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The True Risk of Living Kidney Donation

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Abstract

Purpose of Review: The safety of living donor nephrectomy is essential to the continued success, growth, and sustainability of the clinical practice of living donor kidney transplantation. This review summarizes recent advances in our understanding of the perioperative and long-term risks faced by living kidney donors.

Recent Findings: Although adverse perioperative complications are extremely rare, donors particularly male, black, or obese, frequently experience minor complications that result in delayed return to normal duties at home and work. Similarly, although long-term complications such as end-stage renal disease (ESRD) are rare, recent studies suggest a relative increase in risk of ESRD that is attributable to donation. Several risk calculators have been developed to help donors and their care providers quantify the baseline- and post-donation risk of ESRD based on demographic and health characteristics. Thresholds of risk may help define what is an acceptable level of risk to the donor and the transplant center.

Summary:

Individualized risk calculators now allow care providers and potential donors to objectively and transparently participate in shared decision-making about the safety of living kidney donation.

Keywords

kidney donation; decision-making; ESRD risk; informed consent; living donation

Introduction:

Living donor kidney transplantation is associated with superior survival, graft function, and quality of life when compared to deceased donor kidney transplantation [1, 2]. It is also associated with only a one-year waiting period from ESRD diagnosis – initiation of dialysis or joining the waitlist – to transplantation [3, 4]. The benefits of live donor kidney transplantation are thus timely and directly apparent to the recipient, but also more nuanced

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in being indirectly beneficial to those on the waitlist for deceased donor transplantation. The waitlist and waiting times would have been substantially longer were it not for live kidney donation. In the words of a donor, “When I take this recipient off the list, everyone moves up” [5].

Yet perioperative and long-term risks to the live kidney donor pose a ***potential*** threat to all these outlined patient and societal benefits. Also, the substantial decline over the last two decades in the annual number of donors in the US presents a ***definite*** threat to all these benefits. As such, the transplant community is presently being challenged to responsibly promote live donation, while ensuring the safety of those who choose to donate [6]**. The evidence to date suggests that the absolute risk of adverse outcomes such as ESRD and mortality is acceptably low and the medical community may justify the practice [7]. But it remains unclear how informed the donors themselves are about these and other risks they might face, including other medical, financial, and psychosocial risks [8, 9]. Risk communication across all the U.S. transplant centers [10], and in most international settings [11], is highly variable. Donors may often fail to fully grasp the various risks associated with donation [12–15].

The purpose of this review is to closely examine current literature on the perioperative and long-term risks of living kidney donation to improve risk assessment and communication.

Perioperative safety:

The risks to the donor in the first 90 days of nephrectomy range from the minor to the adverse and are viewed with different emphases by donors, recipients, and transplant professionals. Donors identify time-to-recovery, common surgical complications, and effect on family as their foremost concerns [16, 17]. Kidney transplant recipients cite potential lost income by the donor, often a family member, as a leading concern that impedes donor referral [18]. Transplant professionals might be less concerned about perioperative risks (adverse events are extremely rare), but more about the increased lifetime risk of ESRD, non-ESRD outcomes, and mortality that might be attributed to nephrectomy [19–22].

The perioperative complication rate is approximately 16.8% [23, 24]: the rate for low-grade complications of Clavien Grade II or higher is 8.8%, that for Clavien Grade III or higher is 7.3%, and the one for Clavien Grade IV or higher is 2.5%. The most frequent types of perioperative complications are gastrointestinal (4.4%), bleeding (3.0%), respiratory (2.5%), and surgical or anesthesia related injuries (2.4%) [24–26]. Perioperative mortality is extremely rare (0.03%) [27], as is subsequent hospital mortality for any cause (0.007%) [24]**.

Some subgroups of donors have substantially higher perioperative risks when compared with others including male sex, black race, and those with predonation hypertension. Surgical mortality is higher in men vs. women (5.1 vs. 1.7 per 10,000 donors, risk ratio [RR], 3.0; 95% CI, 1.3–6.9; P=.007), in black vs. white and Hispanic individuals (7.6 vs 2.6 and 2.0 per 10 000 donors; RR, 3.1; 95% CI, 1.3–7.1; P=.01), and in donors with hypertension vs. without hypertension (36.7 vs 1.3 per 10 000 donors; RR, 27.4; 95% CI, 5.0–149.5; P.001) [27]. Similarly, black donors have higher rates of any complication (18.2% vs. 15.5%, p =

0.005) as well as complications Clavien grade IV or higher (3.7% vs. 2.2%, p = 0.0002) [24]**. Even after accounting for other baseline donor, procedure and center factors, black donors might be more likely to experience vascular complications (aOR 1.80, p = 0.03), hernias (aOR 1.77, p = 0.02), gastrointestinal complications (aOR 1.46, p = 0.004), and other complications (aOR 1.37, p = 0.04) [24]**.

The relative likelihood of any perioperative complication might increase by 1% with each increase in year of donor age (adjusted odds ratio [aOR] 1.01, p < 0.0001). Women are 14% less likely to experience any perioperative complication post-donation (aOR 0.86, p = 0.001) [24]**. Obese donors are 55% more likely to experience the most severe perioperative complications (aOR 1.55, p = 0.0005). Predonation genitourinary conditions (aOR 1.92, p < 0.0001), hematologic disorders (aOR 1.60, p = 0.003), and psychiatric diagnoses (aOR 1.29, p = 0.002) have been associated with increased risk of a perioperative complication [24]**. The effect of predonation hypertension on surgical risk remains uncertain with one study finding no association between predonation hypertension and perioperative complication [24]**, while another found an increased risk of surgical mortality (36.7 vs. 1.3 per 10,000 donors; RR, 27.4; 95%CI 5.0–149.5; p<0.001), albeit based on only two deaths among 545 donors [27].

Robotic nephrectomy and lower center volume are other factors that might be associated with higher rates of perioperative complications. Donors who underwent planned open nephrectomy were 31% more likely to experience any perioperative complication compared with donors who underwent laparoscopic nephrectomy (aOR 1.31, p = 0.02). Those who underwent robotic nephrectomy were twice as likely to experience severe perioperative complications (aOR 2.07, p = 0.002 for Clavien grade IV or higher events) [24]**.

Long-term safety:

Prior to 2014, all studies that investigated the long-term risks associated with living donation used the general population as a reference when assessing donor risk [28, 29]. However, two landmark studies published in 2014 demonstrated an increased risk of ESRD in donors compared to matched, healthy controls [19, 20]*. In Norway, Mjoen and colleagues compared the risk of ESRD in a cohort of 1901 donors to a cohort of 32,621 healthy nondonors over a median of 24.9 years and found an eleven-fold higher risk in donors (HR 11.38, 95%CI 4.37–29.6) [19]*. Similarly, in the US, Muzaale and colleagues compared the risk of ESRD in a cohort of 96,217 donors to a cohort of 20,024 healthy nondonors over a median of seven years and found an eight-fold higher risk donors (risk of ESRD 15 years after donation was 30.8 per 10,000 vs. 3.9 per 10,000 in nondonors; $P < .001$). This difference was observed across race (74.7 per 10,000 black donors vs 23.9 per 10,000 black nondonors; 32.6 per 10,000 Hispanic donors vs. 6.7 per 10,000; and 22.7 per 10 000 white donors vs 0.0 per 10,000 white nondonors). Estimated lifetime risk of ESRD was 90 per 10 000 donors, 326 per 10,000 unscreened nondonors (general population), and 14 per 10,000 healthy nondonors [20]*. However, it is important to note that although donors have a higher risk of ESRD compared to healthy donors, the absolute risk is very small.

As with perioperative risks, some subgroups of donors also have a substantially higher long-term risk of ESRD when compared with others including male sex (adjusted hazard

ratio [aHR], 1.88; 95%CI 1.50 to 2.35; P<0.001), black race (aHR at age 40, 2.96; 95% CI 2.25 to 3.89; P<0.001), and predonation hypertension (aHR 3.04; 95%CI: 1.28–7.22; P=.01) [30]. Higher BMI is also associated with higher risk of ESRD (aHR per 5 kg/m2, 1.61; 95% CI 1.29 to 2.00; P<0.001) [31]. It is plausible that the substantially higher risk of ESRD in black donors is attributable to high-risk APOL1 variants found only in individuals with recent African ancestry [32].

Given how common these high-risk variants are among black donors with a family history of ESRD [33], and how little we know about the pathways that lead from gene expression to ESRD in this risk group, it remains unclear whether two high-risk variants should connote an absolute contraindication to kidney donation. By extension, it remains controversial as to whether all potential black donors should be screened for APOL1. One downside to screening is the psychological ramification for donors who test positive, provoking anxiety and psycho-social burden. Furthermore, screening positive for two high-risk alleles is not a specific test for predicting disease. The majority of individuals who have two high-risk alleles may not develop ESRD [34–37]. Indeed, in the Natural History of APOL1-Associated Nephropathy Study, in which healthy relatives of African Americans with nondiabetic kidney disease were screened for APOL1 risk alleles, the majority of patients with high-risk alleles had neither proteinuria nor a reduced estimated GFR [33]. But following a “second hit”, such as incident diabetes, or chronic infection such as HIV, APOL1 might be associated with the collapsing variant of focal segmental glomerulosclerosis and very rapid progression to ESRD. For all these outlined reasons, APOL1 screening remains somewhat controversial and there is very limited live kidney donor literature to inform practice.

Communicating about safety:

Although it is critical for physicians to use the existing literature to inform potential donors of risk factors they possess for developing ESRD after donation, large studies fall short of providing physicians with individualized risk profiles for potential donors. Ideally, physicians should be able to inform each patient of their individualized perioperative and long-term risks of donating a kidney, including if and by how much donation reduces life expectancy as well is if and when donors develop health complications, such as ESRD. Because we cannot predict the impact of donation on life expectancy, the next best option is determining the long-term risk attributable to donation.

In communicating risk to potential donors, it is important to discuss their baseline risk (without donating), the absolute risk (after donation), and the attributable risk to donation. Recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines encourage providing donor candidates with individualized quantitative estimates of short and long-term risks from donation [7]. Using quantitative tools can allow centers to more accurately estimate patient specific risk on the basis of composite risk factors. Risk calculators can help clinicians appreciate the relationships between health characteristics for an individual and the long-term risk of end-stage renal disease (ESRD) but are not meant to supplant a comprehensive evaluation of a donor candidate by an expert physician who considers the circumstances of each candidate.

In 2016, Grams and colleagues released a risk calculator that determines pre-donation risk, the risk of an individual developing ESRD without donating a kidney. This calculator uses risk equations to estimate long-term risk of ESRD if the potential donor does not donate. Their calculator incorporates thirteen demographic and health characteristics, using risk associations from a meta-analysis of seven general population cohorts calibrated to the population level incidence of ESRD and mortality in the United States [21]**. The 15-year predonation projection of the risk of ESRD for the average kidney-donor candidate varied according to age, sex, and race but the highest risk group were middle-aged black men. For a 20-year-old base-case candidate, the 15-year projected risk of developing ESRD was 0.08% among black men, 0.05% among black women, 0.02% among white men, and 0.01% among white women. For a 40-year-old base-case candidate, the estimates were 0.24%, 0.15%, 0.06%, and 0.04%; for a 60-year-old base-case candidate, the estimates were 0.32%, 0.18%, 0.13%, and 0.08%. The lifetime projections were generally higher than the 15-year projections, especially among younger persons, though the risks were less than 2% for all base-case scenarios [21]**. Using Grams risk calculator in combination with a post-donation risk calculator can potentially shed light on the attributable risk of donation. The two calculators developed by Massie et al. and Ibrahim et al. calculate post-donation absolute risk.

Massie and colleagues used data from the Scientific Registry of Transplant Recipients (SRTR) of 133,824 living kidney donors in the United States between 1978 and 2015 to construct a risk calculator that includes sex, age, race, BMI, and first-degree biological relationship [31]**. Estimates of 5, 10, 15, and 20-year ESRD median risk among all donors in the study, 1 (IQR 1–2) cases per 10,000 donors at 5 years, 6 (IQR 4–11) per 10,000 at 10 years, 16 (IQR 10–29) per 10,000 at 15 years, and 34 (IQR 20–59) per 10,000 at 20 years post donation. However, the full range of risk was wide: the 1% of donors with lowest predicted risk had predicted risk below 0.2 cases per 10,000 donors at 5 years post-donation; 1.2 per 10,000 at 10 years post-donation; 3 per 10,000 at 15 years post-donation; and seven per 10,000 at 20 years post-donation. In contrast, the 1% of donors with highest predicted risk had predicted risk exceeding eight cases per 10,000 donors at 5 years post-donation; 48 per 10,000 at 10 years post-donation; 125 per 10,000 at 15 years post-donation; and 256 per 10,000 at 20 years post-donation [31]**. Because the results of these study draw upon national data, these results are likely generalizable to most potential donors.

Ibrahim and colleagues used data from their center at the University of Minnesota from 3956 white kidney donors between 1963 and 2013 [38]**. Their calculator estimates ESRD risk in white donors using age, BMI, and systolic blood pressure all measured at the time of donation. Exclusion criteria for donation included any proteinuria, hypertension, BMI >30 kg/m2 unless physical examination results warranted acceptance, and elevated fasting glucose levels, or, in potential donors with fasting glucose levels in the pre-diabetic range, abnormal glucose tolerance test results. After a mean follow-up of 16 years, 215 (6.1%) donors developed proteinuria. Men had a higher risk of proteinuria (HR 1.56; 95%CI 1.18 to 2.05; P<0.001) as did those with higher body mass index (HR 1.10; 95% CI, 1.06 to 1.13; P<0.001). ESRD was associated with older age (HR 1.07; 95% CI 1.05 to 1.09; P<0.001), higher body mass index (HR 1.08; 95% CI 1.04 to 1.13; P<0.001), and higher systolic BP (HR 1.02; 95% CI 1.00 to 1.04; P=0.01) at donation. Post-donation diabetes and

hypertension associated with a fourfold higher risk of proteinuria and a more than 2-fold higher risk of ESRD [38]**.

None of the online calculators provide estimates for perioperative risks. None provides separate estimates of risk for identical twin donors, full-sibling donors, offspring donors, parent donors, half-sibling donors, and other biological relatives. And none stratifies these familial risks by race, as the basis for familial risks might be partly genetic and related to ancestry as seen with APOL1 genes and recent African ancestry [39]. These are the most urgent updates that are needed to the existing calculators if at all the transplant community is to communicate ***meaningful information*** about safety to specific donor candidates.

Conclusion:

It is imperative that the transplant community educates living donors about the medical risks they undertake. While mortality and morbidity surrounding living donor nephrectomy is low, donors should be made aware that more frequent minor complications may lead to a longer than expected return to recovery, potentially leading to lost wages. Living donors may be at increased risk of developing ESRD compared to healthy nondonors, but the absolute risk is quite low. The development of individualized risk calculators can allow providers to more accurately inform potential donors of their medical risks and address their concerns, although updates to the calculators are needed to provide patients and physicians with the most accurate assessment of their risk.

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Box 1.

Key Points

- Living kidney donation offers individuals with end stage renal disease their best chance at survival, but the number of living donors has declined in the past decade
- The transplant community is being challenged to responsibly promote live donation while also ensuring the safety of those who choose to donate
- Perioperative complications from living donor nephrectomy are rare, but some donors, particularly male, black, or obese, may be at increased risk of complications that may result in a delayed return to normal duties at home and work
- Recent studies suggest a relative increase in the risk of end stage renal disease that is attributable to donation, particularly among males, donors with a high BMI, and African Americans
- Several risk calculators have been developed to help potential donors and their providers quantify the baseline- and post-donation risk of ESRD during the donor evaluation process based on individual demographic and health characteristics