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Long-Term Outcome of Live Kidney Donation in South Korea

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Statistical Analysis C
Data Interpretation D
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Background: Kidney donors may be at increased risk for end-stage renal disease (ESRD) as well as cardiovascular and all-cause mortality. In particular, data on long-term safety after kidney donation in Asian populations are lacking. We aimed to assess the safety of live kidney donation in Korean donors by using a matched control group.

Material/Methods: We conducted a retrospective cohort study using a hospital-based database (Asan Medical Center, Seoul, Korea) and a control group from the national health insurance claims database in South Korea. We analyzed the health status of 1608 kidney donors who underwent donation between September 1990 and December 2015, and we compared their characteristics with those of matched 6426 non-donors (1: 4 ratio). We also measured the glomerular filtration rate (GFR) with ^{51}Cr EDTA and urinary albumin excretion and assessed the prevalence of hypertension, diabetes, and general health status in 200 volunteer donors.

Results: Mortality was significantly lower in kidney donors compared with the matched controls (130.2 *vs.* 185.4 per 100,000 person-years, *P*=0.02). There was no significant difference in mortality if a donor had hypertension or was a current smoker at the time of donation. There was also no significant difference in ESRD (43.1 *vs.* 35.2 per 100,000 person-years, *P*=0.07) between the 2 groups regardless of hypertension and smoking status. Among the 200 donors with measured GFR, 11.5% had GFR values <60 ml/min/1.73 m^2 at 9.4±5.3 years after donation. Older age (*P*=0.001) and female sex (*P*=0.021) were significantly associated with GFR values <60 mL/min/1.73 m^2.

Conclusions: Mortality and ESRD were uncommon in carefully selected kidney donors. However, donors with pre-existing risk factors should be followed up more closely to ensure long-term safety.

MeSH Keywords: Kidney Failure, Chronic • Kidney Transplantation • Risk Factors • Tissue and Organ Procurement

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Background

Recognizing the long-term adverse effects of kidney donation is important for both selecting proper donors and ensuring their safety. Ibrahim et al. [1] demonstrated that after careful kidney donor selection, the survival and the risk of end-stage renal disease (ESRD) appeared to be similar to those in the general population, as most the donors had preserved glomerular filtration rate (GFR), normal albumin excretion, and excellent quality of life. In contrast, it has been reported that kidney donors are at increased long-term risk for ESRD as well as cardiovascular and all-cause mortality compared with non-donor controls who would have been an eligible donor [2,3]. Although living kidney donation is common in Asian countries, previous studies on the long-term outcomes of live kidney donation have been mostly performed in Western countries [4,5]. Recent analyses of long-term ESRD risk were reported in a prospective national cohort in the United States, and studies from Norway and the United States revealed increased risk of ESRD post donation compared with healthy controls [2,3]. In addition, the Donor Nephrectomy Outcomes Research (DONOR) Network has studied a number of potential postdonation problems mostly in Caucasians [6,7].

The increase in the rate of living-donor kidney transplantation has been accompanied by changes in donor characteristics, including racial diversity and more unrelated donors, and an increased number of donations from people with pre-existing morbidities including hypertension and obesity [8,9]. There are concerns that GFR decline after nephrectomy will subsequently have a direct impact on donors' health such as the development of diabetes and hypertension [4]. Although several guidelines for the assessment of live kidney donors have been suggested, pathophysiologic sequences after kidney donation have been less well-defined, especially for donors with pre-existing morbidities [8,10].

We aimed to assess the long-term safety of live kidney donation in Korean donors by using a matched control group selected from the general Korean population.

Material and Methods

Design and setting

We conducted a retrospective cohort study using a hospital-based database and the national health insurance claims database in South Korea, where its citizens have universal access to hospital care and physician services. The Korean National Health Insurance Service (NHIS) established the National Health Information Database (NHID), which incorporates all data from 5 databases [11]: an eligibility database, a national health screening database, a healthcare usage database, a long-term care insurance database, and a healthcare provider database. The NHID covers the entire population of Korea (50 million), and a representative 2% constitutes the NHIS-National Sample Cohort (NHIS-NSC) [12]. Under the current National Health Insurance Act, the data can be used without patients' individual consent only for research purposes. This study follows the STROBE guidelines for the reporting of observational studies. This study was approved by the institutional review board of Asan Medical Center (Approval Number: 2016-0389). Informed consent was obtained from all kidney donors.

Live kidney donor population

From September 1990 to December 2015, a total of 3265 nephrectomies were performed in living kidney donors at Asan Medical Center, Seoul, Korea. We contacted all donors to assess their general health status and renal outcomes as well as the prevalence of hypertension and diabetes. All efforts were made to contact all donors (N=3265), and all donors who could be successfully assessed (N=1607) were included in this study. We measured the GFR with ^{51}Cr EDTA and urinary albumin excretion in 200 living kidney donors who volunteered. Blood pressure was measured at the time of GFR measurement. The presence of hypertension was defined as having been prescribed antihypertensive medications or having an average blood pressure over 140/90 mmHg.

Control population

The control group was selected from the NHIS-NSC which underwent health examinations between 2002 and 2012. In this cohort, medical information was obtained from medical history, physical examination, and radiologic and laboratory test results. We excluded all deaths that occurred within the year of health examination and those with a history of dialysis or renal disease. The nondonors and donors were individually matched at a 4: 1 ratio based on the age group (5-year intervals from 30 years of age), sex, and body mass index (BMI) (Figure 1). Ninety-nine percent outliers and participants with missing data were also excluded from the analyses.

Outcomes and follow-up

We assessed the incidence of ESRD and all-cause mortalities, with a time scale of years following inclusion into the study cohort. In the donor group, ESRD was determined if a donor underwent maintenance dialysis or kidney transplantation, whichever was identified first. In the control group, ESRD was defined as at least one procedure code for hemodialysis or peritoneal dialysis. Study participants were censored at death or at the end of follow-up – December 2013 for the control group and August 2016 for the donor group. In both groups,

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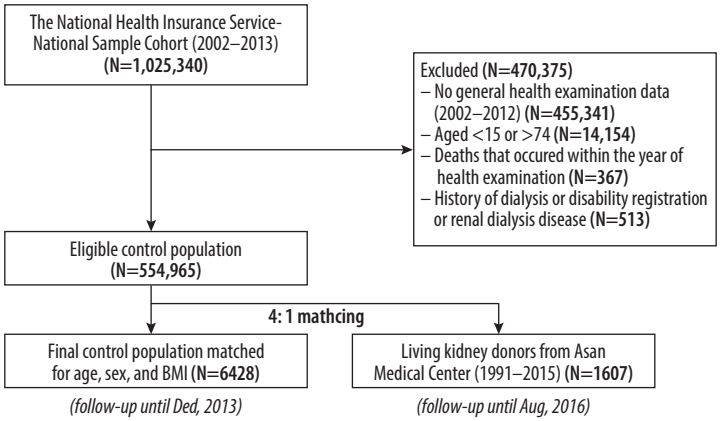

Figure 1. Inclusion and exclusion of control and donor populations.

information on mortality and cause of death were available for all subjects.

Statistical analysis

Baseline characteristics are presented as number (%) compared using the chi-squared test for categorical continuous variables and as the mean±SD compared with Student's *t*-tests for continuous variables. The incidence rates for ESRD and mortality, and 95% confidence intervals (CIs) in each group were calculated by assuming an exact Poisson distribution and expressed as 100,000 person-years. Time to ESRD or death was estimated by the Kaplan-Meier method and compared by log-rank tests. Subgroup analyses were conducted to determine the impact of comorbidities such as hypertension and current smoking. All statistical analyses were performed using the SAS software (version 9.4, SAS Institute, Inc., Cary, NC, USA).

Results

Study populations

A total of 1607 adult kidney donors were successfully contacted and enrolled in this study. Of them, 812 (50.5%) were women, 368 (22.9%) were current smokers at the time of donation, 292 (18.2%) had hypertension, 9 (0.6%) were severely obese (BMI >35), and 6 (0.4%) had diabetes mellitus. The adult controls matched for age, sex, and BMI (n=6426) showed a similar prevalence of hepatitis C, while having a significantly higher prevalence of current smoking, hypertension, diabetes, hepatitis B, and history of malignancy compared with the donors (Table 1).

Overall outcomes after kidney donation

Among the donors, death had occurred in 16 (1.0%) within a median follow-up duration of 5.0 years. There were 2 deaths from cardiovascular disease, 6 from malignancy, 6 from other diseases, and 2 from unknown causes; none of the mortalities were related to perioperative complications. A total of 5 (0.3%) donors had developed ESRD within a median of 19.9 years after donation, and their initial clinical characteristics are summarized in Table 2. Overall, kidney donors had a significantly lower mortality rate compared with the matched controls (130.2 *vs.* 185.4 per 100,000 person-years, P=0.02; Figure 2A). The occurrence of ESRD of donors was 43.1 per 100,000 person-years compared with 35.2 in the control group; however, this difference was not statistically significant (P=0.07, Figure 2B).

Health status after donation in the GFR measurement subgroup

We recruited 200 individuals among the kidney donors and measured their GFR with ^{51}Cr EDTA. The characteristics of the donors according to GFR measurement are summarized in Supplementary Table 1. After a median follow-up of 8.8 years (range: 1–25), the measured GFR (mGFR) group showed increased prevalence of hypertension (39.5%) compared with baseline prior to donation (19.5%; P<0.001); conversely, the prevalence of current smokers had significantly decreased (20.5%) compared with baseline (26.5%; P<0.001).

Multivariate Cox regression analysis revealed that older age (adjusted hazard ratio [HR], 1.097; 95% CI, 1.037–1.161; P=0.001) and female sex (adjusted HR, 3.255; 95% CI, 1.194–8.868; P=0.021) were significantly associated with an increased risk of having mGFR less than 60 mL/min/1.73 m^2 after donation (Table 3).

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Table 1. Characteristics of the living kidney donors and their matched non-donor controls.

Characteristics	Kidney donors (N=1607)	Matched controls (N=6426)	p-Value
Age, yr, median (range)	42 (16–72)	42 (15–74)	1.000
Sex (M: F)	795: 812	3180: 3246	0.991
BMI, kg/m^2, mean±SD	24.0±3.3	24.0±3.3	0.953
Current smoker, n (%)	368 (22.9)	1,687 (26.3)	0.006
Hypertension, n (%)	292 (18.2)	1,553 (24.2)	<0.001
Diabetes mellitus, n (%)	6 (0.4)	362 (5.6)	<0.001
History of Tbc, n (%)	45 (2.8)	114 (1.8)	0.008
Hepatitis B, n (%)	6 (0.4)	95 (1.5)	<0.001
Hepatitis C, n (%)	1 (0.1)	12 (0.2)	0.267
History of malignancy, n (%)	10 (0.6)	217 (3.4)	<0.001
Creatinine clearance, ml/min±SD	114.8±27.3		
Proteinuria, mg/day ±SD	94.74±258.5		
Serum creatinine, mg/dl ±SD	0.8±0.2		

BMI – body mass index; SD – standard deviation; Tbc – tuberculosis.

Table 2. Initial characteristics of the five living kidney donors who developed post-donation end-stage renal disease.

	1	2	3	4	5
Age (yr)	23	49	21	27	28
Sex	Male	Male	Male	Female	Female
BMI, kg/m^2	22.0	23.3	30.1	22.3	18.8
Current smoker	No	Yes	Yes	Yes	No
Hypertension	No	Yes	Yes	No	No
Diabetes mellitus	No	No	No	No	No
History of Tbc	No	No	No	No	No
Hepatitis B	No	No	No	No	No
Hepatitis C	No	No	No	No	No
History of malignancy	No	No	No	No	No
CrCl, ml/min	96	82.2	168.7	97.3	99.2
eGFR (CKD-EPI), ml/min/1.73 m^2	105.6	99.9	107.1	119.1	118.3
Side of donated kidney	Left	Left	Left	Left	Left
Stone in donated kidney	No	No	No	No	No
Stone in remaining kidney	No	No	No	No	No
Donation to ESRD (yr)	20	14	23	21	15
Relation to recipient	Sibling	Unrelated	Son	Sibling	Sibling
Recipient cause of ESRD	Unknown	GN	Unknown	GN	Unknown
Recipient graft survival	13years	13years	18years	>3years	>23years

BMI – body mass index; Tbc – tuberculosis; CrCl – creatinine clearance; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; ESRD – end-stage renal disease.

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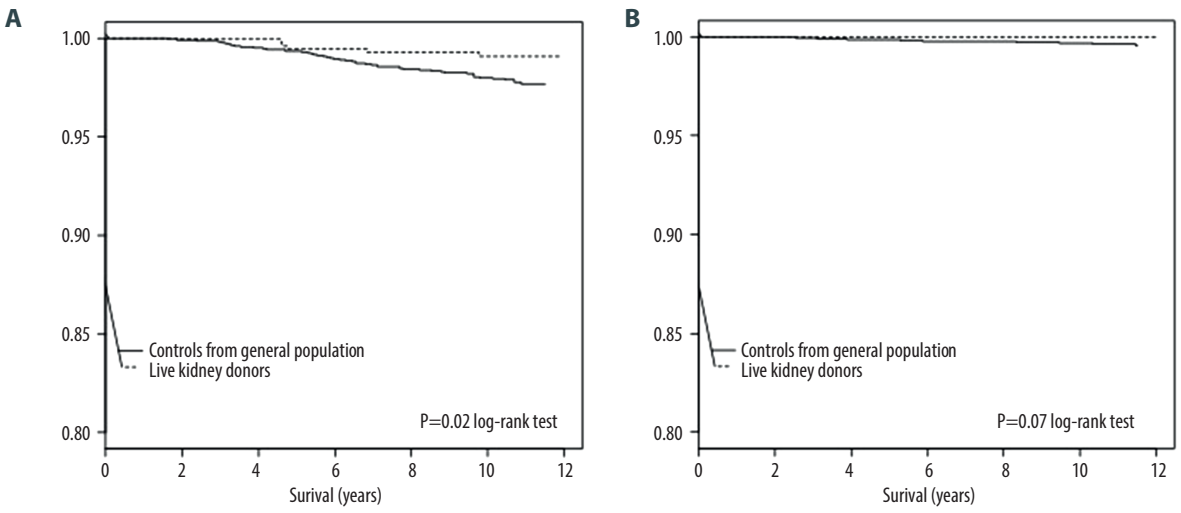

Characteristic	No. of participants	No. of deaths	Follow-up duration (person-years) Median	[min–max]	Sum	Mortality rate (/100,000 person-years)	(95% CI)
NHIS-NSC – Heatlth examination cohort	554,695	14,381	7.5	[0.5–11.5]	4175606.8	344.4	(338.8–350.1)
Matched controls from the NHIS-NSC – Heatlth examination cohort	6,426	89	7.5	[0.8–11.5]	48016.1	185.4	(148.9–228.1)
Kidney donors	1,607	15	5.0	[0.6–25.5]	11518.8	130.2	(72.9–217.8)

Characteristic	No. of participants	No. of ESRD	Follow-up duration (person-years) Median	[min–max]	Sum	Incidence rate of ESRD (/100,000 person-years)	(95% CI)
NHIS-NSC – Heatlth examination cohort	554,695	1,507	8.5	[0.5–11.5]	4227133.8	35.7	(33.9–37.5)
Matched controls from the NHIS-NSC – Heatlth examination cohort	6,426	17	7.5	[1.3–11.5]	48305.7	35.2	(20.5–56.3)
Kidney donors	1,607	5	5.0	[0.6–25.5]	11605.0	43.1	(14.0–100.5)

Figure 2. Kaplan-Meier curves for approximately 12-year survival (**A**) and ESRD-free survival (**B**) between matched control and live kidney donors. ESRD – end-stage renal disease; CI ,– confidence interval; NHIS-NSC – the Korean National Health Insurance Service-National Sample Cohort.

Table 3. Risk of having measured GFR less than 60 ml/min/1.73 m^2 after kidney donation and adjusted HR from multivariate Cox regression.

Variables	HR_{unadj}	HR_{adj}	95% CI	p-value
Age	1.105	1.097		0.001
Female sex	2.755	3.255		0.021
Estimated GFR at donation (CKD-EPIe)	0.974	0.991		0.615

GFR – glomerular filtration rate; HR_{unadj} – unadjusted hazard ratio; HR_{adj} – adjusted hazard ratio; CI – confidence interval; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration.

Survival and health status after donation in kidney donors according to predonation hypertension

Among the kidney donors, 292 (18.2%) had hypertension prior to donation (Table 4). There was no significant difference in mortality between the matched controls with hypertension and donors with predonation hypertension (*P*=0.42), whereas donors without predonation hypertension had significantly lower mortality compared with matched controls without hypertension (79.3 *vs.* 138.0 per 100,000 person-years, *P*=0.03; Figure 3A, 3B). Conversely, the matched controls and the donors did not show any significant difference in the incidence of ESRD either in the presence (*P*=0.16) or absence of hypertension (*P*=0.31; Figure 3C, 3D).

Among the subgroup of 200 kidney donors with mGFR, 39 (19.5%) had hypertension prior to donation. After donation, the donors with predonation hypertension had significantly

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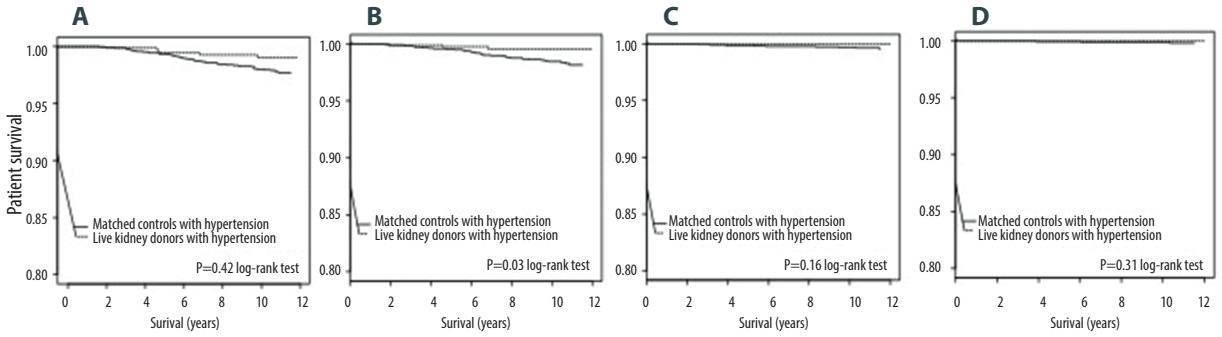
Table 4. Health status after kidney donations of donors according to pre-donation hypertension and smoking status.

	With HTN (N=292)	Without HTN (N=1,315)	P-value	Current smoker (N=368)	Current non-smoker (N=1,237)	P-value
Age, yr, mean±SD	45±11	41±11	<0.001	39±11	42±11	<0.001
Female sex, n (%)	121 (41.4)	691 (52.6)	0.001	40 (10.9)	772 (62.4)	<0.001
BMI, kg/m^2 ±SD	25.1±3.4	23.7±3.4	<0.001	24.4±3.1	23.8±3.3	0.002
Diabetes mellitus, n (%)	16 (6.2)	19 (1.5)	<0.001	11 (3.0)	24 (1.9)	0.194
Dyslipidemia, n (%)	24 (9.3)	104 (8.5)	0.714	24 (6.5)	104 (8.4)	0.309
Coronary artery disease, n (%)	4 (1.6)	5 (0.4)	0.054	1 (0.3)	8 (0.6)	0.693
Cerebrovascular accident, n (%)	2 (0.8)	3 (0.2)	0.214	4 (1.0)	1 (0.1)	0.011
Malignancy, n (%)	12 (4.7)	31 (2.6)	0.100	9 (2.4)	34 (2.7)	0.805

HTN – hypertension; SD – standard deviation; BMI – body mass index.



Characteristic	No. of participants	No. of deaths	Follow-up duration (person-years) Median	[min–max]	Sum	Mortality rate (/100,000 person-years)	(95% CI)
NHIS-NSC – Heatlth examination cohort	554,965	14,381	7.5	[0.5–11.5]	4175606.8	344.4	(338.8–350.1)
Matched controls from the NHIS-NSC – Heatlth examination cohort	6,426	89	7.5	[0.6–11.5]	48016.1	185.4	(148.9–228.1)
with hypertension	1,553	42	8.5	[1.3–11.5]	12503.2	335.9	(242.1–454.1)
without hypertension	4,873	49	7.5	[0.6–11.5]	35512.9	138.0	(102.1–182.4)
Kidney donors	1,607	15	5.0	[0.6–25.5]	11518.8	130.2	(72.9–214.8)
with hypertension	292	8	7.3	[0.6–25.5]	2694.3	295.9	(128.2–585.1)
without hypertension	1,315	7	4.8	[0.6–25.0]	8824.6	79.3	(31.9–163.4)

Characteristic	No. of participants	No. of deaths	Follow-up duration (person-years) Median	[min–max]	Sum	Incidence rate of ESRD (/100,000 person-years)	(95% CI)
NHIS-NSC – Heatlth examination cohort	554,965	1,507	8.5	[0.5–11.5]	4227133.8	35.7	(33.9–37.5)
Matched controls from the NHIS-NSC – Heatlth examination cohort	6,426	17	7.5	[1.3–11.5]	48305.7	35.2	(20.5–58.3)
with hypertension	1,553	12	9.5	[1.3–11.5]	12625.6	95.0	(49.1–166.0)
without hypertension	4,873	5	7.5	[1.5–11.5]	35580.1	14.0	(4.6–32.7)
Kidney donors	1,607	5	5.0	[0.6–25.5]	11605.0	43.1	(14.0–100.5)
with hypertension	292	2	7.5	[0.6–25.5]	2753.3	72.6	(8.8–262.4)
without hypertension	1,315	3	4.9	[0.6–25.0]	8851.8	33.9	(7.0–99.0)

Figure 3. Kaplan-Meier curves for approximately 12-year survival and ESRD-free survival between matched control and live kidney donors with hypertension (**A, B**) and without hypertension (**C, D**). ESRD – end-stage renal disease; CI – confidence interval; NHIS-NSC – the Korean National Health Insurance Service-National Sample Cohort.

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Table 5. Health status after kidney donations of donors according to pre-donation hypertension and smoking status. (Donors with mGFR subgroup)

	With HTN (N=39)	Without HTN (N=161)	p-Value	Current smoker (N=53)	Current non-smoker (N=147)	p-Value
Follow-up, yr, median [range]	10 [1–26]	7 [1–24]	0.001	10 [1–22]	8 [1–26]	0.215
Age, yr ±SD	44±10	40±10	0.018	39±10	41±10	0.236
Female sex, n (%)	20 (51.3)	72 (44.7)	0.479	4 (7.5)	88 (59.9)	<0.001
BMI, kg/m^2 ±SD	24.7±3.7	24.2±2.9	0.348	24.7±2.9	24.1±3.1	0.282
Blood pressure						
Systolic, mmHg ±SD	132.9±15.2	124.3±13.0	<0.001	127.9±12.3	125.3±14.3	0.240
Diastolic, mmHg ±SD	84.1±8.9	82.0±9.0	0.207	85.2±7.7	81.5±9.2	0.006
Systolic ≥140 mmHg or diastolic ≥90 mmHg, n (%)	23 (59.0)	44 (27.3)	<0.001	17 (32.1)	37 (25.2)	0.332
Urinary ACR, mg/g ±SD	55.2±125.8	15.4±35.3	0.057	43.6±111.4	15.7±34.6	0.078
>30, n (%)	13 (33.3)	17 (10.6)	0.001	12 (22.6)	18 (12.2)	0.069
>300, n (%)	1 (2.6)	1 (0.6)	0.353	1 (1.9)	1 (0.7)	0.461
Diabetes, n (%)	3 (7.7)	5 (3.1)	0.189	3 (5.7)	6 (4.1)	0.702
Malignancy, n (%)	2 (5.1)	8 (5.0)	1.000	0	10 (6.8)	0.065
CAD, n (%)	0	1 (0.6)	–	0	1 (0.7)	–
CVA, n (%)	0	0	–	0	0	–
Dyslipidemia, n (%)	10 (25.6)	20 (12.4)	0.047	8 (15.1)	22 (15.0)	0.982
Current smoker, n (%)	6 (15.4)	35 (21.7)	0.508	–	–	–
Hypertension, n (%)	–	–	–	20 (37.7)	47 (32.0)	0.446
mGFR, ml/min/1.73 m^2 ±SD	71.8±17.6	74.9±12.7	0.311	78.6±15.3	73.3±11.4	0.025
Hemoglobin, g/dl ±SD	14.2±1.3	14.4±1.5	0.450	15.2±1.2	14.0±1.4	<0.001
Glucose, mg/dl ±SD	104.3±13.6	99.2±12.5	0.025	104.2±14.8	98.7±11.8	0.018
Hemoglobin A1c, % ±SD	5.7±0.5	5.5±0.7	0.332	5.5±0.4	5.6±0.8	0.841
HDL-cholesterol, mg/dl ± SD	53.9±11.7	51.9±10.3	0.289	49.9±9.9	53.1±10.7	0.057
LDL-cholesterol, mg/dl ± SD	154.9±101.0	141.4±29.1	0.415	156.1±85.6	139±30.7	0.047
Triglyceride, mg/dl ±SD	155.0±93.8	154.5±99.7	0.977	186.6±114.0	143.1±89.7	0.005

mGFR – measured glomerular filtration rate; HTN – hypertension, BMI – body mass index, SD – standard deviation, ACR ;– albumin-to-creatinine ratio, CAD – coronary artery disease; CVA – cerebrovascular accident; HDL; high-density lipoprotein, LDL; low-density lipoprotein.

higher levels of systolic blood pressure (P<0.001) and fasting glucose (P=0.025) as well as higher rates of microalbuminuria (P=0.001) and dyslipidemia (P=0.047) compared with those without predonation hypertension (Table 5).

Survival and health status after donation in kidney donors according to predonation smoking status

A total of 368 (22.9%) donors were current smokers at the time of donation, among whom men were predominant (Table 4). Compared with nonsmokers, current smokers had

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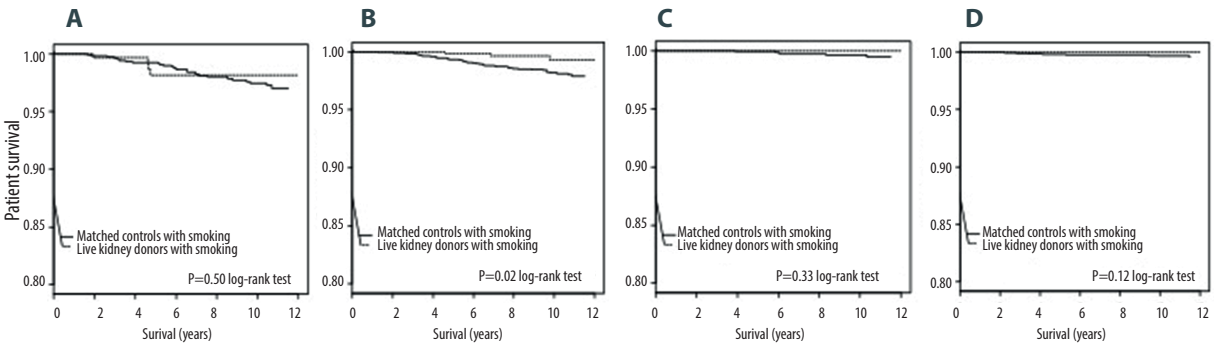

Characteristic	No. of participants	No. of deaths	Follow-up duration (person-years) Median	[min–max]	Sum	Mortality rate (/100,000 person-years)	(95% CI)
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Matched controls from the NHIS-NSC – HeatIth examination cohort	6,426	89	7.5	[0.6–11.5]	48016.1	185.4	(148.9–228.1)
current smoking	1,687	30	7.5	[1.5–11.5]	12662.3	236.9	(159.9–338.2)
no current smoking	4,739	59	7.5	[0.6–11.5]	35353.8	166.9	(127.0–215.3)
Kidney donors	1,607	15	5.0	[0.6–25.5]	11518.8	130.2	(72.9–214.8)
current smoking	368	8	6.0	[0.6–25.4]	3119.0	256.5	(110.7–505.4)
no current smoking	1,239	7	5.0	[0.6–25.5]	8399.9	83.3	(33.5–171.7)

Characteristic	No. of participants	No. of deaths	Follow-up duration (person-years) Median	[min–max]	Sum	Incidence rate of ESRD (/100,000 person-years)	(95% CI)
NHIS-NSC – HeatIth examination cohort	554,695	1,507	8.5	[0.5–11.5]	4227133.8	35.7	(33.9–37.5)
Matched controls from the NHIS-NSC – HeatIth examination cohort	6,426	17	7.5	[1.3–11.5]	48305.7	35.2	(20.5–58.3)
current smoking	1,687	5	8.5	[1.5–11.5]	12761.0	39.2	(12.7–91.4)
no current smoking	4,739	12	7.5	[1.3–11.5]	35544.7	33.8	(17.4–59.0)
Kidney donors	1,607	5	5.0	[0.6–25.5]	11605.0	43.1	(14.0–100.5)
current smoking	368	3	7.1	[0.6–25.4]	3165.6	94.8	(19.5–277.0)
no current smoking	1,239	3	5.0	[0.6–25.5]	8439.4	23.7	(29.0–85.6)

Figure 4. Kaplan-Meier curves for approximately 12-year survival and ESRD-free survival between matched control and live kidney donors with smoking (**A, B**) and without smoking (**C, D**). ESRD – end-stage renal disease; CI – confidence interval; NHIS-NSC – the Korean National Health Insurance Service-National Sample Cohort.

a higher incidence of cerebrovascular accidents after donation (*P*=0.011). There was no significant difference in mortality between the matched controls and donors with predonation smoking (*P*=0.50); in contrast, donors without predonation smoking had significantly lower mortality rate than did the matched controls without predonation smoking (83.3 *vs.* 166.9 per 100,000 person-years, *P*=0.02; Figure 4A, 4B). Conversely, the matched controls and the donors did not show any significant difference in the incidence of ESRD regardless of smoking (Figure 4C, 4D).

Among the subgroup of 200 kidney donors with mGFR, 53 (26.5%) were current smokers prior to donation. In this subgroup, the donors with predonation smoking showed significantly higher levels of diastolic blood pressure, hemoglobin, fasting glucose, triglyceride, and LDL cholesterol after donation compared with their nonsmoking counterparts (Table 5).

Discussion

In this study of 1607 kidney donors compared with a matched control population, we found that the mortality rate was significantly lower in kidney donors, whereas the risk of ESRD showed higher, although statistically insignificant trends. The mean value of mGFR in a subset of the donors was higher than 80 mL/min/1.73 m^2. These results are somewhat consistent with those of previous reports that long-term risks and mortality in kidney donors are not higher than those in a demographically matched general population [1,13]. However, one should be cautious in concluding that the long-term risk of developing ESRD among donors is comparable to their healthy counterparts.

Upon further analyses, however, we found that the long-term safety after kidney donation in terms of mortality and morbidity is not guaranteed if the donor has hypertension or is a current smoker at the time of donation. Although several guidelines have been established regarding the eligibility for

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kidney donation, there are no definite guidelines with strong evidence for predicting the long-term risk of kidney donation for donors with comorbidities. According to these guidelines, patients with blood pressure higher than 140/90 mmHg by ambulatory blood pressure monitoring are generally not accepted as donors [10,14–16]. However, some patients with easily controlled hypertension and low risk for the development of kidney disease are permitted for kidney donation. In contrast, our current results show that hypertension is a significant risk factor for long-term mortality and morbidity after kidney donation. Hypertension is a well-known complication of kidney donation [17–19] and a significant risk factor for chronic kidney disease progression [20], short-term donor complications [21], and donor mortality [22]. Similarly, our study demonstrated that smoking was associated with long-term health risks for the donor. This finding is consistent with the results of recent reports in which current smoking was a strong risk factor for lifetime ESRD after donation [23–25].

In clinical situations, certain proportions of live donors are expected to have at least 1 comorbidity that represents a contraindication to donation. According to the Australia and New Zealand Dialysis and Transplant Living Kidney Donor Registry, 26% of donors had at least 1 relative contraindication for donation and 9% had at least 1 absolute contraindication [26]. Similar gaps between guidelines and practice in donor selection criteria have been well-described [8,27], and it is thus important to assess the risk factors for ESRD and mortality before donation and to inform donors of the possibility of long-term risks after donation.

The main strength of this study is that it is one of the few reports on the long-term safety of live kidney donation in an Asian population, as most reports on donor safety published during the last few decades were from Western countries. For previous studies where race and ethnicity of the population were not provided, it is probable, considering the region of the studies, that the vast majority of donors and controls were Caucasians [4]. These studies are not readily generalizable in Asian populations because Asian donors only composed minor proportions of the cohorts. Furthermore, the introduction of ABO-incompatible kidney transplantation increased the number of living donor kidney transplantation by 12.2%, from 0.3% to 21.7%, during the last decade according to the Korean Organ Transplantation Registry Study Group [28]. In fact, ABO-incompatible kidney transplantation has been routinely performed in Japan, where it constitutes nearly 30% of living kidney transplantations [29]. Another strength of our study is that we utilized the Korean National Health Insurance Service-National Sample Cohort as an unscreened nondonor population for selecting a demographically matched control group, which allowed us to estimate the relative risk of ESRD and mortality of live kidney donors. Additionally, we performed laboratory measurements including GFR with ^{51}Cr EDTA and urinary albumin excretion to assess the deterioration of renal function after donation and to determine the development of morbidity in a selected subgroup.

Notwithstanding these merits, our study has several limitations of note. First, the kidney donors were all from a single center and may thus be subject to selection bias; nevertheless, our study included the largest number of donors in Korea to date. Also, we could not obtain data or information from donors whose contact information was unavailable. This could be a limitation for patient selection criteria and decision on sample size, and these factors may have introduced further bias, which limits the generalizability of our results. Similar to earlier retrospective studies, individual network studies are limited by the quality of the controls, reliance on insurance claims, and a certain degree of bias [4]. Also, while none of the 200 donors who volunteered for GFR measurement had decreased renal function and ESRD, the eGFR value of all 1607 participants could not be obtained and only their follow-up data on dialysis status were assessed. This might possibly omit patients with end-stage renal function of eGFR <30 mL/min/1.73 m^2 prior to initiating dialysis. Another limitation was that the control group had more comorbidities than the donor group even after matching for age, sex, and BMI. Third, it was not feasible to assess the impact of comorbidities other than hypertension and smoking in donors because those with other comorbidities were too few for an appropriate statistical analysis. The inherent limitation of the data source, the National Health Insurance sample database, was that specific data for each comorbidity could not be uniformly matched to the donors. We also acknowledge for further prospective studies that more robust matching could be utilized, and we note that Grams et al. [23] recently developed an algorithm to estimate the kidney-failure risk projection for living kidney donor candidates with multiple demographic and health characteristics. It will be a useful guideline if the system is applied to donors in Asian countries after a proper adjustment in the evaluation and counsel of living kidney donor candidates.

Conclusions

Asian kidney donors had similar long-term risks for ESRD and mortality compared with matched controls. However, candidate donors with hypertension or current smoking status should be informed that they may have a higher risk of long-term morbidity and mortality.

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Supplementary Data

Supplementary Table 1. Characteristics of the 200 donors with measured glomerular filtration rates (mGFR).

	Total donors (N=1607)	With mGFR (N=200)	Without mGFR (N=1407)	p-value
Age, yr, median (range)	42 (16–72)	41 (16–64)	42 (17–72)	0.287
Sex (M: F)	794: 813	108: 92	686: 721	0.174
BMI, kg/m^2, mean±SD	24.0±3.4	23.8±3.2	24.0±3.4	0.459
Current smoker, n (%)	368 (22.9)	53 (26.5)	315 (22.4)	0.208
Hypertension, n (%)	292 (18.2)	39 (19.5)	253 (18.0)	0.624
Diabetes mellitus, n (%)	6 (0.4)	0	6 (0.4)	1.000
History of Tbc, n (%)	45 (2.8)	2 (1.0)	43 (3.1)	0.111
Hepatitis B, n (%)	6 (0.4)	0	6 (0.4)	1.000
Hepatitis C, n (%)	1 (0.1)	0	1 (0.1)	1.000
History of malignancy, n (%)	10 (0.6)	0	10 (0.7)	0.623
Creatinine clearance, ml/min ±SD	115.0±29.8	111.9±26.0	115.4±30.3	0.116
Proteinuria, mg/day ±SD	94.9±242.3	93.8±62.1	95.1±257.8	0.944
Serum creatinine, mg/dl ±SD	0.80±0.20	0.82±0.16	0.79±0.17	0.035
eGFR (CKD-EPI), ml/min/1.73 m^2 ±SD	104.2±13.6	103.3±13.5	104.3±13.6	0.324
Hemoglobin A1c, % ±SD	5.6±0.3	5.6±0.3	5.6±0.3	0.385
Left kidney donation, n (%)	963 (59.9)	113 (56.5)	850 (60.5)	0.334
Stone in donated kidney, n (%)	71 (4.5)	8 (4.0)	63 (4.5)	0.525
Stone in remaining kidney, n (%)	12 (0.8)	1 (0.5)	11 (0.8)	0.536
Follow-up, yr, median (range)	4.9 (0.5–26)	8.8 (1–26)	4.5 (1–26)	< 0.001

BMI – body mass index; SD – standard deviation; Tbc – tuberculosis; eGFR – estimated glomerular filtration rate.

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