PREDICTING OUTCOME OF HEART TRANSPLANTATION

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PREDICTING OUTCOME OF HEART TRANSPLANTATION

Het voorspellen van de uitkomst van harttransplantatie

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor
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door

Yanto Sandy Tjang

geboren op 17 juli 1966
te Jambi, Indonesië

Promotoren: Prof. dr. D.E. Grobbee
Prof. dr. med. dr. h.c. R. Körfer

Co-promotor: Dr. G.J.M.G. van der Heijden

Three passions, simple but overwhelmingly strong, have governed my life: the longing for love, the search for knowledge, and unbearable pity for the suffering of mankind. These passions, like great winds, have blown me hither and thither, in a wayward course, over a deep ocean of anguish, reaching to the very verge of despair. I have wished to understand the hearts of men. I have wished to know why the stars shine. And I have tried to apprehend the Pythagorean power by which number holds sway above the flux. A little of this, but not much, I have achieved.

• Bertrand Russel, 1872 – 1970 •

To my beloved Mother,
Brothers and Sister,
and for everlasting memory of my Father

Manuscripts based on the studies presented in this thesis

Chapter 2

Y.S. Tjang, G.J.M.G. van der Heijden, G. Tenderich, D.E. Grobbee, R. Körfer. Survival analysis in heart transplantation: results from an analysis of 1,290 cases in a single center. *Eur J Cardiothorac Surg 2008; 33:856-61*.

Chapter 3

Y.S. Tjang, G.J.M.G. van der Heijden, G. Tenderich, R. Körfer, D.E. Grobbee. Long-term results of heart transplantation for end-stage valvular heart disease. *Under peer review*.

Chapter 4

Y.S. Tjang, G.J.M.G. van der Heijden, G. Tenderich, R. Körfer, D.E. Grobbee. Impact of recipient age on heart transplantation outcome. *Ann Thorac Surg 2008; 85:2051-5*.

Chapter 5

Y.S. Tjang, G. Tenderich, R. Körfer, D.E. Grobbee, G.J.M.G. van der Heijden. Donor heart refusal in heart transplantation should not be based on donor sodium level. *Under peer review*.

Chapter 6

Y.S. Tjang, G.J.M.G. van der Heijden, G. Tenderich, R. Körfer, D.E. Grobbee. Heart transplantation from donor undergoing cardiopulmonary resuscitation does not adversely affect the outcome. *Under peer review*.

Chapter 7

Y.S. Tjang, E. Suarthana, R. Körfer, G. Tenderich, D.E. Grobbee, G.J.M.G. van der Heijden. Prediction model for the thirty-day mortality risk after adult heart transplantation. *Under peer review*.

Chapter 8

Y.S. Tjang, E. Suarthana, R. Körfer, G. Tenderich, D.E. Grobbee, G.J.M.G. van der Heijden. Predicting the 1- and the 5-year mortality risk after adult heart transplantation. *Submitted*.

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Chapter 1

General introduction

Since the first clinical application in 1967 (1), more than 76,000 heart transplantations have been performed (2). Developments in recipient and donor selection, organ preservation, surgical technique, perioperative management, and postoperative immunosuppressive therapy substantially improved outcome after heart transplantation. Currently, heart transplantation has become the treatment of choice for patients with end-stage heart diseases.

The subsequent increasing demand for heart transplantation has led to the liberalization of the traditional recipient selection criteria (3). There has been a gradual increase of recipient age. The proportion of potential recipients older than 65 years has increased from 5% in 1993 to 12% in 2002. Patients at poor health status, e.g. pretransplant diagnosis of end-stage valvular heart disease and older recipients, are more likely to have a higher morbidity and mortality due to co-existing medical problems.

In the USA, the severe shortage of donor hearts has limited the number of patients placed on the waiting list to about 8,000 per year (4). It is estimated, however, that at least 25,000 patients per year would benefit from heart transplantation. Out of this number, only 2,500 heart transplantations could be performed every year (3). Hence, the increased gap between the demand and supply of donor hearts results in significant prolonged waiting time, which have almost tripled over the past decade, and an increased mortality of recipients on the waiting list (5, 6). In some countries, approximately 50% of all patients on the waiting list will never receive heart transplantation because of extended waiting time and shortage of donor hearts (7). Due to sub-optimal utilization of donor hearts, a rather large proportion of donor hearts has not been transplanted. The maximum non-utilization rate of suitable donor hearts are reported as up to 65% (8-11). Numerous modified protocols regarding the suitability of potential donor hearts have been created (12-14). Recent evidence indicates that certain donor criteria can be liberalized to increase the donor pool, e.g. by accepting marginal donors that are those that under conventional transplant guidelines are rejected (8, 15). Nevertheless, the impact of these trends on the outcome of heart transplantation, in particular on long term, remains uncertain. Special attention should be drawn to the fact that each assessment, especially of marginal donor hearts, should be individualized and recipient-oriented, rather than using a cataloque of theoretical and general acceptability criteria.

There are multiple competing and complementary therapeutic options for end-stage heart diseases, including extensive use of mechanical circulatory support. Heart transplantation should be reserved for those patients most likely to benefit in terms of survival. The concept of survival benefit margin must be balanced with the principle of utility in the selection process (16). In this process, the individual survival risk profil and the availability of suitable donor heart will be crucial in the decision of heart transplantation. To enable predicting the outcome for individual patient based

on recipient and donor characteristics, and their match, a prediction model may play a crucial role in selection of a donor heart to a specific recipient (17).

OUTLINE OF THIS THESIS

This thesis focuses on the impact of various recipient and donor baseline characteristics on outcome after adult heart transplantation, on which information remains limited and disputed. Furthermore, several models have been developed and validated to predict mortality risk after adult heart transplantation.

Chapter 2 gives an overview of the impact of the changes in baseline risk profiles at different transplant period on outcome and the time-specific distribution of causes of death after adult heart transplantation. In **chapter 3**, the long-term outcome of adult heart transplantation for end-stage valvular heart disease is compared to that for other indications. The impact of recipient age on outcome after adult heart transplantation is assessed in **chapter 4**, while the impact of donor sodium level on outcome after adult heart transplantation is evaluated in **chapter 5**. **Chapter 6** outlines the influence of cardiopulmonary resuscitation in donors on outcome after adult heart transplantation. An easily applicable prediction model for the 30-day mortality risk after adult heart transplantation is presented in **chapter 7**. **Chapter 8** demonstrates other easily applicable models for predicting the 1- and the 5-year mortality risk after adult heart transplantation. Finally in **chapter 9**, the major findings of the above studies are discussed in a broader perspective. It outlines the strengths and limitations of the studies, implications for practice and future research, as well as general conclusions and recommendations.

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Chapter 2

Survival analysis in heart transplantation: results from an analysis of 1,290 cases in a single center

Y.S. Tjang, G.J.M.G. van der Heijden, G. Tenderich, D.E. Grobbee, R. Körfer

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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 period on outcome, and the time-specific distribution of causes of death.

Patients and methods

Adult heart transplantations were performed consecutively on 1,290 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 transplant status, need of ventricular assist device, waiting time (to transplantation and on ventricular assist device), donor age and body mass index, donor–recipient mismatch for body mass index, 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 period (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.

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 period on outcome, and to determine the distribution of causes of death after heart transplantation.

PATIENTS AND METHODS

Study population

The study population comprised 1,290 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 Figure 1.

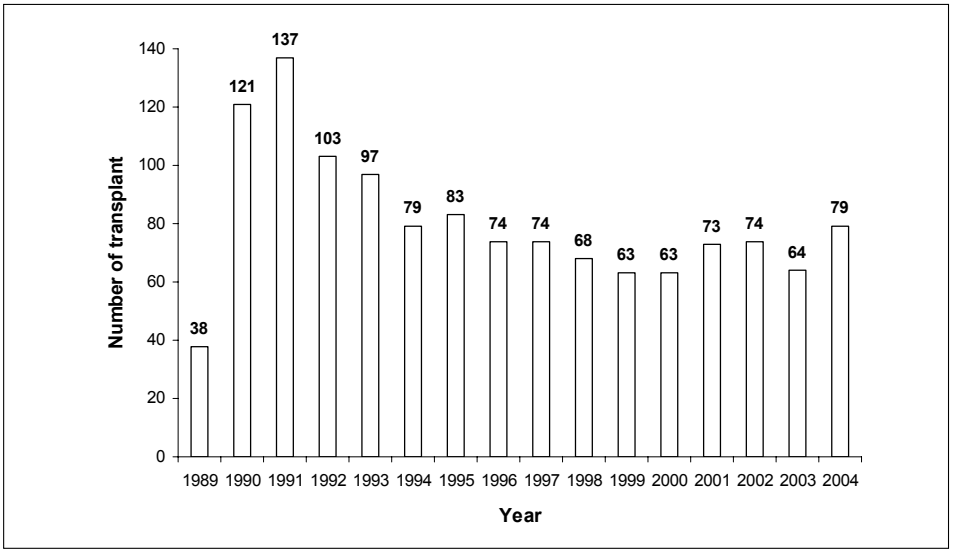


Figure 1. Annual distribution of adult heart transplantation.

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 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.

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.

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 × 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 × 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.

Design of data collection and follow-up

Pre- and perioperative data were retrieved from patient records and prospectively documented in a computerized database. Three transplant periods were defined: 1989 - 1993, 1994 - 1998, and 1999 - 2004. Early mortality was defined as any death within 30 days posttransplantation. 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.

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 (categoric variables). For comparisons, Pearson χ^2-test or Fisher's exact test (categoric 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.

RESULTS

Baseline characteristics

The indications for adult heart transplantation were: dilated cardiomyopathy (631 of 1,290), ischemic cardiomyopathy (543 of 1,290), valvular heart disease (75 of 1,290), heart retransplantation (28 of 1,290), and other (13 of 1,290). 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 for body mass index significantly increased ($p < 0.001$), while ischemic time varied ($p < 0.001$). The cardiopulmonary bypass time increased over the three subsequent transplant periods ($p < 0.001$).

Table 1. Baseline characteristics across the transplant periods.

Variable	Total (n = 1,290)	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)	1,085 (84)	426 (86)	314 (83)	345 (83)	0.39
BMI (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 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
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
BMI (kg/m^2)[a]	23.9 (3.5)	23.4 (2.9)	23.6 (3.3)	24.8 (3.9)	< 0.001
CPR	194 (15)	69 (14)	60 (16)	65 (16)	0.67
Donor-recipient mismatch					
Gender	550 (43)	225 (45)	153 (41)	172 (41)	0.29
BMI (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 data					
Ischemic time[a]	194.4 (40.4)	186.7 (39.7)	199.4 (44.6)	199.1 (35.6)	< 0.001
CPB time[a]	114.8 (48.2)	97.8 (41.1)	119.8 (55.6.9)	130.5 (41.9)	< 0.001

BMI: body mass index, CPB: cardiopulmonary bypass, CPR: cardiopulmonary resuscitation, VAD: ventricular assist device.
Values are count (%) 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.

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 for body mass index (Table 2). The 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).

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

	Total		198 - 1993		1994 - 1998		1999 - 2004		*P*-
Numbers (%)	**Death**	**Survivor**	**Death**	**Survivor**	**Death**	**Survivor**	**Death**	**Survivor**	**value***
Overall	115 (9)	1,175 (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 minutes	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.

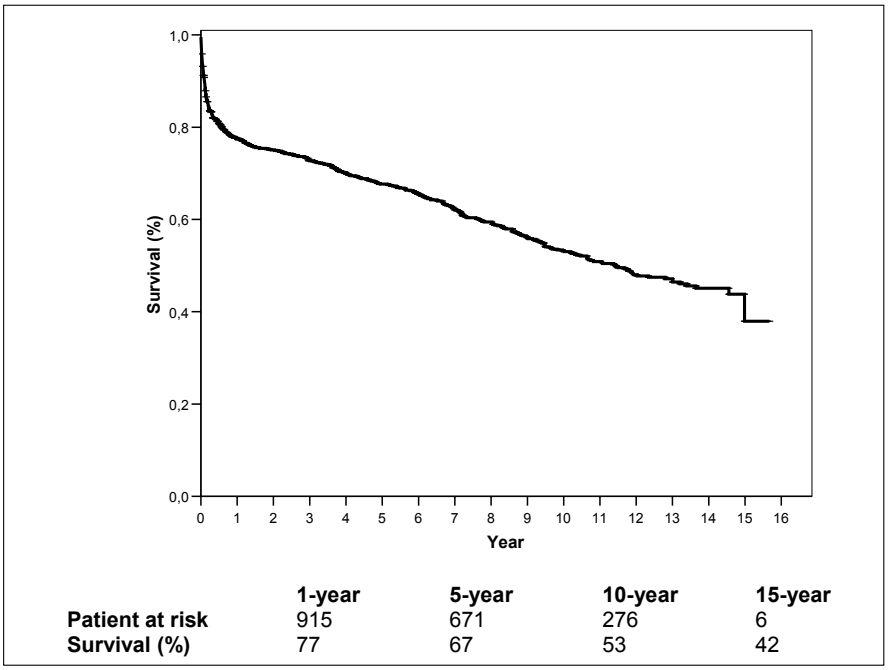
Table 3. Time-specific distribution of causes of death after adult heart transplantation.

Total population (N = 1,290)	**Overall (n = 537)**	**≤30 days (n = 115)**	**31 days - 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)
Other	97 (18)	30 (26)	21 (12)	17 (16)	20 (18)	9 (26)

CAV: cardiac allograft vasculopathy.
Values are count (%). Because of rounding, not all percentages total to 100.

Long-term follow-up

The total follow-up time was 7,256 patient-years. Overall, 537 recipients died during follow-up period, resulting in 74 per 1,000 patient-years of overall mortality rate. The mortality rate for those who survived the first month was 58 per 1,000 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); and 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% (Figure 2). There was no difference in survival by different transplant period (p = 0.68, Figure 3) and the same holds for the cause of death.



	1-year	5-year	10-year	15-year
Patient at risk	915	671	276	6
Survival (%)	77	67	53	42

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

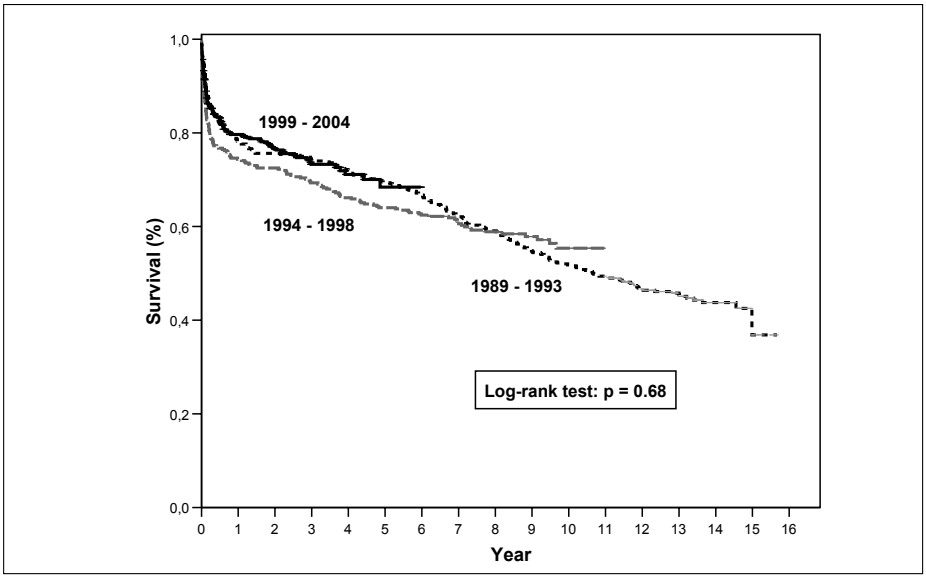


Figure 3. Long-term survival of adult heart transplantation by different transplant period.

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 donor-recipient mismatch for body mass index.

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 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). Studies confirm that centers that perform 50 cardiac transplants per year have better outcome 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 mismatch for body mass index 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 posttransplant 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 posttransplantation (17). The development of malignancy has been well recognized in immunosuppressed transplant recipients (18), with an incidence of 33% after 5 years posttransplantation (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 posttransplantation, 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). 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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Chapter 3

Long-term results of heart transplantation for end-stage valvular heart disease

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Under peer review

ABSTRACT

Background

In general, heart transplantation for patients with heart failure improves survival. However, the outcome of adult heart transplantation for end-stage valvular heart disease is not very well documented. This is a substantial group of patients of which many have had previous cardiac surgery. They, therefore, may be considered a subgroup with a poor prognosis. This study reports the outcome of adult heart transplantation for end-stage valvular heart disease.

Patients and methods

From March 1989 to December 2004, 75 consecutive adult heart transplantations for end-stage valvular heart disease were performed. Pre- and perioperative data were retrieved from computerized database.

Results

Early mortality risk in adult heart transplantation for end-stage valvular heart disease was 13% compared to 8% in that for other indications (p = 0.12). The main causes of early death were rejection (20%) and right ventricular failure (20%). The total follow-up time was 415 patient-years. During the follow-up period, another 23 patients died (55 per 1,000 patient-years of late mortality rate), mostly due to infection (43%) and multi organ failure (22%). Multivariable analysis identified waiting time to heart transplantation (HR = 0.998, 95% CI: 0.996 – 0.999) as an independent predictor for overall mortality in adult heart transplantation for end-stage valvular heart disease. The survival at 1, 5, 10, and 15 years was respectively 70%, 64%, 56%, and 46% in adult heart transplantation for end-stage valvular heart disease compared to 78%, 68%, 53%, and 41% in that for other indications (p = 0.5).

Conclusion

The outcome of adult heart transplantation for end-stage valvular heart disease is similar to that for other indications. Apparently, the longer the waiting time to heart transplantation the better the outcome becomes.

INTRODUCTION

Dilated and ischemic cardiomyopathy are the established indications for heart transplantation, for which the risks and prognosis have been well documented (1). However, the outcome of adult heart transplantation for end-stage valvular heart disease is not very well documented (2-4). Heart transplantation is increasingly recommended in these patients when all other therapeutic means have been considered, and when there is potential benefit for better quality of life and chance of prolonged survival than offered by conventional medical treatment (5) or non-transplant surgical options (6). To arrive at rational decision in these patients, more insight in the short and long-term prognosis after heart transplantation is necessary. This study aimed to evaluate the long-term outcome of adult heart transplantation for end-stage valvular heart disease.

PATIENTS AND METHODS

Study population

We studied 1,406 consecutive patients undergoing heart transplantation from March 1989 to December 2004. Heart retransplantation (n = 28) and pediatric heart transplantation (n = 116) were excluded. From this data set, we identified 75 adult patients with a pretransplant diagnosis of end-stage valvular heart disease for which there was no other possible optimal medical or surgical option. The determinants of prognosis that were considered were recipient characteristics, notably age, gender, body mass index, previous cardiac surgery, transplant status, waiting time to heart transplantation, need of ventricular assist devices; donor characteristics, notably age, gender, body mass index, cause of death, cardiopulmonary resuscitation; donor-recipient mismatch, notably gender, weight or body mass index, blood type; and operative data, notably ischemic and cardiopulmonary bypass time. Patient's waiting time started at the time of the registration on the waiting list. Patients could become temporary non-transplantable, e.g. when suffering from infection. Their waiting-list status then changed to 'non-active'. Only 'active' patients were considered if a donor heart was available. The total waiting time was calculated as the total time listed as 'active' on the waiting list. The outcome variable was the overall mortality which included all deaths until the end of follow-up. This study was approved by our research ethics committee, and the need for individual informed consent was waived.

Surgical technique and immunosuppressive protocol

All orthotopic heart transplantations were performed by a same group of senior heart surgeons, using the biatrial technique (7). Donor procurement was conducted by using a standard technique. Myocardial protection was achieved by infusion of histidine-buffered tryptophane-ketoglutarate cardioplegia solution (Breitschneider-Custodiol; Kohler Chemie, Alsbach-Hahnlein, Germany). Immunosuppressive

protocol was based on initial combination of cyclosporine A, azathioprine and methylprednisolone without using of monoclonal or polyclonal antibodies for induction therapy. Long-term immunosuppressive therapy consisted of cyclosporine A and azathioprine, while steroid maintenance was preferably avoided. Other posttransplant management followed a standardized protocol.

Data collection and follow-up

The pre- and perioperative data of patients were retrieved from computerized database which have been recorded ad hoc since the initiation of our heart transplant program. There were no missing values related to the studied variables. Autopsies were obtained in all death cases. Early mortality was defined as death within 30 days after heart transplantation. Death after this period was defined as late mortality. Overall mortality included early and late mortality. Information regarding follow-up was obtained for all hospital survivors, either through outpatient clinic reports or by telephone interview with the patients/their relatives/referring physician, and was 100% complete.

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

Statistical analysis

All calculations were performed by SPSS software package, version 13.0 (Chicago, IL, USA). Results were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables and count and percentage (%) for categoric variables. Univariable association between predictors and outcome was examined by means of Pearson χ^2 test or Fisher's exact test (categoric variables) and unpaired 2-tailed *t*-test or Mann-Whitney-U test (continuous variables). Those variables which are found to be associated at a *p*-value of 0.5 or below were subsequently entered into a multivariable Cox proportional hazard regression model to identify the independent predictors of overall mortality. The cumulative survival between groups was compared by using the Kaplan-Meier method. The difference between both groups was analyzed by the log-rank test. Results were considered significant if a *p*-value was smaller or equal to 0.05.

RESULTS

Seventy five consecutive adult patients undergoing heart transplantation for end-stage valvular heart disease were included in the analysis. In total, seventy-nine percent (59 of 75) of patients were men and 21% (16 of 75) were women. Recipient mean age was 54 (SD: 12) years (range: 18 - 74). Table 1 presents the baseline characteristics of adult heart transplantation for end-stage valvular disease.

Table 1. Baseline characteristics of adult heart transplantation for end stage valvular heart disease.

Variable	Death (n = 33)	Survivors (n = 42)	*P*-value
Recipient			
Age at transplantation (years)*	54.6 (11.6)	53.6 (12.5)	0.75
Male gender	24 (73)	35 (83)	0.39
Body mass index (kg/m^2)*	22.8 (2.8)	23.3 (2.9)	0.46
Previous cardiac surgery	33 (100)	41 (98)	1.00
High-urgency status	5 (15)	4 (10)	0.49
Waiting time (days)†	66 (15 - 209)	137 (31 - 534)	0.03
Ventricular assist devices	7 (21)	6 (14)	0.54
Donor			
Age (years)*	35.1 (14.3)	34.3 (14.6)	0.84
Male gender	16 (49)	23 (55)	0.59
Body mass index (kg/m^2)*	23.4 (3.3)	23.1 (2.7)	0.61
Cause of death			
Trauma	14 (42)	14 (33)	0.54
Cerebrovascular accident	13 (40)	22 (53)	
Other	6 (18)	6 (14)	
Cardiopulmonary resuscitation	4 (12)	8 (19)	0.53
Donor-recipient mismatch			
Gender	15 (46)	22 (52)	0.55
Body weight	9 (27)	8 (19)	0.42
Body mass index	8 (24)	4 (10)	0.12
Non-identical blood type	4 (12)	3 (7)	0.69
Operative data			
Ischemic time (minutes)*	210.1 (32.9)	199 (45.9)	0.27
Cardiopulmonary bypass time (minutes)*	136.7 (53)	127.8 (51.9)	0.47

Values are count (%) unless otherwise indicated. * Mean (± SD). † Median (IQR).

All patients were in NYHA status class IV. Seventeen percent (13 of 75) of patients were bridged to heart transplantation with different kinds of ventricular assist devices (Thoratec BVAD [Thoratec Laboratories Corp, Pleasanton, CA], n = 4; Thoratec LVAD, n = 3; TCI HeartMate [Thoratec Laboratories Corp, Pleasanton, CA], n = 2; Cardiowest TAH [SynCardia Systems, Inc, Tucson, AZ], n = 2; Novacor

[Baxter Healthcare, Oakland, CA], n = 1; Abiomed LVAD [Abiomed Cardiovascular Inc, Danvers, MA], n = 1). Ninety-nine percent (74 of 75) of patients had undergone prior valve replacement without any prosthetic dysfunction. Seventy-three percent (55 of 75) of them have had one previous cardiac surgery, while 25% (19 of 75) have had two. Univariable analysis revealed waiting time as a significant predictor related to overall mortality after adult heart transplantation for end-stage valvular heart disease. Other predictors showing a trend toward increased overall mortality were recipient gender and body mass index, transplant status, donor-recipient mismatch for body weight and body mass index, increased ischemic and cardiopulmonary bypass time.

Overall, 33 patients died, mostly due to infection (33%) and multiorgan failure (18%, Table 2). Ten patients died within 30 days after heart transplantation for end-stage valvular heart disease, for an early mortality risk of 13% (10 of 75) compared to 8% (96 of 1,187) after that for other indications (p = 0.12). The causes of early death were mostly due to rejection (20%) and right ventricular failure (20%). Median follow-up time of the hospital survivors was 6.3 years (IQR: 1.4 - 10.4 years) (total: 415 patient-years). During the follow-up period, another 23 patients died, for a late mortality rate of 55 per 1,000 patient-years. The main causes of late death were infection (43%) and multiorgan failure (22%).

Table 2. Causes of death after adult heart transplantation for end-stage valvular heart disease.

Causes of death	Early (n = 10)	Late (n = 23)	Overall (n = 33)
Rejection	2 (20)	1 (4)	3 (9)
Right ventricular failure	2 (20)	1 (4)	3 (9)
Infection	1 (10)	10 (43)	11 (33)
Multiorgan failure	1 (10)	5 (22)	6 (18)
Cardiac allograft vasculopathy	-	3 (13)	3 (9)
Abdominal complication	2 (20)	-	2 (6)
Cerebrovascular accident	-	1 (4)	1 (3)
Technical issues	1 (10)	-	1 (3)
Other	1 (10)	2 (9)	3 (9)

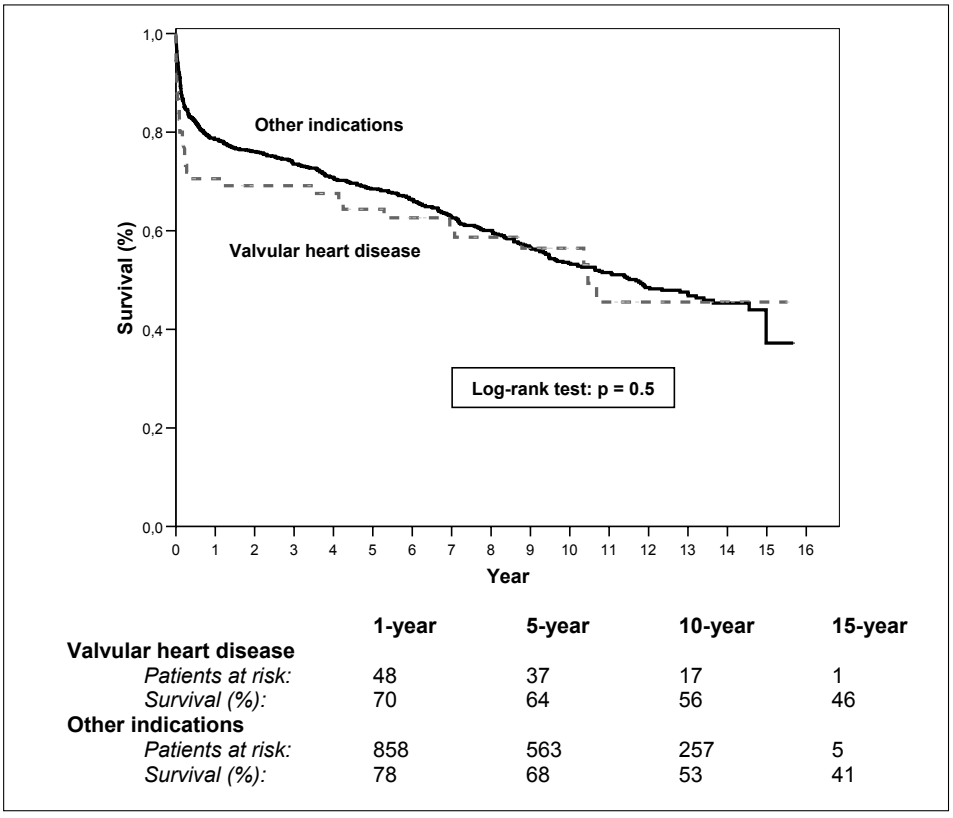
Values are count (%). Because of rounding, not all percentages total 100.

Multivariable analysis identified waiting time to heart transplantation (HR = 0.998, 95% CI: 0.996 - 0.999) as an independent predictor of overall mortality after heart transplantation for end-stage valvular heart disease (Table 3). The actuarial survival at 1, 5, 10, and 15 years was respectively 70%, 64%, 56%, and 46% in adult heart transplantation for end-stage valvular disease compared to 78%, 68%, 53%, and 41% in that for other indications (p = 0.5, Figure 1).

Table 3. Independent predictor of overall mortality after adult heart transplantation for end-stage valvular heart disease.

Variable	Coefficient	*P*-value	Hazard ratio	95% confidence interval
Waiting time (days)	-0,002	0.04	0.998	0.996 - 0.999

Variable(s) entered into multivariable analysis: waiting time, recipient gender and body mass index, transplant status, donor-recipient mismatch for body weight and body mass index, ischemic and cardiopulmonary bypass time.



	1-year	5-year	10-year	15-year
Valvular heart disease				
Patients at risk:	48	37	17	1
Survival (%):	70	64	56	46
Other indications				
Patients at risk:	858	563	257	5
Survival (%):	78	68	53	41

Figure 1. Survival comparison between adult heart transplantation for end-stage valvular heart disease and that for other indications.

DISCUSSION

Patients suffering from treatment resistant end-stage valvular heart disease may derive benefit from heart transplantation. But, because they represent a small proportion compared to dilated or ischemic cardiomyopathy, information on its outcome after heart transplantation is very scarce (2-4). To our knowledge, this study

is the first which specifically describes the long-term outcome of adult heart transplantation for end-stage valvular heart disease in a relatively large number of study populations. Our results show that prognosis after adult heart transplantation for end-stage valvular heart disease is similar to that for other indications. Early mortality appeared to be somewhat increased but not significant difference, whereas a longer waiting time to heart transplantation significantly improved survival.

In the registry of the International Society for Heart and Lung Transplantation (1), more than 70,000 heart transplantations have been reported worldwide between 1982 and 2004; Heart transplantation for end-stage valvular heart disease represents up to 4% of all adult heart transplantations. The La Pitie group in France reported that among all transplant patients from 1968 to June 2005, 7% (105 of 1,452) of orthotopic heart transplantations were performed for patients with valvular pathology (8). In our study, end-stage valvular heart disease represents 6% (75 of 1,262) of all adult heart transplantations. The early mortality risk was 13% (95% CI: 5 - 21%), which is comparable to previous study by Livi et al. (3). Among 19 patients, they reported an early mortality risk of 21% (95% CI: 3 - 39%). Our encouraging outcome is likely explained to our consistency in surgical approach, where all heart transplantations were performed by a same group of experienced heart surgeons. The mid-term (5-year) survival in adult heart transplantion for end-stage valvular heart disease has been reported as high as 74% compared to 77% in that for other indications (3). In our study, the actuarial survival at 1, 5, 10, and 15 years was respectively 71%, 64%, 56%, and 46% in adult heart transplantation for end-stage valvular disease compared to 79%, 69%, 53%, and 37% in that for other indications (p = 0.5).

Heart transplantation for end-stage valvular heart disease is recommended if the life expectancy of patients is less than one year. Indications vary according to the valve pathology. For chronic aortic valve insufficiency with worsened heart failure, heart transplantation should be only considered when the patient develops recurrent heart failure after aortic valve replacement with persistent heart failure (8;9). In patients with aortic valve stenosis, there is rarely a choice to be made between aortic valve replacement or heart transplantation due to patient's advanced age and irreversible left ventricular dysfunction (5). The first logical choice for patient with heart failure due to mitral valve pathology is usually to cure the valvular lesion, especially when the ejection fraction is still above 20%.

Increased pulmonary vascular resistance (PVR) carries a high risk of both early and late mortality and remains a major problem for recipient selection (10). In patients having elevated PVR, we started early in the preoperative management with phosphodiesterase inhibitors, early LVAD implantation, and liberal use of perioperative inhaled nitric oxide. Use of beta-agonists is minimized. Cardiac output was maintained by external pacing (heart rate: 120 - 140) for the first 5 to 7 days. Patients were ventilated on optimal PEEP, and extubated as soon as possible. If

hemodynamic deterioration and signs of right heart failure occur, epoprostenol or nitric oxide are administered (11). Inability of the transplanted heart to adapt to pre-existing significant pulmonary hypertension usually results in right ventricular failure (12), as noted in 3 postoperative deaths in our cohort.

A significant proportion of patients had previous cardiac surgery and might be subject to an increased risk due to technical and other factors inherent in a redo operation. Patients who have undergone multiple operations are considered at higher risk and impaired overall survival (13;14). However, similar to Ott et al. (15), we did not find previous cardiac surgery as an independent predictor for worse prognosis. We routinely perform preliminary exposure of the femoral vessels because severe hemodynamic instability or sudden ventricular fibrillation may develop in many recipients during sternotomy or dissection of the dense mediastinal and pericardial adhesions. With this additional precaution, femorofemoral cardiopulmonary bypass may be instituted very rapidly if it is necessary. Even so, our common policy is to perform aortic and biatrial cannulation whenever it is possible.

Waiting time to heart transplantation remains a crucial issue. In 1991, Stevenson et al. (16) reported that there was no survival benefit from heart transplantation for patients who had been on the transplant waiting list for over 6 months. In contrast, Aaronson et al. (17) demonstrated that the mortality of patients who had been on the waiting list more than 6 months remained high. Our experience shows that longer waiting time to heart transplantation is associated with slightly increased overall survival (HR = 0.998, 95% CI: 0.996 - 0.999). Advances in medical and surgical treatment of end-stage heart failure, including different mechanical circulatory supports can stabilize and keep the end-stage heart failure patients on the waiting list for a much longer time than before. In fact, 17% (13 of 75) of our patients were on mechanical circulatory support by means of ventricular assist devices at the time of transplantation, a likely consequence for longer waiting time to heart transplantation due to widespread use of ventricular assist devices in our center (18-20). The use of ventricular assist devices not only aims to decrease pulmonary vascular resistance which is usually found in end-stage valvular heart disease, but also to bridge the patients to heart transplantation with a more suitable donor heart in an elective manner. Both of these conditions may explain the encouraging posttransplant survival in our cohort. Our finding supports the fact that watchful waiting is not deleterious in the final outcome after heart transplantation (21). A careful balance of risks and survival benefit is of major importance.

In conclusion, our study demonstrates that the outcome of adult heart transplantation for end-stage valvular heart disease is similar to that for other indications. Apparently, the longer waiting time to heart transplantation the better the outcome becomes.

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Chapter 4

Impact of recipient age on heart transplantation outcome

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ABSTRACT

Background

The shortage of donor hearts stimulates the debate whether heart transplantation is justified for older recipients. We studied the effect of recipient age on heart transplantation outcome in a large cohort of recipients.

Patients and methods

Between March 1989 and December 2004, 1,262 adult recipients underwent heart transplantation. Recipients were divided into two groups: 540 recipients aged younger than 55 years and 722 aged 55 years and older.

Results

The overall 30-day mortality risk was 9%, at 6% for recipients younger than 55 years, and 10% for recipients 55 years and older ($p = 0.005$). Rejection, multiorgan failure, infection, and right heart failure dominated the causes of early death in both groups. The 1-, 5-, 10-, and 15-year survival was respectively 84%, 75%, 60%, and 50%, respectively, for recipients younger than 55 years, and 73%, 63%, 48%, and 35% for recipients aged 55 years and older ($p < 0.001$). The mortality rate for those who survived the first month was 58 per 1,000 patient-years. The main causes for late mortality were cardiac allograft vasculopathy, rejection, and infection for recipients younger than 55 years; and infection, malignancies, and rejection for recipients aged 55 years and older. Both the crude and adjusted hazard ratio increased with increasing recipient age.

Conclusion

The outcome of heart transplantation in older recipients is less favorable than in younger recipients. The decision to offer heart transplantation to recipients older than 55 years should be considered cautiously.

INTRODUCTION

Initially, heart transplantation was restricted to recipients aged younger than 50 years (1). As outcomes of heart transplantation improved, the number of patients waiting for heart transplantation has markedly increased. Subsequently, the upper limit of recipient age has been liberalized, from 55 years to currently older than 70 years (2-5). Owing to a shortage of donor hearts, the debate remains whether heart transplantation is justified for older recipients (6). To date, solid data on the outcome of heart transplants, in particular on the effect of increasing recipient age on survival, are limited and controversial. Some studies have reported equivalent survival and lower rejection rates in older recipients (4;5;7-11), but others have reported older recipients have reduced survival after heart transplantation (2;3;12). We set out to study the effect of the recipient age on heart transplantation outcome in a large cohort of patients who underwent transplantation in our center.

PATIENT AND METHODS

Study population

Our study comprised 1,262 adult recipients undergoing heart transplantation at the Department of Thoracic & Cardiovascular Surgery, Heart & Diabetes Center North Rhine Westphalia in Bad Oeynhausen, Germany, between March 1989 and December 2004. Heart transplantations in recipients younger than 18 years and heart retransplantations were excluded from the analysis. Our research ethics committee approved the study, and the need for individual informed consent was waived. The cohort consisted of 1,065 men (84%) and 197 women (16%), and their average age was 54 years (standard deviation, 11; range, 18 to 77 years). Dilated cardiomyopathy (631 of 1,262) and ischemic cardiomyopathy (543 of 1,262) were the most frequent indications for adult heart transplantation.

Recipients were divided into two groups: 540 recipients aged younger than 55 years and 722 aged 55 years and older. All heart transplant recipients met the same eligibility criteria (13). Recipient evaluation involved assessment of clinical conditions that commonly related to advanced age, such as malignancies and diabetes mellitus, with associated carotid and peripheral vascular disease, and end-organ dysfunction. The absolute and relative contraindications for donor hearts in our center have been previously published (14). Donor and recipient were matched on ABO blood type compatibility and body weight.

Surgical techniques

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 tryptophane-ketoglutarate cardioplegia solution (Bretschneider-Custodiol, Kohler Chemie, Alsbach-Hahnlein, Germany) and

topical hypothermia. All orthotopic heart transplantations were performed according to the biatrial technique (15).

Immunosuppression therapy

All recipients received comparable immunosuppressive regimens, based on initial triple-drug therapy with cyclosporine A, azathioprine, and steroid. Long-term immunosuppressive therapy consisted of cyclosporine A and azathioprine. Steroid maintenance was preferably avoided. Rejection was diagnosed by routine endomyocardial biopsy. In case of significant rejection, defined as International Society of Heart and Lung Transplantation (ISHLT) grade 3A or higher rejection (16), pulsed steroids with methylprednisolone were given for 3 days. If more than three episodes of ongoing rejection occurred, prednisone was given orally and then tapered slowly.

Outcome measure

Primary posttransplant outcome included early death and long-term survival. Death within 30 days after transplantation was defined as early mortality. Death occurring after 30 days of heart transplantation was considered as late mortality.

Follow-up and data collection

All recipients have been monitored closely by their family physicians as well as by periodical medical evaluations in our outpatient's clinic. Generally, recipients were referred to our center for further diagnostic and medical management if major complications developed. All data on recipients and donors were collected prospectively and maintained on a computerized database. Follow-up was 100% complete.

Data analysis

Statistical evaluations were performed with SPSS 13.0 software (SPSS Inc, Chicago, IL). Categoric variables are reported as number and percentage. Continuous variables are expressed as mean and standard deviation or median and interquartile range (IQR). For comparative evaluations, the Pearson χ^2 test (categoric variables) and the unpaired two-tailed *t*-test (continuous variables) were used. To avoid any possible confounding effect by baseline characteristics apart from recipient's age on outcomes, a Cox proportional hazard model adjusted for significant differences in baseline characteristics between groups was used. Survival rates were calculated with the Kaplan-Meier product-limit estimator. The log-rank test was used to compare groups. A value of $p \leq 0.05$ (two-tailed test) was considered statistically significant.

RESULTS

Baseline characteristics

The recipient, donor, and operative baseline characteristics were compared across both groups and some differences were found (Table 1).

Table 1. Comparison of baseline characteristics by recipient age.

Variable[a]	Total	Recipient age		*P*-value
		< 55 years	≥ 55 years	
Patients, No.	1,262	540	722	
Recipient				
Age, mean (SD) years	53.9 (11.1)	43.8 (9.3)	61.5 (4.3)	< 0.001
Male gender	1,065 (84)	444 (82)	621 (86)	0.07
BMI, mean (SD) kg/m^2	23.5 (3)	23.1 (3.1)	23.7 (2.9)	< 0.001
Pretransplant diagnosis				
Dilated cardiomyopathy	631 (50)	342 (63)	289 (40)	< 0.001
Ischemic cardiomyopathy	543 (43)	153 (28)	390 (54)	
Other	88 (7)	48 (8)	40 (6)	
High-urgency status	120 (10)	76 (14)	44 (6)	< 0.001
Prior cardiac surgery	411 (33)	141 (24)	270 (40)	< 0.001
Intraaortic balloon pump	37 (3)	18 (3)	19 (3)	0.47
Ventricular assist device	223 (18)	121 (22)	102 (14)	< 0.001
Donor				
Age, mean (SD) years	36.5 (13.6)	32.8 (12.3)	39.3 (13.9)	< 0.001
Male gender	635 (50)	303 (56)	332 (46)	< 0.001
BMI, mean (SD) kg/m^2	23.9 (3.4)	23.8 (3.4)	24 (3.5)	0.29
Cause of death				
Trauma	478 (38)	239 (44)	239 (33)	< 0.001
Cerebrovascular accident	561 (45)	209 (39)	352 (49)	
Other	223 (18)	92 (17)	131 (18)	
Donor-recipient mismatch				
Gender	536 (43)	197 (37)	339 (47)	< 0.001
BMI	257 (20)	111 (21)	146 (20)	0.88
Non-identical blood type	74 (6)	39 (7)	35 (5)	0.08
Operative data				
Ischemic time, mean (SD) min	194.5 (40.4)	193.9 (41.1)	194.9 (39.9)	0.68
CPB time, mean (SD) min	113.9 (45.6)	115.1 (48.6)	113.1 (43.3)	0.44

BMI: body mass index, CPB: cardiopulmonary bypass, SD: standard deviation.
[a] Data are shown as number (%), unless otherwise indicated. Because of rounding, not all percentages total 100.

Recipients aged 55 years and older were more likely to have ischemic cardiomyopathy as an indication for heart transplantation ($p < 0.001$). Fewer of these recipients were in high-urgency status at transplantation ($p < 0.001$), and fewer

required a ventricular assist device ($p < 0.001$). Still, a higher proportion of recipients in this group had prior cardiac surgery ($p < 0.001$). The average age of donors was significantly higher in recipients aged 55 years and older ($p < 0.001$). Younger recipients were more likely to receive a male donor heart ($p = 0.001$). A cerebrovascular accident as the cause of death in the donor was more common in recipients aged 55 years and older ($p < 0.001$), and donor-recipient mismatch for gender was more frequent ($p < 0.001$). All other factors were distributed similarly across both age groups (no significant differences).

Early outcomes

There were 107 deaths within 30 days after transplantation, for an overall 30-day mortality risk of 9%: 6% for recipients younger than 55 years, and 10% for recipients 55 years and older ($p = 0.005$). The main causes of early death for recipients younger than 55 years were acute rejection in 7 (22%), multiorgan failure in 6 (19%), infection in 5 (16%), and right heart failure in 4 (13%). A similar distribution of causes of early death was seen in recipients aged 55 years and older (Table 2).

Table 2. Distribution of causes of early and late mortality by recipient age[a].

	Total No. (%)[a]		Recipient age < 55 years No. (%)[a]		Recipient age ≥ 55 years No. (%)[a]	
Causes of death	**Early**	**Late**	**Early**	**Late**	**Early**	**Late**
Patients, No.	107	414	32	152	75	262
Primary graft failure	6 (6)	2 (0)	1 (3)	1 (1)	5 (7)	-
Right heart failure	13 (12)	6 (1)	4 (13)	5 (3)	9 (12)	1 (0)
Acute rejection	29 (27)	81 (20)	7 (22)	37 (24)	44 (29)	44 (17)
Multiorgan failure	17 (16)	26 (6)	6 (19)	5 (3)	11 (15)	21 (8)
CAV	-	71 (17)	-	38 (25)	-	33 (13)
Infection	12 (11)	94 (23)	5 (16)	26 (17)	7 (9)	68 (26)
Malignancy	-	68 (16)	-	18 (12)	-	50 (19)
Surgical complication	9 (8)	-	2 (6)	-	7 (9)	-
Other	21 (20)	66 (16)	7 (22)	22 (14)	14 (19)	44 (17)

CAV: cardiac allograft vasculopathy
[a] Because of rounding, not all percentages total 100.

Long-term outcomes

The total follow-up time was 7,173 person-years (median, 5.7; IQR, 1.8 to 10.1 years). During the follow-up period, 521 recipients died, resulting in a mortality rate of 73 per 1,000 patient-years. The mortality rate for the 414 patients who survived the first month was 58 per 1,000 patient-years. In recipients younger than 55 years, the

main causes of late death were cardiac allograft vasculopathy in 38 (25%), rejection in 37 (24%), and infection in 26 (17%); and in recipients aged 55 years and older were infection in 68 (26%), malignancies in 50 (19%), and rejection in 44 (17%;Table 2).

Table 3 reports the hazard ratios for late death according to increasing age. Because of the relatively large number in this category, the recipient age category of 46 to 55 years was used as the reference for outcome comparison among the five categories. The overall mortality risk progressively increased from lowest to highest age category. This trend remained after adjustment for differences in baseline characteristics.

Table 3. Hazard ratios by age categories for adult heart transplant recipients.

	Patients,	Hazard ratio (95% CI)	
Recipient age	**No.**	**Crude**	**Adjusted[a]**
Category, years			
≤ 35	102	0.57 (0.37 - 0.88)	0.67 (4.3 - 1.04)
36 - 45	143	0.77 (0.55 - 1.09)	0.84 (0.59 - 1.19)
46 - 55	346	1 [Reference]	1 [Reference]
56 - 65	535	1.25 (1.01 - 1.53)	1.21 (1.18 - 1.49)
≥ 66	136	1.58 (1.18 - 2.12)	1.40 (1.04 - 1.90)

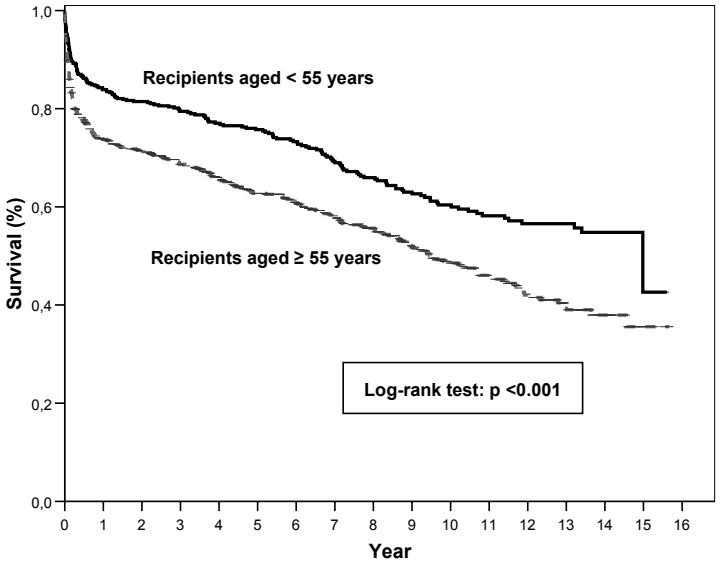
CI: confidence interval.
* Adjusted for recipient body mass index, pretransplant diagnosis, transplant status, prior cardiac surgery, need of ventricular assist device, donor age and gender, donor cause of death, and donor-recipient mismatch for gender.

The 1-, 5-, 10-, and 15-year survival was respectively 84%, 75%, 60%, and 50% for recipients younger than 55 years; and 73%, 63%, 48%, and 35% for recipients aged 55 years and older ($p < 0.001$, Figure 1).

DISCUSSION

This large cohort study of 1,262 heart transplant recipients found that advanced recipient age (≥ 55 years) was associated with increased early death and reduced long-term survival. Our data show a clear trend for recipient age on the outcome of heart transplantation; that is, older recipients have less favorable outcome than younger recipients. The hazard ratios increased with increasing recipient age; that is, relative risk increases 25% (adjusted: 21%) for recipient age category of 56 to 65 years and 58% (adjusted: 40%) for recipient age older than 66 years. Decline of physical condition and physiologic organ function by decay of life may contribute to the adverse outcome. Initially, recipient age between 50 and 55

years was considered as an important criterion to assure a better survival (17). However, despite significant decreased posttransplant survival for older recipients (2;3;12), the upper age limit for heart transplant candidates has significantly increased in recent decades, leading to continued debate about the role of the recipient age in making decision about heart transplantation (18). Expanding the recipient upper age limit beyond 55 years may cause a further growth of the waiting list in heart transplant centers, and the more frequent use of marginal donor hearts for high-risk recipients may contribute to an increase in posttransplant death (6).



	1-year	5-year	10-year	15-year
Recipients aged < 55 years:				
Patient at risk:	409	281	138	3
Survival (%):	84	75	60	50
Recipients aged ≥ 55 years:				
Patient at risk:	497	319	135	3
Survival (%):	73	63	48	35

Figure 1. Survival comparison by recipients aged younger than 55 years (black line) vs 55 years and older (gray line).

However, the advances in heart transplantation during the recent decades have considerably changed the heart transplant practice in most centers; thus, heart transplant outcome for older recipients have been reported to improve. Richenbacher and colleagues (19), for example, showed similar survival risk for recipients older and younger than 54 years, with respectively the 1-year survival of 78% and 81%; and the 5-year survival of 52% and 66%. This finding was confirmed by several comparable single-center studies (17;20;21). The conflicting results between single-center studies may be related to problems in design and conduct of studies, notably limited follow-up time or small number of patients (22). However, recent ISHLT registry data revealed higher mortality in older transplant recipients (23).

Despite significant older donor hearts and a more common pretransplant diagnosis of ischemic cardiomyopathy, we find that late mortality due to cardiac allograft vasculopathy is less frequent in older transplant recipient, a similar finding to other studies (2). We believe that avoiding the use of steroid in our long-term immunosuppression protocol and prophylactic and aggressive treatment of hypertension and hypercholesterolemia may attribute to the lower incidence of cardiac allograft vasculopathy. The lower risk of late mortality due to rejection in older heart transplant recipients in our study is similar to previous studies (19;24). An age-related decrease of immune responsiveness and T-cell function may be responsible for this effect (24).

At the same time, we found a higher risk of infectious complications and malignancies after heart transplantation. This may also be explained by a decreased immune reactivity in the older recipients and their increased susceptibility to the effects of the immunosuppressive regimen (3;4). Reduction of immunosuppression levels in older recipients may perhaps decrease their risk of infection and malignancies without changing the rate of rejection (2).

In conclusion, our data support the view that the outcome of heart transplantation in older recipients is less favorable than in younger recipients. The decision to offer heart transplantation to recipients older than 55 years should be considered cautiously in view of the scarcity of donor hearts

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Chapter 5

Donor heart refusal in heart transplantation should not be based on donor sodium level

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Under peer review

ABSTRACT

Background

The impact of donor sodium level on outcome after heart transplantation remains disputed. We aimed to evaluate whether donor sodium level, in particular > 155 mmol/L, affects the outcome of adult heart transplantation.

Patients and methods

Data from 1,262 primary adult heart transplantations were analysed, and classified into 2 groups: donor sodium level ≤ 155 mmol/L (normo-natremic, n = 1,016) and > 155 mmol/L (hypernatremic, n = 246).

Results

Median donor sodium level was 144 mmol/L for normo-natremic group and 161 mmol/L for hypernatremic group. Except recipient gender and body surface area, donor body surface area, and ischemic time, there were no significant differences between both groups at the time of heart transplantation. The overall 30-day mortality risk was 8.5% (normo-natremic: 8.4%, hypernatremic: 8.9%; $p = 0.77$). The adjusted odds ratio for 30-day mortality by donor sodium level was not significant. There was no difference in cause of death due to primary graft failure between both groups ($p = 0.57$). The adjusted hazard ratio for donor sodium level > 155 mmol/L was 1.05 (95% CI: 0.85 - 1.31). The survival at 1, 5, 10, and 15 years was respectively 79%, 69%, 53%, and 36% for normo-natremic group; and 75%, 65%, 56%, and 46% for hypernatremic group ($p = 0.76$).

Conclusion

Donor sodium level has no major impact on the mortality risk after adult heart transplantation. Organ shortage could be reduced when refusal of donor hearts based on high donor sodium level is abandoned. We suggest adjusting for donor heart selection accordingly.

INTRODUCTION

There is a serious problem in finding sufficient number of suitable donors for heart transplantation. The limited number of suitable donors has a high impact on the life of those currently on the waiting list. Increasing the number of suitable donors would lead to a decrease in waiting time, and thereby would reduce the individual and societal burden of waiting list. Donor hypernatremia, which is usually observed in brain-dead patient (1), is an important risk factor for graft failure after liver (2;3) and kidney transplantation (4). But its impact on outcome after adult heart transplantation remains disputed (5;7-9). While intracellular sodium concentration contributes to reperfusion injury, donor hypernatremia is considered to cause myocardial stunning leading to higher incidence of primary graft failure after heart transplantation (6). Due to the shortage of suitable donor hearts there is a pressure to expand the donor pool by relaxing the criteria for donor sodium level. During quality control of our data, we noticed that this practice eventually applied to about 19% of all our heart transplant procedures. We wondered whether this had an impact on the survival. Therefore, we aimed to evaluate whether donor sodium level, in particular > 155 mmol/L, affects the outcome after adult heart transplantation.

PATIENTS AND METHODS

Study population

All primary heart transplantations (n = 1,262 patients) performed in the Heart & Diabetes Center North Rhine Westphalia in Bad Oeynhausen, Germany between March 1989 and December 2004 were included in this study. Pre- and perioperative data were retrieved from patient records which were documented in a computerized database. The study was approved by our research ethics committee, and the need for individual informed consent was waived. The recipient selection criteria have been previously published (10); briefly they include irreversible end-stage heart failure without any other feasible medical or surgical treatment option, limited untreated life expectancy (estimated < 6 months), age < 65 years old and no 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 sodium level was measured before organ procurement. Hypernatremia was defined as donor sodium level > 155 mmol/L (11). Patients were categorized into two groups: Donor sodium level ≤ 155 mmol/L (normo-natremic, n = 1,016) and > 155 mmol/L (hypernatremic, n = 246). Primary graft failure was defined as death due to severe impairment of systolic graft function affecting the right, left or both ventricles accompanied by hypotension, low cardiac output and high filling pressures (12).

Donor and recipient were matched for ABO blood-type compatibility and body weight (ratio: 1 ± 0.2).

Surgical techniques

Donor heart procurement and preservation was achieved by combination of cold cardioplegic arrest, mainly using Histidine-buffered tryptophane-ketoglutarate cardioplegia solution (Bretschneider-Custodiol, Kohler Chemie, Alsbach-Hahnlein, Germany) and topical hypothermia. All heart transplantations were performed orthotopically (13).

Immunosuppresion therapy

The initial immunosuppressive regimen included cyclosporine A, azathioprine, and steroid. After early postoperative phase, double-drug therapy with cyclosporine A and azathioprine was preferred. In case of clinical- or biopsy-proven rejection, steroid-pulse therapy was initiated. Oral steroid maintenance was given only in case of recurrent rejection.

Follow-up and data collection

All survivors were regularly followed-up through our out-patient's service unit or by telephone interview with the patients, their relatives or family/referring physician. All data of recipients and donors were collected prospectively and maintained on a computerized database. Follow-up was 100% complete. The diagnosis of rejection was based on clinical findings, electrocardiographic and echocardiographic data. In the first 6 months after heart transplantation, it was performed monthly and every 3 months for the next half year. Thereafter, it was examined 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. Endomyocardial biopsy was performed routinely during the 1-, 5-, and 10-year after heart transplantation. When indicated, endomyocardial biopsies were performed regardless of time.

Statistical analysis

Categoric variables were reported as number and percentage (%). Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). For comparative evaluations, Pearson χ^2 test or Fisher's exact test (categoric variables) and unpaired 2-tailed *t*-test or Mann-Whitney-U test (continuous variables) were used. To avoid possible confounding effects on outcome, a logistic regression and Cox proportional hazard model adjusted for differences in baseline characteristics between both groups was performed. The cumulative

survival was calculated with the Kaplan–Meier product-limit estimator. The log–rank test was used to compare both groups. A *p*-value of ≤ 0.05 (two-tailed test) was considered statistically significant. All calculations were performed with the SPSS statistical package, version 13.0 (Chicago, IL, USA).

RESULTS

Baseline characteristic

Baseline characteristics for both groups are presented in Table 1. Mean (SD) recipient age was 54 (11) years. Mean (SD) donor age was 37 (14) years. The overall mean (SD) donor sodium level was 148 (10) mmol/L (range: 11 - 208 mmol/L). Eighty one percent (1,016 of 1,262) of the recipients were normo-natremic and 19% (246 of 1,262) were hypernatremic.

The median (IQR) donor sodium level was 144 (140 - 149) mmol/L for normo-natremic group and 161 (158 - 166) mmol/L for hypernatremic group (Figure 1). Overall mean (SD) ischemia time was 195 (40) minutes. Except recipient gender and body surface area, donor body surface area, and ischemic time, there were no significant differences between both groups at the time of heart transplantation.

Table 1. Baseline characteristics by donor sodium level in adult heart transplantation.

Variable	Total (n = 1,262)	Donor sodium level ≤ 155 mmol/l (n = 1,016)	Donor sodium level > 155 mmol/l (n = 246)	*P*-value
Recipient age (years)*	53.9 (11.1)	53.9 (11.1)	54 (11.4)	0.94
Male recipient	1,065 (84)	867 (85)	198 (81)	0.05
Recipient body surface area (m^2)*	1.9 (0.2)	1.9 (0.2)	1.8 (0.2)	0.03
Primary cardiac disease				
Dilated cardiomyopathy	631 (50)	518 (51)	113 (46)	0.28
Ischemic cardiomyopathy	543 (43)	431 (42)	112 (45)	
Other	88 (7)	67 (7)	21 (9)	
Previous sternotomy	411 (33)	328 (32)	83 (34)	0.66
Donor age (years)*	36.5 (13.6)	36.5 (13.5)	36.7 (13.9)	0.81
Male donor	635 (50)	518 (51)	117 (48)	0.34
Donor body surface area (m^2)*	1.8 (0.2)	1.9 (0.2)	1.8 (0.2)	0.03
Donor cause of death				
Trauma	478 (38)	390 (38)	88 (36)	0.54
Spontaneous hemorrhage	561 (44)	452 (45)	109 (44)	
Other	223 (18)	174 (17)	49 (20)	
Ischemic time (minutes)*	195 (40)	196 (40)	190 (42)	0.05
Cardiopulmonary bypass (minutes)†	103 (83 - 131)	104 (84 - 131)	103 (81 - 133)	0.59

Values are count (%) unless otherwise indicated. * Mean (± SD). † Median (IQR).

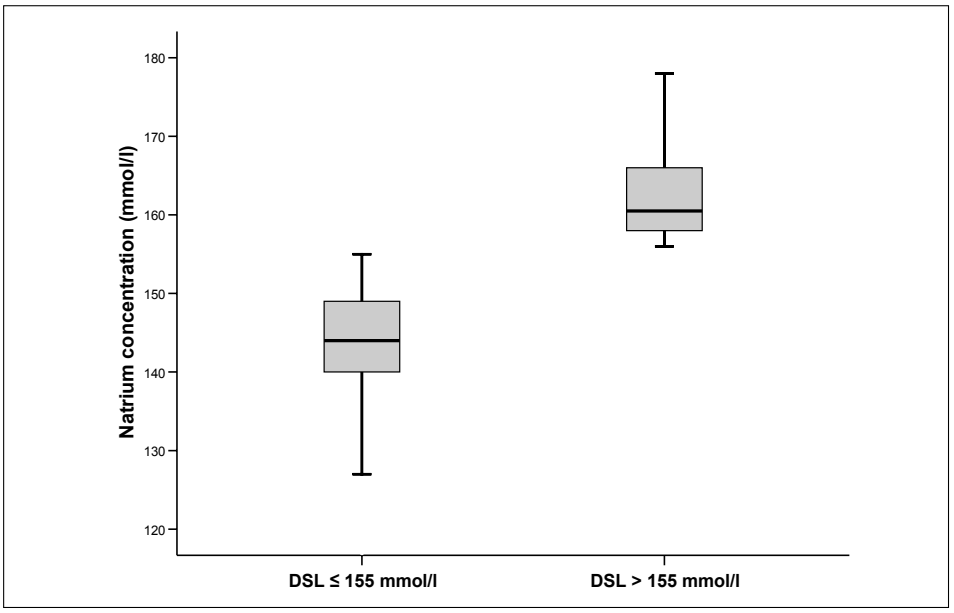

Figure 1. Boxplot of distribution of donor sodium level (DSL) in adult heart transplantation. The black line indicates median of donor natrium concentration.

Overall, there were 107 deaths within 30 days after heart transplantation, for a 30-day mortality risk of 8.5% (normo-natremic: 8.4%, hypernatremic: 8.9%, p = 0.77). A total of 19 out of 107 patients (18%) died due to primary graft failure and there was no significant differences in cause of death between both groups with respect to primary graft failure (Table2).

Table 2. Causes of 30-day mortality after heart transplantation by donor sodium level in adult heart transplantation.

		Donor sodium level		*P*-
Causes of death	**Total (n = 107)**	**≤ 155 mmol/l (n = 85)**	**> 155 mmol/l (n = 22)**	**value**
Primary graft failure	19 (18)	16 (19)	3 (14)	0.57
Rejection	29 (27)	26 (31)	3 (14)	0.18
Multiorgan failure	17 (16)	13 (15)	4 (18)	0.75
Infection	12 (11)	7 (8)	5 (23)	0.07
Other	30 (27)	23 (27)	7 (32)	0.66

Values are count (%) unless otherwise indicated. Because of rounding, not all percentages total 100.

Table 3 shows the 30-day crude mortality risk and adjusted odds ratio for the 30-day mortality by donor sodium level. The total follow-up time was 7,173 patient-years [median (IQR): 4.7 (0.8 - 9.6) years]. The crude hazard ratio for a donor sodium level > 155 mmol/L was 1.03 (95% CI: 0.83 - 1.29). After adjusting for recipient gender and body surface area, donor body surface area and ischemic time, the hazard ratio changed very little (1.05, 95% CI: 0.85 - 1.31) (Table 4). The cumulative survival at 1, 5, 10, and 15 years was respectively 78%, 69%, 53%, and 41% for normo-natremic group; and 75%, 65%, 56%, and 46% for hypernatremic group (p = 0.76, Figure 2). When we analyzed our data with donor sodium level on a continuous scale of mmol/l, we found that a statistically non-significant risk increase of 0.2% per mmol/l; and a statistically non-significant risk increase of 0.3% per mmol/l after adjustment for recipient gender and body surface area, donor body surface area, and ischemic time. Further analysis using a cut-value for donor sodium level through or above 170 mmol/L failed to show a significant result.

Table 3. Thirty-day mortality risk and adjusted odds ratio for 30-day mortality by donor sodium level in adult heart transplantation.

Donor sodium level (mmol/l)	No. of cases	No. of death	30-day crude mortality risk (%)	Adjusted odds ratio* for 30-day mortality (95% CI)
≤ 135	105	6	6	1 [Reference]
136 - 145	464	38	8	1.6 (0.6 - 3.8)
146 - 155	447	41	9	1.7 (0.7 - 4.2)
156 - 165	180	14	8	1.4 (0.5 - 3.8)
≥ 166	66	8	12	2.4 (0.8 - 7.5)

CI: confidence interval.
* Adjusted for recipient gender and body surface area, donor body surface area, and ischemic time.

Table 4. Hazard ratio of recipients undergoing adult heart transplantation by different donor sodium level.

	Crude		Adjusted*	
Donor sodium level	**Hazard ratio**	**95% CI**	**Hazard ratio**	**95% CI**
≤ 155 mmol/L	1	Reference	1	Reference
> 155 mmol/L	1.03	0.83 - 1.29	1.05	0.85 - 1.31

CI: confidence interval.
* Adjusted for recipient gender and body surface area, donor body surface area, and ischemic time.

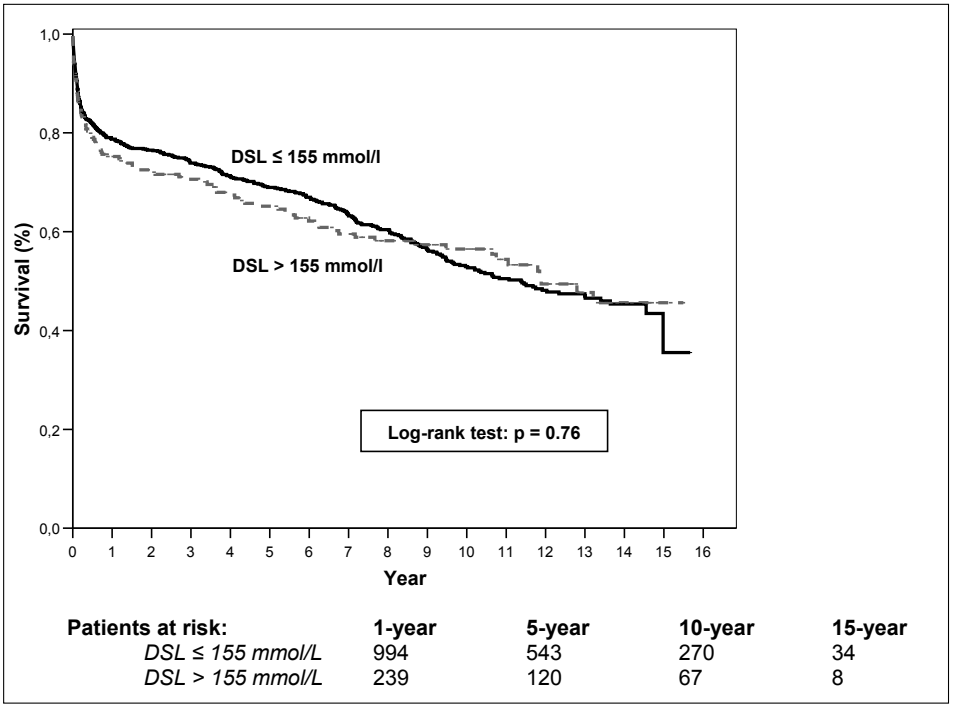

Figure 2. Recipient survival comparison by donor sodium level (DSL) after adult heart transplantation.

DISCUSSION

The findings in this follow-up study among a large group of adult heart transplant patients do not show an increased mortality risk in patients receiving heart transplantations from hypernatremic donors. Eurotransplant considers a donor sodium level of higher than 150 mmol/l as a risk factor of adverse outcome after heart transplantation. Therefore, heart transplantation using donor hearts with high donor sodium level is not recommended (5). Hoefer et al. (7) suggested that donor hypernatremia, defined as donor sodium level exceeding 170 mmol/L, may adversely impact the outcome after orthotopic heart transplantation. Our findings corroborate other studies (5;8;9). We showed that a donor sodium level exceeding 155 mmol/L at the time of organ procurement does not significantly increase the risk of primary graft failure or decrease survival after adult heart transplantation, and the same holds for donor sodium level exceeding 170 mmol/l.

The mechanism of hypernatremia-induced cardiac allograft dysfunction is uncertain. Reduced vasopressin (arginin-vasopressin) production in the pituitary glands, which is seen after brain death, commonly induces a diabetes insipidus like state. The resulting loss of free water may lead to dehydration, hypovolaemia, and

blood electrolyte abnormalities such as hypernatremia (14;15). Although graft damage could occur at the time of graft procurement, during storage and transportation or on reperfusion, it is generally believed to be due to reperfusion injury (6). Intracellular Na^+ accumulation in myocardium during ischemia may induce contractile dysfunction, ventricular fibrillation (lethal arrhythmias) during reperfusion, or both (16). Such condition may explain the risk of primary graft failure, which may occur in up to 25% of all heart transplantations within 24 hours after heart transplantation (17, 18), and may account a 30-day mortality risk of nearly 40% (12;19). Apart from allograft intrinsic myocardial dysfunction due to ischemia-reperfusion injury, primary graft failure can also occur as result of humoral mechanisms and poor donor heart function (20). Recently, we use inhaled nitric oxide or iloprost to reduce pretransplant pulmonary vascular resistance, that may also give risk to primary graft failure (21). Moreover, all of our patients had normal range of pulmonary vascular resistance at the time of heart transplantation.

Our study has some limitations. Apart from a follow-up study, 99% of our donor heart preservation was achieved by infusion of histidine-buffered tryptophane–ketoglutarate cardioplegia solution which has superior effects in heart preservation (22). This solution reduces the extracellular sodium concentration to a cytoplasmatic level. At the same time the free extracellular calcium concentration is minimized, whereby both electrical and (complete) mechanical inactivation of the cardiac muscle cells is achieved. Contraction band necrosis is avoided through the relatively low potassium concentration (23). These favorable effects may counteract the impact of increased donor sodium level on the posttransplant outcome. Moreover, the impact of time interval between declaration of brain death and graft explantation requires further investigations because it could contribute to the accumulation of intracellular natrium in the graft myocardium. An alternative explanation of our results might be the selection of a subgroup of donor hearts from the pool of donor hearts with high donor sodium level that were in very good condition. But since the outcome of our study shows hardly any effect of donor sodium level, this is considered very unlikely.

In conclusion, donor sodium level does contribute very little to the mortality risk after adult heart transplantation. Orthotopic heart transplantation from a donor with hypernatremia (sodium level > 155 mmol/L) can be performed successfully without adversely affecting early and long-term outcome. Organ shortage could be reduced when refusal of donor hearts based on high sodium level is abandoned. We suggest adjusting for donor heart selection accordingly.

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Chapter 6

Heart transplantation from donor undergoing cardiopulmonary resuscitation does not adversely affect the outcome

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Under peer review

ABSTRACT

Background

To date the impact of cardiopulmonary resuscitation (CPR) in donors on the outcome after heart transplantation remains unclear. We set out to study the influence of CPR in donors on outcome after adult heart transplantation.

Patients and methods

Data from 1,262 adult heart transplantations were reviewed, and categorized into two groups on the basis of CPR status in donors (CPR, n = 192; without CPR, n = 1,070).

Results

Mean (SD) recipient age was 54 (11) years. Mean (SD) donor age was 37 (14) years. Mean (SD) ischemic time was 195 (40) minutes. The overall 30-day mortality risk was 8.5% (CPR: 8.3%, without CPR: 8.5%; $p = 0.94$). Apart from donor age, body mass index, cause of death, need of catecholamine, creatine kinase, and creatine kinase isoenzyme MB, there were no significant differences between both groups at the time of heart transplantation. After adjustment for these differences the odds ratio for 30-day mortality and hazard ratio by CPR status in donors was not significantly different. The survival at 1, 5, 10, and 15 years was respectively 81%, 73%, 54%, and 21% for CPR group; and 77%, 67%, 54%, and 43% for without CPR group ($p = 0.55$).

Conclusion

Using donor hearts that have been subject to CPR does not adversely affect the outcome after adult heart transplantation. Accepting such donor hearts will add to the enlargement of the donor pool. We suggest adjusting for donor heart selection accordingly.

INTRODUCTION

In general, heart transplant teams and surgeons are reluctant to accept a heart from donor undergoing cardiopulmonary resuscitation (CPR) because of the fear of poor early and late cardiac function resulting from myocardial injury (1). Some studies (2-4), however, have demonstrated a reversible myocardial contractile failure following successful CPR. Therefore, the increasing demand for donor hearts to treat end-stage heart failure has led heart transplant centers to extend the classical criteria for donor selection criteria, and include hearts from donors who have undergone CPR. Still, there are few data reporting the outcome of heart transplantation with donor hearts that have been subject to CPR (1, 5, 6). We set out to study the influence of CPR in donors on outcome after adult heart transplantation.

PATIENTS AND METHODS

Study population

We reviewed 1,262 adult patients undergoing heart transplantation between March 1989 and December 2004 at the Heart & Diabetes Center North Rhine Westphalia in Bad Oynhausen, Germany. Heart retransplantations and heart transplantation in recipients younger than 18 years were excluded from the study. Our research ethics committee approved the study, and the need for individual informed consent was waived. The recipient selection criteria have been previously published (7), briefly they include irreversible end-stage heart failure without any other feasible medical or surgical treatment option, limited untreated life expectancy (estimated < 6 months), age < 65 years old and no 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 and recipient were matched for ABO blood-type compatibility and body weight (ratio: 1 ± 0.2).

Surgical techniques

Donor heart procurement and preservation was achieved by combination of cold cardioplegic arrest, mainly using Histidine-buffered tryptophane-ketoglutarate cardioplegia solution (Bretschneider-Custodiol, Kohler Chemie, Alsbach-Hahnlein, Germany) and topical hypothermia. All heart transplantations were performed orthotopically (8).

Immunosuppression therapy

The initial immunosuppressive regimen consisted of on cyclosporine A, azathioprine, and steroid. After early postoperative phase, double-drug therapy with

cyclosporine A and azathioprine was preferred. In case of clinical- or biopsy-proven rejection, steroid-pulse therapy was initiated. Oral steroid maintenance was given only in case of recurrent rejection. All survivors were regularly followed-up through our out-patient's service unit or by telephone interview with the patients, their relatives or family/referring physician.

Data collection and follow-up

Information regarding CPR in donors was obtained from the hospital where the donor was available. Cardiopulmonary resuscitation was defined as an attempt to restore spontaneous circulation by performing chest compressions with or without ventilations (9). All survivors after heart transplantation were regularly followed-up through our out-patient's service unit or by telephone interview with the patients, their relatives or family/referring physician. All data of recipients and donors were collected prospectively and maintained on a computerized database. Follow-up was 100% complete. The diagnosis of rejection was based on clinical findings, electrocardiographic and echocardiographic data. In the first 6 months after heart transplantation, it was performed monthly and every 3 months for the next half year. Thereafter, it was examined 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. Endomyocardial biopsy was performed routinely during the 1-, 5-, and 10-year after heart transplantation. When indicated, endomyocardial biopsies were performed regardless of time.

Statistical analysis

Patients were categorized into two groups on the basis of CPR status in donors. Categoric variables were reported as number and percentage (%). Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). For comparative evaluations, Pearson χ^2 test or Fisher's exact test (categoric variables) and unpaired 2-tailed *t*-test or Mann-Whitney-U test (continuous variables) were used. To avoid possible confounding effects on outcomes, a logistic regression and Cox proportional hazard model adjusted for differences in baseline characteristics between both groups was performed. Survival rates were calculated with the Kaplan-Meier product-limit estimator. The log-rank test was used to compare both groups. A *p*-value of ≤ 0.05 (two-tailed test) was considered statistically significant. All calculations were performed with the SPSS statistical package, version 13.0 (Chicago, IL, USA).

RESULTS

Baseline characteristics for both groups are presented in Table 1. There were 192 (15%) donor hearts with CPR and 1,070 (85%) without CPR. The mean (SD) recipient age was 54 (11) years. Mean (SD) donor age was 37 (14) years. Overall mean (SD) ischemic time was 195 (40) minutes.

Table 1. Baseline characteristics of patients undergoing adult heart transplantation by CPR status in donors.

Variable	Total (n = 1,262)	CPR (n = 192)	No CPR (n = 1,070)	*P*-value
Recipient				
Age (years)*	53.9 (11.1)	53.3 (11.9)	54 (10.9)	0.39
Male gender	1,065 (84)	157 (82)	908 (85)	0.28
Body mass index (kg/m^2)*	23.5 (3.1)	23.6 (3.1)	23.4 (3.1)	0.49
Pretransplant diagnosis				
Dilated cardiomyopathy	631 (50)	90 (47)	541 (51)	0.62
Ischemic cardiomyopathy	543 (43)	87 (45)	456 (43)	
Other	88 (7)	15 (8)	73 (7)	
High-urgency status	120 (10)	18 (9)	102 (10)	0.95
Prior sternotomy	411 (33)	64 (33)	347 (32)	0.81
Ventricular assist device (VAD)	223 (18)	29 (15)	194 (18)	0.31
Donor				
Age (years)*	36.5 (13.6)	33.8 (13.8)	37.1 (13.5)	0.003
Male gender	635 (50)	87 (45)	548 (51)	0.13
Body mass index (kg/m^2)*	23.9 (3.4)	23.3 (3.7)	24.0 (3.4)	0.007
Cause of death				
Trauma	478 (38)	43 (22)	435 (41)	< 0.001
Cerebrovascular accident	561 (45)	62 (32)	499 (47)	
Other	223 (18)	87 (45)	136 (13)	
Catecholamine	772 (61)	138 (72)	634 (59)	0.001
Creatine kinase (µg/l)†	100 (30 - 317.3)	155 (35 - 462)	96 (29 - 297)	0.01
CK-MB (µg/l)†	6 (1 - 17)	10 (1 - 25.8)	6 (1 - 15.5)	0.008
Donor-recipient mismatch				
Gender	536 (43)	85 (44)	451 (42)	0.58
Non-identical blood type	74 (6)	12 (6)	62 (6)	0.81
Body mass index ratio				
< 0.8	79 (6)	18 (9)	61 (6)	0.09
> 1.2	178 (14)	22 (12)	156 (15)	
Operative data				
Ischemic time (minutes)*	195 (40)	194 (39)	195 (41)	0.71
CPB time (minutes)*	114 (46)	112 (42)	114 (46)	0.43
Postoperative VAD support	44 (4)	2 (1)	42 (4)	0.06

CPB: cardiopulmonary bypass, CK-MB: creatine kinase isoenzyme MB, CPR: cardiopulmonary resuscitation,
Values are count (%) unless otherwise indicated, *p*-value based on χ^2-test. * Mean (± SD), *p*-value based on *t*-test. † Median (IQR), *p*-value based on Mann-Whitney-U test.

Except donor age, body mass index, cause of death, need of catecholamine, creatine kinase, and creatine kinase isoenzyme MB, there were no significant differences in other characteristics between both groups at the time of transplantation.

Overall, there were 107 deaths within 30 days after heart transplantation, for a 30-day postoperative mortality risk of 8.5% (CPR: 8.3%, without CPR: 8.5%, p = 0.94). There was no significant difference in causes of death between both groups (Table2).

Table 2. Causes of early and late mortality of patients after adult heart transplantation by CPR status in donors.

	Early mortality				Late mortality			
	Total (n = 107)	**CPR (n = 16)**	**No CPR (n = 91)**	***P*-value**	**Total (n = 414)**	**CPR (n = 62)**	**No CPR (n = 352)**	***P*-value**
Causes of death				0.81				0.84
Primary graft failure	6 (6)	1 (6)	5 (6)		1 (0)	-	1 (0)	
Right heart failure	13 (12)	1 (6)	12 (13)		6 (1)	1 (2)	5 (1)	
Acute rejection	29 (27)	7 (44)	22 (24)		81 (20)	13 (21)	68 (19)	
Multiorgan failure	17 (16)	3 (19)	14 (15)		16 (6)	3 (5)	23 (7)	
CAV	-	-	-		71 (17)	12 (19)	59 (17)	
Infection	12 (11)	1 (6)	11 (12)		94 (23)	15 (24)	79 (22)	
Malignancy	-	-	-		68 (16)	6 (10)	62 (18)	
Surgical complication	9 (8)	1 (6)	8 (9)		-	-	-	
Other	21 (20)	2 (13)	19 (21)		67 (16)	12 (19)	55 (16)	

CAV: cardiac allograft vasculopathy, CPR: cardiopulmonary resuscitation.
Values are count (%) unless otherwise indicated. Because of rounding, not all percentages total 100.

The total follow-up time was 7,173 patient-years [median (IQR): 4.7 (0.8 - 9.6) years]. Table 3 shows the odds ratio (OR) for 30-day mortality and hazard ratio (HR) according to CPR status in donors. The crude OR for 30-day mortality and HR for CPR group was 0.98 (95% CI: 0. 56 - 1.71) and 0.93 (95% CI: 0.73 - 1.18). After adjusting for donor age, body mass index, cause of death, the need of inotropic support, creatine kinase, and creatine kinase isoenzyme MB, the OR for 30-day mortality and HR did not materially change (OR = 1.18, 95% CI: 0.59 - 2.35 and HR = 1.01, 95% CI: 0.75 - 1.34).

Table 3. Odds ratio for 30-day mortality and hazard ratios of patients after adult heart transplantation by CPR status in donors.

	Odds ratio (95% CI)		Hazard ratio (95% CI)	
Variable	**Crude**	**Adjusted***	**Crude**	**Adjusted***
No CPR	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
CPR	0.98 (0.56 - 1.71)	1.18 (0.59 - 2.35)	0.93 (0.73 - 1.18)	1.01 (0.75 - 1.34)

CI: confidence interval, CPR: cardiopulmonary resuscitation.
* Adjusted for donor age, body mass index, cause of death, need of catecholamine, creatine kinase, and creatine kinase isoenzyme MB.

The cumulative survival at 1, 5, 10, and 15 years was respectively 81%, 73%, 54%, and 21% for CPR group; and 77%, 67%, 54%, and 43% for without CPR group (p = 0.55) (Figure 1).

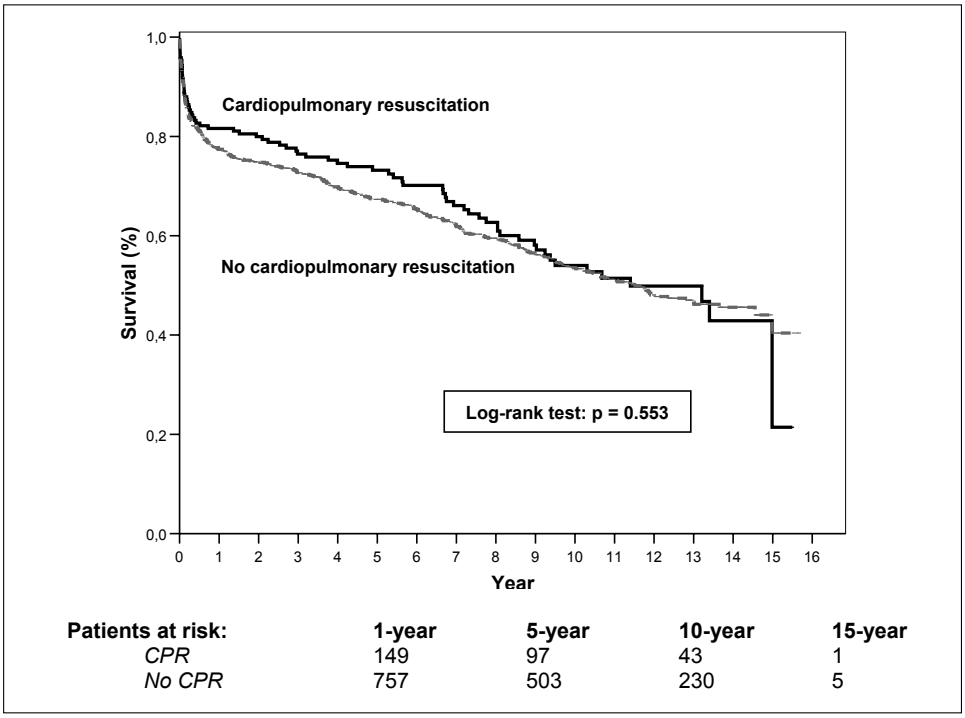

Figure 1. Survival comparison of patients after adult heart transplantation by CPR status in donors.

DISCUSSION

An important factor limiting for heart transplantation in the treatment of patients with end-stage heart failure is the lacking of donor hearts. In recent years, different attempts to expand the donor pool by promoting donor odicils appear to have reached a plateau. Liberalizing donor criteria is a following alternative to increase the number of heart transplantation.

There are many reasons for refusal of donor hearts for transplantation, of which one is the need for CPR in donors during the initial management. Our data however show that the outcome of adult heart transplantation, either 30-day mortality risk or overall survival, is similar when hearts are used from donors with and without CPR. This remains after adjustment for differences between the groups in donor age, body mass index, cause of death, need of catecholamine, and cardiac enzymes.

CPR during the initial donor management will maintain the beating of the heart at a cardiac output of 25% to 50% (10, 11). Thereby, CPR may prepare the heart mechanically to resume circulation by decompressing the right ventricle and filling the left ventricle and coronary arteries (12). Hence, CPR is considered to simultaneously limit ischemia and reduce ischemia-reperfusion injury.

Myocardial damage following CPR may increase the incidence of donor organ dysfunction immediately following heart transplantation. Only two patients who received a heart from donors undergoing CPR developed this complication (primary graft failure = 1, right heart failure = 1); they subsequently died. Although there was an increased need of inotropic support in donors requiring CPR, this did not show to influence our results. Both groups were similar with respect to ischemic time. Donors with CPR were significantly younger than donors without CPR. A similar percentage of patients in both groups (CPR: 15%, without CPR: 18%, p = 0.31) required temporary circulatory support before heart transplantation. After heart transplantation, 1% (2 of 192) of patients who received donors with CPR and 4% (42 of 1,070) of patients who received donors without CPR required a ventricular assist device for temporary circulatory support (p = 0.06). Analyzing the causes of death after heart transplantation, we could not find any statistical differences between donor with and without CPR.

In conclusion, our results demonstrated that using donor hearts that have been subject to CPR does not adversely affect the outcome of heart transplantation. Accepting such donor hearts will add to the enlargement of the donor pool. We suggest adjusting the guidelines for donor selection accordingly.

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Chapter 7

Prediction model for the thirty-day mortality risk after adult heart transplantation

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Under peer review

ABSTRACT

Background

A comprehensive prediction model that provides information on survival after heart transplantation to patients and their families may also help the heart transplant team to classify patients according to their mortality risk. We aimed to develop an easily applicable prediction model for the 30-day mortality risk after adult heart transplantation.

Patients and methods

A comprehensive database including 1,262 adult patients undergoing primary heart transplantation between March 1989 and December 2004 was available to develop a prediction model, using logistic regression analysis. The predictive accuracy and internal validity of the model was assessed. The agreement between the predicted probability and the observed mortality (calibration) was evaluated graphically and with Hosmer-Lemeshow test. The ability of the model to correctly discriminate between the discordant survival pairs was determined by calculating the area under the receiver operating characteristic curve (ROC area).

Results

Recipient age and gender, pretransplant diagnosis, transplant status, waiting time, donor age and gender, donor-recipient mismatch for body mass index and blood type, and cardiopulmonary bypass time were selected as independent predictors for 30-day mortality risk after adult heart transplantation. The model showed good calibration (*p*-value: 0.36) and discrimination (ROC area: 0.74, 95% CI: 0.69 - 0.79). The internal validity of the model was acceptable and the corrected ROC area was 0.71. The prediction model was converted to an easy to use nomogram to enhance its application in clinical practice.

Conclusion

Our prediction model provides an easily applicable instrument for predicting the 30-day mortality risk after adult heart transplantation. It can be used in clinical practice for matching donor to recipient and to assist decision on optimal allocation of a donor heart to a patient waiting for heart transplantation.

INTRODUCTION

Heart transplantation is the treatment of choice for patients with end-stage heart failure, in particular when it is severely impacting daily life (New York Heart Association class III or IV) despite maximal medical therapy, notably for those with left ventricular ejection fraction of 25% or less (1). Several studies on risk factors of mortality in heart transplantation have been published (2-6). Yet, a comprehensive prediction model for posttransplant survival is lacking. Using a comprehensive database from a previous study including recipient, donor, and operative characteristics (7), we set out to develop a model for predicting the 30-day mortality risk after adult heart transplantation. This outcome was chosen for the model because it is a principal bench mark for a successful outcome in surgical procedures. The model should be able to accurately discern patients at high and low 30-day mortality risk. In addition, the prediction model should be well calibrated and easily applicable. Apart from providing important information to patients and their families, the model could support cardiac transplant team and surgeons to classify patients according to their mortality risk, and hence support decision on optimal allocation of donor hearts to patients waiting for heart transplantation.

PATIENTS AND METHODS

Study population

The study population consisted of 1,262 adult patients undergoing primary heart transplantation between March 1989 and December 2004 at the Heart & Diabetes Center North Rhine Westphalia in Bad Oeynhausen, Germany. Our institutional review board approved this clinical follow-up study and waived individual consent. Donor and recipient were matched for ABO blood-type compatibility and body weight.

Surgical techniques

Donor heart procurement and preservation was achieved by combination of cold cardioplegic arrest, mainly using Histidine-buffered tryptophane-ketoglutarate cardioplegia solution (Bretschneider-Custodiol, Kohler Chemie, Alsbach-Hahnlein, Germany) and topical hypothermia. All heart transplantations were performed orthotopically (8).

Immunosuppresion therapy

The initial immunosuppressive regimen included cyclosporine A, azathioprine, and steroid. After early postoperative phase, double-drug therapy with cyclosporine A and azathioprine was preferred. In case of clinical- or biopsy-proven rejection, steroid-pulse therapy was initiated. Oral steroid maintenance was given only in case of recurrent rejection.

Follow-up and data collection

All survivors were regularly followed-up through our out-patient's service unit or by telephone interview with the patients, their relatives or family/referring physician. All data of recipients and donors were collected prospectively and maintained on a computerized database. Follow-up was 100% complete. The main outcome was the 30-day mortality after heart transplantation, which was defined as death within 30 days after heart transplantation.

Predictors

Using reported findings on risk factors of early mortality after heart transplantation (7), we selected the predictors for inclusion in the model. We selected 4 clusters of predictors relating to recipient characteristics, notably age, gender, body mass index, blood type, pretransplant diagnosis, previous sternotomy, transplant status, waiting time, and need of ventricular assist device; donor characteristics, notably age, gender, body mass index, blood type, cause of death, need of cardiopulmonary resuscitation, and catecholamine; donor-recipient mismatch, notably gender, body mass index, and blood type; and operative data, notably ischemic time and cardiopulmonary bypass time. All these variables were routinely recorded in our clinical database.

Modeling

First, we tested the univariable association of each predictor with 30-day mortality by using chi-square test for categoric variables, and the unpaired 2-tailed *t*-test or Mann-Whitney U test for continuous variables. Predictors for which the Wald test for the coefficient of association with the outcome showed a *p*-value equal to or below 0.25 were selected for inclusion in the subsequent multivariable analysis. In building the final multivariable model we used a hierarchical approach that follows routine practice as close as possible. Our intention was to retain the most easily obtainable clinical predictors with the highest predictive value. For this we applied a backward stepwise selection procedure and we excluded predictors for which the Wald test for the coefficient of association with the outcome showed a *p*-value exceeded 0.25. We did not include interaction terms in any step of building the prediction model (9). We used SPSS software, version 14.0 (SPSS Inc., Chicago, Illinois).

Predictive accuracy

The predictive accuracy of the final model was quantified by using calibration and discrimination measures. Calibration, i.e., the agreement between the predicted probability and the observed death, was assessed graphically and tested with the Hosmer–Lemeshow test, for which a *p*-value larger than or equal to 0.10 reflects

good calibration. The discriminative ability was determined with the area under the receiver operating characteristic curve (ROC area). The ROC curve plots the true-positive proportion (Y-axis) against the false-positive proportion (X-axis) of death. The ROC area represents the probability of correct discrimination between discordant survival pairs, i.e., one dies and one survives (10). If the ROC area is equal to 0.5, i.e., the true and false positive proportions describe a 45° line of identity throughout the score range, this means that the model is not able to discriminate between discordant survival pairs. The ROC area approaches 1.0 if the ROC curve reaches higher and towards the left in the diagram, indicating that the prediction model approaches optimal accuracy in discrimination (10).

Validation

To prevent for optimism (i.e. too low or too high estimates) in a new population, we used a bootstrap approach to estimate a 'shrinkage factor', ranging between 0 and 1 (11). The regression coefficients of all predictors in the model were subsequently multiplied with this shrinkage factor. Bootstrap samples were drawn from the full data set with replacement and 100 replications. The backward selection of variables and model fitting was repeated within each bootstrap sample. The model's performance obtained after bootstrapping can be considered as the performance that can be expected in similar future patients (11,12). For these analyses we used S-plus 6.2 Professional (Insightful Corp., Seattle, WA, USA).

Nomogram

To facilitate the application of the prediction model in practice, the prediction model was converted to a nomogram (S-Plus *Hmisc* and *Design* library, function *nomogram*). Nomogram is convenient tool for clinical practice, which can be used to manually obtain predicted values from a regression model. A nomogram has a reference line for reading the score for each predictor in the model (default range 0-100). Once the reader manually totals the scores, the predicted probabilities can be read at the bottom, and can be used to predict the 30-day mortality risk in individual patient.

RESULTS

Of 1,262 patients, 107 died within 30 days after heart transplantation (30-day mortality risk: 9%, 95%CI: 7% - 11%). Table 1 presents the baseline characteristics and univariable association with the 30-day mortality risk after adult heart transplantation. We started the multivariable modeling with 14 variables with a univariable *p*-value ≤ 0.25.

Tabel 1. Baseline characteristics and univariable association with the 30-day mortality risk after adult heart transplantation.

Variable	Total (n = 1,262)	Death (n = 107)	Survivor (1,155)	*P*-value
Recipient				
Age (years)*	53.9 (11.1)	57 (10.8)	53.6 (11.1)	0.003
Female gender	197 (16)	24 (22)	173 (15)	0.04
Body mass index (kg/m^2)*	23.5 (3)	23.2 (3)	23.5 (3)	0.33
Blood type				
A	558 (44)	51 (48)	507 (44)	0.45
B	138 (11)	8 (8)	30 (11)	
O	478 (38)	43 (40)	435 (38)	
AB	88 (7)	5 (5)	83 (7)	
Pretransplant diagnosis				
Dilated cardiomyopathy	631 (50)	40 (37)	591 (51)	0.01
Ischemic cardiomyopathy	543 (43)	55 (51)	488 (42)	
Other	88 (7)	12 (11)	76 (7)	
Previous sternotomy	411 (33)	44 (41)	367 (32)	0.05
High-urgency status	120 (10)	6 (6)	114 (10)	0.15
Waiting time (months)†	3.3 (0.9 - 10.8)	6.4 (1.8 - 13.9)	3.1 (0.9 - 10.4))	0.002
Ventricular assist device	223 (18)	22 (21)	201 (17)	0.41
Donor				
Age (years)*	36.5 (13.6)	41.2 (12.6)	36.1 (13.6)	< 0.001
Female gender	627 (50)	72 (67)	555 (48)	< 0.001
Body mass index (kg/m^2)*	23.9 (3.4)	24.1 (4.2)	23.9 (3.4)	0.45
Blood type				
A	539 (43)	47 (44)	492 (43)	0.41
B	137 (11)	10 (9)	127 (11)	
O	523 (42)	48 (45)	475 (41)	
AB	63 (5)	2 (2)	61 (5)	
Cause of death				
Trauma	478 (38)	28 (26)	450 (39)	0.002
Cerebrovascular accident	561 (44)	65 (61)	496 (43)	
Other	223 (18)	14 (13)	209 (18)	
Cardiopulmonary resuscitation	192 (15)	16 (15)	176 (15)	0.94
Catecholamine	772 (61)	64 (60)	708 (61)	0.76
Donor-recipient mismatch				
Gender				
Male donor to female recipient	55 (4)	5 (5)	50 (4)	0.04
Female donor to male recipient	485 (38)	53 (50)	432 (37)	
Body mass index ratio				
< 0.8 (undermatch)	79 (6)	8 (8)	71 (6)	0.1
> 1.2 (overmatch)	178 (14)	22 (21)	156 (14)	
Non-identical blood type	74 (6)	9 (8)	65 (6)	0.24
Operative data				
Ischemic time (minutes)*	194.5 (40.4)	206.6 (40.2)	193.4 (40.3)	0.001
Cardiopulmonary bypass time (minutes)*	114 (45.6)	139.6 (67)	111.6 (42.4)	< 0.001

Values are count (%) unless otherwise indicated. Mean (± SD). † Median (IQR).

Previous sternotomy, donor cause of death, donor-recipient mismatch for gender, and ischemic time subsequently showed a *p*-value > 0.25 for their multivariable association with the 30-day mortality risk after adult heart transplantation and thus, were not included in the final model.

Table 2 presents estimates of the predictors in the final prediction model after backward stepwise selection, i.e. recipient age and gender, pretransplant diagnosis, transplant status, waiting time, donor age and gender, donor-recipient mismatch for body mass index and blood type, and cardiopulmonary bypass time.

Table 2. Multivariable association of the predictors in the final prediction model for the 30-day mortality risk after adult heart transplantation.

Variable	B	SE	OR	95% CI
Recipient age (years)	0.02	0.01	1.02	0.99 - 1.04
Female recipient	0.61	0.28	1.83	1.07 -3.14
Pretransplant diagnosis				
Dilated cardiomyopathy			1	Reference
Ischemic cardiomyopathy	0.29	0.24	1.33	0.84 - 2.12
Other	0.57	0.37	1.78	0.86 - 3.66
High-urgency status	-0.87	0.48	0.42	0.16 - 1.09
Waiting time (months)	0.03	0.01	1.03	1.01 - 1.05
Donor age (years)	0.02	0.01	1.02	1.01 - 1.04
Female donor	0.59	0.23	1.81	1.15 - 2.84
Donor-recipient body mass index ratio				
0.8 - 1.2			1	Reference
< 0.8 (undermatch)	0.19	0.42	1.21	0.53 - 2.77
> 1.2 (overmatch)	0.47	0.27	1.61	0.94 - 2.74
Donor-recipient blood type (non identical)	0.68	0.41	1.97	0.89 - 4.38
CPB time (per 15 minutes)	0.15	0.03	1.17	1.11 - 1.23

B: beta, CPB: cardiopulmonary bypass, SE: standard errors, OR: odds ratio, CI: confidence interval.

The resulting multivariable prediction model yielded a ROC area of 0.74 (95% CI: 0.69 - 0.79) (Figure 1) and Hosmer-Lemeshow *p*-value of 0.36. Figure 2 shows the calibration of the resulting prediction model. The plotted points are rather close to the 45° line, demonstrating good calibration over the whole range of the predictions. From the bootstrapping procedure, a shrinkage factor of 0.81 was obtained. When the multivariable regression coefficients of all predictors of 30-day mortality risk were multiplied with this shrinkage factor in order to correct for optimism ROC area was 0.71, showing good discrimination.

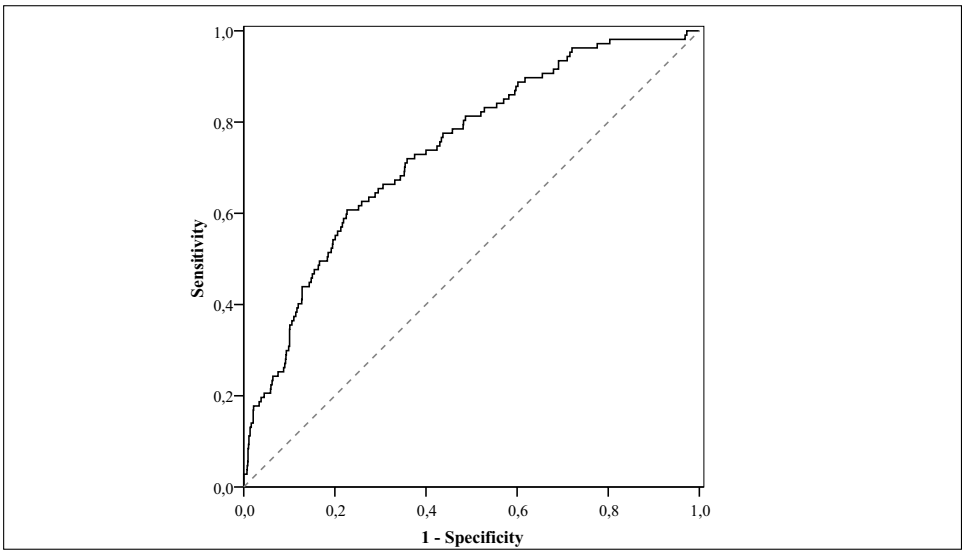

Figure 1. Discriminative ability of the final model for prediction of the 30-day mortality risk after adult heart transplantation. The area under the receiver operator characteristic curve (ROC area) was 0.74, which reflects a good discrimination.

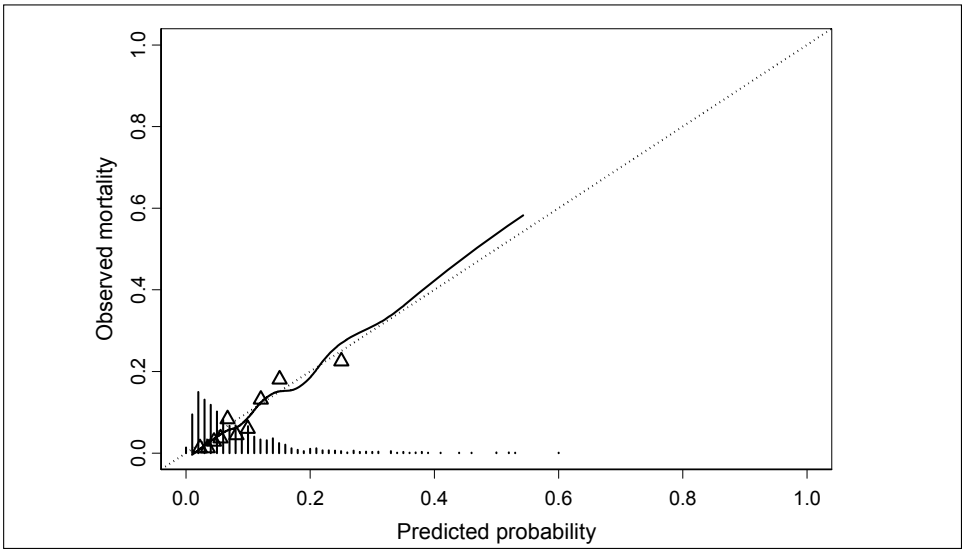

Figure 2. Calibration plot showing the observed mortality versus the predicted probability of the 30-day mortality after adult heart transplantation. The solid line demonstrates the correlation between the predicted probability and the observed mortality. Ideally, this line fits the diagonal dotted line that represents perfect calibration. Triangles indicate the observed mortality risk per equal-size-deciles of predicted probability of the 30-day mortality. Distribution of the predicted probabilities is indicated with vertical lines at the bottom.

Figure 3 shows the normogram for predicting the 30-day mortality risk after adult heart transplantation. As an example how to use the nomogram, a 60-year old female recipient, who has pretransplant diagnosis of ischemic cardiomyopathy and transplanted in high-urgency status after waiting heart transplantation for 10 months, receive a heart from a 50-years old female donor with donor-recipient body mass index > 1.2 (overmatch) and non-identical blood type after an operation with cardiopulmonary bypass time of 2 hours, has total points of 111 (15+0+7+0+6+18+14+12+16+23) which corresponds to a predicted probability of the 30-day mortality of 0.18.

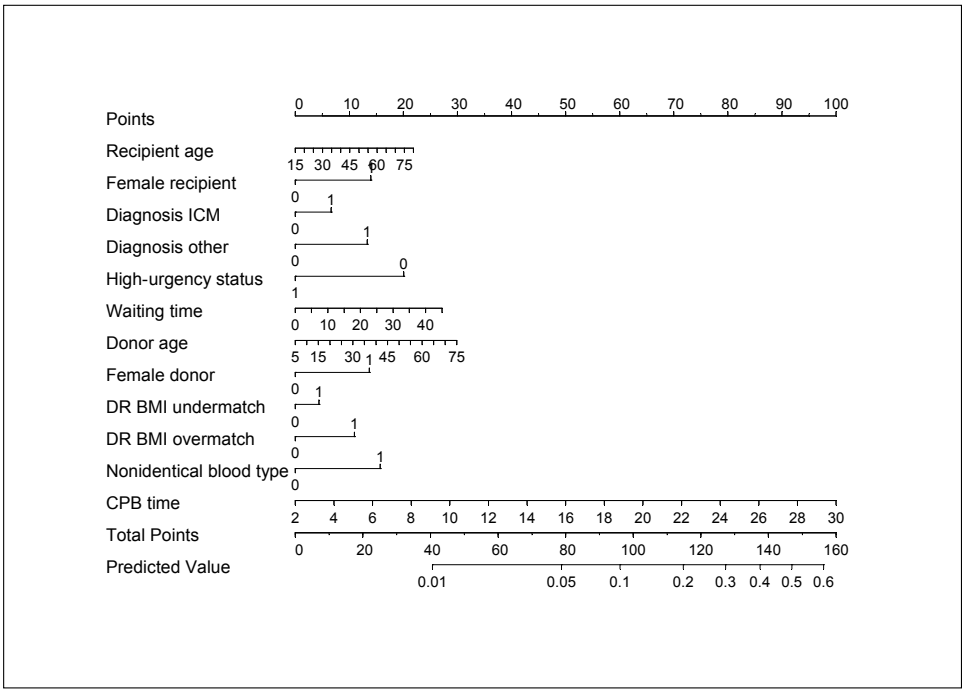

Figure 3. Nomogram for manual calculation of the predicted probability of the 30-day mortality risk after adult heart transplantation. Each predictor has a reference line for reading scoring points (default range 0-100). DR BMI undermatch means donor-recipient body mass index ratio < 0.8. DR BMI overmatch means donor-recipient body mass index > 1.2. CPB (cardiopulmonary bypass) time represents every 15 minutes. Waiting time represents every month. Diagnosis ICM means ischemic cardiomyopathy. Diagnosis other means other than ischemic and dilated cardiomyopathy. Once the reader manually totals the points, the predicted probabilities can be read at the bottom.

DISCUSSION

The results of the present analysis based on data from a large cohort of heart transplant patients provide a simple model that may be used to adequately predict the 30-day mortality risk after adult heart transplantation.

We show that recipient age and gender, pretransplant diagnosis, transplant status, waiting time, donor age and gender, donor-recipient mismatch for body mass index and blood type, and cardiopulmonary bypass time are accurate independent predictors for the 30-day mortality risk after adult heart transplantation.

Our prediction model is easily applicable in clinical practice since it comprises predictors which are commonly available and easily obtainable pre- or perioperatively for most heart transplant patients. In building our model we followed routine clinical practice as much as possible. For this, we used data obtained from a large heart center with a large study population with a complete follow-up of adult patients undergoing heart transplantation from about 16 subsequent years.

There are few previous studies which attempted to predict mortality risk (13-15), but to our knowledge no comprehensive prediction models has been published yet. Some preoperative risk stratification model for heart transplantation have been developed (14,15), but their predictive accuracy, i.e., calibration and discrimination has not been reported. This limits their generalizability and clinical applicability. Anyanwu et al. (13) attempted to derive a simple model for risk stratification after heart transplantation, but unfortunately their study population was too small to allow adequate statistical modeling.

Our prediction model accurately predicts the 30-day mortality risk after adult heart transplantation. The calibration plot shows that the predicted probability categories are close to the ideal line. Hence, our model is rather well calibrated over the complete range of predicted probabilities. After correction for optimism, the ROC area changed from 0.74 to 0.71, which shows good discrimination between deceased patients and survivors at 30-day after adult heart transplantation.

The small number of events relative to the high number of potential predictors is a limitation in every single-center study. For developing a reliable prediction model, the rule of thumb is that per candidate predictor there should be at least 10 events (1 to 10 ratio) (16). In our cohort, 107 events occurred which allowed us to include 10 predictors. Bootstrapping procedures should be used to check whether a developed model is reasonably valid or needs to be adjusted. This has been shown to be superior to split-sample or cross-validation methods (16). We obtained a shrinkage factor of 0.81, which implies only limited over-optimism and so marginal adjustment was needed. Still, external validation in a new population should ideally follow to apply our prediction model to other populations with confidence.

In conclusion, we have developed and validated a prediction model for the 30-day mortality risk after adult heart transplantation by using simple predictors which are generally available in the clinical setting. Our prediction model may serve

clinicians as well as patients and their family in predicting the outcome after adult heart transplantation. Moreover, the nomogram may assist the heart transplant team and surgeon in risk stratification. Thereby, our prediction model can be used for matching donor to recipient and to assist decision on optimal allocation of a donor heart to a patient waiting for heart transplantation.

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Chapter 8

Predicting the 1- and the 5-year mortality risk after adult heart transplantation

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Submitted

ABSTRACT

Background

A clinical model that can accurately predict mortality after heart transplantation at longer term can be of crucial concern for the community and in health care. The aim of this study was to develop models that could predict the 1- and the 5-year mortality risk after adult heart transplantation based on pretransplant characteristics of recipient and donor as well as perioperative data.

Patients and methods

Data for developing the prediction models were obtained from all adult patients undergoing primary heart transplantation between March 1989 and December 2004 at the Heart & Diabetes Center North Rhine Westphalia in Bad Oeynhausen, Germany. The predictive accuracy and internal validity of the models was assessed. The agreement between the predicted probability and the observed mortality (calibration) was evaluated graphically and with Hosmer-Lemeshow test. The ability of the models to correctly discriminate the discordant survival pairs was determined by calculating the area under the receiver operating characteristic curve (ROC area).

Results

The independent predictors were: recipient age and gender, transplant status, donor age, donor-recipient mismatch for body mass index, and cardiopulmonary bypass time for the 1-year model; and recipient age and gender, transplant status, donor age, need of catecholamine in donor, and cardiopulmonary bypass time for the 5-year model. The models showed good calibration (*p*-value: 0.21 for the 1-year model; 0.89 for the 5-year model) and fair discrimination (ROC area: 0.67, 95% CI: 0.63 - 0.71 for the 1-year; and 0.66, 95% CI: 0.63 - 0.69 for the 5-year model). The internal validity of the models was acceptable and the corrected ROC area was 0.64 for the 1-year model and 0.65 for the 5-year model. The prediction models were converted to easy to use nomograms to enhance its application in clinical practice.

Conclusion

Our normograms provide easily applicable instruments for predicting the 1- and the 5-year mortality risk after adult heart transplantation. They can be used in clinical practice for matching donor to recipient in an optimal way and to assist a heart transplant team to estimate mortality risk for potential heart transplant recipients and their relatives objectively.

INTRODUCTION

Heart transplantation is the major therapeutic modality for improving long-term survival in end-stage heart diseases. The feasibility of long-term survival is an important consideration, especially with the development of newer treatment options for end-stage heart diseases. Despite many advances in recent years, the 1- and 5-year survival rates of most large series remain at around 80% and 60% (1). Different studies have reported that some perioperative factors and several pretransplant characteristics of donor and recipient are associated with survival after heart transplantation (1, 2). However, a comprehensive prediction model for posttransplant mortality risk is lacking. Therefore, the development of a clinical model that can accurately predict mortality after heart transplantation at longer term can be of crucial concern for the community and in health care. We believe that a reliable prediction model may help physicians to advise their patients regarding to potential mortality, to prioritize organ use, and can be used for comparison of outcome across transplant centers. The aim of this study was to develop models that can predict the 1- and the 5-year mortality risk after adult heart transplantation by using pretransplant characteristics of recipient and donor, as well as perioperative data.

PATIENTS AND METHODS

Study population

Data for this study were obtained from a database of all adult patients undergoing primary heart transplantation between March 1989 and December 2004 at the Heart & Diabetes Center North Rhine Westphalia in Bad Oeynhausen, Germany. In this analysis, we considered survival to at least 1 year and 5 years. Patients were included in the analysis at each time point only if they had the chance to live up to the specified time point. Our institutional review board approved this clinical follow-up study and waived individual consent. Donor and recipient were matched for ABO blood-type compatibility and body weight.

Surgical techniques

Donor heart procurement and preservation was achieved by combination of cold cardioplegic arrest, mainly using Histidine-buffered tryptophane-ketoglutarate cardioplegia solution (Bretschneider-Custodiol, Kohler Chemie, Alsbach-Hahnlein, Germany) and topical hypothermia. All heart transplantations were performed orthotopically (3).

Immunosuppresion therapy

The initial immunosuppressive regimen included cyclosporine A, azathioprine, and steroid. After early postoperative phase, double-drug therapy with cyclosporine A and azathioprine was preferred. In case of clinical- or biopsy-proven rejection,

steroid-pulse therapy was initiated. Oral steroid maintenance was given only in case of recurrent rejection.

Follow-up and data collection

All survivors were regularly followed-up through our out-patient's service unit or by telephone interview with the patients, their relatives or family/referring physician. All data of recipients and donors were collected prospectively and maintained on a computerized database. Follow-up was 100% complete. The main outcome was the 1- and the 5-year mortality after heart transplantation.

Predictors

Using reported findings on risk factors for mortality after heart transplantation (1), we selected 4 clusters of predictors of mortality at 1 and 5 years relating to recipient characteristics, notably age, gender, body mass index, blood type, pre-transplant diagnosis, previous sternotomy, transplant status, waiting time, and need of ventricular assist device; donor characteristics, notably age, gender, body mass index, blood type, cause of death, need of cardiopulmonary resuscitation, and inotropic support; donor-recipient mismatch, notably gender, body mass index, and blood type, and operative data, notably ischemic time and cardiopulmonary bypass time. All these variables are routinely recorded in our clinical database.

Modeling

First, we tested the univariable association of each predictor with the 1- and the 5-year mortality by using chi-square test for categorical variables, and the unpaired 2-tailed *t*-test or Mann-Whitney U test for continuous variables. Predictors for which the Wald test for the coefficient of association with the outcome showed a *p*-value equal to or below 0.25 were selected for inclusion in the subsequent multivariable analysis. In building the final multivariable models we used a hierarchical approach that follows routine practice as close as possible. Our intention was to retain the most easily obtainable clinical predictors with the highest predictive value. For this, we applied a backward stepwise selection procedure and we excluded predictors for which the Wald test for the coefficient of association with the outcome showed a *p*-value exceeded 0.25. We did not include interaction terms in any step of building the prediction models (4). We used SPSS software, version 14.0 (SPSS Inc., Chicago, Illinois).

Predictive accuracy

The predictive accuracy of the final models was quantified by using calibration and discrimination measures. Calibration, i.e., the agreement between the predicted probability and the observed death, was assessed graphically and tested with the

Hosmer–Lemeshow test, for which a *p*-value larger than or equal to 0.10 reflects good calibration. The discriminative ability was determined with the area under the receiver operating characteristic curve (ROC area). The ROC curve plots the true-positive proportion (Y-axis) against the false-positive proportion (X-axis) of death. The ROC area represents the probability of correct discrimination between discordant survival pairs, i.e., one dies and one survives (5). A ROC area equals to 0.5 means that the model is unable to discriminate between discordant survival pairs. The ROC area approaches 1.0 if the ROC curve reaches higher and towards the left upper corner in the diagram, indicating that the prediction model approaches optimal accuracy in discrimination (5).

Validation

To prevent for optimism (i.e. too low or too high estimates) in a new population, we used a bootstrap approach to estimate a corrected ROC area and a 'shrinkage factor', ranging between 0 and 1 (6). The regression coefficients of all predictors in the models were subsequently multiplied with this shrinkage factor. Bootstrap samples were drawn from the full data set with replacement and 100 replications. The backward selection of variables and model fitting was repeated within each bootstrap sample. The model's performance obtained after bootstrapping can be considered as the performance that can be expected in similar future patients (6, 7). For these analyses we used S-plus 6.2 Professional (Insightful Corp., Seattle, WA, USA).

Nomograms

To facilitate the application of the prediction models in practice, the prediction models were converted to nomograms (S-Plus *Hmisc* and *Design* library, function *nomogram*). Nomograms are convenient tools for clinical practice, which can be used to manually obtain predicted values from regression models. A nomogram has a reference line for reading the score for each predictor in the model (default range 0-100). Once the reader totals the scores, the predicted probabilities can be read at the bottom, and can be used to predict the 1- and the 5-year mortality risk in individual patient.

RESULTS

A total of 1,204 patients and 995 patients were included for developing the 1-year and the 5-year model. Table 1 presents the baseline characteristics and univariable association with the 1- and the 5-year mortality risk after adult heart transplantation. The 1-year mortality risk was 23% (274 of 1,204, 95% CI: 21% - 25%); and the 5-year mortality risk was 38% (377 of 995, 95% CI: 35% - 41%).

Tabel 1. Baseline characteristics and univariable association with the 1- and the 5-year mortality risk after adult heart transplantation.

Variable	1-year (n=1,204)			5-years (n=995)		
	Death (n=274)	Survivor (n=930)	*P*-value	Death (n=377)	Survivor (n=618)	*P*-value
Recipient						
Age (years)*	56.6 (9.8)	53.3 (11.4)	< 0.001	56.4 (9.9)	53.2 (11)	< 0.001
Female gender	49 (18)	136 (15)	0.19	65 (17)	89 (14)	0.23
Body mass index (kg/m^2)*	23.6 (3)	23.4 (3)	0.46	23.6 (3.1)	23.3 (2.8)	0.11
Blood type						
A	125 (46)	402 (43)	0.12	170 (45)	268 (43)	0.37
B	21 (8)	111 (12)		33 (9)	75 (12)	
O	113 (41)	348 (37)		150 (40)	231 ((37)	
AB	15 (6)	69 (7)		24 (6)	44 (7)	
Pretransplant diagnosis						
Dilated cardiomyopathy	121 (44)	477 (51)	0.07	163 (43)	322 (52)	0.03
Ischemic cardiomyopathy	128 (47)	394 (42)		184 (49)	253 (41)	
Other	25 (9)	59 (6)		30 (8)	43 (7)	
Previous sternotomy	172 (63)	102 (37)	0.06	133 (35)	182 (29)	0.06
High-urgency status	13 (5)	107 (12)	0.001	25 (7)	71 (12)	0.01
Waiting time (months)†	4.6 (1.3 - 12.3)	3.1 (0.9 - 10.7)	0.01	4.2 (1.5 - 9.9)	4.3 (1.3 - 12.6)	0.32
Ventricular assist device	48 (18)	162 (17)	0.97	64 (17)	107 (17)	0.89
Donor						
Age (years)*	39.8 (13.6)	35.5 (13.5)	< 0.001	39.2 (13.9)	34.7 (13.5)	< 0.001
Female gender	154 (56)	436 (47)	0.01	202 (54)	294 (48)	0.07
Body mass index (kg/m^2)*	24.1 (3.7)	23.8 (3.4)	0.25	24 (3.5)	23.5 (3.1)	0.04
Blood type						
A	118 (43)	390 (42)	0.28	161 (43)	257 (42)	0.75
B	25 (9)	104 (11)		35 (9)	69 (11)	
O	122 (45)	383 (41)		163 (43)	258 (42)	
AB	9 (3)	53 (6)		18 (5)	34 (6)	
Cause of death						
Trauma	78 (29)	378 (41)	0.001	128 (34)	255 (41)	0.004
Stroke	146 (53)	385 (41)		191 (51)	247 (40)	
Other	50 (18)	167 (18)		58 (15)	116 (19)	
CPR	35 (13)	151 (16)	0.16	49 (13)	100 (16)	0.17
Catecholamine	171 (62)	594 (64)	0.67	241 (64)	458 (74)	0.001
Donor-recipient mismatch						
Gender						
MD to FR	10 (4)	44 (5)	0.29	16 (4)	31 (5)	0.69
FD to MR	115 (42)	344 (37)		153 (41)	236 (38)	
Non-identical blood type	19 (7)	52 (6)	0.41	23 (6)	36 (6)	0.86
Body mass index ratio						
< 0.8	25 (9)	54 (6)	0.06	30 (8)	34 (6)	0.17
> 1.2	44 (16)	125 (13)		55 (15)	77 (13)	
Operative data						
Ischemic time (minutes)*	198.8 (41.3)	193 (40.7)	0.04	198.7 (40.9)	190.9 (42.7)	0.004
CPB time (minutes)*	123.9 (57.1)	110.5 (42)	< 0.001	119.4 (53.9)	105.2 (42.3)	< 0.001

CPB: cardiopulmonary bypass, CPR: cardiopulmonary resuscitation, FD: female donor, FR: female recipient, MD: male donor, MR: male recipient.
Values are count (%) unless otherwise indicated. * Mean (± SD). † Median (IQR).

We started the multivariable modeling for the 1- and the 5-year mortality risk with each 15 variables with a univariable *p*-value ≤ 0.25. Table 2 presents the estimates of the predictors in the final prediction model after backward stepwise selection, i.e. recipient age and gender, transplant status, donor age, donor-recipient mismatch for body mass index, and cardiopulmonary bypass time for the 1-year model; and recipient age and gender, transplant status, donor age, need of catecholamine in donor, and cardiopulmonary bypass time for the 5-year model.

Table 2. Multivariable association of the predictors in the final prediction model for the 1- and the 5-year mortality risk after adult heart transplantation.

	1-year mortality			5-years mortality		
Variable	B	SE	OR (95% CI)	B	SE	OR (95% CI)
Recipient age (years)	0.02	0.01	1.02 (1.01 - 1.04)	0.02	0.07	1.02 (1.01 - 1.03)
Female recipient	0.34	0.19	1.41 (0.96 - 2.05)	0.39	0.19	1.47 (1.02 - 2.12)
High-urgency status	-0.97	0.32	0.38 (0.21 - 0.71)	-0.64	0.26	0.53 (0.32 - 0.88)
Donor age (years)	0.02	0.01	1.02 (1.01 - 1.03)	0.02	0.01	1.02 (1.01 - 1.03)
Catecholamine in donor				-0,41	0.15	0.67 (0.51 - 0.89)
Donor-recipient BMI ratio						
< 0.8 (undermatch)	0.59	0.27	1.81 (1.07 - 3.07)			
> 1.2 (overmatch)	0.19	0.21	1.21 (0.81 - 1.79)			
CPB time (per 15 minutes)	0.11	0.02	1.11 (1.05 - 1.14)	0.11	0.02	1.11 (1.05 - 1.14)

B: beta, BMI: body mass index, CPB: cardiopulmonary bypass, SE: standard errors, OR: odds ratio, CI: confidence interval.

The resulting multivariable prediction model yielded a ROC area of 0.67 (95% CI: 0.63 - 0.71) and Hosmer-Lemeshow *p*-value of 0.21 for the 1-year model, and a ROC area of 0.66 (95% CI: 0.63 - 0.69) and Hosmer-Lemeshow *p*-value of 0.89 for the 5-year model (Figure 1).

From the bootstrapping procedure, a shrinkage factor of 0.78 and 0.82 was obtained for prediction model of the 1- and the 5-year mortality risk, respectively. The corrected ROC area for the prediction model of the 1- and the 5-year mortality after heart transplantation was 0.64 and 0.65, respectively, showing fair discrimination.

Figure 2 shows the calibration of the resulting prediction models. For prediction model of the 1-year mortality risk, the plotted points were rather close to the ideal agreement line, demonstrating good calibration. Note that for mortality probabilities below 20%, the predicted mortality probabilities were slightly too high (Figure 2a). The prediction model for the 5-year mortality risk showed systematically too high predicted mortality probabilities (Figure 2b).

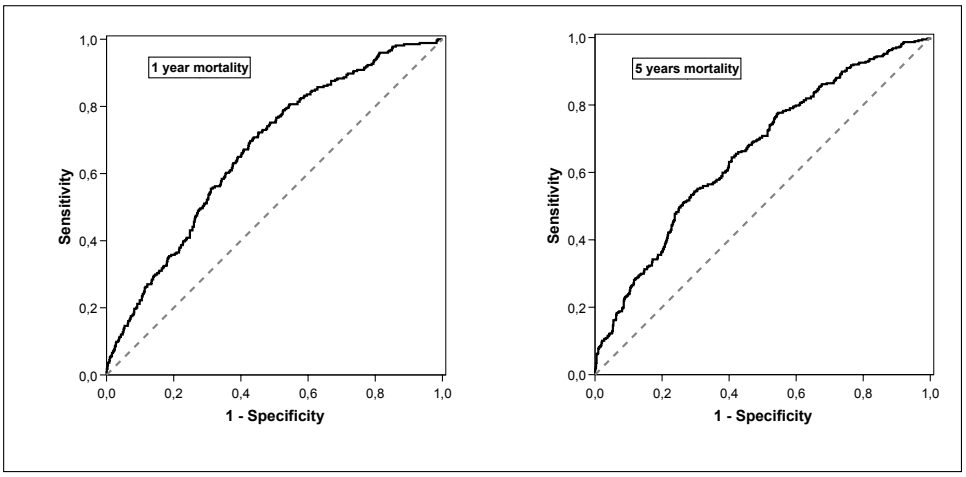

Figure 1. Discriminative ability of the final model for prediction of the 1- and the 5-years mortality risk after adult heart transplantation. The area under the receiver operator characteristic curve (ROC area) was 0.67 (for the 1-year model) and 0.66 (for the 5-year model), which reflects a fair discrimination.

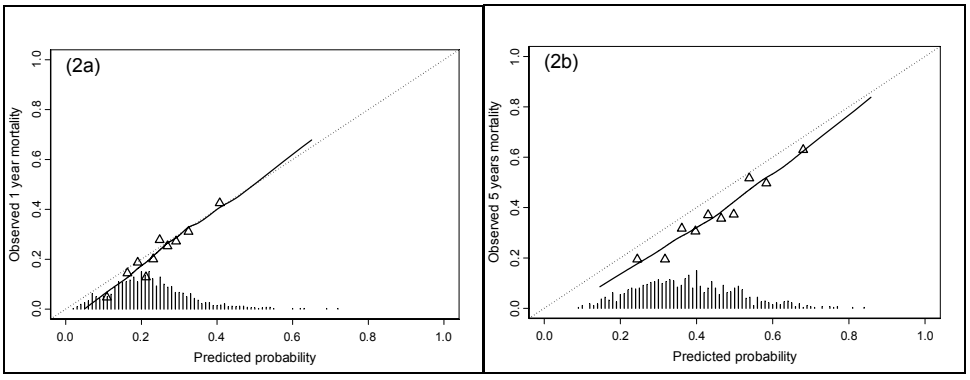

Figure 2. Calibration plot showing the observed mortality versus the predicted probability of the 1-year mortality (2a) and the 5-years mortality (2b) after adult heart transplantation. The solid line demonstrates the correlation between the predicted probability and the observed mortality. Ideally, this line fits the diagonal dotted line that represents perfect calibration. Triangles indicate the observed mortality risk per equal-size-deciles of predicted probability of mortality. Distribution of the predicted probabilities is indicated with vertical lines at the bottom.

Figure 3 and 4 shows the normograms for predicting the 1- and the 5-year mortality risk after adult heart transplantation. As an example how to use the nomogram, a 50-year old male recipient, who was transplanted in high-urgency

status, receive a heart from a 35-years old donor who required catecholamine and with donor-recipient body mass index < 0.8 (undermatch) after an operation with cardiopulmonary bypass time of 2 hours, had total a point of 89 (25+0+0+20+22+22) which corresponded to a predicted probability of the 1-year mortality of 0.16. The same patient had a total point of 66 (24+0+0+20+0+22) which corresponded to a predicted probability of the 5-year mortality of 0.2.

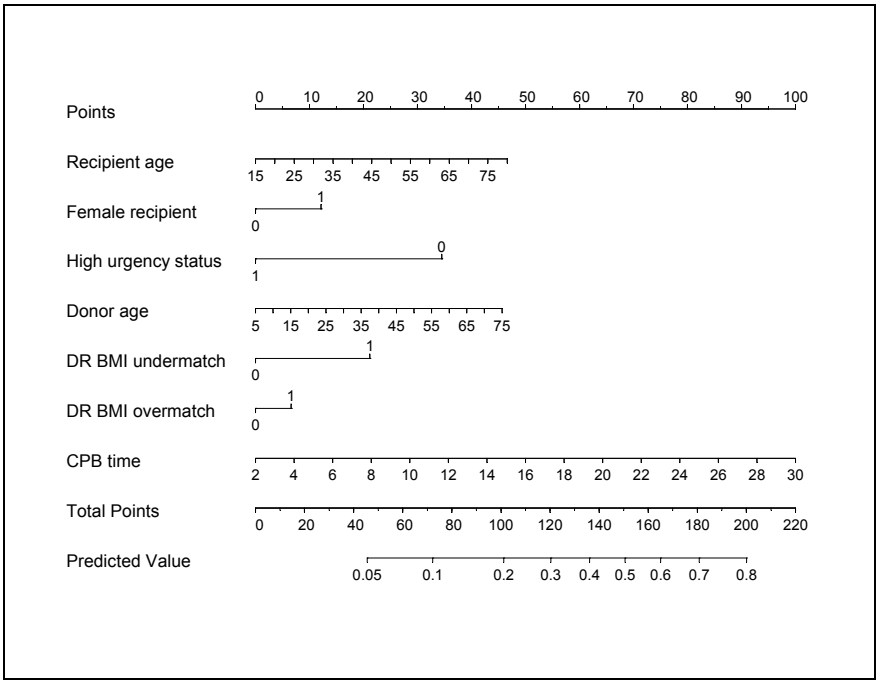

Figure 3. Nomogram for manual calculation of the predicted probability of the 1-year mortality risk after adult heart transplantation. Each predictor has a reference line for reading scoring points (default range 0-100). DR BMI undermatch means donor-recipient body mass index ratio < 0.8. DR BMI overmatch means donor-recipient body mass index > 1.2. CPB (cardiopulmonary bypass) time represents every 15 minutes. Once the reader manually totals the points, the predicted probabilities can be read at the bottom.

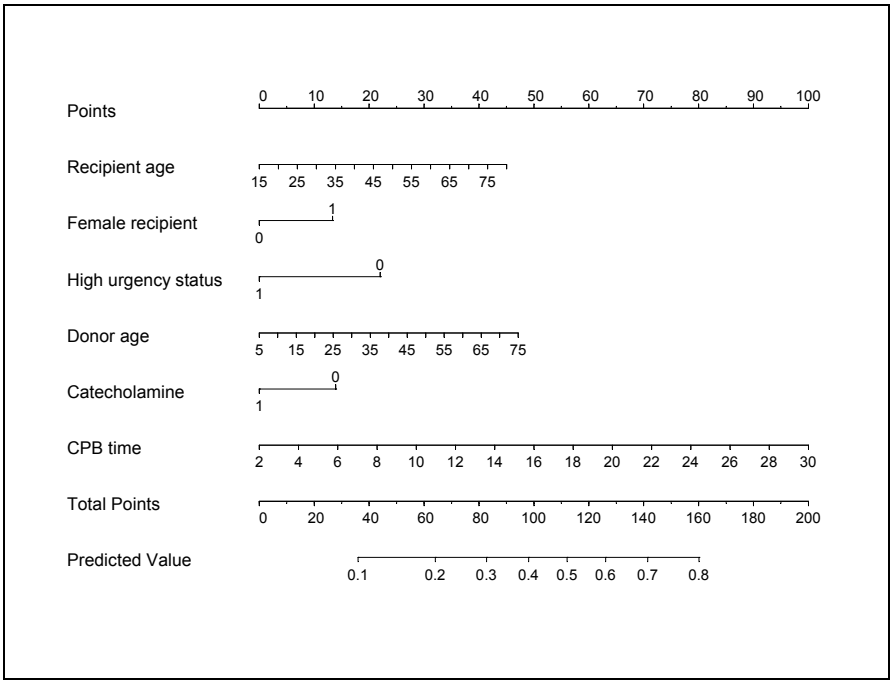

Figure 4. Nomogram for manual calculation of the predicted probability of the 5-year mortality risk after adult heart transplantation. Each predictor has a reference line for reading scoring points (default range 0-100). CPB (cardiopulmonary bypass) time represents every 15 minutes. Once the reader manually totals the points, the predicted probabilities can be read at the bottom.

DISCUSSION

In this study, we have shown that the 1- and the 5-year mortality risk after adult heart transplantation can be predicted with reasonable accuracy by using pretransplant characteristics of recipient and donor, as well as perioperative data. Simultaneously, we have developed user-friendly nomograms that can help heart transplant team to estimate the 1- and the 5-year mortality risk after adult heart transplantation. The pretransplant variables that had a significant influence on outcome after adult heart transplantation were recipient age and gender, transplant status, donor age, donor-recipient mismatch for body mass index, and cardiopulmonary bypass time for the 1-year model; and recipient age and gender, transplant status, donor age, need of catecholamine in donor, and cardiopulmonary bypass time for the 5-year model. All of these predictors are commonly available and easily obtainable pre- or perioperatively.

Some relatively small studies that attempted to predict survival with multivariable regression models with mixed results used both recipient and donor

characteristics to determine mortality risk after heart transplantation (8-10). However, we believe that our study is the most comprehensive one. We have developed and validated our model using a very large single-center data set and converted the prediction models to nomograms which are convenient and easily use in clinical practice.

The calibration plot for the 1-year model showed that the model was rather well calibrated. But it should be noted that the predicted mortality probabilities below 20% were little bit too high, i.e. resulted in a slight overestimation of mortality risk. After correction for optimism, the ROC area changed from 0.67 to 0.64, which shows fair discrimination between deceased patients and survivors at 1-year after adult heart transplantation. The prediction model for the 5-year mortality risk shows rather too high predicted probabilities over the full range, resulting in overestimation of the mortality risk. The ROC area changed from 0.66 to 0.65, which shows fair discrimination between deceased patients and survivors at 5-year after adult heart transplantation. These findings might be explained by other patient's characteristics, e.g. postoperative characteristics, which were not documented in our database, but may to some extent have influenced the intercept of the model. Despite the relative robustness of our results, the implementation of our models in clinical practice should be treated with caution. A prediction model should be used as a decision-support system. It can not replace clinical judgment (11).

In conclusion, we have developed and validated prediction models for the 1- and the 5-year mortality risk after adult heart transplantation by using simple predictors which are generally available in the clinical setting. We believe that our normograms can be used for matching donor to recipient in an optimal way. Such normograms may help a heart transplant team to estimate mortality risk for potential heart transplant recipients and their relatives objectively. Moreover, information on mortality risk may be useful for heart transplant center to internally assess their own programs and compare their outcome to others. Nevertheless, it is important to externally validate our prediction models in a new population before they could be widely applied with confidence.

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Chapter 9

General discussion

The clinical practice of heart transplantation has evolved over time. Initially, recipient and donor selection criteria were developed to minimize the morbidity and mortality after heart transplantation. Unfortunately, the number of donor hearts has not kept pace with the demand from the heart transplant waiting lists. In the USA, 3,011 new patients were added between July 2006 and June 2007 to the already existing 2,878 patients on the heart transplant waiting list while only 2,232 heart transplants were performed. The mortality risk per year on the transplant waiting list is reported as high as 15% (1). Overtime, older and sicker patients have been referred for heart transplantation. Co-morbidity is known to increase the mortality risk after adult heart transplantation. Proper selection of potential recipients and careful expansion of donor pool is considered crucial issue for achieving an overall success after adult heart transplantation (2). Accurate preoperative estimation of mortality risk after adult heart transplantation may support decision on allocation of the limited number of donor hearts to patients waiting for heart transplantation in the most optimal manner. It may also provide objective information to patients or their families, support heart transplant teams and surgeons to classify patients according to their mortality risk.

In subsequent chapters of this thesis, we have examined the impact of changes in baseline risk profiles at different transplant period, pretransplant diagnosis, recipient age, donor sodium level, and cardiopulmonary resuscitation in donors on outcome after adult heart transplantation. Finally, we have developed and validated models for predicting the 30-day as well as the 1- and the 5-year mortality risk after adult heart transplantation. In this chapter, the major findings of the above studies are discussed in a broader perspective. The strengths and limitations of our studies, implications for practice and future research, as well as main conclusions and recommendations are outlined.

CHANGING BASELINE RISK PROFILES OVER TIME

Only few studies (3-6) exist in the literature outlining experience with heart transplantation addressing the impact of changed baseline risk profiles on outcome after heart transplantation. Our study in **chapter 2** demonstrated that 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 adult heart transplantation. Simultaneously, older donors were more frequently used. In particular, there was a gradual increase in ischemic time, and in the acceptance of donors despite the body mass index mismatch. Our results reflect the generally recognized trends toward liberalization of recipient criteria and expansion of the donor pool (3, 7-9). We found that despite of these changes, the early and late survival remained stable and encouraging, presumably due to significant improvements in clinical management, including pretransplant medical therapy,

timing and route of hemodynamic support, myocardial protection, steady progress in surgical experiences, perioperative intensive care, and immunosuppression protocol.

The major causes of deaths were: acute rejection, multiorgan failure, and right heart failure (≤ 30 days); infection and acute rejection (31 days - 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 period (p = 0.68).

SELECTION OF POTENTIAL RECIPIENTS

Heart transplantation for end-stage valvular disease accounts for only 3% of cases in the Registry of the International Society for Heart and Lung Transplantation (10). The immediate and long-term results are not very well documented (11-14). Most of patients transplanted for end-stage valvular heart disease have had previous cardiac surgery and frequently increased pulmonary vascular resistance which have been considered as risk factors for heart transplantation (15). Similar to recent study (14), our study in **chapter 3** found that prognosis after adult heart transplantation for end-stage valvular disease was similar to that for other indications. Early mortality appeared to be somewhat increased, but not statistically significant, whereas a longer waiting time to heart transplantation significantly improved survival (HR = 0.998, 95% CI: 0.996 - 0.999). Advances in medical and surgical treatment of heart failure, including different mechanical circulatory supports can stabilize and keep the end-stage heart failure patients on the waiting list for a much longer time than before. Ventricular assist device is used to decrease pulmonary vascular resistance which commonly seen in end-stage valvular heart disease, and also for bridging patients to heart transplantation with a more suitable donor heart. Our finding supports the fact that watchful waiting is not deleterious in the final outcome after heart transplantation (16). A careful balance of risks and survival benefit is of major importance.

The increasing shortage of donor hearts in relation to the number of patients waiting for heart transplantation necessitates allocating organs to recipients with the greatest need and highest chance to derive the maximum benefit. The most common recipient-dependent risk factors for mortality after heart transplantation are: pulmonary vascular resistance > 3 Wood units, mechanical circulatory support (either left ventricular assist device or intraaortic balloon pump), advanced recipient age, female recipient, increased serum creatinine concentration, ischemic cardiomyopathy, previous sternotomy, and liver failure (10, 17-23). Among them, advanced recipient age, pulmonary vascular hypertension, and patients who are dependent on mechanical circulatory support are widely identified risk factors. In large multi-center studies (24, 25), advanced recipient age (defined as age ≥ 55 years) was associated with increased mortality risk after adult heart transplantation. However, a variety of single-center studies (23, 26-31) suggest that recipient age (in

carefully selected patients) does not adversely impact survival. In contrast, Borkon et al. (18) demonstrated that recipients older than 55 years had poorer survival than those younger than 55 years. Although older recipients are typically considered high-risk for transplantation because of co-morbid conditions, John et al. (32) hypothesized that age-related changes in immunity may (paradoxically) improve outcome in elderly recipients. Our study in **chapter 4** showed a clear trend for recipient age on the outcome after adult heart transplantation, i.e. older recipients have less favorable outcome than younger recipients; the hazard ratios increased with increasing recipient age. A clear guideline for recipient age is difficult to give. Practice may vary per institution and may hinder consensus about the question of recipient age in selection of adult heart transplant recipient.

EXPANSION OF DONOR POOL

The effort to increase the number of heart transplant procedures has led to liberalizing the standard donor acceptance criteria. This includes accepting sub-optimal or marginal donor hearts (33-36). Recent data indicated that the outcome of heart transplant recipients who received marginal donor hearts is not significantly different from those who received ideal donor hearts. Subsequently, several centers have included the acceptance of older donors, non-beating heart donors, longer ischemic time, donors with systemic infection or those who are hepatitis positive or have prolonged hypotension, undersized hearts, hearts with conduction abnormalities, hearts after cardiopulmonary resuscitation and with an increased sodium level, high-dose intravenous catecholamine, moderately depressed left ventricular function, and donors supported by cardiopulmonary bypass (37-40).

While intracellular sodium concentration contributes to reperfusion injury, donor hypernatremia is considered to cause myocardial stunning leading to higher incidence of primary graft failure after heart transplantation (41). Therefore, donor sodium levels exceeding 150 mmol/l are believed to be associated with adverse outcome after adult heart transplantation. Hoefer et al. (42) suggested that donor sodium level exceeding 170 mmol/L increased the mortality risk after adult heart transplantation. But recently, it was shown that donor sodium level has no impact on outcome after adult heart transplantation (38, 39, 43). Similarly, our study in **chapter 5** found that heart transplantation from donors with sodium level > 155 mmol/L could be performed successfully without adversely affecting early and long-term results. Although donor hypernatremia might be considered as an epiphenomenon of brain death and it may serve as an indicator of sub-optimal donor management with the need for careful donor examination, it does not contribute to adverse outcome. Refusal of such grafts is therefore not considered as justified.

In general, heart transplant teams and surgeons are reluctant to accept a heart from donor undergoing cardiopulmonary resuscitation (CPR) because they fear of poor early and late cardiac function resulting from myocardial injury (34). In

contrast, some studies (44-46) have demonstrated a reversible myocardial contractile failure following successful CPR. Our results in **chapter 6** demonstrated that the outcome after adult heart transplantation, either 30-day mortality risk or overall survival was similar when hearts are used from donors with and without CPR. On the one hand, myocardial damage following CPR may increase the incidence of donor organ dysfunction immediately following heart transplantation; on the other hand, CPR during the initial donor management will maintain the beating of the heart at an cardiac output of 25% to 50% (47, 48). Thereby, CPR may prepare the heart mechanically to resume circulation by decompressing the right ventricle and filling the left ventricle and coronary arteries (49). Hence, CPR is considered to simultaneously limit ischemia and reduce ischemia-reperfusion injury. Given the limited number of donors and the increasing number of patients on the waiting list, it may be prudent to re-evaluate the current standard recommendations for accepting donor hearts. By liberalizing the donor criteria, it may be possible to expand the donor pool without influencing the outcome after adult heart transplantation. Meanwhile, assessing other possibilities to increase donor availability is warranted.

PREDICTION MODELS FOR MORTALITY RISK

A careful developed and validated prediction model may assist heart transplant team to estimate the posttransplant mortality risk. To date, however, comprehensive models for predicting early and late mortality after heart transplantation are lacking. In developing the prediction models for mortality risk, we used a hierarchical approach in building multivariable models that follow routine practice as close as possible. The predictive accuracy of our final models was quantified by using calibration and discrimination measures. To prevent over-testing and correct for over-optimism of the resulting prediction models, we used a bootstrap approach to estimate a 'shrinkage factor' (between 0 and 1). This technique has shown its superiority compared to other techniques (50). With bootstrapping techniques all data is used to develop and validate a prediction model, obviously yielding better and more precise estimates of the predictor's odds ratios and the model's ROC area.

Our prediction models are easily applicable in clinical practice since they comprise predictors which are commonly available and easily obtainable pre- or perioperatively for most heart transplant patients. We showed in **chapter 7** that recipient age and gender, pretransplant diagnosis, transplant status, waiting time, donor age and gender, donor-recipient mismatch for body mass index and blood type, and cardiopulmonary bypass time were the independent predictors for the 30-day mortality risk after adult heart transplantation. Our prediction model can accurately predict the 30-day mortality risk after adult heart transplantation. The ROC area of 0.74 demonstrates relatively strong discriminatory ability. The calibration plot shows that the predicted probability categories are close to the ideal line. This

indicates that in general the model is rather well calibrated over the complete range of predicted probabilities. After correction for optimism, the ROC area was 0.71, which implies good discrimination between deceased patients and survivors at 30-day after adult heart transplantation. After bootstrapping, we obtained a correction factor of 0.81, which implies only limited over-optimism and so marginal adjustment was needed.

Furthermore, we demontrated in **chapter 8** that the 1- and the 5-year mortality risk after adult heart transplantation could be predicted with reasonable accuracy based on pretransplant characteristics of recipient and donor as well as perioperative data. The pretransplant variables that had a significant influence on the posttransplant outcome were recipient age and gender, transplant status, donor age, donor-recipient mismatch for body mass index, and cardiopulmonary bypass time for the 1-year model; and recipient age and gender, transplant status, donor age, need of catecholamine in donor, and cardiopulmonary bypass time for the 5-year model. The calibration plot for the 1-year model shows that predicted mortality probabilities below 20% are slightly too high. But in general the model is rather well calibrated. After correction for optimism, the ROC area changed from 0.67 to 0.64, which shows fair discrimination between deceased patients and survivors at 1-year after adult heart transplantation. The prediction model for the 5-year mortality risk shows rather too high predicted over the full range, resulting in overestimation of the mortality risk. The ROC area changed from 0.66 to 0.65, which shows fair discrimination between deceased patients and survivors at 5-years after adult heart transplantation. These findings might be explained by other patient characteristics, e.g. postoperative characteristics, which were not documented in our database, but may to some extent have influenced the intercept of the model.

Our prediction models may be used together with data on the expected mortality on the transplant waiting list to determine whether or not a heart should be used for transplantation, or to form the basis for future discussions on expanding donor criteria in addressing the imbalance between organ supply and demand in heart transplantation. In addition, our prediction models may be used by heart transplant team to stratify heart transplantation into high risk (lower graft survival and higher risk of posttransplant complications) and low risk (higher graft survival and lower risk of posttransplant complications). Finally, these prediction models may be used in the future to inform potential heart transplant recipients and their relatives objectively. In particular, given the limited availability of donor hearts, they may be helpful for matching donor to recipient and to assist in decision on optimal allocation of a donor heart to a patient waiting for heart transplantation.

STRENGTHS AND LIMITATIONS OF THE STUDIES

Our studies harbour certain strengths. Being large single-center studies, inherent inconsistencies in management and reporting can be avoided. In addition, the data are of high quality. Variables were clearly defined. Follow-up for a period of nearly 16 years was 100% complete and no one was lost of follow-up. However, we obtained clinical data by means of electronic database review which has inherent limitations such as access and accuracy of the data. Our studies include only the pre- and perioperative variables which are available on our database. It is possible that other additional important factors that are not recorded in our database may to some extent influence the outcome after adult heart transplantation. Moreover, it is likely that the perceived quality of a potential donor may influence the decision on who the recipient of that donor heart will be. For instance, recipients who are very sick may, if there is choice, be given a higher-quality donor heart to improve their otherwise low posttransplant survival. Alternatively, it is possible that hearts from donors who are considered high-risk or marginal will be transplanted in recipients who are very sick and cannot wait any longer for a better heart to become available. Otherwise, a marginal donor heart may perhaps be used only in a relatively healthy recipient. These considerations suggest that there is a high dependence of recipient and donor characteristics in decision on heart transplantation. The results of our studies contribute to disentangling the dependency of donor and recipient characteristics.

The strength of our prediction models is the possibility to calculate an absolute risk at individual patient level. Still, limitations of such models for the prediction of an individual patient outcome must be considered (50), for example, the precision of a model for predicting outcome is greatest in the average patients (51). Despite the relative robustness of our results, the implementation of our models in clinical practice should be treated with caution. A prediction model should be used as a decision-support system. It can not replace clinical judgment (52).

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

Analyzing recipient and donor characteristics that may influence the outcome after adult heart transplantation is important to optimally utilize the limited resources in heart transplantation. With an increased need and a limited number of donor hearts, our prediction models may assist decision on donor heart allocation to those patients that are likely to benefit most from heart transplantation (16, 53). Moreover, the use of our comprehensive and easily applicable prediction models in clinical decision making on donor hearts allocation may maximize recipient benefits. Our prediction models may be helpful to the heart transplant team when taking a decision on patient requiring heart transplantation (54). Our prediction models may be transformed into an electronic version which could be programmed in a PC or PDA to calculate the mortality risk after adult heart transplantation. This may improve the

clinical usefulness of our prediction models. Therefore, an important objective for future research is to study which patient risk categories benefit most from heart transplantation. Validation of our models in an independent cohort as well as prospective analysis of patients undergoing adult heart transplantation is an important next step in evaluating the robustness of our prediction models.

CONCLUSIONS AND RECOMMENDATIONS

The studies presented in this thesis indicate that careful selection of recipient and considerable expansion of donor criteria are crucial factors to achieve an optimal outcome after adult heart transplantation. The mortality risk after adult heart transplantation can be predicted accurately by using pretransplant characteristics of recipient and donor, as well as perioperative data.

The main conclusions and recommendations of this thesis are:

- Despite increased baseline risk profiles over time, the outcome after adult heart transplantation remains stable and encouraging.
- The outcome of adult heart transplantation for end-stage valvular heart disease is similar to that for other indications. Apparently, the longer the waiting time to heart transplantation the better the outcome becomes.
- The outcome of heart transplantation in older recipients is less favorable than in younger recipients. The decision to offer heart transplantation to recipients older than 55 years should be considered cautiously.
- Donor sodium level has no major impact on the mortality risk after adult heart transplantation. Organ shortage could be reduced when refusal of donor hearts based on high donor sodium level is abandoned. We suggest adjusting for recipient and donor heart selection accordingly.
- Using donor hearts that have been subject to CPR does not adversely affect the outcome after adult heart transplantation. Accepting such donor hearts will add to the enlargement of the donor pool. We suggest adjusting for recipient and donor heart selection accordingly.
- Our prediction models provide easily applicable instruments for predicting the 30-day, the 1-year, and the 5-year mortality risk after adult heart transplantation. Our prediction models can be used in clinical practice to assist a heart transplant team to estimate mortality risk for potential heart transplant recipients and their relatives objectively, for matching donor to recipient in an optimal way, to assist decision on optimal allocation of a donor heart to a patient waiting for heart transplantation, and to compare outcome among centers.
- It is important to externally validate our prediction models in a new population before they are widely applied.

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Summary

Heart transplantation has become the treatment of choice for patients with end-stage heart diseases. Originally, strict recipient and donor selection criteria were developed to minimize morbidity and mortality after heart transplantation. However, the increasing demand for heart transplantation has led to the liberalization of the traditional recipient selection criteria. There has been a gradual increase of recipient age. Patients at poor health status, e.g. pretransplant diagnosis of end-stage valvular heart disease and older recipients, are more likely to have a higher morbidity and mortality due to co-existing medical problems. The increased gap between the demand and supply of donor hearts results in significant prolonged waiting time and an increased mortality of recipients on the waiting list. To increase donor supply, acceptance criteria of donor hearts have been expanded to include the sub-optimal or marginal donor hearts. Nevertheless, the impact of these trends on the outcome of heart transplantation, in particular on long term, remains uncertain. Heart transplantation should be reserved for those patients most likely to benefit in terms of survival. To enable predicting the outcome for individual patient based on recipient and donor characteristics, and their match, a prediction model may play a crucial role in selection of a donor heart to a specific recipient.

The focus of this thesis is on the impact of various recipient and donor baseline characteristics on the outcome after adult heart transplantation. This thesis also includes several models that have been developed and validated to predict mortality risk after adult heart transplantation.

The clinical profiles of recipients and donors eligible for heart transplantation as well as the procedure itself have changed over time. In **chapter 2**, we determined the impact of changes in baseline risk profiles at subsequent transplant periods on outcome, and the time-specific distribution of causes of death after adult heart transplantation. We found statistically significant and clinically relevant changes in recipient characteristics prior to transplantation, notably higher age and increased body mass index, more previous cardiac surgery, high-urgency transplant status, prolonged waiting time to transplantation, and more often with ventricular assist device. Simultaneously, hearts from older donors were more frequently used. In addition, there was an increase in the proportion of body mass index mismatch and in ischemia time. We demonstrated that despite of these changes, the early and late survival remains stable and encouraging. 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 period (p = 0.68), and the same holds for cause of death. The major causes of death were acute rejection, multiorgan failure and right heart failure (for ≤ 30 days); infection and acute rejection (for 31 days - 1 year); malignancy, acute rejection, and cardiac allograft vasculopathy (for >1 - 5 years); cardiac allograft vasculopathy and malignancy (for >5 - 10 years); and malignancy and infection (for > 10 years).

Heart transplantation for end-stage valvular heart disease has been considered to have a poor prognosis due to having previous cardiac surgery and frequently increased pulmonary vascular resistance. The outcome is, however, not very well documented. In **chapter 3**, we compared the long-term outcome of adult heart transplantation for end-stage valvular heart disease to that for other indications. We showed that prognosis after adult heart transplantation for end-stage valvular heart disease is similar to that for other indications. The survival at 1-, 5-, 10-, and 15-year was respectively 70%, 64%, 56%, and 46% in adult heart transplantation for end-stage valvular heart disease compared to 78%, 68%, 53%, and 41% in that for other indications (p = 0.5). Although with end-stage valvular heart disease early mortality was somewhat increased, this difference was not statistically significant (13% vs. 8%, p = 0.12). However, a statistically significant improvement of survival was seen with a longer waiting time to heart transplantation (HR = 0.998, 95% CI: 0.996 - 0.999).

The shortage of donor hearts stimulates the debate whether heart transplantation is justified for recipients with an elevated pretransplant mortality risk. In view of the results of chapter 2 this in particular concerns older recipients. In **chapter 4**, we studied the effect of recipient age on outcome after adult heart transplantation. We showed a clear trend for recipient age on the outcome of heart transplantation. The 30-day mortality risk was 6% for recipients younger than 55 years, and 10% for recipients 55 years and older (p = 0.005). The advantageous survival for recipients younger than 55 years of age remained statistically significant thereafter: the 1-, 5-, 10-, and 15-year survival was respectively 84%, 75%, 60%, and 50% for recipients younger than 55 years, and 73%, 63%, 48%, and 35% for recipients aged 55 years and older (p < 0.001). The hazard ratio increased with increasing recipient age, that is, relative risk increases 25% (adjusted: 21%) for recipient age category of 56 to 65 years, and 58% (adjusted: 40%) for recipient age older than 66 years. We concluded that decision to offer heart transplantation to recipients older than 55 years should be considered cautiously in view of the scarcity of donor hearts.

While intracellular sodium concentration contributes to reperfusion injury, donor hypernatremia is considered to cause myocardial stunning leading to higher incidence of primary graft failure after heart transplantation. But, the impact of donor sodium level on outcome after adult heart transplantation remains disputed. In **chapter 5**, we evaluated whether donor sodium level, in particular exceeding 155 mmol/l, affects the outcome after adult heart transplantation. We found that the 30-day mortality risk after adult heart transplantation is quite similar when using a normo-natremic heart (8.4%) or a hypernatremic donor heart (8.9%, p = 0.77). The same holds for primary graft failure as cause of death (p = 0.57). The adjusted hazard ratio for donor sodium level exceeding 155 mmol/l was 1.05 (95% CI: 0.85 - 1.31). The survival at 1, 5, 10, and 15 years was respectively 79%, 69%, 53%, and

36% with normo-natremic donor hearts; and 75%, 65%, 56%, and 46% with hypernatremic donor hearts (p = 0.76). We concluded that donor sodium level has no major impact on the mortality risk after adult heart transplantation. Organ shortage can be reduced when refusal of donor hearts based on high donor sodium level is abandoned. We suggest adjusting for donor heart selection accordingly.

In general, heart transplant team and surgeons are reluctant to accept a heart from donors undergoing cardiopulmonary resuscitation (CPR), because they fear poor early and late cardiac function resulting from myocardial injury. In **chapter 6**, we analyzed the influence of CPR in donors on outcome after adult heart transplantation. We found a very small and statistically non-significant difference in the 30-day mortality risk after adult heart transplantation when using donor hearts with CPR (8.3%) or without CPR (8.5%, p = 0.94). The overall survival at 1, 5, 10, and 15 years was respectively 81%, 73%, 54%, and 21% for CPR group; and 77%, 67%, 54%, and 43% for without CPR group (p = 0.55). This very small statistically non-significant difference remained after adjustment for differences between the groups in donor age, body mass index, cause of death, need of catecholamine, and cardiac enzymes. We concluded that using donor hearts that have been subject to CPR did not have large impact on the outcome after adult heart transplantation. Accepting such donor hearts will add to the enlargement of the donor pool. We suggest adjusting for donor heart selection accordingly.

A comprehensive prediction model that provides information on survival after heart transplantation to patients and their families may also help the heart transplant team to classify patients according to their mortality risk. Such models can be used to assist clinical decision-making. In **chapter 7**, we developed and validated an easily applicable prediction model for the 30-day mortality risk after adult heart transplantation. We showed that recipient age and gender, pretransplant diagnosis, transplant status, waiting time, donor age and gender, donor-recipient mismatch for body mass index and blood type, and cardiopulmonary bypass time were accurate independent predictors for the 30-day mortality risk after adult heart transplantation. Our prediction model accurately predicted the 30-day mortality risk after adult heart transplantation. The calibration plot showed that the predicted probability categories were close to the ideal line. Hence, our model was rather well calibrated over the complete range of predicted probabilities. After correction for optimism, the area under the receiver operating characteristic curve (ROC area) changed from 0.74 to 0.71, which showed good discrimination between deceased patients and survivors at 30-day after adult heart transplantation. To facilitate the application of our prediction model in practice, the model was converted to a nomogram. Our prediction model can be used in clinical decision-making, in particular in matching donor to recipient, that is, given the limited availability of donor hearts, assist in decision on optimal allocation of a donor heart to a patient waiting for heart transplantation.

Given the limited number of donors and the growing number of patients waiting for heart transplantation, a clinical model that can accurately predict mortality after heart transplantation at longer term can be of crucial concern for the community and in health care. In **chapter 8**, we used pretransplant characteristics of recipients and donors as well as perioperative data to develop models that could predict the 1- and the 5-year mortality risk after adult heart transplantation. We found that the pretransplant variables that had a significant influence on mortality after adult heart transplantation were recipient age and gender, transplant status, donor age, donor-recipient mismatch for body mass index, and cardiopulmonary bypass time for the 1-year model. Recipient age and gender, transplant status, donor age, need of catecholamine in donor, and cardiopulmonary bypass time had a significant influence on mortality of adult heart transplantation for the 5-year model. The calibration plot for the 1-year model showed that the model was rather well calibrated. But it should be noted that the predicted mortality probabilities below 20% were little bit too high, i.e. resulted in a slight overestimation of mortality risk. Consequently, the model showed fair discrimination between deceased patients and survivors at 1-year after adult heart transplantation; the area under the ROC curve was 0.67, and after correction for optimism it was 0.64. The 5-year model provided too high predicted over the full range, resulting in overestimation of the mortality risk. Consequently, the model showed fair discrimination between deceased patients and survivors at 5-year after adult heart transplantation; the area under the ROC curve was 0.66, and after correction for optimism it was 0.65. The prediction models were converted to easy to use nomograms to enhance their application. The nomograms can be used in clinical practice for matching donor to recipient in an optimal way. Such nomograms may assist a heart transplant team to estimate mortality risk for potential heart transplant recipients and their relatives objectively.

Lastly, the major findings of the above studies were discussed in a broader perspective in **chapter 9**. It outlined the strengths and limitations of the studies, implications for practice and future research, as well as general conclusions and recommendations. The studies presented in this thesis indicate that careful selection of recipients and considerable expansion of donor criteria are crucial factors to achieve an optimal outcome after adult heart transplantation. The mortality risk after adult heart transplantation can be predicted accurately by using pretransplant characteristics of recipient and donor, as well as perioperative data. However, external validation of our models is an important next step in evaluating their robustness.

Everything should be as simple as possible, but not simpler

• Albert Einstein, 1879 – 1955 •

Samenvatting

(Summary in Ducth)

Het voorspellen van de uitkomst van harttransplantatie

Harttransplantatie is de behandeling van voorkeur voor patiënten met eindstadium van chronisch hartfalen. Aanvankelijk werden, met het oog op beperking van morbiditeit en mortaliteit, strikte criteria gebruikt bij de selectie van donoren en ontvangers. Echter door de toename in aantal kandidaten voor harttransplantatie worden deze selectie criteria steeds vaker meer pragmatisch gehanteerd; in het bijzonder de leeftijd van patiënten die een harttransplantatie ondergaan is geleidelijk toegenomen. Echter, bij een mindere algemene gezondheidssituatie, bijvoorbeeld op oudere leeftijd, bij het eindstadium bij hartklepziekten, of co-existente ziekten is het risico op morbiditeit en mortaliteit na harttransplantatie toegenomen. Tegelijkertijd is door een toename in de vraag en het beperkte aanbod van donor harten is de gemiddelde wachttijd tot transplantatie toegenomen, waarbij de mortaliteit van patiënten op de wachtlijst is gestegen. Vanwege de toegenomen vraag zijn de acceptatie criteria voor donorharten uitgebreid dan wel meer pragmatisch gehanteerd, waardoor steeds vaker marginaal geschikte donor harten worden geaccepteerd. Maar de impact van de liberalisatie van de selectiecriteria voor kandidaten voor harttransplantatie en acceptatie van donor harten op de uitkomsten van harttransplantatie is onduidelijk.

Vanwege de ingrijpendheid ervan, dient harttransplantatie voorbehouden te worden aan patiënten, waarvoor de grootste baat verwacht mag worden in termen van reductie van morbiditeit en mortaliteit. De individuele kenmerken van de donor en de ontvanger, en de match daarvan, spelen een belangrijke rol bij de accurate voorspelling van morbiditeit en mortaliteit.

In dit proefschrift wordt de impact bestudeerd van diverse individuele kenmerken van de donor en de ontvanger, en de match daarvan, op de uitkomst van harttransplantatie bij volwassenen. Dit proefschrift bevat ook enkele ontwikkelde en gevalideerde voorspelmodellen voor de mortaliteit na harttransplantatie bij volwassenen.

Niet alleen de klinische kenmerken van donoren en ontvangers, maar ook de procedures van harttransplantatie zijn sinds de introductie gewijzigd en verbetert. In **hoofdstuk 2** hebben we de impact van de veranderingen in de klinische kenmerken van donoren en ontvangers en de verdeling van de doodsoorzaken bepaald voor opeenvolgende tijdsperioden van harttransplantatie. We vonden statistisch significante en klinisch relevante veranderingen in de pretransplantatie profielen van ontvangers, in het bijzonder toename van de leeftijd en body mass index, meer voorafgaande cardiochirurgische ingrepen, hogere urgentie bij indicatie, langere wachttijd tot transplantatie, en groter aantal patiënten met een ventriculair assist device. Tegelijkertijd nam de leeftijd van de donoren van getransplanteerde harten toe, nam de donor-ontvanger mismatch toe aangaande body mass index, en nam de ischaemie tijd tijdens transplantatie toe. Ondanks deze veranderingen bleven de vroege en late posttransplantatie sterfte cijfers stabiel. De kans op overleving van 1-, 5-, 10-, en 15 jaar was 77%, 67%, 53%, and 42%. Daarbij bestond er tussen de

opeenvolgende perioden geen verschil in de doodsoorzaken of de mortaliteit (p = 0.68). De belangrijkste doodsoorzaken binnen 30 dagen na transplantatie waren acute afstoting, multiorgaan falen en rechtszijdig hartfalen; tussen 30 dagen en 1 jaar waren dat acute afstoting en infecties; tussen 1 en 5 jaar waren dat acute afstoting, maligniteiten en cardiale allograft vasculopathy; tussen 5 en 10 jaar maligniteiten en cardiale allograft vasculopathy; en na 10 jaar maligniteiten en infecties.

De prognose na harttransplantatie bij patiënten in het eind-stadium van hartfalen door een gebrek van een hartklep wordt doorgaans ongunstig verondersteld wegens eerdere cardiochirurgie en toegenomen pulmonale vaatweerstand. De uitkomst van harttransplantatie bij patiënten is echter niet goed beschreven. In **hoofdstuk 3** vergelijken we de mortaliteit van deze patiënten op lange termijn met die van patiënten na harttransplantatie om een andere reden. Daaruit blijkt dat de mortaliteit na harttransplantatie bij beide groepen patiënten redelijke vergelijkbaar is (13% vs. 8%, p = 0.12). De overlevingskansen op 1, 5, 10, en 15 jaar na transplantatie bij patiënten in het eind-stadium van hartfalen door een gebrek van een hartklep bedroeg 70%, 64%, 56%, en 46% en in de overige patiënten bedroeg de overleving 78%, 68%, 53%, en 41% (p = 0.5). Geen van de gevonden verschillen was statistisch significant. Uit de analyse van de gecorrigeerde overlevingkans na harttransplantatie bij patiënten in het eind-stadium van hartfalen door een gebrek van een hartklep bleek deze toe te nemen naarmate de wachttijd tot harttransplantatie toenam (HR = 0.998, 95% CI: 0.996 - 0.999).

Door het tekort aan donor harten blijft de keuze van de juiste kandidaten voor harttransplantatie, in het bijzonder met het oog op rechtvaardiging aan de hand van overlevingskansen, een cruciaal onderwerp van debat. Uit hoofdstuk 2 bleek een stijging van de mortaliteit bij een toename van de leeftijd. Voor **hoofdstuk 4** is onderzocht wat het effect is van de leeftijd van de transplantatie kandidaat op de uitkomst na hart transplantatie bij volwassenen. Daaruit blijkt een duidelijke trend voor leeftijd bij transplantatie als risicofactor voor verhoging van de mortaliteit. De mortaliteit na 30 dagen bedroeg 6% voor patiënten jonger dan 55 jaar, en 10% voor patiënten vanaf 55 jaar (p = 0.005). Het verschil in mortaliteit in het voordeel van patiënten onder de 55 jaar blijft daarna klinisch relevant en statistisch significant: de overlevingskansen 1, 5, 10, en 15 jaar na transplantatie zijn 84%, 75%, 60%, en 50% voor patiënten jonger dan 55 jaar, en 73%, 63%, 48%, en 35% voor patiënten vanaf 55 jaar (p < 0.001). Het relatieve risico voor mortaliteit neemt toe bij een toename van de leeftijd, van 25% (gecorrigeerd: 21%) voor patiënten van 56 tot 65 jaar oud, en 58% (gecorrigeerd: 40%) voor patiënten ouder dan 66 jaar. Bij de keuze van kandidaten voor harttransplantatie van 55 jaar of ouder dient, in verband met de schaarste aan donor harten, rekening gehouden te worden met de lagere overlevingskansen.

Omdat hoge intracellulaire natriumconcentratie reperfusie schade veroorzaakt, kan hypernatremie van het donorhart myocardial schade veroorzaken, en vervolgens

tot primair graft falen van het donorhart leiden. De impact van een natrium spiegel in het donorhart op de uitkomst van hart transplantatie bij volwassenen wordt betwist. Voor **hoofdstuk 5** hebben we de invloed bestudeerd van een verhoogde natriumconcentratie in het donorhart, in het bijzonder boven 155 mmol/l, op de uitkomst van hart transplantatie bij volwassenen. Daarbij bleek dat de mortaliteit 30 dagen na transplantatie van een donorhart met een normale natriumconcentratie (8.4%) niet wezenlijk te verschillen met die van een donorhart met een verhoogde natriumconcentratie (8.9%, p = 0.77). Ook het risico op primair graft falen als doodsoorzaak was voor beide groepen gelijk (p = 0.57). Het gecorrigeerde risico ratio voor mortaliteit met een natriumconcentratie boven 155 mmol/l was 1.05 (95% CI: 0.85 - 1.31). De overlevingskans 1, 5, 10, en 15 jaar na harttransplantatie was 79%, 69%, 53%, en 36% met donorharten met een normale natriumconcentratie, en 75%, 65%, 56%, en 46% met donorharten met een verhoogde natriumconcentratie (p = 0.76). OP basis van deze bevindingen concluderen we dat een verhoogde natriumconcentratie van het donorhart geen wezenlijke invloed heeft op het sterfte risico na harttransplantatie bij volwassenen. Het tekort aan donorharten kan worden gereduceerd door deze niet langer op basis van de natriumconcentratie te weigeren. Wij bevelen aan de richtlijnen voor selectie van donorharten dienovereenkomstig aan te passen.

Harttransplantatie team en chirurgen zijn niet erg geneigd harten van donoren na cardiopulmonale reanimatie te accepteren, omdat ze daarbij hartspierschade verwachten die tot een slechte cardiale functie zal leiden. In **hoofdstuk 6** beschrijven we de analyse van de impact van cardiopulmonale reanimatie van donoren op de uitkomst van harttransplantatie bij volwassenen. Daarbij vonden we een klein statistisch niet significant verschil in mortaliteit 30 dagen na transplantatie voor donorharten na cardiopulmonale reanimatie (8.3%) en zonder reanimatie (8.5%, p = 0.94). De overlevingskans 1, 5, 10, en 15 jaar na transplantatie was 81%, 73%, 54%, en 21% na cardiopulmonale reanimatie, en 77%, 67%, 54%, en 43% zonder reanimatie (p = 0.55). Ook na correctie voor verschillen tussen de groepen met en zonder cardiopulmonale reanimatie voor leeftijd van de donor, body mass index, catacholaminen voor de donor, cardiale enzymen en doodsoorzaak bleef dit verschil klein en statistisch niet significant. Op basis hiervan concluderen we dat cardiopulmonale reanimatie de uitkomst van hart transplantatie bij volwassenen niet noemenswaardig beïnvloeden. Het tekort aan donorharten kan worden gereduceerd door ze na cardiopulmonale reanimatie niet langer te weigeren. Wij bevelen aan de richtlijnen voor selectie van donorharten dienovereenkomstig aan te passen.

Een voorspelmodel voor een accurate individuele voorspelling van de overleving na harttransplantatie bij volwassenen, kan helpen bij de selectie van patiënten. Een accuraat voorspelmodel kan de besluitvorming van de patiënt en familie, en in het harttransplantatie team ondersteunen. In **hoofdstuk 7**, beschrijven we de ontwikkeling en validering van een eenvoudig toe te passen model voor de

voorspelling van de sterftekans 30 dagen na harttransplantatie bij volwassenen. Op basis van de leeftijd en geslacht van de patiënt, pretransplantie diagnose, urgentie van transplantatie status, wachttijd tot transplantatie, leeftijd en geslacht van de donor, donor-ontvanger mismatch voor body mass index en bloedgroep, en de cardiopulmonary bypass tijd blijkt een accurate voorspelling van de sterftekans 30 dagen na harttransplantatie bij volwassenen mogelijk. Zoals uit de calibratieplot blijkt is de overeenkomst tussen de waargenomen en de voorspelde mortaliteitkans over de gehele range van de voorspelde kansen zeer groot. Hieruit blijkt dat de ijking van het voorspelmodel voldoende goed is. Na correctie voor optimisme, nam het oppervlak onder de receiver operating characteristic (ROC area) kromme van 0.74 iets af tot 0.71. Hieruit blijkt dat met het model accuraat de doden en overlevenden 30 dagen na harttransplantatie bij volwassenen kan voorspellen. Om het gebruik van het voorspelmodel in de patiëntenzorg te bevorderen hebben we een nomogram gemaakt. Hierdoor kan het voorspelmodel eenvoudig gebruikt worden bij de besluitvorming van de patiënt en familie, en in het harttransplantatie team. Deze ondersteuning van de besluitvorming is van belang bij de optimale toewijzing van het beperkte aanbod van het aantal donorharten.

Vanwege het beperkte aanbod van het aantal donorharten en het groeiende aantal patiënten op de wachtlijst voor harttransplantatie is een klinisch eenvoudig toepasbaar model dat de langer termijn uitkomst van harttransplantatie bij volwassenen kan voorspellen is uit maatschappelijk oogpunt en het perspectief van de gezondheidszorg van groot belang. In **hoofdstuk 8** beschrijven we de ontwikkeling en validering van een model ter voorspelling van de individuele sterftekans 1 en 5 jaar na harttransplantatie bij volwassenen. Op basis van de leeftijd en geslacht van de patiënt, urgentie van transplantatie, leeftijd en geslacht van de donor, donor-ontvanger mismatch voor body mass index, en de cardiopulmonary bypass tijd blijkt een accurate voorspelling van de sterftekans 1 jaar na harttransplantatie bij volwassenen mogelijk. Een individuele voorspelling van de sterftekans 5 jaar na harttransplantatie bij volwassenen blijkt mogelijk op basis van de leeftijd van de patiënt, urgentie van transplantatie, leeftijd van de donor, catacholamine voor de donor, en de cardiopulmonary bypass tijd. Uit de calibratieplot blijkt dat de overeenkomst tussen de waargenomen en de voorspelde mortaliteitkans na 1 jaar en de voorspelde kans groot is. Voor de voorspelde kansen lager van 20% blijkt het model in een overschatting van de mortaliteit te resulteren. Als gevolg hiervan is de het oppervlak onder de receiver operating characteristic (ROC area) kromme relatief gering; na correctie voor optimisme nam dit oppervlak af van 0.67 tot 0.64. Het 5-jaars model resulteerde over de hele range in een systematische overschatting van de mortaliteitskansen. Als gevolg hiervan is de het oppervlak onder de receiver operating characteristic (ROC area) kromme relatief gering; na correctie voor optimisme nam dit oppervlak af van 0.66 tot 0.65. Om het gebruik van beide voorspelmodellen in de patiëntenzorg te bevorderen hebben we ook nu weer

nomogrammen gemaakt. Hierdoor kan het voorspelmodel eenvoudig gebruikt worden bij de besluitvorming van de patiënt en familie, en in het harttransplantatie team. Deze ondersteuning van de besluitvorming is van belang bij de optimale toewijzing van het beperkte aanbod van het aantal donorharten.

De belangrijkste bevindingen van de onderzoeken beschreven in dit proefschrift worden in **hoofdstuk 9** in samenhang en in een breder perspectief besproken. In dit hoofdstuk worden ook de kracht en de zwakte van de onderzoeken besproken, alsmede de implicaties van onze bevindingen voor de patiëntenzorg en toekomstig onderzoek. Tevens worden algemene conclusies en aanbevelingen geformuleerd. Uit de gepresenteerde onderzoekingen blijkt dat zorgvuldige selectie van patiënten en verruiming van de criteria voor acceptatie van donorharten cruciale factoren zijn om een optimale overlevingskans na harttransplantatie bij volwassenen te garanderen. De individuele sterftekans na harttransplantatie bij volwassenen kan met voldoende accuratesse voorspeld worden op basis van pretransplantie gegevens van de patiënt en de donor, en enkele perioperatieve gegevens. De robuustheid van de voorspelmodellen dient onderzocht te worden in externe validatie studies.

De meest opmerkelijke ontdekking die ooit door wetenschappers is gemaakt,
is de wetenschap zelf.

• *Jacob Bronowski, 1908 - 1974* •

Rangkuman

(Summary in Bahasa Indonesia)

Prediksi hasil transplantasi jantung

Transplantasi jantung telah menjadi tindakan pengobatan pilihan bagi pasien penyakit jantung stadium akhir. Pada awalnya, kriteria seleksi resipien dan donor yang ketat dikembangkan untuk mengurangi kesakitan (*morbidity*) dan kematian (*mortality*) setelah transplantasi jantung. Namun bertambahnya kebutuhan transplantasi jantung telah menyebabkan liberalisasi kriteria tradisional seleksi resipien. Usia resipien secara perlahan telah meningkat. Pasien dengan status kesehatan yang jelek, misalnya diagnosis penyakit katub jantung stadium akhir sebelum transplantasi dan resipien yang lebih tua, cenderung memiliki angka kesakitan dan kematian yang lebih tinggi akibat permasalahan medis penyerta lainnya. Meluasnya jurang pemisah antara kebutuhan dan penyediaan donor jantung menyebabkan memanjangnya waktu tunggu secara bermakna dan meningkatnya angka kematian resipien yang berada di daftar tunggu. Untuk memperbanyak penyediaan donor, kriteria penerimaan donor jantung telah diperluas dengan memasukkan donor jantung yang kurang optimal atau marjinal. Namun dampak kecenderungan ini terhadap hasil transplantasi jantung terutama jangka panjang masih belum jelas. Transplantasi jantung seharusnya diperuntukkan bagi pasien yang mempunyai kelangsungan hidup (*survival*) yang paling menguntungkan. Agar mampu memprediksi hasil (*outcome*) transplantasi jantung pada seorang pasien berdasarkan karakteristik resipien dan donor, serta kecocokannya, sebuah model prediksi berperanan penting dalam penyeleksian sebuah donor jantung kepada resipien tertentu.

Fokus disertasi ini adalah pada dampak berbagai karakteristik dasar resipien dan donor terhadap hasil setelah transplantasi jantung dewasa. Disertasi ini juga mencakup beberapa model yang telah dikembangkan dan divalidasi untuk memprediksi resiko kematian setelah transplantasi jantung dewasa.

Profil klinis resipien dan donor yang layak bagi transplantasi jantung maupun prosedur transplantasi itu sendiri telah berubah seiring waktu. Di **bab 2**, kami mempelajari dampak berubahnya profil resiko dasar pada periode transplantasi yang berbeda terhadap hasil, dan menentukan penyebaran penyebab kematian berkaitan dengan waktu setelah transplantasi jantung dewasa. Kami menemukan perubahan yang secara statistik bermakna dan secara klinis relevan pada karakteristik resipien, antara lain usia yang lebih tua dan peningkatan indeks masa tubuh, lebih banyak bedah jantung sebelumnya, status transplantasi urgensi tinggi, memanjangnya waktu tunggu ke transplantasi, dan lebih sering membutuhkan alat bantu ventrikel sebelum transplantasi. Secara simultan, lebih sering dipakai donor berusia lebih tua. Sebagai tambahan, terdapat peningkatan dalam proporsi ketidakcocokan indeks masa tubuh dan waktu iskemik. Kami memperlihatkan bahwa meski dengan adanya perubahan ini, kelangsungan hidup awal dan lebih lanjut tetap stabil dan menyakinkan. Kelangsungan hidup secara keseluruhan di tahun ke-1, -5, -10, dan -15 berturut-turut adalah 77%, 67%, 53%, dan 42%. Tidak terdapat perbedaan kelangsungan hidup berdasarkan periode transplantasi yang berbeda (p = 0.68), dan begitu juga untuk

penyebab kematian. Penyebab utama kematian berturut-turut adalah: penolakan akut, kegagalan organ ganda, dan gagal jantung kanan (untuk ≤ 30 hari); infeksi dan penolakan akut (untuk 31 hari – 1 tahun); keganasan, penolakan akut, dan vaskulopati alograft jantung (untuk >1 – 5 tahun); vaskulopati alograft jantung dan keganasan (untuk >5 – 10 tahun); dan keganasan dan infeksi (untuk >10 tahun).

Transplantasi jantung bagi penyakit katub jantung stadium akhir telah dipertimbangkan memiliki prognosis jelek karena adanya bedah jantung sebelumnya dan sering meningkatnya tahanan pembuluh darah paru. Namun begitu, hasilnya kurang sekali didokumentasikan. Di **bab 3**, kami membandingkan hasil jangka panjang transplantasi jantung bagi penyakit katub jantung stadium akhir terhadap transplantasi jantung bagi indikasi lainnya. Kami menunjukkan bahwa prognosis setelah transplantasi jantung bagi penyakit katub jantung stadium akhir menyerupai transplantasi jantung bagi indikasi lain. Kelangsungan hidup di tahun ke-1, -5, -10, dan -15 berturut turut adalah 70%, 64%, 56%, dan 46% pada transplantasi jantung dewasa bagi penyakit katub jantung stadium akhir dibandingkan dengan 78%, 68%, 53%, dan 41% pada transplantasi jantung dewasa bagi indikasi lainnya (p = 0.5).
Meski angka kematian awal pada penyakit katub jantung stadium akhir nampak sedikit lebih tinggi, perbedaannya secara statistik tidak bermakna (13% vs. 8%, p = 0.12). Namun begitu, peningkatan kelangsungan hidup bermakna secara statistik dengan semakin lamanya waktu tunggu ke transplantasi jantung [*Hazard ratio* (HR) = 0.998, 95% interval kepercayaan (IK): 0.996 - 0.999].

Keterbatasan donor jantung memacu perdebatan apakah transplantasi jantung diperkenankan bagi resipien dengan resiko kematian sebelum transplantasi yang lebih tinggi. Ini khususnya berkenaan dengan resipien berusia lebih tua, jika memandang hasil dari bab 2. Di **bab 4**, kami mempelajari efek usia resipien terhadap hasil transplantasi jantung dewasa. Kami menunjukkan adanya kecenderungan yang jelas antara usia resipien terhadap hasil transplantasi jantung. Resiko kematian 30 hari adalah 6% bagi resipien berusia lebih muda dari 55 tahun, dan 10% bagi resipien berusia 55 tahun dan lebih tua (p = 0.005). Keunggulan kelangsungan hidup lebih lanjut bagi resipien berusia lebih muda dari 55 tahun secara statistik tetap bermakna: kelangsungan hidup di tahun ke-1, -5, -10, dan -15 berturut-turut adalah 84%, 75%, 60%, dan 50% bagi resipien berusia lebih muda dari 55 tahun; dan 73%, 63%, 48%, dan 35% bagi resipien berusia 55 tahun dan lebih tua (p < 0.001). *Hazard ratio* meningkat seiring meningkatnya usia resipien, yaitu, resiko relatif meningkat sebesar 25% (setelah penyesuaian: 21%) bagi kelompok usia resipien 56 - 65 tahun, dan 58% (setelah penyesuaian: 40%) bagi resipien berusia lebih dari 66 tahun. Kami menyimpulkan bahwa keputusan menawarkan transplantasi jantung pada resipien berusia lebih dari 55 tahun seharusnya dipertimbangkan secara hati-hati mengingat begitu kurangnya donor jantung.

Karena konsentrasi sodium intraseluler berkontribusi pada jejas reperfusi, hipernatremi pada donor diperkirakan dapat menyebabkan lumpuhnya miokardium

(*myocardial stunning*), sehingga meningkatkan angka kejadian (*incidence*) gagal graft primer setelah transplantasi jantung. Tetapi dampak kadar sodium donor terhadap hasil setelah transplantasi jantung dewasa masih diperdebatkan. Di **bab 5**, kami mengevaluasi apakah kadar sodium donor, khususnya > 155 mmol/l, mempengaruhi hasil setelah transplantasi jantung dewasa. Kami menemukan bahwa resiko kematian 30 hari setelah transplantasi jantung dewasa agak serupa jika menggunakan donor jantung normo-natremia (8,4%) atau hipernatremia (8,9%, p = 0,77). Keadaan ini berlaku bagi gagal graft primer sebagai penyebab kematian (p = 0.57). *Hazard ratio* yang telah disesuaikan bagi kadar sodium donor > 155 mmol/l adalah 1.05 (95% IK: 0.85 - 1.31). Kelangsungan hidup di tahun ke-1, -5, -10, dan -15 berturut-turut adalah 79%, 69%, 53%, dan 36% bagi kelompok normo-natremia; dan 75%, 65%, 56%, dan 46% bagi kelompok hipernatremia (p = 0.76). Kami menyimpulkan bahwa kadar sodium donor tidak memiliki dampak besar terhadap resiko kematian setelah transplantasi jantung dewasa. Keterbatasan organ dapat berkurang jika penolakan donor jantung berdasarkan kadar sodium donor yang tinggi dihindarkan. Oleh sebab itu, kami menyarankan penyesuaian kriteria seleksi donor jantung.

Pada umumnya, team transplantasi jantung dan ahli bedah enggan menerima sebuah jantung dari donor yang telah menjalani resusitasi jantung-paru (RJP), karena takut akan jeleknya fungsi jantung baik awal maupun lebih lanjut akibat dari jejas miokardium. Di **bab 6**, kami menganalisa pengaruh RJP pada donor terhadap hasil setelah transplantasi jantung dewasa. Kami menemukan perbedaan yang sangat kecil dan secara statistik tidak bermakna dalam resiko kematian 30 hari setelah transplantasi jantung dewasa ketika menggunakan donor jantung dengan RJP (8,3%) atau tanpa RJP (8,5%, p = 0,94). Kelangsungan hidup secara keseluruhan di tahun ke-1, -5, -10, dan -15 berturut-turut adalah 81%, 73%, 54%, dan 21% bagi kelompok RJP; dan 77%, 67%, 54%, dan 43% bagi kelompok tanpa RJP (p = 0.55). Perbedaan sangat kecil ini yang secara statistik tidak bermakna menetap setelah penyesuaian bagi perbedaan antar kelompok mengenai usia, indeks masa tubuh, penyebab kematian, keperluan bantuan inotropik, dan enzym jantung donor. Kami menyimpulkan bahwa penggunaan donor jantung yang telah menjalani RJP tidak berdampak besar terhadap hasil setelah transplantasi jantung dewasa. Penerimaan donor jantung semacam ini akan menambah perluasan jumlah donor. Oleh sebab itu, kami menyarankan penyesuaian kriteria seleksi donor jantung.

Sebuah model prediksi komprehensif yang dapat menyediakan informasi kelangsungan hidup setelah transplantasi jantung kepada pasien dan keluarganya juga dapat membantu team transplantasi jantung untuk mengklasifikasikan pasien menurut resiko kematiannya. Model semacam ini dapat digunakan untuk membantu pembuatan keputusan klinis. Di **bab 7**, kami mengembangkan dan mengvalidasi sebuah model prediksi yang mudah dipakai untuk resiko kematian 30 hari setelah

transplantasi jantung dewasa. Kami memperlihatkan bahwa usia dan jenis kelamin resipien, diagnosa sebelum transplantasi, status transplantasi, waktu tunggu, usia dan jenis kelamin donor, ketidakcocokan donor-resipien dalam indeks masa tubuh dan golongan darah, dan waktu pintas jantung-paru adalah prediktor independen yang akurat bagi resiko kematian 30 hari setelah transplantasi jantung dewasa. Model prediksi kami memprediksi secara akurat resiko kematian 30 hari setelah transplantasi jantung dewasa. Garis kalibrasi menunjukkan bahwa kategori probabilitas yang diprediksi mendekati garis ideal. Oleh karena itu, model kami terkalibrasi secara baik meliputi keseluruhan batas probabilitas yang diprediksi. Setelah koreksi bagi optimisme, area di bawah *receiver operating characteristic curve* (ROC area) berubah dari 0,74 menjadi 0,71, yang menunjukkan hasil diskriminasi yang baik antara pasien yang meninggal dan hidup pada hari ke-30 setelah transplantasi jantung dewasa. Untuk memudahkan penggunaannya dalam praktek, model prediksi kami ini dikonversi menjadi sebuah normogram. Model prediksi kami dapat digunakan dalam pembuatan keputusan klinis, terutama dalam mencocokkan donor kepada resipien, dan mengingat keterbatasan donor jantung, membantu keputusan alokasi donor jantung kepada pasien yang menunggu transplantatsi jantung.

Karena keterbatasan jumlah donor dan bertambahnya jumlah pasien yang menunggu transplantasi jantung, sebuah model klinis yang dapat memprediksi resiko kematian jangka lebih lama setelah transplantasi jantung menjadi perhatian penting bagi masyarakat dan pelayanan kesehatan. Di **bab 8**, kami menggunakan karakteristik resipien dan donor sebelum transplantasi maupun data perioperatif untuk mengembangkan model yang dapat memprediksi resiko kematian di tahun ke-1 dan -5 setelah transplantasi jantung dewasa. Kami menemukan bahwa variabel sebelum transplantasi yang secara bermakna mempengaruhi hasil setelah transplantasi jantung dewasa adalah usia resipien dan jenis kelamin, status transplantasi, usia donor, ketidakcocokan donor-resipien dalam indeks masa tubuh, dan waktu pintas jantung-paru bagi model tahun ke-1. Usia resipien dan jenis kelamin, status transplantasi, usia donor, keperluan katekolamin pada donor, dan waktu pintas jantung-paru berpengaruh secara bermakna terhadap kematian setelah transplantasi jantung dewasa bagi model tahun ke-5. Garis kalibrasi bagi model tahun ke-1 menunjukkan bahwa model tersebut terkalibrasi secara baik. Tetapi perlu diperhatikan bahwa probabilitas kematian yang diprediksi di bawah 20% sedikit terlalu tinggi, yaitu mengakibatkan sedikit overestimasi resiko kematian. Konsekuensinya, model tersebut menunjukkan diskriminasi yang memuaskan antara pasien yang meninggal dan hidup pada tahun ke-1 setelah transplantasi jantung dewasa; ROC area adalah 0,67, dan setelah koreksi bagi optimisme adalah 0,64. Model tahun ke-5 memberikan probabilitas yang diprediksi terlalu tinggi meliputi keseluruhan batas, mengakibatkan sedikit overestimasi resiko kematian. Konsekuensinya, model tersebut menunjukkan diskriminasi yang memuaskan antara

pasien yang meninggal dan hidup pada tahun ke-5 setelah transplantasi jantung dewasa; ROC area adalah 0,66, dan setelah koreksi bagi optimisme adalah 0,65. Model-model prediksi ini dikonversi menjadi normogram-normogram yang mudah dipakai untuk meningkatkan aplikasinya. Normogram-normogram tersebut dapat digunakan dalam praktek klinis untuk mencocokkan donor kepada resipien dengan cara yang optimal, karena normogram-normogram semacam ini dapat membantu team transplantasi jantung untuk mengestimasi resiko kematian bagi resipien transplantasi jantung yang potensial dan keluarganya secara obyektif.

Akhirnya, penemuan-penemuan penting dari penelitian-penelitian di atas didiskusikan dalam perspektif yang lebih luas di **bab 9**, Diuraikan kelebihan dan keterbatasan penelitian-penelitian tersebut, implikasi bagi praktek dan penelitian di masa yang akan datang maupun kesimpulan dan rekomendasi secara umum. Penelitian-penelitian yang dipresentasikan dalam disertasi ini mengindikasikan bahwa seleksi resipien secara hati-hati dan perluasan kriteria donor yang dapat dipertimbangkan merupakan faktor penting untuk mencapai hasil yang optimal setelah transplantasi jantung dewasa. Resiko kematian setelah transplantasi jantung dewasa dapat diprediksi secara akurat dengan menggunakan karakteristik resipien dan donor sebelum transplantasi maupun data perioperatif. Namun begitu, validasi eksternal model kami merupakan langkah penting berikutnya dalam menilai kekuatan prediksinya (*robustness*).

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yang telah kita ketahui dengan sendirinya
atau yang hanya kita ketahui dimana ia bisa didapatkan

• *Samuel Johnson, 1709 - 1784* •

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We must see that it is not happiness that makes us grateful,
but the gratefulness that makes us happy

• *Albert Clarke, 1890 - 1917* •

Curriculum vitae

Yanto Sandy Tjang was born in Jambi, Indonesia on July the 17th, 1966. After graduation from the Xaverian Senior High School in Jambi, Indonesia, he started the Medical School at one of the most prestigious state universities in Indonesia, the Gadjah Mada University in Yogyakarta in August 1986 and obtained the Medical Doctor degree in December 1992. During his Medical School, he performed several epidemiological and clinical studies, resulting in publication in the Journal of the Indonesian Medical Association. From March 1993 to February 1996, he worked at the General Hospital of Sambas in West Borneo, Indonesia, where he provided medical care for the mostly poor inhabitants from the remote area. Subsequently, he obtained the full recognition as a General Practitioner from the Indonesian Ministry of Health.

In December 1996, he started his residency training at the Dept. of General Surgery (Head: Prof. Dr. med. A. Encke) and Dept. of Thoracic & Cardiovascular Surgery (Head: Prof. Dr. med. A. Moritz), Johann Wolfgang Goethe University Hospital of Frankfurt, Germany. In June 1997, his residency training was continued at the Dept. of Thoracic & Cardiovascular Surgery (Head: Prof. Dr. med. Dr. h.c. R. Körfer), Heart & Diabetes Center North Rhine Westphalia Bad Oeynhausen/ Ruhr-University Hospital of Bochum, Germany. Between July 2002 and January 2003, he was trained at the Dept. of Thoracic & Cardiovascular Surgery (Head: Prof. Dr. med. R. Autschbach), University Hospital of Aachen, Germany with special interest in minimally invasive surgical techniques. After returning to the Heart & Diabetes Center North Rhine Westphalia Bad Oeynhausen, he completed his residency training, and passed the German Board's examination in December 2003. One of his scientific works entitled atrial fibrillation after heart surgery published in the Journal of the Indonesian Medical Association was selected as the third winner of the best articles and received an award from the Indonesian Medical Association in October 2003. Later on in November 2003, he was elected as a Fellow of the International College of Surgeons (Headquarters: Chicago, USA). Apart from his tight clinical works, he studied at the Frederick Institute of Technology in Nicosia, Cyprus through its representative in Cologne, Germany (*BWL-Akademie* Dr. Braunschweig) and obtained the Master of Business Administration degree in Health Care in February 2005.

Following his sabbatical leave, he went to Erasmus Medical Center Rotterdam, The Netherlands in August 2004 and subsequently obtained the Master of Science degree in Clinical Epidemiology from the Netherlands Institute for Health Sciences (Erasmus University Rotterdam, The Netherlands) in June 2005. Furthermore, from October 2005 to May 2006, he was appointed as a Visiting Surgeon at the Dept. of Thoracic & Cardiovascular Surgery (Head: Prof. Dr. G. Engström), Norrland's University Hospital Umeå, Sweden. During the similar period, he studied at the Umeå International School of Public Health, Sweden and obtained the Master of Public Health degree in May 2006. In June 2006, he earned the Doctor of Science degree in Clinical Epidemiology from the Netherlands Institute for Health Sciences (Erasmus University Rotterdam, The Netherlands).

Before returning to the Heart & Diabetes Center North Rhine Westphalia Bad Oeynhausen in August 2006, he was awarded a travel grant from the European Association for Cardio-Thoracic Surgery and spent the wonderful summer time as a Visiting Fellow at the Dept. of Cardio-Thoracic Surgery (Head: Prof. Dr. R. Dion), Leiden University Medical Center, The Netherlands and the Dept. of Cardiovascular Surgery (Head: Assoc. Prof. Dr.

J.I. Aramendi), Hospital de Cruces Barakaldo/ University of the Basque Country, Bilbao, Spain. In November 2007, he obtained the "Doktor der Medizin" (Doctor in Medicine) degree from the Ruhr-University of Bochum, Germany. He has been a Reviewer for several international medical journals and written numerous articles on health issues in different Indonesian newspaper.

He conducted the studies described in this thesis under the supervision of Prof. Dr. D.E. Grobbee and Dr. G.J.M.G. van der Heijden from the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands, as well as Prof. Dr. med. Dr. h.c. R. Körfer from the Dept. of Thoracic & Cardiovascular Surgery, Heart & Diabetes Center North Rhine Westphalia Bad Oeynhausen/ Ruhr-University Hospital of Bochum, Germany. Apart from his research activities, he was clinically attached as a Fellow to the Dept. of Pediatric Cardio-Thoracic Surgery (Head: Prof. Dr. med. F. Haas), Wilhelmina Children's Hospital Utrecht, as well as the Dept. of Cardio-Thoracic Surgery (Head: Prof. Dr. L.A. van Herwerden) and Dept. of Vascular Surgery (Head: Prof. Dr. F.L. Moll), University Medical Center Utrecht, The Netherlands.

In the future, he is planning to work as a Thoracic & Cardiovascular Surgeon as well as to continue his research in his Motherland, Indonesia.

Every challenge might as well provide an opportunity

• *Albert Einstein, 1879 – 1955* •

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An investment in knowledge pays the best interest

• Benjamin Franklin, 1706 – 1790 •