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Influence of donor sex and age on graft outcome in kidney transplantation

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Abstract

Background and hypothesis

There is a known recipient sex-dependent association between donor sex and kidney transplant survival. We hypothesized that donor age also modifies the association between donor sex and graft survival.

Methods

First deceased donor kidney transplant recipients (1988-2019, n=461,364) recorded in the Scientific Registry of Transplant Recipients, Australia and New Zealand Dialysis and Transplant Registry, and the Collaborative Transplant Study were analyzed. We used multivariable Cox regression models to estimate the association between donor sex and death censored graft loss, accounting for the modifying effects of recipient sex and donor age; donor age was categorized as 5-19, 20-34, 35-49, 50-59, and ≥60 years. Results from cohort-specific Cox models were combined using individual patient data meta-analysis.

Results

Among female recipients of donors aged <60 years, graft loss risk did not differ by donor sex; recipients of female donors ≥60 years showed significantly lower graft loss risks than recipients of male donors of the same age (combined adjusted hazard ratio, aHR 0.90, 95% CI 0.86-0.94).

Among male recipients, female donors aged <50 years were associated with significantly higher graft loss risks than same-aged male donors (5-19 years: aHR 1.11, 95% CI 1.02-1.21; 20-34 years: aHR 1.08, 95% CI 1.02-1.15; 35-49 years: aHR 1.07, 95% CI 1.04-1.10). There were no significant differences in graft loss by donor sex among male recipients of donors aged ≥50 years.

Conclusion

Donor age modifies the association between donor sex and graft survival. Older female donors were associated with similar or lower risk of graft failure than older male donors in both male and female recipients, suggesting a better functional reserve of older female donor kidneys.

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Key learning points:

What was known:

- The association between donor sex and kidney graft survival is modified by recipient sex.
- Older donor age is associated with poorer graft outcomes.

This study adds:

- The association between donor sex and graft survival is modified by donor age.
- Female recipients: no difference in graft loss with younger donors, but significantly lower graft loss with older female donors.
- Male recipients: higher graft loss with younger female donors, but no difference by donor sex with older donors.

Potential impact:

- Graft outcomes with female donors ≥50 years are similar or better compared with male donors the same age.
- Greater confidence in accepting older female donor organs.

Keywords: sex differences, donor age, kidney graft survival, individual patient data meta-analysis

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Introduction

Kidneys from male donors are believed to offer an advantage compared with kidneys from female donors due to a greater number and size of nephrons[1-4]. However, female recipients do not appear to derive the same benefit as males from the larger nephron 'dose' offered by a male donor – likely due to immune reaction against the HY-antigen found on all male tissues[5-9]. At the same time, kidneys are less susceptible to acute kidney injury[10] and ischemia reperfusion injury in a female environment, at least partly due to a protective effect of estrogen[11]. Kidney graft survival is also independently associated with recipient sex[12].

Donor age is among the most powerful predictors of graft survival[13]. Older donor age is associated with poorer regeneration after acute rejection, higher rates of delayed graft function and higher incidence of functional loss due to chronic changes[14, 15]. A higher senescent cell burden in older donors is believed to result in poorer capacity for repair and a profibrotic and proinflammatory milieu[15-17]; this in turn may provoke an immune response[18, 19].

While both donor sex and donor age are known to be associated with graft survival, it is not known whether the association between donor sex and graft survival is modified by donor age. We aimed to determine the independent association between donor sex and death-censored graft loss, accounting for the modifying effects of both donor age and recipient sex, in three of the largest transplant databases worldwide: the American Scientific Registry of Transplant Recipients (SRTR), the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), and the international Collaborative Transplant Study (CTS) database.

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Methods

Data sources and population

This was a retrospective cohort study of recipients of all ages of a first kidney-only deceased donor transplant recorded in the SRTR (transplants January 1, 1988 to December 31, 2018, followed until June 1, 2019), ANZDATA (transplants January 1, 1988 to December 31, 2019, followed until December 31, 2019), or CTS (transplants January 1, 1988 to December 31, 2018, followed until October 28, 2020). We only included patients with at least 90 days of graft survival to focus on long term outcomes rather than losses due to surgical complications. Recipients with a donor <5 years old were excluded due to the known poorer outcomes with very young donors[20-22].

The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the U.S., submitted by the members of the Organ Procurement and Transplantation Network (OPTN). 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 ANZDATA aims to include data for all transplant recipients in Australia and New Zealand with an opt-out consent process. The ANZDATA is linked to the Australia and New Zealand Organ Donor Registry (ANZOD) to optimize capture of transplant activity[23]. The CTS is among the largest voluntary international registries[24]. The CTS includes data from more than 400 centers. Countries with: <1000 transplants, >10% loss to follow-up, or <80% 1-year graft survival were excluded (9.6% of transplants) because recipients from these countries were highly likely to represent a biased sample[12, 25]. To avoid duplicates, recipients from USA, Australia and New Zealand were excluded from the CTS cohort. Countries represented in the CTS cohort are listed in the Supplement.

Exposure and outcome definitions

The primary exposure was *donor sex*. The relation between donor sex and graft failure risk differs by recipient sex[26], due at least partly to immune reaction by female recipients against the HY-antigen on male donor tissues[8]. Therefore, we considered donor-recipient sex combinations to allow us to investigate the association between donor sex and graft survival from the perspective of a female recipient separately from the perspective of a male recipient. We considered the possibility that magnitude or direction of the association between donor sex and graft survival may also differ by donor age by including a donor-recipient sex combination by donor age interaction term in all models. Donor age was categorized as 5-19 (child/adolescent), 20-34 (young adult), 35-49 (early middle-age), 50-59 (late middle-age), and ≥60 (older) years.

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The primary outcome was the *death-censored graft loss,* defined as return to dialysis or re-transplantation, with observation censored at death.

Data harmonization

The distributions of all variables considered for inclusion in the models were examined within each cohort. Where differences between cohorts existed, new variables were generated. E.g., harmonized primary disease categories were created to allow uniform representation across cohorts. Due to significant differences in recipient race distribution between cohorts, race was dichotomized as white vs. other. PRA had to be classified as 0% vs. >0% due differences in the way panel reactive antibody (PRA) was captured between cohorts and over time.

Statistical analysis

Analyses were first performed for each cohort separately, then combined using two-stage individual patient data (IPD) meta-analysis[12, 27, 28]. Descriptive statistics were combined across the 3 cohorts weighted for observation time.

Association between donor sex and graft survival

Cox proportional hazards models were used to estimate the association between donor sex and graft survival for female and male recipients with donors of different ages. Unadjusted analyses were followed by analyses adjusted for the following known potential confounders: recipient age at transplant (piece-wise linear spline), recipient race (white/other), primary diagnosis (diabetes, hypertension, glomerulonephritis, congenital anomalies of the kidneys or urinary tract, cystic kidney disease, other), pre-transplant dialysis (yes/no), PRA (0% vs. >0%), HLA mismatch (continuous), donor-recipient weight ratio (<0.7, 0.7 to <0.9, ≥0.9; not available for CTS), transplant year (continuous), donor cytomegalovirus (CMV; not included for ANZDATA as it was missing in >40%), donor cerebrovascular accident (CVA), donor hypertension, and cold ischemia time (≤18, >18-24, >24-36, >36 hours). Missing data were imputed using multiple imputation methods (15 imputations) based on the fully conditional specification method[29].

Adjusted HR (aHR) represent the hazard for female donor relative to male. Proportionality was assessed by refitting the models, censoring all observation at 5 and 10 years. Results were unchanged, indicating that hazards were proportional.

In the meta-analysis, we used a random-effects model to estimate pooled HR across all 3 cohorts. A random-effects model assumes the observed HR estimates may vary across cohorts due to real

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differences in the association between donor sex and graft loss across cohorts or due to sampling variability. The random effects model synthesizes heterogeneous data as a weighted average of the effect sizes of the cohorts. Heterogeneity in outcome between cohorts was evaluated by Higgins I^2 and the chi-square test of heterogeneity.

Fitted graft failure rates by donor-recipient sex combination

Crude failure rates may be misleading because they do not account for either the changing graft loss risk over time since transplant or for the impact of confounders. To avoid this problem, we calculated fitted cumulative failure rates for each donor-recipient sex and donor-age combination based on the adjusted Cox survival model with multiple imputations described above, at a fixed time point (10 years post-transplant) and the failure rate in recipients with a fixed profile of characteristics.

Sensitivity Analyses

Donor:recipient weight ratio was not available in the CTS. Therefore, models for SRTR and ANZDATA were re-fitted excluding donor:recipient weight ratio. Data on donor CMV were missing in 41% of the CTS and 21.5% of the ANZDATA population, so we also refitted the model for SRTR excluding donor CMV and excluding both donor:recipient weight ratio and donor CMV. Compared to SRTR and CTS cohorts, ANZDATA is a much smaller cohort possibly contributing to greater heterogeneity; therefore, we also refitted the model excluding the ANZDATA.

Data analyses were performed using Statistical Analysis System 9.4 (SAS Institute, Carry NC) and R (version 4.2.0). The study was approved by the McGill University Health Center Research Ethics Board and the Westmead Research Ethics Board.

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Results

We identified 242,030 recipients recorded in the SRTR (69.3% male), 205,399 in the CTS (62.8% male), and 13,935 in ANZDATA (62.4% male) who met inclusion criteria. Overall, there were 62,647 graft losses (25.9%) over a follow-up of 5.4±4.8 years in the SRTR, 50,613 graft losses (24.6%) over a follow-up of 7.1±6.1 years in the CTS, and 3,379 graft losses (24.3%) over a follow-up of 8.5±7.0 years in ANZDATA.

Patient characteristics

An overview of the characteristics of each cohort are presented in Table 1. The distribution of primary disease varied by cohort, with greater proportions in SRTR having diabetes or hypertension as the primary disease than in CTS or ANZDATA. Donors in the SRTR were younger than in ANZDATA or CTS. A larger proportion of SRTR patients underwent pre-emptive transplantation compared to the other two cohorts. The proportion of patients with a PRA >0% was lowest in CTS (19.0%), versus 30.0% in the SRTR and 49.6% in ANZDATA. Cold ischemia times were shortest in the ANZDATA.

Tables 2a (female recipient) and 2b (male recipient) summarize the composition of the observed experience for recipients of female and male donors within each donor age group, pooled across all 3 cohorts. Among both female and male recipients across all donor age groups, a greater proportion of the observation time was contributed by recipients of male donors. Regardless of the recipient sex and across all donor ages, a greater proportion of the observation time contributed by recipients of female than male donors was for transplants where the donor:recipient weight ratio was <0.9. Conversely, a greater proportion of the observation time contributed by recipients of male than female donors represented transplants where the donor:recipient weight ratio was >0.9. Similarly, a greater proportion of the observation time for recipients of donors with cerebrovascular accident as the cause of death and with positive CMV status was contributed by recipients of female than male donors.

Supplemental Tables S1a (SRTR), S1b (CTS) and S1c (ANZDATA) summarize the composition of the observed experience for recipients of male and female donors within each donor age interval for each cohort separately.

Comparison of death-censored graft loss rates by donor sex

There was a significant interaction between donor age and donor-recipient sex combination in both SRTR ($p<0.0001$) and CTS ($p<0.001$); this interaction was not significant in the smaller ANZDATA cohort ($p=0.34$). Forest plots (Figure 1) show the combined adjusted hazard ratios (aHR) for death-censored

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graft loss for recipients of a female versus male donor in each donor age category in the setting of a (a) female recipient, and (b) male recipient as well as for each cohort separately.

As illustrated in Figure 1, the association between donor sex and graft loss differed by recipient sex and by donor age. When the recipient was female, there were no differences in the risk of graft loss by donor sex when the donor was <60 years. However, among female recipients with a donor ≥60 years, the risk of graft loss was significantly lower with a female than a male donor (combined aHR 0.90, 95% CI 0.86-0.94). When the recipient was male and the donor was <50 years, a female donor was associated with a significantly higher risk of graft loss than a male donor: for donors 5-19 years the aHR was 1.11 (95% CI 1.02-1.21), for donors 20-34 years the aHR was 1.08 (95% CI 1.02-1.15), and for donors 35-49 years the aHR was 1.07 (95% CI 1.04-1.10). There was no difference in graft loss risk by donor sex among male recipients of a donor 50-59 years old. Among male recipients of a donor aged ≥60 years, the combined aHR suggested a slightly lower risk of graft loss with a female than male donor (combined aHR 0.92, 95% CI 0.82-1.03), but this was not statistically significant.

Between Cohort Heterogeneity

Among both male and female recipients, the aHRs for each cohort were similar. However, there was some heterogeneity between cohorts, even after excluding the ANZDATA (Supplemental Table S2).

Fitted Absolute Graft Loss Rates

Fitted absolute graft loss rates were comparable across cohorts. Overall, rates were lowest in CTS and highest in ANZDATA, though differences were small. Even where there were statistically significant differences by donor sex, absolute differences in graft loss rates by donor sex were quite small (Table 3). Among female recipients with a donor ≥60 years, graft loss rates were only lower by 0.5 per 100 person-years of observation (pyr) in ANZDATA, 1.5 per 100 pyr in CTS and 1.9 per 100 pyr in SRTR. Among male recipients with donors <50 years, graft loss rates were 0.7 per 100 pyr lower to 0.8 per 100 pyr higher with a male than female donor in ANZDATA, 1.3 to 1.9 per 100 pyr lower with a male than female donor in CTS, and 0.7 to 0.9 per 100 pyr lower with a male than female donor in SRTR.

Sensitivity Analyses

For both female and male recipients across all donor age categories, the HR from models excluding donor:recipient weight ratio (Supplemental Table S3) were slightly higher than those from models including this variable. The results of models excluding the donor CMV were identical to those that included it (Supplemental Table S4). The model excluding ANZDATA showed similar estimates to the main analyses (Supplemental Table S2).

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Discussion

This study combined the data of 461,364 transplants recipients from three of the largest transplant registries worldwide in an individual patient data meta-analysis to demonstrate an association between donor sex and the risk of graft loss that differs not only by recipient sex but also by donor age. When the recipient was female, kidneys from female donors <60 years showed similar outcomes to kidneys from male donors of the same age, whereas kidneys from female donors ≥60 years showed lower graft loss rates than kidneys from male donors ≥60 years. In contrast, when the recipient was male, graft loss rates were higher with female than male donors <50 years, but did not differ by donor sex when the donor was ≥50 years. In fact, the point estimate suggested that when the donor was ≥60 years, female donors may be associated with a lower graft loss risk than male donors.

Female sex and older donor age have been described as markers of inferior donor organ quality[1, 2, 13]. Our data provide evidence that the association between donor sex and graft loss differs by donor age and by recipient sex. Older female donors are not inferior to older male donors among male recipients and even provide superior outcomes among female recipients. These findings, which suggest that functional reserve may be better in kidneys from older women than older men, are supported by a recent study showing sex differences in age-related GFR decline[30]. While GFR was lower in women than in men, a steeper GFR decline over time was observed in men ≥60 years compared with the same aged women [30]. An analysis of American adult kidney transplant recipients showed male donors to be associated with higher rates of delayed graft function than female donors[11]. Our data suggest that older female kidneys may have advantages even outside the female environment; mechanisms for this advantage need further exploration.

Among male recipients, female donors under 50 years old were associated with a higher risk of graft loss than male donors under 50 years old. It is likely that age-related nephron loss is minimal among young donors such that the greater nephron mass afforded by male kidneys provides an advantage. The possibility that androgens promote kidney growth[31] post-transplant differently by donor sex must also be considered. Among female recipients with donors <60 years old, we saw no association between donor sex and graft loss rate. It is likely that the advantage of greater nephron mass offered by a male donor is counterbalanced by the disadvantage of an immunologic reaction against the HY antigen[8, 9] resulting in no net difference in outcome by donor sex. This finding is consistent with a USRDS study that showed a smaller advantage associated with a male (vs. female) donor for female recipients than for male recipients[26]. A UK Transplant Registry study of 1,309 pediatric kidney transplant recipients (mean donor age 28-32 years) showed no independent association between donor sex and graft loss rates for either male or female recipients[32], but power was limited to detect

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differences. An earlier analysis from CTS including 124,911 adult-only, first kidney transplantations demonstrated a higher risk of death or graft loss in female recipients of male donors compared to female recipients of female donors and similarly a higher risk of death or graft loss in male recipients of female than male donors[1]. This study analyzed the outcome graft failure or death (including death with graft function), while our study analyzed death-censored graft survival making a direct comparison difficult.

This is the largest and the first study investigating the modifying effects of both recipient sex and donor age on the association between donor sex and graft survival. Despite its strengths, this study has some limitations. Due to the nature of observational studies, drawing causal inferences is not possible. While most variables were similarly recorded across registries, there were some differences. Information on donor weight was not available in the CTS, therefore donor-recipient weight ratio could not be included in the CTS analysis. The sensitivity analyses excluding donor:recipient weight ratio from the models for SRTR and ANZDATA suggest that HR may have been overestimated in the CTS models, resulting in overestimation of pooled HR. If this was the case, then it is possible that older female donors are associated with a slightly larger advantage over older male donors among female recipients and may even have an advantage over older male donors in male recipients. Overestimation of the HR may also mean that the poorer outcomes observed for younger female than male donors among male recipients may be exaggerated. The observed heterogeneity between cohorts may be partly related to the inability to adjust for donor:recipient weight ratio in CTS. Lastly, reporting to the SRTR and ANZDATA is obligatory, but the CTS is a voluntary registry; the possibility of reporting bias could not be excluded.

Conclusions

By combining data from three large registries, we demonstrate a modifying effect of donor age on the association between donor sex and graft survival. Among male recipients of young donor kidneys, graft loss risk was higher with female than male donors, whereas among female recipients of young donor kidneys, there were no differences in graft loss rates by donor sex. Notably, among both male and female recipients of kidneys from donors over 60 years, graft loss rates were lower with female than male donors – though only significantly for female recipients. Our findings point towards better functional reserve of older female donor kidneys and should result in greater confidence in accepting such organs.

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Data Availability Statement

The SRTR and ANZDATA data are publicly available. Procedures to request data are available at www.srtr.org and www.anzdata.org.au.

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Some data reported here have been supplied by the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the Australia and New Zealand Dialysis and Transplant Registry.

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Authors' Contributions

A.M. and R.I.S contributed equally. A.M. interpreted the data, drafted, finalized and approved the article. R.I.S. interpreted the data, drafted, finalized and approved the article. X.Z. prepared, analyzed, interpreted the data, revised and approved the article. M.D. prepared, analyzed, interpreted the data, revised and approved the article. B.D. prepared, analyzed, interpreted the data, revised and approved the article. C.S. interpreted the data, revised and approved the article. R.S.P. interpreted the data, revised and approved the article. G.W. interpreted the data, revised and approved the article. B.J.F. designed the study, acquired funding, interpreted the data, revised, finalized and approved the article.

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Conflict of Interest Statement

All authors declared no competing interests.

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Table 1: Overview of patient characteristics (patient n, %)

	SRTR	CTS	ANZDATA
Patients	242,030	205,399	13,935
Censoring			
Graft loss	62,647 (25.9)	50,613 (24.6)	3,379 (24.3)
Death	60,163 (24.9)	40,152 (19.5)	2,921 (21.0)
Follow-up			
(years, mean ± SD)	6.1 ± 5.4	7.1 ± 6.1	8.5 ± 7.0
(years, median, IQR)	4.8 (2.0-8.9)	6.0 (2.0–10.6)	6.8 (2.7–12.6)
Donor-recipient sex combination (%)			
Female-Female	38,549 (15.9)	33,035 (16.1)	2,286 (16.4)
Male-Female	56,771 (23.5)	43,595 (21.2)	2,961 (21.2)
Female- Male	57,093 (23.6)	53,533 (26.1)	3,594 (25.8)
Male-Male	89,617 (37.0)	75,236 (36.6)	5,094 (36.6)
Recipient age at transplant			
(years, median, IQR)	51 (40-61)	50 (38–60)	51 (40-60)
Recipient race			
White	204,210 (84.4)	131,264 (91.2)	10,043 (72.1)
Other	37,820 (15.6)	12,615 (8.8)	3351 (27.9)
Missing	0 (0)	61,520 (30.0)	541 (3.9)
Primary disease			
Diabetes	63,674 (26.3)	16,429 (8.4)	1,804 (13.0)
Hypertension	60,647 (25.1)	18,545 (9.5)	823 (5.9)
Glomerulonephritis	58,267 (24.1)	66,898 (34.3)	5,889 (42.4)
CAKUT	7,835 (3.2)	22,171 (11.4)	1,272 (9.2)
Cystic	22,384 (9.3)	28,081 (14.4)	2,022 (14.6)
Other	28,987 (12.0)	42,837 (22.0)	2,086 (15.0)
Missing	236 (0.1)	10,438 (5.1)	39 (0.3)
Donor age			
(years, median, IQR)	38 (23-51)	47 (32–58)	45 (29-57)
Donor age			
5-19	40,495 (16.7)	21,549 (10.5)	1,751 (12.6)
20-34	66,250 (27.4)	36,335 (17.7)	2,760 (19.8)
35-49	69,310 (28.6)	54,523 (26.5)	3,778 (27.1)
50-59	45,323 (18.7)	45,928 (22.4)	2,948 (21.2)
≥ 60 years	20,652 (8.5)	47,064 (22.9)	2,698 (19.4)
Transplant year			
1988–1994	41,822 (17.3)	44,298 (21.6)	2,513 (18.0)
1995–1999	32,306 (13.6)	33,747 (16.4)	1,650 (11.8)
2000–2004	34,778 (14.4)	34,183 (16.6)	1,691 (12.1)
2005–2009	41,843 (17.3)	34,066 (16.6)	1,718 (12.3)
2010–2013	43,777 (18.1)	35,018 (17.0)	2,672 (19.2)
2014–2019	47,504 (19.6)	24,087 (11.7)	3,691 (26.5)
Cold ischemia time (hours)			
0-18	117,398 (52.0)	106,712 (57.9)	10,885 (80.9)
>18–24	50,742 (22.5)	47,614 (25.8)	2,131 (15.8)
>24-36	46,640 (20.6)	25,920 (14.1)	431 (3.2)
>36	11,177 (5.0)	4,010 (2.2)	12 (0.1)
Missing	16,073 (6.6)	21,143 (10.3)	476 (3.4)
Transplantation type			

For Peer Review

Pre-emptive	18,738 (8.1)	4,054 (2.2)	145 (1.0)
With prior dialysis	214,003 (92.0)	177,672 (97.8)	13,790 (99.0)
Missing	9,289 (3.8)	23,673 (11.5)	0
Donor-recipient weight ratio (%)			
<0.7	33,593 (16.1)	N/A	1,536 (11.7)
0.7-<0.9	48,697 (23.4)		2,925 (22.4)
≥0.9	125,877 (60.5)		8,627 (65.9)
Missing	33,863 (14.0)		847 (6.1)
HLA mismatches			
Mean ± SD	3.9 ± 1.6	2.99 ± 1.42	3.6 ± 1.6
Missing	839 (0.4)	21,360 (10.4)	9 (0.1)
PRA (%)			
0%	161,743 (69.6)	118,854 (81.0)	7,016 (50.4)
>0%	70,696 (30.4)	27,844 (19.0)	6,902 (49.6)
Missing	9,591 (4.0)	58,701 (28.6)	17 (0.1)
Donor CMV			
Positive	147,801 (61.2)	97,031 (60.2)	6,929 (84.3)
Negative	93,642 (38.8)	64,245 (39.8)	1,289 (15.7)
Missing	587 (0.2)	44,123 (21.5)	5,717 (41.0)
Donor cause of death			
CVA	83,960 (34.7)	102,690 (56.6)	6,463 (47.8)
Other	157,922 (65.3)	78,656 (43.4)	7,048 (52.2)
Missing	148 (0.1)	24,053 (11.7)	424 (3.0)
Donor hypertension			
Yes	52,378 (25.8)	21,161 (11.6)	2,607 (22.0)
No	150,865 (74.2)	160,935 (88.4)	9,260 (78.0)
Missing	38,787 (16.0)	23,303 (11.3)	2,068 (14.8)

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Table 2: Composition of the contrasted experience, pooled across SRTR, ANZDATA, and CTS, by donor age and sex, for **(A)** female and **(B)** male recipients

(A) Female recipients	Percentage of person-years of observation									
Donor age	**5-19 years**		**20-34 years**		**35-49 years**		**50-59 years**		**≥ 60 years**	
Donor sex	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
Number of patients	8,555	17,633	12,765	28,116	22,032	26,971	17,294	18,377	13,224	12,230
Person-years of observation	67,771	142,009	91,575	207,402	151,765	186,022	108,230	113,307	70,938	64,017
Graft failures	2,325	5,042	3,029	6,666	5,793	6,812	4,674	4,728	3,510	3,303
Age in years at transplant (%)										
0-12	7.2	6.5	3.1	2.6	1.6	1.2	0.4	0.5	0.1	0.2
13-24	11.6	11.8	8.4	8.5	5.4	5.3	3.0	2.6	1.0	1.0
25-44	36.6	36.3	37.2	37.9	35.5	34.9	26.9	27.2	15.1	13.7
45-59	32.0	33.5	36.2	36.4	40.2	40.8	46.5	45.4	36.6	37.2
≥ 60 years	12.7	11.8	15.1	14.7	17.3	17.7	23.1	24.3	47.0	47.9
Recipient race (%)										
White	74.9	74.8	74.6	74.2	75.0	74.8	76.0	75.4	78.7	79.7
Others	25.1	25.2	25.4	25.8	25.0	25.2	24.0	24.6	21.3	20.3
Missing	7.3	7.9	9.3	8.6	11.4	11.4	14.4	15.2	26.0	26.2
Primary disease (%)										
Diabetes	11.7	12.0	13.5	12.8	13.2	12.3	14.2	13.0	12.3	12.6
Hypertension	11.6	12.1	12.8	13.5	13.2	13.6	13.6	14.0	14.2	13.1
GN	32.5	33.0	31.3	32.4	31.0	30.4	28.7	28.5	26.2	25.3
CAKUT	11.9	10.7	10.0	9.9	10.0	9.8	9.1	9.5	8.7	9.2
Cystic	13.0	13.6	14.2	14.0	14.8	16.3	17.3	17.5	19.6	21.2
Other	19.2	18.6	18.2	17.4	17.8	17.5	17.0	17.5	18.6	18.7
Missing	1.5	1.7	1.5	1.7	2.2	2.3	2.8	2.5	3.5	3.8
Cold ischemia time (hours)										
0-18	50.9	49.1	51.6	51.2	53.9	52.0	55.1	53.5	60.1	58.9
19-24	25.7	26.6	25.7	26.0	25.6	26.3	26.0	25.5	24.0	25.2
25-36	19.5	20.5	18.8	19.3	17.3	17.9	15.9	17.7	13.7	13.7
>36	3.9	3.8	3.9	3.5	3.2	3.8	3.1	3.3	2.1	2.3
Missing	8.9	8.8	8.2	7.7	8.7	7.5	7.8	7.4	7.4	7.6
Transplant year										

For Peer Review

1988-1994	32.0	34.7	31.1	31.6	22.2	23.7	16.6	17.0	10.3	10.2
1995-1999	21.6	22.4	18.7	18.6	19.8	19.2	18.0	16.9	15.7	15.3
2000-2004	19.6	18.6	16.8	17.2	21.2	20.0	22.4	21.0	22.4	22.0
2005-2009	15.0	13.7	15.7	16.0	19.2	19.0	21.6	22.6	25.1	25.0
2010-2013	8.7	7.9	12.7	12.2	13.3	13.3	16.0	16.5	19.9	20.8
2014-2018	3.1	2.6	4.9	4.5	4.3	4.8	5.3	5.9	6.6	6.8
Pre-emptive transplant										
Yes	7.5	6.8	6.9	6.5	6.1	5.9	5.7	5.6	4.8	4.5
Missing	7.1	6.9	7.5	6.3	6.7	6.0	6.1	5.9	4.9	5.1
Donor-recipient weight ratio*										
<0.7	40.1	26.3	13.5	4.4	10.6	3.2	10.2	3.1	9.7	2.4
0.7-<0.9	22.3	17.8	23.9	14.3	22.0	13.0	23.7	12.8	22.9	12.8
>0.9	37.6	55.8	62.6	81.3	67.5	83.7	66.1	84.1	67.4	84.8
Missing**	47.9	49.3	50.1	49.2	54.3	54.5	56.7	58.5	69.6	71.0
Missing (SRTR & ANZ)***	18.1	20.5	16.1	16.7	14.4	13.0	12.2	10.9	12.4	11.3
HLA mismatches										
0-1	15.4	15.5	16.8	15.5	16.5	16.9	16.5	15.0	11.5	11.1
2-3	34.7	35.7	35.6	35.6	37.7	38.1	37.7	38.3	35.6	37.7
4-6	49.9	48.9	47.6	48.9	45.8	45.0	45.8	46.7	52.9	51.3
Missing	3.7	3.7	3.7	3.7	4.2	4.0	5.1	4.6	6.7	6.8
PRA										
0%	66.4	66.0	65.3	64.1	65.1	65.8	68.0	67.7	72.5	71.5
>0%	33.6	34.0	34.7	35.9	34.9	34.2	32.0	32.3	27.5	28.5
Missing	11.6	11.5	13.4	12.5	14.8	13.8	15.5	16.1	17.5	17.9
Donor cause of death										
CVA	13.4	7.7	32.8	14.4	66.0	45.0	75.7	59.8	81.0	67.5
Others	86.6	92.3	67.2	85.6	34.0	55.0	24.3	40.2	19.0	32.5
Missing	7.0	6.4	7.3	6.8	5.7	6.2	4.7	5.3	4.7	4.3
CMV positive donor										
Yes	52.4	50.9	61.3	53.9	64.8	57.4	69.9	62.9	75.4	68.8
Missing	9.0	9.8	9.8	9.8	10.0	10.1	11.1	10.8	16.4	16.8
Donor hypertension										
Yes	0.6	0.7	5.6	3.3	19.9	17.0	26.7	27.5	30.2	29.5

For Peer Review

Missing	21.2	23.6	20.2	20.6	14.2	14.9	10.8	10.9	8.1	7.3

(B) Male recipients	**Percentage of person-years of observation**									
Donor age	**5-19 years**		**20-34 years**		**35-49 years**		**50-59 years**		**≥ 60 years**	
Donor sex	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
Number of patients	11,793	25,814	19,483	44,981	33,612	44,996	26,958	31,570	22,374	22,586
Person-years of observation	90,449	205,105	136,614	327,261	223,773	302,437	160,860	185,999	111,167	111,864
Graft failures	3,260	6,747	4,449	9,720	8,788	10,567	7,195	7,984	5,938	5,878
Age in years at transplant (%)										
0-12	8.5	7.7	3.1	2.7	1.5	1.3	0.5	0.3	0.1	0.1
13-24	11.7	11.4	7.9	7.9	4.8	4.5	2.9	2.4	1.9	0.8
25-44	36.5	37.3	38.5	38.7	35.3	35.3	27.7	26.1	11.4	13.3
45-59	31.5	32.6	35.9	36.5	40.8	41.6	45.0	46.1	42.6	36.7
≥ 60 years	11.8	11.0	14.7	14.2	17.5	17.4	23.9	25.1	42.4	49.2
Recipient race (%)										
White	77.9	77.4	76.7	76.6	76.8	76.9	77.8	77.8	82.3	82.9
Others	22.1	22.6	23.3	23.4	23.2	23.1	22.2	22.2	17.7	17.1
Missing	8.7	8.2	9.6	9.5	12.0	12.5	15.1	16.0	27.6	26.9
Primary disease (%)										
Diabetes	12.5	13.4	14.9	14.6	15.8	15.5	16.7	17.4	17.4	17.1
Hypertension	15.5	16.2	17.1	16.9	17.0	17.6	17.3	17.5	17.3	16.8
GN	33.1	33.4	32.8	33.7	33.0	33.0	30.7	31.1	30.7	30.4
CAKUT	11.6	10.3	8.1	8.1	6.4	6.5	5.8	5.4	4.6	4.9
Cystic	10.8	10.6	10.3	10.7	11.5	11.5	12.9	13.4	12.7	12.9
Other	16.5	16.1	16.8	15.9	16.4	16.0	16.6	15.2	17.5	17.9
Missing	1.7	2.0	1.9	1.8	2.4	2.2	3.0	2.9	4.6	4.3
Cold ischemia time (hours)										
0-18	49.1	50.3	52.0	50.8	53.6	52.8	54.9	54.2	61.0	60.2
>18-24	26.5	26.1	24.8	26.2	25.7	26.3	25.6	26.1	23.5	24.2
>24-36	19.9	19.4	19.4	19.1	17.3	17.4	16.2	16.4	13.2	13.2
>36	4.5	4.2	3.8	3.9	3.4	3.6	3.3	3.2	2.3	2.4
Missing	9.6	8.3	8.5	7.9	8.5	8.1	8.2	7.5	7.6	7.2

For Peer Review

Transplant year										
1988-1994	34.2	36.2	30.2	32.4	22.2	23.3	15.9	16.4	9.5	9.7
1995-1999	22.3	22.6	19.0	19.0	20.5	19.7	17.6	16.7	14.5	13.7
2000-2004	18.5	17.8	17.2	17.1	21.1	19.8	21.9	20.4	20.5	21.6
2005-2009	14.2	13.6	15.6	15.5	18.5	19.0	22.7	22.8	26.5	25.1
2010-2013	8.2	7.4	12.9	11.5	13.4	13.3	16.5	17.6	21.8	22.5
2014-2018	2.6	2.4	5.1	4.4	4.4	4.9	5.5	6.1	7.2	7.5
Pre-emptive transplant										
Yes	5.8	6.2	6.1	5.6	4.6	4.8	4.6	4.1	3.3	3.2
Missing	8.2	7.4	7.3	6.2	6.7	6.2	5.9	5.3	5.1	4.5
Donor-recipient weight ratio*										
<0.7	47.6	32.1	26.7	10.7	22.0	8.6	21.0	8.8	20.0	7.0
0.7-<0.9	27.0	24.9	30.0	25.3	31.0	23.5	31.3	23.1	34.1	24.4
>0.9	25.4	43.1	43.3	64.1	47.0	68.0	47.7	68.1	45.9	68.6
Missing**	51.0	50.8	52.0	51.4	55.7	55.4	58.8	59.6	70.9	71.9
Missing (SRTR & ANZ) ***	19.7	20.5	16.3	17.0	14.2	12.5	12.3	10.6	11.2	10.2
HLA mismatches										
0-1	14.7	13.3	14.1	14.2	15.1	14.3	14.3	13.6	10.2	9.8
2-3	37.1	36.6	36.4	36.4	38.4	38.2	38.4	37.9	34.8	36.4
4-6	48.3	50.1	49.5	49.4	46.6	47.5	47.3	48.5	55.0	53.8
Missing	3.8	3.8	4.2	3.7	4.7	4.1	5.4	5.2	7.2	7.2
PRA										
0%	78.6	78.3	78.4	78.2	79.5	79.5	80.7	79.6	81.1	80.1
>0%	21.4	21.7	21.6	21.8	20.5	20.5	19.3	20.4	18.9	19.9
Missing	12.6	11.6	13.4	12.1	15.2	14.5	16.8	16.3	18.1	18.1
Donor cause of death										
CVA	13.2	7.4	32.1	14.1	66.4	44.8	76.3	60.0	80.3	66.1
Others	86.8	92.6	67.9	85.9	33.6	55.2	23.7	40.0	19.7	33.9
Missing	6.8	7.6	6.7	7.5	5.7	6.6	4.6	5.5	4.5	4.6
CMV positive donor										
Yes	53.5	50.8	60.1	53.4	65.3	57.6	69.5	62.4	74.4	68.1
Missing	9.9	10.5	9.9	10.5	10.2	10.1	11.2	11.8	18.5	17.7
Donor hypertension										

For Peer Review

Yes	0.6	0.6	5.0	3.2	19.1	16.2	27.3	27.5	29.9	30.0
Missing	22.1	24.4	18.8	20.8	14.0	14.5	10.2	10.4	7.7	7.2

* data not available from CTS

** Proportion of missing was calculated for population from all 3 cohorts.

*** Proportion of missing was calculated for population from SRTR and ANZDATA.

Because the unit analysis was person-time, rather than person, the characteristics presented are weighted by a factor derived from the number of person-years of observation and number of events. For example, 26.2% of the person-years contributed by female recipients of female donors ≥60 years had glomerulonephritis (GN) as the primary kidney disease.

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Table 3: Fitted graft loss rates per 100 person-years at 10 years post-transplant

Donor age	Female recipient				Male recipient			
	Female donor		Male donor		Female donor		Male donor	
	Graft loss rate	95% CI	Graft loss rate	95% CI	Graft loss rate	95% CI	Graft loss rate	95% CI
SRTR								
5-19	13.3	12.6-14.0	13.8	13.3-14.4	13.5	12.8-14.1	12.6	12.2-13.1
20-34	14.2	13.5-14.9	14.3	13.8-14.8	13.9	13.3-14.5	13.2	12.8-13.7
35-49	17.2	16.5-17.9	17.2	16.6-17.9	17.2	16.6-17.8	16.4	15.8-16.9
50-59	20.6	19.8-21.5	20.1	19.2-21.0	21.5	20.7-22.4	21.3	20.6-22.1
60+	24.8	23.5-26.2	26.7	25.3-28.2	26.9	25.7-28.1	28.9	27.6-30.2
CTS								
5-19	12.8	11.9–13.7	12.3	11.6–12.9	13.2	12.4–14.0	11.3	10.8–11.9
20-34	13.0	12.2–13.8	12.5	12.0–13.1	12.5	11.9–13.2	11.2	10.7–11.6
35-49	15.5	14.8–16.2	15.5	14.9–16.2	15.8	15.1–16.4	14.5	14.0–15.1
50-59	19.0	18.2–19.9	19.8	18.9–20.7	19.0	18.2–19.7	19.4	18.7–20.1
60+	25.7	24.6–26.8	27.2	26.1–28.4	27.4	26.4–28.4	26.7	25.8–27.7
ANZDATA								
5-19	13.0	9.1-18.5	15.0	10.7-20.7	13.6	9.7-19.0	12.9	9.2-17.8
20-34	16.5	11.9-22.8	18.4	13.4-25.0	17.1	12.4-23.3	16.9	12.4-23.0
35-49	20.9	15.3-28.2	22.5	16.6-30.1	21.3	15.6-28.6	22.1	16.3-29.5
50-59	26.2	19.3-34.9	27.3	20.2-36.4	26.3	19.5-35.0	28.5	21.3-37.6
60+	32.5	23.9-43.2	33.0	24.2-43.9	32.3	24.0-42.7	36.4	27.3-47.3

The fitted rates were calculated based on the Cox proportional hazard models with covariates held fixed as: recipient age 51 years at transplant, recipient race: White, primary diagnosis: glomerulonephritis, D:R weight ratio ≥0.9 (not available in CTS), pre-transplant dialysis: yes, PRA: 0%, HLA mismatch: 4, transplant year: 2010, donor cerebrovascular accident as cause of death: no, donor hypertension: no, and cold ischemia time: ≤18.

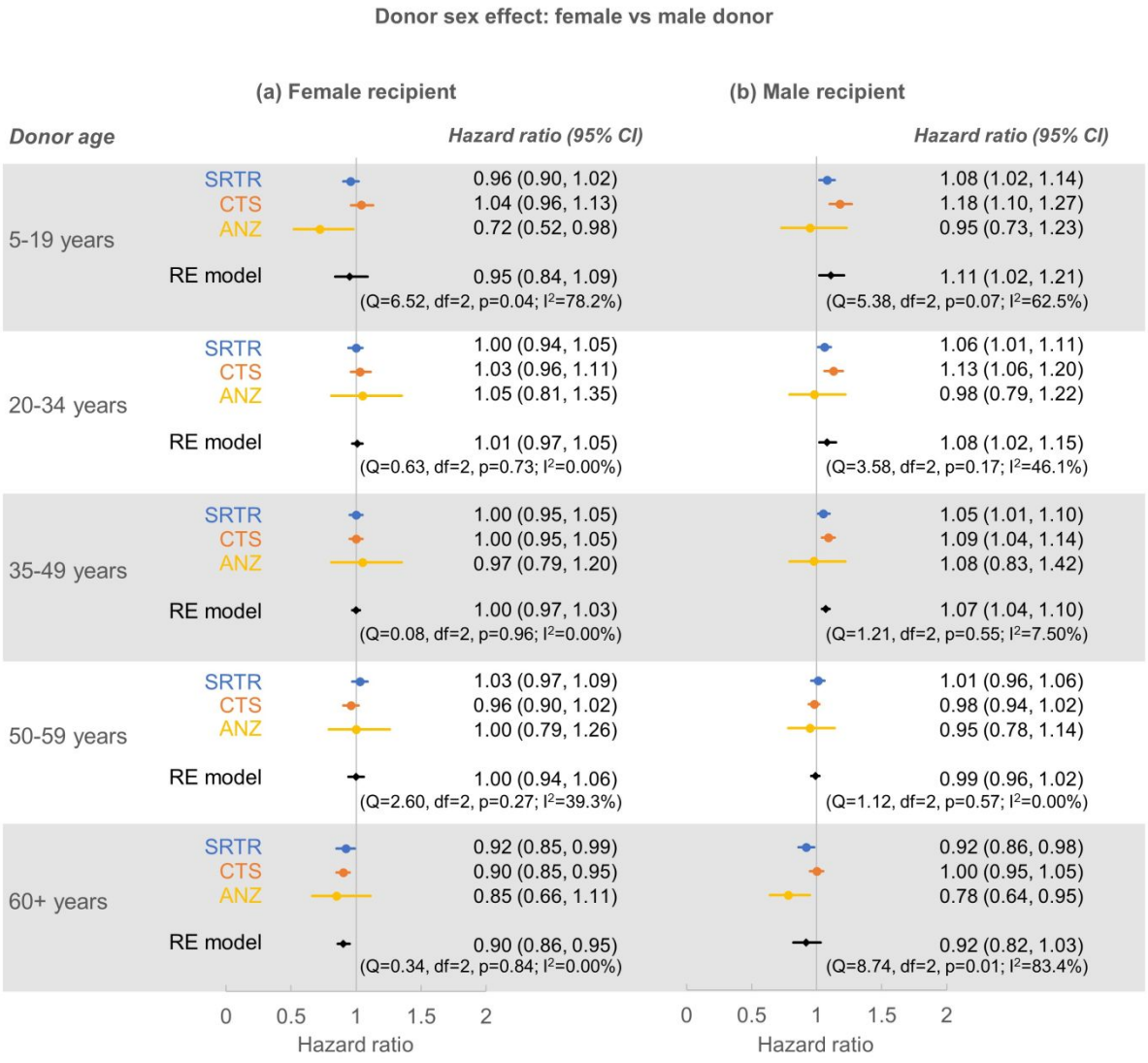
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Figure 1: Individual patient data meta-analyses combining data from SRTR, CTS, and ANZDATA donor age-specific relative hazards of death-censored graft failure in (a) female recipients and (b) male recipients of female donor compared to male donor. Models were as adjusted for recipient age at transplant (piece-wise linear spline), recipient race (White/other), primary diagnosis (diabetes, hypertension, glomerulonephritis, congenital anomalies of the kidneys or urinary tract, cystic kidney disease, other), pre-transplant dialysis (yes/no), PRA (0% vs. >0%), HLA mismatch (continuous), donor-recipient weight ratio (<0.7, 0.7 to <0.9, ≥0.9; not available for CTS), transplant year (continuous), donor cytomegalovirus (CMV; not included for ANZDATA as it was missing in >40%), donor cerebrovascular accident (CVA), donor hypertension, and cold ischemia time (≤18, >18-24, >24-36, >36 hours), conditioned on graft function >90 days. HR are interpreted as the risk of death censored graft loss associated with a female donor relative to that with a male donor.

RE model= random effects model (pooled estimate)

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Figure 1


Donor sex effect: female vs male donor
(a) Female recipient
(b) Male recipient
Donor age
Hazard ratio (95% CI)
Hazard ratio (95% CI)
5-19 years
SRTR 0.96 (0.90, 1.02) 1.08 (1.02, 1.14)
CTS 1.04 (0.96, 1.13) 1.18 (1.10, 1.27)
ANZ 0.72 (0.52, 0.98) 0.95 (0.73, 1.23)
RE model 0.95 (0.84, 1.09) 1.11 (1.02, 1.21)
(Q=6.52, df=2, p=0.04; I²=78.2%) (Q=5.38, df=2, p=0.07; I²=62.5%)
20-34 years
SRTR 1.00 (0.94, 1.05) 1.06 (1.01, 1.11)
CTS 1.03 (0.96, 1.11) 1.13 (1.06, 1.20)
ANZ 1.05 (0.81, 1.35) 0.98 (0.79, 1.22)
RE model 1.01 (0.97, 1.05) 1.08 (1.02, 1.15)
(Q=0.63, df=2, p=0.73; I²=0.00%) (Q=3.58, df=2, p=0.17; I²=46.1%)
35-49 years
SRTR 1.00 (0.95, 1.05) 1.05 (1.01, 1.10)
CTS 1.00 (0.95, 1.05) 1.09 (1.04, 1.14)
ANZ 0.97 (0.79, 1.20) 1.08 (0.83, 1.42)
RE model 1.00 (0.97, 1.03) 1.07 (1.04, 1.10)
(Q=0.08, df=2, p=0.96; I²=0.00%) (Q=1.21, df=2, p=0.55; I²=7.50%)
50-59 years
SRTR 1.03 (0.97, 1.09) 1.01 (0.96, 1.06)
CTS 0.96 (0.90, 1.02) 0.98 (0.94, 1.02)
ANZ 1.00 (0.79, 1.26) 0.95 (0.78, 1.14)
RE model 1.00 (0.94, 1.06) 0.99 (0.96, 1.02)
(Q=2.60, df=2, p=0.27; I²=39.3%) (Q=1.12, df=2, p=0.57; I²=0.00%)
60+ years
SRTR 0.92 (0.85, 0.99) 0.92 (0.86, 0.98)
CTS 0.90 (0.85, 0.95) 1.00 (0.95, 1.05)
ANZ 0.85 (0.66, 1.11) 0.78 (0.64, 0.95)
RE model 0.90 (0.86, 0.95) 0.92 (0.82, 1.03)
(Q=0.34, df=2, p=0.84; I²=0.00%) (Q=8.74, df=2, p=0.01; I²=83.4%)
0 0.5 1 1.5 2
Hazard ratio
0 0.5 1 1.5 2
Hazard ratio

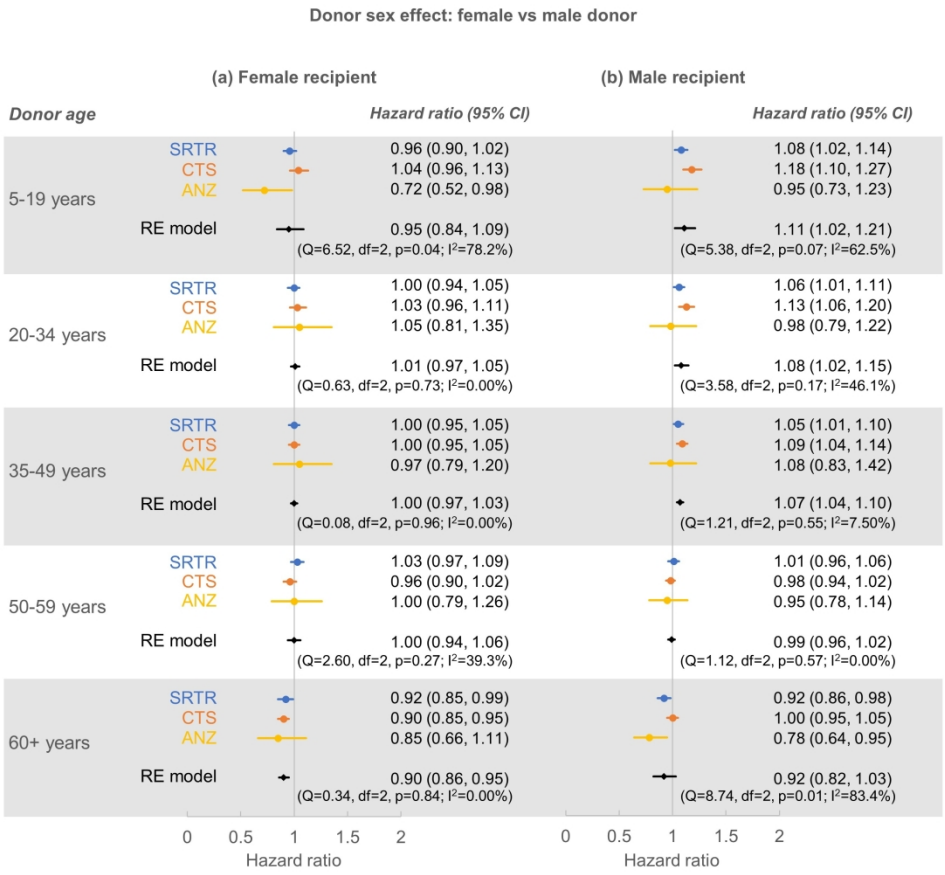


Figure 1: Individual patient data meta-analyses combining data from SRTR, CTS, and ANZDATA donor age-specific relative hazards of death-censored graft failure in (a) female recipients and (b) male recipients of female donor compared to male donor. Models were as adjusted for recipient age at transplant (piece-wise linear spline), recipient race (White/other), primary diagnosis (diabetes, hypertension, glomerulonephritis, congenital anomalies of the kidneys or urinary tract, cystic kidney disease, other), pre-transplant dialysis (yes/no), PRA (0% vs. >0%), HLA mismatch (continuous), donor-recipient weight ratio (<0.7, 0.7 to <0.9, ≥0.9; not available for CTS), transplant year (continuous), donor cytomegalovirus (CMV; not included for ANZDATA as it was missing in >40%), donor cerebrovascular accident (CVA), donor hypertension, and cold ischemia time (≤18, >18-24, >24-36, >36 hours), conditioned on graft function >90 days. HR are interpreted as the risk of death censored graft loss associated with a female donor relative to that with a male donor.
RE model= random effects model (pooled estimate)

241x254mm (300 x 300 DPI)

Influence of donor sex and age on graft outcome in kidney transplantation

Donor sex | **Donor age** | **Recipient sex**

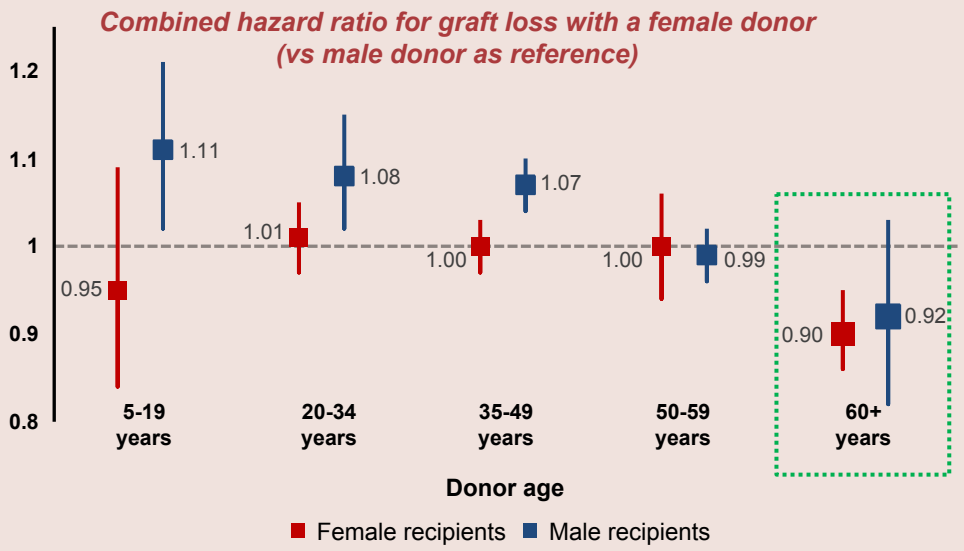
Death-censored graft loss

Population
First deceased donor kidney transplant recipients
(1988-2019, n=461,364)

SRTR | CTS | ANZDATA

Multivariable cox regression models

Individual patient data meta-analysis



- Donor age modified the association between donor sex and graft survival.
- Older female donors were associated with lower or similar risk of graft loss than older male donors in female and male recipients, potentially suggesting a better functional reserve of older female kidneys.

Melk, A. *et al.*
Nephrol Dial Transplant
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