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Sex-Based Disparities in Hepatocellular Carcinoma Recurrence After Liver Transplantation

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Abstract

Background: Women with chronic liver disease have lower rates of **hepatocellular carcinoma (HCC)** as compared to men; it is unknown if there are sex-based differences in HCC recurrence post-liver transplant.

Methods: We conducted an analysis of patients who underwent liver transplant for HCC in the United Network for Organ Sharing/Organ Procurement and Transplantation Network from January 1, 2012 through December 31, 2017.

Results: A total of 12,711 patients underwent liver transplant for HCC: 2,909 (23%) women and 9,802 (73%) men. Women had significantly lower rates of post-liver transplant HCC recurrence than men (4.0 v. 5.4%, p=0.002). A cox-regression analysis for post-liver transplant HCC recurrence highlighted that even after accounting for etiology of cirrhosis, alpha-fetoprotein (AFP) at liver transplant, tumor diameter, tumor pathology, and vascular invasion, female sex was associated with a 25% lower risk of post-liver transplant HCC recurrence (95CI 0.57–0.99). There were no interactions between female sex and the following variables: age, type of locoregional therapy, AFP, donor sex, body mass index, or nonalcoholic steatohepatitis etiology (p>0.05 for each).

Conclusions: This study demonstrates an independent effect of sex on risk for HCC recurrence post-liver transplant. Our data highlight an opportunity to better understand HCC tumor biology by investigating the drivers of this sex-based difference in HCC recurrence.

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N.M.: Study concept and design; analysis and interpretation of data; critical revision of the manuscript
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E.V.: Study concept and design; analysis and interpretation of data; critical revision of the manuscript; study supervision
J.L.: Study concept and design; analysis and interpretation of data; critical revision of the manuscript; obtained funding; study supervision

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INTRODUCTION

The burden of hepatocellular carcinoma (HCC) is rising rapidly, with an incidence that has nearly tripled in the United States (US) over the past decade.[1,2] Consequently, there has been a steady increase in the number of liver transplants performed for HCC—HCC now represents the most common indication for liver transplantation in the US.[1] In light of these trends, there is an urgent need to understand the determinants of HCC recurrence after liver transplantation. Several prognostic models have been developed to predict HCC recurrence, including the risk estimation of tumor recurrence after transplant (RETREAT) score, Metroticket 2.0, French-AFP, and the model of recurrence after liver transplant (Post-MORAL). Each of these indices have been shown to identify those patients at highest risk for HCC recurrence with varying degrees of accuracy.[3–7] However, these models have not accounted for one major factor that has been shown to be associated with the development of HCC in the *non*transplant setting—patient sex. Among patients with end-stage liver disease or viral hepatitis, women have between a 50 – 75% lower risk of HCC as compared to men.[8] Moreover, a single study has suggested that women have a 75% and 31% lower risk of HCC recurrence and HCC-related mortality after hepatic resection, respectively.[9] These differences suggest that there are sex-based differences in HCC biology that might persist into the post-liver transplant setting as well.[10,11]

Herein, we present a study focused on determining the association between sex and HCC recurrence post-liver transplant. We hypothesized that sex would have a significant impact on post-liver transplant HCC recurrence.

Materials and Methods

All adult (≥ 18 years) patients listed for liver transplantation in the United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) registry from January 1, 2012 through December 31, 2017 were evaluated for inclusion in this study.

Recipient and donor characteristics—Data used in this analysis were obtained from the UNOS/OPTN registry as of March 15, 2019, which includes post-liver transplant mortality, as reported to the Social Security Death Master File. The Model for End-Stage Liver Disease with serum sodium (MELDNa) score at listing and transplant, or waitlist removal was calculated and capped at 6 and 40. Ascites and hepatic encephalopathy were considered present if they were recorded at waitlist removal/transplant. Liver donor characteristics included those used to calculate the donor risk index (DRI), a summary metric to quantify liver allograft quality.[12]

Hepatocellular carcinoma and cirrhosis etiology—Patients were included this study for undergoing liver transplantation for HCC if any of the following were true: (1) they were granted HCC exception points; (2) their primary or secondary diagnosis at listing or transplant was HCC; or (3) they were designated as ever having had HCC. Listing diagnoses were grouped into the following common diagnostic categories: hepatitis C virus (HCV), nonalcoholic steatohepatitis (NASH, including cryptogenic cirrhosis), alcohol-related cirrhosis, autoimmune etiologies (including primary biliary cirrhosis, primary

sclerosing cholangitis, and autoimmune hepatitis), and other etiologies of cirrhosis (any other listing code that met inclusion criteria).

Tumor Characteristics—We analyzed all tumor characteristics included in the UNOS/OPTN database. These included size and number of HCC tumors at the time of listing and transplant, AFP at time of listing and transplant, peak and nadir AFP, and type and frequency of locoregional therapy (LRT). These are the variables provided as part of the explant data that is included in the UNOS/OPTN database in recent years.

Outcomes—To better understand the impact of sex on HCC recurrence post-liver transplant, we analyzed the following outcomes: Primary Outcome: HCC Recurrence, defined as cancer (primary hepatic, metastatic liver, malignant pretransplant tumor) after liver transplant; Secondary Outcome: Post-liver transplant mortality. We analyzed post-liver transplant mortality outcomes after 30 days, to focus on post-liver transplant deaths that were secondary to HCC, as opposed to post-liver transplant complications. For both of these outcomes, follow-up time was defined as the time between the date of transplant and the date of death or last follow-up. Patients remaining alive at the last follow-up were censored at that time.

Statistical analysis

Demographics analysis: Categorical variables were compared by sex by the chi-square test. Continuous variables were compared between groups by the Wilcoxon rank-sum test given nonparametric distributions.

Survival analysis: For the outcome of post-liver transplant HCC recurrence, Cox proportional hazard regression models were used to associate sex with recurrence. Covariables with $P < 0.2$ were considered for inclusion in multivariable models. Backward elimination was used for final models, with covariables not reaching significance of $P < 0.05$ being sequentially eliminated. Two-sided P values <0.05 were considered statistically significant. Posttransplant patient mortality was estimated by sex and HCC status using Kaplan-Meier plots. Plots were compared using a log-rank test. For the secondary outcome of post-liver transplant survival, the same methodology was followed. However, patients who died within 30 days of their transplant were censored, as these deaths were unlikely to be the result of HCC recurrence. We completed competing risk analysis to ensure no significant differences from Cox-regression analysis. These analyses are included in supplemental tables and figures (Table S1 and Figure S1 http://links.lww.com/TP/C70).

Hypothesized Interactions: To better understand what factors may be driving any sex-based difference in the primary outcome, HCC recurrence, there was an *a priori* plan to test for a number of interactions: type of LRT, AFP, donor sex, body mass index (BMI), age, and a cirrhosis etiology of nonalcoholic steatohepatitis (NASH).

Software and database: All analyses were performed using Stata 15.0 statistical software (College Station, TX). This study was approved by the institutional review board at the University of California, San Francisco. The interpretation and reporting of these data are

the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the U.S. Government.

Results

Demographics and clinical characteristics by sex—There were 12,711 patients who underwent liver transplant for HCC: 2,909 (23%) were women and 9,802 (73%) were men. Baseline characteristics are shown in Table 1. Compared to men, women were older at time of liver transplant (62 v. 61 years, p= 0.004), were more likely to have NASH (22 v. 13%, p<0.001), and were more likely to be Hispanic (19 v. 15%, p<0.001). Women and men had similar laboratory MELDNa score at listing and MELDNa score at liver transplant. Overall, women as compared to men received liver allografts with a higher DRI (DRI 1.55 v. 1.46, p<0.001).

There were significant differences between women and men with respect to HCC tumor biology and treatments (Table 2). Women, as compared to men, had significantly higher AFP at listing (10.0 v. 8.0 ng/mL, p<0.001) and at the time of transplant (8.0 v. 7.0 ng/mL, p<0.001). Women had a smaller diameter of the lesion (2.3 v. 2.5 cm, p<0.001) and women had smaller total tumor size (3.2 v. 3.8 cm, p<0.001). Women had less microvascular invasion (12% v. 14%, p<0.001) and had less moderately or poorly differentiated tumors (51 v. 57%, p<0.001). Women were less likely than men to receive transarterial chemoembolization (TACE) than men (22 v. 26%, p<0.001), and women were less likely to receive combination therapy (30 v. 35%, p<0.001). There were otherwise no differences by sex in the proportion of patients who received radiofrequency ablation (RFA) or thermal ablation.

Predictors of HCC Recurrence After Liver Transplantation: We next evaluated the impact of sex on HCC recurrence after liver transplantation. In total, there were 640 (5%) HCC recurrences at a median of 1.1 (0.70 – 2.0) years. Significantly fewer women had a recurrence of their HCC as compared to men (4.0 v. 5.4%, p=0.002). Women and men had similar times to HCC recurrence (1.1 v. 1.1 years, p=0.79).

In unadjusted analyses the following were significantly associated with HCC recurrence post-liver transplant: female sex (HR 0.74, 95CI 0.60 – 0.91); diagnosis of NASH as compared to alcohol (HR 0.58, 95CI 0.39 – 0.85); AFP at liver transplant (HR 1.02 per 10 ng/mL, 95CI 1.01 – 1.03); total tumor diameter (HR 1.11 per 1 cm, 95CI 1.09 – 1.13); moderately and poorly differentiated tumors as compared to no viable tumor (*moderately differentiated:* HR 3.00, 95CI 2.16 – 4.16; *poorly differentiated:* HR 9.33, 95CI 6.52 – 13.34); microvascular and macrovascular invasion as compared to no invasion (*microvascular:* HR 3.49, 95CI 2.86 – 4.25; *macrovascular:* HR 5.91, 95CI 4.12 – 8.46) (Table 3). After adjusting for the etiology of cirrhosis, AFP at liver transplant, total tumor diameter, tumor pathology, and degree of vascular invasion, female sex was associated with a 25% lower risk of HCC recurrence after liver transplant (adjusted HR 0.75, 95CI 0.57 – 0.99) (Figure 1).

Interactions of Sex and Clinical Factors: We next tested a number of interactions to inform the mechanism that may be driving this sex-based difference in HCC recurrence.

We found no significant interactions between sex and the following variables in the final adjusted model: age at liver transplant (adjusted HR 1.01, 95CI 0.97 – 1.06); treatment with locoregional therapy (adjusted HR 0.74, 95CI 0.10 – 5.70); AFP at liver transplant (adjusted HR 0.99, 95CI 0.96 – 1.02); BMI (adjusted HR 0.98, 95 CI 0.93 – 1.03); diagnosis of NASH (adjusted HR 0.89, 95CI 0.32 – 2.50) (Table 4). To pay particular attention to the impact of donor sex, we created a categorical variable with the following categories: Female Recipient/Female Donor (1 469 [12%]); Female Recipient/Male Donor (1 441 [11%]); Male Recipient/Female Donor (3 590 [28%]); Male Recipient/Male Donor (6 211 [49%]). Regardless of donor sex, we found that female recipients had a significantly lower proportion of HCC recurrence: Female Recipient/Female Donor (59 [4.0%]); Female Recipient/Male Donor (56 [3.9%]); Male Recipient/Female Donor (192 [5.4%]); Male Recipient/Male Donor (333 [5.4%]), p=0.03. We found no significant interactions between recipient sex and donor sex in the final adjusted model (adjusted HR 1.12, 95CI 0.65 – 1.93) (Table 4).

Predictors of Post-Liver Transplant Mortality: Between 30 days post-liver transplant and 5 years post-liver transplant, there were 1,632 (13%) deaths. There were 329 (11%) deaths among women and 1,309 (13%) deaths among men (p=0.005). In unadjusted analyses the following factors were significantly associated with post-liver transplant mortality at 5 years: female sex (HR 0.84, 95CI 0.75 – 0.95); age at liver transplant (HR 1.02 per year, 95CI 1.01 – 1.02); presence of ascites at transplant (HR 1.30, 95CI 1.15 – 1.46); presence of hepatic encephalopathy at transplant (HR 1.33, 95CI 1.11 – 1.60); presence of diabetes mellitus (HR 1.12, 95CI 1.01 – 1.24); MELDNa at time of liver transplant (HR 1.02 per point, 95CI 1.00 – 1.03); donor risk index (HR 1.25 per 1 point, 95CI (1.11 – 1.41)); AFP at liver transplant (HR 1.02 per 10 ng/mL, 95CI 1.01 – 1.03); total tumor size (HR 1.07 per 1 cm, 95CI 1.05 – 1.09); degree of tumor differentiation (as compared to no viable tumor, *moderately differentiated* [HR 1.79, 95CI 1.49 – 2.14]; *poorly differentiated* [HR 3.74, 95CI 3.00 – 4.67]); degree of vascular invasion (as compared to no invasion, *microvascular invasion* [HR 2.11, 95CI 1.83 – 2.43]; *macrovascular invasion* [HR 2.90, 95CI 2.16 – 3.91]) (Table 5). After adjusting for recipient and donor characteristics, female sex was associated with a 17% lower risk of post-liver transplant mortality between 30 days and 5 years (HR 0.83, 95CI 0.71 – 0.98) (Figure 2).

Discussion

While multiple studies have demonstrated sex-based differences in rates of HCC, these studies have been limited to the pre-liver transplant setting—no study has investigated the impact of sex on HCC recurrence after liver transplant. Using US national registry data, we observed that female sex is associated with a 25% lower risk of HCC recurrence, even after adjusting for recipient tumor characteristics and donor characteristics. Finally, we highlight that among patients undergoing liver transplant for HCC, we found that female sex was associated with a 17% lower risk of mortality between 30 days and 5 years post-liver transplant.

We next investigated a number of possible interactions to inform the mechanism by which sex impacts tumor biology and HCC recurrence. It has become clear that hormonal

pathways drive oncogenesis among patients with end-stage liver disease—androgen and the androgen receptor are involved in the initiation of carcinogen-related HCC and estrogen and the estrogen receptor repress HCC growth.[13–17] That being said, we observed no significant interactions between sex and other correlates of hormonal phenotypes or other factors associated with the development of HCC, including BMI, age, and diagnosis of NASH. Additionally, the impact of sex on the risk of post-liver transplant HCC recurrence was independent of explant pathology, pre-liver transplant locoregional therapy, AFP dynamics, and donor characteristics—an important finding, given that previous studies have highlighted that female sex is associated with "high risk" explant pathology.[18] These results confirm that there are likely multiple, complex mechanisms by which sex impacts HCC[19,20]—collectively, our results highlight the need for more granular studies to measure differences in the physiologic (e.g., hormonal) or demographic (e.g., behavioral) factors that may be driving this sex-based difference in recurrence and are not currently captured in the UNOS/OPTN database.

We acknowledge the following limitations to this study. The accuracy of this study is subject to appropriate reporting in the UNOS registry. We address this in two ways: 1. A previous study has established the accuracy and reliability of the UNOS/OPTN database to study post-liver transplant HCC recurrence[21]; 2. By including an analysis of post-liver transplant mortality and cross-referencing with the Social Security Administration, as performed in this study, we are likely to improve the ascertainment of HCC recurrence.[22] These limitations notwithstanding, there should be no differences in reporting by patient sex. Therefore any underreporting or missing data should be at random and consequently have little impact on the results described. Additionally, the cause of death was not reliably available, and thus it is possible that our findings regarding post-liver transplant survival may be partly a reflection of the higher age-adjusted mortality rate seen in men, and not directly related to HCC recurrence. Finally, this study represents a large cohort with the statistical power to make clinically insignificant differences statistically significant. That being said, we argue that the effect size seen here is clinically meaningful and demonstrates that the inclusion of sex may serve to improve the accuracy of our most used HCC recurrence models.

Despite these limitations, this is an early study highlighting the impact of sex on HCC recurrence. Our data demonstrate that female sex is independently associated with lower post-liver transplant HCC recurrence—our data justify future efforts to investigate the sex-based drivers of post-liver transplant HCC recurrence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CI	confidence interval
DRI	donor risk index
HCC	hepatocellular carcinoma
HCV	hepatitis C
HR	hazard ratio
IQR	interquartile range
MELD	Model for End-Stage Liver Disease
MELDNa	Model for End-Stage Liver Disease including serum sodium
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
UNOS/OPTN	United Network for Organ Sharing/Organ Procurement and Transplantation Network
US	United States

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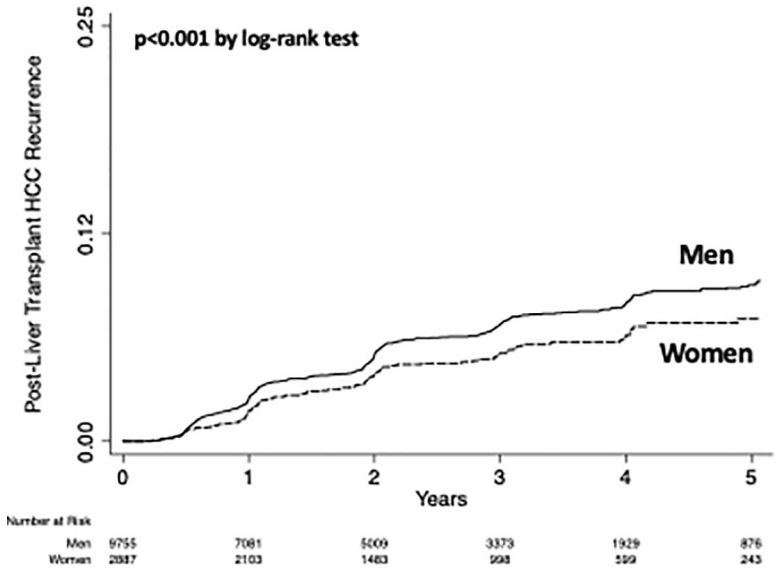

Figure 1.
Kaplan Meier Plot for HCC Recurrence by Sex.

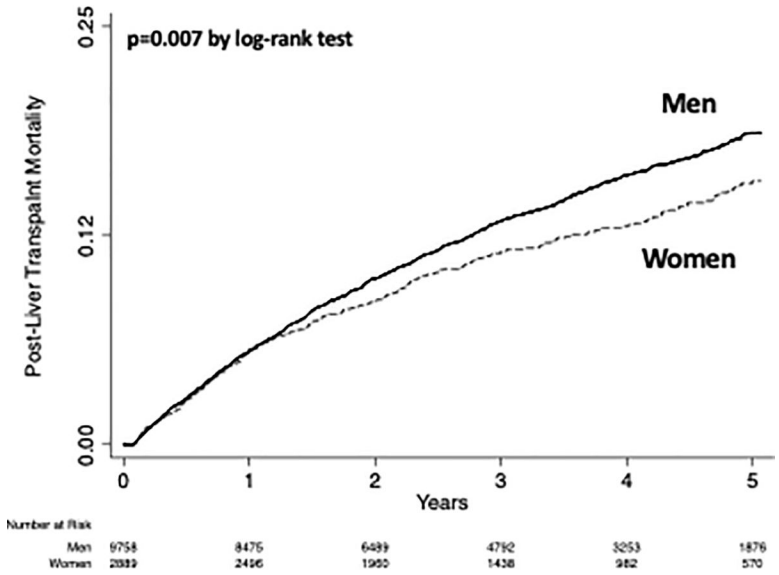

Figure 2.
Kaplan Meier Plot for Post-Liver Transpalnt 5-Year Mortality by Sex.

Table 1.

Characteristics of liver transplant recipients with HCC as an indication by sex.

	Female (n=2 909)	Male (n=9 802)	P
Days on waitlist, m(IQR)	215 (85 – 378)	209 (80 – 369)	<0.001
Age at LT, m(IQR)	62 (57 – 66)	61 (57 – 65)	<0.001
Listing diagnosis, no. (%)			
Alcohol	146 (5)	1 187 (12)	
HCV	1 497 (52)	5 699 (58)	
NAFLD/NASH	628 (22)	1 259 (13)	<0.001
Autoimmune[a]	216(7)	129 (1)	
Other	422 (15)	1 528(16)	
Race, no. (%)			
White	1 776 (61)	6 707 (68)	
African American	343 (12)	924 (9)	
Hispanic	556 (19)	1 430 (15)	<0.001
Asian	187 (6)	619 (6)	
Other	47 (2)	122 (1)	
BMI Category			
≤ 18.5	32 (1)	38 (0)	
18.6 – 24.9	734 (25)	2 074 (21)	
25.0 – 29.9	941 (32)	3 878 (40)	<0.001
30.0 – 34.9	1 048 (36)	3 515 (36)	
35.0 – 39.9	121(4)	242 (2)	
≥ 40	33 (1)	55 (1)	
Ascites at Txp, no. (%)	499 (17)	1 810(18)	0.11
Diabetes, no. (%)	958 (33)	3 287 (34)	0.55
Hepatic encephalopathy at Txp, no. (%)	184 (6)	589 (6)	0.53
MELDNa at listing, m(IQR)	12 (8 – 17)	12(9 – 17)	0.80
MELDNa at delisting, m(IQR)	14 (9 – 22)	13 (9 – 21)	0.14
Donor Risk Index, m(IQR)	1.54 (1.24 – 1.87)	1.46 (1.20 – 1.76)	<0.001

Hepatitis C (HCV); Non-Alcoholic Steatohepatitis (NASH); Model for End-Stage Liver; Body Mass Index (BMI); Transplant (Txp); dDisease including Sodium (MELDNa); median (m); interquartile range (IQR)

[a]Autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis

Table 2.

Tumor and treatment characteristics by sex

	Female (n=2 909)	Male (n=9 802)	P
AFP at Listing in ng/mL, m(IQR)	215 (85 – 378)	209 (80 – 369)	<0.001
AFP at Transplant in ng/mL, m(IQR)	62 (57 – 66)	61 (57 – 65)	<0.001
Largest Tumor Size in cm, m(IQR)	2.3 (1.5 – 3.4)	2.5 (1.6 – 3.5)	<0.001
Total Tumor Size in cm, m(IQR)	3.2 (2.0 – 5.0)	3.8 (2.4 – 5.8)	<0.001
Number of Viable Tumors, m(IQR)	1 (0 – 1)	1 (0 – 2)	<0.001
Largest Tumor + Number, m(IQR)	4.0 (3.0 – 5.3)	4.4 (3.3 – 5.8)	<0.001
Tumor Differentiation, no. (%)			
Complete Necrosis	489 (26)	1 407 (21)	
Well	452 (24)	1 520 (22)	<0.001
Moderate	863 (45)	3 343 (49)	
Poor	117(6)	541 (8)	
Retreat Score, no. (%)			
0	334 (11)	1 036 (11)	
1	877 (30)	2 743 (28)	
2	516 (18)	1 907 (19)	0.003
3	795 (27)	2 592 (26)	
4	225 (8)	844 (9)	
≥ 5	162 (6)	690 (7)	
Vascular Invasion			
None	1 671 (87)	5 704 (84)	
Microvascular	222 (12)	963 (14)	<0.001
Macrovascular	26 (1)	144 (2)	
Any TACE, no. (%)	543 (22)	2 214 (26)	<0.001
Any RFA, no. (%)	48 (2)	164 (2)	0.97
Any Thermal, no. (%)	116 (5)	472 (6)	0.07
Combination Therapy, no. (%)			
0	1 756 (70)	5 563 (66)	
1	682 (27)	2 612 (31)	<0.001
2	64 (3)	64 (3)	
3	0 (0)	18 (0)	

Transarterial chemoembolization (TACE); Radiofrequency ablation (RFA)

Table 3.

Cox Regression Analysis for Post-Liver Transplant HCC Recurrence

	Univariable			Multivariable		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Female Sex	0.74	0.60 – 0.91	0.003	0.75	0.57 – 0.99	0.03
Age per Year	1.00	0.98 – 1.01	0.39			
Etiology						
Alcohol	-	-	-	-	-	-
HCV	1.19	0.90 – 1.56	0.22	1.04	0.73 – 1.47	0.82
NASH	0.58	0.39 – 0.85	0.005	0.60	0.37 – 0.98	0.04
Autoimmune[a]	0.62	0.32 – 1.21	0.16	0.42	0.13 – 1.37	0.15
Other	1.19	0.87 – 1.63	0.28	1.10	0.74 0 1.64	0.63
Non-Hispanic White	0.98	0.83 – 1.16	0.84			
BMI Categories						
≤ 18.5	1.49	0.61 – 3.61	0.38			
18.6 – 24.9	1.07	0.87 – 1.31	0.52			
25.0 – 29.9	-	-	-			
30.0 – 34.9	0.99	0.83 – 1.19	0.92			
35.0 – 39.9	1.11	0.69 – 1.80	0.66			
≥ 40	0.76	0.24 – 2.36	0.63			
Ascites	0.95	0.77 – 1.1l	0.59			
HE	1.00	0.72 – 1.39	1.00			
Diabetes	0.97	0.82 – 1.15	0.71			
MELDNa at Liver Transplant per 1 point	0.99	0.99 – 1.01	0.26			
Donor Risk Index per 1 point	1.10	0.91 – 1.34	0.33			
AFP at Liver Transplant per 10 ng/mL	1.02	1.01 – 1.03	<0.001	1.05	1.04 – 1.06	<0.001
Total Tumor Size per 1 cm	1.11	1.09 – 1.13	<0.001	1.10	1.08 – 1.12	<0.001
Differentiation						
None	-	-	-	-	-	-
Well	1.16	0.77 – 1.75	0.47	1.02	0.66 – 1.57	0.93
Moderate	3.00	2.16 – 4.16	<0.001	2.02	1.42 – 2.88	<0.001
Poor	9.33	6.52 – 13.34	<0.001	5.38	3.62 – 8.00	<0.001
Invasion						
None	-	-	-	-	-	-
Microvascular	3.49	2.86 – 4.25	<0.001	2.30	1.07 – 2.88	<0.001
Macrovascular	5.91	4.12 – 8.46	<0.001	3.01	2.01 – 4.50	<0.001

Body Mass Index (BMI); Hepatitis C (HCV); Hepatic Encephalopathy (HE); Non-Alcoholic Steatohepatitis (NASH); Model for End-Stage Liver Disease including Sodium (MELDNa); median (m); interquartile range (IQR)

[a]Autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis

Table 4.

Interaction Between Variables of Interest and Recipeint in Sex

Adjusted Model[a]			
	aHR	**95% CI**	**p-value**
Female Sex and Age	1.01	0.97 – 1.06	0.21
Female Sex and Treatment with Locoregional Therapy	0.74	0.10 – 5.70	0.40
Female Sex and AFP at Transplant	0.99	0.96 – 1.02	0.48
Female Sex and BMI at Transplant	0.98	0.93 – 1.03	0.41
Female Sex and a Diagnosis of NASH	0.89	0.32 – 2.50	0.77
Female Sex and Donor Sex	1.12	0.65 – 1.93	0.68

Body Mass Index (BMI); Hepatitis C (HCV); Hepatic Encephalopathy (HE); Non-Alcoholic Steatohepatitis (NASH); Model for End-Stage Liver Disease including Sodium (MELDNa); median (m); interquartile range (IQR)

[a]Adjusted for tumor differentiation, presence of vascular invasion, AFP at transplant, total tumor size, diagnosis and female sex

Table 5.

Cox Regression Analysis for Post-Liver Transplant 30 Day to 5 Year Mortality

	Univariable			Multivariable		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Female Sex	0.84	0.75 – 0.95	0.006	0.83	0.71 – 0.98	0.03
Age per Year	1.02	1.01 – 1.02	<0.001	1.02	1.01 – 1.03	0.002
Etiology						
Alcohol	-	-	-			
HCV	1.11	0.93 – 1.31	0.24			
NASH	0.95	0.77 – 1.17	0.62			
Autoimmune[a]	0.82	0.57 – 1.18	0.28			
Other	0.91	0.74 – 1.11	0.34			
Non-Hispanic White	1.09	0.98 – 1.21	0.12			
BMI Categories						
≤ 18.5	0.92	0.46 – 1.84	0.81			
18.6 – 24.9	1.13	0.99 – 1.28	0.07			
25.0 – 29.9	-	-	-			
30.0 – 34.9	0.94	0.84 – 1.05	0.28			
35.0 – 39.9	1.10	0.82 – 1.48	0.53			
≥ 40	1.36	0.80 – 2.32	0.25			
Ascites	1.30	1.15 – 1.46	<0.001			
HE	1.33	1.11 – 1.60	0.002			
Diabetes	1.12	1.01 – 1.24	0.03			
MELDNa at Liver Transplant per 1 point	1.02	1.01 – 1.02	<0.001	1.01	1.00 – 1.02	0.03
Donor Risk Index per 1 point	1.25	1.11 – 1.41	<0.001	1.34	1.15 – 1.56	<0.001
AFP at Liver Transplant per 10 ng/mL	1.02	1.01 – 1.03	<0.001	1.03	1.02 – 1.04	<0.001
Total Tumor Size per 1 cm	1.07	1.05 – 1.09	<0.001	1.05	1.03 – 1.07	<0.001
Differentiation						
None	-	-	-	-	-	-
Well	1.22	0.99 – 1.52	0.07	1.25	0.99 – 1.57	0.06
Moderate	1.79	1.49 – 2.14	<0.001	1.55	1.27 – 1.91	<0.001
Poor	3.74	3.00 – 4.67	<0.001	3.10	2.41 – 3.99	<0.001
Invasion						
None	-	-	-	-	-	-
Microvascular	2.11	1.83 – 2.43	<0.001	1.50	1.27 – 1.78	<0.001
Macrovascular	2.90	2.16 – 3.91	<0.001	1.95	1.40 −2.70	<0.001

Body Mass Index (BMI); Hepatitis C (HCV); Hepatic Encephalopathy (HE); Non-Alcoholic Steatohepatitis (NASH); Model for End-Stage Liver Disease including Sodium (MELDNa); median (m); interquartile range (IQR)

[a]Autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis