ABSTRACT

Background. Kidney transplants from living donors with an estimated glomerular filtration rate (eGFR) < 80 mL/min per 1.73 m² may be at risk for increased graft loss compared with a recipient who receives a kidney from a living donor with a higher eGFR.

Methods. This retrospective cohort study considered 2057 living kidney donors and their recipients from July 1993 to March 2010 at five centres in Ontario, Canada, and linked them to population-based, universal healthcare databases. Recipients were divided into five groups based on their donor’s baseline eGFR. The median (inter-quartile range) for the lowest eGFR group was 73 (68–77) mL/min per 1.73 m². Subjects were followed for a median of 6 years (IQR: 3–10 years).
isotope clearance (51Crom EDTA) [3, 4]. The objective of the

Conclusions. Further research in this setting should clarify

INTRODUCTION

Over the past decade, the selection criteria for living kidney
donors have evolved. While variability across centres exists,
published reports indicate that many factors have become more inclusive, such as the acceptable upper age limit for
donors, and the eligibility of donors with treated hypertension
[1, 2]. This liberalization is, in part, a consequence of an insuf-
ficient number of organs from deceased organ donors. Despite
this trend, one factor that has become more restrictive is the
minimum baseline level of kidney function in living donors
[1]. This may relate to centres attempting to better align their
practice with one set of consensus guidelines published in
2004, citing that individuals with a glomerular filtration rate
(GFR) <80 mL/min should be generally precluded from
donation [3]. Notably, these guidelines were based primarily
on a single study showing a 2.28-fold risk of graft loss for reci-
pients of kidneys <80 versus ≥80 mL/min per 1.73 m² [95% confidence interval (95% CI) 1.18–4.38; GFR assessed by
isotope clearance (51Crom EDTA)] [3, 4]. The objective of the
current study was to assess the impact of incremental differ-
ences in baseline donor kidney function on recipient graft loss
and all-cause mortality.

MATERIALS AND METHODS

Design and setting

This was a population-based, retrospective cohort study
linking living kidney donor and recipient transplant data to
electronic healthcare databases in Ontario, Canada, housed at
the Institutes for Clinical Evaluative Sciences (ICES). This
study was approved by the University Health Network and
Sunnybrook Health Sciences Centre research ethics boards
(Toronto, Ontario, Canada) (REB # 11-0596-AE).

Data sources

Donor and recipient data were abstracted from original
medical records across five major transplant centres for con-
secutive transplants occurring between 1 July 1992 and 31
March 2010. All transplant data were managed centrally by the

Results. There was no significant difference in the adjusted
hazard ratio (HR) for graft loss when comparing recipients in
each eGFR category to the referent group (≥110 mL/min
per 1.73 m²). The adjusted HRs (95% CI) from the lowest (<80
mL/min per 1.73 m²) to highest (100–109.9 mL/min per 1.73
m²) eGFR categories were 1.27 (0.84–1.92), 1.43 (0.96–2.14),
1.23 (0.86–1.77) and 1.23 (0.85–1.77), respectively. Similar
results were observed when dichotomizing the baseline donor
eGFR using a cut-point of 80 mL/min per 1.73 m²—adjusted
HR 1.01 [95% confidence interval (95% CI) (0.76–1.44)].

Registrants

All consecutive adult recipients of living kidney donor trans-
plants, who were permanent residents of Ontario, were regis-
tered. Follow-up began from the date of transplantation.
Baseline donor GFR was estimated using the Chronic Kidney
Disease Epidemiology (CKD-EPI) Collaboration equation
based on the serum creatinine measured during the living
donor assessment [10]. Among potential kidney donors, CKD-
EPI has been shown to have lower bias, higher precision and
higher accuracy compared with the Modification of Diet in
Renal Disease (MDRD) equation [11]. Recipients were divided
into five categories according to their donors’ CKD-EPI esti-
imated glomerular filtration rate (eGFR) (mL/min per 1.73 m²):
<80, 80–89, 90–99, 100–109 and ≥110 (referent). Recipients
were also assessed using an eGFR cut-point of 80 mL/min per
1.73 m² (referent: ≥80 mL/min per 1.73 m²).

Transplant outcome

The primary outcome was time from kidney transplan-
tation to graft loss. Death was treated as a competing risk, a
non-rare event in this population that must be accounted for
to avoid overestimation of the absolute risk of graft loss [12].
Graft loss was defined based on the presence of electronic
healthcare codes for chronic dialysis over ≥3 consecutive
months, or record of a new kidney transplant within the
TGLN database. Death due to all causes was ascertainment via
the RPDB. Patients were censored due to emigration from the
province, or at the end of study (i.e. 31 March 2011). Secondary
outcomes included the composite of graft loss or death,
and death (with or without graft loss).

Statistical analysis

Baseline characteristics were compared using ANOVA or χ²
tests, as appropriate. Multivariable Cox proportional hazards
models for the sub-distribution hazard of graft loss were fit
using first-time transplants [13]. As described by Fine and
Gray, this function uses an estimate of the survivor function of
the censoring distribution to re-weight contributions to the risk
sets for failures from competing causes [13, 14]. The factors that
were adjusted for include recipient age, recipient sex, recipient
Charlson comorbidity index, dialysis duration, peak panel reac-
tive antibody (PRA), donor age, donor sex, laparoscopic or
open surgery, donor-recipient relationship and year of trans-
plant. Models were stratified by transplant centre to allow for

Live kidney donor eGFR and transplant outcome
distinct baseline hazard functions across all centres. Hazard ratios (HR) were reported with corresponding 95% CIs. The proportional hazards assumption was assessed using the likelihood ratio test or a time interaction term (Wald $\chi^2$ test), as appropriate. All analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA) and R version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

From 1 July 1992 to 31 March 2010, there were 2057 first-time, living kidney donors transplants performed across five major centres in Ontario. The distribution of recipients across categories of baseline donor eGFR (mL/min per 1.73 m²) was <80 ($n = 289$, 14%), 80–89 ($n = 334$, 16%), 90–99 ($n = 464$, 23%), 100–109 ($n = 472$, 23%) and $\geq 110$ ($n = 498$, 24%). The median (inter-quartile range) for the lowest eGFR group was 73 (68–77) mL/min per 1.73 m².

Baseline recipient characteristics are shown in Table 1. The median age of all recipients in the cohort was 45 years, and 39% were women. Overall, 367 (18%) recipients received pre-emptive living donor kidney transplants. The remaining recipients spent a median of 11 months on dialysis prior to transplantation. There was also no significant difference across the groups in comorbidity score ($P = 0.94$) or peak PRA ($P = 0.11$). Table 2 shows various baseline renal function parameters of the living kidney donors. The median age of donors was 43 years; as a function of the estimating equation, those with lower eGFR

| Table 1. Recipient characteristics by donor eGFR at the time of transplantation |
|---------------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Total ($N = 2057$) | Donor baseline eGFR (mL/min per 1.73 m²) | $P$-value* |
| | <80 ($n = 289$) | 80–89.9 ($n = 334$) | 90–99.9 ($n = 464$) | 100–109.9 ($n = 472$) | $\geq 110$ ($n = 498$) |
| Age (years) | 45 (35–55) | 47 (37–56) | 45 (35–56) | 46 (35–56) | 46 (35–56) | 40 (33–51) | <0.001 |
| Women | 795 (39%) | 119 (41%) | 138 (41%) | 176 (38%) | 180 (38%) | 182 (37%) | 0.58 |
| Race | | | | | | |
| White | 1519 (74%) | 213 (74%) | 250 (75%) | 357 (77%) | 336 (71%) | 363 (73%) | 0.03 |
| Black | 59 (3%) | 17 (6%) | 9 (4%) | 10 (2%) | 11 (2%) | 12 (2%) |
| Other | 479 (23%) | 59 (20%) | 75 (22%) | 97 (21%) | 125 (26%) | 123 (25%) |
| Months on dialysis* | 11 (1–23) | 9 (0–21) | 10 (0–24) | 11 (1–23) | 11 (1–24) | 12 (2–23) | 0.46 |
| Charlson Score | | | | | | |
| 2–3 | 1464 (71%) | 207 (72%) | 234 (70%) | 328 (71%) | 344 (73%) | 351 (71%) | 0.94 |
| 4–5 | 500 (24%) | 70 (24%) | 83 (25%) | 111 (24%) | 108 (23%) | 128 (26%) |
| $\geq 6$ | 93 (5%) | 12 (4%) | 17 (5%) | 25 (5%) | 20 (4%) | 19 (4%) |
| Peak PRA | | | | | | |
| <20 | 1632 (79%) | 228 (79%) | 272 (81%) | 352 (76%) | 382 (81%) | 398 (80%) |
| 20–49.9 | 116 (6%) | 23 (8%) | 18 (5%) | 26 (6%) | 15 (3%) | 34 (7%) | 0.11 |
| $\geq 50$ | 184 (9%) | 23 (8%) | 30 (9%) | 51 (11%) | 43 (9%) | 37 (7%) |
| Missing | 125 (6%) | 15 (5%) | 14 (4%) | 35 (8%) | 32 (7%) | 29 (6%) |
| Transplant year | | | | | | |
| 1992–95 | 181 (9%) | 40 (14%) | 27 (8%) | 40 (9%) | 33 (7%) | 41 (8%) | <0.001 |
| 1996–99 | 357 (17%) | 24 (8%) | 41 (12%) | 64 (14%) | 85 (18%) | 143 (29%) |
| 2000–05 | 774 (38%) | 127 (44%) | 154 (46%) | 182 (39%) | 170 (36%) | 141 (28%) |
| 2006–10 | 745 (36%) | 98 (34%) | 112 (34%) | 178 (38%) | 184 (39%) | 173 (35%) |

Data presented as median (inter-quartile range) or as number (%).
The Charlson score is a validated index of comorbidity [31].
PRA, panel reactive antibody.
*Includes 367 recipients of pre-emptive living donor kidney transplants (i.e. months on dialysis = 0).
*P-value comparing categories of donor baseline eGFR.
Table 2. Donor renal function parameters at the time of transplantation

<table>
<thead>
<tr>
<th>Total (N = 2057)</th>
<th>Donor baseline eGFR (mL/min per 1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;80 (n = 289)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43 (34–51)</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>74 (65–86)</td>
</tr>
<tr>
<td></td>
<td>68 (59–76)</td>
</tr>
<tr>
<td>MDRD GFR (mL/min per 1.73 m²)</td>
<td>93 (82–108)</td>
</tr>
<tr>
<td></td>
<td>71 (64–79)</td>
</tr>
<tr>
<td>CKD-EPI GFR (mL/min per 1.73 m²)</td>
<td>98 (87–109)</td>
</tr>
<tr>
<td></td>
<td>74 (66–85)</td>
</tr>
</tbody>
</table>

Data presented as median (inter-quartile range). MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate.

**Figure 1:** Frequency distribution of pre-donation CKD-EPI eGFR values of living kidney donors.

Outcomes

The median follow-up time of the entire cohort was 6 years (IQR: 3–10 years; maximum follow-up: 18 years). Of the 2057 recipients, 1523 (74%) reached the end of the study (31 March 2011) without experiencing graft loss or death and <1% were censored due to provincial emigration. Recipient transplant outcomes are summarized in Table 3. At last follow-up, 315 grafts were lost. Cumulative incidence functions for graft loss (death as a competing risk), with donor eGFR divided into five categories, are shown in Figure 2a.

There was no significant difference in the adjusted subdistribution HR for graft loss when comparing recipients in each eGFR category to the referent group (≥110 mL/min per 1.73 m²). Adjusted HRs (95% CI) from lowest (<80 mL/min per 1.73 m²) to highest (100–109.9 mL/min per 1.73 m²) were 1.27 (0.84–1.92), 1.43 (0.96–2.14), 1.23 (0.86–1.77) and 1.23 (0.85–1.77), respectively (P values ranged from 0.08 to 0.27) (Figure 3). Similarly, there was no significant difference in graft loss when dichotomizing the baseline donor eGFR using a cut-point of 80 mL/min per 1.73 m²: HR: 1.01 (95% CI: 0.76 to 1.37) (Figure 3). Similarly, there was no statistically significant difference in the composite outcome when comparing recipients of donor kidneys with eGFR < and ≥80 mL/min per 1.73 m², there was also no significant difference in the composite outcome [HR (95% CI) 1.14 (0.91–1.43)]. For the outcome of death, 294 events were observed over the study period. Similarly, there was no statistically significant difference observed (HRs ranged from 0.87 to 1.24).

**DISCUSSION**

Transplant from a living kidney donor is heralded as the best possible treatment option for patients with kidney failure. Today, one of the key challenges faced by the transplant community is that of potential donors with evaluations that are deemed ‘borderline acceptable’. Examples include the acceptability of living donors in the context of older donor age [7], obesity [15] or high blood pressure [16]. This study focused on one criterion that potentially impacts organ quality and donor selection—borderline donor kidney function. We found that the risk of graft loss was not significantly different for recipients of kidneys with eGFR levels <80 mL/min per 1.73 m².
In 2004, the Amsterdam Forum provided guidelines on the level of kidney function that defines an acceptable living kidney donor [3]. Consensus recommendations were based on a single-centre study from Sweden by Norden et al. They observed 344 living donor kidney transplants, including 26 with measured GFR of <80 mL/min per 1.73 m². They found that kidneys from live donors with measured GFR < 80 mL/min per 1.73 m² are associated with relative risk of graft loss of 2.28 (95% CI 1.18–4.38) compared with those with greater pre-nephrectomy measured GFR [4]. Other studies available at the time provided limited additional information [17, 18]. A more recent single-centre study of 83 living kidney transplants found that poor pre-donation effective renal plasma flow was not associated with an increased rate of decline of allograft function [19].

In our study, when comparing recipients of living donor kidneys with eGFR < 80 mL/min per 1.73 m² to those ≥110 mL/min per 1.73 m², the hazard ratio for the outcome of graft loss after a median follow-up of 6 years was 1.23 (95% CI 0.84–1.92, P = 0.26). To facilitate inter-study comparisons, we dichotomized the baseline donor eGFR at 80 mL/min per 1.73 m², resulting in a hazard ratio of 1.01 (95% CI 0.76–1.44). This attenuation in the magnitude of effect compared with the study by Norden et al. may be influenced by several methodological considerations. First, we studied a larger cohort of living kidney donors and recipients—2057 transplant events, which is six times that of the other study. The number of donors with low absolute renal function (i.e. <80 mL/min per 1.73 m²) was also much larger with 289 donors meeting our criteria. We performed a multi-centre study to improve generalizability. These data were validated by manual review of medical charts on donor registrants. Follow-up time in this and previous work were comparable (~6 years); however, our study includes a more contemporary cohort of donors and recipients, with loss to follow-up of <1% over time. Finally, our analyses of graft loss accounted for the competing risk of death; this differs from traditional Cox models that censors for death, which has been shown to overestimate actual risks in the presence of significant competing events [20].

Prior to the Amsterdam Forum guidelines, ~30% of living kidney donors in the United States had eGFR levels <80 mL/min per 1.73 m² [21]. In 2005, a survey of transplant programs done by Mandelbrot et al. found that 67% of respondents used a creatinine clearance cut-off of <80 mL/min per 1.73 m², an increase compared with the 59% of centres that reported using this cut-off criteria in 1995 [2]. They also reported that 6% of centres required a creatinine clearance of at least 90 mL/min per 1.73 m² to avoid taking donors who could be classified as CKD Stage II (defined as 60–89 mL/min per 1.73 m²) [1]. Fewer centres had no cut-off criteria compared with 1995 (11 versus 2%).

More recently in 2011, a survey of centre practices by Brar et al. showed similar findings: 66% of centres used a cut-off of ≥80 mL/min, 13.5% used 90 mL/min and 7% used 100 mL/min for exclusion of living kidney donors [22]. Indeed, this

### Table 3. Outcomes for recipients receiving kidneys of varying baseline donor eGFRs

<table>
<thead>
<tr>
<th>Donor baseline eGFR (mL/min per 1.73 m²)</th>
<th>&lt;80</th>
<th>80–89.9</th>
<th>90–99.9</th>
<th>100–109.9</th>
<th>≥110</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graft loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number at risk, n</td>
<td>289</td>
<td>334</td>
<td>464</td>
<td>472</td>
<td>498</td>
</tr>
<tr>
<td>No. of graft loss events (%)</td>
<td>45 (16%)</td>
<td>57 (17%)</td>
<td>73 (17%)</td>
<td>69 (15%)</td>
<td>71 (14%)</td>
</tr>
<tr>
<td>Rate of graft loss^a</td>
<td>24.3</td>
<td>26.5</td>
<td>25.8</td>
<td>23.6</td>
<td>20.3</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graft loss or death (composite)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number at risk, n</td>
<td>291</td>
<td>337</td>
<td>471</td>
<td>480</td>
<td>508</td>
</tr>
<tr>
<td>No. of graft loss or death events</td>
<td>88 (30%)</td>
<td>90 (27%)</td>
<td>124 (26%)</td>
<td>121 (25%)</td>
<td>126 (25%)</td>
</tr>
<tr>
<td>Rate^a</td>
<td>47.4</td>
<td>41.4</td>
<td>43.4</td>
<td>40.9</td>
<td>35.8</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, n</td>
<td>291</td>
<td>337</td>
<td>471</td>
<td>480</td>
<td>508</td>
</tr>
<tr>
<td>No. of death events</td>
<td>53 (18%)</td>
<td>44 (13%)</td>
<td>72 (15%)</td>
<td>64 (13%)</td>
<td>61 (12%)</td>
</tr>
<tr>
<td>Event rate^a</td>
<td>25.6</td>
<td>17.7</td>
<td>22.4</td>
<td>19.3</td>
<td>15.7</td>
</tr>
</tbody>
</table>

^aAll rates are reported per 1000 patient years.
trend is also reflected in our study: from 2000 to 2005, 16.4% of living kidney donors in Ontario had an eGFR of <80 mL/min per 1.73 m², and dropped to 13.2% from 2006 to 2010. Notably, while kidney function criteria have become more conservative, the use of older living kidney donors has become more liberalized, in light of findings of superior outcomes compared with either deceased donor kidney transplantation or remaining on dialysis [7, 23–26]. Kidney function declines progressively with age [27], leaving a tendency for other age-related donor characteristics to co-exist with lower GFR. In our study, 15% of donors with eGFR < 80 mL/min per 1.73 m² were also over the age of 60 years. The findings in this study

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**FIGURE 2:** (a) Cumulative incidence function for the primary outcome of graft loss (by five eGFR categories). (b) Cumulative incidence function for graft loss (eGFR< and ≥80 mL/min per 1.73 m²).

**FIGURE 3:** Transplant outcomes for recipients comparing varying categories of baseline eGFR (reference group: ≥110 mL/min per 1.73 m² for all comparisons). Error bars represent 95% confidence intervals around the hazard ratio point estimate.
support the results of studies of older living kidney donors, speculating that mildly reduced kidney function among some older potential donors may be attributable to physiologic rather than pathologic processes, and may not substantially affect the quality of the donated organ.

The results of this study provide renewed data on the impact of baseline donor kidney function on kidney transplant recipient outcomes, but must be interpreted with consideration of its limitations. A key limitation of this study is that the results are based on estimated (versus measured) GFR using the CKD-EPI equation [10]. Serum creatinine was assessed in all living kidney donors in the province, allowing for abstraction from retrospective chart review for every donor in this study. This differs from the study by Norden et al. [4], where donor renal function was assessed by isotope clearance ($^{51}$Cr-EDTA). In recent years, some centres in the province have begun performing measured GFR on some potential living kidney donors; however, such data were not sufficiently available to allow for meaningful analyses. Other centres also perform 24-h urine collection for creatinine clearance on all potential donors, and if the eGFR is deemed borderline, proceed to obtaining more precise renal function assessment via isotopic clearance. This latter practice is consistent with recommendations from the Amsterdam Forum [3].

There is bias associated with currently used estimating equations based on serum creatinine in the living donor population. On average, the MDRD, Cockcroft-Gault (corrected for body surface area) and the newer CKD-EPI estimating equations all underestimate measured GFR both 4 months before and 2 months after kidney donation—median point estimate differences anywhere between 10 and 22 mL/min per 1.73 m$^2$ [28]. Both the Cockcroft-Gault and CKD-EPI had more accurate pre-donation estimates than the MDRD equation, with 89–90% of measures within 30% of the measures GFR. Despite their biases, estimating equations continue to be a useful tool as they can be readily applied in the common setting where direct measurements of GFR may not be available due to issues of feasibility and cost [11, 29]. In this study, it is possible that all the patients with eGFR < 80 mL/min per 1.73 m$^2$ also had evidence of a kidney from a living donor with an eGFR < 80 mL/min per 1.73 m$^2$ was no different than when the kidney came from a living donor with a higher eGFR. These results add to the current literature, suggesting different outcomes than previous work. Despite its strengths, our study does not provide definitive evidence to warrant changes in clinical practice. Acknowledging that recipient outcomes are multi-factorial in nature, these results encourage further efforts to examine this particular association. Future directions should include further analyses to guide the assessment of renal function in potential donors whose eGFR is considered borderline (i.e. should isotope GFR or another method of assessment be above a certain threshold prior to proceeding), and whether these values should be standardized to body surface area. And, of course, the issue of donor health (which is beyond the scope of this particular study) must always be considered prior to liberalizing any selection criteria [30], particularly for younger donors who may expect to live many decades with one kidney.

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CONFLICT OF INTEREST STATEMENT

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(See related article by Wang et al. Implications of predonation GFR to recipient and donor outcomes. Nephrol Dial Transplant 2014; 29: 5–9.)
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