Long-term results of pediatric heart transplantations: Single-center experiences

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ABSTRACT

Background: Heart failure (HF) is characterized by significant mortality in both adults and children. Characteristics of pediatric HF are feeding problems, poor weight gain, exercise intolerance, or dyspnea. These changes are often accompanied by endocrine disorders. The main causes of HF are congenital heart defects (CHD), cardiomyopathies, arrhythmias, myocarditis, or heart failure secondary to oncological treatment. Heart transplantation (HTx) is the method of choice for treatment of end-stage HF in pediatric patients.

Aims: This article aimed to summarize the single-center experience in heart transplantation in children.

Methods: Between 1988 and 2021 in the Silesian Center for Heart Diseases in Zabrze, 122 pediatric cardiac transplantations were performed. In the group of recipients with failing Fontan circulation, HTx was performed in 5 children. The study group was evaluated for the postoperative course: rejection episodes depending on the medical treatment scheme, coinfections, and mortality.

Results: One-, 5-, and 10-year survival rates between 1988 and 2001 were 53%, 53%, and 50%, respectively. One-, 5-, and 10-year survival rates between 2002 and 2011 were 97%, 90%, and 87%, respectively; between 2012 and 2021 (1-year of follow-up), the survival rate was 92%. The main cause of mortality both in early and late periods after transplantation was graft failure.

Conclusions: Cardiac transplantation in children remains the main method of treatment for end-stage heart failure. Our results at both early and long-term posttransplant periods are comparable to those obtained in the most experienced foreign centers.

Key words: cardiomyopathy, congenital heart defect, heart failure, pediatric heart transplantation

INTRODUCTION

Heart failure (HF) in children is a clinical and pathophysiological syndrome resulting from ventricular dysfunction and pressure or volume overload of the circulatory system. Characteristics of pediatric heart failure include feeding problems, poor weight gain, exercise intolerance, or dyspnea. These changes are often accompanied by changes in the endocrine system. There is a complex etiology of HF in children. The main causes are congenital heart disease (CHD) and cardiomyopathies. Less frequent causes are cardiac arrhythmias and acquired heart diseases, such as myocarditis, Kawasaki disease, or heart failure secondary to oncological treatment. In the United States, 12 000 to 35 000 children suffer from heart failure caused by CHD or cardiomyopathy. This gives an incidence of HF in the pediatric population of 16.4–48 cases per 100 000 children [1]. Each year, these patients require 14 000 hospital admissions, of which 65% are caused by CHD. According to a Belgian study, CHD accounts for about 50% of all hospital ad-

WHAT'S NEW?

This article presents an overview of the unique pediatric heart transplant program in Poland. Heart transplantation is the method of choice for treatment of end-stage heart failure in pediatric patients. This is a rare pediatric procedure, related to high operational risk. This article presents the valuable Polish operating and immunosuppression treatment protocol. The results obtained in the second and third periods are consistent with the data presented by leading centers in the world.

missions for HF exacerbation. Fourteen percent of patients with single ventricle physiology require multiple hospital stays due to HF exacerbations. Many of these patients will require mechanical circulatory support (MCS) or HTx qualification in the future [2]. Cardiomyopathies occur with a frequency of 1.13–1.24 cases per 100 000 children. They are especially frequent in the group <1 year of age, where the prevalence of cardiomyopathy is estimated at 7.8–8.3 cases per 100 000 infants. Severe HF is also more common in this age group [3, 4]. Not all patients with cardiomyopathy will develop HF. The prevalence of HF in children with cardiomyopathy is estimated at 0.87 cases per 100 000 children under 16 years of age. Seventy-one percent of HF episodes occur in patients with dilated cardiomyopathy (DCM) [5]. Heart transplantation (HTx) is considered the method of choice for the treatment of end-stage HF in pediatric patients.

Historical overview

In 1960, Lower and Shumway [6] published the results of experiments with orthotopic cardiac transplantation in dogs using an oxygenator. They described the technique of preparation of the recipient and donor atrium (Shumway's technique), which is still used but not commonly. On December 3, 1967, Christian Bernard performed the first successful heart transplant in humans in Groote Schuur Hospital in Cape Town (Republic of South Africa). Despite the use of advanced immunosuppression (local irradiation, azathioprine, prednisolone, and actinomycin C) and the sanitary regime, the patient died 18 days after the transplant due to infection caused by *Pseudomonas Pneumoniae* [7]. Three days later, on December 6, 1967, Adrian Kantrovitz of the Maimonides Medical Center in Brooklin (US) performed the first successful heart transplant in a child. Kantrovitz assumed that the underdevelopment of the immune system of the infant would facilitate surgery and subsequent treatment. The patient was a 3-week-old infant with critical CHD (tricuspid atresia type IA). The procedure was performed in deep hypothermia with full cardiac arrest. Due to post-transplant complications, the patient died after 6 hours [8].

Heart transplantation in the world

The introduction of effective and safe immunosuppressive drugs directly increased the number of successful transplants and extended patients' survival time [9, 10]. According to data from the International Society for Heart and Lung Transplantation (ISHLT) in 1982, 187 heart transplants were performed in the world, including 10 in children. In 1992, the number of transplanted hearts was 4 735, of which 406 were performed in children. This represented a 40-fold increase in the number of heart transplantations in children compared to the year 1982 in fewer than 10 years. Twenty-five percent of transplanted pediatric patients were under one year old. According to data for 2021, the total number of heart transplants in children from 1992 ranged from 458 to 663 per year. With the increase in transplant procedures, the number of pediatric centers where this procedure is performed has also grown. Currently, there are 120 pediatric centers in the ISHLT database, of which 54% are located in North America (US and Canada). Indications for cardiac transplantation in children include three main types of diseases: myocardial diseases such as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and arrhythmogenic ventricular cardiomyopathy (AVC); congenital heart defects (including hypoplastic left heart syndrome [HLHS]), Ebstein's anomaly, transpositions of the great arteries (TGA), and other diseases that impair heart function, such as myocarditis. Retransplantations account for 2%–3% of indications for HTx in children [11, 12]. The main indication for HTx in children under 1 year of age is CHD (53% of indications). In older pediatric recipients, this relation changes to cardiomyopathy, which accounts for 55% of indications in patients in the 11–17 age group [13]. The increase in the experience of transplantation teams and the improvement of immunosuppressive treatment noticeably influenced recipient survival time. In the years 1982–1989, 1-, 5-, and 10-year survival rates in the pediatric population were 63.7%, 57.2%, and 51.6%, respectively. In the years 2004–2008, they increased to 81.8%, 70.8%, and 66.2%, respectively. In the years 2009–2015, the 1- and 5-year survival rates were 87.1% and 80.0%, respectively. The observed mean (standard deviation [SD]) survival time increased from 9.9 (6.9) years in 1982–1991 to 14.3 (3.4) years in the next decade. Mean survival time in the years 1982–2015 was: 22.3 years in the group of children <1 year of life, 18.4 years in the group aged 1–5 years; 14.4 years in the group aged 6–10 years, and 13.1 years in the group aged 11–17 years. Longer survival time occurs in patients who received transplants due to cardiomyopathy compared to patients with congenital heart disease, regardless of the age at which HTx was performed [11]. The type of induction and immunosuppression as well as complications influenced the mean survival time. The most common complications after HTx are primary graft failure, acute

rejection, coronary artery disease (CAV), severe renal insufficiency, or posttransplant lymphoproliferative disorder (PTLD). Early mortality during the first 30 days after transplantation is caused by graft failure and corresponds to 36.2% mortality. This often occurs in the group of children <5 years old, where it corresponds to 45% mortality. The next causes are stroke episodes (15.1%), multiple organ failure (11.2%), acute rejection of the transplanted heart (7.3%), and non-cytomegalovirus infections (6.5%). From the 3rd to the 5th and from the 5th to the 10th year after HTx, the main cause of mortality is graft failure, corresponding to 36.4% and 40.5% mortality, respectively. The episode of acute rejection as well as an increasing percentage of CAV are responsible for poor outcomes in those groups (15.3% and 11.7%, respectively) and also responsible for nearly 25% mortality in children 10 years after HTx [11].

Heart transplantation in Poland

The first Polish heart transplant was performed on April 1, 1969, by Jan Moll, Antoni Dziatkowiak, and Kazimierz Rybiński at the S. Sterling Clinical Hospital in Łódź. Due to unrecognized pulmonary hypertension associated with heart failure, the recipient died shortly after surgery [14]. The development of the Polish heart transplant program is related to Zbigniew Religa, who on December 5, 1985, together with the team of the Provincial Cardiology Center in Zabrze (currently the Silesian Center for Heart Diseases in Zabrze), performed the first successful heart transplant in an adult in Poland. Three years later, on February 8, 1988, in the same Center, a team of cardiac surgeons under the leadership of Zbigniew Religa performed the first successful heart transplant in a pediatric patient. In subsequent years, HTx was performed in increasingly younger patients. In 1998, a heart transplant program was initiated for the youngest children (R. Przybylski, M. Zembala, B. Chodór). In 2008, HTx was performed in 2 infants at the age of 9 and 10 months (R. Przybylski, Sz. Pawlak). In 2010, the 5th and youngest infant (6-month-old) received a transplant due to severe HF in the course of DCM. Currently, in Poland there is one center performing heart transplants in children: the Silesian Center for Heart Diseases in Zabrze. In the period between the years 2010 and 2021, 1333 heart transplants were performed in Poland, of which 609 (45.7%) were in our Center and 75 were pediatric patients. Pediatric heart transplantations in our country remain low, at about 6.9% of all heart transplants. The average number of HTx performed per year was 73 in adults and 7 in children in the last decade (2012–2021) in Poland [15]. The number of potential donors has remained stable for many years but is still not sufficient.

METHODS

Study group

Between 1988 and 2021 in the Silesian Center for Heart Diseases in Zabrze (formerly the Provincial Center of Cardiology in Zabrze), 122 pediatric cardiac transplantations were performed: 30 in the first period before the year 2001, 31 in the second period (2002-2011), and 61 in the third period (2012–2021). The median age of the patients for the whole group was 12.3 (8.0–14.7) and in the individual periods: period I — 13.3 (6.4–14.8), period II —12.7 (8.9–16.1), period III — 11.5 (8.0–14.5) years. The age of the patients ranged from 6 months to 17 years and 10 months. The main indication for HTx in the period between 2002 and 2021 (n = 92) was severe HF as a consequence of cardiomyopathy (n = 66, 71.7 %). In 25 recipients (27.2%), severe HF resulted from a congenital heart defect. Primary and post-inflammatory dilated cardiomyopathy was the most common indication (n = 59; 57.6%); hypertrophic cardiomyopathy (n = 13; 14.1%), restrictive cardiomyopathy (n = 10; 10.9%), arrhythmogenic ventricular cardiomyopathy (n = 1; 1.1%), and heart failure after oncological treatment (n = 1; 1.1%) caused heart failure requiring HTx. In the group of recipients with failing Fontan circulation, HTx was performed in 5 children (5.4%). The endpoint of the study was the time when medical follow-up was completed or the patient died. The death was confirmed in the personal identification number database. It was a retrospective study, and the institutional review board, ethics committee, and patient written informed consent were not required.

Induction and immunosuppression

From 2006 to August 2014, basiliximab (Simulect), a chimeric human-mouse monoclonal antibody administered on day 0 and day 5 after HTx was used as the induction of immunosuppression as a standard procedure until the manufacturer recommended withdrawal. Triple-drug immunosuppressive therapy included the administration of methylprednisolone infusion in the operating room before reperfusion. The infusions were continued for 5 days and then changed to the oral form of prednisone. All recipients were treated with cyclosporine A (CyA) and mycophenolate mofetil (MMF) intravenously in 24 hours after HTx. After the beginning of oral feeding, they were switched to oral forms of the drugs under the control of serum drug levels measured regularly (Table 1). In 2006, CyA was changed to tacrolimus (TAC).

Rejections

Rejection assessment was based on endomyocardial biopsies (EBM). The full EBM protocol is shown in Table 2. EBM was performed by puncturing a peripheral vein: the internal jugular or femoral vein using the Seldinger method. After assessing the pressure in the right atrium and right ventricle, 5 to 10 fragments of myocardium were collected from the interventricular septum. The myocardial fragments were fixed with 4% formalin and then stained with hematoxylin and eosin (HE) according to the standard protocol. Specimens were evaluated for the presence of acute cellular rejection (ACR) using the ISHLT 1995 classification (Table 3) [16, 17].

Table 1. Immunosuppressive drugs levels

Drug	0–6 months	6–10 months	>12 months
Cyclosporine A (CyA)	200–300 ng/ml	150–200 ng/ml	100–150 ng/ml
Mycophenolate mofetil (MMF)	1.5–2.0 ng/ml	1.5–2.0 ng/ml	1.5–2.0 ng/ml
Tacrolimus (TAC)	10–15 ng/ml	10–12 ng/ml	8–10 ng/ml

Table 2. EBM protocol

Days after HTx	
0–30	4 EBM every 7 days
31–60	2 EBM every 14 days
61–180	1 EBM every month
181–270	1 EBM
271–360	1 EBM
720	1 EBM with coronary angiography
Additional EBM	3–5 days after rejection treatment

Abbreviations: EBM, endomyocardial biopsies

Rejection episodes were treated with 3-day use of methylprednisolone infusions and enlarged MMF and TAC dosages. In the group of patients under 5 years of age, either a single EBM or no EBM was performed (n = 12; 13%). In those cases, rejection screening was based on echocardiography evaluation and blood levels of biochemical markers: N-terminal prohormone of brain natriuretic peptide (NT-pro BNP), highly-sensitive troponin T, creatine kinase (CK-MB), and lactate dehydrogenase (LDH).

Statistical analysis

Data were presented as median with interquartile range for quantitative variables with other than normal distribution and mean SD for variables with normal distribution. The number and percentage of cases with percent was presented for qualitative ones. A test for two proportions was used to assess the significance of differences between percentages. The Shapiro-Wilk test was used for the normality assumption check.

The Kaplan-Meier curves displayed the estimated survival probability. Differences in survival between groups were estimated using the Mantel test for more than two groups. Statistical analysis was performed using the statistical package SOFA Statistic (open source AGPL3 license). Survival analysis was performed using R language in Rstudio Environment (RStudio Team [2020]). RStudio is the Integrated Development for R (RStudio, PBC, Boston, MA, US, www.rstudio.com/), with additional packages survimner and survarium (https://cran.rproject.org/package=survminer, https://cran.r-project.org/package=survival). Five-year survival with *P*-value <0.05 was considered statistically significant.

RESULTS

One-, 5-, and 10-year survival rates between 1988 and 2001 were 53%, 53%, and 50%, respectively. One-, 5-, and 10-year survival rates between 2002 and 2011 were 97%, 90%, and 87%, respectively; between 2012 and 2021 (1--year follow-up), the survival rate was 92%. Median survival time in the years 2002–2011 was 9.2 (0.03–22.3) years, and 2012–2021 — 11.6 (10.2–13.7). Median survival was not analyzed in the years 2012-2021 because not all of the patients completed the 10-year follow-up. The main cause of mortality both in early and late periods after transplantation was graft failure (n = 5, 6.4% and n = 5, 6.4%, respectively). In the study group, primary graft failure was the cause of 57% of hospital deaths. In two cases (2.5%) the cause of mortality was PTLD. The distribution of HTx indications, characteristics of the study group, survival

Table 3. Comparison of the ISHLT 2004 and 1995 standardized EBM grades of acute cellular rejection (ACR) [16, 17]

ISHLT 2004		ISHLT 1995	
Grade	**Description**	**Grade**	**Description**
0R	No rejection	0	No rejection
1R, mild	Interstitial and/or perivascular infiltrate with at least one focus of myocyte damage	1, mild	
		A – focal	Focal perivascular and/or interstitial infiltrate without myocyte damage
		B – diffuse	Diffuse infiltrate without myocyte damage
		2, moderate (focal) diffuse	One focus infiltrate with associated myocyte damage
2R, moderate	Two or more foci of infiltrate with associated myocyte damage	3, moderate	
		A – focal	Multifocal infiltrate with myocyte damage
3R, severe	Diffuse infiltrate with multifocal damage and/or edema and/or hemorrhage and/or vasculitis	B – diffuse	Diffuse infiltrate with myocyte damage
		4, severe	Diffuse, polymorphous infiltrate with extensive myocyte damage and/or edema and/or hemorrhage and/or vasculitis

Abbreviations: EBM, endomyocardial biopsies; ISHLT, International Society for Heart and Lung Transplantation

Table 4. Demographic characteristics of the recipients

		Sex	
		Male	Female
n		67	55
%		54.9	55.1
Age of HTx, years			
Median (IQR)	12.3 (8.0–14.7)	14.0 (10.4–15.8)	10.2 (6.2–13.4)
Min	0.54	0.54	0.76
Max	17.82	17.82	17.41
Weight, kg			
Median (IQR)	38.9 (24.0–53.8)	44.6 (29.0–57.0)	30.0 (22.0–46.0)
Min	6.00	6.00	11.00
Max	110.00	110.00	66.00
Height, cm			
Median (IQR)	147 (131–165)	152 (133–170)	138 (122–159)
Min	65.0	65.0	84.0
Max	195.0	195.0	170.0

Abbreviations: HTx, heart transplantation

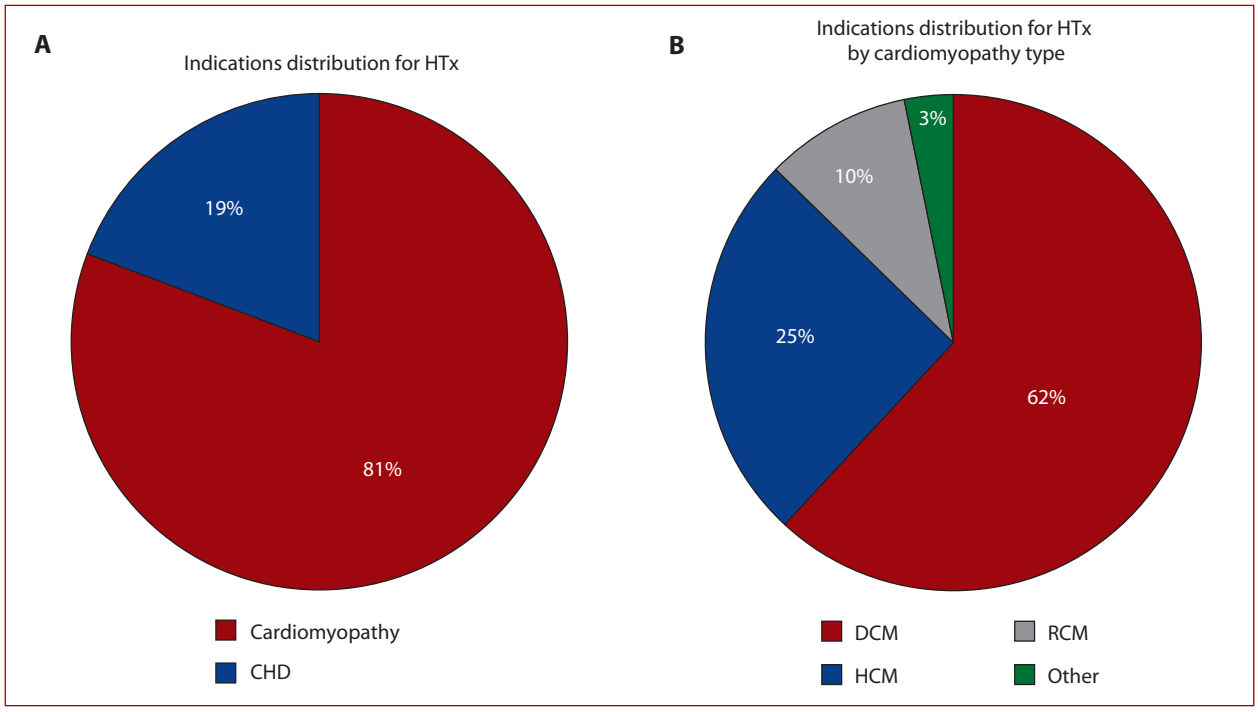

Figure 1. Indications for heart transplants in the Silesian Center for Heart Diseases in Zabrze

Abbreviations: DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HTx, heart transplantation; RCM, restrictive cardiomyopathy; CHD, congenital heart defect

curve, and the number of HTx performed were presented in Table 4 and Figures 1–4.

In 2010, the program of mechanical circulatory support (MCS) in children was initiated in Silesian Center for Heart Diseases in patients diagnosed with severe HF. Up to date, 45 implantations with MSC have been performed with the use of the extracorporeal pulsatile systems produced in Poland (POLCAS, currently ReligaHeart EXT — 2 implantations) or Germany (Berlin Heart EXCOR — 40 implantations). There were also three implantations with the completely implantable heart assist system (Berlin Heart INCOR). MSC was used as a bridge to transplantation in 20 patients (18%) including 2 from another Center. One- and 5-year survival was 92.6% each, and there was no difference in survival between the two groups ($P = 0.11$).

DISCUSSION

Advances in surgical and anesthetic techniques, new immunosuppressive drugs, and thus new post-transplantation protocols, have a significant impact on the survival time of pediatric patients after heart transplantation. The observed survival times of our study group, in different periods, are comparable to those from the most experienced foreign centers. Mean survival time for children who underwent

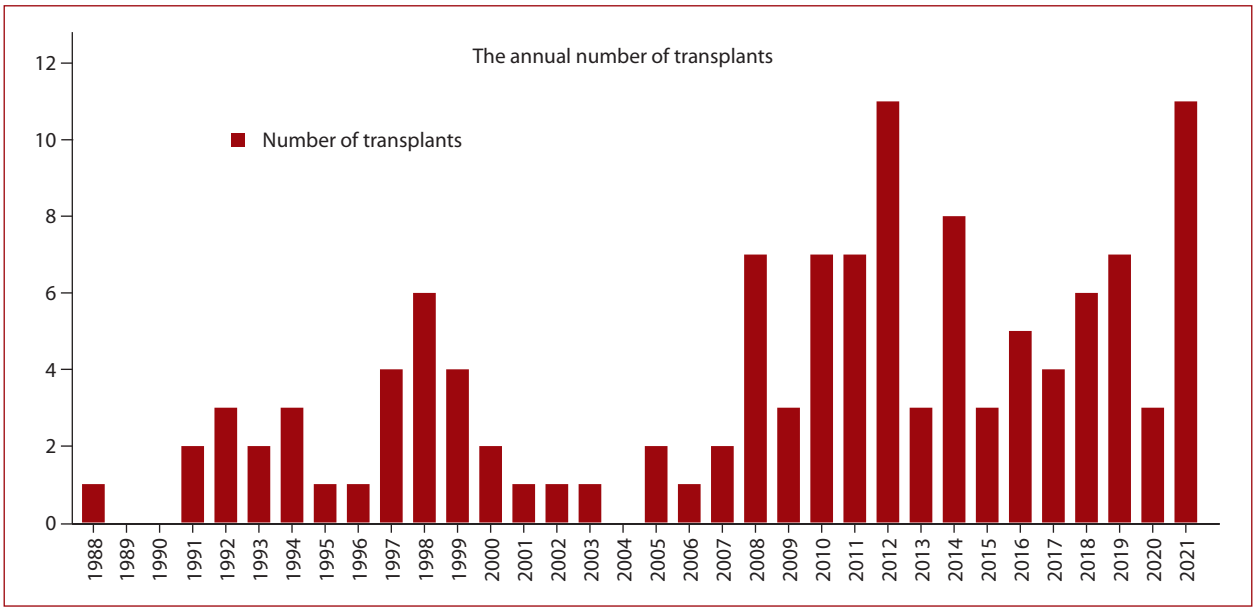

Figure 2. Number of pediatric heart transplants in the Silesian Center for Heart Diseases in Zabrze by year

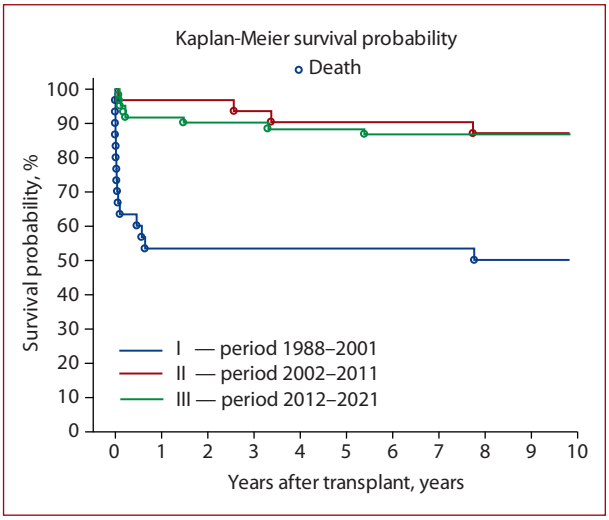

Figure 3. Kaplan-Meier survival curve after pediatric heart transplant in the Silesian Center for Heart Diseases in Zabrze. I 1988–2001; II 2002–2011; III 2012–2021

HTx at the age <1 year of age was 20.1 (SD, 0.8) years; at the age 1–5 years was 17.2 (SD, 7.1); at the age 6–10 years was 13.9 (SD, 1.8), and at the age 11–17 years was 12.4 (SD, 6.8) years [11]. One-, 5-, and 10-year survival rates were slightly better in the group of patients with cardiomyopathy, compared to patients with congenital heart disease as an indication for HTx (91.5% vs. 79.0%, 80.4% vs. 70% and 76.2% vs. 66.1%, respectively) [11, 12]. In the observed group, the survival rate was: 89.3% vs. 85.2%; 87.5% vs. 76.7%, and 84.2% vs. 62.7%, respectively. The population of children supported with MSC before HTx also increased. In this group of patients, there was a survival rate difference depending on the type of MCS. A longer survival time was observed in the group of patients on pulsatile extracorporeal ventricular assist devices (VAD) or total artificial hearts (TAH) in comparison to the group in which extracorporeal membrane oxygenation (ECMO) was used before HTx (1-year survival, respectively, 91.7% vs. 66.1%). In pediatric patients who underwent HTx after MCS in SCCS (n = 20; 18%), 1- and 5-year survival rates were 93.7% with no statistical significance (P >0.05). The immunosuppressive induction protocol with the use of steroids and calcineurin inhibitors also had an impact on long-term survival. The occurrence of episodes of rejection significantly affected long-term survival although 1-year survival of patients who had experienced heart rejection versus patients who had not was comparable (81.6% vs. 89.8%); the 5- and 10-year survival rates were significantly different: 70.1% vs. 79.3%, respectively. In 8.1% to 21.4% of patients, the first episode of rejection occurred in the first year after transplantation [11, 12]. In almost 15% of patients, the treated rejection occurred in the first year after HTx, less frequently in patients who did not receive any induction and TAC had been used as immunosuppressive therapy regardless of age. In recipients with TAC treatment and no induction, rejection occurred in 14.6% of patients compared to the group with TAC treatment and induction, CyA treatment and induction, and CyA treatment and no induction (17.7%, 26.0%, and 26.9%, respectively) [11, 12]. In our study group rejection episodes requiring additional medical treatment occurred more frequently than in the ISHLT registry database. In the group of patients without MSC before HTx, rejection was confirmed in 33.3% of patients compared to the group with MCS — 38.5%. The difference was not significant (P = 0.74).

The development of CAV affected approximately 16% of infants who had HTx, 26% of children at the age 1–5, 27% at the age 6–10, and 37% at the age 11-17. The risk of CAV depends not on the type of induction and immunosuppressive protocols used, but on the donor's age, the recipient's weight, and the need for retransplantation.

The higher risk of CAV affects patients with higher levels of circulating antibodies (PRA-panel reactive antibody) at the time of transplantation [11, 12]. The diagnosis of CAV reduces 1- and 3-year survival to 66%–77% and 52%–60%, respectively.

Cytomegalovirus (CMV) reinfection after HTx is associated with increased morbidity and mortality in solid organ recipients. CMV reinfection has been shown to play a role in graft failure, acute rejection, development of CAV, and PTLD [12, 18]. It occurs in the first two months after HTx, mostly in seronegative CMV recipients who receive a seropositive donor's organ. In our study group, CMV reinfection occurred in 2.45% (n = 3) of patients transplanted between 2008 and 2021, despite using prophylactic antiviral treatment with intravenous and oral valganciclovir for up to 100 days after HTx. Another posttransplant complication is malignant disease, especially in pediatric recipients. Lymphomas originating from B-lymphocytes associated with Epstein-Barr virus (EBV) reinfection are the most frequently occurring malignancies. The risk of developing malignancies increases with time after HTx: 1.6%; 4.7%, and 9.7% in years 1, 5, and 10, respectively. Fifteen years after HTx, neoplastic proliferative lesions occur in as many as 17% of patients [11, 12]. In the study group, PTLD occurred in 3 (2.45%) patients, two of whom died (1.64%).

CONCLUSION

Cardiac transplantation in both adults and children remains the main method of treatment of end-stage heart failure despite the development of artificial circulatory techniques, using both pulsatile and continuous flow pumps. Our results at both early and long-term posttransplant periods, are comparable to those obtained in the most experienced foreign centers. An inadequate number of pediatric donors remains a problem, which is related not only to local conditions but mainly to lack of awarness of benefits of transplantation in society. In comparison to countries with smaller populations, such as the Czech Republic or Croatia, the organ donation rate in Poland remains low, amounting to 14.6 donors per 1 million inhabitants, and varies among regions. In 2017, there were 24.7 donors per 1 million inhabitants in West Pomerania in Poland. In the same period, there were only 5.2 donors per 1 million inhabitants in the Podkarpackie Region. In Croatia, the donation rate is 33.0 donors per 1 million inhabitants, in the Czech Republic there are 25.5 donors per 1 million inhabitants, and in the best functioning donation system in Spain, the rate is 46.9 donors per 1 million inhabitants [19]. The low rate of donations in Poland continues to be of concern to national institutions, including Poltransplant, and is the main topic of not only social campaigns but also development programs for healthcare professionals.

In conclusion, heart transplantation is an effective treatment method for heart failure but still requires further research, especially in the area of early and noninvasive diagnosis of acute allograft rejection that influences long-term outcomes. EMB remains the gold standard for the diagnosis of rejection in adults, but it is not performed in small children. There are publications on the important possible role of cardiovascular magnetic resonance (CMR) to support acute cardiac allograft rejection as an alternative to EBM [20], but the pediatric recipient population is still subject to technical limitations. Small children do not cooperate during the procedure, especially in breath holding, and they must be deeply anesthetized and often intubated. If the CMR procedure was simplified and shortened, there would be a possibility to implement the standard protocol for evaluation in the pediatric population. But still the role of CMR remains to be confirmed in prospective multicenter studies.

Article information

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