Quantifying the benefit of early living-donor renal transplantation with a simulation model of the Dutch renal replacement therapy population

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Abstract

Background. Early living-donor transplantation improves patient- and graft-survival compared with possible cadaveric renal transplantation (RTx), but the magnitude of the survival gain is unknown. For patients starting renal replacement therapy (RRT), we aimed to quantify the survival benefit of early living-donor transplantation compared with dialysis and possible cadaveric transplantation and to estimate the population benefit from increasing the early transplantation rate.

Methods. We used a decision-analytic computer-simulation model, with a lifetime time horizon, simulating patients starting RRT, using data from the Dutch End-Stage Renal Disease Registry and published data. We compared the (quality adjusted) life expectancy (LE) of ‘early living-donor RTx’ and ‘dialysis’ (with possible cadaveric RTx if available).

Results. LE and quality-adjusted LE benefits of the early living-donor RTx compared with the dialysis strategy for 40-year-old patients ranged from 7.5 to 9.9 life years (LYs) [6.7–8.8 quality-adjusted life years (QALYs)] depending on the primary renal disease. For 70-year-old patients, the benefit was 4.3–6.0 LYs (4.3–6.0 QALYs). Increasing the early transplantation rate from currently 5.8 to 22.2% (the highest in Europe) would increase average LE by 1.2 LYs and total LE for annual incident cases in the Netherlands by >1800 LYs.

Conclusions. Efforts to increase early living-donor RTx could potentially substantially increase LE for patients starting RRT, especially in younger patients.

Keywords: decision analysis; dialysis; living-donor renal transplantation; preemptive renal transplantation; survival

Introduction

The number of years spent on renal dialysis prior to renal transplantation (RTx) has been shown to be negatively correlated with renal graft and patient survival, both in cadaveric and living-donor transplant recipients [1–3]. Several studies of preemptive transplantation have shown improved patient or graft survival [2, 4–8], so timely, preferably preemptive RTx has been advocated for patients nearing end-stage renal disease [2, 4–6]. Because waiting time for a cadaveric transplant cannot be accrued before starting renal replacement therapy (RRT) in countries participating in the Eurotransplant organ procurement system, preemptive transplantation can only be performed with a living donor. Moreover, graft survival of a living-donor transplant has been shown to be significantly better than for cadaveric donor transplants (10-year graft survival of 55.2 versus 41.7%) [3].

Although living donors are exposed to an operative risk, they are reported to have a long-term survival comparable to the general population [9]. Recent studies have indicated, however, that donors might be at risk for hypertension and stable chronic kidney disease [10, 11]. In spite of these low risks for the living donor, patients requiring RRT have been shown to be reluctant to accept a transplant from a living donor because of uncertainty about the long-term consequences associated with dialysis and with living-donor transplantation [12].

It is difficult to inform patients about these risks using data from the current literature. Studies comparing the
survival of patients following preemptive renal transplants from living donors with the survival of patients following cadaveric renal transplants do not account for the possibility that patients starting dialysis will receive a cadaveric transplant. Moreover, observational studies comparing preemptive transplantation with postdialysis transplantation report relative mortality rates [2, 4, 5] rather than life expectancy (LE) benefits.

Therefore, we used a computer-simulation model to quantify the LE benefit of early living-donor RTx compared with dialysis while waiting for possible cadaveric RTx for patients starting RRT of different ages and gender, with varying primary renal diseases (PRDs). Secondly, we estimated the population benefit that could be accrued from increasing the early transplantation rate in the Netherlands.

Methods

Model

We developed a state transition model to estimate the LE of patients commencing RRT, comprising four states: (i) hemodialysis (HD), (ii) peritoneal dialysis (PD), (iii) RTx and (iv) death. Two treatment strategies were evaluated for these patients. In the first strategy, ‘dialysis’, patients start dialysis therapy with the chance of being waitlisted and of receiving a renal transplant from a cadaveric donor. Dialysis therapy is subdivided into HD and PD; subsequent switches were not modeled explicitly but were reflected in the source data. If patients receive a renal transplant, graft failure may occur and patients return to HD or PD. Patients can receive a maximum of two renal transplants. With the second strategy, ‘early transplantation’, patients receive a preemptive or early renal transplant (within the first 90 days of dialysis) from a living donor. This 90-day time frame accounts for acute decisions that might influence treatment assignment and the subsequent prognosis assigned to that treatment. If the transplant fails, patients will be treated with HD or PD. Patients may receive a cadaveric transplant at a later stage. A schematic overview of the model is presented in Figure 1.

We used a Markov process model with a cycle length of 3 months. State transition rates dependent on patient covariates were estimated from Cox models and transformed into 3-monthly transition probabilities. We estimated the Cox models for death and for transitions to other treatments for three treatment periods: initial dialysis, transplantation and posttransplant dialysis. Patient history in terms of type of previous dialysis modality and previous transplants was tracked using additional health states. Outcome measures were LE and quality-adjusted LE (QALE) from the perspective of the patients receiving RRT. In this Methods section, we discuss our main data sources and assumptions; a technical appendix containing more detailed information on the construction of the model is available as Supplementary Material.

Data sources and assumptions

Patient sample. We used a sample of 15 435 patients from the Dutch End-Stage Renal Disease Registry, RENINE, who started RRT between 1 January 1987 and 31 December 2002 (Table 1). Registry data included age, gender, PRD, year of start of RRT, dialysis center, date and type of transplantation (living donor or cadaveric), transplantation center and date of death. In RENINE, primary renal diagnosis was coded according to the classification of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA). We aggregated these into five categories: glomerulonephritis (PRD-GN), hypertension (PRD-HT), renovascular disease (PRD-RVD), diabetes mellitus (PRD-DM) and a category for all other renal diagnoses (PRD-OTH).

Initial dialysis models. With the initial dialysis models, we estimated dialysis mortality and transplantation rate. Information on transplantability was available for another subset of RENINE data. We used the hazard ratios of transplantable patients compared with the entire initial dialysis population for both mortality and transplantation rates as relative risks to adjust the mortality and transplantation rates obtained from the initial dialysis models, so that the patients starting on dialysis in the model represented waitlisted dialysis patients.

Transplant models (first and second transplant). RTx patient mortality and graft failure for first and second transplants were modeled from patients in the dialysis mortality model that were transplanted before 31 December 2002 (4699 first and second transplants), and from patients that received an early transplant (772 first and second transplants) (Table 2).

Posttransplant dialysis models. Posttransplant dialysis mortality was based on the data of patients included in the transplant models that returned to dialysis after failure of a first (n = 893) or a second renal transplant (n = 102). The rate of receiving a second transplant was modeled on the sample that returned to dialysis after failure of a first renal transplant (n = 893).

Extrapolating survival data beyond observed follow-up time. We extrapolated our survival data beyond the observed follow-up time to allow for a lifetime time-horizon by fitting weighted quadratic regression functions on the baseline cumulative hazard over time for each Cox model.

Quality of life. For estimates of utilities of HD, PD and RTx patients, we used EuroQol EQ-5D estimates from a recently published systematic review of the literature [13] in accordance with recommendations from the Panel on Cost-Effectiveness in Health and Medicine to prefer values from an indirect method [14]. The means and standard deviations (SDs) were 0.5560 (0.0283) for HD, 0.5817 (0.0385) for PD and 0.8077 (0.0407) for RTx patients. To account for short-term disutilities from procedures, we deducted the duration of procedure-related hospitalization, i.e. assumed

Fig. 1. Schematic overview of the simulation model. A patient enters the model through one of two strategies, the dialysis or the early transplantation strategy and can experience transplantation and transplant failure with return to dialysis.
a quality of life of 0 for those days. The duration of hospitalization was based on expert opinion (J.F.M.W.) for HD shunt and PD catheter implantation and on data from the Dutch Organ Transplant Registry for cadaveric and living RTx [15].

Uncertainty and variability

We performed second-order Monte Carlo simulations to account for parameter uncertainty. Parameter uncertainty of transition probabilities was accounted for by estimating the Cox proportional hazards models on 1000 bootstrap samples of the RENINE patient sample and estimating a weighted quadratic regression model on the baseline cumulative survival of each of the 1000 Cox models. Bootstrapping was performed separately for the three different treatment periods (R, version 2.5.1, The R Foundation for Statistical Computing, Vienna, Austria). For the uncertainty in quality of life estimates, we fitted beta distributions on the means and SDs of the EQ-5D values that we obtained from our meta-analysis.

Analyses

We calculated LE, expressed in life years (LYs), and QALE, expressed in quality-adjusted LYs (QALYs), for the two strategies for patients commencing RRT. We assessed the outcome measures for different scenarios defined by age (40, 50, 60 or 70 years), gender and PRD. The LEs associated with the dialysis and early transplantation strategies, respectively, decreased from 25.3 to 34.1 LYs for 40-year-old patients to 6.5 and 11.9 LYs for 70-year-old patients. For all ages, LE was higher for women versus men.

Table 1. Patient characteristics initial dialysis models (N = 15 435)a

<table>
<thead>
<tr>
<th>Dialysis modality (%)</th>
<th>HD</th>
<th>63.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD</td>
<td>36.7</td>
</tr>
<tr>
<td>Transplanted (%)</td>
<td>C-RTx</td>
<td>23.7</td>
</tr>
<tr>
<td></td>
<td>LD-RTx</td>
<td>4.9</td>
</tr>
<tr>
<td>Age (SD) (yr)</td>
<td>57.5 (14.5)</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>41.2</td>
<td></td>
</tr>
<tr>
<td>PRD (%)</td>
<td>GN</td>
<td>14.2</td>
</tr>
<tr>
<td></td>
<td>HT</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td>RVD</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>DM</td>
<td>15.7</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>50.8</td>
</tr>
<tr>
<td>Year of first RRT (%)</td>
<td>1987–90</td>
<td>17.6</td>
</tr>
<tr>
<td></td>
<td>1991–94</td>
<td>23.9</td>
</tr>
<tr>
<td></td>
<td>1995–98</td>
<td>28.4</td>
</tr>
<tr>
<td></td>
<td>1999–2002</td>
<td>30.0</td>
</tr>
<tr>
<td>Years of follow-up (SD)</td>
<td>2.31 (2.06)</td>
<td></td>
</tr>
</tbody>
</table>

*C-RTx, cadaveric RTx; LD-RTx, living-donor RTx; yr, year; GN, glomerulonephritis; HT, hypertension; RVD, renal vascular disease; DM, diabetes mellitus; Other, other/unknown PRD; RTx, renal replacement therapy.

Table 2. Patient characteristics transplant models (N = 5471)a

| Age at RTx (SD) (yr) | 46.8 (12.9) |
| Female (%)           | 39.0 |
| PRD (%)              | GN | 23.7 |
|                       | HT | 7.7 |
|                       | RVD | 2.2 |
|                       | DM | 8.7 |
|                       | Other | 57.6 |
| Year of RTx (SD)     | 1996 (4) |
| RTx-duration (SD) (yr) | 4.6 (3.8) |

*a yr, year; GN, glomerulonephritis; HT, hypertension; RVD, renal vascular disease; DM, diabetes mellitus; Other, other/unknown PRD.

Results

Figure 2 shows the estimated LEs and 95% confidence intervals associated with the dialysis and early transplantation strategies for the scenarios defined by patient age and gender with early transplantation yielding a higher LE than dialysis. The LEs for the dialysis and for the early transplantation strategies, respectively, decreased from 25.3 to 34.1 LYs for 40-year-old patients to 6.5 and 11.9 LYs for 70-year-old patients. For all ages, LE was higher for women versus men.

Figure 2 also denotes the LE of the Dutch general population according to age and gender in the year 1996 (the mean year of start of dialysis in our analyses). When compared with identically aged individuals from the general population, the need for dialysis reduced LE substantially, ranging from a loss of 13.0 LYs for 40-year-old patients to 6.4 LYs for 70-year-old patients. Substituting early transplantation also resulted in a diminished LE compared with the general population. The difference also decreased with increasing age, but the general population estimates fell...
If the Dutch early living-donor RTx rate could be increased, the average estimated survival was 10.5 LYs and 7.3 QALYs. For a cohort of incident RRT patients of which 5.8% received an early living-donor RTx and 93.2% started on dialysis, the estimated QALEs were 6.9 and 13.9 QALYs. For a plantation with increasing age, found for the entire population, was similar for all disease categories. The decrease in survival benefit of early transplantation increased LE from 7.5 to 9.9 LYs for 40-year-old patients and from 4.3 to 6.0 LYs for 70-year-old patients.

The survival benefit of early transplantation for subgroups defined by age and PRD is shown in Figure 3. Early transplantation increased LE from 7.5 to 9.9 LYs for 40-year-old patients and from 4.3 to 6.0 LYs for 70-year-old patients with no significant differences among the PRD categories. The decrease in survival benefit of early transplantation with increasing age, found for the entire population, was similar for all disease categories.

When comparing the QALE benefit of early transplantation for different combinations of age and PRD (Figure 4), the benefit varied from 6.7 to 8.8 QALYs for 40-year-old patients and from 4.3 to 6.0 QALYs for 70-year-old patients. For patients aged 40 through 60 years, the absolute QALE survival benefit of early transplantation was smaller than the LE benefit, but for 70-year-old patients, the absolute benefit was similar or slightly higher in QALYs than in LYs.

Of the 1565 incident RRT patients on Day 91 in 2005, 93.2% were treated with dialysis, 5.8% with an early living-donor RTx and 1% with an early cadaveric RTx (excluded in the calculations below). Using the average characteristics of the cohort, 61.2 years old and 39% female, LEs associated with the dialysis and early transplantation strategies were 10.1 and 17.4 LYs, respectively, and estimated QALEs were 6.9 and 13.9 QALYs. For a cohort of incident RRT patients of which 5.8% received an early living-donor RTx and 93.2% started on dialysis, the average estimated survival was 10.5 LYs and 7.3 QALYs. If the Dutch early living-donor RTx rate could be increased to 22.2%, that occurring in Iceland and the highest incidence rate reported among ERA-EDTA countries), then the LE and QALE for average incident RRT patients would rise to 11.7 LYs and 8.4 QALYs. Thus, the increase in LE (QALE) would on average be 1.2 LYs (1.1 QALYs). Based on the 2005 incidence of Dutch RRT patients, the higher living donor RTx rate would increase survival by >1800 LYs or >1700 QALYs in the 1565 incident RRT patients.

**Discussion**

From our analyses, we conclude that early transplantation resulted in a considerable LE and QALE survival benefit compared with dialysis in all scenarios. Specifically, the LE (QALE) survival benefits of the early transplantation versus dialysis ranged from 7.5 to 9.9 LYs (6.7–8.8 QALYs) for 40-year-old patients and from 4.3 to 6.0 LYs (4.3–6.0 QALYs) for 70-year-old patients. This benefit decreased with increasing age. Improving the early transplantation rate of 5.8% in the Netherlands to the highest rate reported from the ERA-EDTA of 22.2% would increase average LE (QALE) for RRT patients by 1.2 LYs (1.1 QALYs) and increase survival by 1800 LYs or >1700 QALYs in a cohort of 1565 incident RRT patients in the Netherlands.

We compared our results with the survival for incident RRT patients reported in the literature for incident wait-listed dialysis patients. Inrig et al. [18] reported a 2-year survival of 93.3% for PD and 93.2% for HD patients (average age 47 years) in the USA. The 2-year survival estimates from our dialysis strategy for 40- and 50-year-old patients were on average 95.8 and 92.5%, respectively, suggesting good external validity of our model. A study in a Swedish population by Medin et al. [19],

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**Fig. 3.** Survival benefit of early transplantation in terms of LE. Survival benefit and 95% confidence intervals in terms of LE for the early transplantation compared with the dialysis strategy by age and PRD. DM = diabetes mellitus, GN = glomerulonephritis, HT = hypertension, other = other/unknown PRD, RVD = renal vascular disease.

**Fig. 4.** Survival benefit of early transplantation in terms of quality-adjusted LE. Survival benefit and 95% confidence intervals in terms of QALE for the early transplantation compared with the dialysis strategy by age and PRD. DM = diabetes mellitus, GN = glomerulonephritis, HT = hypertension, other = other/unknown PRD, RVD = renal vascular disease.
however, showed a 5-year survival of 60% for waitlisted patients (average age 49 years old at wait listing). The 5-year survival estimate from our dialysis strategy for 50-year-old patients was on average 80.5%. This discrepancy might be explained by differences in case mix. The patients included in the study by Medin had started dialysis in earlier years (1987–96), a lower percentage was treated with PD, and there was a lower proportion of females, which could all have contributed to a lower survival. In addition, Medin et al. analysed patients from the moment of wait-listing and not from the start of dialysis as we did. Lastly, if our dialysis survival estimates were more similar to those of Medin’s, then the estimated benefit from transplantation would be even larger, making our results conservative.

The most important advantage of our study lies in the comparison of strategies from the initiation of RRT, thereby avoiding lead time bias, which would have occurred in studies comparing the survival of postdialysis cadaveric RTx and preemptive living donor RTx or in studies comparing the survival of waitlisted dialysis patients and cadaveric RTx patients.

Our model provides several important insights. We found that the estimated LE of patients receiving an early transplant approached the LE of the general population, particularly as age increased. Although this might in part be explained by a slight overestimation of early transplantation LE due to lack of long-term follow-up of these patients in our data, registry data suggest that older patients receiving an RTx have an LE that approached that of the general population [20]. In addition, we found that the survival benefit of early transplantation decreased with increasing age, as might be expected. Our results suggest that efforts to increase early transplantation should particularly be aimed at younger patients, but the benefit in older patients remains substantial and justifies an active approach to achieve higher rates of early transplantation in all age groups.

Increasing the national rate of early transplantation from 5.8 to 22.2% substantially increased the average LE for incident dialysis patients by 1.2 LYs (1.1 QALYs). In the absence of data on variation in rate of early transplantation by age, gender and PRD in different countries, our calculation was based on average patient characteristics and on average rates of early transplantation and assumed that increasing the preemptive RTx rate would not change the characteristics of the preemptively transplanted population. With this assumption, the result suggests substantial gains in LE and QALE from increasing early transplantation rates. How to achieve a higher early transplantation rate remains a challenge. Previous research suggested that timely referral of patients with chronic renal disease to a nephrologist may be one factor [21]. Early referral to a nephrologist has been shown to be associated with both a lower dialysis mortality [22] and better access to the waiting list and cadaveric transplantation [23], therefore enhanced awareness of the importance of early diagnosis of renal disease and subsequent referral may markedly improve transplantation rates.

Some limitations of our study need mentioning. Firstly, the model did not account for outcomes for the living donor and the influence of those effects on the quality of life of the recipient. Recent studies have shed some light on shorter-term outcomes [10, 11], but long-term outcomes are lacking and prospective studies are currently underway. Secondly, we assumed that a living donor was sought and available only at the commencement of RRT. In reality, patients may receive a first or subsequent living-donor transplant in the course of their treatment. However, many factors may influence the availability and eligibility of a living donor and the impact of dialysis on subsequent living-donor organ and patient survival are less well known; therefore, we chose to restrict ourselves to the presented situation. However, when interpreting the results of the model, it must be kept in mind that the early transplantation strategy reflects a combination of two advantageous treatments: living-donor over cadaveric RTx and preemptive over postdialysis RTx. Another limitation is that we did not distinguish between early (<3 months of start of dialysis) transplants and actual preemptive transplants. Several studies have shown, however, that patients receiving an early transplant within 6 months [24] or within 1 year [25] of the start of dialysis have a survival comparable to preemptively transplanted patients. As for generalizability, the model was based on Dutch registry data from the period 1987–2002. Since the Dutch end-stage renal disease population may differ from other countries’ populations with respect to demographics and clinical characteristics, we have presented results for subgroups. However, we cannot exclude differential effects of risk factors in different populations. In future research, this model could be applied to external populations to assess its predictive validity.

In conclusion, we found and quantified substantial survival benefits in terms of LE and QALE for patients commencing RRT with an early RTx compared with those starting on dialysis and being listed for a deceased donor organ. This benefit decreased with advancing age, so efforts to increase the rate of early transplantation should particularly focus on younger patients. Increasing rates of early transplantation to the highest rate reported among ERA-EDTA countries would be estimated to increase LE for an average patient with 1.2 years, amounting to an increase of >1800 LYs for an annual cohort of 1565 patients commencing RRT in the Netherlands. Therefore, increasing early transplantation rates may substantially improve LE of RRT patients and national policies and research to promote organ donation should be pursued.

Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

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Conflict of interest statement. None declared.
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