Patient survival after renal transplantation; more than 25 years follow-up

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Abstract
Background. The determinators of patient survival after renal transplantation are incompletely known, and conflicting results have been reported. This may have been influenced by time-related changes in patient selection, post-transplantation management and immunosuppressive regimens. This study was performed to evaluate in recipients of a first renal transplant the effect of patient characteristics, transplantation era, and the immunosuppressive regimen on patient survival.

Methods. We used data from the Leiden Renal Transplant Database of all first renal transplantations performed between 1966 and 1994 in Leiden, the Netherlands. The effect of the following parameters on mortality was investigated: era of transplantation, sex, age at transplantation, cause of renal failure, immunosuppressive regimen, type and duration of pretransplantation dialysis, hypertension, diabetes mellitus, and smoking. In addition we analysed the causes of death. Results were expressed as crude mortality rates, relative risks of mortality, and standardized mortality ratios as compared with death rates in the Dutch population.

Results. The analysis comprised 86 living donor transplant recipients and 916 cadaver transplant recipients. After adjustment for age and sex, the relative risk of mortality for living donor transplant recipients compared with cadaver transplant recipients was 0.5 (95% CI 0.2 to 1.03, P = 0.06). In first cadaver kidney transplant recipients the risk of first-year mortality improved significantly with time, which coincided with the introduction of cyclosporin. The risk of mortality after the first year was higher in patients aged over 40 years at transplantation, men, smokers, and in the presence of hypertension or diabetes, but the effect of individual factors on mortality was small. We found no effect of the type of pretransplantation dialysis or the duration of pretransplantation haemodialysis on post-transplantation mortality. The standardized mortality ratio for recipients of first renal transplants was 14 times the population average in the first year after transplantation and was still four times in the remaining years.

Conclusion. In the present study, time-related changes in patient management were responsible for improved patient survival in the first year after transplantation during the study period. Many individual factors contributed moderately to the risk of mortality after the first year. Compared to the general population the mortality rate of renal transplant recipients was significantly higher during the whole follow-up period.

Key words: age; azathioprine; cyclosporin; diabetes mellitus; dialysis; era; hypertension; immunosuppression; renal transplantation; survival analysis

Introduction
Survival after renal transplantation is the most important outcome measure when transplantation results are analysed. While graft survival improved significantly after cyclosporin was introduced in 1983 [1,2], the influence of various characteristics on short-term and long-term patient survival is incompletely known. This may have been influenced by time-related changes in patient selection, post-transplantation management, and immunosuppressive regimens. Since cadaver kidney transplant recipients are now primarily treated with cyclosporin, time-dependent changes in post-transplantation care and the effect of cyclosporin are interwoven. With time older patients are being accepted for transplantation [3–5]. The acceptance of older transplant recipients is a matter of debate [6–8].

The present study identifies the effect of era, immunosuppressive regimen, and pretransplantation patient characteristics, including atherogenic factors, on survival in recipients of a first donor kidney, transplanted between 1966 and 1994 in Leiden, the Netherlands. In the present analysis we used follow-up data that had been recorded for all renal transplant recipients since 1966.
Subjects and methods

In the Leiden Renal Transplant Database pre- and post-transplantation patient characteristics and follow-up data have been recorded prospectively for all renal and combined renal–pancreas transplantations, performed in the University Hospital of Leiden, the Netherlands since 1966. We used this database as the primary source of information. Where necessary, data were supplemented from the transplantation charts or Eurotransplant data.

Subjects

This study was restricted to first renal transplants. Cadaver and living donor kidney transplantations were separately analysed. All patients were followed until 1 January 1994. Mortality was separately determined within and after the first year post-transplantation. Graft failure was defined as the need for renal function replacement therapy, from any cause. Because the follow-up of patients after the occurrence of graft failure was incompletely recorded in the Database, such patients were regarded as withdrawn alive at the time of graft failure. In all other cases the patient was assumed to be lost to follow-up.

The cause of death was classified as due to (1) cardiovascular or cerebrovascular accident (2) infection (3) malignancy, including lymphoreticular as well as solid tumours, (4) miscellaneous known causes, including gastrointestinal or hepatic causes, trauma or uraemia, and (5) cause unknown or missing. The cause of death was investigated in relation to sex and the immunosuppressive regimen.

The effect of the following parameters on mortality was investigated: (1) Era of transplantation; the period of interest was divided into four periods: 1966–1974, 1975–1983, 1984–1989, and 1990–1994. (2) Sex. (3) The age at transplantation, divided into four categories (under 40 years, 40–50 years, 50–60 years, and over 60 years). (4) The cause of renal failure, which was subdivided into primary glomerulonephritis, diabetes mellitus, polycystic kidney disease, hypertension, miscellaneous known causes, mostly consisting of chronic pyelonephritis, urological diseases, analgesic nephropathy, systemic lupus erythematosus, and other secondary forms of glomerulonephritis. The remaining category consisted of renal failure of unknown origin. (5) The immunosuppressive regimen consisted of azathioprine with prednisone before the second half of 1984. After introduction of cyclosporin in 1984 practically every cadaver kidney transplant recipient has been primarily treated with cyclosporin and prednisone. In a number of patients, azathioprine had been substituted for cyclosporin 3–6 months after transplantation, mostly as a part of a randomized trial, the results of which have been published earlier [9,10]. (6) Pretreatment dialysis was divided into no dialysis, haemodialysis only, peritoneal dialysis only or a combination of haemodialysis and peritoneal dialysis. The duration of dialysis was recorded in months. (7) Hypertension, defined as the use of antihypertensive medication at the time of transplantation, irrespective of the blood pressure measured. This approach is used as an alternative for 24-h blood pressure measurements [11]. (8) Diabetes mellitus. (9) The smoking status at the time of transplantation, which was coded as yes or no. No data were available on the duration and number of cigarettes smoked. Serum cholesterol values had only been recorded in a limited number of probably selected high-risk patients and therefore the effect of serum cholesterol on mortality could not be investigated.

Statistical methods

The crude mortality rates per 100 person years of follow up were calculated in the various separate categories. Mortality to all causes was also compared to the expected mortality obtained as an average of the death rates in the general Dutch population during the follow-up period, standardized for age, sex and calendar period (standardized mortality ratio). The 95% confidence limits of the standardized mortality ratio were calculated under the assumption that the variance of the observed mortality follows a Poisson distribution. The cumulative survival was estimated with the product-limit method (Kaplan–Meier). To quantify the different determinants for death and to adjust for possible confounding variables, we used a Cox proportional hazard model. Dummy variables were created for all determinants, with the first category as reference category. Statistical analysis was performed using the PYORS and SPSS software packages.

Results

Of the 1098 first renal transplantations performed between 1966 and 1994, 96 cases were lost to follow-up (8.7%). Of the 1002 evaluable transplantations 916 were cadaver kidney transplantations, comprising 163 deaths (18%), 330 patients (36%) withdrawn alive because of graft failure, and 423 patients (46%) with follow-up completed up to 1 January 1994. The remaining 86 cases were living donor kidney recipients, including 8 deaths (9%), 12 graft failures (14%), and 66 patients (77%) with follow-up to 1 January 1994. The 86 living donors consisted of four identical twins, 28 HLA-identical siblings, 20 haplo-identical siblings, three non-identical siblings, 19 parents, six children, one other related donor, and eight unrelated donors. The mean (SD) age of transplant recipients at transplantation was 41.0 (13.7) years for the cadaver kidney transplant recipients, compared with 35.8 (14.3) years for living donor transplant recipients. Because the number of living donor kidney recipients was small, the analysis of the effect of specific factors on mortality in these patients lacked statistical power and only overall mortality rates are therefore presented for these patients.

Overall rates and relative risks of mortality

Survival of recipients of cadaver and living donor kidneys is depicted in Figure 1. The crude mortality rate for cadaver kidney transplant recipients was 3.3/100 person-years of follow-up, i.e. 5.8/100 person-years within the first year post-transplantation and 2.8/100 person-years thereafter. Actually the decrease in mortality occurred at 3 months post-transplantation, the mortality rate in the first 3 months being 10.0/100 person-years and 3.0/100 person-years thereafter.

For living donor kidney transplant recipients the overall mortality rate was 1.3 per 100 person-years of follow-up. 3.7/100 person-years within the first post-transplantation year and 0.9/100 person-years thereafter. After adjustment for age and sex in a multivariate
Cox model, the relative risk of mortality for living donor transplant recipients compared with cadaver transplant recipients was 0.5 (95% CI 0.2 to 1.0, $P = 0.06$). The relative risk was 0.7 (95% CI 0.2 to 2.1, $P = 0.5$) for mortality in the first year and 0.5 (95% CI 0.2 to 1.1, $P = 0.1$) thereafter.

**Mortality rate in relation to sex and age at transplantation**

The 916 cadaver kidney transplantations were performed in 558 men (61%) and 358 women (39%). Survival was better in women. For both sexes the crude mortality rate for the first post-transplantation year was double the rate for the remaining follow up period (Table 1). Compared to men, women had lower mortality both in the first year post-transplantation and during the long-term follow-up ($P = 0.03$).

For all age categories the crude first-year mortality rates were roughly similar (comparison, $P = \text{NS}$). In contrast, the relative risk of mortality after the first year increased significantly over age ($P < 0.001$ for comparison of all categories), but no further increase was found in the highest age category. The disproportionally low mortality rate in patients transplanted at an age lower than 40 years is explained by an overrepresentation of patients with a very long follow-up time (i.e. low mortality).

Because the age at transplantation and sex were strongly related to the post-transplantation risk of mortality, although only so after the first year, adjustment for age and sex was made in all of the following analyses.

**Underlying cause of renal failure**

In roughly half of the 916 first cadaver kidney transplant recipients the cause of renal failure was primary glomerulonephritis or autosomal dominant polycystic kidney disease (Table 2). The mean age at transplantation and the sex distribution differed considerably between the diagnostic categories. The high percentage of women with miscellaneous causes of renal failure was due to a disproportionately large number of women with chronic pyelonephritis (75/358 women vs 25/558 men), analgesic nephropathy (23/358 women vs 11/558 men), and diabetes (144/358 women vs 47/558 men)
vs 12/558 men) and systemic lupus erythematosus (12/358 women vs 6/558 men).

The cause of renal failure had no significant effect on the risk of mortality in the first year after transplantation (comparison, \(P = \text{NS}\)). Compared with glomerulonephritis, the relative risk of mortality after the first year was different for the other causes of renal failure (\(P = 0.0001\) for comparison of all categories), being highest for patients with diabetes mellitus or nephrosclerosis, and lowest for patients with miscellaneous known causes.

### Era of transplantation and immunosuppressive regimen

The mean age (SD) at transplantation increased from 33.4 (11.6) years in the era 1966–1974 to 48.3 (13.1) in the years 1990–1994. The sex distribution remained similar in all eras. The crude first-year mortality rate decreased from 10.2 to 2.6/100 person-years from 1966 to 1994 onwards, whereas the mortality rate after the first year remained essentially unchanged at about 3.0/100 person-years (Table 3). The relative risk of first-year mortality was significantly related to the transplantation era and was highest in the early phase of transplantation (\(P = 0.03\)). The overall Kaplan–Meier’s survival curve (Figure 1) may overestimate the true long-term survival of patients transplanted in the era 1966–1974. After a mean follow-up of 25 years, the true survival of patients transplanted before 1974 was 44%. In addition, survival of patients with a functioning graft overestimates overall survival of transplanted patients, because mortality after graft loss is high. When death after graft failure was included in the analysis, the estimated 25-year survival of patients transplanted before 1974 was 36%.

Before 1983, the immunosuppressive regimen for first cadaver kidney transplantations consisted of azathioprine and prednisone. From 1983 onwards it consisted of cyclosporin and prednisone, but in 71 of these patients cyclosporin was replaced by azathioprine at 3–6 months post-transplantation (conversion group). The relative risk of first-year mortality was significantly lower in patients receiving cyclosporin and in the conversion group compared with patients treated with azathioprine only (\(P = 0.009\)). After addition of the era of transplantation into this model, the effect of immunosuppression on the risk of mortality was no longer statistically significant.

### Type and duration of dialysis

Mortality in patients treated with peritoneal dialysis (\(n = 82\)) before transplantation was not different from
Table 3. The effect of the era of transplantation on mortality in 916 recipients of a first cadaveric kidney transplant

<table>
<thead>
<tr>
<th>Era of transplantation</th>
<th>No. of patients</th>
<th>&lt;1 Year post-transplantation</th>
<th>&gt;1 Year post-transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mortality rate (No/100 PY*)</td>
<td>RR (95% CI)*</td>
</tr>
<tr>
<td>1966–1974</td>
<td>160</td>
<td>10.2</td>
<td>1.0</td>
</tr>
<tr>
<td>1975–1983</td>
<td>309</td>
<td>8.0</td>
<td>1.6 (0.9–2.6)</td>
</tr>
<tr>
<td>1984–1989</td>
<td>250</td>
<td>3.6</td>
<td>0.7 (0.4–1.3)</td>
</tr>
<tr>
<td>1990–1994</td>
<td>197</td>
<td>2.6</td>
<td>0.5 (0.2–1.0)</td>
</tr>
</tbody>
</table>

*PY, person-years; RR, relative risk of mortality; CI, confidence interval. The relative risks were estimated in a Cox proportional hazards model, adjusting for age and sex.

mortality in patients treated with haemodialysis (n = 665) (relative risk 1.0, 95% CI 0.2 to 5.2, P = 1.0 for the first year of follow-up; relative risk 0.3, 95% CI 0.1 to 1.4, P = 0.1 for the remaining follow-up period). In the 665 patients who underwent only haemodialysis the age at transplantation was positively correlated with the duration of prior haemodialysis (P < 0.0001). No significant additional effect of the duration of haemodialysis on the risk of post-transplantation mortality was detected.

**Hypertension, smoking, and diabetes mellitus**

Hypertension, smoking, and diabetes mellitus had no significant effect on the first year mortality. Smoking and diabetes were associated with a higher risk of mortality for the follow-up episode after 1 year (P = 0.002 and P = 0.04 respectively) (Table 4). In hypertensive patients a similar trend was identified, but this was just not statistically significant (P = 0.06).

Table 4. The effect of classic risk factors on mortality in 916 recipients of a first cadaveric kidney transplant

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No. (%) of patients</th>
<th>&lt;1 Year post-transplantation</th>
<th>&gt;1 Year post-transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RR (95% CI)*</td>
<td>RR (95% CI)*</td>
</tr>
<tr>
<td>Smoking†</td>
<td>394 (49)</td>
<td>0.7 (0.3–1.5)</td>
<td>2.2 (1.4–3.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>35 (4)</td>
<td>1.3 (0.3–5.4)</td>
<td>2.9 (1.4–6.0)</td>
</tr>
<tr>
<td>Hypertension‡</td>
<td>249 (30)</td>
<td>0.6 (0.3–1.3)</td>
<td>1.5 (1.0–2.3)</td>
</tr>
</tbody>
</table>

*RR, relative risk of mortality; CI, confidence interval. The relative risks were estimated in a Cox proportional hazards model, adjusting for age and sex. †In 804 patients the smoking histories were known. ‡In 822 patients data on the use of antihypertensive medication were known.

**Death patterns**

Compared to the general Dutch population, mortality in recipients of a first cadaveric kidney transplant was higher in the first year after transplantation, the standardized mortality ratio being 14.7 (95% confidence interval 10.2–19.2) (Table 5). The standardized mortality ratio after the first year was still 4.4 (95% confidence interval: 3.6–5.2). The standardized mortality ratio for cardiovascular death was elevated to a similar extent within the first year and after the first year. The standardized mortality ratio for death caused by malignancy was significantly elevated only after the first year. As population death rates for infectious causes of death were not available the standardized mortality ratio for infections could not be calculated separately. However, the standardized mortality ratio for non-cardiovascular and non-malignant causes of death in the first year was most markedly elevated and half of the observed deaths (14/29) in this category were caused by infection.

Table 5. Causes of death in 163 patients who died after a first cadaveric renal transplantation

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Mean age (SD)</th>
<th>No. of men/women</th>
<th>Death &lt;1 year</th>
<th>Death &gt;1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No (%) observed</td>
<td>SMR* (95% CI)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>45.8 (10.7)</td>
<td>51/14</td>
<td>11 (27)</td>
<td>12.1 (4.9–19.2)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>40.5 (12.6)</td>
<td>12/11</td>
<td>1 (2)</td>
<td>1.0 (–0.9–2.8)</td>
</tr>
<tr>
<td>All other causes†</td>
<td>41.3 (13.3)</td>
<td>51/24</td>
<td>29 (71)</td>
<td>34.1 (22.2–47.7)</td>
</tr>
<tr>
<td>All causes</td>
<td>43.0 (12.5)</td>
<td>114/49</td>
<td>41 (100)</td>
<td>14.7 (10.2–19.2)</td>
</tr>
</tbody>
</table>

*SMR, standardized mortality ratio, as calculated with death rate numbers from the Netherlands. †All other causes of death include infections (see text).
Cardiovascular events were the single most frequent cause of death (65/163, 40%). The proportion of cardiovascular deaths in men (45%) was higher than in women (29%), while death due to a malignancy was relatively less frequent in men (11%) compared with women (22%). Death within the first year after transplantation was caused most often by infection (14/41; 34%), whereas death after the first year was caused predominantly by cardiovascular events (54/122; 44%) or malignancy (22/122; 18%) (Table 5).

Immunosuppression with azathioprine, either from the day of transplantation or from 3 months post-transplantation, was associated with a higher proportion of deaths caused by a malignancy (17 vs 5% in patients treated with cyclosporin only). After adjustment for age, sex, and era of transplantation, the relative risk of mortality caused by malignancy, as a separate outcome parameter, was 0.8 (95% CI 0.3 to 2.0, \( P = 0.6 \)) for patients treated with cyclosporin, compared with those patients whose immunosuppression consisted of azathioprine either from transplantation or from 3 months after transplantation. In a similar analysis the relative risk of cardiovascular mortality was 1.2 (95% CI 0.8 to 1.8, \( P = 0.4 \)) for patients treated with cyclosporin, compared with those patients whose immunosuppression consisted of azathioprine.

Discussion

In this retrospective cohort study we analysed the effect of various patient characteristics, transplantation era, and immunosuppressive treatment on patient survival in 1002 first renal transplants performed between 1966 and 1994 in Leiden, the Netherlands. Different mortality rates in the first year after transplantation and in later years justified a separate analysis. The standardized mortality ratio for recipients of first renal transplants was highest in the first year after transplantation. The more than 10-fold excess risk in the first year was probably accounted for by the transplant procedure, intensity of the immunosuppression, and related complications. Mortality was still four times the population average in the remaining follow-up period, alike in recipients of cadaver and living donor kidneys.

The relative risk of mortality was lower for recipients of living donor compared to cadaver kidneys, although just not statistically significant after adjustment for age and sex. These results were based on only 86 recipients of living donor kidneys and a larger number of evaluable patients might have given different results. Moreover, patients were regarded as withdrawn alive at the time of graft failure. While graft failure is more frequent in recipients of cadaver kidneys as compared with living donor kidney transplant recipients, and mortality after graft failure is probably increased, this may have led to an underestimation of the difference in mortality. Better 2-year age- and sex-adjusted survival rates in living donor kidney transplant recipients have been reported [12].

Our results indicate that patients with a prolonged history of dialysis have equal mortality to those with a shorter episode of dialysis pretransplantation, in accordance with the results of a study of paediatric patients [13] and of a study of diabetic adult patients [14]. This finding could be explained by selection bias, because death rates of patients on haemodialysis are high [15] and survival of a long period of haemodialysis can be expected to select patients with the strongest constitution. Peritoneal dialysis before renal transplantation lowered the relative risk of mortality, but this effect was not statistically significant. O’Donoghue et al. [16] similarly found no effect of the dialysis modality on patient survival after 10 years of follow-up.

Patients aged 40 years and over at transplantation had a higher relative risk of mortality after the first year but not in the first year following transplantation. This is partly in contrast with previous studies, reporting higher mortality rates for older patients in the first year after transplantation too [1,17]. We found no further increase in risk in the highest age category, which is in accordance with previous data [18], and may reflect selection of healthier older patients for renal transplantation. However, in other studies higher mortality rates were found in patients aged over 60 years at transplantation [6,19].

Men had a twofold elevated relative risk of mortality after the first year, as was previously found [1]. The proportion of female transplant recipients was less than half, in accordance with previous reports [12,20]. The higher survival rate in women suggests that allocation of donor kidneys to women is advantageous in terms of patient survival. In addition, improved graft survival has been reported in women [1].

Despite the acceptance of ever older patients, mortality in the first year after transplantation has decreased in the two most recent eras, in accordance with previous studies [3–5]. It was not possible to separate the effect of time perchance from the effect of cyclosporin. Because the risk of mortality was lowest in patients who were converted to azathioprine after 3 months’ use of cyclosporin, this indicates that time-related improvements are at least partly responsible for the improved survival in the recent eras. Mortality after the first year remained unaltered. This could still be interpreted as a positive finding, because the trend has been to accept patients with more risk factors for transplantation [21].

Randomized conversion from cyclosporin to azathioprine at 3 months after transplantation was associated with similar 3-year and improved long-term patient survival [9,10]. Conflicting results have been published with respect to the effect of cyclosporin on long-term patient survival [9,10,22–24]. Better 5-year patient survival when cyclosporin use was continued has been reported [23].

The underlying disease responsible for end-stage renal failure affected only the relative risk of mortality
after the first year. Diabetes mellitus and nephrosclerosis roughly doubled the risk compared with glomerulonephritis. Mortality in renal transplant recipients with autosomal dominant polycystic disease was similar to those with glomerulonephritis, as was previously reported [25].

The classic cardiovascular risk factors smoking, diabetes mellitus and hypertension were associated with a higher relative risk of mortality after the first year, although moderately so, presumably brought about by the increased occurrence of vascular disease before and after transplantation [26]. In a previous study mortality of diabetic renal transplant recipients was higher if transplanted before 1988, but became equal after that time [27]. Smoking roughly doubled the risk of mortality after 1 year post-transplantation, which is similar to the increase in risk of mortality for smokers in the general population [28].

Our study has several limitations. We did not compare the survival rates of transplant recipients with those of patients on the transplantation waiting list treated with haemodialysis. Such an analysis was done by Port et al. [20], who observed an initial excess risk of mortality in the post-transplantation period, followed by a lower risk. The equal mortality risk and equal cumulative mortality rate occurred on day 117 ± 28 and day 325 ± 91 respectively [20]. A survival advantage brought about by renal transplantation therefore seems to start at 1 year after transplantation. In the study by Schaubel et al. [29], the risk of mortality in patients aged 60 years and over on haemodialysis was roughly double the risk of transplanted patients.

In conclusion, in the present study the standardized mortality ratio for recipients of first renal transplants was 14 times the population average in the first year after transplantation and four times in the remaining years, indicating that mortality still remains elevated after the first year. In first cadaver kidney transplant recipients the risk of first year mortality has improved with time, which coincided with the introduction of cyclosporin. The risk of mortality after the first year was higher in patients aged over 40 years at transplantation, men, smokers, and in the presence of hypertension or diabetes, but the effect of individual factors on mortality was small and the presence of these factors should therefore not hamper transplantation. We found no effect of the type of pretransplantation dialysis or the duration of pretransplantation haemodialysis on post-transplantation mortality, indicating that patients surviving a long period of haemodialysis are eligible candidates for transplantation. With regard to patient survival the ideal renal transplant recipient would be a young, non-smoking female patient with a urological cause of renal failure.

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