Commentary

The Unjustified Classification of Kidney Donors as Patients with CKD: Critique and Recommendations

Arthur J. Matas* and Hassan N. Ibrahim†

Summary

Unilateral nephrectomy for kidney donation results in loss of about 30% of baseline GFR, leaving some donors with GFR <60 ml/min per 1.73 m², the threshold for the diagnosis CKD. This has resulted in insurability problems for some donors. This article reviews the definition of CKD, risks associated with CKD, and large follow-up studies on the vital status and risk of ESRD in kidney donors. It also provides evidence that kidney donors, despite having reduced GFR, are not at increased risk for CKD-associated morbidity and mortality. Epidemiologic studies, most with follow-up <10 years, have shown an association between GFR <60 ml/min per 1.73 m² and higher mortality and progression to ESRD. Low GFR in the absence of any other markers for kidney disease, however, conveys attenuated or minimal risk. Of note, studies of long-term kidney donor outcomes (6–45 years) have not shown excess mortality or ESRD. The limitation of the collective evidence is that the increased risks associated with GFR <60 ml/min per 1.73 m² were demonstrated in much larger cohorts than those reported for kidney donor outcomes, but donor outcome studies have substantially longer follow-up. On the basis of current findings, kidney donors with low GFR and no other signs of kidney disease should not be classified as having CKD. This is definitely not the reward they deserve, and, more important, the implications of reduced GFR in donors are not associated with unfavorable outcomes.


Patients with ESRD have a limited number of options: dialysis, transplant, or death. Compared with dialysis, a transplant is associated with longer survival and better quality of life (1,2). Patients wanting a transplant must make a critical decision—to go on the waiting list for a deceased-donor (DD) transplant or (if there is a willing living donor [LD]) to have an LD transplant. Compared with a DD transplant, an LD transplant is associated with longer patient and graft survival. In addition, the increasing number of patients who are interested in and are eligible for a kidney transplant has not been associated with a commensurate increase in the number of DD organs. This has resulted in a markedly longer waiting time on the list. The increasing waiting time for a DD transplant and the poor short- and mid-term results with dialysis have put increased emphasis on living donation.

The major disadvantage of an LD transplant is the risk to the donor. Studies over the last three decades have noted a perioperative donor mortality rate of 3 in 10,000 (0.03%) and a major complication rate of <1% (3–5). Laparoscopic nephrectomy is associated with quicker recovery than open nephrectomy but carries similar risk. To date, long-term follow-up studies report that donors, compared with controls, have similar or better survival rates, and perhaps lower rates of development of ESRD (5–14). In addition, donor quality of life after donation is excellent (15). Of concern, however, is that recent studies in the nondonor general population have suggested that reduced renal function is associated with increased cardiovascular and all-cause mortality; consequently, some former donors have had problems obtaining life and health insurance or are being forced to pay higher premiums (16,17). At the same time, some former donors with stable renal function have been labeled as having CKD. Herein, we review level of renal function after donation and the data on long-term survival and risk of ESRD after kidney donation.

Definition of CKD

Many observation studies have shown the association between reduced renal function and increased cardiovascular and all-cause mortality (18–20). For example, Go et al., using a large integrated database (n=1,120,155), reported the risk for cardiovascular events and death as estimated GFR (eGFR) decreased to <60 ml/min per 1.73 m² (18). Median follow-up was 2.84 years. For those with eGFR of 45–59 ml/min per 1.73 m², the adjusted risk for cardiovascular events was 1.4 (95% confidence interval, 1.4 to 1.5) and the adjusted risk for death was 1.2 (95% confidence interval, 1.1 to 1.2), and lower eGFR was incrementally associated with increased hazard ratio for both outcomes. Additional studies and meta-analyses have confirmed that reduced eGFR is an independent risk factor for adverse outcomes in both high- and low-risk populations (19–21). Of note, in these analyses, the average follow-up has been <10 years (Table 1); thus, the increased risk associated with reduced eGFR has occurred in a relatively short interval.
In 2002, the National Kidney Foundation (NKF) and the Kidney Disease Outcomes Quality Initiatives (KDOQI) Clinical Practice Guidelines group defined CKD and classified severity on the basis of eGFR (Table 2) (22). The goal was to develop a system to identify early stages of disease that could progress or lead to complications and to provide objective diagnostic criteria (22-24); the rationale was that “therapeutic interventions at earlier stages can prevent or ameliorate most of the complications of CKD as well as slow the progression to kidney failure” (23). CKD was defined as the presence, for ≥3 months, of (1) kidney damage as defined by structural or functional abnormalities of the kidney (with or without decreased GFR) or (2) GFR <60 ml/min per 1.73 m², irrespective of cause. Earlier this year, the new Kidney Disease Improving Global Outcomes (KDIGO) practice guidelines have become available (25). The new CKD classification uses GFR level, urinary albumin, and cause of CKD. However, eGFR <60 ml/min per 1.73 m² for >3 months is still classified as CKD stage 3 (Table 3). Tables 4 and 5 show the percentage of 255 former donors (from our institution) with iohexol-measured GFR who would fall into each of the CKD stages according to each classification.

The CKD Definition: Limitations, Harms, and Unintended Consequences

GFR can be estimated from the serum creatinine level; thus, eGFR is an inexpensive screening test. Developing a screening tool that has prognostic significance is important for assisting in patient care (early detection), clinical research, epidemiologic studies, and drafting public health policies (24). Undoubtedly, reduced eGFR has reasonable sensitivity and specificity to detect true reduction in kidney function, and its performance may be enhanced further by incorporating urinary protein level, as recently done by the KDIGO group. But using the criterion of eGFR <60 ml/min per 1.73 m² (for >3 months) without any other evidence of kidney damage to define CKD, as stated in the 2002 guidelines (and continued in the current guidelines), has engendered considerable debate (26-33). Concerns have centered on several issues:

1. The NKF guidelines recommended that eGFR be calculated using the Modification of Diet in Renal Disease (MDRD) study equation. This formula was developed in patients with well-defined kidney disease and underestimates true GFR in healthy persons and donors. When the MDRD formula is used, a significant percentage of the population with true GFR >60 ml/min per 1.73 m² are classified as having CKD; this is particularly true for those with eGFR of 45–59 ml/min per 1.73 m². Given that GFR declines with aging, using this single cutoff for GFR without considering age significantly overestimates CKD in the older population, particularly women (34). In addition, the MDRD study equation was based on a North American population and may not necessarily apply to other population groups. The newly introduced and recommended CKD-Epidemiology Collaboration (CKD-EPI) estimating model may provide further improvement over the MDRD study equation. Of note, the bias with the CKD-EPI model is trivially different from that with the MDRD study equation but is more precise. It is critical to realize that unless the isotope dilution mass spectrometry–traceable creatinine assay is used, one cannot use this model to estimate GFR.

2. Use of the word “disease” has specific connotations and may be inappropriate for some groups who have no progressive deterioration of renal function, no other sign of kidney disease (e.g., albuminuria), no other comorbidity, and perhaps no increased long-term risks. Glassock and Winearls note, “The major flaw of using eGFR to categorize...
4. Neither the KDOQI nor KDIGO definitions diagnose. As Using MDRD-calculated eGFR for risk strati
dif
other patients having unilateral nephrectomy), including has resulted in problems for donors (and presumably
unintended consequences effects (anxiety) (26,28). What has not been stressed are the unnecessary referrals and investigations, adverse events from follow-up tests, increased costs, and psychological increased premiums (16,17). This is not a trivial or isolated problem; in fact, it has been estimated that 2%–11% of former donors have had insurability problems (17). In addition, fear of insurance problems or future job changes in which they would be labeled as having a preexisting condition have discouraged some candidates from donating. To some extent, these problems may be unique to the United States and do not exist in countries with universal health care. It is hoped that the upcoming health legislation in the United States would prevent these donors from being labeled as having preexisting conditions.

Table 3. 2013 National Kidney Foundation and Kidney Disease Outcomes Quality Initiatives CKD classification

<table>
<thead>
<tr>
<th>GFR Stage</th>
<th>eGFR (ml/min per 1.73 m²)</th>
<th>Albuminuria Stage</th>
<th>ACR (mg/g)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>A1: optimal</td>
<td>&lt;10</td>
<td>Diabetes</td>
</tr>
<tr>
<td>2</td>
<td>60–89</td>
<td>High normal</td>
<td>10–29</td>
<td>Hypertension</td>
</tr>
<tr>
<td>3</td>
<td>30–59</td>
<td>A2: high</td>
<td>30–299</td>
<td>Glomerular disease</td>
</tr>
<tr>
<td>3a</td>
<td>45–59</td>
<td>A3: very high</td>
<td>300–1999</td>
<td>Others</td>
</tr>
<tr>
<td>3b</td>
<td>30–44</td>
<td>Nephrotic</td>
<td>&gt;2000</td>
<td>Transplant</td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td></td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 (or dialysis)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from reference 25. ACR, albumin-to-creatinine ratio.

Table 4. Former donors (N=255) with measured iohexol GFR and percentage falling into each CKD classification by Kidney Disease Improving Global Outcomes 2002 guidelines

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>eGFR (ml/min per 1.73 m²)</th>
<th>Iohexol GFR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>8.6</td>
</tr>
<tr>
<td>2</td>
<td>60–89</td>
<td>77.0</td>
</tr>
<tr>
<td>3</td>
<td>30–59</td>
<td>14.5</td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>0</td>
</tr>
</tbody>
</table>

Kidney Donor Evaluation, Selection Criteria, and Kidney Function after Nephrectomy

Kidney donor candidates undergo extensive medical and psychosocial evaluation. Criteria for acceptance include having two kidneys, normal kidney function, no identifiable risk of disease transmission (e.g., hepatitis C), and ability to tolerate the procedure with no (or minimal) increased risk (versus age-matched healthy general population). However, transplant centers’ criteria for the minimal accepted GFR vary widely (39). Most centers insist on a minimal GFR of 80 ml/min per 1.73 m². Some, however, recognizing the decline in GFR with age, are willing to accept older donors with GFR <80 ml/min per 1.73 m². Donor nephrectomy results in the immediate loss of 50% of kidney function. The remaining kidney quickly compensates so that within a few weeks GFR returns to approximately 70% of prenephrectomy levels. Recent data indicate that for some donors, especially younger donors, GFR progressively improves over time (11,40).

Given that some donors have an eGFR of 80 ml/min per 1.73 m² at donation and a loss of approximately 30% of GFR after uninephrectomy, some will certainly have a future GFR <60 ml/min per 1.73 m² and thus, when the KDOQI or KDIGO systems are used, be classified as having CKD. Age-related decline in GFR will result in increased numbers so classified. Garg et al. estimated that within 10 years of donation, 12% of donors had GFR <60 ml/min per 1.73 m² (41). Subsequent single-center studies have reported rates as high as 85% (42–44). Tent et al. studied measured GFR (mGFR) versus eGFR as determined by three equations (MDRD, Cockcroft-Gault, and the CKD-EPI) in LDs before and after donation (45). All three equations significantly underestimated mGFR. Mean mGFR (ml/min per 1.73 m²) ± SD was 66±11;
mean eGFR by MDRD was 51±9, by CKD-EPI was 56±11, and by Cockcroft-Gault was 63±13. Reported risk factors for postdonation eGFR <60 ml/min per 1.73 m² include older age at donation, hypertension, and body mass index (11,42,46).

We have recently investigated the performance of four GFR estimating models in 255 donors who underwent iohexol GFR measurement (3–45 years after donation using isotope dilution mass spectrometry–traceable creatinine assay and also standardized cystatin C) (Table 6). For donors with eGFR <60 ml/min per 1.73 m² by MDRD, 34.6% had mGFR >60 ml/min per 1.73 m²; of those with eGFR <60 ml/min per 1.73 m² by CKD-EPI-creatinine, 58.5% had mGFR >60 ml/min per 1.73 m²; of those with eGFR <60 ml/min per 1.73 m² by CKD-cystatin C, 73% had mGFR >60 ml/min per 1.73 m²; and for those with eGFR <60 ml/min per 1.73 m² by CKD-EPI-creatinine + cystatin C, 70.3% had mGFR >60 ml/min per 1.73 m². For GFR >60 ml/min per 1.73 m², eGFR (CKD-EPI-creatinine + cystatin C) was concordant in 97.2% of the cases. Of note, the three models fully agreed when measured GFR was <45 ml/min per 1.73 m².

Table 5. Former donors (N=255) with measured iohexol GFR and percentage falling into each CKD classification by Kidney Disease Improving Global Outcomes 2013 guidelines

<table>
<thead>
<tr>
<th>GFR Categories (ml/min per 1.73 m²)</th>
<th>Albuminuria Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A1: ACR &lt; 30 mg/g</td>
</tr>
<tr>
<td>G1 (&gt;90)</td>
<td>7.0</td>
</tr>
<tr>
<td>G2 (60–89)</td>
<td>70.3</td>
</tr>
<tr>
<td>G3a (45–59)</td>
<td>12.9</td>
</tr>
<tr>
<td>G3b (30–44)</td>
<td>1.2</td>
</tr>
<tr>
<td>G4 (15–29)</td>
<td>0</td>
</tr>
<tr>
<td>G5 (&lt;15)</td>
<td>0</td>
</tr>
</tbody>
</table>

ACR, albumin-to-creatinine ratio.

Table 6. Accuracy of estimated GFR models in classifying donors as having GFR <60 or >60 ml/min per 1.73 m²

<table>
<thead>
<tr>
<th>eGFR Estimating Model</th>
<th>Iohexol GFR &lt; 60 ml/min per 1.73 m² (%)</th>
<th>Iohexol GFR ≥ 60 ml/min per 1.73 m² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD</td>
<td>63.4</td>
<td>82.9</td>
</tr>
<tr>
<td>CKD-EPI-creat</td>
<td>41.5</td>
<td>94.4</td>
</tr>
<tr>
<td>CKD-EPI-cystatin C</td>
<td>27.0</td>
<td>96.7</td>
</tr>
<tr>
<td>CKD-EPI-creat + Cystatin C</td>
<td>29.7</td>
<td>97.2</td>
</tr>
</tbody>
</table>

Long-term Survival after Donation

The first successful kidney transplantation was done between identical twins in Boston in 1954. In the next two decades, only a limited number of kidney transplants were done. Early studies showed no increase in long-term mortality (6,7), but until recently no truly long-term (>20 year) data were available. However, >20-year outcome after unilateral nephrectomy done for cause (e.g., trauma, cancer) has been reported. Baudoin et al. noted no increased risks up to 50 years after uninephrectomy in 111 children, 75% of whom had GFR 75% of baseline; Narkun-Burgess et al. reported similar findings 45 years after uninephrectomy for trauma during World War II (37,38). The degree of CKD in earlier studies cannot be ascertainment because the use of the GFR threshold of 60 ml/min per 1.73 m² to diagnose CKD is a new development.

Several studies from around the world have now compared long-term survival after donor nephrectomy with survival in the general population (Table 5) (8,11–14). In a single-center study from Sweden, Fehrman-Ekholm et al. compared donor survival (n=430) with expected survival calculated from mortality data in the Swedish general population using age-, sex-, and calendar-year-specific mortality rates, concluding that kidney donors live longer than would be expected (8). In a single-center study in the United States, Ibrahim et al. compared donor survival (n=3698) with survival in the age-, sex-, and ethnicity-matched general population and found no difference between groups (11). Similar findings have now been reported from Japan, Norway, and France (12–14). Each of these studies has two limitations: (1) the relatively small n values (especially compared with the population studies showing a relationship between reduced GFR and mortality) (Table 1 versus Table 7) and (2) the use of general population controls. Kidney donors are a subgroup selected from the general population to be healthy at the time of donation, so it may be that donors should be expected to have better survival than the general population. However, an important strength of these studies is that they show no increased risk even after >20 years of follow-up. As shown in Table 1, studies showing increased risk associated with reduced eGFR have had an average follow-up <10 years.

Two studies, albeit with shorter follow-up, have addressed some of the limitations highlighted in the previous paragraph (Table 5). Segev et al. compared survival of 80,347 donors reported to the Organ Procurement and Transplantation Network in the United States with survival of participants of the Third National Health and Nutrition Examination Survey (NHANES III) (5). Participants in NHANES III who had comorbid conditions or other factors that would have made them ineligible to be donors...
Kidney Donors Are Not Protected from Risk

Determining risk is critical for informing future donor candidates (50). Donor evaluation can determine health only at the time of evaluation, and donors will always be at risk for surgical complications and of developing diseases later in life. Steiner has stressed that ESRD in the United States is primarily a disease of older individuals (51) and that evaluation at a young age will neither detect a prodrome nor reduce the baseline lifetime risk of ESRD. He notes that annually only 13% of new ESRD cases in the United States occur in patients younger than age 45 years. Thus, it is unlikely that evaluation at age 20 or 25 years will minimize the estimated lifetime risk of 2%–2.5% in whites and 7%–8% in blacks. The most common diseases causing ESRD in the general population are hypertension and diabetes; both have a familiar pattern. Additional studies are necessary to determine risks in donors from younger cohorts and those with familial disease (50). Questions that need to be answered include whether nephrectomy will accelerate development of hypertension or shorten the time to CKD stage 3, or progression from stage 3 to ESRD, in those developing hypertension or diabetes after donation.

Because of the organ shortage and the long waits on dialysis, acceptance criteria for LDs have been expanded. Currently, many centers will accept older donors with hypertension well controlled with a single drug or donors with a body mass index >30 kg/m²; both are potential risks for CKD, and it is also important to perform long-term follow-up studies in these cohorts (50).

Data on donors who develop hypertension or diabetes after donation are limited. Short-term studies have shown that selected white donors with hypertension well controlled by a single drug or donors with a body mass index >30 kg/m² had similar serum creatinine. Of the total, 64 had ESRD or shortened the time to CKD stage 3, or progression from stage 3 to ESRD, in those developing hypertension or diabetes after donation. The annual eGFR change in these donors was $-0.8 \pm 0.9$ ml/min per 1.73 m²; the annual change in 522 donors without diabetes who were $\geq$15 years postdonation was $-0.7 \pm 0.80$ ml/min per 1.73 m² ($P=0.43$).

In consideration of other manifestations of reduced GFR, kidney donors may also be at higher risk for the development of preeclampsia (55,56). This risk, however, is indistinguishable from that in white controls from the United States.
general population. It is also important to point out that donors have higher levels of fibroblast growth factor-23 and parathyroid hormones, the implications of which are not known (57). Kidney donors, however, are not at increased risk of fractures (58).

Kidney Donation in Minorities

Minorities, particularly African Americans (AAs), are overrepresented in the ESRD population, mainly because of a higher incidence of hypertension, diabetes, and recently recognized genetic predispositions. The safety of donation in this population is critical as the proportion of minority donors is approaching 15% of all donors. Data to date suggest the following:

1. Lentine et al. reported that the prevalence of hypertension and diabetes in AA donors is similar to that in AA with two kidneys (49). However, a recent matched cohort study of 103 AA donors revealed a 40.8% prevalence of hypertension versus 17.9% in controls after 6.8±2.3 years of follow-up (59). This prevalence is strikingly similar to that reported in Aboriginal kidney donors (42% versus 19% in white controls) (60).

2. AA donors made up 40% of the 126 donors reported by Gibney et al. to have gone on the DD waiting list (61). Only one ESRD case was seen in the series by Lentine et al., and none were seen in the matched cohort study by Doshi et al. (49,59).

3. Regarding lifespan of donors from minority groups to date, no data suggest inferior long-term outcomes (5).

Going Forward: Modification of CKD Staging

There is a disconnect between the KDOQI and KDIGO CKD definitions, the increased mortality and ESRD rates associated with having CKD, and the relatively benign long-term course after unilateral nephrectomy (with a normal contralateral kidney). One possibility is that the total number of studied LDs is not yet sufficient to demonstrate an increased risk. Another is that patients undergoing unilateral nephrectomy have reduced GFR for reasons totally different from the reasons in patients with kidney disease, and as a result they do not have the same long-term risks. In addition, the association between CKD and cardiovascular disease might not be causal but a result of shared risk factors for both conditions (32). As noted above, reduced GFR without other markers of kidney disease may not be associated with increased risks (34,35). It is important—both for determining how aggressively to follow former donors and for better providing information to future donor candidates—to ascertain whether a GFR <60 ml/min per 1.73 m² for >3 months after uninephrectomy, in the absence of any other markers of disease, is a long-term risk factor.

Recognizing the flaws in the 2002 KDOQI system, the NKF-KDOQI group, on the basis of an international consensus conference, has suggested that the classification of CKD be revised and the clinical practice guidelines on CKD be updated (Table 2) (24,25). The group recommended three revisions (Table 2). First is the addition of an albuminuria stage (albumin-to-creatinine ratio [ACR] [mg/g] <30, 30–299, and >300). Second involves splitting CKD stage 3 into two subgroups—3a (eGFR of 45–59 ml/min per 1.73m²) and 3b (eGFR of 30–44 ml/min per 1.73m²)—basically identical to the new KDIGO guidelines. Although reported risks are similar for patients with ACR <10 mg/g and ACR of 10–29 mg/g, the group suggested independent study of risks for those in stage 3a (GFR of 30–49 ml/min per 1.73 m²) with an ACR <10 g/ml. This would be important for donors in that the overwhelming majority of donors with reduced eGFR continue to have optimal ACR (11). However, the revised guidelines leave former donors with stable eGFR <60 ml/min per 1.73 m² with the same problem; they meet the definition of CKD stage 3. The third revision was to emphasize clinical diagnosis, the group recommended incorporating six diagnoses into the classification (diabetes, hypertension, glomerular disease, many others, transplant, and unknown). We suggest that an additional diagnosis be added incorporating all cases with unilateral nephrectomy and a normal contralateral kidney; alternatively, given that evaluation is so extensive before donor nephrectomy, the diagnosis of “donor nephrectomy” should be added. In this way, future epidemiologic studies will be able to better determine whether this subgroup of patients is at any increased long-term risk.

In summary, the definition of CKD classifies patients with eGFR <60 ml/min per 1.73 m² for >3 months as stage 3 CKD even when they have no other signs or symptoms of kidney disease. Given the acceptance criteria for living donation and the normal decline of GFR with aging, some asymptomatic donors are being classified as CKD stage 3. Consequently, some donors have difficulty obtaining life or health insurance; other potential donors shy away from donation because of fear of being labeled by insurance companies as having a preexisting condition. Yet long-term follow-up studies have not shown any increased risks for patients (donors and nondonors) undergoing unilateral nephrectomy while having a normal contralateral kidney. We recommend changes to the current CKD classification to differentiate those having reduced GFR due to nephrectomy from those having reduced GFR from other pathogenic causes. At the same time, we strongly believe that additional long-term studies after living donation are necessary.

Acknowledgments

We would like to thank Hang McLaughlin for assistance in preparation of the manuscript. This manuscript was supported by National Institutes of Health grant DK-13083.

Disclosures

None.

References


