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Pre- and early postoperative risk factors for death after cardiac transplantation: A single center analysis

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Abstract Due to the limited number of donor organs, death on the waiting list and waiting time for cardiac transplantation have markedly increased. A pressing need of appropriate selection criteria for patients who would benefit most from transplantation is apparent. The purpose of this study is to identify pre- and early postoperative risk factors that influence long term survival after cardiac transplantation. 702 consecutive patients who underwent cardiac transplantation between 3/1984 and 12/1997 were analyzed retrospectively for the influence of different pre- and early postoperative risk factors on early (30 days) and late death (5 years). Univariate and multivariate regression analysis revealed risk factors

for early as well as late death. Predictors of early death were higher preoperative PVR, retransplantation, longer ischemic time, postoperative acute kidney failure and longer intubation time. Risk factors for late death were early transplant era, previous cardiac surgery, patients awaiting transplantation in a hospital, prolonged stay in an intensive care unit, and any rejection during the first month after transplantation. These results demonstrate that pre- and early postoperative risk factors have significant influence on early and long term survival.

Key words Cardiac transplantation · Risk factors for outcome

Introduction

Cardiac transplantation is a highly effective life-saving procedure for end-stage heart failure [31]. Improved immunosuppression and management of infectious complications have markedly improved quality of life and short- and long-term survival of transplant recipients [3, 11]. These encouraging results have contributed to progressive extension of recipient selection criteria [27]. Meanwhile, donor heart availability has remained relatively constant. Consequently, the number of patients waiting for heart transplantation has dramatically increased. Mortality on the waiting list has increased up to 25% [22]. As the cardiac donor shortage crisis will definitely not improve over the next years, there is a pressing need of appropriate selection criteria for pa-

tients who would most benefit from transplantation. A number of studies have addressed this issue with controversial results [1, 2, 4, 7]. These previous reports have either focused on preoperative or postoperative variables. The aim of this single center analysis is to identify the pre- and postoperative risk factors for short- and long term survival after cardiac transplantation.

Patients and methods

Patients and immunosuppression

In the period from 3/84 through 12/97, 702 patients underwent orthotopic heart transplantation for end stage cardiac disease at the University of Vienna. By means of a mechanical assist device, 35 patients were bridged to transplantation; 27 patients underwent re-

Table 1 Patient Demographics

Patients (<i>n</i>)	702
Sex (m/f)	590/112
Age	
Mean	49.7 ± 12.4
Range	0.5–70
Diagnosis	
CAD	406
CMP	211
Other	85
PVR (Wood units)	2.63 ± 1.59
Status	
At home	367
Hospital	209
ICU	126
Ischemic time (min)	166.0 ± 60.4
Donor age	31.6 ± 11.9

transplantation. Selected recipient- and donor criteria are listed in Table 1. The series comprised 590 male and 112 female recipients, ranging from 6 months to 70 years of age, a means of 49.7 ± 12.4 years. The cause of heart disease before transplantation included idiopathic cardiomyopathy in 406 (57.9%), ischemic cardiomyopathy in 211 (30.1%), and other diagnoses in 85 (12.7%) patients. There were 700 orthotopic and 2 heterotopic transplantations.

All patients received triple drug maintenance therapy consisting of Cyclosporine, azathioprine and prednisolone and anti-lymphocyte induction therapy.

Follow-up and data collection

All patients were followed in the outpatient clinic of our institution. Mean follow-up time was 61.2 ± 65.8 months (range 5 to 156 months). Patient data have been prospectively collected and entered into a database.

Surveillance of rejection and graft arteriosclerosis

The ISHLT grading system was used to detect cardiac rejection from serial endomyocardial biopsy. Rejection was defined as either grade ≥ 2 or grade ≤ 2 with hemodynamic compromise. Biopsies were performed weekly during the first month, monthly in the first six months, and once at the end of the first year, or as clinically indicated. All patients received coronary angiograms 12, 36 and 60 months after undergoing transplantation. Angiograms were also performed whenever the clinical situation suggested occurrence of graft arteriosclerosis.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Nominal variables were expressed as percentages and analyzed by Chi² test. Survival data were analyzed with standard Kaplan-Meier actuarial technique for estimation of survival probabilities. Univariate analysis of risk factors for late death (5 years) after heart transplantation was carried out by comparing survival

Table 2 Variables examined in uni- and multivariate analysis

Pretransplantation variables
Recipient age < 60 years vs. > 60 years
Recipient sex male: vs. female
Cause of recipient heart disease: CMP vs. CAD vs. Other
Preoperative status: stable at home vs. stable in hospital vs. intravenous drug support vs. mechanical assist device
Admission to transplantation: out of hospital vs. in hospital vs. intensive care unit
Previous cardiac operation
Diabetes mellitus: diabetes type 1 and 2 vs. no diabetes
Obesity: BMI > 30 vs. < 30
Pulmonary embolism (< 6 weeks prior transplantation)
Preoperative resuscitation
Retransplantation
Pulmonary vascular resistance: < 3.5 WOOD units vs. > 3.5 WOOD units
Preoperative intubation
Mechanical assist device (any kind)
Preoperative renal function: creatinine < 1.5 mg/dl vs. creatinine > 1.5 mg/dl
Operative/donor variables
Operation date: 1984–1990 vs. 1991–1997
Donor age: < 40 years vs. > 40 years
Donor sex: male vs. female
Sex mismatch (donor/recipient)
Ischemic time: < 240 min vs. > 240 min
CMV match donor/recipient: pos/pos; pos/neg; neg/neg; neg/pos
Perioperative variables
Perioperative renal failure within first postoperative week (need of hemofiltration)
Prolonged postoperative intubation time: < 4 days vs. > 4 days
Prolonged postoperative stay in intensive care unit < 7 days vs. > 7 days
Any clinical relevant rejection during first 30 days (need for steroid therapy)
Infection during first 30 days with need for therapy (bacterial, viral and fungal combined)

curves for two or more independent subsets of patients with the Wilcoxon and log-rank test. A forward stepwise logistic regression analysis was performed to identify specific risk factors associated with 30-day death (early death) or late death (60 months). Analysis for late death was performed only on patients that survived for more than 30 days, in order to exclude any risk factors, which may have influenced only the early phase after transplantation. The specific variables examined are listed in Table 2. Variables were retained in the final multivariate risk factor analysis if the *P* value was 0.15 or less in univariate analysis. Statistical significance was assumed at *P* value of < 0.05.

Results

Overall survival

702 patients were included in the study. Overall survival was 91%, 85% and 73% after 30 days, 1 year and 5 years respectively. A total of 189 patients died

Table 3 Distribution in time of causes of death after cardiac transplantation

Cause of death	< 30 days		> 30 days	
	<i>n</i>	% of 93	<i>n</i>	% of 96
Infection	33	35 %	25	26 %
Acute rejection	11	12 %	18	19 %
Early graft failure	20	22 %	–	–
Multiple organ failure	10	11 %	5	5 %
Graft arteriosclerosis	–	–	12	12 %
Malignancy	–	–	21	22 %
Other	19	20 %	15	16 %
Total	93	100 %	96	100 %

within the follow-up period of 5 years. 49 % of the deaths were early (within the first month posttransplant).

Causes of death

The distribution in time of the causes of death is shown in Table 3. In the early period the most common causes of death were infection (35 %), followed by early graft failure (22 %), and acute rejection (12 %). After the first month, infection (26 %), malignancy (22 %), rejection (19 %), and graft arteriosclerosis (12 %), were the main causes of death. Univariate analysis revealed eight different risk factors of early death after transplantation. After multivariate regression analysis, six independent risk factors for early death remained significant (Table 4). Patients with preoperative PVR higher than 4 Wood units died at a significantly higher rate. High preoperative values of PVR were associated with a significantly higher incidence of right heart failure after transplantation ($P < 0.001$).

Table 4 Univariate and multivariate analysis of risk factors for early death after cardiac transplantation

Incremental risk factor for early death	Log-rank test (<i>P</i> -value)	Logistic regression analysis (<i>P</i> value)
Acute kidney failure (need of hemofiltration)	0.0001	0.0001
Retransplantation	0.0001	0.0001
PVR > 4 Wood units	0.0001	0.0001
Intubation prior transplantation	0.0001	
Stay in ICU > 7 days post transplant	0.0001	
Admission to transplantation from hospital or ICU	0.0002	
Ischemic time > 240 min	0.0003	0.0099
Mechanical or pharmacologic bridging	0.0007	
Previous cardiac surgery	0.0016	
Postoperative intubation > 4 days	0.0030	0.0009
> 0 infections during first postoperative month	0.0079	
Pretransplant CPR	0.0296	
Transplantation performed before 1990	0.1023	
Pretransplant creatinine > 1.5	0.1170	
Indication for transplantation	0.1399	
Mechanical assist device	0.1455	

Patients with primary cardiac transplants had significantly better short-term survival than patients undergoing retransplantation. Infectious complications as cause of death were significantly higher in the retransplantation group ($P < 0.05$). Analysis of donor variables showed no significant risk for early death after transplantation. However, an ischemic time longer than 4 h was a significant risk factor of early death from acute graft failure. Patients suffering from acute kidney failure early after transplantation are under a high risk of death. For patients in need of postoperative hemofiltration, death from infection occurred significantly more often than for patients with normal kidney function ($P < 0.001$). A postoperative intubation time of more than 4 days was also associated with a higher risk of death. Patients with more than 4 days of intubation died significantly more frequently of infectious complications ($P < 0.001$) or right heart failure ($P < 0.01$).

In a second analysis, risk factors for late death (5 years) were examined. Only patients who survived the first postoperative month were included in this analysis. Univariate analysis showed a total of 12 different risk factors for late death. Multivariate logistic regression revealed 5 independent risk factors (Table 5).

Patients who were operated before 1990 had a higher risk of late death than patients who underwent a transplantation after 1990. Transplant patients of the early era had a higher risk of death from rejection ($P < 0.05$) or graft arteriosclerosis ($P < 0.05$). Patients who were admitted to transplantation from an intensive care unit or who awaited transplantation in the hospital (with or without inotropic support) had a significantly worse late outcome. Patients who awaited transplantation at home had a significantly lower risk of dying from acute rejection after the first postoperative month ($P < 0.01$). Furthermore, previous cardiac operations were an independent risk factor for late death after transplantation.

Table 5 Univariate and multivariate analysis of risk factors for late death after cardiac transplantation

Incremental risk factor for late death	Log-rank test (<i>P</i> -value)	Logistic regression analysis (<i>P</i> value)
Acute kidney failure (need of hemofiltration)	0.0001	
Stay in ICU > 7 days post transplant	0.0001	0.0001
Transplantation performed before 1990	0.0001	0.0066
Mechanical assist device	0.0004	
Admission to transplantation from hospital or ICU	0.0007	0.0282
Mechanical or pharmacologic bridging	0.0016	
> 0 rejections during first postoperative month	0.0041	0.0271
Pretransplant CPR	0.0044	
> 0 infection during first postoperative month	0.0066	
Intubation prior transplantation	0.0091	
Preoperative obesity	0.0169	
Previous cardiac surgery	0.0237	0.0185
Indication for transplantation	0.1321	

These patients died more frequently of infectious complications ($P < 0.05$). A longer postoperative stay in an intensive care unit (> 7 days) was associated with lower long-term survival rate. Death occurred more frequently because of infection ($P < 0.001$) or rejection ($P < 0.001$). Rejection episodes during the first month after transplantation were an independent risk factor of late death. Death from late acute rejection was observed significantly more frequently than in patients without rejection episodes.

The combination of these results allowed us to identify subgroups of patients at low risk of early and late death after cardiac transplantation. Patients with primary transplantation, low preoperative PVR, an ischemic time under 4 h, with normal kidney function after transplantation, and short intubation times, had a significantly better short term survival rate (92% vs. 80% at 1 month; $P < 0.01$), as well as better long term survival (71% vs. 51% at 5 years; $P < 0.01$).

Moreover, among patients who survived the first month, a subgroup could be identified which had significantly better long-term survival rates. Patients who underwent transplantation after 1990 had had no previous cardiac operation, had been at home before transplantation, who, furthermore, could be transferred from the intensive care unit within 7 days, and had no acute rejection episode during the first postoperative month, showed survival rates of 96% at one year, 91% at three years, and 83% at five years. Results were significantly better than those of patients with any of the late risk factors (87%, 77%, and 67%; $P < 0.01$). Patients bearing one or more risk factor died significantly more often of infectious complications than patients without risk factors (12% vs. 4.5%; $P < 0.01$).

Discussion

This single-center analysis of 702 cardiac transplant patients revealed pre- and early postoperative risk factors that influence short- and long-term survival. Risk factors for early death were: higher preoperative PVR, retransplantation, longer ischemic time, postoperative acute kidney failure, and longer intubation time. In contrast, risk factors for late death were early transplantation era, previous cardiac surgery, awaiting transplantation in a hospital, prolonged stay in an intensive care unit, and rejections during the first month after transplantation.

As the number of cardiac donors will definitely not increase over the next years, appropriate selection criteria for patients who may most benefit from transplantation is an apparent need. A number of studies, focussing either on preoperative or postoperative variables, have addressed this issue with controversial results. The aim of this single center analysis is to identify the pre- and early postoperative risk factors for short- as well as for long term survival after cardiac transplantation.

Elevated PVR has long been identified as a risk factor of early death after cardiac transplantation [4, 15, 26]. According to our analysis, patients with high PVR values are exposed to a higher risk of right ventricular failure and infectious death. Kirklin et al., have shown that the risk of premature death increases with increasing PVR, rather than abruptly increasing at some specific level [14]. At our institution, patients are now routinely tested for reversibility of elevated PVR, and intravenous PGE1 or inhaled NO are administered routinely during cardiac transplantation on patients with high PVR, in order to decrease the danger of right heart failure [13].

Retransplantation, too, is a well-known risk factor of early death after transplantation [11]. Earlier reports showed that the time-span between transplants, graft failure, and mechanical assistance before retransplanta-

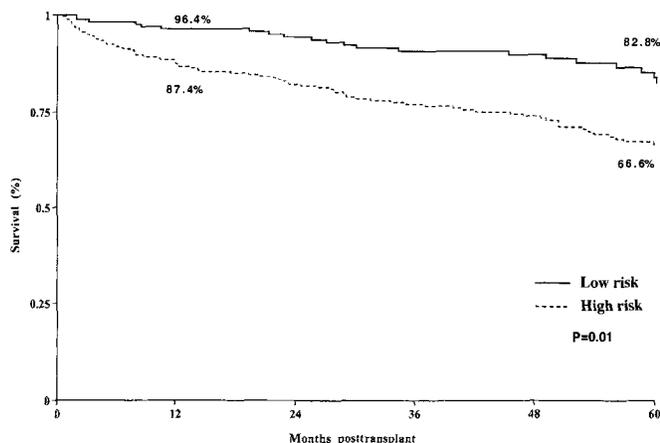


Fig. 1 Survival rates of patients with or without one or more early risk factors (12 and 60 months survival rates are stated in numbers)

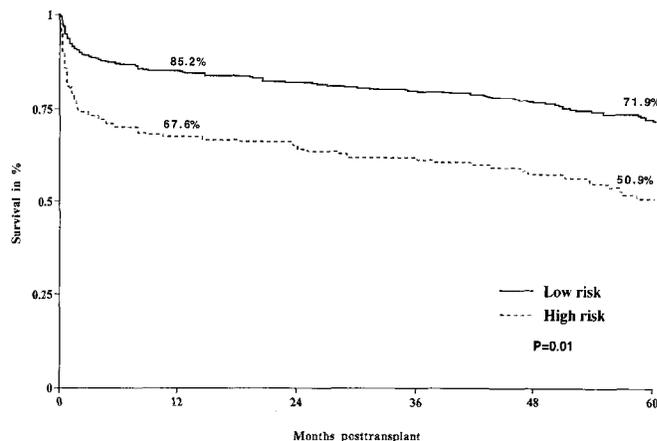


Fig. 2 Survival rates of patients with or without one or more late risk factors (12 and 60 months survival rates are stated in number)

tion are associated with especially high mortality after retransplantation [6]. This is in accordance with our results. Especially patients who underwent retransplantation for acute graft failure, and were mechanically bridged to retransplantation, had a high risk of death. Although some authors suggest that allocation of donor organs for this group of recipients is not justified, we offer retransplantation for both acute- and chronic graft failure at our institution [23, 24].

In contrast to earlier reports, a donor ischemic time of more than 240 min was an independent risk factor of early death in our institution. Sweeney and co-workers suggested that it is even acceptable to use less than ideal donor hearts with ischemic times longer than 5 h [33]. Only when the ischemic time was more than 360 min was there an increased risk noted in the registry of the ISHLT [11]. These findings are contradictory to those of Bourge et al. who report that donor ischemic times of more than 300 min are associated with a higher risk of death [2]. Possibly the use of new preservation solutions promotes a longer safe ischemic times [12].

Although renal dysfunction before transplantation has long been viewed as an important risk factor of early death, our results did not show an increased risk [19, 20]. However, there was a high risk for patients with acute kidney failure after transplantation. Recipients in need of postoperative hemofiltration had the worst outcome. This supports the work by De Maria et al, who report that postoperative acute kidney failure is an independent risk factor for early death [5]. Therefore, we avoid the use of potentially nephrotoxic substances as long as possible, early after transplantation. Especially cyclosporine therapy is delayed during the first postoperative week as long as patients have creatinine levels above 1.5 mg/dl. To minimize the danger of early rejection, patients routinely receive a 7-day course of ATG-induction therapy. No increase in rejection rates has

been observed, and postoperative kidney failure has usually been prevented by this regimen.

Another early postoperative risk factor of death is prolonged intubation time. This is usually observed in combination with severe cardiac or pulmonary problems and is a sign of a complicated immediate postoperative course. These Patients run a high risk of dying from pulmonary infection (24%) or graft dysfunction (13%).

In contrast to earlier reports, older recipient age as well as older donor age are no risk factors for early or late death [29, 33]. Kirsch et al. show that a recipient age above 60 is an independent risk factor for early death [15]. However, other groups report good survival rates among older patients undergoing cardiac transplantation [8, 10, 34]. These studies are limited by the use of univariate methods comparing patients groups and a small percentage of patients in the older groups (14–30%). By using recipients' age as continuous variable, Bourge et al. demonstrate a progressive increase in the expected mortality rate for patients above the age of 50 [2]. The percentage of older patients in our analysis is about the same as in the work by Bourge et al. Yet, in our patient population neither a recipient age above 50, nor one above 60 showed an increased risk of death.

Because of limited availability of donor organs, criteria for donor acceptance have broadened, particularly with respect to donor age. Previous studies at our, as well as other institutions, have shown that transplant recipients with donor hearts aged above 40 years have the same chances of survival as those with younger donor hearts [25, 32, 34]. There was, however, a trend to a higher incidence of graft arteriosclerosis 5 years after transplantation. Luciani et al. demonstrate that transplanting donor hearts above 40 years to recipients above 55 years of age has excellent short- and mid-

term results [18]. At our institution, donor age has risen continuously, and we follow a similar graft allocation policy with good results.

Some earlier studies reveal risk factors for late death without excluding patients who died during the first month after transplantation. As the risk of dying is highest during the first month after transplantation, some late risk factors in these studies may have been influenced by the increased risk of the early period, without actually having an influence on late death. In contrast, this study analyzes late risk only in patients, who survived the first postoperative month.

Patients undergoing transplantation before 1990 had significantly worse long-term survival rates. This is in accordance with other studies and registries that show significantly better survival rates since 1990 [11]. Better patient selection, more experience with post transplant problems, and better understanding of immunosuppression have helped to increase long-term patient survival. Supporting these results is work by McGriffin et al., who demonstrated a reduction in the likelihood of dying of rejection in a later- compared with an earlier era [21]. According to our analysis, patients undergoing transplantation before 1990 have a higher risk of dying of acute rejection or graft arteriosclerosis, than those operated after 1990. McGriffin, however, could not find an improvement in the rate of death from graft arteriosclerosis in the later era [21]. In our institution the overall incidence of graft arteriosclerosis and the incidence of death caused by graft arteriosclerosis is less than some reports indicate [9, 30]. Better antibody induction therapy since 1990 is a possible reason for this improvement.

In contrast to other studies, previous cardiac surgery is an independent risk factor for late death after transplantation [29]. Although most late deaths occur within the first 6 months after transplantation, the difference between high- and low risk patients remains significant even after 5 years. Ott et al. find no difference in mortality of patients with previous cardiac surgery [29]. Lammeriere report similar survival rates but defined a trend of increased morbidity, due especially to a higher rate of postoperative hemorrhage [17].

Preoperative clinical status of a patient is another independent risk factor for late death. Patients awaiting

transplantation in a hospital or intensive care unit are in worse clinical condition and are more prone to infectious complications after transplantation. In these patients, immunosuppression is administered at a low level (no ATG, low cyclosporine target levels) to minimize the risk of life-threatening infections. Therefore, these patients may be at a higher risk of developing late rejection. This argument is also supported by a higher rate of late death caused by acute rejection in this patient group.

Patients with a prolonged stay in an intensive care unit after transplantation are also under an increased risk of dying after the first month. Most of them are in such poor clinical condition even one month after undergoing transplantation that any late complication (infection, rejection) is associated with a high death rate. In consequence, we now tailor immunosuppressive therapy individually for every patient according to his individual problems.

Finally, rejection episodes during the first month after transplantation are associated with a higher risk of late death. Patients experiencing one or more clinical rejection episode (requirement of steroid or antibody therapy) during the first month after transplantation are also under a significantly higher risk of death from recurrent rejection. This finding is in accordance with work by Kubo et al. who report that patients with rejection episodes have a high likelihood of developing subsequent rejection within 2 months [16]. Recurrent rejection episodes may increase the risk of graft arteriosclerosis, a common cause for late morbidity and mortality after cardiac transplantation. On the other hand, early rejection episodes may lead to augmentation of immunosuppression and subsequently increase the risk of infection, cyclosporine induced nephrotoxicity, and malignancy. All these factors may decrease long term survival significantly.

These results suggest that short- and long term results may be improved by either avoiding transplantation with high-risk patients or developing strategies to minimize their pre- and postoperative risk.

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