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Fontan Associated Liver Disease: Screening, Management, and Transplant Considerations.

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Abstract

Surgical innovation and multidisciplinary management have allowed children born with univentricular physiology congenital heart disease to survive into adulthood. There is an estimated global population of 70,000 patients who have undergone the Fontan procedure alive today, most of whom are under 25 years old. There are several unexpected consequences of the Fontan circulation, including Fontan-Associated Liver Disease (FALD). Surveillance biopsies have

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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 due to advanced liver disease including bridging fibrosis, cirrhosis, and hepatocellular carcinoma in this population. In the absence of a transplant option, these young patients face a poor quality of life and death. Acknowledging that there are no consensus guidelines for diagnosing and monitoring FALD or when to consider heart-transplant versus combined heart-liver transplantation in these patients, a multidisciplinary working group reviewed the literature surrounding FALD, with a specific focus on considerations for transplantation.

Keywords

Fontan-associated liver disease; heart transplant; combined heart-liver transplant

Introduction

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 patients post-Fontan 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 and a lack of pulsatility, resulting in passive venous congestion and impaired hepatic blood flow (Figure 1)[2]. While it is generally accepted that all patients post-Fontan have some degree of FALD, it is unclear what proportion of patients post-Fontan will develop clinically significant advanced liver disease. Similarly, the prevalence of and preferred algorithm to provide surveillance for FALD-related hepatocellular carcinoma (HCC) is 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 transplant alone versus combined heart liver transplant (CHLT), a multidisciplinary group of American Society of Transplantation members collaborated to review FALD specifically from the perspective of the transplant 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 post-Fontan who may benefit from liver transplant. It is projected that the mean age of patients post-Fontan will be 23 years by 2025, with an estimated global population of 70,000 patients post-Fontan that could double over the next decade. It is therefore imperative that the transplant community proactively develops algorithms for managing patients post-Fontan with FALD[3,4].

Brief Review of the Fontan Physiology

Most children born with unrepaired univentricular physiology face an early death during infancy. Due to 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 where bi-ventricular 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 sub-pulmonic 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 non-pulsatile flow in the inferior vena cava.

The primary characteristic of Fontan hemodynamics is a lack of a subpulmonary ventricle, which automatically leads to high central venous pressure (CVP). This creates additional driving pressure for the pulmonary circulation and diminished cardiac preload for the systemic ventricle (SV), resulting in chronically low cardiac output (CO)[1,5]. Mild but significant low arterial blood oxygen saturation is also a major hemodynamic feature, which likely results from intrapulmonary ventilation-perfusion mismatch as well as the development of veno-venous collaterals[6]. Thus, it is postulated that the pathophysiologic complications after the Fontan operation are driven by the following conditions: multi-end-organ congestion due to high central venous pressure (CVP), chronic heart failure due to low CO, and mild but significant hypoxia which over time may contribute to multi-organ dysfunction[7]. Possible causes of elevated CVP include (but are not limited to) pre-capillary factors, such as stenosis of the Fontan conduit and high pulmonary vascular resistance (PVR), or post-capillary factors, like systolic and/or diastolic SV dysfunction and atrioventricular valve regurgitation and/or stenosis.

In the U.S., more than 900 Fontan operations are performed each year, with 97% early survival[3]. To put that in perspective, there are an estimated 500–600 children born with biliary atresia each year in the U.S., and approximately half will undergo primary liver transplant, which makes up the majority of pediatric liver transplants performed each year[8,9]. The Fontan operation is usually performed in children two to five years of age, but the effects of the post-Fontan physiology continue to impact these patients through adulthood[10]. Only one third of adult patients post-Fontan are in ‘optimal condition’, defined as acceptable cardiac function with no clinically evident end-organ disease[11]. While 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 as well as chronic systemic inflammation.

Which patients post-Fontan are at risk for FALD?

FALD, including the development of cardiac cirrhosis and liver neoplasms, is recognized to be highly prevalent in patients post-Fontan[12–16]. Chronic passive congestion of the liver due to 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 due to passive pulmonary blood flow results in elevated systemic venous pressure, causing liver congestion[17]. Additionally, cardiac output and cardiac index are diminished, and as a result zone three 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 due to chronic congestion results in reactive fibrogenesis due to centrilobular hepatocyte atrophy, sinusoidal fibrosis and eventual bridging fibrosis and then cardiac cirrhosis[20,21].

In a retrospective study at a single center, 13/32 patients post-Fontan evaluated for heart transplant 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 patients post-Fontan, most had advanced liver disease. Histologic evidence of fibrosis was present in all biopsies and was classified as severe based on a gross architectural distortion score (modified from METAVIR staging) of 3–4 in 68% of the patients[12,22]. Complications of portal hypertension including varices and ascites were present in over 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. While 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 histologic findings are incompletely evaluated in FALD and may not accurately represent all aspects of the disease.

Over the last decade, several studies have attempted to identify relationships between hemodynamics and the extent of liver fibrosis in patients post-Fontan. A recent study involving 33 patients post-Fontan 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 approximately 100 adolescent patients undergoing surveillance cardiac catheterization and liver biopsy ≥ 10 years post-Fontan[24,25]. Another surveillance cardiac catheterization and liver biopsy cohort involving 49 patients 15.2 years post-Fontan reported that all patients had histologic evidence of liver fibrosis, and Fontan pressure ≥ 14 mmHg and MR 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 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). Notably, 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 patients post-Fontan with 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 patients post-Fontan 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; i.e., 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 heart catheterization in the management of Fontan patients remains ‘for cause’; i.e. 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 10–15 years post-Fontan with minimal procedural complications, and these studies have shown that the prevalence and severity of FALD-related liver histopathology most strongly correlates with overall time post-Fontan[13,15,24–26,29].

Diagnosis and Monitoring Progression of FALD

Serum biomarkers

While 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, as the majority of patients will have no detectable abnormalities. In 74 patients 15 years post-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 (F3–4) and sinusoidal fibrosis was an elevated INR ($P = 0.046$ and $P = 0.018$, respectively)[30]. The MELD score is generally not elevated in patients post-Fontan. The MELD excluding INR (MELD-XI) score has been explored to eliminate the impact of therapeutically elevated INR among patients who are being pharmacologically anticoagulated. In a cohort of 70 patients post-Fontan, the MELD-XI 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 (US), computed tomography (CT) and magnetic resonance imaging (MRI) have traditionally been employed to detect findings suggestive of cirrhosis and its complications. A study of 55 patients post-Fontan screened with US imaging found heterogeneous hepatic echotexture or surface or liver surface nodularity in 67% of patients, and this correlated with time from 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 CT or MRI in patients post-Fontan include signs of portal hypertension: altered portal venous phase enhancement of the liver periphery when compared with the hilar region, heterogeneous reticular enhancement of the liver

parenchyma in the portal venous phase, as well as ascites, venous collaterals, and/or dilated hepatic veins with contrast reflux and intrahepatic venous-venous collaterals[33,34].

The Role of Elastography

Elastography, a non-invasive approach to measure liver stiffness, may be useful for patient evaluation and management in the Fontan population. While elastography is not specific for hepatic fibrosis, as it also detects congestive hepatopathy from hepatic venous outflow obstruction, liver stiffness increases as fibrosis progresses[35]. Currently, three major modalities are employed 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.

There are only small case series which have evaluated the performance of imaging and elastography to determine the degree of fibrosis in FALD. A recent study of 38 patients post-Fontan who underwent multiple modalities of hepatic surveillance detected biopsy-confirmed cirrhosis in 29%[12]. However, neither transient elastography nor MRI elastography were able to discriminate between mild and severe fibrosis. In a separate study of 50 patients post-Fontan who underwent transient elastography plus hemodynamic testing via 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.

Other liver-related, invasive approaches to monitor FALD

Endoscopy allows for the assessment of esophageal varices and other gastrointestinal pathologies in cirrhosis and may have a role in patients post-Fontan with evidence of liver disease. However, there are few reports detailing the use of screening endoscopy to detect varices in FALD. Chang and colleagues reported that 27% of adult patients at approximately 15 years post-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 post-Fontan[12]. Similarly, a study examining MRI, CT and/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 post-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 may be useful in patients with evidence of liver fibrosis.

Utility of Hepatic Venous Pressure Gradients

Hepatic venous pressure gradients (HVPG) are measured as a surrogate measurement of portal hypertension, comparing the wedged hepatic sinusoidal pressure to the unwedged free hepatic venous pressure (HVPG normally 1–5 mmHg). The value of the hepatic venous pressure gradients in FALD is unclear, as 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 transplant in patients post-Fontan include central venous pressures and cardiac index[28]. It is unknown if 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. Notably, a report of 67 patients post-Fontan who underwent 68 liver biopsies identified hemorrhage in 7.4% as the sole complication; one patient required blood transfusions due to hemobilia[39]. That being said, in a single center's experience with >100 surveillance biopsies performed during cardiac catheterization approximately 10 years post-Fontan, only one patient had a post-biopsy bleed, which did not require transfusion[24,25]. Single center experience at a mature adult congenital and transplant center also suggest, as noted above, the risk of 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. Due to 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 post-Fontan, 56% demonstrated ≥20% collagen deposition on Sirius red staining of liver biopsy specimens[29]. Increasingly, the Congestive Hepatic Fibrosis Score is 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 due to the risk of sampling bias, such that focal areas may be more or less representative of the patient's overall true degree of fibrosis. Many programs are performing two distinct passes during the biopsy procedure to reduce the effect of sampling bias[24,26,29,30,42].

Evaluation of Liver Lesions

Elevated central venous pressures post-Fontan are associated with the growth of hypervascular nodules in the liver[33,43,44]. Large regenerative nodules and focal nodular hyperplasia (FNH) are common and may occur in as many as 20–30% of patients post-Fontan[32,43,45,46]. Nodules in patients with cirrhosis from any etiology including post-Fontan, should be vigorously evaluated as potential HCC[44,47]. Two recent retrospective, single center studies have reported rates of 3–15% for development of HCC in FALD, up to 22 years post-Fontan[48,49]. The American Association for the Study of Liver Diseases (AASLD) guidelines for HCC surveillance in general recommend US and alpha-fetoprotein (AFP) determination every six months[50]. For patients post-Fontan, the optimal imaging modality remains unclear due to unique liver morphology and vascular characteristics, but AASLD 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, though 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, though a liver biopsy is usually necessary as 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 due to underlying FALD from true HCC within the Liver Imaging Reporting and Data System (LiRADS) 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 post-Fontan is the most important predictor of advanced FALD[25,26,28,30]. Thus, any hepatic surveillance strategy can likely be infrequent and non-invasive in the first ten years post-Fontan. However, patients 10–15 years post-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, INR testing, and MELD-XI calculation, as well as for malignancy with ultrasonography or magnetic resonance imaging. Elastography may be helpful to alert the multi-disciplinary team to increased congestive hepatopathy from a failing Fontan and the need to reduce pulmonary pressures. Ideally, these patients should be followed 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

While 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 approximately 10 years post-Fontan, as 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]. Based on the severity of the fibrosis on biopsy, these patients should also undergo baseline MR elastography with continued surveillance to determine liver stiffness and also establish initial anatomical features, identify concerning nodules, and evaluate for signs of portal hypertension and splenomegaly. While liver labs 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 and/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 US and AFP measurements to assess changes over time according to AASLD guidelines is reasonable until FALD-specific approaches can be proven. Finally, for patients with concern for decompensating chronic liver disease, including the presence of ascites, splenomegaly, thrombocytopenia <100,000, 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 transplant evaluation.

When does FALD require liver transplantation?

Once high-grade fibrosis is observed in a patient post-Fontan, 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 following heart transplantation alone, versus those who may unexpectedly decompensate their liver disease post-heart transplant alone, which represents the most feared early-postoperative outcome in these patients. Even with a 'perfect' Fontan, liver transplant alone in this population is not advisable due to 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 patients post-Fontan (summarized in Table 2)[40,54–58].

The impact of FALD on graft and patient survival following heart transplant alone is limited. Since histologic evidence of fibrosis in FALD is typically observed at least 10 years post-Fontan, the discussion surrounding proceeding with heart transplant alone in the setting of underlying FALD generally refers to late adolescent or adult transplant candidates, as opposed to pediatric patients who proceed to heart transplant alone within a few years of the Fontan. These children can achieve acceptable long-term outcomes, presumably with minimal risk for progression of FALD post-heart transplant, although there is very little data surrounding chronic liver disease as an exclusion criteria for proceeding with heart transplant alone (Table 2)[18,64]. A retrospective review of a single institutional experience with heart transplant alone in 30 pediatric patients post-Fontan demonstrated an overall 30% mortality at 4.8 years post-transplant, with no mortalities related to liver etiology[72]. Unfortunately, in the United States there are no diagnostic codes in the OPTN heart dataset that specifically captures patients post-Fontan. Similarly, there are no diagnostic codes to capture FALD in the OPTN liver dataset. Instead, a code for "Congenital Heart Disease with Surgery" has been used a surrogate marker to study these patients from the heart dataset[57]. In this study, there were approximately 900 patients in the 'Congenital Heart Disease with Surgery' category that underwent heart transplant alone, while there were 27 who underwent CHLT. In both circumstances, patients with congenital heart disease had a higher early mortality with superior long-term survival when compared to non-congenital heart disease heart transplant alone recipients. In a recent analysis of the OPTN data, there were ten patients with a history of heart transplant for 'Congenital Heart Disease with Surgery' who were subsequently placed on the liver transplant waitlist. Only one pediatric patient ultimately received a liver transplant, and 4/6 (67%) of the adult patients died on the liver transplant waitlist[73].

There is some evidence that FALD can stabilize following heart transplant alone. In a retrospective histological study of 74 patients post-Fontan, with five who underwent heart transplant alone, the degree of pre-transplant hepatic fibrosis was not predictive of heart

transplant-free survival or overall survival[74]. In another series of 20 patients post-Fontan who received a heart transplant alone, one-year survival was not affected by the presence of pre-existing cirrhosis, although the average time interval between Fontan and heart transplant was only 8.5 years in this study[16]. A recent case report from Switzerland described a 24-year-old patient with Childs-Pugh A cirrhosis who underwent heart transplant alone 14 years post-Fontan. They report histological evidence of regression of bridging fibrosis 18 months post-transplant, suggesting that this phenomenon is possible although this may represent sampling bias[69]. Importantly, this team proceeded with heart transplant alone with a mechanism in place to list the patient for urgent liver transplant should he experience hepatic decompensation post-operatively. It remains to be determined what the long-term risk of developing HCC will be in the heart transplant alone post-Fontan patient population, as it well-recognized that HCC can still occur in the absence of frank cirrhosis and even following regression of other chronic liver diseases[75].

CHLT is one of the rarest multivisceral transplants reported in the OPTN dataset, and as stated above there is no way to know with certainty the proportion of patients who had a history of Fontan[76]. However, there are several recent single-institution series of CHLT, including patients post-Fontan, that provide intriguing results. Stanford has reported their experience with en bloc CHLT in nine adolescent and adult patients post-Fontan since 2006, with 100% one year patient survival and 0% rejection episodes at 30 days and one year post-transplant[58]. The Mayo Clinic has reported their experience between 2004–2013 with 22 CHLT compared to 223 heart transplant alone, with three of the CHLT patients having a diagnosis of congenital heart disease, post-Fontan[54]. In this series, the overall survival for CHLT versus heart transplant alone were similar, while CHLT resulted in a significant decrease in T-cell mediated rejection confirmed by routine surveillance endocardial biopsies, despite similar immunosuppression (31.8% for CHLT vs. 84.8% for heart transplant alone, $p<0.0001$). Recently, the University of Pennsylvania reported their experience, with 33 CHLT versus 283 heart transplant alone; 11 patients post-Fontan were included in the CHLT cohort[40,55]. There was a similar finding with regards to reduced acute cellular rejection, with only 9.1% of CHLT patients experiencing a rejection episode, versus 42.7% of the heart transplant alone patients. Taken together, it is clear that excellent, if not superior outcomes can be achieved for patients post-Fontan that undergo CHLT versus heart transplant alone, and there may be an immunologic benefit to proceeding with CHLT with significantly less acute cellular and humoral rejection episodes.

The most challenging aspect to proceeding with CHLT versus heart transplant alone is patient selection. The University of Pennsylvania transplant team reports that they decide at the time of transplant via direct visualization of the recipient native liver whether to proceed with CHLT. They have also reported discordant explant histology when compared to pre-transplant liver biopsy, with approximately 30% of patients exhibiting more advanced fibrosis on explant (K.O. and J.W., unpublished data). As well, they have proceeded with listing two patients for CHLT based on the diagnosis of HCC, versus the decision being based on a failing Fontan. Ultimately the decision of the multidisciplinary transplant team will be driven by both by biopsy and clinical findings, as well as the presence or absence of malignancy (considerations outlined in Figure 4). Given the potential immunologic benefit of CHLT, programs may consider the degree of HLA allosensitization in their decision to

proceed with heart transplant alone versus CHLT. The frequency of HLA allosensitization has not been reported for patients post-Fontan 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, and 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 for transplant candidacy in a patient who may be deemed unacceptable risk for heart transplant alone[78].

Moving forward with CHLT in the Fontan patient: 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, patients post-Fontan have unique anesthetic management goals due to their distinctive anatomy[79]. Among the most important is the maintenance of a transpulmonary pressure gradient (CVP – atrial pressure) to promote pulmonary blood flow. Since there is no active pumping of blood through the lungs, CO is dependent on passive pulmonary blood flow. A satisfactory transpulmonary gradient is reliant upon several factors: 1) adequate preload, 2) minimized PVR, 3) satisfactory ventricular function, 4) proper AV valve function, and 5) sinus rhythm[80,81].

Assuming a normal atrial pressure of 5–10 mmHg, a CVP of 12–15 mmHg should promote adequate forward flow[80–82]. Positive pressure ventilation, though 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 patients post-Fontan with fenestrated patients often having a baseline SpO2 that falls in the 80% range. In CHLT, it is more common that cardiac transplantation precedes liver transplantation and cardiopulmonary bypass is commonly weaned prior to liver transplantation[15,56,83]. Adequate cardiac function is essential to limit hepatic congestion. Depending on an individual center's practice, it is likely that these patients will be transferred to the cardiac surgery intensive care unit post-operatively, with a multidisciplinary approach to post-transplant management.

Conclusions and future directions

In summary, FALD increasingly poses a significant clinical challenge. Without discrete International Classification of Diseases (ICD) codes for 'history of Fontan' or 'FALD', it will be virtually impossible to study these patients over time and determine the lifetime risk of clinically significant chronic liver disease and the need for liver transplant[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. Further, routine monitoring for liver disease starting at 10 years post 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 transplant criteria in these patients.

With over 70,000 patients post-Fontan worldwide now reaching adulthood, our community will face increased decisions about when to proceed with transplant and what the role is for CHLT. In the present OPTN dataset, there is no way to study patients post-Fontan 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 patients post-Fontan, and thus surveillance for FALD is a question of “when” and not “if.” Based on the current 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 for multiple non-invasive data points to be generated and facilitate surveillance of FALD over time. Similarly, the potential for stabilization and/or regression of FALD following heart transplant alone exists but is difficult to predict and may not eliminate the risk for HCC. Most centers would not consider liver transplant alone in patients post-Fontan feasible due to chronic elevation of central venous pressures, and OPTN data demonstrate high mortality for heart transplant recipients who are subsequently placed on the liver transplant waiting list. That being said, recent data suggest that superior outcomes can be achieved with CHLT in this patient population when compared to heart transplant alone, with additional immunologic benefit. It is evident that MELD-Na 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 following heart transplant alone to receive a subsequent liver transplant. With the current allocation policy for CHLT, where the liver follows the heart, CHLT may be the only chance for these patients to receive a liver transplant. Proceeding with CHLT requires an experienced transplant center, collaborative team, and dedicated anesthesiology group that can embrace the unique challenges of transplantation in patients post-Fontan.

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Non-standard abbreviations and acronyms:

FALD	Fontan-Associated Liver Disease
CHLT	Combined Heart-Liver Transplant
CVP	Central Venous Pressure
CO	Cardiac Output
PVR	Pulmonary Vascular Resistance
MELD	Model of End-Stage Liver Disease
US	Ultrasound

CT	Computed Tomography
MRI	Magnetic Resonance Imaging
AFP	Alpha-fetoprotein
AASLD	American Association for the Study of Liver Diseases
HCC	Hepatocellular Carcinoma
OPTN	Organ Procurement and Transplantation Network
ICD	International Classification of Diseases
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ALP	Alkaline Phosphatase
GGT	gamma-glutamyl transferase
INR	International Normalized Ratio
PHTS	Pediatric Heart Transplant Society
CLD	Chronic Liver Disease
ACR	Acute Cellular Rejection
NR	Not Reported

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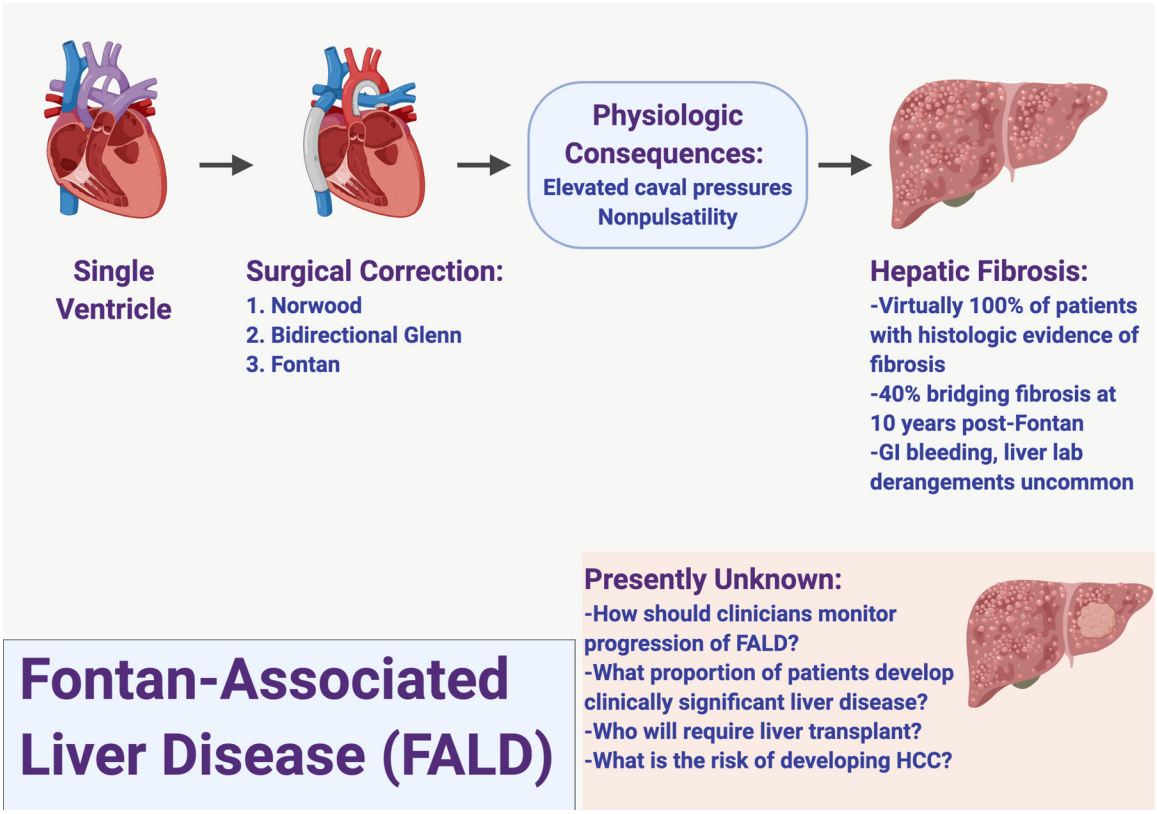

Figure 1:
Fontan-Associated Liver Disease.

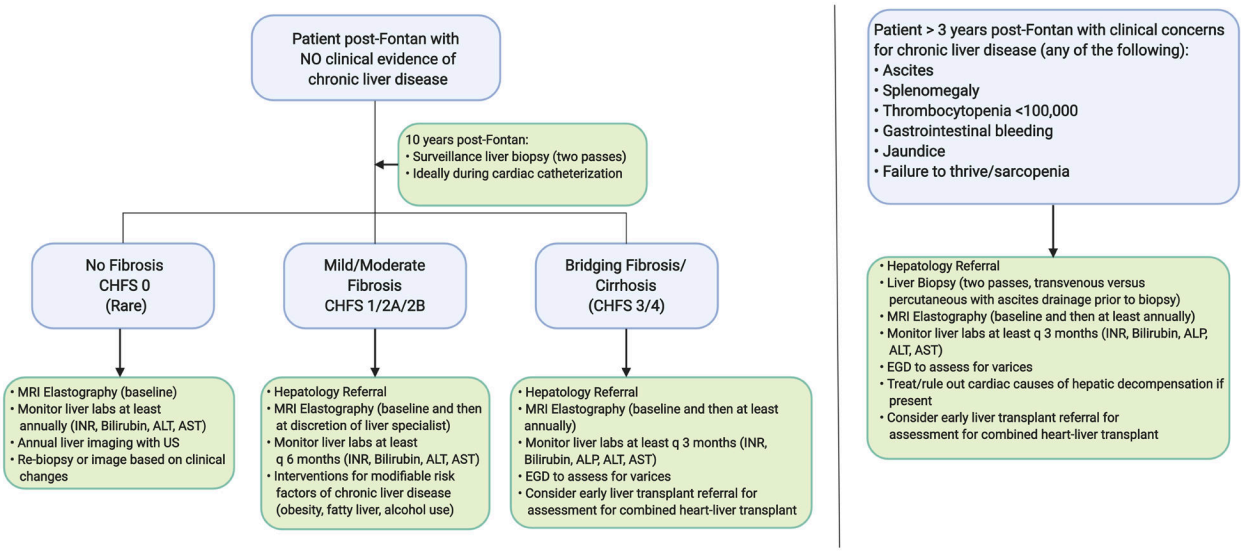

Figure 2: Approach to surveillance of FALD.

Caveats: MR may be challenging in patients with pacemaker devices, and shearwave elastography for liver stiffness and CT abdomen/pelvis with contrast to assess for stigmata of portal hypertension can be considered in these patients. Transvenous biopsy may be safer than 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 AASLD recommend AFP and US every six months in patients with cirrhosis.

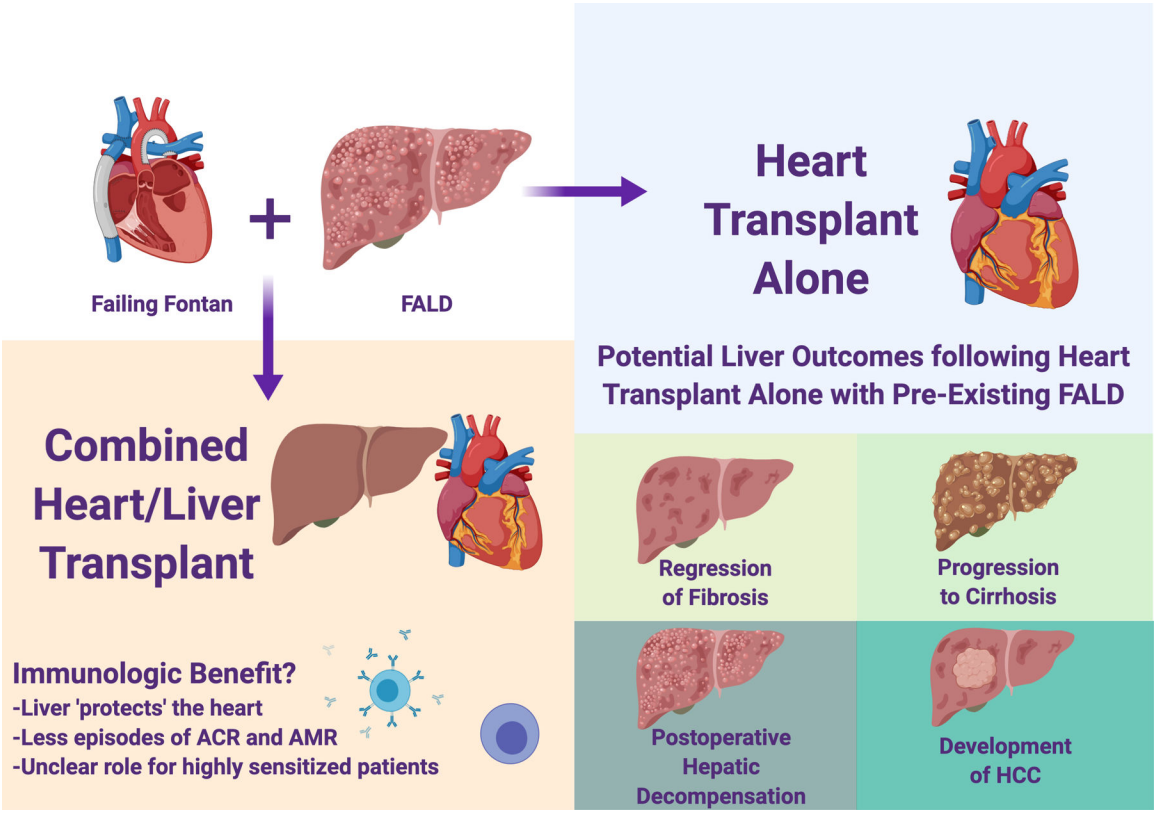

Figure 3:
Transplant Considerations for patients post-Fontan.

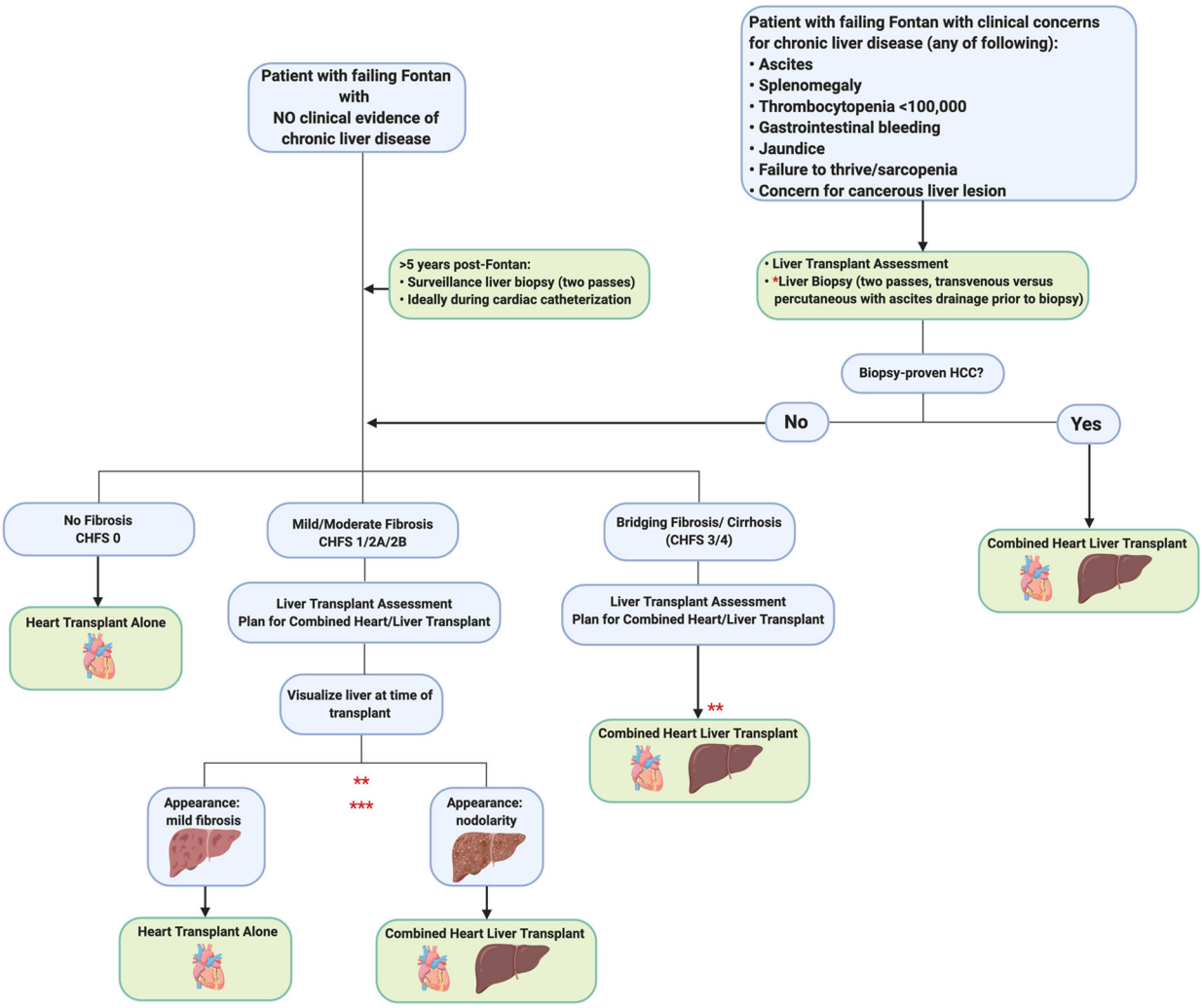

Figure 4: Algorithm for Heart Transplant Alone vs. Combined Heart-Liver Transplant in Patients with FALD.

Caveats: *Transvenous biopsy may be safer than percutaneous approach for patients at higher risk of bleeding (blood thinners, thrombocytopenia, etc). **Decision making for patients with histologic evidence of bridging fibrosis or cirrhosis whose liver disease remains compensated is complex and will require multidisciplinary discussion and further study. ***There may be immunologic benefit of CHLT for patients with high PRA. This has not been studied in patients post-Fontan.

Table 1:

Considerations for diagnostic testing in patients with suspected FALD.

Investigation	Utility	Problems
Liver Biopsy	1) Gold standard for histologic assessment of fibrosis and cirrhosis 2) Transvenous approach allows for simultaneous hemodynamic pressure measurements	1) Risk for procedural complications (low) 2) No universally accepted scoring criteria 2) Useful for screening for FALD
Blood Tests		
Liver Enzymes (ALT, AST)	Assess for hepatocyte injury/dysfunction	1) Rarely elevated in stable FALD 2) Do not correlate with degree of fibrosis in FALD
ALP, Bilirubin, GGT	Evaluate biliary injury or stasis (ALP, Bilirubin, GGT)	1) Rarely elevated in stable FALD 2) Elevated GGT across all patients post-Fontan in one case series 3) 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 one case series
AFP	Serum tumor marker that may be raised in some patients with HCC	1) Does not correlate with disease severity in FALD 2) No data regarding proportion of patients with FALD and HCC that have elevated AFP
MELD-Na	1) Determine mortality risk in patients with end-stage liver disease 2) Calculated with INR, Creatinine, Bilirubin, Na, and presence/absence of renal replacement therapy 3) Used for liver transplant waiting list prioritization	1) Does not correlate with disease severity and is rarely elevated in patients with FALD 2) Can be confounded by systemic anticoagulation in patients post-Fontan
MELD-XI	Modified MELD without INR to risk stratify patients with cirrhosis on anticoagulation	Correlated with degree of fibrosis in FALD in one case series
Imaging Modalities		
MR Elastography	1) Assess global liver stiffness 2) Can perform serial studies to evaluate for progression 3) Evaluate for and characterize liver nodules vs. HCC (with contrast phase) 4) Evaluate portal hypertension, identify complex anatomical variations for surgical planning for liver transplant (with contrast phase)	1) Does not distinguish between passive congestion and fibrosis 2) For high quality liver imaging, patient must be in scanner for at least 30 min. and participate in exam with breath-holding, etc. which may be challenging in pediatric patients or those with a failing Fontan 3) Liver nodules in FALD being evaluated for HCC may be difficult to categorize using OPTN Criteria
Shear Wave US Elastography	1) Assess global liver stiffness 2) Can perform serial studies to evaluate for progression	1) Does not distinguish between passive congestion and fibrosis 2) Limited utility in patients with ascites
Transient Elastography	1) Assess liver stiffness 2) Can perform serial studies to evaluate for progression	1) Does not distinguish between passive congestion and fibrosis 2) Limited utility in patients with ascites
Ultrasound	1) Assess liver morphology 2) Evaluate for liver nodules and vascular patency 3) Evaluate for ascites	1) Difficult to detect small lesions due heterogeneous parenchyma 2) Limited utility in patients with ascites
Contrast CT	1) Assess liver morphology and vascular patency 2) Evaluate for and characterize liver nodules versus HCC 3) Evaluate complex anatomical variations for surgical planning for liver transplant	1) Radiation exposure 2) Nephrotoxic contrast 3) Liver nodules in FALD being evaluated for HCC may be difficult to categorize using OPTN Criteria

ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase, GGT: gamma-glutamyl transferase, INR: International Normalized Ratio, MELD: Model of End-stage Liver Disease, AFP: Alpha-Fetoprotein, OPTN: Organ Procurement and Transplantation Network, HCC: Hepatocellular Carcinoma

Table 2:

Reported experience of Heart Transplant Alone and Combined Heart-Liver Transplant in patients with FALD.

Location	Year	No. of Patients	Years post-Fontan	1 Year Survival	Rate of ACR	Comments	Ref
Heart Transplant Alone							
Italy	2004	14	10.3	86%	50%	No data if CLD was exclusion criteria	59
New York, NY USA	2004	24	6.1	71.5	N.R.	No data if CLD was exclusion criteria	60
Delaware, USA	2012	43	8.6	62.4	N.R.	No data if CLD was exclusion criteria	61
Chicago, IL USA	2013	22	7.1	77	N.R.	No data if CLD was exclusion criteria	62
Europe	2015	61	10.7	81.9	N.R.	No data if CLD was exclusion criteria	63
Atlanta, GA USA	2016	33	8.8	84.8	N.R.	Excluded patients with CLD 2 episodes of ACR per Pt. in Year 1	64
St. Louis, MO USA	2016	47	7.1	90	N.R.	No data if CLD was exclusion criteria	65
Los Angeles, CA USA	2017	36	13.0	75	N.R.	No data if CLD was exclusion criteria	66
Boston, MA USA	2017	30	7.5		N.R.	No data if CLD was exclusion criteria	67
PHTS Registry (US, Canada, UK)	2017	252	6.7	89%	N.R.	No data if CLD was exclusion criteria	68
Switzerland	2018	1	14	100%	0%	Child-Pugh A. Listed for heart only. Plan for urgent liver listing if post-op. decompensation. Regression of bridging fibrosis 18mo. post-transplant	69
Combined Heart-Liver Transplant							
Pittsburgh, PA USA	2011	1	15	100%	0%	Situs ambiguous; Reported alive with no ACR at 2 years post-transplant	70
Omaha, NB USA	2014	1	N.R., Tx at 18yr.	100%	0%	Transplanted across positive T and B-cell XM	71
Mayo Clinic, MN, USA	2016	4**	N.R.	86.4%*	31.8%*	*Survival and rate of ACR include 19 non-Fontan patients. ACR rates may include patients >1-year post-transplant	54
Newcastle, UK	2017	1	41	100%	0%	Explant with cirrhosis, multiple dysplastic nodules, no HCC	56
Los Angeles, CA, USA	2018	5	26.8	N.R.	N.R.	Study published when 3/5 < 1-year post-transplant	15
Stanford, CA, USA	2019	9	16.6	100%	0%	En bloc heart-liver transplantation	58
Philadelphia, PA USA	2019	11	22.9	100%	9.1%	ACR data is includes non-Fontan patients and may extend >1-year post-transplant	40,55

PHTS: Pediatric Heart Transplant Society, CLD: Chronic Liver Disease, ACR: Acute Cellular Rejection; N.R. Not Reported.

** One additional Fontan CHLT since this publication (T.T., personal communication)