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Human Immunodeficiency Virus Infection Does Not Worsen Prognosis of Liver Transplantation for Hepatocellular Carcinoma

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The impact of human immunodeficiency virus (HIV) infection on patients undergoing liver transplantation (LT) for hepatocellular carcinoma (HCC) is uncertain. This study aimed to assess the outcome of a prospective Spanish nationwide cohort of HIV-infected patients undergoing LT for HCC (2002-2014). These patients were matched (age, gender, year of LT, center, and hepatitis C virus (HCV) or hepatitis B virus infection) with non-HIV-infected controls (1:3 ratio). Patients with incidental HCC were excluded. Seventy-four HIV-infected patients and 222 non-HIV-infected patients were included. All patients had cirrhosis, mostly due to HCV infection (92%). HIV-infected patients were younger (47 versus 51 years) and had undetectable HCV RNA at LT (19% versus 9%) more frequently than non-HIV-infected patients. No significant differences were detected between HIV-infected and non-HIV-infected recipients in the radiological characteristics of HCC at enlisting or in the histopathological findings for HCC in the explanted liver. Survival at 1, 3, and 5 years for HIV-infected versus non-HIV-infected patients was 88% versus 90%, 78% versus 78%, and 67% versus 73% ($P = 0.779$), respectively. HCV infection (hazard ratio = 7.90, 95% confidence interval 1.07-56.82) and maximum nodule diameter >3 cm in the explanted liver (hazard ratio = 1.72, 95% confidence interval 1.02-2.89) were independently associated with mortality in the whole series. HCC recurred in 12 HIV-infected patients (16%) and 32 non-HIV-infected patients (14%), with a probability of 4% versus 5% at 1 year, 18% versus 12% at 3 years, and 20% versus 19% at 5 years ($P = 0.904$). Microscopic vascular invasion (hazard ratio = 3.40, 95% confidence interval 1.34-8.64) was the only factor independently associated with HCC recurrence. *Conclusions*: HIV infection had no impact on recurrence of HCC or survival after LT. Our results support the indication of LT in HIV-infected patients with HCC. (HEPATOLOGY 2016;63:488-498)

The widespread use of combined antiretroviral therapy (cART) has dramatically reduced human immunodeficiency virus (HIV)-related mortality and improved the survival rates of patients with HIV infection. Longer survival has made chronic liver disease more clinically relevant, particularly disease associated with hepatitis C virus (HCV) infection.[1,2] Of note, the incidence of hepatocellular carcinoma (HCC) has increased progressively among individuals with HIV infection during recent decades,[3,4] and up to 40% of liver-related mortality in patients with HIV infection is due to HCC.[5] Furthermore, it has been suggested that HCC could have a faster and worse outcome in HIV-infected patients than in non-HIV-infected patients.[6,7]

Liver transplantation (LT) is an effective treatment for HCC.[8] In recent years, LT has been performed in

Abbreviations: cART, combined antiretroviral therapy; CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; LT, liver transplantation; MELD, Model for End-Stage Liver Disease.

patients with HIV infection and HCC.[9,10] However, data showing the impact of HIV infection on the main outcomes (survival and recurrence of HCC after LT) are scant and controversial. One small study suggested a trend toward decreased survival in 16 HIV-infected LT recipients with HCC when compared with a group of 58 non-HIV-infected LT recipients.[6] Conversely, this trend was not observed in a recent report including 30 HIV-infected and 125 non-HIV-infected patients who underwent LT for HCC.[11] Furthermore, the frequency of recurrence of HCC after transplant varied considerably between the two studies: 31%[6] and 7%.[11] Of note, both studies had a relatively short post-LT follow-up period, with a median or mean length of less than 3 years, thus precluding definitive conclusions on the effectiveness of LT in HIV-infected patients.

The aim of the current study, therefore, was to assess the outcome of a sizeable cohort of HIV-infected patients who underwent LT for HCC in comparison with a matched cohort of non-HIV-infected patients.

Patients and Methods

Study Design and Patients. We performed a multicenter cohort study based on 271 consecutive HIV-infected patients who underwent LT between 2002 and 2012 in 19 centers from Spain and who were prospectively followed until August 2014. These patients were matched with 811 non-HIV-infected individuals (1:3) who underwent LT during the same period at the same centers. Other matched criteria were LT calendar year (±1 year), recipient age (±12 years), gender, and indication for LT. Only patients who received LT for HCC were included. Patients with incidental HCC were excluded. The study population finally comprised 74 HIV-infected patients and 222 non-HIV-infected patients, that is, 27% of their respective cohorts.

HCC was diagnosed according to the invasive and noninvasive criteria formulated by the European Association for the Study of the Liver[12] and the American Association for the Study of Liver Disease.[13,14]

All study information was recorded on a standardized case report form at each participating site and managed as described.[9] The main end points were patient survival and recurrence of HCC after LT.

The institutional review boards of all the participating sites approved the study. All patients signed the informed consent form.

Transplant Criteria. HIV-infected patients had to fulfill the HIV-related inclusion criteria for LT described.[9]

The liver disease-related criteria for accepting HIV-infected patients for LT were the same as those recommended in Spain for non-HIV-infected patients. In the case of patients with cirrhosis, the criteria were clinical decompensation with a minimum Model for End-Stage Liver Disease (MELD) score of 12 points. In patients with HCC, the Milan criteria were recommended (solitary tumor ≤5 cm or two or three tumors ≤3 cm in the absence of macrovascular tumor invasion and extrahepatic metastases).[15,16] Once patients were enlisted for LT, radiological imaging was repeated with a minimum frequency of 3 months until transplantation in all participating centers.

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Posttransplant Management. cART was administered until the day of surgery and resumed once the patient was able to tolerate oral medication. Antiretroviral drugs were administered according to Spanish national guidelines.[17] HIV-infected recipients received the same immunosuppressive regimens as non-HIV-infected patients according to local protocols. Post-LT and HIV infection antimicrobial prophylaxis was administered according to national guidelines.[18,19] Thirteen of the 19 (68%) participating centers had a specific protocol for surveillance of HCC recurrence, which consisted of periodic (3-6 months) imaging techniques and alpha-fetoprotein measurements for at least the first 3 years after LT.[15] LT teams from the remaining six centers did not follow any surveillance protocol.[15]

Statistical Analysis. Variables are expressed as median and interquartile range and as percentages when appropriate. Survival was defined as the time interval between LT and death from any cause, unless another time interval was indicated. Time was censored at the date of the last follow-up assessment for patients who were still alive. Patient survival and the cumulative incidence of post-LT recurrence of HCC were calculated using the Kaplan-Meier method, and the curves obtained were compared using the log-rank test. The incidence density rate for recurrence of HCC was calculated as the number of registered new events per person-year during the study period.

Pretransplant and peritransplant variables were assessed as predictors of outcomes using Cox proportional hazards models. The Cox proportional hazards assumption was assessed using smoothed plots of the Schoenfeld residuals. Predictors of outcome were assessed for the overall cohort and for the HIV-infected group alone. Variables associated with a P value <0.10 in the univariate analysis were considered candidate predictors for the multivariate analyses. The hazard ratio (HR) estimates and the associated 95% confidence interval (CI) for each predictor of death/recurrence of HCC were calculated.

Statistical significance was defined as a two-tailed P value <0.05. All statistical analyses were carried out using the STATA package (release 9.2).

Results

Characteristics of Patients. Table 1 shows the baseline characteristics of the 74 HIV-infected and the 222 non-HIV-infected patients. All but two patients (one in each cohort) were Caucasian. All patients had cirrhosis. Most patients were men (85%) and had HCV infection (92%). HIV-infected patients were significantly younger (47 versus 51 years, $P < 0.001$) and had undetectable HCV RNA at the time of LT more frequently than non-HIV-infected patients (19% versus 9%, $P = 0.026$). As expected, genotype 1 was less frequent (45% versus 75%, $P < 0.001$) and genotypes 3 and 4 were more frequent (37% versus 20%, $P = 0.008$, and 15% versus 3%, $P = 0.001$, respectively) in HIV-infected patients than in non-HIV-infected patients.

Table 1. Characteristics of HIV-Infected (HIV^+) and Non-HIV-Infected (HIV^-) LT Recipients With HCC

	HIV^+ n = 74	HIV^- n = 222	*P*
Age (years)*	47 (44-51)	51 (47-55)	<0.001
Male gender	63 (85%)	189 (85%)	1.000
HCV infection	68 (92%)	205 (92%)	0.900
HCV genotype†			
1	27 (45%)	139 (75%)	<0.001
2	2 (3%)	4 (2%)	0.636
3	22 (37%)	37 (20%)	0.008
4	9 (15%)	6 (3%)	0.001
Unknown/undetermined	8	19	0.550
Undetectable HCV RNA at LT‡	13 (19%)	19 (9%)	0.026
MELD score at enlisting*	10 (8-14)	12 (9-15)	0.083
MELD score at LT*	10 (8-14)	12 (9-15)	0.069
Time on waiting list (months)*	4.5 (2.4-7.4)	5.4 (2.9-8.0)	0.356
Time on waiting list >3 months	43 (58%)	126 (66%)	0.254
Donor age (years)*	51 (42-68)	56 (39-65)	0.935
Initial immunosuppressive regimen			
Tacrolimus-based	54 (73%)	173 (82%)	0.114
Cyclosporin-based	20 (27%)	39 (18%)	
mTOR based	0	5 (2%)	NA

*Median and interquartile range.

†Percentages related to patients with HCV infection and known/determined genotype.

‡Eight patients in the HIV^+ cohort and four patients in the HIV^- cohort cleared the HCV infection spontaneously.

Abbreviations: mTOR, mammalian target of rapamycin; NA, not applicable.

No significant differences were seen between HIV-infected and non-HIV-infected patients for the radiological HCC features at the time of inclusion on the waiting list for LT or the histopathological findings for HCC in the explanted livers (Table 2). At inclusion on the waiting list, a trend toward a statistically significantly higher proportion of HIV-infected patients who had HCC exceeding the University of California-San Francisco criteria was observed (1% versus 7%, $P = 0.067$). Nevertheless, this difference was not present at LT (21% versus 18%, respectively, $P = 0.527$). Treatment of HCC did not differ significantly between the two cohorts before transplantation.

The most frequent HIV risk factor was intravenous drug use (80%), followed by heterosexual intercourse (10%). Median (interquartile range) CD4 cells per cubic millimeter in patients with HIV infection was 354

Table 2. Tumor Characteristics in HIV-Infected and Non-HIV LT Recipients With HCC

	HIV+ n = 74	HIV− n = 222	P
Radiological data at LT enlisting			
Single nodule	41 (58%)	141 (65%)	0.293
Multiple nodules	30 (42%)	77 (35%)	
Maximum nodule diameter*	2.7 (2-3)	2.6 (2-3)	0.845
Outside Milan criteria	6 (8%)	26 (13%)	0.343
Outside UCSF criteria	1 (1%)	15 (7%)	0.067
AFP (ng/mL)			
At LT enlisting			
AFP level*	11 (6-37)	11 (5-39)	0.991
>10	40 (55%)	113 (54%)	0.884
>100	9 (12%)	28 (13%)	0.826
>250	4 (5%)	12 (5%)	0.940
At the time of LT			
AFP level*	11 (5-48)	10 (5-31)	0.804
>10	38 (52%)	109 (50%)	0.761
>100	10 (14%)	29 (13%)	0.942
>250	6 (8%)	12 (5%)	0.405
Pre-LT treatment	47 (63%)	135 (61%)	0.679
TACE	38 (51%)	94 (42%)	0.177
RFA	11 (15%)	39 (18%)	0.591
PEI	7 (9%)	27 (12%)	0.528
Liver resection	5 (4%)	9 (7%)	0.343
Histopathological findings in the explanted liver			
Single nodule	30 (41%)	97 (45%)	0.553
Multiple nodules	44 (59%)	121 (55%)	
Maximum nodule diameter*	2.5 (2.0-3.3)	2.7 (2.0-3.5)	0.938
Maximum nodule diameter >3 cm	22 (31%)	59 (28%)	0.580
Microscopic vascular invasion†	17 (25%)	31 (17%)	0.138
Macroscopic vascular invasion	1 (1%)	10 (5%)	0.183
Satellite nodules	9 (14%)	29 (16%)	0.722
Microscopic vascular invasion or satellite nodules	20 (31%)	51 (28%)	0.641
Edmondson grade‡			
Well differentiated	20 (34%)	77 (46%)	0.263
Moderately differentiated	26 (44%)	61 (37%)	
Poorly differentiated or undifferentiated	13 (22%)	29 (17%)	
Outside Milan criteria	22 (31%)	57 (27%)	0.478
Outside UCSF criteria	15 (21%)	38 (18%)	0.527

*Median and interquartile range.

†Available in 68 (92%) HIV-infected and 185 (83%) non-HIV-infected patients. Data not available in the remaining patients due to complete tumor necrosis caused by locoregional treatment.

‡Available in 59 (80%) HIV-infected and 167 (75%) non-HIV-infected patients. Data not available in the remaining patients due to complete tumor necrosis caused by locoregional treatment or not reported.

Abbreviations: AFP, alpha-fetoprotein; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; UCSF, University of California-San Francisco.

(244-523) at inclusion on the waiting list. Most patients (95%) were receiving cART, and HIV plasma viral load was <50 copies/mL in 94%.

All patients received a whole-size organ from deceased donors, with the exception of two HIV-infected patients who received partial grafts from living donors.

Most patients initiated immunosuppressive treatment with tacrolimus-based regimens, with no significant differences between the two cohorts (Table 1).

Survival. After a median of 46 (25-72) months of follow-up, 25 (34%) HIV-infected patients and 64 (29%) non-HIV-infected patients died ($P = 0.421$). The causes of death did not differ significantly between the two cohorts (Table 3). The most frequent were recurrence of HCC and recurrence of hepatitis C infection. Only one HIV-infected patient died of an acquired immune deficiency syndrome-related event (HIV meningoencephalitis 1 month after LT).

Patient probability of survival (95% CI) at 1, 3, and 5 years for HIV-infected patients versus non-HIV-infected patients was 88% (78-93) versus 89% (85-93), 78% (67-86) versus 78% (72-83), and 67% (54-77) versus 73% (66-78), respectively ($P = 0.779$) (Fig. 1).

By considering the two cohorts of HIV-infected and non-HIV-infected patients together, a univariate analysis identified six variables as predictors of mortality with a P value <0.10: HCV infection, increased alpha-fetoprotein, maximum nodule diameter >3 cm,

Table 3. Posttransplant Outcome in HIV-Infected and Non-HIV LT Recipients With HCC

	HIV+ n = 74	HIV− n = 222	P
Follow-up (months)*	48 (31-78)	44 (24-71)	0.187
Mortality	25 (34%)	64 (29%)	0.421
Cause of death			
Recurrence of HCC	8 (32%)	17 (27%)	0.394
Recurrence of HCV infection	7 (28%)	13 (20%)	0.285
Sepsis	2 (8%)	10 (15%)	0.737
De novo tumor	2 (8%)	5 (8%)	0.557
Multiple organ failure	1 (4%)	3 (5%)	0.739
Cardiovascular complications	1 (4%)	2 (3%)	0.580
Rejection	3 (12%)	2 (3%)	0.102
Surgical complications	0	3 (5%)	NA
Other	1 (4%)	9 (14%)	0.239
HCC recurrence	12 (16%)	32 (14%)	0.706
Site of recurrence†			
Intrahepatic	2 (17%)	4 (12%)	0.629
Extrahepatic	7 (58%)	15 (47%)	
Both	3 (25%)	13 (41%)	
Time since LT*	21 (12-33)	20 (9-41)	0.192
Treatment for HCC recurrence†			
RFA	1 (8%)	2 (6%)	0.738
TACE	1 (8%)	5 (16%)	0.634
PEI	1 (8%)	1 (3%)	0.413
Sorafenib	3 (25%)	13 (40%)	0.553
mTOR inhibitors	7 (58%)	14 (44%)	0.360

*Median and interquartile range.

†Percentages related to patients with HCC recurrence.

Abbreviations: mTOR, mammalian target of rapamycin; NA, not applicable; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

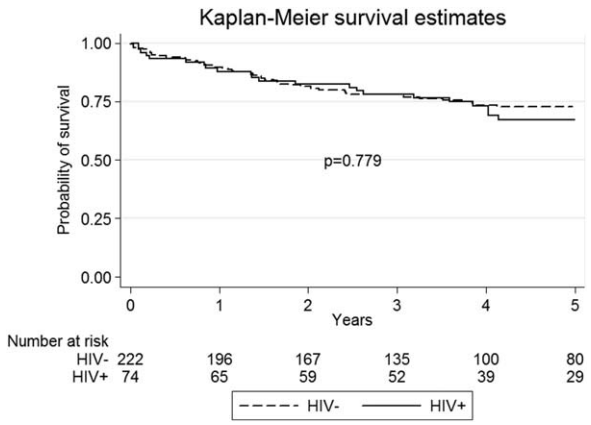

Fig. 1. Survival after liver transplantation in patients with and without HIV infection.

microscopic vascular invasion, satellite nodules, and poorly differentiated Edmondson grade in the explanted liver (Table 4). After the introduction of these six variables into a multivariate analysis, only two remained as independent prognostic factors: HCV infection (HR = 7.79, 95% CI 1.07-56.82) and maximum nodule diameter >3 cm in the explanted liver (HR = 1.72, 95% CI 1.02-2.89) (Table 4). The presence of HIV infection was not significantly associated with mortality (HR = 1.07, 95% CI 0.67-1.70).

In a *post hoc* analysis including only the patients with HCV infection (n = 273), the presence of satellite nodules in the liver explant (HR = 2.00, 95% CI 1.10-3.66) and sustained virological response achievement after LT (HR = 0.27, 95% CI 0.09-0.82) were factors independently associated with death (data not shown).

Recurrence of HCC. Recurrence of HCC was recorded in 12 of the 74 HIV-infected patients (16%) and in 32 of the 222 non-HIV-infected patients (14%) ($P = 0.706$). No significant differences were observed between the two populations in relation to the site of recurrence, the interval from LT to recurrence, or the treatment strategies used for recurrence (Table 3). The

Table 4. Univariate and Multivariate Analysis of Mortality in LT Recipients With HCC

	Alive n = 207	Dead n = 89	Crude HR	P	Adjusted HR	P
Pre-LT characteristics						
Recipient age at LT (1-year increase)*	50 (46-54)	51 (46-54)	1.02 (0.99-1.06)	0.201		
Male gender	182 (88%)	70 (79%)	0.68 (0.41-1.13)	0.141		
HIV infection	49 (24%)	25 (28%)	1.07 (0.67-1.70)	0.768		
HCV infection	185 (89%)	88 (99%)	9.02 (1.26-64.78)	0.029	7.79 (1.07-56.82)	0.043
Undetectable RNA HCV at LT	26 (14%)	6 (7%)	0.51 (0.22-1.17)	0.111		
AFP >11 ng/mL at LT enlisting	97 (49%)	44 (51%)	1.06 (0.7-1.62)	0.777		
MELD score at LT enlisting (1-unit increase)*	11 (9-15)	12 (9-14)	1.02 (0.97-1.06)	0.460		
AFP >10 ng/mL at LT	96 (47%)	51 (59%)	1.48 (0.96-2.27)	0.075		
MELD score at LT (1-unit increase)*	11 (9-15)	12 (9-15)	1.01 (0.97-1.05)	0.574		
HCC treatment pre-LT	122 (59%)	60 (67%)	1.37 (0.88-2.14)	0.161		
Waiting list length (months)*	5.4 (3.0-8.1)	4.4 (2.2-6.9)	0.98 (0.94-1.02)	0.315		
Radiological features at LT enlisting						
Multiple nodules	71 (35%)	36 (41%)	1.25 (0.82-1.92)	0.299		
Maximum nodule diameter >3 cm	46 (24%)	19 (22%)	0.91 (0.55-1.52)	0.731		
Outside Milan criteria	20 (10%)	12 (14%)	1.31 (0.71-2.42)	0.383		
Outside UCSF criteria	11 (5%)	5 (6%)	1.14 (0.46-2.83)	0.767		
Explanted liver						
Multiple nodules	114 (55%)	51 (59%)	1.11 (0.72-1.71)	0.627		
Maximum nodule diameter >3 cm	50 (25%)	31 (36%)	1.69 (1.09-2.63)	0.020	1.72 (1.02-2.89)	0.043
Microscopic vascular invasion	28 (16%)	20 (26%)	1.78 (1.06-2.97)	0.028		
Macroscopic vascular invasion	6 (3%)	5 (6%)	1.99 (0.80-4.93)	0.137		
Satellite nodules	19 (11%)	19 (25%)	1.89 (1.12-3.18)	0.017		
Poorly differentiated Edmondson grade†	84 (53%)	45 (65%)	1.59 (0.97-2.62)	0.065		
Outside Milan Criteria	51 (25%)	28 (33%)	1.35 (0.86-2.12)	0.194		
Outside UCSF Criteria	36 (18%)	17 (20%)	1.18 (0.69-2.00)	0.546		
Transplant characteristics						
2007-2012 transplant period	171 (83%)	60 (67%)	0.85 (0.53-1.35)	0.485		
Donor age (1-year increase)*	53 (40-55)	56 (46-66)	1.01 (0.99-1.02)	0.152		
Tacrolimus-based initial immunosuppressive regimen	166 (82%)	61 (73%)	0.70 (0.43-1.14)	0.150		

All variables reaching $P < 0.10$ in the univariate analysis were included in the multivariate analysis.

*Median and interquartile range.

†Moderately differentiated, poorly differentiated, and undifferentiated Edmondson grade.

Abbreviations: AFP, alpha-fetoprotein; UCSF, University of California-San Francisco.

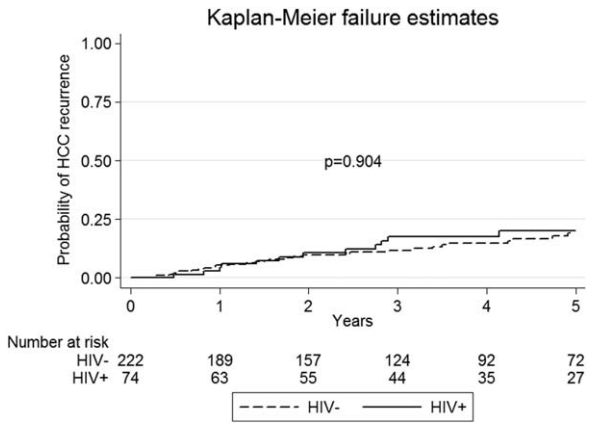

Fig. 2. HCC recurrence in liver transplant recipients with and without HIV infection.

cumulative incidence of recurrence (95% CIs) at 1, 3, and 5 years for HIV-infected patients versus non-HIV-infected patients was 4% (1-13) versus 5% (3-9), 18% (10-30) versus 12% (8-17), and 20% (12-33) versus 19% (13-27), respectively ($P = 0.904$) (Fig. 2). The incidence density rates of recurrence were similar in the two cohorts: 0.236 and 0.263 person-years, respectively ($P = 0.424$). The incidence rate ratio (relative risk) for HIV-infected patients in relation to non-HIV-infected patients was 0.90 (95% CI 0.69-1.17).

In the whole series, the following variables were identified as predictive factors of tumor recurrence with a P value <0.10 in a univariate analysis: maximum nodule diameter >3 cm (in both pre-LT radiological imaging and the explanted livers), microscopic and macroscopic vascular invasion, satellite nodules, poorly differentiated Edmondson grade, and being outside Milan and University of California-San Francisco criteria (Table 5). After introducing these eight variables into a multivariate analysis, only microscopic vascular invasion was found to be independently associated with the recurrence of HCC (HR = 3.40, 95% CI 1.34-8.64) (Table 5). HIV infection was not associated with a significant

Table 5. Univariate and Multivariate Analysis of Recurrence of HCC in LT Recipients With HCC

	No HCC Recurrence n = 252	HCC Recurrence n = 44	Crude HR	P	Adjusted HR	P
Pre-LT characteristics						
Recipient age at LT (1-year increase)*	50 (46-54)	50 (46-54)	1.01 (0.96-1.06)	0.685		
Male gender	217 (86%)	35 (79%)	0.67 (0.32-1.39)	0.281		
HIV infection	62 (25%)	12 (27%)	1.04 (0.54-2.03)	0.897		
HCV infection	229 (91%)	43 (98%)	4.90 (0.67-35.63)	0.116		
Undetectable RNA HCV at LT	28 (12%)	4 (10)	0.74 (0.26-2.08)	0.573		
AFP >11 ng/mL at LT enlisting	118 (49%)	23 (56%)	1.31 (0.71-2.42)	0.391		
MELD score at LT enlisting (1-unit increase)*	11 (9-14)	12 (9-15)	1.04 (0.97-1.10)	0.256		
AFP >10 ng/mL at LT	122 (49%)	25 (61%)	1.61 (0.86-3.00)	0.138		
MELD score at LT (1-unit increase)*	11 (9-15)	11 (9-16)	1.02 (0.97-1.08)	0.451		
Pre-LT treatment of HCC	156 (61%)	26 (59%)	0.97 (0.53-1.76)	0.910		
Time on waiting list (months)*	5.3 (3.1-8.0)	3.7 (1.8-7.3)	0.96 (0.89-1.02)	0.197		
Radiological features at LT enlisting						
Multiple nodules	89 (36%)	18 (41%)	1.27 (0.70-2.32)	0.436		
Maximum nodule diameter >3 cm	50 (22%)	15 (35%)	1.73 (0.92-3.23)	0.088		
Outside Milan criteria	25 (11%)	7 (16%)	1.60 (0.71-3.60)	0.255		
Outside UCSF Criteria	14 (6%)	2 (4%)	0.90 (0.22-3.74)	0.890		
Explanted liver						
Multiple nodules	137 (55%)	28 (64%)	1.38 (0.74-2.54)	0.308		
Maximum nodule diameter >3 cm	61 (25%)	20 (48%)	2.90 (1.57-5.30)	0.001		
Microscopic vascular invasion	29 (13%)	19 (54%)	6.61 (3.39-12.92)	<0.001	3.40 (1.34-8.64)	0.010
Macroscopic vascular invasion	6 (2%)	5 (11%)	4.97 (1.94-12.74)	0.001		
Satellite nodules	24 (11%)	14 (37%)	3.43 (1.77-6.63)	<0.001		
Poorly differentiated Edmondson grade†	104 (54%)	25 (73%)	2.43 (1.13-5.22)	0.022		
Outside Milan criteria	62 (25%)	17 (40%)	1.89 (1.02-3.51)	0.042		
Outside UCSF criteria	40 (16%)	13 (31%)	2.14 (1.11-4.12)	0.023		
Transplant characteristics						
2007-2012 transplant period	198 (79%)	33 (75%)	1.12 (0.56-2.26)	0.745		
Donor age (1-unit increase)*	54 (40-65)	54 (43-68)	1.00 (0.99-1.02)	0.736		
Tacrolimus-based initial immunosuppressive regimen	191 (79%)	36 (84%)	1.31 (0.58-2.94)	0.518		

All variables reaching $P < 0.10$ in the univariate analysis were included in the multivariate analysis.

*Median and interquartile range.

†Moderately differentiated, poorly differentiated and undifferentiated Edmondson grade.

Abbreviations: AFP, alpha-fetoprotein; UCSF, University of California-San Francisco.

Table 6. Univariate Analysis Related to HCC Recurrence in HIV-Infected LT Recipients With HCC

	HCC Recurrence n = 12	Non-HCC Recurrence n = 62	Crude HR (95% CI)	*P*
Pre-LT characteristics				
Recipient age at LT, years (1-unit increase)*	48 (46;53)	46 (43;51)	1.06 (0.96;1.17)	0.214
Male gender	9 (75%)	54 (87%)	0.55 (0.15;2.03)	0.369
HCV infection	11 (92%)	57 (92%)	1.25 (0.16;9.72)	0.829
Undetectable HCV RNA at LT	1 (10%)	12 (21%)	0.45 (0.06;3.59)	0.455
IVDU use (HIV risk factor)	10 (83%)	47 (76%)	1.70 (0.37;7.78)	0.492
Non-HIV inclusion criteria compliance	0	2 (3%)	NA	NA
History of opportunistic infections	2 (17%)	13 (21%)	1.31 (0.28;6.06)	0.728
CD4 cell count >330 cells/mm^3 at LT	6 (50%)	23 (37%)	1.49 (0.48;4.62)	0.491
Serum HIV detectable viremia at LT	0	3 (5%)	NA	NA
AFP >11 ng/mL at enlisting	6 (54%)	29 (47%)	1.16 (0.36;3.82)	0.800
MELD score at enlisting (1-unit increase)*	9 (7;11)	11 (8;14)	0.85 (0.70;1.04)	0.117
AFP >10 ng/mL at LT	6 (54%)	32 (52%)	1.07 (0.32;3.53)	0.905
MELD score at LT (1-unit increase)*	9 (8;11)	10 (8;14)	0.92 (0.79;1.07)	0.297
HCC treatment pre-LT	10 (83%)	37 (60%)	3.59 (0.78;16.42)	0.099
Time on waiting list (months)*	2.8 (1.6;5.9)	4.9 (3.1;7.4)	0.89 (0.75;1.06)	0.206
Radiological features at enlisting				
Multiple nodules at enlisting	8 (67%)	22 (37%)	2.52 (0.76;8.37)	0.132
Maximum nodule diameter >3 cm at enlisting	3 (25%)	13 (22%)	1.34 (0.36;4.99)	0.657
Outside Milan criteria at waiting list	2 (17%)	4 (7%)	2.29 (0.50;10.52)	0.287
Outside UCSF criteria at waiting list	1 (8%)	0	NA	NA
Explanted liver				
Multiple nodules	11 (92%)	33 (53%)	8.6 (1.11;67.07)	0.039
Maximum nodule diameter >3 cm	5 (50%)	17 (28%)	3.2 (0.92;11.15)	0.067
Microscopic vascular invasion	5 (45%)	12 (21%)	3.37 (1.02;11.11)	0.045
Macroscopic vascular invasion	0	1 (2%)	NA	NA
Satellite nodules	4 (36%)	5 (9%)	4.87 (1.41;16.83)	0.012
Microscopic vascular invasion or satellite nodules	6 (54%)	14 (26%)	3.39 (1.03;11.15)	0.044
Poorly differentiated Edmondson grade†	8 (80%)	31 (63%)	2.43 (0.51;11.51)	0.263
Outside Milan Criteria	6 (60%)	16 (26%)	3.97 (1.12;14.09)	0.033
Outside UCSF Criteria	4 (40%)	11 (18%)	2.73 (0.77;9.68)	0.121
Transplant characteristics				
2007-2012 transplant period	10 (83%)	46 (74%)	1.72 (0.38;0.79)	0.483
Donor age, years (1-unit increase)*	52 (43;68)	50 (41;69)	1.00 (0.97;1.03)	0.808
Tacrolimus-based initial immunosuppressive regimen	9 (75%)	45 (73%)	0.96 (0.26;3.54)	0.948
Initial cART after LT based on PIs	1 (8%)	11 (18%)	0.44 (0.57;3.40)	0.430

*Median and interquartile range.

†Moderately differentiated, poorly differentiated, and undifferentiated Edmondson grade.

Abbreviations: BDL, below detection limit; IVDU, intravenous drug use; NA, not applicable; PIs, protease inhibitors.

risk of recurrence of HCC (HR = 1.04, 95% CI 0.54-2.03). In the *post hoc* analysis comprising only the patients with HCV infection, no factor was independently associated with HCC recurrence, although the presence of microvascular invasion in the liver explant had a trend toward statistical significance (HR = 3.02, 95% CI 0.97-9.43) (data not shown). Another *post hoc* analysis was performed with HIV-infected patients alone. In the univariate analysis, four variables proved to be statistically significant predictors of recurrence of HCC in this cohort: multiple nodules (HR = 8.6, 95% CI 1.11-67.07), microscopic vascular invasion (HR = 3.37, 95% CI 1.02-11.11), satellite nodules (HR = 4.87, 95% CI 1.41-16.83), and HCC beyond the Milan criteria (HR = 3.29, 95% CI 1.03-11.15) (Table 6). A multivariate analysis was not performed because of the small number of events (12 recurrences of HCC).

The probability of survival (95% CI) after recurrence in HIV-infected versus non-HIV-infected patients was 57% (25-80) versus 58% (39-73) at 1 year and 25% (5-54) and 33% (15-51) at 3 years, respectively (P = 0.886) (Fig. 3). Few recurrences were treated with local antitumor treatments, whereas sorafenib and mammalian target of rapamycin inhibitors were administered to a larger number of patients after diagnosis of recurrence (Table 3). No significant differences were observed between HIV-infected and non-HIV-infected patients in relation to the type of treatment of HCC recurrence.

No significant differences were observed in the main outcomes between patients from centers with versus

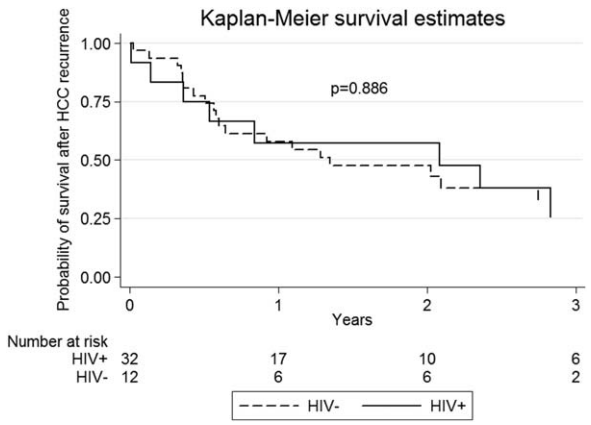

Fig. 3. Survival after HCC recurrence diagnosis in liver transplant recipients with and without HIV infection.

without a protocol of surveillance for HCC recurrence. The rate of HCC recurrence was 15% in the two subsets (29/193 versus 15/103 patients, respectively), with a cumulative incidence of 5% versus 5% at 1 year, 11% versus 15% at 3 years, and 18% versus 20% at 5 years ($P = 0.810$). Survival rates after the diagnosis of HCC recurrence were not significantly different: 65% versus 50% at 1 year and 30% versus 30% at 3 years ($P = 0.678$).

Discussion

We found that rates of survival and recurrence of HCC were similar in HIV-infected patients who underwent LT for HCC and their matched non-HIV-infected controls.

Data on survival of LT recipients with HIV infection and HCC are scarce and inconsistent. Vibert et al.[6] reported a trend toward decreased survival in 16 HIV-infected recipients who were compared with 58 non-HIV-infected patients (74% versus 84% at 3 years, respectively, $P = 0.07$). However, Di Benedetto et al.[11] did not find significant differences in post-LT survival at 1 and 3 years between a group of 30 HIV-infected patients who received LT for HCC and a group of 125 non-HIV-infected patients also receiving LT for HCC (77% and 65% versus 86% and 70%, respectively, $P = 0.32$). The short follow-up in both of these studies (median 27 and 32 months, respectively) precluded the evaluation of long-term survival. In the present study (74 HIV-infected patients with LT for HCC and 222 matched controls followed for a median of 46 months), short-term and long-term survival were similar in the two groups: 88% versus 89% at 1 year, 78% versus 78% at 3 years, and 67% versus 73% at 5 years, respectively. A multivariate analysis highlighted the lack of impact of HIV infection on mortality (HR = 1.07, 95% CI 0.67-1.70). The survival rates in our study were similar to those reported in previous series of non-HIV-infected patients with HCC who underwent LT based on the Milan criteria (approximately 75% at 5 years).[20,21]

Causes of death after LT in HIV-infected and non-HIV-infected patients were similar. As expected, the most frequent causes were recurrence of HCC (32% and 27%, respectively) and hepatitis C (28% and 20%). These findings are not surprising, given the predominance of underlying HCV-related liver disease in our series.

HCV infection and maximum nodule diameter >3 cm in the explanted liver were identified as independent predictors of mortality (HR = 7.79 and 1.72, respectively). In a recent study of LT recipients with HCC,[22] HCV infection was also found to be independently associated with death. The association between HCV infection and a poorer prognosis after LT has two explanations. First, reinfection of the transplanted liver with HCV is universal and leads to accelerated progression of liver damage in most patients.[9,23] Second, sustained virological response rates to the classic regimen of interferon and ribavirin in LT recipients have been low, around 30% in non-HIV-infected patients[24] and 20% in HCV/HIV-coinfected patients.[25,26] However, the introduction of new direct antiviral agents with much higher efficacy against HCV and much better tolerance seems very promising in this setting.[27,28] In fact, interferon-free anti-HCV regimens are currently changing the standards of care for HCV-infected patients before and after LT.

In addition to HCV infection, maximum nodule size in the explanted liver was a statistically independent prognostic factor for survival. This finding is consistent with previous reports involving patients undergoing LT for HCC, in whom tumor burden was the principal determinant of outcome.[20,21]

The present cohort of HIV-infected recipients of LT for HCC, who were mostly coinfected with HCV, achieved better patient survival than the three largest series of HIV/HCV-coinfected patients undergoing LT predominantly indicated for end-stage cirrhosis.[9,10,23] In these studies, survival was around 60% at 3 years and 50% at 5 years after LT, whereas in our study 3-year and 5-year survival of HIV-infected patients reached 78% and 67%, respectively. In two of the three studies mentioned above,[9,23] increased MELD score indicated a poor prognosis. Because many of the HIV-infected patients with HCC in the present study had a low MELD score (median 10 points at the time of LT), we believe that the improved survival in our series was due,

at least in part, to preserved liver function in most patients and, therefore, was not an unexpected finding.

The main concern after LT for HCC is the risk of recurrence, which affects 8%-20% of non-HIV-infected recipients.[16,29] The rate of post-LT HCC recurrence is not well established in HIV-infected patients. One underpowered study[6] found that HCC recurrence was two-fold higher in the HIV-infected group (5/16, 31%) than in the control group (9/58, 15%), although this difference did not reach statistical significance ($P = 0.15$). Conversely, Di Benedetto et al.[11] found that HIV-infected patients had a lower (albeit nonsignificant) rate of recurrence of HCC than non-HIV-infected patients (7% [2/30] versus 14% [18/125], respectively, $P = 0.15$). However, the follow-up periods in both studies were too short to assess recurrence. Our results showed that HIV-infected patients do not have a higher risk of developing recurrence after LT than non-HIV-infected patients: 4% versus 5% at 1 year after LT, 18% versus 12% at 3 years, and 20% versus 19% at 5 years, respectively ($P = 0.904$). In addition, the incidence density rate of recurrence of HCC after LT was similar in both HIV-infected patients and non-HIV-infected patients. Of note, the percentage of recurrence in the two groups (16% and 14%, respectively) was within the range reported elsewhere.[16,29]

In our series, microvascular invasion in the explanted liver was associated with a 3.4-fold increased risk of recurrence of HCC, which is in agreement with the results of previous studies, indicating that this histopathological finding is the strongest predictor of recurrence.[20,21] As no data are available on predictors of recurrence of HCC in LT patients with HIV infection, we performed a *post hoc* analysis in the HIV-infected cohort. Univariate analysis of this population revealed a significant relationship between recurrence of HCC and the following variables: increased number of nodules, satellite nodules, microvascular invasion, and HCC outside the Milan criteria. These variables indicate increased tumor extension and/or aggressiveness, which is consistent with results reported for HCC in non-HIV-infected LT recipients.[21] The small number of events in this cohort (only 12 recurrences) precluded a multivariate analysis.

Some authors recommend surveillance protocols for the early detection and treatment of HCC recurrence.[29,30] However, we found that the incidence of HCC recurrence and survival rates after HCC recurrence in centers with versus without specific surveillance protocols were not significantly different and, thus, do not support such a recommendation.

Concerning HIV infection, in our series it was adequately controlled on cART, with only one death due to HIV meningoencephalitis during the study period.

Our study is subject to a series of limitations. In Spain, the Milan criteria are recommended for indicating LT in patients with HCC; however, we did not adhere fully to this recommendation because a relatively high percentage of patients exceeded the Milan criteria (around 10% at the time of inclusion on the waiting list and 30% in the explanted liver). Nevertheless, given that this limitation is also observed in most previous reports on LT for HCC,[6,11] our series can be considered representative of clinical practice. Furthermore, as the primary aim of the study was to assess post-LT outcomes, we do not have information about the number of patients enlisted for LT or about the waiting list drop-out rate. Therefore, the outcome of patients from their entry on the waiting list could not be assessed. Finally, the relatively small number of patients who experienced recurrence of HCC (12 in the HIV-infected cohort and 32 in the non-HIV-infected cohort) could have left the study underpowered for more accurate identification of predictors of recurrence. Conversely, a major strength of our study is that it is the largest multicenter cohort of HIV-infected patients who underwent LT for HCC with the longest follow-up to date. Our study included all HIV-infected patients who received LT for HCC, which represented 27% of the total cohort of HIV-infected subjects undergoing LT in our country. This percentage is consistent with the figures reported in other studies, ranging from 15% to 34%.[9,10,23,31]

In summary, long-term rates of survival and recurrence of HCC in HIV-infected patients undergoing LT for HCC are satisfactory. These outcomes are similar to those observed in non-HIV-infected patients. Therefore, we strongly recommend considering HIV-infected patients with early-stage HCC as suitable candidates for LT, an effective and life-saving option in most cases.

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