Lung-transplantation in children and young adults: A 20 years single center experience

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Abstract

Lung transplantation in adults is an accepted therapeutic option, whereas in children there is ongoing debate on its positive impact on survival. We report our experience of the first twenty years of pediatric lung transplantation at a single center in Austria.

Patient survival, organ survival and freedom from bronchiolitis obliterans were estimated by Kaplan Meier curves. Pre- and post-transplant parameters were assessed and their influence on patient and organ survival evaluated by univariate tests and stepwise multivariate analyses.

A total of 55 transplantations were performed in 43 patients. One and 5-year patient survival rates were 72.1% and 60.6%, freedom from bronchiolitis obliterans syndrome was found in 52.6% of patients at 5 years post-transplant. Analyzing different eras of transplantation suggests an improvement over the years with a 5-year survival of 70.6% in the second decade. A positive effect of pretransplant diabetes mellitus and immunosuppression with the newer drug tacrolimus, a negative effect of pre-transplant in-hospital admission was found. A high rate of successful re-transplantation prolonged total patient survival.

Introduction

Lung transplantation has emerged as an accepted therapy for end-stage lung disease in adult patients, whereas for the pediatric population it is still controversial [1-3]. Since the first lung transplant after the implementation of cyclosporin in 1983, the number of lung transplants performed has increased to approximately 2500 per year worldwide [4]. Pediatric lung transplantation has scarcely been performed until the 1990's and even today represents only a minority of total procedures performed, accumulating to approximately 80 procedures per year worldwide [5]. Therefore, transplantation in children is preserved to a very small number of centers, with only 30 to 40 institutions reporting pediatric lung transplantations [5]. The reasons are manifold, including the paucity of both donors and recipients, the investment required in developing pediatric lung transplant centers and skepticism about the outcome. Survival after lung transplantation is still well below transplantation of other solid organs but is increasing over the last decades [2, 6, 7] [5]. The subgroup of children and adolescents has been repeatedly reported to have poorer results [3, 6-8], leading to ongoing discussion on the beneficial effect of lung transplantation on survival in these patients [2, 3, 6].

The Department for Thoracic Surgery at the Medical University of Vienna is one of the largest lung transplant centers in Europe, performing the highest per head transplantation rate (14.1 per million inhabitants) worldwide [9]. The first lung transplantation in an adolescent cystic fibrosis (CF) patient treated at the Department of Pediatrics and Adolescent Medicine of the center was performed in 1990. Since then our pediatric department has taken care of 43 patients before and after lung transplantation.

This report describes the experience of the first twenty years of pediatric lung transplantation at a single center in Austria. We assessed patient and graft survival and analyzed which covariates had an effect on the outcome of the procedure.

Material and Methods

The study was approved by the Local Ethics Commitee

Patient collective

The study population includes all lung-transplanted patients that were attended before transplantation at the Department of Pediatrics and Adolescent Medicine of the Medical University of Vienna, Pediatric Pulmonology, from the beginning of the procedure in April 1990 to January 2010. Most of the patients received their post-transplant care at our center, however, some patients died on intensive care unit or received part of their post-transplant care in their respective home country or at the local adult transplant ward. All transplantations were performed at the Department for Thoracic Surgery of the Vienna Medical University.

Our patient collective encompasses twelve young adults (> 17 years at transplantation), which is due to the fact that all patients with CF disregarding age were treated at the pediatric department until 1995.

Due to the geographical situation of Vienna, located at the eastern border of Austria, our patient population includes a high proportion (n=11) of foreign children and adolescents with highly variable social and medical background. Since the first transplantation in an Italian child in 2003, a total of eleven patients from abroad, including Hungary, Italy, Czech Republic, Germany, Romania, and Greece have been transplanted at our center. Selection and preparation for transplantation in these children was performed in cooperation with the respective home country. Post-transplant care was provided in Vienna only in four patients and as shared care in five patients. Two children received long term follow-up at their local center only. Adolescent patients from abroad transplanted by our surgery department but not presented at our pediatric ward before transplantation were not included into the study.

Investigated Parameters

We assessed various pre-and post-transplant parameters and included these data in a detailed patient registry. Pre-transplant parameters were patient age, gender, body mass index (BMI), underlying disease, nationality, lung function, bacterial infections, cytomegalovirus (CMV) status, preformed antibodies, diabetes mellitus as well as invasive ventilation and in-hospital admission at time of transplantation. Perioperative parameters included procedure of choice for transplantation, implementation of extracorporal membrane oxygenation (ECMO), ischaemia time, crossmatch, immunosuppression and induction therapy. Postoperative factors gathered were time on intensive care unit and total in-hospital time post-transplant, occurrence of bronchiolitis obliterans syndrome (BOS) and other post-transplant complications (kidney function impairment, lymphoproliferative disease, neurological complications) as well as causes of graft failure and death.

Statistical analysis

Kaplan-Meier curves were calculated to estimate freedom from BOS, patient survival and organ survival. Tests on all pre- and peritransplant parameters (all measured within 4 months before transplantation) were performed to identify risk factors for post-transplant survival and BOS occurrence. This was done by univariate cox-regression-models for the first transplant for each of the endpoints 'patient survival', 'transplant survival' and 'freedom from BOS'. Finally, a multiple extended cox-regression-model was calculated for each endpoint accounting for the parameters being significant in the univariate analysis (p-value smaller 0.05).

All analyses were performed using SPSS for windows version 17.0 or R 2.9.2

Transplant Procedure

Surgical approach was uni- or bilateral anterolateral thoracotomy or bilateral thoracotomy with transverse sternotomy ('clamshell technique'). Since 2001, intra-operative extracorporal

membrane oxygenation (ECMO) was applied in the majority of patients (69.8%) as reported by Aigner et al 2007 [10]. Mean ischemia time (second lung in double lung transplantation) was 335.3 ± 72.7 minutes.

Immunosuppression at time of transplantation consisted of different combinations of corticosteroids (100%), antiproliferative agents (azathioprine 18.6%, mycophenolate mofetil 79.1%) and calcineurin inhibitors (cyclosporin A 46.5%, tacrolimus 53.5%). In 15 patients, immunosuppression was switched during the post-operative course. Of these, five (11.4%) received rapamycin at some time point post transplantation. Induction was performed in the majority of patients, using antithymocyte globulin (ATG) in 54.8% and anti-IL2-receptor-antibodies in 9.5%. One patient received anti-CD3-antibodies after re-transplantation.

Cytomegalovirus (CMV) prophylaxis was performed with CMV hyperimmune globulin once a week for 4 weeks post-transplant and ganciclovir for 3 months. Since 2006, ganciclovir prophylaxis was given throughout the first post-transplant year in high risk patients (CMV-positive donor, -negative recipient).

Results

Forty-three individuals (m: 22, f: 21) undergoing a total of 55 transplantations (31 double-lung, six single-lung, eight bilateral lobar, two unilateral lobar, seven split-lung and one heart-lung transplantation) were included in the present study. Two living-donor transplantations were performed. At time of analysis, 21 patients had died (three of them after re-transplantation), eight were re-transplanted and two re-re-transplanted.

Mean age at first transplantation was 15.0 ± 6.9 years, ranging from six months to 30.4 years. Thirty-one patients (72.1%) were younger than 18 years, ten (23.3%) were below the age of ten. The most common cause for transplantation was cystic fibrosis (56.4%), followed by bronchiolitis obliterans syndrome (BOS) after first transplantation (21.8%). Indications for transplantation are displayed in table 1. Re-transplantation was performed after a median of 32 months (range: 2 days to 144 months). Almost half of patients (40%) needed in-hospital care at time of transplantation and 25% were on invasive ventilation. Five individuals were bridged to transplantation with ECMO. A detailed listing of pre- and postoperative factors of all transplantations is provided in table 2.

Thirty-day transplant survival was 89.1%; causes of early death or graft failure were multiorgan failure, primary transplant failure, intracerebral haemorrhage, intracerebral infarction and acute rejection. The most common causes of death during total follow-up were infections and BOS (28.6% each). Other causes were intracerebral haemorrhage/infarction and acute rejection (9.5% each) as well as cardiac complications, pulmonary bleeding, primary organ failure, carcinoma and multiorgan failure in one patient each (23.3%). We did not observe recurrence of underlying disease, despite the fact that our collective encompasses eight patients suffering from (possibly) immunologically-mediated diseases (idiopathic lung

fibrosis, idiopathic pulmonary hemosiderosis, graft versus host disease, primary pulmonary hypertension).

Five years post-transplant kidney function was impaired in 66.7% of patients (mild 46.7%, moderate 76.7%), with 9 patients (20.1%) requiring dialysis at some point during transplant follow-up. Fourteen patients (32.6%) showed neurological complications, including cerebral embolism, cerebral bleeding, posterior reversible encephalopathy syndrome (PRES) and epileptic seizures, while no post-transplant proliferative lymphoproliferative disease occurred during total follow-up period. One patient developed adenocarcinoma of the lung.

Median estimated survival (Kaplan-Meier) of all 43 patients was 112 months (95%CI 65.6-158.4), ranging from two days to 201 months (figure 1a). One-year, 5-year and 10-year patient survival rates after transplantation were 72.1%, 60.6% and 38.9%.

Median estimated transplant survival of all 55 transplantations was 71 months (95%CI 26.2-115.8), ranging from 2 days to 158 months (figure 1b). One-year, 5-year and 10-year graft survival rates were 70.9%, 51.2% and 15%, respectively. Graft survival of re-transplantation (median survival 76 months; 95%CI 22.2-115.7) was comparable to that of primary transplantation (median survival 71 months; 95%CI 0-206.6).

Freedom from BOS was found in 96.3% at 1 year and in 53.8% at 5 years post-transplant. Median time to occurrence of BOS was 48 months (95%CI 29.8-66.2). Median transplant survival after occurrence of BOS was 31 months (95%CI 13.9-48.1).

In patients below 18 years at first transplantation (n=31), outcome was comparable to that of the total sample. Median patient survival was 93 month, median organ survival 39 months (95%CI 0-88.4; figure 2a). One- and 5-year patient survival rates were 71% and 57.1%; 1- and 5-year organ survival rates 71% and 42.9%. Freedom from BOS was present in 93.6% 1 year and 53.6% 5 years after transplantation (median time to BOS 40 months; 95%CI 30.4-49.6).

When comparing the outcome according to different eras of the observation period (1990-1999 versus 2000-2009), there was a trend for better results in the second decade (figure 2b). Median transplant survival increased from 37 (95%CI 0-89.9) to 75 months (95%CI 25.5-124.5). One-year organ survival increased from 62.5% to 77.8% and 5-year survival from 43.8% to 52.9%. The same trend was found regarding patient survival (1-year survival 62.7% versus 77.8%, 5-year survival 50% to 70.6%). However these differences were not statistically significant. Freedom of BOS at 5-years post-transplant increased significantly from 14.3% to 75% (p=.019). Time to occurrence of BOS increased from a median of 39 to 81 months (n.s.).

Pretransplant diabetes mellitus was associated with a significant better patient (p=0.007) but not organ survival as well as with increased 5- year patient survival rates (47.8% versus 90.0%; p=0.023; figure 3a). This effect persisted in multivariate analysis.

A better survival of patients receiving the newer immunosuppressive drug tacrolimus compared to patients treated with CsA was observed in uni-and multivariate analysis. This was found for median patient (p<.03; figure 3b) and organ survival (borderline, p=.049) as well as for 5-year patient (p<.01) and organ survival rates (borderline, p=.056). We also observed a non-significant advantage of mycophenolate mofetil over azathioprine in patient (37 vs. 158 months) and organ survival rates (12 vs. 72 months). Both CsA and mycophenolate were used more frequently in the recent years, thus other non-assessed time-dependent parameters might interact with the results.

Moreover, in-hospital admission at time of transplantation was a significant parameter in univariate analysis. Patients needing in-hospital care (40%) had worse 1-year transplant survival than patients who were well enough to be treated at home (p=.009). This effect was not present for 5-year survival, which was similar in both groups. A similar trend was found for patients on invasive ventilation (25%) before transplantation (1-year transplant survival 50% vs. 76%), but this showed only borderline significance (p=.06).

We found no statistically significant effect on post-transplant occurrence of BOS, patient and organ survival for the parameters patient age, underlying disease (CF versus non-CF), nationality, kind of transplantation; lung function (FVC, FEV1, MEF50), BMI, bacterial colonization (*Burkholderia cepacia, Staphylococcus aureus*, *Pseudomonas aeruginosa*), time on waiting list, cross-match, presence of preformed antibodies, transplantation on ECMO, induction therapy, CMV-status or intraoperative ischemia time.

In multivariate analysis, both diabetes and immunosuppression with tacrolimus were found to have a positive influence on patient survival (p=.033), whereas for organ survival and freedom of BOS no independent risk factor was identified.

Discussion

Analyzing the first twenty years of lung transplantation in children, adolescents and young adults at our center, we observed a median estimated total patient survival of 112 months. One-year, 5-year and 10-year patient survival rates after transplantation were 72.1%, 60.6% and 38.9%. Stratification of data according to different eras of transplantation (1990-1999 vs. 2000.2009) points towards an improvement of transplant and organ survival as well as decreased occurrence of BOS over the years, with a 5-year survival rate in the second decade of 70.6%. Moreover, pre-transplant diabetes mellitus and the newer immunosuppressant tacrolimus has been shown to be associated with an improved survival, whereas pre-transplant in-hospital admission was associated with decreased early survival in univariate analysis.

Our results exceed the worldwide results presented by the ISHLT registry in 2010 (5yr survival 1990-2008 48%, 2002-2008 52% [11]. Analyzing the data of large single centers, we show comparable results (Hannover 2009, 1yr survival 69%, 5yr 44% [7]; London, Great Ormond Street Hospital 2004: 5yr survival 10 years ago 27%, more recent era 57% [12]); US, St. Louis Children's Hospital 1990-2002: 1yr survival 77%, 5yr 54% [13], Zurich 1992-2007, children and adults: 1yr survival 86%, 5yr 68% [2]). Likewise, improvement over the years has been demonstrated in other reports of pediatric and adult lung-transplantation [2, 5, 12]. However, comparison of our results to other lung transplant centers is difficult due to various special characteristics of our sample.

First, we have an increasing amount of patients from abroad, with a varying degree of shared care before and after transplantation. This is challenging in many ways. On site pre-transplant evaluation, especially regarding psychosocial aspects, is limited in time and quality due to language barriers. Language barriers are also complicating early post-transplant care, which takes place at our transplant center. Long-term follow-up is done as shared or local care at the patient's home country; in this period most problems arise from limited access to experienced

transplant units, communication problems between the different health care centers and financial issues. We show a similar short-term-survival of foreign patients compared to patients residing in Austria, however, long-term data are still missing and often difficult to obtain.

Second, we have a high rate of critically ill children demonstrated by the high proportion of patients that had to be treated in-hospital (40%), were on invasive ventilation (25%) or on ECMO (12.4%) before transplantation (table 2). This might account for the rather high mortality in the first post-transplant year in our collective. In fact, we showed a statistically significant decreased 1-year survival in patients that were admitted in-hospital before transplantation (p=<.01) as well as in patients on invasive ventilation (borderline significance). This is in line with other reports, describing pre-transplant mechanical ventilation to be a significant risk factor for morbidity and mortality in adults and children [5, 14, 15].

Third, we have a high proportion of patients that received re- or re-re-transplantation (23.3%). Re-transplantation remains the only therapeutic option in some cases of severe primary graft dysfunction, severe untreatable acute rejection and advanced BOS: However, due to the overall scarcity of donor organs and uncertain outcome its value has been questioned. One explanation for our high re-transplant rate might be the donor legislation in Austria ('presumed consent' system), leading to a comparable good organ supply [16]. Overall numbers of pediatric re-transplantations are low, with only 74 pediatric transplantations performed worldwide since 1994 [5] Re-transplantation has repeatedly been reported to have a poorer survival compared to primary transplantation in children and adults [17-21]. At our center, re-transplantation has previously been shown to have good survival rates in selected adult patients [22]. Equally, in the present study in pediatric recipients, we show survival rates after re-transplantation that are comparable to those after primary transplantation. This leads to an increased overall patient survival, resulting in very good long-term survival rates.

Finally, our sample involves some young adults transplanted in the first years of the program as a consequence of the lacking care centers for adult CF patients at that time. As we planned the study as a single center analysis, we decided to include these patients into general analysis. Outcome did not differ significantly between children and young adults.

We show a trend for a better outcome of patients transplanted in the second decade. However, while occurrence of BOS at five year post-transplant was significantly lower after 2000, neither increase in patient survival nor in transplant survival showed statistical significance. Several factors might contribute to these results, including the multiple time-dependent factors (induction therapy, immunosuppressive and anti-microbial therapy, transplant technique, intensive care and experience of involved care takers) changing over the follow-up period. In addition, small patient numbers may limit statistical analysis. In the annual registry of the International Society of Heart and Lung Transplantation (ISHLT), including data from all pediatric transplantations performed worldwide, significantly improved survival rates can be demonstrated only for the last few years [5]. In our collective, patients transplanted in the first and second era of the transplant program (table 3) differed in age, underlying disease, proportion of transplantation on ECMO, immunosuppressive therapy, FEV1 and pseudomonas colonization. Some of these factors, such as newer immunosuppressive drugs might have a positive impact on outcome, whereas others, such as younger patient age, might impair survival.

Interestingly, we found a significant better patient survival in both univariate and multivariate analysis for patients that suffered from diabetes mellitus before transplantation This was previously reported by other authors [2, 3], however, reasons for this observation are not exactly clear. An additional, yet unknown beneficial effect of insulin treatment [2] or a less severe effect on post-transplant survival if diabetes manifests before transplantation compared to new development after transplantation [3] has been discussed.

In many transplant centers, the use of tacrolimus and MMF has replaced CsA and azathioprine despite the fact that consistent data favoring one drug over the other in the treatment of pediatric lung transplant recipients are missing [23-26]. In our collective we found a clear positive impact on survival by the newer immunosuppressive drug CsA and probably also MMF. The use of these drugs was not evenly distributed over time, with tacrolimus and MMF being used much more commonly in the later years. As the beneficial effect of tacrolimus was confirmed in multivariate analysis, it seems unlikely that its advantage is only a marker for the better outcome in more recently transplanted patients. However, interaction with other non-assessed parameters, which changed over time cannot be excluded.

There are no randomized trials to assess the survival benefit of lung transplantation, so the outcome needs to be approached by statistical modeling [27]. In 2008, T. Liou presented a study using data from the U.S. CF Foundation Patient Registry and the Organ Procurement and Transplantation Network. He applied a proportional hazard model using multiple clinical covariates and the interactions of these covariates with lung transplantation as a time-dependent covariate. He stated that the majority of patients assessed (514 children suffering from cystic fibrosis) had an increased risk of death by transplantation, whereas clearly improved survival was shown for only less than 1% of patients [28]. However, several authors have questioned this results and shown clear survival benefit after pediatric lung transplantation [29-31].

The conflicting data on survival benefit of pediatric data adds up to general ethical problems of organ transplantation, such as donor rights, patient allocation, re-transplantation, and living donor transplantation. An important point in this aspect is quality of life (QoL) improvement by transplantation, which is an essential parameter besides survival benefit. Unfortunately, data on QoL, especially after lung transplantation in the pediatric age, is scarce [32, 33] [34]. Therefore conclusions need to be drawn from organ function data. According to the ISHLT

registry, the functional status of survivors is very satisfying, with the majority reporting no activity limitations [35]. In our experience, despite the high number of complications especially in the first months after transplantation, if the patient survives the early post-operative period, QoL generally improves clearly. Our patients generally live a rather normal life, go to school and attend sports as long as their lung function is not significantly impaired by BOS. Psychological problems, such as panic attacks or depression, that are frequently observed in the first weeks after transplantation, generally wane when the patients get better, however, this reflects only personal experience and was not systematically assessed in our study.

Another limitation of our study is the small patient number, which decreases the power of statistical analysis. We focused on the accuracy of pre-transplant parameters, only including data within four months before transplantation. This leads to missing data in some patients and thus further limits analysis. Low patient number is a general obstacle for the evaluation of pediatric transplantation. According to the ISHLT registry data of 2008, of the 36 centers reporting pediatric transplantations, only 5 reported more than 5 procedures per year [5]. Literature on pediatric lung transplantation includes predominantly single center descriptive studies with relatively few patients. Accordingly, to date most of recommendations and practical handling in the field of pediatric lung transplantation is based on extrapolation of adult lung transplant or other solid organ transplant data, which often is not feasible. Therefore, in the future, multicenter studies are essential to provide information, especially on distinct pediatric aspects of lung transplantation, such as developmental parameters, quality of life or pharmacokinetics of applied drugs.

Tables

Table 1.

	N	%
Cystic fibrosis	31	56.4
Primary pulmonary hypertension	4	7.3
Graft versus host disease after bmt	2	3.6
Bronchopulmonary dysplasia	1	1.8
Cystic adenoid malformation	1	1.8
Idiopathic pulmonary haemosiderosis	1	1.8
Idiopathic lung fibrosis	1	1.8
Congenital Alveolarproteinosis (ABCA3-Mutation)	1	1.8
Cardiac malformation with SPH	1	1.8
Re-transplantation :		
BOS	7	12.7
Untreatable acute rejection	3	5.5
Insufficient lung function after 1st tx	2	3.6

Table 1. Underlying disease (n=55)

bmt, bone marrow transplantation, SPH, secondary pulmonary hypertension, tx, transplantation

Table 2

Variable	
Gender (m / f), %	**51.2 / 48.8**
Age at tx, mean (range)	**15.0** (0.5-30.4)
BMI, mean (range)	**15.5** (11.0-25)
Lung function, median (range)	
FVC%pred	**37.6** (17.0-93.3)
FEV1%pred	**23.9** (14.0-107.6)
MEF50%pred	**10.6** (2.8-97.3)
Shared care, %	**25.6**
Waiting time (days), median (range)	**66.5** (1-339)
Preformed antibodies, %	**36.4**
Positive crossmatch, %	**33.3**
CMV high risk, %	**31**.0
Diabetes mellitus, %	**25.6**
Invasive ventilation before tx, %	**25**
In-hospital admission before tx, %	**40**
Bacterial colonization, %	
Staphylococcus aureus	27.9
Pseudomonas aeruginosa	67.4
Burkholderia cepacia	7.0
Kind of transplantation, %	
double lung	69.8
bilateral lobar	16.3
single lung	-
unilateral lobar	2.3
split lung	9.3
heart lung	2.3
Operation on ECMO, %	**73.2**
Ischemia time 2nd lung (minutes), mean (range)	**337.3** (172-555)
30-day transplant survival, %	**89.1**
Postoperative days on ICU, mean (range)	**22.4** (3-100)
Postoperative days in hospital, mean (range)	**43.7** (3-100)
Induction therapy, %	
None	35.7
ATG	54.8
IL2R-antagonists	9.5
Immunosuppression, %	
CsA /Tacrolimus	46.5 / 53.5
Azathioprine / MMF	19.0 / 81.0
Cause of graft failure / death, %	
Infection	28.6
BOS	28.6
Acute rejection	9.6
Intracerebral bleeding / infarction	9.6
Other (acute rejection, primary organ failure, multiorgan failure, cardiac complications, intracerebral hemorrhage, pulmonary bleeding)	23.8

Table 2: Patient characteristics of all patients at first transplantation (n=43)

ATG, antithymocyte globulins; BMI, body mass index, BOS, bronchiolitis obliterans syndrome, CF, cystic fibrosis; CsA, cyclosporine A; ECMO, extracorporeal membrane oxygenation, f, female; FEV1%pred, forced expiratory volume in one second, percent of predicted value; FVC, forced vital capacity, percentage of predicted value; ICU; intensive care unit; IL2R, interleukin 2 receptor; m, m ale; MEF50, maximum expiratory at 50% of FVC, percent of predicted value; MMF, mycophenolate mofetil; tx, transplantation

Table 3

	1990-1999 n=18	2000-2009 n=37	p
Gender (m / f), %	61.1 / 38.9	43.2 / 56.8	n.s.
Age at tx (years), mean (range)	18.3 (4.3-30.4)	13.0 (0.5-21.2)	.027
BMI, mean (range)	14.9 (12.3-17.4)	15.8 (11.0-25)	n.s.
Shared care, %	18.8	29.6%	n.s.
Lung function, median (range)			
FVC%pred	30.2 (17.0-57.0)	41.3 (19.8-93.3)	n.s.
FEV1%pred	20.5 (14.0-31.0)	27.7 (15.7-107.6)	.031
MEF50%pred	9.0 (2.8-26.3)	11.5 (4.3-97.3)	n.s.
Underlying disease, CF, %	93.8%	59.3%	.017
Diabetes mellitus, %	37.5	18.5	n.s.
Ischemia time (minutes), mean (range)	299.4 (172-360)	358.3 (280-555)	n.s.
Preformed antibodies, %	0	46.2	.024.
Positive crossmatch, %	40.0	29.6	n.s.
CMV high risk, %	37.5	26.9	n.s.
Invasive ventilation before tx, %	30.8	21.7	n.s.
In-hospital admission before tx, %	40.0	40.0	n.s.
Waiting time (days), median (range)	57 (1-199)	88 (1-339)	**n.s.**
Bacterial colonization, %			
Staphylococcus aureus	31.3	25.9	n.s.
Pseudomonas aeruginosa	87.5	55.6	.031
Burkholderia cepacia	12.5	3.7	n.s.
Transplantation on ECMO, %	35.7	92.6	<.001
Induction therapy, %			
ATG	75.0	42.3	n.s.
IL2R-antagonist	6.3	11.5	n.s.
Immunosuppression, %			
CsA / tacrolimus	87.5 / 12.5	22.2 / 77.8	<.001
Azathioprine / MMF	50.0 / 50.0	- / 100	<.001

Patient characteristics according to different eras of transplantation

ATG, antithymocyte globulins; BMI, body mass index, CF, cystic fibrosis; CsA, cyclosporine A; ECMO,
extracorporeal membrane oxygenation, f, female; FEV1%pred, forced expiratory volume in one second, percent
of predicted value; FVC, forced vital capacity expressed; percent of predicted value; IL2R, interleukin 2 receptor;
m, male; MEF50, maximum expiratory at 50% of FVC, percent of predicted value; MMF, mycophenolate mofetil;
tx, transplantation

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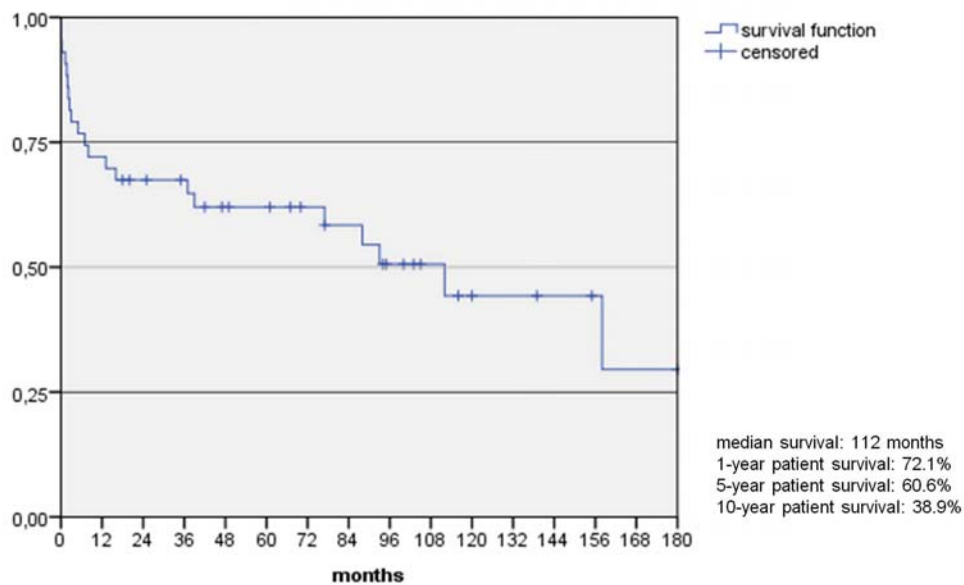
Figures

Figure 1

median survival: 112 months
1-year patient survival: 72.1%
5-year patient survival: 60.6%
10-year patient survival: 38.9%

Figure 1a. Patient survival (n=43)

median survival: 71 months
1-year organ survival: 70.9%
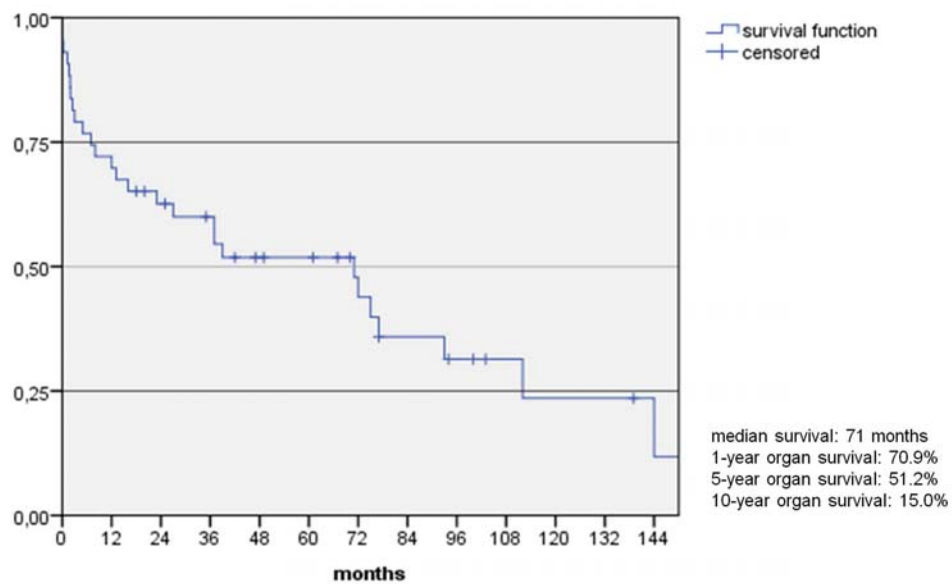5-year organ survival: 51.2%
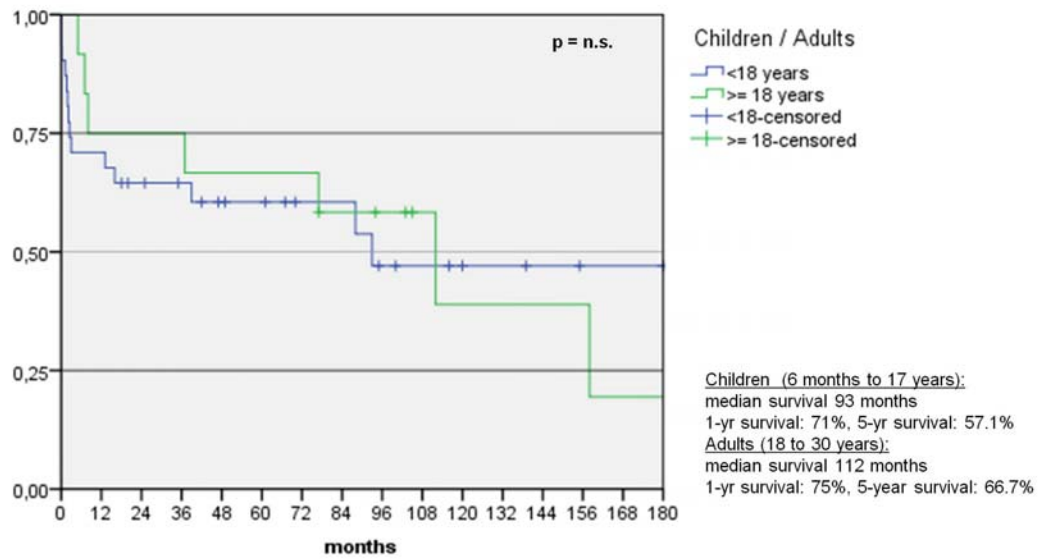10-year organ survival: 15.0%

Figure 1b. Transplant survival (n=55)

Figure 2

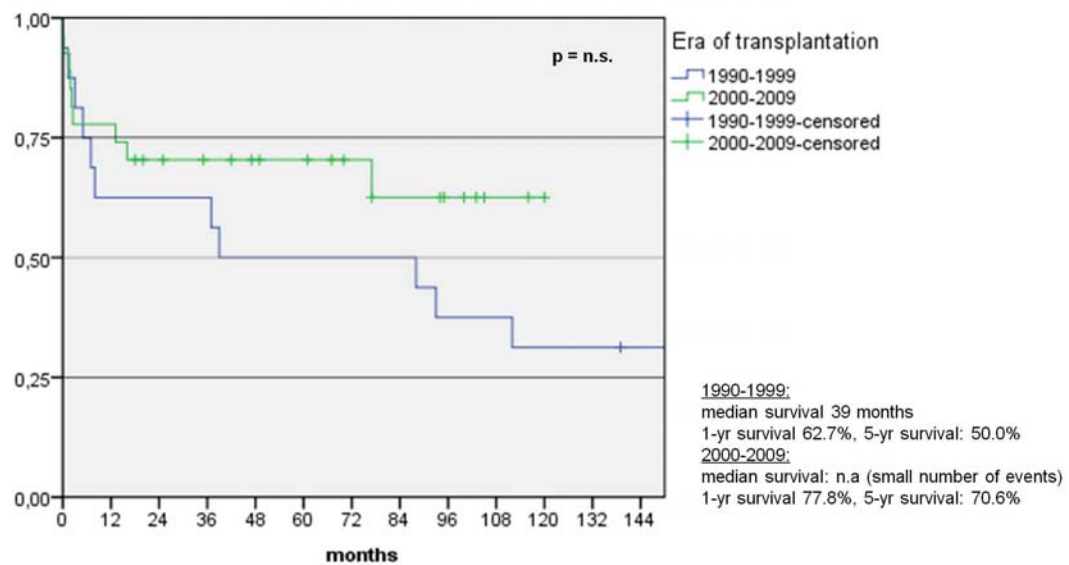Figure 2a. Patient survival according to age at 1st transplantation

Figure 2b. Patient survival according to transplant era (1990-1999 vs. 2000-2009)
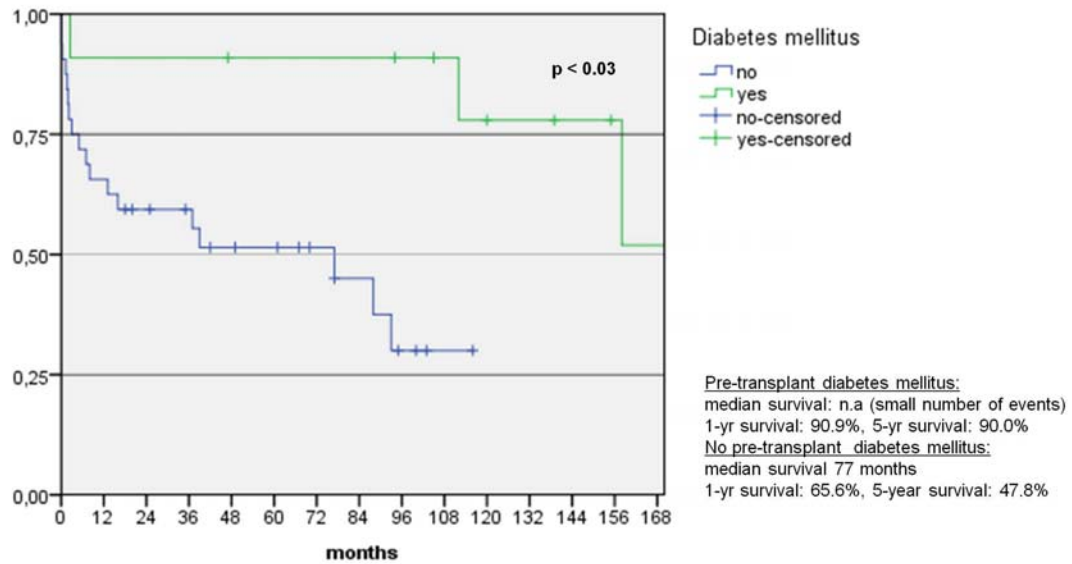
Figure 3

Figure 3a. Patient survival according to pretransplant diabetes mellitus
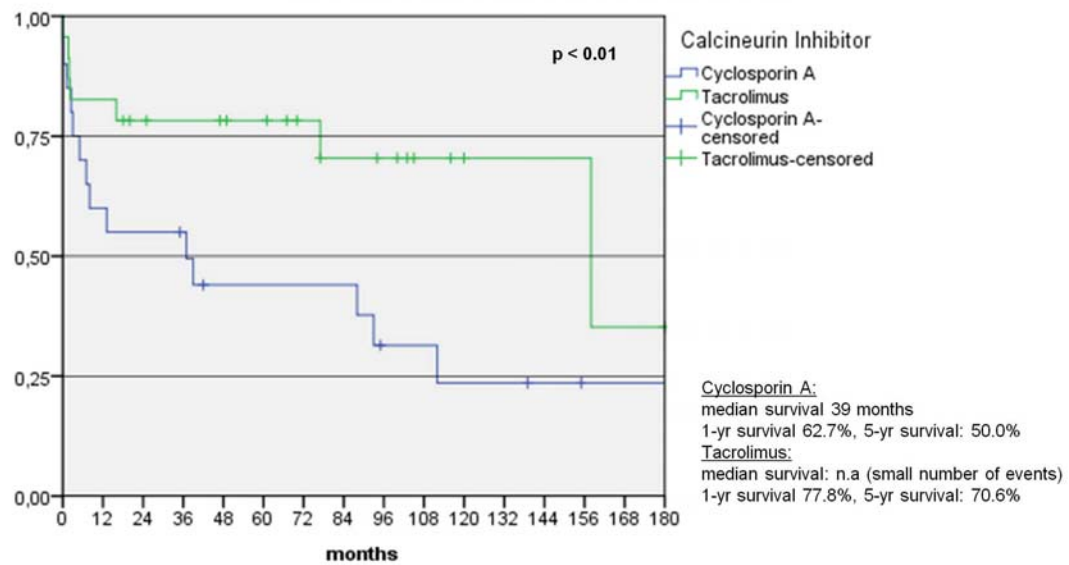

Figure 3b. Patient survival according to calcineurin inhibitor (cycloporin A versus tacrolimus)