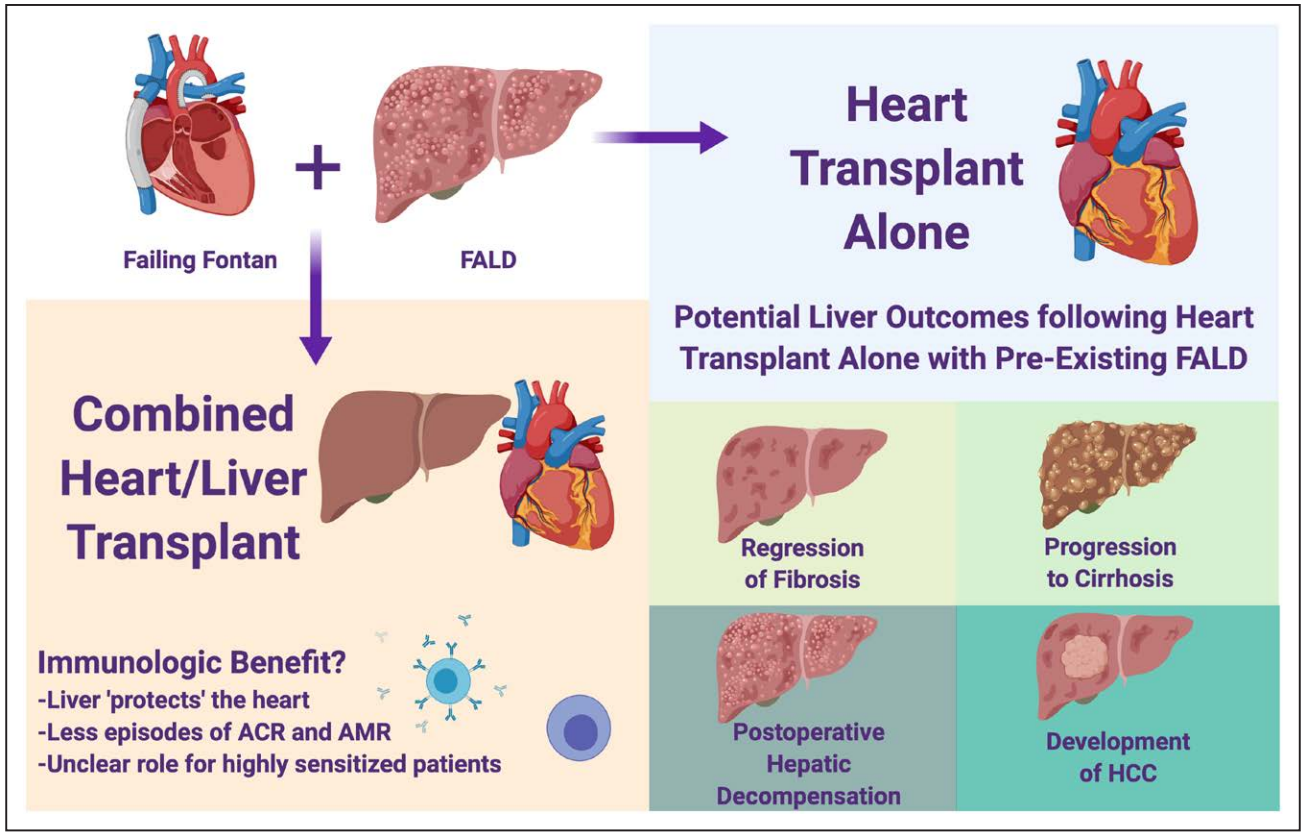

Figure 3. Transplantation considerations for patients after Fontan.
ACR indicates acute cellular rejection; AMR, antibody-mediated rejection; FALD, Fontan-associated liver disease; and HCC, hepatocellular carcinoma.

1 year after transplant.[58] The Mayo Clinic has reported its experience between 2004 and 2013 with 22 CHLTs compared with 223 heart transplantations alone, with 3 of the patients receiving CHLT having a diagnosis of congenital heart disease after Fontan.[54] In this series, the overall survivals for CHLT and heart transplantation alone were similar, although CHLT resulted in a significant decrease in T cell–mediated rejection confirmed by routine surveillance endocardial biopsies despite similar immunosuppression (31.8% for CHLT versus 84.8% for heart transplantation alone; $P<0.0001$). Recently, the University of Pennsylvania reported its experience with 33 CHLTs versus 283 heart transplantations alone; 11 post-Fontan patients were included in the CHLT cohort.[40,55] There was a similar finding with regard to reduced acute cellular rejection, with only 9.1% of patients receiving CHLT experiencing a rejection episode compared with 42.7% of the patients receiving heart transplantation alone. These findings taken together make it clear that excellent, if not superior, outcomes can be achieved for post-Fontan patients who undergo CHLT versus heart transplantation alone, and there may be an immunological benefit to proceeding with CHLT with significantly fewer acute cellular and humoral rejection episodes.

The most challenging aspect to proceeding with CHLT versus heart transplantation alone is patient selection. The University of Pennsylvania transplantation team reports that it decides at the time of transplantation through direct visualization of the recipient native liver whether to proceed with CHLT. That group has also reported discordant explant histology compared with pretransplantation liver biopsy, with ≈30% of patients exhibiting more advanced fibrosis on explantation (K.O. and J.W., unpublished data, January 2020). In addition, they have proceeded with listing 2 patients for CHLT on the basis of the diagnosis of HCC rather than being based on a failing Fontan. Ultimately, the decision of the multidisciplinary transplantation team will be driven by both biopsy and clinical findings, as well as the presence or absence of malignancy (considerations outlined in Figure 4). Given the potential immunological benefit of CHLT, programs may consider the degree of HLA allosensitization in their decision to proceed with heart transplantation alone versus CHLT. The frequency of HLA allosensitization has not been reported for post-Fontan patients specifically, but up to 20% of patients with congenital heart disease are reportedly sensitized, presumably secondary to the transfusion requirement associated with multiple cardiac procedures.[77] There are data that CHLT can overcome antibody-mediated rejection; thus, it is possible that in the highly sensitized Fontan patient with mild to moderate FALD, proceeding with CHLT will result in the best overall outcome for that patient and allow transplantation candidacy in a

Table 2. Reported Experience of Heart Transplantation Alone and Combined Heart-Liver Transplantation With Fontan-Associated Liver Disease

Location	Year	Patients, n	Years Since Fontan	1-y Survival	Rate of ACR, %	Comments	Reference
Heart transplant alone							
Bergamo, Italy	2004	14	10.3	86	50	No data if CLD was exclusion criteria	59
New York, New York	2004	24	6.1	71.5	NR	No data if CLD was exclusion criteria	60
Wilmington, Delaware	2012	43	8.6	62.4	NR	No data if CLD was exclusion criteria	61
Chicago, Illinois	2013	22	7.1	77	NR	No data if CLD was exclusion criteria	62
Europe	2015	61	10.7	81.9	NR	No data if CLD was exclusion criteria	63
Atlanta, Georgia	2016	33	8.8	84.8	NR	Excluded patients with CLD; 2 episodes of acute cellular rejection per patient in year 1	64
St Louis, Missouri	2016	47	7.1	90	NR	No data if CLD was exclusion criteria	65
Los Angeles, California	2017	36	13.0	75	NR	No data if CLD was exclusion criteria	66
Boston, Massachusetts	2017	30	7.5		NR	No data if CLD was exclusion criteria	67
Pediatric Heart Transplant Society Registry (United States, Canada, United Kingdom)	2017	252	6.7	89	NR	No data if CLD was exclusion criteria	68
Geneva, Switzerland	2018	1	14	100	0	Child-Pugh A; listed for heart only; plan for urgent liver listing if postoperative decompensation; regression of bridging fibrosis 18 mo after transplantation	69
Combined heart-liver transplantation							
Pittsburgh, Pennsylvania	2011	1	15	100	0	Situs ambiguous; reported alive with no acute cellular rejection at 2 y after transplantation	70
Omaha, Nebraska	2014	1	NR, transplant at 18 yr	100	0	Transplanted across positive T- and B-cell cross-match	71
Mayo Clinic, Rochester, Minnesota	2016	4*	NR	86.4	31.8	Survival and rate of acute cellular rejection include 19 patients without Fontan; acute cellular rejection rates may include patients >1 y after transplantation	54
Newcastle, United Kingdom	2017	1	41	100	0	Liver explant with cirrhosis, multiple dysplastic nodules, no hepatocellular carcinoma	56
Los Angeles, California	2018	5	26.8	NR	NR	Study published when 3 of 5 were <1 y after transplantation	15
Stanford, California	2019	9	16.6	100	0	En bloc heart-liver transplantation	58
Philadelphia, Pennsylvania	2019	11	22.9	100	9.1	Acute cellular rejection data include patients without Fontan and may extend >1 y after transplantation	40, 55

CLD, chronic liver disease; and NR, not reported.
*One additional Fontan combined heart-liver transplantation since this publication (T.T., personal communication, January 2020).

patient who may be deemed at unacceptable risk for heart transplantation alone.[78]

MOVING FORWARD WITH CHLT IN THE PATIENT WITH FONTAN: ANESTHETIC CONSIDERATIONS

The anesthetic management of CHLT in a patient with Fontan circulation is exceedingly complex. Hemodynamic instability, large-volume blood loss, coagulopathy, and metabolic derangements are commonplace. To complicate matters further, post-Fontan patients have unique anesthetic management goals because of their distinctive anatomy.[79] Among the most important is the maintenance of a transpulmonary pressure gradient (CVP – atrial pressure) to promote pulmonary blood flow. Because there is no active pumping of blood through the lungs, cardiac output depends on passive pulmonary blood flow. A

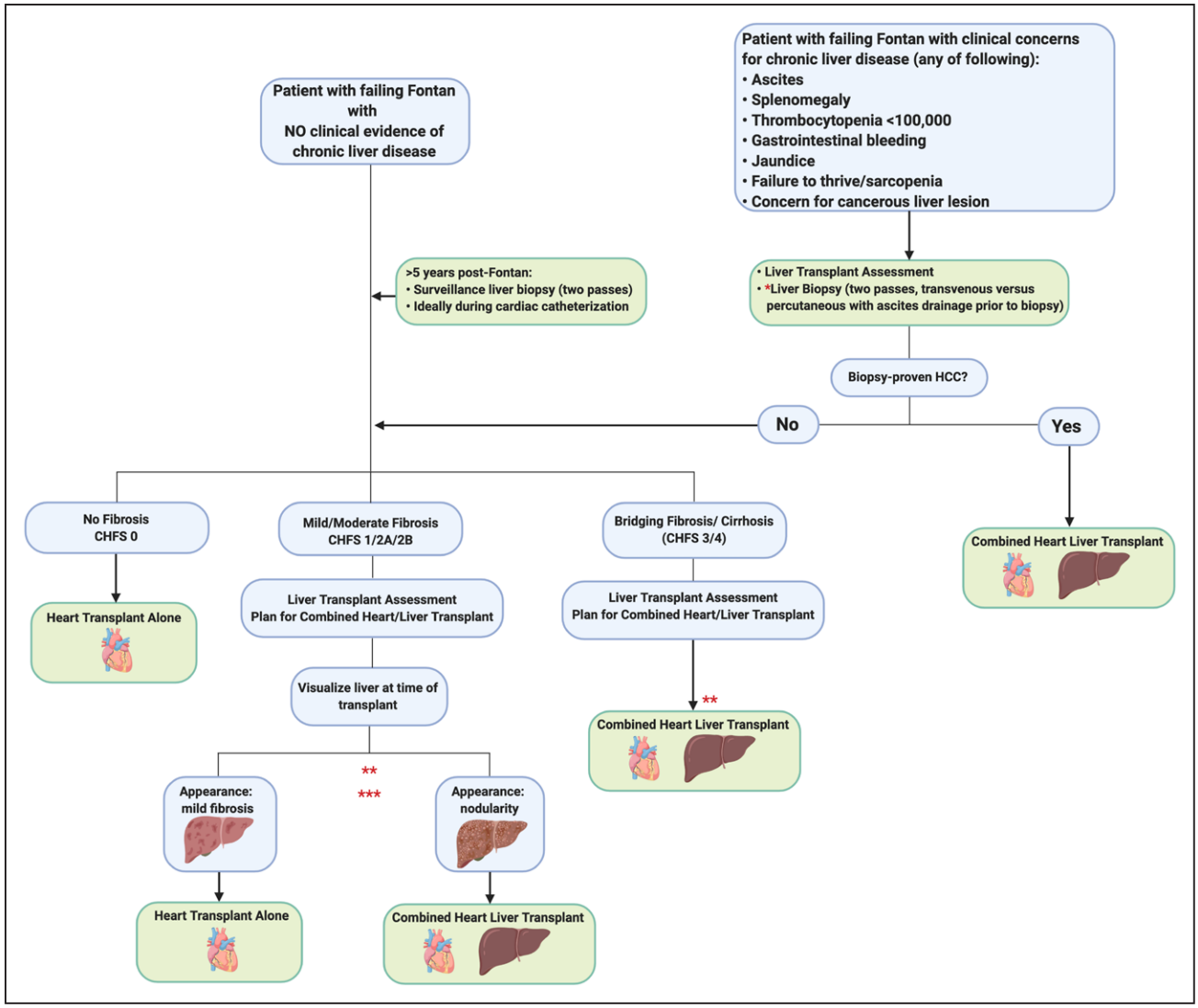

Figure 4. Algorithm for heart transplantation alone vs combined heart-liver transplantation in patients with Fontan-associated liver disease. CHFS indicates Congestive Hepatic Fibrosis Score; and HCC, hepatocellular carcinoma. *Transvenous biopsy may be safer than the percutaneous approach for patients at higher risk of bleeding (blood thinners, thrombocytopenia, etc). **Decision making for patients with histological evidence of bridging fibrosis or cirrhosis whose liver disease remains compensated is complex and will require multidisciplinary discussion and further study. ***There may be immunological benefit of combined heart-liver transplantation for patients with high panel-reactive antibody. This has not been studied in patients after Fontan.

satisfactory transpulmonary gradient relies several factors: adequate preload, minimized pulmonary vascular resistance, satisfactory ventricular function, proper atrioventricular valve function, and sinus rhythm.[80,81]

Assuming a normal atrial pressure of 5 to 10 mm Hg, a CVP of 12 to 15 mm Hg should promote adequate forward flow.[80–82] Positive pressure ventilation, although unavoidable for this operation, is not often well tolerated. The loss of sinus rhythm requires prompt correction and can lead to ventricular failure.[82] Hypoxia is not uncommon in post-Fontan patients, with fenestrated patients often having a baseline Spo_2 that falls in the 80% range. In CHLT, it is more common that cardiac transplantation precedes liver transplantation and cardiopulmonary bypass is commonly weaned before liver transplantation.[15,56,83] Adequate cardiac function is essential to limit hepatic congestion. Depending on the practice at individual centers, it is likely that these patients will be transferred to the cardiac surgery intensive care unit postoperatively, with a multidisciplinary approach to posttransplantation management.

CONCLUSIONS AND FUTURE DIRECTIONS

FALD increasingly poses a significant clinical challenge. Without discrete *International Classification of Diseases* codes for history of Fontan or FALD, it is virtually impossible to study these patients over time and determine the lifetime risk of clinically significant chronic liver disease and the need for liver transplantation.[73] In the short term, the establishment of multi-institutional, collaborative

registries with liver-specific outcome measures is imperative to develop evidence-based management guidelines. Prospective studies aimed at correlating liver biopsy findings and imaging features that can adequately diagnose FALD are necessary. Furthermore, routine monitoring for liver disease starting at 10 years after Fontan surgery is recommended. Similarly, defining imaging findings that correlate with malignant liver lesions in the setting of FALD specifically will be important to monitor for HCC and define OPTN transplantation criteria in these patients.

With >70 000 post-Fontan patients worldwide now reaching adulthood, our community will face increased decisions about when to proceed with transplantation and what the role is for CHLT. In the present OPTN data set, there is no way to study post-Fontan patients or FALD directly. Adopting a policy change so that these diagnoses can be tracked moving forward will provide crucial data in understanding this population in the context of solid organ transplantation. Hepatic fibrosis will develop in all post-Fontan patients; thus, surveillance for FALD is a question of "when" and not "if." On the basis of the present data, the most reliable method to diagnose FALD requires liver biopsy, but large, multicenter studies and further refinement of MELD-XI scoring and elastography techniques may allow multiple noninvasive data points to be generated and facilitate surveillance of FALD over time. Similarly, the potential for stabilization or regression of FALD after heart transplantation alone exists but is difficult to predict and may not eliminate the risk for HCC. Most centers would not consider liver transplantation alone feasible in post-Fontan patients because of chronic elevation of CVPs, and OPTN data demonstrate high mortality for heart transplantation recipients who are subsequently placed on the liver transplantation waiting list. That being said, recent data suggest that superior outcomes can be achieved with CHLT in this patient population compared with heart transplantation alone, with additional immunological benefit. It is evident that the MELD-Na score does not adequately capture FALD, and with the challenges in diagnosing HCC in these patients, it may be difficult for a patient with stable or worsening FALD after heart transplantation alone to receive a subsequent liver transplantation. With the current allocation policy for CHLT in which the liver follows the heart, CHLT may be the only chance for these patients to undergo liver transplantation. Proceeding with CHLT requires an experienced transplantation center, collaborative team, and dedicated anesthesiology group who can embrace the unique challenges of transplantation in post-Fontan patients.

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