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Impact of Renal Cadaveric Transplantation on Survival in End-Stage Renal Failure: Evidence for Reduced Mortality Risk Compared with Hemodialysis during Long-Term Follow-Up

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Abstract. Despite a superior quality of life and a favorable cost effectiveness, it has not been well established thus far whether renal cadaveric transplantation contributes to superior survival probability of end-stage renal disease patients in Europe, because the mortality rate on dialysis is lower compared with the United States. This analysis was undertaken to compare the mortality of wait-listed patients and transplant recipients during long-term follow-up, including the possibility of a retransplant in a single-center study. The study cohort included 309 consecutive patients, ages 17 to 72 yr, being registered on the waiting list of the Renal Transplantation Center of Mannheim since the initiation of the transplantation program on June 3, 1989. Follow-up was terminated on September 30, 1997, with a mean of 4.15 yr. A total of 144 renal cadaveric transplants (four retransplants) was performed during the follow-up period. A Cox regression model considering the time-dependent exposure to the different therapy modalities was applied for statistical analysis. Patients being removed from the waiting list or coming back to dialysis after transplantation were censored at time of withdrawal or graft failure. Transplantation resulted in a lower hazard ratio, which was 0.36 (95% confidence interval, 0.15 to 0.87) when the hazard of the wait-listed group was taken as 1.00. The underlying incidence rate of death was 0.026 per patient-year (0.032 on dialysis *versus* 0.016 with functioning graft). Performing the evaluation on an intention-to-treat basis without censoring the lower risk of the transplanted group was still pronounced according to a hazard ratio of 0.44 (95% confidence interval, 0.22 to 0.89). Thus, patients receiving a renal cadaveric transplantation have a substantial survival advantage over corresponding end-stage renal disease patients on the waiting list even in the setting of a single transplantation center where mortality on regular dialysis therapy was comparatively low.

Kidney transplantation provides an important option in the treatment of end-stage renal disease. Improvements of immunosuppressive therapy, organ preservation, and recipient selection by HLA matching have resulted in increased graft survival, currently ranging from 80 to 90% after 1 yr and 55 to 70% after 5 yr since transplantation, respectively (1–5). Furthermore, it has been shown that renal transplantation is associated with superior health-related quality of life and a favorable cost-effective ratio (6,7). However, survival remains an essential measure for the evaluation of the relative benefits when dialysis and kidney transplantation are compared in the replacement of renal function. Epidemiologic studies that were performed in the precyclosporine era could not show a substantial survival advantage of transplant recipients over dialysis patients on a waiting list (8–11). Recent data from diverse national registries suggest that kidney transplantation reduces patient mortality (1–4). However, only few population-based studies were performed using a Cox regression model to assess the mortality risk of transplant recipients and patients on hemodialysis (12,13). The comparison of survival outcome needs to be done in patients eligible for transplantation (14,15). Selection bias is likely to cause a disparity in mortality rates, because dialysis patients with serious comorbid conditions are not accepted for transplantation (16). Port and colleagues have shown that transplant recipients have a substantial survival advantage over corresponding dialysis patients on a waiting list; however, retransplantation and patients with failed grafts were not studied (14). Transferring the results from the United States to Western European countries might be conflicting, because survival of dialysis patients is superior in Europe (1,4,17,18). Moreover, it has been shown recently that a "center effect" is a determinant of mortality on regular dialysis therapy as well (19). Thus far, no data are available proving the impact of kidney transplantation on patient survival in Western Europe. In the present study a Cox regression model with a time-varying explanatory covariate was applied on the data-

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base of a single center considering all consecutive patients awaiting a renal cadaveric transplantation, including the possibility of a retransplant.

Patients and Methods

The study cohort consisted of all end-stage renal disease (ESRD) patients, ages 17 to 72 yr, who were registered on the waiting list of the Renal Transplantation Center of Mannheim between June 3, 1989, and September 30, 1997 (Figure 1).

Eight individuals were excluded from analysis because they never participated in the Eurotransplant kidney allocation procedure during the study period: One patient with hemolytic uremic syndrome recovered from renal failure, two patients had not yet started renal replacement therapy, and five additional ones had never been in a transplantable condition. Of these, two died within 6 and 22 mo, respectively, after withdrawal from the waiting list. Thus, a total of 301 individuals, 295 on hemodialysis and six on continuous ambulatory peritoneal dialysis, was considered for analysis. Two hundred fifty-eight patients were awaiting a primary transplant, and 53 patients were awaiting a retransplant. Each subject's history was represented by one or two observations in the data set.

One hundred sixty-one patients (167 cases) did not receive a transplant during the study period. Of these, 26 died while on the waiting list after a mean duration of 2.6 yr since registration (range, 3 mo to 7.5 yr). Nineteen patients were removed from the waiting list while alive. They were counted as censored and contributed follow-up to the dialysis group until date of withdrawal: 13 patients were no longer in a transplantable condition. Of these, six died between 2 mo and 3.8 yr after censoring (mean 1.75 yr). Six patients moved to a different transplantation center; four of them received an allograft but did not contribute follow-up to the transplant group in the primary analysis.

A total of 144 renal cadaveric transplants was performed in 140 individuals. Four patients were transplanted twice during the study period. One hundred four patients with stable graft function counted for complete follow-up until the end of study time. Eight patients died with a functioning graft. Mean duration of follow-up since transplantation was 3.25 yr (range, 7 mo to 6.6 yr). Another 28 patients (32 cases) came back to regular renal replacement therapy after graft failure. They were counted as censored in the transplant group. Of these, five died on dialysis after a mean follow-up of 2.5 yr since censoring (range, 1.5 mo to 5.6 yr). One patient was lost to follow-up 1 yr after graft failure. Ten patients were readmitted on the waiting list. They were counted as cases again. Of these, four underwent a retransplantation.

A secondary evaluation was done on the basis of an intention-to-treat design. Each individual was left in the pre- or posttransplant group until death occurred or the end of study time was met. Censoring was not performed even after a patient had been withdrawn from the waiting list or the graft had failed. Individuals undergoing a primary transplantation after moving to a foreign center accounted for the transplantation group from date of transplantation.

Data on each individual were obtained from pretransplant clinical files proving suitability as a transplant candidate before admission on

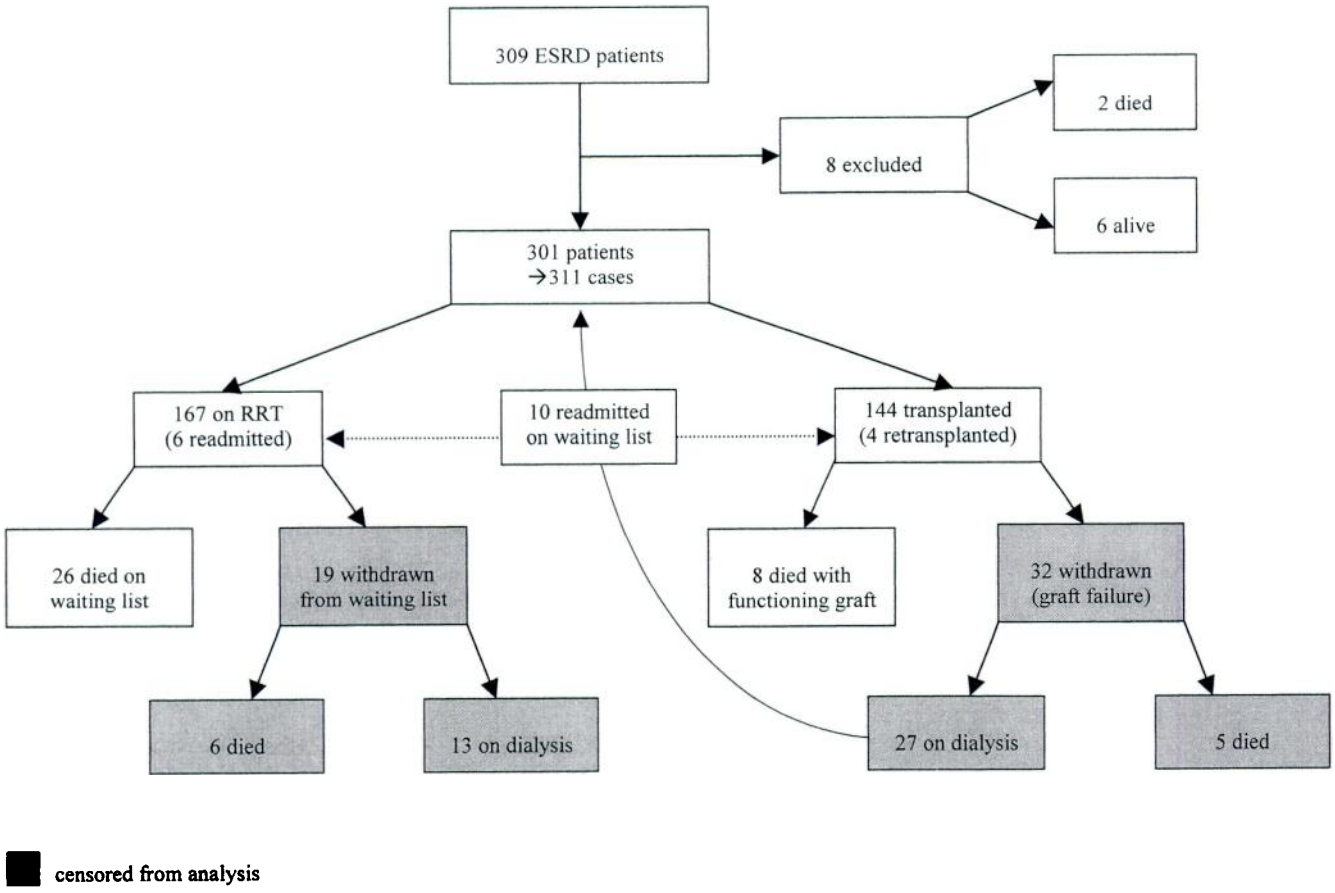

Figure 1. Participant flow and trial profile.

the waiting list. Evaluation of the patients included medical history, physical examination, HLA typing, viral titers (cytomegalovirus, HIV, hepatitis B or C), routine laboratory studies, electrocardiogram, chest radiograph, abdomen ultrasonogram, voiding cystourethrogram, and endoscopy of the upper gastrointestinal tract. Cardiac catheterization was performed in diabetic patients and patients older than 55 yr, or if indicated by patient history.

Donor organs were allocated according to the Eurotransplant rules of organ sharing. Almost 55% of the kidneys retrieved were shipped, and 45% were transplanted locally with permission by Eurotransplant. Since the implementation of the XCOMB algorithm in 1996, a higher proportion of long-waiting patients has been transplanted. This new computerized procedure of organ allocation has been proven to reduce the average waiting time of renal transplant recipients by adjustment for rare HLA phenotypes and HLA homozygosity, providing for an almost optimal HLA match distribution and a reasonably balanced kidney exchange rate among the transplantation centers (20).

All patients undergoing renal transplantation received a cyclosporine-based triple drug immunosuppressive regimen. Since 1996, azathioprine has been replaced by mycophenolate mofetil. Antirejection therapy was initiated with high-dose steroids. In case of a steroid-resistant rejection, polyclonal anti-T lymphocyte globulins and/or OKT3 were applied.

The Cox regression model (21) with time-varying explanatory variables was applied for statistical analyses because exposure to different therapy modalities (pretransplant *versus* posttransplant) changed over time (22,23). Study entry was defined as the date of admission on the waiting list. Follow-up was terminated on September 30, 1997, or at the earlier date of censoring from study group or death, respectively. Each subject contributed follow-up to the dialysis group. Subjects changing the exposure group by transplantation contributed follow-up to the posttransplant group from the date of allografting.

Several pretransplant characteristics were obtained for multivariate analysis: Age at admission on waiting list, time interval between initiation of renal replacement therapy and admission on waiting list, number of previous transplants, quantity of antihypertensive drugs, residual diuresis on regular dialysis therapy, and body mass index were introduced as continuous variables. Gender and original disease (diabetes, yes/no) were coded as dichotomous variables.

Relative risk of death was calculated from the ratio of death rates among transplant recipients relative to patients awaiting a transplant for the same time interval since placement on the waiting list. Results are presented with 95% confidence interval (CI).

Survival curves were generated according to the Kaplan–Meier method. The equality of the survivor function across the different therapy groups (transplant recipients *versus* dialysis patients) was tested using the log-rank test.

Differences in proportions and means were tested with the χ^2 test and t test, respectively. A P value of <0.05 was taken as significant. Statistical analysis of the data set was performed with Stata Statistical Software for Microsoft Windows (version 5.0).

Results

A total of 301 patients with ESRD were included in the analysis. Mean follow-up was 4.2 (SD 3.7) yr for the total study population, when censoring was performed in case of graft failure or withdrawal from the waiting list. Patient demographics and clinical characteristics at admission on waiting list are presented in Table 1. The retrospective analysis of the data does not show a significant difference between patients who were transplanted and those who remained on dialysis. The patient groups did not differ with regard to body mass index or severity of hypertension, estimated by the quantity of prescribed antihypertensive drugs and residual renal function during renal replacement therapy. Corresponding data were available in 98.1, 98.6, and 92.0% of patients, respectively. Average age at baseline (48.3 *versus* 44.0 yr, $P < 0.001$) and the prevalence of diabetes (13.8% *versus* 4.9%, $P < 0.008$) were higher in the dialysis group, reflecting an increasing proportion of elderly and diabetic patients who were accepted for transplantation as time went on, while the average waiting time was not affected.

The overall incidence rate of death was 0.026 per patient-year (0.032 on dialysis *versus* 0.016 with functioning graft). Using the Cox model with a time-dependent covariate to control for the span of time until transplantation, a hazard ratio of 0.36 (95% CI, 0.15 to 0.87) was calculated in favor of the transplant recipients. The relative risk of mortality controlled for age, gender, and underlying disease (diabetes, yes/no) was 0.23 (95% CI, 0.03 to 1.82), 0.34 (95% CI, 0.10 to 1.21), and 0.31 (95% CI, 0.10 to 0.87) at 3, 5, and 8 yr since placement on the waiting list, respectively. A Kaplan–Meier plot is shown in Figure 2.

In the multivariate analysis, age at admission, severity of hypertension, and the presence of diabetes as underlying disease for ESRD were associated with increased hazards, whereas the volume of the residual diuresis at entry to the waiting list had a small but statistically significant beneficial effect. However, transplantation was the most important discriminating variable to reduce mortality (Table 2).

Applying the intention-to-treat design, the mean follow-up of the study population was 4.7 (SD 3.4) yr. Transplantation still had a beneficial effect on patient survival (Figure 3) according to a hazard ratio of 0.44 (95% CI, 0.22 to 0.89). The underlying incidence rate of death was 0.032/patient-year (0.038 pretransplant *versus* 0.023 posttransplant). The adjusted relative risk of mortality for the 3-, 5-, and 8-yr interval since placement on the waiting list was 0.37 (95% CI, 0.08 to 1.63), 0.43 (95% CI, 0.16 to 1.19), and 0.52 (95% CI, 0.24 to 1.11), respectively.

Discussion

This study provides evidence that long-term survival is superior in transplant recipients compared to waiting-list transplant candidates in the setting of a single-center analysis. Our data are supported by previous observations suggesting a beneficial effect of renal transplantation with regard to long-term morbidity and mortality in patients with ESRD: Transplantation leads to regression of uremic cardiomyopathy (24) and decreases cardiovascular mortality as well (25). According to the registry of the U.S. Renal Data System, cardiovascular causes of death predominate in the ESRD patient population (1). It was recently published that hepatitis C virus-positive renal transplant recipients had a better survival than similar hepatitis C virus-positive patients awaiting transplantation after a follow-up of 2 yr minimum (26). Various studies assessing the suitability of elderly patients for transplantation conclude that it can be done safely and successfully in patients over age

Table 1. Demographics of the study population and comparison of the different therapy groups at baseline after admission on waiting list[a]

Characteristic	All Cases (n = 311)	Transplant Group (n = 144)	Dialysis Group (n = 167)	P Value
Age at admission on waiting list (yr)	46.3 ± 11.8 (17.0 to 72.1)	44.0 ± 11.7 (17.0 to 67.2)	48.3 ± 11.5 (19.1 to 72.1)	0.001
Gender				
male	190 (61.1%)	87 (60.4%)	103 (61.7%)	0.820
female	121 (38.9%)	57 (39.6%)	64 (38.3%)	
Previous transplantation				
n = 0	258 (83.0%)	122 (84.7%)	136 (81.4%)	0.442
n = 1	39 (12.5%)	18 (12.5%)	21 (12.6%)	
n = 2	10 (3.2%)	3 (2.1%)	7 (4.2%)	
n = 3	4 (1.3%)	1 (0.7%)	3 (1.8%)	
Time spent on waiting list (yr)	2.56 ± 2.25 (0.02 to 15.0)	2.55 ± 2.22 (0.05 to 15.0)	2.58 ± 2.29 (0.02 to 10.52)	0.903
Interval ESRD to wait-listing (yr)	3.16 ± 4.79 (0.02 to 25.03)	2.89 ± 4.19 (0.02 to 22.44)	3.39 ± 5.26 (0.02 to 25.03)	0.360
Original disease				
diabetes mellitus	30 (9.7%)	7 (4.9%)	23 (13.8%)	0.008
glomerulonephritis	130 (41.8%)	65 (45.1%)	65 (38.8%)	
hypertensive nephropathy	11 (3.5%)	5 (3.5%)	6 (3.6%)	
interstitial nephritis	31 (10.0%)	13 (9.0%)	18 (10.8%)	
polycystic kidneys	33 (10.6%)	18 (12.5%)	15 (9.0%)	
other	35 (11.2%)	16 (11.1%)	19 (11.4%)	
unknown	41 (13.2%)	20 (13.9%)	21 (12.6%)	
Body mass index (kg/m^2)	22.3 ± 3.5 (14.3 to 34.3)	23.0 ± 3.3 (14.3 to 32.5)	23.6 ± 3.7 (15.7 to 34.3)	0.113
Antihypertensive medication (drug/person)	1.4 ± 1.2 (0 to 5)	1.3 ± 1.1 (0 to 5)	1.5 ± 1.3 (0 to 5)	0.164
Residual urine volume (ml/24 h)				
<500 ml	127 (44.4%)	58 (43.3%)	69 (45.4%)	0.690
500 to 1000 ml	56 (19.6%)	20 (20.9%)	28 (18.4%)	
>1000 ml	109 (36.0%)	35 (35.8%)	55 (36.2%)	

[a] ESRD, end-stage renal disease.

60 (27–31). These data were confirmed by a population-based study comparing the impact of transplantation *versus* dialysis on mortality in this age group. Using a Cox regression, the time-dependent hazard ratio was estimated at 0.47. However, these studies tend to overestimate the transplantation effect due to selection bias, since renal transplant candidates exhibit less comorbid conditions than the average dialysis population (16). The overall mortality of ESRD patients in the United States was calculated at 168.2 per 1000 patient-years at risk (1). Comparing transplant patients and all regular dialysis patients, the death rate is eightfold higher in the latter group (30.2 *versus* 247.1), which cannot only be explained by the transplantation effect. In our series, the crude death rate was 32.6 *versus* 16.2 per 1000 patient-years in the pre- and posttransplant group, respectively. Thus, for the assessment of the transplantation effect on survival, the analysis needs to be restricted to patients who have been screened as eligible for transplantation, *i.e.*, patients on the waiting list.

It is unlikely that confounding-by-indication accounted for a relevant bias in the present study, because the allocation of donor organs to the individual recipient was centrally directed by Eurotransplant, delivering a computerized, mainly HLA-based allocation algorithm. A limited number of only three individuals received a transplantation on a special urgency mode. On the other hand, patients coded to be in a temporarily nontransplantable condition were not considered in the allocation algorithm. This may have biased the equality of organ allocation in that healthier patients were favored to receive an allograft. Nevertheless, it is rather unlikely that this caused major selection bias because the rate of temporarily nontransplantable patients was low during the entire study period, ranging between 5 and 8%.

Demographics of transplant recipients and candidates at baseline revealed no differences, except for a higher mean age and an elevated percentage of diabetic patients in the waiting list group (Table 1). Looking at our data in detail, it was quite

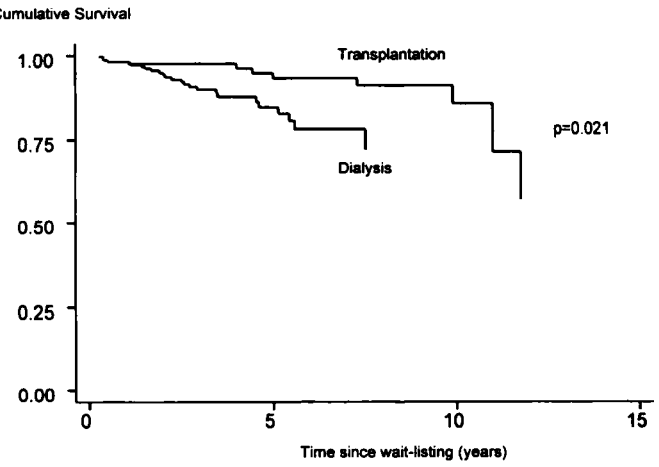

Figure 2. Kaplan–Meier survival estimates of waiting list and transplanted patients.

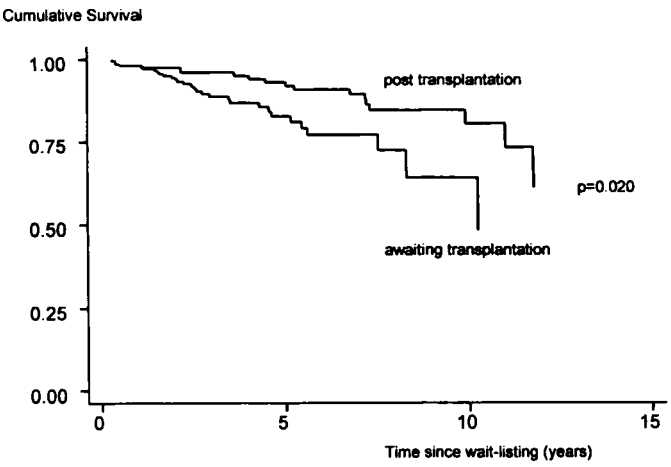

Figure 3. Kaplan–Meier survival estimates of waiting list and transplanted patients. Intention-to-treat design.

clear that the proportion of elderly and diabetic patients being accepted for transplantation increased with time. However, average waiting time was not affected, resulting in a higher percentage of this patient category awaiting a transplant. When eliminating diabetic patients from analysis or censoring patients over age 60, the hazard ratio still ranged between 0.33 and 0.30 (95% CI, 0.12 to 0.87) in favor of the transplant recipients, indicating that this had no influence on the study outcome. Moreover, the changes of patient demographics with time reveal a trend to include an increasing number of high-risk patients into the transplantation programs worldwide (32). These patients are more likely to be older, diabetic, or obese, as was demonstrated in the 30-yr Cleveland Clinic experience (33). To control for this, we introduced these variables for the statistical analysis when using the Cox regression model.

Apart from diabetes, several individual characteristics contribute to the risk of mortality in the hemodialysis population (34). The number of antihypertensive drugs prescribed on admission to the waiting list was indicative of the severity of hypertension. Data from patient files revealing the 24-h urine

Table 2. Multivariate Cox regression analysis with time-varying covariate

Variable	Hazard Ratio (95% CI)	*P* Value
Transplantation	0.37 (0.14 to 0.97)	0.045
Age (admission on waiting list)	1.05 (1.01 to 1.09)	0.011
Gender	1.41 (0.61 to 3.27)	0.415
Diabetes mellitus	4.36 (1.60 to 11.86)	0.004
No. of previous transplants performed	0.78 (0.31 to 1.92)	0.588
Time interval since ESRD	1.10 (0.99 to 1.21)	0.084
Body mass index	1.07 (0.97 to 1.18)	0.175
No. of prescribed antihypertensive drugs	1.41 (1.01 to 1.96)	0.043
Residual urine volume	0.999 (0.998 to 0.999)	0.017

collection at study entry were used to evaluate the residual renal function. In the multivariate analysis, the amount of BP-lowering medication and the 24-h urine volume were found to be independent variables affecting survival (Table 2). With some limitations, these results are consistent with previous studies quantifying the impact of hypertension on survival in the hemodialysis population and after renal transplantation as well (35–37). The persistence of residual renal function was shown to reduce the risk of death in patients on regular dialysis therapy (38).

Retransplantation is associated with the potential for inferior success rates due to increased risk of allograft rejection (5). It is remarkable that waiting for a retransplant did not predict an elevated mortality risk in the multivariate analysis (Table 2), although the total duration of ESRD is longer in this patient category. This could be explained by selection bias, because patients in a nontransplantable condition are excluded from readmission to the waiting list. However, taken together, the previous transplantation might have conferred survival benefit to these patients as well.

Alterations of treatment modalities are in principle a methodologic problem of any observational study. In 1996, azathioprine was replaced by mycophenolate mofetil in the standard immunosuppressive protocol at our center. However, it is unlikely that this had a major effect on the outcome of the current study. Data from controlled clinical trials confirmed a beneficial effect of mycophenolate mofetil on the cumulative incidence of biopsy-proven rejections 0 to 6 mo after transplantation (39–41). Nevertheless, there was no impact on graft loss and patient mortality in the pooled, 1-yr efficacy analysis (42).

One-year graft function is between 80 and 90% worldwide due to the general use of the new generation immunosuppressants. However, mainly because of chronic rejection, graft survival barely exceeds 65% at 5 yr after transplantation (1–5).

Port and colleagues demonstrated in a population-based evaluation from the Michigan Kidney Registry that patients receiving a primary transplantation have a substantial survival advantage over corresponding dialysis patients on the waiting list. The analysis was done on an intention-to-treat basis, leaving patients in the transplanted group even after the graft had failed. Patients who were removed from the waiting list due to illness were analyzed as if they remained on the waiting list eligible for transplantation (14). It was argued that this procedure is useful to advise transplant candidates prospectively (14,15). In other words, the evaluation mainly addresses the issue of whether it is favorable to receive a transplant, regardless of graft outcome in follow-up, which is comparable to a safety analysis to some extent. However, the intention-to-treat evaluation results in selection bias and could overestimate the survival benefit of transplantation if patients who are no longer in a transplantable condition are considered as transplant candidates for analysis. On the other hand, the percentage of transplant recipients returning to dialysis because of chronic rejection is getting higher with time. Therefore, the efficacy analysis of transplantation on patient survival is offended due to a mixing of the effects of alternative therapeutic modalities in long-term follow-up unless patients with graft failure or those who are no longer eligible for transplantation are censored. When applying the intention-to-treat design to our data, a statistically significant effect of transplantation was still detectable. The hazard ratio was calculated to be 0.44 (95% CI, 0.22 to 0.89). However, the relative risk adjusted for age, gender, and presence of diabetes as underlying disease tended to rise with time due to an increasing proportion of patients coming back to dialysis therapy after graft failure.

To our knowledge, the current study is the first to prove the beneficial effect of renal transplantation on survival by applying a Cox regression model with a time-dependent covariate in a single-center study. Due to the completeness of the database, it was possible to calculate the impact of transplantation with high internal validity in long-term follow-up. Furthermore, retransplants were considered in the analysis as well, which is appropriate in a clinical setting. It was emphasized by Port *et al.* that mortality is raised in the perioperative phase, which is counterbalanced by the beneficial effect of transplantation after 325 d. Crude mortality of the waiting list dialysis population was calculated to be 10.7% per year, and the relative risk of mortality was shown to rise to 2.43 during 30 d after transplantation in this population-based study (14). Thus, an additional lethality risk of 15% due to transplant surgery can be estimated. In our series, no death occurred within 6 mo after surgery. Actuarial patient survival at 1 and 5 yr after transplantation was 98.5 and 92.8%, respectively. These results are comparable with a larger single-center study from the United States (43). Taking recent data from the United Network for Organ Sharing Scientific Registry, the overall patient survival rates at 3 mo and 1 yr after transplantation were 97.3 and 94.7%, respectively. For comparison, the corresponding survival rates of waiting list patients can be calculated approximately from the incidence rate of death. According to the data of the Michigan Group and our study, the estimated patient survival is between 97.3 and 99.2% at 3 mo, indicating that the lethality risk due to transplant surgery is low today. Early mortality is obviously related to various recipient characteristics (14); however, the existence of a "center effect" cannot completely be excluded. Nevertheless, significant improvements in the prevention and treatment of potentially lethal complications after renal transplantation have generally been achieved during the past decade. Thus, encouraging patients to undergo renal transplantation should not overemphasize the potential of an elevated perioperative mortality risk.

In summary, this center-based analysis demonstrates that renal cadaveric transplantation offers a substantial survival advantage to patients with ESRD. The beneficial effect is pronounced even in long-term follow-up. Besides the improved quality of life and cost effectiveness, nephrologists should take this survival advantage into consideration when advising patients eligible for transplantation. Pointing out the life-saving advantage to the public might promote organ donation, as organ shortages are still the most important limitation in clinical transplantation today.

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