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P-640. HIV Infection Does Not Worsen Prognosis of Liver Transplantation in Patients With Hepatocellular Carcinoma

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Background: Small series of liver transplantation (LT) in HIV-infected patients with hepatocellular carcinoma (HCC) have been reported in recent years. However, data on recurrence of HCC and survival after LT are limited and controversial. The aim of this study was to assess the impact of HIV on clinical outcome in patients undergoing LT for HCC.

Methods: Prospective cohort study of HIV-infected patients with HCC who received LT at 22 Spanish centres (FIPSE cohort) and were matched with non–HIV-infected LT recipients (1:3 ratio). The study started in 2002, and follow-up ended in July 2014. The matched criteria were age, gender, calendar year of LT, HCV or HBV coinfection, and HCC. The main outcomes were recurrence of HCC and survival. Patients with incidental HCC were excluded.

Results: In total, 74 HIV-infected patients and 222 non–HIV-infected patients underwent LT for HCC. Most were men (86%) and had HCV infection (92%). HIV-infected patients were younger (47 vs 51 y) and the frequency of HCV replication at LT was lower (80% vs 90%) than in HIV-negative patients. At LT, median (IQR) CD4 cells/mm^3 was 347 (238-523) and most HIV-infected patients (96%) were on antiretroviral therapy. HIV plasma viral load was <50 copies/mL in 93%. No differences were seen between HIV-infected and non–HIV-infected recipients in the pathological characteristics of HCC in the explanted liver (Table). After a median of 46 (25-72) months of follow-up, recurrence was recorded in 12 (16%) HIV-infected patients and 32 (14%) HIV-negative patients, Recurrence at 1, 3, and 5 years (Kaplan-Meier estimates) for HIV-infected patients vs non–HIV-infected patients was 7% vs 5%, 17% vs 11%, and 20% vs 19%, respectively (p=0.876), with a similar rate of recurrence: 0.229 and 0.266 person-year, respectively. The incidence rate ratio was 0.86 (95% CI, 0.66-1.12). In the whole series, microscopic vascular invasion (HR, 3.79 95% CI, 1.67-8.57) was the only factor independently associated with recurrence of HCC. Survival at 1, 3, and 5 years for HIV-infected patients vs non–HIV-infected patients was 87% vs 89%, 78% vs 78%, and 69% vs 73% (p=0.905). HCV coinfection (HR, 8.85 95% CI, 1.23-63.64) and satellite nodules (HR, 1.92 95% CI, 1.13-3.24) were the variables independently associated with mortality.

Conclusions: HIV-infection did not have any impact on recurrence of HCC or survival after LT. These results support the indication of LT in HIV-infected patients with HCC.

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BACKGROUND

Data illustrating the impact of HIV infection on the main outcomes of LT (survival and recurrence of HCC) in HIV-infected liver recipients are scant and controversial.

OBJECTIVE

To assess the outcome of a large cohort of HIV-infected patients who underwent LT for HCC, in comparison with a matched control cohort of non–HIV-infected patients.

PATIENTS AND METHODS

- Spanish nationwide prospective multicenter cohort study of all HIV-1-infected patients who underwent LT for HCC matched with non–HIV-infected LT recipients (1:3 ratio).
- The criteria for LT and HCC were the same as for non–HIV-infected patients.
- Study period: 2002-2014
- Variables: Sociodemographic, HIV (stage, CD4 cell count, plasma HIV-1 RNA viral load, ART), liver disease (etiology, HCC, MELD, AFP, radiological features), and LT characteristics at baseline and at follow-up were collected using a standardized CRF.

HIV inclusion criteria for primary LT in Spain

Previous C events	
- Opportunistic infections	Tuberculosis, *Pneumocystis jiroveci* pneumonia, or esophageal candidiasis
- Neoplasms	No
CD4 cell count/mm^3	>100 §
Plasma HIV-1 RNA VL BDL on cART*	Yes
Drug abuse	No heroin or cocaine abuse for >2 years; No alcohol abuse for >6 months

§ Patients with previous OIs had to have >200 CD4 cells/mm^3; *If plasma VL was detectable, post-OLT suppression with HAART was envisaged in all patients; BDL, below detection limit.

HCC inclusion criteria for LT

Milan Criteria (Mazzafero *et al*., 1996)
Single tumor ≤ 5 cm
2-3 nodules, none exceeding 3 cm
No vascular invasion and/or extrahepatic spread
UCSF* Criteria (Yao *et al*, 2001)
Single tumor ≤ 6.5 cm
2-3 nodules, none exceeding 4.5 cm with total nodule diameter ≤ 8 cm
No vascular invasion and/or extrahepatic spread

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STATISTICAL ANALYSIS

- Comparisons between continuous variables: Mann-Whitney test. Comparisons between categorical variables: chi-square or Fisher exact test.
- Survival analyses: start date = date of LT and HCC recurrence. Death from any cause = failure. Survival time estimated using the Kaplan-Meier method; curves compared using log-rank test.
- Pre- and peritransplant variables assessed as predictors of outcomes using univariate and multivariate Cox proportional hazards models. Variables associated with a *P* value <0.10 in the univariate analysis considered candidate predictors for the multivariate analyses
- Statistical significance set as a 2-tailed *P* value <0.05.

Characteristics of HIV+ and HIV-LT recipients with HCC (1)

	HIV+ N=74	HIV– N=222	*P* value
Pre-LT characteristics			
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	14	36	0.591
Undetectable HCV RNA at LT	13 (20)	19 (9)	0.026
MELD score at listing for LT*	12 (7,17)	12 (7,17)	0.225
MELD score at LT*	12 (7,17)	13 (8,18)	0.126
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

*Mean and standard deviation; ** Percentages for patients with HCV infection and known/determined genotype: ***Median and interquartile range

Characteristics of HIV+ and HIV-LT recipients with HCC (2)

	HIV+ N=74	HIV– N=222	*P* value
Transplant characteristics			
Transplant period 2002-2006 2007-2012	 18 (24) 56 (76)	 47 (21) 175 (79)	0.570
Donor age (years)*	54 (37,71)	52 (34,70)	0.473
Initial immunosuppressive regimen			
- Tacrolimus-based	54 (73)	173 (82)	0.114
- Cyclosporine-based	20 (27)	39 (18)	
- mTOR based	0	5 (2)	NA

*Mean and standard deviation
LT, liver transplantation; HCC, hepatocellular carcinoma; NA, not applicable.

Characteristics of the tumor in HIV+ and HIV-LT recipients with HCC (1)

	HIV+ N=74	HIV– N=222	*P* value
At the time of listing for LT			
Radiological data			
Single nodule	41 (58)	141 (65)	0.293
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*	11 (6;37)	11 (5;39)	0.991
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
At the time of LT			
AFP*	11 (5;48)	10 (5;31)	0.804

*Median and interquartile range;
LT, liver transplantation; HCC, hepatocellular carcinoma; UCSF, University of California San Francisco; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; AFP, alphafetoprotein.

Characteristics of the tumor in HIV+ and HIV-LT recipients with HCC (2)

	HIV+ N=74	HIV– N=222	*P* value
Explanted liver			
Single nodule	30 (41)	97 (45)	0.553
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
Edmonson grade			
Well differentiated	20 (34)	77 (46)	0.263
Moderately differentiated	26 (44)	61 (37)	
Poorly differentiated/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;
LT, liver transplantation; HCC, hepatocellular carcinoma; UCSF, University of California San Francisco.

Post-transplant outcome in HIV+ and HIV-LT recipients with HCC (1)

	HIV+ N=74	HIV– N=222	P value
Follow-up (months) *	48 (31;78)	44 (24;71)	0.187
Mortality	25 (34)	64 (29)	0.421
Cause of death			
HCC recurrence	8 (32)	17 (27)	0.394
HCV recurrence	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

*Median and interquartile range;
LT, liver transplantation; HCC; hepatocellular carcinoma; NA, not applicable.

Post-transplant outcome in HIV+ and HIV-LT recipients with HCC (2)

	HIV+ N=74	HIV– N=222	*P* value
HCC recurrence	12 (16)	32 (14)	0.706
Site of recurrence			
Intrahepatic	2 (3)	4 (2)	0.629
Extrahepatic	7 (9)	15 (7)	
Both	3 (4)	13 (5)	
Time since LT*	21 (12;33)	20 (9;41)	0.192
Treatment for HCC recurrence			
RFA	1 (1)	2 (1)	0.738
TACE	1 (1)	5 (2)	0.634
PEI	1 (1.4)	1 (0.5)	0.413
Sorafenib	3 (4)	13 (6)	0.553
mTOR inhibitors	7 (9)	14 (6)	0.360

*Median and interquartile range

LT, liver transplantation; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; PEI, percutaneous ethanol injection.

Univariate and multivariate analysis of mortality in LT recipients with HCC

	Crude HR	*P* value	Adjusted HR	*P* value
Pre-LT characteristics				
HCV infection*	9.02 (1.26;64.78)	0.029	7.79 (1.07;56.82)	0.043
Explanted liver				
Maximum nodule diameter >3 cm*	1.69 (1.09;2.63)	0.020	1.72 (1.02;2.89)	0.043
Microscopic vascular invasion*	1.78 (1.06;2.97)	0.028		
Satellite nodules*	1.89 (1.12;3.18)	0.017		
Moderately/Poorly differentiated/ Undifferentiated Edmonson grade*	1.59 (0.97;2.62)	0.065		

*Variables associated with a *P* value <0.10 in the univariate analysis were considered candidate predictors for the multivariate analyses.

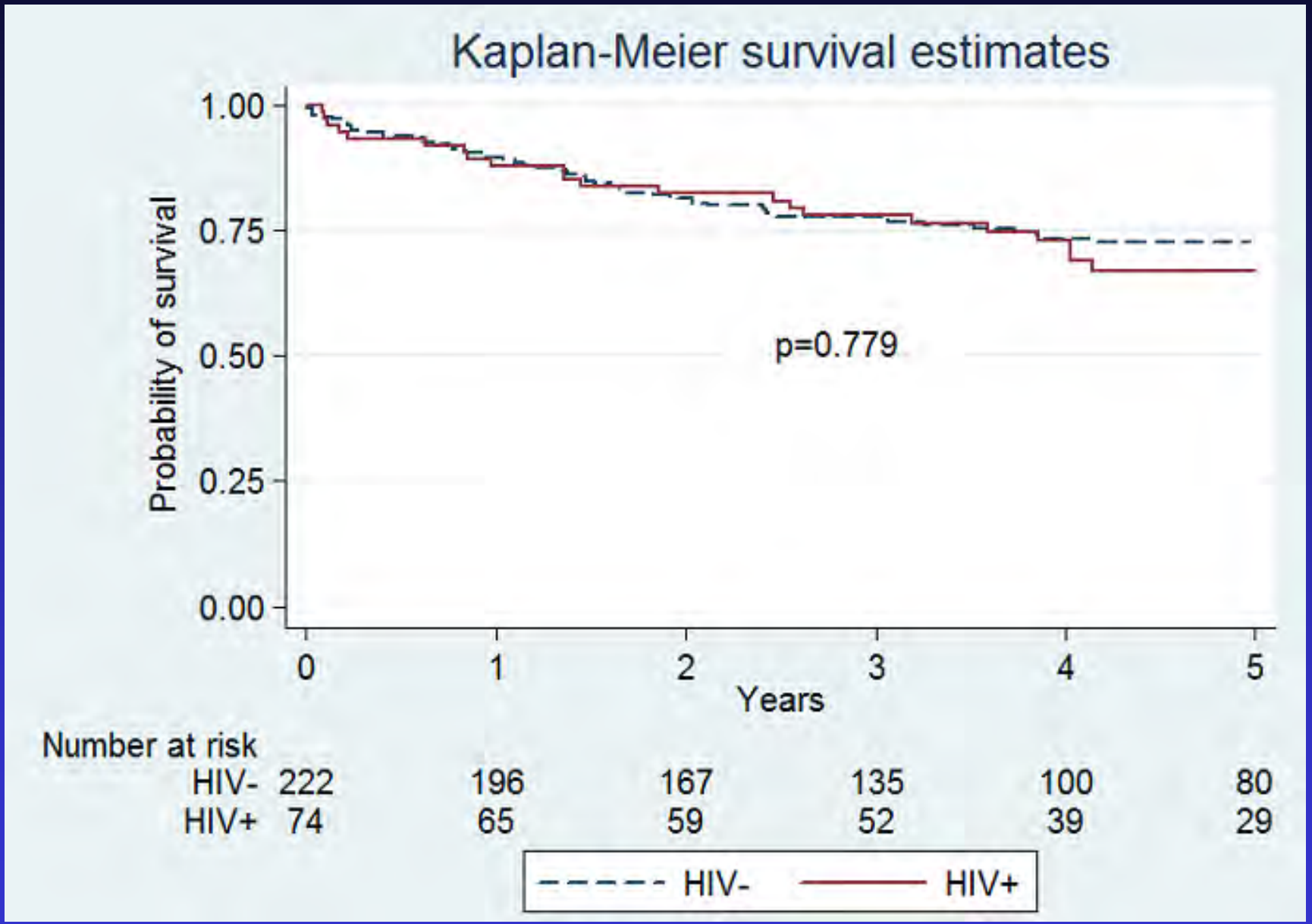
LT, liver transplantation; HCC, hepatocellular carcinoma; AFP, alphafetoprotein; UCSF; University of California San Francisco.

Univariate and multivariate analysis related to HCC recurrence in LT recipients with HCC

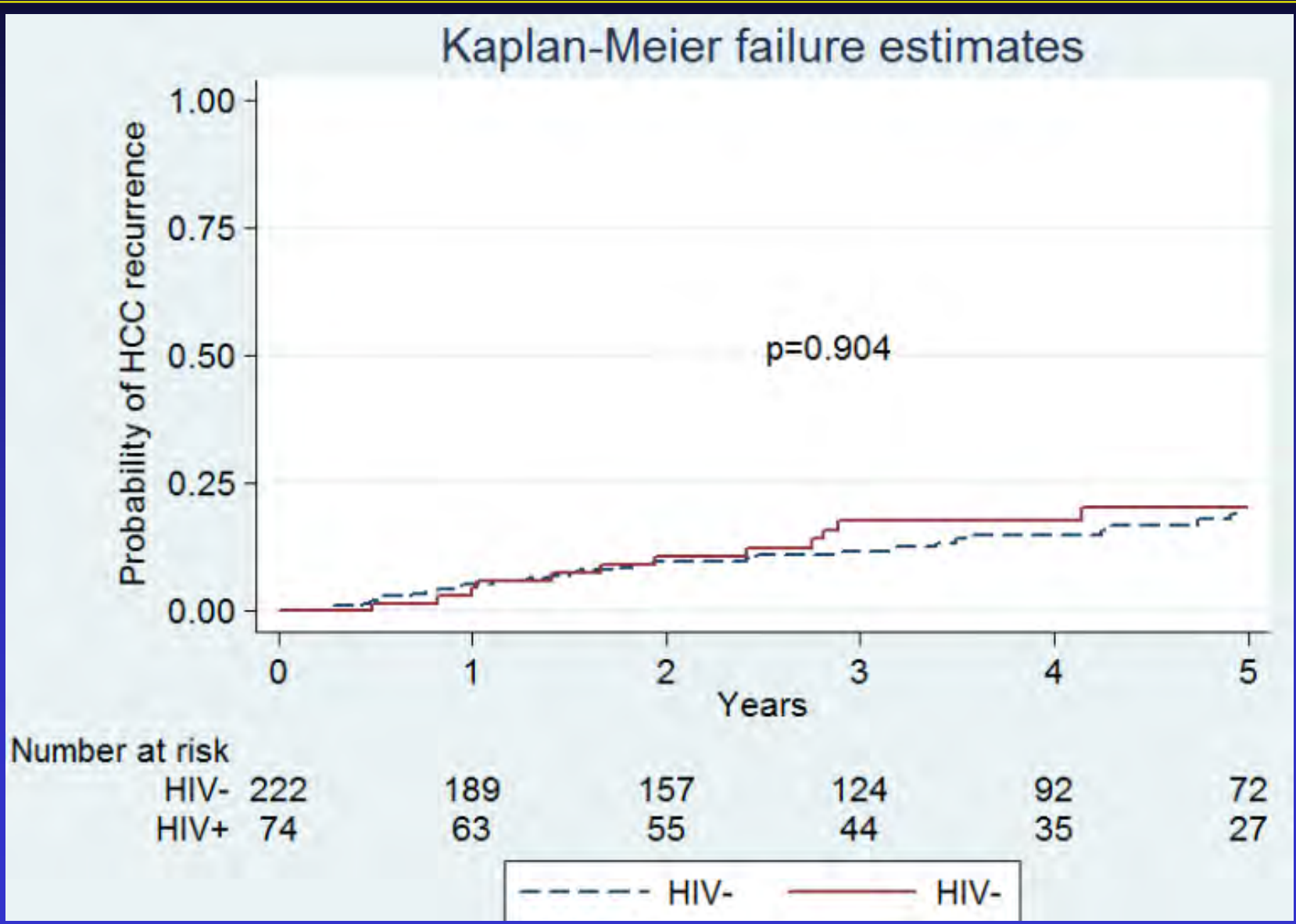
	Crude HR	*P* value	Adjusted HR	*P* value
Explanted liver				
Maximum nodule diameter >3 cm	2.90 (1.57;5.30)	0.001		
Microscopic vascular invasion	6.61 (3.39;12.92)	<0.001	3.40 (1.34;8.64)	0.010
Macroscopic vascular invasion	4.97 (1.94;12.74)	0.001		
Satellite nodules	3.43 (1.77;6.63)	<0.001		
Moderately/Poorly differentiated/ Undifferentiated Edmonson grade	2.43 (1.13;5.22)	0.022		
Outside Milan criteria	1.89 (1.02;3.51)	0.042		
Outside UCSF criteria	2.14 (1.11;4.12)	0.023		

*Mean and standard deviation; **Median and interquartile range
LT, liver transplantation; HCC, hepatocellular carcinoma; UCSF, University of California San Francisco.

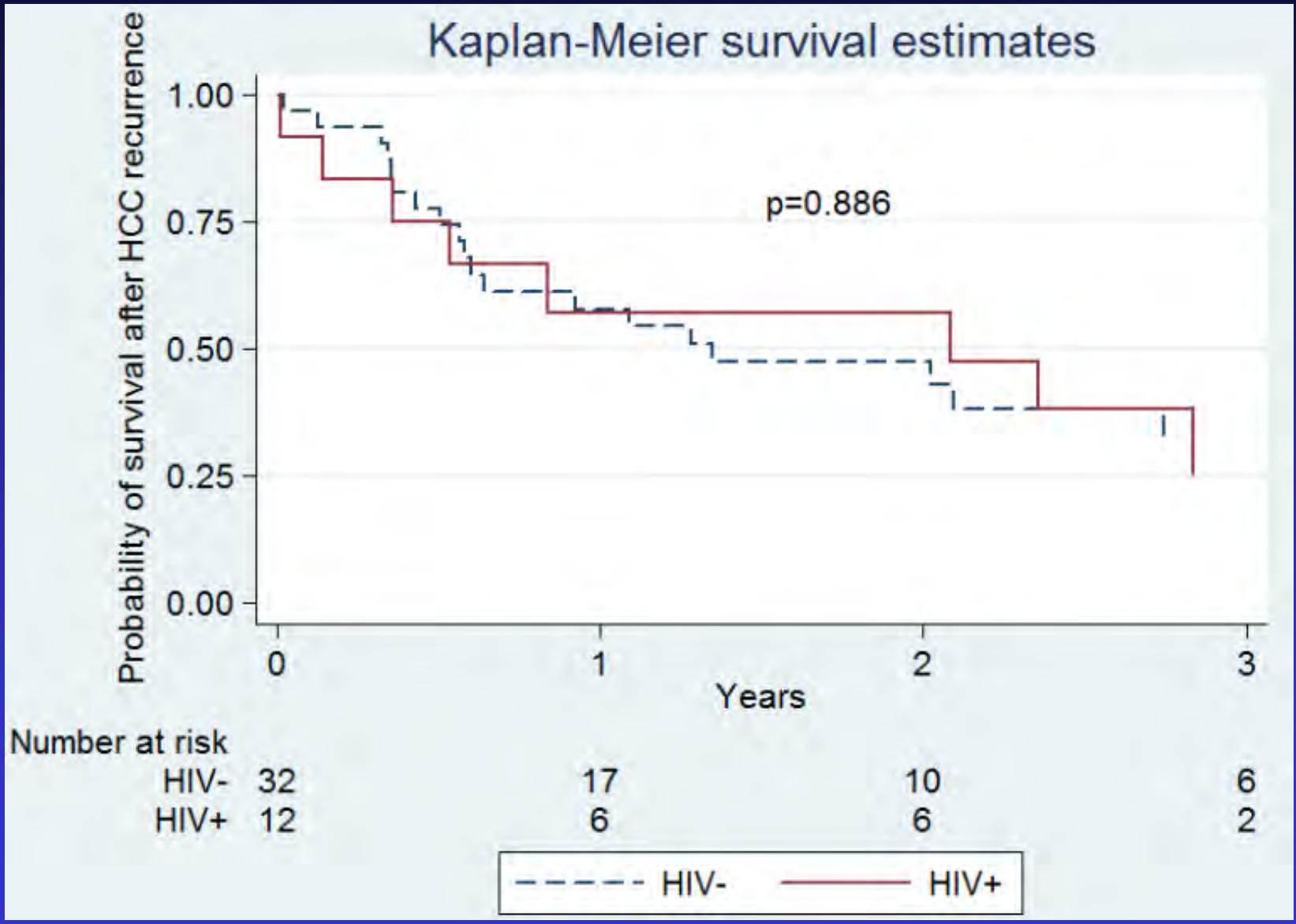
Post-LT patient survival rate according to HIV status



Cumulative incidence of HCC recurrence after LT according to HIV status



Patient survival rate after HCC recurrence according to HIV status



CONCLUSIONS

- Largest multicenter cohort of HIV-infected patients undergoing LT for HCC with the longest follow-up to date.
- HIV-infected LT recipients with HCC achieved satisfactory outcomes with rates of survival and HCC recurrence similar to those of non–HIV-infected controls.
- HCV infection and maximum nodule diameter >3 cm in the explanted liver identified as independent predictive factors for mortality.
- Microvascular invasion associated with an increased risk of HCC recurrence.
- HIV infection per se not a predictor of death or HCC recurrence.
- Results support the indication of LT in HIV-infected patients with HCC.

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