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Outcome of HCV/HIV-Coinfected Liver Transplant Recipients: A Prospective and Multicenter Cohort Study

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Eighty-four HCV/HIV-coinfected and 252-matched HCV-monoinfected liver transplant recipients were included in a prospective multicenter study. Thirty-six (43%) HCV/HIV-coinfected and 75 (30%) HCV-monoinfected patients died, with a survival rate at 5 years of 54% (95% CI, 42–64) and 71% (95% CI, 66 to 77; p = 0.008), respectively. When both groups were considered together, HIV infection was an independent predictor of mortality (HR, 2.202; 95% CI, 1.420–3.413 [p < 0.001]). Multivariate analysis of only the HCV/HIV-coinfected recipients, revealed HCV genotype 1 (HR, 2.98; 95% CI, 1.32–6.76), donor risk index (HR, 9.48; 95% CI, 2.75–32.73) and negative plasma HCV RNA (HR, 0.14; 95% CI, 0.03–0.62) to be associated with mortality. When this analysis was restricted to pretransplant variables, we identified three independent factors (HCV genotype 1, pretransplant MELD score and centers with <1 liver transplantation/year in HIV-infected patients) that allowed us to identify a subset of 60 (71%) patients with a similar 5-year prognosis (69% [95% CI, 54–80]) to that of HCV-monoinfected recipients. In conclusion, 5-year survival in HCV/HIV-coinfected liver recipients was lower than in HCV-monoinfected recipients, although an important subset with a favorable prognosis was identified in the former.

Key words: HCV infection, HIV infection, Liver Transplantation, Spain, Survival

Abbreviations: AIDS, acquired immunodeficiency syndrome; cART, highly active combined antiretroviral therapy; CI, confidence interval; CMV, cytomegalovirus; FIPSE, Spanish Foundation for the Investigation and Prevention of Acquired Immunodeficiency Syndrome; GESIDA, Spanish Group for the Study of Acquired Immunodeficiency Syndrome; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IQR, interquartile range; OLT, orthotopic liver transplantation; MELD, Model for End Stage Liver Disease; MSM, men who have sex with men; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitors; SVR, sustained virological response.

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Introduction

The life expectancy of patients infected by the human immunodeficiency virus type-1 (HIV) has improved dramatically since the introduction of combined antiretroviral treatment (cART) in 1996 (1). However, HIV-infected patients are currently dying of non–AIDS-defining events, especially liver disease related mainly to hepatitis C virus (HCV) infection (2–4). Consequently, orthotopic liver transplantation (OLT) is increasingly necessary in this population (5). At present, HIV-infection is not an absolute contraindication for OLT (6), and this life-saving intervention is performed in most developed countries in selected HIV-infected patients with end-stage liver disease.

In the cART era, excellent results have been achieved with OLT in HIV-infected patients with liver diseases not

related to HCV (7–9); however, results in HCV/HIV-coinfected patients are poorer than those obtained in HCV-monoinfected patients (9–11). Published studies usually analyze small case series from single institutions and have relatively short follow-up periods. Cohort studies involving large series are in progress in several European countries and the United States.

In Spain, the first OLT in an HIV-infected patient was performed in 2002 (12). Since then, most Spanish liver transplant units have been performing OLT in this group, leading to the creation of a sizeable cohort, on which this study is based. Our objectives were to compare post-OLT survival between HCV/HIV-coinfected patients and HCV-monoinfected patients and to identify prognostic factors in HCV/HIV-coinfected patients.

Methods

Study design

This is a prospective, multicenter cohort study including 84 consecutive HCV/HIV-coinfected patients who underwent OLT between 2002 and 2006 in 17 centers in Spain and who were followed until July 2010. HIV-infected recipients were matched with 252 HCV-monoinfected patients (1:3 ratio) who underwent OLT during the same period at the same sites. Other matched criteria were calendar year (±1 year), age (±12 years), gender, presence of HBV coinfection and presence of hepatocellular carcinoma (HCC). The study was approved by the Institutional Review Boards of all the participating sites. All patients signed the informed consent form.

Definitions, data collection, data entry and data management

For each patient, pre-, peri- and post-OLT variables listed in Table 1 were collected. The donor risk index, a score derived from seven donor variables (Table 2) that helps to estimate the influence of donor characteristics on patient and graft outcome after transplantation, was calculated according to the criteria of Feng et al. (13). All variables were collected at each site using a standardized case report form. Information for each patient was recorded at registration on the OLT waiting list, every 3 months until OLT, and at OLT. After OLT data were recorded at 1, 3, 6, 9, 12, 15, 18, 24, 30, 36 months and annually thereafter for up to 10 years. Patient information was sent every 6 months to the coordinating center and entered into the FIPSE OLT-HIV-05-GESIDA 45–05 database (available at https://www.seif88.com/gesida/asp/login.asp). Two data entries were made per patient, and queries and missing data were sent periodically to local investigators for resolution. An audit was performed at all participating sites by checking information from patients selected at random. Overall, the error and missing data rates were less than 5% per site.

The definitions of HIV, HCV and HBV infections, AIDS-defining events (14) and bacterial, fungal and viral infectious and other posttransplant complications were based on standard criteria (15,16). Severe infections were defined as follows: any bacterial infection with bacteremia, pneumonia, intraabdominal and/or central nervous system involvement, invasive fungal infection, cytomegalovirus disease, any invasive viral infection and mycobacterial disease. As habitually in the setting of liver transplantation, the transplant activity of the participating centers was based on the number of transplants performed per year in HIV-infected patients and was considered low if the center performed less than 1 per year.

Data for HIV-negative recipients were obtained from the Spanish Liver Transplant Registry. Variables not included in the registry were collected at the participating sites according to a common protocol. Data were managed and analyzed blind at the coordinating center.

Transplant criteria

HIV-infected patients had to fulfill the following criteria according to their infection status (17): no AIDS-defining events except tuberculosis, esophageal candidiasis, or *Pneumocystis jiroveci* pneumonia, CD4+ T cell count >100 cells/μL (>200 cells/μL in cases with a history of opportunistic infection) and a plasma HIV-RNA viral load that was undetectable or suppressible with cART. Former intravenous drug users had to have abstained from heroin or cocaine use for more than 2 years. The minimum period of abstinence for alcohol was 6 months. As for liver disease, the criteria for accepting HIV-infected patients for transplantation were the same as those followed in Spain for HIV-negative patients: a minimum Child-Turcotte-Pugh score of 7 for patients with cirrhosis, and, for patients with HCC, 1 tumor of <5 cm or 2–3 tumors of <3 cm in the absence of hepatic macrovascular tumoral invasion and extrahepatic metastases.

Posttransplant management

Combined antiretroviral therapy was administered until the day of surgery and resumed once the patient was stable and oral intake was reintroduced. Antiretroviral drugs were administered according to national guidelines (18).

HIV-infected recipients received the same immunosuppressive regimens as HIV-negative patients according to local protocols. Rejection was diagnosed according to the Banff criteria (19). Post-OLT and HIV infection antimicrobial prophylaxis were administered according to national guidelines (20,21).

During follow-up, liver biopsies were performed according to the protocols of each center and were mostly annual or biannual. Fibrosing cholestatic hepatitis (FCH) was defined according to standard histologic criteria (22). In chronic hepatitis, fibrosis stage was established according to the METAVIR system (23). Severe graft fibrosis was defined as the development of FCH or stage F3/F4 fibrosis as assessed by the METAVIR score. HCV recurrence was treated with pegylated interferon α-2a or α-2b and ribavirin and was based on the same criteria for HCV monoinfected OLT recipients according to local protocols. Sustained virological response (SVR) was defined as a persistently negative plasma HCV-RNA viral load at 24 weeks of follow-up after the end of treatment.

Statistical analysis

Variables are expressed as the mean and standard deviation, median and interquartile range (IQR), or as proportions, as appropriate. Patient and graft survival and time to severe graft fibrosis were analyzed with the date of transplantation as the start date. Survival time from OLT was estimated using the Kaplan-Meier product-limit method; the curves obtained in different groups were compared using the generalized log-rank test (univariate Cox model analysis). Predictors associated with a p value <0.10 in the univariate analysis were considered as candidate predictors for the multivariate analyses. We used both forward stepwise and backward elimination subset selection methods to identify variables that predicted survival. The significance level for entering effects was <0.1 and the significance level for removing effects was 0.05. The hazard ratio (HR) and the associated 95% confidence interval (CI) for each predictor were calculated. Statistical significance was defined as a bilateral p value <0.05. All statistical analyses were carried out using the Stata package (release 9.2).

Results

The annual distribution of OLT in HCV/HIV-coinfected patients and the number of cases per center are depicted in Figures 1(A) and (B). Pre-, peri- and postoperative

Table 1: Main characteristics of HCV/HIV-coinfected liver transplant recipients and risk donors

	All cases	Survivors	Dead	p-Value
No. of cases	84	48	36	
Pretransplant variables				
Age (year)[1]	42(39; 45)	42(39; 45)	41(39; 46)	0.8191
Male recipients, n (%)	64(76%)	36(75%)	28(78%)	0.5431
Caucasian race, n (%)	82(98%)	47(98%)	35(97%)	0.9059
Body mass index	24(22; 26)	24(22; 27)	23(21; 26)	0.4487
HIV-1 risk factors, n (%)				0.5367
Drug use	63(75%)	37(77%)	26(72%)	
MSM	2(2%)	1(2%)	1(3%)	
Heterosexual relations	10(12%)	3(6%)	7(19%)	
Hemophilia	4(5%)	3(6%)	1(3%)	
Other	4(4%)	3(6%)	1(3%)	
Duration of HIV-1 infection (mo)	157(116; 200)	164(121; 208)	139(108; 191)	0.9165
AIDS-defining events[2], n (%)	17(20%)	8(17%)	9(25%)	0.4813
Fulfill HIV inclusion criteria[3], n (%)	74(88%)	43(90%)	31(86%)	0.6925
HBV coinfection, n (%)	13(15%)	12(25%)	1(3%)	0.0419
Duration of HCV infection (mo)	97(52; 181)	91(50; 181)	99(65; 172)	0.9165
HCV genotype, n (%)				0.0681
1	46(55%)	20(42%)	26(72%)	
2	3(4%)	1(2%)	2(6%)	
3	16(19%)	12(25%)	4(11%)	
4	12(14%)	8(17%)	4(11%)	
Other	3(4%)	3(6%)		
Nontypable/others	4(5%)	4(8%)		
Plasma HCV RNA viral load U $\times$ 10^6/mL	5.67(5.16; 6.20)	5.52(4.36; 5.91)	5.85(5.50; 6.30)	0.007
Negative plasma HCV RNA viral load before OLT, n (%)	7(8%)	6(13%)	1(3%)	0.2497
Hepatocellular carcinoma, n (%)	15(18%)	9(19%)	6(17%)	0.9152
Child-Turcotte-Pugh class at listing, n (%)				0.0344
A	10(12%)	8(17%)	2(6%)	
B	38(45%)	25(52%)	13(36%)	
C	35(42%)	14(29%)	21(58%)	
MELD score at listing[4]	15(11; 18)	14(11; 16)	17(12; 20)	0.0259
MELD score before OLT[4]	16(12; 19)	14(11; 17)	18(13; 21)	0.0072
Delta MELD	0(1; −2)	0(2; −2)	−0.5(0.5; −4)	0.2147
Type of cART, n (%)				0.8210
NRTI-based	11(13%)	6(13%)	5(14%)	
PI-based	21(25%)	13(27%)	8(22%)	
Efavirenz-based	37(44%)	20(42%)	17(47%)	
Other regimens	15(18%)	9(19%)	6(17%)	
Plasma HIV-1 RNA below 200 copies/mL at listing, n (%)	80(95%)	46(96%)	34(94%)	0.9025
CD4 cell count at listing	296(200; 420)	262(193; 424)	309(208; 408)	0.5651
Time on waiting list (mo)	4(2; 7)	4(2; 7)	5(2; 7)	0.9245
Transplants in centers with < 1 OLT in HIV-infected patients/year, n (%)	13(15%)	4(8%)	9(25%)	0.0039
Donor characteristics and other peritransplant variables				
Donor risk index	1.40(1.17; 1.77)	1.35(1.03; 1.55)	1.53(1.37; 1.78)	0.0019
Donor characteristics				
Age (year)	52(40; 68)	48(34; 62)	61(43; 71)	0.0197
Male gender, n (%)	48(57%)	29(60%)	19(53%)	0.5814
Caucasian race, n (%)	77(92%)	45(94%)	32(89%)	0.5814
Cause of donor brain death, n (%)				0.0367
Vascular	44(52%)	20(42%)	24(67%)	
Cranial trauma	25(30%)	20(42%)	5(14%)	
Other	16(19%)	8(17%)	7(19%)	
Donor type, n (%)				0.3728
Deceased	81(98%)	46(96%)	35(97%)	
Living-donor	2(1%)	1(2%)	1(3%)	
Domino	1(1%)	1(2%)		

Continued

Table 1: Continued

	All cases	Survivors	Dead	p-Value
Cold ischemia time (min)	390(310; 535)	378(297; 535)	420(333; 455)	0.7738
Peri-operative transfusion requirements (units)[5]	3(1; 6)	2(0; 5)	4(3; 7)	0.0015
Posttransplant variables				
Length of follow-up (year)	3.63(1.41; 4.68)	4.44(3.73; 6.00)	1.38(0.79; 2.38)	NA
Initial immunosuppression, n (%)				0.9418
Cyclosporine-based	26(31%)	15(31%)	11(31%)	
Tacrolimus-based	49(58%)	29(60%)	20(56%)	
Other regimens	9(11%)	4(8%)	5(14%)	
Time to re-start cART (d)	9(5; 17)	9(4; 16)	10(7; 24)	0.1152
Type of cART, n (%)				0.8210
NRTI-based	11(13%)	6(13%)	5(14%)	
PI-based	21(25%)	13(27%)	8(22%)	
Efavirenz-based	37(44%)	20(42%)	17(47%)	
Others	15(18%)	9(19%)	6(17%)	
Acute rejection, n (%)	32(38%)	18(38%)	14(39%)	0.9893
Chronic rejection, n (%)	2(2%)	–	2(6%)	0.0865
Peak plasma HCV RNA viral load increase after transplantation (log_{10})	6.66(5.88; 7.17)	6.48(5.70; 7.02)	6.89(6.16; 7.37)	0.059
Anti-HCV treatment, n (%)	47(56%)	26(54%)	21(58%)	0.825
SVR to anti-HCV treatment, n (%)	13/47(28%)	12/26(46%)	1/21(5%)	0.013
At least one infection, n (%)	58(69%)	29(60%)	29(81%)	0.077
Severe infection, n (%)	39(46%)	16(33%)	23(64%)	0.006
Invasive fungal infection[6], n (%)	6(7%)	1(2%)	5(14%)	0.008
CMV disease, n (%)	2(2%)	1(2%)	1(3%)	1.000
Tuberculosis, n (%)	2(2%)	1(2%)	1(3%)	1.000
Re-transplantation[7], n (%)	4(5%)	2(4%)	2(6%)	0.201

cART = combined antiretroviral therapy; MSM = men who have sex with men; NRTI = nucleotide reverse transcriptase inhibitor; OLT = orthotopic liver transplant; PI = protease inhibitor; SVR = sustained virological response. Delta MELD: difference between MELD at inclusion on the waiting list and MELD at the time of transplantation; NA = not applicable.

[1]All quantitative variables are expressed as median and interquartile range, unless otherwise stated.

[2]Seventeen patients (20%) had a history of 24 AIDS-defining events: tuberculosis, 11; *Pneumocystis jiroveci* pneumonia, 5; esophageal candidiasis, 5; cerebral toxoplasmosis, 2; grade III intracervical neoplasia, 1.

[3]Ten cases did not fulfill these criteria: 3 cases had <100 CD4+ T cells/μL; 4 cases had a permitted opportunistic infection but a CD4+ T-cell count between 100 and 200 cells/μL; and, 3 had >200 CD4+ T cells/μL but an opportunistic infection other than tuberculosis, esophageal candidiasis, or *Pneumocystis jiroveci* pneumonia.

[4]Calculated MELD score, without extra-points in patients with hepatocellular carcinoma.

[5]Red blood cell transfusion requirements during surgery.

[6]Zygomycosis, 2 cases; esophageal candidiasis, 2 cases; aspergillosis, 1 case; and *Pneumocystis jiroveci* pneumonia, 1 case.

[7]Primary graft failure, 2 cases; hepatic artery thrombosis, 1 case; and HCV recurrence, 1 case.

variables in HCV/HIV-coinfected recipients and characteristics of their donors are shown in Table 1. Donors were HIV, HCV and HBV negative. No patients underwent combined liver–kidney transplantation. Median (IQR) follow-up was 3.63 (1.41; 4.68) years and no patients were lost to follow-up. No recurrences of HBV infection were recorded.

Post-OLT survival in HCV/HIV-coinfected patients and HCV-monoinfected patients

Table 2 shows the main characteristics of both cohorts. HCV/HIV-coinfected patients underwent the procedure in the same institutions and calendar year and, as matched criteria, they had a similar age and similar proportions of male gender, HBV coinfection and HCC as HCV-monoinfected recipients. Patients exposed and non-exposed to HIV had a similar MELD score. HIV-infected patients had a lower rate of HCV genotype 1 ($p = 0.001$), although the rates of sustained virological response after anti-HCV therapy were similar in both groups. Donor risk index was the same in both cohorts. The rate of acute rejection was almost two times higher in HIV-infected patients (38% vs. 20%; $p = 0.001$). CD4+ T-cell count remained stable in HIV-infected patients in most cases between 200 cells/μL and 300 cells/μL and most patients (>90%) remained virologically suppressed on cART during the post-OLT study period (Table 3). Four coinfected patients (5%) and 17 monoinfected patients (7%) underwent a second transplant.

Mortality was significantly higher among HCV/HIV-coinfected recipients. Thirty-six (43%) HCV/HIV-coinfected

Table 2: Characteristics of HCV/HIV-coinfected and HCV-monoinfected liver transplant recipients and their donors, and posttransplant outcomes

	HCV/HIV coinfection	HCV monoinfection	p-Value
No. of cases	84	252	
Matching recipient variables:			
Age (year)[1]	42 (39;45)	47 (43;53)	
Male gender	20 (76%)	63 (74%)	
HBV coinfection	13 (15%)	13 (5%)	
Hepatocellular carcinoma	15 (18%)	40(16%)	
Other recipient variables:			
Pre-OLT MELD score[1]	15 (11;18)	15 (13;18)	0.363
Delta MELD[1]	0 (-1;2)	0 (-2;2)	0.593
HCV genotype 1	46 (55%)	173 (69%)	< 0.001
RNA—before OLT	7 (8%)	25 (10%)	0.830
SVR/No. treated after OLT	13/47 (28%)	39/117 (33%)	0.603
Donor variables:			
Donor age > 60 years	23 (27%)	74 (29%)	0.781
Donor brain death by trauma	25 (30%)	90 (36%)	0.388
Caucasian race	77(92%)	235 (93%)	0.629
Donation after cardiac death	1 (1.2%)	1 (0.4%)	0.440
Partial/Split	2 (2.%)		0.062
Height (cm)[1]	170 (160;170)	170 (161;175)	0.104
Local donation	78 (93%)	251 (99%)	0.046
Cold ischemia time (minutes)[1]	388 (320;535)	377 (300;486)	0.412
Donor risk index[1]	1.40 (1.17;177)	1.38 (1.11;1.65)	0.134
Follow-up (year)[1]	3.63 (1.41;4.68)	4.68 (3.00;5.96)	
Acute rejection[2]	32 (38%)	50 (20%)	0.001
HCV recurrence[3]			
FCH	9 (11%)	10 (4%)	0.029
Stage F3/F4 fibrosis	30/65 (46%)	54/187 (29%)	0.014
Severe graft fibrosis[4]	37/72 (51%)	62/193 (32%)	0.004
Retransplantation[5]	4 (5%)	17 (7%)	0.611
Mortality	36 (43%)	75 (30%)	0.033
Causes of death[6]			
HCV recurrence	18 (21%)	31 (12%)	0.049
Infection	7 (8%)	15 (6%)	0.612
Tumors	3 (4%)	4 (2%)	0.373
Technical problems	–	6 (2%)	0.343
Other causes	8 (10%)	19 (8%)	0.643

SVR = sustained virological response; FCH = fibrosing cholestatic hepatitis. Delta MELD: difference between MELD at inclusion on the waiting list and MELD at the time of transplantation.

[1]Median and interquartile range.

[2]Biopsy-proven.

[3]Only patients with follow-up biopsies were considered.

[4]Two cases in the coinfected population and six cases in the monoinfected cohort had both complications (FCH and stage F3/F4 fibrosis).

[5]Two HIV-infected patients and three HIV-negative recipients died after retransplantation.

[6]Number of deaths (percentage related to the whole group).

patients and 75 (30%) HCV-monoinfected patients died ($p = 0.033$) during a median (IQR) of 3.63 (1.41; 4.68) and 4.68 (3.00; 5.96) years of follow-up, respectively. As shown in Table 2, HCV recurrence was the most important cause of death—21% and 12% of cases ($p = 0.049$), respectively—but was more frequent in HIV-infected patients ($p = 0.049$).

Figures 2(A),(B) and Table 4 show patient and graft survival in HCV-infected liver recipients according to their HIV status. Patient survival (95% CI) rates at 1, 3 and 5 years for HCV/HIV-coinfected and HCV-monoinfected patients were 88% (79–93) versus 90% (86–93), 62% (51–72) versus 76% (70–80) and 54% (42–64) versus 71% (66–77), respectively (overall, $p = 0.008$). Similar differences were observed in graft survival ($p = 0.042$).

The multivariate analysis adjusted for the variables included in Table 2 that yielded a p-value <0.10 showed that HIV infection was an independent predictor of post-OLT mortality (HR, 2.20; 95% CI, 1.42–3.41; $p < 0.001$). HCV genotype 1 (HR, 2.14; 95% CI, 1.24–3.41; $p = 0.006$) and donor risk index (HR, 3.03; 95% CI, 1.57–5.83; $p < 0.001$) were also independently associated with death. A negative HCV RNA

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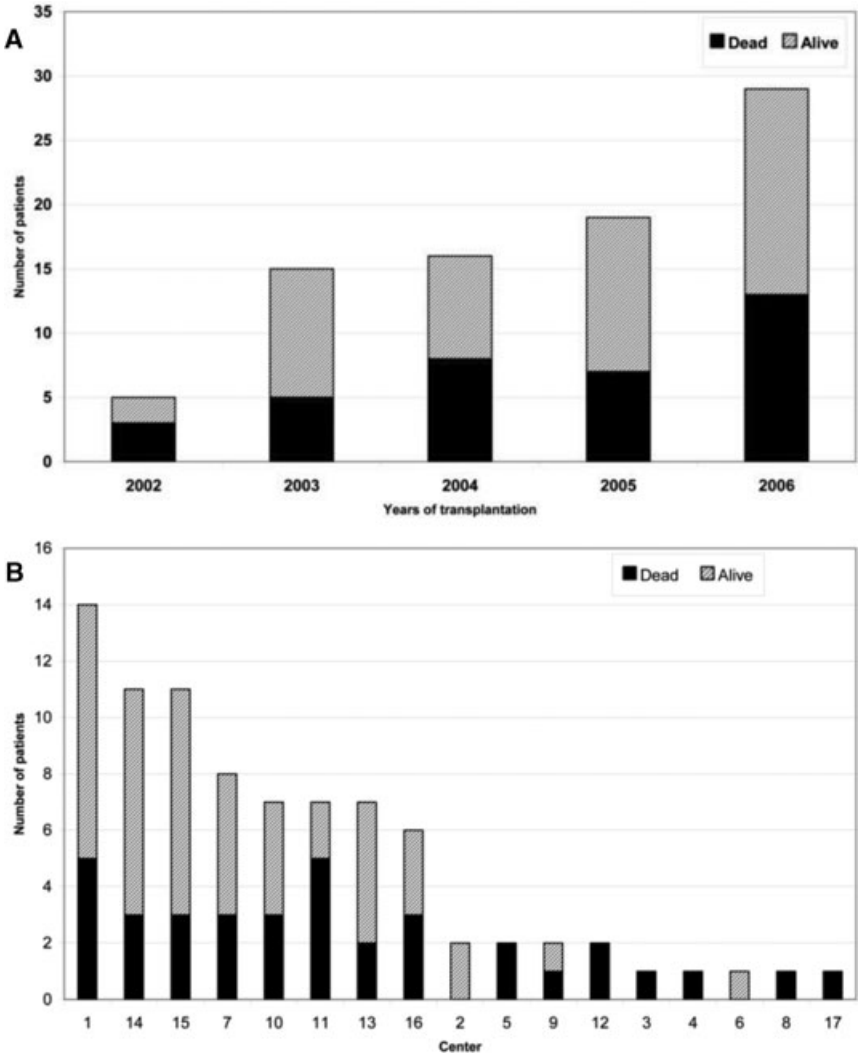

Figure 1. (A) Annual number of liver transplants in HCV/HIV-coinfected patients performed in Spain between 2002 and 2006. (B) Number of liver transplants performed in HCV/HIV-coinfected patients in the 17 participating centers.

viral load before or after OLT was a protective factor (HR, 0.23; 95% CI, 0.10–0.49; $p < 0.001$).

Severity of HCV recurrence after OLT in HCV/HIV-coinfected patients and HCV-monoinfected patients

Coinfected patients had a higher rate of FCH than monoinfected patients (11% vs. 4%; $p = 0.029$) and a higher rate of stage F3/F4 fibrosis (46% *vs.* 29%, $p = 0.014$; Table 2). Severe graft fibrosis was also more frequent in coinfected patients (Table 2). Figure 3 shows the probability of severe graft fibrosis in patients according to their HIV status. The probability (95% CI) of remaining free from severe graft fibrosis at 1, 3 and 5 years for HCV/HIV-coinfected and HCV-monoinfected patients was 84% (73–91) versus 90% (85–94), 42% (27–54) versus 66% (56–73) and 24% (12–39) versus 49% (38–59), respectively (overall, $p < 0.001$).

Predictive factors of mortality among HCV/HIV-coinfected patients

The results of the univariate analysis of prognostic factors in HCV/HIV-coinfected liver recipients are shown in Table 5. A multivariate analysis including all variables reaching a p value ≤ 0.1 in the univariate analysis revealed the following independent risk factors for death: HCV genotype 1 (HR, 2.98; 95% CI, 1.32–6.76; $p = 0.008$), donor risk index (HR, 9.48; 95% CI, 2.75–32.73; $p < 0.001$) and a negative HCV RNA viral load before or after OLT (HR, 0.14; 95% CI, 0.03–0.62; $p = 0.009$). When we included pretransplant variables only, MELD score (HR, 1.06; 95% CI, 1.01–1.11; $p = 0.023$), transplant at a center with less than 1 OLT per year in HIV-infected patients (HR, 2.82; 95% CI, 1.30–6.94, $p = 0.009$) and HCV genotype 1 (HR 2.27; 95% CI, 1.09–4.76; $p = 0.029$) were independently associated with death.

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Table 3: CD4+ T-cell count and plasma HIV-1 RNA viral load below detection levels (<200 copies/mL) on cART in the 84 HCV/HIV coinfected recipients before and after liver transplantation

	CD4+ T-cell counts[1]	Plasma HIV-1 RNA viral load <200 copies/mL
Before transplantation		
At listing (N = 84)	296 (200;420)	80 (95%)
After transplantation		
At one month (N = 81)	296 (200;420)	73 (90%)
At 6 months (N = 77)	268 (175;395)	73 (95%)
At 1 year (N = 73)	269 (178;333)	68 (96%)
At 2 years (N = 60)	294 (189;387)	59 (98%)
At 3 years (N = 49)	334 (229;478)	47 (96%)
At 4 years (N = 35)	309 (246;475)	33 (94%)
At 5 years (N = 23)	344 (257;528)	22 (96%)

[1]Median and interquartile range.
cART = Combined antiretroviral therapy.

As pretransplant variables may be helpful in the selection of HCV/HIV-coinfected OLT candidates, we calculated a risk score for mortality taking into account the three variables identified in the multivariate analysis and their respective regression coefficients (24). The individual risk of mortality of the 84 recipients was calculated with the formula "Exp ([(0.81966* if genotype = 1] + [0.05748* MELD pre-OLT] + [1.03540 if center <1 OLT in HIV-infected patients/year])". A risk score cut-off of 1.07795 classified the 84 recipients as having a low risk (n = 60 patients, 69%) or a high risk of death (n = 24 patients, 31%). This cut-off was chosen to ensure an equal number of deaths in both subsets. Figure 2(C) shows the Kaplan-Meier survival curves for these groups. Survival (95% CI) rates at 1 and 5 years for recipients with a low or high mortality risk score were 93% (83 to 97) versus 74% (51–87) and 69% (54–80) versus 17% (5–35), respectively ($p < 0.001$).

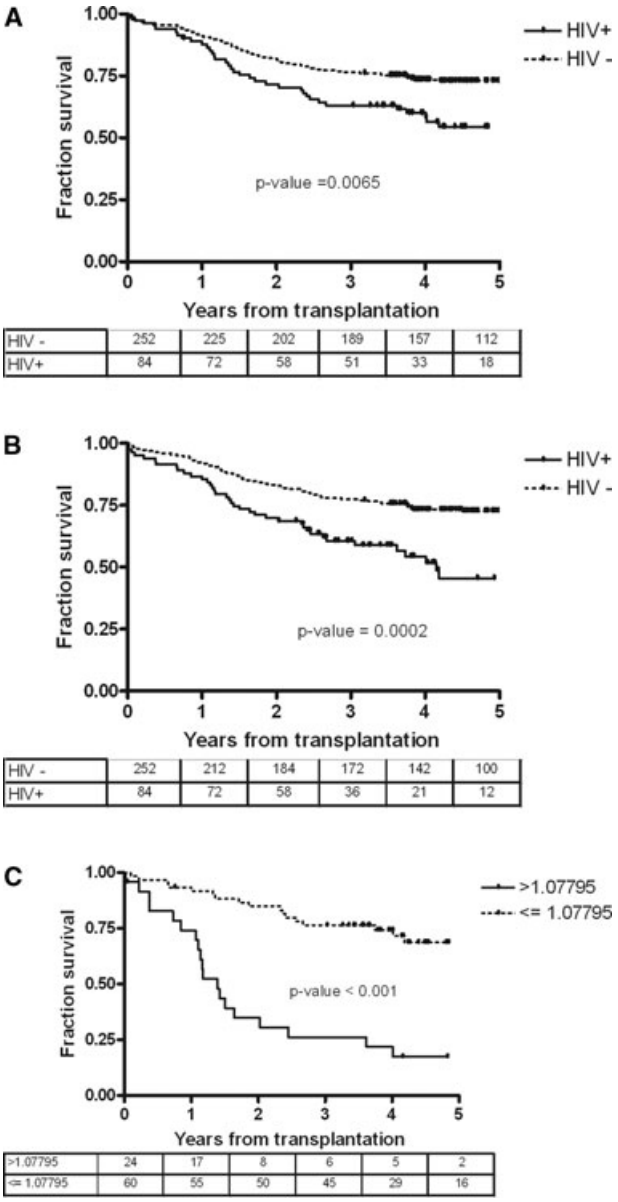


Figure 2. Probability of patient (A) and graft (B) survival in HCV/HIV-coinfected (dashed line) and HCV monoinfected (solid line) liver transplant recipients; (C) Probability of survival among HCV/HIV-coinfected recipients according to risk score of death ≤1.07795: low-risk, dashed line; >1.07795: high-risk, solid line.

Discussion

This study shows that OLT was an effective short-term (1 year) procedure in HCV/HIV-coinfected liver recipients, with a survival rate similar to that observed in HCV-monoinfected patients (88% vs. 90%). However, post-OLT survival in HCV/HIV-coinfected patients after longer follow-up was lower (at 5 years: 54% vs. 71%, $p = 0.008$), although acceptable.

The present cohort had three interesting characteristics: (1) It was a nationwide multicenter study with the participation of 17 out of the 23 units performing OLT in Spain; (2) HIV-specific criteria for OLT were previously agreed by all units (17) and, (3) We started the program in the late cART era and managed to collect a relatively large cohort of HCV/HIV-coinfected OLT recipients (N = 84) over a short period of time (2002–2006). In addition, we waited a minimum of 3 years before reporting our results. Consequently, our findings are even more valid, as previously published studies (5,10,11) in HCV/HIV-coinfected liver transplant patients were performed in single institutions with smaller sample sizes collected over longer periods.

We found that HIV-infection was an independent predictor of death in HCV-infected liver transplant recipients. When we compared the cohort of HCV-infected recipients exposed to HIV infection or not, the results of matched

Table 4: Five-year patient and graft survival and 95% confidence interval after liver transplantation in HCV/HIV coinfected and HCV-monoinfected recipients

	HCV/HIV coinfection	HCV monoinfection	p-Value
No. of cases	N = 84	N = 252	
Patient survival at			p = 0.008
1 year	88% (79%–93%)	90% (86%–93%)	
2 years	71% (60%–79%)	81% (75%–85%)	
3 years	62% (51%–72%)	76% (70%–80%)	
4 years	60% (47%–69%)	73% (67%–78%)	
5 years	54% (42%–64%)	71% (66%–77%)	
Graft survival at			p = 0.042
1 year	86% (76%–92%)	85% (80%–89%)	
2 years	69% (57%–78%)	74% (68%–79%)	
3 years	60% (48%–70%)	69% (63%–74%)	
4 years	54% (41%–65%)	65% (59%–71%)	
5 years	45% (31%–58%)	64% (58%–70%)	

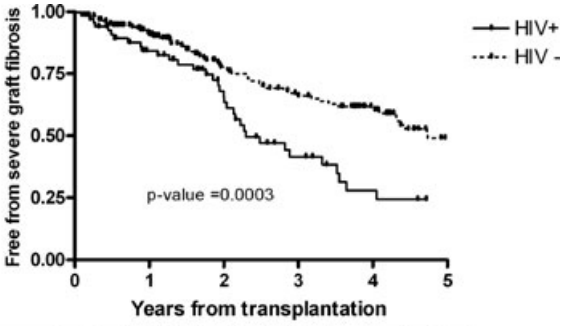
variables were obviously similar, but the MELD score before transplantation, which was not a matching criterion and has been reported to have prognostic value in HCV-infected liver transplant recipients (11), was the same in both cohorts. Furthermore, other variables capable of influencing post-OLT outcome were also similar, such as the donor risk index and its individual components. On the other hand, the rate of HCV genotype 1, a poor prognostic factor for HCV-infected transplant recipients (25,26), was higher in our HCV-monoinfected patients, although this group of patients had a better 5-year survival. The most likely explanation for the worse outcome in HCV/HIV-coinfected patients is HCV recurrence after OLT, which has been reported to be more aggressive in this group than in HCV-monoinfected recipients (10,11). Consistent with this possibility, severe graft fibrosis was observed more often and earlier in HCV/HIV-coinfected patients than in HCV-monoinfected patients (Figure 3), and almost twice as many HIV/HCV-infected recipients as HCV-monoinfected recipients died due to HCV recurrence (21% vs. 12%; p = 0.049; Table 2). The similar survival in both cohorts at 1 year and the lower survival in HCV/HIV-coinfected patients beyond this time point also support this hypothesis, because the negative impact of HCV recurrence predictably becomes apparent in the medium or long term after OLT.

A remarkable finding in our study was the higher incidence of biopsy-proven acute rejection in HCV/HIV-coinfected recipients than in HCV-monoinfected patients: 38% vs. 20% ($p < 0.001$). This high rate of rejection in coinfected patients is consistent with the 30–40% incidence of rejection reported elsewhere (10,11,27). The reasons for this finding are elusive. However, it has been attributed to the

Table 5: Univariate analysis of prognostic factors of mortality in HCV/HIV-coinfected liver recipients[1]

	Hazard ratio (95% confidence interval)	p-Value
Pretransplant variables		
HCV genotype 1	2.55(1.22; 5.29)	0.012
Plasma HCV RNA viral load above the median (400,000 units)	1.89(0.97; 3.67)	0.061
HBV coinfection	0.13(0.02; 0.97)	0.042
MELD score at listing (1-unit increase)	1.06(1.01; 1.12)	0.026
MELD score pre-OLT (1-unit increase)	1.07(1.01; 1.12)	0.007
Child-Turcotte-Pugh C stage at listing	2.38(1.22; 4.62)	0.011
Center with <1 liver transplants in HIV-infected patients/year	3.08(1.43; 6.67)	0.004
Peritransplant variables		
Donor age ≥60 years	2.51(1.29; 4.90)	0.007
Noncranial trauma as cause of donor brain death	3.17(1.23; 8.16)	0.017
Peri-operative red blood cell transfusion ≥3 units	2.73(1.47; 6.25)	0.004
Donor risk index	6.35(1.98; 20.39)	0.002
Posttransplant variables		
Negative plasma HCV RNA viral load at any time (before or after OLT)	0.14(0.03; 0.58)	0.007
Peak plasma HCV RNA viral load increase after OLT (1 $\log_{10}$ increase)	1.53(1.00; 2.34)	0.048
Chronic rejection	3.57(0.83; 15.28)	0.086
Severe infection	2.61(1.32; 5.19)	0.006
Invasive fungal infection	3.73(1.42; 9.81)	0.008

[1]Only variables with a p value < 0.1 are shown.



HIV -	193	144	83	64	46	24
HIV+	72	48	29	15	8	5

Figure 3. Probability of remaining free from severe graft fibrosis in HCV/HIV-coinfected (dashed line) and HCV-monoinfected (solid line) liver transplant recipients.

immunomodulatory effects of HIV and difficulties in achieving optimal immunosuppression due to strong interactions between some antiretroviral agents and immunosuppressive drugs (10,11). On the other hand, because rejecting patients could have received a more powerful immunosuppression as antirejection therapy, the higher incidence of rejection in coinfected recipients could have indirectly contributed to their worse HCV recurrence (26).

Once we realized that survival in HCV/HIV-coinfected recipients was relatively poor, we tried to identify variables with prognostic significance in this population. A multivariate analysis adjusted for pre-, peri- and postoperative variables, revealed that the donor risk index and HCV genotype 1 were independently associated with an increased risk of death, whereas having a negative HCV RNA before or after OLT was a protective factor. It is well established that donor-related factors such as donor risk index correlate clearly with survival after liver transplantation (13). This association has also been seen in HCV-monoinfected liver transplant recipients (28). HCV genotype 1 has been found to be a predictor of mortality in HCV-monoinfected OLT recipients (25,26). Conversely, clearance of HCV after treatment with pegylated-interferon and ribavirin is a protective factor that confers a favorable long-term outcome (29). However, with current anti-HCV therapy, the rate of sustained virological response is very low in HCV/HIV-coinfected recipients, mainly in patients with HCV genotype 1 (29,30). The development of better drugs to treat HCV will probably improve these results.

An additional analysis including only the three pretransplant variables independently associated with post-OLT death (MELD score, HCV genotype 1 and center activity in OLT in HCV/HIV-coinfected patients) identified a subset of HCV/HIV-coinfected patients, comprising two-thirds of our cohort, with a 5-year life expectancy that was very similar to that of HCV-monoinfected recipients (69% vs. 71%). The importance of HCV genotype 1 and MELD score as poor prognostic factors has already been discussed earlier (11,25,26,29,30). In our series, coinfected patients who underwent transplant in centers with a low activity (<1 OLT/year) had almost three times higher mortality. This finding agrees with previous studies indicating that transplant center volume has an impact on survival (31–33). Although not evaluated in our study, a training effect cannot be excluded. Conversely, we also identified a subset of HCV/HIV-coinfected patients, including the remaining third of the cohort, with poor expected survival after OLT: only 17% at 5 years. Therefore, patients with the characteristics of this subset should theoretically be excluded from OLT. Nevertheless, the low number of patients in this subset (only 24), the lack of studies verifying the reproducibility of our results, and the possible improvement for genotype 1 HCV infection with new anti-HCV drugs preclude robust conclusions on this key issue. Further investigations involving large series of patients from other countries, or even the inclusion of more patients in our own study, are necessary before formal recommendations can be made.

Although 12% of our HCV/HIV-coinfected patients did not fulfill the HIV inclusion criteria for OLT, survival did not significantly differ from that of patients fulfilling these criteria, suggesting that some of our criteria were probably too restrictive. Consistent with the findings of previous studies (11,34), our cohort had very good immunological and virological control on cART, with a low rate of opportunistic infections after OLT.

Our study has three main limitations. First, we could not analyze prognostic factors in patients stratified according to the different HCV genotypes. Nevertheless, the prognosis of patients with non-1 HCV genotypes is clearly better; therefore, this group should not be excluded from OLT. Second, the number of recipients who reached at least 5 years of follow-up is small, and the results might change with a larger sample size. Several prospective cohort studies in Europe and the United States and the present cohort may provide more results on this issue either individually or by merging data. Third, although an intention-to-treat analysis from the time of admission of HIV/HCV-coinfected and HCV-monoinfected patients to the OLT waiting list would have been a very interesting addition to our cohort study, we were unable to perform such an analysis, because we did not collect information on patients on the waiting list who had not received a transplant.

In conclusion, OLT is an effective short-term procedure in HCV/HIV-coinfected recipients. Patient and graft survival in the medium term were lower than that of the matched HCV-monoinfected patients, although it remained acceptable. Our study was able to identify subsets of patients with a more favorable prognosis. Liver transplantation in HCV/HIV-coinfected patients restricted to sites with more experience and better anti-HCV therapies could improve long-term outcome in these patients.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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