Graft loss following renal transplantation in Australia: is there a centre effect?

Esther M. Briganti1, Rory Wolfe1, Graeme R. Russ2, Josette M. Eris3, Rowan G. Walker4 and John J. McNeil1

1Department of Epidemiology and Preventive Medicine, Monash University, Victoria, 2Renal Unit, Queen Elizabeth Hospital and ANZDATA Registry, South Australia, 3Statewide Renal Services, Royal Prince Alfred Hospital, New South Wales and 4Department of Nephrology, Royal Melbourne Hospital, Victoria, Australia

Abstract

Background. Assessment of centre variation in renal transplantation outcome provides an opportunity to examine differences in quality of care between centres. However, differences in outcome may represent differences in patient factors between centres and be biased by sampling variability and inadequate data ascertainment.

Methods. Differences in 12-month graft survival in 1986 primary renal transplant adult recipients from 16 centres in Australia between 1993 and 1998 were examined. Fifteen recipient and donor factors known prior to transplantation were examined to determine factors independently predictive of graft survival. Differences between centres in these factors were examined. Unadjusted and multivariable adjusted outcomes for each centre were compared to the average for all centres. Multivariable hierarchical modelling was employed to account for potential bias due to sampling variability.

Results. Factors predictive of reduced 12-month graft survival on multivariable analysis that were significantly different between centres were time on dialysis prior to transplantation, donor age, organ source, and number of human lymphocyte antigen mismatches. Unadjusted 12-month graft survival for all centres was 91.7% and ranged from 83.1 to 96.4%. Although two centres performed significantly lower than average, this poorer outcome was accounted for in one of these two centres after adjusting for factors shown to be independently predictive of outcome. However, multivariable hierarchical modelling failed to identify any centre as performing significantly different to average, with 12-month graft survival ranging from 89.2 to 92.2%. Outcome in patients excluded from the study due to inadequate data ascertainment was significantly worse than patients who were included.

Conclusions. There was no evidence of centre variation after accounting for variation in risk factors predictive of poor outcome between centres, as well as potential bias due to sampling variability. Exclusion of patients due to inadequate data remains an important source of bias in estimating accurate outcomes. Appropriate analytical strategies and consideration of sources of bias are important for the valid identification of centres with poorer outcomes.

Keywords: centre effect; graft loss; hierarchical analysis; registry; renal transplantation; risk adjustment

Introduction

The presence of centre variation in clinical outcome in renal transplantation has been debated in the USA and UK since 1973 [1–8]. Centre-specific outcomes are reported each year by the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry to enable individual renal transplant centres to compare their own outcome with those of other centres and with the Australian average. This process has been anonymous in relation to the identity of the other centres. Since its inception, this mode of reporting has identified discrepancies in outcome amongst the various centres. It is unclear, however, whether these discrepancies represent differences in patient characteristics between centres or reflect differences in quality of care. This study was undertaken to differentiate between these alternatives.

Subjects and methods

Data collection

The ANZDATA registry has compiled information regarding all renal transplants conducted in Australia since 1963.
Baseline clinical information and six-monthly follow-up information on outcome is collected on all renal transplant patients. Outcome measures collected routinely include patient and graft survival. Relevant data relating to recipient and donor characteristics known prior to transplantation and transplant outcome were accessed from the ANZDATA registry for the period 1993–1998 to determine 12-month graft survival for adult renal transplant centres.

**Study population**

Twenty-one Australian transplant centres performed a total of 2304 primary renal transplants between 1 January 1993 and 30 September 1998. Sixteen of these centres are primarily adult renal transplant centres and five are primarily paediatric renal transplant centres. The five paediatric transplant centres were excluded from the analysis. Recipients under 18 years of age and transplanted in a primarily adult renal transplant centre were also excluded. Of the remaining 2187 patients, 201 (9%) were subsequently excluded from the analysis because of missing data relating to recipient or donor characteristics.

**Statistical methods**

**Outcome variable.** The primary outcome variable was 12-month graft survival, which was defined as time elapsing between transplantation and graft loss, either as patient death with a functioning graft or graft failure. Graft failure was defined as the need for permanent dialysis or re-transplantation. Patients who were alive with a functioning graft were censored at the date of last follow-up or at 12 months if their follow-up was greater than 12 months.

The additional outcome of 12-month patient survival, which was defined as time elapsing between transplantation and patient death with or without a functioning graft, was also examined to allow comparison with European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) benchmarks for satisfactory renal transplantation outcomes [9].

**Recipient and donor factors influencing outcome.** Fifteen pre-transplant recipient and donor factors considered possible or likely predictors of graft survival were selected after review of relevant published information. The univariable association between each of these factors and 12-month graft survival was determined by log rank tests for equality of survivor functions. A backward selection Cox proportional hazard regression model that included all of the 15 factors was fitted to determine factors independently predictive of survival. The significance level for removal from the model was a P-value greater than 0.05. The assumption of proportional hazards was confirmed using the scaled Schoenfeld residuals.

**Centre comparisons.** Differences in outcome between renal transplant centres were analysed by including centre as a 16-level covariate in a fixed-effects multivariable Cox proportional hazards regression model that included the recipient and donor factors found to be predictive of outcome. Since analyses of this type are likely to overestimate differences between transplant centres, a hierarchical analysis was performed in which the same model was fitted but with variation between centre being modelled explicitly as a random effect rather than as a 16-level covariate [10]. The 12-month graft survival of each centre was compared to the average outcome for all centres in the fixed-effects multivariable model and to the outcome in the average centre in the hierarchical multivariate model.

**Statistical analysis.** Statistical analyses were undertaken with Stata (Version 6.0, 1999). The hierarchical Cox proportional hazards regression analysis was performed using WinBUGS (Version 1.2, 1999) with processing of the resulting output performed in Stata. Results from the Cox proportion hazard regression analyses for the predictiveness of recipient and donor factors are expressed as hazard ratios and 95% confidence intervals. Centre specific 12-month survival data are derived from the hazard ratio by the following formula:

\[
\text{survival} = e^{(-H)}
\]

where \( H = \text{hazard ratio} \times [-\ln(\text{reference survival})] \)

Differences between the 16 centres in the proportion of patients with risk factors found to be independently predictive of outcome was tested by chi-squared test. A P-value of less than 0.05 was considered significant and all P-values were two-tailed.

**Results**

**Data ascertainment**

Complete information was available on 79–96% of patients from individual centres. Ten of the centres provided complete information on 90% or more of the patients. The number of transplants performed by each of the six centres, which had complete information on less than 90% of patients, was below the median number of transplants for all centres for the period 1993–1998.

Of the 1986 patients included in this analysis, 9 (0.5%) were lost to follow-up within the first year post-transplant at a median time of 2.2 months (range: 1.0–5.7 months). Amongst the remainder, patient death with a functioning graft occurred in 42 patients and graft failure occurred in 135 patients within the first 12 months. Patient death with or without a functioning graft occurred in 65 patients within the first 12 months.

**Recipient and donor factors influencing outcome**

Factors found to be predictive of reduced 12-month graft survival on univariable analysis were older recipient age, presence of vascular disease in the recipient at the time of commencement of renal replacement therapy, higher peak panel reactive antibody levels, longer time on dialysis prior to transplantation, older donor age, cadaveric donor source, brain damage as the cause of donor death, greater number of human lymphocyte antigen (HLA) mismatch, longer cold ischaemia time, and earlier year of transplantation (Tables 1 and 2). On multivariable analysis, longer time on dialysis prior to transplantation, presence of vascular disease in the recipient at the time of commencement of renal replacement therapy, younger and older donor age categories, cadaveric organ source, greater number of HLA mismatches and earlier
year of transplantation were independent predictors of 12-month graft survival.

Centre comparisons

Differences in recipient and donor factors between centres. Of the factors that were predictive of reduced 12-month graft survival on multivariable analysis, time on dialysis prior to transplantation, donor age, organ source, and number of HLA mismatches were significantly different between centres. For time on dialysis prior to transplantation, the percentage of patients on dialysis ≥3 years overall was 22.6% and ranged from 11.8 to 56.7% between centres (P=0.000 for difference). The percentage of donors ≥50 years overall was 28.9% and ranged from 20.1 to 42.1% between centres (P=0.001 for difference). The percentage of cadaveric donors transplanted overall was 75.2% and between centres ranged from 50.0 to 96.7% (P=0.000 for difference). For number of HLA mismatches, the percentage of patients with four to six mismatches overall was 30.8% and ranged from 12.5 to 42.8% between centres (P=0.000 for difference).
For the 201 patients who were excluded from the analysis due to incomplete information for the multivariable analysis, the average 12-month graft survival was 86.0% (95% CI: 80.3%, 90.1%) and ranged from 33.3 to 100% amongst individual transplant centres. The 12-month graft survival for patients excluded from the analysis was significantly less than the average 12-month graft survival for all patients included in the analysis, which was 90.9% (95% CI: 89.6%, 92.1%; P = 0.02 for log rank test).

Twelve-month patient survival. The average 12-month patient survival for all centres was 96.5% (95% CI: 95.5%, 97.2%) and ranged from 91.2 to 100% amongst individual transplant centres.

Discussion

This study has shown that the outcomes amongst Australian renal transplant centres were not different from the average outcome for all centres for patients transplanted between 1993 and 1998, after accounting for key outcome predictors known prior to transplantation and random variability between centres.

The presence of centre variation in renal transplantation outcome has been reported in a number of studies [1–8], however, methodological limitations limit the validity of the conclusions of these studies. Recipient, donor, or centre-specific risk factors, which impacted on reported renal transplantation outcome, were identified in some studies [1,4–8], but were either not accounted for [1,4,6] or incompletely accounted for [5,8] statistically in determining centre variation. Although some of these studies recognized the importance of accounting for transplantation volume in comparing centre-specific outcomes to avoid sampling bias [2,3], this potential bias was explicitly accounted for in the analysis in only one study [3]. None of these studies addressed both the issue of differences in risk factors between centres and the issue of sampling bias for small volume centres when attempting to determine a centre effect.

Appropriate analytical considerations are required in comparing the performance of centres. This particularly relates to the consideration of differences in patient characteristics between centres. An increasing number of patients with older age and associated co-morbidities, which have a negative effect on outcome, have undergone renal transplantation in recent years. It is likely that transplant centres vary on the acceptance of such patients. In fact, of the factors that were independently predictive of 12-month graft loss, a significant difference was found between centres for time on dialysis prior to transplantation, donor age, organ source, and number of HLA mismatches. Use of multivariable models, which account for these differences between centres, allows centres to be compared on an equal level. However, the inclusion of baseline recipient and donor factors potentially predictive of outcome was limited by the data items routinely collected by the ANZDATA registry. While this study aimed to account for recipient and donor factors known prior to transplantation, other post-transplant factors have been reported to be important predictors of graft failure and patient death. These factors included delayed graft function, episodes of acute rejection, hypertension, body mass index, cigarette smoking, and compliance with medication [11–23].

The appropriateness of including particular baseline recipient or donor factors identified as correlating independently with 12-month graft survival in the risk-adjustment process requires consideration of whether centres exercise control over these factors. Prolonged cold ischaemia time, for example, is associated with a less favourable outcome and is often unavoidable, particularly for centres where a larger proportion of cadaveric kidneys are shipped from interstate sources. On the other hand, it might sometimes result from poor organization on behalf of the transplanting centre and if routinely adjusted for may conceal differences that clearly reflect quality of care. In the present study, it was not possible to identify which patient characteristics were clearly under the control of the transplanting centre, and this is likely to vary between centres. Therefore, the approach adopted was to adjust for independent predictors of outcome and some degree of over-adjustment may have resulted.

The degree of availability of complete data relating to recipient and donor factors necessary for appropriate risk adjustment ranged widely between centres, with there being lower ascertainment of complete data for patients transplanted in smaller centres. The presence of missing data and, therefore, the exclusion of these patients from the analysis, is potentially an important source of bias, particularly for the interpretation of outcome for the smaller centres. Although only 9% of patients were excluded from the analysis, the unadjusted 12-month graft survival for this group was significantly less than for those with complete information relating to recipient and donor factors. Such a bias would result in a more favourable outcome than was truly the case in centres with greater numbers of patients with missing data.

A further important methodological issue relates to the difficulty in drawing conclusions from the data provided by smaller centres due to the imprecise estimates of their performance. Large differences may be seen between observed and expected outcomes in smaller centres as a result of sampling variability rather than any true difference in performance between centres. The hierarchical model employed in this analysis accounts for such variation between centres (Figure 1). This methodology tends to draw the relatively imprecise estimates of smaller volume centres towards the average outcome while exerting less effect on the relatively more precise estimates from larger centres [24].

The specific definition of what constitutes a centre effect is an important consideration. In this analysis, centres that performed statistically significantly
worse or better than the average for all centres were considered aberrant. The ERA–EDTA has recently promulgated guidelines for satisfactory renal transplantation outcome [9]. These recommend that for primary renal transplants, 12-month actuarial patient survival should exceed 90% and graft survival should exceed 80%. This definition does not account for variation in patient characteristics between centres nor for sampling variation in smaller centres. All Australian centres examined in this analysis achieved the benchmarks proposed by the ERA–EDTA.

Finally, there has been a significant improvement in short-term outcomes in renal transplantation since the introduction of modern immunosuppressive regimens. In the era prior to cyclosporine, 12-month graft survival rates typically varied over a 30% range (60–90%) between centres compared with the 15% range identified in this study [6]. Modern therapy has significantly reduced the variability in outcomes, making differences between centres more difficult to detect.

Identification of performance extremes can be affected by the analytical strategies used. The availability of relevant and complete patient information to allow for risk-adjustment, the use of appropriate multivariable and hierarchical modelling, and the choice of a suitable reference standard are necessary if a valid comparison of performance is to be made between centres.

Acknowledgements. This study was supported by a grant from the Dialysis and Transplantation Subcommittee, a joint committee of the Australian and New Zealand Society of Nephrology and the Australian Kidney Foundation. We wish to thank Professor John Stewart, Professor Ian Hardie and Associate Professor Andrew Forbes for their valuable advice at the onset of this study.

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Received for publication: 15.8.01
Accepted in revised form: 21.1.02