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ORIGINAL ARTICLE

Variations in graft and patient survival after kidney transplantation in Sweden: caveats in interpretation of center effects when benchmarking

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Summary

Benchmarking and comparisons between transplantation centers are becoming more common. A crude comparison indicated a 50% difference in patient survival between centers in Sweden. A 'task group' was formed to refute or confirm and learn from this observation. Patient survival and graft survival of 5 933 patients transplanted at three different transplantation centers in Sweden (Stockholm, Göteborg, and Malmö) were followed up until February 2007. Patient survival and graft survival were compared between the centers with and without consideration being given to important covariates such as time period, type of donation (living or deceased donor), gender, and age. A refined cohort of 2 956 adult patients that had been transplanted for the first time between 1991 and 2007 was assessed in more detail using Cox regression analysis. The difference in patient and transplant outcome observed in the crude comparison diminished considerably after adjustment for differences in case mix and time period of transplantation, and was neither evident nor significant after 1999. Patient survival and graft survival have improved considerably during the time period since 1991. The adjusted hazards ratio for mortality was 0.39 (95% CI 0.29–0.53) for patients who were transplanted after 1999 when compared with those transplanted between 1991 and 1994. Crude comparisons between results from transplantation centers may be severely confounded not only by case mix but also by differences in the proportion of patients transplanted during different time periods. Patient outcome and graft outcome have improved considerably since 1991, and after 1999 center effects were no longer apparent in Sweden.

Introduction

End-stage renal disease (ESRD) is associated with high mortality despite renal replacement therapy (RRT). Even so, slow but continued improvements in patient survival in RRT have been recorded during recent decades [1,2]. This is mainly the result of generally improved patient and graft survival after kidney transplantation [3]. Survival after kidney transplantation is higher than survival on dialysis, for comparable groups. In dialysis patients who

have been accepted for transplantation and have been transplanted, survival is considerably better than for those patients who have remained on the waiting list [4–6].

Benchmarking to assess results from medical treatments, and in particular surgical procedures, is becoming more common—and is encouraged by the medical profession, grant-awarding bodies, and also the general public. This is also true for long-term follow up of patient survival after kidney transplantation [7–10]. The comprehensive national registry for all RRT patients in Sweden has presented data in its annual report for 2006 showing considerable regional and center-based differences in patient survival after kidney transplantation [11]. Standardized risk ratio for mortality, adjusted for age, gender and presence of diabetes, was calculated for six different regions in Sweden, which correspond to the catchment areas of the four transplantation centers in the country. The national average served as a reference. Rather pronounced differences emerged; in one center/region, the risk ratio for mortality was 1.32 as compared with 0.85 and 0.86 in two of the others [11]. This translates into a greater than 50% difference in apparent mortality between the centers.

With the objective of examining and analysing these results more thoroughly, a 'task force' comprising participants from three of the four transplantation and nephrology centers in Sweden (those centers with a reported risk of mortality ranging from 1.32 to 0.85) was formed in early 2007. If the data were correct, could the pronounced difference in patient survival be confirmed? If so, what was the reason for this discrepancy and what could be learned from this? It was decided that not only patient survival but also graft survival after the first transplantation should be examined, and that as many pertinent confounders as possible should be considered—including donor type, time on the waiting list prior to transplantation, and year of first transplantation.

Material and methods

Patients

All RRT patients who had been reported to the Swedish Renal Replacement Registry [11,12] and who had undergone kidney transplantation at one of the participating transplantation centers (in Stockholm, Göteborg, and Malmö) were initially included. All primary data were carefully scrutinized to confirm that the center assignment for the first transplantation was correct. The calendar year of first transplantation ranged from 1964 to 2007. The total number of patients was 5 933 (Karolinska University Hospital, Stockholm: $n = 1\,988$; University Hospital, Malmö: $n = 1\,232$; and Sahlgrenska University Hospital, Göteborg: $n = 2\,713$).

Statistical analysis

All patients were followed up until February 28, 2007. Patient survival time was calculated from the day of first transplantation until the end of follow up, or until death. Patients who were transplanted a second time remained among surviving patients in the patient survival analysis. Likewise, graft survival of the first transplant was calculated from the day of transplantation until return to dialysis treatment or death, or to the end of follow up (February 28, 2007; not censored for patient death with a functioning graft). We also performed additional graft survival analysis censoring for death with a functioning graft.

The following predictors of survival and potential confounders were considered: gender; age at first transplantation; donor type, whether living or deceased donor; time on waiting list prior to transplantation; primary renal disease categorized into seven groups such as diabetic nephropathy, chronic glomerulonephritis, polycystic kidney disease, miscellaneous, pyelonephritis and interstitial nephritis, renal vascular disease, and renal disease because of other unknown causes; diabetes whether type I or II; time in dialysis before renal transplantation; also, time period of transplantation (1991–94, 1995–99, or 2000–2007). These time periods of about five years were chosen in order to get the cohort divided into roughly similar size subgroups. When center-based comparisons were made using Cox regression analysis, Göteborg (Sahlgrenska University Hospital) (with the largest number of patients) served as reference. Proportionality of variables used in the Cox regression was tested and confirmed not to offend the model used. Cut-off levels for creating intervals in the Cox-regression analysis were selected to produce similarly sized or logical groups.

Information on several other recipient risk factors, such as cardiovascular morbidity, smoking habits, body mass index, plasma cholesterol, or donor-specific ones such as donor age, HLA-matching and many more variables of great importance for graft and patient survival were not available in the data-base and could thus not be analysed.

Most variables were not normally distributed and thus expressed as median and 10–90 percentiles or as percentage of the total. Differences among the three groups were analysed with the nonparametric Kruskal–Wallis analysis of variance. A chi-squared test was used for categorical variables. For survival analysis, we used the Kaplan–Meier survival curve, and the Cox proportional hazards model was used to examine differences in survival after the analysis had been adjusted for potential confounding factors. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SAS statistical software (version 9.1; SAS Institute Inc., Cary, NC, USA).

Results

Average age (44–45 years), cause of ESRD, and proportion of patients transplanted with a kidney from a living donor (LD) (30–32%) were similar for the three centers, but 10.3% of transplanted were aged <19 years in Stockholm when compared with 4.5 and 4.8% in Malmö and Göteborg. Likewise combined kidney–pancreas transplant were more common in Stockholm (2.6%) when compared with the other centers (0.4% and 1.5%).

Pronounced differences in patient survival were noted when the primary cohort was analysed by center (Fig. 1).Five- and 10-year patient mortality after the first kidney transplant was 20% and 38% respectively in Stockholm, when compared with 10% and 22% in Malmö, and 7% and 20% in Göteborg.

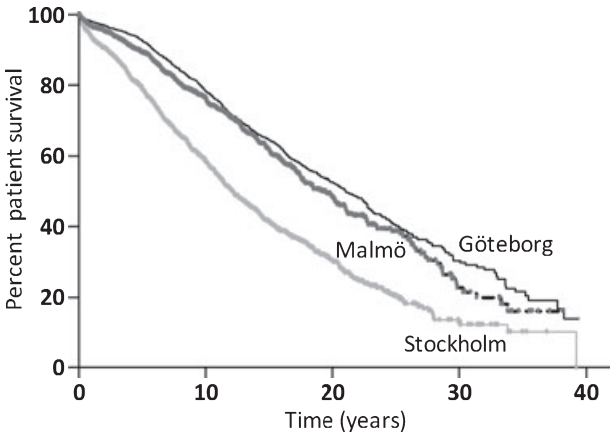

Figure 1 Cumulative proportion of patient survival among 5 933 renal transplant recipients, transplanted 1964–2007, by transplant center; Sahlgrenska University Hospital in Göteborg, Karolinska University Hospital, Stockholm, and the University Hospital, Malmö.

When examining the crude cohort of 5 933 patients, it became evident that the Stockholm and Göteborg subgroups had larger proportions of patients who had their first kidney transplant before 1991 (39% and 42% for Stockholm and Göteborg respectively) whereas this proportion was smaller in Malmö (18%). We also found that the time period when the transplantation was performed had a marked influence on both patient survival and graft survival (data not shown). Consequently, the patient survival comparison was biased, as there were important differences in the three subgroups. Furthermore, it appears that reporting to the national registry had not been comprehensive from all centers until 1991, which was the year when the national Swedish RRT registry began to collect information from all patients in Sweden starting RRT.

We therefore proceeded by creating a more refined cohort (Table 1) to enable more relevant comparisons and benchmarking between the centers. In the refined analyses, which included only patients who had their first transplant some time between January 1, 1991 and up to February 28, 2007, we also excluded patients aged <19 years and those who had received a combined kidney–pancreas transplant.

The refined cohort is presented in Table 1. Certain differences between the groups are evident; female recipients were less common in Stockholm, time on dialysis before transplantation was somewhat longer and the proportion of living donation less. The proportion of all transplantations performed during the first time period

Table 1. Characteristics of the refined cohort of kidney transplant recipients (n = 2 956). Expressed as median and 10–90 percentiles, or percentages.

	Malmö	Stockholm	Göteborg	*P*-value
Number	703	796	1457	
Age, years	49 (19–73)	48 (19–72)	49 (19–73)	NS
Gender, female (%)	36	29	36	0.003
Primary renal disease (%)				
Diabetic nephropathy	18	14	15	0.02
Chronic glomerulonephritis	30	34	34	
Polycystic kidney disease	15	19	17	
Miscellaneous	13	12	13	
Pyelonephritis and interstitial nephritis	9	7	7	
Unknown	5	6	5	
Renal vascular disease	8	7	6	
Time in dialysis before kidney transplantation (years)	1.2 (0–3.4)	1.5 (0–4.5)	1.1 (0–3.9)	<0.001
Living donation (%)	36	31	38	0.006
Number of transplants 1991–94	186	223	362	
Number of transplants 1995–99	217	223	432	
Number of transplants 2000–07	300	350	663	

Malmö, University Hospital, Malmö; Stockholm, Karolinska University Hospital, Stockholm; Göteborg, Sahlgrenska University Hospital, Göteborg.

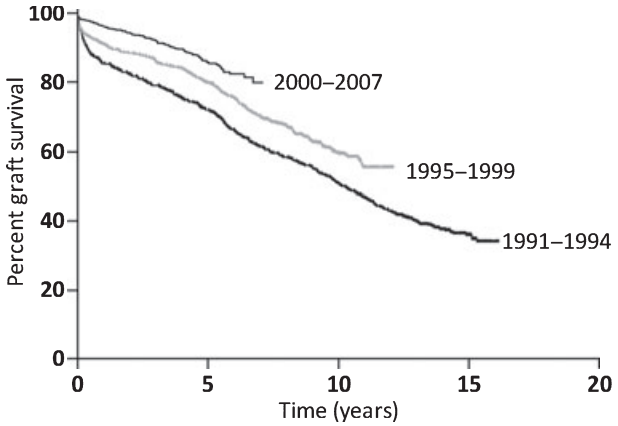

Figure 2 Cumulative proportion of graft survival (first transplants only) by time period in patients transplanted after 1991; refined cohort.

(1991–94) was higher in Stockholm (28%) than in Malmö (26%) or in Göteborg (24%). In particular, the time period of the transplantation had implications for both patient (not shown) and graft survival (Fig. 2).

To allow more accurate comparisons of the patient survival experience between the three centers, Cox regression analysis was performed. Table 2 gives hazards ratios for predictors of survival for the refined cohort during the whole period. From Table 2, it is evident that the risk of mortality increased with age at transplantation, time in dialysis before renal transplantation, presence of diabetes, and transplantation of a kidney from a deceased donor. It decreased in more recent time periods; it became reduced by 71% between 1991–1994 and 2000–2007. There appears also to be a significantly increased risk of mortality (hazards ratio 1.55) in patients transplanted in Stockholm (Table 2). However, when we restrict the analysis to patients transplanted during the period 2000–2007, no significant differences were seen between the centers, (hazards ratio 1.12; 95% CI 0.63–1.98) (Fig. 3). Examination of causes of death among patients transplanted at different centers also revealed noteworthy differences in the early 1990s. Cardiovascular mortality was more common in patients transplanted in Stockholm during the first period (1991–94). Sixty-eight of 223 patients (30%) transplanted during the period 1991–94 in Stockholm had died from cardiovascular causes, whereas the cumulative incidence of cardiovascular death was much lower in patients transplanted in Göteborg (75/362; 20%) and Malmö (36/186; 19%). The proportions of cardiovascular to the overall mortality were 57% in Stockholm, and 50% and 48% in Göteborg and Malmö respectively. For other time periods and causes of death, no differences in patterns of mortality were seen.

Analysis of graft survival showed a similar pattern, with the same risk factors for graft loss as for mortality (increasing age, presence of diabetes, and transplantation from a deceased donor). Overall, there was a significantly increased risk of graft loss in Stockholm (hazards ratio 1.41; 95% CI 1.2–1.64), but again this difference disappeared after 1999 (Table 3, hazards ratio 0.85; 95% CI 0.58–1.26).

Censoring for death with functioning graft, i.e. merely regarding return to dialysis as an event of failure, gave essentially the same result as the analysis of graft survival not censored for death with functioning graft. There was inferior graft survival for Stockholm during the early period (1991–94) but with less (and statistically not

Table 2. Cox hazards regression analysis of mortality in the refined cohort; patients transplanted 1991–2007, excluding those who were <19 years old at transplantation, or who received a combined kidney–pancreas transplant.

Time period 1991–2007	Hazards ratio	95% Confidence limits		*P*-value
Gender (female)	1.08	0.92	1.28	0.34
Age 40–59 years (ref. <40)	2.37	1.87	3.02	<0.0001
Age 60 + years (ref. <40)	5.12	3.94	6.64	<0.0001
Diabetes mellitus (ref. not DM)	2.31	1.92	2.78	<0.0001
Donor type (ref. LD)	1.89	1.50	2.48	<0.0001
Time in dialysis before kidney transplantation >1.4 year (ref <1.4 year)	1.53	1.29	1.83	<0.0001
1995–99 (year of transplant, ref. 1991–94)	0.68	0.57	0.82	<0.0001
2000–07 (year of transplant, ref. 1991–94)	0.39	0.29	0.53	<0.0001
Malmö (ref. Göteborg)	1.13	0.92	1.38	0.23
Stockholm (ref. Göteborg)	1.55	1.29	1.87	<0.0001

Malmö, University Hospital, Malmö; Stockholm, Karolinska University Hospital, Stockholm; Göteborg, Sahlgrenska University Hospital, Göteborg; DM, diabetes mellitus; LD, living donor.
Number of individuals; <40 years n = 862, 40–59 years n = 1 554 and 60- n = 540. Median time in dialysis before transplantation 1.4 years.

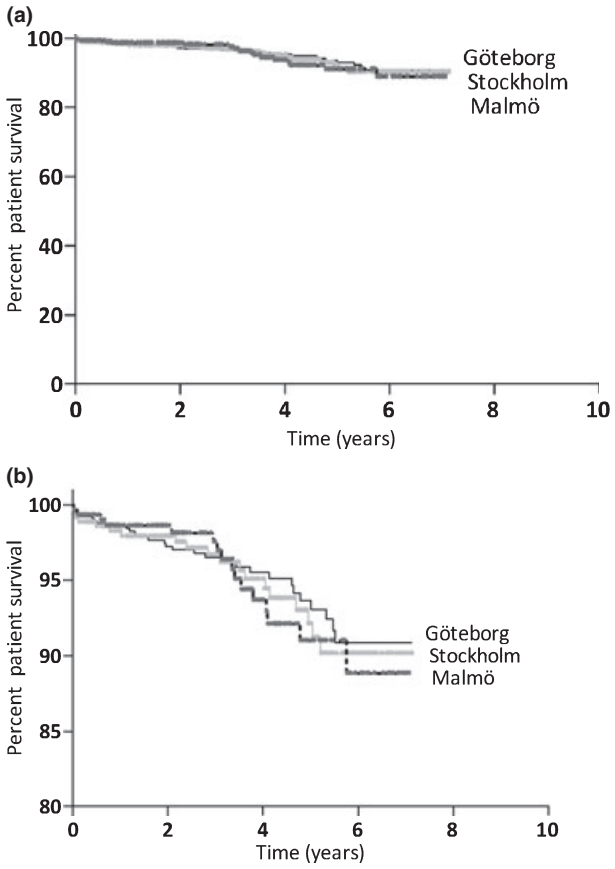

Figure 3 (a) Cumulative proportion of patient survival among renal transplant recipients, transplanted 2000–2007, by transplant center; Sahlgrenska University Hospital in Göteborg, Karolinska University Hospital, Stockholm, and the University Hospital, Malmö; refined cohort. (b) Enlargement of the upper part of the y-axis of Figure 3(a).

Table 3. Cox hazards regression analysis of graft loss in all patients transplanted after 2000–2007; refined cohort.

Time period 2000–2007	Hazards ratio	95% Confidence limits		*P*-value
Gender (female)	1.06	0.75	1.49	0.74
Age 40–59 years (ref <40)	0.86	0.58	1.28	0.45
Age 60 + years (ref <40)	0.87	0.53	1.45	0.61
Diabetes mellitus (ref. not DM)	1.29	0.82	2.04	0.28
Donor type (ref. LD)	3.56	2.20	5.76	<0.0001
Time in dialysis before kidney transplantation >1.4 years (ref <1.4 years)	0.98	0.67	1.45	0.93
Malmö (ref. Göteborg)	0.73	0.47	1.13	0.16
Stockholm (ref. Göteborg)	0.85	0.58	1.26	0.42

Malmö, University Hospital, Malmö; Stockholm, Karolinska University Hospital, Stockholm; Göteborg, Sahlgrenska University Hospital, Göteborg; DM, diabetes mellitus; LD, living donor.

significant) differences between the three centers for the two more recent time periods.

Discussion

Comparisons of outcome and benchmarking between different medical centers are important, and both are being undertaken more frequently [9,13,14]. The results obtained may be of considerable interest to professionals as well as to the general public, and may be used for allocation of resources and patients.

The outcome after kidney transplantation is a clear example of data that are of immense interest to patients. As a rule, the procedure is carried out once during the patient's lifetime and the possible benefits from a successful transplantation are substantial, considering reduction in cost for healthcare services including dialysis, and improvement in quality adjusted life years of the transplanted patients.

It is thus extremely important that benchmarking and comparative quality-control exercises should be carried out in a correct way. Erroneous results and interpretations may have serious consequences. This is illustrated in this study. In the first crude analysis (Fig. 1), pronounced differences in patient survival between the three different transplantation centers in Sweden became apparent. The case mix, including children, adolescents, and recipients of combined kidney–pancreas transplants—and particularly the period when the patients were transplanted for the first time—had an important influence on survival. When these factors were accounted for, the differences between the three centers diminished and were not seen at all after 1999. A higher incidence of cardiovascular mortality in patients from Stockholm during the early period (1991–94) appeared to be the main culprit for the inferior result during this period. Indeed, cardiovascular mortality was recognized as a main cause of death and graft loss in Sweden during the 1990s [15]. After this observation and similar findings made by other investigators, a much more thorough and careful assessment of potential kidney recipients was introduced, with special focus on cardiovascular risk factors [16]. Patients with overt or incipient cardiovascular morbidity are not accepted for kidney transplantation at all, or until steps to reduce the risk have been taken, e.g. coronary bypass operations or other similar procedures to reduce the risk of severe cardiovascular events. However, in Stockholm, this careful cardiovascular assessment was introduced about five years later (mid-1990s) when compared with the other two centers (early 1990s).

The importance of selection of candidates for transplantation was recently discussed in an extensive follow up of patients transplanted in the US during the period

between 1995 and 2005 [10]. It was observed that centers with a high mortality among patients on the waiting list prior to transplantation often also displayed a poor survival after. It was concluded that the health status of centers' transplant candidate pool is a significant determinant of outcomes and performance ratings and that pressures to enhance outcomes may lead centers to exclude high-risk but otherwise viable transplant candidates. In Sweden, the three examined centers under the observation period have converged to a similar acceptance policy.

In addition to cardiovascular morbidity a great number of other factors are well known to influence graft and patient survival, such as obesity, blood lipids, HLA-mismatch, type of immunosuppression etc. Data on this was not available in the registry and could not be accounted or adjusted for in the analysis. Apart from differences in cardiovascular morbidly during the early period (1991–94), which was also evident in the mortality pattern, we however have no reasons to believe that there are important differences between the centres that should have concealed differences in survival after 1995.

Our analysis shows, and this is something quite encouraging, that patient survival and graft survival have improved to a great extent since 1991. The adjusted risk of mortality and graft loss in patients transplanted in the year 2000 and later are less than 50% of the corresponding figures for patients transplanted in the early 1990s. In a comparison of kidney and liver transplantation outcome in the US, Axelrod *et al.*, [13] noticed that 'low-' and 'very low-' volume centers (with <75 and 45 kidney transplantations annually respectively) had a significantly higher incidence of graft failure at 1 year than medium- or high-volume centers. The three transplant centers we have examined are all in the low- or medium-volume category.Even so, the 1-year graft failure rates in the three centers examined during the latest period, since 2000, were between 4% and 7% (data not shown) which is in the same range as, or even better than, those of the large-volume centers in the US reported for renal transplantations performed during the period from 1996 to 2000 [13].

Similar results as ours have been reported from Canada [8].Graft survival and patient survival after kidney transplantation performed between 1988 and 1997 were compared in 20 different Canadian centers using a Cox proportional hazards model, and adjusting for several relevant covariates. Considerable differences between transplant outcomes from the 20 different centers were also seen after adjustment for covariates and case mix. This is similar to what we found when the three time periods were merged together (Table 2), although the differences seen in Sweden are less than those reported from Canada. However, no significant differences in results between centers were seen in Sweden after 1999. In accordance with our observations, Kim *et al.* [8] also observed a considerable improvement in outcome in patients transplanted in a later period (1994–97) when compared with an earlier period (1988–89). A single centre experience from Northern Ireland is also in line with ours [17]; in spite of changes in co-morbidity, age and other characteristics of kidney recipients the overall outcome after renal transplantation had improved considerably since 1967.

To sum up, the message and conclusion from this study is that the differences in mortality initially observed after kidney transplantation, between different centers in Sweden, can mainly be explained by differences in case mix and time period. Since 2000, no significant differences in patient survival or graft survival could be seen between the Swedish centers. Patient and graft survival have improved considerably in the last two decades. This analysis may serve as a reminder of potential caveats in analyses and interpretation of kidney transplant results when benchmarking procedures are performed in other countries or regions.

Authorship

C-GE: initiated the study and wrote the first draft of the report, which all co-authors subsequently critically reviewed and contributed to. C-GE, ARQ: together made the statistical analysis and finalized the report. SS: is general secretary of the Swedish RRT registry and provided all data used in the analysis. HE: chaired the 'task group' and administrated the multi-centre collaboration. HE, PB, IF-E, GJ, GN, SS, LW, ARQ have all contributed substantially to the design, evaluation and reporting of this work.

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