
# Tratamiento e historia natural de la hepatitis crónica C en pacientes coinfectados por VIH-1

Javier Murillas Angoiti

*Tesis Doctoral*

# *TRATAMIENTO E HISTORIA NATURAL DE LA HEPATITIS CRÓNICA C EN PACIENTES COINFECTADOS POR VIH-1*

*Javier Murillas Angoiti*

*Universidad de Barcelona*

*Facultad de Medicina*

*Departamento de Medicina*

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# ANEXO 1:PUBLICACIONES

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ORIGINAL ARTICLE

# The Model for End-Stage Liver Disease Score Is the Best Prognostic Factor in Human Immunodeficiency Virus 1–Infected Patients with End-Stage Liver Disease: A Prospective Cohort Study

AQ: 1

**Javier Murillas,[1] Antonio Rimola,[2,3] Montserrat Laguno,[2] Elisa de Lazzari,[2] Javier Rascón,[1] Fernando Agüero,[2] José L. Blanco,[2] Eduardo Moitinho,[1] Asunción Moreno,[2] José M. Miró,[2] and the** AQ: 2 **ESLD-HIV Working Group Investigators**

*[1]Hospital Son Dureta, Palma de Mallorca, Spain; [2]Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi-Sunyer, University of Barcelona, Barcelona, Spain; and [3]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Barcelona, Spain*

AQ: 3 End-stage liver disease (ESLD) has become the main cause of mortality in patients coinfected by human immunodeficiency virus (HIV) and hepatitis B virus or hepatitis C virus in developed countries. The aim of this study was to describe the natural history of and prognostic factors for ESLD, with particular attention paid to features affecting liver transplantation. This was a prospective cohort study in 2 Spanish community-based hospitals performed between 1999 and 2004. All HIV-infected patients with cirrhosis and a first clinical decompensation of their chronic liver disease or hepatocellular carcinoma were included in the study. One hundred four patients were included in the study. During a median follow-up of 10 months (endpoint: death, liver transplantation, or the last checkup date), 61 patients (59%) died. The probability of mortality (Kaplan-Meier method) at 1, 2, and 3 years was 43% [95% confidence interval (CI), 34%-60%], 59% (95% CI, 48%-70%), and 70% (59%-81%), respectively. In a multivariate analysis, the Model for End-Stage Liver Disease (MELD) score and the inability to reach an undetectable plasma HIV-1 RNA viral load at any time during follow-up were the only variables independently associated with the risk of death ($P < 0.001$). Fifteen (14%) of the 104 patients were accepted for liver transplantation, although only 5 underwent the procedure, and 10 died while on the waiting list. The waiting list mortality rate in patients with a MELD score $< 20$ and in patients with a MELD score $>20$ was 58% and 100%, respectively (median follow-up, 5 months). In conclusion, HIV-1–infected patients with ESLD, especially those with poorly controlled HIV and a high MELD score, have a poor short-term outcome. The MELD score may be useful in deciding whether to indicate liver transplantation in these patients. However, because only a small proportion of the patients in this study were considered candidates AQ: 4 for liver transplantation and most died while on the waiting list, few received a transplant. ***Liver Transpl 15:000-000, 2009.***


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**Abbreviations:** AIDS, acquired immune deficiency syndrome; BDL, below the detection limit; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CTP, Child-Turcotte-Pugh; ESLD, end-stage liver disease; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; IVDA, intravenous drug abuse; MELD, Model for End-Stage Liver Disease; MSM, men who have sex with men; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; OH, chronic alcohol abuse; OLT, orthotopic liver transplantation; PI; protease inhibitor; SPB, spontaneous bacterial peritonitis.

The ESLD-HIV Working Group investigators included Melchor Riera and Concepción Villalonga (Hospital Son Dureta, Palma de Mallorca, Spain); Felipe García, Esteban Martínez, Josep Mallolas, and José M. Gatell (Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi-Sunyer, University of Barcelona (Barcelona, Spain); and Daniel Fuster and Cristina Tural (Hospital Germans Trias i Pujol, Badalona, Spain).

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Address reprint requests to José M. Miró, Infectious Diseases Service, Hospital Clínic, Helios Building, Desk 26, Villarroel 170, 08036 Barcelona, Spain. Telephone: +34-93-2275586; FAX: +34-93-4514438; E-mail: jmmiro@ub.edu

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Human immunodeficiency virus (HIV)–related mortality has declined dramatically since 1996 in Europe and the United States with the widespread use of highly active antiretroviral therapy (HAART). Conversely, end-stage liver disease (ESLD), mainly due to cirrhosis caused by hepatitis C virus (HCV), is becoming an important cause of death among HIV-1–infected patients in developed countries.[1] Even after recent improvements in chronic hepatitis C and B therapy, many coinfected patients will progress to liver cirrhosis, ESLD, and death. Liver transplantation is the only hope for these patients. Until a few years ago, infection by HIV was an absolute contraindication to any type of transplant, although since the introduction of HAART in 1996, liver transplantation has been reconsidered in HIV-infected patients with ESLD; at present, HIV infection is no longer a formal contraindication to transplant,[2] and good results can be achieved, especially in patients coinfected with hepatitis B virus (HBV).[3] In patients coinfected with HIV and HCV, our greater understanding of the mechanisms involved in HCV recurrence after liver transplantation and the improvements in antiviral therapy used after transplantation give hope for the future. In this setting, a better selection of candidates and an accurate scoring of liver disease are needed to improve the results of liver transplantation.[4]

According to current estimates, there are around 130,000 HIV-infected patients in Spain.[5] In 1 cross-sectional study,[6] 61% of HIV-1–infected patients were coinfected with HCV, and 4.8% were coinfected with HBV. Eight percent of coinfected patients had clinical or histological criteria of cirrhosis, and 17% met the Spanish criteria[6,7] for registration on a liver transplant waiting list. In an Italian study, the median time from the diagnosis of cirrhosis to the first liver decompensation or hepatocellular carcinoma (HCC) was only 4 years in HIV-1–infected patients.[8] Furthermore, in 2 recently published case-control studies, patients with ESLD who were coinfected with HIV and HCV had a faster progression to death after the first liver decompensation than HCV-monoinfected patients.[9,10] In these retrospective studies, independent predictors of poor outcome were the severity of liver disease [as assessed by the Child-Turcotte-Pugh (CTP) classification or the development of hepatic encephalopathy], the level of cellular immunosuppression (less than 100 CD4 cells/mm$^3$), and the failure to take HAART during follow-up.[9-11]

The present prospective cohort study examined the outcome of ESLD in HIV-1–infected patients and identified possible prognostic factors. Furthermore, aspects concerning liver transplantation were also analyzed.

## PATIENTS AND METHODS

In order to describe the natural history of ESLD in HIV-1–infected patients, a prospective cohort study was performed between 1999 and 2004 at 2 Spanish hospitals: the Hospital Clínic in Barcelona and Hospital Son Dureta in Palma de Mallorca (whose reference hospital for liver transplantation was also the Hospital Clínic). The study included consecutive HIV-1–infected patients with cirrhosis and ESLD, which was defined as the development of either a first major clinical decompensation of cirrhosis (variceal bleeding, ascites, jaundice, encephalopathy, or spontaneous bacterial peritonitis) or HCC. Complications of cirrhosis were managed with standard recommendations, which have been described elsewhere.[12] The Model for End-Stage Liver Disease (MELD) score was calculated by electronic consultation (the MELD United Network for Organ Sharing modification, which is available at http://www.mayoclinic.org/gi-rst/mayomodel6.html). In all patients, the CTP and MELD scores were determined at the initial visit when liver decompensation or HCC was detected, with the exception of patients with variceal bleeding, for whom these scores were calculated 7 to 30 days after bleeding stopped.

The study started in 1999 in the context of a pilot program of liver transplantation in HIV-1–infected patients promoted by the Transplant Organization of Catalonia (Spain).[7] All patients were evaluated as candidates for liver transplantation and were registered on the liver transplant waiting list if the following HIV-1 selection criteria were met: no history of opportunistic infections (with the exception of tuberculosis) or HIV-related neoplasms [acquired immune deficiency syndrome (AIDS) criteria, Centers for Disease Control and Prevention, 1993], a CD4 cell count $>$ 200 cells/mm$^3$ or $>$ 100 cells/mm$^3$ with a CD4 cell percentage $>$ 20%, and effective antiretroviral treatment. For drug abusers, a 2-year abstinence from heroin and cocaine was required, although patients could be in a methadone program. As for liver disease, the criteria for accepting HIV-infected patients for transplantation were the same as those followed at the Hospital Clínic for non–HIV-infected patients[12]: a minimum CTP score of 7 for patients with cirrhosis and, for patients with HCC, 1 tumor of $<$5 cm or 2 to 3 tumors of $<$3 cm in the absence of hepatic macrovascular tumoral invasion and extrahepatic metastases.

Quantitative data were described with the median (interquartile range). Qualitative data were described with absolute values and percentages. The probability of survival was estimated with the Kaplan-Meier method, and survival functions were compared with the log-rank or Wilcoxon (Breslow) test. The endpoints of the study were death, liver transplantation, and the date on which the follow-up of nontransplanted survivors ended (December 31, 2004). The Cox proportional hazard model was used to identify mortality risk factors. All tests were 2-sided with a significance level of $<$0.05. The analysis was performed with the Stata statistical package (Stata Statistical Software, release 8.2, StataCorp, College Station, TX).

## RESULTS

### Patient Characteristics

The 2 hospitals participating in the study attended 2891 HIV-1–infected patients during the study period

(1910 at the Hospital Clínic and 981 at the Hospital Son Dureta). Of these patients, 104 (3.5%) had ESLD and were included in this study. Table 1 shows the baseline characteristics of these 104 patients. No significant differences were observed between patients from the Hospital Clínic (n = 57) and those from Hospital Son Dureta (n = 47). The median (interquartile range) baseline serum HCV RNA viral load (only available in 19 patients) was 820,000 (470,000-1,660,000) IU/mL. The HCV genotype was available in 13 patients, with genotypes 1 or 4 and 2 or 3 identified in 8 (66%) and 5 cases (34%), respectively. None of the 6 patients treated with interferon alone (n = 3), interferon plus ribavirin (n = 2), or pegylated interferon plus ribavirin (n = 1) achieved a sustained virological response. Patients coinfected with HIV and HBV were on lamivudine or tenofovir-emtricitabine–based antiretroviral regimens. Plasma HBV DNA was available in 7 patients and was undetectable in 6.

Five patients had HCC. In 2 patients, HCC was multinodular, and in the other 3 patients, a solitary nodule measuring 1, 3, or 5 cm in diameter was found. Three patients were treated with chemoembolization, and 1 patient was treated with radiofrequency.

## Outcome

Outcome is summarized in Fig. 1. During the follow-up period [median, 10.3 (3.0-20.6) months], 61 (59%) patients died (59 because of liver-related problems, 1 because of an HIV-related disease, and 1 because of a heroin overdose), 15 patients were registered on the waiting list (Table 2), and 5 (5%) underwent liver transplantation.

Mortality rates [95% confidence interval (CI)] in the first, second, and third years were 43% (34%-60%), 59% (48%-70%), and 70% (59%-81%), respectively (Fig. 2A). Results of the univariate analysis for predictive factors of mortality are shown in Table 3. In the univariate analysis, the CTP classification ($P = 0.034$; Fig. 2B), the MELD score (Fig. 2C; $P < 0.001$), and the inability to achieve an undetectable plasma HIV-1 RNA viral load during follow-up ($P < 0.001$; Fig. 2D) were associated with risk of death. Survival tended to be better in patients with a CD4 cell count $\geq 350$ cells/mm$^3$ ($P = 0.06$) and poorer in patients with ascites ($P = 0.06$) or HCC ($P = 0.101$) and the absence of an intercurrent illness at the time of ESLD ($P = 0.068$), although none of these differences reached statistical significance. Interestingly, didanosine use, antiretroviral class, and duration of HAART were associated with risk of death.

All variables reaching a $P$ value $\leq 0.1$ in the univariate analysis were included in the multivariate analysis (CTP classification, MELD score, intercurrent illness at the time of ESLD, CD4 cell count, ascites and HCC, and the inability to achieve an undetectable plasma HIV-1 RNA viral load during follow-up). The MELD score (hazard ratio per 5-unit increase, 1.53; 95% CI, 1.22-1.92) and the inability to achieve an undetectable plasma HIV-1 RNA viral load during follow-up (hazard ratio, 3.47; 95% CI, 1.94-6.17) were the only 2 variables in-

**TABLE 1. Baseline Demographic Data and Clinical Characteristics of 104 Consecutive HIV-1–Infected Patients with Cirrhosis and ESLD**

| | |
|---|---|
| Age (years), median (IQR) | 40 (37-44) |
| Gender, n (%) | |
| Male | 84 (81) |
| Female | 20 (19) |
| HIV-1 risk factors, n (%) | |
| Intravenous drug use | 74 (71) |
| MSM | 15 (14) |
| Heterosexual relations | 13 (13) |
| Unknown | 2 (2) |
| AIDS criteria (CDC, 1993), n (%) | 55 (53%) |
| CD4 cell count (cells/mm$^3$), median (range) | 202 (129-311) |
| Plasma HIV-1 RNA viral load (copies/mL)* | |
| Median (IQR) | 556 (<200-29,368) |
| Viral load BDL (<200 copies/mL), n (%) | 39 (42) |
| Antiretroviral therapy | |
| PI-based regimen | 21 (20) |
| NNRTI-based regimen | 25 (24) |
| Other regimens | 17 (16) |
| No therapy | 42 (40) |
| Etiology of cirrhosis, n (%) | |
| HCV | 86 (83) |
| HBV | 8 (8) |
| HCV + HBV | 6 (6) |
| Cryptogenic | 4 (4) |
| Duration of HIV infection (months), median (IQR) | 95.4 (56.9-144.0) |
| Duration of HCV infection (months), median (IQR) | 204 (132-252) |
| Alcohol intake > 50 g/day, n (%) | 24 (23%) |
| First manifestation of ESLD, n (%)† | |
| Ascites | 67 (64) |
| Variceal bleeding | 33 (32) |
| Hepatic encephalopathy | 22 (21) |
| Spontaneous bacterial peritonitis | 13 (12) |
| Hepatocellular carcinoma | 5 (5) |
| Intercurrent illness at initial visit, n (%) | 21 (20) |
| Infection | 17 (16) |
| Other | 4 (4) |
| Child-Turcotte-Pugh class | |
| A | 31 (30) |
| B | 37 (36) |
| C | 36 (35) |
| MELD score, median (IQR) | |
| Global | 13 (10-18) |
| Intravenous drug use | 14.8 (10-18) |
| MSM | 15.8 (12-17) |
| HCV(+) | 13.4 (10-18) |
| HVB(+) | 14.7 (12-18) |

**Abbreviations:** AIDS, acquired immune deficiency syndrome; BDL, below the detection limit; CDC, Centers for Disease Control and Prevention; ESLD, end-stage liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI; protease inhibitor;
*Available in 93 patients.
†Either alone or in combination.

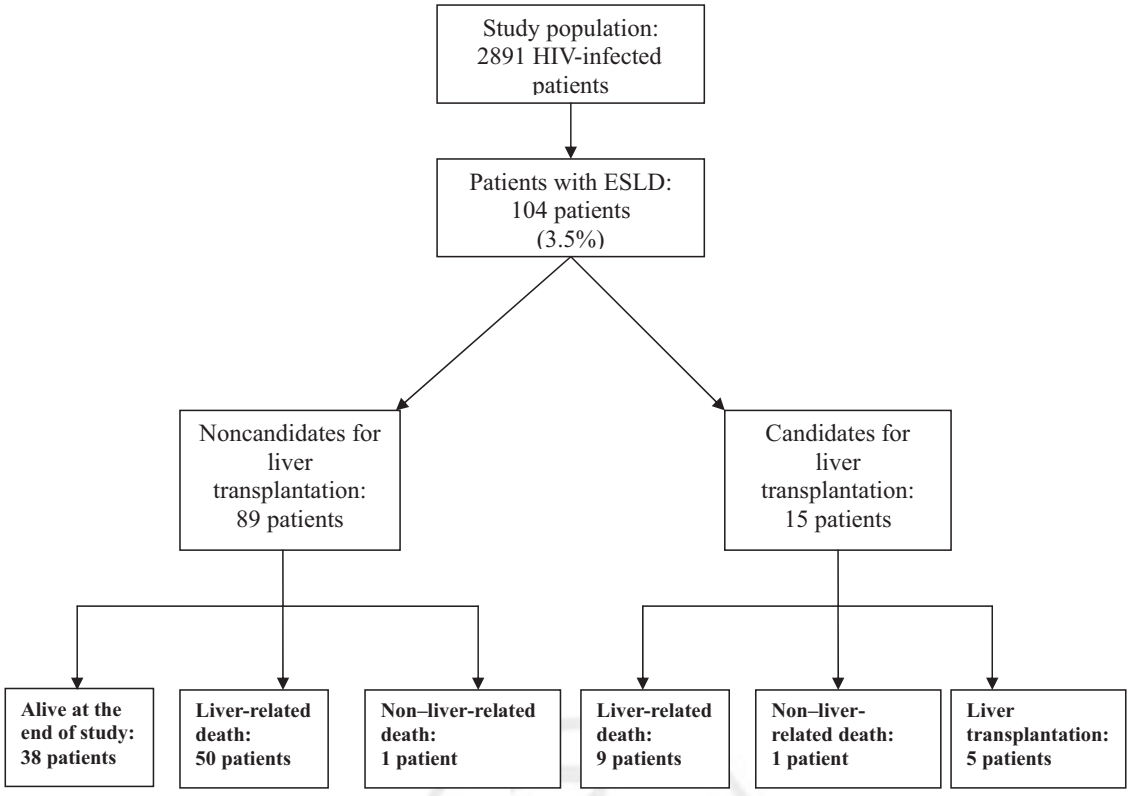


**Figure 1. Outcomes of the 104 HIV-1–infected patients with ESLD included in this study. Patients were or were not candidates according to whether or not they met the acceptance criteria for liver transplantation. Abbreviations: ESLD, end-stage liver disease; HIV, human immunodeficiency virus.**

**TABLE 2. Outcome of the 15 Patients Registered on the OLT Waiting List According to Their Baseline MELD Score**

| No. | Gender | Age | Cause of ESLD | MELD Score | Months on Waiting List | Outcome* |
|---|---|---|---|---|---|---|
| 1 | Female | 47 | HCV | 10 | 6 | OLT |
| 2 | Male | 42 | HCV | 10 | 7 | OLT |
| 3 | Male | 41 | HCV | 11 | 4 | Death |
| 4 | Male | 38 | HCV | 11 | 9 | OLT |
| 5 | Female | 38 | HCV | 11 | 1 | OLT |
| 6 | Male | 43 | HCV | 12 | 5 | Death |
| 7 | Male | 28 | HCV | 13 | 10 | Death |
| 8 | Male | 37 | HCV | 15 | 3 | Death |
| 9 | Male | 39 | HCV | 16 | 18 | Death |
| 10 | Male | 35 | HCV + HBV | 16 | 10 | OLT |
| 11 | Male | 43 | HCV + OH | 16 | 2 | Death |
| 12 | Male | 44 | HCV | 18 | 3 | Death |
| 13 | Male | 40 | HCV + OH | 24 | 1 | Death |
| 14 | Male | 39 | HCV + HBV | 25 | 1 | Death |
| 15 | Female | 35 | HCV | 27 | 2 | Death |

**Abbreviations:** ESLD, end-stage liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; OH, chronic alcohol abuse; OLT, orthotopic liver transplantation.
*The cause of death was liver-related (ESLD) in all but 1 case who died of a drug overdose (case 7).

dependently associated with death ($P < 0.001$). To gain insight into the prognostic value of the MELD score, the same analyses were repeated post hoc in selected subpopulations, and the MELD score maintained its independent association with death in all of them: patients without HCC [hazard ratio per 5-unit increase, 1.55 (95% CI, 1.22-1.98), $P < 0.001$], HCV-infected patients [1.58 (1.27-1.98), $P < 0.001$], patients who were not candidates for liver transplantation [1.49 (1.18-1.90), $P = 0.001$], and patients

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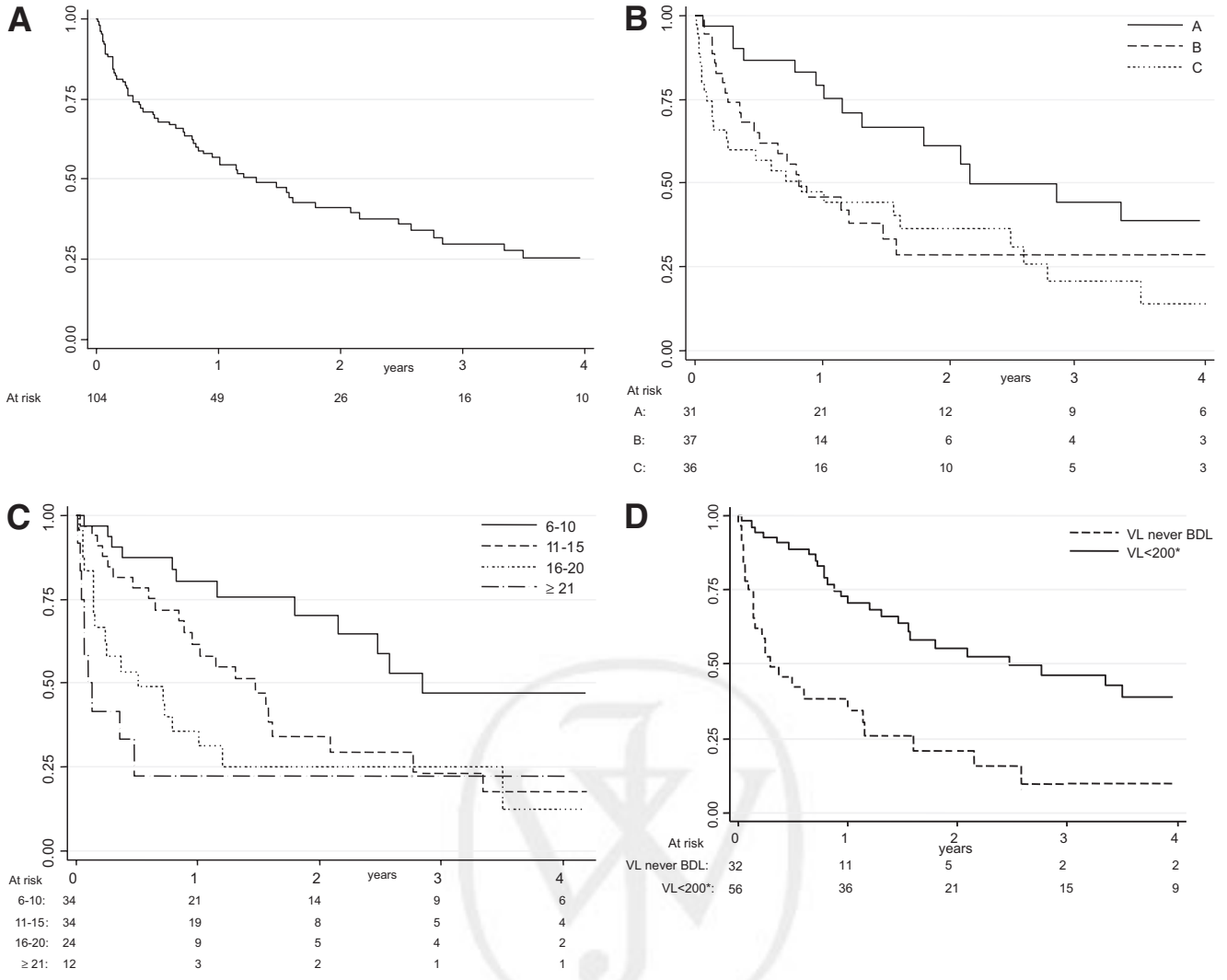


**Figure 2. Probability of survival of human immunodeficiency virus–infected patients with end-stage liver disease according to different predictors of death: (A) overall population, (B) survival according to the Child-Turcotte-Pugh stage, (C) survival according to the Model for End-Stage Liver Disease score, and (D) survival according to plasma human immunodeficiency virus 1 RNA viral suppression on antiretroviral therapy. Abbreviation: BDL, below the detection limit.**

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recently (2002-2004) included in the study [1.59 (1.23-2.04), $P < 0.001$].

We also calculated the risk of death at 1 year using different cutoffs of the MELD score with a receiver operating characteristic curve (figure not shown). A MELD score greater than 10 points had a sensitivity of 90% and a specificity of 39%. Conversely, when the threshold of MELD was 20 points, the sensitivity and specificity were 26% and 94%, respectively.

## Liver Transplantation

Fifteen (14%) of the 104 patients met the criteria to be accepted for liver transplantation and consequently were placed on the transplant waiting list, whereas the remaining 89 (86%) patients were excluded from the option of liver transplantation. The reasons for exclusion were HIV-related conditions in 69 cases (77%; AIDS criteria in 55, immunological criteria in 35, and/or multidrug-resistant virus in 5, alone or in combination), liver-related conditions in 8 (9%; early stage, ie, CPT class A, in 7 and portal vein thrombosis in 1), and other reasons in 12 (13%; active alcohol or drug abuse in 7, unfavorable psychiatric evaluation in 4, and legal problems in 1).

Five (33%) of the 15 patients placed on the transplant waiting list underwent liver transplantation, and the other 10 (67%) died while on the waiting list (median survival, 5 months; range, 1-10). The MELD scores and outcomes of these patients are shown in Table 2. Seven (58%) of the 12 patients with a MELD score $< 20$ died after a median (range) of 5.5 (1-18) months on the waiting list. The 3 patients with a MELD score $> 20$ died 1 to 2 months after being placed on the waiting list. The causes of death in the 10 patients accepted for transplantation but who died while on the waiting list and of

**TABLE 3. Variables at Inclusion and Their Prognostic Value in HIV-Infected Patients with End-Stage Liver Disease**

| Variable | Category | Number of Patients | Number of Deaths (%) | Median Survival (Months) | Crude Hazard Ratio (95% Confidence Interval) | *P* Value |
|---|---|---|---|---|---|---|
| Study site | Hospital Clínic | 57 | 30 (53) | 14 | 1 | 0.889 |
| | Hospital Son Dureta | 47 | 31 (66) | 19 | 1.04 (0.63-1.72) | |
| Age (years) | <40 | 48 | 28 (58) | 14 | 1 | 0.840 |
| | ≥40 | 56 | 33 (59) | 18 | 1.05 (0.64-1.74) | |
| Gender | Male | 84 | 49 (58) | 18 | 1 | 0.508 |
| | Female | 20 | 12 (60) | 9 | 1.24 (0.66-2.33) | |
| Source of HIV infection: IVDA | No | 30 | 19 (63) | 26 | 1 | 0.426 |
| | Yes | 74 | 42 (57) | 12 | 1.25 (0.72-2.17) | |
| AIDS criteria | No | 49 | 29 (59) | 12 | 1 | 0.980 |
| | Yes | 55 | 32 (58) | 16 | 1.01 (0.61-1.66) | |
| Baseline CD4 cell count (cells/mm$^3$) | <100 | 19 | 14 (74) | 14 | 1 | 0.290 |
| | 100-199 | 31 | 19 (61) | 14 | 1.01 (0.50-2.03) | |
| | 200-349 | 35 | 21 (60) | 10 | 0.86 (0.44-1.70) | |
| | ≥350 | 19 | 7 (37) | 34 | 0.45 (0.18-1.11) | |
| Baseline plasma HIV-1 RNA viral load (copies/mL) | ≥200 | 53 | 32 (60) | 14 | 1 | 0.314 |
| | <200 (on HAART) | 39 | 20 (51) | 19 | 0.75 (0.43-1.31) | |
| HAART | No HAART | 42 | 25 (59%) | | 1 | 0.399 |
| | IP | 21 | 13 (61%) | | 0.94 (0.48-1.85) | |
| | NNRTI | 25 | 11 (44%) | | 0.78 (0.38-1.59) | |
| | NRTI | 14 | 10 (71%) | | 1.80 (0.86-3.76) | |
| | Other combinations | 3 | 2 | | 1.10 (0.26-4.68) | |
| Didanosine | Never | 71 | 43 (60%) | | 1 | 0.237 |
| | Previous or currently | 33 | 18 (54%) | | 0.71(0.41-1.24) | |
| Etiology: HCV infection | No | 12 | 6 (50) | 19 | 1 | 0.210 |
| | Yes | 92 | 55 (60) | 14 | 1.72 (0.73-4.04) | |
| Alcohol consumption: >50 g/day | No | 80 | 49 (61) | 14 | 1 | 0.893 |
| | Yes | 24 | 12 (50) | 18 | 0.96 0.51-1.81) | |
| Type of hepatic decompensation (either alone or in combination) | | | | | | |
| Variceal bleeding | No | 71 | 43 (56) | 11 | 1 | 0.235 |
| | Yes | 33 | 18 (54) | 30 | 0.71 (0.41-1.24) | |
| Hepatic encephalopathy | No | 82 | 45 (55) | 14 | 1 | 0.478 |
| | Yes | 22 | 16 (73) | 19 | 1.23 (0.69-2.18) | |
| SBP | No | 91 | 52 (57) | 18 | 1 | 0.605 |
| | Yes | 13 | 9 (69) | 14 | 1.20 (0.59-2.45) | |
| Ascites | No | 37 | 18 (49) | 33 | 1 | 0.06 |
| | Yes | 67 | 43 (64) | 11 | 1.73 (0.99-3.01) | |
| Hepatocellular carcinoma | No | 99 | 57 (58) | 16 | 1 | 0.101 |
| | Yes | 5 | 4 (80) | 2 | 2.36 (0.84-0.57) | |
| Number of signs of decompensation at inclusion | 1 | 77 | 40 (52) | 19 | 1 | 0.286 |
| | >1 | 27 | 21 (78) | 9 | 1.57 (0.89-2.76) | |
| Intercurrent illness at initial visit | No | 83 | 44 (53) | 18 | | 0.068 |
| | Yes | 21 | 17 (81) | 6 | 1.69 (0.96-2.96) | |
| Child-Turcotte-Pugh class | A | 31 | 14 (45) | 26 | 1 | 0.034 |
| | B | 37 | 22 (59) | 10 | 2.03 (1.03-4.00) | |
| | C | 36 | 25 (69) | 10 | 2.33 (1.21-4.50) | |
| MELD score | 6-10 | 34 | 12 (35) | 34 | 1 | 0.000 |
| | 11-15 | 34 | 22 (65) | 18 | 2.22 (1.09-4.49) | |
| | 16-20 | 24 | 18 (75) | 6 | 3.51 (1.68-7.33) | |
| | ≥21 | 12 | 9 (75) | 2 | 6.45 (2.66-15.65) | |
| MELD score | 5-unit increase | NA | NA | NA | 1.53 (1.22-1.92) | 0.000 |
| Inability to achieve an undetectable plasma HIV-1 RNA viral load during follow-up | No | 56 | 26 (46) | | 1 | 0.000 |
| | No | 32 | 25 (78) | | 3.45 (1.96-6.25) | |

**Abbreviations:** AIDS, acquired immune deficiency syndrome; HAART, highly active antiretroviral treatment; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IVDA, intravenous drug abuse; MELD, Model for End-Stage Liver Disease; NA, not applicable; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; SPB, spontaneous bacterial peritonitis.

**TABLE 4. Causes of Death and Survival Time in Candidates and Noncandidates for Liver Transplantation**

| Candidate for liver transplantation | No (n = 53) | Yes (n = 10) |
|---|---|---|
| Gastrointestinal bleeding, n (%) | 20 (38) | 1 (10) |
| Liver failure, n (%) | 14 (26) | 5 (50) |
| Infection, n (%) | 8 (15) | 1 (10) |
| Hepatocellular carcinoma, n (%) | 4 (8) | 0 |
| Hepatorenal syndrome, n (%) | 6 (11) | 2 (20) |
| Non–liver-related, n (%) | 1 (2) | 1 (10) |
| Time to death (months), median (IQR) | 5 (1-11) | 5 (1-13) |

NOTE: No difference was statistically significant.
**Abbreviation:** IQR, interquartile range.

the 53 patients rejected for transplantation who died during follow-up are shown in Table 4.

## DISCUSSION

This prospective study showed that HIV-1–infected patients with ESLD had a rapid progression to death and confirmed the high mortality rates reported in previous retrospective studies in patients coinfected with HIV and HCV.[9,10] After the first major clinical decompensation of their liver disease, our patients had a survival probability of 57% at 1 year of follow-up and 41% at 2 years, although there have been reports of better survival in non–HIV-infected patients with cirrhosis of different etiologies after the onset of hepatic decompensation (74%-90% at 1 year and 65%-80% at 2 years).[9,13-15]

In our cohort, we included HCV and non–HCV-infected patients, and we did not find significant differences in survival according to the etiology of cirrhosis; this suggests that HIV-infected patients with ESLD have an overall poor outcome regardless of the nature of their liver disease.

With respect to immune status and HAART, Merchante et al.[10] showed that a low CD4 cell count and failure to take HAART were also associated with a high risk of death. A higher risk of death among HIV-1–infected patients with liver disease and a low CD4 cell count was also found in the Strategies for Management of Anti-Retroviral Therapy (SMART) study and in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study.[16,17] Another study[18] found that patients with cirrhosis who were able to take HAART during follow-up had a better prognosis. In our series, a reduced CD4 cell count also indicated decreased survival, although the tendency was not significant. We could not find a significant impact of HAART (administered or not and drugs used) on mortality. Nevertheless, those patients that were not able to achieve an undetectable viral load at least intermittently during follow-up had significantly poorer outcomes. This may suggest a protective effect of HAART but could also be the result of a selection bias because the patients with the poorest liver function could have not tolerated HAART long enough to achieve an undetectable viral load or may not even have been offered HAART.

Two other variables related to high mortality in our patients were the CTP and MELD scores, which are the most commonly used methods to estimate the degree of severity of ESLD.[11] This finding agrees with the results obtained by Merchante et al.,[10] who identified a high CTP score and hepatic encephalopathy (one of the components used to calculate the CTP score) as independent predictors of mortality in a series of 153 patients coinfected by HIV and HCV.[10] Girón-González et al.[18] also found that baseline CTP, progression of CTP, and more than 1 decompensation during follow-up were independent predictors of death.

One remarkable finding in our study was that a high MELD score was independently associated with mortality. Subramanian et al.[19] observed similar results for HIV-infected patients on the transplant waiting list in the United States. These authors reported that the MELD score was the only prognostic factor of pretransplant mortality. This allowed us to stratify our patients into different categories according to their MELD score and to accurately assess the risk of death in each category. Interestingly, the mortality in each category of our HIV-infected patients was approximately 2 to 4 times higher than the mortality reported for the corresponding categories of non–HIV-infected patients with cirrhosis,[20] indicating yet again that HIV-infected patients with cirrhosis have a poorer survival than non–HIV-infected patients, regardless of their similar baseline severity of chronic liver disease. The high prognostic value of the MELD score found in our study is also relevant given the increasing interest in MELD as a tool to indicate liver transplantation.[11] According to the survival curves calculated for the different MELD categories (Fig. 2C), liver transplantation could be recommended in HIV-infected patients with cirrhosis with a MELD score greater than 10 because the probability of survival observed in these patients was clearly lower than that currently expected following liver transplantation: <65% versus 85% at 1 year and <30% versus 82% at 2 years, respectively [posttransplant survival data were obtained from the European Liver Transplant Registry at http://www.eltr.org (accessed January 2008)]. This MELD value of 10 is substantially lower than that of 15, which is the MELD value usually considered as the cutoff to decide whether liver transplan-

tation in non–HIV-infected patients gives a true survival benefit (MELD $\geq$ 15) or is a futile procedure (MELD $<$ 15).[21] Therefore, it might also be suggested that liver transplantation in HIV-infected patients should be indicated earlier than in non–HIV-infected patients.

It should be noted, however, that most patients in whom liver transplantation would be indicated primarily on the basis of the MELD score do not fulfill the criteria for this procedure, as observed in our series, in which only 14% of HIV-infected patients with ESLD were included on the liver transplant waiting list. This figure was similar to the figure of 17% reported from a cross-sectional study performed in Spain during the same period.[6] In our study, the conditions most frequently considered exclusion criteria for liver transplantation were related to HIV status, such as previous AIDS-defining disease or marked immunosuppression at the time of evaluation. Other exclusion criteria were liver disease at a stage that was too early for transplantation, namely, CTP class A in the absence of HCC, and psychological problems. Another interesting finding in our study was that, once on the transplant waiting list, HIV-infected patients with ESLD continued to have very high mortality: 67% after a median time of 5 months. In comparison, the mortality rate for non–HIV-infected patients while on the liver transplant waiting list in our center ranged from 8% to 12% per year during the same period. High mortality rates of patients with ESLD who were coinfected with HIV and HCV and were waiting for liver transplantation have been reported elsewhere.[8,22] In one study,[8] mortality rates during pretransplant evaluation among HIV-positive (n = 58) and HIV-negative (n = 1359) patients were 36% and 15%, respectively ($P < 0.001$). This unfavorable comparison of HIV-infected patients with non–HIV-infected patients can be seen in the fact that the calculated mortality rate per 1000 patient years in our patients with a MELD score $<$ 20 (ie, a low-to-moderate score) was 318.1, whereas the corresponding figure for non–HIV-infected patients reported by Merion et al.[23] was 85.4. All our patients with higher MELD scores died after a very short period of time, only 1 or 2 months. Furthermore, by comparing our series with Merion et al.'s series, we found that the calculated mortality rate for each particular MELD category in HIV-infected patients was similar to the mortality rate in non–HIV-infected patients with a MELD category that was roughly 10 points higher (Table 5). Although no robust conclusions can be drawn on this issue because of the small number of HIV-infected patients who died while on the waiting list in our series, these comparisons might have important implications for the prioritization of HIV-1–infected patients according to the MELD score because the same MELD value appears to be associated with a very different expected survival while a patient is on the waiting list and, therefore, with a very different probability of receiving a transplant.

The main limitation of our study is the lack of an HIV-negative control group. Consequently, we had to compare some of our findings, especially those regarding the waiting list for liver transplantation, with the results in HIV-negative patients previously reported by other authors. Therefore, further properly designed studies are necessary to validate our findings on this particular issue.

**TABLE 5. Mortality Rate (per 1000 Patient Years) on the Waiting List for This Study's HIV-Infected Patients and for Non–HIV-Infected Patients Reported by Merion et al.[23] According to Different MELD Categories**

| HIV-Infected Patients (This Study) | | Non–HIV-Infected Patients (Merion et al.[23]) | |
|---|---|---|---|
| MELD Category | Mortality Rate | MELD Category | Mortality Rate |
| 6-14 | 857.1 | 24-26 | 840.7 |
| 15-20 | 1,333.3 | 27-29 | 1,663.8 |
| 21-29 | 9,000 | 30-39 | 13,152.7 |

**Abbreviations:** HIV, human immunodeficiency virus; MELD, Model for End-Stage Liver Disease.

In conclusion, our study shows that HIV-1–infected patients with ESLD, especially those patients with a persistently detectable HIV viral load, have a poor short-term outcome, suggesting a possible protective effect of HAART that warrants further investigation. Survival at 1 year in our study and others[9,18] is only 50% to 60%. In addition, the MELD score is a strong prognostic factor and might be relevant for the selection of these patients for liver transplantation. However, our results also show that only a relatively small proportion of HIV-1–infected patients are adequate candidates for this procedure and that, for those accepted for liver transplantation, a high mortality rate while they are on the waiting list reduces their probability of receiving a transplant.

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