International Journal of Pediatrics & Neonatal Care
Original Article Open Access

Evolving Strategy of Mechanical Bridge to Pediatric Heart Transplantation: A 25-year Single-center Experience

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Abstract

Background: An increasing number of children are being supported with ventricular assist devices (VADs) as a bridge-to-transplantation (BTT) strategy. We aim to investigate the temporal variation in pediatric heart transplant practices in our institution, regarding recipient characteristics and post-transplant outcomes, and correlate these practices with the evolution in pediatric mechanical bridging devices.

Methods: Data from all heart transplant recipients who underwent transplantation at less than 17 years of age from 1995 through 2021 at the National Taiwan University Hospital were retrospectively reviewed.

Results: Sixty-one heart transplantations were included. The cohort was grouped according to the predominate mechanical BTT used in our institution. There were 17 cases before 2006 when the predominate BTT was extracorporeal membrane oxygenation (ECMO) and 44 cases after 2006 when VAD became the predominate BTT. The size of recipients has grown, and more recipients were transplanted with mechanical circulatory support (MCS) in the recent era (MCS BTT: 17.6% before 2006, 38.6% after 2006, p= 0.12). The average duration of MCS support was 1 day for ECMO before 2006 and 42 days for VAD after 2006. Nine of the 16 VADs were transitioned from ECMO. The average duration of ECMO support was 8 days before the transition to VAD. Compared to the ECMO-only group, both the ECMO-to-VAD and direct VAD groups had excellent early outcomes (88.9% and 100% hospital survival).

Conclusion: This study demonstrated that the expanding use of VAD as a bridge to transplantation in pediatric patients accommodated the increasing numbers of critically ill children undergoing transplantation, without compromising post-transplant outcomes in our institution. The early post-transplant survival rates of the ECMO-to-VAD and direct VAD strategies were comparable. More evidence to suggest an optimal device strategy in pediatric heart transplant is warranted.

Publication History:

Received: February 20, 2022
Accepted: March 05, 2022
Published: March 07, 2022

Keywords:

Extracorporeal membrane oxygenation, Heart transplant, Pediatric, ventricular assist device

Introduction

Of all candidates listed for solid organ transplantation in the United States, children in need of heart transplantation face one of the highest waiting list mortalities [1]. In adult patients, mechanical bridge with ventricular assist devices (VAD) has proven to significantly improve functional status, quality of life and waiting list mortality [2,3]. A similar beneficial effect of VAD use on waiting list mortality has been suggested in pediatric patients [4]. As a result, an increasing number of patients are supported with VAD as a bridge-to-transplantation (BTT) strategy, both in adults and in children. In pediatric heart transplant centers, up to 30-40% of heart transplant recipients have been transplanted on VAD in the recent era, compared with only 15.7% recipients in the past decade [5].

Comparable late post-transplant outcomes between adult patients not requiring mechanical circulatory support (MCS) support and patients bridged on VAD have been reported in recent studies, though there was a higher risk of mortality within the first year post-transplant in the VAD group [6,7]. In pediatric patients, transplant on VAD did not have a negative impact on post-transplant survival [8-10].

ECMO is a rapidly applicable and easily accessible first-line short-term MCS. It could be widely used in the pediatric population, especially for small children whose heart failure is most likely to be associated with complex structural heart disease. Traditionally, ECMO is utilized to bridge the most critical pediatric candidates for heart transplantation. However, the resulting increase in left ventricular afterload on ECMO is associated with ventricular arrhythmias, pulmonary edema, thrombotic events, and multiorgan dysfunction [11]. Along with remarkable advances in device technology, VAD has demonstrated excellent durability and complication profiles and improved ventricular unloading. In children awaiting heart transplantation in the U.S., a survival advantage for VAD over ECMO in waitlist outcome as well as in post-transplant outcome has been reported [12].

Berlin Heart EXCOR (Berlin Heart, Inc, Texas, USA) is the only Food and Drug Administration (FDA)-approved VAD for children and was first introduced in Taiwan in 2006. Before 2006, ECMO was the predominant MCS available for bridging pediatric candidates to heart transplantation in our institution. Since the introduction of Berlin Heart EXCOR, adult VAD was permitted for use in selected adolescents. With accumulating data demonstrating the better device performance and clinical outcome of continuous-flow pumps over

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Citation: Fu HY, Chou HW, Tsao CI, Huang SC, Chi NH, et al. (2022) Evolving Strategy of Mechanical Bridge to Pediatric Heart Transplantation: A 25-year Single-center Experience. Int J Pediatr Neonat Care 8: 184. doi: https://doi.org/10.15344/2455-2364/2022/184

pulsatile-flow pumps, we started to implant CentriMag (Abbott, IL, USA), Rotaflow (Maquet, Rastatt, Germany), and the alternative configuration of Berlin Heart or Medos (Aachen, Germany) cannulas connected to a centrifugal pump in our pediatric candidates [13].

Goals

The primary goal of this study was to investigate the temporal variation in pediatric heart transplant practices in our institution, regarding recipient characteristics and post-transplant outcomes, and correlate these practices with the evolution in pediatric mechanical bridging devices. The secondary goal was to identify the potential predictors of post-transplant outcome in our patients.

Materials and method

Study cohort

Databases of all heart transplant recipients who underwent transplantation at less than 17 years of age from 1995 through 2021 at the National Taiwan University Hospital (NTUH) were retrospectively reviewed. Data was extracted from the institution's transplant database. This study was approved by the Institutional Research Ethics Committee (REC, RIN, NTUH 201510022 RIND) on October 23, 2015, and consent from statutory agents or parents was waived.

Clinical variables of pediatric recipients prior to transplantation, including age, weight, etiology of heart failure, cardiac surgery history, MCS use, United Network for Organ Sharing (UNOS) status, prospective complement-dependent cytotoxicity crossmatch, panel reactive antibody, donor demographics and surgical records, were retrieved from prospectively collected transplant databases. Longitudinal data regarding post-transplant follow-up were obtained from medical records or case managers for out-of-hospital events.

Post-transplant management

The immunosuppressant protocol, including the induction and maintenance regimen and intensified therapy for acute rejection in our institution, were described in other reports [14-17]. Basically, most recipients received induction therapy with rabbit antithymocyte globulin (RATG). Maintenance therapy included calcineurin inhibitor (cyclosporine in earlier era, tacrolimus in later era), everolimus, steroid, and/or azathioprine or mycophenolate mofetil (MMF) in three or four combined therapies. Pulse therapy or plasmapheresis with intravenous immunoglobulin (IVIG) was indicated for severe acute rejection.

Pediatric recipients received endomyocardial biopsy (EMB) with routine C4d immunohistochemistry staining every week in the first month and then every three months in the first year after transplantation. Monthly outpatient clinic visits were arranged for echocardiography check-up and immunosuppressant level adjustment within the first year. Beyond the first year, low-risk recipients underwent EMB and echocardiography every year. Additional clinical event-driven examinations could be ordered for high-risk recipients. Annual coronary angiography was not performed regularly in small

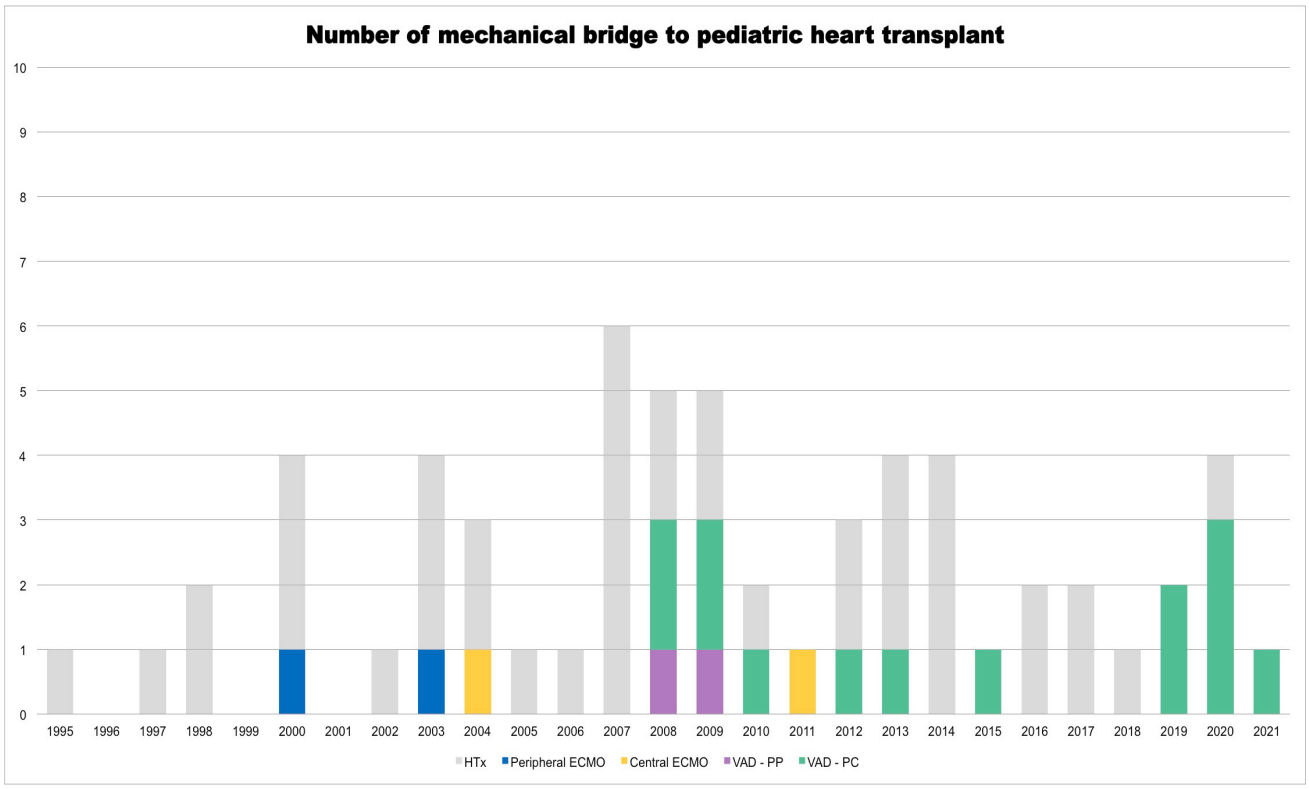

Figure 1: Numbers of pediatric heart transplantations and mechanical bridge-to-transplant by year.
The numbers of pediatric heart transplantations and mechanical bridge-to-transplant by year are shown.
ECMO: extracorporeal membrane oxygenation; HTx: heart transplantation; VAD-PP: ventricular assist device-paracorporeal pulsatile device; VAD-PC: ventricular assist device-paracorporeal continuous device

recipients because of difficulty in vascular access, risk from anesthesia, and potential for coronary injury [18].

Statistical analysis

Descriptive data are expressed as medians with interquartile ranges (IQRs) or ranges for continuous variables and as counts with percentages for categorical variables. Continuous variables were compared using the Mann-Whitney U test, and categorical variables were compared using chi-square tests. Post-transplant survival was estimated using the Kaplan-Meier method and censored at the time of retransplantation. All statistical analyses were performed using the STATA® 13.0 statistical package (StataCorp MP, College Station, TX, USA). A p value below 0.05 was considered statistically significant.

Results

Patient characteristics

The distribution of pediatric heart transplantations and MCS-bridged recipients in our institution by year is plotted in Figure 1.

Sixty-one heart transplantations with recipients less than 17 years of age from 1995 through 2021 at the National Taiwan University Hospital (NTUH) were included in our study. Retransplantation (N = 4) was analyzed as long as recipients were under 17 at the time of retransplantation. The median age at transplant was 9.8 years (range 0.5-16.4 years), with a median weight of 26.8 kg (range 4-70 kg). Dilated cardiomyopathy (DCMP) was the most frequent etiology of pediatric heart failure in our cohort (N = 34). Approximately 50% of the transplantations were performed in UNOS status 2 candidates (N = 29). The median waiting time was 114 days (interquartile range/IQR 28-335 days). Sixteen recipients were intubated, and 20 recipients were implanted with mechanical circulatory support (MCS) prior to transplantation. The median age of accepted donors was 17 years (range 1-52 years), with a median weight of 50 kg (range 8-114 kg). The clinical and demographic characteristics of recipients and donors in our cohort are shown in Table 1. No cases were lost to follow-up.

Temporal variations in pediatric heart transplant practice

The pediatric heart transplant cohort was divided into two groups according to the predominance of ECMO (i.e., before 2006) and VAD (i.e., after 2006). The characteristics of recipients and donors and peritransplant outcomes were compared between the ECMO-predominate era and VAD-predominate era (Table 1). There were 17 and 44 transplantations, respectively. DCMP remained the major cause of pediatric heart transplant across both eras. The age and

		1995-2021	1995-2005	2006-2021	
N(%)		61	17	44	P value
Etiology	DCMP	34 (55.7%)	13 (76.5%)	21 (47.7%)	
	CHD	10 (16.4%)	3 (17.6%)	7 (15.9%)	
	Myocarditis	8 (13.1%)	0	8 (18.2%)	
	Kawasaki	2 (3.3%)	1 (5.9%)	1 (2.3%)	
	Re-HTx	4 (6.6%)	0	4 (9.1%)	
	RCM	3 (4.9%)	0	3 (6.8%)	
Age (median, range)		9.8 (0.5–16.4)	7.2 (0.5-15.8)	10.4 (2.3-16.4)	0.04
BW (median, range)		26.8 (4-70)	22 (4-56)	30.6 (10.7-70)	0.03
Gender	M	38	10	28	
	F	23	7	16	
UNOS	1A	21 (35%)	4 (23.5%)	17 (39.5%)	0.24
	1B	10 (16.7%)	4 (23.5%)	6 (14%)	
	2	29 (48.3%)	9 (52.9%)	20 (46.5%)	
Waiting days (median, IQR)		114 (28-335)	NA	114 (28-335)	
ETT before HTx		16/60 (26.7%)	3/17 (17.6%)	13/43 (30.2%)	0.32
MCS BTT		20/61 (32.8%)	3/17 (17.6%)	17/44 (38.6%)	0.12
	ECMO	4	3	1	
	VAD	16	0	16	
Donor age (median, range)		17 (1-52)	16 (1-49)	18 (1-52)	0.21
Donor BW (median, range)		50 (8-114)	40 (8-70)	56 (10-114)	0.01
Ischemic time (median, IQR)		199 (108-237)	204 (119-244)	183 (103-226)	0.51
Hospital survival		56/60 (93.3%)	16/17 (94.1%)	40/43 (93%)	0.88
ICU stay of hospital survivors after HTx (median days, IQR)		14 (7-21)	13 (7-25)	14 (7-21)	0.96
Hospital stay of hospital survivors after HTx (median days, IQR)		36 (28-52)	39 (32-63)	35 (26-51)	0.35

Table 1: Patient demographics.
BTT: bridge to transplant; BW: body weight; CHD: congenital heart disease; DCMP: dilated cardiomyopathy; ECMO: extracorporeal membrane oxygenation; ETT: endotracheal tube, HTx: heart transplantation; ICU: intensive care unit; IQR: interquartile range; MCS: mechanical circulatory support; RCM: restrictive cardiomyopathy; Re-HTx: retransplant; UNOS,:United Network for Organ Sharing; VAD: ventricular assist device

weight of recipients at transplant increased in the recent era (median age: 7.2 years before 2006, 10.4 years after 2006, p= 0.04; median weight: 22 kg before 2006, 30.6 kg after 2006, p= 0.03). Although not significantly different because of the low event frequency in the early era, more patients tended to undergo transplantation at UNOS status 1A (p= 0.24), mainly because the proportion of recipients supported with MCS doubled in the recent era (MCS BTT: 17.6% before 2006, 38.6% after 2006, p= 0.12).

Consistent with the markedly increased use of VAD in pediatric patients, especially for children with DCMP, only one patient was transplanted on ECMO (central ECMO) in the VAD-predominant era [19]. The hospital survival rate was 94.1% before 2006 and 93% after 2006 (p= 0.88), with an average intensive care unit (ICU) stay of 13 days (IQR 7-25 days) and 14 days (IQR 7-21 days, p= 0.96) and an average hospital stay of 39 days (IQR 32-63 days) and 35 days (IQR 26-51 days, p= 0.35), respectively, for survivors (Table 1).

Long-term retransplant-free survival

The cumulative retransplant-free survival rates of the entire cohort were 93.4%, 73.4%, 53.4%, 33.4% and 22.3% at 1 year, 5 years, 10 years, 15 years and 20 years post-transplant, respectively (Figure 2a). No statistically significant difference in cumulative retransplant-free patient survival between eras (Figure 2b) or between patients with and without mechanical bridges was found (Figure 2c).

MCS bridging strategy

The MCS BTT strategy was analyzed in patients who received transplantation on ECMO or VAD (Table 2). The only MCS BTT was

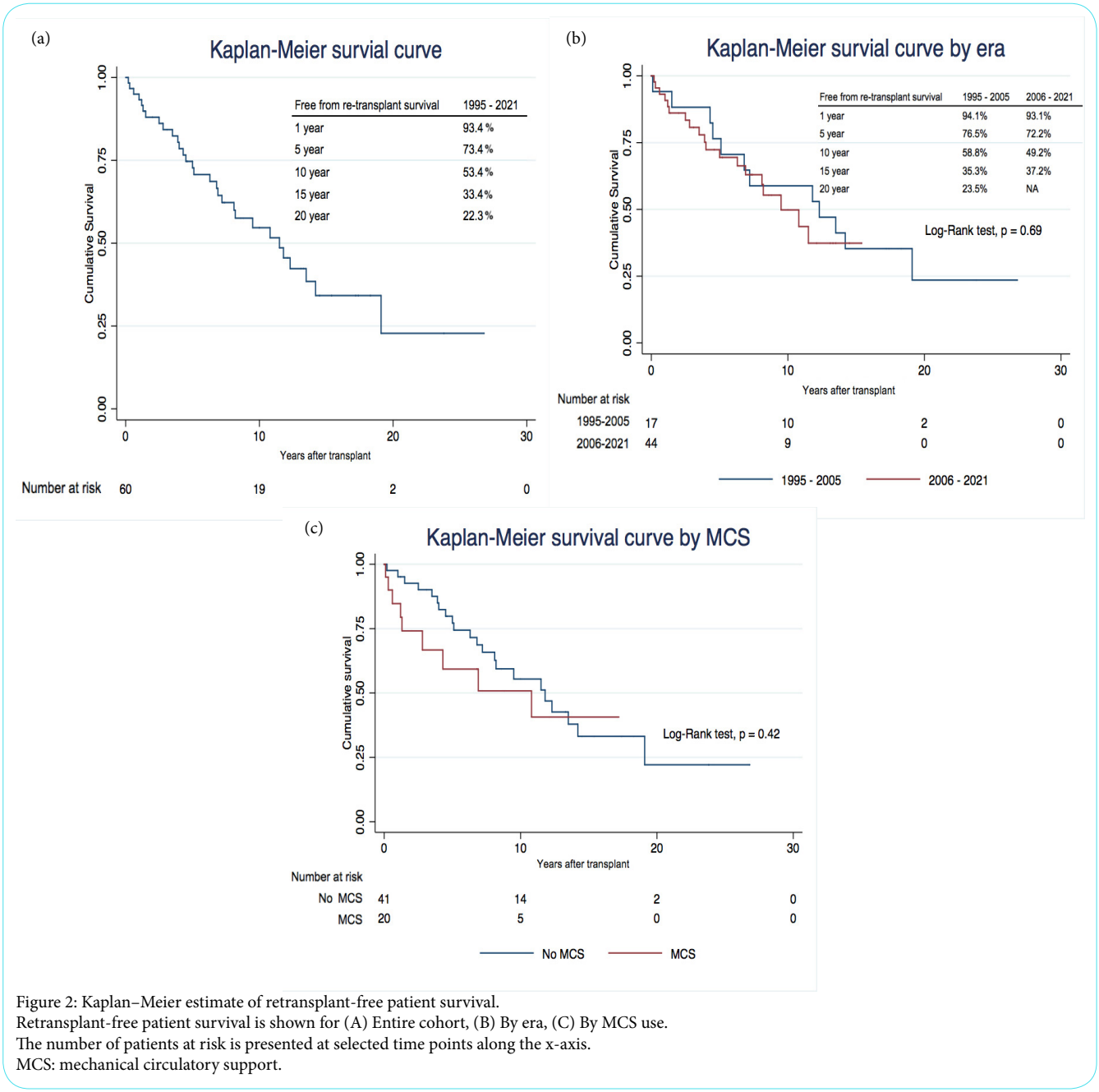

Figure 2: Kaplan–Meier estimate of retransplant-free patient survival.
Retransplant-free patient survival is shown for (A) Entire cohort, (B) By era, (C) By MCS use.
The number of patients at risk is presented at selected time points along the x-axis.
MCS: mechanical circulatory support.

ECMO in the early era (1995-2005). The average duration of ECMO support before transplantation was 1 day (range 1-17 days) in the ECMO-predominant era. The only patient transplanted on ECMO after 2006 was supported on central ECMO for 18 days.

VAD has been the most commonly used device in the recent era (2006-2021). The other 16 patients bridged with MCS after 2006 were supported with VAD, including 2 paracorporeal pulsatile devices and 14 paracorporeal continuous devices for an average of 42 days (range 5-165 days) before transplantation. Nine of the 16 VADs were transitioned from ECMO, and 11 of the 16 VADs were implanted in INTERMACS profile 1 patients. All patients transplanted on ECMO (N= 3 before 2006, N= 1 after 2006) were intubated at the time of transplantation, while 25% (4/16) of patients transplanted on VAD were free from mechanical ventilation. The average waiting time was 69 days (IQR 24-136 days) for MCS-bridged patients (formal waiting time was not available in the early era) and 294 days (IQR 29-623 days) for nonbridged patients (not shown). Hospital survival of MCS-bridged patients was 66.7% before 2006 and 87.5% after 2006.

Because only 3 patients were MCS bridged before 2006, the association between MCS BTT and late post-transplant survival was estimated in patients who underwent transplantation after 2006. The cumulative retransplant-free survival between MCS-bridged patients and patients without MCS was comparable (Figure 3).

ECMO bridge to VAD

In patients transplanted on VAD, 56.3% (9/16) were transitioned from ECMO. Subgroup analysis among patients supported with ECMO only (N= 4), ECMO to VAD (N= 9), and direct VAD (N= 7) was conducted (Table 3).

Compared with patients who transitioned from ECMO to VAD, children receiving direct VAD implantation were marginally smaller in size (median weight: 42.1 kg in the ECMO to VAD group, 26.8 kg in the direct VAD group, p= 0.06). Children who transitioned from ECMO to VAD were most likely to be diagnosed with myocarditis (5/9). The average duration of ECMO support was 9 days (range 1-18 days) before transplantation and 8 days (range 5-14 days) before the transition to VAD.

The average duration of VAD support before transplantation was 75 days (range 22-119 days) in the direct VAD group and 26 days

		1995-2005	2006-2021
N (%)		3	17
Age (median, range)		11.1 (3.3-11.5)	11 (2.3-16.2)
BW (median, range)		49.5 (17.5-55)	37 (10.7-67.5)
Etiology	DCMP	1	8
	CHD	1	2
	Myocarditis	0	7
	Kawasaki	1	0
	Re-HTx	0	0
	RCM	0	0
ECMO		3	1
ECMO duration before HTx (median days, range)		1 (1-17)	18
VAD		0	16
ECMO to VAD		0	9
INTERMACS	1		11
	2		4
	3		1
VAD device	PP		2
	PC		14
	IC		0
VAD duration before HTx (median days, range)			42 (5-165)
ETT before HTx		3/3 (100%)	13/17 (76.5%)
Waiting day (median, IQR)		NA	69 (24-136)
Hospital survival		2/3 (66.7%)	14/16 (87.5%)
ICU stay of hospital survivors after HTx (median days, IQR)		12, 15	19 (10-49)
Hospital stay of hospital survivors after HTx (median days, IQR)		31, 52	42 (29-84)

Table 2: Mechanical bridge to heart transplant.
BW: body weight; CHD: congenital heart disease; DCMP: dilated cardiomyopathy; ECMO: extracorporeal membrane oxygenation; ETT: endotracheal tube, HTx: heart transplantation; IC: intracorporeal continuous; ICU: intensive care unit; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; IQR: interquartile range; PC: paracorporeal continuous; PP: paracorporeal pulsatile; RCM: restrictive cardiomyopathy; Re-HTx: retransplant; UNOS: United Network for Organ Sharing; VAD: ventricular assist device.

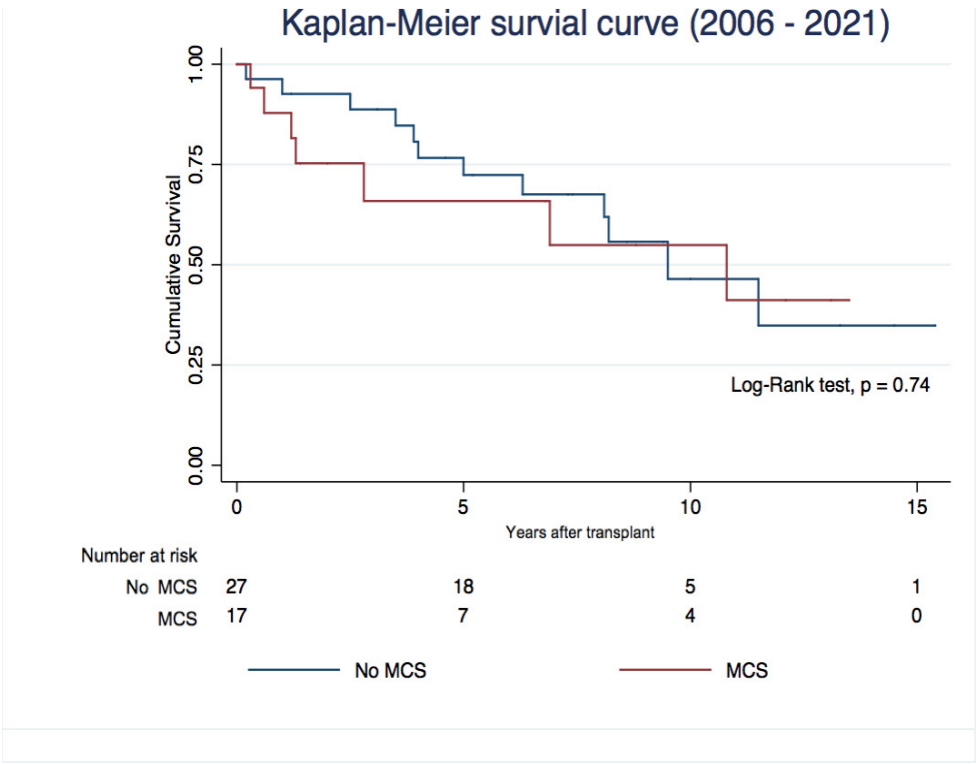

Figure 3: Kaplan–Meier estimate of retransplant-free patient survival in the VAD-predominant era (2006-2021). Retransplant-free patient survival by MCS use after 2006 is shown. The number of patients at risk is presented at selected time points along the x-axis.
ECMO: extracorporeal membrane oxygenation; MCS: mechanical circulatory support.

		ECMO	ECMO to VAD	VAD	P value*
N (%)		4	9	7	
Age (median, range)		11.3 (3.3-13.8)	11.6 (8.4-14.7)	9.7 (9.3-12)	0.31
BW (median, range)		43.8 (17.5-55)	42.1 (29.5-62.7)	26.8 (25.4-31)	0.06
Etiology	DCMP	1	3	5	
	CHD	1	1	1	
	Myocarditis	1	5	1	
	Kawasaki	1			
ECMO duration before HTx (median days, range)		9 (1-18)	8 (5-14)		
VAD duration before HTx (median days, range)			26 (13-70)	75 (22-119)	0.22
INTERMACS	1		9	2	
	2			4	
	3			1	
ETT before HTx		4 (100%)	9 (100%)	3 (42.9%)	0.02
Waiting days (median, IQR)		16	40 (19-68)	129 (112-208)	0.005
Hospital survival		50% (2/4)	88.9% (8/9)	100% (6/6)	1
ICU stay of hospital survivors after HTx (median days, IQR)		12, 15	29 (16-51)	14 (7-53)	0.28
Hospital stay of hospital survivors after HTx (median days, IQR)		31, 52	46 (37-88)	32 (20-97)	0.24

Table 3: Comparisons among device strategies.
* Between ECMO to VAD and VAD
BW: body weight; CHD: congenital heart disease; DCMP: dilated cardiomyopathy; ECMO: extracorporeal membrane oxygenation; ETT: endotracheal tube, HTx: heart transplantation; ICU: intensive care unit; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; IQR: interquartile range; VAD: ventricular assist device.

(range 13-70 days) for the ECMO to VAD group (p= 0.22). All patients in the ECMO-only and ECMO-to-VAD groups were intubated, while 57.1% (4/7) of patients in the direct VAD group were free from mechanical ventilation at the time of transplantation.

Candidates in the direct VAD group had a significantly longer wait time (40 days in the ECMO to VAD group, 129 days in the direct VAD group, p= 0.005). Compared to the ECMO-only group, both the ECMO-to-VAD and direct VAD groups had excellent early outcomes (88.9% and 100% hospital survival, respectively, p= 1.0). No statistically significant difference in long-term retransplant-free survival between subgroups was found (Figure 4).

Predictors of post-transplant survival

Among recipient, donor, and surgical variables, we could not identify a significant association with post-transplant outcomes in our cohort (Table 4).

Cause of retransplantation and late deaths

Four patients underwent retransplantation (re-HTx) under 17 years of age, with 3 re-HTx due to chronic rejection. The median graft survival was 3.4 years (IQR 1.4-6.4 years). The causes of late deaths included sudden cardiac death (N= 13), graft failure (N= 3), sepsis (N= 1), intracranial hemorrhage (N= 1), and post-transplant lymphoproliferative disorders (PTLD, N= 1). The median survival after heart transplantation in patients who died of identified cardiovascular-associated causes (i.e., graft failure and sudden cardiac death) was 7.1 years (IQR 3.2-11.6 years, Figure 5a and Figure 5b).

Discussion

This study described the temporal change in recipient characteristics in pediatric heart transplantation in our hospital, primarily focusing on MCS use, which paralleled the results of the 24th ISHLT annual report in general. VAD offered more durable support than did ECMO and allowed better functional restoration before transplantation in MCS-bridged children. Both the ECMO-to-VAD and direct VAD strategies achieved excellent early post-transplant outcomes.

Significant changes in the recipient profile over time with advances in congenital heart disease surgery, particularly for children with single ventricle disease, and the development and widespread use of VAD as a BTT in pediatric heart transplantation were described in the latest ISHLT pediatric heart transplantation report. During the past 3 decades, the number of pediatric heart transplantations has increased, and recipients have grown older and larger and are more likely to be hospitalized or supported on inotropes or VAD in the most recent era [20].

Compatible with the results in the ISHLT annual report, we observed a similar trend in pediatric heart transplantation and recipient characteristics, which could be partially attributed to the considerable improvement in the outcome of congenital heart disease and heart failure treatment, including pharmacological, transcatheter, surgical and mechanical therapy, in recent decades in our institution, allowing an increasing population who survived the staged palliation treatment and developed end-stage heart failure till their grow-up.

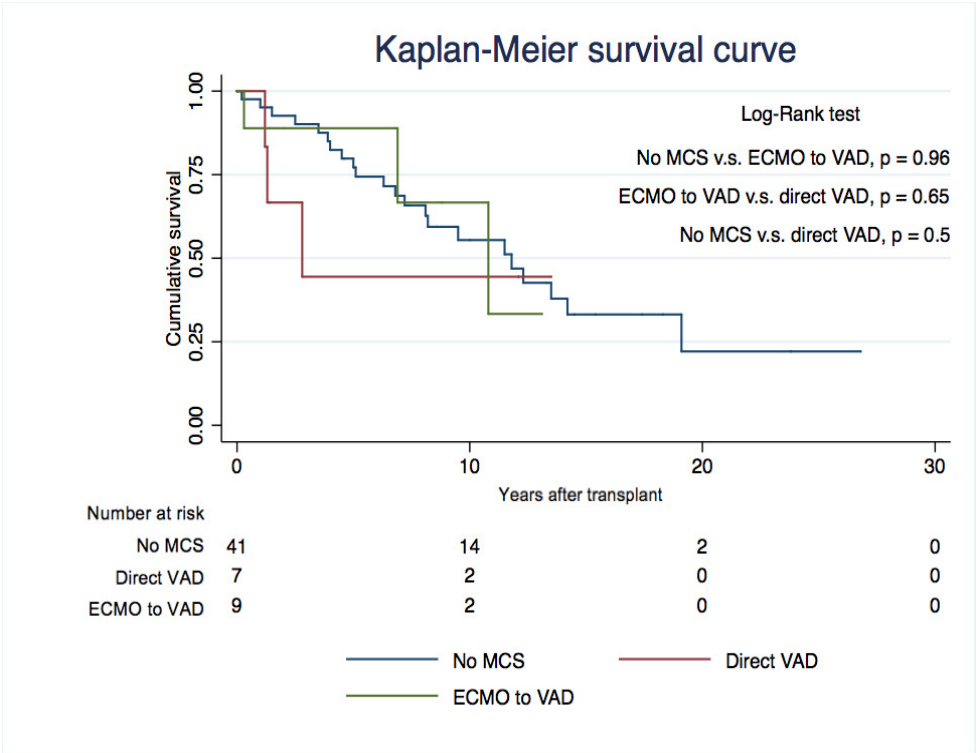

Figure 4: Kaplan–Meier estimate of retransplant-free patient survival by device strategy.
Retransplant-free patient survival by device strategy is shown. The number of patients at risk is presented at selected time points along the x-axis.
ECMO: extracorporeal membrane oxygenation; MCS: mechanical circulatory support; VAD: ventricular assist device.

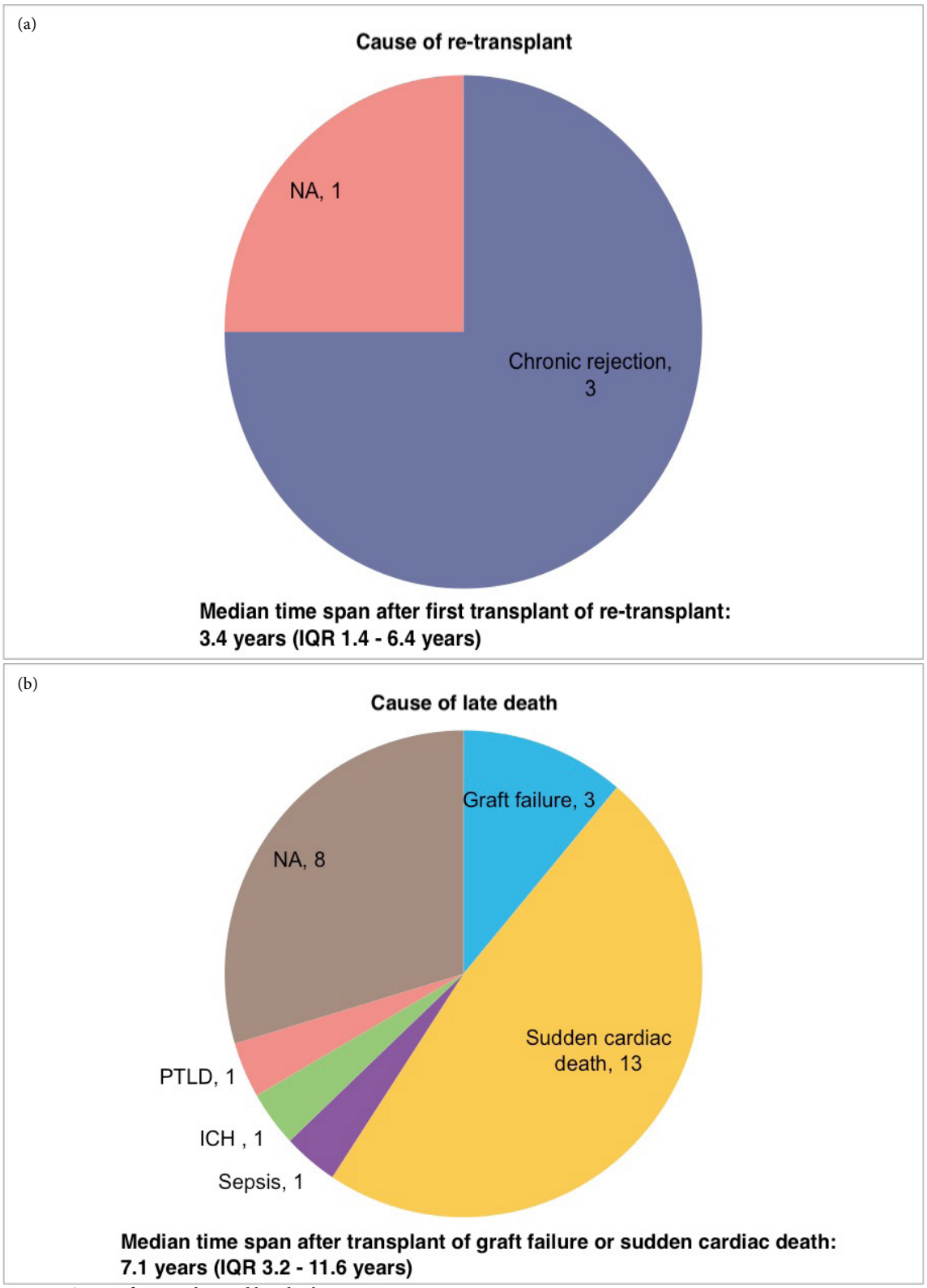

Figure 5: Causes of retransplant and late death.
(A) The causes of retransplantation and median graft survival are shown.
(B) The causes of late deaths and median survival of patients who died of identified cardiovascular-associated causes are shown.
ICH: intracranial hemorrhage; IQR: interquartile range; NA: not available; PTLD: posttransplant lymphoproliferative disorders.

Features of patients on MCS

Although the small numbers of ECMO BTTs in our study limited the effective comparison between different modalities of MCS BTTs, the clinical features of patients transplanted on MCSs, in general, corroborated the fact that VAD offers more durable support and allows better functional reserve (i.e., all patients without mechanical ventilation prior to transplantation were supported on VAD) over ECMO.

In contrast to the relatively rare configuration of ECMO + VAD analyzed in pediatric registries, we noticed that 56.3% of our pediatric VAD patients were transitioned from ECMO. Wehman et al. [8] reported that 12.1% of the VAD BTT cohort was supported with ECMO at the time of listing before being transitioned to VAD from an earlier UNOS registry. Edelson et al. [10] described a small group of only 54 children with VAD+ECMO within the ISHLT registry, while there were 1,030 patients with VAD in the same period. Consistent between both large registries, the use of VAD BTT was more likely to occur in older, larger children, the use of ECMO BTT was more commonly observed in smaller, younger children, and the group of ECMO + VAD consisted of children aged in between (3 years old/16 kg and 4 years old/15 kg, respectively [8,10]). However, in our report, compared with patients who transitioned from ECMO to VAD, children receiving direct VAD implantation were marginally smaller in size, which could possibly be explained by the increasing experience in pediatric VAD, the concept of early support to avoid urgent implantation with INTERMACS profile 1 or 2, and the prevailing trend in using VAD over ECMO as BTT.

Impact of MCS as a BTT on post-transplant survival

In adults, there was no significant difference in post-transplant survival between patients not requiring MCS support and patients bridged on VAD, although a higher risk of mortality within the first year post-transplant was found in the VAD group [6,7]. Post-transplant survival in patients with VAD BTT, both durable and temporary devices, was proven superior to that in patients with ECMO [7]. Although patients with ECMO BTT remained a small group within the enlarging MCS BTT population, there has been increasing use of ECMO as a bridge to heart transplant or VAD over the past decade, with the number of ECMO-to-VAD implantations surpassing the number of ECMO BTTs between 2017 and 2019, which was likely explained by the change in the U.S. heart allocation system in October 2018 [21,22]. In children, patients transplanted on VAD had similar outcomes in both the acute post-transplant period and long-term survival as patients without MCS. Corresponding with studies in adults, ECMO BTT was identified as a risk factor for post-transplant mortality, especially during the early post-transplant period and in children with CHD [8,10].

Currently, the vast majority of studies on pediatric MCS outcomes are conducted in North America, where durable VAD use predominates [19]. The general algorithm of MCS BTT practice and mid-term post-transplant outcomes of different bridging strategies in our institution were reported recently. ECMO-to-temporary VAD was the most frequently adopted strategy in our heart recipients during the past decade and offered a noninferior mid-term survival compared to VAD [23]. Although most pediatric patients underwent planned device exchange throughout the course of MCS support, there has been limited evidence on the ECMO-to-VAD strategy, especially regarding post-transplant survival.

In Wehman's et al. [8] subgroup analysis, there was no difference in short-term or mid-term post-transplant survival between ECMO-to-VAD and direct transplantation. In contrast, ECMO-to-VAD was reported to have significantly worse outcomes than those supported exclusively by a VAD, with predischarge mortality rates of 13.7% in VAD+ECMO, 3.5% in VAD, and 4.2% in no MCS, from a more recent report based on the ISHLT registry. Because these data did not describe the length of support time for each modality, the authors proposed that it is not ECMO itself that confers risk but instead the accompanying deconditioning, intubation, and poor nutritional status of many of these patients, implying that the observed risk of poor transplant outcomes in this subgroup may be mitigated by a prompt conversion from ECMO to VAD and minimizing the period of ECMO support [10]. In the present study, we described an average duration on ECMO support of 8 days before shifting to VAD with excellent hospital survival in both the ECMO-to-VAD and direct VAD groups (88.9% and 100%, respectively), and a possible trend in reducing peri-transplant ICU stay and hospital stay in the direct VAD group.

Predictors (univariate)	Hospital survival			5 year re-HTx free survival (1995-2016)			10 year re-HTx free survival (1995-2011)		
	OR	P	95% CI	OR	P	95% CI	OR	P	95% CI
MCS	0.13	0.09	0.01-1.38	0.37	0.14	0.10-1.37	0.83	0.8	0.20-3.42
ETT	0.1	0.06	0.01-1.08	0.23	0.04	0.06-0.91	0.4	0.26	0.08-1.94
UNOS 1A	0.15	0.11	0.01-1.54	0.38	0.15	0.10-1.41	1	1	0.25-4.00
Non DCMP	0.44	0.43	0.06-3.36	0.28	0.05	0.07-1.02	0.49	0.34	0.11-2.09
BW < 25 kg	2.6	0.42	0.25-26.5	2.37	0.2	0.63-8.93	0.89	0.86	0.24-3.24
Male	1.8	0.57	0.24-13.8	0.66	0.54	0.17-2.50	0.36	0.14	0.09-1.42
Blood type O	0.47	0.47	0.06-3.64	2.5	0.21	0.60-10.5	1.4	0.64	0.34-5.76
BW ratio > 2	1.31	0.82	0.13-13.5	3.25	0.16	0.63-16.8	1.08	0.92	0.25-4.60
Age gap	1.06	0.43	0.91-1.24	1	1	0.94-1.07	1.02	0.57	0.95-1.10
Gender discrepancy	0.49	0.49	0.06-3.74	0.98	0.97	0.27-3.52	0.53	0.36	0.13-2.09
Ischemic time	1	0.93	0.99-1.01	1	0.21	1.0-1.02	1	0.61	0.99-1.01

Table 4: Predictors of hospital survival and re-HTx-free late survival.
BW: body weight; CI: confidence interval; DCMP: dilated cardiomyopathy; ETT: endotracheal tube; MCS: mechanical circulatory support; OR: odds ratio; UNOS: United Network for Organ Sharing.

Pediatric device strategy

The device strategy should be individualized after thorough consideration of all relevant factors, including patient size and heart anatomy, type of support needed (LVAD vs. BiVAD vs. RVAD), severity and acuity of the clinical situation, possible myocardial recovery (such as fulminant myocarditis and primary graft dysfunction), anticipated duration, goal of support, device availability, and for patients bridged to transplant, difficulty in matching an acceptable organ, predicted waiting time, and post-transplant outcome [9,23]. Commonly, when patients with critical cardiogenic shock are stabilized on temporary devices at first, the optimal timing of device crossover to permit an evaluation of eligibility for durable devices and cardiac transplantation needs to be addressed [24].

Because of the complicated clinical spectrum of children with end-stage heart failure, pediatric organ scarcity and even more challenging device strategies, including the size constraints from device profiles and the relatively high cost, the use of durable pediatric VAD has been limited in our country. Intracorporeal continuous VAD started to be reimbursed by Taiwan's National Health Insurance in 2018 and first implants in our pediatric patients were conducted after the FDA's approval of HeartMate 3 (Abbott, Chicago, IL, USA) for use in pediatric patients at the end of 2020. However, increasing experience with pediatric temporary VADs has been noted in the data from pediatric heart transplant studies, and crossover among the different support strategies has become more prevalent in the most recent era [9]. Therefore, we hope that this study adds evidence to the granular discussion on pediatric temporary device and device crossover strategies.

Long-term outcomes and causes of late death in the pediatric heart transplant population

Most analyses of the long-term outcome of pediatric heart transplantation have been subjected to inadequate statistical power due to low transplant volume outside of North America, which is further complicated by the phenomenon of immunological advantage for infants < 1 year old and medication noncompliance in adolescents [20]. Daly et al. [25] previously reported an incidence of 10-20% of sudden death after heart transplant in children. UNOS status 2 at transplant and recipient age > 1 year were identified as risk factors, while ECMO and VAD support had no association with post-transplant sudden death. We noticed a higher incidence (48.1%, 13/27) of late sudden death in our study, although a significant portion of the causes of late deaths were undetermined. The long-term outcome of our pediatric heart transplant patients in the era of VAD warrants further exploration.

Limitations

The small numbers of cases from a single institution's 25 years of experience precluded a powerful analysis to identify important factors associated with post-transplant survival and to compare long-term survival in our study. The retrospective, nonrandomized study design came with many caveats, given that the device strategy is influenced by many variables. For example, as one of the few pediatric heart transplant centers in Taiwan, a portion of our patients were rescued by ECMO at first in other hospitals and then transferred to our institution to be evaluated for heart transplantation candidacy. In that condition, the initial device strategy might differ from our own practice.

Conclusions

This study demonstrated that the expanding use of VAD as a bridge to transplantation in pediatric patients collaborated with the increasing numbers of critically ill children to be transplanted, without compromising early post-transplant outcomes in our institution. VAD offered more durable support than did ECMO and allowed better functional restoration before transplantation in MCS-bridged children. The early post-transplant survival rates of the ECMO-to-VAD and direct VAD strategies were comparable. More evidence to suggest an optimal device strategy in pediatric heart transplant is warranted.

Competing Interests

The authors declare that they have no competing interests.

Author's Contributions

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Analysis and interpretation of data: H.Y. Fu, C.I. Tsao, H.W. Chou.

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