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Similar survival but higher and delayed hepatocellular carcinoma recurrence in HIV-positive compared to negative cirrhotics undergoing liver transplantation

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ABSTRACT

Background: Liver transplantation (LT) represents the best therapeutic option for hepatocellular carcinoma (HCC) and end-stage liver disease (ESLD). Although HIV infection does not seem to lower survival rates, HCV and HCC recurrence appear more harmful.
Aims: To compare the overall survival after LT; evaluate the impact of anti-HCV direct-acting agents (DAA); assess the rate of HCC recurrence in HIV-positive and negative patients.
Methods: Subjects with HCV/HBV infection who underwent LT for HCC or ESLD from 2012 to 2019 were retrospectively evaluated.
Results: Study population included 299 individuals, 31 (10.4%) were HIV-positive. Overall mortality was similar (16.1% versus 19.0%, $p = 0.695$). HCC recurrence was observed in 6 HIV-positive (19.4%) and in 17 negative subjects (6.3%, $p = 0.022$). Time to relapse was 831 days in HIV-positive and 315 days in negative patients ($p = 0.046$). Cox model found a significant role for HIV in univariate analysis but, after adjusting for variables, extra-hepatic tumor was the only factor associated to recurrence (aHR 56.379, $p < 0.001$).
Conclusions: Post-LT survival improved after DAA availability and HIV has no impact on mortality. A higher and delayed rate of HCC recurrence was observed in co-infected individuals: surveillance protocols should be strengthened along time in this population.

1. Introduction

Liver transplantation (LT) is acknowledged as the best treatment option for end-stage liver disease (ESLD), hepatocellular carcinoma (HCC), acute fulminant hepatic failure (AFHF), and several metabolic and autoimmune disorders. Recent improvements in surgical technique, perioperative management and immunosuppressive therapy led to good graft and patient survival outcomes [1].

Liver disease among people living with HIV is mainly related to HBV and HCV [2]: these co-infections are more likely to progress to ESLD or liver failure than those with HBV or HCV alone. In the past, HIV infection was an absolute contraindication to LT for concerns about reduced overall survival and immunosuppression-related opportunistic infections, but several studies showed an acceptable short-term survival without increased risks of infective complications [3,4].

Historically, outcomes in HIV/HCV co-infected recipients were worse providing controversial indications for LT in this population because of the high rate of hepatitis relapse [5–9]. Nevertheless, direct-acting antivirals (DAAs) proved to be safe and effective also in co-infected cirrhotics so this disparity could be reduced even if DAAs impact on HCC relapse is still under debate [9]. Oncologic recurrence in presence of HCV infection is a major issue [10], and with HIV co-infection the overall outcome is even worse because of a more common and harmful HCC relapse [11]. HIV/HCV co-infected cirrhotics frequently present infiltrative and portal-obstructing tumors, resulting in a considerably shorter survival [12].

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So far, few data are available about the impact of DAAs on these outcomes [13]. Aims of the present study are to compare the overall survival of HIV-positive and HIV-negative patients who underwent LT in the DAA era identifying factors associated with mortality; to assess whether and how the presence of HCC affects clinical outcomes in the two populations.

2. Methods

This retrospective, monocentric analysis included all patients with HCV or HBV infection who consecutively underwent LT for HCC, ESLD or AFHF from 2012 to 2019. Patients with HCC were considered eligible for LT if the Milan criteria (MC) were fulfilled [14]. Patients outside MC were still considered eligible for LT if an adequate down-staging approach could be performed to bring these patients within MC. The current criteria for LT eligibility in HIV-infected patients are like those indicated for the general population with limitations related to the virologic and immunologic parameters [15]. According to the Italian recommendations, a T lymphocyte CD4+ cell count higher than 200 cells/mL (100 cell/mL if no previous AIDS-defining events were recorded in medical history) is required. A detectable HIV RNA is considered acceptable only in subjects who are intolerant to antiretroviral therapy but with an available genotypic resistance test that predicts possible virological suppression post-LT [16].

A pre-LT multidisciplinary evaluation among transplantation surgeons, gastroenterologists, and infectious diseases physicians sharing clinical, radiological, and laboratory data was performed for all patients. HCC was diagnosed with abdominal computed tomography scan, abdominal magnetic resonance, and liver ultrasound, according to the European Association for the Study of the Liver (EASL) criteria [17], or with biopsy samples of liver nodules. Each patient was evaluated regarding past medical history and complete blood tests. Pre-LT screening also included a psychiatric evaluation, an upper gastrointestinal endoscopy, a colonoscopy, assessment of pulmonary and cardio-circulatory functions. The severity of the underling liver disease was assessed via the Child-Pugh-Turcotte (CPT) classification and MELD score. If needed, HCC down-staging was performed with trans-arterial chemoembolization (TACE), radiofrequency ablation (RFA), or liver resection.

Antiretroviral treatment was continued until the day of surgery and restarted after LT once the patient was able to tolerate oral medication or via nasogastric tube if the patient remained mechanically ventilated or sedated for more than 48 h. HIV-positive and negative patients received the same immunosuppressive regimens and antimicrobial prophylaxis according to local protocols and international guidelines. DAA regimens were prescribed according to the EASL recommendations [18] even though treatment combinations changed over time according to drug availability (sofosbuvir was available for compassionate use since 2013, daclatasvir was available for compassionate use since December 2014; marketed sofosbuvir was available for clinical use since December 2014; thereafter, the other drugs were available after the approval by the European and Italian Medicine Agencies). The choice to treat before or after LT was taken according to drug availability, clinical conditions and at treating physician's discretion. To evaluate the impact of DAAs availability on survival, the study period was dichotomously divided in LT performed before and after 2015.

Demographic, virologic and biochemical parameters, clinical and liver pathology features of included subjects were retrieved from hospital electronic patient records. Data about alfa-fetoprotein levels, immune-virologic parameters, Eastern Cooperative Oncology Group (ECOG) performance status, Barcelona Clinic Liver Cancer (BCLC) stage, number and size of HCC lesions were collected from the last evaluation before LT. Macroscopic features of explanted livers were used to assess the MC fulfillment. Grading system was based on the conventional 3-scale that in our hospital is preferred to the traditional 4-scale Edmonson and Steiner system. Study population was stratified according to the presence of HIV infection. Since all HIV-positive LT recipients were Caucasian, HIV-negative individuals belonging to other races were excluded from the analysis to avoid possible confounding genetic-related factors.

The study was conducted in accordance with the ethical standards of the Helsinki Declaration. The data collected are part of the routine clinical management of LT recipients, so no specific local Ethics Committee approval was required. At enlisting, all patients signed a written informed consent to allow the use of their anonymized data for further clinical research.

Descriptive statistics (median and interquartile range [IQR] for continuous variables, absolute and relative [%] values for categorical variables) were used. Mann Whitney U for non-normally distributed and t-student for normally distributed continuous variables were applied to compare the groups. Chi-square and Fisher's exact tests were employed for categorical variables. Patient survival and cumulative incidence of HCC recurrence were calculated using the Kaplan Meier method; the curves obtained were compared using the log-rank test. Pre-, peri– and post-LT variables were assessed as predictors of outcomes using Cox proportional hazards models. The Cox proportional hazards assumption was assessed using the Breslow method to handle tied failures. Two-tailed p-values were calculated and a value <0.05 was considered statistically significant. Data management and analysis were performed using STATA package, version 16.1.

3. Results

In the study period, 329 LT were performed: after excluding 30 non-Caucasian subjects, 299 individuals resulted eligible for the analysis. They were mainly men (249, 83.1%), with a median age of 57 (IQR 52–63) years; 230 (76.9%) were HCV-Ab positive and 69 (23.1%) HBsAg positive. HCC was the indication for LT in 199 (66.6%) of cases. The median follow-up was 33 (IQR 11–57) months after LT. HIV co-infected individuals were 31 (10.4%): Table 1 shows demographic and clinical baseline features of the two groups.

Among HIV-infected subjects the median T lymphocyte CD4+ count was 368 (IQR 220–518) cells/mL, and none had a detectable HIV RNA. The majority was on treatment with tenofovir-based (either disoproxil fumarate or alafenamide, 51.6%) and integrase strand transfer inhibitors (INSTI, 64.5%).

HIV-positive individuals received more down-staging treatments before transplantation compared to HIV-negative ones (2.3 versus 1.8, $p = 0.004$). No difference was observed in terms of type of down-staging approach even though surgical resection tended to be less common in HIV-positive subjects (0% versus 20.4% in HIV-negative patients, $p = 0.189$). The overall mortality was 16.1% in HIV-infected and 19.0% in HIV-uninfected subjects ($p = 0.695$). Fig. 1 shows Kaplan Meier survival estimates for both groups. The probability of being alive 1, 3 and 5 years after LT was 92.3%, 81.8% and 74.4% versus 88.0%, 80.0% and 77.9%, respectively (overall log-rank 0.13, $p = 0.714$). Although the main causes of death were oncologic issues for HIV-positive (40.0%) and liver-related disease for HIV-negative patients (29.4%), no statistically significant differences between groups were observed ($p = 0.933$). Even stratifying according to LT indication, no difference was observed in terms of mortality (overall log-rank 0.22, $p = 0.640$, see Supplementary Materials Fig. 1). Table 2 shows Cox proportional hazards model for survival: factors associated to death were age, HCV genotypes other than 1a, calendar year of LT performance, extra-hepatic HCC, ECOG performance status and BCLC stage. HIV status had no impact on survival ($p = 0.339$).

Table 1
Baseline demographic, clinical and virologic features of study population.

		HIV-positive subjects ($N = 31$)	HIV-negative subjects ($N = 268$)	p
Age, years, median (IQR)		53 (50–56)	58 (53–63)	**<0.001**
Male sex, N (%)		26 (83.9)	223 (83.2)	0.926
BMI, median (IQR)		23 (21–25)	25 (23–28)	**0.001**
Viral hepatitis co-infection, N (%)	HBV	5 (16.1)	64 (23.9)	**0.018**
	HCV viremic	12 (38.7)	145 (54.1)	
	HCV in SVR	14 (45.2)	59 (22.0)	
HCV Genotype, N (%)	1a	11 (42.3)	29 (14.2)	**0.004**
	1b	5 (19.2)	88 (431)	
	2	–	14 (6.9)	
	3	6 (23.1)	57 (27.9)	
	4	4 (15.4)	16 (7.8)	
Alcohol intake, N (%)	No use	13 (41.9)	199 (74.3)	**<0.001**
	Moderate	13 (41.9)	21 (7.8)	
	Severe	5 (16.1)	48 (17.9)	
Diabetes, N (%)		4 (12.9)	82 (30.6)	**0.039**
Radiologic evidence of a single lesion, N (%)		7 (38.9)	72 (37.1)	0.882
Number of lesions for patients with radiologic evidence of >1 lesion, median (IQR)		2 (2–2.3)	3 (2–3)	0.080
AFP, ng/dL, median (IQR)		5.3 (3.5–12.8)	7.0 (3.5–17.7)	0.390
	AFP>100 ng/dL, N (%)	4 (12.9)	23 (8.6)	0.427
	AFP>300 ng/dL, N (%)	2 (6.5)	14 (5.2)	0.774
Time in waiting list, weeks, median (IQR)		18 (7–32)	18 (7–35)	0.682
Number of down-staging treatments, N (SD)		2.3 (1.2)	1.8 (0.9)	**0.004**
Type of down-staging approach, N (%)	TACE	14 (77.8)	106 (58.6)	0.135
	RFA	6 (33.3)	72 (39.8)	0.801
	Surgery	–	37 (20.4)	0.133
	No treatment	–	32 (17.7)	0.157
	Combined approach	5 (27.8%)	71 (39.2)	0.448
Calendar year of LT, median (IQR)		2016 (2014–2017)	2015 (2013–2017)	0.057
Indication for LT, N (%)	HCC	18 (58.1)	181 (67.5)	0.414
	ESLD	12 (38.7)	83 (31.0)	
	AFHF	1 (3.2)	4 (1.5)	
CPT score in patients undergoing LT for HCC, median (IQR)		7 (5–9)	6 (6–8)	0.697
MELD score in patients undergoing LT for HCC, median (IQR)		13 (9–17)	12 (9–15)	0.322
CPT score in patients undergoing LT for ESLD, median (IQR)		11 (10–11)	10 (9–11)	0.050
MELD score in patients undergoing LT for ESLD, median (IQR)		22 (16–31)	17 (16–24)	0.168
Classification according to the MC*, N (%)	Milano IN	19 (61.3)	183 (68.3)	0.431
	Milano OUT	12 (38.7)	85 (31.7)	
Grading*, N (%)	G1	4 (26.7)	26 (15.8)	0.418
	G2	9 (60.0)	98 (59.4)	
	G3	2 (13.3)	41 (24.8)	
Presence of portal thrombosis*, N (%)		6 (19.4)	37 (13.8)	0.405
Presence of extra-hepatic HCC*, N (%)		5 (16.1)	13 (4.9)	**0.012**
Vascular invasion*, N (%)		8 (53.3)	53 (32.1)	0.097
ECOG performance status, N (%)	0	9 (29.0)	74 (27.6)	**0.031**
	1	8 (25.8)	90 (33.6)	
	2	3 (9.7)	53 (19.8)	
	3	7 (22.6)	44 (16.4)	
	4	4 (12.9)	7 (2.6)	
BCLC Stage°, N (%)	A	15 (83.3)	99 (54.7)	0.106
	B	3 (16.7)	40 (22.1)	
	C	–	41 (22.7)	
	D	–	1 (0.6)	
Overall deaths, N (%)		5 (16.1)	51 (19.0)	0.695
	Deaths in subjects transplanted for ESLD, N (%)	2 (6.4)	21 (7.8)	0.724
	Deaths in subjects transplanted for HCC, N (%)	3 (9.7)	30 (11.2)	0.997
Causes of death, N (%)	Infective complications	1 (20.0)	8 (15.7)	0.933
	Oncologic progression	2 (40.0)	10 (19.6)	
	Liver-related complications	1 (20.0)	15 (29.4)	
	Surgical complications	–	7 (13.7)	
	Other	1 (20.0)	10 (19.6)	
T CD4+ lymphocyte cell count, cell/mmc, median (IQR)		368 (220–518)		
T CD4+ lymphocyte cell count,%, median (IQR)		33.1 (26.3–36.1)		
CD4/CD8 ratio, median (IQR)		0.69 (0.64–0.92)		
Undetectable HIV RNA, N (%)		31 (100)		
TXF-based regimens, N (%)		16 (51.6)		
NNRTI-based regimens, N (%)		1 (3.2)		
PI-based regimens, N (%)		3 (9.7)		
INSTI-based regimens, N (%)		20 (64.5)		
Other regimens, N (%)		7 (22.6)		

BMI: body mass index; SVR: sustained virologic response; AFP: alfa-fetoprotein; TACE: trans-arterial chemoembolization; RFA: radiofrequency ablation; HCC: hepatocellular carcinoma; ESLD: end-stage liver disease; AFHF: acute fulminant hepatic failure; CPT: Child Pugh Turcotte; MELD: model for end-stage liver disease; ECOG: Eastern cooperative oncology group; BCLC: Barcelona clinic liver cancer; TXF: tenofovir disoproxil fumarate or tenofovir alafenamide; NNRTI: non-nucleoside reverse transcriptase inhibitors; PI: protease inhibitors; INSTI: integrase strand transfer inhibitors.

* Data obtained after surgery and from explanted livers.

° Calculated on data available at the last clinical evaluation before LT.

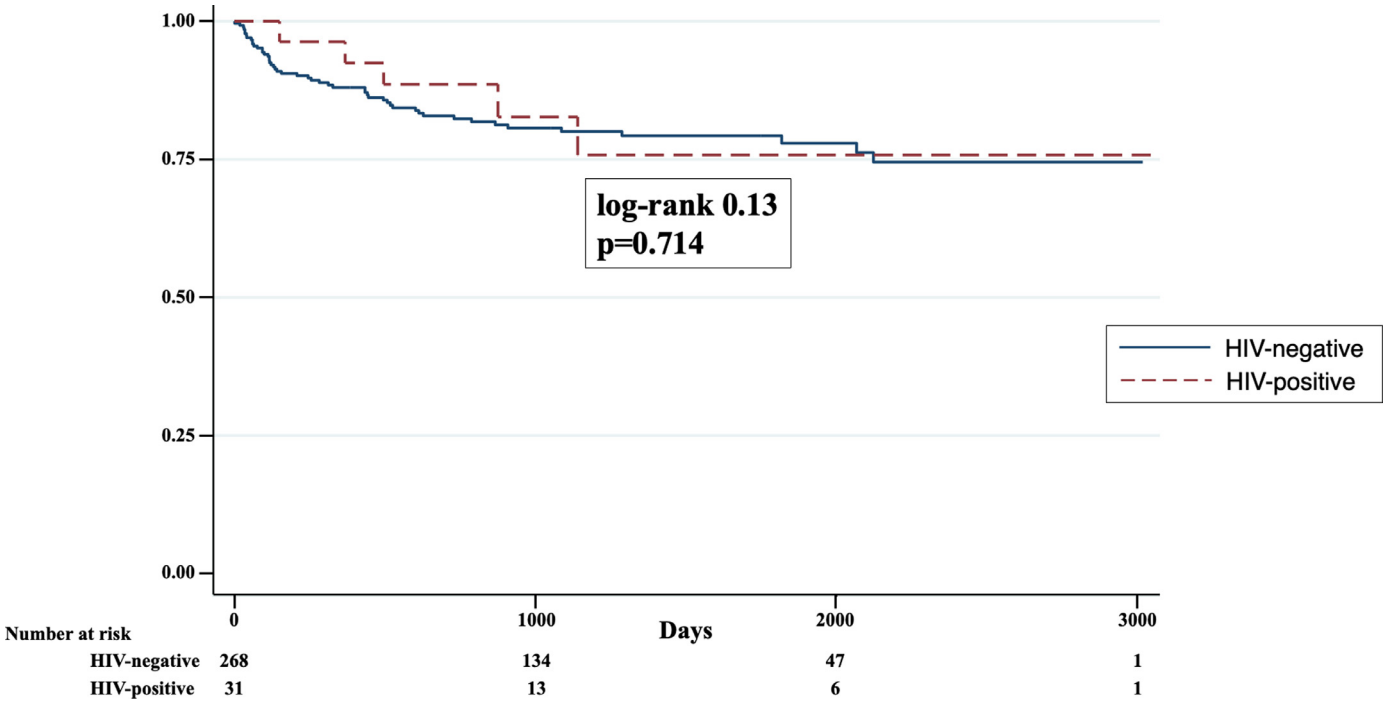

Fig. 1. Kaplan Meier survival estimates for HIV-positive and HIV-negative liver transplantation recipients.

Table 2
Cox proportional hazards model calculated for factors associated to overall mortality.

		HR	95% Confidence Interval	p	aHR*	95% Confidence Interval	*p*
HIV infection		0.842	0.336–2.109	0.713	0.310	0.028–3.415	0.339
Age		**1.041**	**0.999–1.084**	**0.051**	**1.114**	**1.013–1.224**	**0.025**
Male sex		0.985	0.497–1.952	0.965			
BMI		0.973	0.905–1.046	0.460	1.139	0.986–1.315	0.077
Diabetes		1.065	0.602–1.884	0.829	1.573	0.525–4.709	0.418
Alcohol use	No	ref			ref		
	Moderate	1.117	0.502–2.486	0.787	0.631	0.134–2.974	0.561
	Abuse	0.699	0.314–1.557	0.381	2.691	0.705–10.279	0.148
Viral co-infection	HBV	ref					
	Viremic HCV	1.338	0.699–2.562	0.787			
	HCV in SVR	0.549	0.205–1.467	0.231			
HCV genotype	1a	ref					
	1b	**1.129**	**0.528–2.415**	**0.755**	**0.250**	**0.069–0.910**	**0.035**
	2	1.075	0.291–3.973	0.913	0.734	0.101–5.356	0.761
	3	**0.284**	**0.087–0.922**	**0.036**	**0.201**	**0.045–0.899**	**0.036**
	4	0.409	0.088–1.895	0.253	0.000		
HCC as indication for LT vs ESLD/AFHF		0.714	0.413–1.236	0.229			
Calendar year of LT performance		**0.837**	**0.731–0.960**	**0.011**	**0.703**	**0.545–0.908**	**0.007**
Single HCC vs multiple lesions		0.818	0.396–1.687	0.586			
Number of HCC lesions on explanted livers		1.015	0.921–1.119	0.762			
Pre-LT alfa-fetoprotein value		1.000	0.999–1.003	0.145			
Time in the waiting list		0.995	0.985–1.006	0.389			
CPT classification		1.084	0.977–1.203	0.126			
MELD score		1.017	0.984–1.050	0.327			
Milan criteria OUT		0.923	0.527–1.618	0.780			
HCC Grade 1 vs grade 2–3		1.527	0.668–3.487	0.316			
Portal vein thrombosis		1.368	0.690–2.712	0.370			
Infiltration of surrounding hepatic tissue		0.816	0.438–1.519	0.521			
Extra-hepatic HCC		**2.603**	**1.231–5.503**	**0.012**	**10.672**	**2.005–56.804**	**0.006**
Vascular invasion		1.508	0.771–2.949	0.230			
ECOG Performance	0	ref					
Status	1	1.428	0.569–3.583	0.448	1.023	0.288–3.636	0.971
	2	**3.257**	**1.347–7.874**	**0.009**	**5.344**	**1.393–20.500**	**0.015**
	3	**2.825**	**1.139–7.007**	**0.025**	1.809	0.273–12.009	0.539
	4	**6.623**	**2.110–20.980**	**0.001**	**108.739**	**0.003–0.876**	**0.040**
BCLC Stage	1	ref					
	2	1.002	0.439–2.291	0.996	0.449	0.155–1.304	0.141
	3	0.554	0.188–1.630	0.283	0.334	0.083–1.355	0.125
	4	**4.723**	**1.096–20.352**	**0.037**	**0.048**	**0.003–0.875**	**0.040**

* Adjusted for HIV, age, BMI, diabetes, alcohol use, HCV genotype, calendar year of LT, extra-hepatic HCC, ECOG performance status, BCLC stage.BMI: Body Mass Index; SVR: Sustained Virologic Response; LT: liver transplantation; HCC: hepatocellular carcinoma; ESLD: end-stage liver disease; AFHF: Acute Fulminant Hepatic Failure; CPT: Child-Pugh-Turcotte; MELD: Model for End-stage Liver Disease; ECOG: Eastern Cooperative Oncology Group; BCLC: Barcelona Clinic Liver Cancer.

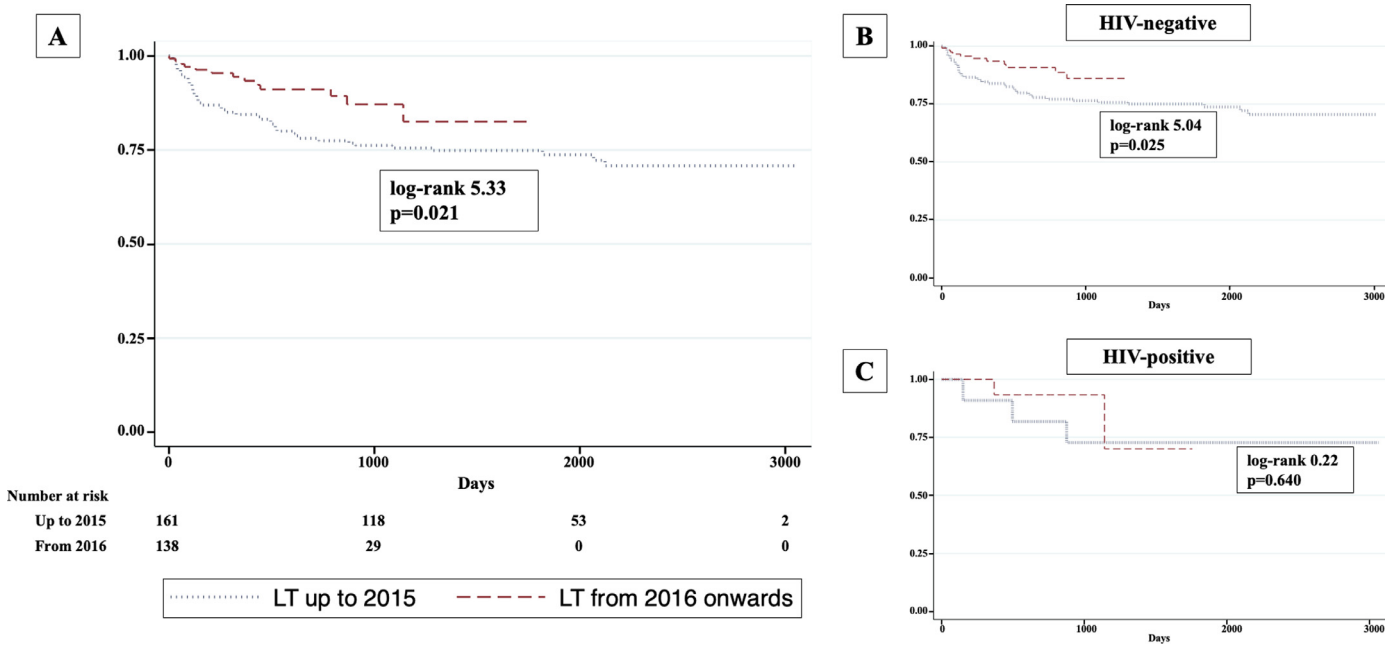

Fig. 2. Kaplan Meier survival estimates for liver transplantations performed up to 2015 versus from 2016 onwards (A) and stratified according to HIV status (B-C).

The overall mortality decreased from 26.7% in LT performed up to 2015 to 9.4% in those performed from 2016 onwards ($p < 0.001$). Kaplan Meier survival estimates according to calendar year of LT performance found that those who underwent LT up to 2015 had a worse likelihood to survive compared to those who were transplanted from 2016 onwards (log-rank 5.33, $p = 0.021$, Fig. 2). DAA availability had an impact on mortality for HIV-negative patients (from 26.7% to 9.3%, $p < 0.001$) but not for HIV-positive subjects (from 27.3% to 9.5%, $p = 0.233$).

HCC recurrence was observed in 6 HIV-positive (19.4%) and in 17 HIV-negative subjects (6.3%, $p = 0.022$). The rate of recurrence was 2.057 (95% CI 0.834–4.279) per 10,000 patients/year in HIV-infected subjects and 0.574 (95% CI 0.345–0.899) per 10,000 patients/year in HIV-negative individuals (incidence rate ratio 3.588, 95% CI 1.297–8.859, $p = 0.008$). The median time to relapse was 831 (IQR 715–1334) days in HIV-positive and 315 (IQR 219–489) days in HIV-negative patients ($p = 0.046$). Even after excluding those with extrahepatic HCC, time to recurrence was longer in HIV-positive than in HIV-negative subjects (752 versus 304 days, $p = 0.012$). Fig. 3 shows Kaplan Meier estimates for HCC recurrence in both groups. The probability of relapse 1, 3 and 5 years after LT was 4.0%, 16.1% and 33.9% in HIV-infected versus 5.4%, 7.7% and 7.7% in HIV-uninfected individuals (overall log-rank 9.06, $p = 0.003$). The Cox proportional hazards model found a significant role for HIV in univariate analysis (HR 3.047, 95% confidence interval 1.201–7.320, $p = 0.019$) but, after adjusting for all the variables included in the model, the infection was no more associated to relapse (aHR 0.662, 95% confidence interval 0.180–2.432, $p = 0.534$). Table 3 shows the results of the Cox proportional hazards model: the only factor associated to HCC recurrence — although with a wide confidence interval — was extra-hepatic tumor (aHR 56.379, 95% confidence interval 15.453–205.697, $p < 0.001$). Indeed, after excluding those with baseline extra-hepatic cancer, the rate of recurrence was 0.352 (95% CI 0.018–1.736) per 10,000 patients/year in HIV-infected subjects and 0.176 (95% CI 0.064–0.390) per 10,000 patients/year in HIV-negative individuals (incidence rate ratio 0.245, 95% CI 0.010–1.772, $p = 0.445$).

4. Discussion

The present study included a large sample of HIV-positive and negative recipients who underwent LT. As previously reported, the overall survival was similar regardless HIV status (around 75% at 5 years) [19] and is consistent with mortality data from recent published literature (see Supplementary Materials Table 1). Mortality was mainly associated to HCC recurrence and liver-related complications, while HIV-related immunodepression was not a significant concern for HIV-positive recipients. Of note, HIV-positive subjects enrolled in this study were mainly treated with INSTI, and had excellent immunologic and virologic conditions, so the differences in terms of interactions with immunosuppressive regimens and of infective complications were minimized.

The availability of safe and effective anti-HCV regimens allowed to treat patients with advanced liver disease and those on the waiting list for LT. Published literature proved that SVR achievement led to a noteworthy clinical improvement allowing the delisting of around 20−30% of patients with low risks of further liver-related complications [20,21], thus decreasing LT both in patients with HCV-related ESLD (by 60%) and HCC (by 41%). Furthermore, the overall survival of HCV-related LT recipients improved noticeably reaching results like what observed in HBV-infected recipients [22]. Several papers reported the efficacy and safety of pre-, peri– and post-transplantation anti-viral treatment [23–25], but no data are available about the impact of DAAs on survival of HIV/HCV co-infected LT recipients. Our study confirmed the decrease in mortality in the HIV-negative population but failed to see any improvement in HIV-positive subjects. This discrepancy should be attributed to the different timing of DAAs therapy: co-infected patients were mainly treated before LT and underwent surgery with undetectable HCV RNA (45.2%) while HIV-negative subjects were in SVR only in a small proportion (22.0%) and received DAAs afterwards. Thus, the beneficial effect of DAAs could not be observed because of the small number co-infected subjects who underwent LT with detectable HCV RNA.

HCC recurrence after LT is another main issue in HIV-positive recipients. The studies by Vibert et al. [26] and Di Benedetto

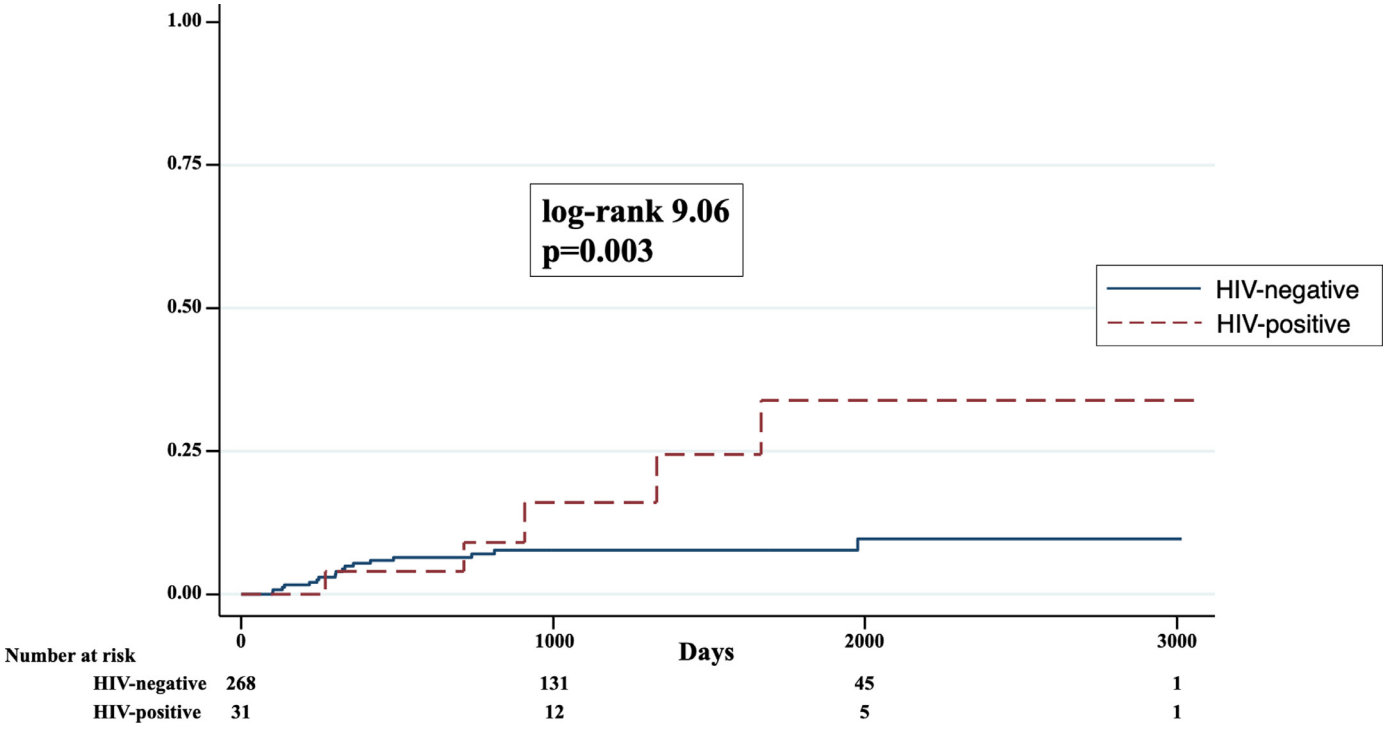

Fig. 3. Kaplan Meier estimates for hepatocellular carcinoma recurrence in HIV-positive and HIV-negative liver transplantation recipients.

Table 3
Cox proportional hazards model calculated for factors associated to hepatocellular carcinoma recurrence.

			HR	95% Confidence Interval	p	aHR*	95% Confidence Interval	p
HIV infection			**3.047**	**1.201–7.320**	**0.019**	0.662	0.180–2.432	0.534
Age			0.996	0.938–1.058	0.900			
Male sex			4.821	0.650–35.780	0.124			
Diabetes			0.508	0.172–1.494	0.218			
Viral co-infection	HBV		ref					
	Viremic HCV		0.567	0.228–1.410	0.222			
	HCV in SVR		0.591	0.176–1.986	0.395			
HCV genotype	1a		ref					
	1b		$7.17e^{-16}$	0	1			
	2		1.588	0.308–8.199	0.581			
	3		0.855	0.077–9.440	0.898			
	4		1.246	0.258–6.025	0.784			
Pre-LT alfa-fetoprotein value			**1.003**	**1.001–1.005**	**<0.001**	1.000	0.999–1.001	0.715
CPT classification			**0.742**	**0.592–0.929**	**0.009**	1.215	0.711–2.078	0.476
MELD score			**0.911**	**0.836–0.993**	**0.034**	0.955	0.760–1.200	0.690
Milan criteria OUT vs IN			**4.589**	**1.866–11.038**	**0.001**	0.668	0. 117–3.814	0.650
Single HCC vs multiple lesions			1.183	0.506–2.770	0.330			
Number of HCC lesions on explanted liver			**1.073**	**1.006–1.448**	**0.032**	0.971	0.714–1.320	0.850
HCC Grade 2–3 vs grade 1			$4.93e^{-16}$	0	1			
Portal vein thrombosis			1.797	0.667–4.842	0.247			
Infiltration of surrounding hepatic tissue			1.472	0.623–3.478	0.377			
Extra-hepatic HCC			**64.858**	**25.268–166.477**	**<0.001**	**56.379**	**15.453–205.697**	**<0.001**
Vascular invasion			**2.728**	**1.202–6.188**	**0.016**	1.498	0.285–7.874	0.633
BCLC Stage		A	ref			ref		
		B	0.707	0.230–2.173	0.545	2.045	0.452–9.261	0.353
		C	0.786	0.256–2.414	0.674	1.021	0.202–5.162	0.980
		D	**13.230**	**2.906–60.238**	**0.001**	1.624	0.211–12.503	0.641

* Adjusted for HIV, pre-LT alfa-fetoprotein value, CPT classification, MELD score, Milan criteria fulfillment, number of HCC lesions on explanted livers, extra-hepatic HCC involvement, vascular invasion and BCLC stage.SVR: Sustained Virologic Response; LT: liver transplantation; HCC: hepatocellular carcinoma; CPT: Child-Pugh-Turcotte; MELD: Model for End-stage Liver Disease; BCLC: Barcelona Clinic Liver Cancer.

et al. [27], characterized by a short follow-up of less than 3 years, showed relapse rates in HIV-positive subjects of 31% and 7%, respectively. The study by Agüero, with a follow up of 5 years, found a recurrence rate of 16% with microscopic vascular invasion and satellite nodules being the only factors associated to relapse [28]. All these studies failed to find any difference with the HIV-negative population. In contrast, we observed a higher incidence of HCC recurrence in HIV-positive subjects, with a significantly longer time-to-recurrence compared to the HIV-negative counterpart: it might be speculated that our longer follow up, which reached 8 years, allowed to highlight a delayed phenomenon. HIV infection was associated to HCC relapse in univariate analysis, but the statistical significance was not confirmed after adjusting for all the variables included in the model. Indeed, tumor burden played the main role:

HIV-positive subjects showed more commonly an extra-hepatic HCC involvement that seemed to be the most important determinant of recurrence. A different oncogenic pathway for the development of HCC in HIV-infected cirrhotics was speculated since they show a risk of developing hepatic cancer four-fold higher than the general population [29]. These mechanisms might partially persist despite HCV eradication leading to HCC development over a longer time. Consequently, some authors recommended specific surveillance protocols for early detection and treatment of HCC recurrence [30,31].

This study has several limitations. First, the retrospective nature of the analysis may suffer from several weaknesses such as selection bias and misclassification or information bias. Secondly, study population is large, but the size of HIV-infected patients is relatively small — although comparable to existing literature — thus the power of the statistical analyzes might be limited. For instance, the numbers of acute graft rejections and re-transplantations were small in both groups so these variables could not be included in Cox proportional hazards models. Indeed, the impact of the large use of INSTI with minor drug-drug interactions with immunosuppressive regimes could not have been appreciated. With relatively small numbers of events and many factors evaluated in regression models, over-fitting could be a concern. Additionally, the two samples were not homogeneous so we could not control for all the possible exposures such as co-morbidities and concomitant medications, not allowing to ascertain confounding effects of other diseases on outcomes. Lastly, the long interval of time included in the analysis encompassed the availability of different antiretrovirals and DAAs, and variations in immunosuppressive drugs management, so some features that changed over time were difficult to assess.

Long-term rates of survival in HIV-infected patients undergoing LT are satisfactory and comparable to those observed in HIV-negative patients. Nevertheless, the recurrence of HCC seems higher although delayed. Further studies are required to clarify this issue. Additional studies including more sites and a larger population of HIV-positive individuals are required to confirm these observations. Hence, HIV-infected patients are suitable candidates for LT but surveillance protocols for early detection of HCC recurrence should be kept attentive for a long time after transplantation.

Declaration of Competing Interest

none of the Authors has conflicts of interests to declare.

CRediT authorship contribution statement

Roberto Rossotti: Resources, Formal analysis, Data curation, Writing – original draft. **Marco Merli:** Writing – original draft, Supervision. **Chiara Mazzarelli:** Supervision. **Riccardo Maria De Carlis:** Visualization. **Giovanna Travi:** Resources, Supervision, Supervision. **Marta Vecchi:** Supervision. **Raffaella Viganò:** Supervision. **Andrea Lauterio:** Visualization. **Alessandro Raimondi:** Supervision. **Luca Saverio Belli:** Supervision, Writing – review & editing. **Luciano Gregorio De Carlis:** Visualization. **Massimo Puoti:** Methodology.

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Data availability statement

All the anonymized data used to perform this analysis will be available for any further revision.

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Supplementary materials

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