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ORIGINAL ARTICLE

Hypertension and renal outcomes in normotensive kidney donors with multiple renal arteries

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SUMMARY

Having multiple renal arteries (MRA) has been linked to hypertension development. Whether kidney donors who are left with MRA in the nondonated kidney incur a higher risk of hypertension has not been studied. We compared the development of hypertension, reduced estimated glomerular filtration rate (eGFR), cardiovascular disease, and mortality in 2624 normotensive kidney donors with MRA in the nondonated kidney and to 2624 propensity score matched normotensive donor controls with a single renal artery. In total, 35% of donors had MRA. Donors with MRA were less likely to have undergone a left nephrectomy (51% vs. 83%). Post-donation hypertension was associated with age, male gender, non-White ethnicity, obesity, and family history of hypertension. Having MRA was not associated with risk of hypertension; aHR 0.92 (95% CI 0.82–1.03), $P = 0.16$. After 17 ± 11 years from donation, a similar proportion of donors with and without MRA developed cardiovascular disease, proteinuria and eGFR <30, <45 and <60 mL/min/1.73 m^2 and the multivariable risks of developing these outcomes were similar in the two groups. Our study did not show increased risk for hypertension, reduced eGFR, proteinuria or cardiovascular disease in donors with MRA in the remaining kidney and without hypertension at donation.

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Key words
multiple renal arteries, kidney transplantation, kidney donors, hypertension

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Introduction

Kidney failure in many former kidney donors has been attributed to hypertension [1,2]. Sanchez *et al.* reported that a third of mainly White kidney donors developed hypertension after donation but the prevalence of hypertension in donors was significantly lower than what is reported in the general population [3]. A recent analysis, however, demonstrated that a third of kidney donors developed hypertension 15 years after donation compared to <10% in nondonor healthy controls [4]. We have recently shown that hypertension development in kidney donors is associated with older age, male gender, a higher body mass index (BMI), and a higher fasting plasma glucose [5]. Importantly, hypertension at donation was not associated with an increased risk of

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kidney failure [5]. In contrast, Al-Ammary *et al.* suggested that predonation hypertension in older donors (>50 years of age) was associated with an increased risk (1.0%) of end-stage kidney disease (ESKD) [6].

Kidney donors typically achieve 70% of predonation GFR shortly after donation and their GFR continues to rise for many years thereafter [7,8]. Therefore, postdonation level of renal function is more than sufficient to excrete a typical dietary amount of sodium. In addition, animals undergoing nephrectomy only develop hypertension if given a large amount of salt or mineralocorticoids [9]. Moreover, the characteristics identified that may be associated with post-donation hypertension, namely age, male, higher BMI, and higher fasting plasma glucose, are analogous to what has been reported in people with a full complement of nephrons. Therefore, if kidney donors are indeed at an increased risk for hypertension, other factors should be considered in order to explain the heightened risk. There is some evidence to suggest that having multiple renal arteries (MRA) may be associated with hypertension in the general population and aberrant renal arterial anatomy has been noted in as many as 80% of those with essential hypertension [10–12]. The possibility that donors left with a kidney with MRA might be predisposed to hypertension development has not been studied. Herein, we describe the prevalence of MRA determined from angiographic studies at the time of donation in a large cohort of kidney donors and compare the development of hypertension, renal and nonrenal outcomes in kidney donors without hypertension at donation who are left with multiple arteries versus a single renal artery in the remaining kidney.

Patients and methods

The RELIVE Study evaluated outcomes of 8922 kidney donors from three US transplant centers: University of Minnesota, Mayo Clinic-Rochester, and the University of Alabama-Birmingham. All donations took place in 1963–2007. Donors' medical records were abstracted for baseline demographic and laboratory data. Prior, or current diagnosis or treatment for hypertension, hyperlipidemia, family history of hypertension, diabetes mellitus, kidney disease, stroke, or heart disease were recorded, as previously described [5,13]. Conventional angiograms, CT and MR angiogram reports were reviewed by study personnel to provide the number of renal arteries in both donated and nondonated kidneys. Blood pressure readings were obtained on multiple occasions during the donor evaluation and the average of the three lowest readings was used as baseline. Hypertension at baseline was defined as having BP ≥140/90 mmHg or requiring anti-hypertensive agents. Between 2010 and 2012, donors were contacted by mail requesting participation in the RELIVE Study. If no response was received, a follow-up letter and at least two phone calls were made by study personnel. In addition, a fee-based Internet service was used to update donors' addresses and phone numbers. Donors were asked about developing diabetes, hypertension, kidney disease, cardiovascular disease (CVD), cancer and other conditions. A subset also provided quality of life surveys. Participating centers provided all follow-up data they had on their donors. In many instances, recipients also provided information about their donors. Postdonation diabetes was considered present if it was self-reported by the donor, a verified fasting plasma glucose ≥126 mg/dL from laboratory work done any time after donation, the requirement for insulin, oral hypoglycemic agents, or evidence of end organ damage (retinopathy or nephropathy). Postdonation hypertension was defined as use of antihypertensive medications specifically used for hypertension treatment or a documented home, center or office-based BP ≥ 140/90 mmHg. CVD was defined as a diagnosis of myocardial infarction, congestive heart failure, stroke, need for coronary or peripheral arterial interventions or coronary artery bypass surgery. Proteinuria was defined by one or more of the following: urine dipstick protein ≥2+, urine protein/osmolality ratio >0.42, urine random protein >15 mg/dL or 24-h protein >300 mg/day. The CKD-EPI equation was used to estimate the eGFR [14]. ESKD was defined by the need for dialysis, being listed for or receiving a kidney transplant. The ascertainment of ESKD in this public dataset was from centers' records, donors themselves or their recipients. These studies were exempt from Institutional Review Board approval as it used publicly available de-identified data. The dataset is available at https://immport.org/shared/study/SDY289.

Statistical analysis

Baseline characteristics were reported as frequencies and proportions for categorical variables and as median and interquartile range (IQR) for continuous variables. Differences between donors with 1 renal artery versus >1 renal artery in the nondonated kidney were compared using the Pearson's chi-square or Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. Propensity score matching without replacement was conducted between donors having a single renal artery in the nondonated kidney versus

donors having MRA in the nondonated kidney with a match ratio of 1:1, caliper of 1 and matching criteria of age, gender, ethnicity, BMI, baseline systolic (SBP) and diastolic blood pressure (DBP), and also baseline serum creatinine. Multiple imputations by chained equations were used to impute missing baseline data: donor relationship to recipient (0.7% missing), BMI (2.7% missing), fasting plasma glucose (1.4% missing), eGFR (0.1% missing), and family history of hypertension (2.3% missing). In the analyses using the complete data, the matched data were obtained from the complete dataset and in the analyses using the multiple imputation, the matched data were obtained from the imputed dataset.

Cox proportional hazard modeling was conducted for postdonation mortality. Postdonation outcomes other than mortality were evaluated using the Fine and Gray competing risk (sub-distribution hazard) modeling [15]. The final Cox proportional hazard and competing risk models were run on both complete and imputed datasets but since both datasets yielded very similar results only the output from the complete dataset is presented. The selection of variables for the Cox proportional hazard and competing risk models were conducted using the least absolute shrinkage and selection operator (Lasso or LASSO) method with the cross-validation selection option and clinical importance of the covariates [16,17]. The number of renal arteries in the nondonated kidney was retained in all multivariable models. Cumulative incidence of postdonation hypertension was estimated using the competing risk method and difference between groups was compared using the sub-distribution hazard ratio.

The eGFR trajectory in donors with serial creatinine measurements was presented with a cubic spline plot. Difference in the eGFR change over time between donors with 1 vs. >1 renal artery was compared using the multivariable generalized linear mixed model. The model used eGFR as the dependent variable and number of renal arteries (1 vs. >1) as the independent variable and employed subject-specific random intercepts and slopes with an unstructured covariance option. Additional evaluated covariates were age, gender, ethnicity, family history of hypertension, BMI, fasting plasma glucose, systolic blood pressure, left nephrectomy, center, and donation year. The coefficient (slope) and 95% CI, which represented the mean change over time in years 0–30 after donation, were reported for each group. As the eGFR slope appeared to change direction after 10 years, a sub-analysis using the piecewise generalized linear model for years 0–10 and years 10–30 were conducted. Since not all donors had serial creatinine measurements, additional propensity score matching without replacement, ratio of 1:1 and caliper of 0.01, was conducted for donors who had and did not have serial creatinine measurement. The matching criteria included the number of renal arteries in nondonated kidney, age, gender, ethnicity, BMI, baseline systolic BP, baseline diastolic BP, and also baseline serum creatinine.

Observed and predicted systolic and diastolic blood pressure readings over time are presented as scatter plots with regression line. The relationship between blood pressure (SBP and DBP) and years from donation was analyzed via a multivariable linear regression model, where we distinguished between the effects of year after donation for both donor groups. Regression diagnostics were conducted for all assumptions. The models were adjusted for: age, gender, ethnicity, family history of hypertension, BMI, fasting plasma glucose, pre-donation systolic blood pressure, left kidney removal, center, and donation year and corrected for the violation of the heterogeneity assumption. The incidence of postdonation outcomes observed at study end was reported as the proportion of the number of new outcomes occurred during the study period divided by the number of donors with data available. All the analyses were performed on Stata version 16.1 (StataCorp LLC, College Station, TX, USA). A P-value of <0.05 was considered statistically significant.

Results

General characteristics

There was a total of 8922 live donations at the three centers between 1963 and 2007. A total of 1331 donors were excluded from this analysis: 46 for missing vital status, 381 did not have information on the number of renal arteries, 184 for not having baseline blood pressure measurements and since hypertension is the main outcome of interest of this analysis we also excluded 909 donors who had BP $\geq$ 140/90 mmHg or were receiving anti-hypertensive medications at the time of donation (Fig. 1). Donors excluded from the analysis, compared to those included, were older (45 vs. 38 years), more likely to be men (47.3% vs. 43.1%), had higher systolic and diastolic blood pressure (since the majority of those excluded had hypertension at donation) and a lower eGFR at donation (84 vs. 89 mL/min/1.73 m^2). There were no differences in relationship to the recipient or laterality of removed kidney (Table S1).

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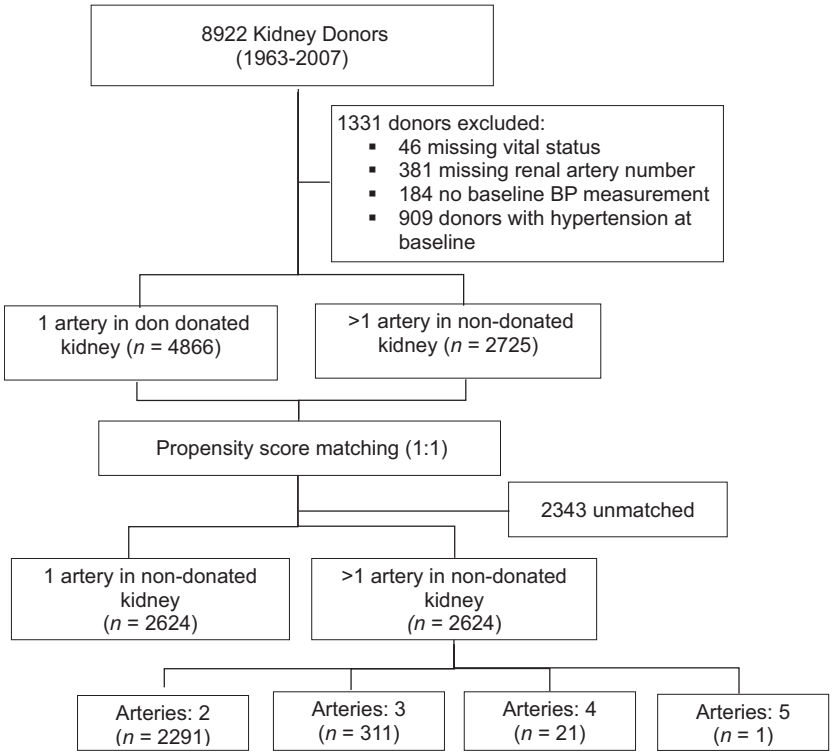

Figure 1 Study participants.

Baseline laboratory and demographic information was available in 91.5–100% of 7591 donors who were included in the analysis (Table S2). Information regarding development of postdonation CVD, diabetes, hypertension, and proteinuria was available for 6929–7591 donors; depending on the outcome (Table S3). All 7951 donors had one serum creatinine measurement after donation; 72% had two or more and 52% had three or more measurements (Table S4).

For the 7591 donors included in the analysis, median age was 39 years, 57% were women, 85% were non-Hispanic White, 9.2% were non-Hispanic Black, 1.8% were Hispanic, 0.9% were Asian, and 3% were categorized as other. The majority (81%) donated to a family member; 71% had at least one first-degree relative with kidney disease and 41% had at least one first-degree relative with hypertension. The median BMI was 25.8 kg/m^2 and eGFR was 88 mL/min/1.73 m^2.

Characteristics of donors by number of renal arteries

Data regarding renal arterial anatomy was available for 8541/8922 donors; 61.2% had single renal arteries bilaterally, 9.1% had >1 artery bilaterally, 3.2% had >1 artery in the donated kidney only and 26.1% had >1 artery in the nondonated kidney. Of the 7591 donors included in the analysis, 4866 had a single renal artery. Donors with >1 renal artery in the remaining kidney were more likely to be men (46.2% vs. 41.3%), White (87% vs. 84%) and were more likely to have undergone a right nephrectomy (49.3% vs. 17.3%) (Table 1). In those individuals with MRA bilaterally, 63.7% donated the left kidney. After propensity score matching donors with single and MRA were highly comparable with the exception of fewer left nephrectomies in donors with multiple arteries (Table 2). Of the 2624 propensity score matched donors with >1 artery in the non-donated kidney, 2291 (87%) had 2 arteries, 311 (12%) had 3, 21 (0.8%) had 4 and one donor had 5 arteries (0.04%) (Fig. 1). Both SBP and DBP were similar in the two donor groups; median at baseline; 120 mmHg and 73 mmHg, respectively (Fig. 2).

Postdonation hypertension development

At study close in 2010–2012 (17 $\pm$ 11 years after donation), 30% of donors, regardless of number of renal arteries, developed hypertension. Development of hypertension was associated with age; adjusted hazard ratio (aHR) 1.01 (95% CI 1.00–1.02), $P = 0.001$, BMI; aHR 1.04 (95% CI 1.02–1.05), $P < 0.001$, a higher fasting plasma glucose at donation; aHR 1.01 (95% CI 1.01–

Table 1. Baseline characteristics of the overall cohort (n = 7591).

Variable	Number of arteries in nondonated kidney		*P*-value
	1 (n = 4866)	>1 (n = 2725)	
Age (years)	39 (30, 47)	38 (30, 46)	0.34
Male	2011 (41.3)	1258 (46.2)	<0.001
Race/ethnicity			
White	4082 (84)	2376 (87)	<0.001
Black	491 (10.1)	187 (6.9)	
Hispanic	101 (2.1)	45 (1.7)	
Asian	44 (0.9)	27 (1.0)	
Other	59 (1.2)	45 (1.7)	
Unknown	89 (1.8)	45 (1.7)	
Related to recipient	3933 (81.1)	2197 (80.8)	0.76
1st degree relative with hypertension	1804 (40.8)	999 (39.6)	0.33
1st degree relative with diabetes	1791 (39.7)	992 (38.5)	0.32
1st degree relative with kidney disease	3341 (72.0)	1910 (72.3)	0.79
1st degree relative with heart disease	1204 (27.3)	738 (29.3)	0.08
Body mass index (kg/m^2)	25.6 (22.8, 29.1)	25.4 (22.7, 28.9)	0.14
Fasting plasma glucose (mg/dL)	92 (85, 99)	92 (85, 99)	0.77
Systolic BP (mmHg)	120 (112, 127)	120 (112, 127)	0.91
Diastolic BP (mmHg)	73 (68, 79)	73 (68, 78)	0.14
Serum creatinine	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.07
eGFR (mL/min/1.73 m^2)	89 (77, 103)	89 (77, 102)	0.76
Left kidney removed	4009 (82.7)	1380 (50.7)	<0.001

Values are in frequency, (%) and median (interquartile range) unless otherwise specified; BP, blood pressure; eGFR, estimated glomerular filtration rate.

1.02), $P < 0.001$, predonation SBP; aHR 1.03 (95% CI 1.02–1.04), $P < 0.0001$ (Table 3). Donation in more recent years was also associated with increased risk of hypertension; aHR 2.80 (95% CI 2.04–3.68), $P < 0.001$ for 2004–2007 compared to 1963–1973 (Table 3). Having MRA was not associated with increased risk of hypertension; aHR 0.95 (95% CI 0.84–1.08), $P = 0.43$ in those with 2 arteries and 1.11 (95% CI 0.87–1.40), $P = 0.40$ in those with >2 arteries (Table 3, Fig. 3).

To obtain more insight into blood pressure evolution in donors by number of renal arteries, we evaluated the relationship between blood pressure (SBP and DBP) and the years from donation in donors with 1 renal artery versus donors >1 renal artery (Fig. 4). Systolic BP rose by 3.56 mmHg/decade in donors with 1 artery and 3.23 mmHg/decade in those with multiple arteries, $P = 0.53$. Diastolic BP rose by 0.86 mmHg/decade and 1.19 mmHg/decade in the two groups respectively, $P = 0.84$.

Incidence of major outcomes at study end

After 17 ± 11 years from donation, there was no difference in the incidence of mortality, CVD, proteinuria or reduced eGFR between donors with versus without MRA. In total, 12% of donors developed CVD, 8% developed diabetes (DM), 30% developed hypertension, 14% developed proteinuria, and 11% developed an eGFR <45 mL/min/1.73 m^2. Death occurred in 5% of donors and cause of death is provided in Table S5. There was a total of 27 cases of ESKD: 9 in donors with a single renal artery and 18 in donors with MRA.

Since developing an eGFR <45 mL/min/1.73 m^2 or kidney failure were rare events, we compared the profile of eGFR in the two donor groups. The mean eGFR change in the first 15 years after donation increased in both donors with one artery and donors with MRA, 1.82 vs. 1.92 mL/min/1.73 m^2 per year respectively; $P = 0.60$. Both groups exhibited a decline in eGFR from years 15–30 postdonation, −2.14 vs. −2.55 mL/min/1.73 m^2 per year respectively; $P = 0.61$ (Fig. 5). Of note, donors with available serial creatinine measurements were more likely to have a first degree relative with hypertension, diabetes and kidney disease (Table S6). In addition, donors with serial measurements were more likely to have developed CVD, diabetes, hypertension, proteinuria, and were more likely to die.

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Table 2. Baseline characteristics of the propensity score matched cohort (n = 5428).

Variable	Number of arteries in nondonated kidney		*P*-value
	1 (n = 2624)	>1 (n = 2624)	
Age (years)	38 (30, 46)	38 (30, 46)	0.78
Male	1201 (46)	1191 (45)	0.78
Race/ethnicity			
White	2308 (88)	2287 (87)	0.18
Black	188 (7.2)	179 (6.8)	
Hispanic	47 (1.8)	44 (1.7)	
Asian	19 (0.7)	25 (1.0)	
Other	25 (1.0)	45 (1.7)	
Unknown	37 (1.4)	44 (1.7)	
Related to recipient	2118 (80.9)	2110 (80.6)	0.74
1st degree relative with hypertension	946 (39.8)	972 (40.0)	0.91
1st degree relative with diabetes	964 (39.6)	959 (38.6)	0.47
1st degree relative with kidney disease	1824 (72.8)	1832 (72.0)	0.54
1st degree relative with heart disease	639 (27.0)	718 (29.6)	0.045
Body mass index (kg/m^2)	25.4 (23, 29)	25.5 (23, 29)	0.88
Fasting plasma glucose (mg/dL)	92 (85, 99)	92 (85, 99)	0.80
Systolic BP (mmHg)	120 (112, 127)	120 (113, 127)	0.63
Diastolic BP (mmHg)	73 (67, 78)	73 (68, 78)	0.97
Serum creatinine	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.64
eGFR (mL/min/1.73 m^2)	89 (77, 103)	89 (77, 102)	0.46
Left kidney removed	2182 (83)	1328 (51)	<0.001

Values are in frequency, (%) and median (interquartile range) unless otherwise specified; BP, blood pressure; eGFR, estimated glomerular filtration rate.

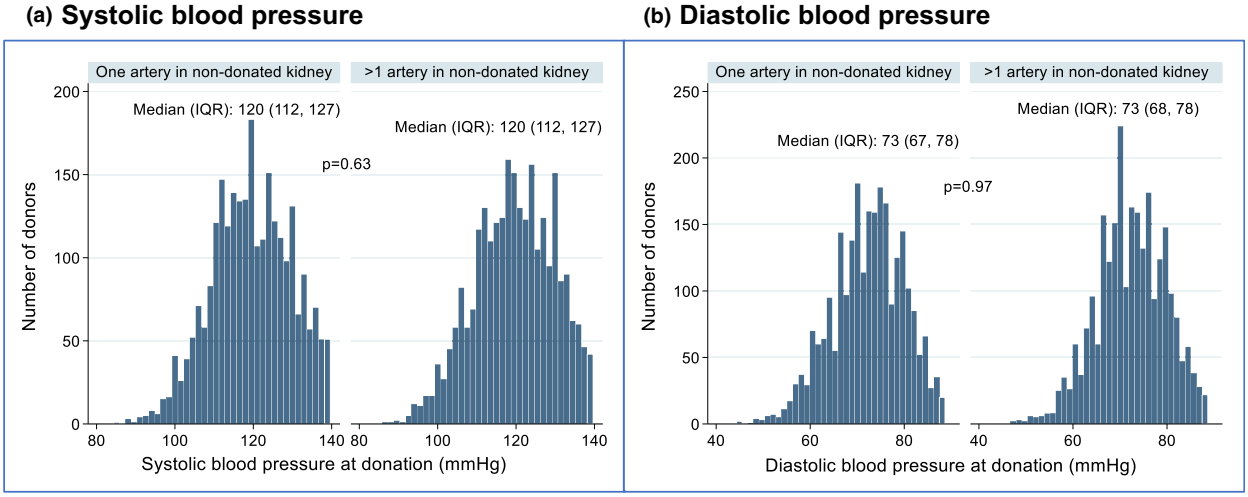


Figure 2 Distribution of baseline blood pressure at donation.

Multivariable competing risks of renal and nonrenal outcomes

The risks of death, CVD, diabetes, proteinuria, and reduced eGFR were not different in those with single versus MRA (Table 4). For ESKD, the aHR 1.84 (95% CI 0.68–5.01), P = 0.23 and for the composite of ESKD or eGFR < 30 mL/min/1.73 m^2, it was 1.27 (95% CI 0.76–2.04), P = 0.32. Tables S7-S14 provide the unadjusted and adjusted risk for mortality and also characteristics associated with CVD, diabetes, proteinuria, eGFR < 60, eGFR < 30 mL/min/1.73 m^2, ESKD or

Table 3. Univariable and multivariable risk of postdonation hypertension: competing risk model in the propensity score matched cohort.

	Unadjusted SHR (95% CI)	*P*-value	Adjusted SHR (95% CI)	*P*-value
Number of arteries in in nondonated kidney				
1	(reference)		(reference)	
2	0.90 (0.81, 1.01)	0.06	0.95 (0.84, 1.08)	0.43
>2	1.10 (0.91, 1.34)	0.32	1.11 (0.87, 1.40)	0.40
Age (years)	1.02 (1.01, 1.02)	<0.001	1.01 (1.00, 1.02)	0.001
Male	1.35 (1.22, 1.49)	<0.001	1.06 (0.94, 1.19)	0.35
Non-White (vs. White)	1.53 (1.31, 1.80)	<0.001	1.02 (0.83, 1.24)	0.88
Related to recipient	0.78 (0.67, 0.91)	0.002	--	--
1st degree relative with hypertension	1.24 (1.12, 1.39)	<0.001	1.12 (1.00, 1.27)	0.06
1st degree relative with diabetes	0.93 (0.84, 1.03)	0.19	--	--
1st degree relative with kidney disease	0.72 (0.63, 0.83)	<0.001	--	--
1st degree relative with heart disease	1.16 (1.04, 1.30)	0.01	--	--
Body mass index (kg/m^2)	1.08 (1.07, 1.09)	<0.001	1.04 (1.02, 1.05)	<0.001
Fasting plasma glucose (mg/dL)	1.02 (1.01, 1.02)	<0.001	1.01 (1.01, 1.02)	<0.001
Predonation systolic BP (mmHg)	1.05 (1.05, 1.06)	<0.001	1.03 (1.02, 1.04)	<0.001
Predonation diastolic BP (mmHg)	1.04 (1.03, 1.04)	<0.001	1.01 (1.00, 1.02)	0.01
Predonation serum creatinine	1.83 (1.38, 2.42)	<0.001	--	--
Predonation eGFR (mL/min/1.73 m^2)	1.00 (0.99, 1.00)	0.002	1.00 (1.00, 1.01)	0.27
Left kidney removed	1.20 (1.08, 1.33)	0.001	1.16 (1.02, 1.32)	0.03
Center				
A	1.66 (1.44, 1.91)	<0.001	1.41 (1.21, 1.65)	<0.001
B	3.67 (3.19, 4.21)	<0.001	3.39 (2.88, 4.00)	<0.001
C	(reference)		(reference)	
Donation year				
1963–1973	(reference)		(reference)	
1974–1983	1.47 (1.20, 1.80)	<0.001	1.37 (1.08, 1.75)	0.01
1984–1993	2.68 (2.15, 3.35)	<0.001	2.09 (1.58, 2.77)	<0.001
1994–2003	4.42 (3.52, 5.57)	<0.001	3.05 (2.30, 4.06)	<0.001
2004–2007	3.70 (2.82, 4.85)	<0.001	2.80 (2.04, 3.86)	<0.001

CI, confidence interval; BP, blood pressure; eGFR; estimated glomerular filtration rate; SHR, sub-distribution hazard ratio.

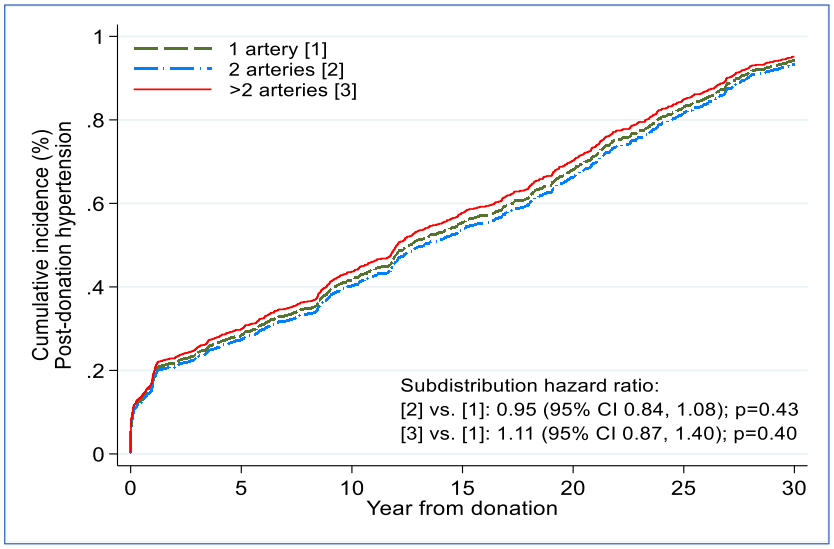
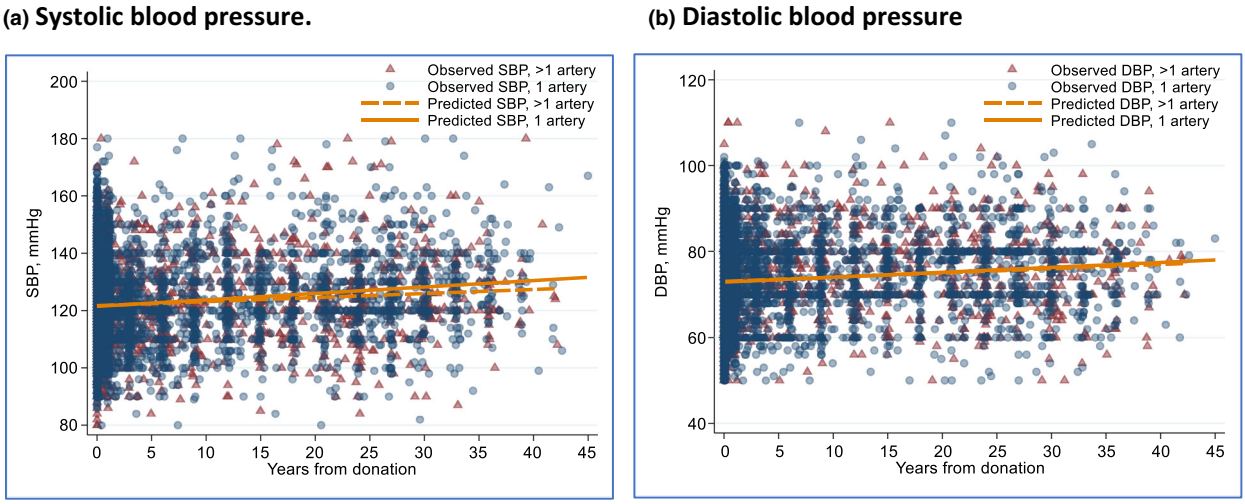
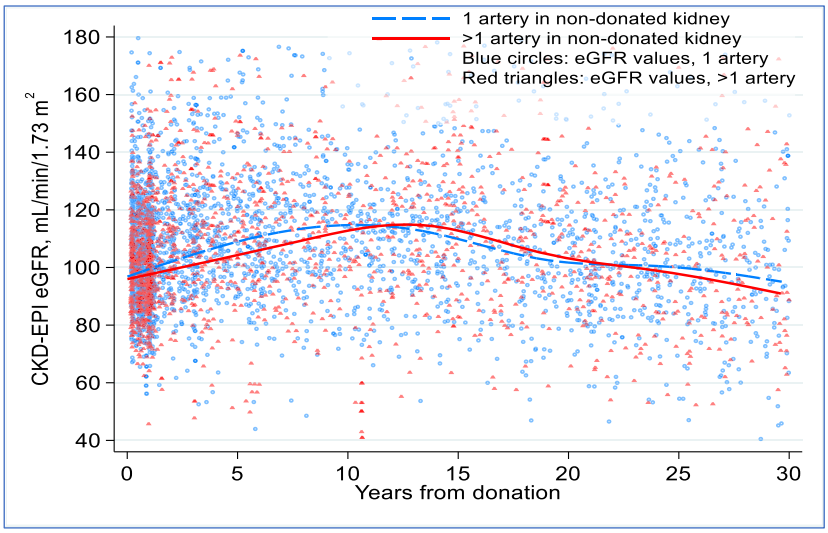


Figure 3 Cumulative incidence of postdonation hypertension.



	Blood Pressure Change/Decade		
	Number of arteries in non-donated kidney		
	1 artery	>1 artery	p-value
Systolic blood pressure(mmHg)	3.56 (2.96, 4.16)	3.23 (2.44, 4.02)	0.98
Diastolic blood pressure(mmHg)	0.86 (0.45, 1.28)	1.19 (0.64, 1.74)	0.11

Figure 4 Observed and predicted postdonation blood pressure profile. (a) Systolic blood pressure. (b) Diastolic blood pressure.



	Mean eGFR change (mL/min/1.73m2 per year)		
	Number of arteries in non-donated kidney		p-value
	1 artery	>1 artery	
Years 0-15	1.82 (1.65, 1.99)	1.92 (1.68, 2.17)	0.60
Years 15-30	-2.14 (-2.53, 1.74)	-2.55 (-3.12, -1.99)	0.61

Figure 5 Estimated glomerular filtration rate trajectory in donors with available serial creatinine in the entire cohort, n = 5284.

eGFR <30 mL/min/1.73 m^2; all employing a competing risk model. Having MRA was not associated with any of these outcomes.

Discussion

These results suggest that kidney donors whose remaining kidney has >1 renal artery are not at an increased

Table 4. Multivariable risk for outcomes other than post-donation hypertension between donors having >1 vs. 1 artery in nondonated kidney in the propensity score matched cohort.

	Adjusted HR or SHR (95% CI)	*P*-value
Death	1.19 (0.90, 1.58)	0.22
Cardiovascular disease	1.01 (0.86, 1.19)	0.92
Diabetes	1.12 (0.83, 1.52)	0.46
Proteinuria	1.10 (0.93, 1.31)	0.27
eGFR < 60 mL/min/1.73 m^2	1.06 (0.99, 1.14)	0.07
eGFR < 45 mL/min/1.73 m^2	1.01 (0.85, 1.21)	0.89
eGFR < 30 mL/min/1.73 m^2	1.19 (0.73, 1.95)	0.48
ESKD	1.84 (0.68, 5.01)	0.23
ESKD or eGFR < 30 mL/min/1.73 m^2	1.27 (0.79, 2.04)	0.32

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SHR, sub-distribution hazard ratio; For death, the reported result is HR (95% CI) and obtained from the multivariable Cox regression model; for outcomes other than death, the reported result is SHR (95% CI) and obtained from the complete risk models.

risk for hypertension and their rate of development of CVD, diabetes, proteinuria and reduced eGFR is similar to those left with a remaining single artery. Donors with MRA were, however, more likely to undergo a right nephrectomy.

Hypertension occurs in a third of kidney donors after donation [3,4]. Risk factors associated with hypertension development are similar to those observed in the general population. Namely, age, male gender, non-White ethnicity, BMI, and having a family history of hypertension. While those covariates are statistically significant, many of the aHR are close to 1 (age, BMI, and higher fasting glucose). This indicates that our study may underestimate the true impact of these variables on the development of hypertension potentially due to the healthy nature of the population of interest and possibly the large sample size. Therefore, if more insight is to be gained regarding why donors may have a higher risk of hypertension development, other demographic, anthropometric, or laboratory variables should be considered.

Multiple renal arteries have been reported in 20–56% of people [10–12]. The marked variability of this estimate reflects variability in the methods used to study arterial anatomy (autopsies vs. angiographic determination) and the characteristics of the populations studied [10]. The available evidence also suggests that MRA are more prevalent in hypertensive individuals; 23–80%. Importantly, in one study utilizing arteriography, 95% of the 400 hypertensive individuals studied had MRA [18]. The prevalence of renal arteries in deceased and live donor transplant is estimated at 19–22% [19–22]. The prevalence of multiple arteries in the 7591 donors included in this analysis who had no hypertension at donation is 35% and in the 909 donors excluded from the analysis for having hypertension at donation was 33%; $P = 0.23$. Collectively, our results, in contrast to the studies cited above, found no difference in the prevalence of MRA in normotensive versus hypertensive donors.

The mechanism postulated to explain the possible link between MRA and hypertension centers around heightened activity of the renin–angiotensin–aldosterone system [10]. This increased activity is postulated to stem from increased renin production in areas supplied by a small caliber accessory renal artery and therefore transporting lower volume and consequently lower pressure [10]. In a small series of 62 individuals undergoing angiography, those with MRA had a higher plasma renin activity at baseline and also after furosemide administration [11]. These studies have not been confirmed in larger cohorts.

Donors with MRA were less likely to undergo a left nephrectomy. We suspect this reflects the general preference of surgeons to remove the kidney with a singular vessel for technical reasons and for easier implantation in the recipient. In fact, in this cohort, the donated kidney had a single renal artery 97% of the time.

Moreover, in donors with bilateral MRA, the left kidney was preserved more often. Data from Lafranca *et al.* suggests that there is quite a bit of variability amongst transplant centers regarding candidacy of donor with MRA [23]. In a survey that was sent to 1128 European Society of Transplantation (ESOT) members and was returned by 331 responders (55% of whom were surgeons), 7% indicated that MRA constituted a contraindication to donation [23]. Moreover, 40–55% of responders said they would only consider donors with a maximum of two renal arteries [23].

The impact of receiving an allograft with MRA has been studied by many investigators. Carvalha *et al.* demonstrated that operative time was slightly longer in those recipients receiving an allograft with MRA (2.43 vs. 2.28 h) [24]. Delayed graft function, patient and allograft survival were, however, similar to those seen in recipients receiving a singular renal artery graft. In a study of 951 recipients of allografts with MRA from live donors, Lafranca *et al.* demonstrated a longer warm ischemia time (by 1.1 min) and a 24-min longer skin-to-skin time [25]. Recipients of these grafts were twice more likely to develop delayed graft function and

interestingly a lower rate of biopsy proven acute rejection. In a meta-analysis of 23 studies of 18 289 kidney transplant recipients, it was noted that delayed graft function and complication rates were higher in recipients of kidneys with MRA [26]. The 5-year patient and graft survival were, however, not different between recipients of single versus multiple renal artery allograft.

To our knowledge, this is the largest study to determine prevalence of MRA using conventional, CT and MR angiography kidney donors. Importantly, the number of arteries in both the donated and nondonated kidneys was determined. There were minimal missing baseline data and the outcomes of interest were available for most donors. Unfortunately, the dataset does not provide information regarding size of the arteries, their location or the practice patterns of the participating centers. Moreover, arterial anatomy was determined via conventional angiography between 1963 and 2000 and CT or MR angiography thereafter. While these methods are highly comparable, it is certainly possible that the prevalence of multiple arteries would be different if one method was used consistently. In a study of 288 live donation, MR angiography failed to predict arterial anatomy in 10% compared 3% with conventional angiography [27]. These rates of discordance between CT and MR angiography and what is encountered at the time of nephrectomy is consistent with other publications which quote 2–14% discordance rates [28–34]. Importantly, it is unclear what the protocols were in the three centers regarding approach to donors with MRA and the observed center effect regarding hypertension development in this analysis is very difficult to explain considering the long period of the study and the evolution of surgical technique from open to largely laparoscopic nephrectomy. It would have also been ideal if serial blood pressure measurements were available for each donor as only the most recent measurement was used to construct blood pressure profile after donation. This approach does not allow precise estimation of the rate of blood pressure change after donation for the individual donor but simply provides a cross-sectional appraisal of blood pressure thus allowing depiction of blood pressure rise with aging. This analysis is also limited by its retrospective nature and the issue of recall bias as this study spans over four decades of kidney donation. Some of the outcomes studied were by self-report. The reliability of self-reported diabetes and hypertension requiring treatment is however excellent [35,36]. Lastly, donors with available serial creatinine measurements were more likely to develop many of the outcomes studied suggesting that these measurements were triggered by clinical events and therefore subject to ascertainment bias.

In summary, the prevalence of MRA in kidney donors is similar to what is reported in the general population. Donors without hypertension at donation who are left with MRA do not appear to have a higher incidence postdonation hypertension and their long-term outcomes are similar to other donors. Barring technical reasons, donors with MRA should not be excluded from donation.

Authorship

HNI: conceived of the idea, design, and contributed to the analysis and manuscript preparation. NVG and DNM: contributed to study design and manuscript preparation. DTN and EAG: conducted the analysis and contributed to manuscript preparation.

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Conflict of Interest

The authors declare no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics: Included versus excluded donors.

Table S2. Data available for baseline variables for donors included in the analysis, (N = 7591).

Table S3. Extent of availability of outcome data in included donors (N = 7591).

Table S4. Availability of serial creatinine measurements (N = 7591).

Table S5. Primary cause of death.

Table S6. Baseline donor characteristics and outcome development in donors with vs. without serial creatinine measurements.

Table S7. Characteristics associated with post-donation mortality: Cox regression model.

Table S8. Characteristics associated with post-donation CVD: competing risk model.

Table S9. Characteristics associated with post-donation diabetes: competing risk model.

Table S10. Characteristics associated with post-donation proteinuria: competing risk model.

Table S11. Characteristics associated with post-donation eGFR < 60 mL/min/1.73 m^2: competing risk model.

Table S12. Characteristics associated with post-donation eGFR < 30 mL/min/1.73 m^2: competing risk model.

Table S13. Characteristics associated with post-donation ESKD: competing risk model.

Table S14. Characteristics associated with post-donation ESKD or eGFR < 30 mL/min/1.73 m^2: competing risk model.

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