Comparison of early renal function parameters for the prediction of 5-year graft survival after kidney transplantation

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Abstract

Background. Early graft function (EGF) has an enduring effect on the subsequent course after kidney transplantation. This study compares quantitative parameters of EGF for the prediction of graft survival.

Methods. We involved 300 consecutive transplant recipients from deceased donors from 1989 to 2005. Urine output during 24 h post-transplant (UO), and serum creatinine after 1 week (Cr7) were taken for explanatory variables. We generated Kaplan–Meier (K–M) estimates of graft survival, by quintiles of the explanatory variable. Cox regression was applied to control for various recipient factors.

Results. K–M survival estimates indicate a threshold effect of UO and Cr7, which can dissect the risk of graft failure. The thresholds referring to the 2nd quintile correspond to a UO > 630 ml and a Cr7 < 2.5 mg/dl and were associated with a proportional hazard ratio of 0.52 (95% CI 0.33–0.84) and 0.34 (95% CI 0.18–0.65), respectively. Combining both of the parameters predicted a 5-year graft survival probability > 90%, according to a hazard ratio of 0.21 (95% CI 0.09–0.46). Requirement of dialysis post-transplant lost its discriminative power and was not a significant explanatory variable in the multivariate analysis.

Conclusion. Routine parameters for monitoring of EGF display a threshold effect allowing accurate prediction of 5-year graft survival at the earliest point in time. The quantitative threshold levels for an optimum discriminatory power require validation in a larger, preferably multicentre database.

Keywords: delayed graft function; graft survival; kidney transplantation; serum creatinine; urine output post-transplant

Introduction

Delayed graft function (DGF) is both an outcome and a predictor of the subsequent course of a kidney transplant [1]. DGF comprises the common final path of various aetiologial factors that accumulate in harm to the graft. Donor-related factors, such as age and tissue quality, brain death, and variables related to the donation and transplantation process are crucial for the early performance and affect the long-term function of the graft [2–5]. Several recipient characteristics may add to the risk of DGF. Among these, prerenal causes, immunosuppressive medications, HLA-mismatches, sensitization, and a repeat transplant also have a major influence on graft survival. DGF enhances the susceptibility of tissues for an alloimmune-mediated attack [6–8]. Some analyses conclude that DGF in the absence of rejection does not affect graft loss [9,10], while others come to converse findings [11–13]. Various definitions for DGF have been used [10,14–16], the most common referring to the requirement for any dialysis in the first week after transplantation. However, criteria for the use of dialysis after transplantation are not well defined. Some investigators also advocated urine output post-transplant, creatinine concentrations 1 week after transplantation, or a combination of these for the assessment of early renal function [17–19]. Creatinine reduction ratio on the 2nd post-transplant day (CRR2) has recently been proposed as a more accurate criterion for DGF, bearing the potential to predict graft dysfunction at an earlier point in time. The main drawback of the CRR2 criterion comes from the interference with early dialysis post-transplant arbitrarily distorting the serum creatinine levels [20]. Given the enormous impact for the subsequent prognosis in the long term, a quantitative measure of DGF, which is not mandated by a treatment only, could allow more precise predictions. Indeed, an objective and reliable
parameter that is generally accepted has not been evaluated to date. The current study compares in quantitative terms the prognostic accuracy and reliability of different measures for early graft function in a cohort of 300 consecutive renal transplant recipients from deceased heart-beating donor. The focus of the analyses is directed at graft survival after 5 years.

Materials and methods

Study population

A prospective database was created of all consecutive renal transplants carried out at the University Hospital of Mannheim, Germany, between June 1989 and December 2005. We excluded four patients with an early graft loss due to vascular thrombosis, and all recipients of a living donor kidney. Thus, the study population involved 300 transplant recipients of a kidney graft from a brain dead donor. Besides standard donor and recipient characteristics like age, gender, panel reactivity, HLA-matching, serological CMV status, the database also includes information on serial serum creatinine concentrations during the in-hospital stay after transplantation, urine output on the first and second post-operative day, requirement of haemodialysis post-transplant and occurrence of acute rejection during the first month.

Allocation of the donor kidneys to the individual recipient was centrally directed by Eurotransplant delivering a computerized algorithm mainly based on waiting time and HLA-matching. Study entry was defined by the date of transplantation, and follow-up was terminated on 31 December 2005 or at the earlier date of graft failure and recipient death, respectively. The observation period for the current study was limited to a maximum of 5 years. No patient was lost to follow-up. Mean duration of follow-up was 3.4 years, and a total of 77 kidney grafts failed during the study period. Chronic allograft nephropathy and death with a functioning graft accounted for the most common causes of graft failure.

Perioperative fluid management, immunosuppressive medication and acute rejection episodes

All patients, except those on continuous peritoneal dialysis (n = 9) received a dialysis session immediately before transplantation targeting 1–2 kg over the former dry weight. Perioperative hydration was initiated with intravenous 0.9% saline at a rate of 1–1.5 ml/kg/h and was subsequently adapted according to urine output and fluid balance. Mannitol 20% (250 ml) and a single bolus of i.v. furosemide (40–80 mg) were administered before opening of the arterial vessel clamp. No additional doses of diuretics were given over the first 24 h post-operatively. Immunosuppressive therapy was mainly based on a ciclosporin containing triple-drug regimen (95% of all cases). Ciclosporin was given orally on the first post-operative day, and the initial dose (5 mg/kg bid) was adjusted according to a target trough level between 180 and 250 ng/ml. In 1996, azathioprine was replaced by mycophenolate mofetil, and anti-CD25 monoclonal antibodies have been routinely applied for induction of immunosuppression since 1999.

Diagnosis of acute transplant rejection was proven by renal core biopsy (52 patients) or based on clinical criteria (28 patients). Renal core biopsies were graded according to the Banff classification [21]. Clinical criteria consisted of a sustained rise of serum creatinine, a marked reduction of urine production in the absence of drug toxicity or urinary tract obstruction, and response to steroid bolus therapy within 3 days after administration. Anti-rejection therapy was initiated with high dose methylprednisolone. In cases of steroid resistant rejection, polyclonal anti-T-lymphocyte globulines were applied and/or plasmapheresis was performed in instances of a positive C4d staining in peritubular capillaries suggesting humoral rejection.

Measures of early graft function and definition of study outcomes

Urine output during the first 24 h, serum creatinine 1 week after transplantation and dialysis dependency during the first week were the target variables of interest and were compared with one another with regard to 5-year allograft survival. Analyses were done with patient death and with censoring for death with functioning graft.

Requirement of haemodialysis was coded dichotomously in the original database. The number of dialysis sessions and days of dialysis requirement before a sufficient graft function occurred were also documented. Measures of urine output and serial creatinine concentrations were entered as continuous variables. The primary survival analysis was performed by dividing the continuous variables of interest into quintiles. Cut-off levels were derived from quintiles to dissect patients at risk by a simple dichotomous measure for a secondary analysis. We also assessed the risk of graft failure by doing a multivariate analysis to control for potential confounding factors. The following parameters were considered in the multivariate analysis: donor and recipient age (age groups: <30 years; 30–45 years; 46–60 years; >60 years), donor and recipient gender, repeat transplant, number of HLA mismatches (classes I and II), panel reactive antibodies >5%, occurrence of rejection episodes, occurrence of vascular rejection episodes (Banff grade II/III), and transplantation era (1989–1995; 1996–2000; 2001–2005).

Statistics

Numerical data are reported as mean±SD, and comparisons among groups were done by using the two-sided Student’s t-test. Differences in the distribution of categorical variables were tested with the chi-squared test or with Fisher’s exact test if appropriate. Kaplan–Meier (K–M) survival analysis (log rank test) and the Cox regression model were applied for the comparison of graft survival. Results of the Cox regression model are expressed as proportional hazard ratios (HRs), with a 95% confidence interval (95% CI) for a one-unit change in the variable. Significance was defined according to a P-value <0.05. Statistical analyses were carried out using Stata Statistical Software for MS Windows (release 5.0; Stata Corp., College Station, TX).
Early renal function parameters and graft survival

Results

Measures of early graft function and graft survival

K–M graft survival curves, by quintiles of 24 h urine output, and serum creatinine concentration at 1 week are displayed in Figure 1. The survival curves clearly indicate the existence of a quantitative threshold that separates patients with an increased risk of graft failure from those with an excellent prognosis in the long-term. In particular, urine output during the first 24 h post-transplant above the 2nd quintile was associated with a 5-year graft survival of 78.8%, whereas graft survival was 56.9%, if the post-operative urine production did not exceed the 2nd quintile. When death with a functioning graft was censored for the analysis, graft survival was 82.7 and 65.1%, respectively. The cut-off level corresponded clinically to a urine volume of 630 ml during 24 h after transplantation. Likewise, the cut-off level for the serum creatinine concentration at 1 week (2.5 mg/dl) was derived from the upper limit of the 2nd quintile. Accordingly, graft survival rates after 5 years were 88.1 vs 57.7% and 91.6 vs 64.8% when censoring for death was performed. The particular effect on long-term graft survival is underscored when splitting the observation period in two intervals, up to 2 years and beyond 2 years after transplantation (Figure 2). Compared with urine output post-transplant, the cut-off level for serum creatinine after 1 week provided a better discriminatory power regarding graft survival, because this measure separated a smaller fraction of patients at risk from the whole study population at a later point in time. Combining the criteria [UO >630 ml and 1 week (Cr7) ≤2.5 mg/dl] resulted in a further rise of 5-year graft survival, which was 93.6 vs 65.4% and 91.6 vs 58.0% when doing the analysis with and without censoring for death, respectively.

Dialysis independency post-transplant discriminated graft survival probability to almost the same degree of magnitude as the upper limit of the 2nd quintile of the 24 h urine production. Overall graft survival after 5 years was 76.4 vs 57.6% and 82.3 vs 63.8% when death with a functioning graft was disregarded for failure. As shown in Figure 3, there was a great variation in the length of time and in the number of dialysis sessions, before recovery of graft function occurred. In addition, the indication varied with ongoing duration of dialysis therapy. Duration of dialysis post-transplant and the required number of dialysis sessions had also a major influence on the long-term outcome (Figure 3D and E).

The effect of UO and Cr7 was maintained when doing the analyses only in patients without dialysis dependency. Five-year graft survival conditional on a UO of >630 ml was 81.8 vs 54.6% and 85.9 vs 66.9% after censoring for death. Likewise, 5-year graft survival conditional on a Cr7 <2.5 mg/dl was 89.7 vs 56.6% and 93.3 vs 65.5%, respectively. The survival differences were statistically highly significant (log rank P < 0.001).

Grouping by dichotomous threshold values

Table 1 summarizes a selection of recipient and donor related characteristics and transplant variables. Grouping is performed according to the surrogate parameters of immediate graft function and the threshold levels described above. Separation of the data by the cut-off levels bore an inverse association with donor age and cold ischaemia, which was statistically significant in each of the groups. No interrelationship was seen with transplant factors such as HLA matching, panel reactivity, changes of the immunosuppressive medication and with recipient related characteristics—except in the category serum creatinine after 1 week, owing to the well-known linkage between body weight and gender and the extent of the serum creatinine values. It was a consistent finding in all groups that the dichotomous cut-off levels were also determinants of clinically diagnosed and biopsy proven rejection episodes occurring during the first month. In this regard the measure of urine output post-transplant missed the level of statistical significance.

Risk of graft failure in the multivariate analysis

Figure 4 puts into graphs the relative risk of 5-year graft failure conditional on the aforementioned surrogate parameters for early graft function. Urine output, serum creatinine 1 week after transplantation and the combined criterion remained to be significant explanatory variables for the prediction of graft failure, when multivariate Cox regression analysis was applied to control for various potential confounding factors in the long-term. In contrast, independence from dialysis during the first week, although highly predictive of a minor risk in the univariate analysis, lost its prognostic accuracy and was no longer a significant determinate in the multivariate Cox regression model. This was mainly caused by the addition of both any rejection episode and vascular rejection as an explanatory variable. The multivariate Cox proportional HR of dialysis independence referred to 0.69 (95% CI 0.43–1.12) and 0.63 (95% CI 0.36–1.08) after censoring for death with a functioning graft, respectively.

Discussion

This study shows that early clinical parameters, such as urine volume and serum creatinine measurement collected on a routine basis to monitor graft function immediately after transplantation also provide an insight into the long-term function of the graft. Our data indicate the existence of threshold levels that can dissect the risk of graft failure after 5 years.
Fig. 1. K–M graft survival during 5 years of follow-up. Survival curves are displayed by quintiles of urine output in the first 24 h after transplantation (A, B) and serum creatinine concentration at 1 week (C, D).
Fig. 2. K–M graft survival including patient death, by quintiles of urine output in the first 24 h after transplantation (A, B) and serum creatinine concentration at 1 week (C, D) diagrammed in intervals up to 2 years (A, C) and beyond 2 years (B, D).
Fig. 3. Histograms of duration (A) and number of sessions (B) in patients requiring any dialysis during the first week post-transplant. Indications for dialysis in patients requiring maximal two sessions post-transplant, by duration of DGF (C). K–M graft survival including patient death, by duration of dialysis (D) and number of sessions (E).
Table 1. Comparison of recipient/donor characteristics and transplant variables. Grouping is performed according to the cut-off levels derived from quantitative routine parameters for the assessment of early graft function

<table>
<thead>
<tr>
<th></th>
<th>24h urine output post-op.</th>
<th>Serum creatinine at 1 week</th>
<th>Dialysis dependency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥630 ml (n = 180)</td>
<td>&lt;630 ml (n = 120)</td>
<td>P-value</td>
</tr>
<tr>
<td>Recipient age, (years)</td>
<td>50 ± 13</td>
<td>48 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Recipient gender male, n (%)</td>
<td>106 (59)</td>
<td>79 (66)</td>
<td>NS</td>
</tr>
<tr>
<td>Recipient weight, (kg)</td>
<td>69 ± 14</td>
<td>70 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Previous transplant, n (%)</td>
<td>29 (16)</td>
<td>26 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>HLA mismatches, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>1.5 ± 1.1</td>
<td>1.5 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Class II</td>
<td>0.6 ± 0.6</td>
<td>0.5 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Panel reactivity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5%</td>
<td>168 (93.3)</td>
<td>106 (88.3)</td>
<td>NS</td>
</tr>
<tr>
<td>6–85%</td>
<td>8 (4.4)</td>
<td>10 (8.3)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;85%</td>
<td>4 (2.2)</td>
<td>4 (3.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Immunosuppression, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMF</td>
<td>112 (62)</td>
<td>72 (60)</td>
<td>NS</td>
</tr>
<tr>
<td>Anti-CD25</td>
<td>76 (42)</td>
<td>43 (36)</td>
<td>NS</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>42 ± 17</td>
<td>46 ± 15</td>
<td>0.04</td>
</tr>
<tr>
<td>Donor gender male, n (%)</td>
<td>95 (53)</td>
<td>73 (61)</td>
<td>NS</td>
</tr>
<tr>
<td>Cold ischaemia (h)</td>
<td>20 ± 7</td>
<td>24 ± 8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute rejection 1st month, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>47 (26.1)</td>
<td>43 (35.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Biopsy proven</td>
<td>26 (14.4)</td>
<td>26 (21.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Banff II/III</td>
<td>16 (8.9)</td>
<td>10 (8.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Dialysis post-transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any, n (%)</td>
<td>25 (14)</td>
<td>86 (72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Of these, 1 session max., n (%)</td>
<td>8 (32)</td>
<td>16 (19)</td>
<td>NS</td>
</tr>
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</table>
This holds particularly true for the threshold levels derived from the quantitative measure of the urine output during the first 24 h post-transplant, and the serum creatinine concentration 1 week after transplantation, respectively. The predictive accuracy remained when recipient-related factors which affect the outcome during the ongoing follow-up were included for multivariate survival analyses.
Moreover, the discriminatory variables also revealed an explicit association with donor age and cold ischaemia, which are well-known risk factors for DGF [6,22,23]. In detail, it is clear that the different parameters select different patient groups at risk at a different point of time. Compared with the criterion of the urine output post-transplant, the cut-off level for serum creatinine 1 week after transplantation discriminates a smaller fraction of patients with a lower risk of graft failure, in other words provides a higher specificity for the prediction of graft survival after 5 years. The explanation comes in part from the fact that the 1-week period already covers interferences with an early alloimmune mediated attack. Recipients who reached a serum creatinine concentration under the cut-off level of 2.5 mg/dl were less frequently prone to acute rejection, which was statistically highly significant (Table 1). It is well-established that acute rejection substantially adds to a detrimental prognosis of early graft dysfunction [24]. It should be noted though that the impact of acute rejection episodes cannot reliably be delineated from our retrospective data set, because only a minority of patients got a graft biopsy and no protocol biopsies were done to rule out subclinical rejections.

Because serum creatinine is a rather crude measure of renal function, it seems conceivable that a more accurate measurement, such as an estimated GFR, may have provided a better discriminatory power for the prediction of graft survival. Reanalysing our data by using the Cockroft–Gault clearance [25] did not enhance the diagnostic specificity. Obviously, the dichotomous threshold of the serum creatinine offers a similar accuracy in predicting graft survival. Apart from this, the crude measure of serum creatinine has also advantages, because it is simpler and therefore easy to apply in clinical praxis. The diagnostic accuracy of various GFR estimates, including the Cockroft-Gault formula, has recently been evaluated in renal transplant patients. The predictive performance of these formulas has been questioned though, because agreement with the reference method was generally poor [26–28].

Given that low urine output post-transplant provides an appropriate measure for the quality of the transplanted tissue including graft injury, there is still the potential of some bias. Theoretically, it cannot be excluded that residual renal function contributed to a measurement bias when interpreting the urine output post-transplant. However, it is unlikely that the principle finding of our study was obscured by this shortcoming: first, the existence of the quantitative threshold was derived from quintiles of the urine volume, meaning that each individual patient was categorized according to the rank rather than the exact numeric value of the variable. Second, with regard to the outcome, it is inconceivable that graft failure after 5 years was affected by the size of the residual function of the recipient’s native kidneys. Allowing abstractions away from the residual function has the advantage of giving a more simple parameter to clinicians for the assessment of the graft prognosis.

It should be kept in mind that the worldwide most preferred definition for DGF simply relies on the need for dialysis in the first week post-transplant. However, DGF is nosologically an early condition of the graft rather than a treatment of the recipient. To date there is no general agreement among nephrologists about the criteria for the use of dialysis post-transplant. As shown in Figure 3, some of the indications urging dialysis in our series, such as hyperkalaemia or fluid overload, have emerged from the recipient’s state. Confounding by indication is likely to occur and may be a problem especially in cases that recovered rapidly from impaired graft function or required a limited number of dialysis sessions. In our study population, 22% of the recipients fulfilling the definition of DGF received one dialysis session only (Table 1). Both limited number of dialysis sessions (two sessions maximum) and shorter duration of DGF (<6 days) did not exert a decisive influence on graft survival (Figure 3), which is in line with a previous study assessing the impact of DGF duration on long-term survival of transplanted kidneys from brain-dead donors [14]. Although being significantly associated with graft failure in the univariate analysis, dialysis dependency lost its prognostic accuracy in the multivariate Cox regression model. Confounding, by indication, may in fact explain why mainly centre based studies have provided controversial results [9–13], whereas larger registry based analyses have demonstrated a clear linkage to an adverse effect on graft survival [6,29]. Another disadvantage arises from the definition of DGF excluding kidneys with non-dialysis dependent DGF. Our findings are in accordance with more recent studies indicating that transplants with slow graft function, despite dialysis independency, are prone to harmful outcomes, such as increased acute rejection, reduced GFR and lesserened survival [1,20,30]. An intriguing study from Edmonton, investigating the characteristics of the donor tissue in the contra-lateral kidney from the same donor found that both early dialysis dependency and occurrence of rejection were not significantly paired. In contrast, urine output, serum creatinine values 1 week after transplantation and graft survival showed significant similarities [4].

What are the clinical consequences of the study? Since our data suggest a threshold effect, early functional lesions can be delineated in quantitative terms from simple routine parameters without additional costs. Albeit lacking in diagnostic specificity, the threshold level for the urine output post-transplant indicates potential pathologies, i.e. rejections, at an early stage. These pathologies are maintained during the long term and have also a profound impact on the ultimate prognosis of the graft (Figure 2). The complex interrelationship of DGF, subsequent rejection and the ultimate prognosis of the graft are well recognized [31]. Alloimmune mediated attack in the early phase after...
transplantation is crucial, but can largely be excluded provided a sustained and continuous decline of the serum creatinine concentration occurs. Hence, the combination of both of the criteria, immediate urine production post-transplant and improving graft function during the first week to a reasonable cut-off substantially enhances the predictive value for graft survival. In our series, urine production exceeding 630 ml during 24 h together with a subsequent fall in the serum creatinine below 2.5 mg/dl during the first week was associated with a relative risk reduction of almost 80% in the multivariate analysis, equivalent to a 5-year graft survival probability >90% (Figure 4).

Owing to their discriminatory power for the detection of early function impairment and for the prediction of 5-year graft survival, both in the parameters may serve as a surrogate and/or a composite endpoint in future trials on the prevention of preservation and reperfusion injury at least in recipients of a kidney graft from a deceased heart-beating donor. In addition, they may also be helpful for risk stratification in trials investigating a novel treatment after a given time post-transplant. In contrast, need for dialysis is not an adequate criterion for DGF in terms of long-term outcome prediction. Guidance for doing an early biopsy in cases of perioperative oliguria and impending graft function impairment over the threshold value of 2.5 mg/dl in serum creatinine during the first week could be one of the clinical consequences of our findings. However, this needs to be evaluated prospectively before definite recommendations can be made.

In summary, this study provides evidence that early graft dysfunction can accurately be assessed by quantitative routine parameters that also allow a prediction for the subsequent course until 5 years post-transplant. Both urine output during the first 24 h and serum creatinine concentration 1 week after transplantation have a larger discriminatory power than the conventional definition based on dialysis dependency. Our study suggests the existence of a discernible threshold that can disclose donor influences in real terms, and may be clinically useful. The determination of the optimum threshold level associated with a sharp change of the attributable risk for graft failure in the long term requires further evaluation and confirmation in a larger, preferably multi-center registry.

Conflict of interest statement. None declared.

References


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