Griffiths Eric (Orcid ID: 0000-0001-7679-5151)
Carlo Waldemar F (Orcid ID: 0000-0002-5460-9079)
Nandi Deipanjan (Orcid ID: 0000-0003-0144-1433)
Zangwill Steven (Orcid ID: 0000-0002-1838-4714)
Friedland-Little Joshua M (Orcid ID: 0000-0001-6161-7651)
West Shawn C. (Orcid ID: 0000-0002-4369-4394)
Alejos Juan (Orcid ID: 0000-0002-7653-6114)



# Fontan Associated Liver Disease after Heart Transplant

Eric R. Griffiths MD, Pediatric Cardiothoracic Surgery, University of Utah, Primary Children's Hospital, ORCID: 0000-0001-7679-5151

Linda M. Lambert APRN, Pediatric Cardiothoracic Surgery, University of Utah, Primary Children's Hospital, ORCID: 0000-0002-8572-9874

Zhining Ou MS, Division of Epidemiology, Department of Internal Medicine, University of Utah, ORCID: 0000-0002-7353-6872

Akraam Shaaban MD, Department of Radiology, University of Utah, ORCID: 0000-0002-7748-1258

Maryam Rezvani MD, Department of Radiology, University of Utah, ORCID: 0000-0002-2765-8414

Waldemar F Carlo MD, Department of Pediatrics, University of Alabama Birmingham, ORCID: 0000-0002-5460-9079

Kurt R. Schumacher MD MS, Pediatric Cardiology, C.S. Mott Children's Hospital, University of Michigan ORCID - 0000-0001-8659-736X

Frank DiPaola MD, Department of Pediatrics, Division of Hepatology, University of Virginia Children's Hospital, ORCID: 0000-0003-2344-626X

Matthew J. O'Connor MD, Pediatric Cardiology, Children's Hospital of Philadelphia, University of Pennsylvania, ORCID: 0000-0003-3012-5464

Deipanjan Nandi, MD, MSc, Pediatric Cardiology, Nationwide Children's Hospital, The Ohio State University, ORICD: 0000-0003-0144-1433

Steven Zangwill MD, Pediatric Cardiology, Phoenix Children's Hospital, ORCID: 0000-0002-1838-4714

Michael A. McCulloch MD, Pediatric Cardiology, University of Virginia Children's Hospital, ORCID: 0000-0003-4837-6819

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/petr.14435

Joshua M. Friedland-Little MD, Pediatric Cardiology, Seattle Children's Hospital, University of Washington, Seattle, WA ORCID 0000-0001-6161-7651

Shawn C. West MD, MSc Pediatric Cardiology, Children's Hospital of Pittsburg, University of Pittsburg Medical Center, ORCID: 0000-0002-4369-4394

Teresa M. Lee MD, MS Pediatric Cardiology, Columbia University Medical Center, New York, NY ORCID: 0000-0001-7409-6832

Juan C. Alejos MD, Pediatric Cardiology UCLA Mattel Children's Hospital ORCID: 0000-0002-7653-6114

Sharon Chen MD, MPH, Pediatric Cardiology, Stanford University, ORCID 0000-0002-0576-0856

Kimberly M. Molina MD, Division of Pediatric Cardiology, University of Utah, Primary Children's Hospital, ORCID ID: 0000-0002-8676-7960

**Address for Correspondence**

Eric R. Griffiths, MD

Section of Pediatric Cardiothoracic Surgery

Primary Children's Hospital

100 N Mario Capecchi Dr

Tel: 801-662-5578

FAX: 801-662-5571

Email: Eric.griffiths@hsc.utah.edu

**Word count: 2985**

**Abbreviations**

| | |
|---|---|
| AST | Aspartate aminotransferase |
| ALT | Alanine aminotransferase |
| AV canal | atrioventricular canal |
| CHLT | Combined heart liver transplant |
| Cr | Creatinine |
| DILV | Double inlet left ventricle |
| DORV | Double outlet right ventricle |
| FALD | Fontan associated liver disease |
| HLHS | Hypoplastic left heart syndrome |
| INR | International Normalized Ratio |
| Kpa | Kilopascals |
| LVEF | Left ventricle ejection fraction |
| MR-E | Magnetic Resonance elastography |
| PCWP | Pulmonary capillary wedge pressure |
| PLE | Protein losing enteropathy |
| US-E | Ultrasound elastography |

**Data statement**

Data available on request from the authors.

**Fontan Associated Liver Disease after Heart Transplant**

Fontan associated liver disease (FALD) is a late sequela of single ventricle palliation. The relatively intact synthetic hepatic function in the face of abnormal fibrotic liver imaging is unique and complicates the grading and prognosis of FALD compared to other forms of cirrhosis where synthetic function correlates with imaging abnormalities which, in turn, correlate with survival. In this setting, heart transplant teams evaluating children with failing Fontan circulation are tasked with determining the possible negative impact of FALD and if a combined heart-liver transplant (CHLT) treatment pathway should be pursued.

Because there is no clear definition or grading system of FALD it is hard to extrapolate findings from the literature to the bedside. Multiple single center and a Pediatric Heart Transplant Society registry paper have reported favorable outcomes with heart transplant alone[1]. Several retrospective studies even demonstrated that liver cirrhosis on pre-heart transplant imaging did not affect survival at 1 year[2-4]. However, these studies did not comment on the exclusion of patients due to liver disease. Other centers have advocated for CHLT in older patients with evidence of cirrhosis. They have demonstrated that Fontan patients can safely undergo combined heart-liver transplant with similar short-term outcomes to heart transplant alone.[5-7]

It is largely unknown to what degree the liver can recover after heart transplant in Fontan patients.[8, 9] Case reports and small series suggest there is some improvement.[8, 10] Adults with acquired heart disease who undergo transplantation recover hepatic function when the congestive hepatopathy is alleviated.[11] It is unclear if these findings are translatable to the Fontan population

since the etiology of the liver dysfunction seems to be more complex. There are currently no guidelines for monitoring FALD after heart transplant especially given the concerns for cancer and precancerous nodules that have been identified in patients with FALD.[12, 13]

In an effort to better understand the role of FALD in patients with a Fontan circulation who are being considered for transplantation, we compared the post-transplant imaging and laboratory measurements of liver function with the pre-transplant studies in Fontan patients undergoing heart only transplant. We sought to identify pre-transplant characteristics that were predictors of post-transplant mortality. Additionally, we also sought to characterize the post-heart transplant function of the liver to identify any improvement or deterioration in function.

**Methods**

We conducted a multicenter, retrospective review of patients with a single ventricle who underwent palliation with a Fontan circulation and subsequent heart transplant from January 2000 to June 2019. Twelve pediatric centers were involved in the study. IRB approval was obtained under a waiver of consent at each participating site. Patients with a history of viral hepatitis or other diagnosed non-FALD causes of liver cirrhosis were excluded. We collected demographic data, pre- and post-heart transplant laboratory data, as well as pathology, endoscopy, echocardiography, cardiac catheterization, and hepatic imaging study results. Ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) images were sent to the primary study site for evaluation by local radiologists.

We focused on the following laboratory values relevant to hepatic function: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, platelets, creatinine, and international normalized ration (INR). Patients taking warfarin were excluded

from the INR analysis. The values closest to (and before) the date of transplant were used as the pre-transplant values for this analysis. Post-transplant values were collected at two time points, 24-48 hours after transplant and one-year follow-up.

Echocardiographic and cardiac catheterization data were recorded from the studies closest to the date of transplant. Similar post-transplant data were recorded from the last available data. Hepatic wedge pressures only were collected.

Liver biopsy reports were included, but description of the findings and amount of fibrosis were inconsistent and typical grading scales for fibrosis such as the Ishak or Metavir were rarely used. Therefore, for this analysis, we divided patients into 2 groups based on the presence or absence of bridging fibrosis as indicated in the pathology reports. Pre and post-transplant endoscopy reports were reviewed for evidence of varices.

All pre- and post-heart transplant US, CT, and MRI were reviewed by two radiologists fellowship-trained in abdominal imaging. Not all patients had equivalent pre- and post-heart transplant imaging. The liver was assessed for morphological changes of cirrhosis including nodular contour, elevated caudate lobe to right lobe ratio, liver parenchymal abnormalities (changes in parenchymal echogenicity on ultrasound, abnormal signal intensity on T1, T2 and diffusion-weighted images on MRI), and delayed enhancement on late phase contrast enhanced CT or MRI (indicating the presence of fibrosis). Evidence of liver congestion was also documented (dilated inferior vena cava (IVC) and hepatic veins and abnormal early enhancement on contrast-enhanced CT or MRI). The liver was further assessed for the presence of

parenchymal nodules, and the nodules were assessed for size, location, signal intensity on T1 and T2 MRI, and enhancement pattern on contrast-enhanced CT or MRI. Findings of portal hypertension, including splenomegaly, portosystemic collaterals and ascites, were recorded. The radiologists divided the patients into two cohorts based on imaging findings: advanced and non-advanced fibrosis. Advanced fibrosis was based on by nodular contour, abnormal delayed enhancement and findings of portal hypertension. Dilated veins and abnormal early enhancement (nutmeg) without other features was called "non-advanced fibrosis." This allowed for comparative analysis for prediction of adverse outcomes or death.

Ultrasound elastography (US-E) reports were also inconsistent due to differences in hardware and techniques that evolved over time and prohibited comparisons of patient numerical values. Most reports were interpreted using the 2015 Society of Radiologists in Ultrasound Consensus Conference Statement where patients had low sheer wave elastography (SWE) values consistent with no clinically significant fibrosis (corresponding with METAVIR <F2), indeterminate (F2-F3), or advanced fibrosis/cirrhosis (F3-F4).[14] Therefore, patients were identified as having no significant fibrosis, indeterminate fibrosis, or advanced fibrosis.

Statistical Analysis

We summarized demographics, lab, hemodynamic outcomes of interest, and clinical diagnosis from radiology imaging using median, inter-quartile range (IQR), and count, percentage for continuous and categorical variables, respectively. We compared lab variables between the pre-transplant vs 24 - 48 hour post-transplant, or vs 1 year post-transplant time points using Wilcoxon signed ranks test. We assessed the association between mortality and demographics, or between mortality and the changes of lab measures from pre-transplant to 24–48 hour post-

transplant using univariate Cox proportional hazard regressions with center as a random effect. The Cox proportional hazard regressions included a frailty term to account for heterogeneity in outcomes due to multiple centers Hazard Ratios (HRs), 95% confidence intervals (CIs) and p-values were reported from the models. [15] Statistical significance was assessed at the 0.05 level. Statistical analyses were implemented using R v. 3.6.0 (R Core Team, 2019).[15]

## Results

### Demographics

Of the 156 patients identified across 12 institutions, 35% were female (Table 1). Extracardiac Fontan was the most common type 98 (64%) followed by lateral tunnel 53 (35%), and aortopulmonary 2 (1%) with 3 unknowns. The median age at the time of the Fontan operation was 3.3 years (IQR 2.25, 4.85). Protein losing enteropathy (PLE) and plastic bronchitis were present in 58 (37%) and 15 (10%) of patients, respectively. The mode of Fontan failure leading to transplant was characterized as ventricular dysfunction in 76 (49%), PLE in 48 (31%), plastic bronchitis in 15 (10%), and other in 17 (11%). A hepatologist/gastroenterologist followed 37 patients (24%) prior to transplantation.

The median age at transplant was 13.6 years (IQR 7.8, 17.2). At the time of transplant, 93 (60%) were listed as status 1A, 37 (24%) as status 1B, 24 (16%) as status 2 and two unknowns. The median time from the Fontan operation to heart transplant was 9.3 years (IQR 3.2, 13.4) with a median follow up time post-heart transplant of 3 years (IQR 0.7, 5.0). Post-heart transplant resolution of PLE was documented in 48 of the 57 pre-transplant PLE patients (84%, 1 patient

had no documentation) and resolution of plastic bronchitis in 14 of the 15 pre-transplant plastic bronchitis patients (93%).



Laboratory Results

The median (IQR) for pre- and post-transplant laboratory values are listed in Table 2. There were significant increases in the pre-transplant to early post-transplant values for creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin, while the albumin levels and platelet counts decreased. By one year after transplant, AST, and bilirubin were significantly lower than pre-transplant values, while the platelet count and albumin were significantly higher. The INR in patients not taking warfarin was not elevated and remained similar across time points.

Hemodynamics

After heart transplant, there was an expected increase in ejection fraction, cardiac output and improvement in central venous and pulmonary venous wedge pressures (Table 3). The pre-transplant hepatic wedge pressure was measured in 37 patients with a median value of 17 mm Hg and was only measured in two patients after transplantation.

Pathology

Only 29 patients underwent liver biopsy between the Fontan operation and heart transplant and four patients had post-heart transplant liver biopsies. All patients had evidence of hepatic disease ranging from mild patchy sinusoidal dilation and mild portal fibrosis to bridging fibrosis with regenerative nodules. Mild portal fibrosis was noted in 12 patients while 17 patients had more

severe disease characterized by bridging fibrosis. Of the three patients with a post-transplant liver biopsy, one had a lymphoproliferative disorder diagnosed with no other mention of liver parenchymal changes, one had focal nodular hyperplasia in a liver mass, and one had patchy portal fibrosis two years after heart transplant. None of the three patients had biopsies prior to transplant for comparison.

Endoscopy

Of the 28 patients (18%) who underwent pre-transplant endoscopy, 15 (54%) were entirely normal. Only five patients had evidence of varices: three were grade 1, and two were grade 2. Of the 10 patients with post-transplant endoscopy, none had varices. None of the four patients with both pre- and post-transplant endoscopy had any findings of varices or portal gastropathy either pre- or post-transplant.

Imaging

Pre- and post-transplant imaging was not standardized either between or within participating sites. The timing of imaging relative to transplant varied from weeks to years. Of the 156 patients in the study only 119 (76%) had imaging available for review. Pre-transplant US showed advanced fibrosis on 33% (30/91) of patients. Post-transplant US had advanced fibrosis on 49% (27/55) and 15 patients had both pre- and post-transplant fibrosis. (Table 4) CT or MRI evidence of advanced fibrosis was found in 70% (31/44) pre-transplant patients and 58% (22/38) post-transplant, with 11 patients having fibrosis both before and after transplant. Advanced fibrosis using any modality (US/CT/MRI) was found in 50% (49/98) pre-transplant patients,

54% (38/70) post-transplant patients with 48% (28/58) having both pre- and post-transplant fibrosis.

There were 11 patients with CT/MRI imaging 6 months to 1-year post-transplant. Seven patients had nodular livers and were classified as advanced fibrosis. However, IVC and/or hepatic vein dilation was only seen in 2 patients. Only 3 of the patients had pre-transplant CT/MRI available for comparison. All showed nodularity and advanced fibrosis both pre and post-transplant. There were 15 patients with CT/MRI imaging beyond 1 year of which 7 patients had nodular appearance with advanced fibrosis. IVC and hepatic vein dilation was only seen in 2 patients. Only 4 patients had pre and post-transplant imaging available for comparison. Three of which had continued advanced fibrosis.

Looking specifically at the 7 patients with both pre- and post-transplant MRI showed one scan was performed 2 weeks post-transplant which demonstrated unchanged fibrosis. The remaining six MRIs were performed 3 months to 18 months post-transplant. Fibrotic changes persisted in all studies but the livers appeared generally smaller and/or less congested by caudate lobe to right lobe ratios or lacked IVC dilation.

Liver nodules were seen in 30 patients by one or more imaging modality: 13% (11/87) patients pre-transplant and 25% (13/52) post-transplant by US (Table 5a); 26% (11/42) pre-transplant and 29% (10/34) of post-transplant by CT/MRI. Of the 30 patients with liver nodules, 13 had 1-5 nodules, one had 6-10 nodules, and 16 had > 10 nodules (Table 5b). All nodules showed the

hypervascularity typical of regenerative nodules occurring in the setting of vascular liver disorders. The number of nodules decreased in three patients after transplant. Portosystemic collaterals were identified on CT/MRI in 10 patients before transplant and five patients after transplant.

Elastography was performed in 23 patients: US in 19 patients and MRI in 4 patients. In the US elastography group, 11/15 patients had indeterminate (F2-F3) fibrosis, four had advanced (F4) fibrosis, and none had clinically insignificant fibrosis (<F2) before transplant. All four of the patients with US elastography after transplant had serial exams: one had variable results over time, including no fibrosis→fibrosis→ no fibrosis over the course of 3 years; one improved over the course of a year from indeterminate to no fibrosis; and two remained indeterminate on annual exams. The one patient with US elastography both before and after transplant showed improvement from fibrosis to no evidence of fibrosis. MRI elastography (MR-E) was performed in four patients: two before transplant, one patient after transplant, and one with both pre- and post-transplant studies. All four of these patients demonstrated increased stiffness (4.4-7 Kilopascals). The one patient with serial imaging had decreased liver stiffness (5.9 to 3.1 Kpa) 18 months after transplant.

Death

There were 31 (20%, 31/156) deaths, among all participating sites with six occurring within 48 hours post-transplant. The median time from transplant to death was 0.5 years (IQR 0.0, 3.6). The five-year survival was 73% (Figure 1). Deaths were related to cardiac causes in 61%, (19/31), infection in 16%, (5/31), and post-transplant lymphoproliferative disorder (PTLD) in 2

(6.5%). Death from a gastrointestinal bleed, pulmonary venous malformation and portal hypertension, renal failure, stroke and unknown cause occurred in one patient each. The patient who died from a gastrointestinal bleed did not undergo an endoscopy pre or post-transplant.

No pre-transplant demographic factors were associated with a higher post-transplant mortality (Table 6). Higher total bilirubin (HR: 1.12, 95% CI: 1.03, 1.21; p=0.007) was associated with increased post-transplant mortality while higher platelet count was associated with decreased post-transplant mortality (HR: 0.49, 95% CI: 0.24, 0.97; p=0.041). Higher immediate post-op (24-48 hours) creatinine, AST, ALT and INR elevations were associated with increased post-transplant mortality. (Table 7) Pre-transplant fibrosis on any imaging modality was not associated with post-transplant mortality (Table 6).

## Discussion

This study represents the largest detailed retrospective review of Fontan patients who have undergone cardiac transplant and provides insight into the impact of FALD at the time of transplant. We recognize that the true incidence of FALD is difficult to identify since there is no formal definition of the disease. Despite this, our study provides multicenter, real-world laboratory and imaging assessment of the liver for Fontan patients undergoing transplant that are likely broadly applicable. The presence of advanced fibrosis, identified on 50% of the patients with pre-operative imaging, as evidenced by nodular liver contour, abnormal delayed enhancement and portal hypertension was not a marker of a higher mortality at transplant. This finding is consistent with other studies that found mortality was not impacted by pre-transplant cirrhosis. We were limited in understanding the course of disease progression by imaging

studies by the relatively few studies obtained, variability in modality of imaging, and no standard imaging time points. In spite of the small numbers, elastography showed there was no worsening of FALD, and even some improvement in two patients. The number of liver nodules decreased in three patients suggesting possible hepatic healing after transplantation.

The rare endoscopic findings of only low-grade varices amongst this cohort may suggest these patients are at low risk for variceal bleeding especially considering the selection bias towards these patients having worse liver disease. The development and behavior of varices in FALD may differ from that of cirrhosis given the elevated central venous pressures present in the Fontan circulation. As variceal bleeding is a major cause of mortality in cirrhosis, it is important to determine any differences and similarities which could impact long-term survival of all Fontan patients.

Abnormal higher pre-transplant total bilirubin predicted mortality; however, most lab values were normal or mildly abnormal consistent with the clinical picture of FALD. Half of the patients with liver imaging had evidence of advanced fibrosis with largely normal labs. Although elevated total bilirubin indicates more advanced illness or liver disease, the median and interquartile range of the cohort falls within normal values leaving the question unanswered as to how high a value is prohibitive. Higher platelet levels were found to be protective and may indicate less splenic involvement from portal hypertension. Immediate post-transplant increases in creatinine, AST, ALT, and INR were risk factors for mortality. The question of whether these are general manifestations that can be seen immediately post-transplant (post-cardiopulmonary bypass, primary graft failure, low cardiac output, for example) or evidence of liver insufficiency secondary to FALD remains unanswered. The normalization of post-

transplant lab values overtime, however, is reassuring and may indicate some degree of hepatic regenerative ability that allows recovery as the cardiogenic component of liver congestion is alleviated. Furthermore, there were few late deaths in a setting of a median follow up of 3 years with gastrointestinal bleeding and portal HTN/pulmonary venous malformation in 1 patient each as the only causes of death with a possible link to hepatic dysfunction.

Hepatocellular carcinoma has been reported in long term survivors of the Fontan circulation. There were no cases of hepatocellular carcinoma in this cohort. Therefore, we can provide little guidance on possible surveillance strategies in Fontan patients after transplant. The median age of our cohort is 13 years so these results may not be extrapolated to adults with Fontan circulation. These older patients have already been selected out as a "healthier" Fontan patient, due to their advanced age at the time of transplant evaluation. It is unclear if their livers are actually healthier, retaining regenerative abilities or conversely, near decompensation requiring replacement. A similar review of older patients with a Fontan followed at adult congenital heart centers who have undergone heart transplant could help answer this question.

Limitations

Our retrospective study has several limitations. It is unclear how well this cohort represents the overall population of failing Fontan patients being evaluated for heart transplant. There is a strong potential for selection bias as those with worse FALD may have not been referred for transplant, underwent CHLT, or died on the wait list. This is countered by the fact that many Fontan patients underwent transplant in the early 2000s prior to FALD being recognized thereby potentially negating any selection bias. The lack of standardized imaging protocols, either pre-transplant or post-transplant, limits our ability to define the course of FALD post-transplant. The

imaging practice both pre and post-op may be inherently biased either by institutional practice or generated by patient specific concerns. We tried to account for variability in protocols and imaging quality by having central radiologists review the liver imaging. The average age of cohort is 13 years old. It is unclear how well these findings can be extrapolated to an older Fontan cohort. The follow-up time for some patients was relatively short. As some of the patients were transplanted in late adolescence, the transfer of care to an adult center potentially limited follow-up by the initial pediatric program. Futures studies should include the participation of adult programs where Fontan transplant patients are followed.

## Conclusion

For failing Fontan patients undergoing heart transplant evaluation, abnormal liver synthetic function may indicate increased risk of early post-transplant mortality. Additionally, advanced fibrosis on liver imaging may not be an adequate predictor of transplant mortality and its impact remains poorly defined. Limited post-heart transplant liver imaging shows hepatic fibrosis remains present but with some evidence of decongestion. A prospective MRI study of Fontan patients post-transplant could better define the post-transplant hepatic changes seen and need for ongoing surveillance either short or long term.

## Author Contributions

Each author contributed through study design, data analysis, or writing of the manuscript to warrant authorship. The authors report no financial conflicts of interest.

Table 1. Demographics and Clinical Variables

| | N=156 |
|---|---|
| Age at transplant, median (years) | 13.6 (IQR 7.8, 17.2) |
| Age at Fontan operation, median (years) | 3.33 (IQR 2.25, 4.85) |
| Time from Fontan to transplant, median (years) | 9.3 (IQR 3.2, 13.4) |
| Female | 54 (35%) |
| Status at transplant | |
| 1A | 93 (60%) |
| 1B | 37 (24%) |
| 2 | 24 (16%) |
| Pre-transplant plastic bronchitis | 15 (10%) |
| Pre-transplant PLE | 58 (37%) |
| Followed by a gastroenterologist for liver dysfunction | 37 (24%) |
| Clinical Diagnosis | |
| DILV | 8 (5%) |
| DORV | 19 (12%) |
| HLHS | 68 (44%) |
| Tricuspid atresia | 11 (7%) |
| Unbalanced AV canal | 20 (13%) |
| Other | 30 (19%) |
| Type of Fontan | |
| Extracardiac conduit | 98 (65%) |
| Lateral tunnel | 52 (34%) |
| Atriopulmonary connection | 2 (1%) |
| Time from transplant to last visit, median (years) | 3.0 (IQR 0.7, 5.0) |
| Race | |

| | |
|---|---|
| American Indian | 2 (1%) |
| Asian | 5 (3%) |
| Black/African American | 22 (14%) |
| White/Caucasian | 104 (67%) |
| Other | 20 (13%) |
| Unknown | 2 (1%) |
| **Mode of Failure:** | |
| Plastic Bronchitis (PB) | 15 (10%) |
| Protein-Losing Enteropathy (PLE) | 48 (31%) |
| Ventricular dysfunction | 76 (49%) |
| Other | 17 (11%) |

Missing Values: Status at transplant=2, time from Fontan to transplant=1, type of Fontan=4

Table 2. Laboratory Results summarized in median (IQR).

| | Pre-transplant N=153 | Post-transplant 48hr N=149 | Post-transplant 1 year N=123 | Pre- vs post-transplant 48hr p value | Pre- vs post-transplant 1 year p value |
|---|---|---|---|---|---|
| AST, u/L | 36 (27, 49) | 130 (77, 262) | 33 (25, 41) | <0.001 | 0.013 |
| ALT, u/L, | 33 (24, 43) | 52.0 (33, 105) | 31.5 (23, 46) | <0.001 | 0.38 |
| Bilirubin, mg/dL | 0.7 (0.5, 1.0) | 1.4 (0.9, 2.7) | 0.4 (0.3, 0.6) | <0.001 | <0.001 |
| Creatinine, mg/dL | 0.6 (0.4, 0.8) | 0.8 (0.6, 1.1) | 0.6 (0.4, 0.8) | <0.001 | 0.07 |
| Platelets, k/uL | 210 (162, 296) | 122.0 (87, 170) | 232 (175, 309) | <0.001 | 0.024 |
| Albumin, g/dL | 3.7 (3.0, 4.3) | 3.1 (2.6, 3.5) | 4.1 (3.7, 4.4) | <0.001 | <0.001 |
| INR (no warfarin) | 1.2 (1.1, 1.4) | 1.4 (1.2, 1.7) | 1.1 (1.1, 1.2) | 0.31 | 0.17 |

Missing values by group (Pre/Post 48 hrs/Post 1 year): AST (Aspartate aminotransferase) =10/21/17, ALT (Alanine aminotransferase) =10/21/16, Bilirubin=11/31/19, Creatinine =1/1/2, INR (International Normalized Ratio) =19/13/61, Platelets=4/1/10, Albumin=15/17/27

Table 3. Hemodynamics summarized in median (IQR).

| | Pre-transplant N=152 | Most Recent Post-transplant N=149 |
|---|---|---|
| PCWP, mmHg | 11.0 (8.0, 14.0) | 13.0 (10.0, 18.0) |
| Cardiac index, $L/m^2$ | 3.0 (2.6, 3.6) | 3.2 (2.6, 3.7) |
| Fontan pressure, mmHg | 16.0 (14.0, 19.0) | NA |
| Right atrial pressure, mmHg | NA | 8.0 (5.0, 13.0) |
| LVEF, % | NA | 62.0 (59.0, 67.0) |
| Hepatic wedge pressure, mmHg | 17.0 (15.0, 19.0) | 4.5 (0, 9) |

Missing values by group (Pre / Post): Pulmonary capillary wedge pressure (PCWP) =19/14, Cardiac index =30/27, Fontan pressure=20/149, Hepatic wedge pressure =115/147, Right atrial pressure=152/11, Left ventricle ejection fraction (LVEF) =152/64.

Table 4. Fibrosis on Imaging Studies

| Modality | Pre-transplant | Post-transplant | Both Pre-transplant and Post-transplant |
|---|---|---|---|
| | N=91 | N=55 | N=44 |
| US | 30 (33%) | 27 (49%) | 15 (34%) |
| | | | |
| CT/MRI | N=44 | N=38 | N=14 |
| | 31 (70%) | 22 (58%) | 11 (79%) |
| | | | |
| US, CT/MRI | N=98 | N=70 | N=58 |
| | 49 (50%) | 38 (54%) | 28 (48%) |

US=ultrasound, CT=computed tomography, MRI =magnetic resonance imaging

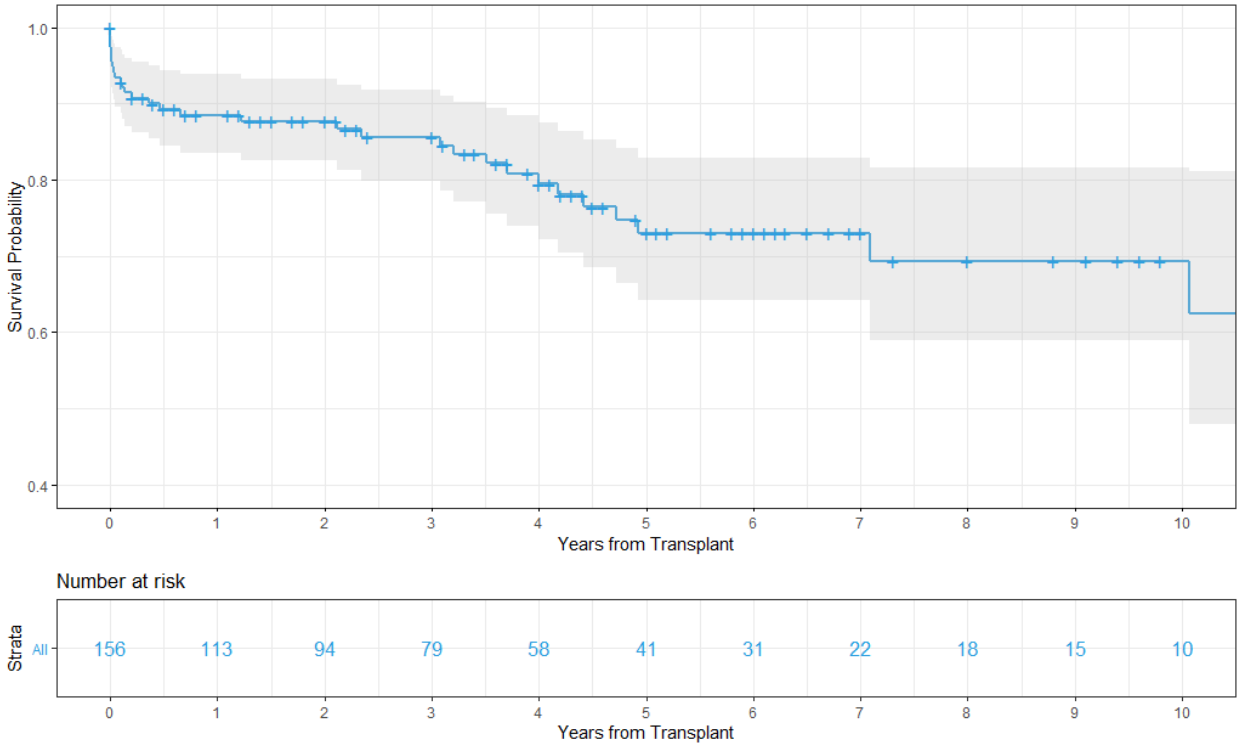
Table 5a. Liver Nodules and Portosystemic Collaterals by Imaging Modality

| Modality | Pre-transplant | Post-transplant |
|---|---|---|
| Liver Nodules | | |
| US | N=87 | N=52 |
| | 11 (13%) | 13 (25%) |
| CT/MRI | N=42 | N=34 |
| | 11 (26%) | 10 (29%) |
| Portosystemic collaterals | | |
| CT/MRI | N=42 | N=34 |
| | 10 (24%) | 5 (15%) |

Table 5b. Frequency of Multiple Liver Nodules by Any Modality

| Number of Liver Nodules by Patient | N=30 |
|---|---|
| 1 to 5 Nodules | 13 |
| 6-10 | 1 |
| >10 | 16 |

Figure 1. Kaplan-Meier Plot for Post-Transplant Survival




Estimated Survival at 5 years from transplant is 73%. (95% CI: 0.17, 0.36).

Table 6. Univariate Survival Analysis Results for Demographic and Clinical Variables (Table 1).

| **Demographic Factors** | **HR (95% CI)** | **p-value** |
|---|---|---|
| Age (years) at transplant | 1.02 (0.96,1.09) | 0.46 |
| Sex - Male | 1.57 (0.67,3.7) | 0.30 |
| Status at transplant - 1B | 1.28 (0.5,3.27) | 0.60 |
| Status 2 | 0.38 (0.09,1.66) | 0.20 |
| Followed for liver dysfunction | 1.64 (0.75,3.58) | 0.21 |
| Age at Fontan operation (years) | 0.95 (0.81,1.1) | 0.47 |
| Years between Fontan and transplant | 1.04 (0.98,1.11) | 0.19 |
| Race - White | 1.04 (0.46,2.37) | 0.93 |
| Clinical diagnosis - HLHS | 0.81 (0.38,1.69) | 0.57 |
| Pre-transplant plastic bronchitis | 0.71 (0.21,2.36) | 0.57 |
| Protein-losing enteropathy | 2.32 (0.84,6.43) | 0.11 |
| Ventricular dysfunction | 0.98 (0.33,2.93) | 0.97 |
| Type of Fontan – Extra-cardiac conduit | 0.87 (0.37,2.02) | 0.74 |
| Pre-transplant fibrosis by US | 1.89 (0.65,5.5) | 0.24 |
| Pre-transplant fibrosis by CT/MRI | 1.53 (0.32,7.26) | 0.59 |
| Pre-transplant fibrosis by any modality | 1.89 (0.69,5.23) | 0.22 |

Table 7. Survival Analysis Results for Laboratory Variables (Table 2).

| | **Pre-transplant** | | **Immediate Post-transplant** | |
|---|---|---|---|---|
| | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| CR (mg/dL) | 0.81 (0.12,5.52) | 0.83 | 1.81 (1.08,3.05) | **0.025** |
| 100 × AST (U/L) | 3.44 (0.96,12.36) | 0.06 | 1.08 (1.01,1.15) | **0.029** |
| 100 × ALT (U/L) | 1.74 (0.31,9.69) | 0.53 | 1.11 (1.03,1.21) | **0.011** |
| Bilirubin total (mg/dL) | 1.12 (1.03,1.21) | **0.007** | 1.3 (0.82,2.07) | 0.26 |
| INR** | 0.93 (0.37,2.34) | 0.87 | 1.87 (1.07,3.3) | **0.029** |
| 100 × PLTs (K/uL) | 0.49 (0.24,0.97) | **0.041** | 1.5 (0.74,3.02) | 0.26 |
| Albumin (g/dL) | 0.84 (0.51,1.36) | 0.48 | 0.49 (0.21,1.14) | 0.10 |

** Excluded patients who are on warfarin.

CR=creatinine, AST=aspartate aminotransferase, ALT=alanine aminotransferase, INR= international normalized ratio, Plts=platelets.

1. Simpson KE, Pruitt E, Kirklin JK, Naftel DC, Singh RK, Edens RE, Barnes AP and Canter CE. Fontan Patient Survival After Pediatric Heart Transplantation Has Improved in the Current Era. *Ann Thorac Surg*. 2017;103:1315-1320.
2. Simpson KE, Esmaeeli A, Khanna G, White F, Turnmelle Y, Eghtesady P, Boston U and Canter CE. Liver cirrhosis in Fontan patients does not affect 1-year post-heart transplant mortality or markers of liver function. *J Heart Lung Transplant*. 2014;33:170-7.
3. Miller JR, Simpson KE, Epstein DJ, Lancaster TS, Henn MC, Schuessler RB, Balzer DT, Shahanavaz S, Murphy JJ, Canter CE, Eghtesady P and Boston US. Improved survival after heart transplant for failed Fontan patients with preserved ventricular function. *J Heart Lung Transplant*. 2016;35:877-83.
4. Kanter KR, Mahle WT, Vincent RN, Berg AM, Kogon BE and Kirshbom PM. Heart transplantation in children with a Fontan procedure. *Ann Thorac Surg*. 2011;91:823-9; discussion 829-30.
5. Sganga D, Hollander SA, Vaikunth S, Haeffele C, Bensen R, Navaratnam M, McDonald N, Profita E, Maeda K, Concepcion W, Bernstein D and Chen S. Comparison of combined heartliver vs heart-only transplantation in pediatric and young adult Fontan recipients. *J Heart Lung Transplant*. 2021;40:298-306.
6. Reardon LC, DePasquale EC, Tarabay J, Cruz D, Laks H, Biniwale RM, Busuttil RW, Kaldas FM, Saab S, Venick RS, Lin JP, Nsair A, Deng MC, Ardehali A, Caderias M, Iygengar A and Aboulhosn JA. Heart and heart-liver transplantation in adults with failing Fontan physiology. *Clin Transplant*. 2018;32:e13329.
7. D'Souza BA, Fuller S, Gleason LP, Hornsby N, Wald J, Krok K, Shaked A, Goldberg LR, Pochettino A, Olthoff KM and Kim YY. Single-center outcomes of combined heart and liver transplantation in the failing Fontan. *Clin Transplant*. 2017;31.
8. Rodriguez DS, Mao C, Mahle WT, Kanter KR, Alazraki A, Braithwaite K, Rytting H, Caltharp S, Magliocca JF and Romero R. Pretransplantation and Post-Transplantation Liver Disease Assessment in Adolescents Undergoing Isolated Heart Transplantation for Fontan Failure. *J Pediatr*. 2021;229:78-85 e2.
9. Emamaullee J, Zaidi AN, Schiano T, Kahn J, Valentino PL, Hofer RE, Taner T, Wald JW, Olthoff KM, Bucuvalas J and Fischer R. Fontan-Associated Liver Disease: Screening, Management, and Transplant Considerations. *Circulation*. 2020;142:591-604.
10. Bouchardy J, Meyer P, Yerly P, Blanche C, Hullin R, Giostra E, Hanquinet S, Rubbia-Brandt L, Sekarski N, Pretre R and Beghetti M. Regression of Advanced Liver Fibrosis After Heart Transplantation in a Patient With Prior Fontan Surgery for Complex Congenital Heart Disease. *Circ Heart Fail*. 2018;11:e003754.
11. Crespo-Leiro MG, Robles O, Paniagua MJ, Marzoa R, Naya C, Flores X, Suarez F, Gomez M, Grille Z, Cuenca JJ, Castro-Beiras A and Arnal F. Reversal of cardiac cirrhosis following orthotopic heart transplantation. *Am J Transplant*. 2008;8:1336-9.
12. Asrani SK, Warnes CA and Kamath PS. Hepatocellular carcinoma after the Fontan procedure. *N Engl J Med*. 2013;368:1756-7.
13. Egbe AC, Poterucha JT, Warnes CA, Connolly HM, Baskar S, Ginde S, Clift P, Kogon B, Book WM, Walker N, Wagenaar L, Moe T, Oechslin E, Kay WA, Norris M, Gordon-Walker T,

Dillman JR, Trout A, Anwar N, Hoskoppal A and Veldtman GR. Hepatocellular Carcinoma After Fontan Operation: Multicenter Case Series. *Circulation*. 2018;138:746-748.
14. Barr RG, Ferraioli G, Palmeri ML, Goodman ZD, Garcia-Tsao G, Rubin J, Garra B, Myers RP, Wilson SR, Rubens D and Levine D. Elastography Assessment of Liver Fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement. *Radiology*. 2015;276:845-61.
15. Vaupel JW, Manton KG and Stallard E. The impact of heterogeneity in individual frailty on the dynamics of mortality. *Demography*. 1979;16:439-54.