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Pediatric Combined Heart-liver Transplantation: A Single-center Long-term Experience

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Background. Combined heart liver transplant (CHLT) continues to gain attention as a surgical treatment for patients with end-stage heart and liver disease but remains rare. We present our institutional longitudinal experience with up to 14 y of follow-up, focused on long-term outcomes in CHLT recipients. **Methods.** We conducted a single-institutional, retrospective review from January 1, 2010, to December 31, 2023, including 7 patients ages 7–17 y who underwent CHLT. **Results.** Most patients were surgically palliated via Fontan procedure pretransplant (n = 6), and all had evidence of advanced fibrosis or cirrhosis before transplant. The 30-d mortality was 14.3% (n = 1, multiorgan failure). During the follow-up period, 1 patient developed acute heart rejection which required treatment and 2 developed acute liver rejection. In all cases, rejection was successfully treated. Two patients developed acute heart rejection which did not require treatment (grade 1R). No patients developed chronic or refractory rejection. No patients developed allograft coronary artery vasculopathy. **Conclusions.** CHLT remains a rarely performed treatment for pediatric patients with end-stage heart and liver disease, but our long-term data suggest that this treatment strategy should be considered more frequently.

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Patients with congenital heart disease necessitating single-ventricle palliation via the Fontan procedure often develop Fontan-associated liver disease, resulting in congestive hepatopathy. As more children survive into adolescence and adulthood with congenital heart disease, the prevalence of congestive hepatopathy, cirrhosis, and liver failure continues to climb dramatically.[1] Combined heart-liver transplant (CHLT) is an uncommon procedure offered to patients with end-stage heart and liver failure.[2] Although the rate of CHLT has increased in the last several years, it remains rare compared with sequential heart and liver transplant[3]; between 1992 and 2017, only 16 pediatric patients underwent CHLT from the same organ donor.

Few studies have examined the long-term outcomes of CHLT in children, which may contribute to the procedure's scarcity despite superior short-term outcomes compared with isolated heart transplant.[4] Here, we present our institutional longitudinal experience with up to 14 y of follow-up, focused on long-term outcomes in CHLT recipients.

We retrospectively reviewed electronic health records of 7 patients younger than 18 y of age who underwent CHLT at our institution from 2010 to 2023. Local institutional review board approval was obtained before review of medical records (institutional review board #52170). Data collected include patient demographics, biopsy results, operative information (time for cross clamp, bypass, and cold ischemia; transfusion requirements; and estimated blood loss), rejection episodes, and immunosuppression data. The mean age at transplant was 14 ± 3 y. Median preoperative weight was 57.8 kg (mean 53.9 ± 11 kg). Five patients were male and 2 were female. Four patients were White, 1 was African American, 1 was Asian, and 1 was Other/Hispanic-Latino. Diagnoses included congenital single-ventricle physiology for 6 patients (hypoplastic left or right ventricle or tricuspid atresia), and double-outlet right ventricle (1 patient). Six patients were surgically palliated through the Fontan procedure (Table 1). Two patients had high

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TABLE 1.
Heart-liver transplant recipient characteristics

Patient No.	Age at transplant (y)	CHD diagnosis	Height percentile (%)	Weight percentile (%)	Preoperative hospital duration (d)	Race/ethnicity	Sex	Preoperative weight (kg)	PELD/MELD score	HLA mismatch level	Blood type	Donor blood type
1	7	DORV with subvalvar PS, VSD, PAPVR. s/p RV to PA conduit, repair of VSD, PAPVR.	74.86	91.13	1	African American/ Non-Hispanic	F	29.8	0	7	AB pos	AB (A1)
2	15	Tricuspid hypoplasia, hypoplastic RV, HLHS, large VSD, s/p PA band, Glenn, PA closure, fenestrated Fontan, PM	2	38	71	Asian/ Non-Hispanic	M	57.8	35	6	B pos	0
3	15	HLHS s/p tricuspid valve annuloplasty and Fontan, tricuspid valve replacement, PM	96	71	36	White/ Non-Hispanic	F	58.5	18	3	A pos	A (A1)
4	17	HLHS s/p Glenn and Fontan, chronic heart failure, ventricular assist device	4	6	4	White/ Non-Hispanic	M	52.6	15	4	A pos	A (not A1)
5	16	Tricuspid atresia, VSD, s/p extracardiac Fontan	7	46	1	Other/Hispanic-Latino	M	62.8	20	3	O pos	0
6	16	Heterotaxy with dextrocardia, common atrium, unbalanced AVSD, DORV, malposed great arteries, s/p Fontan	3	62	17	White/ Non-Hispanic	F	57.6	15	4	O pos	0
7	14	HLHS s/p extracardiac Fontan, Norwood/Sano, BDG with RPA plasty, nonfenestrated Fontan	64	61	19	White/ Non-Hispanic	M	58.4	9	5	A pos	0

AVSD, atrioventricular septal defect; BDG, bidirectional Glenn; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; LVSC, persistent left superior vena cava; MELD, model for end-stage liver disease; NSVT, nonsustained ventricular tachycardia; PAPVR, partial anomalous pulmonary venous return; PELD, pediatric end-stage liver disease; PM, pacemaker; PS, pulmonary stenosis; (R)PA, (right) pulmonary artery; RV, right ventricle; TGA, transposition of the great arteries; VSD, ventricular septal defect.

calculated panel-reactive antibodies; one was de-sensitized pretransplant with IVIg, whereas the other (who additionally was found to have preformed donor-specific antibodies to HLA-B18 by IgG) was not because of volume overload concerns. A third patient was found to be a virtual crossmatch with IgG to HLA-A24. All 3 of these patients received plasmapheresis and IVIg intraoperatively. Pediatric end-stage liver disease score was 0 for the 7-y-old patient, and the median model for end-stage liver disease (MELD) score was 16.5 (mean 18.7 ± 8.8) for the remaining patients. All patients had liver fibrosis confirmed by biopsy or imaging pretransplant which was recapitulated at explant; congestive hepatic fibrosis scores (CHFSs) were 4 (2 patients), 3 (4 patients), and 2b (1 patient).[5] Three patients had ascites pretransplant; of these, 2 had varices confirmed by cross-sectional imaging, whereas 2 of the patients without ascites also had small esophageal varices. One patient had thrombocytopenia (platelets 117 000/μL) and 2 patients had borderline thrombocytopenia (platelets <160 000/μL); 2 of these 3 patients also had varices, but only 1 had concurrent ascites. None of the patients had prior evidence of variceal bleeding. Operative data for CHLT included median cross clamp time of 170 min (mean 206 ± 109 min), bypass time of 290 min (mean 363 ± 151 min), and cold ischemic time of 248 min (mean 238 ± 57 min) (Table 2).

After the surgical intervention, the median hospital stay after transplant was 42 d (mean 41.1 ± 17.4 d). Of 7 patients, 1 (14.3%) underwent hospital readmission within 30 d of initial discharge. The 30-day mortality was 14.3% (1 patient), with cause of death being multisystem organ failure. The operative course for this patient was complicated by significant bleeding requiring massive resuscitation. Postoperative complications for this patient included poor hemodynamics requiring chest reopening and subsequent need for extracorporeal membrane oxygenation, hepatic artery thrombosis requiring reconstruction with an interposition allograft, and cardiac arrest. Three patients had no complications predischarge. Predischarge complications for the remaining 3 patients included atrial fibrillation without hemodynamic changes (1 patient), acute kidney injury requiring dialysis (1 patient), and bile duct obstruction (1 patient).

Postoperative management with induction immunosuppression for all 7 patients included antithymocyte globulin (range: 3–6 doses, 4–6 mg/kg in total) and methylprednisolone. The single patient with preformed donor-specific antibodies received rituximab on postoperative day 10. On postoperative day 30, all surviving patients were receiving tacrolimus (goals 10–12) and mycophenolate. In terms of postoperative rejection, 1 patient had moderate acute heart rejection (2R), 1 had acute heart-liver rejection (1R heart and moderate liver), 2 had mild acute heart rejection (1R, no treatment required), and 1 had mild acute liver rejection during the follow-up period.[6] All episodes of rejection were successfully treated with methylprednisolone and in one case antithymocyte globulin. One patient was started on IVIg because of new donor-specific antibodies discovered as part of rejection evaluation (Table 3). The 1 case of moderate heart rejection occurred in the setting of medication noncompliance. None of the patients developed chronic or refractory rejection. There was an average of 8 negative heart biopsies for those who did not experience heart rejection. There was a total of 3 additional heart and/or liver biopsies performed because of documented follow-up of rejection. One patient had a post-transplant biopsy at 125 mo for follow-up of heart rejection;

TABLE 2.
Preoperative and operative data

Patient no.	Liver pathology	Cross clamp time (min)	Bypass time (min)	Cold ischemia time (min)	Transfusion requirements	Estimated blood loss, L
1	Congested and nodular, pericellular and perivenular fibrosis, bridging fibrosis, perivenular sinusoid dilation and focal nodularity	129	214	248	8 units RBCs, 2 units platelets, 5 units FFP, 3 units cryoprecipitate, 500 mL 5% albumin	2
2	Bridging fibrosis	216	290	276	18 units RBCs, 5 units platelets, 13 units FFP, 7 units cryoprecipitate, 500 units K-centra and FEIBA × 3	1.2
3	Congestive hepatopathy. Bridging fibrosis	360	512	187	30 units RBCs, 6 units platelets, 13 units FFP, 2L crystalloid	7.5
4	Congestive hepatopathy with patchy perisinusoidal fibrosis	170	487	139	27 units RBCs, 4 units platelets, 13 units FFP	Unknown
5	Patchy mild sinusoidal dilation with perisinusoidal fibrosis	129	248	244	11 units RBCs, 5 units platelets, 8 units FFP, 20 units cryoprecipitate, 2L saline, 500 mL 5% albumin	CPB
6	Congestive hepatopathy with sinusoidal dilatation and extensive bridging fibrosis	350	563	258	20 units RBCs + 15 units on pump, 6 units platelets, 12 units FFP + 4 units on pump, 2 units cryoprecipitate	CPB
7	Stage 4 fibrosis	90	224	311	12 units RBCs, 2 units platelets, 7 units FFP, 2 units cryoprecipitate, 0.5 L crystalloid, 250 mL 5% albumin	CPB

CPB, cardiopulmonary bypass; FFP, fresh–frozen plasma; RBC, red blood cell.

another patient had biopsies at 12 and 13 mo posttransplant for follow-up of liver rejection. The remaining patients had postoperative biopsies for surveillance according to our institutional protocol (Table 3). The surviving 6 patients are clinically well as of the last available outpatient clinical note (median follow-up was 2.8 y posttransplant [mean 4.6 ± 4.4 y]). No patients developed transplant coronary allograft vasculopathy.

Since it was first described in 1984, CHLT has become more common but remains available to patients at only a limited number of institutions, and its use in pediatric patients remains even more rare.[7] The implications of heart-only versus CHLT continue to be debated, as few institutions have published long-term outcomes of these patients. The recently published FOSTER (Fontan Outcomes to Improve Transplant Experience and Results) study found that, in adults, even compensated chronic liver disease increased the risk of death after isolated heart transplant.[8] Data in children are scarcer, but in 1 study of 47 pediatric patients with Fontan physiology, 9 underwent CHLT and overall outcomes were similar to the patients who underwent heart-only transplant.[9] However, the 10 patients with pretransplant evidence of cirrhosis who underwent heart-only transplant had a 1-y survival rate of 67% versus 89% in the CHLT group. In another series of 9 pediatric patients with Fontan-associated liver disease, liver biopsy fibrosis scores were overall unchanged post heart transplant.[10] Given the high mortality rate of heart transplant recipients on liver transplant waiting lists, the above data suggest that thresholds for CHLT versus heart-only transplant may need to differ between children and adults, and waiting until pediatric patients have clinical evidence of advanced portal hypertension may lead to inferior outcomes.[11]

In general, patients at our institution who undergo CHLT have higher liver disease scores than those who undergo heart-only transplant.[9] All but 1 patient demonstrated CHFS 3 or 4 liver pathology (bridging fibrosis or cirrhosis); the single patient with CHFS 2b pathology had persistently elevated INR and bilirubin which raised concern for a poor outcome from isolated heart transplant because of compromised hepatic reserve.[12] None of the patients in this study had pretransplant episodes of variceal bleeding, though the development of varices in Fontan-associated liver disease differs from that of other cirrhotic disorders and may be a suboptimal indicator of the degree of hepatic impairment.[12] The majority of patients had evidence of varices on cross-sectional imaging and ascites. Although some of the patients were monitored using ultrasound or magnetic resonance elastography to evaluate liver stiffness longitudinally, this technique has difficulty distinguishing liver fibrosis from congestive hepatopathy and can overestimate stiffness during periods of fluid overload.[13]

In adults who undergo heart transplant, coronary allograft vasculopathy remains a leading cause of graft dysfunction, with a stable incidence in the last 20 y despite improved overall patient survival.[14] In children who undergo heart transplant, the risk of coronary vasculopathy increases with age, the number of episodes of acute rejection, and the presence of chronic rejection.[15] Combined liver transplant with kidney, lung, skin, and intestine has been described, with more recent work demonstrating higher rejection-free survival in combined kidney-liver versus kidney-only transplant; dual-organ transplantation greatly reduced the risk of chronic rejection.[16,17] This pattern of improved clinical and immunologic outcome conferred by the liver was confirmed in a series of

TABLE 3.

Rejection episodes and follow-up

Patient no.	Type of rejection	Grade of heart rejection (months posttransplant)	Grade of liver rejection (months posttransplant)	Treatment (outcome)	Years of follow-up
1	Heart	2R (124)	Unknown	IV steroids, prednisone (resolved)	13 (transitioned to adult care)
	Heart	1R (125)[a]			
2	Heart/Liver	1R (11)	Moderate acute cellular rejection (11)	IV steroids, prednisone (liver resistant)	6 (currently followed)
		1R (12)[a]	Moderate acute cellular rejection (12)	IVIg (new DSA), ATG (liver resolved)	
		1R (13)[a]			
		1R (19)		IVIg (rising DSA)	
		1R (30)			
3	Heart	1R (2)	Unknown		5 (currently followed)
4	Heart	1R (2)	Unknown		3 (transitioned care)
5	None	Unknown	Unknown		3 (currently followed)
6	None	Unknown	Unknown		<1 (deceased)
7	Liver	Unknown	Mild acute cellular rejection (6)	IV steroids, prednisone (liver resolved)	2 (transitioned care)

[a]Biopsy performed for rejection follow-up.
ATG, antithymocyte globulin; DSA, donor-specific antibodies.

patients who underwent heart-kidney and heart-liver transplantation.[18] Although it is difficult to draw definitive conclusions from our small cohort, the fact that none of our patients suffered from chronic rejection or coronary allograft vasculopathy is interesting and warrants further investigation.

Defining which patients may benefit most from CHLT versus heart-only transplant remains a clinical challenge, although our findings build on previous work showing that CHLT should be offered to more patients who have evidence of liver disease.[9]

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