



HAL
open science

MELD Score Kinetics in Decompensated HIV+/HCV+ Patients: A Useful Prognostic Tool (ANRS HC EP 25 PRETHEVIC Cohort Study)

Moana Gelu-Simeon, Tatiana Bayan, Maria Ostos, Faroudy Boufassa, Elina Teicher, Jean-Marc Steyaert, Inga Bertucci, Rodolphe Anty, Georges-Philippe Pageaux, Laurence Meyer, et al.

► To cite this version:

Moana Gelu-Simeon, Tatiana Bayan, Maria Ostos, Faroudy Boufassa, Elina Teicher, et al.. MELD Score Kinetics in Decompensated HIV+/HCV+ Patients: A Useful Prognostic Tool (ANRS HC EP 25 PRETHEVIC Cohort Study). *Medicine*, 2015, 94 (30), pp.e1239. 10.1097/MD.0000000000001239 . hal-01205351

HAL Id: hal-01205351

<https://univ-rennes.hal.science/hal-01205351>

Submitted on 8 Jun 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

MELD Score Kinetics in Decompensated HIV+/HCV+ Patients

A Useful Prognostic Tool (ANRS HC EP 25 PRETHEVIC Cohort Study)

Moana Gelu-Simeon, MD, PhD, Tatiana Bayan, Maria Ostos, PhD, Farouly Boufassa, PhD, Elina Teicher, MD, PhD, Jean-Marc Steyaert, PhD, Inga Bertucci, Rodolphe Anty, MD, PhD, Georges-Philippe Pageaux, MD, PhD, Laurence Meyer, MD, PhD, Jean-Charles Duclos-Vallée, MD, PhD, for the ANRS HC EP 25 PRETHEVIC study group

Abstract: To assess prognostic factors for survival and describe Model for End-Stage liver disease (MELD) dynamics in human immunodeficiency virus+/hepatitis C virus+ (HIV+/HCV+) patients after an initial episode of hepatic decompensation.

An HIV+/HCV+ cohort of patients experiencing an initial decompensation episode within the year preceding enrollment were followed prospectively. Clinical and biological data were collected every 3 months. Predictors for survival were identified using Kaplan–Meier

curves and Cox models. A 2-slope-mixed linear model was used to estimate MELD score changes as a function of survival.

Sixty seven patients were included in 32 centers between 2009 and 2012 (72% male; median age: 48 years [interquartile ratio (IQR):45–52], median follow-up: 22.4 months [range: 0.5–65.3]). Overall survival rates were 86%, 78%, and 59% at 6, 12, and 24 months, respectively. Under multivariate analysis, the MELD score at initial decompensation was predictive of survival, adjusted for age, type of decompensation, baseline CD4 counts, and further decompensation during follow-up as a time-dependent variable. The adjusted hazard ratio of death was 1.32 for a score 3 points higher (95% CI: [1.06–1.63], $P=0.012$). MELD score kinetics within the 6 months after initial decompensation differed significantly between non-deceased and deceased patients, with a decreased (–0.49/month; $P=0.016$), versus a flat (+0.06/month, $P=0.753$) mean change in score.

MELD is an effective tool to predict survival in HIV+/HCV+ patients with decompensated cirrhosis. A non-decreasing MELD score within 6 months following this initial decompensation episode may benefit from privileged access to liver transplantation in this poor prognosis population.

(*Medicine* 94(30):e1239)

Editor: Giuseppe Lapadula.

Received: April 9, 2015; revised: July 1, 2015; accepted: July 2, 2015.

From the AP-HP Hôpital Paul-Brousse, Centre Hépatobiliaire (MG-S, MO, ET, J-CD-V); DHU Hépatinov, Villejuif (MG-S, MO, ET, J-CD-V); Inserm, UMR 1018 CESP, Centre de Recherche en Epidémiologie et Santé des Populations (TB, FB, LM); Université Paris-Sud, Faculté de Médecine Paris-Sud, Le Kremlin-Bicêtre (TB, FB, LM, J-CD-V); École Polytechnique, Laboratoire d'Informatique (LIX), Palaiseau (J-MS); ANRS, Agence Nationale de Recherches sur le Sida et les hépatites virales, Paris (IB); Inserm, UMR 1193, Villejuif (J-CD-V); AP-HP Hôpital de Bicêtre, Service de Médecine Interne, Immunologie Clinique et Maladies Infectieuses, Le Kremlin-Bicêtre (ET); Centre Hospitalier Universitaire de Nice – Hôpital de l'Archet, Service d'Hépatogastroentérologie, Nice (RA); Université de Nice-Sophia-Antipolis, Faculté de Médecine (RA); Inserm, Unité 1065, Nice (RA); Centre Hospitalier Régional Universitaire de Montpellier – Hôpital Saint-Eloi, Service d'Hépatogastroentérologie et Transplantation (G-PP); Université Montpellier 1, Faculté de Médecine, Montpellier (G-PP); CHU de Pointe-à-Pitre, Service d'Hépatogastro-Entérologie, Pointe-à-Pitre Cedex, Guadeloupe (MG-S); Institut National de la Santé et de la Recherche Médicale (Inserm), U.1085, Institut de Recherche Santé Environnement et Travail (IRSET), Rennes (MG-S); and AP-HP Hôpital Bicêtre, Service de Santé Publique, Le Kremlin-Bicêtre, France (LM).

Correspondence: Moana Gelu-Simeon, Jean-Charles Duclos-Vallée, AP-HP Hôpital Paul Brousse, Centre Hépatobiliaire, DHU Hépatinov, 12 Avenue Paul Vaillant-Couturier, 94800 Villejuif, France (e-mail: moana.simeon@gmail.com, jean-charles.duclos-vallee@pbr.aphp.fr).

LM and J-CD-V contributed equally to the work.

Study concept and design: JCDV and LM; acquisition of data: MO and MGS; analysis and interpretation of data: TB, FB, LM, MO, MGS, and JCDV; drafting of the manuscript: TB, FB, LM, MO, MGS, and JCDV; critical revision of the manuscript for important intellectual content: all authors; statistical analysis: TB, FB, and LM; obtaining of funding: JCDV and LM; administrative, technical, or material support: MO; study supervision: MO, MGS, and JCDV; and writing assistance: VH.

ANRS HC EP 25 PRETHEVIC study group, the list of contributors is given in the Appendix section.

The French National Institute for Health and Medical Research – French National Agency for Research on Aids and viral hepatitis (Inserm-ANRS) sponsored this study.

The authors have no conflicts of interest to disclose.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0, where it is permissible to download, share and reproduce the work in any medium, provided it is properly cited. The work cannot be changed in any way or used commercially.

ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001239

Abbreviations: aHR = adjusted hazard ratio, ANRS = Agence Nationale de Recherches sur le Sida et les hépatites virales, ATV = atazanavir, cART = combined antiretroviral therapy, CTP = Child–Turcotte–Pugh, dot = duration of the treatment, ESLD = end-stage liver disease, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HE = hepatic encephalopathy, IQR = interquartile ratio, LT = liver transplantation, MELD = Model for End-Stage liver disease, PHGB = portal hypertensive gastrointestinal bleeding.

INTRODUCTION

Human immunodeficiency virus (HIV) infection increases the rate of liver disease progression in patients with hepatitis C virus (HCV) infection, and HIV/HCV-coinfected patients experience higher rates of hepatic decompensation and severe liver events than HCV-monoinfected patients.^{1–4} The important overall improvement in life expectancy among HIV-infected patients treated with combined antiretroviral therapy (cART) has been accompanied by a higher rate of end-stage liver disease (ESLD) in HIV/HCV-coinfected patients, and a 13% probability of death due to liver failure at 5 years after the diagnosis of cirrhosis.⁵ As in HCV-monoinfected patients, liver transplantation (LT) should be considered for HIV/HCV-coinfected patients whose liver function has deteriorated, despite

previous reports of poorer results in HIV/HCV-coinfected patients than HIV-monoinfected patients.^{6–8} In HIV-uninfected patients, it has been established that the Model for End-Stage liver disease (MELD) score can determine priorities for access to LT.^{9,10} Recent data have demonstrated that the MELD score is also an independent predictor of pretransplant mortality in HIV-infected patients.^{11,12} On the other hand, several studies have suggested that different factors that are not included in the MELD score, such as the type of decompensation, the Child–Turcotte–Pugh (CTP) stage, hepatic encephalopathy (HE), the CD4 count or older age, are associated with mortality due to liver failure.^{3,7,11}

Dynamic predictive factors for mortality have been evaluated in patients with advanced cirrhosis, but not specifically for decompensated cirrhosis after the first episode of decompensation of cirrhosis, in either HIV-infected or HIV-uninfected patients.^{13–15}

The aim of this prospective study was to define prognostic factors for survival in HIV/HCV-coinfected patients after an initial episode of decompensation of cirrhosis and to study the kinetics of MELD scores in this population.

PATIENTS AND METHODS

Study Subjects

The ANRS PRETHEVIC study is a multicenter prospective cohort of HIV/HCV-coinfected patients, which was set up in 2009. A total of 32 centers in France, comprising 17 departments of infectious disease or internal medicine and 15 hepatology departments, were involved in this study. A common database was created to collect the data. HIV/HCV-coinfected patients were included between 2009 and 2012 if they had experienced an initial episode of decompensation of cirrhosis and/or a diagnosis of hepatocellular carcinoma (HCC) during the 12 months preceding their enrollment. HCV infection was identified by the simultaneous presence of serum HCV antibodies and HCV ribonucleic acid. Cirrhosis was diagnosed by histological examination and/or noninvasive tests (transient elastography and/or biological markers of fibrosis). The dates of the HCV and HIV diagnoses were recorded.

Follow-Up and Definitions

The patients were followed prospectively through visits scheduled at least every 3 months as from enrollment. At each visit, clinical, MELD score, CTP score, virological, immunological, and drug toxicity assessments were carried out. Episodes of portal hypertensive gastrointestinal bleeding (PHGB), ascites, HE, non-obstructive jaundice, spontaneous bacterial peritonitis, and HCC were considered as reflecting hepatic decompensation. PHGB was diagnosed according to the Baveno criteria.¹⁶ HE was defined by the physician as an episode of mental confusion reported by the patient or their relatives, or the detection of disorientation in the absence of any other non-hepatic cause. Non-obstructive jaundice was diagnosed if the plasma bilirubin level was 17 $\mu\text{mol/L}$ or higher, and an ultrasound examination revealed a normal biliary tract. When the polynuclear count of ascitic fluid was higher than 250 cells/mL or bacteria grew in a culture of ascitic fluid, and no clinical or image data indicative of secondary peritonitis were present, a diagnosis of spontaneous bacterial peritonitis was made. If HCC was suspected during follow-up in light of the results of a previous ultrasound examination or because of elevated α -fetoprotein levels ($>250 \text{ ng/mL}$), the diagnosis was confirmed

by computed tomography or magnetic resonance imaging according to American Association for the Study of Liver Disease criteria (nodule size greater than 1 cm with arterial phase hyperenhancement and portal venous or delayed phase washout at either computed tomography or magnetic resonance imaging).¹⁷ Hepatorenal syndrome was defined as proposed by Arroyo et al.¹⁸ The treatment of HCC was defined according to the Barcelona Clinic Liver Cancer staging system.¹⁹ The treatment history of each patient for HIV and HCV was recorded from its initiation, before the dates of inclusion and hepatic decompensation, and was subsequently updated during follow-up in the PRETHEVIC database.

Access to Liver Transplantation and Causes of Death

At each visit, the decision (Yes/No) to refer a patient to an LT unit was recorded. The dates of registration on the waiting list and of transplantation were recorded. Mortality data were obtained through direct patient follow-up; an expert group classified the causes of death into liver- or HIV-related causes of death. Deaths were considered to be liver-related when attributable to hepatic failure or HCC.

Statistical Analysis

In this analysis, only patients enrolled because of an initial episode of liver decompensation were considered; therefore, 24 patients from the entire cohort of 91 patients were not considered because the only reason for their inclusion was a diagnosis of HCC. The occurrence of death, due to liver failure or any other cause, after the date of the initial decompensation, was the main endpoint of the survival analysis. The relationship between survival and the following parameters was studied: sex, age at hepatic decompensation, HCV/HIV transmission group, HCV genotype, coinfection with hepatitis B virus (HBV) and D virus, and both alcohol consumption and smoking defined by a variable with 3 modalities: past, active or never, unspecified quantity, baseline CDC stage, MELD, and CTP scores, use of anti-HCV therapy, antiretroviral regimen, HIV ribonucleic acid and CD4 cell levels at enrollment, type of initial hepatic decompensation. The occurrence of a new decompensation episode after the initial episode was also included in models, as a time-dependent variable.

Survival since the diagnosis of the initial hepatic decompensation to death or censoring was studied using Kaplan–Meier curves. Censoring was defined at the last visit during the follow-up or the date of LT, whichever came first. Univariate and multivariate Cox models with late entry were used to assess prognostic factors of survival. Late entry was used in models with time zero as the date of first decompensation; subjects entered the dataset at risk (ie, they were considered as exposed to death) only at the date of inclusion. Since the start of follow-up for some individuals could be different from the specified time origin, correcting for late entry avoided to underestimate mortality rate and produced less biased estimates of hazard ratios. All variables with a P value < 0.20 were included in the final model, plus CD4 cell counts at enrolment to assess the role of this factor in such situation. Further episodes of hepatic decompensation during follow-up after inclusion were included in the Cox models as a time dependent variable.

Finally, the kinetics of MELD scores starting from the initial hepatic decompensation episode and throughout follow-up was modeled. At least 2 points of MELD score were required to perform the kinetic of MELD from the first decompensation.

TABLE 1. Characteristics at Inclusion of HIV/HCV-Coinfected Patients With Decompensated Cirrhosis

Characteristics	N = 67
Age (years; median [IQR])	48 [45–52]
Gender (n; %)	
Male	48 (72)
Country of birth (n; %)	
France	54 (81)
Other	13 (19)
Route of HIV/HCV transmission (n; %)	
IVDU	54 (81)
Transfusion	4 (6)
Sexual	9 (13)
CDC classification (n; %)	
A	22 (33)
B	11 (16)
C	34 (51)
CD4 at inclusion (/mm ³ ; median [IQR])	303 [177–480]
cART treatment (n; %)	
No	2 (3)
Yes	65 (97)
HIV viral load (n; %)	
≤Threshold 50 copies/mL	53 (79)
>Threshold 50 copies/mL (log copies/mL; median [IQR])*	2.7 [2.0–3.5]
HCV treatment (n; %)	
No	29 (43)
Yes	38 (57)
HCV viral load (n; %) (IU/mL)	
≤Threshold 20 IU/mL	9 (14)
>Threshold 20 IU/mL (logIU/mL; median [IQR])*	5.8 [5.1–6.2]
Genotype (n; %)	
1	2 (3)
1a	33 (49)
1b	7 (11)
2	1 (2)
3	13 (19)
4	9 (13)
ND	2 (3)
Creatinin (μmol/L; median [IQR])	76 [58–97]
Bilirubin (μmol/L; median [IQR])	32 [21–63]
Platelets (Giga/L; median [IQR])	68 [50–98]
Albumin (g/L; median [IQR])	28.2 [24–34.7]
INR (median [IQR])	1.4 [1.2–1.6]
CHILD score (n; %)	
A	16 (24)
B	31 (46)
C	20 (30)
MELD score (median [IQR])	13.18 [10.54–16.34]

IQR = interquartile ratio, IVDU = intravenous drug user, ND = not done.
* Only in detectable patients.

MELD scores collected after LT were not included in the models. Several piecewise models (1 or more slopes, nodes at different time points since the initial decompensation) were tested. A 2-slope mixed linear model with a node at 6 months was used to estimate the comparative changes in MELD scores in deceased and non-deceased patients. This model was used in

order to take account of the fact that subjects underwent repeated MELD measurements. The best model was chosen using likelihood ratio tests or Akaike Information Criteria. All statistical analyses were performed using SAS version 9.3 (Cary, NC).

Ethical Aspects

Written informed consent was obtained from all study subjects. The study protocol was conducted according to the Declaration of Helsinki and French law for biomedical research. It was approved by the Ethics Committee CPP Ile de France VII (based at Bicêtre Hospital) and the French Regulatory Authority (French National Agency for Medicines and Health Products).

RESULTS

Characteristics of the Study Population at Inclusion

Between 2009 and 2012, 67 HIV/HCV-coinfected patients, 48 of them male (72%), with a median age of 48 years [interquartile ratio (IQR): 45–52] who had experienced at least 1 episode of decompensation during the previous year, were enrolled in the study. The principal characteristics of this population at enrollment are summarized in Table 1. At inclusion, these patients had been diagnosed with HIV and HCV infection between 21.7 [16.4–24.3] and 15.0 [9.5–18.2] years previously, respectively. Three patients (5%) suffered from HBV coinfection. Past or active alcohol consumption was reported in 32 (48%) and 14 (21%) patients, respectively. Past or active smoking was reported in 13 (20%) and 46 (70%) cases, respectively. The presumed route of infection was via drug injection in 81% of the patients. The median body mass index of the study population was 22.5 kg/m² [19.8–26.2]; only 5 patients (8%) presented with obesity (body mass index above 30 kg/m²). Eight patients (12%) had diabetes mellitus (50% type 1 and 50% type 2) and all were being treated with insulin therapy and/or an oral antidiabetic regimen.

HCV-Related Characteristics

In the 86% patients with replicating HCV at enrollment, the median HCV viral load was 5.8 log IU/mL [5.1–6.2]. Of note, in those with history of antiviral therapy for HCV before enrollment, 16% were non-replicating patients.

HIV-Related Characteristics

At enrollment, 97% of patients (n = 65) were being treated with cART, and 53 of them had an HIV viral load ≤50 copies/mL (82%). Among patients with detectable HIV viral load, the median value was 2.7 log copies/mL [2.0–3.5]. The median baseline CD4 count was 303 cells/mm³ [177–480] and the CD4 nadir was 114.5 cells/mm³ [42–166] (n = 46).

Characterization of the Initial Decompensation Episode

The median time elapsing between the diagnosis of cirrhosis and the initial decompensation episode was 24 months [1.4–64.4]. These initial decompensation episodes could be classified as follows: ascites (n = 30 [45%]), non-obstructive jaundice (n = 6 [9%]), PHGB (n = 3 [4%]), and a combination of 2 or more of these in 28 patients (42%). The median interval between the first episode of decompensation and enrollment was 3 months [1–5.5]; 10 and 5 patients experienced 2 or 3

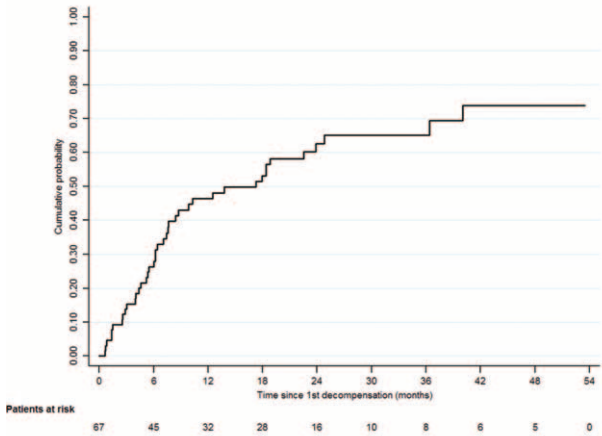


FIGURE 1. Cumulative incidence of further episodes of hepatic decompensation.

episodes of decompensated cirrhosis during this period, respectively.

Twelve (21%) out of the study patients have been treated with cART including atazanavir (ATV) before, at the time of, or after first decompensation of cirrhosis with a median duration of treatment (dot) of 28 months [6.9–46.4]. Four patients started ATV before the first decompensation (median dot: 39 months [IQR: 24–43]) and 1 patient started ATV at the time of the first decompensation (median dot of 9.9 months [2.1–11.8]). The other 7 patients started ATV after the first decompensation. During follow-up, 6 patients stopped ATV and the median duration of cART with ATV for those patients was 8 months [3.7–32.2] from ATV initiation.

Characterization of Other Hepatic Decompensation Episodes and Occurrence of HCC

During follow-up, 35 patients (52%) developed at least 1 new hepatic decompensation episode. Ascites was observed in 10 patients (29%), HE in 4 (11%), and a combination of 2 or

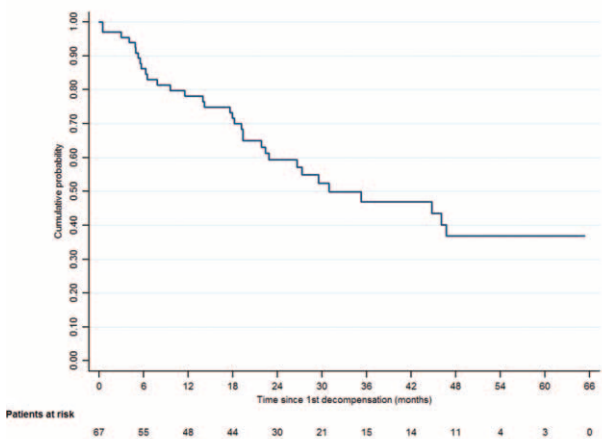


FIGURE 2. Overall survival of HIV/HCV-coinfecting patients after an initial episode of decompensation. HCV = hepatitis C virus, HIV = human immunodeficiency virus.

more types of decompensation in 18 patients (51%). A diagnosis of HCC was made in 12 patients (18%) within a median of 17.4 months [6.5–23.7] since the initial decompensation. The cumulative incidence of new episodes of hepatic decompensation is shown in Figure 1. The probabilities of experiencing at least a second episode of decompensation after the initial 1 were 46% and 63%, at 1 and 2 years, respectively.

Overall Survival and Causes of Death

Thirty three patients (49%) died during a median follow-up period of 22.4 months [7.82–35.28]. Using a Kaplan–Meier estimate, the median survival time was therefore 30.9 months after the initial decompensation episode. Survival rates at 6 months, 1 year, and 2 years were 86%, 78%, and 59%, respectively (Figure 2). Among the 33 patients who died, non-acquired immune deficiency syndrome (AIDS)-classifying infectious disease was the cause of death in 19 (58%), liver disease in 10 (30%), and other causes in 4 (12%). Of the 11 patients who died from liver disease, HCC was the cause of death in 2 patients (20%), and liver failure in 82%, including HE in 4 (40%), PHGB in 3 (30%), and hepatorenal syndrome in 1 (10%).

Evaluation for Liver Transplantation

Among 67 patients with decompensated cirrhosis, 9 patients were not considered for LT and 10 improved their liver function during follow-up without the necessity of performing an evaluation for LT. In contrast, 7 patients died during before being enlisted. Twenty three (34%) patients were contraindicated for LT (the reasons were active alcohol consumption in 13%, not controlled HIV immunosuppression in 6%, HCC outside Milan criteria in 3%, social reasons in 3%, psychiatric disease in 3%, patient refusal in 3%, respiratory failure in 1.5%, and cancer in 1.5%), among these latter 14 (61%) died during follow-up due to septicemia, HCC, or ESLD. Eighteen (27%) patients were enlisted and among them, 9 patients were transplanted, the others died during the waiting period or are still on the waiting list.

Predictive Factors for Survival

Under the univariate Cox proportional hazards regression model, a higher MELD score at initial decompensation was significantly associated with poorer survival (Table 2) as the occurrence of further episodes of decompensation during follow-up. The HIV viral load (≤ 50 vs > 50 copies/mL at baseline) was found to be significantly associated with survival (HR = 2.50; 95% CI: [1.15–5.44], $P = 0.021$). A younger age tended to be associated with poorer survival, but this relationship was of borderline significance ($P = 0.074$). Female patients tended to experience better survival, but this difference was not significant relative risk (HR = 0.48; 95% CI: [0.18–1.24], $P = 0.129$).

Under multivariate analysis, the MELD score remained significantly associated with surviving after an initial episode of decompensation; the adjusted hazard ratio (aHR) was 1.32 (95% CI: [1.06–1.63], $P = 0.012$) for an MELD score that was 3 points higher. The presence of ascites during initial decompensation tended to predict a poorer prognosis compared with jaundice alone, but this relationship was not significant ($P = 0.330$).

The occurrence of a further episode of decompensation during follow-up was associated with a significantly increased risk of death (aHR: 6.54; 95% CI: [2.51–17.02], $P = 0.0001$).

The time elapsing since the diagnosis of HIV, HIV viral load and the CD4 count at enrollment, was not associated with

TABLE 2. Factors Associated With Survival in HIV/HCV-Coinfected Patients After an Episode of Decompensation (n=67), Determined by Univariate and Multivariate Analysis

	Hazard Ratio [95% CI] Univariate Analysis	P Value	Adjusted Hazard Ratio [95% CI]* Multivariate Analysis	P Value
Gender				
Male	1		1	
Female	0.48 [0.18–1.24]	0.129	0.94 [0.32–2.71]	0.90
Age at initial decompensation†	0.95 [0.90–1.005]	0.074	0.95 [0.88–1.02]	0.156
MELD score‡	1.33 [1.11–1.59]	0.002	1.32 [1.06–1.63]	0.012
Type of decompensation				
Jaundice	1	0.157	1	0.330
Ascites	4.30 [0.57–32.51]	0.142	2.90 [0.35–24.34]	0.613
Other	4.55 [0.60–34.36]		1.74 [0.20–15.09]	
Number of signs				
1	1		–	–
>1	1.17 [0.58–2.34]	0.661	–	–
Period between HIV diagnosis and initial decompensation†	0.96 [0.91–1.03]	0.241	–	–
Period between HCV diagnosis and initial decompensation†	1.02 [0.97–1.08]	0.441	–	–
CD4 cell count (/mm ³)§	1.00 [0.85–1.18]	0.973	1.06 [0.89–1.27]	0.521
HIV viral load				
≤Threshold 50 copies/mL	1		1	
>Threshold 50 copies/mL	2.50 [1.15–5.44]	0.021	2.11 [0.83–5.38]	0.117
HCV viral load				
≤Threshold 20 IU/mL	1		–	–
>Threshold 20 IU/mL	1.78 [0.54–5.82]	0.344		
CDC stage				
A	1		–	–
B	1.80 [0.62–5.24]	0.284		
C	1.79 [0.78–4.12]	0.169		
Further episode of decompensation during follow up	7.80 [3.39–17.93]	<0.0001	6.54 [2.51–17.02]	0.0001

CD4 = cell count, viral load and further episode of decompensation during follow-up as a time-dependent covariate, CI = confidence interval, MELD = Model for End-Stage liver disease, type of decompensation.

* Adjusted for age, gender.

† For 1 year higher age or time.

‡ For s MELD score 3 units higher.

§ For an increase of 100 CD4/mm³.

|| As a time-dependent covariate.

survival in this population where the vast majority was being treated with cART and in which no AIDS-related deaths occurred.

Using an ROC analysis, it was found that a cut-off value of 20 for the MELD score was able to discriminate HIV/HCV-coinfected patients with good survival from those with poor survival. The probability of survival was significantly higher in patients whose MELD score at the time of their initial decompensation was ≤ 20 than in patients with a MELD score >20 (79% and 69% vs 64% and 24% at 1 and 2 years, respectively; *P* = 0.0005) (Figure 3).

Dynamic Factors

MELD Score Kinetics During Follow-Up

At the initial decompensation, the median MELD score was 15.5 [12.5–20.0], which included 11 patients (18%) with an MELD score >20. The kinetics of MELD score was calculated from the initial episode of decompensation in 66 patients for

whom at least 2 further MELD measurements were available. Several piecewise models (1 or more slopes, nodes at different time points since the initial decompensation) were tested. The best model was a 2-slope model with a node at 6 months after the initial decompensation. The first slope within the first 6 months following the initial decompensation did not differ significantly from zero (*b* = -0.21, *P* = 0.140), while subsequently there was a significant rise in the mean MELD score (*b* = +0.20/month, *P* = 0.0003).

The kinetics of MELD score after the initial decompensation episode differed significantly between deceased and non-deceased patients (Figure 4). Three different models were tested with a node at 3, 6, or 9 months after the first episode of decompensation. The mean MELD score of patients who remained alive during the study period fell significantly during the first 6 months by -0.49/month, *P* = 0.016, while they remained stable in deceased patients (+0.06/month, *P* = 0.755). After 6 months, the mean MELD score increased significantly by +0.32/month (*P* < 0.0001) in patients who

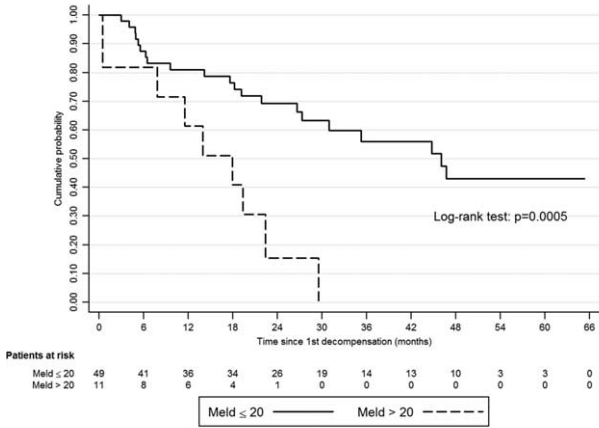


FIGURE 3. Cumulative survival according to MELD score after an initial episode of decompensation in HIV/HCV-coinfected patients. HCV = hepatitis C virus, HIV = human immunodeficiency virus, MELD = Model for End-Stage liver disease.

would die during follow-up, while it did not change significantly (+0.05/month, $P=0.171$) among those who remained alive during the study period. Both slopes differed significantly in deceased and nondeceased subjects ($P=0.054$ and 0.0004 , respectively). Treatment with ATV did not influence the MELD kinetics, the slope of MELD score did not differ between patients treated with ATZ and patients not treated by ATV ($P=0.192$). We also tested CD4 dynamics during follow-up (a fall below 200 CD4/mm^3 as a time-dependent variable) and did not find that this factor exerted any influence.

DISCUSSION

This multicenter, prospective study of 67 HIV/HCV-coinfected patients thus confirmed the very poor prognosis of HCV-related decompensated cirrhosis in the event of HIV coinfection.¹ Survival at 1 and 2 years following the initial episode of decompensation reached only 78% and 59%, respectively. The MELD score was the main predictive factor for the outcome of HIV/HCV-coinfected patients with decompensated cirrhosis: the risk of death was increased by 32% (aHR 1.32; 95% CI: [1.06–1.63]; $P=0.012$) if a 3-point higher MELD score was measured at the time of the initial decompensation. Furthermore, patients who did not survive during the study period generally experienced a stable MELD score during the first 6 months after their initial decompensation, followed by a significant increase, while patients who remained alive generally saw an initial decrease in their MELD score, followed by a stable score over subsequent months. Moreover, the occurrence of a further episode of decompensation during follow-up was associated with a significantly increased risk of death (aHR: 6.54; 95% CI: [2.51–17.02], $P=0.0001$).

These results clearly have strong implications when referring these patients for LT. Following an initial episode of hepatic decompensation, an increase or a stabilization of the MELD score will probably be predictive of poor survival and necessitate a rapid referral for LT. Indeed, we actually need specific validated scores to decide the more timely moment to perform LT in this subgroup of patients. The kinetic of MELD score may help us not only to refer but also to manage patients on the waiting list for LT. This is particularly important in HIV/

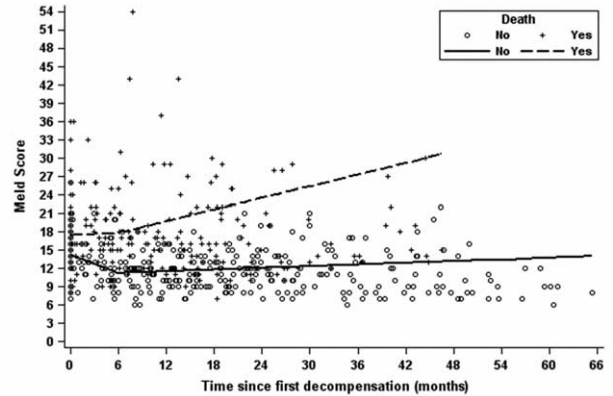


FIGURE 4. Evolution of MELD score in line with survival in HIV/HCV-coinfected patients (N=66) after an initial episode of decompensation. HCV = hepatitis C virus, HIV = human immunodeficiency virus, MELD = Model for End-Stage liver disease.

HCV-coinfected patients who are a risky high population with a more rapid liver disease progression.

In their prospective cohort of 153 HIV/HCV-coinfected patients with decompensated cirrhosis, Merchante et al³ reported that the CTP score (aHR: 1.2, 95% CI: [1.08–1.37], $P=0.001$), a CD4 cell count at decompensation lower than 100 cells/mL (aHR: 2.48, 95% CI: [1.52–4.06], $P<0.001$), and HE at the initial hepatic decompensation (aHR: 2.45, 95% CI: [1.41–4.27], $P=0.001$) were predictive factors for survival. Indeed, HE was the leading cause of death in our study but was not the most common type of decompensation during the initial episode. The most common type was ascites, but this was not significantly associated with survival in our study. An accumulation of signs of decompensation was then observed during the final course of cirrhosis and led to HE, the ultimate complication prior to death. Not surprisingly, a further episode of decompensation was associated with a poor prognosis and of course reflected a particularly rapid kinetic of deterioration in liver function. We evaluated the kinetics of MELD rather than the CTP score in our model, because the former is currently the reference to predict survival in patients with ESLD who are either HCV-monoinfected or suffering from other chronic liver diseases, and is used to prioritize these patients for LT.^{9,10} It was therefore necessary to evaluate the properties of MELD scores in an HIV/HCV-coinfected population. Besides other well-known factors, our data suggested that the MELD score is a strong prognostic factor of survival in HIV/HCV-coinfected patients after an initial episode of decompensation, thus confirming the analysis performed by Subramanian et al.¹² Surprisingly, in the study by Merchante et al,³ MELD scores were not associated with survival under multivariate analysis, and the authors explained this by the absence of HE from this score. We also performed a strict evaluation of MELD scores during the 3-month follow-up interval applied during our study, but this was not the only factor that increased the accuracy of this method as MELD scores were also significantly associated with survival under a transversal evaluation at the initial decompensation episode. For the first time, we have demonstrated in the present study that evaluating the kinetics of MELD scores with a critical time point at 6 months after decompensation is of crucial importance. Changes in MELD scores (DMELD = second MELD score – initial MELD score) were evaluated by Huo et al¹⁵ and DMELD/month >2.5 was the only significant

predictor of survival at 6 (OR: 9.8, $P < 0.001$) and 12 months (OR: 16.3, $P < 0.001$). However, this latter study included a majority of patients with HBV cirrhosis (69%). Moreover, initial median MELD score was low, of 11.8 [6.8–23.4], which signifies that the degree of severity of included patients was quite heterogeneous.

The introduction of new direct-acting antiviral agents raises hopes that HCV-related infections will be better controlled in the near future, even in HIV/HCV-coinfected patients.⁴ Sulkowski et al²⁰ also reported recently on the efficacy of sofosbuvir in HIV/HCV-coinfected patients who had not received treatment for their HCV, and found a 67% to 88% rate for a sustained virological response at 12 weeks after the end of therapy. Such advances will probably contribute to lowering the incidence of advanced liver disease in this population. Consequently, individualization of the prognostic factors that influence a short survival may lead to an introduction of new direct-acting antiviral agents in this particular subgroup of HIV/HCV-coinfected patients with ESLD and to a rapid referring to a liver transplant center.

The present study had some limitations. Although our cohort was of a multicenter and national type, the sample size may have precluded identifying significant risk factors other than the MELD score; our predictive model therefore needs to be evaluated in another larger cohort in order to confirm our findings. Moreover, as the role of HIV infection in this setting has been already identified by Pineda et al¹ and Merchante et al,³ we decided to focus on the determination of prognostic tools in an HIV/HCV-coinfected population experiencing a particularly rapid evolution of their liver disease.

In conclusion, the MELD score can be an effective tool to predict survival in HIV/HCV-coinfected patients after an initial episode of hepatic decompensation. A non-decreasing MELD score within 6 months following this initial decompensation episode may benefit from privileged access to LT. An increase in the MELD slope after 6 months is a second warning. Our findings are particularly important in this population with a poor prognosis and a high risk of a rapid progression in their liver disease, and argue in favor of integrating MELD score kinetics in new prognostic algorithms, a handy, easy to judge the patient's prognosis before and during their incorporation on list.

ACKNOWLEDGMENTS

The authors thank sponsored and funded by the French National Institute for Health and Medical Research – French National Agency for Research on Aids and viral hepatitis (Inserm-ANRS). The authors also thank all members of the ANRS HC EP 25 PRETHEVIC Study Group (listed in the Appendix); especially thank Laura IORDACHE (previously Project Manager), Géraldine BOY (previously Project Manager), Messad Ould-Rabah (Clinical Research Assistant), Laetitia JOHNSON (previously Clinical Research Assistant), and Géraldine ROBERT (previously Clinical Research Assistant), Anne PERSOZ (senior data manager); thank Prof. Daniel Vittecoq, Prof. Jean-François Delfraissy and Prof. Didier Samuel who supported the project; and thanks also go to all the patients who took part in this study.

REFERENCES

- Pineda JA, Romero-Gómez M, Díaz-García F, et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. *Hepatology*. 2005;41:779–789.
- Ragni MV, Eghtesad B, Schlesinger KW, et al. Pretransplant survival is shorter in HIV-positive than HIV-negative subjects with end-stage liver disease. *Liver Transpl*. 2005;11:1425–1430.
- Merchante N, Girón-González JA, González-Serrano M, et al. Survival and prognostic factors of HIV-infected patients with HCV-related end-stage liver disease. *AIDS*. 2006;20:49–57.
- Gelu-Simeon M, Sobesky R, Haïm-Boukobza S, et al. Do the epidemiology, physiological mechanisms and characteristics of hepatocellular carcinoma in HIV-infected patients justify specific screening policies? *AIDS*. 2014;28:1379–1391.
- Pineda JA, Aguilar-Guisado M, Rivero A, et al. Natural history of compensated hepatitis C virus-related cirrhosis in HIV-infected patients. *Clin Infect Dis*. 2009;49:1274–1282.
- Duclos-Vallée J-C, Féray C, Sebagh M, et al. Survival and recurrence of hepatitis C after liver transplantation in patients coinfecting with human immunodeficiency virus and hepatitis C virus. *Hepatology*. 2008;47:407–417.
- Miro JM, Montejo M, Castells L, et al. Outcome of HCV/HIV-coinfected liver transplant recipients: a prospective and multicenter cohort study. *Am J Transplant*. 2012;12:1866–1876.
- Terrault NA, Roland ME, Schiano T, et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. *Liver Transpl*. 2012;18:716–726.
- Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33:464–470.
- Kamath PS, Kim WR. Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). *Hepatology*. 2007;45:797–805.
- Murillas J, Rimola A, Laguno M, et al. 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. *Liver Transpl*. 2009;15:1133–1141.
- Subramanian A, Sulkowski M, Barin B, et al. MELD score is an important predictor of pretransplantation mortality in HIV-infected liver transplant candidates. *Gastroenterology*. 2010;138:159–164.
- Merion RM, Wolfe RA, Dykstra DM, et al. Longitudinal assessment of mortality risk among candidates for liver transplantation. *Liver Transpl*. 2003;9:12–18.
- Bambha K, Kim WR, Kremers WK, et al. Predicting survival among patients listed for liver transplantation: an assessment of serial MELD measurements. *Am J Transpl*. 2004;4:1798–1804.
- Huo T-I, Wu J-C, Lin H-C, et al. Evaluation of the increase in model for end-stage liver disease (DMELD) score over time as a prognostic predictor in patients with advanced cirrhosis: risk factor analysis and comparison with initial MELD and Child-Turcotte-Pugh score. *J Hepatol*. 2005;42:826–832.
- De Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol*. 2005;43:167–176.
- Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;5:1020–1022.
- Arroyo V, Ginès P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology*. 1996;23:164–176.
- Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis*. 1999;19:329–338.
- Sulkowski MS, Naggie S, Lalezari J, et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. *JAMA*. 2014;312:353–361.