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The impact of waiting time and comorbid conditions on the survival benefit of kidney transplantation

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Background. Longer waiting times may limit the survival benefit of kidney transplantation in older patients or those with a high burden of comorbid disease.

Methods. We performed a longitudinal study of mortality among 63,783 transplant candidates who started dialysis between April 1995 and December 2000. We determined the relative risk (RR) of death and increase in life expectancy among subjects who received a first deceased donor transplant after different waiting times compared to subjects who had equivalent waiting times but remained on dialysis.

Results. Transplant recipients had a lower long-term RR of death and the risk reduction was greatest in recipients with longer waiting times (RR of death 12 months after transplantation for recipients with waiting times of 0, 1, 2, 3 years was 0.49, 0.43, 0.38, 0.34, $P = 0.0006$).The average increase in life expectancy in transplant recipients was 9.8 years and was lower in older recipients and recipients with comorbid conditions. Increased waiting times from 1 to 3 years only moderately decreased the overall survival benefit of transplantation from 7.1 to 5.6 years, and all subjects derived a survival benefit from transplantation with waiting times up to 3 years.

Conclusion. These findings do not support limiting access to transplantation for otherwise suitable candidates on the basis of longer anticipated waiting times.

Transplantation is the preferred treatment for patients with end-stage kidney disease. Compared to patients treated with dialysis, transplant recipients live longer, have improved quality of life, and consume fewer health care resources [1–3]. The survival benefit of transplantation compared to dialysis was demonstrated in a cohort of patients activated to the transplant waiting list in the United States between 1991 and 1996 [1]. Since that time, both waiting times for transplantation and the burden of comorbid disease in patients seeking transplantation have increased. In the current era, the shortage of available organs is the dominant issue. As of March 2005 there were 61,192 patients on the United Network of Organ Sharing waiting list for kidney transplantation [4]. By 2010, a projected 95,000 patients will be on the kidney waiting list in the United States, and waiting times of a decade or more are anticipated [5, 6]. The success of kidney transplantation has also contributed to the increased demand, and patients previously denied transplantation because of age or comorbid conditions now routinely seek and receive transplants. For example, between 1991 and 2001, the proportion of deceased donor kidney transplant recipients in the United States who were older than 50 years increased from 29.5% to 47.7% [7].

Previous work evaluating the survival benefit of transplantation compared to dialysis did not consider the impact of death or progression of comorbidity while awaiting transplantation and, hence, its applicability to the care of patients under current conditions is uncertain [1]. As the discrepancy between the supply and demand for kidney transplantation grows, pressure to preferentially allocate organs to patients with the greatest chance of benefit is likely to increase. The purpose of this study was to determine the impact of increased waiting time and comorbid disease on the survival benefit of transplantation in the current era.

METHODS

Data from the United States Renal Data System were used for this study. There were 361,254 subjects under the age of 75 years who began their first chronic dialysis treatment between April 1, 1995 and December 31, 2000. We studied the subset of 63,783 subjects who were also active on the kidney transplant waiting list. Descriptive

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statistics included the chi-square test or ANOVA as appropriate.

Survival was determined from the time of first activation to the transplant waiting list. Patients were followed until death, living donor, or multiorgan transplant, or the end of follow-up (December 31, 2000). Follow-up continued for subjects who were removed from the waiting list or had transplant failure. The relative risk of death in transplant recipients compared to subjects who remained on the waiting list with the same amount of waiting time was determined in a Cox regression analysis. Because mortality among transplant recipients increased sharply during the perioperative period and then declined below the rate observed in comparable subjects remaining on dialysis, the coefficient of the transplant status variable was allowed to vary with time after transplantation. We also permitted the risk of death after transplantation to differ in subjects with longer waiting times prior to transplantation with the use of time-varying coefficients. Analyses were adjusted for age, gender, race, cause of end-stage renal disease, comorbid conditions defined at the time of dialysis initiation (ischemic heart disease, congestive heart failure, stroke, peripheral vascular disease), duration of dialysis exposure prior to wait-listing, and year of placement on the transplant waiting list.

The projected number of life years remaining was determined in time-dependent parametric survival analyses that included the same covariates in the Cox regression analysis described above. The projections of life years remaining in wait-listed dialysis subjects were based on follow-up from activation to the waiting list until live donor or multiorgan transplantation, death, or end of study, and therefore included the impact of death on dialysis during the wait-list period. These projections assumed a Weibull distribution for the survival times in subjects remaining on dialysis, and a log-normal distribution for the survival times in subjects who received a transplant, based on goodness of fit tests and graphical comparison of the parametric hazard curves with the empiric hazards. [8] All analyses were performed with SAS, version 8.2 (SAS Institute, Cary, NC, USA). The study was approved by our university hospital ethics review board.

RESULTS

Of the 63,783 wait-listed dialysis subjects studied, 19,666 received a first deceased donor kidney transplant after a median waiting time of 0.65 years (5th–95th percentile, 24 days–2.65 years). An additional 8568 received either live donor or multiorgan transplants, while 35,549 subjects did not receive transplants and remained on dialysis. Compared to subjects who remained on dialysis, recipients of first deceased donor kidney transplants were younger and more likely to be male and of white race ($P < 0.001$ for all group comparisons) (Table 1). Transplant recipients were also less likely to have diabetic kidney disease, ischemic heart disease, or congestive heart failure ($P < 0.001$ for all group comparisons) (Table 1). Among transplant recipients with waiting time $\leq$12 months, the proportion of recipients aged $\geq$60 years (20%), of white race (72%), with diabetic kidney disease (34%), history of ischemic heart disease (8%), peripheral vascular disease (5%), congestive heart failure (12%), or cerebrovascular accident (3%) was higher than among receipts with waiting times $\geq$36 months (11%, 51%, 23%, 6%, 3%, 9%, 2%; $P < 0.001$ for all group comparisons).

The relative risk of death in transplant recipients who received transplants after 0, 1, 2, or 3 years of waiting time compared to wait-listed subjects with equal waiting time who remained on dialysis is shown in Figure 1. All transplant recipients had an increased relative risk of death in the immediate posttransplant period. The relative risk of death then rapidly declined, and transplant recipients had a lower long-term relative risk of death. The unadjusted annual death rates and hazard for mortality in dialysis subjects increased with each additional year on the waiting list (Table 2, Fig. 2A). In contrast, the annual death rates and hazard for morality in transplant recipients were similar in subjects who received transplants after short or long waiting times (Table 2, Fig. 2B). Consequently, the relative risk of death among transplant recipients tended to decrease with increasing waiting times, compared with subjects who remained on dialysis (Fig. 1).

The projected years of life remaining for subjects who received transplants after different waiting times and subjects who remained on dialysis are shown in Table 3, as well as the projected benefit in life years for transplant recipients. The average projected benefit for subjects who received a transplant at any time during follow-up was 9.8 years. The benefit of transplantation was inversely related to subject age and was lower in subjects with comorbid conditions. For example, transplant recipients who were 0 to 19 years of age or $\geq$70 years at the time of activation to the waiting list derived a projected survival benefit of 17.2 and 3.7 additional life years, respectively, compared with subjects of similar age who remained on dialysis (Table 3).

The benefit of transplantation was greatest in subjects who received transplants with the shortest waiting time. However, the overall survival benefit associated with transplantation was only moderately reduced, from 7.1 years after a waiting time of 1 year to 5.6 years after a waiting time of 3 years (Table 3), and the survival benefit of transplantation was observed in all subject groups even after the maximum observed waiting time of 3 years. The magnitude of the benefit associated with shorter waiting time appeared most pronounced in younger subjects [i.e., transplant recipients aged 0–19 had a 2.6 year