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Differences in Liver Graft Survival by Recipient Sex

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Background. We aimed to characterize patterns of differences in liver graft failure rates by recipient sex, accounting for the modifying effects of donor sex and recipient age. **Methods.** We evaluated 144 212 first deceased donor liver transplant recipients [1988–2019; Scientific Registry of Transplant Recipients (SRTR)]. We used multivariable time-varying Cox models, considering a recipient sex by donor sex by recipient age (0–12, 13–24, 25–44, ≥45 y) interaction. **Results.** Among recipients of male donors, females <45 y had higher graft failure rates than males of the same age, but none of these differences were statistically significant [0–12 y: adjusted hazard ratio (aHR) 1.17 (0.98, 1.40); 13–24 y: aHR 1.18 (0.96, 1.46); 25–44 y: aHR 1.11 (0.96, 1.28)]; there was no material or statistically significant difference between female and male recipients ≥45 y [aHR 1.01 (0.97, 1.06)]. When the donor was female, recipients <45 y showed no statistically significant differences in graft outcomes by recipient sex [0–12 y: aHR 0.91 (0.74, 1.11); 13–24 y: aHR 0.98 (0.77, 1.25); 25–44 y: aHR 0.86 (0.73, 1.01)], whereas female recipients ≥45 y had significantly lower graft failure rates [aHR 0.85 (0.81, 0.89)] than males of the same age. **Conclusions.** Among recipients of female donors, female recipients ≥45 y had significantly better outcomes than males of the same age; there were no clear differences by recipient sex in younger recipients. When the donor was male, there was no material or statistically significant difference in graft failure rates between males and females ≥45 y; among younger recipients point estimates suggested higher failure rates in females than males recipients, but confidence intervals were wide making firm conclusions impossible. Larger studies combining multiple datasets are needed.

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INTRODUCTION

Analyses identifying sex differences highlight areas in which future, mechanistic studies are needed to inform sex-specific approaches to diagnosis and treatment.[1,2] Identification of sex differences in the prevalence and severity of conditions as disparate as asthma,[3,4] HIV,[5] cardiovascular diseases,[6] and Alzheimer's disease[7] led to new insights into disease mechanisms, which may ultimately result in more effective therapies. Organ transplantation lags behind in this area. Despite known sex differences in immune reactivity,[8] immunosuppression strategies are the same for males and females. Characterization of similarities or differences in graft outcomes by recipient sex, in different organ types, may provide clues as to mechanisms and is an important first step to more personalized transplant care.

Phenotypic expression of sexual dimorphism changes with age. Levels of circulating sex hormones differ little by sex among prepubertal children but diverge dramatically following puberty and throughout peak reproductive years.

Following menopause, sex hormone levels drop in women; differences in sex hormone profiles in this age group are smaller. Sex hormones influence immune reactivity. The immune profiles of postmenopausal women differ substantially from those of women of reproductive age, and sex differences in immune reactivity are smaller after menopause.[8,9] If sex hormones play a role in sex differences in graft outcomes, the magnitude of sex differences may differ by age.

Donor sex may also modify the relationship between recipient sex and graft outcomes. Interactions between the recipient and donor sex were previously shown.[10-12] In particular, the HY-antigen, present on all male tissues, may provoke an immunologic reaction in female (but not male) recipients of a male donor.[8,13-15]

Emerging evidence in kidney transplantation suggests that, among young people, recipient sex is a powerful predictor of graft survival.[16] We recently demonstrated donor sex- and recipient age-dependent differences in the risk of death-censored graft failure between male and female kidney transplant recipients.[16] Among recipients of male donors, females of all ages had poorer graft survival than males. In contrast, among recipients of female donors, only adolescent and young adult females had poorer outcomes than males of the same age; females ≥45 y old had *better* graft survival than males of the same age. These findings suggest that sex differences in immune reactivity, driven in part by sex hormones,[13] may play a role in the observed sex differences in graft outcomes.

It is not known whether similar sex differences in graft outcomes exist in liver transplant recipients. The liver is an "immunologically privileged" organ that may be less sensitive than other organs to sex differences in immune reactivity.[17-19] The majority of prior studies in the liver transplant population[20-26] focused on differences in outcomes by either donor sex or by donor–recipient sex combination; few assessed the effect of *recipient sex*,[27,28] and none considered the potentially modifying effect of recipient age. We hypothesized that the pattern of differences in liver graft survival by recipient sex would be similar to that observed for kidney transplant recipients, but of smaller magnitude. We aimed to characterize patterns of difference in graft survival between male and female liver transplant recipients in the prepubertal, adolescent and young adult, mid-adulthood, and postmenopausal age ranges, accounting for the potentially modifying effect of donor sex.

MATERIALS AND METHODS
Data Source and Population
This was a retrospective cohort study of individuals recorded in the Scientific Registry of Transplant Recipients (SRTR) who received first, isolated liver transplantation from a deceased donor in the United States between January 1, 1988 and June 1, 2019. Patients were followed until June 1, 2019. The SRTR includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Exposure and Outcome Definitions
The primary exposure was *recipient sex*. Interactions between donor and recipient sex were shown in prior studies,[16,21] meaning that the association between recipient sex and graft survival differs depending on the donor sex. Therefore, we considered donor–recipient sex combinations: male donor—male recipient (MM), male donor—female recipient (MF), female donor—male recipient (FM), and female donor—female recipient (FF). This approach allowed us to consider the association between recipient sex and graft survival in the setting of a male donor separately from the setting of a female donor. Because biologic differences between males and females differ by recipient current age,[8,13] we included a donor–recipient sex combination by recipient current age interaction term in all models. Including this interaction allowed us to consider the possibility that the magnitude, or even the direction, of differences in graft failure risk by recipient sex, may differ in different age intervals. Current age was a time-varying variable and categorized as 0–12 (prepubertal), 13–24 (adolescence and young adulthood), 25–44 (middle adulthood), and ≥45 y (postmenopausal). This means that each patient started observation (at the time of transplant) in the age category appropriate to their age at transplant, but that the age category was updated as they were followed over time. For example, a patient transplanted at 17 y old would start observation in the 13–24 y age interval, but upon turning 25 (8 y after transplant), would move into the 25- to 44-y interval. This approach ensures that comparisons of failure rates account for recipient age at the time of failure when it is most relevant. Liver, heart, and kidney graft failure rates were previously shown to vary by recipient current age in a nonlinear fashion, peaking in adolescence and young adulthood.[29-31] Because our analytic approach acknowledges that recipients are aging over time (by considering current age), and considers the interaction between donor–recipient sex combination and current age, it is not possible to construct meaningful Kaplan–Meier plots—which require that recipients be classified into static categories at baseline and that these categories do not change over time.

Primary Outcome
The primary outcome was graft failure, defined as retransplantation or death following graft failure.[30] Graft status (failed versus functioning) is reported annually to the SRTR. When a death is reported, it is required to indicate whether the death was a result of graft failure or due to some other factor unrelated to graft failure (ie, death with graft function). It was important to exclude death with graft function from the definition of graft failure for 2 reasons. First, the mechanisms underlying sex differences in graft survival may differ from those underlying sex differences in patient survival, and second, the expected age-specific mortality risk is lower for females than males.[32] Comparisons between males and females of absolute mortality rates or composites including graft failure and death are uninterpretable.[33] Therefore, the observation was censored at death with graft function.

Statistical Analyses
Association Between Recipient Sex and Graft Survival
We used Cox models with time-varying covariates to assess the associations between recipient sex and graft failure. Time

0 was the date of the transplant. Unadjusted analyses were followed by multivariable analyses adjusted for potential confounders. The models included the following covariates: donor and recipient race (White, Black, and other), donor age, donor:recipient weight ratio (a measure of donor–recipient body size match or mismatch), primary liver disease (categorized as biliary atresia/other cholestatic disease, alcoholic disease, liver tumors, metabolic liver disease, fulminant liver failure, autoimmune condition, and other), cold ischemia time, medical condition at transplant (ICU/hospital/no hospital stay), and era of transplant (1988–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2014, and 2015–2019). Transplant era categories were based on changes in immunosuppression practices over time.[34,35] Panel reactive antibodies (a marker of sensitization) and human leukocyte antigen mismatch are not available so could not be included. We considered including insurer (public, private, none) in the models, but the insurer was missing in up to 25%, so was excluded. Missing variables were imputed using multiple imputation methods based on the joint distributions of all other variables in the model.[36]

We first fitted the models setting MM as the reference category. This allowed us to compare graft failure rates between male and female recipients of a male donor (MF versus MM). We then refitted the same model setting FF as the reference category. This allowed us to compare graft failure rates between male and female recipients of a female donor (FM versus FF) (Figure 1). Hazard ratios (HRs) were always expressed as the hazard for females relative to males. HR and adjusted HR (aHR) are presented with 95% confidence intervals.

To determine the proportionality of hazards, we used Kaplan-Meier plots comparing graft survival by donor–recipient sex combination. In addition, proportionality was assessed by refitting the models, censoring all observations at 5 and 10 y. Results were unchanged, indicating that hazards were proportional.

Sensitivity Analyses

We refitted the model described above including insurer using multiple imputations for missing values.

M-M (Male donor- Male Recipient) *Reference*	M-F Effect of recipient sex on graft failure when the donor is male
F-F (Female donor- Female Recipient) *Reference*	F-M Effect of recipient sex on graft failure when the donor is female

FIGURE 1. Interpretation of contrasts between donor–recipient sex combinations. The 2 black boxes on the left show the 2 different reference groups considered: male donor–male recipient (MM) and female donor–female recipient (FF). The grey and white boxes to the right of each reference group represent the contrasts estimating the effects of recipient sex. For example, the contrast between the MM reference and MF gives the effect of recipient sex when the donor is male.

Fitted Absolute Graft Failure Rates by Current Age Stratified on Donor–recipient Sex Combination

Crude failure rates may be misleading because they do not take into account the changing failure risks over time since transplant, resulting in estimates that are highly influenced by the proportion of person-years contributed by incident transplant recipients. Therefore, we calculated fitted failure rates for each current-age interval based on absolute failure rates in male recipients of male donors with a fixed profile of other recipient and donor characteristics (failures per 1000 person-y of observation within that interval) and the HRs from the models described above.

We also calculated crude graft failure rates by donor-recipient sex combination in the 4 current-age intervals (failures per 1000 person-y of observation within that interval).

We performed data analyses using Statistical Analysis Software 9.4 (SAS Institute, Cary, NC) and S-plus (version 6.1). The study was approved by the McGill University Health Center Research Ethics Board.

RESULTS

We identified 144 332 individuals who had a first, single-organ, deceased-donor liver transplant between January 1, 1988 and June 1, 2019. We excluded 108 for whom the status of the graft could not be determined (graft recorded as failed, but no record of death or retransplant), 1 recorded as having died without a date of death, and 11 with unknown donor sex. This left 144 212 (85 929 with a male donor; 58 283 with a female donor). Patients were followed for a median of 5.0 [interquartile range (IQR) 1.5–10.5] y, with a total of 972 370 person-years of observation. The outcomes of liver recipients, by donor sex, are shown in Figure 2a and b.

Recipient and Transplant Characteristics

Table 1 summarizes the composition of the observed experience within each age interval for male and female recipients in the setting of a male donor and of a female donor. There were a few differences in characteristics by recipient sex. Across most ages, a greater proportion of the observation time of females than males was contributed by Blacks and a greater proportion of the observation time of males than females was contributed by Whites. The distribution of primary liver disease differed by age and by recipient sex across almost all current age categories. A greater proportion of observation time of females than males was contributed by patients with biliary atresia or other cholestatic diseases across all ages; in the 2 oldest age categories, a greater proportion of the observation time of males than females was contributed by patients with alcoholic liver disease. Donor age was generally older for male than female recipients.

Comparison of Graft Survival by Recipient Sex

Figure 3 illustrates the relative hazards of graft failure for female compared with male recipients of a: (a) male donor or (b) female donor at different recipient ages. When the donor was male, females <45 y had higher graft failure rates than males of the same age, but none of these differences were statistically significant [0–12 y: aHR 1.17 (0.98, 1.40); 13–24 y: aHR 1.18 (0.96, 1.46); 25–44 y: aHR 1.11 (0.96, 1.28)]; there was no material or statistically significant difference between female and male recipients ≥45 y [aHR 1.01 (0.97, 1.06)].
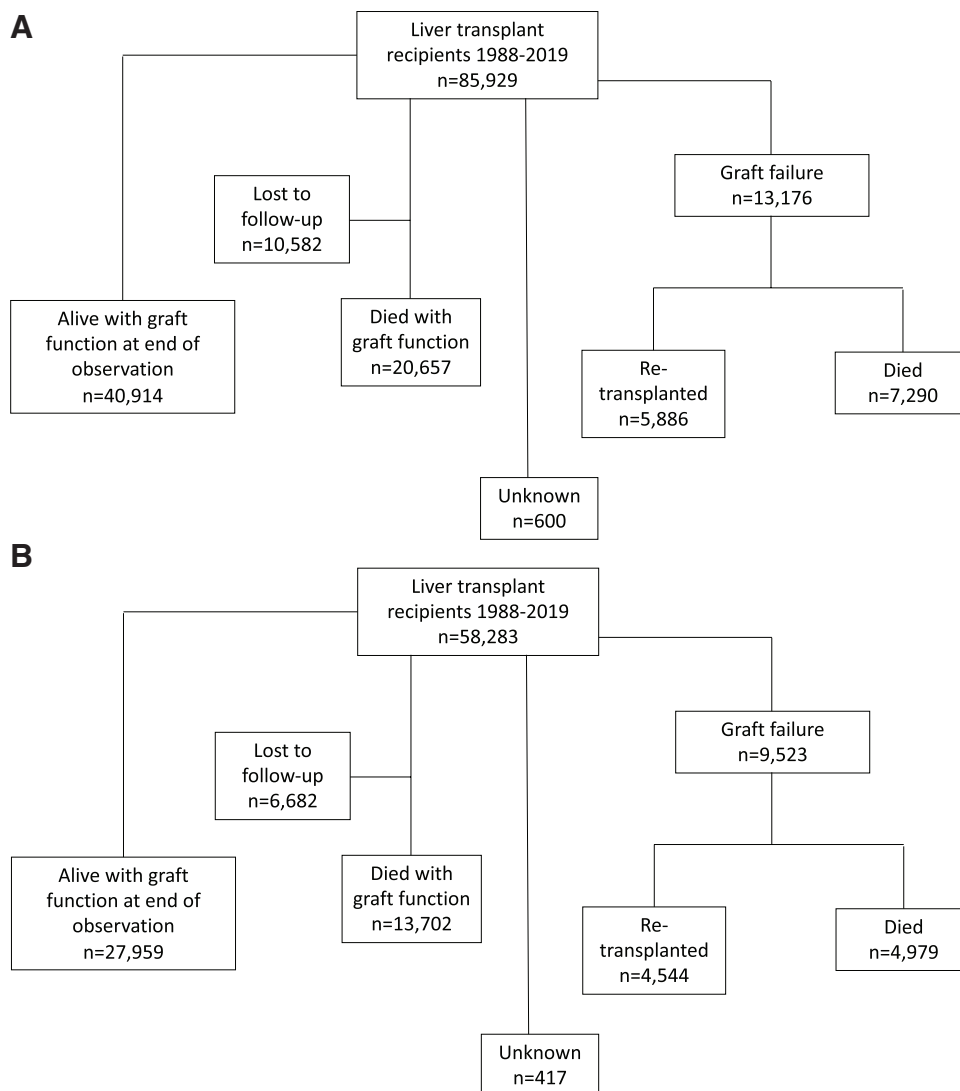
A

```
            Liver transplant
            recipients 1988-2019
            n=85,929
```

Lost to
follow-up
n=10,582

Graft failure
n=13,176

Alive with graft
function at end of
observation
n=40,914

Died with
graft function
n=20,657

Re-
transplanted
n=5,886

Died
n=7,290

Unknown
n=600

B

```
            Liver transplant
            recipients 1988-2019
            n=58,283
```

Lost to
follow-up
n=6,682

Graft failure
n=9,523

Alive with graft
function at end of
observation
n=27,959

Died with
graft function
n=13,702

Re-
transplanted
n=4,544

Died
n=4,979

Unknown
n=417

FIGURE 2. Flow diagrams of LIVER recipient outcomes. Outcomes of recipients of a (A) male donor and (B) a female donor are shown.

When the donor was female, female recipients ≥45 y had significantly *lower* graft failure rates than males of the same age [aHR 0.85 (95% confidence interval [CI] 0.81, 0.89)], but it was not possible to draw firm conclusions about differences in graft failure rates between female and male recipients <45 y because of wide confidence intervals.

Sensitivity Analyses

The model including insurer with multiple imputation for missing values returned results almost identical to those shown in Figure 3.

Fitted Absolute Graft Failure Rates by Donor-recipient Sex Combination and Recipient Age

Figure 4 shows fitted graft failure rates by donor-recipient sex combination in the 4 current-age intervals among those with the following fixed characteristics: White recipient race, donor age ≤35 y, White donor race, cold ischemia of 7 h (median), donor:recipient weight ratio ≥0.9, and transplant era 2005–2009. Comparisons of the fitted absolute failure rates between male and female recipients (adjusted for

potential confounders) are provided by the models used to calculate these rates.

Crude graft failure rates by donor–recipient sex combination in the 4 current-age intervals are shown in Figure S1 (Supplemental Digital Content http://links.lww.com/TXD/A297).

DISCUSSION

Examining the patterns of sex differences in graft outcomes among recipients of different ages, across different organs, may provide insights into the mechanisms for differences. In this study, we show the first comparison of liver graft failure by recipient sex, accounting for the potentially modifying effects of both donor sex and recipient age.

Overall, in the setting of a male donor, the pattern of sex differences among liver transplant recipients appeared to be similar to the patterns observed in kidney and heart transplant recipients.[16] When the donor was male, the point estimates (which are considered the best estimate of effect[37]) suggested that female liver recipients <45 y may have poorer outcomes

TABLE 1.

Composition of the contrasting experience by LIVER recipient sex and age among recipients of a male donor (N = 85 929) and a female donor (N = 58 283)

	0–12 y		13–24 y		25–44 y		≥45 y	
	Females	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**
Male donor (N = 85 929)								
Person-y of observation	19 119	18 524	14 932	14 154	26 404	38 222	141 020	314 593
Retransplants	407	332	234	192	513	841	957	2334
Deaths after failure	148	125	127	80	412	592	1722	3839
Age at transplant (y)								
Median	1	1	10	9	32	35	55	54
IQR	0–2	0–3	2–16	2–15	25–38	29–29	48–60	48–59
Race (%)								
White	72.4	76.7	75.6	80.1	80.4	85.4	87.2	90.1
Black	18.9	16.0	18.6	15.1	15.7	9.7	8.0	5.5
Other	8.7	7.3	5.8	4.8	3.9	4.9	4.8	4.4
Primary disease (%)								
Bililary atresia/other								
Cholestatic	72.0	57.5	47.3	41.1	20.6	15.3	34.8	13.7
Alcoholic disease	0.0	0.0	0.1	0.2	8.1	21.2	11.7	26.7
Liver tumors	5.4	7.7	4.1	4.2	4.0	3.5	7.7	12.8
Metabolic liver disease	10.0	17.7	16.0	20.3	8.3	7.8	2.1	2.9
Fulminant liver failure	7.8	11.7	15.3	17.0	21.3	8.4	6.6	3.1
Autoimmune conditions	1.1	0.8	11.5	10.6	23.6	21.7	12.3	7.5
Others	0.3	0.2	2.0	2.3	11.1	20.7	23.1	32.2
Missing (%)	3.2	4.4	3.8	4.2	3.1	1.6	1.6	1.2
Insurer (%)								
Private	38.8	41.9	44.8	46.8	47.4	49.7	52.5	59.4
Public	42.0	38.3	29.2	26.9	25.2	25.9	31.0	29.7
No coverage	1.7	1.4	2.3	1.9	2.2	1.7	0.8	0.8
Missing	17.5	18.4	23.7	24.4	25.3	22.7	15.8	10.1
Era (%)								
1988–1994	20.5	21.5	28.0	28.9	29.8	27.8	19.7	12.6
1995–1999	17.4	17.9	23.1	24.3	21.2	20.8	21.2	17.3
2000–2004	22.7	17.3	23.2	20.1	16.6	18.1	20.3	23.4
2005–2009	19.3	21.4	13.6	14.8	16.1	16.5	19.3	24.0
2010–2014	14.6	16.3	9.2	9.1	10.8	10.7	14.2	16.6
2015–2019	5.6	5.7	3.0	2.8	5.6	6.2	5.4	6.2
Medical condition at transplant								
ICU	20.9	23.1	27.1	25.3	30.4	18.1	15.7	9.8
Hospital, not ICU	21.0	20.5	17.2	15.6	19.3	18.6	17.7	16.4
Not hospital	58.0	56.3	55.7	59.1	50.3	63.2	66.6	73.8
Missing (%)	0.1	0.1	0.0	0.0	0.0	0.1	0.0	0.1
Donor:recipient weight ratio (kg:kg)								
Median	1.9	2.1	1.2	1.3	1.1	1.1	1.0	0.9
IQR	1.1–5.3	1.2–5.2	0.9–1.8	0.9–1.9	0.9–1.3	0.8–1.2	0.8–1.2	0.8–1.1
Missing (%)	11.7	11.7	12.2	11.6	9.7	8.1	5.9	4.6
Donor age (y)								
Median	5.0	6.0	14.0	14.0	24.0	28.0	28.0	34.0
IQR	1.1–17.0	2.0–19.0	5.0–23.0	5.0–23.0	17.0–39.0	20.0–43.0	19.0–46.0	22.0–49.0
Missing (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Donor race								
White (%)	80.7	79.0	83.7	82.3	83.7	84.2	83.4	83.3
Black (%)	16.1	17.3	13.4	15.1	13.2	13.7	13.8	14.4
Other (%)	3.2	3.7	2.9	2.6	3.1	2.1	2.8	2.3
Cold ischemia time (h)								
Median	7.5	7.2	8.0	7.7	7.5	7.9	7.1	7.1
IQR	5.4–10.0	5.0–10.0	5.8–10.2	5.6–10.7	5.4–10.2	5.6–10.4	5.3–9.8	5.3–9.5
Missing (%)	11.0	10.1	10.5	10.7	8.4	8.4	9.4	6.6

TABLE 1. (Continued).

	0–12 y		13–24 y		25–44 y		≥45 y	
	Females	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**
Female donor (N = 58 283)								
Person-y of observation	15 848	13 809	11 735	9713	22 156	19 450	129 461	163 229
Retransplants	302	282	168	133	463	538	973	1644
Deaths after failure	112	111	98	61	327	333	1520	2240
Age at transplant (y)								
Median	1	1	10	9	32	34	55	54
IQR	0–2	0–2	1–16	1–15	26–38	28–39	49–61	49–60
Race (%)								
White	73.4	78.6	75.3	81.4	79.9	82.2	86.6	87.6
Black	18.3	13.9	19.3	13.2	15.7	10.7	7.7	5.8
Other	8.4	7.6	5.4	5.5	4.3	7.1	5.6	6.5
Primary disease (%)								
Bililary atresia/other								
Cholestatic	73.4	60.5	47.1	43.5	21.0	14.7	36.0	13.0
Alcoholic liver disease	0.0	0.0	0.0	0.2	8.7	18.5	11.5	26.1
Liver tumors	4.1	6.5	3.8	3.5	4.7	4.0	8.1	14.5
Metabolic liver disease	10.6	16.4	15.8	19.3	6.6	8.3	1.8	2.7
Fulminant liver failure	6.3	11.5	14.6	16.4	20.4	9.1	5.8	3.2
Autoimmune conditions	1.0	0.9	11.3	10.5	24.5	22.5	12.8	7.0
Others	0.4	0.3	2.8	2.9	11.3	20.5	22.3	32.2
Missing (%)	4.1	3.9	4.6	3.9	2.9	2.4	1.6	1.3
Insurer (%)								
Private	41.4	40.8	44.1	46.1	47.7	55.0	53.4	60.2
Public	40.1	40.6	32.6	30.0	27.4	26.7	32.1	32.4
No coverage	2.0	1.8	2.7	2.2	2.2	1.7	0.7	1.1
Missing	15.6	16.9	20.6	22.2	22.7	16.6	13.8	6.3
Era (%)								
1988–1994	19.1	22.1	26.0	27.4	26.7	20.2	16.2	8.2
1995–1999	19.9	16.8	26.6	24.4	20.9	21.7	18.9	16.2
2000–2004	20.6	20.4	22.4	23.8	19.6	20.9	22.9	24.1
2005–2009	22.6	23.2	13.9	13.9	16.8	17.0	21.1	25.7
2010–2014	13.4	14.4	8.3	7.6	10.8	13.7	14.8	19.0
2015–2019	4.5	5.1	2.8	2.9	5.2	6.4	5.6	6.8
Medical condition at transplant								
ICU	20.2	22.8	25.2	25.6	27.8	18.7	12.4	10.2
Hospital, not ICU	21.5	18.4	17.1	15.2	17.7	19.1	16.4	16.9
Not hospital	58.3	58.7	57.6	59.3	54.5	62.2	71.2	72.8
Missing (%)	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0
Donor:recipient weight ratio (kg:kg)								
Median	2.1	2.0	1.1	1.2	1.0	0.9	0.9	0.8
IQR	1.2–5.8	1.1–4.9	0.8–1.7	0.9–1.9	0.8–1.2	0.7–1.1	0.8–1.1	0.7–1.0
Missing (%)	14.1	14.3	13.6	12.5	9.2	7.4	5.6	4.2
Donor age (y)								
Median	7.0	6.0	16.0	16.0	37.0	39.0	42.0	44.0
IQR	1.0–24.0	2.0–24.0	5.0–32.0	4.0–32.0	22.0–50.0	25.0–51.0	27.0–54.0	31.0–55.0
Missing (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Donor race								
White (%)	79.8	81.9	83.1	86.0	86.6	85.8	85.7	83.0
Black (%)	15.9	14.0	13.7	11.2	11.2	11.3	11.4	14.1
Other (%)	4.3	4.1	3.1	2.9	2.2	2.9	2.8	3.0
Cold ischemia time (h)								
Median	7.0	7.2	8.0	7.5	7.4	7.4	7.0	7.0
IQR	4.6–9.6	4.8–9.7	5.2–10.4	5.1–0.3	5.4–10.0	5.2–9.8	5.1–9.5	5.1–'9.0
Missing (%)	12.7	11.3	11.1	10.9	8.8	8.5	7.4	6.8

Because age was treated as a time-varying variable, individuals could contribute observation to >1 age interval. Because the unit of analysis was person-time, rather than person, the characteristics presented are weighted by a factor derived from the number of person-y of observation and number of events, and presented as weighted mean ± SD, weighted median [interquartile range (IQR)] or percent (%). For example, 72.4% of the person-y contributed by female recipients of a male donors between 0 and 12 y were by White recipients, when the donor was male.
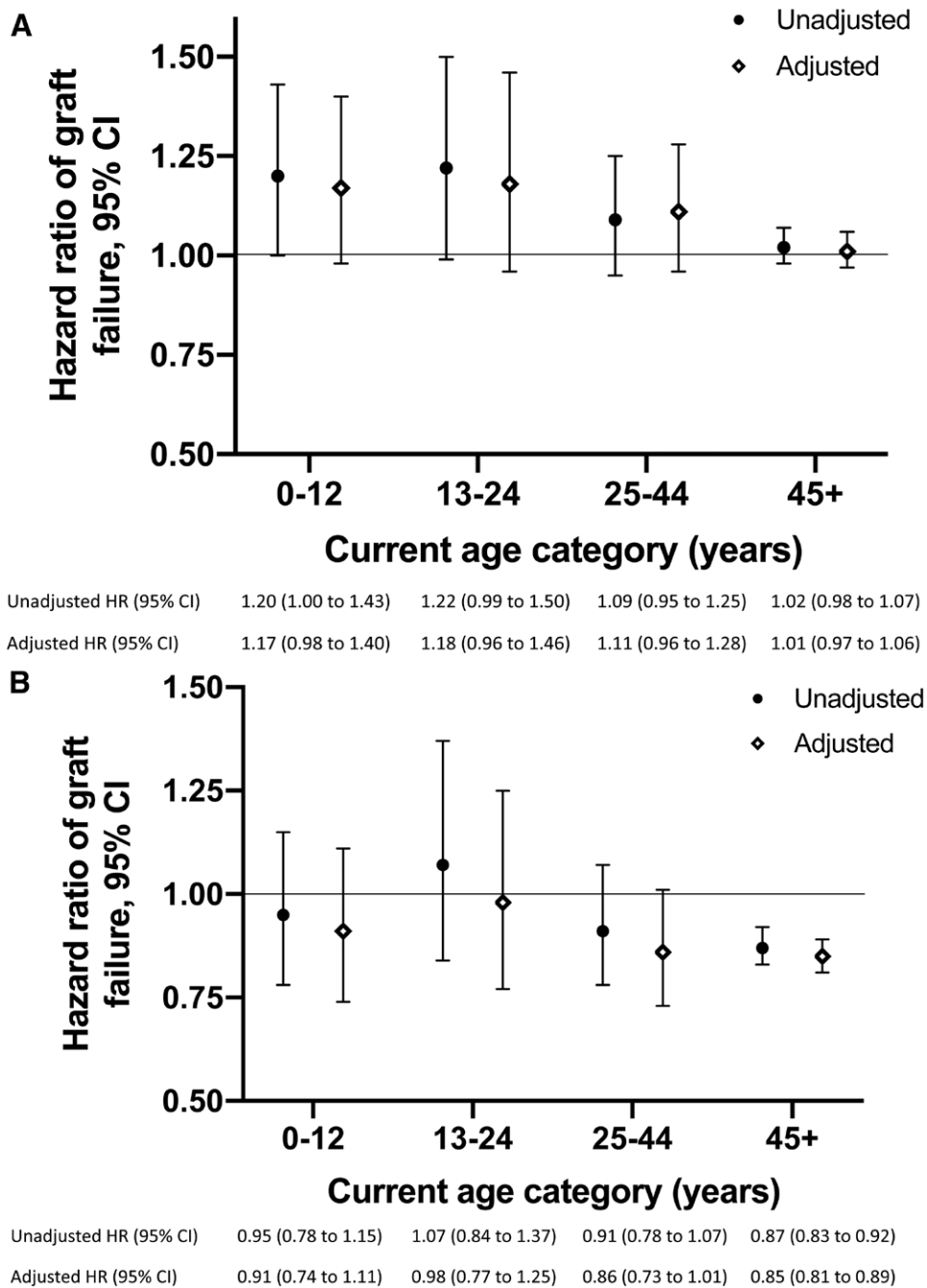
A

Unadjusted HR (95% CI)	1.20 (1.00 to 1.43)	1.22 (0.99 to 1.50)	1.09 (0.95 to 1.25)	1.02 (0.98 to 1.07)
Adjusted HR (95% CI)	1.17 (0.98 to 1.40)	1.18 (0.96 to 1.46)	1.11 (0.96 to 1.28)	1.01 (0.97 to 1.06)

B

Unadjusted HR (95% CI)	0.95 (0.78 to 1.15)	1.07 (0.84 to 1.37)	0.91 (0.78 to 1.07)	0.87 (0.83 to 0.92)
Adjusted HR (95% CI)	0.91 (0.74 to 1.11)	0.98 (0.77 to 1.25)	0.86 (0.73 to 1.01)	0.85 (0.81 to 0.89)

FIGURE 3. Comparisons of LIVER failure rates by recipient sex. Relative hazards of graft failure in female vs male recipients stratified by donor sex. (A) When the donor was male, adjusted hazards of graft failure were higher in female than male recipients <45 y, but the estimates were uncertain; the data were consistent with rates that were higher or lower in females than males. (B) When the donor was female, female recipients ≥25 y had lower graft failure rates than males the same age. The estimate was uncertain in those 25–44 y, with data consistent with higher or lower rates in females than males. Among those ≥45 y, the data were most consistent was lower failure rates in females than males. There were no clear differences in graft failure rates by recipient sex in younger recipients. Hazards ratios are shown with 95% CIs. Final models were adjusted for recipient race, primary liver disease, donor age, donor race, donor:recipient weight ratio, cold ischemia time, medical condition at transplant, and era of transplant. CI, confidence interval; HR, hazard ratio.

than males, whereas no differences by recipient sex were evident among those ≥45 y. Based on the point estimates, the magnitude of the association appears smaller in liver than in kidney or heart; however, the confidence intervals were wide for those <45 y, making firm conclusions about recipient sex differences impossible. It is likely that power was inadequate to precisely estimate effect size due to the low failure rates in liver transplant.[21,29-31] A smaller magnitude of the effect of

recipient sex on outcome may be consistent with the greater tolerogenicity[38] of the liver, compared with kidney or heart transplants.[18,39]

Among recipients of female donors, there was less consistency in the patterns across organs. There were no evident differences in the risk of liver graft failure by recipient sex among prepubertal children who received a female liver, similar to what was seen in recipients of a female donor kidney
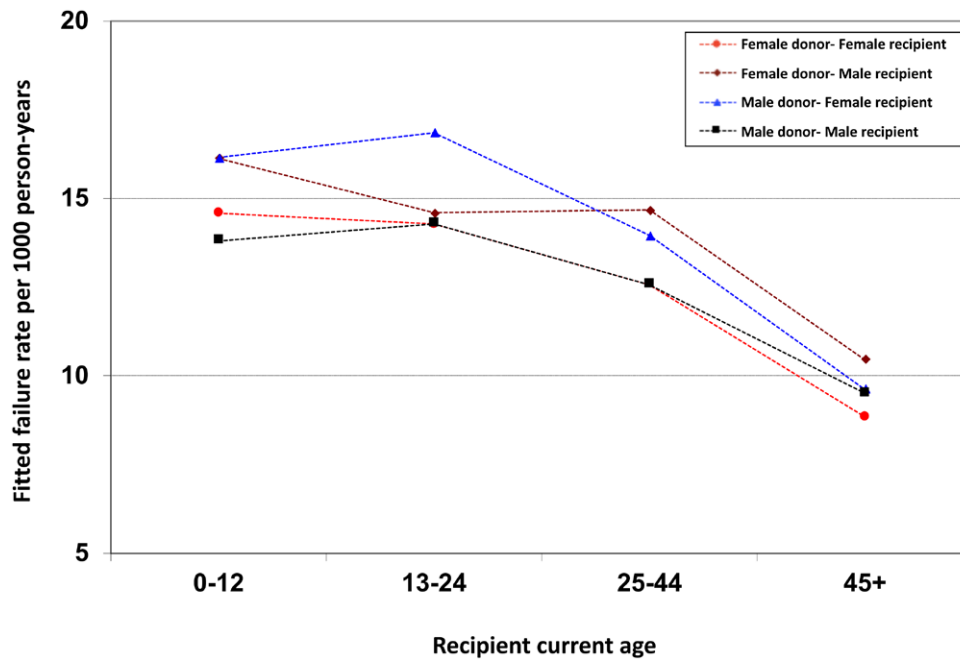
FIGURE 4. Fitted absolute LIVER graft failure rates by donor-recipient sex combination. Fitted graft failure rates (failures per 1000 person-y) within each current age interval (0–12, 13–29, 30–44, ≥45 y) are shown for each donor-recipient sex combination. These estimates are based on the following profile of recipient and donor characteristics: White recipient race, donor age ≤35 y, White donor race, cold ischemia of 7 h (median), donor:recipient weight ratio ≥0.9, and transplant era 2005–2009.

transplant.[16] There was also no apparent difference in liver graft failure rates between male and female adolescent and young adult recipients of a female donor. This contrasts with observations in kidney recipients, in whom female adolescent and young adult recipients showed higher failure rates than male recipients of the same age. However, power was limited in liver recipients to precisely estimate differences, resulting in wide confidence intervals. Similar to observations in kidney transplants, female liver recipients of postmenopausal age who received a liver from a female donor showed significantly lower graft failure rates than their male counterparts who also received a female organ.[16]

Most prior studies examining sex differences in liver transplant outcomes[21,22,24,25,40,41] did not isolate the effects of recipient sex from those of donor sex. Furthermore, none considered the potentially modifying effect of recipient age. One prior study showed poorer long-term outcomes among female than male recipients of a male donor, but only in the setting of hepatitis C virus positivity.[28] Comparisons of outcomes by recipient sex in the setting of a female donor were not made. An additional limitation of prior studies was the inconsistent primary outcome definition across studies; in some, the outcome was graft failure including death with graft function,[21,43] whereas in others death with graft function was excluded.[22,25,28]

We can only speculate as to the possible reasons for sex differences in graft failure rates. Multiple potential contributors to the observed differences in outcomes by recipient sex have been proposed,[16] including higher levels of sensitization among women due to prior pregnancies (not a plausible factor in children and adolescents), higher immune reactivity in females than males due to immune-stimulating influences of estrogen and inhibiting effects of androgens[8,42,43] and greater expression of immune-related genes in XX versus XY individuals,[44] reactions of females against the HY-antigen present

on male donor tissues,[8,13,15] and better medication adherence in women than men.[45-47] Some of these factors may lead to poorer outcomes in females than males, whereas others may favor better outcomes in females. Until more is known about each of these potential contributors to differences in graft failure rates by recipients sex, it is not possible to estimate the combined impact of these factors within each age period. The patterns of differences in graft failure rates by recipient sex observed in liver, kidney, and heart transplant recipients point to an important role for the reaction against the HY-antigen explaining the observed differences. Across all organs, there is a suggestion that female recipients may have higher graft failure rates than males mainly when the donor is male. In the setting of a female donor, recipient sex differences were smaller, and less consistent across organs. In both liver and kidney transplantation, female recipients of postmenopausal age who received a female donor showed lower failure rates than male recipients of the same age who also received a female donor. This may be a result of better medication adherence in women than men,[45-47] combined with immune senescence leading to decreased expression of immune-related genes on the X-chromosome, and a dampening of any sex hormone-related effects on immune activation after menopause. However, other mechanisms must also be considered.

The magnitude of the difference in graft failure risk between male and female recipients that constitutes a clinically meaningful difference is an important question, without an easy answer. One option is to consider the magnitude of associations with other variables considered important to liver graft outcomes. For example, there is widespread concern that adolescent and young adult liver transplant recipients have higher graft failure rates than other age groups. The HR associated with recipient age 21–24 y compared with 30–34 y is ~1.19 and compared with 35–39 y is ~1.25.[30] This magnitude of the effect is in line with the difference observed between

≥45-y-old female and male recipients of a female donor (HR 0.85 for female compared with male, which corresponds to an HR of 1.17 for male compared with female).

We must acknowledge some limitations. Power was limited to produce precise HR estimates while accounting for the potentially modifying effects of recipient age and donor sex. However, the SRTR represents the largest liver transplant cohort worldwide. Furthermore, given the strong biologic rationale for these interactions, and prior observations in the kidney,[16] liver, heart, and pancreas transplant,[20,21,29,30,48] it was important to consider these interactions. Although it is tempting to pool age categories to increase power, doing so would ignore the important impact of age on biologic sex differences. Pooling age categories would likely result in tighter confidence intervals around meaningless point estimates. Our broad goal was to observe patterns, comparing across organs. We highlight the HR point estimates that provide the best estimate available.[37] However, we acknowledge that the confidence intervals around the HR are wide in many instances. Future studies combining data from multiple large databases are needed to get more precise estimates.

This study can only hint at potential mechanisms for sex differences. The SRTR provides no information on sex hormone levels, measures of immune activation, or medication adherence.

The timeframe for our study was long, and there have been changes to both transplant management and outcomes over this interval. We included era as a covariate in the models in an effort to account for this but cannot exclude residual confounding. However, it is very unlikely that the long timeframe for the study would introduce bias in comparisons between males and females. Biologic differences between males and females have not changed over time. Furthermore, transplant management strategies have never (to our knowledge) differed for males and females; as organ allocation and transplant management changed, new approaches were equally applied to both sexes.

Finally, our study was restricted to deceased donor recipients in the United States; conclusions cannot be generalized to recipients of living donor transplants or recipients in other countries. Although biologic differences between females and males will not differ by country, gender-related adherence behaviors and sex and gender biases in medical care may vary by country.

This study adds to the observations in kidney and heart transplantation regarding the impact of recipient sex on graft outcomes and allows comparison of patterns of sex differences at different ages across organ types. Observations in the setting of an immunologically privileged organ[38] may inform the overall understanding of mechanisms underlying recipient sex differences in solid organ transplant outcomes. In the setting of a male donor, liver recipients showed a similar pattern of differences in failure rates by recipient sex to those seen in kidney and heart transplantation, with a suggestion of higher rates in young females than males. However, these preliminary observations are uncertain and require confirmation in larger studies. In the setting of a female donor, females of postmenopausal age showed significantly lower failure rates than males of the same age; this observation is more certain, with narrow confidence intervals. Although better immunosuppressive medication adherence among women than men[45-47] may at least partly explain this observation,

other explanations should also be entertained. Deeper interrogation of the factors contributing to the lower graft failure rates in older female than male recipients of female donors is warranted. When contemplating possible mechanisms for sex differences in graft outcomes for recipients of different ages, it is important to consider the combined impacts of different factors, with individual effects that may be in opposite directions. Future larger studies, combining data from multiple data sources, are needed to get more precise estimates of sex differences in graft outcomes. Additional studies focusing specifically on recipient sex differences in graft rejection rates are also needed, as are studies exploring sex differences in immune reactivity and in the pharmacodynamics of immunosuppressives.

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