Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment a prospective cohort study

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Title.

Clinical outcomes in patients with chronic hepatitis C following direct-acting antiviral therapy: a prospective cohort study.

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Summary

Background

Although direct-acting antivirals (DAAs) have been extensively used to treat patients with chronic Hepatitis C Virus (HCV) infection, their clinical impact has not been well documented. We compared the incidence rates of death, hepatocellular carcinoma (HCC) and decompensated cirrhosis between patients in the French ANRS CO22 Hepather cohort, who were and were not treated with DAAs.

Methods

Between August 6, 2012 and December 31, 2015, adult patients with chronic HCV infection were enrolled in this prospective study from 32 centres in France. Patients with chronic hepatitis B, a past history of decompensated cirrhosis, HCC or liver transplantation, or who were treated with Interferon-ribavirin ± first generation protease inhibitors were excluded. Outcome was based on the incidence rates of all-cause mortality, HCC and decompensated cirrhosis. The association between DAA and the different outcomes was quantified using time-dependent Cox proportional hazards models. This study was registered with ClinicalTrials.gov, number NCT01953458.

Findings

In total, 10,166 patients were eligible and 9,895 (97%) of these were included in the analyses because follow-up information was available. Median follow-up was 33 months (IQR 24-41). DAA treatment was initiated during follow-up in 7,344 patients, while 2,551 patients remained untreated at the final follow-up visit. Death, HCC and decompensated cirrhosis were reported during follow-up in 218, 258 and 106 patients, respectively. Exposure to DAA treatment was associated with an increased risk of HCC and decompensated cirrhosis on the unadjusted Cox model (Hazard

Ratio (HR)=2·77 (95% CI 2·07-3·71) and (HR=3·83 (2·29-6·42)), respectively. On adjusted multivariable analysis, exposure to DAA was associated with a decrease in all cause-mortality (HR=0·48 (95% CI 0·33-0·70)) and HCC (HR=0·66 (0·46-0·93)), and was no longer associated with decompensated cirrhosis (HR=1·14 (0·57-2·27)).

Interpretation

DAA treatment is associated with a reduced risk of mortality and HCC and should be considered in all patients with chronic HCV infection.

Introduction

The recently updated Global Hepatitis Report by the World Health Organization suggests that hepatitis C virus (HCV) has infected 1% of the population worldwide (71 million) and causing approximately 400,000 deaths annually, mainly from cirrhosis and hepatocellular carcinoma (HCC).[1] This significant public health burden can be improved by HCV therapies since this is the only chronic viral infection that may be cured, as defined by a sustained virological response (SVR).[2,3] Since 2014, the combination of 2 or 3 direct-acting antivirals (DAA) targeting viral proteins (NS3/4A protease inhibitors, NS5B nucleos(t)idic and non nucleos(t)idic polymerase inhibitors, NS5A replication complex inhibitors), has been shown to have a pangenotypic efficacy in HCV infection with a SVR rate > 95% and fair tolerance. Treatment lasts from 8 to 16 weeks depending on baseline factors including the stage of fibrosis, genotype, prior treatment history (-naïve or -experienced) and pre-existing resistance-associated variants.[4,5]

Numerous observational studies have reported a reduced risk of HCC, the complications of liver disease and mortality in interferon- or DAA-treated patients who achieve a SVR.[6-12] However, very few studies have compared the clinical outcomes of DAA-treated and similar untreated patients, as would be done in a randomized trial.[13] One single-centre cohort study reported a decrease in mortality in patients receiving either paritaprevir/ritonavir/ombitasvir/dasabuvir or sofosbuvir/ledispasvir compared to untreated patients.[14] However, this study did not report the incidence of liver-related events such as liver decompensation or HCC, which is critical because of the controversy on a potential increase in the risk of HCC with DAA therapy.[15,16]

The goal of this study was to further clarify the benefits or harms of DAA by comparing the incidence rates of death, HCC and decompensated cirrhosis in DAA-

treated and untreated patients from the prospective French ANRS CO22 Hepather cohort.

Methods

Study design and participants

ANRS CO22 Hepather cohort « Therapeutic option for hepatitis B and C: a French cohort » is a national, multicentre, prospective observational cohort study of patients with viral hepatitis B or C started in August 2012 (see [17] for a complete description). The main objectives of this study were to quantify the clinical efficacy and safety of new hepatitis treatments in real-life. The anticipated cohort size was 15,000 patients with existing or past chronic hepatitis C and 10,000 patients with active or inactive chronic hepatitis B, to be followed for a median of 7 years. HCV-positive patients were defined as those with positive HCV-RNA or positive anti-HCV antibodies. Our goal was to include at least 90% of patients with chronic hepatitis C at entry (positive HCV-RNA and anti-HCV antibodies). The main exclusion criteria were HIV-coinfection and ongoing HCV treatment at inclusion. Participants were recruited consecutively during a medical visit in one of the 32 expert hepatology centres. Blood and urines samples were obtained and stored in a centralized biobank (Cell&Co Biorepository, Pont du Château, France). Patients were enrolled from August 6th, 2012 to December 31st, 2015. At this date, 14,389 HCV-positive patients had been recruited, including 11,870 with chronic hepatitis C at entry (figure 1). Detailed demographics, clinical (including fibrosis staging and history of past treatment) and biological data were collected during the inclusion visit using an electronic case-report form. Follow-up included systematic visits (once a year) and spontaneous

reports for particular events on specific data forms (e.g. deaths, HCC, decompensated cirrhosis, the onset of therapy). In April 2014, the follow-up protocol was modified to include local HCV-RNA evaluations and visits with the physician when HCV treatment was started, during treatment, and up to 24 weeks after the last treatment. The study was observational and the choice of treatment combination, treatment timing, and screening for HCC or the progression of fibrosis was left up to the physician, but followed national French recommendations based on European Association for the Study of the Liver (EASL) guidelines.[18] Written informed consent was obtained from each patient before enrolment. The protocol was performed in accordance with the Declaration of Helsinki and French law for biomedical research and was approved by the "CPP Ile de France 3" Ethics Committee (Paris, France) and the French Regulatory Authority (ANSM).

We selected all patients with chronic hepatitis C at entry to explore the clinical impact of DAA. Patients with active HBV coinfection defined by detectable HBsAg (n=95), a past history of HCC (n=653), decompensated cirrhosis (n=1003), or liver transplantation (n=326) at entry were excluded, as well as patients who received peginterferon and ribavirin with or without a first-generation protease inhibitor after entry in the cohort (n=148). Follow-up information was missing in 271 of the remaining 10,166 patients.

Outcomes

Study outcomes were all-cause mortality, which was later classified into liver-related (LR) or non-liver related (NLR) deaths, incident HCC and incident decompensated cirrhosis. The causes of death were classified by an adjudication committee including two hepatologists (HF, MB) and one methodologist (CD). Adjudication was based on medical records, and investigators filled in a specific case report form. Data on incident HCC included the number of lesions at diagnosis, the largest nodule size, total size, diagnostic imaging procedures and treatment. Decompensated cirrhosis was defined as the development of ascites, variceal haemorrhage, encephalopathy, and/or jaundice.[19]

Predictor variables

Exposure to DAA was considered to be a time-dependent covariate, and the first day of the first treatment defined the time point to switch DAA exposure from 0 to 1. If a patient received several DAA treatments during follow-up (e.g. because of virological failure), she/he was considered to be continuously exposed to DAA from her/his first day of first treatment. The other potential predictors of clinical outcome evaluated at entry in the cohort were age, gender, BMI, geographic origin, infection route, time since HCV diagnosis, fibrosis score, HCV treatment-naive, HCV genotype, diabetes, arterial hypertension, past and current alcohol consumption, biological variables (albumin, aspartate aminotransferase, alanine aminotransferase, Gamma glutamyl-transferase, prothrombin time, platelet count, alpha-fetoprotein), and MELD score in patients with a cirrhosis. Patients with a platelet count < 150,000/µL or a prothrombin time < 70%, were considered to have cirrhosis unless specifically specified otherwise (n=1,326).[20,21] These criteria were validated in 757 patients who had also been

evaluated for liver fibrosis less than 1 year before and up to 3 months after inclusion, including 755 (99.8%) who had been classified with cirrhosis by different techniques. Fibrosis was evaluated in other patients by liver biopsy (n=398) or another non-invasive method (liver stiffness measurement (Fibroscan®) (n=3,188), Fibrotest® (n=1,812), Fibrometer® (n=635), or the Hepascore (n=143) that was performed closest to the date of inclusion, but less than 1 year before and up to 3 months after inclusion. If a recent measurement of fibrosis was not available or in case of discrepancies between non-invasive fibrosis markers, physicians were asked to assess the level of fibrosis based on past fibrosis scores and the patient's history of liver-related comorbidities (n=1,521). The baseline fibrosis score remained unknown in 872 eligible patients. Mild fibrosis (F0-F2), severe fibrosis (F3) and cirrhosis (F4) were defined by the Metavir score.[22] The cut-offs for severe fibrosis and cirrhosis by noninvasive methods were 9·5 kPa and 12·5 kPa with Fibroscan®, 0·59 and 0·75 with Fibrotest®, 0·62 and 0·98 with Fibrometer®, 0·61 and 0·84 with the Hepascore, respectively.

Statistical analyses

A post-hoc calculation was performed based on 33% of included patients with cirrhosis at entry, a 2 per 100 person-years annual incidence of all-cause mortality in the absence of treatment in patients with cirrhosis,[23] a multivariable-adjusted Hazard Ratio (HR) of all-cause deaths of 0·43 (95%CI 0·33-0·57) in treated versus untreated patients[14] and showed that 1,500 person-years of follow-up in patients unexposed to DAA and 4,500 person-years of follow-up in patients exposed to DAA achieved a statistical power of 86% to detect a HR of < 0·5

Survival time was calculated as the time between entry (unexposed period) or the start of first therapy (exposed period) to the last follow-up visit, the date of an outcome (death, HCC or decompensated cirrhosis) or January 1st, 2018, whichever occurred first.

Baseline characteristics were compared using the Mann-Whitney test for quantitative variables or the Fisher's exact test for categorical variables. Pseudo Kaplan-Meier curves were drawn using a clock reset procedure for patients exposed to DAA treatment during follow-up.[24] Incidence rates and 95% confidence intervals were estimated with an exact method based on the Poisson distribution. We used a multivariable Cox proportional-hazards model with exposure to treatment modelled as a time-varying covariate in our primary analysis. This analysis was adjusted for the baseline values of all predictor variables listed above and used a time-dependent parameter for the baseline hazard by a smooth function of the time since August 2012 using natural cubic splines with four knots. Categorization of continuous covariates was based on clinically relevant thresholds determined *a priori* (all biological parameters) or quartiles limits (age, time since HCV diagnosis). Missing covariate values were handled using indicators for missing data in the multivariable model. To better characterize the potential impact of a SVR in DAA-exposed patients compared to untreated patients, the exposure period was divided into the on-treatment period (from first to last day of DAA treatment extended by 3 months), and the period with a measurable SVR status (from 3 months after the last day of DAA treatment to the end of follow-up), which were considered as time-dependent covariates in the Cox model (see supplementary figure 3). SVR status was evaluated after the first DAA treatment and was not updated if a patient received several consecutive treatments. These analyses were repeated both in patients with and

without cirrhosis or unknown fibrosis score at entry in the cohort. To deal with a potential residual indication bias, time-dependent censoring, and confounding, the robustness of our findings were also evaluated using inverse probability of treatment weighting[25] and sequential weighted Cox Models.[26] Because the most severe patients could be excluded from treatment due to a high risk of complications, an additional sensitivity analysis was performed including patients with at least 12 months of follow-up. Robust variance estimates were determined for all analyses to obtain conservative 95% confidence intervals. All analyses were performed with SAS 9·4 (SAS Institute Inc., Cary, North Carolina). A P-value < ·05 was considered to be statistically significant.

Role of the funding source

The ANRS CO22 Hepather cohort was sponsored by Inserm-ANRS, which contributed to the study design and drafting of the study. The sponsor played no role in data collection, data analysis or data interpretation. The other funding sources played no role in study design, data collection, data analysis, data interpretation, or drafting the study. FC had full access to all data in the study and FC and SP made the final decision to submit the study for publication.

Results

A total of 10,166 patients were eligible for the study (figure 1). Post-entry follow-up information was available in 9,895 (97%) of these patients (see supplementary Table 1 for a comparison with eligible patients with missing follow-up information) who were included in the analyses. Baseline demographic, clinical and laboratory characteristics of included patients according to exposure to DAA during the follow-up are provided in Table 1. Mean age was 56·7 years old and 53% were men. A total of 7,344 patients began DAA treatment after a median time from entry of 4·3 months (IQR 0·2-17·2) . The median follow-up (untreated + treated periods) in these patients was 33·4 months (IQR 24·0-40·7). At the last follow-up visit, 2,551 patients remained untreated, with a median follow-up of 31·2 months (IQR 21·5-41·0). Patients who received DAA were older, more often men, with a higher BMI, and were often reported past excessive alcohol use than those who remained untreated at the final follow-up. Receiving DAA treatment was also strongly associated with the severity of liver disease and other comorbidities: treated patients had been diagnosed with HCV longer, 42% of these patients had cirrhosis (vs 10% of untreated patients), 57% were HCV treatment-experienced at entry (vs 39%), including 49 (0·7%) vs 3 (0·1%) with past use of IFN-free regimens, 13% had genotype 3 infection (vs 9%), 13% had diabetes (vs 8%) and 30% had arterial hypertension (vs 24%). Of note, 40% of patients with past excessive alcohol use had cirrhosis vs 28% of those without (P<0·0001), explaining why past excessive alcohol users were more likely to initiate DAA treatment. DAA combinations are listed in Supplementary Table 2.

A total of 218 deaths (73 classified as LR, 114 NLR (see supplementary table 3 for details), 31 unclassified), 258 HCC and 106 cases of decompensated cirrhosis were reported during follow-up. Twenty-five patients also underwent liver transplantation

during follow-up. Crude incidence rates of all-cause mortality, LR death, HCC and decompensated cirrhosis were higher in patients exposed to DAA than in unexposed patients (table 2, figure 2). Exposure to DAA was associated with an increased risk of HCC (HR= 2·77 (95%CI 2·07-3·71), P<0·0001) and decompensated cirrhosis (HR=3·83 (2·29-6·42), P<0·0001) on the unadjusted Cox model. On adjusted multivariable analysis, exposure to DAA was associated with a decrease in all-cause mortality (HR= 0·48 (95%CI 0·33-0·70), P=0·0001), LR death (HR=0·39 (0·21-0·71), P=0·0020), NLR death (HR=0·60 (0·36-1·00), P=0·048), and HCC (HR=0·66 (0·46-0·93), P=0·018), and was no longer associated with decompensated cirrhosis (HR=1·14 (0·57-2·27), P=0·72). Similar findings were obtained using inverse probability of treatment weighting and weighted sequential Cox models (Supplementary Table 4) or when analyses were limited to events that occurred after 12 months of follow-up (Supplementary Table 5). Other predictors independently associated with the risk of all-cause mortality, HCC or decompensated cirrhosis are presented Table 3 (see also supplementary Table 6 for a description of events by covariate levels).

A SVR was achieved in 5,615 out of 7,344 patients who started DAA, was not achieved in 341 (SVR rate=94%) and was unknown in 709, while SVR status could not be determined in 679 patients due to insufficient follow-up (Supplementary Table 7, these patients are classified “on-treatment”). Compared to unexposed patients, a SVR in treated patients was associated on adjusted multivariable analysis with a decrease in all-cause, LR and NLR mortalities and HCC and a non-significant decrease in decompensated cirrhosis, while failure to obtain a SVR was associated with a significant increase in HCC (multivariable-adjusted HR=2·23 (95%CI 1·37-3·64), P=0·0012) (Supplementary Table 8). There was no evidence of an increased

risk of HCC during the on-treatment period (multivariable-adjusted HR=0·74 (95%CI 0·49-1·13), P=0·17).

When adjusted multivariable analyses were performed in the patients with baseline cirrhosis, exposure to DAA was strongly associated with a decrease in all-cause (HR=0·34 (95%CI 0·22-0·55), P<0·0001), LR (HR=0·28 (0·15-0·54), P=0·0001) and NLR mortalities (HR=0·40 (0·19-0·83), P=0·015) as well as in HCC (HR=0·57 (0·40-0·81), P=0·0016) (Table 2 and Figure 3). Predictors of clinical events in patients with cirrhosis were similar to those identified in the entire cohort (Supplementary Table 9). A SVR was achieved in 2,329 out of 2,823 patients with cirrhosis who initiated DAA, was not achieved in 195 (SVR rate=92%) and was unknown in 179, while 120 patients were still on-treatment. Multivariable analyses confirmed the association between SVR and a decrease in all-cause, LR and NLR mortalities as well as in HCC and the association between a lack of SVR and an increased risk of HCC (Supplementary Table 8).

We did not find any significant association between exposure to DAA with the studied outcomes in the subset of patients without a cirrhosis or with unknown fibrosis score at entry (Table 2). A SVR was achieved in 3,286 out of 4,521 patients who initiated DAA, was not achieved in 146 (SVR rate=96%) and was unknown in 530, while 559 patients were still on-treatment.

The detailed characteristics of HCC were obtained in 249 (97%) patients with incident HCC. No difference was found in the delay between the last normal imaging test and diagnosis, the macroscopic pattern, the number of tumours at diagnosis, the total nodule size, largest nodule size, or serum alpha-fetoprotein levels in DAA-treated and untreated patients (Supplementary Table 10).

Discussion

This large French cohort study showed that DAA treatment was associated with a reduced risk of mortality and HCC, after adjustment for potential confounding factors. Patients exposed to DAA had a 52% and 34% lower risk of all-cause mortality and HCC, respectively than those who were not exposed. Similar associations were identified in the subgroup of patients with cirrhosis. These inverse associations persisted in the subgroup of patients who achieved a SVR, while those who did not had a higher risk of HCC. It should be noted that there were no signs of an increased risk of HCC during DAA treatment.

Overall, our results are similar to those reported in the ERCHIVES retrospective cohort.[14] In that study a significant (57%) (95%CI 43%-67%) decrease in all-cause mortality was observed in patients receiving DAA compared to propensity-score matched untreated patients. Moreover, results showed that age, cirrhosis, comorbidities (diabetes and chronic kidney disease), and anaemia were positively correlated with mortality. Our study found a strong, independent relationship between all-cause mortality and cirrhosis, markers of liver failure, hypertension, and anaemia. Our results also confirm numerous studies that show a lower risk of death in DAA-treated patients who achieve a SVR compared to those who do not.[10] Our HCC incidence rates in patients with a SVR after DAA treatment were similar to those in studies,[8] while the rate in patients without a SVR was significantly higher (7·19/100 (95%CI 5·16/100-9·76/100) person-years in our study vs 3·45/100 (2·73/100-4·18/100) person-years), because "priority" patients, that is, those with the highest risk of hepatic morbidity and mortality, received DAA in our study.

A striking finding in our study was the lower risk of NLR mortality in DAA-treated compared to untreated patients. Although a decrease in long-term NLR mortality has

been reported in patients with SVR compared to those without following interferon-based therapy,[27] reverse causality could be another possibility if patients with the most severe liver-disease and the highest risk of death from any cause had a lower probability of starting DAA treatment. However, patients with decompensated cirrhosis or a past history of HCC were excluded at baseline. We adjusted for numerous markers of liver insufficiency and comorbidities in our multivariable analyses. Finally, our results were similar when data from the first 12 months of follow-up were excluded. These elements seem to exclude reverse causality.

Our study has several limitations. First, the assessment of fibrosis and cirrhosis were based on patients records at entry in the cohort, were determined by different methods, and were not updated during follow-up or when patients started DAA treatment. We validated the predictive value of platelet count and the prothrombin time for the diagnosis of cirrhosis using other methods for the assessment of fibrosis. The median time between the assessment of fibrosis and the end of follow-up in untreated and treated patients was 32·3 (IQR 22·7-43·0) and 34·5 (25·1-43·0) months, respectively. Fibrosis probably worsened in some patients, thus explaining the development of liver-related complications in patients classified as without a cirrhosis at entry in the cohort. However, any difference in the progression of fibrosis between untreated and treated patients during follow-up would be directly due to the effect of treatment on fibrosis. Thus, this should not be considered a bias but rather a plausible explanation for the inverse relationship between treatment and the risk of liver-related outcomes. Moreover, results in the subgroup of patients with baseline cirrhosis, which should be less biased by the misclassification of fibrosis, were highly consistent.

Second, the duration of follow-up was relatively short, making it impossible to assess long-term outcomes associated with DAA. Nevertheless, an inverse relationship was found between treatment and liver-related mortality or HCC in patients with cirrhosis over this short-term follow-up, and a longer follow-up would probably not change these findings. Third, due to the observational nature of our study, some patients may have undergone less regular HCC screening than recommended, resulting in potentially missed HCC diagnoses. However, the average number of follow-up visits and ultrasound examinations (weighted by person-years of follow-up) were higher in patients during treatment and the year after treatment than in untreated patients or before treatment (9·3 ± 3·9 vs 2·8 ± 1·3, P<0·0001 and 1·5 ± 1·9 vs 0·6 ± 1·1, P<0·0001, respectively). Therefore, any screening bias would result in a decrease in HCC detection in unexposed compared to exposed patients, and would not affect our conclusions. Fourth, no significant association was found between DAA and the risk of decompensated cirrhosis. However, the analysis according to SVR status shows a trend towards an inverse association in patients with cirrhosis at baseline (HR comparing patients who achieved a SVR vs untreated patients of 0·51 (95%CI 0·23-1·14)), and our study probably still lacks statistical power for this outcome. Finally, although numerous multivariable analyses were performed, a residual risk of bias from confounding factors associated with unmeasured prognostic factors or another complex time-dependent selection bias cannot be excluded. We used different statistical methods to take into account these different sources of bias, with similar results.

Because of the observational design of our study, we cannot formally conclude that inverse associations between DAA treatment and mortality or HCC incidence reflect cause and effect relationships. However, we can hypothesize about the plausible

mechanisms: DAA induces a SVR, reducing liver damage and inflammation. This causes liver regeneration, decreasing the risk of progression to liver-related complications or HCC. Our results showing markedly different risks of these liver-related events in patients with and without a SVR support these mechanisms. Several studies have also suggested that a lack of SVR could be a sign of HCC.[28,29] However, the median time between assessment of a SVR and a diagnosis of HCC was 14·0 months (IQR 7·4-21·1) in patients without a SVR vs 12·1 months (5·9-20·1) – P=0·29. This does not support the presence of pre-existing HCC in patients without a SVR.

In summary, this large prospective cohort study showed a significant decrease in the risk of all-cause mortality and HCC associated with DAA treatment. Our results also suggest that DAA does not adversely affect the development of HCC. The long-term influence of DAA on liver decompensation must still be clarified.

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Table 1. Characteristics of patients at entry in the cohort, in relation to DAA treatment during follow-up.

	Did not receive DAA at the last follow-up visit (N=2,551)	Did receive DAA before the last follow-up visit (N=7,344)	P-value
Age - yrs (mean ± SD)	54·6 ± 12·6	57·5 ± 11·0	<0·0001
Male Gender	1,174 (46)	4,105 (56)	<0·0001
BMI (kg/m^2)			
<18·5	82 (3)	219 (3)	<0·0001
[18·5, 25[	1,397 (57)	3,592 (50)	
[25, 30[	683 (28)	2,434 (34)	
≥ 30	295 (12)	994 (14)	
Missing	*94*	*105*	
Geographic Origin			
Asia	76 (3)	173 (2)	<0·0001
Eastern Europe	85 (3)	275 (4)	
France	1,559 (63)	4,555 (63)	
North Africa	245 (10)	788 (11)	
Other	268 (11)	954 (13)	
Subsaharan Africa	258 (10)	479 (7)	
Missing	*60*	*120*	
Infection route			
Injecting drug use	608 (25)	1,862 (26)	0·056
Transfusion	711 (29)	2,254 (31)	
Other or Unknown	1,115 (46)	3,116 (43)	
Missing	*117*	*112*	
Excessive alcohol use*			
At entry in the cohort			
No	2,459 (96)	7,104 (97)	0·41
Yes	92 (4)	240 (3)	
Missing	*0*	*0*	
Past			
No	1,868 (76)	5,251 (72)	0·0018
Yes	603 (24)	2,004 (28)	
Missing	*80*	*89*	
Time since HCV diagnosis – yrs (mean ± SD)	13·7 ± 8·2	14·4 ± 8·5	0·0004
Missing	*157*	*252*	
HCV treatment history			
Treatment-experienced	974 (39)	4,159 (57)	<0·0001
Treatment-naive	1,542 (61)	3,165 (43)	
Missing	*35*	*20*	
HCV genotype			
1	1,531 (64)	4,818 (67)	<0·0001
2	231 (10)	420 (6)	
3	211 (9)	918 (13)	
4	334 (14)	918 (13)	
5/6/7	68 (3)	153 (2)	
Missing	*176*	*117*	
Fibrosis scoring			
F0-F1-F2	1,865 (84)	2,805 (41)	<0·0001
F3	136 (6)	1,172 (17)	
F4	222 (10)	2,823 (42)	
Missing	*328*	*544*	
APRI score (mean ± SD)	0·62 ± 0·85	1·20 ± 1·55	<0·0001

Missing	*449*	*625*	
FIB4 score			
(mean ± SD)	1·78 ± 1·89	2·90 ± 2·96	<0·0001
Missing	*453*	*633*	
MELD Score in patients with cirrhosis			
<13	157 (90)	2,426 (92)	0·15
[13-20[	10 (6)	143 (5)	
≥20	8 (5)	60 (2)	
Missing	*47*	*194*	
APRI score in patients with cirrhosis			
(mean ± SD)	1·68 ± 2·14	1·94 ± 2·05	0·0014
≤2.00	133	1807	0·16
>2.00	49	857	
Missing	*40*	*159*	
FIB4 score score in patients with cirrhosis			
(mean ± SD)	4·39 ± 4·76	4·41 ± 3·85	0·31
<3.25	96	1330	0·49
≥3.25	86	1332	
Missing	*40*	*161*	
Diabetes			
No	2,277 (92)	6,325 (87)	<0·0001
Yes	198 (8)	945 (13)	
Missing	*76*	*74*	
Hypertension			
No	1,878 (76)	5,105 (70)	<0·0001
Yes	589 (24)	2,161 (30)	
Missing	*84*	*78*	
Anaemia†			
No	2,014 (92)	6,303 (92)	0·69
Yes	177 (8)	576 (8)	
Missing	*360*	*465*	
Albumin			
≥ 30g/L	1,751 (99)	6,160 (99)	0·042
< 30g/L	12 (1)	79 (1)	
Missing	*788*	*1105*	
Prothrombin time			
> 70%	1,921 (97)	6,041 (95)	<0·0001
≤ 70%	51 (3)	319 (5)	
Missing	*579*	*984*	
Platelet count			
≥ 10^5/μL	2,106 (98)	6,232 (91)	<0·0001
< 10^5/μL	50 (2)	598 (9)	
Missing	*395*	*514*	
Alanine aminotransferase			
≤ 5 ULN‡	2,247 (98)	6,646 (94)	<0·0001
> 5 ULN	39 (2)	404 (6)	
Missing	*265*	*294*	
Aspartate aminotransferase			
≤ 5 ULN‡			
> 5 ULN	2,198 (97)	6,701 (96)	<0·0001
Missing	58 (3)	312 (4)	
	295	*331*	
Alpha fetoprotein			
< 5·5 ng/mL	1,051 (74)	2,647 (52)	<0·0001
≥ 5·5 ng/mL	365 (26)	2,425 (48)	
Missing	*1,135*	*2,272*	

n (%) otherwise specified.
* defined as at least 15 alcoholic drinks (150g) per week for a woman or 22 alcoholic drinks (220g) per week for a man, or at least 6 consecutive alcoholic drinks (60g) on at least 1 occasion per week.
†Anaemia: HB <12g/dL in women, Hb<13g/dL in men
‡ULN: Upper limit or normal

Table 2. Incidence rates of death, hepatocellular carcinoma and decompensated cirrhosis in patients according to exposure to DAA treatment and corresponding hazard ratios.

	Not exposed to DAA (DAA-)		**Exposed to DAA (DAA+)**		**Exposed vs not exposed (DAA+ vs DAA-)**	
	n/pyrs*	Incidence per 100 pyrs (95%CI)	n/pyrs	Incidence per 100 pyrs (95%CI)	Univariable Hazard Ratio (95%CI)	Multivariable-adjusted Hazard Ratio (95%CI)
All patients (n=9,895)						
All-cause mortality	89/12,709	0·70 (0·56-0·86)	129/13,626	0·95 (0·79-1·12)	1·14 (0·85-1·52)	0·48 (0·33-0·70)
Liver related	25/12,709	0·20 (0·13-0·29)	48/13,626	0·35 (0·26-0·47)	1·46 (0·89-2·39)	0·39 (0·21-0·71)
Non-liver related	53/12,709	0·42 (0·31-0·55)	61/13,626	0·45 (0·34-0·58)	0·92 (0·62-1·37)	0·60 (0·36-1·00)
Hepatocellular carcinoma	71/12,660	0·56 (0·44-0·71)	187/13,375	1·40 (1·20-1·61)	2·77 (2·07-3·71)	0·66 (0·46-0·93)
Decompensated cirrhosis	32/12,698	0·25 (0·17-0·36)	74/13,520	0·55 (0·43-0·69)	3·83 (2·29-6·42)	1·14 (0·57-2·27)
Patients with a cirrhosis (n=3,045)						
All-cause mortality	41/1,578	2·60 (1·86-3·52)	94/6,320	1·49 (1·20-1·82)	0·35 (0·23-0·53)	0·34 (0·22-0·55)
Liver related	19/1,578	1·20 (0·72-1·88)	42/6,320	0·66 (0·48-0·90)	0·32 (0·17-0·59)	0·28 (0·15-0·54)
Non-liver related	15/1,578	0·95 (0·53-1·57)	36/6,320	0·57 (0·40-0·79)	0·36 (0·18-0·71)	0·40 (0·19-0·83)
Hepatocellular carcinoma	57/1,539	3·70 (2·80-4·80)	166/6,104	2·72 (2·32-3·17)	0·63 (0·44-0·90)	0·57 (0·40-0·81)
Decompensated cirrhosis	28/1,567	1·79 (1·19-2·58)	67/6,223	1·08 (0·83-1·37)	0·67 (0·40-1·11)	0·95 (0·48-1·89)
Patients w/o a cirrhosis (n=5,978) or with unknown fibrosis score (n=872)						
All-cause mortality	48/11,131	0·43	35/7,307	0·48	0.94	0.74

		(0·32-0·57)		(0·33-0·67)	(0·58-1·50)	(0·43-1·28)
Liver related	6/11,131	0·05 (0·02-0·12)	6/7,307	0·08 (0·03-0·18)	1·33 (0·46-3·84)	ND[†]
Non-liver related	38/11,131	0·34 (0·24-0·47)	25/7,307	0·34 (0·22-0·51)	0·89 (0·51-1·56)	0·75 (0·42-1·35)
Hepatocellular carcinoma	14/11,120	0·13 (0·07-0·21)	21/7,271	0·29 (0·18-0·44)	2·49 (1·18-5·27)	1·02 (0·40-2·61)
Decompensated cirrhosis	4/11,131	0·04 (0·01-0·09)	7/7,297	0·10 (0·04-0·20)	3·59 (0·66-19·5)	ND[†]

*pyrs: person-years.

[†]ND: Not Done due to insufficient number of events

Table 3. Factors associated with all-cause mortality, hepatocellular carcinoma and decompensated cirrhosis in all analysed patients.

	All-cause mortality	Hepatocellular carcinoma	Decompensated cirrhosis
Exposed to DAA (Y vs N)	0·48 (0·33-0·70)*	0·66 (0·46-0·93)*	1·14 (0·57-2·27)
Age (yrs)			
<50 (ref)	1	1	1
[50-56[	1·37 (0·84-2·26)	1·78 (1·08-2·95)*	1·77 (0·84-3·71)
[56-64[	1·41 (0·86-2·30)	2·41 (1·47-3·95)*	2·08 (1·05-4·14)*
≥64	2·02 (1·27-3·23)*	3·47 (2·07-5·81)*	1·60 (0·79-3·24)
Male Gender (vs Female)	1·43 (1·06-1·92)*	2·37 (1·71-3·29)*	1·39 (0·84-2·31)
BMI (kg/m^2)			
<18·5	2·57 (1·36-4·85)*	0·23 (0·03-1·75)	2·18 (0·63-7·50)
[18·5, 25[(ref)	1	1	1
[25, 30[	0·90 (0·65-1·25)	0·89 (0·67-1·20)	1·92 (1·16-3·16)*
≥ 30	1·00 (0·66-1·51)	0·99 (0·69-1·44)	1·68 (0·92-3·08)
Geographic Origin France (vs others)	1·35 (0·99-1·84)	1·46 (1·11-1·92)*	1·25 (0·80-1·96)
Infection route			
Injecting drug use (ref)	1	1	1
Transfusion	1·62 (1·04-2·53)*	1·36 (0·90-2·07)	1·10 (0·60-2·02)
Other or Unknown	1·18 (0·77-1·81)	1·14 (0·79-1·64)	0·73 (0·41-1·33)
Excessive alcohol use †			
At entry in the cohort (Y vs N)	1·32 (0·67-2·60)	0·78 (0·39-1·53)	1·01 (0·31-3·37)
Past (Y vs No)	1·27 (0·91-1·78)	1·29 (0·95-1·75)	0·83 (0·53-1·29)
Time since HCV diagnosis (yrs)			
<7 (ref)	1	1	1
[7-15[	0·66 (0·43-1·02)	1·08 (0·72-1·64)	1·37 (0·70-2·69)
[15-21[	0·82 (0·54-1·25)	1·06 (0·71-1·59)	1·01 (0·49-2·05)
≥21	0·71 (0·46-1·10)	1·06 (0·70-1·60)	1·24 (0·62-2·48)
HCV treatment-naive (Y vs N)	0·85 (0·61-1·18)	0·83 (0·60-1·15)	1·32 (0·80-2·18)
HCV genotype			
1 (ref)	1	1	1
2	1·14 (0·64-2·00)	1·07 (0·58-1·99)	1·34 (0·60-2·97)
3	1·46 (0·97-2·20)	2·27 (1·63-3·16)*	1·68 (1·01-2·79)*
4	1·13 (0·71-1·80)	0·70 (0·43-1·15)	0·58 (0·28-1·21)
5/6/7	1·18 (0·51-2·76)	1·93 (1·02-3·64)*	1·36 (0·43-4·34)
Fibrosis scoring			
F0-F1-F2 (ref)	1	1	1
F3	1·45 (0·79-2·67)	5·03 (2·29-11·0)*	1·41 (0·32-6·24)
F4	3·69 (2·32-5·87)*	15·3 (7·55-30·9)*	9·01 (3·30-24·6)*
Diabetes (Y vs N)	1·23 (0·86-1·76)	1·05 (0·76-1·43)	1·23 (0·79-1·90)
Hypertension (Y vs N)	1·51(1·10-2·08)*	1·44 (1·09-1·91)*	1·60 (0·99-2·59)
Anaemia (Y vs N)	2·45 (1·69-3·55)*	1·28 (0·89-1·84)	2·10 (1·22-3·62)*
Albumin (<30 g/L vs ≥ 30g/L)‡	2·03 (0·87-4·74)	2·49 (1·23-5·03)*	1·87 (0·73-4·81)
Prothrombin time (≤ 70% vs > 70%)	1·71 (1·07-2·71)*	1·44 (0·97-2·14)	1·72 (1·01-2·94)*
Platelet count (< 10^5/µL vs ≥ 10^5/µL)	1·50 (0·97-2·33)	2·24 (1·66-3·01)*	6·05 (3·75-9·77)*
Alanine aminostransferase (> 5 ULN vs ≤ 5 ULN)§	0·54 (0·24-1·22)	0·79 (0·42-1·48)	0·53 (0·22-1·30)
Aspartate aminotransferase (> 5 ULN vs ≤ 5 ULN)§	1·31 (0·67-2·57)	0·78 (0·44-1·38)	0·95 (0·37-2·42)
Alpha fetoprotein (≥ 5·5 ng/mL vs < 5·5 ng/mL)	1·03 (0·73-1·44)	2·09 (1·48-2·95)*	0·82 (0·51-1·34)

*indicates significant adjusted analysis associations at the P<0.05 level.
†defined as at least 15 alcoholic drinks (150g) per week for a woman or 22 alcoholic drinks (220g) per week for a man, or at least 6 consecutive alcoholic drinks (60g) on at least 1 occasion per week.
‡Anaemia: Hb <12g/dL in women, Hb<13g/dL in men.
§ULN: Upper limit or normal

A time-dependent Cox model was used. Dummy variables were used for missing covariate values. The baseline hazard was modelled as a smooth function of time since the first patient inclusion visit

Figure legends.

Figure 1. Participant flow-chart

Figure 2. Global survival, survival free from hepatocellular carcinoma and survival free from decompensated cirrhosis according to exposure to DAA in all analysed patients. Upper panel represents the unadjusted survival curves. The lower panel represents the multivariable-adjusted survival curves estimated using a time-dependent Cox proportional-hazards model. HR: Hazard-Ratio

Figure 3. Global survival, survival free from hepatocellular carcinoma and survival free from decompensated cirrhosis according to exposure to DAA in patients with cirrhosis. Upper panel represents the unadjusted survival curves. Lower panel represents the multivariable-adjusted survival curves estimated using a time-dependent Cox proportional-hazards model. HR: Hazard-Ratio

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Research in context

Evidence before the study

We searched for evidence of randomized trials or observational studies assessing the risk of mortality, liver cancer, and the complications of liver disease after antiviral treatment with Direct Acting Antivirals (DAA) in patients with chronic hepatitis C infection. We searched PubMed for articles published in any language between Jan 1, 2012 and Jan 1, 2018, using the keywords: ("Hepatitis C, Chronic/drug therapy"[Mesh] OR "Hepatitis C, Chronic/therapy"[Mesh]) AND ("Hepatitis C, Chronic/mortality"[Mesh] OR "Hepatitis C, Chronic/complications"[Mesh]). We identified a 2017 review of 138 randomized trials assessing the effects of 51 different DAAs, indicating that DAA increased the rate of sustained virological response. However, the review did not reach any conclusions on clinical effects. We only found one additional retrospective cohort study reporting a significant decrease in all-cause mortality in patients receiving either paritaprevir/ritonavir/ombitasvir/dasabuvir or sofosbuvir/ledispasvir compared to untreated patients. This study did not report on liver-related mortality or liver-related events such as liver cancer or liver decompensation. No existing prospective study has examined the benefits and harms of DAAs in chronic HCV infection on liver-related clinical outcomes using a time-to-event analyses and a comparison of treated and untreated patients.

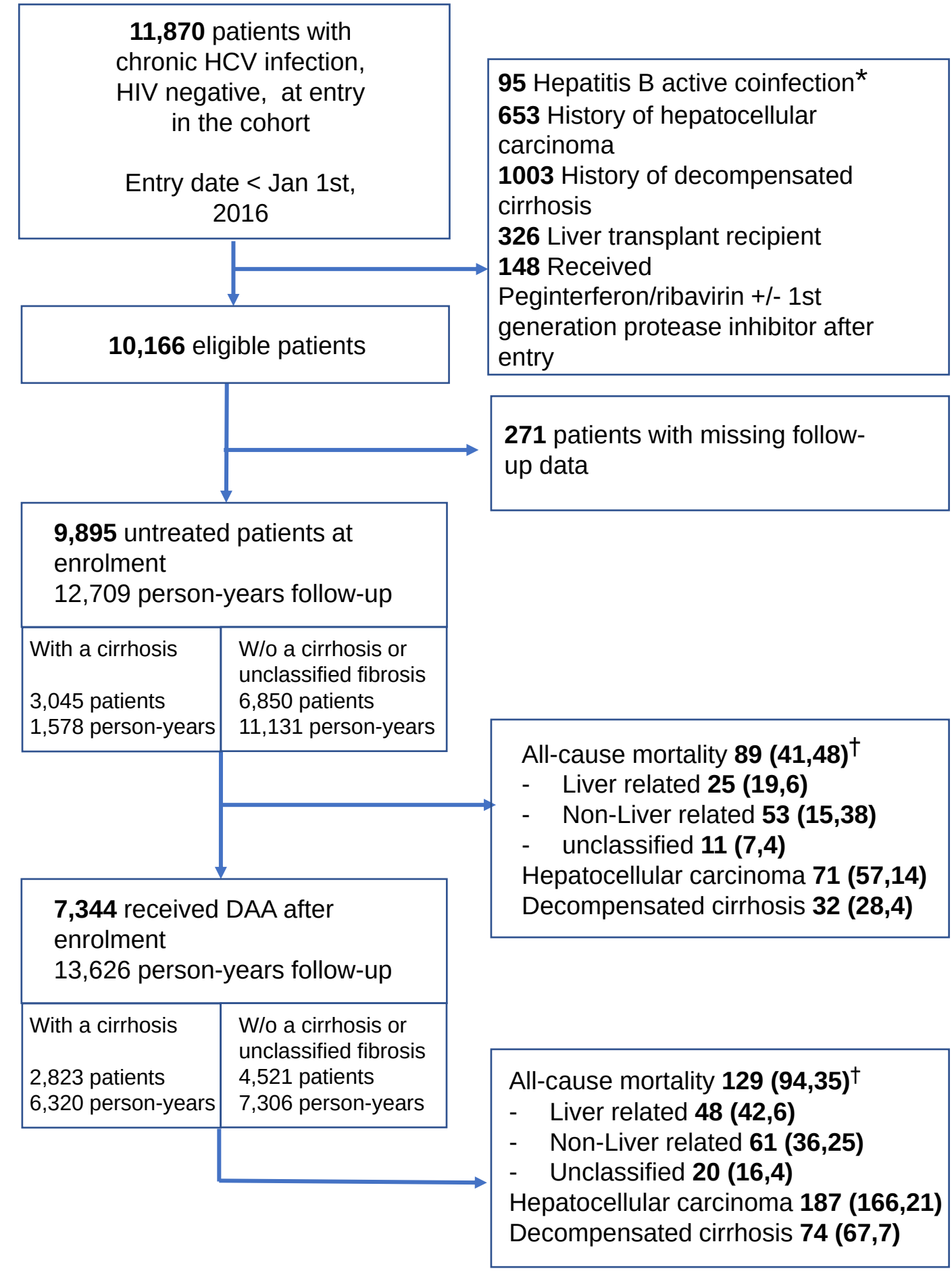
Added value of the study

To our knowledge, the ANRS CO22 Hepather cohort study is the first prospective longitudinal study to explore the clinical outcomes associated with DAA treatment in patients with chronic hepatitis C, by comparing treated versus untreated patients, irrespective of SVR status, with careful control of confounding and indication biases. The adjusted multivariate analyses show that DAA treatment is associated with a

rapid decrease in all-cause mortality and the incidence of hepatocellular carcinoma and that these inverse associations are stronger in patients with cirrhosis.

Implications of all the available evidence

For obvious ethical reasons a trial with an untreated control arm cannot be performed to confirm these findings. We encourage other researchers to perform similar comparisons of DAA-treated and untreated patients using existing observational databases. Whatsoever, our results clearly support urgent treatment of patients with advanced liver disease and to extend the follow-up of treated patients with less severe disease to assess the long-term clinical impact of DAA treatment.



* Patients may experience > 1 exclusion criteria

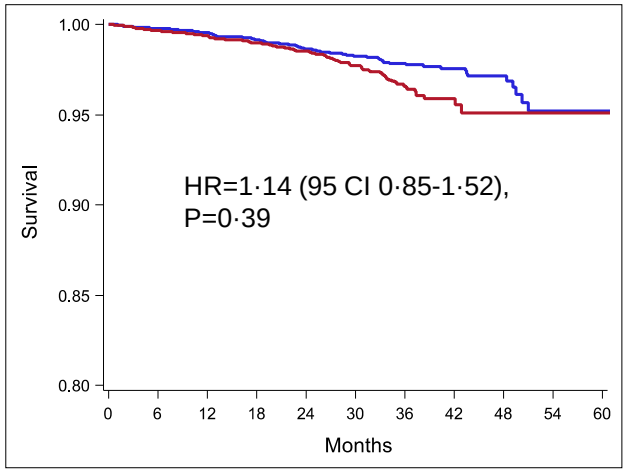
†Numbers in all patients (numbers in patients with a cirrhosis, numbers in patients w/o a cirrhosis or unclassified fibrosis)

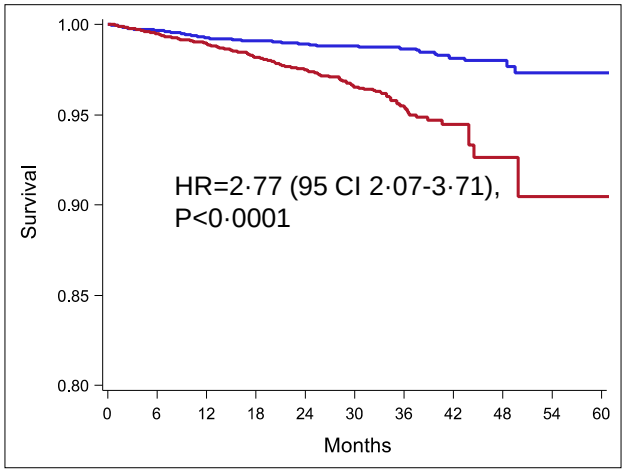
All-cause mortality

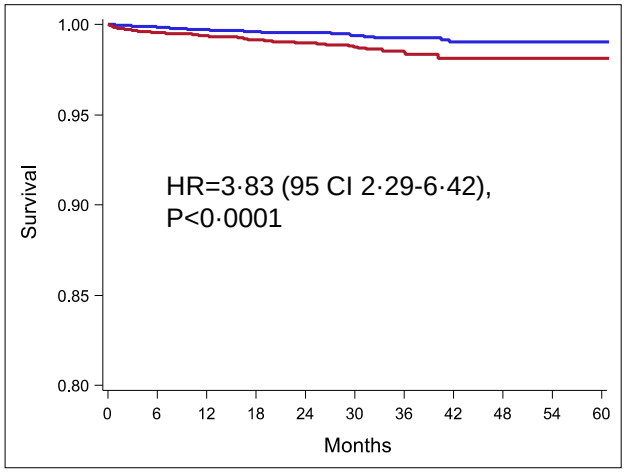
Hepatocellular carcinoma

Decompensated cirrhosis

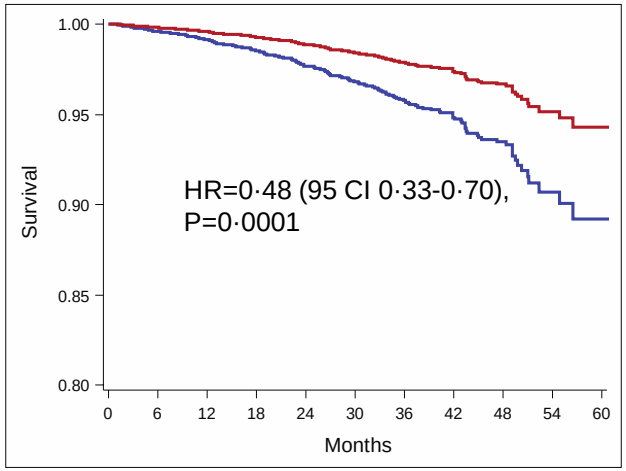
Unadjusted survival curves

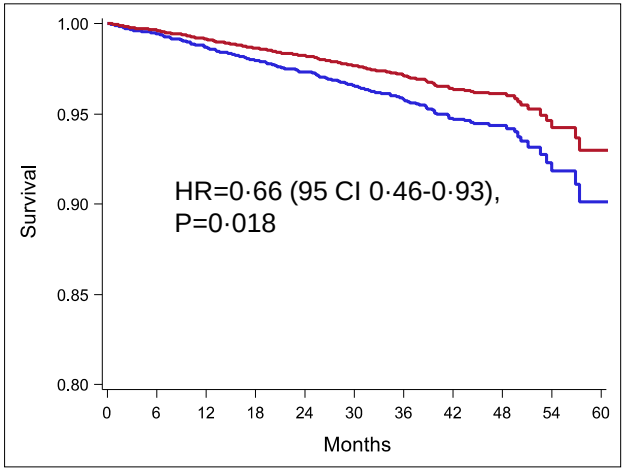


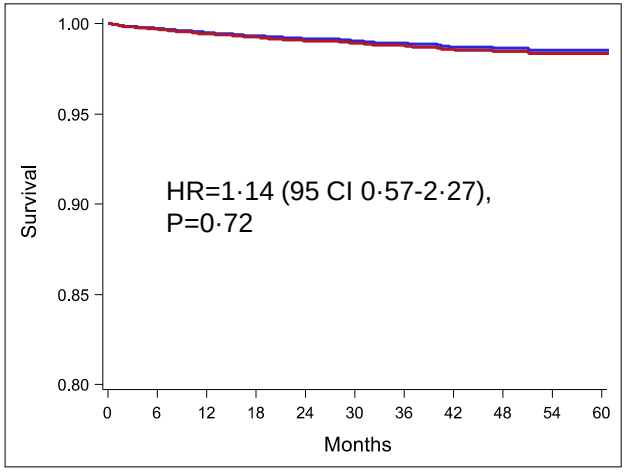




Multivariable-adjusted survival curves







	Months	0	12	24	36	48	60
N at risk	DAA+	7344	5448	3469	1012	59	6
	DAA-	9895	4774	2889	1344	360	10

	Months	0	12	24	36	48	60
N at risk	DAA+	7308	5366	3368	977	57	6
	DAA-	9895	4751	2878	1337	355	10

	Months	0	12	24	36	48	60
N at risk	DAA+	7330	5408	3432	996	59	6
	DAA-	9895	4766	2888	1342	360	10

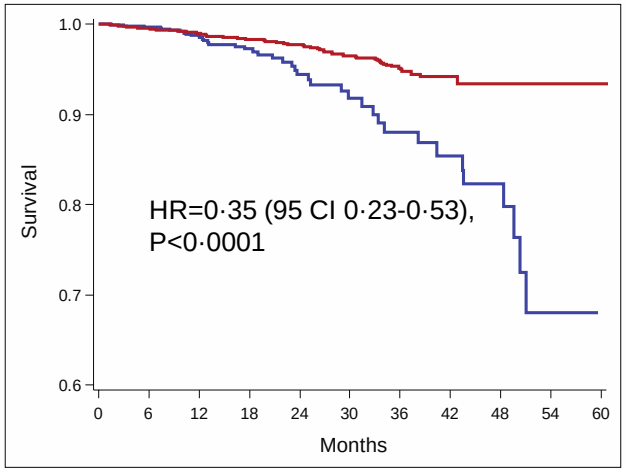
DAA+ DAA-

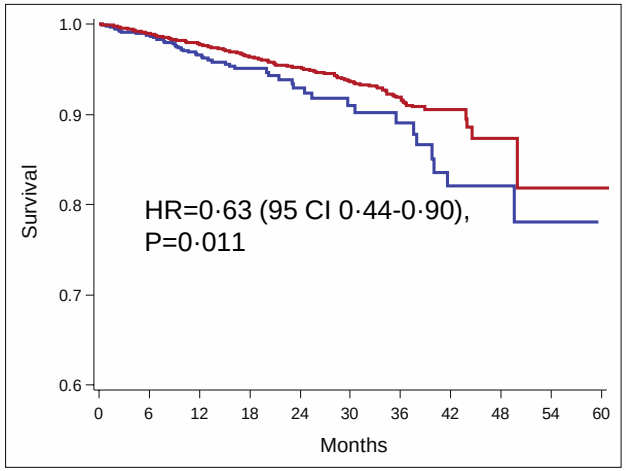
All-cause mortality

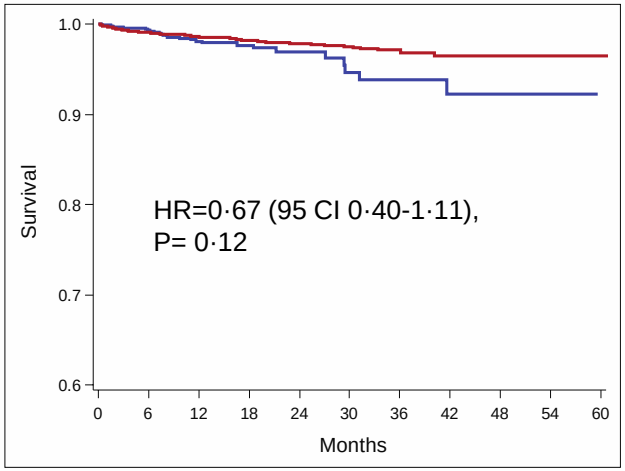
Hepatocellular carcinoma

Decompensated cirrhosis

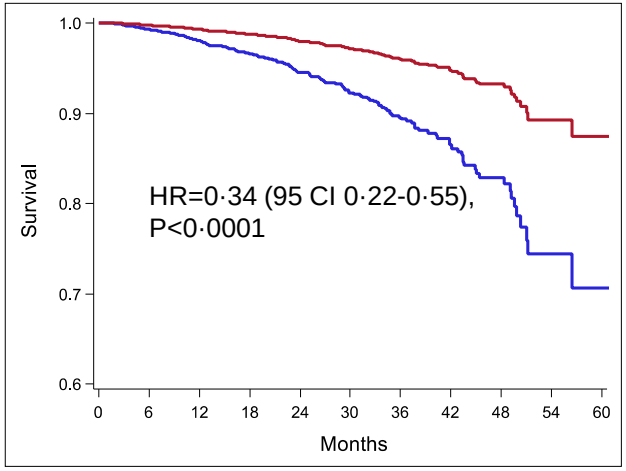
Unadjusted survival curves

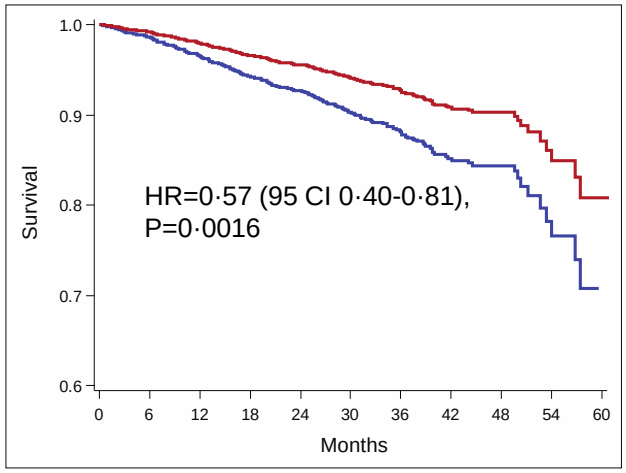


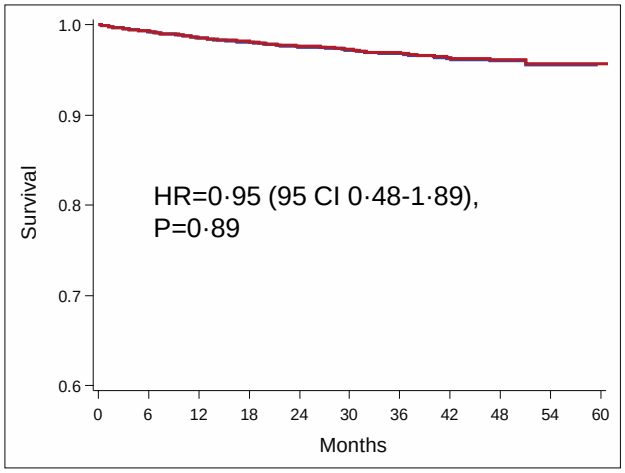




Multivariable-adjusted survival curves







	Months	0	12	24	36	48	60
N at risk	DAA+	2823	2457	1803	610	25	2
	DAA-	3045	560	186	82	37	0

	Months	0	12	24	36	48	60
N at risk	DAA+	2795	2389	1715	575	23	2
	DAA-	3045	543	178	76	33	0

	Months	0	12	24	36	48	60
N at risk	DAA+	2810	2419	1768	596	25	2
	DAA-	3045	552	185	81	37	0

DAA+ DAA-