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CLINICAL INVESTIGATION

Prognostically controlled comparison of dialysis and renal transplantation

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Prognostically controlled comparison of dialysis and renal transplantation. Because the comparison of survival in patients with renal failure treated by dialysis and transplantation may be biased by pretreatment prognostic differences in the patients who receive these two therapies, we quantified the pretreatment prognosis of all 430 dialysis and transplant patients who began therapy for end-stage renal disease at two hospitals from 1970 to 1980. Five pretreatment factors had a statistically significant adverse effect on survival: age, duration of diabetes, left ventricular failure, myocardial infarction, and other serious comorbid illness. Dialysis patients had a worse pretreatment prognosis than transplant patients did. When we controlled for these pretreatment differences, the actuarial 5-year patient survivals were 80% for dialysis (D), 79% for cadaver transplantation (CT), and 91% for living donor transplantation (LDT), ($P = 0.9$ for CT vs. D, and $P = 0.05$ for LDT vs. D). This similarity in survival with dialysis and cadaver transplantation was quite different from the results obtained when pretreatment prognosis was not controlled; the uncontrolled 5-year patient survivals were 43% for D, 77% for CT, and 89% for LDT ($P < 0.001$ for CT vs. D, and $P < 0.001$ for LDT vs. D). Our data suggest that the major factor determining differences in survival with dialysis and renal transplantation is not the relative efficacy of the two treatments but the pretreatment prognostic status of the patients chosen to receive them.

Une comparaison contrôlée de façon pronostique entre la dialyse et la transplantation rénale. Puisque la comparaison de la survie des malades en insuffisance rénale traités par dialyse ou par transplantation peut être biaisée par des différences pronostiques pré-thérapeutiques entre les malades qui reçoivent ces deux traitements, nous avons quantifié le pronostic pré-thérapeutique de l'ensemble des 430 malades dialysés et transplantés qui ont commencé le traitement de leur insuffisance rénale dans deux hôpitaux de 1970 à 1980. Cinq facteurs pré-thérapeutiques possédaient un effet adverse statistiquement significatif sur la survie: l'âge, la durée du diabète, une insuffisance ventriculaire gauche, un infarctus du myocarde, et une autre maladie sérieuse associée. Les dialysés avaient un pronostic pré-thérapeutique plus mauvais que les transplantés. Lorsque nous avons contrôlé ces différences pré-thérapeutiques, la survie actuarielle à 5 ans des malades était de 80% pour la dialyse (D), 79% pour la transplantation cadavérique (CT), et 91% pour la transplantation avec donneur vivant (LDT) ($P = 0{,}9$ pour CT contre D, et $P = 0{,}05$ pour LDT contre D). Cette similitude de survie en dialyse ou après transplantation cadavérique était très différente des résultats obtenus lorsque le pronostic pré-thérapeutique n'était pas contrôlé; les survies non contrôlées à 5 ans des malades étaient de 43% pour D, 77% pour CT, et 89% pour LDT ($P < 0{,}001$ pour CT contre D, et $P < 0{,}001$ pour LDT contre D). Nos données suggèrent que le facteur principal déterminant les différences de survie en dialyse ou après transplantation rénale n'est pas l'efficacité relative des deux traitements, mais l'état pronostique pré-thérapeutique des malades choisis pour les recevoir.

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Although there is a large number of studies [1–11] comparing survival with dialysis and renal transplantation in the treatment of end-stage renal disease, the published results have a potential scientific flaw—the patients chosen for transplantation may be prognostically different from patients continued on dialysis therapy [12–16]. Therefore, apparent beneficial or detrimental effects of transplantation may be related to the better or worse prognosis of the patients who receive a transplant rather than to the efficacy of transplantation itself. To provide a more scientifically valid comparison of these two major therapies for endstage renal disease, we have quantified the pretreatment prognosis and corrected for the prognostic disparities in patients treated by dialysis and transplantation.

Methods

Patients. We studied all patients ($N = 430$) who received their first definitive treatment (dialysis or kidney transplantation) for chronic renal failure at the Royal Victoria Hospital or the Montreal General Hospital from 1 January 1970 to 31 December 1980. They were identified from the lists of patients who had received dialysis or kidney transplantation at either hospital and from the medical records of all patients with discharge diagnoses of chronic renal failure or uremia.

Data collection. We separated the information used to predict prognosis from that related to the effects of replacement therapy by using only pretreatment information to characterize patients' clinical state. For this purpose, replacement therapy was judged to have begun with the start of regular dialysis therapy or with a first kidney transplant, whichever came first. In the initial data collection, which involved patients started on treatment from 1970 to 1975, we examined the patients' medical records for 85 variables in the following categories: demography; primary renal diagnosis; duration, severity and complications of uremia; presence and severity of comorbid illnesses; and the level of general physical, social, and psychological functioning. The results of this study led to the development of an age-equivalence index for predicting survival in renal failure, which has been published [16]. For patients who started treatment from 1976 to 1980, we collected

information on a limited number of factors that were shown to have statistically significant effects on survival in the patients treated during the earlier period.

We used the information collected after the start of replacement therapy to identify major changes in therapy and to ascertain survival. We obtained complete follow-up information on 413 patients (96%). The main reason for loss to follow-up was that patients had moved out of the geographical area. During the study period, 188 patients (45%) died.

We collected the data from medical records using a two-stage procedure that has been described previously [16]. To avoid the bias that might occur if alterations were made in the way that information was collected in patients with different outcomes, we did not tell the person collecting the information the precise purpose of the study, and we usually collected the prognostic information before collecting information on the outcome. Since the person who collected the patient data in the initial study could not be kept blind to the results of that study, we used another person, who was unaware of the first set of results, to collect the data on patients treated from 1976 to 1980.

Statistics. We assessed the effect of various factors on survival, determined by life table analysis, by using the regression approach devised by Cox [17]. The basic assumption of this method is that a worse prognostic status, which can result from a patient having more of one characteristic or an additional different characteristic, multiplies the risk of dying by a factor that remains constant over the period of follow-up. We tested these assumptions on patients treated in the initial period and found that they fitted the data very well [16].

With this approach, we first examined the effect of the treating hospital on survival. Because the survival rates in the two hospitals were similar, we pooled the data in subsequent analysis. Next, as previously reported [16], we examined each of the potential prognostic variables for an effect on survival in the first study period (1970 to 1975). Since this represented an hypothesis-generating study that might produce some statistically significant effects by chance alone, we tested variables that appeared significant in the first data set for an effect in the patients treated later on (1976 to 1980). To obtain the major prognostic characteristics, we then did a stepwise procedure using only variables that had produced statistically significant effects in both data sets. We used the whole data set (1970 to 1980) for this analysis to maximize our power to identify prognostically important variables.

To remove any confounding by the effects of transplantation, we reevaluated prognosis using cadaver and living donor transplantation as time-dependent covariates. The two kinds of transplant were included in the analysis and were treated on an equal basis with the prognostic variables. The analysis estimated the risk or benefit associated with each variable to maximize the accuracy of predicting survival for all the members of the population. Thus, when there was an overlap or potential confounding between the effects of treatment and a prognostic variable, the analysis distributed the overlapping effect between the two in a way that best explained the survival data. By using transplant as a time-dependent covariate, we allowed for the waiting period between starting ESRD treatment and getting a kidney transplant. With this approach dialysis was given credit for keeping patients alive until they received a transplant. At transplantation, patients were changed to the equivalent point on the transplant curve and were compared with dialysis patients who had been on ESRD treatment for the same length of time as the transplanted patient. This method of analysis is essential to avoid the bias that is otherwise created by the waiting period for transplantation [18]. After prognosis had been assessed, we then calculated survival with dialysis and transplantation after adjustment for the prognostic characteristics identified.

Table 1. Characteristics of study population

	1970–75	1976–80	Total
Age (mean ± SD)	45.4 ± 17.4	51.9 ± 17.3	48.6 ± 17.6
Sex			
Male	134 (61%)	118 (56%)	252 (59%)
Female	86 (39%)	92 (44%)	178 (41%)
Renal disease			
Glomerulonephritis	57 (26%)	35 (17%)	92 (21%)
Chronic pyelonephritis	39 (18%)	18 (9%)	57 (13%)
Polycystic kidneys	16 (7%)	17 (8%)	33 (8%)
Diabetic nephropathy	16 (7%)	15 (7%)	31 (7%)
Hypertensive disease	5 (2%)	5 (2%)	10 (2%)
Miscellaneous other disease	18 (8%)	8 (4%)	26 (6%)
Uncertain cause	69 (31%)	112 (53%)	181 (42%)
Treatment			
Cadaver transplant	87 (40%)	44 (21%)	131 (30%)
Living donor transplant	30 (14%)	8 (4%)	38 (9%)
Dialysis alone	103 (47%)	158 (75%)	261 (61%)
Hospital			
Hospital 1	132 (60%)	116 (55%)	248 (58%)
Hospital 2	88 (40%)	94 (45%)	182 (42%)

To assess the impact of transplantation on actual lives saved or lost, we also did pairwise comparisons of mortality after transplantation with that expected if dialysis and the relevant kind of transplant were equivalent treatments. We assumed no difference between dialysis and transplantation (null hypothesis) and calculated the expected mortality by applying the overall mortality rate to the period of follow-up experienced by the transplant patients. The effect of the kind of transplantation that was not being evaluated was removed by including it as a time-dependent covariate in the analysis, and we used the effects of the prognostic variables to adjust the expected mortality for the clinical status of the patients chosen for transplantation. A chi-square test was used to compare observed and expected deaths after transplantation.

Results

Study population. The patients studied are described in Table 1. Because some of the subsequent analyses give separate results for the two study periods (1970 to 1975; 1976 to 1980), we have given the characteristics of patients in each period as well as those for the population as a whole. We cannot describe the exact racial mixture of patients in this study, because race was not routinely recorded in the medical record; however, the majority of patients at both hospitals were white. Hemodialysis was the predominant mode of dialysis; 72% of the patients either started on hemodialysis or switched later to this form of therapy. There is a difference between the patients in the two periods in age, distribution of renal diag-

noses, and the proportion of patients receiving renal transplants. These differences, however, did not affect survival: in the 1970–1975 study period, the 1-year and 5-year survivals were 77% and 54%; in the 1976 to 1980 period, they were 76% and 56%.

Prognostic assessment. Table 2 shows the pretreatment characteristics that had a statistically significant effect in the 1970 to 1975 period and also gives the *P* value for their effect in 1976 to 1980. In addition to the variables originally found to be statistically significant [16], three other variables that were not coded for in the original analysis were found to have a statistically significant effect on survival: ischemia showing on electrocardiogram; other severe comorbid illness; and the ability of patients to care for themselves. The determination of "ischemia on electrocardiogram" was based on probable or definite ischemia diagnosed by the cardiologist making out the official EKG report. Other comorbid illnesses included a variety of illnesses judged to be likely to have a markedly adverse effect on survival by a nephrologist who was blind to the outcome of the patients. There were 5 patients with cancer, 6 with a myeloproliferative disorder, 2 with severe collagen vascular disease, and 6 with miscellaneous other life-threatening illnesses. "Ability to care for self" reflected patients' ability to carry out activities of daily living after they had developed severe renal failure (serum creatinine, greater than 5 mg/dl) but before they started on therapy for end-stage renal disease.

Of the characteristics shown in Table 2, 16 had statistically significant ($P < 0.05$) effects on survival for the 1976 to 1980 period. The prognostic features that had statistically significant effects on survival in both study periods were age and variables relating to the following comorbid illnesses: diabetes, congestive heart failure, atherosclerosis, and miscellaneous other illnesses. To reduce redundant information caused by the high correlation of individual variables with each other, we did a stepwise analysis on the whole data set (1970 to 1980) using these 16 characteristics. With this approach, we identified 5 characteristics that made an independent contribution to survival: age, duration of diabetes, left-sided heart failure as evidenced by pulmonary edema, a history of myocardial infarction, and other severe comorbid illness. The prognostic characteristics identified included 3 variables (age, duration of diabetes, and left-sided heart failure) that we had previously used to construct a prognostic index based on patients treated from 1970 to 1975 [16]. Of the remaining 2 variables, "other severe comorbid illness" was not coded in previous analyses. The addition of myocardial infarction reflects an increased power of the analysis owing to the larger number of patients in the current study (430 vs. 220).

The relative risk associated with the 5 prognostic variables is shown in column one of Table 3. These estimates of prognostic risk might be biased if a prognostic characteristic were associated with an increased likelihood of getting a transplant and if transplantation were to have a significant effect on mortality. To avoid this potential for confounding by the effects of transplantation, we did a second analysis in which the first transplantation (cadaver donor and living related donor transplants were treated separately) was treated as a time dependent covariate: Patients were included in the group receiving dialysis until they had a kidney transplant and after that point were included in one of the two transplant categories. The results of this analysis, which are shown in the second column of Table 3, do not suggest that there was confounding by the effects of transplantation. We did a further check by limiting the analysis to the patients treated by dialysis alone. The results were similar.

Table 2. Pretreatment characteristics that had a statistically significant ($P < 0.05$) effect on survival in the 1970 to 1975 period tested in the 1976 to 1980 period

Characteristic	*P* value for prognostic effects	
	1970 to 1975	1976 to 1980
Age	<0.001	<0.001
Renal diagnosis		
Glomerulonephritis	0.02	0.13
Pyonephrosis	0.001	0.14
Uremia		
Number of physical signs of uremia	0.002	—[a]
Motor neuropathy	0.003	0.68
Pericarditis	0.01	0.12
Comorbid illness		
Diabetes		
Diabetes mellitus	0.004	<0.001
Duration of diabetes	0.001	<0.001
Oral hypoglycemic agents for diabetes	0.001	<0.001
Adult-onset diabetes	<0.001	0.001
Congestive heart failure		
Cardiomegaly	<0.001	<0.001
Pulmonary edema	<0.001	<0.001
Jugular venous distension	<0.001	<0.001
Paroxysmal nocturnal dyspnea	0.001	0.003
Atherosclerosis		
Myocardial infarction	0.03	<0.001
Angina pectoris	0.006	<0.001
Intermittent claudication	<0.001	<0.001
Absent pedal pulses	0.01	0.01
Carotid bruits or absent pulsation	0.009	0.08
Ischemia on electrocardiogram	0.002	0.02
Miscellaneous		
Duration of untreated hypertension	0.001	0.8
Hypertensive retinal complications	0.04	0.2
History of more than one episode of pneumonia	0.005	0.75
Severe depression diagnosed by a psychiatrist	0.008	0.6
Other serious comorbid illness	0.03	<0.001
Ability to care for self	0.004	<0.001

[a] Not tested because data were not collected for the 1976 to 1980 period.

Comparison of dialysis and transplantation (without prognostic adjustment). The survival for patients treated by dialysis and cadaver and living related donor transplantation are shown in Fig. 1. The survival of patients in the dialysis curve is dated from the point of starting dialysis. Patients who were initially dialyzed and later transplanted contributed to dialysis survival up to the point of receiving a transplant and then began to contribute to survival at the *start* of the relevant transplant curve. A newer method of analysis [18] that allows for the variable "waiting period for transplantation" led to similar conclusions: Survival with both cadaver and living related donor transplantation was significantly better than survival with dialysis therapy. The relative risk of death compared with dialysis therapy was 0.38 (95% confidence interval: 0.25 to 0.58; $P < 0.001$) for cadaver transplantation and 0.13 (95%

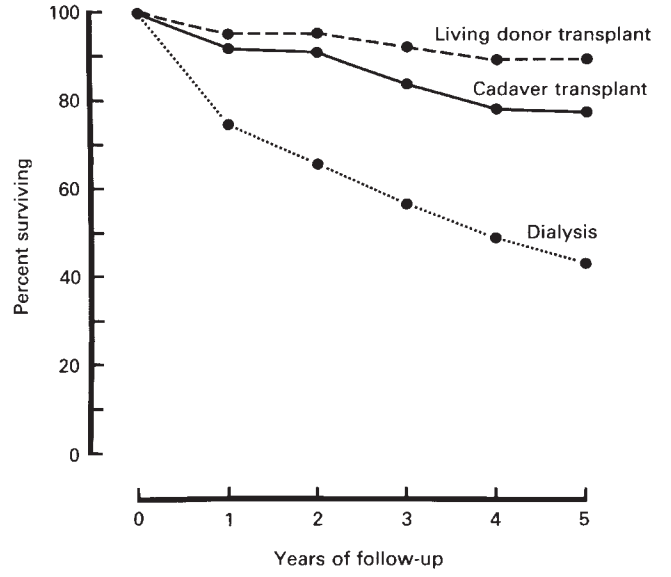

Fig. 1. *Survival with dialysis and transplantation* without *control for pretreatment prognostic differences.*

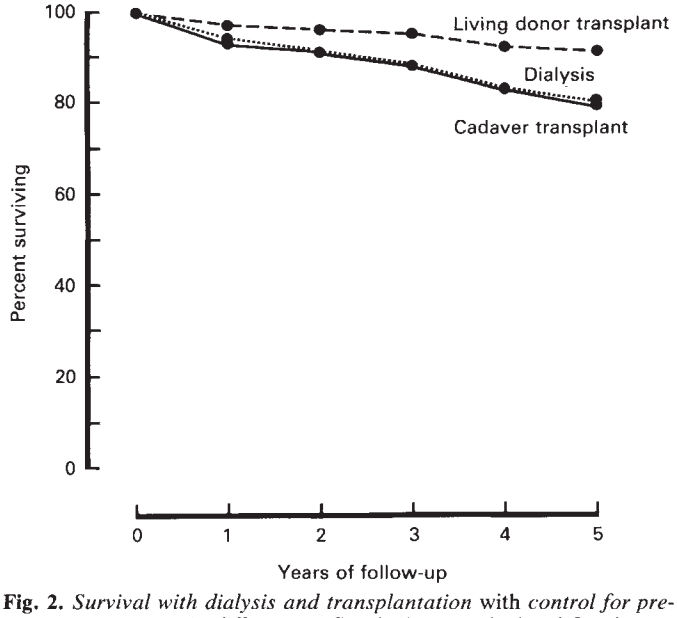

Fig. 2. *Survival with dialysis and transplantation* with *control for pretreatment prognostic differences.* Survivals are calculated for the average pretreatment status of cadaver transplant patients, which corresponds to an age of 41.6 without adverse prognostic factors.

confidence interval: 0.05 to 0.34; $P < 0.001$) for living donor transplantation.

Pretreatment prognosis of dialysis and transplant patients. When we compared the distribution of prognostic factors in dialysis and transplant patients (Table 4), we found that dialysis patients were older and sicker than patients chosen for transplantation. For instance, the average age of patients treated by dialysis alone was 57.1 years as compared with 36.5 years in cadaver transplant patients and 31.8 in living donor transplant patients. The frequencies of diabetes, left ventricular failure, myocardial infarction, and other severe comorbid illness were also higher in dialysis than in transplant patients.

Table 3. Relative risk of death[a] associated with the prognostic characteristics

Prognostic characteristic	Unadjusted for effects of transplantation	*P*	Adjusted for effects of transplantation[b]	*P*
Age (10 years)	1.8	<0.001	1.8	<0.001
Duration of diabetes (10 years)	1.8	<0.001	1.8	<0.001
Left-sided heart failure	1.9	<0.001	1.9	<0.001
Myocardial infarction	1.4	<0.05	1.4	0.10
Other severe comorbid illness	4.2	<0.001	4.3	<0.001

[a] The relative risk of death is the risk of death in patients with a prognostic characteristic divided by the risk of death in those without it. Thus, a relative risk of 1.9 associated with left-sided heart failure means that patients with heart failure had approximately twice the risk of dying as patients without heart failure had.

[b] To remove effects that were due to transplantation rather than to the prognostic characteristics themselves, we included transplantation as an independent variable in this analysis.

Table 4. Distribution of prognostic factors in dialysis and transplant patients[a]

Prognostic characteristic	Dialysis alone ($N = 261$)	Cadaver transplant ($N = 131$)	Living donor transplant ($N = 38$)	Total population ($N = 430$)
Age (mean ± SD)	57.1 ± 15.4	36.5 ± 11.3	31.8 ± 12.5	48.6 ± 17.6
Diabetes mellitus[b]	38 (15%)	13 (10%)	1 (3%)	52 (12%)
Left ventricular failure	166 (64%)	40 (31%)	16 (42%)	222 (52%)
Myocardial infarction	57 (22%)	3 (2%)	0 (0%)	60 (14%)
Other comorbid illness	17 (7%)	0 (0%)	1 (3%)	18 (4%)

[a] The percentages shown in parentheses reflect the proportion of patients on the relevant treatment who had this abnormality. For example, of patients treated by dialysis alone, 38 out of 261 (15%) had diabetes mellitus.

[b] The duration of diabetes was similar in the diabetic patients treated by dialysis alone (mean = 12.9 yrs.), cadaver transplant (mean = 14.4 yrs.) and living donor transplant (mean = 14.0 yrs.).

Comparison of dialysis and transplantation (with prognostic adjustment). To correct for this prognostic bias, we calculated survival curves after adjusting for the pretreatment differences in the patients chosen for dialysis and transplantation. The curves shown in Fig. 2 are calculated for the average prognostic risk of cadaver transplant patients. This corresponds to an age of 41.6 years without comorbid illness. When pretreatment prognostic differences are removed, the curves for cadaver transplantation and dialysis overlap. The estimated relative risk of death for cadaver transplantation compared with dialysis was 1.03 (95% confidence interval: 0.64 to 1.66; $P = 0.9$) showing no difference in the risk of death with these two therapies. The survival curve for living donor transplantation ap-

peared better than for dialysis. The estimated relative risk of death for living donor transplantation compared with dialysis was 0.42 (95% confidence interval: 0.15 to 1.19; $P = 0.05$), suggesting but not proving a beneficial effect. These results contrast with the unadjusted results (Fig. 1), which suggested that both kinds of transplantation had a statistically significant beneficial effect on survival.

To determine whether the results obtained with prognostic adjustment might be affected by an over-conservative method of choosing prognostic variables we tried a less conservative approach: We adjusted for all the 25 variables listed in Table 2. The relative risks for transplantation versus dialysis were unchanged (1.0 for cadaver transplantation and 0.44 for living donor transplantation). We were also concerned that the results might be affected by a change in the risk associated with the prognostic variables over time. For instance, the risk associated with left ventricular failure drops from 4.2 in the first 6 months after starting treatment to 1.05 after 3 years. Because the average risk of 1.9 is applied in our analyses, a patient who was transplanted at 3 years might have been at less risk of dying from left ventricular failure than we allowed for in the prognostic adjustment. When, however, we allowed for these changes in prognostic effects over time, the results were unchanged. The relative risk of death was 0.96 for cadaver transplantation and 0.44 for living donor transplantation.

A further concern relates to the marked difference in age between dialysis and transplant patients, which means that some age groups are not represented in the transplant group—there was only one transplant patient aged 60 or over, whereas 126 of the dialysis patients were in this age group. It might therefore be argued that the effect of age in our analyses is heavily weighted by the poor results of old dialysis patients and that the application of this overall age effect to transplant patients is an extrapolation that may distort the results. To meet this criticism, we excluded patients 60 years of age or older from the analysis and recalculated the effect of age and of transplantation on survival. The results were similar to our previous analyses. The relative risk was 1.7 for each 10 years of age, and the relative risk of death compared with dialysis treatment was 1.17 for cadaver transplantation and 0.39 for living donor transplantation.

A final concern relates to the assumption that the effect of age and other prognostic variables were the same in dialysis and transplant treatment groups. This assumption was testable for three variables (age, duration of diabetes, and left ventricular failure) that had sufficient numbers in the dialysis and transplant groups. For age, the relative risk associated with each 10 years was 1.7 for dialysis and 1.6 for transplantation (P value for the difference, >0.1). For duration of diabetes, the risk associated with each 10 years was 1.7 for dialysis and 1.9 for transplantation (P value for the difference, >0.1). For left ventricular failure, the relative risk was 2.5 for dialysis and 0.8 for transplantation (P value for the difference, <0.05). This discrepancy appeared to be explained by the marked decrease in the effect of left ventricular failure over time—patients were usually transplanted after the major prognostic effect of left ventricular failure had disappeared. This interpretation is supported by the finding that, when the time dependency of the prognostic effect of heart failure was accounted for, transplantation did not significantly modify the effect of the left ventricular failure ($P > 0.1$). The assumption of similar prognostic effects on dialysis and transplantation cannot be tested for the remaining two prognostic variables, which are history of myocardial infarction and other comorbid illness. However, these variables did not appear to have a major effect on the comparison of dialysis and transplantation; when we omitted these two variables from the analysis; the results for comparison with dialysis were a relative risk of 0.95 for cadaver transplantation and 0.41 for living donor transplantation.

Table 5. Deaths after transplantation compared with deaths expected if dialysis and transplantation were equivalent treatments

Type of transplant	Observed deaths	Expected deaths[a]	P[b]
Cadaver (N = 131)	32	31.5	0.9
Living Donor (N = 38)	4	9.1	0.05

[a] The expected deaths were calculated from the overall mortality rate (dialysis and transplant patients) and the pretreatment prognostic risk of the patients who received a transplant.
[b] The P value is based on a χ^2 test comparing observed and expected deaths.

Table 6. Comparison of observed and expected deaths for functioning and failed transplants

Type of transplant	Function of graft	Observed deaths	Expected deaths[a]	P[b]
Cadaver	Functioning	16	20.5	0.2
Cadaver	Failed	16	10.9	0.09
Living donor	Functioning	1	8.3	<0.01
Living donor	Failed	3	0.7	<0.01

[a] The expected deaths were calculated from the overall mortality rate (dialysis and transplant patients) and the pretreatment prognostic risk of patients with a failed or functioning transplant.
[b] The P value is based on a χ^2 test comparing observed and expected deaths.

Impact of transplantation on lives saved or lost. To express the above results in the more tangible form of numbers of lives saved or lost owing to transplantation, we compared observed and expected mortality for the transplant patients. The expected mortality was calculated from the overall mortality rate of the population and the pretreatment prognostic risk of the patients who received a transplant. A similarity of observed and expected deaths would fit with the null hypothesis of no difference in treatment efficacy between dialysis and transplantation. The results are shown in Table 5. Column one shows the observed mortality, and column two gives the expected mortality. The mortality with cadaver transplantation was similar to that expected from pretreatment prognosis: The observed deaths were 32, versus the expected 31.5. For living donor transplantation, observed deaths were 4, and the number expected was 9.1.

Functioning and failed transplants. The above analyses assess the effect of the clinical decision to give a dialysis patient a renal transplant. They do not, however, distinguish between the biological effects of a functioning graft and a failed one, and they do not show which phase of transplant therapy accounted for the mortality observed. Therefore, we did a further analysis to distinguish between the mortality with a functioning

versus a failed transplant. The results are shown in Table 6. A functioning transplant appeared to have a beneficial effect on survival, whereas a failed transplant appeared to have a detrimental effect. For cadaver transplantation, neither result was statistically significant. For living donor transplantation, the beneficial effect while the transplant was functioning and the detrimental effect after it failed were both statistically significant.

Discussion

Our study is not the first to compare the survival of patients treated by dialysis and transplantation. The majority of published studies [1–5, 7–9], however, fail to allow for the different pretreatment prognoses of patients treated by dialysis and transplantation. Of the studies that do attempt to equalize prognosis [6, 10, 11], only one study [10] corrects for factors others than age. After excluding patients with diabetes and those with hypertension, the authors [10] compared survival with dialysis and transplantation after adjustment for age, renal diagnosis, and number of associated diseases. The relative risk of death on transplantation compared with dialysis was 1.26 ($P = 0.7$) for cadaver transplants and 0.51 ($P < 0.01$) for living donor transplants. Confidence in these results is limited, however, because the authors did not make a thorough search for all of the factors other than treatment that might have affected the survival of their patients. Also, no direct comparison was made of the pretreatment prognosis of the dialysis and transplant patients in their study.

In our study, we did an extensive search involving a large number of potential prognostic factors. We also demonstrated a potent bias in favor of transplantation. When we adjusted for this prognostic bias, cadaver transplantation had no effect on the survival expected with dialysis therapy. Living donor transplantation had a beneficial effect that did not quite reach statistical significance. The lack of overall effect of transplantation was explained by a favorable effect while the transplant was functioning and a detrimental effect after it had failed. Our data suggest that the main explanation for differences in survival with dialysis and transplantation is not the relative efficacy of the two treatments. The major determining factor in our study was the pretreatment prognostic status of the patients chosen for transplantation.

The main potential limitations of this research relate to the number of patients studied, the choice of the prognostic variables and estimate of risk associated with them, and the effect of graft survival on patient survival. Although the number of patients studied was not small ($N = 430$), it did allow for a sizeable type II error (the chance of concluding that no difference exists between treatments that are really different). The confidence intervals for relative risk obtained in our study do not exclude a beneficial or detrimental effect on survival for either cadaver or living related transplants. Further studies with very much larger numbers of patients are needed to exclude the possibility that we missed real differences in our study.

Although we cannot exclude the possibility that we overlooked prognostically important variables, we did an extensive search that included 85 variables in five categories—demographic, renal diagnosis, uremic severity and complications, comorbid illness, social and psychologic functioning. The final variables used in prognostic adjustment represented a conservative approach to avoid overcorrecting for variables whose effect might be due to chance alone. When we used a less conservative approach, however, and adjusted for 25 variables that had statistically significant effects in the first data set, we got similar results.

The estimate of risk that we used to adjust for prognostic characteristics in our study do not appear to be biased by confounding with the effects of transplantation or by a change in the effect of the prognostic variables over time. The risk estimates that we used were adjusted for the effects of transplantation. Furthermore, when we used the risk estimates obtained in patients treated by dialysis alone, the results were similar. The effects of the prognostic characteristics do tend to change over time; however, when we did an analysis allowing for this change, the results for the comparison of dialysis and transplantation were unchanged. A further issue related to our estimates of prognostic risk is whether the effects of the prognostic variables were similar in dialyzed and transplanted patients. For the three variables for which such a test could be made (age, duration of diabetes, and left ventricular failure), the results supported a similar effect in different treatment groups. The other two characteristics (history of myocardial infarction and other comorbid illness) were too infrequent in transplanted patients to allow the similarity of their effect to be tested. These two variables, however, did not appear to have a major effect on the results of treatment comparison. Omission of a history of myocardial infarction and other comorbid illness from the analysis did not change the results for comparison of dialysis and transplantation.

With the functioning transplants appearing to be more beneficial than failed transplants (Table 6), it is possible that the rate of graft failure affected our results. The one-year graft survival was 76% for cadaver transplants and 87% for living donor transplants. Because these graft survivals are better than many in the published literature [19–21], it seems unlikely that poor graft survival has biased our results. Nevertheless, higher graft survival rates may be achievable with newer therapies such as cyclosporin A [22, 23]. To the extent that these improved graft survivals are achievable without having long-term adverse effects on the patient [24], the effects of cadaver transplantation may be more favorable in the future than our study suggests. Conversely, transplantation would be a less attractive therapy in centers with substantially lower graft survivals than the levels reported in our study.

It may be that transplantation has beneficial effects on the quality of life that are not revealed in our study, which focuses solely on duration of survival. A recent study of quality of life in cadaver transplant patients [25] showed, however, a similar pattern of results. The quality of life in patients with functioning transplants was slightly better than it was in patients on dialysis who had not been transplanted. This slight superiority of transplantation was offset, however, by a poorer quality of life after the transplant had failed. Taken together with our data showing an increased risk of death in patients with failed transplants, these findings suggest that perhaps cadaver transplantation should be limited to patients who have a high probability of prolonged graft survival. Further work is needed to determine the break-even point—the duration of graft survival necessary to confer an overall beneficial effect on the duration and quality of life of transplanted patients.

Although our study focuses on the comparison between dialysis and transplantation, other comparisons of treatment for end-stage renal disease may also be biased by differences in the patients chosen to receive them. For instance, differences in survival on home versus hospital dialysis [26] may be explained by the better pretreatment prognosis of patients who are well enough to carry out their own dialysis at home [14]. The conventional method for removing such biases is to randomize allocation of therapy. However, surveys such as ours have some attractive features as another method for dealing with the same questions. First, they are more feasible, cost less, and avoid some of the ethical dilemmas [27] posed by clinical trials. Second, they yield results that are more easily extrapolated to patient care for several reasons: *(a)* The patients studied are not preselected by their willingness to give informed consent or by their absence of comorbid illnesses, which often lead to exclusion from a trial. *(b)* The treatment evaluated is the one actually administered to patients in routine care and is not altered by the structure of a trial, an alteration that may lead to more rigid adherence to protocol, more use of ancillary investigations and treatments, and potential placebo effects in patients who receive both the experimental and comparison treatments. *(c)* The rapidity with which results can be obtained decreases the likelihood that the technology being evaluated will be superseded by newer methods by the time the study has been completed.

These advantages of sophisticated survey methods do not mean that they can replace experimental clinical trials as the gold standard for determining therapeutic efficacy. All such studies, including ours, involve major assumptions that are not completely provable. The main assumptions of the method that we used are (a) that individual prognostic factors and treatments multiply the risk of dying by a factor that remains constant over the period of follow-up, *(b)* that the effect of two or more prognostic factors is the multiplication of their individual risks, *(c)* that we have not missed major prognostic variables, and *(d)* that pretreatment status is a good indicator of prognostic risk throughout the period of follow-up. We have dealt with assumptions *a, b,* and *c* in this and previous publications [16]. The issue raised in *d* is the subject of ongoing research. However, regardless of the thoroughness of our testing, some element of doubt will remain. It is the reduction or elimination of such doubt that is the main advantage of well-conducted experimental studies. We would suggest that the two methodologies (surveys and experiments) should be seen as complementing each other. A rational approach would be to begin with a survey that can identify prognostic factors and estimate treatment effects using the most sophisticated methodology available. The data from such studies can then provide estimates on which clinicians can base decision until trials are performed, can suggest hypotheses to be tested in clinical trials, and can provide information that will be useful in the planning and analysis of those trials that are performed. We believe that this combined approach can increase the efficiency and scientific validity of therapeutic evaluation, both in nephrology and in other areas of clinical medicine.

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