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Research Article

Living Kidney Donation: What's the Risk?

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Kidney transplantation is currently the treatment of choice for end-stage renal disease (ESRD) in terms of survival and quality of life compared with other renal replacement therapies [1-4]. In certain developing countries, it may be the only feasible treatment option for patients with ESRD given the financial burden of maintenance dialysis. As of June 2013, approximately 108,000 patients wereregistered on the kidney transplant waiting list at the United Network for Organ Sharing (UNOS) in the United States [5]. The median waiting time to transplant for new patients, i.e.the number of days by which 50 percent of these patients have been transplanted, has ranged approximately from 850 to 1800 days depending on blood type [5]. Amongst the successful approaches that have been studied to concomitantly ease the waiting time and improve post-transplant outcome is the expansion of living donor (LD) transplantation [6].

Every year for the past decade, approximately 6000 healthy adults in the US willinglyundertake the risks of donor nephrectomy [5]. Oftentimes, these donors are wholly reliant upon us to provide them with updated and relevant data surrounding donation. It is our professional and moral obligation, therefore, as physicians to these donors to educate ourselves with the potential risks and benefits of donation, and convey these to prospective donors so they may be in a position to give informed consent or refusal.

Studies have consistently shown that the perioperative morbidity and mortality is rare in healthy kidney donors (Table 1) [7-9].

Table 1. Recent published studies on risks of perioperative morbidity and mortality in living donors.

Study (Reference)	Study Type	Sample Size	Control Group	Outcomes	Duration of Study	Results
Najarian JS *et al.* (7)	Prospective cohort study Survey	57 live donors 65 non-donors	Siblings of donors	Renal function, blood pressure, and proteinuria Perioperative mortality	Mean of 23.7 years	No evidence of progressive renal deterioration, proteinuria and hypertension in both donors and control group. 17 perioperative deaths after living donation, which estimates peri-operative mortality to be 0.03%.
Segev*et al.* (8)	Prospective cohort study	80,347 live kidney donors 9,364 non-donors	Screened population (excluded those with contraindications to kidney donation	Surgical mortality Long-term survival.	Within 90 days of live kidney donation for perioperative mortality Median follow-up was 6.3 (3.2-9.8) years for long-term risk of death	Surgical mortality from live kidney donation was 3.1 per 10,000 donors (95% confidence interval [CI], 2.0-4.6). Long-term risk of death was no higher for live donors than for age- and comorbidity-matched NHANES III participants for all patients and also stratified by age, sex, and race.
Matas et al. (9)	Survey	10 828 donor nephrectomies	None	Perioperative mortality Reoperations Complications not requiring reoperation Readmission rate	Not specified	Of the 10828 donors, three donors died, the calculated overall mortality was 0.03%. Reoperation has been performed in 25 (0.4%) open, 23 (1.0%) hand-assisted (HA) laparoscopic nephrectomy (LN), and 21 (0.9%) non-HA LN donors (p = 0.001). Complications not requiring reoperation were for 19 (0.3%) open, 22 (1.0%) HA LN, and 24 (0.8%) non- HA LN cases (p=0.02). Readmission rate was higher for LN (1.6%) vs. open (0.6%) donors (p<0.001).

In one study drawn from a mandated national registry of 80,347 live kidney donors, surgical mortality was 3.1 per 10,000 donors, a rate that has been unchanged over the last 15 years despite differences in practice and donor selection, albeit subject to race-specific variations [8]. Discord has arisen, however, with studies looking at the long-term risks, all-cause and cardiovascular mortality observed in kidney donors, specifically studies which have probed the development of ESRD (Table 2). Numerous studies has suggested that the risk of ESRD is no higher among donors compared to the general population [10-12].

have been ineligible for kidney donation and were unequal controls forrigorously screened donors. Another criticism that these studies received was that few individuals have ample follow-up time adequate to assess the long-term risk of ESRD (Table1).

To overcome this selection bias, two recent studies used a highly selected control group from the general population (meaning that these people may have been eligible to donate if they had wished to) and have shown results that have raised questions within the transplant community.

Table 2. Recent published studies on risks of perioperative morbidity and mortality in living donors.

Study (Reference)	Study Type	Sample Size	Control Group	Outcomes	Duration of Study	Results
Cherikh*et al.* (10)	Retrospective cohort	56, 458 donors	Unscreened general population	ESRD	Average duration of follow-up of 9.8 years.	Of the 56 458 LKDs, 126 LKDs (0.22%) developed ESRD.The overall LKD ESRD rate was 0.134 per 1000 years at risk. ESRD rates for LKDs overall and for Black, White, male and female donors compared favorably to the ESRD incidence in the general population.
Ibrahim *et al.* (11)	Cohort	3,698 donors	Unscreened general population	ESRD Survival Glomerular filtration rate (GFR) Urine protein excretion	No data	ESRD developed in 11 donors, a rate of 180 cases per million persons per year, as compared with a rate of 268 per million per year in the general population. At a mean (±SD) of 12.2±9.2 years after donation, 85.5% of the subgroup of 255 donors had a GFR of 60 ml per minute per 1.73 m^2 of body-surface area or higher, 32.1% had hypertension, and 12.7% had albuminuria, similar to those of matched controls.
Fehrman*et al.* 12)	Cross sectional follow-up	402 donors	Unscreened general population	GFR Urine protein excretion Hypertension	Mean time since donation was 12 years (SD:8).	The average estimated GFR was 72% (SD:18) of the age-predicted value. The ratio of the estimated to the predicted GFR showed no correlation to the time since donation, indicating that there is no accelerated loss of renal function after donation. GFR below 30 ml/min was found in five donors. One donor required dialysis treatment. Hypertension was present in 38% of the donors but the age-adjusted prevalence of hypertension among donors was not higher than in the general population. Significant proteinuria (>=1.0 g/L) was found in 3% and slight proteinuria (<1.0 g/L) in 9% of the donors.
Mjøen G *et al.* (13)	Cohort	1901 donors 32,621 non-donors	Healthy screened non-donors	All-cause mortality Cardiovascular mortality ESRD	Median follow-up of 15.1 years.	Hazard ratio for all-cause death was significantly increased to 1.30 (95% confidence interval 1.11-1.52) for donors compared with controls. There was a significant corresponding increase in cardiovascular death to 1.40 (1.03-1.91), while the risk of ESRD was significantly increased to 11.38 (4.37-29.6).
Muzaale AD *et al.* (15)	Cohort	96,217 kidney 9364 non-donors	Healthy screened non-donors	ESRD	Median follow-up of 7.6 years for donors, 15 years for non-donors	Estimated risk of ESRD at 15 years after donation was 30.8 per 10,000 (95% CI, 24.3-38.5) in kidney donors and 3.9 per 10,000 (95% CI, 0.8-8.9) in their matched healthy non-donor counterparts (P < .001).

In an analysis of 56, 458 living kidney donors in the US, the rate of ESRD was 0.134 per 1000 years at risk over an average follow-up period of 9.8 years [10]. The incidence of ESRD was 0.22 percent, which was not statistically higher than that of the general population. Another study by Ibrahim et al., evaluated the lifetime risk of ESRD in 3,698 kidney donors and showed a rate of ESRD of 180 cases per million persons per year which was comparable with a rate of 268 per million per year in the general population [11]. The aforementioned studies, amongst others, were flawed and received a number of criticisms. Primarily, the general population samples, which were used ascomparator groups in these studies, were not appropriate controls for comparison since they included adults that are unscreened for general medical conditions which may have contributed to adverse long term outcomes including mortality and ESRD. Consequently they would

These studies have suggested that the risk of ESRD in kidney donors is relatively higher when compared with similarly selected non-donor counterparts.

The first study published by Mjoen and colleagues compared1,901 living kidney donors in Norway with 32,621 highly selected control group from the general population and showed that the risk of all-cause death, cardiovascular death and ESRD was higher among donors (with HR adjusted for age, gender, systolic blood pressure, smoking, and BMI of 11.4, 95% CI 4.4-29.6) [13]. Hazard ratio for all-cause death was significantly increased to 1.30 (95% confidence interval 1.11-1.52) for donors compared with controls. There was a significant corresponding increase in cardiovascular death to 1.40 (1.03-1.91), while the risk of ESRD was significantly increased to 11.38 (4.37-29.6). The overall incidence of ESRD among donors was 302 cases per million

person-years, whereas the estimated incidence of ESRD in the general population in Norway is 100 million per person-years.

It is important to note that in this nationwide cohort of predominantly Caucasian origin, 80 percent of studied donors were first-degree relatives ofkidney recipients. Furthermore, the etiology of ESRD among donors was mostly immunologic in nature suggesting that the possible increase in the risk of ESRD was related to genetically determine immunologic factors rather than the nephrectomy itself [14]. In addition, as the authors acknowledge in their study, the control group lived within one county in Norway,which may not be representative of the screened non-donor population. Moreover, the observation period of the living donor cohort was different from that of the non-donor controls, i.e. 1963–2007 for the living donors and 1984–1987 for the non-donor controls, making comparison between the two cohorts challenging.

In the other study, Muzaale et al, compared 96,217 donors with matched non-donor population drawn from the Third National Health and Nutrition Examination Survey (NHANES III).15Matching was based on age, sex, self-identified race, educational background, BMI, smoking history, and systolic blood pressure. Non-donors were individually matched with replacement to live donors using a sophisticated process callediterative expanding radius matching. By this method, individual selected NHANES participants served as multiple controls for kidney donors. Crude analyses showed that 99 of 96, 217 kidney donors developed ESRD (incidence of 10.3 per 10,000). In contrast, crude analyses for NHANES III participants showed that 17 of 9364 participants developed ESRD (incidence of 18.2 per 10,000). Using the matched sample, the estimated cumulative incidence of ESRD at 15 years was 30.8 per 10,000 in donors and 3.9 per 10,000 in healthy non-donors, an 8-fold higher cumulative risk of ESRD in donors compared to non-donors. The risk was particularly high in African American individuals (risk of 74.7 per 10,000 in donor'svs 23.9 per 10,000 in race matched non-donors). The lifetime risk of ESRD in donors was still noted to be significantly lower than unscreened non-donors (i.e. general population) at 90 per 10,000 vs 326 per 10,000.

The risk of ESRD may have been underestimated in the control group for several reasons [16]. As previously noted, because of the discrepancy in the number of donors and screened healthy non-donors, the study was designed such that individual controls are allowed to be matched to multiple donors, which may have resulted in the repeated inclusion of long event-free survival times. Moreover, there were differences in methods used in identifying ESRD between donors and controls. While donors were identified as having ESRD by requirement for dialysis, transplantation, or by activation to the deceased-donor transplant list, ESRD in controls was identified by requirement for dialysis or elective transplantation. Further, compared to controls, donors had significantly higher BMI, systolic blood pressure and were two times as likely to be smokers.

Most importantly, whereas the latter studies show that compared with a matched cohort of healthy US non-donors, kidney donors had an increased relative risk of ESRD over a lifetime, the magnitude of the absolute risk increase was indeed small (0.1%). Similarly, the Norweigan study provides analogous result of this low absolute risk of ESRD in living donors (0.47%). These two studies therefore also underscore the limitations of relative measures of risk for rare events. In view of the low absolute risk, the authors in both publications, state that they will not change their stance in the promotion of live kidney donation but that informed consent must be expanded to encompass thisincreased, albeit, small risk. Living donor education should now more than ever before stress on the adoption of healthier lifestyle practices to minimize this now apparent risk. These studies also call upon the transplant community to ensure regular, sustained and careful follow-up of kidney donors to detect, pre-empt and optimally control the risk factors for CVS disease and ESRD that appear to be slightly more likely to arise in kidney donors. Ultimately, these studies highlight the need for further genotypic and phenotypicresearch that may better delineate modifiable and non-modifiable factors that predispose certain individuals to develop kidney disease after living donation, who could benefit from more aggressive follow-up or rarely even non-donation.

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