Immediate Graft Function Positively Affects Long-Term Outcome of Renal Allografts From Older But Not From Younger Donors

P. Messa, B. Brezzi, D. Cresseri, L. Berardinelli, F. Poli, M. Scalamogna, G. Tripepi, and C. Ponticelli

ABSTRACT

There is disagreement about the impact of delayed graft function (DGF) on renal allograft outcome. This may depend on several variables including the age of the donor. We evaluated whether DGF could have different effects in recipients of kidneys from donors aged more than 60 years versus well-matched recipients of younger kidney donors. Patients were retrospectively subdivided into 3 groups. Immediate graft function (IGF), DGF without dialysis (DGF-ND), DGF requiring dialysis (DGF-D). DGF-ND and DGF-D occurred more frequently among 198 older than 198 younger donors ($P = .016$ and $P = .044$, respectively). The 5-year patient (96% vs 93%) and pure graft (96% vs 89%) survivals were significantly better in younger recipients, while the incidence of acute rejection was similar. After a mean follow-up of 66 $\pm$ 44 months in older donor recipients, the graft survival was significantly better among IGF than patients in the DGF-ND ($P = .046$) or DGF-D ($P = .003$) groups. Instead, in younger recipients there was no difference in graft survival between IGD and DGF-ND. Only patients with DGF-D showed a significantly worse outcome. Upon multivariate analysis of older donors, their recipients, showed the pattern of graft function recovery to be the only variable associated with allograft outcome. Instead in younger donor recipients, acute rejection and time on dialysis were the main variables associated with a poor outcome. In older donor recipients, DGF was an independent variable associated with a poor graft outcome. In younger donor recipients, duration of dialysis and rejection were the most important predictors of poor graft outcomes.

DELAYED GRAFT FUNCTION (DGF) has been reported with variable frequency after cadaveric renal transplantation.1–4 DGF negatively affects short-term clinical outcomes, prolongs hospitalization, facilitates infections, and impairs patient rehabilitation.1,5,6 However, it is still unclear whether DGF may also affect long-term renal allograft outcome.7–9 Evidence of the possible negative impact of DGF on long-term allograft outcome is hindered by the frequent association of DGF with acute rejection episodes (ARE), which can per se negatively affect allograft outcomes.7,9,10–14

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Both the difference in the reported rate of occurrence of DGF and the dispute about its possible role on long-term outcome might at least in part be accounted for by the unsatisfactory definition of DGF. In fact, DGF is commonly defined as the requirement for dialysis in the first week after transplantation. However, this definition has many major drawbacks: for example, different criteria for dialysis prescription, and the possibility of including in the same group completely different causes of failed allograft function. It has been reported that graft survival is consistently lower among patients with a slow reduction of creatinine levels during the early posttransplantation period, independently of the need for dialysis.\textsuperscript{15,16} However, this aspect cannot be captured by the common definition of DGF. To overcome these drawbacks, first Govani et al\textsuperscript{17} and thereafter Rodrigo et al\textsuperscript{18} proposed to define immediate graft function (IGF) versus DGF, based on creatinine reduction ratio. They observed a good correlation between the creatinine reduction ratio at posttransplantation day 2 and renal function throughout the first year.

Because of the shortage, the criteria for donor acceptance have been widened in recent years with an increasing use of kidneys from older donors.\textsuperscript{19} A potential drawback of this policy is that the elderly age of the donor may be a prominent risk factor for DGF\textsuperscript{20} as well as poorer renal function at 1 year after transplantation.\textsuperscript{21} In this single center retrospective study, we evaluated the prognostic impact of our proposed criteria for IGF versus DGF on the major outcome variables of all patients transplanted in our center who were stratified by donor age above versus below 60 years.

**PATIENTS AND METHODS**

Among 1276 adult patients who received a kidney transplant from January 1986 to December 2004, we selected patients who had received a renal graft from a donor older than 60 years. As a control group, we selected for each older donor patient one recipient of a kidney from a donor younger than 60 years seeking a transplant source (cadaver/living donor), type of immunosuppression, fraction of reduction rate (FRR\textsubscript{2}), and creatinine serum levels at 24 and 48 hours after transplantation.\textsuperscript{22} The groups were matched for most of the main variables and immunosuppressive therapy, but importantly recipient age was slightly, but significantly, higher among subjects receiving organs from older donors. By Kaplan-Meier analysis, the cumulative patient and graft survivals were significantly better from younger vs older kidneys: 5-year patient survival: 96% vs 93%, respectively (P = .0351). The death censored 5-year graft survivals were 96% vs 89%, respectively (P = .001). The 2 groups of recipients showed a similar cumulative incidence of ARE: namely, 31.2% vs 29.0%, respectively (P = .639). Cox univariate and multivariate models did not reveal correlation among either patient or graft survival and all considered variables, including recipient age.

IGF occurred more frequently in younger than in older donor kidney recipients: 56.6% vs 34.9% (P < .0001). DGF occurred significantly more frequently in older than younger donor grafts, both for DGF-ND (42.4% vs 30.3%, P = .016) and for DGF-D (18.2% vs 10.6%, P = .044). PNF incidence was slightly, but not significantly, higher in older kidney recipients (4.5% vs 2.5%). Old donor kidney patients displayed 3 patterns of graft functional recovery which were not associated with the occurrence of ARE (31.9%, 27.4%, and 38.9% for IGF, DGF-ND, and DGF-D, respectively; $\chi^2 =$...
In younger donor recipients, a trend toward a significant association between DGF and ARE was observed (23.1%, 33.3%, and 47.6% for IGF, DGF-ND, and DGF-D, respectively; $\chi^2 = 5.9, P = .052$).

In the older donor group, IGF was associated with the lowest creatinine levels at 6 months without any major difference between DGF-ND and DGF-D. At month 12, the same trend was evident, but at a lower level of statistical significance. In young donor recipients, the IGF group showed the lowest month 6 creatinine levels; however, the month 12 creatinine levels were not different between the IGF and the DGF-ND groups, while DGF-D was associated with the highest levels (Table 1).

Figure 1 describes the graft survival in elderly donor kidney recipients, grouped according to the graft function recovery pattern. The IGF group showed significantly better survival than either the DGF-D ($P = .003$) or the DGF-ND group ($P = .046$). In contrast, graft survival was not significantly different between DGF-ND and DGF-D patients.

In a univariate Cox model, the only variable associated with long-term graft survival in elderly donor recipients was the pattern of graft function recovery after renal transplantation. There was no significant impact for ARE, time on dialysis, HLA mismatches, PRA, recipient age, or recipient/donor BMI ratio. By multivariate analysis the functional recovery pattern was the only variable that was significantly associated with graft survival; DGF-ND and DGF-D recipients showed a 3 to 4 times greater risk of graft loss than IGF patients (Table 2).

The graft survivals for the 3 graft function recovery patterns in young donor kidney recipients are shown in Fig 2. At variance with the elderly group, the DGF-D recipients displayed worse graft outcomes for IGF ($P = .012$) and DGF-ND ($P = .003$), with significant difference between IGF and DGF-ND ($P = .677$).

The Cox univariate model showed that ARE and time on dialysis were the main variables associated with worse graft survivals. Only DGF-D was related to a worse graft prognosis, without any significant difference between IGF and DGF-ND. The multivariate analysis reinforced the role of both ARE and time on dialysis as predictors of poor graft outcomes in young donor recipients, without any significant role for the pattern of early functional recovery (Table 2).

### Table 2. Multivariate Analyses (Cox Model) Among Each of the Most Relevant Variables and Graft Survival in Older and Younger Donor Kidney Recipients

<table>
<thead>
<tr>
<th>Older Donor Kidney Recipients</th>
<th>Multivariate Analysis</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft function recovery pattern</td>
<td>DGF-ND vs IGF</td>
<td>.031</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>DGF-D vs IGF</td>
<td>.006</td>
<td>4.1</td>
</tr>
<tr>
<td>ARE (yes vs no)</td>
<td>.14</td>
<td>1.7</td>
<td>0.84–3.46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Younger Donor Kidney Recipients</th>
<th>Multivariate Analysis</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft function recovery pattern</td>
<td>DGF-ND vs IGF</td>
<td>.170</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>DGF-D vs IGF</td>
<td>.140</td>
<td>2.6</td>
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<tr>
<td>Months on dialysis</td>
<td>.004</td>
<td>1.01</td>
<td>1.0–1.02</td>
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<tr>
<td>ARE (yes vs no)</td>
<td>.002</td>
<td>8.2</td>
<td>2.15–31.34</td>
</tr>
</tbody>
</table>
DISCUSSION

The pattern of early functional recovery based on creatinine reduction rate in the first 2 days after renal transplantation has been claimed to better predict long-term renal graft survival compared with the classical DGF definition.\(^\text{18,19}\) However, this suggestion was based on data from a nonselected population of transplanted patients. The aim of our study was to assess whether this diagnostic approach might offer advantages in predicting the long-term prognosis of grafts harvested from elderly donors, which are particularly prone to the risk of DGF.

We arbitrarily considered an elderly donors kidney to be from an individual aged 60 years or over, comparing their allograft outcomes with those of patients transplanted from donors younger than 60. The 2 groups were well matched for most donor- and recipient-related variables, except importantly for recipient age, which was also older in the elderly kidney group. However, we considered this difference of marginal clinical relevance. As expected, long-term death censored graft survival was better among recipients of younger vs older donor kidneys consistent with previous data.\(^\text{22}\) Acute rejection episodes did not seem to play a significant role, since their incidence was almost the same in the 2 groups. An unexpected finding was the lower patient survival rate among recipients of elderly kidneys, which when tested by univariate and multivariate Cox models, was not explained by any of the considered variables, including recipient age.

The probability of IGF was significantly lower, while those of both DGF-ND and DGF-D were significantly higher among patients who received an older kidney, data in agreement with previous studies\(^\text{20}\) and probably reflecting a limited capacity to adapt to stress and injury.\(^\text{23}\) The impact of early functional recovery on renal outcome was different for the two sets of recipients. Recipients of older kidneys showed immediate recovery of function to be significantly associated with lower serum creatinine levels at both 6 and 12 months and better 5-year graft survival, not only when compared with patients with DGF-D, but also patients with DGF-ND. Furthermore, by both univariate and multivariate analyses the patterns of graft function recovery were the only variables affecting graft outcome: the risk of graft loss was 3 and 4-fold greater among DGF-ND and DGF-D, respectively, compared with IGF patients. This observation implies that donor-related factors and ischemia-reperfusion damage probably play prominent roles to influence outcomes. It is reasonable to suppose that a severe injury to a frail kidney enhances cell damage caused by a direct lesion amplifying the immune and adaptive immune host defense, eventually resulting in early and long-term adverse outcomes.

In contrast, recipients of younger kidneys do not display a major role of the pattern of early renal functional recovery. Both the occurrence of ARE and time on dialysis were most relevant factors affecting long-term graft survival. In other words recipients of a kidney from a nonold donor show the most prominent role of the recipient-related factors.

In contradistinction to Rodrigo et al,\(^\text{18}\) our data confirmed the prognostic usefulness of Govani et al’s\(^\text{17}\) definition of DGF only for of elderly donors recipients, but not for patients receiving a graft from donors younger than 60 years. A possible explanation for this partial discrepancy may be that in Rodrigo’s study the donor age of patients...
who experienced DGF-ND and DGF-D was significantly higher than in patients who had IGF.

In conclusion, the pattern of immediate functional recovery showed an overwhelming impact on long-term graft outcome only for kidneys harvested from elderly donors. We speculated that the younger kidney probably adapts better to cell damage caused by ischemia-reperfusion associated mechanisms. In these recipients, the long-term outcome seems to be mainly related to recipient-dependent factors. However, the possibility of foreseeing long-term graft outcomes from the early posttransplantation phase may help to fine-tune immunosuppressive therapy for patients who are recipients of marginal kidneys.

REFERENCES