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A meta-analysis of renal outcomes in living kidney donors

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Abstract

Given the increased burden of end-stage renal disease (ESRD), renal outcomes of kidney donation by living donors are of particular interest. PubMed, ProQuest, MEDLINE, EMBASE, Chinese national knowledge infrastructure, and Wanfang databases were searched for clinical outcomes of living kidney donors (LKDs) including renal death, ESRD, proteinuria/albuminuria, and renal function after donation. We included 62 studies from 19 countries involving 114,783 kidney donors and nondonors to evaluate the renal consequences less than 6 months, 6 months to 5 years, 5 to 10 years, and 10 years onward after donation. The pooled data showed that uninephrectomy significantly decreased glomerular filtration rate and creatinine clearance rate in parallel with increased serum creatinine concentration (all $P < 0.05$). The drastic changes in renal function occurred within 6 months rather than 5 to 10 years after donation. Ten years and onward, rate of proteinuria/albuminuria increased gradually: microalbuminuria from 5.3% to 20.9%, proteinuria from 4.7% to 18.9%, and overt proteinuria from 2.4% to 5.7% (all $P < 0.05$). Prevalence of ESRD was 1.1%. All-cause mortality was 3.8% and all the renal deaths on average occurred 10 years postnephrectomy. LKDs might have aggravated glomerular filtration and creatinine clearance within 6 months after donation. Five years and onward, albuminuria, proteinuria, ESRD, and death might be the major concerns of LKDs. Long-term studies may clarify the survival time after donation.

Abbreviation: Ccr = creatinine clearance rate, CI = confidence interval, ESRD = end-stage renal disease, GFR = glomerular filtration rate, LDKT = living donor kidney transplantation, LKD = living kidney donor, sCr = serum creatinine, WMD = weighted mean difference.

Keywords: albuminuria, end-stage renal disease, glomerular filtration rate, kidney transplantation, living kidney donor

1. Introduction

Patients with end-stage renal disease (ESRD) outnumber deceased kidney donors available for transplantation.[1] Living donor kidney transplantation becomes an important option for ESRD treatment, owing to prolonged waiting times on transplant list, superior outcomes for recipients, and evolving criteria for donor acceptance.[2–4] Increasing transplantations should not mean increasing risk to donors. A recent study highlights an increased cumulative incidence and lifetime risk of ESRD following donation.[5] Previously, we have reported that uninephrectomized rats progressively developed renal impairments and glomerulosclerosis accompanied by insulin resistance, hyperglycemia, hyperlipidemia, fat redistribution, and remnant kidney cancer.[6–11] Definitive outcome assessment is precluded by lacking of a comprehensive system or registry for follow-up. Safety remains in obscurity because of the inferences at single centers with limited generalizability, restrictive sample size, and inappropriate comparison groups.[12] All these findings generate concerns about postnephrectomy outcomes with special focus on the remnant kidney. Therefore, we conducted a systematic review and meta-analysis to investigate the short-, mid-, and long-term changes in renal function relative to proteinuria/albuminuria, ESRD, and mortality in living kidney donors (LKDs).

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement was used as a guide in the present study that ensures a standard method for transparent and complete reporting of systematic reviews and meta-analyses.[13] The present study was approved by the Ethics Committee Board of Guilin Medical University (GLMC20120308HL). We had reviewed each included studies and found 19 studies mentioned in the methods section that ethical approval and written informed consent were obtained.

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SSL, YMH, MW, and JS equally contributed to this work.

LSS searched the studies, performed the meta-analyses, and wrote the manuscript. WM, SJ, and SY checked the studies and revised the manuscript. HYM and LBJ performed the literature searching. ZHL designed the project, revised the manuscript, and approved for submission.

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2.1. Search strategy

Four reviewers (LSS, HYM, SJ, and LBJ) systematically searched 5 English databases including PubMed, ProQuest, Cochrane Library, MEDLINE, and EMBASE; 4 Chinese and Japanese databases including Wanfang database, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, and Japan Science and Technology Information Aggregator Electronic; and other electronic databases including the United Network for Organ Sharing and Organ Procurement and Transplantation Network. The search terms "living kidney donation," "living kidney transplantation," "renal transplantation," "nephrectomy," and "unilateral nephrectomy" were used in various combinations with "renal outcomes," "renal function," "kidney function," "creatinine clearance rate," "serum creatinine," "plasma creatinine," "glomerular filtration rate," "proteinuria," "albuminuria," "ESRD," "mortality," and "death." In addition, relevant studies were also identified through manual search of the bibliographies and reference lists.

2.2. Eligibility criteria

All published articles had to meet the following inclusion criteria[1]: original interventions were conducted with comparing renal outcomes before and after donation or between donors and nondonors[2]; available data were the remnant kidney outcomes including glomerular filtration rate (GFR), estimated GFR, creatinine clearance rate (Ccr), serum creatinine (sCr), and urinary protein excretion[3]; reports showed rate of mortality, ESRD and proteinuria/albuminuria, or reports disclosed sufficient data to calculate these values; and[4] one of 4 postnephrectomy durations was defined by <6 months (short term), 6 months to 5 years (mid-term), 5 to 10 years (prolonged term), and >10 years (long-term). For the LKDs, time at risk was accrued from the date of uninephrectomy. Nondonors were accrued from the enrollment into study. All potential articles were in English or Chinese and published in their entirety. If there are multiple publications from the same 1 investigation, we cited the most representative publication with largest number of donors and longest time of follow-up.

Literatures meeting the following criteria were excluded: nonclinical nature, duplication, studies that did not investigate duration after donation as a variable or renal function as an outcome, nonhuman studies, unclear of outcome evaluation, and nonoriginal reports including reviews, editorials, letters, and commentaries. The chance-corrected agreement between 4 reviewers for study inclusion was applicative (kappa = 0.87).

Initially, we downloaded 1271 full-text articles of potential studies, of which 975 publications were excluded due to nonclinical nature (Fig. 1). After detailed evaluation, 234 more were subsequently excluded according to our inclusion and exclusion criteria. Eventually, 62 studies published from 1973 to 2014 and from 19 countries involving a total of 114,783 participants were included in this meta-analysis.

2.3. Data extraction

Four coauthor of this study (LSS, HYM, SY, and SJ) independently extracted the data from the 62 eligible studies. The extracted data were as follows: study descriptions, participants' characteristics, follow-up duration after donation, renal function measurements, and methods of these measurements and calculation (Tables 1 and 2). To avoid age-related kidney dysfunction after donation, we conducted comparison of long-term outcomes between donors and nondonors.

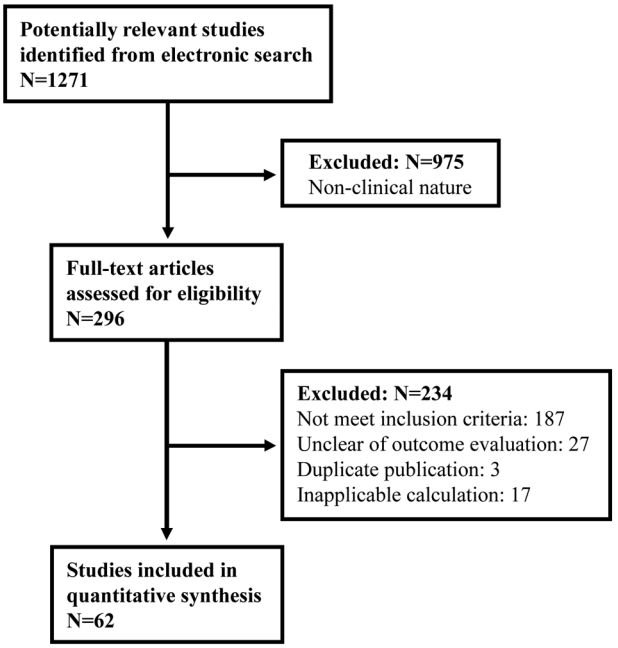

Figure 1. Flow chart of study selection process.

2.4. Outcome measures

The primary outcomes included rates of mortality, ESRD, and proteinuria/albuminuria. The secondary outcomes were the remnant kidney function parameters such as GFR, Ccr, and sCr.

2.5. Validity assessment

We used the risk of bias assessment tool for nonrandomized studies to evaluate the quality of the included studies for the purpose of reliability, feasibility, and validity.[14] The risk of bias assessment tool for nonrandomized studies tool tests the selection of participants, confounding variables, measurements of intervention, blinding of outcome assessments, incomplete outcome data, and selective reporting.

2.6. Statistical analysis

The fixed-effect or random-effects models with generalized least-squares estimation were used to calculate the summarized mean estimates. Q-test was used to compare the mean effect between different duration after donation. In order to explore the potential sources of heterogeneity, subgroup meta-analyses and meta-regression analyses were conducted based on participants' gender, age, geographic region, measurements, and quality of the studies. Additionally, we also conducted sensitivity analyses to assess the robustness in this study.

The heterogeneity among the literatures was examined using I^2 statistics. $I^2 < 50\%$ indicates low heterogeneity and fixed-effect model as appropriate, random-effects model on the contrary. Publication bias was assessed by visual inspection of funnel plot and then tested by the Egger regression and trim and fill analyses. The P values for the Egger test are less than 0.05 in the presence of

publication bias. All of the statistical analyses were performed using the Review Manager 5 software package (version 5.1; The Nordic Cochrane Center, Copenhagen, Denmark) and Stata 11.0SE statistical software package (StataCorp, College Station, TX).

3. Results

3.1. Study description and quality and bias assessment

3.1.1. Study characteristics. Tables 1 and 2 show the 62 studies included 114,783 participants. Among the 62 studies (Table 2), 62 showed comparison between predonation and postdonation (GFR in 23, Ccr in 22, sCr in 43, and urinary protein excretion in 6), while 8 had comparison of donors and nondonors (GFR in 4, Ccr in 5, sCr in 6, and urinary protein excretion in 3). Rate of ESRD, albuminuria/proteinuria, and mortality were documented in 12, 26, and 19 studies, respectively.

In general, 72.6% commendably followed the total number of donors, 47.3% depicted the characteristics of donors lost to follow-up, 38.4% described types of surgery, and 74.7% had scheduled renal outcomes measured. Definitions of albuminuria/proteinuria were reported in 77.2%, and criteria for ESRD were described in 52.3%. Details of measuring GFR, Ccr, sCr, and urinary protein excretion were found in 87.0%, 54.5%, 97.3%, and 87.4%, respectively.

3.2. Methodological quality and bias of studies

In this meta-analysis of the 62 studies, the risk of bias analysis revealed concerns about low- versus high-risk of bias for selection of participants (96.8% vs 3.2%), confounding variables (57.1% vs 4.8%), measurements of intervention (98.4% vs 0), blinding of outcome assessments (98.4% vs 1.6%), incomplete outcome data (63.5% vs 4.8%), and selective reporting (95.2% vs 4.8%), as shown in Fig. 2 and Supplemental Table 1, http://links.lww.com/MD/B21.

The vast majorities of the funnel plots assessed by Egger regression test and trim and fill analysis showed no significant publication bias (Table 3).

3.3. Changes of renal functions between pre- and postdonation

Table 3 summarizes the outcomes along with time after donation. A random-effect model was selected due to the heterogeneity of reporting GFR ($I^2=99\%$), Ccr ($I^2=98\%$), urinary protein excretion ($I^2=98\%$), and sCr ($I^2=98\%$). Pooled analysis revealed a significant reduction of GFR (weighted mean difference [WMD], −14.80; 95% confidence interval [CI], −19.89 to −9.70) and Ccr (WMD, −22.32; 95% CI, −25.65 to −18.99) in parallel to elevation of urinary protein excretion (WMD, 24.25; 95% CI, 3.32–45.17) and sCr (WMD, 22.10; 95% CI, 19.64–24.57).

Consistently, the largest absolute number of WMD for GFR, Ccr, and sCr generated within 6 months postnephrectomy while urinary protein excretion progressively aggravated along with time after donation (Table 3, Fig. 3).

3.4. Comparison of renal functions between donors and nondonors

Eight studies included 792 donors and 562 nondonors 5 to 20 (mean 10) years after donation. Table 4 shows the donors contrasting nondonors to have decreased GFR and Ccr in parallel to increased sCr and urinary protein excretion (all $P<0.031$). Funnel plot was detected by Egger test and trim and fill analysis (Table 4).

3.5. Rate of proteinuria postdonation

The cut-off points and rates of proteinuria and albuminuria in relation to donation were given in 26 studies of 5337 LKDs. Table 1 shows that rate of microalbuminuria, proteinuria, and overt proteinuria increased along with time after donation ($P<0.050$).

3.6. Rate of ESRD postdonation

Rate of ESRD was described in 12 studies. A total of 516 donors had defined ESRD diagnosed 14±9 years after donation. In general, total pooled rate of ESRD was 1.1% 10 years onward and 0.5% 6 months to 5 years after donation (Table 1).

Table 1

Summary of renal outcomes after donation.

Time after donation			5 to 20 years	>10 years	5 to 10 years	6 months to 5 years	<6 months
Comparison			Donors vs nondonors	Post- vs predonation	Post- vs predonation	Pre- vs postdonation	Pre- vs postdonation
Glomerular filtration rate			Decrease	Decrease	Not significant ($P=0.490$)	Decrease	Decrease
Creatinine clearance rate			Decrease	Decrease	Decrease	Decrease	Decrease
Serum creatinine concentration			Increase	Increase	Increase	Increase	Increase
Urinary protein excretion			Increase	Increase	Increase	Not significant ($P=0.340$)	Not significant ($P=0.850$)
Rate	Microalbuminuria		No reports	20.9%*	25.6%*	8.7%*	5.3%*
	Macroalbuminuria		No reports	4.1%*	No reports	No Reports	No reports
	Proteinuria	>150 mg/d	OR: 1.64 (95% CI: 0.94–2.86)*	18.9%*	18.7%*	4.7%*	No reports
		>300 mg/d		5.7%*	14.0%	2.4%*	No reports
	ESRD		No reports	1.1%*	No reports	0.5%	No reports
	All-cause mortality		3.8% on average 10 years after donation				

Proteinuria was defined as total urinary protein excretion >150 and >300 mg/d, overt proteinuria was defined as >300 mg/d.
CI = confidence interval, ESRD = end-stage renal disease, OR = odds ratio
* $P<0.05$.

Table 2

Characteristics of the 63 studies included in the meta-analysis.

Source	City, country	No. participants	Lost to follow-up (%)	Women (%)	Age at donation (year)	Duration of follow-up	Outcome	GFR estimation	Ccr estimation	Proteinuria
Abdu et al, 2011	Witwatersrand, South Africa	571	59.7	55.0	35±8	(9±6) Y	Ccr, sCr, ESRD	NR	NR	NR
Alnimri et al, 2011	New York, America	341	69.8	63.1	40±10	1 Y	GFR	MDRD formula	NR	NR
Antoniewicz et al, 2012	Warsaw, Poland	33	0	41.7	62	3 M	GFR, sCr	MDRD formula	NR	NR
Azar et al, 2007	Tabriz, Iran	86	0	33.0	29±5	(17±5) M	Mortality, proteinuria	NR	NR	24-hour urine
Bieniasz et al, 2009	Warsaw, Poland	46	19.6	61.0	39 (25–57)	(1–24) M	sCr, ESRD, mortality, proteinuria	NR	NR	NR
Chen et al, 2008	Guangzhou, China	89	0	57.3	42 (23–54)	1 D–3 M	GFR, Ccr, sCr	(99 m)Tc-DTPA	NR	NR
Chien et al, 2010	Taoyuan, Taiwan	51	0	47.1	45 (23–68)	22 (1–72) M	Ccr, sCr	NR	24-hour Ccr	NR
Chung et al, 2013	Seoul, Korea	207	47.8	52.8	39±11	(7±4) M	GFR, sCr	MDRD formula	NR	NR
Connie et al, 2004	Washington, America	78	0	NR	37	>20 Y	Ccr, sCr, proteinuria	NR	24-hour Ccr	24-hour urine
Dunn et al, 1986	Tennessee, America	314	20.3	43.3	34 (18–67)	(53±38) M	Ccr, sCr, mortality, proteinuria	NR	24-hour Ccr	24-hour urine
Edgren et al, 1976	Helsinki, Finland	46	NR	30.4	45 (20–70)	3 Y	Ccr	NR	24-hour Ccr	NR
Enger et al, 1973	Oslo, Norway	26	NR	34.6	42 (19–65)	4 Y	Ccr, sCr	NR	24-hour Ccr	NR
Fang et al, 2011	Henan, China	68	0	21.0	19–74	1Y	sCr, proteinuria	NR	NR	24-hour urine
Fehrman-Ekholm et al, 2006	Huddinge, Sweden	1112	0	16.7	54 (31–68)	20 (14–27) Y	ESRD	NR	NR	NR
Fehrman-Ekholm et al, 2010	Huddinge, Sweden	1110	0	NR	62±12	(14±9) Y	GFR, ESRD, mortality, proteinuria	MDRD formula	NR	NR
Goldfarb et al, 2001	Cleveland, America	180	61.1	58.6	40±10	(25±3) Y	Ccr, sCr, mortality, proteinuria	NR	Cockcroft-Gault	24-hour urine
Gossmann et al, 2005	Frankfurt, Germany	152	11.2	71.0	45±11	(11±7) Y	GFR, Ccr, sCr, mortality, proteinuria	MDRD formula	24-hour Ccr	24-hour urine
Guo et al, 2010	Shandong, China	62	0	73.3	21–78	1 W-12 M	GFR, sCr, mortality	NR	NR	NR
Hakaim et al, 1997	Massachusetts, America	16	NR	NR	39±5	(6–60) D	sCr, mortality	NR	NR	NR
Han et al, 2008	Shanghai, China	60	56.7	69.2	40±7	(4±2) Y	sCr, mortality	NR	NR	NR
Hassan et al, 2009	Minnesota, America	3698	NR	NR	53±10	(12±9) Y	GFR, sCr, ESRD, mortality, proteinuria	MDRD formula	NR	An urine sample
Hida et al, 1982	Tokyo, Japan	34	0	58.8	24–66	6 M-5 Y	sCr	NR	NR	NR
Hu et al, 2009	Beijing, China	19	0	42.1	58 (55–69)	(1–48) W	Ccr, sCr, proteinuria	NR	NR	NR
Johnson et al, 1997	Minneapolis, America	871	NR	56.0	38 (17–74)	5 (2–14) D	Mortality	NR	NR	NR
Kim et al, 2012	Seoul, Korea	1356	88.6	NR	NR	1 Y	ESRD	NR	NR	NR
Li et al, 2007	Guangzhou, China	93	0	44.0	53±13	(1–12) M	Ccr, Proteinuria	NR	24-hour Ccr	NR
Li et al, 2010	Chengdu, China	107	0	45.8	20–64	(1–12) M	sCr, proteinuria	NR	NR	24-hour urine
Lu et al, 2009	Nanjing, China	102	NR	68.6	52 (34–62)	1D-8Y	GFR, sCr	NR	NR	NR
Meng et al, 2009	Wuhan, China	63	0	22.2	36.0±11.5	1W, 1Y	sCr, proteinuria	NR	NR	NR
Miller et al, 1985	New York, America	46	0	67.4	46 (21–78)	(6±3) Y	sCr, proteinuria	NR	NR	24-hour urine
Mimran et al, 1993	Montpellier, France	18	0	55.6	47±3	(14±1) M	sCr, Ccr	NR	NR	NR
Mohammad et al, 2009	California, America	601	83.7	64.0	44±11	(11±7) Y	GFR, sCr, proteinuria	MDRD formula	NR	NR
Muzaale et al, 2014	Baltimore, America	96217	0	NR	NR	8 Y	ESRD	NR	NR	NR
Najarian et al, 1992	Minneapolis, America	57	0	NR	61±8	(24±2) Y	Proteinuria	NR	NR	24-hour urine
O'Donnell et al, 1986	Johannesburg, South Africa	33	0	45.5	43±11	6 (3–18) Y	Ccr, GFR, sCr, mortality, proteinuria	NR	NR	24-hour urine
Ramcharan et al, 2002	Minneapolis, America	773	40.0	NR	NR	(29±4) Y	ESRD, mortality, proteinuria	NR	NR	NR
Rayhan et al, 2012	Xinjiang, China	57	3.5	46.0	32 (18–46)	(6–68) M	Ccr, sCr	NR	NR	NR
Rizvi et al, 2005 a	Karachi, Pakistan	736	0	47.6	36±11	(3±3) Y	Ccr, sCr, ESRD, proteinuria	24-hour Ccr	24-hour Ccr	24-hour urine
Rosenblatt et al, 2008	New York, America	1195	0	NR	42	16 (7–24) Y	ESRD	NR	NR	NR
Sahay et al, 2007	Hyderabad, India	50	0	56.0	41±8	63 (3–264) M	GFR, mortality, proteinuria	NR	24-hour Ccr, standard UV/P formula	NR

Source	City, country	No. participants	Lost to follow-up (%)	Women (%)	Age at donation (year)	Duration of follow-up	Outcome	GFR estimation	Ccr estimation	Proteinuria
Samhan et al, 1999	Hawaly, Kuwait	36	0	61.1	32 (21–63)	(3–30) D	sCr, mortality, proteinuria	NR	NR	24-hour urine
Siebels et al, 2003	Munich, Germany	160	0	66.7	51 (21–77)	38 (1–62) M	sCr, mortality, proteinuria	NR	NR	24-hour urine
Sobh et al, 1989	Mansoura, Egypt	65	0	53.0	26 (22–64)	23 (13–122) M	Ccr, sCr, proteinuria, GFR	NR	NR	24-hour urine
Song et al, 2008	Qingdao, China	61	0	73.8	47 ± 11	(15 ± 2) M	GFR, sCr	24-hour Ccr	NR	NR
Song et al, 2014	Sichuan, China	45	0	75.6	48 ± 8	1 W-1 Y	GFR, sCr	Cockcroft–Gault	NR	NR
Talseth et al, 1986	Oslo, Norway	74	8.1	47.0	46 (33–55)	11 (10–12) Y	Proteinuria	NR	NR	Ponceau S-method
Tan et al, 2011	Singapore	86	0	57.0	41 ± 10	6 (1–21) Y	GFR, Ccr, sCr, ESRD, mortality, proteinuria	MDRD formula	NR	24-hour urine
Tent et al, 2010	Groningen, Netherlands	253	0	57.0	NR	2 M	GFR, sCr	MDRD formula	NR	NR
Ter Wee et al, 1990	Amsterdam, Netherland	20	0	30.0	46 (22–72)	3 M	GFR, sCr	^{125}I-iothalamate, formula UV/120 × P	NR	NR
Wafa et al, 2011	Mansoura, Egypt	2000	0	52.4	22–59	16 (5–27) Y	ESRD, proteinuria	NR	NR	24-hour urine
Wang et al, 2007	Shenyang, China	250	0	40.0	45 ± 16	1 W	sCr	NR	NR	
Wang et al, 2008	Henan, China	30	0	60.0	NR	(2–85) M	Proteinuria	NR	NR	24-hour urine
Watnick et al, 1988	New Haven, America	29	24.1	45.0	NR	14 (9–18) Y	Proteinuria, GFR, Ccr, sCr	Insulin and PAH clearance	NR	NR
Wiesel et al, 1997	New York, America	118	43.2	NR	NR	(8 ± 1) Y	sCr, mortality	NR	NR	NR
Xia et al, 2002	Zhejiang, China	10	0	90.0	50 ± 4	1 W	Ccr, sCr	NR	NR	NR
Xiao et al, 2012	Guangzhou, China	84	0	36.0	33 ± 10	6 M	GFR	MDRD formula	NR	NR
Yasumura et al, 1988	Kyoto, Japan	247	0	66.0	50 ± 10	2 W	Ccr, mortality	NR	NR	NR
Yazawa et al, 2011	Kanagawa, Japan	63	42.9	63.9	58 ± 10	944 (279–3979) D	GFR, proteinuria	Equation from Japanese Society of Nephrology	NR	NR
Zhang et al, 2009	Guangzhou, China	46	0	33.0	35 ± 13	(7–10) D	GFR, Ccr, sCr	MDRD formula	Cockcroft-Gault	NR
Zhao et al, 2009	Guangzhou, China	251	0	53.4	47 (22–72)	10 D	GFR, Ccr, sCr	24 h urine	24-hour Ccr	NR
Zhao et al, 2010	Hefei, China	38	2.6	19.0	58 ± 13	3 M	GFR, sCr	(99 m)Tc-DTPA	NR	NR
Zhu et al, 2006	Wuhan, China	43	0	79.0	26–61	1 W	sCr	NR	NR	NR

Data are shown as mean ± standard deviation and n (range). Ccr = creatinine clearance rate, D = days, DTPA = diethylene triamine pentacetic acid, GFR = glomerular filtration rate, M = months, MDRD = modification of diet in renal disease, NR = no reports, PAH = p-aminohippuric acid, sCr = serum creatinine, UV = ultra violet, W = weeks, Y = years.

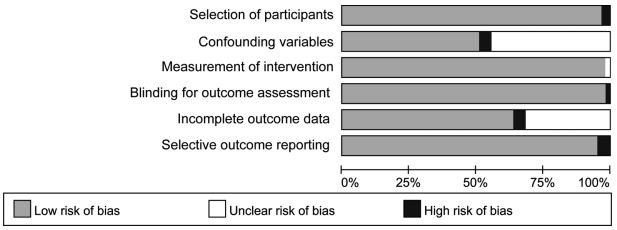

Figure 2. Risk of bias graph of all included quasi-randomized controlled trials using the risk of bias assessment for nonrandomized studies (RoBANS) tool.

3.7. Mortality after donation

Nineteen studies of 8098 donors addressed total mortality after donation. All-cause mortality was reported less than 10.0% in the majority of studies. The pooled overall mortality was 3.8% (95% CI, 1.15%–6.45%). Nephrectomy-related deaths were extracted from 15 studies involving 5301 donors. Among 19 studies reporting mortality, 2 studies revealed deaths attributable to renal failure. The pooled renal death rate was 0.3% and the renal deaths on average occurred 10 years after donation. One donor died of renal failure 32 years after nephrectomy at the age of 76.[15]

3.8. Potential sources of heterogeneity and sensitivity analyses

Subgroup analysis (Table 5) and meta-regression analyses (Table 6) disclosed sex, age at donation, and study location as potential sources of between-study variance in this study. Age at donation could account for 24.4% of the heterogeneity for Ccr and 18.6% of the heterogeneity for sCr. Moreover, 61.2% of the heterogeneity for urinary protein excretion could be explained by study location. In contrast, sex, age at donation, and study location had no significant impact on the heterogeneity exploration of GFR (Table 6).

After exclusion of 3 studies that had a low risk of bias, sensitivity analysis yielded similar results of Ccr, GFR, sCr, and urinary protein excretion after donation (data not shown). Stepwise elimination of the studies was also used in the sensitivity meta-analysis. Overall, the sensitivity analysis yielded a nearly identical set of pooled WMD for Ccr, GFR, sCr, and urinary protein excretion (Fig. 4).

4. Discussion

4.1. Summary of findings

Findings from this study of LKDs are as follows[1]: donation-induced renal dysfunction is evident by decreased GFR and Ccr in parallel to increased urinary protein excretion and sCr concentration[2]; the drastic change in the donors' renal function consistently occurs within 6 months after donation rather than 6 months to 10 years postnephrectomy[3]; the rate of micro-albuminuria, proteinuria, and ESRD gradually increase at 5-year intervals postkidney donation; and[4] the LKDs would see less than 5.0% of overall morality and less than 1.0% of renal deaths on average 10 years after donation. In the present study, we also have performed subgroup analysis and meta-regression to validate the contribution of women proportion, age at donation,

Table 3

Changes in donors' renal function in relation to duration after donation.

	No. of study	N		Type of model	Pooled-WMD (95% CI) post- vs predonation	P^*	I^2 (%)	$P^\dagger$	No. of trim‡
		Post-	Pre-						
GFR									
Donation <6 months	14	1961	1961	Random	−18.64 (−27.34, −9.94)	<0.001	99	0.386	0
Donation 6 months to 5 years	13	1530	1792	Random	−12.22 (−20.92, −3.52)	<0.001	99	0.193	2
Donation 5 to 10 years	3	270	599	Random	−6.16 (−23.80, 11.48)	0.490	99	0.918	0
Donation 10 years longer	4	1116	1316	Random	−17.84 (−27.39, −8.28)	<0.001	98	0.175	0
Total	23	4877	5668	Random	−14.80 (−19.89, −9.70)	<0.001	99	0.116	3
Ccr									
Donation <6 months	11	1296	1296	Random	−28.59 (−35.21, −21.97)	<0.001	98	0.718	0
Donation 6 months to 5 years	11	1391	1410	Random	−18.42 (−24.16, −12.69)	<0.001	98	0.660	0
Donation 5 to 10 years	6	1325	1372	Random	−18.23 (−28.92, −7.55)	<0.001	96	0.331	0
Donation 10 years longer	3	262	283	Fixed	−22.36 (−26.59, −18.13)	<0.001	51	0.587	0
Total	22	4274	4361	Random	−22.32 (−25.65, −18.99)	<0.001	98	0.857	0
Urinary protein excretion									
Donation <6 months	2	357	357	Fixed	−1.04 (−12.04, 9.97)	0.850	53	0.580	0
Donation 6 months to 5 years	2	950	950	Random	7.22 (−7.53, 21.96)	0.340	86	0.190	0
Donation 5 to 10 years	1	55	55	Random	48.82 (38.01, 59.63)	<0.001	–	–	1
Donation 10 years longer	2	168	168	Random	99.48 (0.51, 198.46)	0.050	99	–	1
Total	6	2266	2309	Random	24.25 (3.32, 45.17)	0.020	98	0.498	0
sCr									
Donation <6 months	27	3937	3937	Random	27.55 (23.50, 31.59)	<0.001	97	0.015	11
Donation 6 months to 5 years	27	3147	3471	Random	17.97 (14.60, 21.34)	<0.001	97	0.280	5
Donation 5 to 10 years	9	1474	1785	Random	20.22 (12.45, 27.99)	<0.001	98	0.004	4
Donation 10 years longer	5	615	636	Random	14.26 (8.89, 19.54)	<0.001	85	0.203	0
Total	43	9178	9824	Random	22.10 (19.64, 24.57)	<0.001	98	<0.001	22

Ccr = creatinine clearance rate, CI = confidence interval, GFR = glomerular filtration rate, sCr = serum creatinine, WMD = weighted mean difference.

* Derived from *z* test.

† Derived from Egger test.

‡ Derived from trim and fill analysis.

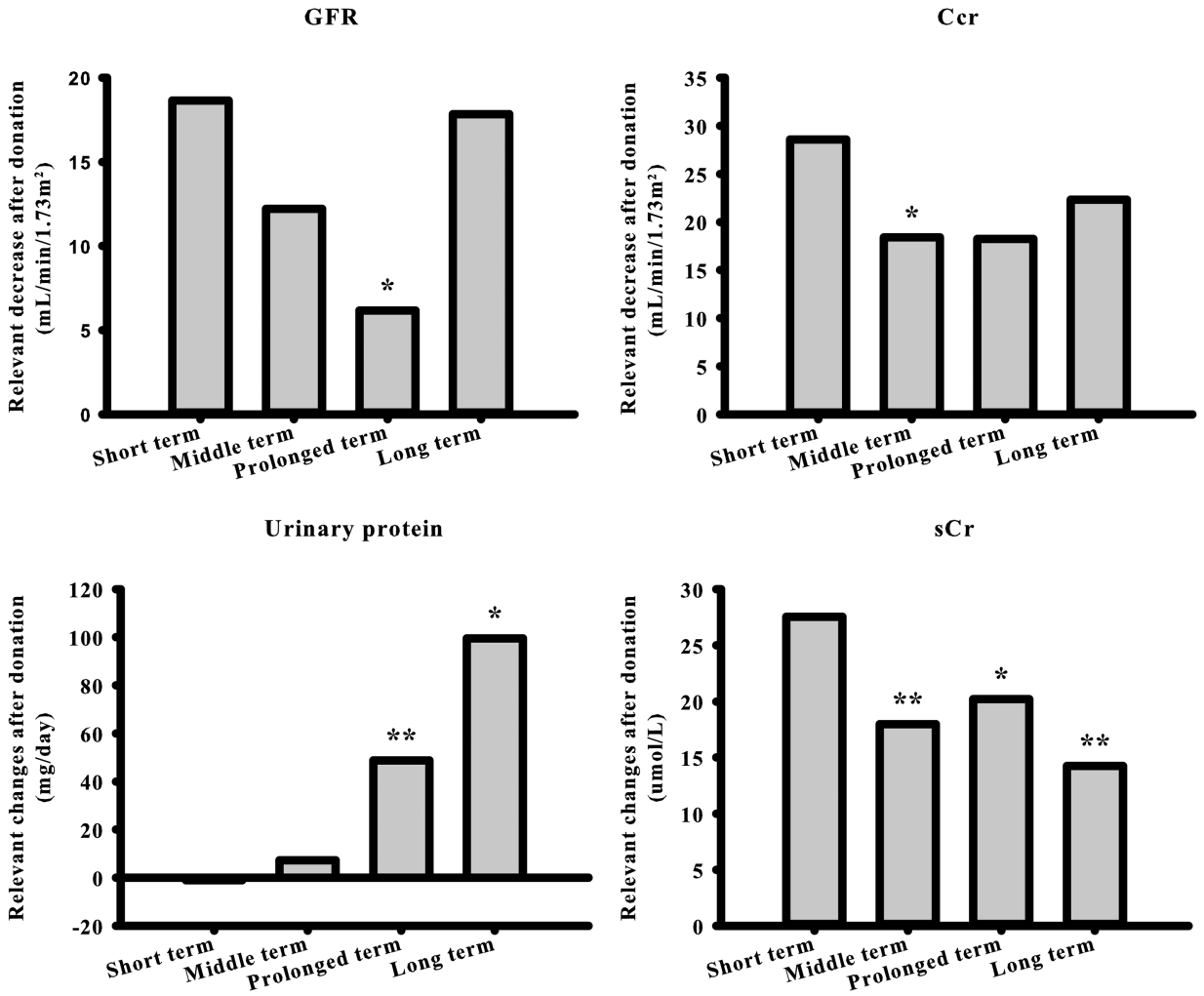

Figure 3. Changes of renal function in relation to different duration after donation. *P* value derived from *Q*-test by comparing with short-term group. $^{*}P<0.05$, $^{**}P<0.001$. Ccr = creatinine clearance rate, GFR = glomerular filtration rate, sCr = serum creatinine.

and study location to heterogeneity among the studies and between-study variance. In general, publication bias, as examined by funnel plots and sensitivity analyses, is unlikely in most studies included for this meta-analysis.

4.2. Interpretation of findings

The drastic renal dysfunction observed within 6 months after donation indicates incomplete compensation of the remnant kidney. It may take a few months for the remnant kidney to compensate for glomerular filtration and creatinine clearance. Indeed, there is a humoral substance acting specifically on the kidney that promotes renal compensatory hyperplasia in uninephrectomized rats.[16] The renal compensatory hyperplasia may ameliorate the stressful demand for creatinine clearance at the cost of glomerular hyperfiltration subsequently followed by increased urinary protein excretion.

Table 4

Changes in renal function between donors and nondonors 5 to 20 years after donation.

	No. of study	n		Type of model	Pooled-WMD (95% CI) donors vs nondonors	P^{*}	I^2 (%)	$P^{\dagger}$	No. of trim‡
		Donor	Nondonor						
GFR (mL/min·1.73 m^2)	4	610	419	Random	−14.60 (−16.76, −12.44)	<0.001	85	0.107	0
Ccr, (mL/min·1.73 m^2)	5	235	205	Random	−15.49 (−29.46, −1.52)	0.030	93	0.353	0
Urinary protein excretion (mg/d)	3	106	83	Random	19.91 (5.44, 34.38)	0.007	96	0.557	0
sCr (μmol/L)	6	250	220	Random	14.87 (4.17, 25.57)	0.006	94	0.007	0

Ccr = creatinine clearance rate, CI = confidence interval, GFR = glomerular filtration rate, sCr = serum creatinine, WMD = weighted mean difference.

* Derived from *z* test.

† Derived from Egger test.

‡ Derived from trim and fill analysis.

Table 5

Subgroup analyses to explored sources of heterogeneity.

Subgroups	No. of study	Pooled-WMD (95% CI)	P^*	I^2 (%)
GFR				
Sex				
Women <50%	6	−18.22 (−30.51, −5.93)	0.004	97.6
Women ≥50%	15	−12.41 (−18.67, −6.14)	<0.001	99.3
Mean age at donation (year)				
Middle†	16	−22.45 (−30.14, −14.76)	<0.001	99.0
Elderly‡	8	−7.46 (−14.56, −0.36)	0.040	99.3
Location				
Africa	–	–	–	–
Asia	17	−13.88 (−19.80, −7.96)	<0.001	99.2
America	3	−24.66 (−30.41, −18.92)	<0.001	90.9
Europe	5	−14.87 (−30.11, 0.38)	0.056	99.1
Ccr				
Sex				
Women <50%	19	−21.45 (−26.25, −16.66)	<0.001	98.1
Women ≥50%	6	−26.13 (−30.52, −21.74)	<0.001	84.4
Mean age at donation (year)				
Middle†	9	−28.84 (−32.05, −25.66)	<0.001	93.9
Elderly‡	13	−19.63 (−24.62, −14.65)	<0.001	97.7
Location				
Africa	3	−7.89 (−20.51, 4.74)	<0.001	88.0
Asia	15	−22.59 (−27.03, −18.14)	<0.001	98.3
America	3	−32.73 (−44.43, −21.03)	<0.001	92.1
Europe	4	−27.42 (−35.67, −19.18)	0.016	71.1
Urinary protein excretion				
Sex				
Women <50%	2	3.93 (−5.95, 13.80)	0.436	80.3
Women ≥50%	4	59.80 (3.82, 115.78)	0.036	98.3
Location				
Africa	–	–	–	–
Asia	5	8.51 (−2.60, 19.62)	0.133	90.8
America	2	99.48 (0.51, 198.46)	0.049	99.0
Europe	–	–	–	–
sCr				
Sex				
Women <50%	17	19.96 (16.15, 23.76)	<0.001	97.4
Women ≥50%	27	24.21 (21.01, 27.41)	<0.001	96.4
Mean age at donation (year)				
Middle†	36	21.00 (17.95, 24.04)	<0.001	97.0
Elderly‡	9	25.92 (22.51, 29.32)	<0.001	95.8
Location				
Africa	3	19.79 (14.19, 25.39)	<0.001	56.5
Asia	32	21.80 (18.97, 24.62)	<0.001	97.9
America	8	17.75 (11.89, 23.61)	<0.001	93.0
Europe	8	32.65 (23.49, 41.81)	<0.001	94.3

Ccr = creatinine clearance rate, CI = confidence interval, GFR = glomerular filtration rate, sCr = serum creatinine, WMD = weighted mean difference

* Derived from the *z* test.

† Middle, <50 years.

‡ Elderly, ≥50 years.

Table 6

Meta-regression to explored sources of heterogeneity.

	Adjusted-R^2 (%)*	$P^\dagger$
GFR		
Model 1	1.0	0.228
Model 2	3.6	0.106
Model 3	0	0.699
Model 4	0	0.689
Ccr		
Model 1	0	0.978
Model 2	24.4	0.001
Model 3	0.9	0.230
Model 4	0	0.398
Urinary protein excretion		
Model 1	21.5	0.118
Model 2	13.4	0.253
Model 3	61.2	0.003
sCr		
Model 1	0	0.565
Model 2	18.6	<0.001
Model 3	0	0.442

Model 1 = covariate including proportion of women, model 2 = covariate including age at donation, model 3 = covariate including study location, model 4 = covariate including calculated formulas of GFR or Ccr. Ccr = creatinine clearance rate, GFR = glomerular filtration rate, sCr = serum creatinine.

* Proportion of between-study variance explained by covariates.

† *P* value derived from the joint test for all covariates with Knapp–Hartung modification.

Increased urinary protein excretion results in albuminuria and proteinuria. In the present study, the rate of albuminuria and proteinuria aggravated along with time after donation (Table 1). Proteinuria is a well-known marker of disease progression.[17] In this meta-analysis, the estimated rate of ESRD in donors was approximately 1.0%, higher than 0.1% to 0.5% reported in previous studies.[5,18,19] In fact, a recent study has shown similar findings of increased risk of ESRD in LKDs.[5] Moreover, the estimated lifetime risk of ESRD is higher in black donors than in white donors. Furthermore, the hazard of ESRD should not be neglected when considering conditions including older age, diabetes, obesity, and hypertension are no longer classified as absolute contraindications for living kidney donation.[20,21]

The lifetime impact of albuminuria/proteinuria should never be underestimated. Albuminuria/proteinuria is an important marker for endothelial dysfunction predisposing to the development of ESRD,[22,23] cardiovascular disease,[24–26] and cerebrovascular accident.[27] ESRD may lead to renal deaths whereas cardiovascular disease and cerebrovascular accident will escalate all-cause mortality. Although there is cautious optimism concerning perioperative mortality, survival, and the risk of ESRD in carefully screened kidney donors,[1,28,29] the lifetime risk for LKDs should be clarified in relation to coexisting medical conditions, age, gender, and race.[20,30]

In general population, renal function declines with aging. In the present study, comparisons between donors and nondonors have suggested donation-induced renal dysfunction echoed by the results of the paired comparisons (Tables 3 and 4). Although age is deliberately an important factor for renal outcomes, LKDs should aware the potential risks of donation-associated renal hyperplasia and deficiency.

4.3. Limitations and future studies

This study has potential limitations that may confound the results.[1] In addition to time after donation, factors such as comorbidities, genetic predisposition, ethnic, and racial disparities may also influence donor's renal outcomes. A recent study has demonstrated that persons with metabolic syndrome are at an increased risk for ESRD and death.[31] And, we plan further studies in this area considering more confounding factors to confirm this hypothesis.[2] Each transplantation center has established methods for the measurement of GFR, Ccr, sCr, and urinary protein excretion. Here we used model 4, stratified by different calculation of estimated GFR and Ccr, heterogeneity remains unchangeable. Details in methodological description in many studies included in this meta-analysis are unknown.

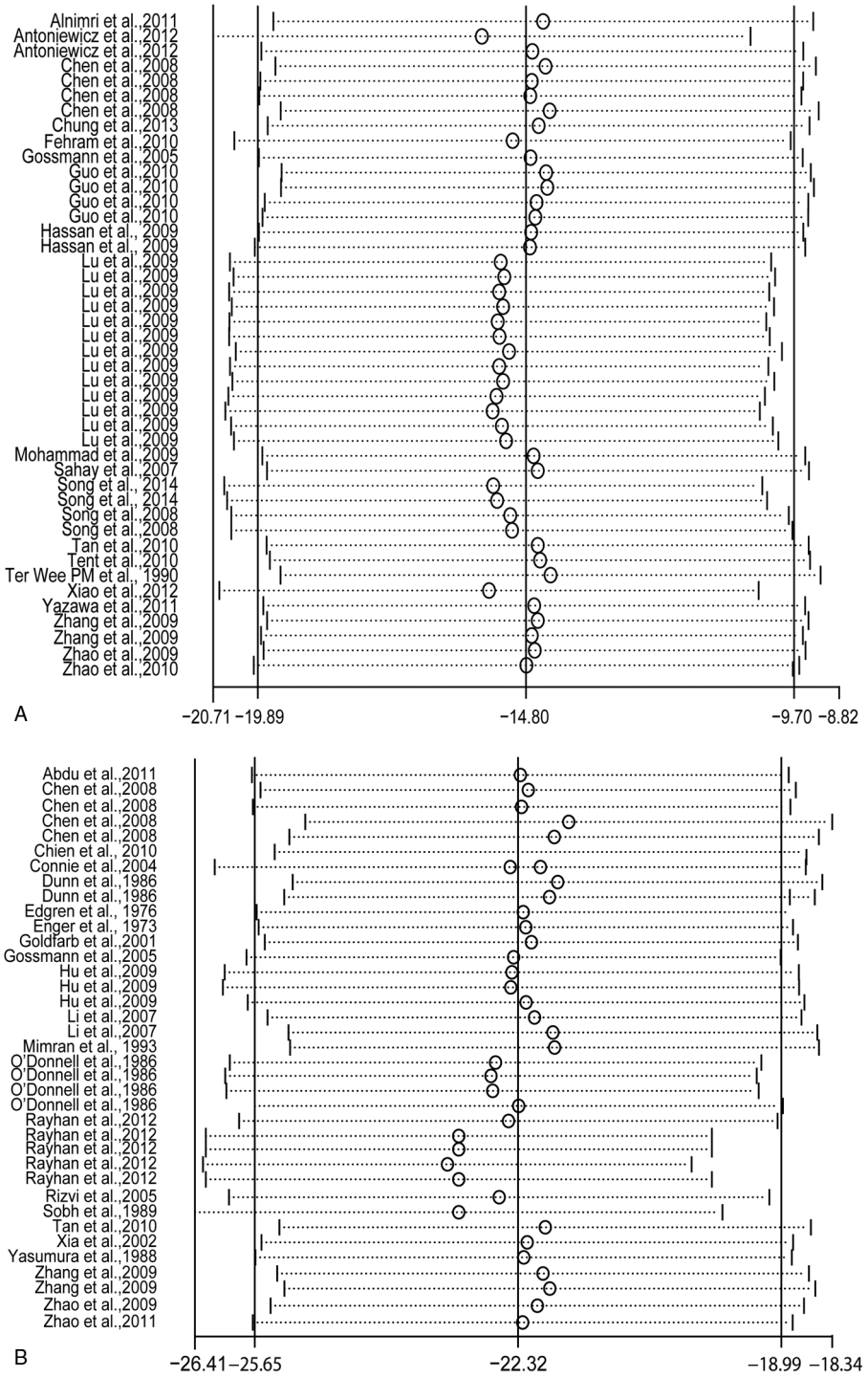

Figure 4. Sensitivity analyses for renal functions (A) glomerular filtration rate, (B) creatinine clearance rate, (C) urinary protein excretion, and (D) serum creatinine.

Moreover, estimated GFR calculated from the Cockroft-Gault and Modification of Diet in Renal Disease formulas are verified only in Caucasian population. This is particularly relevant when comparing GFR between worldwide donors. Although there is modified GFR estimating equation for Chinese patients with chronic kidney disease,[32] whether the equation is appropriate for Chinese kidney donors remains uncertain.[3] Albuminuria and proteinuria were not defined according to a uniform urine collection. A 24-hour urine collection was used in most of the included studies while a spot urine collection used in the others. Therefore, the rate of albuminuria and proteinuria in donors and nondonors may differ due to different urine collections. Hereby, we selected the studies using 24-hour urine collection for pooled analysis and the results unaltered.

In our future works, we will compare GFR estimated by the equations and GFR measured by the (99m)Tc-diethylene triamine pentacetic acid plasma clearance method. The mechanisms underlying uninephrectomy-induced glomerular hyperfiltration and subsequent proteinuria are also of our interest.

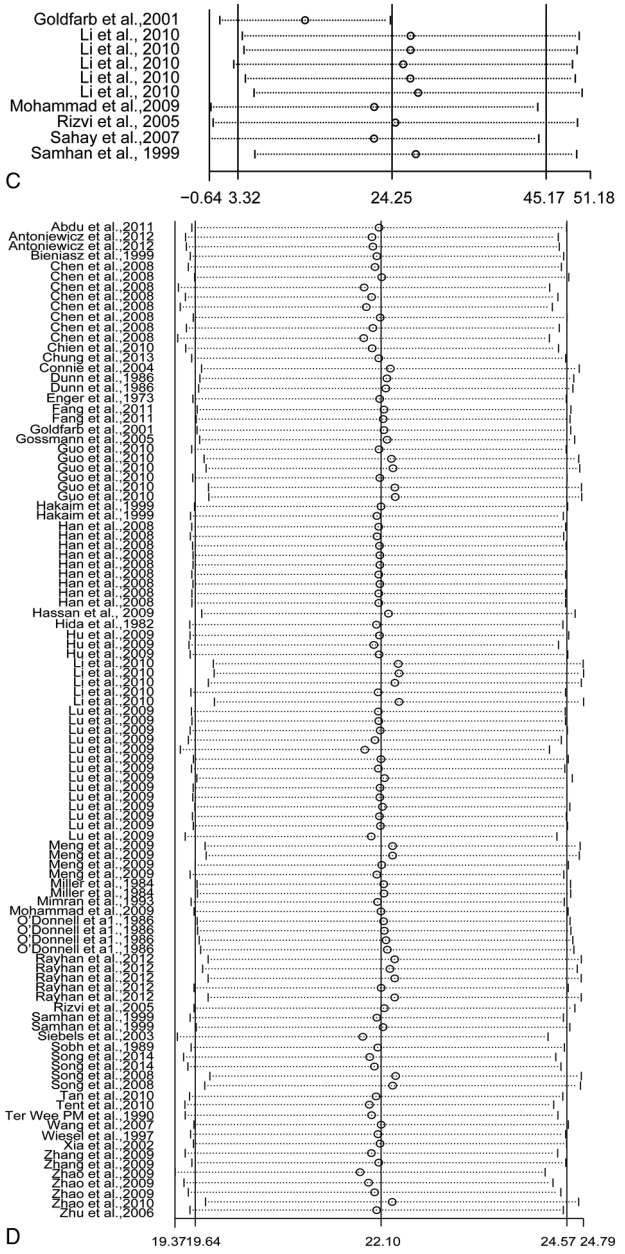

Figure 4. Continued.

5. Conclusions

LKDs may see renal deficiency aggravated within 6 months after donation, followed by an increased risk of proteinuria and ESRD 5 years and onward. These findings alert LKDs to avoid using renal toxic chemicals and to take cautious action for renal protection.

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References

[1] Segev DL, Muzaale AD, Caffo BS, et al. Perioperative mortality and long-term survival following live kidney donation. JAMA 2010;303:959–66.
[2] Stoves J, Lindley EJ, Barnfield MC, et al. MDRD equation estimates of glomerular filtration rate in potential living kidney donors and renal transplant recipients with impaired graft function. Nephrol Dial Transplant 2002;17:2036–7.
[3] Mitus A, Tefft M, Fellers FX. Long-term follow-up of renal functions of 108 children who underwent nephrectomy for malignant disease. Pediatrics 1969;44:912–21.
[4] Muzaale AD, Dagher NN, Montgomery RA, et al. Estimates of early death, acute liver failure, and long-term mortality among live liver donors. Gastroenterology 2011;142:273–80.
[5] Hosokawa Y, Tanaka N, Mibu H, et al. Follow-up study of unilateral renal function after nephrectomy assessed by glomerular filtration rate per functional renal volume. World J Surg Oncol 12:59.
[6] Dols LF, Ijzermans JN, Wentink N, et al. Long-term follow-up of a randomized trial comparing laparoscopic and mini-incision open live donor nephrectomy. Am J Transplant 2015;10:2481–7.
[7] Reese PP, Simon MK, Stewart J, et al. Medical follow-up of living kidney donors by 1 year after nephrectomy. Transplant Proc 2009;41:3545–0.
[8] Andersen MH, Bruserud F, Mathisen L, et al. Follow-up interviews of 12 living kidney donors one yr after open donor nephrectomy. Clin Transplant 2007;21:702–9.
[9] Godbole PP, Wilcox DT, Mushtaq I. Follow-up after unilateral nephrectomy in children: is an estimate of glomerular filtration rate necessary? BJU Int 2005;95:635–7.
[10] Vlaovic PD, Richardson RM, Miller JA, et al. Living donor nephrectomy: follow-up renal function, blood pressure, and urine protein excretion. Can J Urol 1999;6:901–5.
[11] Shirai T, Matuura S, Konomi G, et al. Follow-up study of unilateral nephrectomized patients. Preliminary report: long-term effects of unilateral nephrectomy. Fukuoka Shika Daigaku Gakkai Zasshi 1988;15:9–18.
[12] Robitaille P, Mongeau JG, Lortie L, et al. Long-term follow-up of patients who underwent unilateral nephrectomy in childhood. Lancet 1985;1:1297.
[13] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62:e1–34.
[14] Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol 2013;66:408–14.
[15] Mandelbrot DA, Pavlakis M, Danovitch GM, et al. The medical evaluation of living kidney donors: a survey of US transplant centers. Am J Transplant 2007;7:2333–43.
[16] Lowenstein LM, Stern A. Serum factor in renal compensatory hyperplasia. Science 1963;142:1479–80.
[17] Soliman AR, Fathy A, Khashab S, et al. Comparison of abbreviated modification of diet in renal disease formula (aMDRD) and the Cockroft-Gault adjusted for body surface (aCG) equations in stable renal transplant patients and living kidney donors. Ren Fail 2012;35:94–7.
[18] Rosenblatt GS, Nakamura N, Barry JM. End-stage renal disease after kidney donation: a single-center experience. Transplant Proc 2008;40:1315–8.
[19] Aiken JW, Vane JR. The renin–angiotensin system: inhibition of converting enzyme in isolated tissues. Nature 1970;228:30–4.
[20] Muzaale AD, Massie AB, Wang MC, et al. Risk of end-stage renal disease following live kidney donation. JAMA 2014;311:579–86.
[21] Lentine KL, Patel A. Risks and outcomes of living donation. Adv Chronic Kidney Dis 2012;19:220–8.
[22] Ritz E. Albuminuria and vascular damage—the vicious twins. N Engl J Med 2003;348:2349–52.
[23] Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA 2015;313:837–46.
[24] Matsushita K, van der Velde M, et al. Chronic Kidney Disease Prognosis ConsortiumAssociation of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010;375:2073–81.
[25] Jackson CE, Solomon SD, Gerstein HC, et al. Albuminuria in chronic heart failure: prevalence and prognostic importance. Lancet 2009;374:543–0.
[26] Nielsen SH, Jensen JE, Magid E. Episodic albuminuria in acute ischaemic heart disease. Lancet 1994;343:732.
[27] Remuzzi G, Weening JJ. Albuminuria as early test for vascular disease. Lancet 2005;365:556–7.

[28] Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. N Engl J Med 2009;360:459–69.
[29] Najarian JS, Chavers BM, McHugh LE, et al. 20 years or more of follow-up of living kidney donors. Lancet 1992;340:807–10.
[30] Lin J, Kramer H, Chandraker AK. Mortality among living kidney donors and comparison populations. N Engl J Med 2010; 363:797–8.
[31] Uchikura T, Kobayashi M, Hashiguchi M, et al. Expected value of the additional state in evaluating the method of quantification and uncertainty of additional states in an analytical model of grade I hypertension. J Pharm Health Care Sci 2015;1:3.
[32] Ma Y-C, Zuo L, Chen J-H, et al. Modified glomerular filtration rate estimating equation for chinese patients with chronic kidney disease. J Am Soc Nephrol 2006;17:2937–44.