Perioperative Mortality and Long-term Survival Following Live Kidney Donation

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Context More than 6000 healthy US individuals every year undergo nephrectomy for the purposes of live donation; however, safety remains in question because longitudinal outcome studies have occurred at single centers with limited generalizability.

Objectives To study national trends in live kidney donor selection and outcome, to estimate short-term operative risk in various strata of live donors, and to compare long-term death rates with a matched cohort of nondonors who are as similar to the donor cohort as possible and as free as possible from contraindications to live donation.

Design, Setting, and Participants Live donors were drawn from a mandated national registry of 80 347 live kidney donors in the United States between April 1, 1994, and March 31, 2009. Median (interquartile range) follow-up was 6.3 (3.2-9.8) years. A matched cohort was drawn from 9364 participants of the third National Health and Nutrition Examination Survey (NHANES III) after excluding those with contraindications to kidney donation.

Main Outcome Measures Surgical mortality and long-term survival.

Results There were 25 deaths within 90 days of live kidney donation during the study period. Surgical mortality from live kidney donation was 3.1 per 10 000 donors (95% confidence interval [CI], 2.0-4.6) and did not change during the last 15 years despite differences in practice and selection. Surgical mortality was higher in men than in 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; $P<.001$). However, 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.

Conclusion Among a cohort of live kidney donors compared with a healthy matched cohort, the mortality rate was not significantly increased after a median of 6.3 years.

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With a significant organ shortage in the United States and with minimal expansions of the deceased donor pool in recent decades, many patients with end-stage renal disease are turning to live donor kidney transplantation to improve survival and quality of life.[1-5] Although many healthy adults are eager and willing to accept the risk of donor nephrectomy to help their loved ones, the responsibility lies within the medical community to quantify these risks as best as possible and to make this information available to those considering donation.

Evidence to date suggests that live kidney donation is safe.[3,6-14] In fact, some studies show that live donors have better outcomes than their population counterparts.[1,3] But inferences have thus far been limited by lack of generalizability, restrictive sample size, and inappropriate comparison groups. Most studies that have evaluated live donor outcomes have been conducted at single academic centers with carefully selected, primarily white individuals who receive close follow-up and are often involved in funded research studies. Furthermore, although some single centers have studied as many as 3700 donors,[3] the event rate for long-term death in live donors is so low that the power to detect differences in outcomes is limited with these sample sizes. Finally, comparison groups for long-term outcomes have been limited to published population-based life tables or heavily confounded reference populations and as such lack the ability to select healthy controls in a manner comparable with the screening process for kidney donors.

The goal of our study was to extend previous studies of live donor outcomes to a large generalizable cohort of all live kidney donors in the United States during a 15-year period, to study national trends in live kidney donor selection and outcome, to estimate short-term operative risk in various strata of live donors, and to improve the long-

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term comparison group by identifying a matched cohort of nondonors who are as similar to the donor cohort as possible and as free as possible from contraindications to live donation.

METHODS

Study Population

Live Donors. By national mandate, all live kidney donors are reported to the Organ Procurement and Transplantation Network through the United Network for Organ Sharing (UNOS). A total of 80 347 live kidney donors between April 1, 1994, and March 31, 2009, were included in this study, excluding only 24 donors where age was not recorded and 12 donors where age was recorded as younger than 18 years. All donor characteristics are reported by the transplant centers to UNOS and are shown as entered on the donor registration form. Postdonation death was ascertained by linking donors to the Social Security Death Master File as of March 31, 2009, using the social security number and confirming with 1 or more of the following identifiers: first name, last name, middle initial, and date of birth, as has been previously reported in other studies of live donors.[3]

Matched Cohort. Potential comparison patients were identified from among participants of the third National Health and Nutrition Examination Survey (NHANES III) conducted between 1988 and 1994. NHANES III was a national household survey conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention using a complex oversampled multistage sample design. Baseline comorbidities and other medical information was obtained through home interviews, physical examinations, and radiographic and laboratory test results. Death among NHANES III participants was similarly ascertained by linkage as described above for the live donors, allowing for a reasonable comparison of death rates. Of 20 024 adults in the NHANES III, 9458 with recorded comorbidities or other factors that would have deemed them ineligible at most transplant centers were excluded. Exclusion comorbidities included kidney disease, diabetes, heart disease, and hypertension. Although some transplant programs accept donors with hypertension, the degree of hypertension is not recorded in either data set, and it is likely that donors with hypertension are well-controlled; therefore, for the sake of a reference group, donors with hypertension were held to the comparison standard of controls without hypertension.

Additional exclusion factors included answering "yes" to any of the questions listed in the eTable (available at http://www.jama.com). Finally, NHANES III participants who were missing information on kidney disease, diabetes, heart disease, or hypertension could not serve as part of a comparison cohort and were thus excluded (n=1228). A total of 9364 NHANES III participants remained who were without contraindications to live donation; 1 matched control for each live kidney donor was selected from this remaining NHANES III population with replacement, as fully delineated in the eMethods (available at http://www.jama.com).

Statistical Analysis

Mortality estimates were obtained by Kaplan-Meier curve methods, with administrative censoring at the time of linkage to the Social Security Death Master File. For live donors, time at risk was accrued from the date of donation. For NHANES III controls, time at risk was accrued from the date of enrollment into the study. Early postsurgical (3-month and 12-month) death rates were calculated per 10 000 donors with 95% confidence intervals (CIs) derived using Poisson exact intervals. Differences in early postsurgical deaths across donor characteristics were analyzed by using χ^2 tests of independence. Associations between donor characteristics and long-term death (all deaths including early deaths) were analyzed using nested Cox proportional hazards regression models. Long-term death rates between live kidney donors and the matched cohort were compared using log-rank tests. Based on the number of patients for whom we had 10-year follow-up and a 10-year survival of 97%, we had 80% power to detect a difference of 1%; in other words, if live donor survival at 10 years was 96% or lower and matched cohort survival was 97%, we would anticipate having the power to detect this difference. All analyses were performed by using multiprocessor Stata version 11.0/MP for Linux (StataCorp, College Station, Texas), with $\alpha=.05$. When applicable, all hypothesis tests were 2-sided.

RESULTS

Donor Demographics

There was a significant increase in live donor kidney transplants in the United States during the last 15 years (from 3009 in 1994 to 5968 in 2008). Donor age changed considerably over time, with 13.9% of donors older than 50 years in 1994 compared with 22.8% in 2008. A total of 58 683 live kidney donors (73.1%) were white, 10 505 (13.1%) were black, and 9846 (12.3%) were Hispanic (TABLE 1). Educational backgrounds varied, with 38.4% of live kidney donors educated at grade school or high school level, 28.0% with some college, and 33.6% with a bachelor's degree or postcollege. Of donors where body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) information was available (after 2003), 22.6% were obese (BMI $\geq$30). Very few individuals (1.8%) were categorized as having hypertension in the same era.

Early Postsurgical Death

In general, the risk of death in the first 90 days following live donor nephrectomy was 3.1 per 10 000 donors in the first 90 days (95% CI, 2.0-4.6) (TABLE 2). Although more conservative than the commonly used 30-day perioperative mortality metric, death in the first 90 days seemed a good measure of surgical mortality, because this rate greatly exceeded the risk of death

in the first 90 days for the NHANES III matched cohort (0.4 per 10 000 donors; 95% CI, 0.1-1.1; $P<.001$) compared with live donors. By 1 year following nephrectomy, risk of death in the matched cohort was similar (4.6 per 10 000 donors; 95% CI, 3.2-6.3; vs 6.5 per 10 000 donors; 95% CI, 4.8-8.5; $P=.11$) to the live donor cohort, likely representing deaths attributable to comorbidity rather than surgical mortality.

Surgical mortality did not change during the 15-year period, despite differences in surgical practice and donor selection (Table 2). Men had a statistically significantly higher surgical mortality than women did (5.1 per 10 000 donors; 95% CI, 3.0-8.2; vs 1.7 per 10 000 donors; 95% CI, 0.7-3.4; risk ratio [RR], 3.0; 95% CI, 1.3-6.9, $P=.007$), as did black individuals vs white and Hispanic individuals (7.6 per 10 000 donors; 95% CI, 3.3-15.0; vs 2.6 per 10 000 donors; 95% CI, 1.4-4.2; and 2.0 per 10 000 donors; 95% CI, 0.2-7.3; RR, 3.1; 95% CI, 1.3-7.1; $P=.01$ vs nonblack individuals). Donors with hypertension also had a statistically significantly higher surgical mortality than did donors without hypertension (36.7 per 10 000 donors; 95% CI, 4.4-132.6; vs 1.3 per 10 000 donors; 95% CI, 0.4-3.4; RR, 27.4; 95% CI, 5.0-149.5; $P<.001$), although this was based on only 2 deaths among 545 donors with hypertension; therefore, as indicated by the wide CI, the magnitude of the excess surgical risk remains quite uncertain. No statistically significant difference in surgical mortality was observed by age, smoking status, BMI, or systolic blood pressure (SBP).

Long-term Donor Survival

Similar associations were observed when studying long-term mortality after live kidney donation as were shown in postsurgical death rates. When analyzing the entire cohort of live donors, individuals aged 50 to 59 years (hazard ratio [HR], 3.3; 95% CI, 2.6-4.1; unadjusted 3.5% 12-year mortality for this subgroup vs 1.3% 12-year mortality for those adults younger than 40 years), aged 60 years or older (HR, 9.4; 95% CI, 7.3-12.1; unadjusted 9.4% 12-year mortality for this subgroup), male sex (HR, 1.7; 95% CI, 1.5-2.0; unadjusted 2.7% 12-year mortality for men vs 1.9% 12-year mortality for women), and black race (HR, 1.3; 95% CI, 1.0-1.6; unadjusted 2.8% 12-year mortality for black individuals vs 1.7% 12-year mortality for white individuals) were associated with higher rates of long-term death (model 1 in TABLE 3). These associations were also observed in the cohort of donors between 2000 and 2009, where information about SBP was also available (model 2 in Table 3). In this cohort, SBP of 140 mm Hg or higher was also associated with a higher rate of death (HR, 1.7; 95% CI, 1.1-2.9; unadjusted 4.0% 9-year mortality vs 1.4% 9-year mortality for SBP of <120 mm Hg) (model 2 in Table 3).

Missing covariate data resulted in a cohort limited to donors between 2004 and 2009 when studying the effect of smoking and hypertension (model 3 in Table 3). This cohort was one-fourth the size of the full cohort, with about one-third of the follow-up time (median [interquartile range], 2.1 [1.0-3.1] years; vs 6.3 [3.2-9.8] years for the full cohort), and many of the associations observed in the larger cohorts with longer follow-up were not detected in this model. In fact, the only statistically significant associations were SBP of 140 mm Hg or higher (HR, 3.3; 95% CI, 1.1-9.7; unadjusted 4% 9-year mortality vs 1% 9-year mortality for SBP of <120 mm Hg) and smoking (HR, 5.3; 95% CI, 2.6-10.8; unadjusted 1.0% 4-year mortality vs 0.7% 4-year mortality for nonsmokers), while hypertension was not associated with increased risk of death (HR, 0.9; 95% CI, 0.1-6.6; unadjusted 0.7% 3-year mortality vs 0.5% 3-year mortality for those donors without hypertension).

Matched NHANES III Cohort

Although 90-day death rates were higher for live kidney donors (Table 2), long-term mortality was similar or lower for live kidney donors than for the matched NHANES III cohort throughout the 12-year period of follow-up (5-year follow-up: 0.4% vs 0.9% and 12-year follow-up: 1.5% vs 2.9%; $P<.001$ by log-rank test) (FIGURE 1).

Table 1. Demographic and Predonation Characteristics of Live Kidney Donors[a]

Characteristics	No. (%) of Donors
Age, y	
18-39	39 516 (49.2)
40-49	24 375 (30.3)
50-59	13 439 (16.7)
≥60	3017 (3.8)
Sex	
Men	33 380 (41.5)
Women	46 967 (58.5)
Race/ethnicity	
White	58 683 (73.1)
Black	10 505 (13.1)
Hispanic	9846 (12.3)
Other	1252 (1.6)
Education	
Grade school	910 (2.3)
High school	14 497 (36.1)
Some college	11 259 (28.0)
Bachelor degree	9660 (24.1)
Postcollege	3820 (9.5)
BMI	
15-24	7343 (37.0)
25-29	8016 (40.4)
≥30	4473 (22.6)
SBP, mm Hg	
<120	25 713 (53.3)
120-139	19 114 (39.6)
≥140	3430 (7.1)
Hypertension	
No	29 848 (98.2)
Yes	545 (1.8)
Smoking (ever)	
No	19 391 (76.0)
Yes	6114 (24.0)
Creatinine values, mean (SD)[b]	
Serum creatinine, mg/dL	0.9 (0.2)
Creatinine clearance, mL/min	117 (36)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SBP, systolic blood pressure.

SI conversions: To convert serum creatinine to µmol/L, multiply by 88.4; and creatinine clearance to mL/s, multiply by 0.0167.

[a] Characteristics for age, sex, and race/ethnicity were available throughout the study period. For race/ethnicity, other included American Indian, Native Hawaiian, Alaskan Native, Pacific Islander, and multiracial. Education was only available after 1998 (46% missing between 1999-2004; 24% missing between 2005-2009). BMI was only available after 2003 (49% missing between 2004-2006; 31% missing between 2007-2009). SBP was only available after 1999 (22% missing between 2000-2005; 9% missing 2006-2009). Hypertension was only available after 2003 (41% missing in 2004; 3% missing in 2005; 1% missing between 2006-2008). Smoking was only available after 2004 (23% missing in 2005; 0.06% missing between 2006-2008).

[b] Serum creatinine (n=58 599) was only available after 1998 (49% missing between 1999-2000; 4% missing between 2001-2009). Cockcroft-Gault formula was used to obtain creatinine clearance estimates (n=21 295).

Similar patterns were observed when comparing live kidney donors with matched controls stratified by age (FIGURE 2), sex (FIGURE 3), and race (Figure 3) ($P<.001$ for all comparisons by log-rank test).

COMMENT

The benefits of live donation for the recipient in terms of reduction in waitlist mortality and longevity after transplantation have been well demonstrated. It is incumbent on the transplantation community to show that these lives are not saved at the cost of placing the donors at risk for excess perioperative or long-term mortality. In our study of all live donors during a 15-year period in the United States, 25 of 80 347 donors died within 3 months of donation, for an estimated surgical mortality of 3.1 per 10 000 cases. This compares with reported surgical mortality of approximately 18 per 10 000 cases for laparoscopic cholecystectomy[15] and approximately 260 per 10 000 cases for nondonor nephrectomy.[16] Although the proportion of donors older than 50 years nearly doubled, the death rate did not change over time. Similarly, although more than 20% of live donors were obese (BMI ≥30), surgical mortality was not associated with obesity. Although it is possible that surgical mortality was higher for older adults, this difference was also not statistically detectable. Surgical mortality was demonstrably higher for men (RR, 3.0), black individuals (RR, 3.1), and those reported to have hypertension (RR, 27.4), consistent with higher rates of death after other surgical procedures for these subgroups.[17-21] These factors were also associated with higher risk of long-term death, consistent with known population factors associated with

Table 2. Death Within 3 and 12 Months of Live Donor Nephrectomy[a]

	Within 3 Months			Within 12 Months		
Characteristic	No. of Deaths	Rate per 10 000 Donors (95% CI)	*P* Value	Deaths	Rate per 10 000 Donors (95% CI)	*P* Value
Live donors (n = 80 347)	25	3.1 (2.0-4.6)	<.001	52	6.5 (4.8-8.5)	.11
Matched cohort (n = 80 347)	3	0.4 (0.1-1.1)		37	4.6 (3.2-6.3)	
Age, y						
18-39	12	3.0 (1.6-5.3)	.46	24	6.1 (3.9-9.0)	.08
40-49	9	3.7 (1.7-7.0)		18	7.4 (4.4-11.7)	
50-59	2	1.5 (0.2-5.4)		5	3.7 (1.2-8.7)	
≥60	2	6.6 (0.8-23.9)		5	16.6 (5.4-38.7)	
Sex						
Men	17	5.1 (3.0-8.2)	.007	34	10.2 (7.1-14.2)	<.001
Women	8	1.7 (0.7-3.4)		18	3.8 (2.3-6.1)	
Race/ethnicity						
White	15	2.6 (1.4-4.2)	.04	32	5.5 (3.7-7.7)	.08
Black	8	7.6 (3.3-15.0)		12	11.4 (5.9-20.0)	
Hispanic	2	2.0 (0.2-7.3)		6	6.1 (2.2-13.3)	
BMI						
15-24	2	2.7 (0.3-9.8)	.49	3	4.1 (0.8-11.9)	.76
25-29	1	1.2 (0.0-7.0)		4	5.0 (1.4-12.8)	
≥30	0	0.0 (0.0-8.2)		1	2.2 (0.1-12.4)	
SBP, mm Hg						
<120	4	1.6 (0.4-4.0)	.37	9	3.5 (1.6-6.6)	.07
120-139	7	3.7 (1.5-7.5)		14	7.3 (4.0-12.3)	
≥140	1	2.9 (0.1-16.2)		4	11.7 (3.2-29.9)	
Hypertension						
No	4	1.3 (0.4-3.4)	<.001	13	4.3 (2.3-7.4)	.001
Yes	2	36.7 (4.4-132.6)		2	36.7 (4.4-132.6)	
Smoking						
No	3	1.5 (0.3-4.5)	.40	8	4.1 (1.8-8.1)	.45
Yes	2	3.3 (0.4-11.8)		4	6.5 (1.8-16.8)	
Year						
1994-1997	2	1.5 (0.2-5.4)	.33	6	4.5 (1.7-9.8)	.44
1998-2001	8	3.9 (1.7-7.6)		16	7.7 (4.4-12.6)	
2002-2005	11	4.2 (2.1-7.6)		20	7.7 (4.7-11.9)	
2006-2009	4	2.0 (0.5-5.0)		10	4.9 (2.3-9.0)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; SBP, systolic blood pressure.
[a] Poisson exact 95% CIs reported. *P* values were calculated by χ^2 test across all values (rows) for a given category. Matched controls were identified among participants in the third National Health and Nutrition Examination Survey.

vulnerability to mortality. Most importantly, long-term death rates were no higher for live donors than for the matched cohort of NHANES III participants selected to most closely resemble live donors.

The strength of our study lies in its generalizability, sample size, and choice of comparison group. This is the first longitudinal survival study to our knowledge that draws from the entire population of live US donors during a 15-year period. The use of a complete national population is critical, as most single-center studies to date have involved white donors without hypertension from large-volume transplant centers. For example, the largest longitudinal study of donors to date (3700 live donors at the University of Minnesota), although important and informative, is limited to a population that is nearly 100% white.[3] However, we have shown that 26% of US donors are nonwhite and outcomes differ by race/ethnicity, with higher surgical and long-term mortality in black individuals. With more than 10 000 black individuals in our study, we were also able to compare survival of these donors with their NHANES III controls; this comparison has not been possible in previous studies.

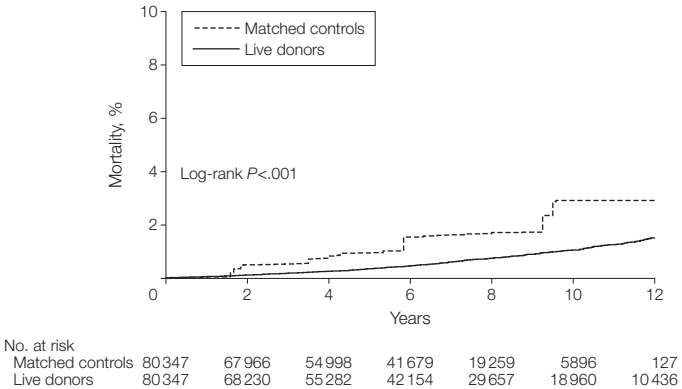
The large sample size of more than 80 000 live donors allows for more robust inferences about surgical mortality, which is a rare event (3.1 per 10 000 cases overall), and for comparison of death rates by various strata, including age, sex, race/ethnicity, BMI, SBP, and smoking. This is particularly relevant in terms of donor counseling, because risk awareness is the essence of informed consent when a healthy person embarks on a major operation. Previous surgical mortality estimates have been based mostly on self-report and literature review, with the risk of reporting bias, recall bias, and publication bias. Estimates currently quoted to candidate donors range from 0.03% based on a self-reported survey of members of a professional society conducted in 1992[8] to 0.06% based on a study of 8200 live donors drawn from the literature and a self-reported survey conducted in 1987.[22] Surgical mortality in the recent era has not been estimated in general or for any stratified populations. The 15-year period included in our study is inclusive of the transition from the predominance of the open nephrectomy to the laparoscopic nephrectomy.[23,24] Although not statistically significant, it is entirely possible that the increase in surgical mortality between 1994-1997

Table 3. Characteristics Associated with Survival Among Live Donors[a]

Characteristic	Hazard Ratio (95% CI) Model 1 (n = 80 287)	Model 2 (n = 47 695)	Model 3 (n = 22 745)
Age, y			
18-39	1 [Reference]	1 [Reference]	1 [Reference]
40-49	1.6 (1.2-2.0)	1.2 (0.8-1.8)	1.0 (0.4-2.3)
50-59	3.3 (2.6-4.1)	1.8 (1.2-2.8)	0.9 (0.3-2.4)
≥60	9.4 (7.3-12.1)	5.5 (3.3-9.2)	2.4 (0.8-7.6)
Sex			
Men	1.7 (1.5-2.0)	1.5 (1.1-2.1)	1.3 (0.6-2.6)
Women	1 [Reference]	1 [Reference]	1 [Reference]
Race/ethnicity			
White	1 [Reference]	1 [Reference]	1 [Reference]
Black	1.3 (1.0-1.6)	2.0 (1.3-3.0)	1.6 (0.6-4.2)
Hispanic	0.6 (0.4-0.9)	0.7 (0.4-1.2)	1.0 (0.3-3.2)
SBP, mm Hg			
<120	NA	1 [Reference]	1 [Reference]
120-139	NA	1.2 (0.8-1.6)	2.1 (1.0-4.6)
≥140	NA	1.7 (1.1-2.9)	3.3 (1.1-9.7)
Smoking (ever)			
Yes	NA	NA	5.3 (2.6-10.8)
Hypertension			
Yes	NA	NA	0.9 (0.1-6.6)
Follow-up, y			
Median (IQR)	6.3 (3.2-9.8)	4.2 (2.1-6.5)	2.1 (1.0-3.1)
Maximum	15.1	9.3	4.3

Abbreviations: CI, confidence interval; IQR, interquartile range; NA, not applicable; SBP, systolic blood pressure.
[a] Number of observations (changes because of missing data; see Table 1 for covariate availability). Hazard ratios (95% CIs) were estimated from Cox proportional hazards regression models. Model 1 includes demographics only (age, sex, race/ethnicity); model 2 includes demographics and SBP; and model 3 includes demographics, SBP, smoking, and hypertension.

Figure 1. Kaplan-Meier Curves Comparing Cumulative Mortality of Live Kidney Donors and Matched Controls for the Entire Cohort of Live Donors



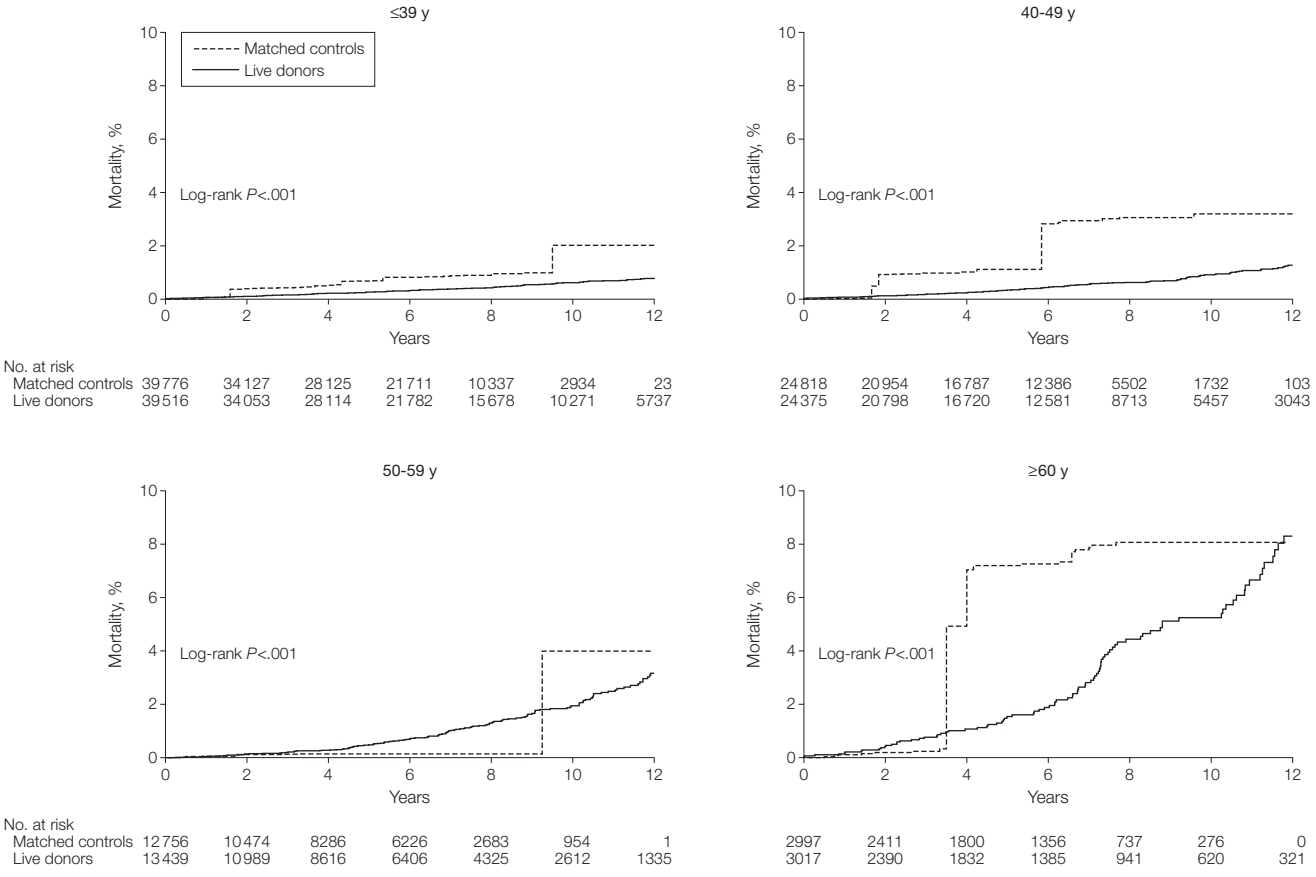
Matched controls were identified among participants in the third National Health and Nutrition Examination Survey.

and 1998-2005, and the subsequent reduction thereafter, reflects the learning curve with new technology.[12] If this is true, a mortality between 1.5 per 10 000 donors (from 1994-1997) and 2.0 per 10 000 donors (from 2006-2009) may be more representative as live donor nephrectomy moves forward.

Long-term live donor survival has traditionally been compared with population-based survival estimates. For example, Fehrman-Ekholm et al[6] compared live donor survival to expected survival using national mortality rates. Recently, Ibrahim et al[3] compared live donor survival with general population life tables from the National Center for Health Statistics. However, clearly live donors are very carefully selected and an appropriate comparison group should be selected in a similar manner. In applying our exclusion criteria, which were based on standard live donor candidate workup[4] as best ascertained by NHANES III data, more than half of the NHANES III cohort were found to be ineligible for live donation, illustrating the bias that is inherent in population-based comparison groups. Our matched cohort was thus carefully constructed to represent (within the limitations of the data) potential candidates for live donation and oversampled to represent the demographic distribution of the live donor cohort. Despite these efforts, unmeasured confounding still likely explains the lower observed survival among the matched cohort, given that candidate live donors are very carefully screened by multidisciplinary teams and significant laboratory and radiographic testing, while we were only able to exclude a proportion of the NHANES III controls based on approximately 30 screening questions.

Our study is limited by availability of data, duration of follow-up, and statistical artifacts resulting from an oversampled matched cohort. Of the 80 347 donors registered by national mandate through UNOS, all had information about age, sex, race/ethnicity, and vital status throughout the study period. However, more granular information about education, BMI, SBP, hypertension, and smoking was only available in the later periods. As a result, our ability to estimate early surgical mortality stratified by these factors was limited to a smaller (yet still very large and nationally representative) subset of donors (n = 22 745-47 695). Furthermore, our ability to make inferences about the ef-

Figure 2. Kaplan-Meier Curves Comparing Cumulative Mortality of Live Kidney Donors and Matched Controls by Age Category



Matched controls were identified among participants in the third National Health and Nutrition Examination Survey.

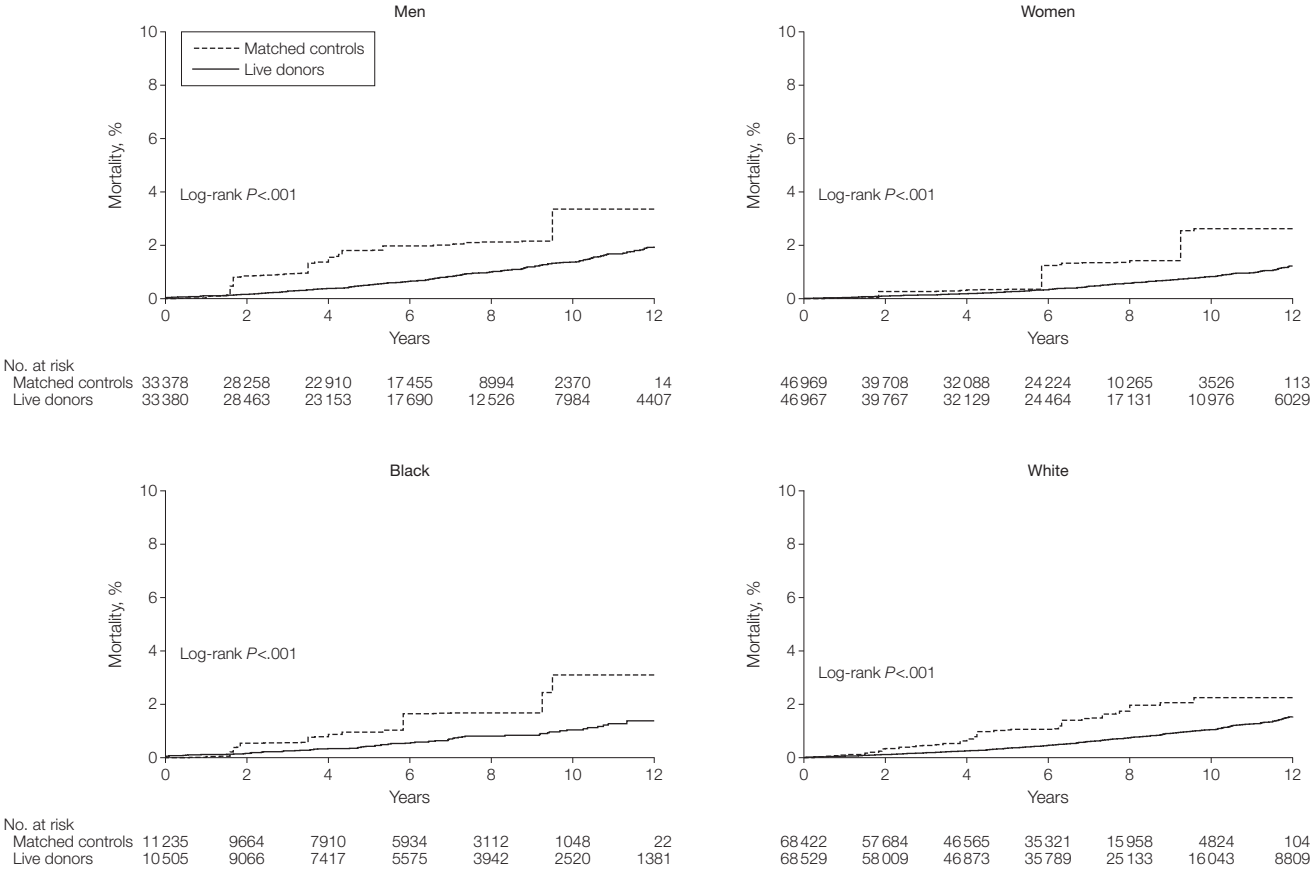
fects of SBP, hypertension, or smoking on long-term survival was limited by shorter follow-up (maximum follow-up, 4.3-9.3 years vs 15.1 years for those donors with only age, sex, and race/ethnicity information).

Although NHANES III is a large, representative, and commonly studied population of potential comparison patients, this cohort was one-eighth the size of the live donor cohort after appropriate exclusions. As a result, in generating a matched cohort based on these patients, we had to sample with replacement (some patients were used more than once in the matched cohort). Although this accounted for confounding by making the matched cohort similar in demographics to the live donor cohort, the oversampling caused an artificially larger sample size for the purposes of standard error estimates. Of all statistical analyses performed in our study, the only one affected was the statistical comparison of the live donor survival with the matched cohort survival, where we found that live donors had a statistically significantly better survival than their NHANES III counterparts. Although it is unlikely that this substantial difference was driven by the artificial increase in sample size, we can still safely conclude that live donors did not have statistically significantly worse survival than their NHANES III counterparts.

We have shown that live kidney donation is safe and free from significant long-term excess mortality. Although perioperative mortality is low (3.1 of 10 000 cases), some subgroups seem to be at higher risk and individuals from these demographic groups should be counseled accordingly. Importantly, although selection criteria have changed over time and more adults older than 50 years are donating, we found no evidence that these adults are at higher risk of surgical mortality and no evidence that surgical mortality is changing over time. This suggests that current screening practices, even in older age groups, still result in a well-selected group of healthy adults.

Regardless of what physiologic changes might occur in a healthy adult after kidney donation, our findings of similar long-term survival between donors and healthy comparison patients suggest that these physiologic changes do not result in premature death. Although additional studies are clearly needed to better understand the physiologic changes after kidney donation, the current practice of live kidney donation should continue to be consid-

Figure 3. Kaplan-Meier Curves Comparing Cumulative Mortality of Live Kidney Donors and Matched Controls by Sex and Race



Matched controls were identified among participants in the third National Health and Nutrition Examination Survey.

ered a reasonable and safe modality for addressing the profound shortage in deceased donor organs.

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Study concept and design: Segev.
Acquisition of data: Segev, Taranto, McBride.
Analysis and interpretation of data: Segev, Muzaale, Caffo, Mehta, Singer, Taranto, Montgomery.
Drafting of the manuscript: Segev, Muzaale.
Critical revision of the manuscript for important intellectual content: Segev, Muzaale, Caffo, Mehta, Singer, Taranto, McBride, Montgomery.
Statistical analysis: Segev, Muzaale, Caffo, Mehta, McBride.
Administrative, technical, or material support: Montgomery.
Study supervision: Segev.
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REFERENCES

1. Poggio ED, Braun WE, Davis C. The science of stewardship: due diligence for kidney donors and kidney function in living kidney donation—evaluation, determinants, and implications for outcomes. *Clin J Am Soc Nephrol*. 2009;4(10):1677-1684.
2. Delmonico FL, Dew MA. Living donor kidney transplantation in a global environment. *Kidney Int*. 2007; 71(7):608-614.
3. Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. *N Engl J Med*. 2009; 360(5):459-469.
4. Delmonico F; Council of the Transplantation Society. A report of the Amsterdam forum on the care of the live kidney donor: data and medical guidelines. *Transplantation*. 2005;79(6)(suppl):S53-S66.
5. United Network for Organ Sharing Web site. http://www.unos.org. Accessed February 5, 2010.
6. Fehrman-Ekholm I, Elinder CG, Stenbeck M, Tyden G, Groth CG. Kidney donors live longer. *Transplantation*. 1997;64(7):976-978.
7. Garg AX, Muirhead N, Knoll G, et al; Donor Nephrectomy Outcomes Research (DONOR) Network. Proteinuria and reduced kidney function in living kidney donors: a systematic review, meta-analysis, and meta-regression. *Kidney Int*. 2006;70(10):1801-1810.
8. Najarian JS, Chavers BM, McHugh LE, Matas AJ. 20 years or more of follow-up of living kidney donors. *Lancet*. 1992;340(8823):807-810.
9. Goldfarb DA, Matin SF, Braun WE, et al. Renal outcome 25 years after donor nephrectomy. *J Urol*. 2001; 166(6):2043-2047.
10. Okamoto M, Akioka K, Nobori S, et al. Short- and long-term donor outcomes after kidney donation: analysis of 601 cases over a 35-year period at Japanese single center. *Transplantation*. 2009;87(3): 419-423.
11. Andersen B, Hansen JB, Jorgensen SJ. Survival after nephrectomy. *Scand J Urol Nephrol*. 1968; 2(2):91-94.
12. Friedman AL, Peters TG, Jones KW, Boulware LE, Ratner LE. Fatal and nonfatal hemorrhagic complications of living kidney donation. *Ann Surg*. 2006; 243(1):126-130.
13. Johnson EM, Remucal MJ, Gillingham KJ, Dahms RA, Najarian JS, Matas AJ. Complications and risks of living donor nephrectomy. *Transplantation*. 1997; 64(8):1124-1128.
14. Matas AJ, Bartlett ST, Leichtman AB, Delmonico FL. Morbidity and mortality after living kidney donation, 1999-2001: survey of United States transplant centers. *Am J Transplant*. 2003;3(7):830-834.
15. Steiner CA, Bass EB, Talamini MA, Pitt HA, Steinberg EP. Surgical rates and operative mortality for open and laparoscopic cholecystectomy in Maryland. *N Engl J Med*. 1994;330(6):403-408.
16. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med*. 2002;346(15):1128-1137.
17. Lucas FL, Stukel TA, Morris AM, Siewers AE, Birkmeyer JD. Race and surgical mortality in the United States. *Ann Surg*. 2006;243(2):281-286.
18. Nathan H, Frederick W, Choti MA, Schulick RD, Pawlik TM. Racial disparity in surgical mortality after major hepatectomy. *J Am Coll Surg*. 2008;207 (3):312-319.
19. Sheikh K, Jiang Y, Bullock CM. Effect of comorbid and fatal coexistent conditions on sex and race differences in vascular surgical mortality. *Ann Vasc Surg*. 2007;21(4):496-504.
20. Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical risk factors, morbidity, and mortality in elderly patients. *J Am Coll Surg*. 2006;203(6):865-877.
21. Nguyen GC, Laveist TA, Segev DL, Thuluvath PJ. Race is a predictor of in-hospital mortality after cholecystectomy, especially in those with portal hypertension. *Clin Gastroenterol Hepatol*. 2008; 6(10):1146-1154.
22. Bay WH, Hebert LA. The living donor in kidney transplantation. *Ann Intern Med*. 1987;106(5): 719-727.
23. Schulam PG, Kavoussi LR, Cheriff AD, et al. Laparoscopic live donor nephrectomy: the initial 3 cases. *J Urol*. 1996;155(6):1857-1859.
24. Ratner LE, Kavoussi LR, Schulam PG, Bender JS, Magnuson TH, Montgomery R. Comparison of laparoscopic live donor nephrectomy versus the standard open approach. *Transplant Proc*. 1997;29(1-2): 138-139.