Creatinine Reduction Ratio and 24-Hour Creatinine Excretion on Posttransplant Day Two: Simple and Objective Tools to Define Graft Function

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Abstract. To devise objective criteria for early diagnosis of delayed graft function (DGF), 59 adult living donor kidney transplants with immediate graft function (IGF) and 51 cadaveric kidney transplants were investigated for creatinine reduction ratio (CRR2) from posttransplant day 1 to day 2 and 24-h urine creatinine excretion (UC2) on day 2. The mean CRR2 in living donor transplants was 53% (SD ± 11); the distribution of CRR2 was gaussian, and all of them had UC2 >1000 mg. Criteria for DGF were developed on the basis of living donor transplant: CRR2 (range, 8 to 50%) and all of them had UC2 >1000 mg. Overall, 24 cadaver transplant recipients (47%) developed DGF (CRR2 ≤30%); 13 patients (25%) had mild DGF (UC2 >1000 mg), and the remaining 11 (22%) had severe DGF (UC2 ≤1000 mg). All the patients with severe DGF had a measured creatinine clearance <25 ml/min on day 7, and 8 of 11 were dialyzed within the first week of transplantation. Patients with IGF and mild DGF had a creatinine clearance of ≥25 ml/min on or before day 7, and none of them were dialyzed. Calcineurin inhibitors were avoided or delayed in five patients with mild DGF and all patients with severe DGF. In conclusion, diagnosing DGF within 48-h after transplantation is simple and may be valuable in the management of these patients.

Delayed graft function (DGF) is a common complication after cadaveric kidney transplantation, affecting approximately 25% (range, 8 to 50%) of the recipients, and there is significant evidence that it is associated with acute rejection episodes and directly or indirectly with poor short-term and long-term graft survival (1–6). It also increases the cost and complexity of posttransplant management (7–9). The diagnosis of DGF, which is virtually considered synonymous with ischemic acute tubular necrosis due to perioperative insults, is made after exclusion of other causes of acute renal failure (e.g., mechanical complications). However, the need for dialysis within the first week of transplantation, a common definition of DGF, is less than satisfactory for several reasons. First, the criteria for dialysis requirement can vary among nephrologists. Second, the modality of dialysis treatment (hemodialysis versus peritoneal dialysis) and the timing of pretransplant hemodialysis affects requirement for dialysis postoperatively. Third, the diagnosis of DGF may be delayed up to a week because some patients may not need dialysis until posttransplant day 7. Although calcineurin inhibitors play an important role in immunosuppressive strategy despite their nephrotoxicity, many clinicians delay their introduction until they are confident of sufficient renal function. With the availability of new immunosuppressive agents like sirolimus, mycophenolate mofetil (MMF), and others, calcineurin inhibitors can be avoided altogether instead of just delaying their introduction or they can be delayed for a longer period of time. Developing criteria for diagnosis of DGF at earlier than 1 wk can facilitate this alternative strategy. Fourth, only the patients with the most severe impairment of renal function are likely to require dialysis; therefore, this definition does not differentiate between the patients with mild to moderate graft dysfunction and those with immediate graft function. Finally, the need for dialysis during the first week after transplantation is usually because of fluid and/or solute accumulation, which depends on poor graft function and increased solute generation (increased intake in case of fluid accumulation). In other words, dialysis requirement is not an absolute criterion of poor graft function.

To overcome these shortcomings, we retrospectively investigated creatinine reduction ratio (CRR2) and 24-h urine creatinine excretion (UC2) from posttransplant day 1 to day 2 in living donor kidney transplants, devised criteria for IGF and DGF, and applied them to the data available on cadaveric transplant recipients. We used living donor transplant recipients as reference patients because procurement-related damage is minimal to the graft.

Materials and Methods
A retrospective review of charts was performed on 63 adult living donor and 57 consecutive adult cadaveric kidney transplant recipients at Indiana University Medical Center. All cadaver and 35 living donor transplants were performed between January 1, 2000, and November 2001. A retrospective review of charts was performed on 63 adult living donor and 57 consecutive adult cadaveric kidney transplant recipients at Indiana University Medical Center. All cadaver and 35 living donor transplants were performed between January 1, 2000, and November 2001.

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7, 2000; the remaining living donor transplants, which were carried out during 1998 and 1999, were selected randomly to increase the number of subjects in the reference group. Six cadaveric transplant recipients were excluded because of inadequate data or mechanical complications within a week of transplantation. Four living donor transplants were excluded from analysis because they met one or more of the following exclusion criteria: (1) inadequate data; (2) mechanical complication within a week of transplantation; (3) serum creatinine ≥2.0 mg/dl by day 5; (4) creatinine clearance ≤30 ml/min by day 5; and (5) requirement of dialysis within a week of transplantation. Stringent exclusion criteria were applied to living donor transplants because they were used as reference IGF patients to develop criteria for IGF and DGF. All living donor transplants were managed with basiliximab, calcineurin inhibitor, MMF, and corticosteroids. Introduction of calcineurin inhibitor was delayed until the graft function was well established.

Day of surgery (release of vascular clamps) was considered day 0. At Indiana University Medical Center, it is routine to collect 24-h urine for daily creatinine clearance in all renal transplant patients during their postoperative hospital stay. The following formulae were used for creatinine reduction ratio (CRR2) and 24-h urine creatinine excretion (UC2) between day 1 and day 2:

\[
\text{CRR2} = \left( \frac{(C1 - C2)}{C1} \times 100 \right)
\]

where C1 and C2 are serum creatinines on posttransplant day 1 and day 2, respectively.

\[
\text{UC2} = \frac{U \times V}{24}
\]

where U is urine creatinine (mg/dl) and V is urine volume (dl/24 h) collected between posttransplant days 1 and 2.

Day 1 and day 2 were selected because time 0 (release of vascular clamps) on day 0 is unpredictable and serum creatinine is usually not available just before time 0. Day 2 and day 3 would have been an alternative; however, that would delay the diagnosis of DGF. Also, many recipients with IGF have serum creatinine within the normal range by day 2, and a further reduction in serum creatinine is minimal, which would make our first parameter invalid. The 24-h urine creatinine excretion can be measured accurately during the first few days after transplantation because the patient is in the hospital and an indwelling catheter is in place.

These parameters were studied on living donor transplants, and criteria for immediate and delayed graft function (IGF and DGF) were developed. These criteria were applied to cadaveric transplant recipients, and they were followed for a mean duration of 9.8 mo (range 4 to 14 mo).

For statistical analysis, one-way ANOVA or t test were used for continuous variables as appropriate and \(\chi^2\) was used for categorical variables.

### Table 1. Results of living donor transplant patients

<table>
<thead>
<tr>
<th>Patients (N)</th>
<th>Male (38)</th>
<th>Female (21)</th>
<th>All (59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1* mg/dl (SD, range)</td>
<td>5 (± 2, 2.1–9.7)#</td>
<td>3.3 (± 1.7, 1.4–7.6)</td>
<td>4.4 (± 2.1, 1.4–9.7)</td>
</tr>
<tr>
<td>C2* mg/dl (SD, range)</td>
<td>2.2 (± 0.8, 1.1–3.8)#</td>
<td>1.4 (± 0.5, 0.9–2.6)</td>
<td>1.9 (± 0.8, 0.9–3.8)</td>
</tr>
<tr>
<td>CRR2 % (SD, range)</td>
<td>54 (± 10, 30–72)##</td>
<td>53 (± 13, 31–76)</td>
<td>53 (± 11, 30–76)</td>
</tr>
<tr>
<td>UC2 mg/24 hr (SD, range)</td>
<td>3024 (± 1086, 1404–5204)#</td>
<td>1728 (± 561, 1150–3178)</td>
<td>2563 (± 1119, 1150–5204)</td>
</tr>
</tbody>
</table>

* C1 serum creatinine on day 1, C2 serum creatinine on day 2.
# p<0.5 in comparison to female patients.
## p>0.05 in comparison to female patients.

### Results

#### Living Donor Transplants

As shown in Table 1, 38 (64%) of 59 recipients were male; mean age was 42 yr (SD ± 12); 55 were white, 1 was African American, and 3 were of other ethnicity; mean weight was 76 kg (SD ± 18; range, 39 to 124 kg). Fourteen patients were not on dialysis before transplantation, 21 patients received dialysis for less than 1 yr, and the remaining 24 patients received dialysis for more than 1 yr. Mean creatinine on posttransplant day 1 (C1) was 4.4 mg/dl (SD ± 2.1; range, 1.4 to 9.7 mg/dl); mean creatinine on post-transplant day 2 (C2) was 1.9 mg/dl (SD ± 0.8; range, 0.9 to 3.8 mg/dl), and mean CRR2 was 53% (SD ± 11; range, 30 to 76%). Mean UC2 was 2563 mg/24 h (SD ± 119; range, 1150 to 5204 mg/24 h).

Mean and median CRR2 were 53%; modes were 52 and 53%. Thirty (67.8%) of 59 patients had their CRR2 within 1 SD of mean (42 to 64%), and 57 (96.6%) of 59 had their CRR2 within 2 SD of mean (31 to 75%). These data suggest that the distribution of CRR2 was gaussian. The lowermost UC2 was 1150 mg/24 h.

To see the effect of residual renal function, data were analyzed excluding the recipients who had no pretransplant dialysis and those who were on dialysis less than 1 yr; mean CRR2 was 54% (SD ± 10; range, 30 to 72%), and mean UC2 was 2992 mg/24 h (SD ± 1250; range, 1150 to 5204 mg/24 h).

#### Criteria for IGF and DGF

On the basis of the results of the living donor transplant recipients, IGF was defined as having CRR2 >30% and UC2 >1000 mg/24 h; mild DGF was defined as having CRR2 ≤30% with UC2 >1000 mg, and severe DGF was defined as CRR2 ≤30% with UC2 ≤1000 mg. CRR2 value of 30% was selected as the watershed between IGF and DGF because 2 SD of the mean CRR2 (53%) of living transplant recipients ranged from 31 to 75%. Considering that the recipient’s body is loaded with creatinine and that the generation of creatinine is relatively high because of recent surgery and corticosteroids between posttransplant day 1 and day 2 and all living donor transplant recipients had UC2 >1000 mg, UC2 ≤1000 mg was selected to reflect severe impairment of renal function. If the recipient required dialysis on posttransplant day 1, severe DGF was thought to have occurred, because CRR2 or UC2 would not reflect graft function in that situation. Urine volume <200
ml over 24 h between posttransplant day 1 and day 2 was also considered to have fulfilled the criteria for severe DGF.

**Cadaver Transplants**

Of 51 cadaver transplant recipients, 31 (61%) were male; mean age was 45 (SD ± 13) years; white/African American/other ethnic distribution was 38/12/1; mean weight was 75 kg (SD ± 18; range, 41 to 120 kg). Overall, 24 patients (47%) met criteria for DGF; 13 had mild DGF, and the remaining 11 had severe DGF (Table 2). Mean CRR2, UC2, C1, and C2 of the recipients with IGF, mild DGF, and severe DGF are shown in Table 3. Four (19%) of 27 patients with IGF and one (8%) of 13 patients with mild DGF were on dialysis before transplantation for <1 yr; one IGF recipient (4%) was never dialyzed; all the remaining cadaver transplant recipients were dialyzed for longer than a year.

Mean CRR2 in IGF patients was 51% (SD ± 11; range, 34 to 77%), and mean UC2 was 2627 mg/24 h (SD ± 1322; range, 1260 to 6234 mg/24 h). All the patients with IGF had creatinine clearance of at least 25 ml/min on day 7 or earlier, and none of them required dialysis. Five of 27 recipients (19%) with IGF developed acute rejections, and their serum creatinine (mean ± SD) at the end of follow-up was 1.2 ± 0.2 mg/dl. One patient died with the functioning graft approximately 2 mo after transplantation. All IGF recipients were managed with immunosuppressive regimen similar to that used for living donor transplants.

Three patients (27%) with severe DGF were dialyzed on posttransplant day 1, and one more patient had urine volume <200 ml over 24 h between posttransplant day 1 and 2. Mean UC2 in the remaining seven patients was 493 mg/24 h (± 200); mean CRR2 in eight patients (excluding those who were dialyzed on day 1) was −18% (± 10).

As shown in Table 2, the patients with severe DGF (11 recipients) developed significantly more rejections (55 versus 19%; P = 0.026), and their creatinine at the end of follow-up was significantly higher (1.6 ± 0.6 versus 1.2 ± 0.2 mg/dl; P = 0.0008) than the patients with IGF. There was no significant difference in acute rejections between the recipients with mild DGF (13 recipients) and those with severe DGF, but creatinine of the latter was significantly higher at the end of follow-up (1.6 ± 0.6 versus 1.3 ± 0.3 mg/dl; P = 0.047). Creatinine clearance was <25 ml/min on day 7 in all 11 patients with severe DGF; however, only eight of them required dialysis within a week of transplantation. All patients with severe DGF were managed with a calcineurin inhibitor avoiding (CIA) regimen consisting of sirolimus, MMF, and prednisone for at least 6 wk, starting immediately after transplantation.

The rate of acute rejections in the recipients with mild DGF was higher than that in the recipients with IGF (23 versus 19%), but it did not reach statistical significance. However, three (23%) patients with mild DGF were managed with polyclonal antibody during DGF phase, and two more patients received the CIA regimen. All 13 patients with mild DGF had creatinine clearance >25 ml/min by day 7; none of them required dialysis, and their creatinine at the end of follow-up was 1.3 ± 0.3 (mean ± SD) mg/dl.

**Discussion**

This study demonstrates that DGF can be diagnosed early and reliably by simple and objective criteria: UC2 and CRR2. CRR2 is easy to calculate from available serum creatinine values, and UC2 can be measured by routine urine collection. Moreover, the vagaries of 24 h urine collection are minimized because of the routine use of an indwelling catheter during the immediate postoperative period.

CRR2 in living donor transplants was 53% (SD ± 11; range, 30 to 76%) with a gaussian distribution. The distribution of CRR2 was not surprising considering that the main determinant of CRR2 is creatinine clearance of the graft and that all living donors had creatinine clearance in the normal range (assuming that the grafted kidney and the remaining kidney had similar function).

In transplant recipients with IGF, true graft function should reflect demographics (age, gender, ethnicity, and size) of the donor rather than those of the recipient, especially during the early posttransplant period. However, one has to use parameters of the recipient to measure graft function. The criteria of severe DGF, used in this study, unlike the dialysis requirement, depend mainly on the creatinine clearance of the grafted kidney (provided there is no residual renal function) and relatively less on solute generation and fluid intake. The criterion, UC2

### Table 2. Classification of cadaver transplant recipients by the studied criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>IGF</th>
<th>Mild DGF</th>
<th>Severe DGF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients [N (%)]</strong></td>
<td>UC2 &gt; 1000mg &amp; CRR2 &gt; 30%</td>
<td>UC2 &gt; 1000mg &amp; CRR2 ≤ 30%</td>
<td>UC2 ≤ 1000mg &amp; CRR2 ≤ 30%</td>
</tr>
<tr>
<td>Dialysis requirement# [N (%)]</td>
<td>27 (53)</td>
<td>13 (25)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>CrCl &gt; 25 ml/minute## [N (%)]</td>
<td>0</td>
<td>0</td>
<td>8 (73%)</td>
</tr>
<tr>
<td>Acute rejections [N (%)]</td>
<td>27 (100)</td>
<td>13 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine (mg/dl) (mean ± SD)</td>
<td>1.2 ± 0.2</td>
<td>1.3 ± 0.3*</td>
<td>1.6 ± 0.6**</td>
</tr>
</tbody>
</table>

# No. of subjects requiring dialysis during the first week.
## No. of subjects with creatinine clearance > 25 ml/minute by day 7.
* P<0.05 in comparison to patients with Severe DGF.
** P<0.05 in comparison to patients with IGF.
Table 3. Results of cadaver transplant recipients

<table>
<thead>
<tr>
<th>Category</th>
<th>IGF (N = 27)</th>
<th>Mild DGF (N = 13)</th>
<th>Severe DGF (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 mg/dl (SD, range)</td>
<td>6.7 (± 2.6, 3.0–11.8)</td>
<td>7.1 (± 3.0, 2.9–11.4)</td>
<td>9.6 (± 3.5, 4.6–18.6)</td>
</tr>
<tr>
<td>C2 mg/dl (SD, range)</td>
<td>3.3 (± 1.4, 1.2–6.7)</td>
<td>6.8 (± 3.6, 2.7–12.9)</td>
<td>10.1 (± 2.3, 6.2–14.7)</td>
</tr>
<tr>
<td>CRR2 % (SD, range)</td>
<td>51 (± 11, 34–77)</td>
<td>7.0 (± 11, –10–20)</td>
<td>–18 (± 10, –6–35)*</td>
</tr>
<tr>
<td>UC2 mg/24hr (SD, range)</td>
<td>2627 (± 1322, 1260–6234)</td>
<td>1468 (± 231, 1185–1836)</td>
<td>493 (± 200, 204–775)*</td>
</tr>
</tbody>
</table>

*Three patients were dialyzed on day 1 and they were excluded from CRR2 calculations. One more patient had 24-hr. urine volume from post-op day 1 to day 2 < 200 ml. All 4 patients were excluded from UC2 calculations.

≤1000 mg, which reflects very low creatinine clearance, is also unlikely to be related directly to the donor demographics. This means that, when one uses UC2 ≤1000 mg, especially with CRR2 ≤30, the recipient and donor demographics and excesses of perioperative fluid intake are less of a concern in defining severe DGF. However, the recipient and donor demographics may influence criteria for mild DGF. Nevertheless, our criteria of IGF and DGF are not different for male and female patients because there was no significant difference in CRR2 between male and female living donor transplant recipients and all of them had UC2 >1000 mg. These criteria should be used with caution in African Americans, Hispanics, and other minority groups, as they were underrepresented in this study.

UC2 in the male living donor transplants was significantly higher than their female counterparts (P < 0.5). This can be explained by the significantly higher C1 and C2 in male patients.

C1 and C2 in living donor transplants were significantly lower than those in cadaver transplants with IGF (4.4 versus 6.7 and 1.9 versus 3.3, respectively; P < 0.05). This difference may be because of the fact that more living donor transplant recipients had residual renal function at the time of transplantation. Also, difference in timing of the transplant procedures between living donor and cadaver transplants on day 0 may have contributed to this observation. However, there was no significant difference in CRR2 between the two groups.

Residual renal function data were not available on these patients. We assumed that those who are most likely to have significant residual renal function would be the patients on dialysis for less than a year or those with no dialysis history at all. None of our cadaver kidney transplant patients with severe DGF and only one patient with mild DGF had dialysis less than a year. CRR2 was not significantly different in the living donor transplant recipients, who had no pretransplant dialysis or who were on dialysis for less than a year, from those who were on dialysis for longer than a year. This can be explained on the basis that all the recipients with or without residual renal function have high and stable creatinine and any significant reduction in creatinine after transplantation will be dependent on the graft function. However, UC2 ≤1000 mg, the criterion for severe DGF would not be a reliable criterion in the patients with residual renal function unless the values of 24 h urine creatinine excretion from urine samples collected shortly before transplantation are available. It is impractical to expect that these values could be available in cadaver transplant recipients. In this situation, one may have to use CRR2 alone to define the severity of graft dysfunction, although it is less accurate. In our study, none of the patients with mild DGF had CRR2 < –10, and only one patient with severe DGF had CRR2 > –10, suggesting that CRR2 < –10 can be used to define severe DGF in the patients with residual renal function. Further studies are necessary to validate this observation.

We did not have any patients who had UC2 ≤1000 mg and CRR2 > 30%. This combination is highly unlikely unless the patient is a very small adult, a child, or someone with very low muscle mass (e.g., bilateral amputee). Therefore, these criteria are not applicable to the patients with these characteristics.

With the availability of sirolimus, MMF, and anti-CD25 monoclonal antibodies, it has become possible to avoid potentially nephrotoxic immunosuppressive agents, calcineurin inhibitors, in renal transplant patients (10–12). DGF contributes significantly to poor long-term graft survival either directly or indirectly by increasing the rate of acute rejections (1–4, 6). The use of nephrotoxic agents like calcineurin inhibitors may enhance this harmful effect of DGF (13, 14); therefore, it is even more desirable to avoid these agents in the patients with DGF. In our study, calcineurin inhibitors were avoided for at least 6 wk in all 11 patients with severe DGF and in two patients with mild DGF. At the end of follow-up, serum creatinine and the rate of acute rejections were significantly higher in the recipients with severe DGF than in those with IGF; however, there was no graft loss in the severe DGF group.

Among cadaver transplant recipients, there was no significant difference in acute rejections and follow-up creatinine values between IGF and mild DGF patients; however, three patients with mild DGF received polyclonal antibody and two more patients were managed with the CIA regimen. It is possible that larger samples, longer follow-up, and/or similar immunosuppressive management of both groups could have shown a significant difference.

In summary, UC2 and CRR2 are simple, safe, objective, and convenient tools that help early and reliable diagnosis of DGF. The conventional definition of DGF (requirement of dialysis within a week) has many problems as described earlier, which leads to many controversies including incidence and significance. Our criteria, if validated by large studies and used on a large scale, may help in solving these controversies. IGF and DGF are segments of the spectrum characterized by best graft function at one end and worst graft function at the other.
pilot study provides partial resolution of this spectrum by defining IGF, mild DGF, and severe DGF. Future studies may provide “high definition” of this spectrum by dividing mild DGF into two subcategories depending on the therapeutic and prognostic significance.

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References

Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/