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Risk of subsequent health disorders among living kidney donors

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Abstract

Few studies have investigated the risk of physiological sequelae in living kidney donors (KDs). We conducted a population-based cohort study using the National Health Insurance Research Database of Taiwan, which covers more than 99% of citizens.

We comprehensively investigated the risk of medical disorders after kidney donation in living KDs using a maximum follow-up of 13 years. From January 1997 to December 2010, 1081 living KDs and 1082 age- and sex-matched non-KDs were eligible. Primary outcomes comprised end-stage renal disease, chronic kidney disease, stroke, cancer, acute myocardial infarction, acute renal failure (ARF), and diabetes.

The adjusted hazard ratios (HRs) for developing ARF, diabetes, hyperlipidemia, hypertension, cancer, end-stage renal disease, acute myocardial infarction, and stroke were similar between the KD and non-KD cohorts ($P > .05$). Although differences in the adjusted HRs of ARF were nonsignificant, the cumulative incidence rate of ARF 13 years after donation was 7.48 per 1000 person-years in the KD cohort compared with 3.46 in the matched non-KD cohort. The incidence rate ratio for ARF between donors and nondonors significantly increased to 2.16 (95% confidence interval, 1.61–2.71).

Living KDs experienced no significant health disorders following kidney donation but should be alert to the higher incidence rate of ARF.

Abbreviations: AMI = acute myocardial infarction, ARF = acute renal failure, CI = confidence interval, CKD = chronic kidney disease, ESRD = end-stage renal disease, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, KD = kidney donor, KT = kidney transplantation.

Keywords: acute renal failure, end-stage renal disease, kidney transplantation, living kidney donor, retrospective cohort study

1. Introduction

Since the first operation in 1954, kidney transplantation (KT) has achieved more favorable outcomes for patients with end-stage renal disease (ESRD) than maintenance dialysis.[1,2] Despite the advantages of KT, the increasing prevalence of ESRD has drastically increased the demand for KT; thus, the extreme shortage of available cadaveric organs is exacerbated.[3] Research has noted that half of older candidates for KT could not endure a long waiting period for an available cadaveric renal allograft.[4] Therefore, KT using living donors has inevitably become a global trend to benefit both the recipient and graft kidney.[5]

Studies have shown that living kidney donations are generally accepted, with minimal risk of complications noted during nephrectomy or in long-term follow-up periods.[6,7] However,

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other studies have reported living kidney donors (KDs) who developed ESRD and found themselves on the waiting list for KT.[7,8] Thus, the effect of reduced renal mass remains a concern for donors. Taiwan has considerably higher incidence and prevalence rates of chronic kidney disease (CKD) and ESRD than any other country.[9] Because patients with ESRD generally receive kidneys from living donors, a pilot study in an area with high ESRD prevalence to assess the long-term effects of kidney donation on living KDs would be both compelling and beneficial. Therefore, we conducted a nationwide retrospective cohort study using a 13-year well-organized tracking database to evaluate the long-term outcomes of living donors to provide more comprehensive risk evaluation for hypertension, diabetes, hyperlipidemia, acute renal failure (ARF), renal diseases, ESRD, stroke, acute myocardial infarction (AMI), and cancer.

2. Methods

2.1. Study setting

The National Health Insurance (NHI) program of Taiwan is a single-payer social insurance program that was established in 1995 through the consolidation of 13 insurance programs into one national system. By the end of 1999, more than 99% of the 23.7 million citizens of Taiwan were enrolled in the program.[10] The National Health Research Institutes (NHRI) has been in charge of maintaining and updating the National Health Insurance Research Database (NHIRD). This study obtained inpatient claims data of the insured population from the NHIRD for the period of 1996 to 2010. For data analysis, we retrieved information on patients' sociodemographic characteristics and medical care records from inpatient care claims, the Registry for Catastrophic Illness Patient Database (CIPD), and the registry for beneficiaries. In Taiwan, patients with a catastrophic illness certificate (CIC) are exempted from certain medical insurance premiums and costs. The NHI strictly evaluates and reviews CICs. Therefore, CIC data in Taiwan are highly accurate and reliable.[11] We used scrambled personal identification numbers to link data files to ensure privacy protection. Diagnoses of diseases were defined according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes.

2.2. Ethics statement

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved by the Institutional Review Board (IRB) of China Medical University and fulfilled the conditions for exemption (CMUH104-REC2-115-CR3). The IRB also specifically waived the consent requirement.

2.3. Data sharing statement

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW), which must approve applications to access the data. Any researcher interested in accessing this dataset can submit an application form to the MOHW requesting access. Please contact the staff of MOHW (Email: stcarolwu@mohw.gov.tw; Taiwan MOHW address: No. 488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan [R.O.C.]; Phone: +886-2-8590-6848) for further assistance. All relevant data are included within the paper.

2.4. Study participants

Based on inpatient care claims, we identified KDs during the period of 1997 to 2010 from the CIPD (ICD-9-CM code V594) as the KD cohort. Individuals with a history of diabetes, CKD, other renal disease, stroke, cancer, AMI, or ARF, with major outcomes such as ESRD, or with invalid information at the baseline were excluded. We excluded any persons with prior liver disease, rheumatic diseases, tuberculosis, or human immunodeficiency virus. The index date was the date of KT. The comparison cohort, defined as the non-KD cohort, was randomly identified from the general population without kidney donation in the NHIRD, also for the period of 1997 to 2010, using exclusion criteria similar to those for the KD cohort. For each KD, we selected one non-KD control whose frequency was matched by baseline age (for 5-year spans), sex, index date, income, urbanization level, and comorbidity of hypertension, hyperlipidemia, obesity, or chronic obstructive pulmonary disease (COPD).

2.5. Outcome measures

We identified new events of ESRD, CKD, other renal diseases, stroke, cancer, AMI, and ARF during 1997 to 2010 for each cohort. We followed both cohorts until the occurrence of events of interest, loss to follow-up, death, withdrawal from the insurance system, or the end of 2010. Other renal diseases comprised ICD-9-CM codes 580 (acute glomerulonephritis), 581 (nephrotic syndrome), 582 (chronic glomerulonephritis), 791 (nonspecific findings on examination of urine, which indicate ICD-9-CM codes 791.0, proteinuria; 791.1, chyluria; 791.2, hemoglobinuria; 791.3, myoglobinuria; 791.4, biliuria; 791.5, glycosuria; 791.6, acetonuria; 791.7, other cells and casts in urine convert; and 791.9, other nonspecific findings on examination of urine), and 753.1 (cystic kidney disease). We also noted any new diagnosis of diabetes (ICD-9-CM code 250) for both cohorts in the follow-up period. We adjusted for hypertension to eliminate its effects on the risk of ESRD and other events. ARF was determined on the basis of ICD-9-CM diagnosis codes and defined as "the sudden, severe onset of inadequate kidney function," as in a previous study.[12] We used one main code (584) as well as five subcodes (584.5, 584.6, 584.7, 584.8, and 584.9) to indicate ARF. ARF data in the NHIRD, as recorded by ICD-9-CM codes, were validated, with sensitivity of 1 and specificity of 0.99.[13]

2.6. Statistical analysis

Data analysis entailed comparing baseline distributions of sex, age, income (New Taiwan dollars), urbanization level, and comorbidities between the KD and non-KD cohorts. We examined categorical variables using a chi-squared test or Fisher's exact test and continuous variables using a *t* test. The follow-up time in person-years was estimated for each participant. We measured incident density rates of ESRD and other disorders for each cohort and the incidence rate ratio (IRR) between the cohorts as well as the corresponding 95% confidence interval (CI) for each event. Poisson regression was used to estimate the IRR of the KD cohort to the non-KD cohort with a 95% CI. Factors significant in the single-variable Cox model were included in the multivariable model. We estimated the hazard

Table 1

Demographic and comorbidity comparison of kidney donors and nondonors at baseline.

	Kidney donors				*P*-value
	No (N = 1081)		Yes (N = 1082)		
	n	%	n	%	
Age (years)					0.99
≤35	392	36.3	392	36.2	
35–55	546	50.5	547	50.6	
55+	143	13.2	143	13.2	
Mean (SD)*	39.8	13.6	40.1	13.3	0.64
Sex					0.98
Female	552	51.1	552	51.0	
Male	529	48.9	530	49.0	
Income (NTD)					0.99
<15,000	375	34.7	375	34.7	
15,000–22,799	465	43.0	466	43.1	
≥22,800	241	22.3	241	22.3	
Urbanization level†					0.99
1 (highest)	327	30.3	327	30.2	
2	338	31.3	338	31.2	
3	196	18.1	196	18.1	
4 (lowest)	220	20.4	221	20.4	
Comorbidity					
Hypertension	40	3.70	40	3.70	0.99
Hyperlipidemia	7	0.65	8	0.74	0.72
Obesity‡	0	0.00	1	0.09	0.09
Chronic obstructive pulmonary disease‡	3	0.28	3	0.28	0.99

Chi-squared test. NTD = New Taiwan dollar, SD = standard deviation.
* *t* test.
† The urbanization level was categorized into four levels by population density of the residential area, with level 1 being the most urbanized and level 4 being the least urbanized.
‡ Fisher's exact test.

ratio (HR) of medical disorders and the corresponding 95% CI using multivariable Cox proportional hazards regression with adjustment for hypertension. We further evaluated whether the risk changed over time for disorders with higher incidence by stratifying the follow-up period into two segments (≤3 and >3 years), with both the IRR and HR measured for the KD and non-KD cohorts. Statistical analyses were performed using the SAS statistical package (version 9.2 for Windows; SAS Institute, Inc., Cary, NC, USA). Results with statistical significance ($P < .05$) were accepted.

3. Results

3.1. Demographic characteristics of KD and comparison cohorts

This study identified 1082 patients in the KD cohort and selected 1081 frequency-matched individuals for the non-KD cohort. Table 1 shows that the cohorts were similar in terms of mean age (approximately 40 years) and sex distribution (49% men). Both cohorts had a low income (34.7%), and most individuals lived in urbanized areas (Table 1).

3.2. Incidence of ESRD, CKD, other renal diseases, stroke, cancer, AMI, ARF, and diabetes

Table 2 presents the incidence rates and adjusted relative risk of ESRD, CKD, other renal diseases, stroke, cancer, AMI, ARF, and diabetes. During the follow-up period, the incidence of ESRD, CKD, other renal diseases, and ARF was higher in the KD and non-KD cohorts. The IRRs of ESRD, CKD, other renal diseases, and ARF of the KD and non-KD cohorts were significantly different in the follow-up period, at 1.50 (95% CI, 1.06–1.95), 2.53 (95% CI, 1.88–3.41), 1.44 (95% CI, 1.03–2.03), and 2.16 (95% CI, 1.61–2.91), respectively. After adjustment for hypertension, the risks of ESRD, CKD, other renal diseases, stroke, cancer, AMI, ARF, and diabetes in the KD cohort were not significantly higher than those in the non-KD cohort (Table 2).

Table 3 presents the IRR of donors to nondonors for CKD, which increased from 2.05 within the first 3 years to 3.05 in the later follow-up period. The IRR of cancers decreased from 1.37 within the first 3 years to 0.57 in the later follow-up period. After adjustment for hypertension, the risk of ESRD, CKD, other renal diseases, stroke, cancer, AMI, ARF, and diabetes by follow-up years (≤3 years or >3 years) in the KD cohort was not statistically significantly higher than in the non-KD cohort.

Figure 1A–H demonstrate that the KD cohort did not exhibit a significantly higher cumulative proportion of ESRD ($P = .75$,

Table 2

Incidence of ESRD, chronic kidney disease, other renal diseases, stroke, cancer, AMI, ARF, and diabetes diagnosed in follow-up period in kidney donors and nondonors.

	Kidney donors						Donors to non-donors	
	No			Yes				
Outcome	Event	PY	Rate#	Event	PY	Rate#	IRR (95% CI)	Adjusted HR† (95% CI)
ESRD	1	5770	1.73	1	4010	2.49	1.50 (1.06, 1.95)*	1.76 (0.11, 28.4)
Chronic kidney disease	4	5763	6.94	8	3983	20.1	2.53 (1.88, 3.41)***	2.69 (0.78, 9.23)
Other renal diseases&	2	5764	3.47	2	3993	5.01	1.44 (1.03, 2.03)*	1.33 (0.19, 9.43)
Stroke	13	5749	22.6	5	3890	12.5	0.55 (0.41, 0.74)***	0.60 (0.22, 1.70)
Cancer	25	5739	43.6	15	3987	37.6	0.86 (0.67, 1.12)	0.90 (0.47, 1.70)
AMI	3	5765	5.20	2	3995	5.01	0.96 (0.70, 1.32)	0.93 (0.16, 5.58)
ARF	2	5775	3.46	3	4008	7.48	2.16 (1.61, 2.91)***	2.50 (0.41, 15.2)
Diabetes	44	5613	78.4	30	3900	76.9	0.98 (0.76, 1.24)	0.99 (0.62, 1.58)

AMI = acute myocardial infarction, ARF = acute renal failure, CI = confidence interval, ESRD = end-stage renal disease, HR = hazard ratio, IRR = incidence rate ratio, PY = person-years.
# Incidence rate, per 10,000 person-years
† Hazard ratio from multiple analysis including hypertension.
& Other renal diseases comprised acute glomerulonephritis, nephrotic syndrome, chronic glomerulonephritis, nonspecific findings on examination of urine, and cystic kidney disease.
* $P < .05$.
** $P < .01$.
*** $P < .001$.

Table 3

Incidence of chronic kidney disease, stroke, cancer, diabetes, and ARF by follow-up years in kidney donors and nondonors.

	Non-donors			Donors				
Follow time	**Event**	**PY**	**Rate[#]**	**Event**	**PY**	**Rate[#]**	**IRR (95% CI)**	**Adjusted HR[&] (95% CI)**
Chronic kidney disease								
≤3	2	2688	7.44	4	1968	20.3	2.05 (1.48, 2.84)***	2.56 (0.47, 14.0)
>3	2	3075	6.50	4	2016	19.9	3.05 (2.10, 4.44)***	3.54 (0.64, 19.6)
Stroke								
≤3	3	2686	11.2	2	1970	10.2	0.91 (0.66, 1.25)	0.88 (0.15, 5.28)
>3	10	3063	32.6	3	2020	14.9	0.46 (0.31, 0.68)	0.51 (0.14, 1.86)
Cancer								
≤3	9	2682	33.6	9	1967	45.8	1.37 (1.03, 1.80)*	1.34 (0.53, 3.39)
>3	16	3057	52.3	6	2020	29.7	0.57 (0.39, 0.82)**	0.60 (0.23, 1.55)
Diabetes								
≤3	22	2660	82.7	13	1960	66.3	0.80 (0.62, 1.04)	0.79 (0.40, 1.57)
>3	22	2954	74.5	17	1939	87.7	1.18 (0.85, 1.63)	1.22 (0.64, 2.29)
ARF								
≤3	1	1265	7.91	1	929	10.8	1.39 (0.09, 22.2)	1.29 (0.08, 20.7)
>3	1	3086	3.24	2	2035	9.83	3.77 (0.34, 42.5)	3.37 (0.30, 38.0)

ARF = acute renal failure, CI = confidence interval, HR = hazard ratio, IRR = incidence rate ratio measured by Poisson regression analysis controlling for hypertension, PY = person-years.

[#] Incidence rate, per 1,000 person-years.

[&] Hazard ratio from multiple analysis including hypertension.

* $P < .05$.

** $P < .01$.

*** $P < .001$

Fig. 1A), CKD ($P = .06$, Fig. 1B), other renal diseases ($P = .76$, Fig. 1C), stroke ($P = .33$, Fig. 1D), cancer ($P = .74$, Fig. 1E), AMI ($P = .94$, Fig. 1F), ARF ($P = 0.31$, Fig. 1G), or diabetes ($P = .99$, Fig. 1H) than the non-KD cohort.

4. Discussion

The general health status of living KDs was not inferior to that of the matched comparison non-KD cohort. The results regarding the risk of metabolic syndrome, ESRD, stroke, AMI, and cancers were similar for the KD and non-KD cohorts during the follow-up period. However, KDs were tended to have a higher incidence rate of ARF than non-KDs.

Our data suggest the favorability of living kidney donation, similar to previous studies.[14,15] Notably, living KDs did not have a significantly higher risk of metabolic syndrome or diabetes. Other studies have focused on the mortality and renal function reserves of living KDs. Researchers have found that renal insufficiency is associated with hyperuricemia and metabolic syndrome.[16,17] Mildly elevated uric acid levels, blood

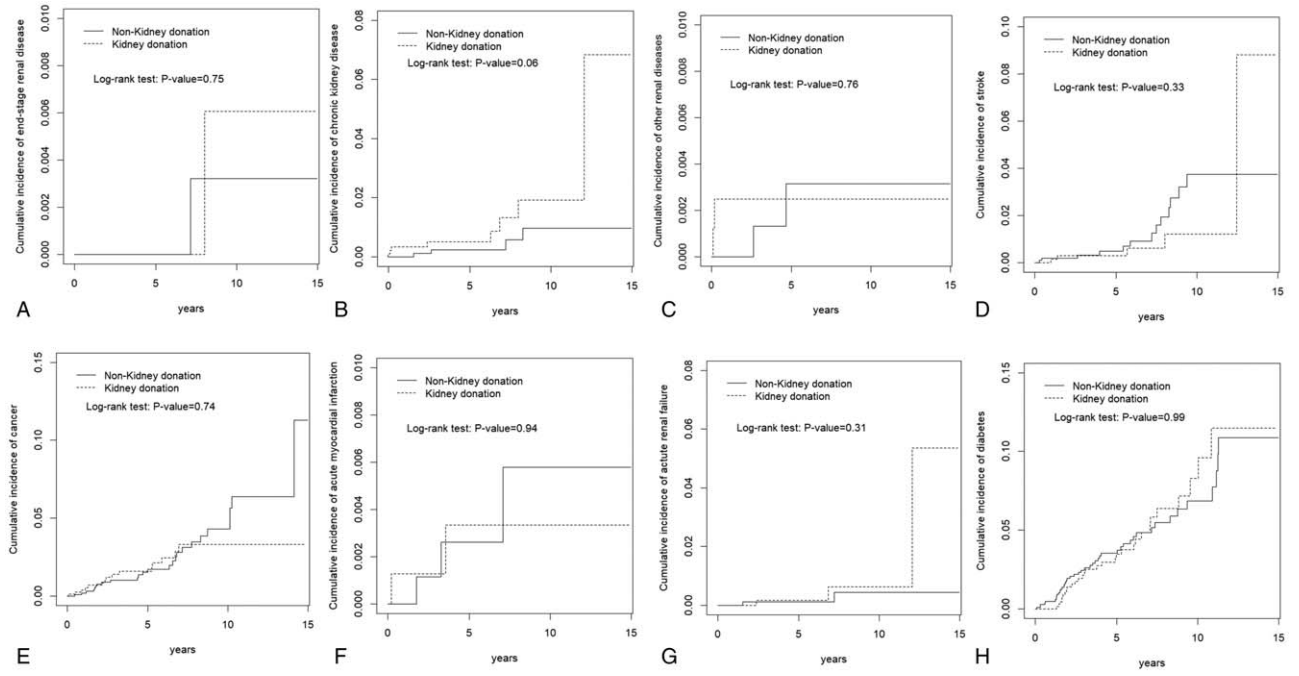

Figure 1. Cumulative incidence of end-stage renal disease (A), chronic kidney disease (B), other renal diseases (C), stroke (D), cancer (E), acute myocardial infarction (F), acute renal failure (G), and diabetes (H) for kidney donors (dashed line) and nondonors (solid line).

pressure, and insulin resistance can cause endothelial cell dysfunction and glomerular sclerosis.[18–20] Moreover, mildly reduced renal reserve can reduce the excretion of uric acid, leading to vicious cycles of renal function decline, hypertension, endothelial cell dysfunction, and hyperuricemia.[21] In our study, the risks of metabolic syndrome, ESRD, stroke, and AMI were similar for the KD and non-KD cohorts. Our data might complement previous findings that living kidney donation is not related to major health disorders.[14,22–25] However, two KD studies have demonstrated that the risk of developing diabetes after kidney donation varies among ethnic groups.[26,27] Canadian aboriginal and US African American populations are both disadvantaged with respect to health care compared with their countries' respective general populations and thus are at a higher risk of diabetes following kidney donation.[26–28] Our data suggest the benefit of kidney donation for Asian populations or for *medicare beneficiaries* in well-covered countries such as Taiwan.

Although the difference in the risk of ARF was nonsignificant between the KD cohort and non-KD cohorts, the higher incidence rate of ARF in the KD cohort warrants special attention. Kido et al described the clinical course of ARF leading to CKD or ESRD in several living KDs.[29] Reduced renal mass might remain a concern for renal reserve capacity in living KDs. Remaining kidney capacity after kidney donation might be insufficient for some KDs when facing illness or stress. Our further analysis revealed that no ARF cases in the KD or non-KD cohorts required temporary dialysis (data not shown). Our result was consistent with that of Lam et al[30] who used acute dialysis as a primary outcome and found no statistically significant difference in the risk of receiving acute dialysis between KDs and nondonors.[30] Interestingly, most ARF events occurred after the first 3 years following kidney donation (too few events to compare); events were not concentrated immediately after kidney donation. Thus, a single contributing cause such as perioperative morbidity or renal aging might not completely account for this finding. We propose that events or stresses may cause ARF in the first 3 years after kidney donation in KDs with insufficient renal reserves for coping with potential prerenal, renal, or postrenal insults.

Our KD cohort exhibited lower incidence rates of all types of cancer than the non-KD cohort. This finding is consistent with that of Lentine et al who reported that the rate of total nonskin cancers was significantly lower among donors than among controls.[28] One possible reason for this finding is that a malignancy exclusion protocol was used to select living donor candidates; therefore, the risk of cancer for KT donors was reduced.[31]

Our study has several strengths. First, the study applied a longitudinal design that was based on the NHIRD that covers more than 99% of Taiwan's citizens and contains comprehensive medical claims data.[10] Therefore, the results are reliable and representative. Second, the selection criteria for the comparison cohort were strict. Because living KDs receive careful physical and psychological evaluations before donation, they are believed to be healthier than the general population.[32] We cautiously selected a comparison cohort through not only age and sex matching but also the exclusion of all comorbidities to achieve an ideal comparison between cohorts. To our knowledge, only Segev et al made such an effort to select appropriately matched cohorts.[7] Third, the follow-up period was relatively long and accompanied by the nationwide and comprehensive longitudinal medical claims of each individual in the cohorts. Because KDs are believed to be healthier than the general population, the long-term medical consequences of KT would not appear until after a long period. Other studies with long follow-up periods of living KDs have been conducted at single academic centers; thus, they lacked generalizability and involved a limited number of patients who completed the follow-up study or employed nationwide data but inappropriately selected comparison cohorts, possibly resulting in statistical artifacts.[24] Our study also has several limitations. First, we did not have the actual blood pressure, glucose level, or glomerular filtration rate data of the study participants, as one previous study did.[33] However, to determine the diagnosis of these disorders correctly, we utilized the ICD-9-CM codes of HTN, diabetes, and renal diseases based on the NHIRD, which is strictly evaluated under the supervision of the NHRI. Moreover, the NHIRD lacks information about smoking, body mass index (BMI), and family history, which might affect the development of conditions including stroke, AMI, and ESRD. Research has suggested creating suitable comparison cohorts for KDs.[22] We adopted a similar study design and used proxies such as obesity for BMI, COPD, and smoking habits. Thus, the comparison controls in this study were not only age and sex matched but also matched in terms of primary cardiovascular risk factors. The possible bias of some unavailable information might have been minimized in this study. Because of the limitations of ICD-9-CM codes, data regarding classification (prerenal, intrinsic, postrenal) of ARF in donors and nondonors were unavailable in this study. Thus, we could not analyze the causes of ARF.

Long-term outcomes, including metabolic risk factors, AMI, ESRD, cancer, and stroke, of living donors were similar to those of the general population in this 13-year follow-up study. Our results bolster the evidence that kidney donation might have nonsignificant physiological or medical sequelae. We recommend carefully informing living donors about the risk of ARF and associated sequelae before donation; educating them to avoid nephrotoxins and regularly following them are necessary for the prevention, early identification, and modification of sequelae associated with ARF.

Author contributions

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Formal analysis: Cheng-Li Lin.
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Project administration: Chia-Hung Kao.
Resources: Chao-Hsiang Chang, Chia-Hung Kao.
Software: Cheng-Li Lin.
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Writing – review & editing: Shih-Yi Lin, Fung-Chang Sung, Chao-Jung Chen, Chia-Hung Kao.

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