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Impact of cadaveric renal donor morbidity on long-term graft function

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Abstract The significance of donor age, cause of death, and morbidity for the outcome of renal cadaveric transplantation was evaluated in 534 cases from 1994 through 2001. Half of the kidneys (49.4%) were from donors without identified risk, the others were age 50–64 or ≥65 years, had died of cerebrovascular lesion (CVL), or had known cardiovascular disease, or hypertension. Only death from CVL influenced cumulative graft survival ($P=0.04$), the actual survival at 6 months being 87% vs 95% with other donors ($P=0.004$). Clearance of ^{51}Cr EDTA (glomerular filtration rate, GFR) after 1 year was a more sensitive marker of graft quality and was significantly reduced with each tested risk factor. For instance, the median GFR (range) in the three donor age groups was 52 (9–125), 37 (13–83), and 29 (15–60) ml/min, respectively ($P<0.0001$). Combinations of risk factors significantly increased their impact on GFR. However, the overall results with such suboptimal donors should rather encourage a widening of the donor acceptance criteria.

Keywords Cadaveric kidney donor · Glomerular filtration rate · Graft function · Marginal donors · Renal transplantation

Introduction

There are no strict criteria for the acceptance of cadaveric kidneys offered for transplantation. The decision whether to use the kidneys from a potential donor or not is made by the transplant surgeon. It involves consideration of information procured by the transplant coordinator regarding factors that might be contraindications, such as the donor's age, cause of death, and any history of cardiovascular disease. The prognostic significance of such factors is, however, not fully known. Although the prognosis is worse with a kidney from an elderly donor [1, 2, 3, 4, 5], the survival rates might be quite acceptable to some patients who are now refused transplantation [5, 6, 7, 8, 9]. Furthermore, chronologic age is a surrogate for aging, or rather the rate at which nephrosclerosis develops. This process differs between individuals. It may be better determined by cause of death or history of cardiovascular disease than by actual age. We decided to analyze in retrospect the impact of donor morbidity and age, both alone and in combination, on survival.

Patients and methods

Among 900 kidney transplantations performed at Sahlgrenska University Hospital in 1994 through April 2001, 534 were cadaveric kidneys procured by a local team of transplant surgeons. The other kidneys were either from living donors or shipped. The decision to accept the donors was based on information on donor age, case history, serum creatinine at the time of admittance and later, and urine yield. Proteinuria was not tested for routinely, and a biopsy was obtained only in the rare case of a systemic disease. The number of approved donors for the 534 kidneys was 337. In the majority of cases, when only one kidney was used in the unit, the other was shipped as part of the Scandiatransplant cooperation. The donors were classified as to their age being less than 50 years, 50–64 years, or older; as to death from cerebrovascular lesion

(CVL), subarchnoid hemorrhage (SAH), or other, mainly trauma; and as to any previously known cardiovascular morbidity, treated hypertension, or any other disease known to affect the kidney. The latter group comprised seven kidneys from donors with diabetes and four from donors with systemic lupus erythematosus (SLE). Cardiovascular disease, defined as stroke, myocardial infarction, angina pectoris, cardiac failure, or claudication, was termed so irrespective of any concomitant hypertension; therefore, hypertension means hypertension alone. The data were also combined in a risk score ranging from 0–3, where age 65 years or higher, death from CVL, and previously known hypertension, cardiovascular disease, diabetes, or SLE each counted one point.

These basic data were used in survival calculations. Survival was calculated as actual survival after 6 months, analyzed by χ^2-test, as well as cumulative survival according to Kaplan-Meier, analyzed by Mantel-Cox. Grafts lost due to patient death were censored, i.e., considered lost to follow-up. A Cox proportional hazards analysis was also performed, including the possible risk factors with a *P*-value of below 0.1 in the univariate analyses.

The glomerular filtration rate (GFR) was determined after 1 year as plasma clearance of ^{51}Cr EDTA or iohexol and expressed as ml/min per 1.73 m^2 body surface area. Differences between categories were calculated with ANOVA and evaluated by Fisher's PLSD.

Results

In Fig. 1, three pie charts show demographic donor data on age, cause of death, and morbidity known before the final event. Half of the kidneys (49.4%) were from donors without identified risk, 29.1% had one risk factor, 15.9% had two, and 5.6% had three risk factors, i.e., they were from elderly donors with known hypertension, diabetes, or cardiovascular disease who died of stroke.

Graft survival

After 6 months, actual graft survival was significantly less when the cause of death was CVL, rather than SAH or trauma, namely 87% vs 95% and 95%, respectively ($P < 0.0001$). In univariate analyses, cumulative survival was also reduced when CVL was the cause of death ($P = 0.04$, Fig. 2). There was only a trend for better survival with grafts from younger donors ($P = 0.09$), whether calculated after 6 months or as cumulative survival. No impact of previously known disease was seen on survival, even though the small groups of diabetic donors and such with rare disorders were excluded from the calculations in order to increase strength.

As seen in Fig. 3, the combined risk index did not turn out to be significant for graft survival after 6 months and showed only borderline significance in the cumulative analysis ($P = 0.07$), with index 3 tending to come out worse than the other three groups. In the Cox proportional hazards analysis, where age and cause of death were included, none of them remained significant.

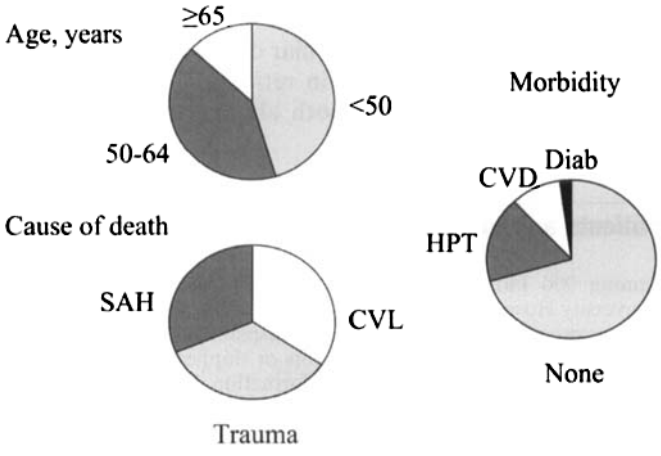

Fig. 1 Pie charts indicating demographic donor risk profiles for 534 kidney grafts, regarding age, cause of death, and previously known morbidity (*SAH* subarachnoid hemorrhage, *CVL* cerebrovascular lesion, *HPT* hypertension, *CVD* cardiovascular disease, *Diab* diabetes)

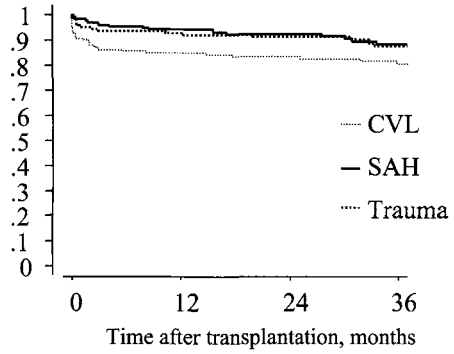

Fig. 2 Cumulative graft survival of 534 kidney grafts according to Kaplan-Meier. Graft loss due to patient death was calculated as lost to follow-up. Groups separated according to cause of death, cerebrovascular lesion (*CVL*): $n = 186$, subarachnoid hemorrhage (*SAH*): $n = 181$, trauma: $n = 167$. $P = 0.04$

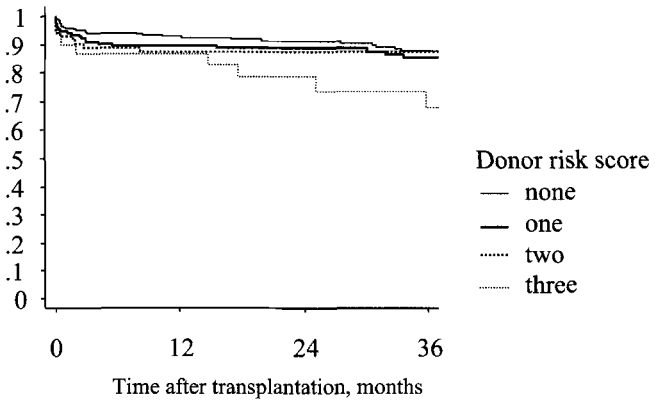

Fig. 3 Cumulative graft survival of 534 kidney grafts according to Kaplan-Meier. Graft loss due to patient death was calculated as lost to follow-up. Groups separated according to a combined donor risk score, based on age, cause of death, and previous morbidity. The number of grafts (with increasing risk score) is 265, 154, 85, and 30. $P = 0.07$

Graft function—GFR

Figure 4 shows how the GFR at 1 year was influenced by the isolated donor risk factors and by the combined score. Donor age of less than 50 years conferred a significantly higher GFR than the older age groups ($P < 0.0001$). Cause of death also influenced the GFR at 1 year, death from trauma leading to a higher GFR than both other causes ($P < 0.0001$), while the difference between SAH and CVL was not significant. Within each cause of death, the effect of age on GFR was similar. A weaker, but clearly significant effect of previous morbidity on GFR was observed for no known disease vs each of the diagnosis groups ($P < 0.02$). In the donor risk score 0–3, the GFR differed significantly between all steps except score 2 and 3.

Discussion

This study is a contribution to the discussion of "marginal donors" [1, 5, 6, 8, 9, 10, 11, 12]. The lack of cadaveric donor organs and the growing waiting lists have initiated a widening of acceptance criteria, particularly with respect to donor age, individual reports defining "marginal" kidneys as being from donors aged ≥40 [13], ≥55 [1, 11], ≥60 [3, 8, 14], and even ≥70 years [12]. We did not see any impact of age on graft survival. This may be due to the fact that the influence of donor age is gradual, with a noticeable increase starting already around the age of 30 years [4, 5, 7]. This effect is also evident in histopathologic investigations of time zero biopsies [10]. Chronologic age does not fully reflect such change.

In recent years, the proportion of donors to have suffered traumatic death has decreased and the acceptable age range has been extended [1, 9, 12]. Therefore, interest has also been focused on the impact of cause of donor death, i.e., whether cardiovascular or not, and of known donor morbidity, such as hypertension or diabetes [1, 4, 5, 8, 9, 14]. We found a limited effect of cause of death on cumulative survival, but previous morbidity had no impact.

The fact that multiple risk factors should be evaluated in consort has been stressed [1, 9]. Therefore, we ▶

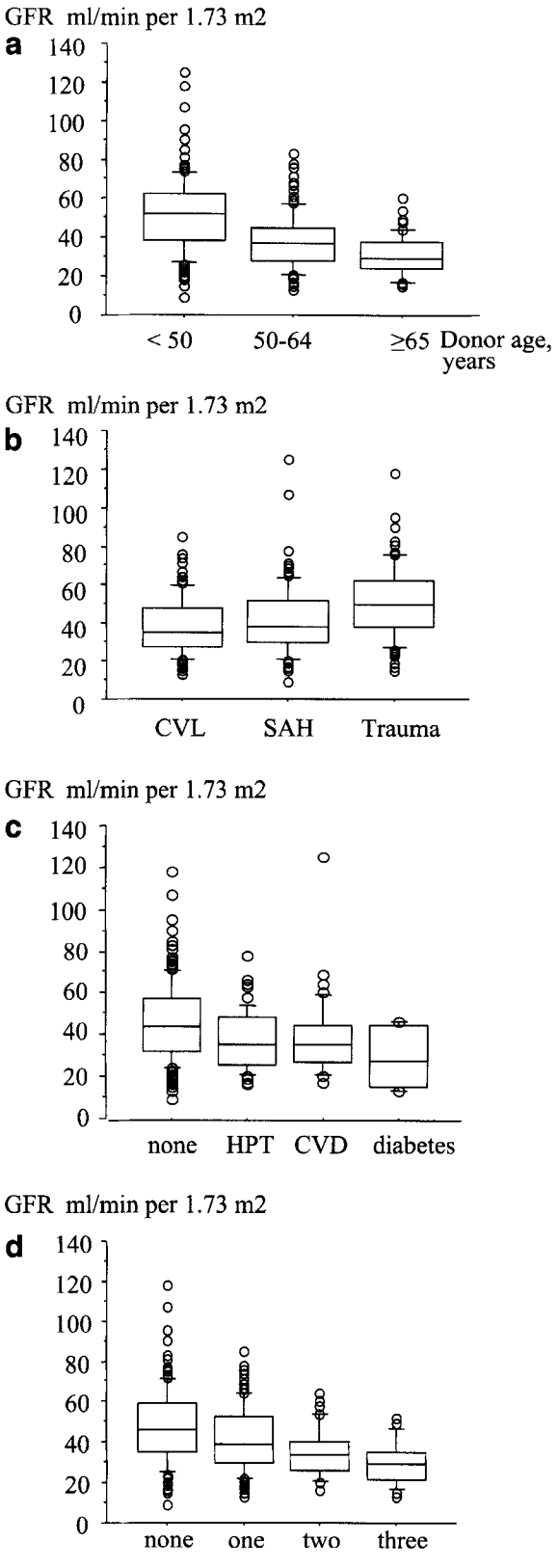

Fig. 4 Box plots demonstrating the impact on recipient glomerular filtration rate (*GFR*) at 1 year of follow-up of (**a**) donor age (*P*-values for differences between donor age groups are < 0.0001 and 0.007), (**b**) cause of death (cerebrovascular lesion [*CVL*] different from both subarachnoid hemorrhage [*SAH*] and trauma, $P < 0.0001$), (**c**) donor morbidity ("none" significantly different from the respective diagnoses, $P = 0.0006$ vs hypertension [*HPT*], $P = 0.02$ vs cardiovascular disease [*CVD*], and $P = 0.02$ vs diabetes), and (**d**) the combined donor risk score (*P*-values for each step 0.003, 0.01, and 0.2)

created a combined donor risk score based on age, cause of death, and previous morbidity. There were only 30 grafts from donors with the highest risk score, i.e., from donors aged 65 years or more, dead of stroke, and with known cardiovascular disease, hypertension, or diabetes. Graft survival from such donors was not significantly worse in the first years, but then seemed to drop (Fig. 3). This is probably a result of the lower nephron mass provided [14]. An excess risk has been reported for a combination of high donor age, longstanding hypertension, and a calculated creatinine clearance below 80 ml/min [1].

In this study, we showed that the GFR at 1 year is a much more sensitive marker of graft quality than survival. It is profoundly influenced by donor risk factors. We know of no other study in which GFR has been measured and evaluated in relation to donor data. Cosyns et al. found a significant impact of donor age on serum creatinine after 6 months in a subset of recipients who had not suffered acute rejection episodes [10]. The impact of donor data we found was evident, even though rejection had often occurred and had certainly caused some graft damage. Comparing serum creatinine levels in recipients of pair kidneys 6 months after transplantation, Cosio et al. estimated that donor data explained 64% of the variability and that only 36% was due to recipient factors [2]. Had the grafts in our series that had already failed after 1 year been included in these calculations as GFR 0 ml/min, the effect would clearly have been much stronger since all survival trends went in the same direction as the differences in GFR.

Though donor risk factors are clearly identified, our main conclusion is that the results are good even with these suboptimal donors. Furthermore, if only the ideal donor had been used, i.e., less than 50 years of age, with no known cardiovascular disease, and dead of trauma, only half of the recipients in our series would have been offered transplantation.

An offer to the recipient to opt for "marginal" donors with the possibility of shorter waiting time has been practised in Malmö, Sweden [12]. Other transplant centers give patients the opportunity to accept or reject a kidney when offered [15]. One problem with the separate "marginal donor" waiting list approach is the definition of "marginal donor". Our results—and the much different definitions given in various publications—clearly show that there is no sharp limit where a risk donor profile makes a kidney "marginal" and another kidney "optimal" or "normal" [5, 11, 12, 13, 14]. All transplant candidates must be aware that the quality of cadaveric kidneys varies and cannot be ascertained beforehand in detail.

The outcome of this study should rather encourage a widening of the donor acceptance criteria, allowing more patients with relative contraindications to submit themselves to the risk and the chance.

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