Cost-effectiveness of the National Pediatric Heart Transplantation Program in Australia

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ABSTRACT

Objectives: Cost data for pediatric heart transplantation are scarce. We examined hospital cost of the national pediatric heart transplantation program in Australia and assessed factors associated with increased costs.

Methods: The hospital cost of all children who underwent heart transplantation at a national referral center between January 2003 and June 2015 and were followed more than 1 year was retrospectively analyzed. Lifetime follow-up costs were adjusted for quality of life and projected to life expectancy. All costs were reported in 2016 US dollars.

Results: Of 70 children who underwent heart transplantation in the study period, 61 were followed more than 1 year after transplantation (mean, 4.3 ± 2.5 years). Mean cost of primary heart transplantation was \$278,480 (95% confidence interval, 219,282-337,679) and did not change over time. Pretransplant mechanical circulatory support was required in 36% (22/61) of children. On multivariable analysis, greater admission costs were associated with ventricular assist device and pretransplant length of stay. Mean annual follow-up cost after discharge was \$55,823 (95% confidence interval, 47,631-64,015) in the first year and \$12,119 (95% confidence interval, 8578-15,661) thereafter. Increased first-year follow-up costs were associated with endomyocardial biopsies and length of readmissions. Cost per quality-adjusted life-year gained varied from \$29,161 to \$44,481 on sensitivity analysis. Freedom from treated rejections was 65.5% at 1 year, 63.2% at 3 years, and 59.5% at 5 years. Endomyocardial biopsies contributed to 52% of first-year follow-up costs.

Conclusions: Primary pediatric heart transplantation in Australia is cost-effective for long-term survivors, even for those supported by ventricular assist device. Surveillance endomyocardial biopsy was a major contributor to post-transplantation costs. Selective targeting of surveillance biopsies may be cost-saving. (J Thorac Cardiovasc Surg 2019;157:1158-66)

Endomyocardial biopsies contributed to 52% of first-year follow-up cost after discharge.

Central Message

Pediatric HT in Australia is cost-effective, even for those supported by VAD. EMB is a major contributor to post-transplant cost.

Perspective

Primary pediatric HT in Australia is cost-effective, even for those supported by durable VAD. Endomyocardial biopsies contributed to 52% of cost in first-year follow-up. Selective targeting of surveillance biopsies may be cost-saving.

See Commentary on page 1167.

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Heart transplantation (HT) is resource intensive but remains the standard of care for children with end-stage cardiomyopathy or congenital heart disease (CHD). In the United States, national expenditure on adult HT increased more than 50% over 4 years to reach \$375 million in 2009.¹

Scanning this QR code will take you to the article title page to access supplementary information.

Abbreviations and Acronyms

CHD	= congenital heart disease
CI	= confidence interval
ECMO	= extracorporeal membrane oxygenation
EMB	= endomyocardial biopsy
HT	= heart transplantation
ISHLT	= International Society for Heart and Lung Transplantation
MCS	= mechanical circulatory support
QALY	= quality-adjusted life-year
RCH	= Royal Children's Hospital
USD	= US dollar
VAD	= ventricular assist device

Recent analysis of a nationwide database in the United States found that mean charges for pediatric HT hospitalizations increased more than 60% from 1997 to 2006.² With increasing case complexity and use of ventricular assist devices (VADs) among candidates,³ costs associated with pediatric HT are likely to increase further. Given the country's small population and low donor rate,⁴ a cost-utility study on pediatric HT in Australia is of interest.

Since 1991, the Royal Children's Hospital (RCH) in Melbourne has been the sole National Funded Center for pediatric HT in Australia.⁵ The first VAD was implanted in 2005. In this government-funded program, all hospital costs were reimbursed by the public health system, with no role for private insurance or patient out-of-pocket expenses. Compared with the United States, data in Australia are more likely to reflect true costs rather than hospital charges, with the former generally being less.

In this study, we sought to determine the hospital costs of the national pediatric HT program in Australia. We also assessed factors associated with increased costs.

MATERIALS AND METHODS

Study Design

We performed a retrospective analysis of hospital costs associated with all children who underwent primary HT between January 2003 and June 2015 at the RCH and were followed at this institution for more than 1 year. The study was approved by the hospital's human research ethics committee (#36271C).

The age at transplantation was a mean of 9.9 ± 5.0 years (median, 10.7 years; range, 5.3 months to 18.7 years). Of the cohort, 7% (4/61) were infants (aged <1 year).

Clinical data were collected by retrospective chart review. Costs were retrieved by the finance department on all clinical episodes from the patient's first contact with our hospital until death, transition to an adult center, or June 30, 2016, whichever occurred first. Initial transplantation costs included all costs associated with the admission during which the HT occurred and that of any pretransplant VAD implantation leading up to HT. These included the costs of patient and organ transport, but not organ procurement performed at other hospitals. Costs of admissions and clinics included that of any laboratory tests and prescribed medications.

Children receiving a HeartWare (HeartWare Inc., Framingham, Mass) device implantation were allowed to go home while awaiting transplant, whereas those receiving the Berlin Heart EXCOR (Berlin Heart GmbH, Berlin, Germany) stayed in admission. Induction therapy was generally used in patients with CHD or VAD, or those at risk of donor dysfunction (eg, with pulmonary hypertension, long-distance donors). After hospital discharge, patients were routinely seen at weekly intervals for the first month, fortnightly for 2 months, monthly for the remainder of the first year, and then every 3 months, with additional visits scheduled as required. Each visit involved an electrocardiogram, echocardiogram, medical consultation, and blood tests. Routine surveillance endomyocardial biopsies (EMBs) were performed at 2, 4, 8, and 12 weeks, and then at 6, 9, and 12 months. Sensitized patients and those at increased risk of rejection, including patients with CHD and VAD, also had a biopsy at 4 to 5 months. Additional biopsies were performed if there were clinical concerns. Infants had fewer biopsies, but this varied according to their characteristics and venous access.

Acute cellular rejections and antibody-mediated rejections were graded according to International Society for Heart and Lung Transplantation (ISHLT) guidelines.⁶ Treated rejections were those graded 2R/3R for acute cellular rejection, 1 for antibody-mediated rejection, or the presence of humoral rejection before 2008. Sensitization was panel-reactive antibody 10% or greater. Mechanical circulatory support (MCS) included durable VAD and extracorporeal membrane oxygenation (ECMO). Prolonged mechanical ventilation was 72 hours or greater.⁷ Sepsis was defined as per the 2002 International Consensus Conference on Pediatric Sepsis.⁸ Renal impairment was creatinine clearance less than 40 mL/min/1.73 m². Patients were divided into 3 cohorts according to age at transplantation: preschool (0-5 years), school-age (6-12 years), and teenagers (13-18 years).

In our projection of the lifetime follow-up costs for long-term survivors, we excluded the cost data of children who died or required retransplantation during the study period and used the data of only children who survived for 2 years or more and were still under routine surveillance at the latest follow-up. The mean follow-up cost per patient-year of these children was then assumed to be the mean annual follow-up cost for all long-term survivors.

Costs were adjusted for inflation rates in Australia.⁹ Costs were then converted to US dollars (USD) using the average rate of exchange in 2016, which was \$1 Australian dollar = \$0.7445 USD.¹⁰ All costs were reported in 2016 USD.

Cost-Utility Analysis

Post-transplant life expectancy was assumed to be 25 years for infants, 21.5 years for children aged 1 to 5 years, 16.5 years for children aged 6 to 10 years, and 15.7 years for adolescents aged 11 to 18 years, conditional on survival to 1 year after HT.¹¹ Post-transplant life expectancy for the entire cohort was assumed to be 16 years, age matched to the ISHLT registry.¹¹ Children who required VAD were assumed to have equivalent post-transplant survival as those not requiring MCS.¹¹ Total costs were the sum of initial transplantation plus lifetime follow-up costs.

To calculate the cost per quality-adjusted life-year (QALY) gained over the lifetime of long-term survivors, we calculated a utility score of 0.89 from published quality-of-life data on pediatric HT recipients and healthy children,¹² in which healthy children were presumed to have perfect health (utility score = 1). Life expectancy was multiplied by the utility score to yield the number of QALYs gained. For simplicity, we assumed that children with end-stage heart failure who did not receive HT had negligible QALY. We compared the cost per QALY gained of HT recipients with that of those who would have died without HT at no additional cost.¹³ All future costs were discounted at an annual rate of 3%.

Sensitivity analyses were performed on key assumptions in the model. We varied the post-transplant life expectancy from 14 to 18 years and the utility score from 0.75 to 0.95. Children who required retransplantation were assumed to have a utility score of 0.75.

Statistical Analysis

Continuous variables were reported as mean $\pm$ standard deviation, mean (95% confidence interval [CI]), or median (range) and compared between groups using the Kruskal–Wallis test followed by Dunn test with Bonferroni adjustment. Categorical variables were reported as frequencies and percentages and compared between groups using the Fisher exact test. Freedom from treated rejections was analyzed using the Kaplan–Meier method. Cox regression analysis was performed to evaluate predictors of treated rejections. Linear regression analysis was performed to evaluate differences in continuous variables across the study period. Multiple linear regression models were created to evaluate predictors of increased costs. Variables with at least moderate evidence against the null hypothesis ($P < .10$) in univariable analysis were included in the multivariable analysis. Data were analyzed using Stata version 14 (StataCorp, LP, College Station, Tex). Statistical significance was $P < .05$.

RESULTS

A total of 70 patients underwent primary HT at the RCH during the study period. Patients who were followed at other institutions ($n = 5$) or died ($n = 4$) within the first year were

excluded, none of whom was an infant. Patient characteristics are shown in Table 1.

The mean follow-up time was 4.3 years (median, 4.1 years; range, 1.0–12.1 years). Follow-up time for the entire cohort was 264.7 patient-years. As of June 30, 2016, 35 patients continued follow-up at our institution, 22 transitioned to adult centers, 3 died without retransplantation, and 1 died after retransplantation.

Cost of Initial Heart Transplantation

Mean cost of primary HT was \$278,480 (95% CI, 219,282–337,679; median, \$177,414). The mean length of stay was 53 days (95% CI, 38–68 days; median, 30 days). There was no significant change in mean HT admission length of stay ($P = .73$) or cost ($P = .39$) over the study period. However, the interquartile range of HT admission costs increased through the study period, from \$141,190 in 2003 to 2006 to \$348,464 in 2011 to 2015. The

TABLE 1. Patient characteristics by age at pediatric heart transplantation

Factors	Entire cohort (n = 61)	Age ≤ 5 y (n = 16)	Age 6–12 y (n = 23)	Age 13–18 y (n = 22)	P value
Female, n (%)	29 (48)	7 (44)	15 (65)	7 (32)	.07
Gender mismatch, n (%)	30 (49)	7 (44)	13 (57)	10 (45)	.69
CHD, n (%)	20 (33)	4 (25)	4 (17)	12 (55)	.03
Oversize DRWR (>2.0), n (%)	18 (30)	9 (56)	6 (26)	3 (14)	.02
Sensitization, n (%)	18 (30)	7 (44)	5 (22)	6 (27)	.36
ABO mismatch, n (%)	4 (7)	4 (100)	0 (0)	0 (0)	<.01
Previous sternotomy, n (%)	30 (49)	6 (38)	8 (35)	16 (73)	.02
HT admission LOS, d	30 (8–325)	64 (9–206)	17 (8–65)	39 (9–325)	.01
Pretransplant LOS, d	1 (0–270)	45 (0–181)	0 (0–57)	1 (0–270)	<.01
Post-transplant LOS, d	15 (8–120)	17 (8–40)	14 (8–49)	16 (9–120)	.14
ICU stay, h	117 (22–2446)	148 (48–376)	94 (28–375)	110 (22–2446)	.26
Pretransplant MCS, n (%)	22 (36)	10 (63)	4 (17)	8 (36)	.02
MCS duration, d	61 (2–237)	74 (2–173)	19 (6–223)	43 (4–237)	.67
Pretransplant ECMO, n (%)	10 (16)	5 (31)	1 (4)	4 (18)	.07
ECMO duration, d	5 (2–10)	7 (2–10)	8 (8–8)	4 (2–5)	.34
Pretransplant VAD, n (%)	19 (31)	9 (56)	3 (13)	7 (32)	.02
VAD duration, d	65 (1–235)	74 (1–164)	30 (6–223)	58 (13–235)	.64
Perioperative complications, n (%)					
Additional cardiac procedures*	34 (56)	13 (81)	8 (35)	13 (59)	.01
Delayed chest closure	9 (15)	7 (44)	0 (0)	2 (9)	<.001
Emergency chest exploration	14 (23)	5 (31)	2 (9)	7 (32)	.12
Pretransplant MV, n (%)	11 (18)	6 (38)	1 (4)	4 (18)	.03
Prolonged MV post-transplant (≥ 72 h)	18 (30)	9 (56)	5 (22)	4 (18)	.03
Renal impairment	20 (33)	1 (6)	6 (26)	13 (59)	<.01

Data are presented as median (range) or number (%). **Bold P values** were statistically significant. CHD, Congenital heart disease; DRWR, donor–recipient weight ratio; ABO, ABO blood group; HT, heart transplantation; LOS, length of stay; ICU, intensive care unit; MCS, mechanical circulatory support; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device; MV, mechanical ventilation. *Additional cardiac procedures included aortic valve repair/replacement, central venous catheter insertion, chest exploration, ECMO de/cannulation, femoral embolectomy, pacemaker explant, thoracotomy, and wound revision.

breakdown of cost components according to age at transplantation is shown in [Table E1](#). Children undergoing transplantation in the preschool or teenage years incurred significantly higher HT costs than school-age children ($P < .01$), driven by longer admissions, more prevalent requirement of MCS, and more perioperative complications ([Table 1](#)).

Twenty-two patients (36%, 22/61) required pretransplant MCS, including 7 supported by ECMO and then VAD, 3 supported by ECMO only, and 12 supported by VAD only. The duration of MCS is shown in [Table 1](#). Patients who required MCS incurred significantly higher HT costs than other patients ($\$493,564 \pm \$229,995$ vs $\$157,151 \pm \$129,396$, $P < .001$). Of the 19 patients bridged to HT with VAD, the Berlin Heart device was implanted in 9 patients, the HeartWare device was implanted in 2 patients, and the Thoratec Para-corporeal VAD (Thoratec Corp, Pleasanton, Calif) was implanted in 8 patients. More than half (53%, 10/19) of all VADs were implanted in 2011 to 2015.

Predictors of increased HT costs are shown in [Table 2](#). No cost difference was found between patients with CHD and patients with cardiomyopathy ($\$261,930 \pm \$214,888$ vs $\$312,407 \pm \$276,979$, $P = .44$). There was a trend toward lower cost among patients with the HeartWare versus the Berlin Heart device ($\$394,071 \pm \$52,938$ vs $\$641,650 \pm \$171,196$, $P = .08$). Pretransplant length of stay and VAD were independent predictors of increased costs.

Costs in First Year After Transplantation

Mean first-year follow-up cost after discharge was $\$55,823$ (95% CI, 47,631-64,015; median $\$48,886$, [Table E1](#)). Teenagers incurred significantly higher biopsy costs

than younger children ($\$38,807 \pm \$18,293$ vs $\$26,532 \pm \$17,707$, $P < .01$), contributing to higher follow-up costs overall ($\$71,978 \pm \$37,262$ vs $\$46,710 \pm \$26,060$, $P < .01$). Patients undergoing transplantation in the last 4 years of the study period had fewer follow-up EMBs (4.3 ± 1.8 vs 9.5 ± 1.7 , $P < .001$) and shorter readmission stays (2 ± 3 vs 11 ± 14 days, $P = .02$) than those undergoing transplantation in the first 4 years, incurring lower first-year follow-up costs ($\$45,952 \pm \$20,512$ vs $\$82,682 \pm \$23,297$, $P = .003$). There was no significant difference in outpatient medication costs between patients on cyclosporine versus tacrolimus ($\$11,042 \pm \8436 vs $\$16,913 \pm \$20,810$, $P = .12$). Factors associated with increased first-year follow-up costs are shown in [Table 3](#). There was a trend toward older age at HT and CHD being associated with increased follow-up costs. EMBs and hospital readmissions independently predicted higher costs.

Patients underwent an average of 7.8 ± 3.3 EMBs in the first year, including 5.7 ± 2.9 after hospital discharge. Teenagers had significantly more follow-up biopsies than younger children (6.7 ± 2.4 vs 5.1 ± 2.9 , $P = .03$). Patients with treated rejections before discharge ($n = 8$) also had more follow-up biopsies than patients without (7.9 ± 2.9 vs 5.3 ± 2.7 , $P = .03$). The mean cost of each EMB episode was $\$5474$ (95% CI, 5154-5794), which included the costs of associated catheterization and hospital admissions. The mean cost of EMBs in the first year postdischarge was $\$30,959$ (95% CI, 26,258-35,661) ([Table E1](#)). Of all surveillance EMBs performed in the first year, 81% (280/345) were day procedures with a mean cost of $\$4933$ (95% CI, 4668-5198); 15% (53/345) required an overnight stay with a mean cost of $\$6598$ (95% CI, 5969-7227, $P < .001$); and 3% (12/

TABLE 2. Predictors of increased primary pediatric heart transplantation cost

Factors	Univariable analysis*			Multivariable analysis			
	Mean initial HT cost (\$)	95% CI (\$)	P value	β coefficient (\$) [†]	95% CI (\$)	P value	VIF
VAD	534,532	435,626-633,438	<.001	154,812	56,736-252,887	.003	2.15
Pretransplant length of stay (per day)	3442	2777-4106	<.001	1998	1194-2802	<.001	2.01
Age ≤ 5 y	423,530	283,479-563,581	.02	n/a	n/a	.82	1.56
Additional cardiac procedures [‡]	392,654	306,420-478,888	<.001	n/a	n/a	.30	1.70
ECMO	531,507	349,421-713,593	<.001	n/a	n/a	.84	1.64
Emergency chest exploration	514,663	378,582-650,744	<.001	n/a	n/a	.17	1.54
Delayed chest closure	442,045	234,300-649,790	.049	n/a	n/a	.67	1.73
Prolonged MV post-transplant (≥ 72 h)	429,081	287,743-570,419	<.01	n/a	n/a	.28	1.39

Bold P values are statistically significant. HT, Heart transplantation; CI, confidence interval; VIF, variance inflation factor; VAD, ventricular assist device; n/a, not applicable; ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation. *Variables included in univariable analysis were additional cardiac procedures, age ≤ 5 years, CHD, delayed chest closure, ECMO, emergency chest exploration, female, gender mismatch, number of years since 2003, oversize donor-recipient weight ratio (>2.0), previous Fontan, sensitization, prolonged MV, pulmonary hypertension, renal impairment, respiratory infection, sepsis, stroke, treated rejection episode before discharge, univentricular physiology, and VAD. Only listed variables had $P < .10$. [†]The β coefficient indicates how a 1-unit change in the value of the independent variable would affect the value of HT admission cost if all other variables in the model were constant. [‡]Additional cardiac procedures included aortic valve repair/replacement, central venous catheter insertion, chest exploration, ECMO de/cannulation, femoral embolectomy, pacemaker explant, thoracotomy, and wound revision. All costs are presented in 2016 USD.

TABLE 3. Predictors of increased follow-up cost in the first year from discharge after pediatric heart transplantation

Factors	Univariable analysis*			Multivariable analysis			
	Mean first-year follow-up cost (\$)	95% CI (\$)	P value	β coefficient (\$) [†]	95% CI (\$)	P value	VIF
EMBs in first year after discharge (per episode)	7929 [†]	5791-10,066	<.001	5254	3122-7386	<.001	1.82
Readmission in first year after discharge (per day)	2434 [†]	1775-3093	<.001	1533	897-2169	<.001	1.73
Age at HT (per year)	2639 [†]	1100-4179	.001	n/a	n/a	.06	1.40
CHD	69,550	51,874-87,226	.04	n/a	n/a	.08	1.29
Renal impairment during HT admission	69,589	49,555-89,623	.02	n/a	n/a	.99	1.52
Sepsis during HT admission	92,801	56,091-129,511	.02	n/a	n/a	.45	1.51
Treated rejection during first year after discharge	73,453	60,538-86,368	<.001	n/a	n/a	.94	1.62

Bold P values are statistically significant. CI, Confidence interval; VIF, variance inflation factor; EMB, endomyocardial biopsy; HT, heart transplantation; n/a, not applicable; CHD, congenital heart disease. *Other variables examined in univariable analysis included ABO mismatch, additional cardiac procedure, concomitant reconstruction of the great vessels, delayed chest closure, emergency chest reexploration, female, gender mismatch, hypoplastic left heart syndrome, oversize donor-recipient weight ratio (>2.0), preoperative length of stay >1 week, pretransplant MCS, previous Fontan, previous sternotomy, treated rejection episode during admission, and univentricular physiology. Only listed variables had $P < .10$. [†]The β coefficient indicates how a 1-unit change in the value of the independent variable would affect the value of first-year follow-up cost if all other variables in the model were constant. All costs are presented in 2016 USD.

345) required admission 2 days or more with a mean cost of \$11,263 (95% CI, 8958-17,322, $P < .001$). Surveillance EMBs contributed 52% of follow-up costs during the first year (Figure 1, A).

Costs Beyond First Year After Transplantation

As of June 30, 2016, 48 patients were followed for 2 years or more after HT. Of these, 44 patients had routine follow-up at 5.2 ± 2.2 years after HT, incurring a mean annual follow-up cost of \$12,119 (95% CI, 8578-15,661) beyond the first year (Table E1). One patient received retransplantation at 5.2 years after primary HT and then died 3.8 years after retransplantation, incurring a retransplantation cost of \$103,865 and then an annual follow-up cost of \$101,092 until death. The remaining 3 children died at 2.2, 2.6, and 8.6 years after HT, respectively, with a mean annual follow-up cost of \$147,840 (95% CI, 37,984-257,696) until death.

Beyond the first year, the mean cost of EMB was \$7786 per episode. Costs of EMBs contributed 19% of annual costs beyond the first year (Figure 1, B).

Treated Rejection Episodes

Freedom from treated rejections for the entire cohort was 65.5% at 1 year, 63.2% at 3 years, and 59.5% at 5 years (Figure 2, A). There was a trend toward a lower risk of rejection among infants ($P = .089$, Figure 2, B), none of whom had an episode of rejection during 3.9 ± 2.3 years of follow-up. Risk factors for treated rejections are shown in Table E2. On multivariable analysis, gender mismatch was the only significant predictor.

Cost-Utility Analysis

Overall cost analysis is summarized in Table 4. The mean lifetime cost for long-term survivors was \$483,319 (95% CI, 372,389-594,263). After adjusting for quality of life, the cost per QALY gained was \$33,941 (95% CI, 26,151-41,732) for long-term survivors, \$46,346 (95% CI, 35,704-56,988) for those supported by VAD without ECMO, and \$123,407 for the 1 patient who required retransplantation. On sensitivity analysis, the cost per QALY gained for primary HT varied from \$29,161 to \$44,481 (Table 5).

FIGURE 1. Components of the follow-up cost during the first year (A) and per patient-year beyond the first year (B) from discharge after pediatric HT.

FIGURE 2. Kaplan–Meier curves demonstrating freedom from treated rejection events for the entire cohort (A) and according to age at the time of pediatric HT (B). Shaded areas are 95% CIs. *CI*, Confidence interval.

DISCUSSION

Data on costs of pediatric HT are scarce. Gajarski and colleagues¹⁴ from Houston reported mean hospital charges of \$49,249 and yearly follow-up charges of \$35,225 for pediatric HT in 1993, which equate to \$81,800 and \$58,500 in 2016, respectively.¹⁵ Laboratory, physician, nursing, and ventilator charges were not available, which likely have led to underestimation of the total costs. Dayton and colleagues¹³ in Atlanta found that the mean cost of initial hospitalization and organ procurement exceeded \$220,000 in 2004 dollars, which equates to \$281,000 in 2016.¹⁵ Annual follow-up costs were estimated at \$18,141 in the first year and \$18,480 per year thereafter. The cost per QALY gained

was just under an arbitrary cost-effectiveness threshold of \$50,000. The costs of VADs were not included, because most of their transplantations were performed in the pre-VAD era. Recently, Law and colleagues² examined a nationwide US database and found that mean hospital charges increased more than 60% over 10 years to \$451,738 in 2006, which equates to \$539,000 in 2016.¹⁵ However, hospital charges may not equate to true costs, but rather reflect individual hospital's cost-to-charge ratios. Our study suggests that the cost-utility of pediatric HT in Australia may appear more favorable than that reported in the United States. Our mean primary HT cost of \$278,480 and mean total lifetime cost of \$483,319 were similar to

TABLE 4. Cost-utility analyses of lifetime follow-up after primary pediatric heart transplantation

	Entire cohort (n = 61)	Infants (n = 4)	Age 1-5 y (n = 12)	Age 6-10 y (n = 16)	Age 11-18 y (n = 29)	VAD (n = 12)
Initial HT cost	\$278,480 (219,282-337,679)	\$417,660 (96,092-739,228)	\$425,487 (263,449-587,525)	\$157,485 (103,909-211,061)	\$265,209 (185,050-345,369)	\$461,944 (367,318-556,570)
Year 1 follow-up cost	\$55,823 (47,631-64,015)	\$41,226 (29,746-52,706)	\$38,861 (27,983-49,740)	\$47,477 (31,898-63,056)	\$69,460 (56,873-82,047)	\$49,006 (35,636-62,376)
Annual follow-up cost after year 1*	\$12,119 (8578-15,661)	\$12,119 (8578-15,661)	\$12,119 (8578-15,661)	\$12,119 (8578-15,661)	\$12,119 (8578-15,661)	\$12,119 (8578-15,661)
Life expectancy after HT, conditional on 1-y survival (y)	16	25	21.5	16.5	15.7	16
Total lifetime cost	\$483,319 (372,389-594,263)	\$670,285 (275,469-1,065,118)	\$656,767 (427,629-885,922)	\$361,757 (246,789-476,738)	\$483,685 (347,399-619,985)	\$659,966 (508,430-811,515)
Cost per year of life gained	\$30,207 (23,274-37,141)	\$26,811 (11,019-42,605)	\$30,547 (19,890-41,206)	\$21,925 (14,957-28,893)	\$30,808 (22,127-39,489)	\$41,248 (31,777-50,720)
Cost per QALY gained†	\$33,941 (26,151-41,732)	\$30,125 (12,381-47,870)	\$34,323 (22,348-46,299)	\$24,634 (16,805-32,464)	\$34,616 (24,862-44,370)	\$46,346 (35,704-56,988)

Data are presented as mean (95% CI). Future costs were adjusted by 3% per annum. All costs are presented in 2016 USD. VAD, Ventricular assist device; HT, heart transplantation; QALY, quality-adjusted life year. *Assuming the mean annual follow-up cost of patients followed 2 years or more and still under routine surveillance at last follow-up (ie, \$12,119) to be the expected mean annual follow-up cost for all long-term survivors. †Quality-of-life utility score was assumed to be 0.89.

the findings of Dayton and colleagues¹³ after adjusting for inflation, whereas our cost per QALY gained of \$29,161 to \$44,481 was substantially lower than their reported range of \$44,943 to \$57,628.¹³ However, there are underlying differences between the 2 country's healthcare systems, such that direct comparison of cost-utility may not be feasible. The pediatric HT program in Australia is single-payer and government funded, and operates at a single center. In contrast, variations in cost-to-charge ratios between hospitals and insurance providers in the multipayer US system may lead to large discrepancies in surgical costs.¹⁶ A more appropriate comparison would be one with other single-payer systems such as the United Kingdom or Canada, but cost data from outside the United States are scarce at the present. Furthermore, geographic variations in patient demographics may contribute to cost differences. According to the ISHLT registry,¹¹ infants and children with CHD were both more common in North America than in other parts of the world. Moreover, later calendar year was independently associated with increased mean charges in the United States, even after accounting for greater morbidities.² In contrast, we found no significant change in the mean cost of pediatric HT hospitalizations in Australia over the study period. This suggests that other nonclinical cost drivers may be at play in the United States. Nevertheless, our study demonstrates that primary pediatric HT in Australia is cost-effective for long-term survivors. Our cost per QALY gained was well below the commonly cited threshold of \$50,000 and in line with World Health Organization recommendations of less than 3 times gross domestic product per capita,¹⁷ which was \$48,178 USD for Australia

in 2016.¹⁸ The patient who required retransplantation incurred a less favorable cost-effectiveness ratio, costing approximately 4 times as much per QALY gained. However, given that only 2% of our cohort required retransplantation, pediatric HT is likely cost-effective for the majority of recipients.

We demonstrated that hospital length-of-stay and VAD were associated with increased cost of pediatric HT, consistent with findings in the United States.² We also found that children undergoing transplantation in the preschool or teenage years incurred significantly higher costs than school-age children, which has not been reported previously. The substantial HT costs associated with children aged 5 years or less likely relate to their heightened clinical urgency, as evident in prolonged pretransplant admission, more prevalent requirement for MCS, and more perioperative complications. This is in keeping with previous studies reporting a high risk of early mortality among infants due to early graft failure.¹⁹ Furthermore, preschool-age children had significantly higher readmission costs after the first year, consistent with the findings of Joffe and colleagues²⁰ that adverse neurodevelopmental outcomes and rehospitalizations were common in this age group. Nonetheless, these young children achieved similar cost-utility as older children, because their higher lifetime costs were offset by greater survival gain. Likewise, the substantial cost associated with teenagers likely relate to their increased clinical complexity, especially of children with palliated CHD who commonly present with cardiac failure at this age. We have previously reported that children with CHD undergoing HT more often underwent complex vascular

TABLE 5. Sensitivity analysis: Cost per quality-adjusted life-year gained for long-term survivors after primary pediatric heart transplantation

	Quality-of-life utility score		
	0.75	0.89	0.95
Life expectancy after pediatric HT			
14 y	\$44,481 (34,369-54,595)	\$37,484 (28,963-46,007)	\$35,117 (27,134-43,101)
16 y	\$40,277 (31,032-49,522)	\$33,941 (26,151-41,732)	\$31,797 (24,499-39,096)
18 y	\$36,937 (28,388-45,487)	\$31,127 (23,923-38,332)	\$29,161 (22,412-35,911)

Data are presented as mean (95% CI). Future costs were adjusted by 3% per annum. All costs are presented in 2016 USD. HT, Heart transplantation.

reconstructions and required more prolonged intraoperative preparation,³ which are likely to increase costs. Furthermore, older children more frequently underwent surveillance EMBs than younger children, which incurred substantial follow-up costs.

Similar to previous studies,^{13,14} our study demonstrated that the cost of initial admission contributed the greatest proportion toward total costs. Furthermore, admissions involving MCS were particularly expensive, costing 3 times as much as other admissions. Mahle and colleagues²¹ in North America reported cost-utility of \$119,937 per QALY saved for VAD bridge-to-transplant in children, concluding that it was not cost-effective. In contrast, we demonstrated that VAD bridge-to-transplant in Australia yields a cost-utility of \$46,346 per QALY gained for children who survived to transplantation. We have previously reported that children supported with VADs before HT had similar survival as those without.²² Our findings are a proof of concept that VAD bridge-to-transplant in children can be cost-effective, at least in those who survive to transplantation. However, the cost-effectiveness of our pediatric VAD program overall certainly warrants further study.

A major finding of our study was that EMBs contributed 52% of follow-up costs within the first year after discharge and independently predicted increased follow-up costs. Dayton and colleagues¹³ similarly reported that costs of catheterization and EMBs accounted for 42% of follow-up costs within the first year. In our cohort, overnight admissions were required after 15% of follow-up EMBs and admissions more than 2 days were required after 3%, which accrued significantly higher costs. Thus, it would be beneficial to reduce the frequency of routine EMBs.

In our cohort, freedom from treated rejections was 65% at 1 year and remained relatively stable thereafter, in keeping with the known fact that rejection rate is highest in the first 3 months post-transplantation.²³ In fact, the value of EMBs beyond 6 months after HT has been questioned.²⁴ Wagner and colleagues²³ showed a time-dependent decrease in the diagnostic yield of EMB in children. Likewise, Zinn and colleagues²⁵ demonstrated that freedom from rejection was 93% at 3 years in children who survived the first year without rejection. In light of these findings, it

has been proposed that surveillance intensity should be focused on children with rejection in the first year and reduced in those without.²⁵

Our study also identified associations among gender mismatch, infancy, and rejection episodes. Gender mismatch is a known risk factor for poor post-transplant outcomes in both adults²⁶ and children,²⁷ including increased incidence of rejections in the first year.²⁶ Thus, intense surveillance may be more cost-effective if devoted to gender-mismatched recipients. Likewise, none of our infants had clinically significant rejection during a mean follow-up of 3.9 years, consistent with the observations of Ibrahim and colleagues.²⁸ It has been argued that surveillance EMBs are unnecessary beyond 6 months in infants without clinical suspicion of rejection.²⁹ Limiting surveillance EMBs to children with known risk factors for rejection, such as gender mismatch or transplantation after infancy, may potentially be cost-saving.

Study Limitations

Healthcare costs may be more regulated under the Australian healthcare system than in other countries; thus, reported costs may not be generalizable. Cost data on retransplantation were available from only 1 patient, which may not allow meaningful extrapolation to the entire cohort. Follow-up costs from our pediatric center were projected into adulthood, which may not reflect actual costs in adult centers.

CONCLUSIONS

Primary pediatric HT in Australia is cost-effective for long-term survivors, even for those supported by VAD. VAD implantation and pretransplant length of stay were independently associated with increased costs. Surveillance EMB was a major contributor to post-transplantation costs. Selective targeting of surveillance biopsies may be cost-saving.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: cost, endomyocardial biopsy, heart transplantation, pediatrics, rejection

TABLE E1. Cost components of pediatric heart transplantation admission and follow-up, according to age at time of transplantation

	Entire cohort (n = 61)	Age ≤5 y ^a (n = 16)	Age 6-12 y ^b (n = 23)	Age 13-18 y ^c (n = 22)	P value
Primary HT, \$					
Total admission cost	278,480 (219,282-337,679)	423,530 (283,479-563,581)	148,536 (110,070-187,002)	308,840 (210,066-407,614)	<.01 (a > b*; b < c†)
Surgical and theatre	86,855 (69,819-103,892)	127,426 (77,796-177,056)	52,307 (41,469-63,145)	93,468 (72,591-114,345)	<.01 (a > b*; b < c*)
ICU	59,637 (40,105-79,168)	80,088 (45,723-114,453)	27,579 (16,481-38,677)	78,278 (34,028-122,528)	.01 (a > b*)
Medical	41,274 (28,926-53,622)	77,769 (42,896-112,642)	23,644 (14,502-32,786)	30,758 (18,863-42,653)	.02 (a > b†; a > c†)
Nursing	38,934 (26,343-51,526)	68,414 (31,667-105,161)	19,306 (12,468-26,144)	38,015 (19,781-56,249)	.049 (a > b†)
Pathology/laboratory	19,887 (15,090-24,683)	26,517 (16,797-36,237)	11,620 (7142-16,098)	23,707 (14,241-33,173)	.01 (a > b*; b < c†)
Pharmacy	13,920 (8672-19,168)	10,580 (5679-15,481)	7613 (4335-10,891)	22,942 (9904-35,980)	<.01 (b < c*)
Prostheses‡	11,694 (5421-17,967)	19,524 (2686-36,362)	4307 (0-9685)	13,386 (3057-23,715)	<.01 (a > b*; b < c*)
Allied health	6410 (4204-8616)	9737 (5340-14,134)	3049 (1726-4372)	7503 (2735-12,271)	.03 (a > b†)
Imaging	2792 (2009-3576)	3517 (2006-5028)	1710 (977-2443)	3397 (1744-5050)	.06
First year after discharge, \$					
Annual follow-up cost	55,823 (47,631-64,015)	39,452 (30,970-47,934)	51,758 (39,472-64,044)	71,978 (56,407-87,549)	<.01 (a < c*; b < c†)
Endomyocardial biopsies	30,959 (26,258-35,661)	23,654 (15,678-31,630)	28,534 (20,881-36,187)	38,807 (31,163-46,451)	.02 (a < c†)
Cardiology clinic and medications	7122 (5664-8580)	5496 (3564-7428)	791 (4768-8814)	8651 (5551-11,751)	.47
Hospital readmissions§	6127 (2860-9394)	2502 (954-4050)	6935 (923-12,947)	7920 (1497-14,343)	.89
Allied health	2666 (1908-3424)	2209 (976-3442)	2823 (1711-3935)	2992 (1240-4744)	.69
Echocardiography	2919 (2581-3257)	1996 (1469-2523)	2128 (1759-2497)	2349 (1903-2795)	.45
Noncardiology clinic and medications	1775 (1166-2383)	661 (316-1006)	2249 (861-3637)	2149 (1332-2966)	.07
ED attendance without admission	849 (443-1255)	814 (139-1489)	944 (204-1684)	768 (36-1500)	.97
After first year, \$ per patient-year of follow-up (n = 44)¶		n = 10	n = 19	n = 15	
Follow-up time post HT (y), median (range)	4.1 (1.0-12.1)	3.0 (1.2-8.6)	4.8 (1.0-12.1)	3.9 (1.0-6.9)	.07
Annual follow-up cost	12,119 (8578-15,661)	16,145 (4758-27,532)	8477 (5098-11,856)	14,048 (8549-19,547)	.32
Hospital readmissions§	2999 (1264-4735)	6854 (598-13,110)	1135 (8-2262)	2054 (279-3829)	.03 (a > b†)
Cardiology clinic and medications	2899 (2222-3577)	1932 (1379-2485)	2263 (1282-3244)	4274 (2999-5549)	.01 (a < c†; b < c*)
Endomyocardial biopsies	2796 (1787-3805)	1833 (469-3197)	1941 (868-3014)	3907 (1762-6052)	.31
Noncardiology clinic and medications	1517 (588-2446)	1833 (0-3679)	750 (146-1364)	2216 (0-4441)	.25
ED attendance without admission	1028 (93-1963)	1177 (154-2200)	102 (0-227)	2304 (0-5472)	.04 (a > b†)
Allied health	448 (252-644)	434 (175-693)	321 (135-507)	616 (119-1113)	.71
Echocardiography	445 (363-526)	323 (227-419)	363 (272-454)	614 (447-781)	<.01 (a < c*; b < c†)
Day admissions	391 (153-628)	452 (0-1088)	233 (0-497)	537 (96-978)	.25

Bold P values are statistically significant. Data are presented as mean (95% CI) unless otherwise specified. All costs are reported in 2016 USD. HT, Heart transplantation; ICU, intensive care unit; ED, emergency department. ^aAge ≤5 years. ^bAge 6 to 12 years. ^cAge 13 to 18 years. *P < .01. †P < .05. ‡Prostheses were all implanted material, including biological tissues, pacemaker, wires, lines, and other medical devices, excluding VADs and ECMO. §Hospital readmissions other than those after endomyocardial biopsies. ||Assuming each echocardiography costs \$230.65 Australian dollar (\$171.72 USD) in 2016 value. ¶Patients followed for at least 2 full years (n = 48), excluding patients who subsequently died (n = 3) or required retransplantation (n = 1).

TABLE E2. Predictors of treated rejection episodes after pediatric heart transplantation

Factors	Univariable analysis*		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age >5 y	3.0 (0.89-10.0)	.08	2.5 (0.7-8.9)	.16
CHD	2.3 (1.007-5.2)	.048	1.8 (0.7-4.3)	.20
EBV mismatch	2.3 (0.95-5.6)	.07	1.5 (0.6-3.9)	.38
Gender mismatch	3.5 (1.4-8.9)	.01	2.9 (1.1-7.8)	.03
Oversize DRWR (>2.0)	0.3 (0.1-0.99)	.05	0.7 (0.2-2.8)	.65

Bold P values are statistically significant. HR, Hazard ratio; CI, confidence interval; CHD, congenital heart disease; EBV, Epstein-Barr virus; DRWR, donor-recipient weight ratio.

*Variables included in univariable analysis were gender mismatch, age >5 years, CHD, oversize DRWR, EBV mismatch, ever had VAD, ever had ECMO, sensitization, cytomegalovirus serology mismatch, preoperative transfusion, and previous sternotomy. Only listed variables had $P < .10$.