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ORIGINAL ARTICLE

Heart transplantation and in-hospital outcomes in adult congenital heart disease patients with Fontan: A decade nationwide analysis from 2004 to 2014

Gabriel A. Hernandez MD[1] | Alejandro Lemor MD[2] | Daniel Clark MD[3] | Vanessa Blumer MD[4] | Danielle Burstein MD[5] | Ryan Byrne MD[6] | Rachel Fowler RN[3] | Benjamin Frischhertz MD[3] | Emily Sandhaus RN[3] | Kelly Schlendorf MD[3] | Sandip Zalawadiya MD[3] | JoAnn Lindenfeld MD[3] | Jonathan N. Menachem MD[3]

[1]Cardiovascular Division, Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi

[2]Cardiovascular Division, Department of Medicine, Henry Ford Hospital, Detroit, Michigan

[3]Cardiovascular Division, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

[4]Cardiovascular Division, Department of Medicine, Duke University, Durham, North Carolina

[5]Cardiology Division, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[6]Department of Medicine, Vanderbilt University Medical Cente, Nashville, Tennessee

Correspondence
Jonathan Menachem, MD, Assistant Professor of Medicine and Pediatrics, Director, Advanced Congenital Cardiac Therapies (ACCT), Vanderbilt University Medical Center, 1215 21st Ave. South, South Tower – 5209, Nashville, TN 37232-8802.
Email: Jonathan.n.menachem@vumc.org

Abstract

Introduction: Treatment of adult congenital heart disease patients who require advanced therapies remains challenging due to high perioperative and wait-list mortality and limited donors. Patients palliated with Fontan are at the highest risk of early mortality due to multiorgan involvement and few centers able to safely transplant them. We sought to evaluate the early outcomes of heart transplants in these adult Fontan patients.

Methods: Using the Nationwide Inpatient Sample database, we identified all adults aged at least 18 years old who underwent heart transplantation across U.S. hospitals from 2004 to 2014. We then identified those with specific ICD-9 codes to include tricuspid atresia, hypoplastic left heart syndrome and common ventricle. Multivariate regression models were created to adjust for potential confounders.

Results: A total of 93 Fontan patients underwent heart transplant during the study time (0.5% of all heart transplants). Compared to non-Fontan heart transplantations, Fontan patients were younger, with a higher incidence of liver disease and coagulopathy. Fontan patients receiving heart transplant had higher mortality during transplant hospitalization compared to non-Fontan patients (26.3% vs 5.3% OR, 18.10, CI, 5.06-65.0 $P < .001$). Extracorporeal membrane oxygenator (ECMO) usage and bleeding were also higher in the Fontan cohort with an OR of 5.30 ($P = .016$) and 5.32 ($P = .015$) for ECMO and bleeding, respectively. The remaining outcomes were similar for both cohorts.

Conclusion: Adults with Fontan palliation undergoing heart transplantation have exceptionally high inpatient mortality, which is nearly five times that of non-Fontan heart transplant recipients, perhaps related to a delayed referral, surgical complexity, and coexistent, underrecognized liver failure.

KEYWORDS
congenital heart defect, Fontan procedure, heart failure, heart transplantation

1 | INTRODUCTION

Treatment of heart failure (HF) in adults with congenital heart disease (ACHD) requiring advanced therapies remains challenging due to limited donors, high rate of delisting due to worsening condition, high perioperative and wait-list mortality, and lack of experience with ventricular assist devices.[1] Despite early perioperative mortality with heart transplant (HT), long-term outcomes conditional on 30-day survival is at least equivalent; if not better, than transplant outcomes in non-ACHD patients.[2] However, the outcomes and risks differ depending on the patient's native anatomy and subsequent surgical corrections. Single ventricle patients palliated with a Fontan are known to be at the highest risk of early mortality for a multitude of reasons including increased risk of bleeding, multiple previous cardiac operations, and multiorgan dysfunction – notably the liver. As a result, few centers are able to safely transplant them.[3] We sought to evaluate the early outcomes of HT specifically in the adult Fontan population.

2 | METHODS

2.1 | Data source

The study cohort was derived from the 2004 to 2014 Nationwide Inpatient Sample (NIS) database. Institutional Review Board (IRB) review and approval was not required as the NIS is a publically available database that contains deidentified patient information. The NIS contains all-payer data on hospital inpatient stays from states participating in the Healthcare Cost and Utilization Project. The NIS database is a sample of discharges from the United States and contains data about 7 to 8 million discharges per year. The NIS data is originated from billing data submitted by hospitals to statewide data organizations across the United States and contains discharge-level weights to calculate national estimates for discharges. Before 2012, a 20% probability sample of all hospitals within each stratum was collected, all discharges from these hospitals were recorded and then weighted to ensure that they were nationally representative. Starting in 2012, the NIS sample design was changed, now including 20% of discharges among all the hospitals in the NIS universe. As many as 30 discharge diagnoses and 15 procedures are recorded for each patient by using the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes (ICD-9-CM).

NIS is based on a complex sampling design that includes stratification, clustering, and weighting. We used a survey analysis that accounted for stratification and clustering, as well as the weights for each hospital discharge. Pearson's Chi-square and Wilcoxon rank-sum tests were used to calculate the *P*-value for the differences among the baseline characteristics of patients. Multivariate regression models were created to adjust for potential confounders (age, gender, race, hospital bed size, teaching hospital, elective admission, and hospital region). Stata version 13.0 was used for all statistical analyses.

2.2 | Study sample and variables

We used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure code to identify all adults aged at least 18 years old who underwent HT (37.51) across the U.S. hospitals from 2004 to 2014. We then identified those with specific ICD-9 codes to include single ventricle ACHD (tricuspid atresia [746.1], hypoplastic left heart syndrome [746.7] and common ventricle [745.3]) who, to survive to age 18, most likely have been palliated with a Fontan procedure (from now on referred to as Fontan).

The NIS variables were used to identify patients' demographic characteristics including age, gender, and race (Table 1). Comorbid conditions, such as hypertension, diabetes, liver disease, and chronic kidney disease were identified using ICD-9 codes in the diagnosis fields. The ICD-9 procedure code 50.50 was used to identify those receiving liver transplants during the same hospitalization. The severity of comorbid conditions was defined using the Deyo modification of the Charlson Comorbidity Index (CCI). The CCI contains 17 comorbid conditions with differential weights. The score ranges from 0 to 33, with higher scores corresponding to greater comorbidity burden. Furthermore, given that coagulopathy is a characteristic comorbid condition in Fontan patients, the definition of coagulopathy included the following ICD-9-CM discharge diagnosis: 286.0 to 9, 287.1, 287.3, 287.5, 289.81 to 82; similar methodology has been used before in adult HT recipients.[4]

2.3 | Outcomes

The primary outcome was in-hospital mortality, which was provided within the NIS for each discharge. Secondary outcomes included the mean length of hospital stay (LOS), cardiac arrest, stroke, need for extracorporeal membrane oxygenator (ECMO), acute kidney injury (AKI) and mean total hospital costs. In addition, code 996.83 was used to identify complications of the transplanted heart organ, including failure or rejection.

3 | RESULTS

We identified a weighted total of 93 (0.5% of all HT) adult patients palliated with Fontan who underwent HT during the study time. These patients were most commonly male (52%) and white (68.3%). Compared to all adult HT, Fontan patients were younger (24 years IQR 21-40 vs 55 years IQR 45-62), $P < .001$), female (48% vs 25.3%, $P = .038$), and there was a noteworthy signal of higher rates of Hispanic patients (25.3% vs 8.5%, $P = .013$). Fontan patients undergoing transplants were less likely to have diabetes, obesity (BMI > 30 kg/m^2), chronic obstructive lung disease, or coronary disease. No Fontan patients had an implantable cardiac defibrillator. As expected, these patients had a higher incidence of liver disease (31.3% compared to 2.7% in non-Fontan cohort $P < .001$) and coagulopathy

TABLE 1 Baseline characteristics of the patient that underwent heart transplantation

	Overall (%)	Fontan (%)	No Fontan (%)	*P* value
Number of patients	19,814	93 (0.5%)	19,721	
Age (median), y	55	24	55	<.001
18-34	33.9	89.4	33.6	
35-54	53.6	10.6	53.8	
55-74	12.5	0.0	12.6	
>75	0.0	0.0	0.0	
Gender				.038
Male	74.6	52.0	74.7	
Female	25.4	48.0	25.3	
Race				.401
Caucasian	66.5	68.3	66.5	
African American	18.3	6.4	18.4	
Hispanic	8.5	25.3	8.5	
Asian	3.3	0.0	3.3	
Other	3.4	0.0	3.3	
Comorbidities				
Hypertension	51.6	26.7	41.6	.259
Diabetes mellitus	31.2	0.0	31.3	.004
End-stage renal disease	3.5	5.4	3.5	.662
Obesity (BMI ≧ 30 kg/m2)	7.3	0.0	7.4	.210
Chronic pulmonary disease	11.7	0.0	11.7	.112
Peripheral vascular disease	5.0	5.4	5.0	.944
Hypothyroidism	12.3	10.6	12.4	.805
Depression	10.0	26.8	9.9	.032
Smoking	12.9	0.0	12.9	.097
Prior MI	14.3	0.0	14.4	.074
Prior PCI	6.5	0.0	6.5	.259
Prior CABG	8.5	0.0	8.5	.180
Prior stroke/TIA	5.7	5.4	5.7	.959
Known CAD	27.9	0.0	28.0	.008
Atrial fibrillation	29.1	21.1	29.1	.460
Prior ICD	17.6	0.0	17.6	.063
Anemia	23.5	16.0	23.5	.507
Liver disease	279.0	31.3	2.7	<.001
Cancer	0.7	5.4	0.6	.012
Fluid and electrolyte disorders	50.9	58.2	50.8	.513
Coagulopathy	32.7	58.2	32.5	.028
Charlson Comorbitiy Index				.898
0	24.4	21.4	24.4	
1	36.1	41.9	36.1	
2	22.1	16.0	22.1	
≧3	17.4	20.7	17.4	
Other characteristics				
Teaching hospital	69.9	63.9	69.6	.569
Median household income				.474
0-25th quartile	22.0	26.0	22.0	
26th-50th quartile	25.0	21.1	25.1	
51st-75th quartile	25.3	37.2	25.2	
76th-100th quartile	27.7	15.8	27.8	
Elective admission	25.6	31.8	25.6	.599
Primary payer				.559
Medicare/medicaid	46.8	52.7	46.8	
Private insurance	47.5	47.3	47.5	
Self-pay/other	5.7	0.0	5.7	
Discharge disposition				.766
Home	87.8	100.0	87.8	
Nursing home/facility	10.9	0.0	10.9	
Transfer to another hospital	1.3	0.0	1.3	

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; ICD, implantable cardioverter defibrillator; PCI, percutaneous coronary intervention; MI, myocardial infarction; TIA, transient ischemic attack.

(58.2% vs 32.5% $P = .028$); comorbid depression was also more likely among Fontan HT patients (26.8% vs 9.9%, $P = .032$). A list of comorbidities and the relation with the non –Fontan cohort are listed in Table 1.

Fontan patients receiving HT had exceptionally high mortality during their index transplant hospitalization (26.3% vs 5.3% OR, 18.10, CI, 5.06-65.0 $P < .001$). The median hospital costs were 1.53 times higher for Fontan patients, though this difference did not reach statistical significance ($203 952 vs $132 945 $P = .119$).

Secondary outcomes of ECMO usage and bleeding were higher in the Fontan cohort with an OR of 5.30 ($P = .016$) and 5.32 ($P = .015$) for ECMO and bleeding, respectively. The remaining outcomes were similar for both cohorts (Table 2). There was no difference in rates of early post-transplant rejection, despite a high rate of sensitization in these patients due to a multitude of previous operations. Furthermore, compared to the non-Fontan cohort where 10.9% of patients were discharged to a nursing home or long term care facility, all of the Fontan patients were discharged home.

We identified a weighted total of 10 patients receiving simultaneous liver transplants during the same hospitalization. Given that the unweighted number of patients undergoing heart and liver transplant is small (<10), NIS does not permit reporting baseline characteristics to avoid patient identification. There were no in-hospital deaths in this group.

TABLE 2 In-Hospital outcomes of post-transplant patients

Outcome	Overall (%)	Fontan (%)	No Fontan (%)	Odds ratio[a]	95% CI	*P* value
Mortality	5.4	26.3	5.3	18.10	5.06-65.0	<.001
Stroke	3.0	5.2	3.0	1.71	0.29-10.1	.557
Cardiogenic shock	27.3	31.9	27.3	1.06	0.35-3.22	.923
Acute respiratory failure	12.6	5.4	12.6	...	...	...
Cardiac arrest	3.5	0.0	3.5	...	...	...
Acute kidney injury (AKI)	46.8	47.8	46.8	1.71	0.64-4.54	.283
AKI requiring hemodialysis	4.3	0.0	4.3	...	...	...
Major bleeding	4.3	15.8	4.2	5.30	1.39-20.4	.015
Use of ECMO	4.0	16.1	3.9	5.32	1.37-20.6	.016
Cardiac complications	12.2	16.1	12.2	1.87	0.51-6.82	.345
Post-transplant complications/rejection	29.2	37.1	29.2	1.17	0.47-2.88	.737
Transfusion	33.7	47.3	33.6	2.48	1.01-6.07	.046
Median hospital costs (US$)	133,366	$203,952	$132,945	...	...	.119
Median length of stay (days [IQR])	21 (12-43)	23 (15-134)	21 (12-43)	...	...	.267

Abbreviation: ECMO, extracorporeal membrane oxygenator.
[a]Adjusted for age, gender, race, hospital bed-size, teaching hospital, elective admission, and hospital region.

4 | DISCUSSION

Our study, which evaluates Fontan patients in the most recent era, yields several important findings and highlights a number of important factors during the index transplant care of this complex group of patients. Foremost, despite these patients being highly selected, younger, and with less co-morbid conditions such as diabetes and chronic lung disease, Fontan patients undergoing HT are at a much higher risk of inpatient mortality compared to the non-Fontan cohort. Possible explanations for this mortality difference include the high prevalence of the underlying liver disease, resultant coagulopathy, complex anatomy, and multiple prior sternotomies, leading to possibly prolonged pump and ischemic time for their transplantation.[3,5]

In 2009, Lamour et al[5], demonstrated that patients with congenital heart disease (CHD) have a lower 3-months survival compared to their cardiomyopathic counterparts; survival at 3-months for patients with CHD was 86%, compared to 91% and 94% for adults and children with cardiomyopathy. Although there were no specific survival analyses between pediatric and adult patients, they found that older recipient age at transplant (30 years vs 10 years) had a 1.5-fold increased risk of death. In addition, the one-year survival in Fontan patients was lower than other CHD patients (71% vs 83%), which is likely driven by the elevated index admission mortality seen in our study. Moreover, while our findings suggest higher early mortality for Fontan patients undergoing HT, the long-term survival conditional on 30-day survival is known to be better for ACHD patients undergoing heart transplant than for non-ACHD patients.[6,7] This is likely related to a younger population with less preexisting comorbidities, such as diabetes, tobacco use, coronary artery disease, or vascular disease.

Over 60% of the CHD population in North America has now reached adulthood due in large part to improvement in pediatric surgical and advanced medical care[8,9] and there are an estimated 273 000 adults with moderate-severe congenital heart disease age 20 to 64 years old living in the United States as of 2010.[10] For these patients, heart failure is the leading cause of death, accounting for an estimated 26% of deaths, placing ACHD patients with heart failure at over a threefold increased mortality risk compared to ACHD patients without heart failure.[11,12] However, few complex ACHD patients are referred for advanced heart failure therapies.

A recent publication using the NIS suggests that there has been a progressive increase in complex ACHD admissions in the United States, with an increasing prevalence of comorbid conditions such as hypertension, diabetes, obesity, and chronic kidney disease. Interestingly, close to 22% of the complex ACHD admissions were due to heart failure or arrhythmias.[9] Extrapolating from these estimates, the annual rate of HT for failing Fontan in the NIS database over the 11-year period we studied was 0.003%. While there is both a limited epidemiologic data about annual rates of Fontan failure in the United States, as well as a lack of a consensus definition of Fontan failure, this likely represents under-referral and under-transplantation of failing Fontan, especially considering the limited mechanical circulatory support options and utilization for these patients.[13]

Mitigating the perioperative risk is paramount to successfully transplanting Fontan patients. First and foremost is the clinical recognition and appropriate treatment of worsening heart failure or Fontan failure. However, even after these patients demonstrate evidence of clinical failure, there is a paucity of data in these patients regarding the timing of advanced therapies. ACHD patients are known to have higher waitlist mortality and delisting rate compared to non-ACHD patients.[1] As such, early referral for transplant

evaluation is recommended in those patients with declining NYHA class, progressive ventricular dysfunction, increased burden of arrhythmias, worsening peak oxygen uptake (VO_2 max), repeated HF hospitalizations or emergency room visits, escalating diuretic dose, or worsening end-organ function. Advanced HF referral is also recommended in those with idiosyncratic complications suggesting increased short-term mortality risk, such as protein-losing enteropathy (PLE) in Fontan patients.[14,15]

Over the last 50 years of heart transplantation, centers have faced higher standards of care and lower acceptable 1-year mortality rates. While new transplant centers arise, there are still few centers comfortable or capable of caring for high-risk congenital patients. Furthermore, more recent data demonstrated that low volume transplant centers have statistically significant worse outcomes in transplanting ACHD patients.[16] In addition, timing of listing and transplant is complicated in these patients as they are listed as UNOS status 4, competing with the growing group of patients supported with a left ventricular assist device, an option limited for Fontan patients; it is imperative to recognize subtle changes in symptoms and petition to list by exception as these patients rarely meet the standard non-ACHD criteria for transplant.

One of the biggest barriers for successful transplants in the Fontan population is the underlying and poorly understood impact of subclinical liver failure. Fontan-associated liver disease is highly prevalent, as these patients are exposed to systemic venous hypertension, hepatic congestion, and low cardiac output leading to various stages of liver disease ranging from clinically silent cirrhosis to hepatocellular carcinoma.[17,18] A recent study found that adults with Fontan palliation universally have biopsy-proven hepatic fibrosis despite normal synthetic function.[19] How to best proceed with heart vs combined heart-liver transplant remains a controversial and under studied area. One single-center experience reported 100% 30-day and 1-year survival for all Fontan patients who underwent combined heart-liver transplantation.[20] Thus, it is possible that the early mortality seen in our Fontan cohort could potentially be reduced by combined heart-liver transplantation. Inclusion of liver transplant has been postulated to reduce the risk of postoperative liver dysfunction and bleeding complications.[21] The lack of mortality among the small cohort of patients receiving a combined heart-liver transplant in our study further supports this theory. However, despite these potential advantages, it remains unclear whether combined heart-liver transplant should be recommended in all Fontan patients. It is important to note that a recent UNOS study reported equivalent survival in CHD patients undergoing isolated heart vs combined heart-liver transplantation.[22]

One helpful tool, the MELD-XI score has emerged as an important prognostic tool for identification of risk associated with Fontan patients.[23] This modified version of MELD-Na excludes international normalized ratio (INR) given that many Fontan patients require anticoagulation for their hypercoagulable state, comorbid atrial arrhythmias, and higher risk for paradoxical emboli. A MELD-XI score >18 among Fontan patients has been associated with increased recipient mortality after HT.[24] This highlights the fact that decompensated liver disease in Fontan patients undergoing transplant worsens the outcomes. Validation of this score on a larger scale will be important before integrating into transplant selection criteria.

Finally, there are substantial opportunities for further research to better define Fontan failure, validate MELD-XI as a prognostic tool, more clearly define indications for advanced heart failure therapies referral, study outcomes among different ACHD subgroups post-heart transplantation and develop a registry to follow more than single-center cohorts of these patients.

5 | LIMITATIONS

The limitations of our study partly relate to the analysis of a large nationwide administrative database using ICD-9-CM codes. There are currently limited ways to retrospectively investigate outcomes in patients with Fontan and relying on administrative databases to identify them may currently be the only way. Similarly, the UNOS database does not capture these patients either and also relies on coding parameters to identify Fontan patients. We acknowledge that our method of identifying adult patients with Fontan palliation likely underestimates the actual number of Fontan patients given our use of only 3 ICD-9 codes.

Furthermore, the NIS lacks clinical details such as information about biochemical parameters (for example MELD-XI), liver biopsy data, anatomic characteristics, and number and types of prior surgeries. We also lack long-term follow-up data, as we could only determine in-hospital events for a particular admission.

6 | CONCLUSIONS

Adult Fontan patients undergoing HT have exceptionally high inpatient mortality, which is nearly five times that of non-Fontan HT recipients despite having a similar cumulative comorbidity profile. This finding is likely related to but not limited to delayed referral, imprecise methods for identifying risk, and surgical and medical comorbidities along with limited experience in transplanting these patients. For now, a case-by-case approach is recommended at a medium or high volume transplant center and a combined heart-liver transplant should be considered. Moving forward, more intentional training and multi-disciplinary collaboration and research between ACHD and HF providers is necessary to expedite advanced heart failure therapies for these patients.

REFERENCES

1. Alshawabkeh LI, Hu N, Carter KD, et al. Wait-list outcomes for adults with congenital heart disease listed for heart transplantation in the U.S. *J Am Coll Cardiol*. 2016;68(9):908-917. https://doi.org/10.1016/j.jacc.2016.05.082
2. Burchill LJ, Edwards LB, Dipchand AI, Stehlik J, Ross HJ. Impact of adult congenital heart disease on survival and mortality after heart

transplantation. *J Heart Lung Transplant*. 2014;33(11):1157-1163. https://doi.org/10.1016/j.healun.2014.05.007
3. Shi WY, Saxena P, Yong MS, et al. Increasing complexity of heart transplantation in patients with congenital heart disease. *Semin Thorac Cardiovasc Surg*. 2016;28(2):487-497. https://doi.org/10.1053/j.semtcvs.2015.09.007
4. Mujib M, Khanna N, Mazumder NK, et al. Pretransplant coagulopathy and in-hospital outcomes among heart transplant recipients: a propensity-matched nationwide inpatient sample study. *Clin Cardiol*. 2015;38(5):300-308. https://doi.org/10.1002/clc.22391
5. Lamour JM, Kanter KR, Naftel DC, et al. The effect of age, diagnosis, and previous surgery in children and adults undergoing heart transplantation for congenital heart disease. *J Am Coll Cardiol*. 2009;54(2):160-165. https://doi.org/10.1016/j.jacc.2009.04.020
6. Burchill LJ. Heart transplantation in adult congenital heart disease. *Heart*. 2016;102(23):1871-1877. https://doi.org/10.1136/heartjnl-2015-309074
7. Patel ND, Weiss ES, Allen JG, et al. Heart transplantation for adults with congenital heart disease: analysis of the United network for organ sharing database. *Ann Thorac Surg*. 2009;88(3):814-822. https://doi.org/10.1016/j.athoracsur.2009.04.071
8. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation*. 2014;130(9):749-756. https://doi.org/10.1161/CIRCULATIONAHA.113.008396
9. Agarwal S, Sud K, Menon V. Nationwide hospitalization trends in adult congenital heart disease across 2003-2012. *J Am Heart Assoc*. 2016;5(1), https://doi.org/10.1161/JAHA.115.002330
10. Benziger CP, Stout K, Zaragoza-Macias E, Bertozzi-Villa A, Flaxman AD. Projected growth of the adult congenital heart disease population in the United States to 2050: an integrative systems modeling approach. *Popul Health Metr*. 2015;13:29. https://doi.org/10.1186/s12963-015-0063-z
11. Verheugt CL, Uiterwaal CSPM, van der Velde ET, et al. Mortality in adult congenital heart disease. *Eur Heart J*. 2010;31(10):1220-1229. https://doi.org/10.1093/eurheartj/ehq032
12. Krieger EV, Valente AM. Heart failure treatment in adults with congenital heart disease: where do we stand in 2014? *Heart*. 2014;100(17):1329-1334. https://doi.org/10.1136/heartjnl-2014-305667
13. Menachem JN. Advanced heart failure in the ACHD population: finding the fellows' role in a growing field. *J Am Coll Cardiol*. 2017;69(15):1986-1989. https://doi.org/10.1016/j.jacc.2017.03.012
14. John AS, Johnson JA, Khan M, Driscoll DJ, Warnes CA, Cetta F. Clinical outcomes and improved survival in patients with protein-losing enteropathy after the Fontan operation. *J Am Coll Cardiol*. 2014;64(1):54-62. https://doi.org/10.1016/j.jacc.2014.04.025
15. Mertens L, Hagler DJ, Sauer U, Somerville J, Gewillig M. Protein-losing enteropathy after the Fontan operation: an international multicenter study. PLE study group. *J Thorac Cardiovasc Surg*. 1998;115(5):1063-1073. http://www.ncbi.nlm.nih.gov/pubmed/9605076
16. Menachem JN, Lindenfeld J, Schlendorf K, et al. Center volume and post-transplant survival among adults with congenital heart disease. *J Hear Lung Transplant*. 2018;37:1351-1360. https://doi.org/10.1016/j.healun.2018.07.007. Article in.
17. Josephus Jitta D, Wagenaar LJ, Mulder BJM, Guichelaar M, Bouman D, van Melle JP. Three cases of hepatocellular carcinoma in Fontan patients: review of the literature and suggestions for hepatic screening. *Int J Cardiol*. 2016;206:21-26. https://doi.org/10.1016/j.ijcard.2015.12.033
18. Rychik J. The relentless effects of the Fontan paradox. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2016;19(1):37-43. https://doi.org/10.1053/j.pcsu.2015.11.006
19. Surrey LF, Russo P, Rychik J, et al. Prevalence and characterization of fibrosis in surveillance liver biopsies of patients with Fontan circulation. *Hum Pathol*. 2016;57:106-115. https://doi.org/10.1016/j.humpath.2016.07.006
20. Menachem JN, Golbus JR, Molina M, et al. Successful cardiac transplantation outcomes in patients with adult congenital heart disease. *Heart*. 2017;103(18):1449-1454. https://doi.org/10.1136/heartjnl-2016-310933
21. Greenway SC, Crossland DS, Hudson M, et al. Fontan-associated liver disease: implications for heart transplantation. *J Heart Lung Transplant*. 2016;35(1):26-33. https://doi.org/10.1016/j.healun.2015.10.015
22. Bradley EA, Pinyoluksana K-O, Moore-Clingenpeel M, Miao Y, Daniels C. Isolated heart transplant and combined heart-liver transplant in adult congenital heart disease patients: insights from the united network of organ sharing. *Int J Cardiol*. 2017;228:790-795. https://doi.org/10.1016/j.ijcard.2016.11.121
23. Assenza GE, Graham DA, Landzberg MJ, et al. MELD-XI score and cardiac mortality or transplantation in patients after Fontan surgery. *Heart*. 2013;99(7):491-496. https://doi.org/10.1136/heartjnl-2012-303347
24. Lewis M, Ginns J, Schulze C, et al. Outcomes of adult patients with congenital heart disease after heart transplantation: impact of disease type, previous thoracic surgeries, and bystander organ dysfunction. *J Card Fail*. 2016;22(7):578-582. https://doi.org/10.1016/j.cardfail.2015.09.002

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