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The impact of recipient and donor gender-match and mismatch on the post-liver transplant outcomes of patients with primary biliary cholangitis

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ABSTRACT

Background & aims: In this study, we evaluate the effects of donor gender on post-liver transplant (LT) prognosis. We specifically consider patients with primary biliary cholangitis (PBC).
Methods: The 2005 to 2019 UNOS transplant registry was used to select patients with PBC. The study cohort was stratified by donor gender. All-cause mortality and graft failure hazards were compared using iterative Cox regression analysis. Subanalyses were performed to evaluate gender mismatch on post-LT prognosis.
Results: There were 1885 patients with PBC. Of these cases, 965 entries had male donors and 920 had female donors. Median follow-up was 4.82 (25–75% IQR 1.83–8.93) years. Having a male donor was associated with higher all-cause mortality (aHR 1.28 95%CI 1.03–1.58) and graft failure (aHR 1.70 95%CI 1.02–2.82). Corresponding incidence rates were also relatively increased. In the sub-analysis of female recipients (n = 1581), those with gender-mismatch (male donors, n = 769) were associated with higher all-cause mortality (aHR 1.41 95%CI 1.11–1.78) but not graft failure. In the male recipient subanalysis (n = 304), no associations were found between gender-mismatch (female donors, n = 108) and all-cause mortality or graft failure.
Conclusion: This study shows that recipients who have male donors experienced higher rates of all-cause mortality following LT. This finding was consistent in the female recipient-male donor mismatch cohort.

1. Introduction

In patients with primary biliary cholangitis (PBC), hepatobiliary inflammation elicits a fibrotic wound-healing response from stellate cells [1–3]. This condition eventually progresses to cirrhosis and end-stage liver disease [3–6], with manifestations including portal hypertension, ascites, jaundice, encephalopathy, and variceal bleeding [1,3,5]. While options are available to attenuate these complications, the ultimate resolution of end-stage PBC is liver transplant therapy (LT), effectively replacing the diseased liver with a healthy graft [3,4,6].

Risks associated with LT can depend on donor and recipient characteristics [7,8]. Gender and gender-mismatch may influence prognosis [9–11]; for example, females are thought to mount a more robust immune response post-LT [9,10,12]. Other studies have suggested the existence of sex-specific metabolic complications, reporting higher incidences of sarcopenia in males after graft insertion [13–15]. Although the general LT literature has supported these claims with clinical evidence, there is limited data describing gender-specific outcomes post-LT in patients with PBC. This is despite the fact that PBC in non-transplant literature has demonstrated association between disease severity and sex [4,6,11].

We sought to analyze patients transplanted for PBC are investigated using a UNOS-derived database, stratified by donor gender to assess its relationship to all-cause mortality and graft failure.

2. Methods

2.1. Database

This study analyzes data extracted from the UNOS STAR registry, querying files compiled between January 2005 and June 2019. Periprocedural data, recipient and donor information, and

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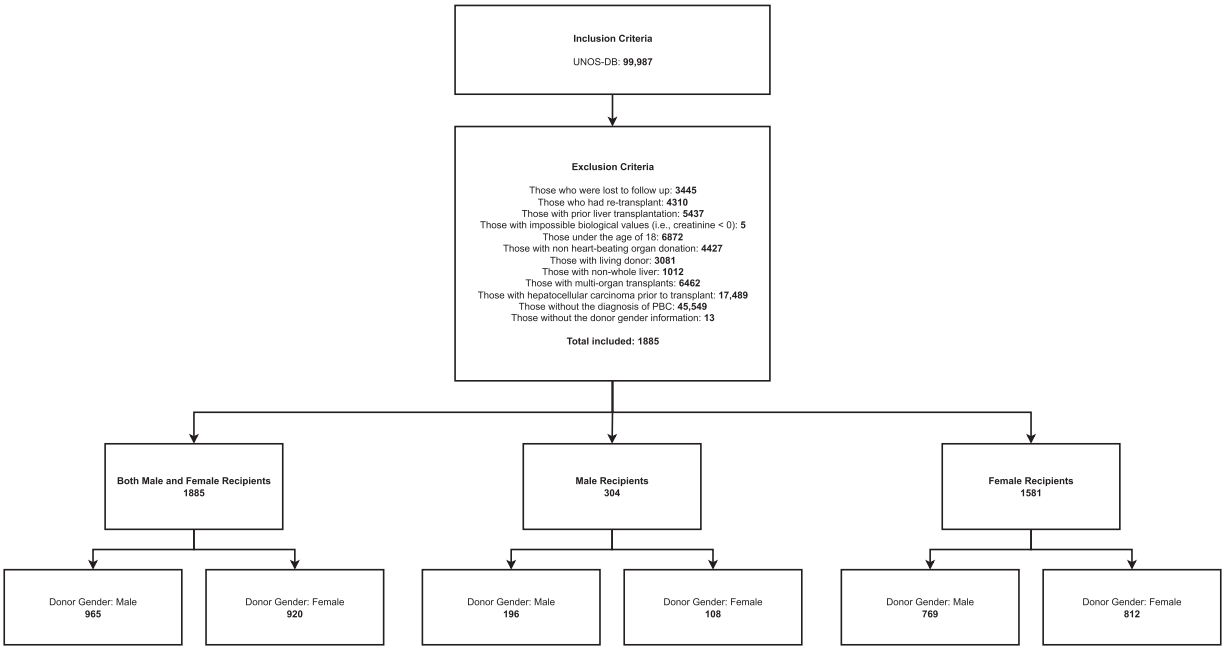


Fig. 1. This figure shows the patient selection process of this study.

longitudinal outcomes are contained within UNOS STAR. The database employs safety protocols to maintain the confidentiality and anonymity of patient information, and data-use agreements allow for access by biomedical researchers. This study is solely the responsibility of the authors alone. It does not reflect the opinions of the Department of Health and Human Services, nor any other regulatory agency.

2.2. Study population and covariates

There were 99,987 LT entries found in UNOS STAR from 2005 to 2019. A stepwise exclusionary procedure was then applied to isolate a specific PBC population. Patients who were lost to follow-up (n=3445) or who underwent retransplant were excluded (n=4310). Patients with prior LT were also removed (n=5437). Further exclusionary criteria were as follows, with the number of cases eliminated noted: Those with impossible biological values (e.g., creatinine $<$ 0, n=5), those under 18 years of age (n=6872), those with donors of cardiac death (n=4427), those with living donors (n=3081), those with non-whole livers (n=1012), those with multiple organs being transplanted (n=6462), and those with hepatocellular carcinoma prior to transplant (n=17,489). Patients without the diagnosis of PBC were removed (n=45,549), and finally, patients without donor gender information were removed (n=13), resulting in a cohort of 1885 patients. PBC diagnosis was defined as having PBC listed as a primary indication for LT, either at UNOS waitlist registration or at the time of hospital admission during which transplant occurred. Fig. 1 demonstrates the patient selection process for this study.

2.3. Study variables and outcomes

The study exposure was donor gender, which was a two-level variable (male or female). Primary outcomes were all-cause mortality and graft failure, and secondary outcomes were mortality from recurrent liver disease and mortality from post-LT hepatic malignancy. Covariates were recipient and donor demographics, laboratory markers, recipient comorbidities, hepatic function variables, and MELD score. The 'assistance' term within the comorbidities group was an ordinal variable based on the Karnofsky score [16], in which 1 corresponded to scores between 80 and 100% (high functional status), 2 corresponded to scores between 50 and 70% (intermediate functional status), 3 corresponded to scores between 10 and 40% (low functional status), and 0 represented no data. Other information collected included immunosuppressant regimens, and critical care and life support descriptors.

Two supplementary cohorts were produced that included all patients of the main cohort; however, groups were restricted across donor obesity or tacrolimus-containing regimen. Transplant cases whose donors had a body mass index (BMI) $>$ 30kg/m2 were separated from cases whose donors had a lower BMI. Similarly, patients who received tacrolimus as part of their immunosuppressant regimen were studied independently from patients who did not receive tacrolimus.

2.4. Statistical methods

Baseline characteristics were compared via mean-based and nominal-based statistics. Fisher's Exact or Chi-square comparisons were conducted for categorical data. Continuous data was assessed for parametricity and then measured with Student's t-tests and Whitney-Mann tests accordingly. Sets of Cox regression analyses were performed to describe the relationship between exposure and outcome. Each iterative model included four steps, which were as follows: model 1—adjusted for recipient age, race, sex, and BMI; model 2—further adjusted for comorbidities (i.e., diabetes, hepatitis B, hepatitis C, and alcoholic liver disease); model 3—further adjusted for MELD score, liver laboratory markers, and hepatic function terms; model 4—further adjusted for donor age, race, sex, and BMI. Statistical significance was determined using the standard two-sided 95% confidence interval and p-value $<$ 0.05. Cumulative hazard-event analyses were used to compare freedom from outcome, and crude incidence rates were also derived for each stratum. Forest plots showing adjusted hazard ratios from the final model of the multivariate Cox regression were constructed to help isolate the exposure's effect on each primary outcome, for the combined-sex analysis only. While both supplementary cohorts (groups restricted across tacrolimus use or donor obesity) contained gender mismatch subanalyses and underwent baseline char-

acteristic and Cox regression evaluations, forest plots were not generated.

For only the main cohort, a proportional subdistribution hazards model, as outlined in the cumulative incidence function by Fine and Gray [17], was employed to analyze the competing risk regression for graft failure versus mortality. This analysis was conducted according to the iterative process described previously, with four models generated.

Aside from endpoints, all variables were graphically evaluated to assess missingness patterns and processed through random forest plot generation for optimized statistical power [18]. All analyses in this study used RStudio version 1.2.5042 with R code version 3.6.3.

3. Results

3.1. Baseline characteristics

A total of 1885 subjects were included in the study cohort, with 965 subjects in the male donor cohort and 920 subjects in the female donor cohort. Median follow-up was 4.82 (25–75% IQR 1.83–8.93) years. The male donor cohort featured a higher proportion of male recipients than the female donor cohort (20.30 vs. 11.70%, $p<0.001$). There were no statistically significant differences in race or age between cohorts. Regarding MELD score, recipients of the male donor cohort featured a higher average score than recipients of the female donor cohort (24.30 ± 8.81 vs 23.40 ± 8.41, $p<0.04$). Assistance level did not differ significantly between the donor cohorts. Female donors were generally older than male donors (47.90 ± 17.70 vs 39.60 ± 17.40 years, $p<0.001$), and racial profiles of the donors also showed significant variation. Table 1 demonstrates further comparisons of background characteristics.

Table 1 also includes subanalyses of gender mismatch, produced by restricting the study cohort to include either male or female recipients only. There were 1581 female recipients, with 812 of these cases having a female donor and 769 having a male donor (gender mismatch). Among the remaining 304 male recipients, there were 108 entries in the female donor (gender mismatch) cohort and 196 in the male donor cohort.

Solely considering female recipients, the female donor cohort had a higher average recipient age than that of the male donor cohort (56.80 ± 8.88 vs. 55.80 ± 9.51 years, $p = 0.05$). Average recipient MELD score of the male donor category was significantly higher than the score of the female donor category (24.40 ± 8.75 vs 23.30 ± 8.41, $p = 0.01$). No significant differences in assistance level were detected. When considering donor characteristics, the female donor group was older on average (47.60 ± 18.00 vs 39.00 ± 17.40 years, $p < 0.001$) and had a greater proportion of White donors among other differences (Female vs Male donors: White 70.10 vs 58.10%, Asian 2.22 vs 2.34%, Black 14.50 vs 18.90%, Hispanic 11.50 vs 17.90%, $p<0.001$).

When isolating male recipients, there were only significant differences in baseline characteristics along donor qualities. Donors of the female donor group were older (50.10 ± 15.10 vs 42.10 ± 17.10 years, $p<0.001$). Male donors of this framework were found to have higher levels of serum creatinine (1.72 ± 1.61 vs 1.42 ± 1.40 mg/dL, $p<0.001$) and total bilirubin (1.13 ± 1.05 vs 0.66 ± 0.56 mg/dL, $p<0.001$).

3.2. Clinical outcomes

Table 2 demonstrates the sequential Cox regression analyses of all-cause mortality and graft failure. Those with male donors were associated with a higher risk of post-LT all-cause mortality (aHR 1.28 95% confidence interval [CI] 1.03–1.58, $p = 0.02$) and graft failure (aHR 1.70 95%CI 1.02–2.82, $p = 0.04$). Each comparison corresponded with a higher indexed incidence rate in the male-donor cohort (expressed as events per 1000 person-years, all-cause mortality: 42.28 vs 33.34; graft failure: 8.65 vs 5.46).

Further subanalysis was done to assess primary outcomes of mismatched donor gender. Mismatched female recipients of male donors exhibited a significantly higher risk of all-cause mortality than matched female recipient-donor cases (aHR 1.41 95%CI 1.11–1.78, $p = 0.005$). There was also a trend toward a greater hazard of graft failure (aHR 1.65 95%CI 0.96–2.84, $p = 0.07$). Additionally, each comparison returned a higher indexed incidence rate in female recipients of male donors (expressed as events per 1000 person-years, all-cause mortality: 41.75 vs 31.17; graft failure: 8.89 vs 5.71). In male recipients, there were no associations between donor gender and post-LT all-cause mortality (aHR 0.82 95%CI 0.49–1.38, $p = 0.46$) and graft failure (aHR 2.36 95%CI 0.42–13.42, $p = 0.33$).

Fig. 2 shows cumulative hazard analysis of the combined-sex and sex-restricted cohorts. Having a male donor was significantly associated with a higher risk of all-cause mortality and trended toward higher risk for graft failure ($p = 0.026$ and $p = 0.061$, respectively). The female-recipient-restricted subanalysis saw similar results along these same endpoints ($p = 0.014$ for all-cause mortality and $p = 0.096$ for graft failure). Male-recipient-restricted analysis showed no significant associations.

3.3. Competing risks, secondary outcomes, and forest plots with adjusted hazard ratios

Using donor sex as a prognostic risk factor, Supplementary Table 1 demonstrates competing risk regression analyses for both all-cause mortality and graft failure. There was no significant difference in the incidence of all-cause mortality between the male and female donor cohorts (aHR 1.19 95% CI 0.94–1.51, $p = 0.15$), but there was a significant difference in graft failure (aHR 1.65 95% CI 1.01–2.68, $p = 0.04$). In female-recipient-restricted analysis, there was an increased risk for all-cause mortality in cases who had male donors (aHR 1.34 95%CI 1.03–1.75, $p = 0.03$). Male recipient analyses did not show any associations. Supplementary Table 2 describes a Cox regression of the main cohort with the outcome of mortality secondary to recurrent liver disease. No significant associations were detected in combined-sex or sex-restricted analyses. Furthermore, no diagnoses of hepatic malignancy were detected in follow-up for any case. Supplementary Figure 1 shows the relationships between covariates and all-cause mortality for the combined-sex analysis, whereas Supplementary Figure 2 represents these variables' associations with graft failure.

3.4. Donor obesity and tacrolimus use: restricted analysis

When restricting to non-obese donors, male donors were associated with increased mortality hazard in the combined-sex (aHR 1.28 95% CI 1.01–1.62, $p = 0.04$) and female-only (aHR 1.34 95% CI 1.03–1.74, $p = 0.03$) cohorts. Regarding solely obese donors, no significant relationships with either primary outcome were found. Patients on regimens without tacrolimus and male donors were associated with increased hazard for all-cause mortality (aHR 2.19 95% CI 1.33–3.61, $p = 0.002$) and graft failure (aHR 5.80 95% CI 1.09–30.81, $p = 0.04$). Discrepant risks persisted in female-only subanalysis as well (all-cause mortality: aHR 3.36 95% CI 1.83–6.15, $p<0.001$; graft failure: aHR 16.19 95% CI 1.78–147.42, $p = 0.01$). In contrast, patients who were on tacrolimus regimens showed no donor sex associations with any of the primary outcomes. Associated case-incidence rates were elevated in the reported significant findings. Non-tacrolimus-prescribed male donor cases experienced a mortality rate of 146.54 deaths per 1000 person-years, compared to non-tacrolimus female donor cases featuring a rate of 80.84

Table 1
Baseline Characteristics of PBC-Indicated Liver Transplant Recipients and Donors—Combined, Male-Restricted, and Female-Restricted Analyses.

	Male vs Female Donors in All Recipients			Subanalysis: Male vs Female Donors in Male Recipients			Subanalysis: Male vs Female Donors in Female Recipients		
	Female	Male	*P*-value	Female	Male	*P*-value	Female	Male	*P*-value
Number of Patients	**920**	**965**		**108**	**196**		**812**	**769**	
Recipient Demographics									
Age, mean ± SD, y	56.40 ± 9.37	55.70 ± 9.93	0.14	54.10 ± 12.30	55.40 ± 11.50	0.32	56.80 ± 8.88	55.80 ± 9.51	0.05*
Male sex, *n* (%)	108 (11.70)	196 (20.30)	< 0.001*						
Race, *n* (%)			0.97			0.46 †			0.84
White	647 (70.30)	693 (71.80)		81 (75.00)	153 (78.10)		566 (69.70)	540 (70.20)	
Black	87 (9.46)	84 (8.70)		11 (10.20)	15 (7.65)		76 (9.36)	69 (8.97)	
Hispanic	147 (16.00)	149 (15.40)		13 (12.00)	17 (8.67)		134 (16.50)	132 (17.20)	
Asian	26 (2.83)	26 (2.69)		2 (1.85)	10 (5.10)		24 (2.96)	16 (2.08)	
Other	13 (1.41)	13 (1.35)		1 (0.93)	1 (0.51)		12 (1.48)	12 (1.56)	
BMI, mean ± SD, kg/m²	26.50 ± 5.69	27.40 ± 5.60	< 0.001*	25.80 ± 4.59	26.70 ± 5.00	0.13	26.60 ± 5.82	27.60 ± 5.73	< 0.001*
Comorbidities									
Hepatitis B, *n* (%)	7 (0.76)	10 (1.04)	0.70	3 (2.78)	1 (0.51)	0.13 †	4 (0.49)	9 (1.17)	0.17 †
Hepatitis C, *n* (%)	23 (2.50)	33 (3.42)	0.30	3 (2.78)	5 (2.55)	1.00 †	20 (2.46)	28 (3.64)	0.22
Alcoholic Liver Disease, *n* (%)	5 (0.54)	9 (0.93)	0.47	2 (1.85)	3 (1.53)	1.00 †	3 (0.37)	6 (0.78)	0.33 †
Diabetes, *n* (%)	121 (13.20)	155 (16.10)	0.09	15 (13.90)	39 (19.90)	0.25	106 (13.10)	116 (15.10)	0.28
Assistance, *n* (%) ‡			0.49			0.29 †			0.48
0 (%)	27 (2.93)	18 (1.87)		4 (3.70)	4 (2.04)		23 (2.83)	14 (1.82)	
1 (%)	177 (19.20)	192 (19.90)		23 (21.30)	57 (29.10)		154 (19.00)	135 (17.60)	
2 (%)	340 (37.00)	354 (36.70)		42 (38.90)	61 (31.10)		298 (36.70)	293 (38.10)	
3 (%)	376 (40.90)	401 (41.60)		39 (36.10)	74 (37.80)		337 (41.50)	327 (42.50)	
Hepatic Variables									
Ascites, *n* (%)			0.51			0.42			0.81
Absent	156 (17.00)	181 (18.80)		17 (15.70)	41 (20.90)		139 (17.10)	140 (18.20)	
Slight	464 (50.40)	465 (48.20)		57 (52.80)	90 (45.90)		407 (50.10)	375 (48.80)	
Moderate	300 (32.60)	319 (33.10)		34 (31.50)	65 (33.20)		266 (32.80)	254 (33.00)	
Encephalopathy, *n* (%)			0.62			0.95			0.64
None	291 (31.60)	296 (30.70)		34 (31.50)	65 (33.20)		257 (31.70)	231 (30.00)	
1–2	521 (56.60)	566 (58.70)		65 (60.20)	116 (59.20)		456 (56.20)	450 (58.50)	
3–4	108 (11.70)	103 (10.70)		9 (8.33)	15 (7.65)		99 (12.20)	88 (11.40)	
MELD Scores, mean ± SD	23.40 ± 8.41	24.30 ± 8.81	0.04*	24.30 ± 8.39	23.80 ± 9.04	0.50	23.30 ± 8.41	24.40 ± 8.75	0.01*
Immunosuppressants									
Mycophenolate Mofetil, *n* (%)	737 (80.10)	799 (82.80)	0.15	88 (81.50)	170 (86.70)	0.29	649 (79.90)	629 (81.80)	0.38
Cyclosporine, *n* (%)	49 (5.33)	49 (5.08)	0.89	9 (8.33)	16 (8.16)	1.00	40 (4.93)	33 (4.29)	0.63
Tacrolimus, *n* (%)	839 (91.20)	869 (90.10)	0.44	97 (89.80)	175 (89.30)	1.00	742 (91.40)	694 (90.20)	0.49

(*continued on next page*)

Table 1 (*continued*)

	Male vs Female Donors in All Recipients			Subanalysis: Male vs Female Donors in Male Recipients			Subanalysis: Male vs Female Donors in Female Recipients		
	Female	Male	*P*-value	Female	Male	*P*-value	Female	Male	*P*-value
Sirolimus, *n* (%)	16 (1.74)	13 (1.35)	0.61	1 (0.93)	3 (1.53)	1.00 †	15 (1.85)	10 (1.30)	0.50
Steroids, *n* (%)	857 (93.20)	900 (93.30)	1.00	98 (90.70)	185 (94.40)	0.34	759 (93.50)	715 (93.00)	0.77
Laboratory Markers									
Albumin, mean ± SD, mg/dL	2.95 ± 0.75	2.95 ± 0.77	0.94	2.86 ± 0.67	2.94 ± 0.71	0.29	2.97 ± 0.76	2.96 ± 0.79	0.74
Creatinine, mean ± SD, mg/dL	1.32 ± 0.92	1.42 ± 1.04	0.19	1.50 ± 1.04	1.58 ± 1.15	0.95	1.30 ± 0.91	1.39 ± 1.01	0.41
INR, mean ± SD	1.85 ± 1.00	1.98 ± 1.57	0.07	1.86 ± 0.73	1.87 ± 0.84	0.61	1.84 ± 1.03	2.01 ± 1.70	0.03*
Total Bilirubin, mean ± SD, mg/dL	13.80 ± 12.10	13.80 ± 12.10	0.89	13.90 ± 12.20	12.50 ± 12.80	0.13	13.80 ± 12.10	14.10 ± 11.90	0.45
Critical Care and Life Support									
Primary Inotropic Agent, *n* (%)			0.05			0.75 †			0.12
Dobutamine	20 (2.17)	21 (2.18)		3 (2.78)	3 (1.53)		17 (2.09)	18 (2.34)	
Dopamine	175 (19.00)	194 (20.10)		24 (22.20)	41 (20.90)		151 (18.60)	153 (19.90)	
Epinephrine	11 (1.20)	7 (0.73)		1 (0.93)	1 (0.51)		10 (1.23)	6 (0.78)	
Levophed	165 (17.90)	132 (13.70)		20 (18.50)	29 (14.80)		145 (17.90)	103 (13.40)	
	165 (17.90)	149 (15.40)		17 (15.70)	26 (13.30)		148 (18.20)	123 (16.00)	
Neosynephrine									
None	362 (39.30)	437 (45.30)		41 (38.00)	92 (46.90)		321 (39.50)	345 (44.90)	
Other	22 (2.39)	25 (2.59)		2 (1.85)	4 (2.04)		20 (2.46)	21 (2.73)	
Secondary Inotropic Agent, *n* (%)			0.65 †			0.94 †			0.57 †
Dobutamine	8 (0.87)	4 (0.42)		0 (0.00)	1 (0.51)		8 (0.99)	3 (0.39)	
Dopamine	10 (1.09)	11 (1.14)		2 (1.85)	5 (2.55)		8 (0.99)	6 (0.78)	
Epinephrine	8 (0.87)	9 (0.93)		2 (1.85)	2 (1.02)		6 (0.74)	7 (0.91)	
Levophed	32 (3.48)	32 (3.32)		4 (3.70)	5 (2.55)		28 (3.45)	27 (3.51)	
	42 (4.57)	43 (4.46)		5 (4.63)	8 (4.08)		37 (4.56)	35 (4.55)	
Neosynephrine									
None	811 (88.20)	848 (87.90)		95 (88.00)	173 (88.30)		716 (88.20)	675 (87.80)	

(*continued on next page*)

Table 1 (*continued*)

	Male vs Female Donors in All Recipients			Subanalysis: Male vs Female Donors in Male Recipients			Subanalysis: Male vs Female Donors in Female Recipients		
	Female	Male	*P*-value	Female	Male	*P*-value	Female	Male	*P*-value
Other	9 (0.98)	18 (1.87)		0 (0.00)	2 (1.02)		9 (1.11)	16 (2.08)	
Tertiary Inotropic Agent, *n* (%)			1.00 †			0.79 †			0.99 †
Dobutamine	0 (0.00)	1 (0.10)		0 (0.00)	0 (0.00)		0 (0.00)	1 (0.13)	
Dopamine	1 (0.11)	0 (0.00)		0 (0.00)	0 (0.00)		1 (0.12)	0 (0.00)	
Epinephrine	2 (0.22)	2 (0.21)		0 (0.00)	0 (0.00)		2 (0.25)	2 (0.26)	
Levophed	4 (0.43)	4 (0.42)		1 (0.93)	1 (0.51)		3 (0.37)	3 (0.39)	
	4 (0.43)	4 (0.42)		0 (0.00)	0 (0.00)		4 (0.49)	4 (0.52)	
Neosynephrine									
None	903 (98.20)	948 (98.20)		107 (99.10)	193 (98.50)		796 (98.00)	755 (98.20)	
Other	6 (0.65)	6 (0.62)		0 (0.00)	2 (1.02)		6 (0.74)	4 (0.52)	
ICU admission, *n* (%)			0.51			0.64			0.47
ICU	120 (13.00)	137 (14.20)		9 (8.33)	21 (10.70)		111 (13.70)	116 (15.10)	
No ICU	800 (87.00)	828 (85.80)		99 (91.70)	175 (89.30)		701 (86.30)	653 (84.90)	
Ventilator Support, *n* (%)	37 (4.02)	45 (4.66)	0.57	4 (3.70)	5 (2.55)	0.73 †	33 (4.06)	40 (5.20)	0.34
TIPS Procedure, *n* (%)	85 (9.24)	90 (9.33)	1.00	12 (11.10)	19 (9.69)	0.85	73 (8.99)	71 (9.23)	0.94
Donor Demographics									
Donor Age, mean ± SD, y	47.90 ± 17.70	39.60 ± 17.40	< 0.001*	50.10 ± 15.10	42.10 ± 17.10	< 0.001*	47.60 ± 18.00	39.00 ± 17.40	< 0.001*
Donor Male sex, *n* (%)	0 (0.00)	965 (100.00)	< 0.001 †***	0 (0.00)	196 (100.00)	< 0.001 †***	0 (0.00)	769 (100.00)	< 0.001 †***
Donor Race, *n* (%)			< 0.001*			0.24 †			< 0.001*
White	649 (70.50)	575 (59.60)		80 (74.10)	128 (65.30)		569 (70.10)	447 (58.10)	
Black	129 (14.00)	176 (18.20)		11 (10.20)	31 (15.80)		118 (14.50)	145 (18.90)	
Hispanic	103 (11.20)	164 (17.00)		10 (9.26)	26 (13.30)		93 (11.50)	138 (17.90)	
Asian	23 (2.50)	22 (2.28)		5 (4.63)	4 (2.04)		18 (2.22)	18 (2.34)	
Other	16 (1.74)	28 (2.90)		2 (1.85)	7 (3.57)		14 (1.72)	21 (2.73)	
Donor BMI, mean ± SD, kg/m²	27.80 ± 6.84	26.30 ± 4.91	< 0.001*	29.70 ± 7.65	27.90 ± 5.05	0.22	27.60 ± 6.69	25.90 ± 4.79	< 0.001*
Donor Laboratory Markers									
Donor Creatinine, mean ± SD, mg/dL	1.42 ± 1.69	1.76 ± 1.88	< 0.001*	1.42 ± 1.40	1.72 ± 1.61	< 0.001*	1.42 ± 1.73	1.77 ± 1.95	< 0.001*
Donor Total Bilirubin, mean ± SD, mg/dL	0.75 ± 0.61	1.02 ± 0.86	< 0.001*	0.66 ± 0.56	1.13 ± 1.05	< 0.001*	0.76 ± 0.62	0.99 ± 0.80	< 0.001*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
† Fisher's Test.

Table 2
Sequential Cox Regression Analysis Using Donor Gender as a Prognostic Risk Factor for All-Cause Mortality and Graft Failure.

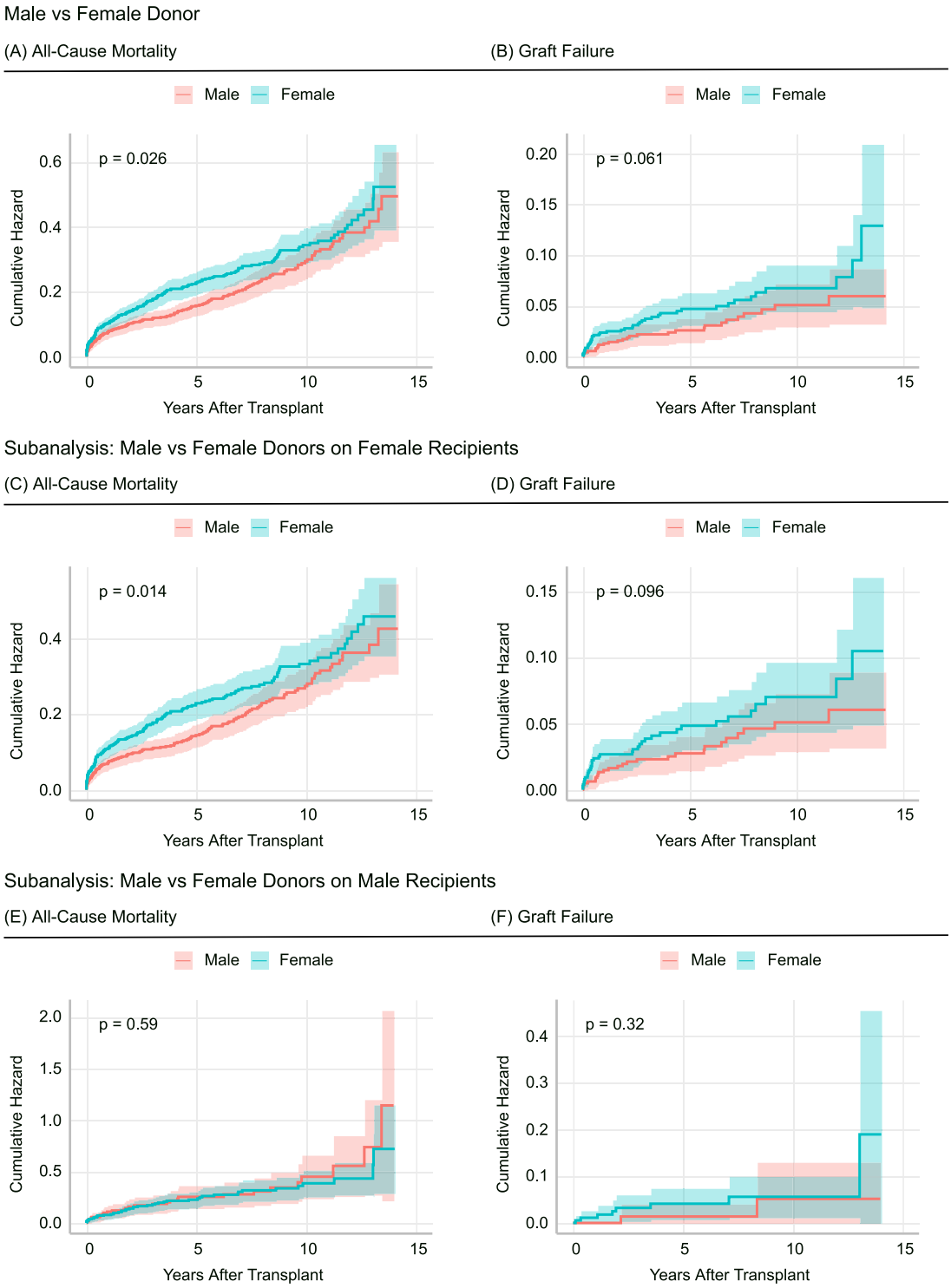
(A) All-Cause Death

Male vs Female Donor					Subanalysis: Male vs Female Donors in Male Recipients				Subanalysis: Male vs Female Donors in Female Recipients				
Incidence Rates per 1000 Person-Years					**Incidence Rates per 1000 Person-Years**				**Incidence Rates per 1000 Person-Years**				
Male Donor			42.28	(36.91–48.18)	**Male Donor**		44.34	(32.64–58.70)	**Male Donor**			41.75	(35.80–48.37)
Female Donor			33.34	(28.59–38.62)	**Female Donor**		50.58	(34.13–71.83)	**Female Donor**			31.17	(26.31–36.63)
Sequential Cox Regression Analysis					**Sequential Cox Regression Analysis**				**Sequential Cox Regression Analysis**				
Model	**p-value**		**aHR**	**95% CI**	**Model**	**p-value**	**aHR**	**95% CI**	**Model**	**p-value**		**aHR**	**95% CI**
1	0.06		1.22	(0.99–1.49)	1	0.52	0.86	(0.53–1.38)	1	0.02	*	1.31	(1.04–1.63)
2	0.07		1.21	(0.99–1.49)	2	0.49	0.85	(0.52–1.36)	2	0.02	*	1.30	(1.04–1.63)
3	0.05		1.22	(1.00–1.50)	3	0.58	0.87	(0.54–1.41)	3	0.02	*	1.32	(1.05–1.65)
† FM	0.02	*	1.28	(1.03–1.58)	† FM	0.46	0.82	(0.49–1.38)	† FM	0.005	**	1.41	(1.11–1.78)

(B) Graft Failure

Male vs Female Donor					**Subanalysis: Male vs Female Donors in Male Recipients**				**Subanalysis: Male vs Female Donors in Female Recipients**				
Incidence Rates per 1000 Person-Years					**Incidence Rates per 1000 Person-Years**				**Incidence Rates per 1000 Person-Years**				
Male Donor			8.65	(6.29–11.60)	**Male Donor**		7.71	(3.33–15.14)	**Male Donor**			8.89	(6.24–12.29)
Female Donor			5.46	(3.63–7.88)	**Female Donor**		3.49	(0.42–12.54)	**Female Donor**			5.71	(3.73–8.35)
Sequential Cox Regression Analysis					**Sequential Cox Regression Analysis**				**Sequential Cox Regression Analysis**				
Model	**p-value**		**aHR**	**95% CI**	**Model**	**p-value**	**aHR**	**95% CI**	**Model**	**p-value**		**aHR**	**95% CI**
1	0.08		1.54	(0.95–2.48)	1	0.24	2.56	(0.53–12.34)	1	0.14		1.47	(0.88–2.44)
2	0.08		1.54	(0.95–2.49)	2	0.23	2.67	(0.54–13.25)	2	0.14		1.47	(0.88–2.45)
3	0.06		1.60	(0.99–2.59)	3	0.30	2.33	(0.47–11.61)	3	0.09		1.55	(0.93–2.59)
† FM	0.04	*	1.70	(1.02–2.82)	† FM	0.33	2.36	(0.42–13.42)	† FM	0.07		1.65	(0.96–2.84)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
† FM indicates Final Model.
Footnote: *Model 1 includes VOI (variable of interest) and demographics; Model 2 includes Model 1 terms with the addition of comorbidities, and liver disease etiologies; Model 3 includes Model 2 terms with the addition of hepatic variables, MELD score, and liver laboratory markers; Model † FM includes Model 3 terms with the addition of donor demographics.



(A) and (B) represent the cumulative hazards for all-cause mortality and graft failure in liver transplant recipients, who received their grafts from male versus female donors. (C) and (D) represent the cumulative hazards for all-cause mortality and graft failure in female liver transplant recipients who received their grafts from male versus female donors. (E) and (F) represent the cumulative hazards for all-cause mortality and graft failure in male liver transplant recipients who received their grafts from male versus female donors.The p-value indicates the respective log-rank p-value for each curve.

Fig. 2. This figure shows the prognostic differences in the cumulative hazards using all-cause mortality (Fig. 2a) and graft failure (Fig. 2b) as primary endpoints. Fig. 2c, 2d, 2e, and 2f show these same outcomes for the sex-restricted subanalyses.

deaths per 1000 person-years. Meanwhile, tacrolimus-prescribed male donor cases and female donor cases demonstrated mortality rates of 35.49 and 30.07 deaths per 1000 person-years, respectively. Evaluation of baseline characteristics are shown in Supplementary Tables 3.1 through 3.4 and Cox regression analyses are included in Supplementary Tables 4.1 through 4.4.

4. Discussion

Using a select PBC population, this study investigated the implications of donor sex on post-LT outcomes. A primary motivating factor of this work came from non-transplant literature; PBC in males is typically characterized by greater morbidity than in females, including higher incidences of hepatocellular carcinoma, extrahepatic complications, and overall mortality [6,19]. Reasons for these phenomena are unclear. Recent literature has suggested that males are consistently diagnosed late in the PBC disease course and have lower rates of response to temporizing treatments such as ursodeoxycholic acid [20,21]. Some authors trace their hypotheses back to a hormonal level, such as Trivedi et al. (2016) who propose that estrogen could protect against hepatocellular carcinogenesis [22]. This literature raises the question of male donors in the transplant PBC setting, if these grafts are risk factors for adverse outcomes. Indeed, livers from male donors experienced significantly increased risk for all-cause mortality and graft failure. When restricting the study cohort to female recipients, having a male donor was similarly associated with an increased all-cause mortality rate. In male recipients, no significant associations were found. These observations of male donor status being a risk factor for poor outcomes contrast with other reviews. A meta-analysis combining seven studies found that female-to-male LT schemes predicted the worst outcomes, but no such relationships were identified in the reverse design of male-to-female designs [23]. Older research has also found that livers from female donors, regardless of recipient sex, were associated with increased rates of adverse outcomes [24]. However, these investigations did not specifically consider the PBC-indicated LT population. It is worth mentioning that a small cohort study from the United Kingdom found that males transplanted for PBC exhibited symptom exacerbation compared to non-transplanted controls, whereas no differences in clinical status were found when comparing female transplanted and non-transplanted cases [25].

Supplementary analyses were conducted with restrictions across donor obesity and tacrolimus use. When considering non-obese donors, similar results were observed, with male donors being associated with increased all-cause mortality in the combined-sex and female-restricted cohorts. However, differences in mortality hazard fell out of significance when restricting to obese donors. This finding could be secondary to increased prevalence of hepatic steatosis in obese donors. Fatty pre-transplant insults could impair hepatic function and insulin and glucagon sensitivity, ultimately predisposing the graft recipient to metabolic derangements and suboptimal health [26].

Meanwhile, patients who did not receive tacrolimus experienced profound survival discrepancies between donor sex, with higher adjusted hazards for both all-cause mortality and graft failure in the combined-sex and female-restricted cohorts. All relationships with the primary outcomes (all-cause mortality and graft failure) fell out of significance when evaluating recipients who were on tacrolimus, the larger of the medication-based cohorts.

The effect of immunosuppressive therapies in LT is an area of active research, especially in cases with PBC as a primary indication. The type of calcineurin inhibitor has been shown to profoundly affect the clinical courses of transplanted PBC patients; for example, tacrolimus use has been associated with improved survival but more severe forms of recurrent PBC (rPBC) [27,28]. It should be noted that tacrolimus use is associated with superior mortality outcomes across LT indications [29]. With regard to sex-dependent pharmacokinetics, clearance rates of both cyclosporine and tacrolimus appear to be increased in females, with mechanisms potentially linked to CYP3A and P-glycoprotein activity in the liver and intestine [30]. Applying these findings to the present analysis is complicated by classifying the 'sex' of the donated liver after allocation, especially in mismatch cases. UNOS contains data on medication names, but dosages and T-cell counts are not sampled. Immunological data that specifically evaluates lymphocyte levels across sex with different suppressant regimens could be helpful in correlating pharmacodynamic mechanisms with the present findings.

In the combined-sex cohort, cumulative hazard curves for both graft failure and all-cause mortality showed divergence between sex early, within three years. This result could provide clues to etiologies of mortality rate disparities, as literature on post-LT prognosis has reported that infection is an especially prominent cause of death in short-term follow-up [31]. Immunosuppression is also closely linked to infectious phenomena, with worse outcomes typically accompanying higher drug concentrations [32]. More specifically, Jacob et al. (2008) reported ten deaths out of one hundred transplanted PBC patients, with four deaths having infectious etiologies within one year post-LT [33]. Patient sex was not reported. Notably, research on the general population has found male sex to be correlated with higher mortality in sepsis, with mechanisms attributed to higher interleukin (IL)−6 cytokine levels and low-estrous states [34,35].

Basic science research has evidenced the sexually dimorphic nature of the liver, and this *quality may affect hormone receptor concentrations. Della Torre* et al. *(2016) demonstrated that* male and female mouse models exhibit different levels of estrogen receptor α (ERα) [36]. This specific protein-steroid combination may have implications in surviving severe inflammatory responses—an investigation by Harada et al. (2004) reported that all ERα-negative male mice and 60% of ERα-negative female mice died within one week of a liver ischemia and reperfusion event, whereas untreated females or males given estrogen survived indefinitely [37]. Both receptor and ligand had to be present to achieve a protective effect against mortality, and evidence suggests that both of these variables are modified by sex. The persistence of poor outcomes in female PBC patients with male grafts may depend on these pathways, such that male-derived grafts could contain lower concentrations of specific estrogen receptors that enhance survival in the context of systemic inflammation. Regardless of the environment's estrogen content, patients may be at a higher risk for mortality from inflammatory causes such as sepsis, given their grafts' sex receptor profile. This mechanism could be modulated by calcineurin inhibitor subtype, with the risk of severe infection and inflammatory responses attenuated in both donor sexes when using tacrolimus, but patients with male donors experiencing higher risks on alternative regimens. As previously mentioned, more efficient female clearance of certain immunosuppressants [30] may be related to these observations, but further investigations into drug effects and metabolism are needed before making definitive conclusions. With respect to why other LT indications do not see similar sex-based outcomes, the underlying immune dysregulation of PBC may provide clarity. Peripheral blood mononuclear cells of PBC patients appear to more readily produce pro-inflammatory cytokines, such as IL-6 and IL-1β [38]. Such abnormalities might be key in causing the mortality rates reported by this study.

In general, PBC is associated with excellent post-transplant outcomes relative to other liver diseases [39]. Beyond the highlighted etiology of infection, two prominent threats to patient health in the post-LT PBC landscape are graft rejection and rPBC [40,41]. There have been numerous reports of rPBC, with investigations

demonstrating incidence between 17 and 46% [42]. Recurrent disease has historically been rendered innocuous, but recent experiences have highlighted a potentially pernicious role and an association with male sex [42–45]. Mortality from recurrent liver disease, which served as a proxy for mortality from rPBC, was evaluated between sex in this study. No evidence was found for this condition's occurrence to translate into differential death rates. In light of the previous literature, this result may suggest that any deleterious effects of rPBC are felt by males and females alike, or that the study sample is limited by inadequate follow-up time.

4.1. Implications, limitations, and future directions

Even with an incomplete understanding of the pathophysiology, it can be argued that PBC-indicated transplants should involve a female native liver. This is especially relevant in male-to-female discordant pairings, as hazards were significantly increased along both graft failure and all-cause mortality outcomes. As PBC remains a leading cause of LT, future studies of PBC post-transplant could be clinically useful. Limitations of this study include the retrospective, national database design of the study precluded further collection of follow-up and relevant information. Considering the potential selection bias of male patients being predisposed to worse outcomes due to sicker pre-LT health status, MELD score was included as a covariate in Cox regression, and functional status was assessed as a baseline characteristic between cohorts (coded as 'assistance'). Furthermore, patients with hepatocellular carcinoma were excluded due to reported disparate rates between sex in PBC [6]. Mortality subtype etiologies did not reach significance between the sex strata, indicating potential underpowering despite utilization of a national database. UNOS data collection is conducted through various documents, including the Transplant Candidate Registration, Transplant Recipient Registration, and Transplant Recipient Follow-up forms [46]. Individual criteria used to make a PBC diagnosis therefore depend on each registering hospital's protocols, but it can be presumed that centers followed the formal guidelines in establishing the diagnosis, using both histological markers and laboratory findings [47].

5. Conclusion

An analysis of PBC patients post-transplant found male donor gender to be associated with adverse outcomes of graft failure and all-cause mortality. This effect remained in gender-discordant matches, although stratifications across tacrolimus use and donor obesity affected the strength of these relationships. Using native female grafts may improve outcomes in LT for PBC, especially in female patients. Tacrolimus-containing regimens may also contribute to better patient survival.

Declaration of Competing Interest

The authors of this manuscript certify they share no affiliation or involvement with any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. None declared.

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Supplementary materials

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