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Clinical outcomes and prognostic factors after HCV clearance with DAA in HIV/HCV-coinfected patients with advanced fibrosis/cirrhosis

Juan Berenguer[1,2,3] | Teresa Aldámiz-Echevarría[1,2,3] | Víctor Hontañón[3,4,5] | Chiara Fanciulli[1,2,3] | Carmen Quereda[3,6,7] | Carmen Busca[3,4,5] | Lourdes Domínguez[3,8,9] | Cristina Hernández[10] | Jorge Vergas[11,12] | Gabriel Gaspar[13] | Lucio J. García-Fraile[3,14,15] | Cristina Díez[1,2,3] | Marta De Miguel[16] | José M. Bellón[1,2,3] | Rafael Bañares[2,17,18,19] | Juan González-García[3,4,5]

[1]Infectious Diseases/Clinical Microbiology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[2]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain

[3]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Madrid, Spain

[4]HIV Unit/Internal Medicine, Hospital Universitario La Paz, Madrid, Spain

[5]Instituto de Investigación Hospital Universitario La Paz (IdiPAZ), Madrid, Spain

[6]Infectious Diseases, Hospital Universitario Ramón y Cajal, Madrid, Spain

[7]Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain

[8]HIV Unit/Internal Medicine, Hospital Universitario 12 de Octubre, Madrid, Spain

[9]Instituto de Investigación Sanitaria Hospital 12 de Octubre (I+12), Madrid, Spain

[10]Infectious Diseases/Internal Medicine, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Spain

[11]Infectious Diseases/Internal Medicine, Hospital Clínico de San Carlos, Madrid, Spain

[12]Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain

[13]Internal Medicine, Hospital Universitario de Getafe, Getafe, Spain

[14]Infectious Diseases, Hospital Universitario de la Princesa, Madrid, Spain

[15]Instituto de Investigación del Hospital de La Princesa (IIS-Princesa), Madrid, Spain

[16]Fundación SEIMC-GeSIDA, Madrid, Spain

[17]Departamento de Medicina Universidad Complutense, Madrid, Spain

[18]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain

[19]Liver Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain

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Correspondence
Juan Berenguer, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Doctor Esquerdo 46, Madrid 28007, Spain.
Email: jbb4@me.com

Abstract

Background and Aims: We assessed long-term clinical outcomes and prognostic factors for liver disease progression after sustained viral response with direct-acting antivirals in patients coinfected with HIV/HCV with advanced fibrosis or cirrhosis.

Approach and Results: A total of 1300 patients who achieved sustained viral response with direct-acting antivirals from 2014 to 2017 in Spain were included: 1145 with compensated advanced chronic liver disease (384 advanced fibrosis and 761 compensated cirrhosis) and 155 with decompensated cirrhosis. The median follow-up was 40.9 months. Overall, 85 deaths occurred, 61 due to non-liver non-AIDS–related causes that were the leading cause of death across all stages of liver disease. The incidence (95% CI) of decompensation per 100 person-years (py) was 0 in patients with advanced fibrosis, 1.01 (0.68–1.51) in patients with compensated cirrhosis, and 8.35 (6.05–11.53) in patients with decompensated cirrhosis. The incidence (95% CI) of HCC per 100 py was 0.34 (0.13–0.91) in patients with advanced fibrosis, 0.73 (0.45–1.18) in patients with compensated cirrhosis, and 1.92 (1.00–3.70) per 100 py in patients with decompensated cirrhosis. Prognostic factors for decompensation in patients with compensated advanced chronic liver disease included serum albumin, liver stiffness measurement (LSM), and fibrosis 4. In this population, LSM and LSM-based posttreatment risk stratification models showed their predictive ability for decompensation and HCC.

Conclusions: Non-liver non-AIDS–related events were the leading causes of morbidity and mortality after direct-acting antiviral cure among coinfected patients with advanced fibrosis/cirrhosis. Among those with compensated advanced chronic liver disease, baseline LSM and posttreatment LSM-based models helped to assess decompensation and HCC risk.

INTRODUCTION

Over the last decade, the introduction of all-oral direct-acting antivirals (DAAs) against the HCV has revolutionized the treatment of hepatitis C.[1] The high effectiveness, safety, and lack of contraindications for DAA have improved clinical outcomes for patients with hepatitis C, including those with compensated and decompensated cirrhosis.[2–5] Broad access to DAA has also contributed dramatically to reducing the burden of HCV-related liver disease,[6] significantly affecting the evolution of the number and results of liver transplantation due to this indication.[7,8]

DAA therapy has had a significant impact on persons with HIV (PWH) coinfected with HCV, a population group difficult to treat in the interferon plus ribavirin era[1,9] with sustained viral response (SVR) rates over 90% in real-world practice.[10,11] Despite all the

progress, the burden of HCV-related liver disease among PWH will persist in the years to come, as a substantial number of those with chronic hepatitis C clearing the infection with anti-HCV therapy have cirrhosis.[12] Studies in the interferon era confirmed the clinical benefits of SVR in patients coinfected with HIV/HCV, including a reduction in liver-related complications and mortality[13] and a decrease in HIV progression and mortality not related to liver disease.[14] However, information on the long-term effects of SVR following DAAs in PWH, particularly in those with more severe liver disease, is limited.[15]

We aimed to assess the long-term clinical outcomes and prognostic factors for liver disease progression after HCV clearance in a large cohort of patients coinfected with HIV/HCV with advanced fibrosis or cirrhosis who achieved SVR following oral DAA therapy.

METHODS

Design and study population

This multicenter retrospective study was carried out by the AIDS Study Group (Grupo de Estudio del SIDA [GeSIDA]) of the Spanish Society of Infectious Diseases and Clinical Microbiology (Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica [SEIMC]). It included previously untreated and anti-HCV therapy–experienced patients coinfected with HIV/HCV with advanced fibrosis or cirrhosis who achieved SVR following all-oral DAA therapy from 2014 to 2017 in 21 centers across 5 regions in Spain (GeSIDA 10318-Study). Patients were included in 3 prospective observational cohort studies, 2 of which were conducted by GeSIDA[16,17] and 1 within the Madrid Coinfection Registry (Madrid-CoRe).[10] The censoring date of the study was December 31, 2019.

Investigations

We leveraged the databases from the 3 studies to obtain baseline data for the working database for this new investigation. New fields for follow-up data have been added as needed. The electronic case report form was built using REDCap electronic data capture tools[18] and hosted by the SEIMC/GeSIDA Foundation.

Baseline variables included demographics, height and weight, clinical data on HIV and its treatment, HCV-related liver disease, several comorbid conditions, current smoking, high alcohol intake, and whether the participants were on methadone maintenance programs (see below). Laboratory parameters included complete blood counts, international normalized ratio, biochemical parameters (serum lipids, alanine aminotransferase, aspartate aminotransferase, serum albumin concentration, and serum creatinine concentration), HCV-RNA quantification, HCV genotype, HBsAg, cluster of differentiation 4 (CD4) + T lymphocyte count, and HIV-RNA load. Liver fibrosis was estimated by liver stiffness measurement (LSM) assessed by transient elastography and the fibrosis 4 (FIB-4) index.[19] Other noninvasive biomarkers include the triglyceride and glucose index, a screening index for insulin resistance and NAFLD,[20] and the hepatic steatosis index, which is another screening index for NAFLD.[21] Furthermore, LSM and various laboratory parameters were recorded 1 year (± 2 mo) following treatment completion to evaluate posttreatment LSM-based risk stratification models developed in patients with compensated advanced chronic liver disease (cACLD) who had undergone HCV treatment with DAAs.

Patients underwent follow-up visits at least twice a year with surveillance for HCC using abdominal ultrasound. Interim and final data monitoring was performed by clinical research monitors from the SEIMC/GeSIDA Foundation to ensure data consistency with medical records. The study was conducted in accordance with the Declarations of Helsinki and Istanbul and was approved by the ethics committee of the Hospital General Universitario Gregorio Marañón, which waived informed consent for the collection of clinical data (FHG-AAD-2018-01). All the processes satisfied the local data confidentiality requirements.

Definitions

SVR was defined as undetectable serum HCV-RNA level 12 weeks after discontinuing anti-HCV therapy. Advanced fibrosis was defined by bridging fibrosis in liver biopsy or an LSM value > 9.9 and ≤ 12.5 kPa. Liver cirrhosis was defined by liver biopsy, an LSM > 12.5 kPa, or clinical-biological or imaging-compatible parameters. Liver decompensation was defined by a history of clinically detectable ascites, variceal bleeding, or portosystemic encephalopathy.[22] To encompass advanced fibrosis and compensated cirrhosis, we used the term cACLD.[23] HCC was defined using imaging criteria (CT or magnetic resonance) defined by the European Association for the Study of the Liver (EASL) and the European Organization for Research and Treatment of Cancer (EORTC) guidelines.[24]

Non-liver non-AIDS–related comorbidities were defined according to the Spanish AIDS Research Network (CoRIS) criteria, as described elsewhere.[25] These included arterial hypertension, hyperlipidemia, diabetes mellitus, obesity, ischemic cardiovascular disease (myocardial infarction, angina, stroke, peripheral artery disease, and mesenteric artery ischemia), heart failure, chronic kidney disease, bone events (fractures and avascular necrosis), and biopsy-confirmed non-liver–related non-AIDS–related cancer. Metabolic syndrome was assessed according to the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI),[26] while a high intake of alcohol was defined as the consumption of more than 50 g of alcohol per day for at least 12 months.

Investigators classified the cause of death at each center according to the following criteria: (a) liver-related death when the train of events that ended in death was caused by liver decompensation or HCC, (b) AIDS-related death when death was directly related to an AIDS-defining condition, and (c) non-liver non-AIDS–related death when the 2 previous criteria were not met.

Study outcomes

We first analyzed overall and cause-specific mortality in the entire study cohort. Next, we analyzed other outcomes separately for patients with compensated

and decompensated liver disease owing to their differing natural histories and prognostic factors.[27] The primary study outcomes for patients with cACLD were decompensation and HCC. The primary study outcome for patients with decompensated cirrhosis was the first episode of further decompensation defined according to the Baveno II consensus statement.[22] The secondary outcomes for all patients included new AIDS-defining conditions and incident non-liver non-AIDS–related events.

Statistics

Each participant was followed from the date of finalization of the DAA therapy to the last follow-up visit, death, or administrative censoring date, which-ever occurred first. Descriptive statistics are expressed as absolute numbers, percentages, medi-ans, and IQRs. Differences between groups were analyzed using the chi-square test, *t* test, or Mann-Whitney test, as appropriate. Normality was analyzed using the Kolmogorov-Smirnov test. We calculated the frequency and incidence rate of events per 100 person-years (100-py) of follow-up for different liver disease stages. When assessing non-liver, non-AIDS–related events, those with a history of a specific event at baseline were excluded from the population at risk when considering the incidence of such events. We used Poisson regression to calculate the inci-dence rate ratio and 95% CI of clinical events between categories of liver disease. When assessing the study outcomes of patients with decompensated cirrhosis, we categorized them according to the type of prior decompensation: ascites, variceal hemor-rhage (with or without ascites), and portosystemic encephalopathy (with or without ascites or variceal hemorrhage).

Multivariable Fine-Grey competing-risk regression analyses, with multiple imputations by chained equa-tions for missing data, were used to assess the effect of the independent variables on the outcomes. In patients with cACLD, competing events for the analysis of decompensation included death and HCC, as it can precipitate decompensation,[22] whereas the competing event was death while for the examination of HCC. In patients with decompensated cirrhosis, competing events were death and liver transplantation. In patients with cACLD, the independent variables analyzed included liver disease stage (advanced fibrosis or compensated cirrhosis), sex, age, current smoking, high alcohol intake, the presence of metabolic syn-drome, serum albumin concentration, CD4+ T-cell count, liver stiffness, FIB-4, and triglyceride and glucose index. In patients with decompensated cirrhosis, the independent variables analyzed included the type of decompensation before the initiation of DAA therapy,

sex, age, albumin concentration, the Model for End-Stage Liver Disease score, and platelet count. The selection of potential predictor variables was based on the underlying conceptual framework, and they were included in the multivariable models regardless of statistical significance.

To assess the performance of pretreatment LSM in predicting liver decompensation among patients with cACLD, we used time-dependent receiver operating characteristic (t-ROC) curves for censored event times and applied the inverse probability of censoring weighting estimators to address competing risks.[28] In the absence of a parallel metric to Youden's index for determining the optimal cutoff value within the context of t-ROC curves for censored event times with competing risks, various cutoff values for LSM were systematically explored. To rule out decompensation, we identified the highest LSM cutoff value associated with the maximum negative predictive value over a 42-month follow-up period.

In addition, 4 posttreatment LSM-based risk strati-fication models developed in patients with cACLD who had undergone HCV treatment with DAAs were assessed. The model by Semmler et al[29] was based on posttreatment LSM and platelet count that was developed to estimate the probability of clinically significant portal hypertension and to evaluate the risk of decompensation, and 3 models that were devel-oped to assess the risk of HCC: the model by Pons et al[30] based on posttreatment LSM and albumin concentration, Semmler et al[31] based on age, alcohol consumption, posttreatment LSM, and albumin con-centration, and Alonso Lopez et al[32] based on baseline LSM, the percentage of reduction in LSM at 1-year posttreatment (1-year DeltaLSM), and albumin concentration. To achieve this, the incidence rate of events for distinct risk categories defined by these indices was computed. A detailed description of the calculation of posttreatment LSM-based risk stratifica-tion models is provided in Supplemental Table S1, http://links.lww.com/HEP/I336.

Statistical analyses were performed using the Stata software (version 15.0; Stata Corporation). We used R version 4.3.2 (R Core Team, 2023) for calculations and graphical representations of t-ROC curves, leveraging the "timeROC" package.

RESULTS

Study cohort

A total of 1300 patients were included in the study, 384 of whom had advanced fibrosis (29.5%), 761 had compensated cirrhosis (58.5%), and 155 had decom-pensated cirrhosis (11.9%). Their characteristics before initiating DAA therapy, categorized by liver

TABLE 1 Baseline characteristics of 1300 patients coinfected with HIV/HCV with advanced fibrosis/cirrhosis with sustained viral response following all-oral direct-acting antiviral therapy against HCV

Characteristic	Advanced fibrosis (N = 384)	Compensated cirrhosis (N = 761)	Decompensated cirrhosis (N = 155)	Total (N = 1300)
Demographics and anthropometry				
Sex, male, N/total N (%)	303/383 (79.1)	621/761 (81.6)	105/155 (67.7)[ab]	1029/1299 (79.2)
Age, median (IQR), y	51.6 (48.3–54.6)	51.9 (48.9–55.1)	52.4 (49.3–55.2)	51.9 (48.9–55)
White race, N/total N (%)	362/364 (99.5)	712/717 (99.3)	149/149 (100)	1223/1230 (99.4)
BMI, median (IQR), kg/m^2	23.6 (20.9–26.8)	24.1 (21.3–26.7)	23.9 (21.9–27.1)	24 (21.2–26.8)
HIV data				
HIV acquired by IDU, N/total N (%)	328/375 (87.5)	668/742 (90)	132/152 (86.8)	1128/1269 (88.9)
Prior AIDS defining conditions, N/total N (%)	152/369 (41.2)	296/740 (40)	61/152 (40.1)	509/1261 (40.4)
Antiretroviral therapy, N/total N (%)	375/384 (97.7)	744/761 (97.8)	154/155 (99.4)	1273/1300 (97.9)
CD4+ T-cell count, median (IQR)	613 (406–827)	518 (319–729)[a]	356 (209–573)[ab]	525 (324–742)
HIV RNA <50 copies/mL, N/total N (%)	318/334 (95.2)	631/681 (92.7)	136/139 (97.8)	1085/1154 (94.0)
Liver disease data				
HBsAg positive, N/total N (%)	9/340 (2.6)	9/684 (1.3)	3/144 (2.1)	21/1168 (1.8)
HCV-RNA genotypes, N/total N (%)	384/384 (100)	759/761 (99.9)	155/155 (100)	1298/1300 (99.8)
1a	165 (43.0)	301 (39.7)	63 (40.6)	529 (40.8)
1b	54 (14.1)	130 (17.1)	23 (14.8)	207 (15.9)
1 non-subtyped	9 (2.3)	16 (2.1)	6 (3.9)	31 (2.4)
2	3 (0.8)	6 (0.8)	2 (1.3)	11 (0.8)
3	66 (17.2)	151 (19.9)	27 (17.4)	244 (18.8)
4	80 (20.8)	145 (19.1)	30 (19.4)	255 (19.6)
Mixed	7 (1.8)	10 (1.3)	4 (2.6)	21 (1.6)
Prior liver transplantation, N/with data (%)	2/384 (0.5)	5/758 (0.7)	4/155 (2.6)	11/1297 (0.8)
Naïve for anti-HCV treatment, N/with data (%)	238/384 (62.0)	412/761 (54.1)[a]	67/155 (43.2)[ab]	717/1300 (55.2)
Anti-HCV treatment regimen, N/total N (%)				
Sofosbuvir/ledipasvir	225/384 (58.6)	491/761 (64.5)	67/155 (43.2)[ab]	783/1300 (60.2)
Sofosbuvir and daclatasvir	63/384 (16.4)	112/761 (14.7)	49/155 (31.6)[ab]	224/1300 (17.2)
Ombitasvir/paritaprevir/ ritonavir and dasabuvir	59/384 (15.4)	86/761 (11.3)	2/155 (1.3)[ab]	147/1300 (11.3)
Other direct-acting antivirals	37/384 (9.6)	72/761 (9.5)	37/155 (23.9)[ab]	146/1300 (11.2)
Liver stiffness, median (IQR), kPa	10.7 (10.1–11.8)	19.5 (14.6–28.4)[a]	28 (19 – 45.0)[ab]	15.8 (11.8–26.0)
Fibrosis-4 index (FIB4), median (IQR)	1.90 (1.36–2.69)	3.22 (2.05–5.64)[a]	5.52 (3.27–8.81)[ab]	2.84 (1.83–5.13)
Triglyceride and glucose index (TyG), median (IQR)	4.66 (4.50–4.87)	4.70 (4.53–4.89)	4.64 (4.45–4.83)	4.68 (4.52–4.87)
Hepatic steatosis index (HSI), median (IQR)	34 (30.3–39.1)	33.7 (29.4–36.9)	31.4 (28.7–36.2)	33.5 (29.4–37.4)
Current substance use				
Smoking, N/with data (%)	245/348 (70.4)	522/724 (72.1)	100/141 (70.9)	867/1213 (71.5)
Alcohol abuse, N/with data (%)	36/299 (12.0)	108/651 (16.6)	14/138 (10.1)	158/1088 (14.5)
Methadone use, N/with data (%)	73/363 (20.1)	162/745 (21.7)	35/155 (22.6)	270/1263 (21.4)

TABLE 1. (continued)

Characteristic	Advanced fibrosis (N = 384)	Compensated cirrhosis (N = 761)	Decompensated cirrhosis (N = 155)	Total (N = 1300)
Comorbid conditions, N/with data (%)				
Arterial hypertension	81/382 (21.2)	186/756 (24.6)	34/154 (22.1)	301/1292 (23.3)
Hyperlipidemia	72/380 (18.9)	138/751 (18.4)	24/155 (15.5)	234/1286 (18.2)
Metabolic syndrome	56/384 (14.6)	139/761 (18.3)	27/155 (17.4)	222/1300 (17.1)
Diabetes mellitus	32/383 (8.4)	111/757 (14.7)[a]	31/155 (20.0)[a]	174/1295 (13.4)
Obesity	23/250 (9.2)	49/522 (9.4)	17/111 (15.3)	89/883 (10.1)
Bone fractures or avascular necrosis	37/380 (9.7)	58/744 (7.8)	20/151 (13.2)	115/1275 (9.0)
Ischemic cardiovascular disease[c]	25/382 (6.5)	52/751 (6.9)	7/154 (4.5)	84/1287 (6.5)
Chronic kidney disease	24/381 (6.3)	43/755 (5.7)	17/155 (11.0)	84/1291 (6.5)
NLR-NAR cancer (active)	11/378 (2.9)	36/737 (4.9)	9/154 (5.8)	56/1269 (4.4)
Heart failure	5/379 (1.3)	13/749 (1.7)	5/154 (3.2)	23/1282 (1.8)
Laboratory results, median (IQR)				
Platelet count×10^9 per liter	168 (130–216)	128.5 (88–172)[a]	80 (55–114)[ab]	136 (92–182)
ALT, IU/L	55 (36–90)	66 (42–105)[a]	42 (29–74)[ab]	61 (37–97)
AST, IU/L	47.5 (33–67)	66 (43–102)[a]	58 (36–92)[a]	59 (38–92)
Albumin, g/dL	4.3 (4.1–4.5)	4.2 (3.8–4.41)[a]	3.7 (3.3–4.1)[ab]	4.2 (3.8–4.5)
Total bilirubin, mg/dL	0.6 (0.4–0.8)	0.8 (0.56–1.16)[a]	1.0 (0.7–1.7)[ab]	0.7 (0.5–1.1)
INR	1.00 (0.98–1.06)	1.06 (1–1.14)[a]	1.17 (1.09–1.28)[ab]	1.05 (1–1.13)
Creatinine, mg/dL	0.87 (0.76–1.01)	0.85 (0.74–0.98)	0.84 (0.71–1.02)	0.85 (0.75–1)
Triglycerides, mg/dL	117 (88–171)	122 (90–167)	103 (75–152)[ab]	118 (88–167)
Total cholesterol, mg/dL	164 (138–189)	158 (134–181)	144.5 (121–176)[ab]	159 (133–183)
LDL cholesterol, mg/dL	91 (70–113)	86 (64.4–107)	79.5 (56–106.5)[a]	87 (65–109)
HDL cholesterol, mg/dL	43 (35–54)	42 (33–54.9)	43.4 (32.25–55)	42.3 (34–54.9)

[a]Statistically significant differences with F3.
[b]Statistically significant differences with F4 comp.
[c]Myocardial infarction, angina, cerebrovascular disease, and peripheral artery ischemic disease.
Abbreviations: CD4, cluster of differentiation 4; NLR-NAR, non-liver-related non-AIDS-related.

disease stage, are shown in Table 1. In brief, 79.2% of patients were male, the median age was 51.9 years, 88.9% had acquired HIV by injection drug use, 40.4% had prior AIDS-defining conditions, 97.9% were on antiretroviral therapy, the median CD4 cell count was 525 cells/mm^3, and 94.0% had an HIV viral load lower than 50 copies per mL. Fifty-two percent of patients were naïve to anti-HCV in 60.2%, was the most frequent DAA regimen. The median baseline liver stiffness and FIB-4 values were 15.8 kPa (IQR: 11.8–26.0) and 2.84 (IQR: 1.83–5.13), respectively. Current smoking and a high alcohol intake were registered in 71.5% and 14.5% of patients, respectively. In addition, 21.4% of the patients were on methadone maintenance programs. The most frequent comorbidities were arterial hypertension (23.3%), hyperlipidemia (18.2%), diabetes mellitus (13.4%), and obesity (10.1%). Metabolic syndrome was detected in 17.1% of the participants.

Statistically significant differences between the groups were found for age, CD4+ T-cell count, history of prior anti-HCV treatment, DAA regimens employed, liver stiffness and FIB-4 values, diabetes mellitus, and most laboratory parameters analyzed.

The median follow-up time after the completion of DAA therapy was 40.9 (34.5–45.1) months. Eighty-nine patients were lost to follow-up for an incidence rate of 2.16 (95% CI: 1.76–2.66) per 100-py (Table 2).

Mortality

Overall, 85 patients died during the study period, 61 due to non-liver non-AIDS–related events, and 24 due to a liver-related event, with no AIDS-related deaths identified in the entire cohort. Non-liver non-AIDS–related deaths outnumbered liver-related deaths across all liver disease stages (Table 2). The relative risk of overall, liver-related, and non-liver non-AIDS–related mortality was significantly higher for decompensated cirrhosis versus advanced fibrosis and decompensated versus compensated cirrhosis. However, no statistically

TABLE 2 Frequency and incidence rate of losses to follow-up and events in 1300 patients coinfected with HIV/HCV with advanced fibrosis and cirrhosis and sustained viral response with all-oral direct-acting antivirals

Event by liver-disease categories	Number at risk	Person-years of follow-up	Number of events	Incidence rate of events per 100 PY (95% CI)
Lost to follow-up				
All patients	1300	4121	89	2.16 (1.76–2.66)
Advanced fibrosis	384	1190	28	2.35 (1.62–3.41)
Compensated cirrhosis	761	2439	55	2.26 (1.73–2.94)
Decompensated cirrhosis	155	492	6	1.22 (0.55–2.72)
Mortality				
Overall mortality				
All patients	1300	4121	85	2.06 (1.67–2.55)
Advanced fibrosis	384	1190	13	1.09 (0.63–1.88)
Compensated cirrhosis	761	2439	47	1.93 (1.45–2.57)
Decompensated cirrhosis	155	492	25	5.08 (3.43–7.52)
Non-liver non-AIDS–related mortality				
All patients	1300	4121	61	1.48 (1.15–1.90)
Advanced fibrosis	384	1190	12	1.00 (0.57–1.78)
Compensated cirrhosis	761	2439	34	1.39 (0.99–1.95)
Decompensated cirrhosis	155	492	15	3.05 (1.84–5.06)
Liver-related mortality				
All patients	1300	4121	24	0.58 (0.39–0.87)
Advanced fibrosis	384	1190	1	0.08 (0.01–0.60)
Compensated cirrhosis	761	2439	13	0.53 (0.31–0.92)
Decompensated cirrhosis	155	492	10	2.03 (1.09–3.78)
AIDS-related mortality				
All patients	1300	4121	0	–
Liver-related events				
Liver decompensation				
All patients	1266	3996	61	1.53 (1.19–1.96)
Advanced fibrosis	374	1181	0	–
Compensated cirrhosis	737	2373	24	1.01 (0.68–1.51)
Decompensated cirrhosis	155	443	37	8.35 (6.05–11.53)
HCC				
All patients	1236	3967	30	0.76 (0.53–1.08)
Advanced fibrosis	372	1171	4	0.34 (0.13–0.91)
Compensated cirrhosis	721	2328	17	0.73 (0.45–1.18)
Decompensated cirrhosis	143	468	9	1.92 (1.00–3.70)
AIDS-defining events[a]				
All patients	1251	4040	12	0.30 (1.17–0.52)
Advanced fibrosis	372	1168	2	0.17 (0.04–0.69)
Compensated cirrhosis	732	2387	7	0.29 (0.14–0.62)
Decompensated cirrhosis	147	485	3	0.62 (0.20–1.92)
Non-liver non-AIDS–related events[a]				
Ischemic cardiovascular event				
All patients	1265	4003	44	1.10 (0.82–1.48)
Advanced fibrosis	376	1167	6	0.51 (0.23–1.15)
Compensated cirrhosis	740	2364	30	1.27 (0.89–1.82)
Decompensated cirrhosis	149	473	8	1.69 (0.85–3.38)
Heart failure				
All patients	1236	3987	14	0.35 (0.21–0.59)
Advanced fibrosis	370	1165	3	0.26 (0.08–0.80)

TABLE 2. (continued)

Event by liver-disease categories	Number at risk	Person-years of follow-up	Number of events	Incidence rate of events per 100 PY (95% CI)
Compensated cirrhosis	723	2357	5	0.21 (0.09–0.51)
Decompensated cirrhosis	143	465	6	1.29 (0.58–2.88)
Chronic renal failure				
All patients	1181	3776	27	0.72 (0.49–1.04)
Advanced fibrosis	350	1097	7	0.64 (0.30–1.34)
Compensated cirrhosis	699	2247	18	0.80 (0.51–1.27)
Decompensated cirrhosis	132	431	2	0.46 (0.12–1.85)
Bone event				
All patients	1124	3599	32	0.89 (0.63–1.26)
Advanced fibrosis	330	1039	6	0.58 (0.26–1.29)
Compensated cirrhosis	666	2146	21	0.98 (0.64–1.50)
Decompensated cirrhosis	128	415	5	1.21 (0.50–2.90)
Diabetes mellitus				
All patients	1092	3476	41	1.18 (0.87–1.60)
Advanced fibrosis	343	1077	7	0.65 (0.31–1.36)
Compensated cirrhosis	630	2018	28	1.39 (0.96–2.01)
Decompensated cirrhosis	119	382	6	1.57 (0.71–3.50)
Non-liver non-AIDS–related cancer				
All patients	1202	3841	49	1.28 (0.96–1.69)
Advanced fibrosis	365	1154	10	0.87 (0.47–1.61)
Compensated cirrhosis	698	2235	34	1.52 (1.09–2.13)
Decompensated cirrhosis	139	452	5	1.11 (0.46–2.66)

[a]When assessing new AIDS-related events, those with prior AIDS were excluded from the analysis. When assessing non-liver non-AIDS–related events, those with a history of the event at baseline were excluded from the population at risk when considering the incidence of events.

significant differences in relative risk or overall and cause-specific mortality were found between compensated cirrhosis and advanced fibrosis (Supplemental Table S2, http://links.lww.com/HEP/I336). Kaplan-Meier and cumulative incidence plots of overall death over 3½ years of follow-up are shown in Figure 1.

## Clinical events and prognostic factors in patients with cACLD

Table 2 shows the number of clinical events and their corresponding incidence rates. Notably, no instances of liver decompensation were observed in patients with advanced fibrosis, while 24 patients (3.3%) with compensated cirrhosis experienced decompensation, resulting in an incidence rate of 1.01 (95% CI: 0.68–1.51) per 100-py. Detailed information regarding the different types of liver-related, AIDS-related, and non-liver non-AIDS–related events in patients with cACLD during follow-up is shown in Supplemental Table S3, http://links.lww.com/HEP/I336.

The median time to decompensation following the completion of therapy among patients with compensated cirrhosis was 13.9 (6.7–32.8) months. The cumulative incidence plots of liver decompensation in patients with compensated cirrhosis and advanced fibrosis are shown in Figure 2A.

Newly diagnosed HCC was observed in 4 (0.3%) patients with advanced fibrosis and 17 (2.4%) patients with compensated cirrhosis, resulting in incidence rates of 0.34 (95% CI: 0.13–0.91) and 0.73 (95% CI: 0.45–1.18) per 100-py, respectively. The median time to HCC diagnosis after the end of therapy was 15.6 (IQR: 9.9–32.4) months for the former and 19.3 (IQR: 7.6–23.1) months for the latter. The cumulative incidence plots of HCC over 3½ years of follow-up for patients with compensated cirrhosis and advanced fibrosis are shown in Figure 2B.

The most frequent non-liver non-AIDS–related events during follow-up among the patients with cACLD were non-liver non-AIDS–related cancer, ischemic cardiovascular events, and diabetes mellitus. The relative risks of clinical events in patients with compensated cirrhosis and advanced fibrosis are shown in Table 3. No statistically significant differences were observed between the 2 groups regarding the risk of HCC, new AIDS-defining events, or most non-liver non-AIDS–related events. However, a notable exception was ischemic cardiovascular events, where individuals with
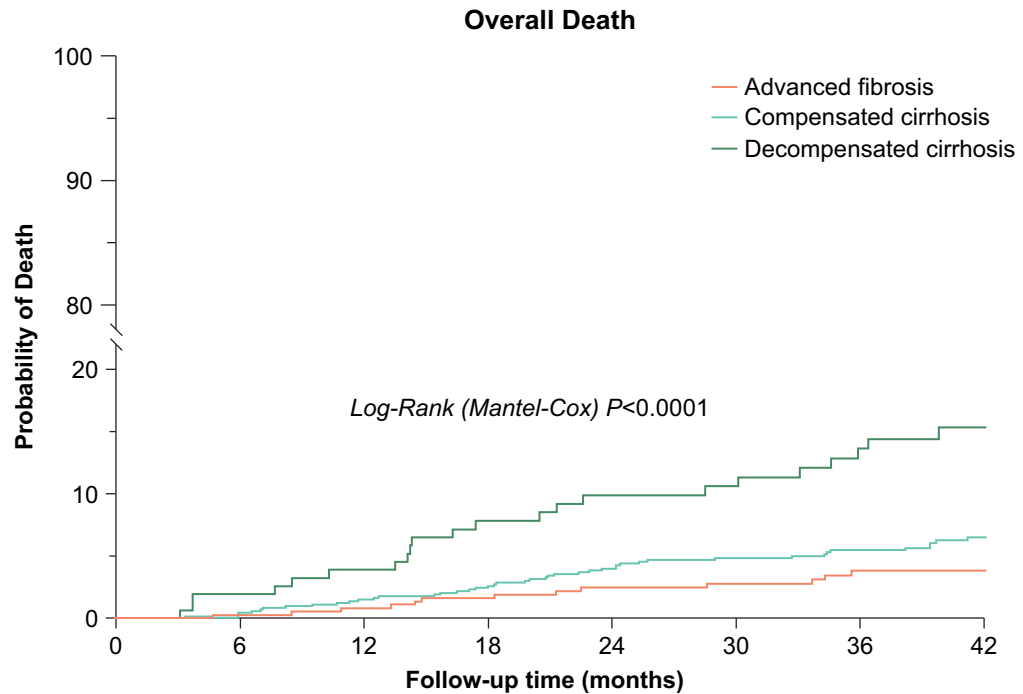
Overall Death

FIGURE 1 Kaplan-Meier plots of overall death over 3½ years of follow-up among 1300 patients coinfected with HIV/HCV with advanced fibrosis or cirrhosis following DAA-induced SVR. Abbreviations: DAA, direct-acting antiviral; SVR, sustained viral response.

compensated cirrhosis exhibited a 2.47-fold higher relative risk (95% CI: 1.03–5.93) compared to those with advanced fibrosis.
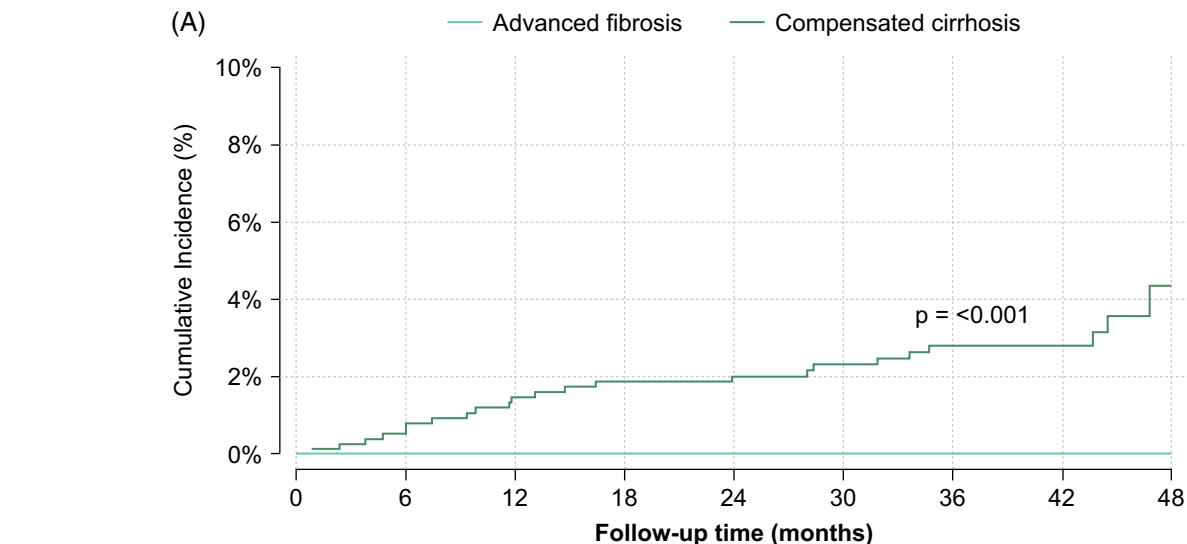
Baseline factors associated with decompensation in patients with cACLD are summarized in Table 4. Serum albumin concentration (adjusted subhazard ratio [aSHR] [95% CI]: 0.51 [0.28–0.94] per g/L increase) and LSM (aSHR [95% CI]: 1.05 [1.03–1.07] per kPa increase), and FIB-4 (aSHR [95% CI]: 1.04 [1.00–1.09] per unit increase) were independently associated with decompensation risk.

The median (IQR) LSM for patients without decompensation or competitive events (N = 1045), those with a competitive event (N = 63), and those with decompensation (N = 24) were 14.4 (11.5–22.0), 17.1 (12.2–27.0), and 36.9 (23.2–64.5) kPa, respectively. The utility of LSM as a predictive tool for decompensation over 42 weeks after therapy assessed using t-ROC curves, and accounting for competing risks is shown in Supplemental Table S4, http://links.lww.com/HEP/I336 and Supplemental Figure S1, http://links.lww.com/HEP/I336. In brief, the areas under the t-ROC curves for LSM predicting decompensation at 12, 24, and 42 months were 82.7%, 85.2%, and 84.0%, respectively, with a cutoff of 13.5 kPa exhibiting a 100% negative

predictive value at different time points up to 42 months of follow-up (Supplemental Table S5, http://links.lww.com/HEP/I336).

The risk of decompensation assessed 1 year after therapy using the posttreatment LSM/platelet count criterion developed by Semmler and colleagues among 631 patients is summarized in Table 5. The incidence rate of decompensation per 100-py was null among the 206 patients who were categorized as low risk (LSM <12 kPa and platelet count > 150×10^9 platelets/L). For patients in the gray zone or at high risk (LSM > 25 kPa), the incidence rates of decompensation were 0.36 (0.12–1.13) and 1.70 (0.55–5.28) per 100-py, respectively.

Serum albumin concentration (aSHR [95% CI]: 0.56 [0.36–0.87] per g/L increase) was the sole factor independently associated with HCC risk (Table 6). The risk of developing HCC, assessed 1 year after therapy using 3 post-SVR HCC risk stratification models, is summarized in Table 5. The incidence rates of HCC (95% CI) per 100-py of follow-up among patients in the low-risk category in the models by Pons et al,[30] Semmler et al,[31] and Alonso Lopez et al[32] were 0.20 (0.05–0.79), 0.40 (0.17–0.97), and 0, respectively.
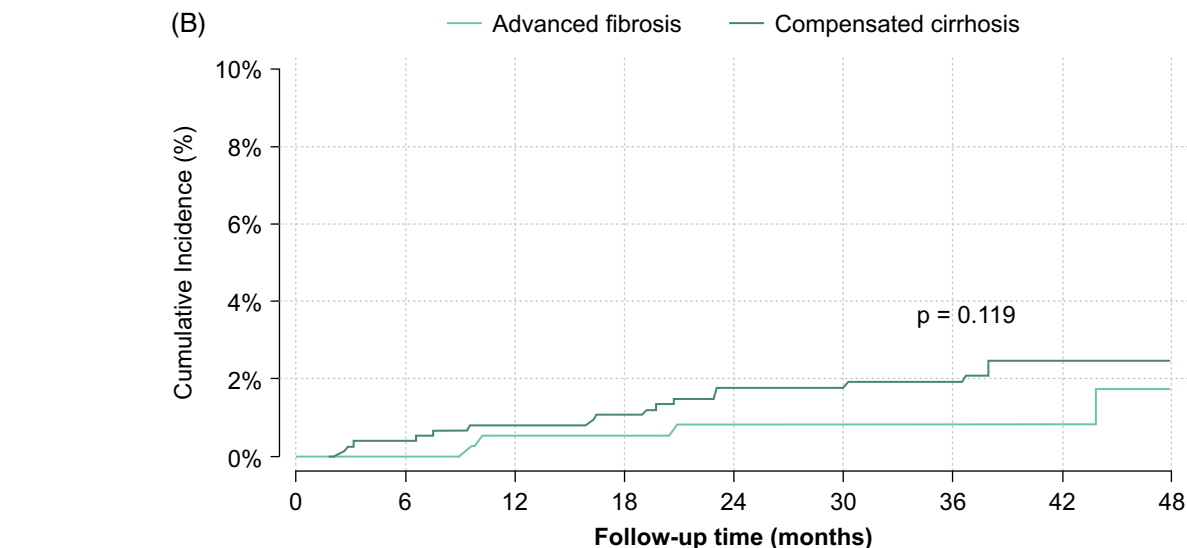
FIGURE 2 Cumulative incidence plots of liver decompensation (A) and HCC (B) for patients with compensated cirrhosis and advanced fibrosis. *p* values were calculated using the Gray tests.

Clinical events and prognostic factors in patients with decompensated cirrhosis

Before the initiation of DAA therapy, 219 episodes of liver decompensation occurred among 155 patients with decompensated cirrhosis, including ascites (N = 128), portosystemic encephalopathy (N = 48), and variceal bleeding (N = 43). Detailed information about the different types of liver-related, AIDS-related, and non-liver non-AIDS–related events in patients with decompensated cirrhosis during follow-up are shown in

Supplemental Table S3, http://links.lww.com/HEP/I336. During follow-up, 37 patients (23.9%) developed 48 new episodes indicating further decompensation, including ascites (N = 20), variceal bleeding (N = 14), and portosystemic encephalopathy (N = 14). In addition, 9 patients (6.3%) were diagnosed with de novo HCC. As shown in Table 2, the incidence rates of further decompensation and HCC for patients with decompensated cirrhosis were 8.35 (95% CI: 6.05–11.53) and 1.92 (95% CI: 1.00–3.70) per 100-py. Table 2 also shows the frequency and incidence rates

TABLE 3 Incidence rate ratio of clinical events according to the severity of liver disease among 1145 patients coinfected with HIV/HCV with advanced fibrosis or compensated cirrhosis and sustained viral response with direct-acting antivirals (Poisson regression)

	Compensated cirrhosis vs. advanced fibrosis incidence rate ratio (95% CI)
Liver-related events	
Liver decompensation	NA
HCC	2.14 (0.72–6.35)
New AIDS-defining event	1.71 (0.36–8.25)
Non-liver–related non-AIDS–related events	
Ischemic cardiovascular event	2.47 (1.03–5.93)
Heart failure	0.82 (0.20–3.45)
Chronic renal failure	1.26 (0.52–3.01)
Bone events	1.69 (0.68–4.20)
Diabetes mellitus	2.13 (0.93–4.89)
Non-liver non-AIDS–related cancer	1.75 (0.87–3.55)

Abbreviation: NA, not assessable due to the absence of events among patients with advanced fibrosis.

of AIDS-defining and non-liver non-AIDS–related events among patients with decompensated cirrhosis.

The prognostic factors of further liver decompensation in patients with decompensated liver disease are shown in Table 6. Male sex (aSHR [95% CI]: 2.95 [1.24–7.03]) was the only factor independently associated with further decompensation.

DISCUSSION

This study provides a comprehensive analysis of mortality, clinical events, and prognostic factors in a cohort of 1300 patients coinfected with HIV/HCV with advanced fibrosis or cirrhosis over a median follow-up of almost 3½ years after HCV clearance following all oral DAA therapy. Non-liver–related and non-AIDS–related conditions were the leading cause of death across all stages of liver disease. Among patients with cACLD, baseline LSM and LSM-based posttreatment risk stratification models showed predictive abilities. Among patients with decompensated cirrhosis, the risk of further decompensation remains high despite HCV clearance.

The liver-related mortality and HCC rates observed in individuals with cACLD in our cohort were comparable to those reported after HCV clearance with DAAs in patients without HIV who had similar liver disease stages and follow-up durations.[33,34] This suggests that the long-term benefits of successful DAA therapy in altering the natural course of liver disease among individuals with chronic hepatitis C and cACLD are not compromised by well-controlled HIV infection. Notably, there were no AIDS-related deaths in our study

TABLE 4 Multivariable Fine-Grey regression analysis evaluating baseline factors associated with liver decompensation and with HCC among 1145 patients coinfected with HIV/HCV with compensated advanced chronic liver disease and SVR following all oral DAA therapy

Variable	N[c]	Liver decompensation[a]			HCC[b]		
		Adjusted sHR	95% CI	*p*	Adjusted sHR	95% CI	*p*
Liver-disease stages[d]	1145						
Advanced fibrosis	384	—			Reference		
Compensated cirrhosis	761	—	—	—	1.43	0.45–4.55	0.539
Demographics and clinical variables							
Sex, male[e]	1144	2.20	0.41–11.69	0.361	—	—	—
Age (per 10 years)	1145	0.71	0.32–1.55	0.387	1.52	0.81–2.85	0.187
High intake of alcohol	950	0.99	0.30–3.30	0.984	0.71	0.16–3.19	0.655
Metabolic syndrome	1145	0.40	0.10–1.59	0.192	0.49	0.11–2.15	0.344
Laboratory parameters and noninvasive indexes							
Serum albumin (per mg/dL)	1057	0.51	0.28–0.94	0.030	0.56	0.36–0.87	0.009
CD4+ cell count (per 100 cells/mm^3)	1143	0.95	0.80–1.13	0.546	0.95	0.81–1.11	0.533
Liver stiffness measurement (per kPa)	1132	1.05	1.03–1.07	<0.001	1.01	0.98–1.03	0.515
FIB-4 index (per unit)	1064	1.04	1.00–1.09	0.043	1.03	0.97–1.09	0.354
TyG index (per unit)	1087	1.42	0.19–10.48	0.729	1.01	0.16–6.25	0.991

[a]A total of 24 patients experienced decompensation during follow-up.
[b]A total of 21 patients developed HCC during follow-up.
[c]Number of patients with the variable available; values were imputed when the variable was unavailable.
[d]sHR of decompensation could not be estimated due to the absence of cases of decompensation among patients with advanced fibrosis.
[e]sHR of HCC for sex could not be determined due to the absence of cases among females.
Abbreviations: CD4, cluster of differentiation 4; DAA, direct-acting antivirals; FIB-4, fibrosis 4; sHR, sub hazard ratio; SVR, sustained viral response; TyG, triglyceride and glucose index.

TABLE 5 Risk of decompensation and risk of developing HCC according to posttreatment risk stratification models assessed 1 year after the finalization of DAA therapy among patients with cACLD

Posttreatment risk stratification indexes[a]	Patients at risk	Person-years of follow-up	Patients with competitive events	Patients with event	Incidence of event 100-PY (95% CI)
Liver decompensation					
LSM/platelet count (Semmler et al[29])					
LSM < 12 kPa and PLT > 150×10⁹/L	206	455.0	4	0	0
Gray-zone	349	825.3	12	3	0.36 (0.12–1.13)
LSM > 25 kPa	76	176.3	5	3	1.70 (0.55–5.28)
Total	631	1456.6	21	6	0.41 (0.19–0.92)
Hepatocellular carcinoma					
LSM/albumin (Pons et al[30])					
Low risk	441	1006.8	8	2	0.20 (0.05–0.79)
High risk	178	421.5	5	6	1.42 (0.64–3.17)
Total	619	1428.3	13	8	0.56 (0.28–1.12)
Age/alcohol/LSM/albumin (Semmler et al[31])					
Low risk	539	1235.8	10	5	0.40 (0.17–0.97)
High risk	80	192.5	3	3	1.56 (0.50–4.83)
Total	619	1428.3	13	8	0.56 (0.28–1.12)
LSM/1yDelta-LSM/albumin (Alonso Lopez et al[32])					
Low risk	182	411.5	3	0	0
Intermediate risk	215	487.6	4	1	0.21 (0.03–1.46)
High risk	149	356.6	3	4	1.12 (0.42–2.99)
Very high risk	72	171.9	0	3	1.74 (0.56–5.41)
Total	618	1427.6	10	8	0.56 (0.28–1.12)

[a]A detailed description of the calculation of the posttreatment LSM-based risk stratification models is provided in Supplemental Table S1, http://links.lww.com/HEP/I336.
Abbreviations: 1yDelta-LSM, percentage of reduction in LSM at 1 year posttreatment; cACLD, compensated advanced chronic liver disease; DAA, direct-acting antivirals; LSM, liver stiffness measurement; PY, patient-years.

population, most of whom were on antiretroviral therapy and had fully suppressed HIV viremia.

Furthermore, we found that non-liver–related and non-AIDS–related mortality exceeded liver-related mortality across all liver disease stages. This observation aligns with other reports assessing the impact of DAAs on mortality in individuals with and without HIV,[35] highlighting the influence of concurrent health risk behaviors and comorbidities on mortality in patients with chronic hepatitis C.[36] In our cohort, all-cause mortality rates were higher among patients with cACLD than among those described after HCV clearance with

TABLE 6 Multivariable Fine-Grey regression analysis evaluating factors associated with further liver decompensation in 155 HIV/HCV-coinfected patients with decompensated cirrhosis and SVR following all oral DAA therapy

Variable	N[b]	Further liver decompensation[a]		
		SHR	95% CI	p
Type of previous decompensation	155			
Ascites (only)	77	Reference	—	—
Hemorrhage (with or without ascites)	30	1.73	0.80–3.74	0.166
Portosystemic encephalopathy	48	0.79	0.33–1.84	0.579
Sex, male	155	2.95	1.24–7.03	0.015
Age (y)	155	1.32	0.69–2.54	0.400
Serum albumin (g/dL)	146	0.77	0.42–1.38	0.376
MELD score	136	1.03	0.94–1.14	0.503
Platelets (per 10⁴/μL)	154	1.04	0.96–1.13	0.285

[a]A total of 37 patients experienced further decompensation during follow-up.
[b]Number of patients with the variable available; values were imputed when the variable was unavailable.
Abbreviations: DAA, direct-acting antiviral; SVR, sustained viral response.

DAAs in patients without HIV who had similar liver disease stages.[33] This discrepancy must be considered in the context of a higher burden of aging-related comorbidities, coinfections, and substance use disorders among people living with HIV than among age-matched and sex-matched individuals without HIV.[37] Notably, cancer, ischemic cardiovascular events, and diabetes mellitus were the most frequently observed non-liver, non-AIDS–related events in our cohort, with no significant differences in the incidence rate ratio between patients with advanced fibrosis and those with compensated cirrhosis, except for ischemic cardiovascular events, which exhibited a significantly higher risk in patients with compensated cirrhosis than in those with advanced fibrosis. This finding should be considered taking into account that the prevalence of diabetes mellitus, a common comorbidity among patients with cirrhosis[38] and a recognized risk factor for cardiovascular disease, was significantly higher among patients with compensated cirrhosis than among those with advanced fibrosis.

Significantly, we did not observe substantial differences in the overall or cause-specific mortality risk between patients with advanced fibrosis and those with compensated cirrhosis. However, the risk of HCC was somewhat higher among individuals with cirrhosis than among those with advanced fibrosis, with the latter group experiencing no liver decompensation during the follow-up.

Serum albumin concentration, LSM, and FIB-4 index emerged as the only factors independently associated with the risk of decompensation among patients with cACLD. No significant associations with decompensation were found for demographics, CD4+ cell counts, high alcohol intake, or metabolic-related variables. However, it should be noted that our cohort displayed a high degree of homogeneity regarding these variables, as patients were predominantly males in their late forties and early fifties, receiving antiretroviral therapy with full suppression of HIV viremia, high CD4+ T cell counts, and low prevalence of harmful alcohol consumption and obesity.

To assess the performance of LSM before the initiation of DAA therapy in predicting the risk of decompensation among patients with cACLD, we used t-ROC curves for censored event times, accounting for competing risks. Our results demonstrated good discrimination of pre-therapy LSM for this purpose, with a consistent 100% negative predictive value over 3½ of follow-up for a cutoff value of 13.5 kPa. In line with the growing body of evidence supporting the utility of LSM-based noninvasive indexes in prognosticating patients with cACLD following HCV eradication with DAAs, we evaluated the index developed by Semmler et al.[29] This index, utilizing LSM and platelet count at the time of SVR, aimed to predict the likelihood of clinically significant portal hypertension and the risk of decompensation after HCV cure with DAA therapy. Our assessment of 631 patients, with both parameters recorded 1 year after completing therapy, showed that none of those categorized as low risk (LSM <12 kPa and platelet count >150×10^9/L) experienced decompensation during follow-up. This supports the current recommendation that patients who are at low-risk, in the absence of cofactors, may be exempted from ongoing surveillance for portal hypertension, including LSM and endoscopy.[22]

During the follow-up period, we documented 4 incident cases of HCC in patients with advanced fibrosis and 17 in those with compensated cirrhosis, yielding incidence rates of 0.37 and 0.73 events per 100-py, respectively. A recent systematic review and meta-analysis reported HCC incidence rates following HCV cure with DAAs of 0.63 per 100-py for patients with advanced fibrosis and 2.99 per 100-py for patients with patients with cirrhosis (without differentiation between compensated and decompensated disease), with values ranging from 0.32 to 11.47 across the 31 individual studies analyzed.[33] In our cohort, the upper limits of the CI for the incidence rate of HCC in patients with advanced fibrosis and compensated cirrhosis were 0.91 and 1.18 per 100-py, respectively. Incidence rates below the threshold of >1.32 per 100-py were proposed for cost-effective HCC screening in patients with DAA-cured HCV by employing current screening methodologies.[34]

Among the pretreatment variables, serum albumin concentration was found to be independently associated with HCC risk. In addition, we assessed 3 LSM-based post-SVR HCC risk stratification models in a group of 618/619 patients with LSM determined 1 year after the end of treatment and free of HCC at the same time point.[30–32] These selection criteria were adopted, as 2 of the mentioned studies[30,32] did, to preclude including patients with malignant transformation before clinical recognition. All 3 indices could categorize patients according to their risk of developing HCC and identify individuals with incidence rates above the cost-effective HCC screening threshold. Notably, the model developed by Alonso-Lopez et al[32] showed a lower incidence of HCC in the low-risk group (0 per 100-py), suggesting a potentially better ability to rule out HCC during follow-up in this population.

The advent of all-oral DAA therapy has enabled HCV cure in patients with HCV-related decompensated liver disease, both with and without HIV.[5,10,39,40] However, it is worth noting that the success rates are slightly lower in individuals with decompensated liver disease than in those with compensated disease.[10,40] Although DAA-induced viral clearance in patients with HCV-related decompensated cirrhosis has been associated with short-term improvements in liver function,[39,40] it has not been linked to reduced disease progression, even in patients with sustained improvements in liver function, as demonstrated in a large multinational observational

study.[4] Among the 115 patients with decompensated cirrhosis in our cohort, nearly a quarter experienced further episodes of decompensation despite HCV clearance. These findings are concordant with the observations that in patients with HCV-related decompensated cirrhosis, the disappearance of clinically significant portal hypertension is rarely, if ever, achieved[17,41] and underscores that they remain at a high risk of experiencing further decompensation or developing HCC, which may ultimately necessitate liver transplantation.

Our study had several limitations and strengths worth noting. The main limitation stems from the retrospective evaluation of the mortality and clinical events. However, the patient's scheduled follow-up in the participating centers may have lessened their relevance. The study was also limited by missing observations, which were partially mitigated by implementing a strategy for imputing missing values. A major limitation, shared with many past studies, is the limited follow-up duration (median 3½ years), which hinders the assessment of the long-term risk of HCC development after SVR with DAAs, which may be observed beyond 5 years. A significant strength of our study was the large cohort of participants with comprehensive and prospectively captured baseline information. All patients were treated within a relatively short timeframe, decreasing the potential impact of changes in clinical management practices over time. Finally, interim and final independent monitoring was carried out, to ensure the reliability of our data set.

This study has important practical implications. First, it highlights the critical role of age-related comorbidities among patients coinfected with HIV/HCV with cACLD as they emerge as the principal determinants of morbidity and mortality after DAA treatment. In addition, our study provides valuable insights into the prognostication and risk stratification of decompensation and HCC in patients with cACLD following HCV eradication with DAAs. Furthermore, it supports the use of LSM-based noninvasive indexes to assess risk and guide targeted surveillance strategies. Finally, our study reaffirms that patients with HCV-related decompensated cirrhosis continue to face a substantial risk of further decompensation or HCC despite achieving HCV clearance. Although our study sheds crucial light on these critical aspects, there are still critical knowledge gaps, particularly in identifying specific subgroups of PWH and cACLD who may remain at negligible risk of developing HCC and can safely forgo HCC screening. This question demands further research to better guide clinical decision-making and improve outcomes for PWH with cACLD.

AUTHOR CONTRIBUTIONS

Juan Berenguer and Juan González-García conceptualized and designed the study with later input from Rafael Bañares. Teresa Aldámiz-Echevarría, Víctor Hontañón, Chiara Fanciulli, Carmen Quereda, Carmen Busca, Lourdes Domínguez, Cristina Hernández, Jorge Vergas, Gabriel Gaspar, Lucio J. García-Fraile, and Cristina Díez contributed substantially to data acquisition. José M. Bellón and Marta De Miguel curated the databases and managed the global data collection. José M. Bellón, Juan Berenguer, Rafael Bañares, and Juan González-García analyzed and interpreted the data. Juan Berenguer drafted the manuscript and all authors critically reviewed the manuscript. All authors were responsible for the final decision to submit for publication and have seen and approved the manuscript.

CONFLICTS OF INTEREST

ORCID

Juan Berenguer https://orcid.org/0000–0001–8541–8200

Teresa Aldámiz-Echevarría https://orcid.org/0000–0002–4374–6940

Víctor Hontañón https://orcid.org/0000–0003–3070–2647

Chiara Fanciulli https://orcid.org/0000–0003–2175–9027

Carmen Busca https://orcid.org/0000–0002–4549–7749

Lourdes Domínguez https://orcid.org/0000–0001–6018–9026

Cristina Hernández https://orcid.org/0000–0002–2467–9965

Jorge Vergas https://orcid.org/0000–0002–4894–9763

Gabriel Gaspar https://orcid.org/0000–0002–7144–8959

Lucio J. García-Fraile https://orcid.org/0000–0002–2512–6107

Cristina Díez https://orcid.org/0000–0002–3508–9979

José M. Bellón https://orcid.org/0000–0002–8492–1565

Rafael Bañares https://orcid.org/0000–0002–0412–8437

Juan González-García https://orcid.org/0000–0002–3652–002X

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