The natural history of liver cirrhosis in HIV-HCV coinfected patients

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Objective: To provide detailed information about the natural history of HIV–HCV coinfected patients with cirrhosis.

Methods: Prospective cohort including 340 HIV-HCV coinfected patients with compensated (n = 248) or decompensated (n = 92) cirrhosis. We evaluated predictors of survival and of first hepatic decompensation.

Results: The mortality rate for patients with decompensated and compensated cirrhosis was 27.14 deaths per 100 person-years (95% CI, 18.93–35.35) and 3.98 deaths per 100 person-years (95% CI, 2.42–5.54) respectively. Rate of first hepatic decompensation in patients with compensated cirrhosis was 4.62 per 100 persons-years (95% CI 2.91–6.33). In the complete cohort, permanent HAART interruption during follow-up, CD4 cell count nadir and baseline CPS-B or C were significantly associated with shorter survival. In patients with compensated cirrhosis factors significantly associated with decreased survival were having the first hepatic decompensation during follow-up, permanent HAART discontinuation, and Child-Pugh scores B and C at baseline. For patients with compensated cirrhosis, time since diagnosis of HCV infection, Child-Pugh score B and C and permanent HAART discontinuation were significantly associated with the risk of first hepatic decompensation. Sustained viral response to anti-HCV therapy was not independently associated with better survival in patients with compensated cirrhosis.

Conclusion: HIV-HCV coinfected patients with cirrhosis have a relatively good three year survival (87%). In contrast, two year survival of patient with decompensated liver cirrhosis is only 50%. Three-year survival was mostly impacted by liver related factors and HAART maintenance.

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Introduction

Since the advent of highly active anitretroviral therapy (HAART) survival of HIV infected patients has continuously improved due to the dramatic decrease in the incidence of classical opportunistic diseases. Concomitantly with this decrease of mortality due to opportunistic diseases, the relative importance of mortality due to end-stage liver disease has progressively increased [1].

It has been reported that HIV-HCV coinfected patients have a worse prognosis than patients monoinfected with HCV [2–8]. Several cohorts have detailed the natural history of end-stage liver disease in HIV-HCV coinfected patients [9–11]. In addition the natural history of compensated cirrhosis in coinfected patients has been described in smaller cohorts including less than 200 patients [12,13]

The goal of our study was to describe in detail the natural history and prognostic factors of compensated and decompensated liver cirrhosis in a larger cohort of HIV-HCV coinfected patients who have been followed for approximately three years.

Patients and methods

Study design

To be included in this multicentre (nine hospitals in Spain), prospective cohort, patients had to be HIV-HCV coinfected and had a diagnosis of liver cirrhosis. Patients enrolled from June, 2004 to June 2005 and are still under follow-up. Median follow up for this report is 2.8 years (IQR 1.47–3.02). The study was approved by the local ethics committees and all patients gave dated and written informed consent

Liver cirrhosis was diagnosed by a biopsy [14], by a prior diagnosis of liver decompensation or by a Bonacini score of $\geq$ 8 [15]. Liver cirrhosis was classified as decompensated or compensated based on the presence or absence of a history of hepatic decompensation. Patients with decompensated cirrhosis were enrolled only if the first episode of decompensation had occurred during the year prior to baseline visit.

Hepatitis C was diagnosed based on a positive serology or positive HCV plasma RNA by PCR. Hepatitis C genotyping was also routinely performed. Hepatitis B was diagnosed based on a positive serology.

All patients had a baseline visit and then one follow-up visit in monographic HIV clinics every six months. In each visit we reviewed clinical events, laboratory data, Child-Pugh score (CPS), consumption of alcohol and illicit drugs, type of HAART regimen, type of treatment for hepatitis C and/or B and liver transplant criteria.

The primary endpoint was survival defined as time from baseline visit to liver transplant, liver cancer or death (all causes). Death was considered liver-related if the cause of death was progressive liver insufficiency, liver cancer or if death occurred within 40 days after an episode of liver decompensation. Secondary endpoints were first episode of liver cirrhosis decompensation in patients with compensated liver cirrhosis at baseline and recurrent episodes of liver cirrhosis decompensation during follow-up in patients with decompensated liver cirrhosis at baseline.

Statistical analysis

Qualitative variables are described with frequencies and percentages. Quantitative variables are described with mean, standard deviation, median and interquartile range. Comparisons between categorical variables were made by the chi-square of the Fisher test when appropriate. Comparisons between continuous variables were made using the Student t test or Mann-Whitney U test, depending on the normality of distributions. Normality of the variables was tested with the Kolmogorov-Smirnov-Lilliefords test.

Time to event was calculated as months from baseline visit to primary endpoint diagnosis.. For secondary endpoints, time to event has been calculated as the number of months from baseline visit until the episode of liver decompensation. Survival functions for primary and secondary endpoints were done by the Kaplan-Meier method. Survival curves were compared using the Log-Rank test.

We analyzed the impact of prognostic factors upon primary and secondary endpoints Univariant analysis was performed using bivariate Cox regression. Those variables which showed a p value < 0.05 in the univariate analyis were included in the Cox regression mulitvariate model. SPSS 16.0 software was used for analysis. For all test we considered as statistically significant a bilateral p value < 0.05.

Results

Three-hundred and forty HIV-HCV coinfected patients were included (Table 1). The overall mortality rate was 8.55 deaths per 100 person-years (95% CI, 6.51–10.60). Of the 67 deaths, 45 (67.2%) were liver-related, 15 (22.4%) non-liver related and in 7 (10.4%) the cause was unknown. Mortality rate for patients with decompensated cirrhosis was 27.14 deaths per 100 person-years (95% CI, 18.93–35.35) and 3.98 deaths per 100 person-years (95% CI,

Table 1. Baseline characteristcs of HIV-HCV coinfected patients with liver cirrhosis by compensation status.

VARIABLE	COMPENSATED (n = 248)	DESCOMPENSATED (n = 92)	p value
Male sex – n (%)	193 (77.8)	74 (80.4)	0.658
Age-yr			
Median	42.4	40.9	0.088
Interquartile range	39.8–45.4	38.5–44.3	
Diagnosis – n (%)			
Liver biopsy	212 (85.5)	0	
Clinical decompensation	0	92 (100)	
Bonacini Score > 8	36 (14.5)	0	
Time-yr since cirrhosis diagnosis,			
Median (interquartile range)	2.2 (0.9–3.7)	0.0 (0.0–0.2)	0.0001
Time-yr since HIV diagnosis,			
Median (interquartile range)	13.4 (9.0–17)	13.7 (10.2–17.1)	0.821
CDC C3 stage– n (%)	55 (22.3)	43 (46.7)	0.0001
Route of HIV infection– n (%)			
Injection-drug use	213 (85.9)	85 (92.4)	
Male homosexual sex	33 (13.3)	6 (6.5)	0.137
Heterosexual sex	4 (1.6)	0 (0)	
Receiving HAART– n (%)	218 (88.3)	73 (79.3)	0.053
CD4 cells per μL, Median (interquartile range)	179 (83.0–272.0)	97.5 (58.0–178.0)	
Nadir	437 (284.0–646.0	235 (139.0–364.0	0.0001
Baseline			0.0001
Plasma HIVRNA HIV <50 copies/ml – n (%)	150 (62.8)	47 (55.9)	0.299
Hepatitis B virus coinfection– n (%)	9 (4.3)	5 (6.2)	0.546
Hepatitis C virus genotype 2–3– n (%)[a]	59 (23.8)	15 (16.3)	0.183
Hepatitis C virus therapy – n (%)	184 (74.2)	29 (31.5)	0.0001
Response to Hepatitis C virus therapy – n (%)		4 (13.8)	0.203
Sustained virologic response	45 (24.5)	25 (86.2)	
Only End of treatment or no response	135 (73.4)	0 (0)	
Still on treatment	4 (2.17)		
Child Pugh score at baseline – n (%)			
A	223 (90.3)	26 (28.3)	0.0001
B	22 (8.9)	28 (30.4)	
C	2 (0.8)	38 (41.3)	

[a]Determined in 262 patients

2.42–5.54) for patients with compensated cirrhosis. Liver-related deaths were also significantly more frequent in patients with decompensated cirrhosis than in patients with compensated cirrhosis (33.7%, vs. 5.6%; $p < 0.001$).

A liver transplant was performed in 13 patients, 8 (8.7%) in patients with decompensated cirrhosis and 5 (2%) in patients with compensated cirrhosis at baseline. Six patients suffered liver cancer (2 occurred in the decompensated group and 4 in the compensated group).

After three years of follow-up survival was 75% (95% CI: 70%–80%). One, two and three year survival of patients with decompensated versus compensated cirrhosis at baseline was 66% (95% CI: 56%–76%), 50% (95% CI: 39%–61%), 43% (95% CI: 32%–54%) and 96% (95% CI: 93%–99%), 90% (95% CI: 86%–94%) and 87% (95% CI: 82%–92%) respectively ($p < 0.001$. Fig. 1a). Three year survival of patients with CPS-A, B and C at baseline was 89% (95% CI: 85%–93%), 50% (95% CI: 35%–65%) a 16% (95% CI: 3%–29%) respectively ($p < 0.001$ for all comparisons. Fig. 1b).

In the complete cohort, multivariant analysis showed that only permanent HAART interruption during follow-up, CD4 cell count nadir and baseline CPS-B or C remained significantly associated with survival. If we excluded from the analysis CPS, then the variable decompensation at baseline was significantly associated with survival both in the univariant and multivariant analyisis

In patients with compensated cirrhosis at baseline factors significantly associated with a shorter survival in the multivariant analysis were having the first hepatic decompensation during follow-up, permanent HAART discontinuation, and CPS-B and C at baseline. In patients with decompensated cirrhosis at baseline, the only factors that were significantly associated with a shorter survival were permanent discontinuation of HAART during follow up and CPS-C at baseline.

During follow-up 74 liver decompensations (21.8%) occurred. One, two and three year probability of a new episode of hepatic decompensation in patients with decompensated versus compensated cirrhosis at baseline was 47%, 55%, 69% and 5%, 9% and 13% respectively ($p < 0.001$). Rate of first hepatic decompensation in patients with compensated cirrhosis at baseline was 4.62 per 100 persons-years (95% CI 2.91–6.33). Three year probabilities of continuing with compensated cirrhosis of patients with CPS-A, B and C at baseline were 0.91, 0.39 and 0 respectively ($p < 0.0001$; Fig. 1c).

Table 2. Variables associated with surival in HIV-HCV coinfected patients with cirrhosis. Univariant and multivariant analysis.

VARIABLE	UNIVARIANT ANALYISIS HR (95% CI). p value	MULTIVARIANT ANALYSIS HR (95% CI). p value
Decompensation at baseline	6.38 (4.05–10.06) 0.0001	...
Time since HCV infection	0.32 (0.19–0.49) 0.0001	...
Hepatitis C virus therapy	1.00 (0.95–1.1) 0.929	
Sustained virologic response after therapy for Hepatitis C	0.615 (0.33–1.14) 0.123	...
On HAART at baseline	0.53 (0.31–0.89) 0.019	...
Non continuous HAART during follow-up	1.31 (0.64–2.67) 0.463	...
Permanent HAART discontinuation	4.06 (2.51–6.57) 0.0001	3.53 (1.96–6.37) 0.0001
Plasma HIV RNA <50 copies/ml at baseline	0.58 (0.37–0.92) 0.019	...
CD4+ cells per μL		
<100 at baseline	2.67 (1.28–5.57) 0.009	...
Nadir	0.99 (0.99–1.00) 0.018	0.99 (0.99–1.00) 0.017
Child Pugh Score at baseline		
B	6.67 (3.82–11.65) 0.0001	5.22 (2.67–10.18) 0.0001
C	17.59 (10.17–30.43) 0.0001	9.96 (4.41-22-53) 0.0001

Univariant and multivariant analyises showed that time since HCV infection diagnosis, permanent HAART discontinuation and CPS-B and C at baseline were significantly associated with the risk of having the first hepatic decompensation.

Finally, in an analysis restricted to patients with compensated cirrhosis at baseline and who received anti hepatitis C treatment at any point since the diagnosis of cirrhosis we evaluated a combined endpoint of death and/or hepatocarcinoma and/or liver transplant and/or first

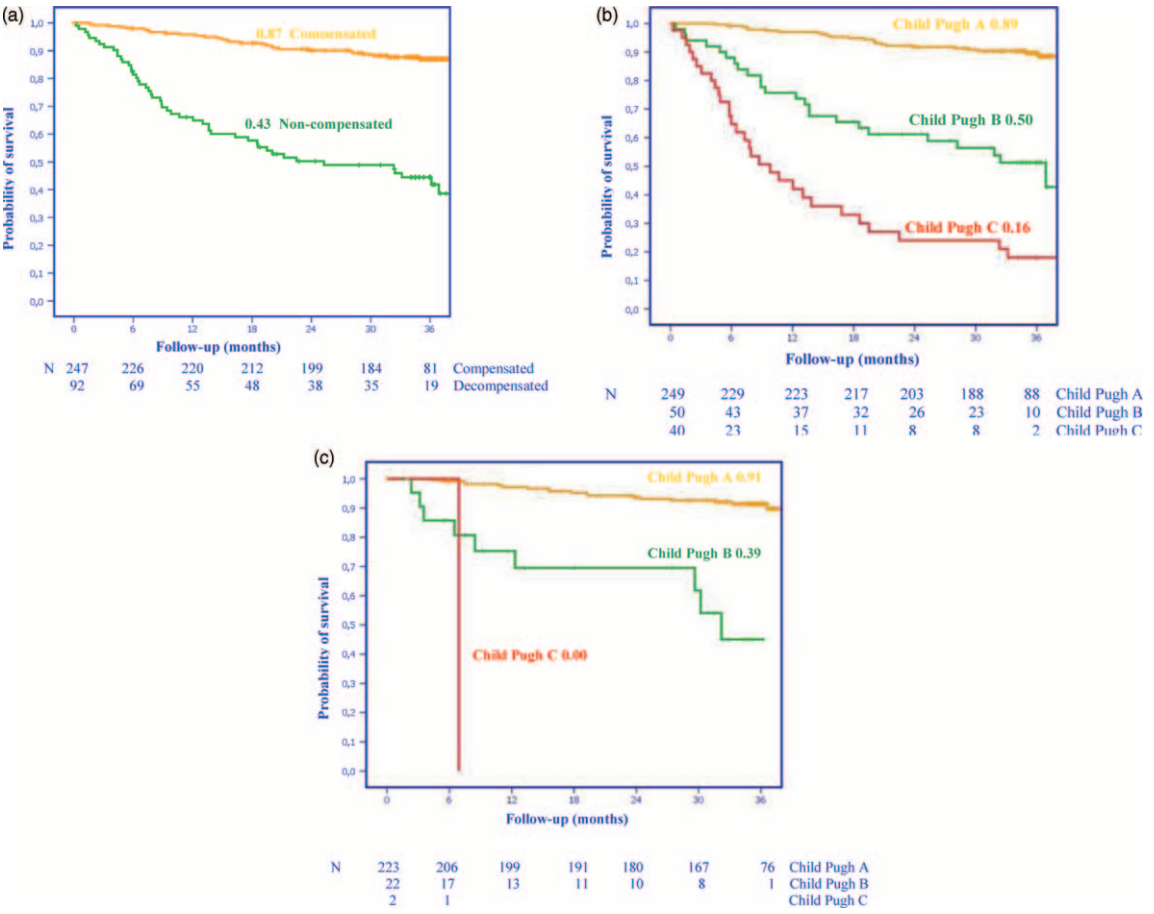

Fig. 1. ?? (a). Survival of HIV-HCV coinfected patients with compensated and decompensated cirrhosis.. Figure 1 (b). Survival of HIV-HCV coinfected patients with cirrhosis according to Child-Pugh score. Figure 1 (c). Probability of first hepatic decompensation in HIV-HCV coinfected patients with compensated cirrhosis according to baseline Child-Pugh score.

liver decompensation during follow-up. There were 25 endpoints, two in patients who achieved a sustained virological response (SVR) and 23 in patients who did not achieve SVR. By log-rank test this difference was statistically significant ($p = 0.042$). However when we performed Cox regression analysis in this group of patients including response to anti-HCV therapy as a time dependent variable the only factors significantly associated with survival were the baseline CPS and lack of HAART or permanent interruption of HAART.

Discussion

Our cohort shows that three year survival of HIV coinfected patients with compensated liver cirrhosis is relatively high (87%), but slightly lower to what has been described in other studies of HCV monoinfected patients [6]. Once decompensation has occurred, prognosis rapidly worsens with a two-year survival of just 50%. In patients with compensated cirrhosis at baseline the highest risk of first hepatic decompensation was in those patients with CPS-B and C.

We have also found that in patients with compensated cirrhosis permanent HAART discontinuation was independently associated with the risk of first hepatic decompensation. The apparent benefit associated with HAART maintenance in our cohort might be due to prescription bias. Clinicians might have decided to stop HAART precisely in patients with more advanced liver disease unable to tolerate antiretrovirals and consequently with worse survival prognosis. However, at a minimum our study shows that HAART, does not worsen the prognosis of coinfected patients with compensated or decompensated cirrhosis and might even improve survival. It is also possible that HAART might be beneficial for coinfected patients due to relatively preservation of the immune function or even by decreasing the HIV-induced progression of liver fibrosis or hepatocyte apoptosis [16–18].

We have not found conclusive evidence that achieving a SVR to anti HCV treatment improved the three-year survival or the risk of decompensation of our patients with compensated cirrhosis. In a smaller cohort of coinfected patients with compensated cirrhosis, Pineda and cols [12] found that having received anti HCV therapy decreased the risk of decompensation but did not improve survival. In addition, Berenguer and collaborators [19] have reported that having a fibrosis score F3 or F4 was independently associated with liver related events regardless of having achieved a SVR.

It is possible that the reason why we have not found a survival benefit associated to SVR is lack of power and/or insufficient follow-up. The data from our cohort suggest that in patients who have achieved SVR the probability of suffering death, hepatocarcinoma, liver transplant or first liver decompensation is rather low. Longer follow-up of our cohort would confirm if SVR improves survival and the incidence of liver decompensation beyond three years..

As it has been shown previously [9,10,12] our study supports the use of the CPS to estimate the prognosis of coinfected patients with liver cirrhosis. There are other scores that evaluate the risk of liver disease progression such as APRI [20], HGM-3 [21] or MELD [22], but in contrast with the CPS none of them include liver decompensations in the score which, as our study shows, have critical impact on survival.

Our study provides also a very precise estimate of the risk of first hepatic decompensation in coinfected patients. Based in our findings, the risk is relatively low with a three-year probability of liver decompensation of 0.13. This risk is similar to the 0.12 reported in HCV monoinfected patients [6]. Our data also show that once the first liver decompensation has occurred, time to the next decompensation is critically reduced.

In summary, our study shows a relatively good three year survival of HIV-HCV coinfected patients with compensated liver cirrhosis. In contrast, two year survival of patient with decompensated liver cirrhosis is only 50%. Our study also emphasizes the clinical utility of the CPS in this population. Further follow up is needed to confirm a possible survival benefit for patients with cirrhosis who achieve a SVR.

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