ORIGINAL ARTICLE

Long-term kidney function and survival in recipients of allografts from living kidney donors with hypertension: a national cohort study

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SUMMARY

Allografts from living kidney donors with hypertension may carry subclinical kidney disease from the donor to the recipient and, thus, lead to adverse recipient outcomes. We examined eGFR trajectories and all-cause allograft failure in recipients from donors with versus without hypertension, using mixed-linear and Cox regression models stratified by donor age. We studied a US cohort from 1/1/2005 to 6/30/2017; 49 990 recipients of allografts from younger (<50 years old) donors including 597 with donor hypertension and 21 130 recipients of allografts from older (≥50 years old) donors including 1441 with donor hypertension. Donor hypertension was defined as documented predonation use of antihypertensive therapy. Among recipients from younger donors with versus without hypertension, the annual eGFR decline was −1.03 versus −0.53 ml/min/m^2 ($P = 0.002$); 13-year allograft survival was 49.7% vs. 59.0% (adjusted allograft failure hazard ratio [aHR] 1.23; 95% CI 1.05–1.43; $P = 0.009$). Among recipients from older donors with versus without hypertension, the annual eGFR decline was −0.67 versus −0.66 ml/min/m^2 ($P = 0.9$); 13-year allograft survival was 48.6% versus 52.6% (aHR 1.05; 95% CI 0.94–1.17; $P = 0.4$). In secondary analyses, our inferences remained similar for risk of death-censored allograft failure and mortality. Hypertension in younger, but not older, living kidney donors is associated with worse recipient outcomes.

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Key words
GFR, graft survival, hypertension, kidney function, kidney transplantation, living donors

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Introduction

The practice of accepting allografts from living kidney donors with hypertension is growing in an effort to increase living donor kidney transplantation [1–5]. However, limited guidance exists to help inform decision-making—choosing between multiple living kidney donors or evaluating offers in kidney paired donation when considering donors with hypertension. Allografts from donors with hypertension may carry undetected subclinical kidney disease from the donor to the recipient and, thus, lead to adverse outcomes in the recipient [6–14].

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Single-center studies have reported similar outcomes in recipients of allografts from donors with hypertension as compared with recipients of allografts from donors without hypertension [15–17]. But inferences from these studies are based on short-term data (<3 years of follow-up) of only recipients of allografts from older donors with hypertension and insufficiently powered statistical analyses. The intrinsic factors underlying donor pre-existing hypertension may differ by donor age. Hypertension in younger (<50 years old) donors may be the consequence of earlier life-course events such as low birth weight, premature birth, or kidney injury [18–22], and hypertension in older donors (≥50-year-old) donors may reflect glomerular senescence [23–25]. We hypothesized that these two donor phenotypes would pose different long-term risks to the recipient.

We aimed to study the long-term clinical significance of donor hypertension on recipient outcomes addressing the concern that the clinical phenotype of a younger donor with hypertension might be substantively distinct from the older donor with hypertension. To accomplish this, we drew on a national cohort of adult living-donor kidney transplant recipients in the United States (US) and examined the change in kidney function over time and all-cause allograft failure for those with allografts from donors with versus without hypertension, stratified by donor age.

Methods

Data source and study population

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere [26,27]. The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. The SRTR data system includes linkages to the Centers for Medicare & Medicaid Services data and the Social Security Death Master File (SS-DMF) for end-stage kidney disease (ESKD) and mortality ascertainment. We studied a cohort of adult (≥18 years old) living-donor kidney transplant recipients in the US between January 1, 2005 and June 30, 2017.

Exposure

The study exposure of interest was hypertension in the living donor prior to donation. Donor hypertension was defined as both documented predonation use of antihypertensive therapy and history of hypertension, regardless of systolic and diastolic blood pressure (BP). Postdonation new-onset hypertension was not considered an exposure in this analysis [28].

Recipient outcomes

The recipient outcomes of interest were change in kidney function over time and all-cause allograft failure. Death-censored allograft failure and mortality were assessed in secondary analyses. *A priori*, we stratified the study analyses by donor age: younger (<50 years old) and older (≥50 years old) donors because of the following: (i) the pathophysiology of pre-existing hypertension may differ in younger versus older donors [18–23,29]; (ii) high prevalence of hypertension in individuals older than 50 years [30]; (iii) the rise in systolic BP continues throughout life, in contrast to diastolic BP, which rises until approximately 50 years [31,32]; (iv) the practice of accepting individuals with primary hypertension for donation is increasing with the most common cutoff age being 50 years [1,33,34]; and (v) by the age of 50 years, underlying kidney disease in screened individuals with predonation hypertension is less likely to be missed [35–37]. Recipients were followed from the date of transplantation to the date of allograft failure, death, or administrative censorship on June 30, 2019. Kidney function over time was assessed using the post-transplant estimated glomerular filtration rate (eGFR) at 6 months and subsequent eGFR trajectories. The CKD Epidemiology Collaboration (CKD-EPI) creatinine equation was used to calculate eGFR [38]. The CKD-EPI eGFR is not biased by age, given that the equation does adjust for age to account for age-related confounding, and its performance appears comparable in older individuals with that reported in younger individuals [39–41]. We restricted the analysis of eGFR trajectories to 10 years post-transplantation because the eGFR follow-up beyond 10 years was limited. Recipients were censored for death in this analysis and were additionally censored for allograft failure and at 5 years post-transplantation in sensitivity analyses. All-cause allograft failure was defined as the earliest of resumption of maintenance dialysis, relisting for kidney transplantation, retransplantation, or death.

Statistical analyses

Chi-square and Wilcoxon rank-sum tests were used to compare the distribution of recipients' baseline categorical and continuous characteristics, as appropriate, by donor hypertension status. Baseline covariates included in regression models were donor characteristics (age, gender, Black race, obesity [body mass index, BMI ≥30], and biological relationship with the recipient); recipient characteristics (age, gender, Black race, obesity, diabetes, time on dialysis, year of transplantation, private insurance, and peak panel-reactive antibody [PRA]); and transplant characteristics (ABO-incompatibility, human leukocyte antigen [HLA] mismatch, and history of previous transplant).

Multivariable mixed-effects linear regression models were used to estimate the change in kidney function over time in recipients of allografts from donors with versus without hypertension, adjusting for donor, recipient, and transplant characteristics. To account for individual variations in baseline eGFR and its change, random intercepts and random slopes were analyzed.

Kaplan-Meier methods were used to estimate allograft failure and mortality by donor hypertension status. Multivariable Cox regression models were used to estimate risk of allograft failure and mortality in recipients of allografts from donors with versus without hypertension, adjusting for donor, recipient, and transplant characteristics.

Sensitivity analyses were performed to evaluate the robustness of our results after further adjustment for donor systolic BP. We did not adjust for donor systolic BP in our primary analyses because donors with hypertension are cleared for nephrectomy with presumably controlled systolic BP. Sensitivity analyses were also performed to further adjust for donor eGFR. We did not adjust for donor eGFR in our primary analyses because we consider it conceptually not a confounder, but a mediator, of the association between donor hypertension and recipient outcomes. Other sensitivity analyses were conducted to exclude recipients whose donors had hypertension and were on diet control-only therapy ($N = 236$). Multiple imputation with chained equations (20 imputations) was used to account for missing data as per the methods of White and Royston [42]. Missing data comprised recipient BMI [3.6%], recipient diabetes status [0.6%], recipient time on dialysis [1.2%], recipient PRA [1.1%], donor BMI [2.8%], and transplant HLA mismatch [0.8%]. The proportions of missingness of these variables were similar between recipients of allografts from donors with vs. without hypertension.

All analyses were performed using Stata 16.0/MP for Linux (Stata Corp., College Station, TX, USA). All hypothesis tests were 2-sided ($\alpha = 0.05$).

Results

Study population

Our study included 71,120 adult living-donor kidney transplant recipients in the US between January 1, 2005, and June 30, 2017. The median follow-up time was 6.8 (interquartile range [IQR], 4.0–10.0; maximum, 14.5) years.

Among recipients of allografts from younger donors, 597 received allografts from younger donors with hypertension and 49 393 received allografts from younger donors without hypertension. Compared with younger donors without hypertension, younger donors with hypertension were more likely to be of higher age (mean age of 42 vs. 36 years, $P < 0.001$), male (48% vs. 40%, $P < 0.001$), White (73% vs. 64%, $P < 0.001$), and obese (40% vs. 24%, $P < 0.001$). Compared with recipients of allografts from younger donors without hypertension, recipients of allografts from younger donors with hypertension were more likely to be of higher age (mean age of 50 vs. 47 years, $P < 0.001$), White (71% vs. 62%, $P < 0.001$), and obese (37% vs. 31%, $P = 0.001$) (Table 1).

Among recipients of allografts from older donors, 1441 received allografts from older donors with hypertension and 18 689 received allografts from older donors without hypertension. Compared with older donors without hypertension, older donors with hypertension were more likely to be older (mean age of 58 vs. 56 years, $P < 0.001$), male (42% vs. 34%, $P < 0.001$), White (85% vs. 82%, $P = 0.02$), and obese (30% vs. 20%, $P < 0.001$) (Supplementary Appendix, Table S1). Compared with recipients of allografts from older donors without hypertension, recipients of allografts from older donors with hypertension were more likely to be older (mean age of 53 vs. 52 years, $P < 0.001$), White (81% vs. 77%, $P = 0.02$), and obese (35% vs. 31%, $P = 0.004$) (Table 1).

Patterns of blood pressure in living kidney donors

Among younger donors, the prevalence of hypertension at the time of donation rose from 0.9% in 2005 to 1.7% in 2017. For younger donors with versus without hypertension, predonation mean (standard deviation [SD]) systolic and diastolic BP were 130 (14) and 80

Table 1. Baseline characteristics of recipients of allografts from living-kidney donors in the United States between 1/1/2005 and 6/30/2017 by donor hypertension status, stratified by donor age.

	Younger donors (age < 50 years)			Older donors (age≥50 years)		
	Hypertension status*			Hypertension status*		
Recipients of allografts	Yes (*N* = 597)	No (*N* = 49,393)	*P*-value	Yes (*N* = 1,441)	No (*N* = 18,689)	*P*-value
Donor characteristics						
Age at transplant, mean (SD), y	42 (7)	36 (8)	<0.001	58 (6)	56 (5)	<0.001
Male	48%	40%	<0.001	42%	34%	<0.001
Race			<0.001			0.015
White	73%	64%		85%	82%	
Black	13%	14%		5%	6%	
Other	14%	22%		10%	12%	
BMI, median (IQR), kg/m2	29 (27, 31)	27 (24, 30)	<0.001	28 (25, 31)	26 (24, 29)	<0.001
Obesity	40%	24%	<0.001	30%	20%	<0.001
Biologically related with the recipient	53%	56%	0.12	43%	43%	0.98
eGFR at time of transplant, mean (SD)	98 (16)	102 (18)	<0.001	86 (13)	87 (14)	0.001
Systolic BP, mean (SD), mm Hg	130 (14)	120 (13)	<0.001	132 (15)	124 (14)	<0.001
Diastolic BP, mean (SD), mm Hg	80 (9)	73 (9)	<0.001	78 (9)	74 (9)	<0.001
Recipient characteristics						
Age at transplant, mean (SD), y	50 (14)	47 (14)	<0.001	53 (14)	52 (14)	0.002
Male	63%	61%	0.37	64%	62%	0.20
Race			<0.001			0.018
White	71%	62%		81%	77%	
Black	14%	16%		7%	9%	
Other	15%	22%		12%	14%	
BMI, median (IQR), kg/m2	28 (24, 32)	27 (23, 31)	<0.001	28 (24, 32)	27 (24, 31)	0.050
Obesity	37%	31%	0.001	35%	31%	0.004
Diagnosis for ESKD			0.56			0.81
Glomerulonephritis	32%	32%		28%	29%	
Diabetes	23%	23%		24%	23%	
PKD	12%	11%		15%	16%	
Others	33%	34%		33%	32%	
Years on dialysis, median (IQR)	0.5 (0.0, 1.7)	0.6 (0.0, 1.7)	0.10	0.5 (0.0, 1.5)	0.5 (0.0, 1.6)	0.73
Year of transplant			<0.001			<0.001
2005–2008	29%	35%		19%	29%	
2009–2012	31%	32%		31%	33%	
2013–2017	40%	33%		50%	38%	
Private insurance	59%	57%		58%	60%	0.11
Peak PRA, median (IQR)	0 (0, 10)	0 (0, 13)	0.90	0 (0, 12)	0 (0, 12)	0.57
Transplant characteristics						
ABO incompatibility	2%	2%	0.93	2%	2%	0.36

Table 1. Continued.

	Younger donors (age < 50 years)			Older donors (age≥50 years)		
	Hypertension status*			Hypertension status*		
Recipients of allografts	Yes (*N* = 597)	No (*N* = 49,393)	*P*-value	Yes (*N* = 1,441)	No (*N* = 18,689)	*P*-value
HLA zero mismatch	10%	7%	0.027	7%	8%	0.62
History of previous transplant	11%	13%	0.16	11%	12%	0.65

BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; BP, blood pressure; eGFR, estimated glomerular filtration rate; HLA, human leukocyte antigen; IQR, interquartile range; PKD, polycystic kidney disease; PRA, panel reactive antibody; SD, standard deviation.

*Hypertension was defined as documented predonation use of antihypertensive therapy with history of hypertension.

(9) mm Hg versus 120 (13) and 73 (9) mm Hg. Among younger donors with hypertension, 66% had a history of hypertension for 5 years before donation, 6% for 6–10 years, 3% for >10 years, and 25% for an unknown duration; majority (49%) were on nondiuretic only, 11% on diuretic only, 3% on dual therapy of nondiuretic and diuretic, 18% on diet control only therapy, and 19% on an unknown type of therapy.

Among older donors, the prevalence of hypertension at the time of donation rose from 4.1% in 2005 to 10.6% in 2017. For older donors with versus without hypertension, predonation mean (SD) systolic and diastolic BP were 132 (15) and 78 (9) mm Hg versus 124 (14) and 74 (9) mm Hg. Among older donors with hypertension, 57% had a history of hypertension for 5 years before donation, 11% for 6–10 years, 7% for >10 years, and 25% for an unknown duration; majority (62%) were on nondiuretic only, 15% on diuretic only, 7% old donors on dual therapy of nondiuretic and diuretic, 9% on diet control only therapy, and 7% on an unknown type of therapy (Supplementary Appendix, Table S2).

Recipient eGFR trajectories

Among recipients of allografts from younger donors with versus without hypertension, the median unadjusted post-transplant eGFR was 59.8 vs. 62.8 ml/min/m^2 at 6 months, 61.1 vs. 63.5 ml/min/m^2 at 1 year, 59.7 vs. 64.2 ml/min/m^2 at 3 years, 61.3 vs. 63.8 ml/min/m^2 at 5 years, and 56.1 vs. 63.3 ml/min/m^2 at 10 years (Fig. 1a). After adjustment for donor, recipient, and transplant characteristics, the median post-transplant eGFR was similar (61.8 vs. 61.9 ml/min/m^2, $P = 0.92$). The adjusted annual eGFR decline was more rapid in recipients of allografts from younger donors with versus without hypertension (−1.03 vs. −0.53 ml/min/m^2, $P = 0.002$) (Table 2). In sensitivity analyses, our inferences remained unchanged after further adjustment for donor systolic BP (−1.05 vs. −0.53 ml/min/m^2, $P < 0.001$), donor eGFR (−1.02 vs. −0.57 ml/min/m^2, $P = 0.01$), censored for allograft failure (−1.04 vs. −0.53 ml/min/m^2, $P = 0.004$), or censored at 5 year post-transplantation (−0.80 vs. −0.19 ml/min/m^2, $P = 0.011$).

Among recipients of allografts from older donors with versus without hypertension, the median unadjusted post-transplant eGFR was 50.6 vs. 52.4 ml/min/m^2 at 6 month, 50.1 vs. 52.8 ml/min/m^2 at 1 year, 51.2 vs. 52.8 ml/min/m^2 at 3 years, 51.1 vs. 52.0 ml/min/m^2 at 5 years, and 47.4 vs. 51.1 ml/min/m^2 at 10 years

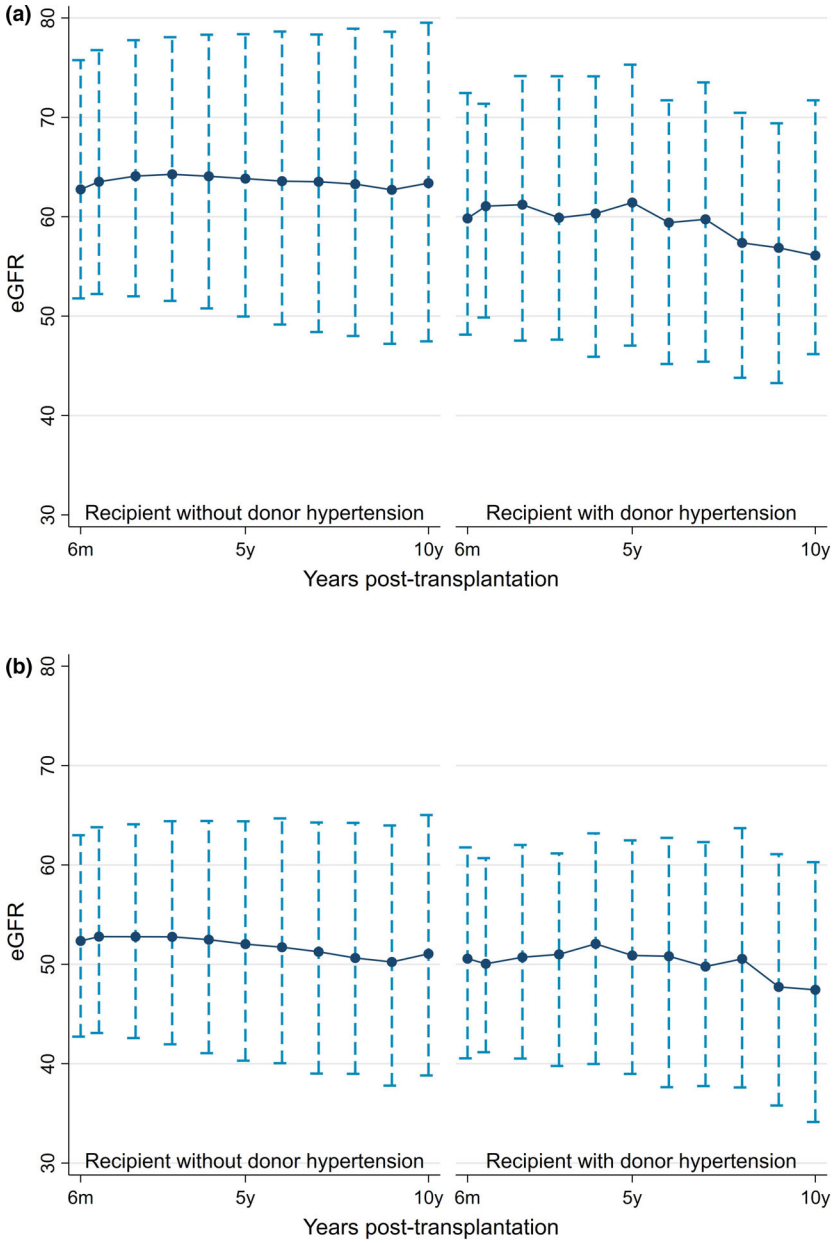

Figure 1 Unadjusted post-transplant eGFR in recipients of allografts from living kidney donors in the united states between 1/1/2005 and 6/30/2017 by Donor Hypertension Status, Stratified by Donor Age. (a) Recipient of allografts from younger donors (age < 50 years), median eGFR (IQR). (b) Recipient of allografts from older donors (age≥50 years), median eGFR (IQR).

(Fig. 1b). After adjustment for donor, recipient, and transplant characteristics, the median post-transplant eGFR was minimally different (51.4 vs. 52.8 ml/min/m^2, $P = 0.003$). The adjusted annual eGFR decline was similar in recipients of allografts from older donors with versus without hypertension (−0.67 vs. −0.66 ml/min/m^2, $P = 0.9$) (Table 2). In sensitivity analyses, our inferences remained unchanged after further adjustment for donor systolic BP (−0.66 vs. −0.65 ml/min/m^2, $P = 0.9$), donor eGFR (−0.71 vs. −0.68 ml/min/m^2, $P = 0.7$), censored for allograft failure (−0.69 vs. −0.66 ml/min/m^2, $P = 0.8$), or censored at 5 years post-transplantation (−0.43 vs. −0.44 ml/min/m^2, $P = 0.9$).

All-cause allograft failure

Among recipients of allografts from younger donors with hypertension, unadjusted all-cause allograft survival was 96.3% at 1 year, 92.6% at 3 years, 84.7% at

Table 2. Post-transplant eGFR in recipients of allografts from donors with hypertension compared with recipients of allografts from donors without hypertension, stratified by donor age.

	Younger donors (age < 50 years)			Older donors (age ≥ 50 years)		
	Donor with hypertension			Donor with hypertension		
	Yes	No	*P*-value	Yes	No	*P*-value
Post-transplant eGFR*	61.8	61.9	0.92	51.4	52.8	0.003
Annual change in eGFR†	−1.03	−0.53	0.002	−0.67	−0.66	0.9

*The model among younger donors adjusted for donor [age (centered at 37), sex (reference group: female), race (reference group: White), BMI (centered at 27), biological relationship (reference group: no biological relationship with the recipient)]; recipient [age (centered at 47), sex (reference group: female), race (reference group: White), BMI (centered at 27), diagnosis for ESKD (reference group: glomerular disease), time on dialysis (centered at 0.6 years), insurance (reference group: no private insurance)]; and transplant [HLA mismatch (reference group: HLA < 100% matched), previous transplant history (reference group: no previous transplant history), year of transplantation (centered at 2009), and ABO incompatible] characteristics. The model among older donors adjusted for donor [age (centered at 55), sex (reference group: female), race (reference group: White), BMI (centered at 27), biological relationship (reference group: no biological relationship with recipient)]; recipient [age (centered at 54), sex (reference group: female), race (reference group: White), BMI (centered at 27), diagnosis for ESKD (reference group: glomerular disease), time on dialysis (centered at 0.4 years), insurance (reference group: no private insurance)], and transplant [HLA mismatch (reference group: HLA < 100% matched), previous transplant history (reference group: no previous transplant history), and year of transplantation (centered at 2010), ABO incompatible] characteristics.

†Adjusted for donor (age, sex, race, BMI, and biological relationship with recipient), recipient (age, sex, race, BMI, diagnosis for ESKD, time on dialysis, and private insurance), and transplant (HLA mismatch, previous transplant history, year of transplantation, and ABO incompatible) characteristics.

5 years, and 49.7% at 13 years. Among recipients of allografts from younger donors without hypertension, unadjusted all-cause allograft survival was 97.1% at 1 year, 92.7% at 3 years, 87.1% at 5 years, and 59.0% at 13 years (Fig. 2a). In a multivariable regression accounting for donor, recipient, and transplant characteristics, there was a significantly higher risk of all-cause allograft failure in recipients of allografts from younger donors with versus without hypertension (adjusted hazard ratio [aHR]: 1.23; 95% CI 1.05–1.43; $P = 0.009$). In sensitivity analyses, our inferences remained unchanged after further adjustment for donor systolic BP (aHR: 1.21; 95% CI 1.04–1.41; $P = 0.02$). A 10 mmHg increase in systolic BP was associated with higher risk of all-cause allograft failure (aHR 1.02; 95% CI 1.00–1.03; $P = 0.01$) (Table 3). Our inferences remained unchanged as well after further adjustment for donor eGFR (aHR: 1.23; 95% CI 1.05–1.43; $P = 0.009$) or excluding the recipients whose donors had hypertension and were on diet control only therapy (aHR: 1.23; 95% CI 1.05–1.43; $P = 0.009$).

Among recipients of allografts from older donors with hypertension, unadjusted all-cause allograft survival was 96.8% at 1 year, 90.3% at 3 years, 83.4% at 5 years, and 48.6% at 13 years. Among recipients of allografts from older donors without hypertension, unadjusted all-cause allograft survival was 96.3% at 1 year, 91.2% at 3 years, 84.4% at 5 years, and 52.6% at 13 years (Fig. 2b). In a multivariable regression accounting for donor, recipient, and transplant characteristics, there was no evidence of a difference in all-cause allograft failure in recipients of allografts from older donors with versus without hypertension (aHR 1.05; 95% CI 0.94–1.17; $P = 0.37$). In sensitivity analyses, our inferences remained unchanged after further adjustment for donor systolic BP (aHR: 1.02; 95% CI 0.92–1.14; $P = 0.66$). A 10 mmHg increase in systolic BP was associated with higher risk of all-cause allograft failure (aHR 1.04; 95% CI 1.02–1.06; $P < 0.001$) (Table 3). Our inferences remained unchanged as well after further adjustment for donor eGFR (aHR: 1.05; 95% CI 0.94–1.17; $P = 0.38$) or excluding the recipients whose donors had hypertension and were on diet control only therapy (aHR: 1.05; 95% CI 0.94–1.17; $P = 0.37$).

Death-censored allograft failure

Among recipients of allografts from younger donors with hypertension, there was a significantly higher risk of death-censored allograft failure in recipients of allografts from younger donors with vs. without hypertension (aHR: 1.28; 95% CI 1.03–1.60; $P = 0.03$) adjusting for donor, recipient, and transplant characteristics. In

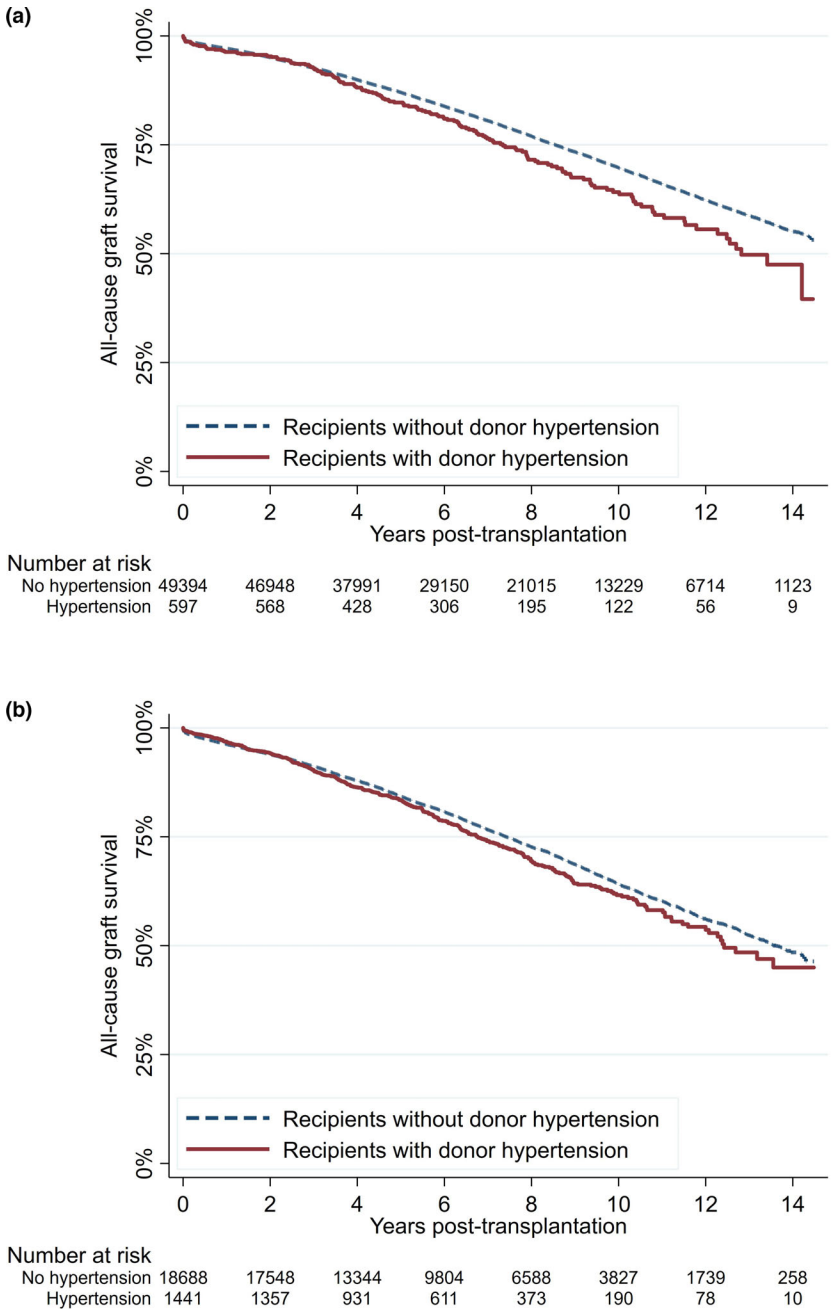

Figure 2 Unadjusted all-cause allograft survival in recipients of allografts from living kidney donors in the United States between 1/1/2005 and 6/30/2017 by donor hypertension status, stratified by donor age. (a) Recipient of allografts from younger donors (age < 50 years). (b) Recipient of allografts from older donors (age ≥ 50 years).

sensitivity analyses, our inferences remained unchanged after further adjustment for donor systolic BP (aHR: 1.27; 95% CI 1.01–1.58; $P = 0.04$). A 10 mmHg increase in systolic BP was associated with non-statistically significant higher risk of death-censored allograft failure (aHR 1.01; 95% CI 0.99–1.04; $P = 0.17$). Our inferences remained unchanged as well after further adjustment for donor eGFR (aHR: 1.29; 95% CI 1.03–1.60; $P = 0.03$) or excluding the recipients whose donors had hypertension and were on diet control only therapy (aHR: 1.35; 95% CI 1.06–1.73; $P = 0.02$).

Among recipients of allografts from older donors with hypertension, there was no evidence of a difference in death-censored allograft failure in recipients of allografts from older donors with versus without hypertension (aHR 1.11; 95% CI 0.95–1.29; $P = 0.2$) adjusting

Table 3. Outcomes in recipients of allografts from donors with hypertension compared with recipients of allografts from donors without hypertension, stratified by donor age.

	Younger donors (age < 50 years) (*N* = 49 990)			Older donors (age≥50 years) (*N* = 20 130)		
All-cause allograft failure	HR	95% CI	*P*-value	HR*	95% CI	*P*-value
Primary analysis model*	1.23	(1.05, 1.43)	0.009	1.05	(0.94, 1.17)	0.4
Sensitivity analysis model†	1.21	(1.04, 1.41)	0.02	1.02	(0.92, 1.14)	0.7

*Hazards ratios for recipients of allografts from donors with hypertension compared with recipients of allografts from donors without hypertension, adjusted for donor characteristics (age, gender, Black race, obesity [body mass index, BMI ≥30], and biological relationship with the recipient); recipient characteristics (age, gender, Black race, obesity, diabetes, time on dialysis, year of transplantation, private insurance, and peak panel-reactive antibody [PRA]); and transplant characteristics (ABO-incompatibility, human leukocyte antigen [HLA] mismatch, and history of previous transplant).

†Sensitivity analysis was performed to evaluate the robustness of the results after further adjustment for donor systolic BP.

for donor, recipient, and transplant characteristics. In sensitivity analyses, our inferences remained unchanged after further adjustment for donor systolic BP (aHR: 1.08; 95% CI 0.93–1.26; $P = 0.3$). A 10 mmHg increase in systolic BP was associated with higher risk of death-censored allograft failure (aHR 1.05; 95% CI 1.02–1.08; $P = 0.001$). Our inferences remained unchanged as well after further adjustment for donor eGFR (aHR: 1.11; 95% CI 0.95–1.29; $P = 0.18$) or excluding the recipients whose donors had hypertension and were on diet control only therapy (aHR 1.10; 95% CI 0.94–1.30; $P = 0.2$).

Mortality

Among recipients of allografts from younger donors with hypertension, there was a significantly higher risk of mortality in recipients of allografts from younger donors with vs. without hypertension (aHR: 1.23; 95% CI 1.02–1.49; $P = 0.03$) adjusting for donor, recipient, and transplant characteristics. In sensitivity analyses, our inferences remained unchanged after further adjustment for donor systolic BP (aHR: 1.21; 95% CI 1.00–1.45; $P = 0.049$). A 10 mmHg increase in systolic BP was associated with higher risk of mortality (aHR 1.03; 95% CI 1.01–1.05; $P = 0.003$). Our inferences remained unchanged as well after further adjustment for donor eGFR (aHR: 1.23; 95% CI 1.02–1.49; $P = 0.03$) or excluding the recipients whose donors had hypertension and were on diet control only therapy (aHR: 1.23; 95% CI 1.02–1.49; $P = 0.03$).

Among recipients of allografts from older donors with hypertension, there was no evidence of a difference in mortality in recipients of allografts from older donors with versus without hypertension (aHR 1.02; 95% CI 0.96–1.16; $P = 0.8$) adjusting for donor, recipient, and transplant characteristics. In sensitivity analyses, our inferences remained unchanged after further adjustment for donor systolic BP (aHR: 1.00; 95% CI 0.87–1.13; $P = 0.9$). A 10 mmHg increase in systolic BP was associated with higher risk of mortality (aHR 1.04; 95% CI 1.01–1.06; $P = 0.002$). Our inferences remained unchanged as well after further adjustment for donor eGFR (aHR: 1.02; 95% CI 0.89–1.16; $P = 0.8$) or excluding the recipients whose donors had hypertension and were on diet control only therapy (aHR 1.02; 95% CI 0.90–1.16; $P = 0.8$).

Discussion

In this US national study of 71 120 adult living-donor kidney transplant recipients from 2005 to 2017, we observed that the overall number of recipients of allografts from donors with hypertension has nearly doubled over time. We found that recipients of allografts from younger donors with hypertension had a more rapid decline in kidney function and 23% higher risk of all-cause allograft failure when compared with recipients of allografts from younger donors without hypertension. By contrast, recipients of allografts from older donors with hypertension had comparable decline in kidney function and risk of all-cause allograft failure when compared with recipients of allografts from older donors without hypertension. Although our results reaffirm the reported 4% increased risk of all-cause allograft failure with each 10 mmHg increase in donor systolic BP, our study inferences remained unchanged after further accounting for donor systolic BP [43]. Likewise,

hypertension in younger, but not older, donors was associated with increased risk of death-censored allograft failure and mortality in secondary analyses.

Our findings among recipients of allografts from older donors with hypertension (mean donor age, 58 years) are consistent with prior, smaller studies. A German single-center study ($N = 174$) reported comparable allograft function three years post-transplant in recipients whose donors had hypertension (mean donor age, 59 years) versus recipients whose donors did not have hypertension [15]. Similarly, a Japanese single-center study ($N = 52$) reported comparable allograft survival two years post-transplant in recipients whose donors had hypertension (mean donor age, 67 years) versus recipients whose donors did not have hypertension [16]. Our study extends these inferences about allografts from older donors with hypertension with data from a large national cohort, followed up for thirteen years. Unlike prior studies where only outcomes in recipients of allografts from older donors with hypertension were investigated, [15–17] here, we additionally studied outcomes in recipients of allografts from younger donors. Our study reveals a higher risk of adverse outcomes among recipients of allografts from younger donors with hypertension (mean donor age, 42 years).

Our findings raise the concern that younger donors with hypertension might have subclinical kidney disease exits at donation. Whereas the proportion of younger donors with hypertension increased between 2005 and 2017, the proportion of young donors overall declined in the US in the same period [2,5]. Given that younger individuals have an increased lifetime risk of ESKD [44], the acceptance of such donors with hypertension is questionable. This may explain why they represent only a small proportion (1.7% in 2017) of donors in this age-group. This is totally coherent with the finding that recipients of allografts from those donors seem to have poorer outcomes with a half-life of all-cause graft survival that is worse than expected in living donor kidney transplantation.

Some limitations of our study are worth noting. Despite having performed the largest study of recipients of allografts from donors with hypertension to date, we recognize the potential limitations of using registry-based data. First, in the absence of implantation biopsy information, we cannot definitively ascertain the presence of subclinical kidney disease in the allograft at implantation nor can we definitively rule out the contribution to our findings of genetic or other unknown clinical factors. Second, there was no information on donor albuminuria; however, clinical practice guidelines specify that donor candidates who have been cleared for nephrectomy should have no evidence of target organ damage (e.g., proteinuria and microalbuminuria) [4,45]. Third, we acknowledge that that our findings likely reflect differences in intrinsic factors underlying donor hypertension between early- and late-onset hypertension, rather than a sudden shift at the age of 50 years. Nevertheless, a *priori*, we stratified the study analyses by donor age with a cutoff of 50 years; within the stratified models, we adjusted for age as a continuous variable.

That said, key strengths of our study include the use of national registry data to study the largest cohort of recipients of allografts from donors with hypertension. This permitted our analyses to be stratified by donor age, which in turn revealed our novel findings. Given the national representativeness of the demographic and clinical characteristics of recipients whose donors had documented hypertension and the reliable ascertainment of the study outcomes, our inferences are likely to be generalizable to the growing number of kidney transplant recipients who receive allografts from donors with hypertension.

In conclusion, we report that hypertension in younger, but not older, donors is associated with worse recipient outcomes through thirteen years after transplantation. These results may help inform decision-making when considering donors with hypertension. Our findings reassure the increasing practice of accepting allografts from older donors with hypertension. However, caution is needed in accepting allografts from younger donors with hypertension.

Authorship

Dr. Al Ammary had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Al Ammary, Yu, Muzaale, and Massie. Acquisition of data: Al Ammary, Massie, and Segev. Analysis and interpretation of data: Al Ammary, Yu, Muzaale, Brennan, Segev, and Massie. Drafting of the manuscript: Al Ammary, Yu, Muzaale, Liyanage, El-Meanawy, and Massie. Critical revision of the manuscript for important intellectual content: Al Ammary, Yu, Muzaale, Liyanage, Crews, Segev, Brennan, El-Meanawy, Alqahtani, Atta, Henderson, Caffo, Welling, and Massie. Statistical analysis: Al Ammary, Yu, Muzaale, Segev, and Massie. Obtained funding: Segev. Administrative, technical, and material support: Segev and Massie. Study supervision: Massie.

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Conflicts of interest

The authors of this article have no conflicts of interest to disclose.

Disclaimer

The analyses described here are the responsibility of the authors alone and do not necessarily reflect the views or policies of the Department of Health and Human Services nor does mention of trade names, commercial products or organizations imply endorsement by the US government. The data reported here have been supplied by the Hennepin Healthcare Research Institute (HHRI) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the US government.

Ethics Statement

This study has been reviewed by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in an appropriate version of the 2000 Declaration of Helsinki as well as the Declaration of Istanbul 2008. This study used deidentified data and was exempted by the Johns Hopkins School of Medicine Institutional Review Board.

SUPPORTING INFORMATION

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

Table S1. Summary table of age and BMI categories among younger and older living kidney donors, stratified by hypertension status.

Table S2. Summary table of systolic and diastolic blood pressures among younger and older living kidney donors with hypertension, stratified by antihypertensive therapy.

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