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Fontan Liver Disease: Review of an Emerging Epidemic and Management Options

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Opinion statement

Adults with complex congenital heart disease that resulted in a Fontan procedure frequently experience late cardiac failure. Increasingly, liver disease is recognized as an important complication of single-ventricle anatomy and Fontan physiology; however, there is no consensus regarding liver evaluation in this population. Here, we review what is known about liver disease in this unique group and propose screening and prevention measures. We also review controversial treatment areas including assist devices and transplantation, with a review of outcomes in isolated heart and combined heart-liver transplant.

Keywords

Single ventricle; Fontan; Liver disease; Cirrhosis

Introduction

Adults living with congenital heart disease (CHD) now outnumber children living with CHD. Within this group, the prevalence of severe CHD has exponentially increased, largely due to improved survival of patients with single-ventricle anatomy who have undergone a Fontan procedure. Although this palliation has allowed such patients to reach adulthood, it has not been without significant consequences. In particular, liver disease is nearly ubiquitous in this population and frequently leaves clinicians scratching their heads with questions about etiology, evaluation, treatment, and prognosis.

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Compliance with Ethics Guidelines

Conflict of Interest

Elisa Bradley, Benjamin Hendrickson, and Curt Daniels each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Fontan physiology and liver cirrhosis

Complex congenital heart disease characterized by a single functioning ventricle was universally lethal until about 40 years ago when the Fontan procedure was developed [1]. The Fontan has evolved over the past several decades; however, intrinsic limitations exist even in the most ideal conditions [2]. Although this palliation relieves cyanosis and has allowed such patients to reach adulthood, alterations in systemic venous return can lead to elevated systemic venous pressure with chronic passive hepatic congestion and limitation of ventricular filling (due to high preload) thereby reducing cardiac output. Ultimately this can contribute to the development of congestive hepatopathy, liver cirrhosis (LC), and liver failure [3–5]. It has been suggested that chronic venous congestion in combination with low cardiac output produce hypoxic stress (exacerbated by perioperative insults) and acute or chronic injury that may trigger inflammation and subsequent liver fibrosis (or cirrhosis) [6].

Laboratory data in these patients usually demonstrate only mild abnormalities even when advanced cirrhosis is present [7], making assessment of liver dysfunction with tools such as the MELD score [8] of limited clinical value. Consequently, the search for a more meaningful measure of liver function in this population is critical and ongoing at the present time.

Fontan liver pathology

Liver involvement after the Fontan procedure was recognized in the early 1980s when cardiac cirrhosis following the Fontan procedure was first published in a case report [9]. This was followed by the first case series ($n=9$) of autopsied patients aged 1–24 years who had undergone a prior Fontan (survival <1–18 years) and showed that the majority had evidence of chronic passive hepatic congestion with half demonstrating centrilobular necrosis or cirrhosis [3]. Centrilobular fibrosis, by definition, affects the area around the central vein and extends along the sinusoids, and so is often referred to as sinusoidal fibrosis (Fig. 1) and has been postulated to result from increased central venous pressure. Subsequent research confirmed the presence of sinusoidal fibrosis in Fontan patients, suggesting that chronic passive congestion is responsible for the liver changes in Fontan patients [4, 10]. A later study predominantly involving pediatric patients reported both sinusoidal and portal-based fibrosis at autopsy, the latter of which is more commonly observed in inflammatory and/or acute hepatitis [11]. Subgroup analysis of patients with the shortest post-Fontan survival in this cohort revealed that Ishak fibrosis stage was associated with longer hospitalization prior to the Fontan and higher pre-Fontan right atrial pressure. This data suggests that there may be liver damage before the Fontan in many single-ventricle patients. The same group demonstrated similar findings (both sinusoidal and portal fibrosis) in an adolescent/young adult cohort (average age 19 years) that underwent liver biopsy after Fontan [12]. Univariate analysis in this cohort indicated that low platelet count correlated with higher fibrosis scores; however, no other variables including traditional measures of synthetic liver function were associated with degree of fibrosis. A subsequent larger postmortem study confirmed the presence of both sinusoidal and portal fibrosis and also showed that longer time to Fontan operation correlated with severity [13].

In total, this pathologic data suggests that liver disease in this population is the result of both pre- and post-Fontan liver damage, making it difficult to target specific insults. Although pathologic specimens can identify fibrosis/cirrhosis, this does not often correlate with the clinical picture or traditional measures of synthetic function, implying that liver structure and hepatic function are not directly related. This probably explains why common lab tests fail to accurately identify significant liver involvement by traditional measures, such as the MELD score [5].

Screening—no panacea

The lack of a reliable test(s) to determine severity and progression of liver disease in the Fontan population is a significant clinical problem. Several research groups have evaluated clinical parameters, laboratory values, imaging, and histopathologic specimens to try and determine what studies provide meaningful information about the state of the liver in Fontan patients. Blood tests that evaluate basic liver function including aminotransferases, alkaline phosphatase, bilirubin, coagulation markers, and protein levels have generally not correlated with degree of liver disease. Blood tests evaluating markers of liver fibrosis such as the AST/platelet ratio index (APRI) [14], AST/ALT ratio (AAR) [15–17], Forns index [18], cirrhosis discriminant score (CDS) [19], and Pohl score [20] have not correlated with the degree of liver involvement, nor has the FibroSURE panel (Fibrotest/ActiTest LabCorp, Burlington, NC, USA) which combines α 2-macroglobulin, haptoglobin, apo-lipoprotein A1, bilirubin, γ -glutamyl transferase (GGT), and alanine transaminase along with age and gender to measure fibrosis activity of the liver. Although laboratory data has not reliably correlated with histologic or image-based liver findings, there is some evidence that the model for end-stage liver disease excluding INR (MELD-IX) is associated with increased risk for cardiac mortality or transplantation in the Fontan population [21].

Pathologic series have identified liver fibrosis and cirrhosis, although initial studies did not correlate these findings with clinical characteristics [22]. When lab tests failed to correlate with degree of liver disease, many clinicians hoped that imaging would correctly identify the extent of liver involvement in Fontan patients, particularly given the knowledge that pathologic disease had been proven. Liver ultrasound, magnetic resonance imaging, and computed tomography have all been evaluated, as have measures of liver stiffness including transient elastography, acoustic radiation force impulse (ARFI), and shear wave elastography (SWE). Although liver imaging can identify abnormal liver architecture, this has not shown any reliable correlation with clinical findings, including liver or cardiac function. Similarly, measures of liver stiffness, which have shown to be abnormal in the Fontan population, did not correlate with blood markers or clinical features of liver disease (Table 1).

Several groups have sought to identify the correlation between markers of liver disease and degree of pathology; to date, 14 manuscripts [23–25, 26•, 27–36] have been published that outline institutional experiences with several clinical, laboratory, imaging, and histopathologic evaluation techniques in these patients. These studies are detailed in Table 1 and highlight that there is not yet a consistent reliable marker that can be used to detect the degree or clinical impact that liver disease has in the Fontan population.

Treatment

- There are no guidelines or widely accepted common practice recommendations for prevention or treatment of liver disease in Fontan patients. The most common approach requires consideration of therapies aimed at treating the underlying cardiac problem(s). Here, we review a reasonable approach to screening and prevention, as well as consideration of mechanical support and surgical options.

Screening and prevention

- When adult Fontan patients are transitioned from pediatric to adult care, they frequently have not had evaluation of their liver. Basic blood chemistries and liver function tests including aminotransferases, alkaline phosphatase, γ -glutamyl transferase (GGT), bilirubin, coagulation markers, albumin, and total protein should be assessed when this transition occurs. Although MELD scores traditionally underestimate the degree of liver disease in this population, MELD or MELD-IX scores should be calculated, because if elevated additional liver tests would be indicated. In the patient with known liver fibrosis or cirrhosis, it is reasonable to monitor MELD or MELD-IX at the predetermined frequency [8] depending on initial score: >25 weekly, 19–24 monthly, 11–18 every 3 months, and <10 yearly.
- The US Preventive Services Task Force (USPSTF) currently recommends screening for hepatitis C virus (HCV) infection in high-risk individuals. This includes current or prior injection drug use, blood transfusion recipient prior to 1992, long-term hemodialysis, incarceration, intranasal drug use, born to HCV-positive mother, getting an unregulated tattoo, and other percutaneous exposures [37]. Similar recommendations are in place for hepatitis B virus (HBV) screening [38]. The CHD population has been found to have a higher prevalence of HCV than the general population [39, 40]. Adult CHD patients, including those with a prior Fontan, have almost always had prior blood transfusions, and therefore, it is reasonable that they receive a minimum of one-time HCV and HBV screening once transitioned to an adult healthcare provider. If hepatitis B testing is negative and the patient has not received vaccination, it should be offered at this time.
- Patients with a prior Fontan palliation are at increased risk for the development of malignant and non-malignant liver lesions [4, 41, 42]. The American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver recommend surveillance in patients at high risk for developing hepatocellular carcinoma (HCC) which include those with cirrhosis from any cause and chronic HBV infection irrespective of cirrhosis [43, 44]. Given the increased risk of HCC as well as non-malignant liver lesions in the Fontan patient, it is reasonable to provide the same screening to this population. This would include a serum alpha fetoprotein (AFP) and liver imaging, typically ultrasound; however, computed tomography and magnetic resonance imaging may also be used. Interval surveillance for HCC in patients

with documented cirrhosis should take place every 6–12 months based on prior establishment of HCC median doubling time. It is unclear whether or not follow-up AFP and imaging surveillance should be done in the Fontan with isolated fibrosis.

- In the general population, a liver biopsy is indicated in those found to have parenchymal liver disease (such as fibrosis, cirrhosis, or mass) in order to determine the etiology and prognosis of liver disease [45]. In the Fontan population, it is not unreasonable to apply the same general criteria. This type of application would result in the majority of Fontan patients receiving a biopsy to confirm diagnosis and estimate prognosis of the liver disease. Biopsy results would play an important role in determining HCC follow-up if cirrhosis is indeed present.

Pharmacologic treatment

- There are no current medical therapies that are recommended for the treatment of fibrosis in the Fontan population. The renin-angiotensin system (RAS) is recognized as an important regulator of liver fibrosis, and there is evidence supporting anti-inflammatory and anti-fibrogenic effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in liver disease [46]. However, no similar studies have been performed in the Fontan population. Moreover, the complex hemodynamics in Fontan patients can be difficult to evaluate, and afterload-reducing agents such as these can have differential effects relative to central venous pressure and underlying ventricular function. Caution in the Fontan patient with liver disease must be taken, as use of this group of medications can precipitate hepato-renal syndrome. Therefore, these pharmacologic agents are not routinely recommended for this group of patients.

Assist devices

- Reports of ventricular assist device use in Fontan patients are rare and in general document technical aspects of the implant, clinical improvement, and a successful bridge to transplantation [47–50]. There is only one reported case using a total artificial heart in a single-ventricle Fontan patient who recovered and eventually went on to have heart transplant [51]. Given the paucity of data using ventricular assist devices in this group, a registry was established in 2013 to collect further data and experience [52]. Mechanical circulatory support was not designed for complex congenital cardiac conditions. However, there has been an increase in research efforts directed at understanding and developing a device that can safely be used in patients with a Fontan procedure [53–58]. There are potential advantages to restoring pulsatile flow to the lungs in this population. A pulmonary pump capable of restoring pulsatile flow, even in the face of elevated pulmonary vascular resistance, may provide a durable bridge to recovery or transplant for Fontan patients by reducing central venous pressures and congestion. To our knowledge, there has been no evaluation of transient effects

on the liver in this group of patients, information which could be useful in determining the “recoverability” of liver function and assist in determination of candidacy for orthotopic heart transplant (OHT) versus combined heart liver transplant (CHLT).

Transplant: heart versus combined heart liver transplant

- The Fontan procedure led to marked improvement in survival of single-ventricle patients, yet despite this, many patients develop late Fontan failure or systemic ventricular failure and are eventually considered for heart transplant. Given the ubiquitous nature of liver disease in Fontan patients, clinicians must determine whether or not OHT versus CHLT is required. Of all CHD, Fontan patients seem to have the highest risk for early morbidity and mortality with OHT [59–66]. In the last decade, advances in surgical technique, postoperative care, and immunosuppressive management may have led to some mild improvements in outcomes [62, 66–69].
- Currently, there are a small number of institutions in the United States that offer CHLT. In general, liver transplant is considered in any patient with cirrhosis and index complication (ascites, hepatic encephalopathy, or variceal hemorrhage) or hepatocellular dysfunction resulting in a MELD score ≥ 15 [70]. For those Fontan patients that have clear cirrhosis with end-stage liver and heart disease, there have been several small studies showing good outcomes for CHLT [71–78] (Table 2). Combined organ transplant outcomes are similar to those in single-organ transplant, irrespective of underlying etiology for CHLT [79–81]. However, as reviewed in this manuscript, determining the degree of liver disease in adult Fontan patients is difficult. We know that histologic presence of fibrosis is present in nearly all Fontan patients, and many have cirrhosis. Despite this, there is evidence that Fontan patients with cirrhosis have similar 1-year postoperative OHT mortality and liver function tests as compared to those with lesser degrees of liver involvement [82•]. The crux of the problem is defining when liver disease in the Fontan patient is irreversible and clinically significant. This problem exists not only in Fontan patients but also in other groups with cardiac cirrhosis, such as amyloid patients. Recently, in a non-congenital heart disease cohort, a liver risk score inclusive of biopsy results and the MELD-XI was found to be correlative with morbidity and mortality [83••]. Future research using this type of predictive tool, along with prospective validation, is required and holds prospect for a more inclusive model to evaluate this complex population when the question of transplant arises.

Conclusion

Adult patients with a prior Fontan procedure are a unique population requiring specialized care for the systemic nature of their disease. Clinicians need to focus on extra-cardiac manifestations of the late Fontan patient, including recognition and management of liver disease as reviewed here. There is no consensus regarding care for Fontan liver disease;

based on current available literature, our approach highlights basic screening, prevention, and ultimately consideration for isolated heart and combined heart-liver transplant if required for Fontan or ventricular failure. Predictive risk score models inclusive of clinical and pathologic components hold promise for evidence-based risk stratification and management options.

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Papers of particular interest, published recently, have been highlighted as

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- Of major importance

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Fig. 1.
Trichrome stain of liver biopsy showing modified Scheuer stage 3 sinusoidal fibrosis.
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Table 1

Pathologic series

Primary author, year	Year(s)	Total, <i>n</i> Men, <i>n</i>	Age mean (years)	Time from Fontan x(years)	Evaluation	Highlighted findings
Baek [23], 2010	1986–2003	139 86	19	12	<ul style="list-style-type: none"> Clinical features, labs (APRI, AAR, CDS, Pohl Score) Imaging: echocardiogram, cardiac CT, liver CT 	<ul style="list-style-type: none"> Compared patients with (<i>n</i>=57) and without (<i>n</i>=82) hepatic complications (LC, liver nodule, thrombocytopenia, hyperbilirubinemia) Hepatic complications more common with longer follow-up, AP type Fontan, poor ventricular function, absence Fontan fenestration, thrombus in Fontan, sinus node dysfunction, and arrhythmia Patients with CT evidence of LC had higher Forns index, APRI, AAR, and Pohl score and there was positive correlation between follow-up duration and Forns index/Pohl score
Furukawa [24], 2011	1994–2008	24 18	12	8	<ul style="list-style-type: none"> Clinical features, labs (type IV collagen, APRI) Post-Fontan catheterization for IVC pressure measurement 	<ul style="list-style-type: none"> Positive correlation between type IV collagen and post-Fontan IVC pressure No significant change in hepatologic markers at varying intervals post-Fontan
Guha [25], 2011		21 14	26	19	<ul style="list-style-type: none"> Clinical features, labs, echocardiogram Enhanced Liver Fibrosis Discriminant Score (ELF): TIMP-1, HA, PIIINP, plasma disappearance rate (PDR), R15 (ICG retention rate after 15 min) Indocyanine green (ICG) elimination by spectrophotometry 	<ul style="list-style-type: none"> Compared parameters in Fontan to cirrhotic (HCV, HAV) cohort, which at baseline was older, had lower NYHA FC, and higher blood pressure ICG clearance and retention were similar in Fontan and viral cirrhotic patients Positive correlation between ELF/PDR and ELF/R15 in cirrhotic, but not Fontan group—indicating “uncoupling” of liver structure and function
Ginde [26••], 2012	2009–2011	16 7	30	21	<ul style="list-style-type: none"> Labs (FibroSURE) Imaging: echocardiogram, cardiac MRI, liver CT Exercise stress test 	<ul style="list-style-type: none"> Elevated FibroSURE correlated with time since Fontan operation and presence of atrial arrhythmia All patients had some type of liver abnormality on imaging, with 81 % demonstrating nodularity Number of abnormal findings on liver CT correlated with length of time from Fontan

Primary author, year	Year(s)	Total, <i>n</i> Men, <i>n</i>	Age mean (years)	Time from Fontan x(years)	Evaluation	Highlighted findings
Elder [27], 2013	2001–2011	73 51	24	17	<ul style="list-style-type: none"> Clinical features, labs Imaging: echocardiogram, liver imaging (MRI, CT, US) VAST score ECG rhythm and QRS duration 	<ul style="list-style-type: none"> No lab findings correlated with presence of liver disease on CT Primary outcome was major adverse event (death, OHT, OHT listing, HCC), <i>n</i>=19 Adverse events more common if: older, increased time from Fontan, type of Fontan, if pacemaker present, reduced systolic function, wider QRS, total protein, albumin, platelet count, alkaline phosphatase, creatinine, or the following liver findings: nodular liver contour, clinical features of portal hypertension, varices, ascites, and splenomegaly VAST score >2 was associated with ninefold increase in adverse events
Kaulitz [28], 2013		51	10 16	11	<ul style="list-style-type: none"> Clinical features, labs Imaging: liver ultrasound Post-Fontan catheterization 	<ul style="list-style-type: none"> GGT correlated with age at follow-up (2 follow-up intervals, average age 10 and 16 years, respectively) Liver nodularity was seen in patients with longer postoperative follow-up Post-Fontan hemodynamics correlated with initial GGT, but not late follow-up GGT There was no correlation between ultrasound liver findings and labs, post-Fontan hemodynamics, or ventricular morphology
Wallihan [29], 2013	2006–2011	42 17	22	20	<ul style="list-style-type: none"> Labs (<i>n</i>=14) Imaging: liver MRI or CT 	<ul style="list-style-type: none"> No relationship between Fontan duration and presence of hypervascular liver nodules or liver function tests Abnormal liver enhancement correlated with low protein levels and curiously, with low total bilirubin and high platelet levels Higher alkaline phosphates levels correlated with imaging findings of cirrhosis
Kutty [30], 014		41 29	14	11	<ul style="list-style-type: none"> Clinical features Imaging: liver ultrasound and shear wave elastography Cardiac catheterization (<i>n</i>=16), liver biopsy (<i>n</i>=10) 	<ul style="list-style-type: none"> Compared Fontan patients to normal controls where hepatic stiffness was greater with histopathology fibrosis score 2 Hepatic stiffness, celiac artery resistive index, and superior mesenteric artery resistive index, and celiac artery pulsatility index were increased in Fontan vs. control subjects SMA acceleration index, velocity time integral, and main portal vein flow were lower in Fontan patients;

Primary author, year	Year(s)	Total, <i>n</i> Men, <i>n</i>	Age mean (years)	Time from Fontan x(years)	Evaluation	Highlighted findings
Ofei [31], 2014	2010–2013	10 5	33	23	<ul style="list-style-type: none"> Labs (<i>n</i>=7, FibroSURE) Imaging g: echocardiogram, liver imaging (MRI, CT, US) Cardiac catheterization, liver biopsy 	<p>main portal vein diameter positive correlation hepatic stiffness, age, duration Fontan</p> <ul style="list-style-type: none"> Ventricular end diastolic pressure and PCWP correlated with shear wave elastography No relationship between FibroSURE and liver biopsy findings No relationship between ventricular end diastolic pressure and degree of fibrosis
Suraj [32], 2014	2010–2013	16	23	18	<ul style="list-style-type: none"> Labs (<i>n</i>=8) Liver MRI with MRE 	<ul style="list-style-type: none"> All patient demonstrated abnormal liver stiffness Liver stiffness was positively correlated with time from Fontan procedure Liver stiffness was greater in AP versus TCPC Fontan possibly due to difference in time from Fontan (15 vs. 25 years)
Wallihan [33], 2014	2011–2013	15 6	18	17	<ul style="list-style-type: none"> Labs Imaging: cardiac MRI, liver MRI with MRE 	<ul style="list-style-type: none"> Negative correlation between cardiac index and Fontan duration, cardiac index and liver stiffness, and EF and liver stiffness No significant lab abnormalities
Won Yoo [34], 2014	2011–2012	46 24	18	14	<ul style="list-style-type: none"> Clinical features, labs (APRI) Imaging: echocardiogram, liver ultrasound, and transient elastography 	<ul style="list-style-type: none"> Compared Fontan patients to right side heart failure patients (RHF; <i>n</i>=26), showing increased total bilirubin, INR, PTT in Fontan vs. RHF and significantly higher liver stiffness in Fontan vs. RHF In the Fontan group, current age, age of Fontan completion, and IVC diameter correlated with liver stiffness, whereas Fontan type, ejection fraction, and Fontan duration did not APRI and total bilirubin correlated positively with liver stiffness whereas white count and albumin had an inverse correlation with liver stiffness; age at Fontan completion and total bilirubin were independent factors associated with liver stiffness as were spleen size and ultrasound liver findings correlated with degree of liver stiffness
Wu [35••], 2014	2011–2012	45 23	13	10	<ul style="list-style-type: none"> Clinical features, labs (APRI, FibroSURE) 	<ul style="list-style-type: none"> Positive correlation between liver stiffness and age, time since Fontan, and platelet count

Primary author, year	Year(s)	Total, <i>n</i> Men, <i>n</i>	Age mean (years)	Time from Fontan x(years)	Evaluation	Highlighted findings
Wu [36], 2015		68 36	23	18	<ul style="list-style-type: none"> Imaging: liver ultrasound and transient elastography Cardiac catheterization Liver biopsy (<i>n</i>=10) 	<ul style="list-style-type: none"> No correlation between liver function tests and liver stiffness, however liver stiffness associated with more severe fibrosis Liver stiffness was strongly associated with the following hemodynamics: Fontan pressure, cardiac index, systemic arterial oxygen saturation, and PVR—all were predictors of liver stiffness either in multiple regression or overall analysis Centrilobular fibrosis was less prominent in biventricular versus dominant right or left ventricle or those with hepatitis C infection Portal fibrosis correlated with alkaline phosphatase and mode of biopsy Overall, no significant correlation between fibrosis, hemodynamics, labs, and clinical outcomes

Metavir scoring system of fibrosis stages=F0 no fibrosis, F1 portal fibrosis, F2 bridging fibrosis with few septa, F3 bridging fibrosis with many septa, F4 cirrhosis

AAR AST/ALT ratio, *ALT* alanine aminotransferase, *APRI* AST/platelet ratio, *AST* aspartate aminotransferase, *CDS* cirrhosis discriminant score, *CT* computed tomography, *EF* ejection fraction, *FibroSURE panel* α 2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, age, and gender, *GGT* gamma-glutamyl transferase, *HAV* hepatitis A virus, *HCV* hepatitis C virus, *INR* international normalized ratio, *LC* liver cirrhosis, *MRE* magnetic resonance elastography, *MRI* magnetic resonance imaging, *PCWP* pulmonary capillary wedge pressure, *Pohl Score* marker of fibrosis based on AST, ALT platelet count; *PTT* prothrombin platin time, *RHIF* right heart failure, *TCP* total cavo-pulmonary connection, *US* ultrasound, *VAST Score* varices, ascites, splenomegaly, thrombocytopenia (<150)

Table 2

Small studies showing outcomes for CHLT

Author, year	Time frame	Total, <i>n</i> Fontan, <i>n</i>	Age(s) or mean ±SD (years)	Time from Fontan (years)	Study description	Pre-transplant findings	Highlighted findings
Aduri [71], 2014	1997–2013	26 6	46±13	21	• Single center case series	• Liver evaluation: liver US, liver function tests, ±liver biopsy	• Survival rates at 1 and 5 years: 87 ±7 %, 83±8 %
					• Heart failure: NICM (18) ICM, CHD (6), ICM (2)	• Creatinine (mg/dL) 1.7±0.9	• No acute graft failure
					• Liver failure: cardiac cirrhosis (23), HCV (2), AIAT (1)	• Bilirubin (mg/dL) 1.4±1.0	• Freedom from rejection 88.5 % (23/26)
						• INR 1.8±1.0	• Amyloidosis not main listing indication
						• PRA (mean %) 6.3±19.3	
						• MELD score: 16.8±6.8	
Raichlin [72], 2014		1 1	18		• Case report of HLHS with CHF/ cardiac cirrhosis	• Donor: EBV positive. Positive T and B complement dependent cross match	• No acute graft rejection
							• Patient developed PTLD 9 months post-transplant, recovered
							• Doing well 2 years post- CHLT without further rejection
Hollander [73], 2013	2006–2010	3 2	17, 14, 7	13, 7	• Case series, all patients single ventricle	• Cirrhosis diagnoses: direct visualization, appearance on CT, MRI, and biopsy findings	• All patients alive at 2, 3, and 5 years post-CHLT
					• Diagnosis: tricuspid atresia post-Fontan (2), DORV with BTS (1)	• No HLA antibodies in Fontan patients	• No rejection in Fontan patients; AMR in DORV patient
						• DORV highly sensitized to class I antibodies	• CHLT performed successfully in patient with situs abnormalities and interrupted inferior vena cava
Nagpal [74], 2013	2006–2012	5 2	15, 50, 58, 59, 64		• Case series	• Creatinine (mg/dL): 1.34–2	• All patients alive, median follow-up 38 (range 11–67) months
						• Liver pathology: HCV (4), amyloidosis (1)	

Author, year	Time frame	Total, <i>n</i> Fontan, <i>n</i>	Age(s) or mean ±SD (years)	Time from Fontan (years)	Study description	Pre-transplant findings	Highlighted findings
					<ul style="list-style-type: none">Diagnoses: CHD (2), amyloidosis (1), NICM (1), HCM (1)	<ul style="list-style-type: none">Cardiac Index (L/min/m²) 2.0–3.4Pulmonary vascular resistance (WU): 1–2Ejection fraction (%): 20–50TAH in patient with HOCMMELD score: 11, 15, 19, 25 (2)	<ul style="list-style-type: none">No episodes of rejection
Vallabhajosyula [75], 2012		1 1	62	30	<ul style="list-style-type: none">Case reportDiagnosis: unbalanced atrioventricular canal with heterotaxy	<ul style="list-style-type: none">Preoperative decompensated heart failure, bridging fibrosis, and protein losing enteropathy 5 sternotomies prior to CHLT	<ul style="list-style-type: none">Describes complicated operative approach and extensive reconstruction for Fontan patient with situs and vascular anomalies
						Childs-Pugh class: A (1), B (4)	<ul style="list-style-type: none">Patient alive and asymptomatic 2 years post-transplant with no episodes of rejection or surgical complication
Vallabhajosyula [76], 2012	2008–2012	14 4			<ul style="list-style-type: none">Case series (abstract)Fontan (4) vs. other CHD (10)All patients had hepatic bridging fibrosis	<ul style="list-style-type: none">Hemodynamics (mmHg): RA 21 vs. 15, PCWP 20 vs. 16.5, PVR (WU): 2.7 vs. 2.6Cardiac index (L/min/m²): 1.9 vs. 2.5Ejection Fraction (%): 29 vs. 33, (<i>P</i>=0.04)INR (1.4 vs. 2.3), bilirubin (mg/dL) (1.1 vs. 1.9)MELD score (14.3 vs. 15.7)	<ul style="list-style-type: none">No graft failure or rejection in Fontan patientsAll Fontan patients alive 1 year post-transplant

Author, year	Time frame	Total, <i>n</i> Fontan, <i>n</i>	Age(s) or mean ±SD (years)	Time from Fontan (years)	Study description	Pre-transplant findings	Highlighted findings
Hill [77], 2012	2006–2010	3 2	14, 17, 7	•	• Single center case series • Fontan diagnoses (2): double inlet and heterotaxy single ventricles • Other (1): double outlet right ventricle	• All had abnormal liver function tests and cirrhosis by liver biopsy • PELD score: 9, 14 (5 in non Fontan) • PRA: 0 % (2 patients), 26 % (1 patient)	• Pediatric CHD patients with successful en bloc CHLT • No acute graft failure • All 3 alive and without evidence of rejection 4 years post-transplant
Horai [78], 2011		1 1	21	15 •	• Case report • Fontan diagnosis: DORV unbalanced atrioventricular canal with heterotaxy, Other: dextrocardia, bilateral SVC, IVC interruption, hemi-azygos continuation	• Preoperative decompensated heart failure, liver cirrhosis on biopsy	• Successful CHLT in Fontan patient with situs abnormalities requiring rotated implantation and SVC reconstruction • Alive and well 2 years post-transplant

AIAT alpha 1-antitrypsin deficiency, *BTS* Blaylock Taussig shunt, *CHD* congenital heart disease, *CHLT* combined heart liver transplant, *CT* computed tomography, *DORV* double outlet right ventricle, *EBV* Epstein Barr virus, *HLA* human leukocyte antigen, *HLHS* hypoplastic left heart syndrome, *HCM* hypertrophic cardiomyopathy, *HCV* hepatitis C virus, *ICM* ischemic cardiomyopathy, *IHT* isolated heart transplant, *ILT* isolated liver transplant, *IVC* inferior vena cava, *MELD* model for end stage liver disease, *MRI* magnetic resonance imaging, *NICM* non-ischemic cardiomyopathy, *PELD* pediatric model for end-stage liver disease, *PCWP* pulmonary capillary wedge pressure, *PVR* pulmonary vascular resistance, *PRA* panel reactive antibody, *PTLD* post-transplant lymphoproliferative disorder, *RA* right atrium, *RCM* restrictive cardiomyopathy, *SVC* superior vena cava, *TAH* total artificial heart, *UNOS* United Network for Organ Sharing, *US* ultrasound, *WU* woods units