

Sex disparities in liver transplantation for hepatocellular carcinoma: long-term outcomes and recurrence predictors

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Background: With a 2- to 3-fold higher incidence in men, hepatocellular carcinoma (HCC) is the leading indication for liver transplantation (LT). Despite this sex disparity in HCC incidence, the influence of recipient sex on long-term LT outcomes, including HCC recurrence, is not well established. This study investigates the impact of recipient sex on the long-term outcomes following LT for HCC.

Methods: All consecutive patients undergoing LT for HCC between 2005 and 2018 were retrospectively analyzed. Data regarding patient demographics, tumor characteristics, and post-transplant outcomes were collected, and recipients were stratified by sex. Kaplan-Meier analysis was used to assess overall and recurrence-free survival (RFS). Multivariable Cox regression models were then used to determine independent predictors of HCC recurrence within each sex group.

Results: Of the 384 adult recipients (mean age was 58.7±8.4 years and mean follow-up of 86.5±51.5 months), 17.2% of patients were female. The main etiology of cirrhosis in the female and male groups was alcohol-related (19.7%, 36.5%), HCV (40.9%, 24.5%) and metabolic dysfunction-associated steatohepatitis (MASH) (10.6%, 12.3%). The Model for End-Stage Liver Disease (MELD) and Child-Pugh scores were similar in both groups. 87.9% and 76.4% of the patients were within the Milan criteria and 95.5% and 91.5% of the patients had an alpha-fetoprotein (AFP) score ≤2 at the time of LT, respectively. The 1-, 3-, 5-, 10- and 15-year survival rates were similar in the male and female groups (91.5%, 81.5%, 72.4%, 57.7% and 44.9% vs. 89.4%, 80.1%, 72.0%, 50.0% and 29.6%, P=0.43). Microvascular invasion was seen in 30.3% and 36.3% of the patients, respectively, P=0.36). Recurrence rates were comparable in female and male groups (19.7% vs. 20.1%, respectively, P=0.94). The 10-year RFS rate was 50.6% in the female group and 54.9% in the male group (P=0.61).

Conclusions: Recipient sex does not impact long-term survival or HCC recurrence after LT. However, sex-specific predictors of HCC recurrence were identified: AFP score >2 and prior hepatectomy in females, and these plus diabetes mellitus and older age in males. Furthermore, female recipients presented with a significantly lower incidence of alcohol-associated cirrhosis as the underlying cause of HCC.

Keywords: Sex; disparity; hepatocellular carcinoma (HCC); recurrence; liver transplantation (LT)

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Introduction

Hepatocellular carcinoma (HCC) is a major global health concern, ranking as the third leading cause of cancer-related death and the sixth most diagnosed cancer (1). Despite advances in the prevention and screening of HCC, mortality and incidence rates of HCC are still two to three times higher in men than in women in different regions of the world (2,3). Disparity of sex in HCC incidence, morbidity and survival is not yet understood, but has been linked to the effects of hormonal, genetic, anatomical and environmental factors on the pre-transplant setting (4).

Highlight box

Key findings

- While recipient sex did not affect post-liver transplantation (post-LT) outcomes for hepatocellular carcinoma (HCC), including survival and recurrence, distinct predictors of recurrence were identified. In male recipients, older age and pre-transplant diabetes mellitus type 2 were predictive factors, whereas prior hepatectomy and alpha-fetoprotein (AFP) >2 were independent predictive factors in both male and female recipients.

What is known and what is new?

- HCC is the leading indication for LT, with a higher incidence and more aggressive behaviour observed in males. Post-LT HCC recurrence rates range from 8–20%. However, the influence of sex on post-transplant long-term outcomes remained poorly understood.
- Despite pre-transplant sex disparities in incidence, etiology and tumor biology of HCC, recipient sex does not impact the outcomes of LT for HCC in survival and recurrence rates.

What is the implication, and what should change now?

- This study highlights the importance of personalized risk assessment in the management of HCC patients undergoing LT. The identification of distinct predictors of HCC recurrence in male and female recipients underscores the importance of considering sex as a crucial biological variable in risk stratification. This highlights the need to move away from a “one-size-fits-all” approach and towards individualized risk assessment strategies that take into account sex-specific factors.
- Post-transplant surveillance protocols for HCC recurrence may need to be tailored based on recipient sex. For example, female recipients with a history of prior hepatectomy or high AFP score at transplant may benefit from more intensive monitoring.

Liver transplantation (LT) is the ideal curative therapy for HCC (5). However, it is associated with disparities in access and survival between men and women (6). In the context of receiving an LT for HCC in the standard allocation system, men were 20% more likely to be transplanted than women at 1 year. This gender disparity is most pronounced at the 1- and 2-year intervals, whereas it is not statistically significant during the first three months and becomes non-significant by the 5-year interval (7-9).

Life expectancy after LT for HCC has been reported to be significantly reduced compared with the normal population; however, there is no difference in overall survival between men and women after LT (10,11). A recent study showed that there is a sex disparity in the recurrence of HCC in patients after curative hepatectomy, with males having a higher risk of HCC recurrence than females (12). Survival from HCC after resection was worse in women over 50 years of age, which has been linked to menopause and a decrease in the protective effect of oestrogen (13). Female liver transplant recipients have comparable, if not better, outcomes than males for various etiologies; however, because of their limited access to LT, female patients become progressively sicker while waiting and are at risk of being removed from the transplant list while their male counterparts undergo successful transplantation (14-16). Upon examination of the drop-out rates for waitlist, it was discovered that men waitlisted for HCC have a lower likelihood of being removed from the list compared to women at 1 and 2 years. These findings cannot be fully accounted for by the natural history of HCC in women (17). Women with HCC are more likely to receive improved follow-up care have lower recurrence after curative treatments and overall survive longer than men (18,19). Thus, it is plausible that factors beyond the biological characteristics of the tumor, such as equitable access to down-staging therapies, may also play a significant role (9).

Further research into sex-related differences in transplant patients is required to identify areas for improvement, with a view to optimizing the organ matching process and the peri- and post-operative care of these patients. Some studies have identified an interaction effect between sex and specific subgroups on LT, yet the impact of sex on HCC recurrence remains uncertain. The objective of this study

is to investigate the impact of recipient sex on long-term outcomes, including recurrence, by conducting a long-term follow-up of a large cohort of adult patients undergoing LT for HCC. We present this article in accordance with the STROBE reporting checklist (available at <https://tgh.amegroups.com/article/view/10.21037/tgh-25-4/rc>).

Methods

Study population

From a database of 1,869 patients who underwent LT between January 2005 and December 2018, a total of 384 consecutive patients with HCC were recruited for the study. This retrospective cohort study was conducted at the Hepato-Biliary Centre of Paul Brousse Hospital in France. Patients with multiple organ transplants (n=4) and re-transplants (n=20) were excluded from the study. The follow-up period extended until August 2024. The collection of data was carried out in accordance with the International Guideline for Ethical Review of Epidemiological Studies, and the principles of the Declaration of Helsinki and its subsequent amendments, with approval from the local committee of the hepatobiliary center at Paul Brousse Hospital. Individual consent for this analysis was waived due to the retrospective nature.

The data set included recipient demographics, such as age, sex, BMI, the etiology of underlying liver disease, biochemical parameters, and various variables at the time of LT. Additionally, the study incorporated calculated Model for End-Stage Liver Disease (MELD) scores, Child-Pugh scores, alpha-fetoprotein (AFP) scores, and AFP levels. Tumor characteristics at the time of HCC diagnosis, the time of transplant and at the final pathology of the explant [size, number of nodules, tumor differentiation and microvascular invasion (MVI)] were all considered.

Patient classification

Patients were divided into two groups according to the recipient's sex: female (n=66) and male (n=318) (Figure S1). The time points of HCC diagnosis, transplant procedure, and HCC recurrence were recorded. Following LT, data were gathered at predefined intervals: 1, 3, 5, 10, and 15 years post-transplant. Overall survival (OS) was measured from the date of transplantation to either death, the last follow-up visit, or the study's end date of 31 August 2024. Recurrence-free survival (RFS) was calculated from the

time of transplant to the occurrence of HCC recurrence or death; patients without recurrence were censored at the last confirmed date of being recurrence-free. Survival after HCC recurrence was assessed from the date of recurrence diagnosis to death, the most recent follow-up, or the conclusion of the study.

Statistical analysis

Categorical data were expressed as percentages and frequencies and compared by the chi-squared test. Continuous variables were expressed as the mean $\pm$ standard deviation (SD) and compared using the independent sample *t*-test. Finally, survival probabilities were assessed using Kaplan-Meier methods and compared by the log-rank test. Statistical significance was accepted with a P value ≤ 0.05 and 95% confidence interval (CI). A univariable Cox regression was applied to identify potential outcome predictors. Variables with a P value less than 0.10 in the univariable analysis were included in the multivariable Cox regression. The results of the multivariable analysis were expressed as hazard ratios (HRs) with 95% CI. All statistical analysis was performed using SPSS version 23 (SPSS, Inc., Chicago, IL, USA) and R software version 4.4.1.

HCC recurrence diagnosis

Recurrence of HCC was defined as the direct identification of metastatic lesions through imaging, with biopsy used to confirm the diagnosis when imaging results were unclear. Our center has previously established comprehensive follow-up protocols tailored to the individual risk of HCC recurrence. These protocols include regular AFP testing and imaging studies conducted during scheduled outpatient visits.

Results

Characteristics of the study population

A total of 384 patients with HCC who underwent transplantation between 2005 and 2018 were included in this analysis. Of these patients, 318 were male (82.8%) and 66 were female (17.2%). At the time of LT, the mean recipient's age in the female and male groups was comparable (58.4 $\pm$ 8.9 vs. 59.1 $\pm$ 7.8 years, respectively; P=0.45). Similarly, BMI at the time of LT was comparable among both groups (26.1 $\pm$ 6.0 vs. 27.1 $\pm$ 5.1 kg/m², respectively; P=0.32).

Regarding the etiology of HCC, the proportions of females and males with chronic hepatitis B cirrhosis (10.6% *vs.* 14.2%, respectively, $P=0.12$) and metabolic dysfunction-associated steatohepatitis (MASH) cirrhosis (10.6% *vs.* 12.3%, $P=0.52$) were found to be similar. However, females were found to have significantly higher hepatitis C cirrhosis (40.9% *vs.* 24.5%, $P=0.04$), while males were found to have significantly higher alcohol-associated cirrhosis (19.7% *vs.* 36.5%, $P=0.04$) (Table 1). The mean MELD score was comparable among both groups (15.3 ± 7.1 *vs.* 13.9 ± 7.3 , $P=0.74$). The majority of patients in both groups had a Child-Pugh score of B or C (43.9% and 37.9% *vs.* 42.1% and 32.1%, respectively; $P=0.36$) (Table 1).

Most of the patients among both groups had cadaveric LT (83.3% *vs.* 73.9%, $P=0.47$). Interestingly, the recipients among female group were transplanted with significantly older grafts (59.9 ± 22.0 *vs.* 53.5 ± 19.1 years, $P=0.02$) compared to male group and significantly more female grafts (54.5% *vs.* 39.6%, $P=0.03$) compared to male group (Table 1).

HCC diagnosis and waiting time

The initial diagnosis of HCC was made much earlier among female patients than male patients, with a significantly reduced waiting time between the initial HCC diagnosis and LT in the female group (18.6 ± 15.2 *vs.* 24.4 ± 22.1 months, $P=0.04$). However, the waiting time between listing and LT was similar in both groups (7.9 ± 7.8 *vs.* 7.5 ± 6.8 months, $P=0.35$) (Table 1). During the waiting period, the majority of recipients received pre-transplant therapy (downstaging/bridging) (73.7% of female recipients *vs.* 75.5% of male recipients, $P=0.43$) (Table 1).

HCC characteristics at transplant

The imaging at the time of LT revealed that the mean tumor size among the female group was significantly smaller than that observed in the male group (22.3 ± 11.8 *vs.* 26.1 ± 12.1 mm, $P=0.02$). The number of nodules was comparable among both groups ($P=0.30$), with most of the nodules detected in one lobe among the females group compared to the male group (80.3% *vs.* 68.9%, $P=0.12$). At the time of LT, a significantly higher percentage of patients in the female group met the Milan criteria compared to the male group (87.9% *vs.* 76.4%, respectively; $P=0.04$), with a small number of patients with an AFP score >2 in both groups (3 patients, 4.5% *vs.* 27 patients, 8.5%; $P=0.38$) (Table 2).

Characteristics of the liver explant tumor

The pathological characteristics of the explanted liver confirmed that most of the tumors were within Milan criteria (63.1% of female recipients *vs.* 60.4% of male recipients, $P=0.67$). However, further analysis revealed that tumor differentiation ($P=0.06$) and MVI ($P=0.36$) were not able to differentiate between the two groups (Table 2).

Post-transplant outcomes

Male recipients had a significantly longer mean follow-up period than female recipients (93.5 ± 53.9 *vs.* 79.6 ± 48.9 months, respectively; $P=0.05$). No significant differences were observed between groups in baseline post-transplant immunosuppression regimens (Table 3).

Similarly, there were no significant differences between male and female recipients in length of intensive care unit (ICU) stay ($P=0.65$), overall mortality rates ($P=0.41$), or causes of mortality ($P=0.52$) (Table 3).

Kaplan-Meier analysis revealed no significant difference in either OS or RFS between female and male recipients following LT. OS rates at 1-, 3-, 5-, 10- and 15-year were 91.5%, 81.5%, 72.4%, 57.7%, and 44.9% for females and 89.4%, 80.1%, 72.0%, 50.0%, and 29.6% for males (log-rank $P=0.43$) (Figure 1A). RFS rates at the same time points were 83.3%, 77.1%, 70.6%, 50.6%, and 30.0% for females and 88.0%, 77.4%, 70.6%, 54.9%, and 41.4% for males (log-rank $P=0.61$) (Figure 1B).

HCC recurrence and outcomes

The incidence of HCC recurrence was comparable between female and male recipients (19.7% and 20.1%, respectively; $P=0.94$). Extrahepatic sites were the most common location of recurrence in both groups, with no statistically significant difference in the distribution of recurrence sites (extrahepatic: 53.8% *vs.* 60.9%; combined intra- and extrahepatic: 30.8% *vs.* 21.9%; intrahepatic: 15.4% *vs.* 17.2%; $P=0.92$) (Table 4). Serum AFP levels at the time of recurrence diagnosis were also similar between female and male recipients ($1,237.5 \pm 3,663.4$ *vs.* $444.3 \pm 1,756.6$ ng/mL; $P=0.54$). Chemotherapy was the predominant treatment strategy for HCC recurrence in both female (84.6%) and male (89.1%) recipients (Table 4).

While long-term follow-up showed similar cumulative HCC recurrence rates between female and male recipients at 1, 3, 5, and 10 years (9.5%, 14.6%, 20.1%, and 22.6%

Table 1 Baseline characteristics according to recipient sex

Variables	Female (N=66)	Male (N=318)	P value
Recipient characteristics at transplant			
Age (years)	58.4±8.9	59.1±7.8	0.45
BMI (kg/m ²)	26.1±6.0	27.1±5.1	0.32
History of DM2	23 (34.8)	126 (39.6)	0.47
Underlying liver disease etiology			<0.01
Alcohol associated cirrhosis	13 (19.7)	116 (36.5)	0.04
HCV cirrhosis	27 (40.9)	78 (24.5)	0.04
HBV cirrhosis	7 (10.6)	45 (14.2)	0.12
MASH cirrhosis	7 (10.6)	39 (12.3)	0.52
Non cirrhotic HCC	3 (4.5)	2 (0.6)	0.43
Others	9 (13.6)	38 (11.9)	0.15
MELD score	15.3±7.1	13.9±7.3	0.74
Child-Pugh score	12 (18.2)	82 (25.8)	0.36
A	29 (43.9)	134 (42.1)	
B	25 (37.9)	102 (32.1)	
C			
eGFR at transplant (mL/min/1.73 m ²)	122.9±31.9	122.9±24.7	0.98
Waiting time between HCC diagnosis and LT (months)	18.6±15.2	24.4±22.1	0.04
Waiting time between listing and LT (months)	7.9±7.8	7.5±6.8	0.35
Type of transplant			0.47
Cadaveric	55 (83.3)	235 (73.9)	
Domino	6 (9.1)	56 (17.6)	
Living	3 (4.5)	20 (6.3)	
Maastricht3	1 (1.5)	3 (0.9)	
Split	1 (1.5)	4 (1.3)	
Pre-transplant therapy for HCC			0.43
No therapy	18 (27.3)	78 (24.5)	
Loco-regional ablation	9 (13.6)	24 (7.5)	
Resection alone	2 (3)	23 (7.2)	
TACE alone	23 (34.8)	117 (36.8)	
TACE + loco-regional ablation	10 (15.2)	45 (14.2)	
TACE+ resection	4 (6.1)	31 (9.7)	
Donor characteristics at transplant			
Age (years)	59.9±22.0	53.5±19.1	0.02
Sex (female)	36 (54.5)	126 (39.6)	0.03
BMI (kg/m ²)	25.4±5.2	25.6±5.0	0.89

Data are presented as number of cases (percentage) or mean ± SD. AFP, alpha-fetoprotein; BMI, body mass index; DM2, diabetes mellitus type 2; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; MASH, metabolic dysfunction-associated steatohepatitis; MELD, Model for End-Stage Liver Disease; SD, standard deviation; TACE, trans-arterial chemoembolization.

Table 2 Tumor characteristics at transplant and pathological features of explant

Variables	Female (N=66)	Male (N=318)	P value
Tumor characteristics at transplant			
Maximum size (mm)	22.3±11.8	26.1±12.1	0.02
Number of nodules			
1	34 (51.6)	120 (37.7)	0.30
2–3	28 (42.3)	179 (56.3)	
>3	4 (6.1)	19 (6.0)	
Site			
Uni-lobar	53 (80.3)	219 (68.9)	0.12
Bi-lobar	9 (13.6)	81 (25.5)	
Un detectable	4 (6.1)	18 (5.7)	
Serum AFP (ng/mL)	46.6±146.2	95.6±339.5	0.17
Within Milan criteria	58 (87.9)	243 (76.4)	0.04
AFP score			0.38
≤2	63 (95.5)	291 (91.5)	
>2	3 (4.5)	27 (8.5)	
Pathological features of the explant			
Maximum size (mm)	24.5±13.3	26.2±12.5	0.34
Number of nodules			
1	22 (33.3)	102 (32.1)	0.99
2–3	25 (37.9)	118 (37.1)	
>3	18 (27.3)	90 (28.3)	
Un-detectable	1 (1.5)	8 (2.5)	
Site			0.57
Uni-lobar	38 (57.6)	179 (56.3)	
Bi-lobar	27 (40.9)	131 (42.2)	
Un-detectable	1 (1.5)	8 (2.5)	
Microvascular invasion	20 (30.3)	115 (36.3)	0.36
Differentiation			0.06
Well	30 (45.5)	170 (53.5)	
Necrotic	11 (16.7)	56 (17.6)	
Moderate	23 (34.8)	57 (17.9)	
Poor	1 (1.5)	18 (5.7)	
Absence of HCC	1 (1.5)	9 (2.8)	
Hepato-cholangiocarcinoma	0	8 (2.5)	
Within Milan criteria	41 (63.1)	183 (60.4)	0.67

Data are presented as number of cases (percentage) or mean ± standard deviation. AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma.

Table 3 Follow up and outcomes following LT for HCC

Variables	Female (N=66)	Male (N=318)	P value
Follow up (months)	79.6±48.9	93.5±53.9	0.05
ICU stay (days)	4.3±3.1	5.7±5.1	0.65
Immunosuppression at baseline			
Corticosteroids	66 (100.0)	302 (95.0)	0.06
MMF	61 (92.4)	296 (93.1)	0.85
Calcineurin inhibitors			0.86
Cyclosporine	9 (13.6)	46 (14.5)	
Tacrolimus	57 (86.4)	272 (85.5)	
Overall mortality	30 (45.5)	141 (44.3)	0.41
Cause of mortality			0.52
HCC recurrence	9 (13.6)	31 (9.7)	
Cardiovascular disease	0	11 (3.5)	
HCV recurrence	1 (1.5)	1 (0.3)	
Malignancy	1 (1.5)	11 (3.5)	
Natural death	3 (4.5)	3 (0.9)	
Septic shock	2 (3.0)	14 (4.4)	
Other causes	13 (19.7)	69 (21.7)	
Time to death (months) [†]	52.9±43.1	63.6±49.3	0.27

Data are presented as number of cases (percentage) or mean ± standard deviation. HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICU, intensive care unit; LT, liver transplantation; MMF, mycophenolate mofetil.

vs. 6.2%, 15.2%, 18.9%, and 22.5%, respectively; log-rank $P=0.91$) (*Figure 2*), there was no statistically significant difference in survival after HCC recurrence (log-rank $P=0.06$), despite a trend towards shorter median survival in females (3 *vs.* 3.7 years in males). Post-recurrence survival rates at 1, 3, 5, and 10 years were 84.6%, 46.2%, 15.4%, and 0% for females and 90.6%, 60.9%, 34.4%, and 15.0% for males (*Figure 3*).

Predictors of HCC recurrence

Potential predictors of HCC recurrence were initially assessed using univariable Cox regression, with variables demonstrating a P value of ≤ 0.01 carried forward to a multivariable Cox regression model. In female recipients, a high AFP score (>2) at the time of transplantation (HR =8.19; 95% CI, 7.20–11.35) and a history of prior hepatectomy (HR =6.51; 95% CI, 4.27–8.67) were identified as strong independent pre-transplant predictors of

HCC recurrence. In male recipients, the same factors (AFP score >2 : HR =1.43; 95% CI, 1.34–1.47; prior hepatectomy: HR =1.60; 95% CI, 1.52–1.92) were also independent predictors, along with diabetes mellitus (HR =1.41; 95% CI, 1.35–1.58) and age at transplantation (HR =1.01; 95% CI, 1.01–1.17) (*Table 5*).

Discussion

This retrospective study of 384 adult patients who underwent LT for HCC and were followed for up to 15 years, we investigated the impact of recipient sex on long-term outcomes. Despite differences in underlying liver disease etiology and tumor presentation at transplant, our findings demonstrated comparable OS at 10 years (50.0% for females *vs.* 57.7% for males) and RFS at 10 years (50.6% for females *vs.* 54.9% for males). While recurrence rates were also similar (19.7% in females *vs.* 20.1% in males), distinct pre-transplant predictors of HCC recurrence

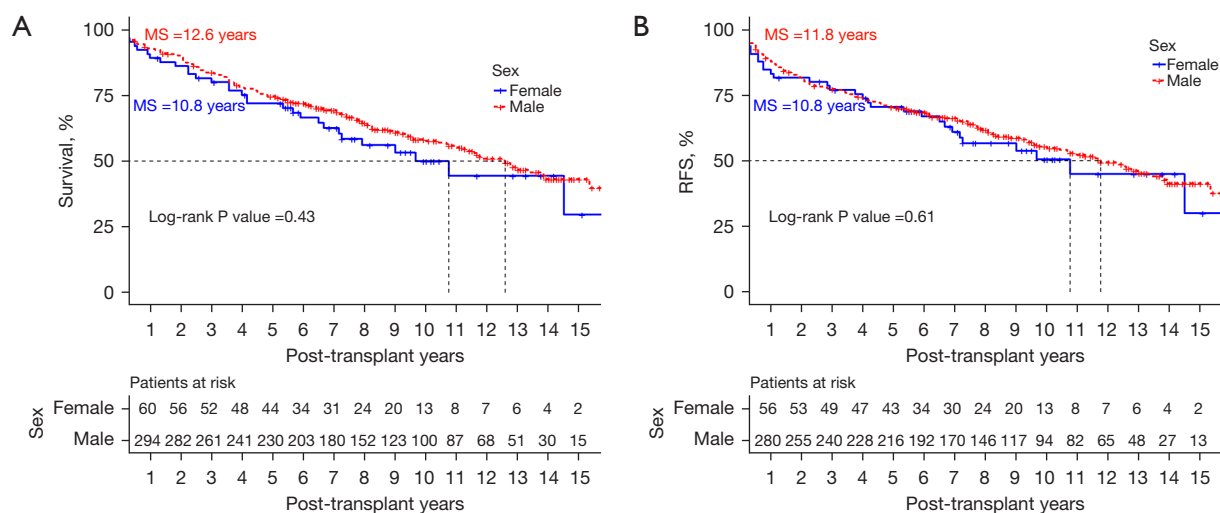


Figure 1 Kaplan-Meier overall survival and RFS curves after liver transplantation for HCC according to recipient sex. (A) Overall survival after liver transplantation for HCC. The 1-, 3-, 5-, 10 and 15-years overall survivals after LT were comparable between female and male groups (91.5%, 81.5%, 72.4%, 57.7% and 44.9% *vs.* 89.4%, 80.1%, 72.0%, 50.0% and 29.6% respectively, log-rank $P=0.43$). Median survival was respectively 10.8 years and 12.6 years, respectively. (B) RFS after liver transplantation for HCC. The 1-, 3-, 5-, 10-, 15-year RFS were 83.3%, 77.1%, 70.6%, 50.6% and 30.0% for females and 88.0%, 77.4%, 70.6%, 54.9% and 41.4% for males (log-rank $P=0.61$). Median RFS was respectively 10.8 and 11.8 years, respectively. HCC, hepatocellular carcinoma; LT, liver transplantation; MS, median survival in years; RFS, recurrence-free survival.

Table 4 Post-transplant HCC recurrence

Variables	Female (N=66)	Male (N=318)	P value
HCC recurrence	13 (19.7)	64 (20.1)	0.94
Time to recurrence (months)	26.4±25.1	30.1±29.9	0.74
Site of HCC recurrence			0.92
Intrahepatic	2/13 (15.4)	11/64 (17.2)	
Intra and extra hepatic	4/13 (30.8)	14/64 (21.9)	
Extrahepatic	7/13 (53.8)	39/64 (60.9)	
AFP level at diagnosis of HCC recurrence (ng/mL)	1,237.5±3,663.4	444.3±1,756.6	0.54
Therapies for HCC recurrence			0.38
Chemotherapy	11/13 (84.6)	57/64 (89.1)	
Palliative therapy	2/13 (15.4)	0	
Radiotherapy	0	2/64 (3.0)	
Re-transplantation	0	1/64 (1.6)	
Resection	0	3/64 (4.7)	
Resection and radiotherapy	0	1/64 (1.6)	
Post HCC recurrence survival (months)	38.1±24.3	50.5±38.6	0.25

Data are presented as number of cases (percentage) or mean ± standard deviation. AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma.

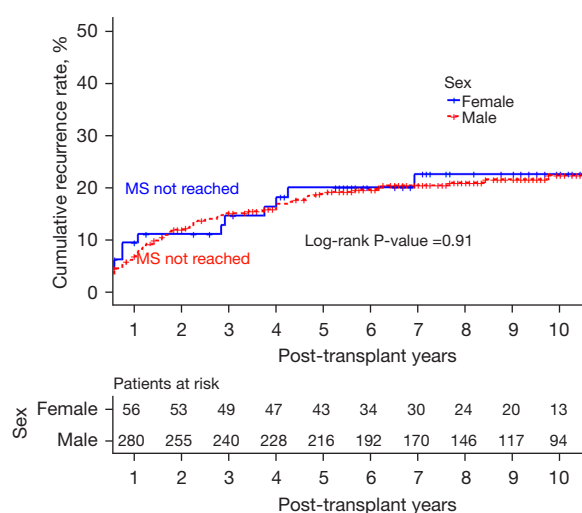


Figure 2 Cumulative HCC recurrence rate according to recipient sex. The 1-, 3-, 5-, and 10-year cumulative HCC recurrence rates were comparable between the female and male groups (9.5%, 14.6%, 20.1%, and 22.6% *vs.* 6.2%, 15.2%, 18.9%, and 22.5%, respectively, log-rank $P=0.91$). HCC, hepatocellular carcinoma; MS, median survival in years.

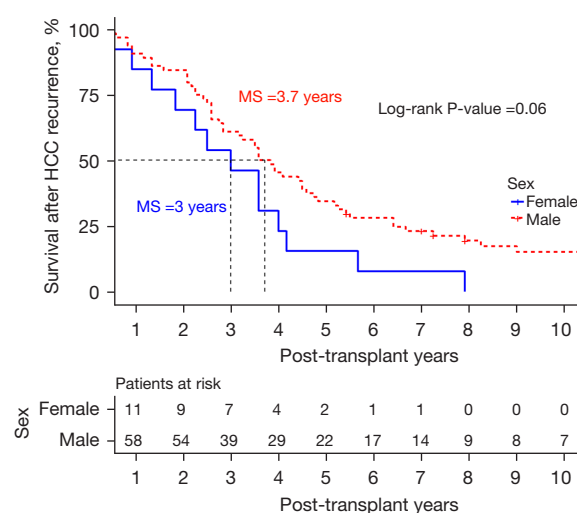


Figure 3 Kaplan-Meier curve on patient survival after HCC recurrence following LT according to recipient sex. The 1-, 3-, 5- and 10-year survival after diagnosis of HCC was 84.6%, 46.2%, 15.4% and 0% among females *vs.* 90.6%, 60.9%, 34.4% and 15.0% among males (log-rank $P=0.06$). Median survival was respectively 3 and 3.7 years, respectively. HCC, hepatocellular carcinoma; LT, liver transplantation; MS, median survival in years.

Table 5 Sex-specific predictors of HCC recurrence

Variable	β (95% CI)	P value	HR (95% CI)
Female			
AFP score at LT (>2)	2.10 (1.97–2.43)	<0.01	8.19 (7.20–11.35)
Prior hepatectomy	1.87 (1.45–2.16)	0.046	6.51 (4.27–8.67)
Male			
AFP score at LT (>2)	0.36 (0.29–0.38)	0.002	1.43 (1.34–1.47)
Prior hepatectomy	0.47 (0.42–0.65)	0.02	1.60 (1.52–1.92)
History of diabetes mellitus	0.34 (0.30–0.46)	0.03	1.41 (1.35–1.58)
Age at LT	0.01 (0.01–0.15)	0.01	1.01 (1.01–1.17)

AFP, alpha-fetoprotein; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; LT, liver transplantation.

were identified in each sex, highlighting the importance of considering sex as a biological variable in post-transplant management.

Despite significant differences in underlying liver disease etiology [females had a higher proportion of HCV-related cirrhosis (40.9% *vs.* 24.5%; $P=0.04$), while males had more alcohol-associated cirrhosis (36.5% *vs.* 19.7%; $P=0.04$)], and the observation that female recipients received significantly

older grafts and grafts from more female donors, overall and RFS after LT were comparable between sexes. This finding is consistent with previous reports (20,21) and a large USA-based study of 51,721 HCC patients listed for LT, which also found no significant difference in post-transplant mortality between male and female recipients (22).

Despite evidence from other studies (6,7,23) suggesting disparities in access to LT for women including a study of

31,725 wait-listed candidates receiving exception scores for HCC, reported that women were 8% less likely to receive a transplant and 6% more likely to die or be removed from the list compared with men, our findings suggest that these disparities may be mitigated by efficient referral and listing practices. In our cohort, females had a significantly shorter waiting time from initial HCC diagnosis to LT, and the time from listing to LT was similar between sexes. This potentially explains the smaller tumor size at transplant and higher proportion meeting Milan criteria observed in females, indicating earlier intervention. These observations are consistent with existing literature reporting smaller HCC tumors and more favorable tumor biology in females (19,20).

Although HCC recurrence after LT is reported in 8–20% of patients despite adherence to eligibility criteria (24,25), our findings revealed comparable recurrence rates between females and males (19.7% *vs.* 20.1%, respectively). This is a noteworthy observation, as females were diagnosed earlier and presented with smaller tumors at the time of transplant, factors typically associated with a lower risk of recurrence. This suggests the involvement of other factors beyond tumor size influencing post-LT recurrence in both sexes. While the influence of sex on HCC recurrence after resection has been previously investigated (13), our study specifically addresses recurrence following LT.

Multivariable analysis identified distinct pre-transplant predictors of HCC recurrence in each sex. In females, a high AFP score (>2) at transplantation and a history of prior hepatectomy were strong independent predictors, with stronger hazard ratios compared to males, suggesting a greater impact on recurrence risk in women. Prior hepatectomy as a predictor of recurrence could reflect the selection of patients with more aggressive tumor biology who initially underwent resection but were later deemed eligible for LT due to recurrence or progression. The strong correlation between a high AFP score (>2) and recurrence among women also suggests that this biomarker can be used as a surrogate for more aggressive tumor behavior in this group. An AFP score ≤ 2 has been used in France as a selection criterion for LT since 2014, associated with a 10% reduction in recurrence risk (26), higher survival rates in patients within Milan criteria, and correlation with less aggressive tumor histology (27), our analysis highlights the independent predictive value of a high AFP score (>2).

These same factors were also predictive in males, along with diabetes mellitus and age at transplantation. The observed sex-specific predictors of HCC recurrence may be explained by underlying biological, clinical, and

environmental factors. In males, the identification of older age and pre-transplant diabetes mellitus type 2 as predictors aligns with existing evidence linking metabolic dysfunction and cumulative exposure to risk factors (e.g., chronic inflammation, oxidative stress, and insulin resistance) to poorer HCC outcomes (28–31). These findings underscore the potential role of hormonal differences, such as the protective effect of estrogen in females, which diminishes with age, and the influence of androgen-mediated pathways in males. Furthermore, the higher prevalence of alcohol-associated cirrhosis in males may contribute to a pro-inflammatory and pro-carcinogenic liver microenvironment, exacerbating recurrence risk. Taken together, these observations highlight the complex interplay of sex-specific biological and clinical factors in shaping post-transplant outcomes.

While 1-, 3-, 5-, and 10-year RFS and overall survival (OS) after LT were comparable between female and male recipients in our cohort, reflecting the similar overall recurrence rates, we observed a trend towards shorter median survival after recurrence in females *vs.* males (3 *vs.* 3.7 years). Although not statistically significant, this trend warrants further investigations in larger cohorts to explore potential biological differences or variations in tumor biology between the sexes.

This study benefits from several key strengths such as: (I) one of the few studies that analyze the recipient sex impact on long-term outcomes of LT for HCC; (II) the inclusion of 384 patients represents a substantial cohort for a single-center liver transplant study, providing adequate statistical power for many of our analyses; (III) the extensive follow-up period of up to 15 years allowed us to assess long-term outcomes including late recurrences; and (IV) furthermore, comprehensive data collection on recipient demographics, clinical parameters, tumor characteristics, and post-transplant outcomes enabled us to control for potential confounding factors.

Nonetheless, several limitations warrant consideration, such as the retrospective nature of the study, the single-center design and lack of statistical adjustment for Confounders. Although we performed multivariable Cox regression to identify independent predictors of HCC recurrence within each sex group, residual confounding cannot be entirely excluded. Variables such as socioeconomic status, access to healthcare, compliance with follow-up protocols, and center-specific practices were not fully accounted for in our analysis. These factors could influence both pre-transplant management and post-

transplant outcomes. Prospective, multicenter studies with standardized data collection and advanced statistical methods are warranted to confirm and expand upon these findings.

Conclusions

Recipient sex does not impact long-term survival or HCC recurrence after LT in our cohort. However, sex-specific predictors of recurrence were identified: older age, pre-transplant diabetes mellitus type 2 in males and prior hepatectomy and AFP score >2 in both sexes. These findings highlight the importance of tailored risk stratification and personalized post-transplant surveillance strategies.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The collection of data was carried out in accordance with the International Guideline for Ethical Review of Epidemiological Studies, and the principles of the Declaration of Helsinki and its subsequent amendments, with approval from the local committee of the hepatobiliary center at Paul Brousse

Hospital. Individual consent for this analysis was waived due to the retrospective nature.

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