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Survival analysis in heart transplantation: results from an analysis of 1290 cases in a single center

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Abstract

Background: The clinical profiles of recipients and donors eligible for the procedure as well as the procedure itself have changed over time. We determined the impact of changes in baseline risk profiles at different transplant periods on outcome, and the time-specific distribution of causes of death. **Patients and methods:** Adult heart transplantations were performed consecutively on 1290 patients. Three transplant periods were defined: 1989–1993, 1994–1998, and 1999–2004. **Results:** Recipient age and body mass index, previous cardiac surgery, high urgency status, need of ventricular assist device, waiting time (to transplantation and on ventricular assist device), donor age and body mass index, donor–recipient body mass index mismatch, and ischemic and cardiopulmonary bypass time were significantly different over the three transplant periods. There was, however, no significant difference in mortality risk. The major causes of deaths were: acute rejection, multiorgan failure, and right heart failure (≤30 days); infection and acute rejection (31 days to 1 year); malignancy, acute rejection, and cardiac allograft vasculopathy (>1–5 years); cardiac allograft vasculopathy and malignancy (>5–10 years); and malignancy and infection (>10 years). The overall 1-, 5-, 10- and 15-year survival was respectively 77%, 67%, 53% and 42%. There was no difference in survival by different transplant periods ($p = 0.68$). **Conclusion:** Despite clearly increased baseline risk profiles over time, the outcome of adult heart transplantation remains stable and encouraging. Cardiac allograft vasculopathy, malignancy, and infection threaten the long-term survival.

Keywords: Transplantation; Heart; Adult; Mortality; Survival

1. Introduction

Heart transplant practices, organ allocation criteria, and demographic characteristics of recipient and donor have evolved over time [1–4]. Several changes occurring during the past decades, including advances in surgical techniques, immunosuppressive therapies, and better understanding of postoperative medical care have allowed heart transplantation to become the treatment of choice for patients with end-stage heart failure. The growing number of patients awaiting heart transplantation and the shortage of donor hearts has encouraged many centers to liberalize the recipient criteria and expand the donor pool. Still, the impact of these changes on outcome after heart transplantation remains unclear. Moreover, understanding the time-specific distribution of causes of death is important to improve survival. We aimed to evaluate the impact of the changes in baseline risk profiles at different transplant periods on outcome, and to determine the distribution of causes of death after heart transplantation.

2. Patients and methods

2.1. Study population

The study population comprised 1290 consecutive adult recipients undergoing heart transplantation from inception of the heart transplant program at the Heart & Diabetes Center North Rhine Westphalia in Bad Oeynhausen, Germany (March 1989) up to the end of December 2004. The annual distribution of the heart transplantation is presented in Fig. 1. Our research ethics committee approved this study, and the need for individual informed consent was waived. Recipient selection criteria for adult heart transplantation have been recently published [5], and included: irreversible end-stage heart failure without any other feasible medical or surgical treatment option, limited life expectancy if untreated (less than 6 months), age < 65 years, and no

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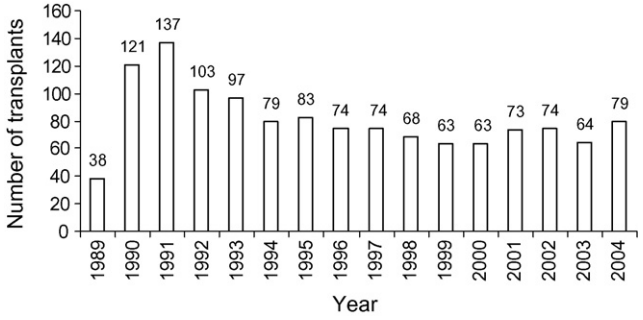

Fig. 1. Annual distribution of adult heart transplantation.

other systemic illness except abnormalities related to heart failure. Exclusion criteria were severe pulmonary hypertension (fixed PVR $>$ 6 Wood Units/m^2), severe irreversible hepatic, renal or pulmonary disease, systemic or local infection in operative site, acute peptic ulcer disease, acute pulmonary infarction, evidence of patient's non-compliance, history of drugs and/or alcohol abuse. Donor hearts were harvested from beating-heart, brain death individuals through cooperation with the Eurotransplant organization. Donor assessment was based on complete clinical-laboratory evaluation and echocardiography, and the selection criteria have been published previously [6]. Males younger than 40 years and females younger than 45 years were considered as suitable donors if there were no pre-existing heart diseases or impaired myocardial dysfunction, and mitral insufficiency. We recommend donor heart's acceptance if hemodynamic parameters are in a normal range on mild-to-moderate inotropic support. A heart from an older donor was accepted if coronary atherosclerotic lesions could be excluded. Since a regular coronary angiogram is practically impossible in potential donors, a bench coronary angiogram was preferably done if the donor heart shows signs of coronary artery disease on palpation at the time of explantation. Donor and recipient were matched for ABO blood-type compatibility and body weight. Marginal donor hearts were considerably accepted in individual cases.

2.2. Surgical technique

Donor hearts were harvested from beating-heart brain-dead persons. Graft procurement and preservation was achieved by combination of cold cardioplegic arrest, mainly using Histidine-buffered tryptophan-ketoglutarate cardioplegia solution (Bretschneider-Custodiol; Kohler Chemie, Alsbach-Hahnlein, Germany) and topical hypothermia. All transplantations were performed orthotopically by senior heart surgeons, using the biatrial technique [7]. Weaning from CPB was done under monitoring of right and left atrial pressure.

2.3. Immunosuppressive protocol

Initial immunosuppressive regimen was based on 300 mg oral or 50 mg intravenous cyclosporine A, 200 mg oral or 100–150 mg intravenous azathioprine (adjusted to renal and hepatic function), and 250 mg intravenous methylprednisolone. 2 ml/kg human immunoglobulin G, 40 mg intravenous omeprazole and 1 pipette oral nystatin were also given. Intraoperative, 3 mg/h cyclosporine A was continually infused. Shortly before releasing the aortic cross-clamping, 1 g methylprednisolone was administered. During a stay in the intensive care unit, the recipient received 4 $\times$ 250 mg/day intravenous methylprednisolone for 3 days. Oral steroid dosage was tapered gradually within 2–3 weeks. Cyclosporine A was continued intravenously, and then orally with the dosage depending on its level in blood, measured directly after transplantation and twice a day for the following course. In addition, twice a day of 2–4 mg/kg azathioprine (adjusted to white blood cell/platelet count and hepatic function), and 2 ml/kg intravenous human immunoglobulin G (until the fifth postoperative day) was administered. Twenty mg intravenous omeprazole was administered until the third postoperative day. Long-term immunosuppressive therapy consisted of cyclosporine A (6 mg/kg/day) and azathioprine (2 mg/kg/day). Target level of cyclosporine A was 200–250 μg/l (monoclonal RIA) within the first year and maintained between 80 and 180 μg/l. If recipient white blood cell count fell below 5000/μl, azathioprine dosage was reduced. If it fell below 3500/μl, azathioprine was completely stopped and not restarted even if the white blood cell count returned to normal (except for rejection episodes). Whenever possible, steroid maintenance (10 mg/day) was avoided. Anti-platelet agents including 50 mg/day aspirin and 300 mg/day dipyridamole were administered as prophylaxis of cardiac allograft vasculopathy. Ninety mg/day calcium channel blocker was added if cardiac allograft vasculopathy was suspected.

The diagnosis of rejection was usually based on clinical findings, electrocardiographic and echocardiographic data. In the first 6 months after heart transplantation, patients were examined monthly and every 3 months after that for the next half year. Thereafter, examinations were performed every 6 months. A clinically proven rejection was assumed when an echocardiography revealed an ejection fraction $<$50%, septal hypokinesia, pericardial effusion, and a mean arterial pressure $<$65 mmHg occurred in parallel with nausea, weakness, abdominal or thoracic pain. Indicated endomyocardial biopsies were performed when rejection was suspected, and routinely during the 1-, 5-, and 10-year after heart transplantation.

Baseline coronary angiography was performed in the recipient having a donor heart older than 50 years or with previous cardiopulmonary resuscitation. Significant rejection was defined as an episode with symptom of graft rejection requiring augmentation of immunosuppression, corresponding to ISHLT grade 3A rejection or above [8] or with newly developed left ventricular function impairment (ejection fraction $<$30%). Routine treatment of rejection consisted of 4 $\times$ 250 mg/day methylprednisolone for 3 days. If there were more than three episodes of ongoing rejection, 1 mg/kg/day oral prednisone was given, and then tapered slowly to at least 0.05 mg/kg/day. In patients with unstable hemodynamic or rejection episodes refractory to intravenous steroid boost, rescue immunosuppressive therapy with antithymocyte globulin or mono-/polyclonal antibodies was initiated.

2.4. Design of data collection and follow-up

Preoperative and intraoperative data were retrieved from patient records and prospectively documented in a computer-

ized database. Three transplant periods were defined: 1989–1993, 1994–1998, and 1999–2004. Early mortality was defined as any death within 30 days post-transplantation. Late mortality was defined as death after 30 days. A donor–recipient size mismatch can occur in two directions: oversizing and undersizing. We use the historic ratio threshold of 20%.

Follow-up information was collected through outpatient's clinic reports or by telephone interview with patients, their relatives and referring physician or both, and was 100% complete.

2.5. Data analysis

The Statistical Package for the Social Sciences (SPSS), version 13.0 (Chicago, IL, USA) was used for data analysis. Results were expressed as mean and standard deviation or median and interquartile range (continuous variables), and counts with percentages (categorical variables). For comparisons, Pearson χ^2-test or Fisher's exact test (categorical variables) and analysis of variance (ANOVA) or the non-parametric Kruskal–Wallis rank test (continuous variables) were used. Survival was calculated by means of the Kaplan–Meier product-limit estimate of the survivorship function. The log-rank test was used to compare groups. A p-value of less than or equal to 0.05 (two-tailed test) was considered statistically significant.

3. Results

3.1. Baseline characteristics

The indications for adult heart transplantation were: dilated cardiomyopathy (631 of 1290), ischemic cardiomyopathy (543 of 1290), valvular heart disease (75 of 1290), heart retransplantation (28 of 1290), and other (13 of 1290). Table 1 compares the baseline characteristics between the three subsequent transplant periods. Mean recipient age rose from 52.8 ± 10.4 years to 54.3 ± 12.1 years ($p = 0.03$). Recipient body mass index significantly increased ($p = 0.002$). Recipients transplanted were more ill as reflected by an increasing need of ventricular assist device prior to transplantation ($p < 0.001$) and a greater percentage of recipients listed with high urgency transplant status ($p = 0.005$). During the later years, the transplantations were more often complicated by previous cardiac surgeries. The waiting time to transplantation varied ($p < 0.001$) but waiting time on ventricular assist devices ($p < 0.001$) increased over the three subsequent transplant periods. Mean donor age ($p < 0.001$) and body mass index ($p < 0.001$) increased significantly. Donor–recipient mismatch regarding to body mass index significantly increased ($p < 0.001$), while ischemia time varied ($p < 0.001$). The cardiopulmonary bypass time increased over the three subsequent transplant periods ($p < 0.001$).

3.2. Early outcomes

In total, 115 recipients died within 30-day postoperative, for an overall 30-day mortality risk of 9% (95% CI: 7–11%). There was no significant variation in 30-day postoperative mortality risk over the three subsequent transplant periods ($p = 0.31$). Similarly, there was no significant difference in mortality risk over the three subsequent transplant periods for significantly different baseline characteristics, notably recipient with previous cardiac surgery, high urgency transplant status, need of ventricular assist device, and donor–recipient mismatch in body mass index (Table 2). The

Table 1
Baseline characteristics across the transplant periods

	Total ($n = 1290$)	1989–1993 ($n = 496$)	1994–1998 ($n = 378$)	1999–2004 ($n = 416$)	p-Value
Recipient					
Age (years)[a]	53.8 (11.2)	52.8 (10.4)	54.7 (11.1)	54.3 (12.1)	0.03
Gender (male)	1085 (84)	426 (86)	314 (83)	345 (83)	0.39
Body mass index (kg/m^2)[a]	23.5 (3)	23.2 (2.9)	23.3 (2.9)	23.9 (3.3)	0.002
Previous cardiac surgery	436 (34)	122 (25)	145 (38)	169 (41)	<0.001
Retransplantation	28 (2)	11 (2)	6 (2)	11 (3)	0.59
High urgency transplant status	123 (10)	35 (7)	51 (14)	37 (9)	0.005
Waiting time (days)[b]	100 (27–324)	42 (13–110)	295 (79–487)	278 (39–401)	<0.001
Ventricular assist device (VAD)	230 (18)	45 (9)	97 (26)	88 (21)	<0.001
Waiting time on VAD[b]	82 (29–189)	12 (5–27)	67 (35–141)	187 (86–315)	<0.001
Donor					
Age (years)[a]	36.4 (13.6)	34.1 (13.4)	37.3 (14)	38.4 (13.2)	<0.001
Gender (male)	651 (51)	255 (51)	203 (54)	193 (46)	0.104
Body mass index (kg/m^2)[a]	23.9 (3.5)	23.4 (2.9)	23.6 (3.3)	24.8 (3.9)	<0.001
Cardiopulmonary resuscitation	194 (15)	69 (14)	60 (16)	65 (16)	0.67
Donor–recipient mismatch					
Gender	550 (43)	225 (45)	153 (41)	172 (41)	0.29
Body mass index (ratio: ±20%)	265 (21)	68 (14)	88 (23)	109 (26)	<0.001
Non-identical blood type	80 (6)	34 (7)	23 (6)	23 (6)	0.71
Operative characteristics					
Ischemic time[a]	194.4 (40.4)	186.7 (39.7)	199.4 (44.6)	199.1 (35.6)	<0.001
Cardiopulmonary bypass time[a]	114.8 (48.2)	97.8 (41.1)	119.8 (55.6.9)	130.5 (41.9)	<0.001

Values are count (percentage) unless otherwise indicated, p-value based on Pearson χ^2 test or Fisher's exact test.
[a] Mean (±SD), p-value based on ANOVA.
[b] Median (interquartile range), p-value based on Kruskal–Wallis rank test.

Table 2
Comparison of 30-day mortality for three transplant periods in adult heart transplantation (overall and for significant difference in baseline characteristics)

Numbers (%)	Total		1989–1993		1994–1998		1999–2004		*p*-Value*
	Death	Survivor	Death	Survivor	Death	Survivor	Death	Survivor	
Overall	115 (9)	1175 (91)	31 (6)	465 (94)	47 (12)	331 (88)	37 (9)	379 (91)	0.31
Previous cardiac surgery	52 (12)	384 (88)	15 (12)	107 (88)	19 (13)	126 (87)	18 (11)	151 (89)	0.49
High urgency status	7 (1)	116 (99)	1 (3)	34 (97)	3 (6)	48 (94)	3 (8)	34 (92)	0.33
Ventricular assist device	26 (11)	204 (89)	3 (7)	42 (93)	9 (9)	88 (91)	14 (16)	74 (84)	0.12
IT > 240 min	20 (13)	135 (87)	1 (2)	40 (98)	11 (18)	50 (82)	8 (15)	45 (85)	0.69
BMI mismatch	30 (11)	235 (89)	4 (6)	64 (94)	13 (15)	75 (85)	13 (12)	96 (88)	0.47

BMI: body mass index, IT: ischemic time; Values are count (percentage).
* Adjusted for recipient and donor age.

Table 3
Time-specific distribution of causes of death after adult heart transplantation

Total population (*N* = 1290)	Overall (*n* = 537)	≤30 days (*n* = 115)	31 days to 1 year (*n* = 174)	>1–5 years (*n* = 104)	>5–10 years (*n* = 109)	>10 years (*n* = 35)
Acute rejection	117 (22)	32 (28)	55 (32)	23 (22)	4 (4)	3 (9)
Multiorgan failure	47 (9)	20 (17)	15 (9)	3 (3)	9 (8)	–
Right heart failure	20 (4)	14 (12)	2 (1)	–	3 (3)	1 (3)
Infection	107 (20)	12 (10)	67 (39)	13 (13)	8 (7)	7 (20)
Primary graft failure	8 (1)	7 (6)	–	–	–	1 (3)
Malignancy	68 (13)	–	3 (2)	30 (29)	26 (24)	9 (26)
CAV	73 (14)	–	11 (6)	18 (17)	39 (36)	5 (14)
Others	97 (18)	30 (26)	21 (12)	17 (16)	20 (18)	9 (26)

Values are count (column %). Because of rounding, not all percentages total to 100.

major causes for 30-day mortality were: acute rejection (32 of 115), multiorgan failure (20 of 115), and right heart failure (14 of 115) (Table 3).

3.3. Long-term follow-up

The total follow-up time was 7256 patient-years. Overall, 537 recipients died during follow-up period, resulting in 74 per 1000 patient-years of overall mortality rate. The mortality rate for those who survived the first month was 58 per 1000 patient-years. The major causes for late mortality were: infection (67 of 174) and acute rejection (55 of 174) (for 31 days to 1 year); malignancy (30 of 104), acute rejection (23 of 104) and cardiac allograft vasculopathy (18 of 104) (for > 1–5 years); cardiac allograft vasculopathy (39 of 109) and malignancy (26 of 109) (for >5–10 years); malignancy (9 of 35) and infection (7 of 35) (for after 10 years) (Table 3). The overall 1-, 5-, 10- and 15- year survival of adult heart transplantation was respectively 77%, 67%, 53% and 42% (Fig. 2). There was no difference in survival by different transplant periods ($p = 0.68$) (Fig. 3), and the same hold for cause of death.

4. Discussion

The effects of temporal changes in donor and recipient characteristics on early and late survival after adult heart transplantation were examined in a single-center experience over a period of 15 years. Our data reflect the generally recognized trends toward liberalization of recipient criteria and expansion of the donor pool [1,9–11]. Significant and clinically relevant changes were seen in the proportion of recipient age and body mass index, previous cardiac surgery, high urgency transplant status, waiting time to transplantation, and need of ventricular assist device prior to transplantation. Simultaneously, older donors were more frequently employed. In particular, there was a gradual increase in ischemic time, and in the acceptance of donors despite the body mass index mismatch. Our results show that despite these changes, the early and late survival remain stable and encouraging, presumably due to significant improvements in clinical management, including pretransplant medical therapy, timing, route of hemodynamic

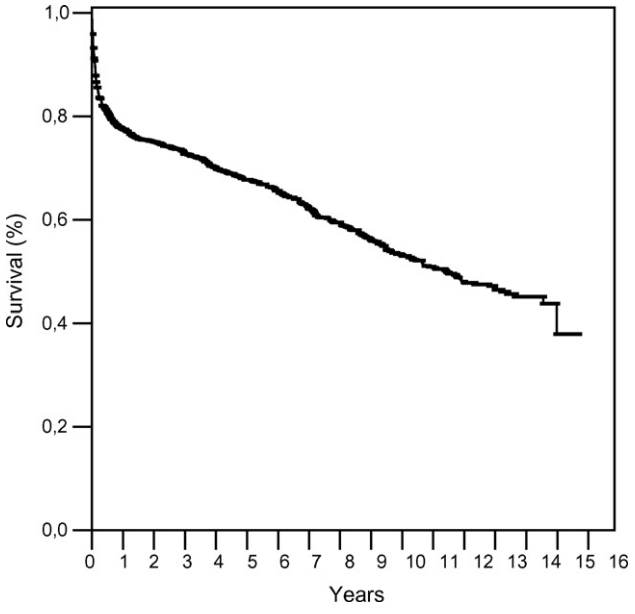

Fig. 2. Overall long-term survival of adult heart transplantation (*n* = 1290).

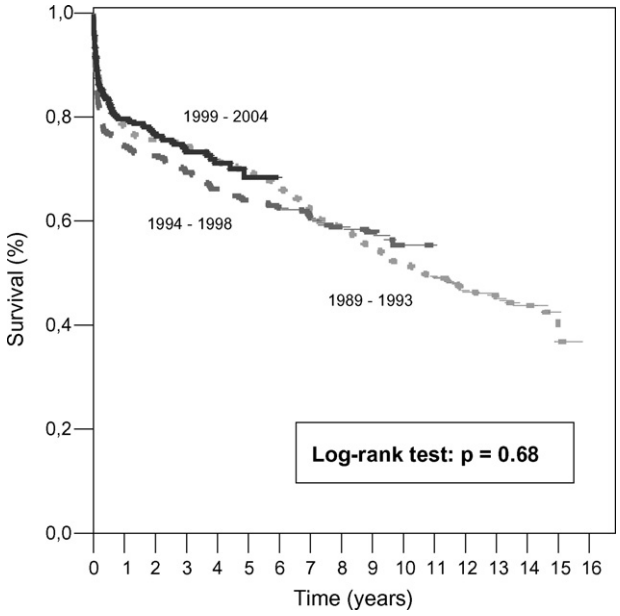

Fig. 3. Long-term survival of adult heart transplantation by different transplant period.

support, myocardial protection, steady progress in surgical experiences, perioperative intensive care, and immunosuppression protocol. We believe that transplant volume and the accumulation of our surgical experiences may correct for the expected worsening survival when higher risk transplantation is performed [12,13]. Recent studies confirm that centers that perform 50 cardiac transplants per year have better outcomes than those with 10 or 100 per year [14]. The increase in the percentage of recipients who had previous cardiac surgery explains, in part, the longer cardiopulmonary bypass and ischemic times. The use of older donors, more frequent donor–recipient body mass index mismatch, and prolonged ischemic time reflects a gradual attempt to expand the donor pool, as waiting time to transplantation steadily increased. Despite these potentially increased risks, the early and late survival in our patients remained unchanged.

The distribution of causes of death depends on the post-transplant interval and deserves separate consideration. A better understanding of transplant-related death may improve survival. Similar to the ISHLT registry [15], the main causes of 30-day mortality in our study are acute rejection, multiorgan failure, and right heart failure. Previous data [14] showed that acute rejection was responsible for 9.4% of 30-day mortality after adult heart transplantation. Death from acute rejection may be reduced by improving rejection surveillance and appropriate treatment. Similar to our results, McGiffin et al. [3] reported cardiac allograft vasculopathy, malignancy, and infection as the causes of late mortality. Cardiac allograft vasculopathy, which is characterized by diffuse and multifocal heterogeneous myointimal hyperplasia, is reported as the most common cause of late mortality [16] with an incidence of 50–60% after 5 years post-transplantation [17]. The development of malignancy has been well recognized in immunosuppressed transplant recipients [18], with an incidence of 33% after 5 years post-transplantation [2]. With increasing age, the long-term effect of immunosuppression increases the likelihood for neoplastic transformation. Patients with a history of prior malignancy are, in particular, at higher risk [15]. Unfortunately, aside from the established association between cytolytic induction therapy and lymphoproliferative disorders [19], we do not have clear insight into which components of an immunosuppressive protocol may in particular increase the risk for malignancy. Within the first month post-transplantation, infection is usually caused by nosocomial pathogens, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterobacteriaceae*. The sites of infection include blood, respiratory/urinary tract and surgical wounds. Late infections are commonly caused by cytomegalovirus, *Pneumocystis jiroveci*, *Legionella* and fungi [20,21]. Early monitoring of immunoglobulin levels might help to identify the risk of developing infection [22].

In conclusion, despite increased baseline risk profiles over time, the outcome of adult heart transplantation remains stable and encouraging. Cardiac allograft vasculopathy, malignancy, and infection threaten the long-term survival.

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