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Direct acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients

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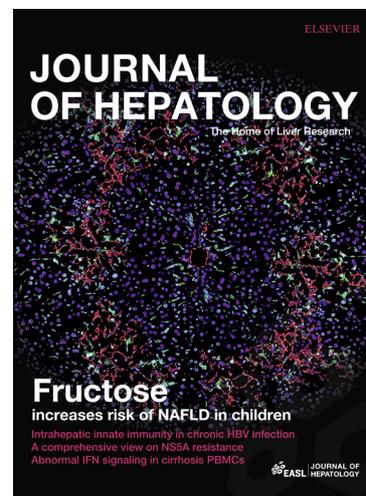
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Title page

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Abbreviations: Hepatocellular carcinoma (HCC); Hepatitis C virus (HCV); Direct acting antivirals (DAAs); Overall survival (OS); Sustained virological response (SVR), Barcelona Clinic Liver Cancer (BCLC), Hazard Ratio (HR), Confidence Interval (CI), Orthotopic Liver Transplantation (OLT), Randomised controlled trials (RCTs), Rete Sicilia Selezione Terapia HCV (RESIST HCV), complete radiological response (CRR), European Association for the Study of the Liver (EASL), Ultrasound (US), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Standard deviations (SDs), Model for end-stage liver disease (MELD), Standardized Mean Differences

(SMD), inverse probability of treatment weighting (IPTW), propensity score (PS), Alanine transaminase (ALT), Body mass index (BMI), Alfafetoprotein (AFP).

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ABSTRACT

Background & Aims: The effectiveness of direct-acting antivirals (DAAs) against hepatitis C virus (HCV) after successful treatment of early hepatocellular carcinoma (HCC) has been studied extensively. However, the benefit in terms of overall survival (OS) remains to be conclusively demonstrated. The aim of this study was to assess the impact of DAAs on OS, HCC recurrence, and hepatic decompensation.

Methods: We enrolled prospectively 163 consecutive patients with HCV-related cirrhosis and at first diagnosis of early Barcelona Clinic Liver Cancer (BCLC) 0/A HCC who had achieved a complete radiologic response after curative resection or ablation, subsequently treated with DAAs. DAA-untreated patients from ITA.LI.CA. cohort (n=328) served as controls. After propensity-score matching, outcomes of 102 DAA-treated (DAA group) and 102 DAA-untreated patients (No DAA group) were compared.

Results: In DAA group, 7/102 patients (6.9%) died, HCC recurred in 28/102 patients (27.5%) and hepatic decompensation occurred in 6/102 patients (5.9%), after a mean follow-up of 21.4 months. OS was significantly higher in DAA group compared with No DAA group (hazard ratio [HR]=0.39; 95% confidence Interval [CI]=0.17–0.91, $p=0.03$). HCC recurrence was not significantly different between DAA and No DAA groups (HR=0.70; 95% CI=0.44-1.13, $p=0.15$). A significant reduction in the rate of hepatic decompensation was observed in DAA group compared with No DAA group (HR=0.32; 95% CI=0.13-0.84, $p=0.02$).

In DAA group, sustained virologic response was a significant predictor of overall survival (HR 0.02, 95% CI 0.00–0.19, $p<0.001$), HCC recurrence (HR 0.25, 95% CI 0.11–0.57, $p<0.001$) and hepatic decompensation (HR 0.12, 95% CI 0.02-0.38, $p=0.02$).

Conclusions: In patients with HCV-related cirrhosis and previous successful treatment of early HCC, DAAs significantly improved OS compared with No DAA treatment.

Word Abstract Count: 274 words

Lay summary: In patients with compensated cirrhosis who are infected with hepatitis C virus (HCV) and at first diagnosis of early hepatocellular carcinoma (HCC) (without history of HCC recurrence before DAA treatment) who had achieved a complete radiologic response after curative resection or ablation, direct-acting antivirals (DAAs) significantly improve overall survival and reduce risk for hepatic decompensation compared with propensity-score-matched patients who did not receive DAAs. In contrast, the risk for HCC recurrence is not significantly reduced in DAA group compared to No DAA group.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death globally, and the leading cause of mortality in cirrhotic patients, with hepatitis C virus (HCV) being the major risk factor in the Western world and Japan.¹ Orthotopic liver transplantation (OLT) is the definitive treatment for HCC and cirrhotic liver, but this approach cannot be offered to all patients due to limited graft availability and rigorous selection criteria.² Alternative curative treatment options for patients with compensated cirrhosis are surgical resection and loco-regional ablation of early (i.e., stage 0/A) Barcelona Clinic Liver Cancer (BCLC).²

Unfortunately, hepatic decompensation of underlying cirrhosis, the major driver of death, and tumor recurrence contribute to long-term mortality after successful treatment of early HCC.³ A recent meta-analysis showed that, among HCV-infected compensated cirrhotic patients in whom early HCC was successfully treated, who remained unexposed to direct-acting antivirals (DAAs), the 2-year actuarial pooled HCC recurrence rate was 47.0% and the 3-year actuarial pooled survival rate was 79.8%.⁴ These data indicate that there is an urgent need for an effective adjuvant strategy given the prior failures of other adjuvant treatments, including sorafenib.⁵

DAAs improve HCV infection outcomes, even in patients with advanced liver disease,⁶⁻⁷ with a good safety profile and a sustained virologic response (SVR) rate exceeding 90% in clinical practice. In 2016, an alarm signal was released about a potentially increased risk for early HCC recurrence after DAA therapy, raising concerns about the safety of DAA use in patients with previously treated early HCC.⁸⁻⁹ Since then, several prospective studies¹⁰⁻¹³ and two meta-analyses¹⁴⁻¹⁵ have provided evidence that the risk of HCC recurrence after treatment with DAAs in patients with history of successful treatment of early HCC is similar, if not lower, than that observed in interferon-treated or DAA-unexposed controls. However, field-practice prospective studies that prove the benefit of DAAs on overall survival and hepatic decompensation are lacking, and the longer-term effect of DAAs on mortality remains to be established. Since DAAs are the accepted standard of care even in patients with previously treated early HCC, randomised controlled

trials (RCTs) comparing DAAs to No DAAs are not feasible, ethical and timely. Therefore, we analysed our observational data, as an attempt to emulate a randomized trial, outlining a framework for comparative effectiveness using observational data.¹⁶ For this reason, an appropriately matched control group of DAA-unexposed patients is needed to assess the benefit of DAA treatment on hepatic decompensation, HCC recurrence and finally overall survival.

The main aim of this prospective multicentre study was to estimate, in patients with compensated cirrhosis who are infected with hepatitis C virus (HCV) and at first diagnosis of early hepatocellular carcinoma (HCC) (without history of HCC recurrence before DAA treatment) who had achieved a complete radiologic response after curative resection or ablation, if DAAs (DAA group) prolong OS compared with an appropriately matched control group of patients who had not received DAAs (No DAA group). As secondary outcomes we considered the impact of DAAs on HCC recurrence and on hepatic decompensation.

Materials and methods

DAA-treated patients after successful treatment of HCV-related early HCC

This multicentre prospective cohort study used data from the RESIST-HCV (Rete Sicilia Selezione Terapia HCV), a web-based regional network (for more details, see Supplementary File 1).¹⁷⁻¹⁸ We analysed data from all consecutive HCV-infected cirrhotic patients, who had previously cured HCC, that were treated with DAAs and included in the RESIST-HCV database from March 1, 2015 to March 27, 2018. The study included all consecutive patients with HCV-related compensated cirrhosis and complete radiologic response (CRR) after successful treatment of early HCC (BCLC 0-A) by ablation or resection. The inclusion criteria were: 1) HCC, at first diagnosis, defined by pathology or by non-invasive criteria according to guidelines published by the European Association for the Study of the Liver (EASL);¹⁹ (2) HCC should have been treated before DAA exposure by resection or ablation; (3) CRR (i.e., absence of residual tumor or complete necrosis evaluated with dynamic computed tomography [CT] or magnetic resonance imaging [MRI]

performed one month after HCC treatment, according to EASL criteria¹⁹); (4) at least one dynamic CT/MRI assessment not later than 6 months before starting DAAs, and (5) treatment with DAA regimens. The exclusion criteria were: (1) treated HCC without CRR; 2) presence of “non-characterized nodules” before starting DAA treatment; (3) history of HCC recurrence before DAA treatment; 4) previous OLT; 5) coinfection with hepatitis B virus and/or human immunodeficiency virus; 6) addiction to intravenous drugs.

Patients with previous successful treatment of HCV-related early HCC who did not receive DAAs

Medical records for DAA-unexposed controls were obtained from the Italian Liver Cancer (ITA.LI.CA.) database. Controls were 328 patients, enrolled from 2007 to 2015, with HCV-related compensated cirrhosis and at first diagnosis of early HCC (BCLC 0/A), who had not been treated with DAAs, who achieved CRR after ablation or resection (for more details, see Supplementary File 2).^{3,11}

Follow-up

The follow-up for HCC patients who achieved CRR (assessed by CT or MRI) included physical examination, laboratory evaluation, and abdominal ultrasound (US) scan every 3 months, in addition to dynamic CT or MRI every 6 months. HCC recurrence was diagnosed on the basis of combined abnormal findings on US and on one of the additional dynamic imaging technique.¹⁹ HCC recurrences were treated, whenever possible, according to BCLC schedule and EASL guidelines.¹⁹ During DAA treatments, all patients were followed up monthly for clinical and laboratory evaluation. US was performed at month 3 of DAA therapy, and at any time when considered by clinical judgement. Hepatic decompensation was defined as the occurrence of portal hypertensive bleeding, hepatic encephalopathy, ascites or jaundice. SVR was defined as quantitative HCV-RNA below the lower limit of quantification at least 12 weeks or more after the end of treatment. Patients were categorized as No SVR if they had HCV-RNA above the limit of

quantification 12 weeks or more after the end of treatment, or if they did not complete DAA treatment for any reason.

Outcomes

The exposure of interest was DAA therapy. The primary outcome of interest was the overall survival after CRR to death (by any cause) or last visit, both for DAA-exposed and DAA-unexposed patients. Survival of patients treated with DAAs was compared with those who were not treated with DAAs, after propensity-score-matching¹⁶ and inverse probability of treatment weighting (IPTW) using propensity score (PS). The secondary outcomes included HCC recurrence and hepatic decompensation.

In order to assess the impact of survivor treatment selection bias in observational studies,^{20,21} we also performed robust analyses with two methods:

A) DAA therapy was also evaluated as a time-dependent covariate both by a time-dependent Cox model after propensity-score matching, and by a marginal structural Cox model using IPTW.²²

B) Emulating a target trial, we also compared overall survival between DAA-exposed and DAA-unexposed patients (after covariate balance with propensity-score-matching and IPTW using PS) starting follow-up from DAA initiation for DAA-exposed and from a comparable index time for DAA-unexposed patients. Index time was obtained subtracting the median time between CRR and DAA initiation for DAA-exposed patients from the beginning of follow up of DAA-unexposed patients.

Statistical analysis

Continuous variables are expressed as means \pm standard deviations and categorical data are reported as counts and percentages. The Kaplan-Meier estimator was used to estimate OS, time to

HCC recurrence, and time to liver decompensation. Log-rank tests were used to assess differences in these outcomes.

Propensity scores were obtained using a logistic regression model, with treatment status regressed on demographic, liver function and cancer-related variables (age, gender, body mass index, ALT, platelets, INR, total bilirubin, albumin, creatinine, MELD score, Child-Pugh [CP] class, oesophageal varices, alpha-fetoprotein, number of HCC lesions, size of main tumor lesion, HCC treatment) in order to provide a one-to-one match between DAA and No DAA groups. Nearest neighbour with a caliper of width equal to 0.2 of the standard deviation of the logit of the propensity score was used.²³ Standardized mean difference (SMD) was used to compare balance between DAA and No DAA groups, with a value more than .10 indicating imbalance.²⁴ To assess the impact of DAA therapy on primary and secondary outcomes, analysis was repeated in the matched sample, using the Huber-White (Robust) Sandwich Estimator to account for the lack of independence. Inverse probability of treatment weighting using PS, following the approach proposed by Xie and Liu,²⁵ was performed allowing the inclusion of all study subjects in the analysis. More details are showed in **Supplementary Figures S1 and S2**.

Univariate and multivariate Cox regression analyses were used to identify variables associated with mortality, HCC recurrence and hepatic decompensation in the DAA group. Variables with p values $\leq .10$ in the univariate analyses were included in the final multivariate model. To avoid co-linearity effects with single variables, Child-Pugh score, MELD, and BCLC were not included in the same multivariate model. For all analyses, $P \leq .05$ were considered statistically significant. All P-values were two-tailed, and all confidence intervals (CIs) were 95%. Analyses and results were performed with The R Statistical Computing Environment (R Foundation for Statistical Computing, Vienna, Austria).

This study met the ethical guidelines of the Helsinki Declaration. The institutional review boards of the participating centres approved this study.

Results

Baseline features of patients

The baseline characteristics of the 163 patients treated with DAAs (DAA-treated) and 328 patients who had not received DAAs (DAA-untreated) are shown in **Table 1**. Most of the DAA-treated patients were male (63%) and Child-Pugh class A (84%). Oesophageal varices were present in 60% of patients. Eighty-two percent had monofocal HCC at the time of tumor diagnosis. The HCC treatment received by a majority of the patients (59.5 %) was thermal ablation. In DAA-treated patients, intention-to-treat analysis indicated that SVR was obtained in 135 of 163 patients (83%). No decompensating events occurred during DAA treatment. Only three patients did not complete the planned DAA treatment course, remained HCV-RNA positive and were qualified as No SVR. DAA treatment data are detailed in **Table S1**. Median time-lag between CRR and DAA start was 2.1 months (range 0.5-6 months). We did not observe any event during this period. No patient was excluded during this time-lag.

Before propensity-score-matching, DAA-treated patients compared to patients who had not received DAAs had significantly more advanced liver disease in terms of alanine transaminase (ALT) levels, liver function (CP class), portal hypertension (oesophageal varices) and tumor burden (mean size of main tumor lesion) (see **Table 1 and Supplementary Figure S1**).

As showed in **Table 2 and Supplementary Figure S3**, matching produced full balance for all baseline variables between 102 patients treated with DAAs (DAA group) and 102 controls who did not receive DAAs (No DAA group).

Outcomes

Table 3 showed the outcomes observed during follow-up of DAA group (n=102) and No DAA group (n=102), after propensity-score-matching. During a mean follow-up of 21.4 months (range 1–37 months), 7 of 102 patients (6.9%) in DAA group and 18 of 102 patients (17.7%) in No DAA group died. Actuarial survival rates at 6, 12, 24, and 36 months between DAA and No DAA

groups are shown in **Table 3** and **Figure 1**. DAA group had a significantly higher survival rate than No DAA group (Hazard Ratio [HR] 0.39, 95% Confidence Interval [CI] 0.17-0.91, $p = 0.03$). Similar results were obtained by IPTW (HR 0.42, 95% CI 0.18-1, $p=0.05$). In order to assess the impact of survivor treatment selection bias in observational studies, four other models were performed using DAA as a time-dependent covariate or starting follow-up from DAA initiation in DAA group and from index time in the No DAA group. In all the robust analyses, the estimate of the DAA treatment effect on overall survival was significant. (see **Supplementary Table S2** and **Figure S4**).

HCC recurred in 28 of 102 patients in DAA group (27.5%) and in 38 of 102 (37.3%) patients in No DAA group. Actuarial 6, 12, 24 and 36 month HCC recurrence rates between DAA and No DAA groups are shown in **Table 3** and **Figure 2**. In DAA group, HCC recurrence rate was lower than in No DAA group, but difference was not statistically significant (HR 0.70, 95% CI 0.44-1.13, $p=0.15$).

During follow-up, 6 of 102 (5.9%) patients in DAA group and 14 of 102 (13.7%) patients in No DAA group experienced hepatic decompensation. The 6, 12, 24 and 36 month actuarial rates of hepatic decompensation are shown in **Table 3** and **Figure 3**. DAA group showed significantly lower decompensation rate than no DAA group (HR 0.32, 95% CI 0.13-0.84, $p=0.02$).

Predictors of mortality, HCC recurrence and hepatic decompensation in DAA group

Predictors of outcomes (mortality, HCC recurrence, hepatic decompensation) in the cohort of 102 DAA-treated patients are showed in **Table 4**. SVR was the only variable associated with a decrease in mortality (HR 0.02, 95% CI 0.00–0.19, $p<0.001$). It is noteworthy that SVR was independently associated with a decrease in HCC recurrence risk (HR 0.25, 95% CI 0.11–0.57,

$p < 0.001$) and hepatic decompensation (HR 0.12, 95% CI 0.02-0.38, $p = 0.02$) by multivariate analyses.

Similar results were obtained in the whole cohort of 163 DAA-treated patients before propensity-score-matching, as showed in **Table S3**. The presence of oesophageal varices at baseline was not significantly associated with long-term outcomes.

Discussion

This prospective real-world multicentre observational study involved a cohort of patients with HCV-related cirrhosis who had received treatment with DAAs after curative resection or ablation of early HCC. According to methods for comparative effectiveness, we used our observational data to emulate a hypothetical randomized trial by comparing DAA exposed versus DAA unexposed patients.^{16,26} Its results show that patients treated with DAAs had significantly better OS and lower hepatic decompensation than propensity-score-matched controls who did not receive DAAs. To the best of our knowledge, the benefit of DAAs on OS and hepatic decompensation was demonstrated for the first time in our matching-propensity analyses adjusted for demographic, liver function, and cancer-related characteristics. In contrast, the risk of HCC recurrence was not significantly different between patients treated with DAAs and propensity-score-matched controls who did not receive DAAs.

Most investigators and clinicians now accept DAAs as the standard of care, even for patients with advanced liver disease and a history of HCC.⁶⁻⁷ As a result, it is not feasible to design RCTs for direct comparison of patients who did versus did not receive DAAs. Therefore, DAA and No DAA groups may be compared only by propensity score methods to correct for potential confounding. Despite the lack of randomization, our findings suggest that DAAs improve OS and hepatic decompensation without affecting HCC recurrence risk, after adjustment by matching-propensity analyses. We underline that DAA-treated patients, compared with controls who did not receive DAAs had more advanced liver disease in terms of higher Child-Pugh score, prevalence of

oesophageal varices and tumor burden. Therefore, our results are particularly relevant considering that a full balance between DAA and No DAA groups was obtained after propensity-score-methods.

It is noteworthy that the reported 2-year HCC recurrence actuarial rate of our matched controls who did not receive DAAs is in keeping with the results of previous meta-analysis of DAA-unexposed patients with compensated cirrhosis,⁴ providing that our control group is a useful benchmark for comparison of DAA benefit on this outcome.²⁷ Among the DAA group, the 2-year HCC recurrence rate, although not significantly different compared to No DAA group, still remains high (27%). This finding is consistent with the results of two recent published studies.^{28,29} Multivariate analysis of our cohort of DAA-exposed patients showed that no SVR after DAAs was an independent risk factor for HCC recurrence. So, our study suggests that future models including SVR could identify patients at higher risk for HCC recurrence reliably and thereby maximize the clinical benefit and the cost/effectiveness of imaging follow-up. Lack of data on other potential risk factors for HCC recurrence, such as microscopic vascular invasion, histology grade, and both cancer and patient gene profile,³⁰ may have affected the accuracy of the results. Incomplete knowledge of molecular characteristics and tumor pathobiology (e.g., neo-angiogenic pathways) may explain why adjuvant therapy in HCC represents an area of high unmet medical need. New markers, such as liver angiopoietin-2, have shown promising results in predicting HCC growth and recurrence, as well as risk for death.³⁰ A recent report suggested that a DAA-mediated increase in VEGF may act as a trigger in patients with highly activated neo-angiogenic pathways in cirrhotic tissue.³¹

Our data provide evidence that DAAs significantly reduce the risk of hepatic decompensation. The findings presented above strongly support the current practice of DAA treatment, even in patients with advanced liver disease and HCC. Exploring causality multifactorial mechanism of the observed reduction in mortality associated with DAAs is outside the purpose of the present study. We can speculate that DAAs improve OS through long-term preservation of liver function, resulting in greater likelihood that the patient will receive curative treatment, even in the

case of HCC recurrence. This result suggests that, although the risk of HCC recurrence remains high, the inefficacy of DAA treatment on HCC recurrence risk could be overcome by way of the proven survival-enhancing benefit with regard to hepatic decompensation.³ In this line, a recent retrospective cohort study by Huang et al. found that DAA use does not change the risk of HCC recurrence after local-regional therapy among waitlisted patients but rather is associated with reduced risk of waitlist dropout due to tumor progression or death.⁷ Although waitlisted patients had more advanced liver disease (half had CP B or C cirrhosis) compared to our cohort of compensated cirrhotic patients, these results add further evidence that DAAs reduce the risk of decompensating events also in patients with advanced liver disease and HCC. These findings align with previous literature showing that DAA therapy is associated with improvement in liver function^{12, 32-34} as well as lower rates of hepatic decompensation.^{12, 32} All these evidences lend support to the use of DAA therapy in patients with advanced liver disease and successfully treated HCC. Finally, treatment of HCV infection even in the sickest patients with more advanced BCLC stage remains a controversial topic.³⁵

Our study has some limitations. First, a methodological issue of the current study is the potential limitation of the generalizability of its results to different populations and settings, given that the results were obtained in a cohort of real-world, compensated patients with cirrhosis and early HCC enrolled in tertiary care centres, who may be different in terms of age, clinical features and comorbidities from patients treated with DAAs in other settings. In particular, we excluded patients with HBV/HCV or HIV/HCV coinfections, as well as those with comorbidities or those who did not receive potential curative HCC treatments like resection or ablation. It should be also emphasized that our cohort included older patients (mean age 70 years) than those recruited in other studies (ranging from 54 to 58 years).^{6, 12, 32-34}

Second, this nonrandomised study regards the issue of survivor treatment selection bias in observational studies, such as immortal and time-lag biases.^{20, 21, 36, 37} The effectiveness of DAAs was also confirmed when DAA treatment was assessed as time-dependent covariate, mitigating

misclassified immortal-time bias. Regarding the time-lag bias²⁰ (i.e. a potential bias due to the fact that patients may change their disease stage during the time-lag between CRR and DAA start), we are confident that this bias did not affect our results because no clinical events occurred during this short interval (median 2.1 months).³⁸ Moreover, in all the robust analyses performed with and without time-dependent methods or starting follow-up from DAA initiation or from CRR, the estimates of the treatment effect of DAAs on survival were similar and significant. Finally, although matching and IPTW were used in order to handle the issue of lack of randomization, residual confounding from both measured and unmeasured variables could not be definitively rule out. Whatever efforts were made to control for confounding and survivor treatment selection bias, “bias-zero” observational studies of drug effects do not exist, remaining randomized controlled trials the gold standard to evaluate the effectiveness of treatments.

Finally, another limitation of our study is the use of historical, instead of contemporaneous controls.³⁹ However, differences in HCC management, regarding diagnosis, follow-up and treatment were not observed between DAA-treated and DAA-untreated patients. Moreover, the 3-year survival and 2-year HCC recurrence of our historical controls from the ITA.LI.CA. cohort are in keeping with the benchmark provided by a previous published meta-analysis of DAA-untreated patients,⁴ as well as by the placebo arm of the STORM trial⁵ (that included patients with successfully treated early HCC), making us confident that our historical controls are representative of the population of DAA-unexposed patients.

In conclusion, the results observed in patients with HCV-related cirrhosis who underwent DAA therapy after successful treatment of early HCC demonstrated that patients treated with DAAs had improved OS compared to those who had not received DAAs. DAA treatment was found to improve OS through reduction of hepatic decompensation. HCC recurrence risk remains high despite DAA therapy, highlighting the need for new adjuvant strategy for prevention of HCC recurrence. Finally, DAA-induced SVR significantly reduces mortality, hepatic decompensation and HCC recurrence. A meta-analysis of individual patient data, including studies performed in

different clinical settings, may prove useful to substantiate the benefit of DAA therapy on long-term outcomes.⁴⁰

ACCEPTED MANUSCRIPT

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Figure legends

Fig. 1. Overall survival after complete radiological response of 102 patients treated with DAAs (DAA group) and 102 patients who did not receive DAAs (no DAA group), after propensity-score-matching.

The Kaplan-Meier method was used to assess overall survival rates, and the log-rank test was used to compare them.

Fig. 2. Cumulative incidence of HCC recurrence after complete radiological response of 102 patients treated with DAAs (DAA group) and 102 patients who did not receive DAAs (no DAA group), after propensity-score-matching.

The Kaplan-Meier method was used to assess cumulative HCC recurrence rates, and the log-rank test was used to compare them.

Fig. 3. Cumulative incidence of hepatic decompensation after complete radiological response of 102 patients treated with DAAs (DAA group) and 102 patients who did not receive DAAs (no DAA group), after propensity-score-matching.

The Kaplan-Meier method was used to assess cumulative hepatic decompensation rates, and the log-rank test was used to compare them.

TABLES

Table 1. Baseline characteristics of 163 patients treated with DAAs and 328 patients who did not receive DAAs, before propensity-score-matching.

	DAA (n=163)	No DAA (n=328)	p value	SMD
Age (y)	70.6±9.2	69.4±9.8	0.215	0.120
Male sex, n (%)	103 (63.2)	217 (66.2)	0.583	0.062
BMI (Kg/m²)	25.7±3.7	25.2±3.5	0.144	0.054
Diabetes, n (%)	46 (28.2)	NA	-	-
ALT (IU/L)	72.61±36.02	58.27±36.88	<0.001	0.732
Platelets (10³/μL)	120±92	123±53	0.700	0.034
INR	1.15±0.27	1.12±0.14	0.915	0.010
Total bilirubin (mg/dL)	1.09±0.55	1.00±0.47	0.065	0.173
Albumin (g/dL)	3.73±0.50	3.68±0.49	0.284	0.102
Creatinine (mg/dL)	0.88±0.50	0.90±0.46	0.666	0.041
MELD score	8.81±2.72	8.74±2.22	0.759	0.028
Child-Pugh class, n(%)				
A	137 (84)	307 (93.6)	0.001	0.307
B	26 (16)	21 (6.4)		
Oesophageal varices, n (%)				
F0	65 (39.9)	205 (62.5)	<0.001	0.509
F1	80 (49.1)	85 (25.9)		
F2/F3	18 (11)	38 (11.6)		
AFP (ng/mL)^a	30.86±83.02	47.31±95.51	0.061	0.184
Number of HCC lesions, (%)^a			0.599	0.096
1	134 (82.2)	281 (85.7)		
2	23 (14.1)	38 (11.6)		
3	6 (3.7)	9 (2.7)		
Mean number of HCC lesions^a	1.21±0.49	1.17±0.44	0.320	0.094
Mean size of main tumor lesion (cm)^a	2.68±0.49	2.23±0.81	<0.001	0.835
HCC treatment before DAA therapy, n (%)				
Thermal ablation	97 (59.5)	240 (73.2)	0.003	0.292
Surgical resection	66 (40.5)	88 (26.8)		

Notes: Values are mean ± standard deviation or numbers (%). The t-test for continuous variables and the chi-squared test for categorical variables were used to compare them between DAA and No DAA groups.

BMI, Body mass Index; ALT, Alanine transaminase; INR, International Normalised Ratio; MELD, model for end-stage liver disease; AFP, alfafetoprotein; HCC, hepatocellular carcinoma; DAA,

direct-acting antivirals; SMD, Standardized Mean Differences. a Data are related to the state before treatment of HCC.

Table 2. Baseline characteristics of 102 patients treated with DAAs (DAA group) and 102 patients who did not receive DAAs (No DAA group), after propensity-score-matching.

	DAA	No DAA	<i>p</i> value	SMD	
Number of patients	102	102			
Age (years)	71.3±9.5	71.9±8.8	0.599	0.074	
Male sex, n(%)	63 (61.8)	65 (63.7)	0.885	0.041	
BMI (Kg/m²)	25.3±2.3	24.8±2.8	0.165	0.076	
ALT (IU/L)	74.54±35.64	75.07±25.84	0.903	0.017	
Platelets (10³/μL)	124±110	118±32	0.649	0.064	
INR	1.13±0.28	1.13±0.16	0.824	0.031	
Total bilirubin (mg/dL)	1.07±0.47	1.09±0.52	0.810	0.034	
Albumin (g/dL)	3.74±0.50	3.72±0.55	0.752	0.044	
Creatinine (mg/dL)	0.84±0.19	0.86±0.19	0.637	0.066	
MELD score	8.69±2.83	8.61±2.06	0.809	0.033	
Child-Pugh class, n(%)	A	90 (88.2)	91 (89.2)	1.000	0.031
	B	12 (11.8)	11 (10.8)		
Oesophageal varices, n (%)	Absent	48 (47.1)	50 (49)	0.889	0.039
	Present	54 (52.9)	52 (51)		
AFP (ng/mL)^a	37.16±100.72	30.49±38.52	0.533	0.087	
Mean number of HCC lesions^a	1.26±0.64	1.24±0.57	0.729	0.049	
Mean size of main tumor lesion (cm)^a	2.44±1.13	2.46±0.93	0.910	0.016	
Thermal ablation as HCC treatment, n(%)	68 (66.7)	66 (64.7)	0.880	0.047	

Notes: Values are mean ± standard deviation or numbers (%). The t-test for continuous variables and the chi-squared test for categorical variables were used to compare them between DAA and No DAA groups.

BMI, Body mass Index; DAA, direct-acting antivirals; ALT, Alanine transaminase; INR, International Normalised Ratio; MELD, model for end-stage liver disease; AFP, alfafetoprotein; HCC, hepatocellular carcinoma; SMD, Standardized Mean Differences. a Data are related to the state before treatment of HCC.

Table 3. Outcomes observed during follow-up in 102 patients treated with DAAs (DAA group) and 102 patients who did not receive DAAs (No DAA group) after propensity-score-matching.

	DAA n= 102	No DAA n= 102	Hazard Ratio (95% C.I.)
Follow-up, mean, range (mo)	21.44 (1-37)	17.5 (1-37)	
Deaths, n (%)	7 (6.9)	18 (17.7)	
Survival rate (95%CI)^a			0.39 (0.17-0.91) <i>p=0.03</i>
6-month <i>N at risk</i>	100 (100-100) 101	99 (97-100) 101	
12-month <i>N at risk</i>	99 (97-100) 88	95 (90-99) 81	
24-month <i>N at risk</i>	90 (83-96) 39	83 (75-92) 59	
36-month <i>N at risk</i>	90 (83-97) 1	66 (60-77) 34	
HCC recurrence during follow up, n (%)	28 (27.5)	38 (37.3)	
HCC recurrence rate (95%CI)^a			0.70 (0.44-1.13) <i>p=0.15</i>
6-month <i>N at risk</i>	6 (1-10) 99	9 (3-14) 93	
12-month <i>N at risk</i>	15 (8-22) 74	20 (11-27) 64	
24-month <i>N at risk</i>	27 (16-36) 33	40 (28-50) 33	
36-month <i>N at risk</i>	70 (22-88) 1	57 (40-65) 17	
Treatment of HCC recurrences, n (%)			-
Surgical resection	2 (7)	2 (5)	
Thermal Ablation	10 (36)	18 (47)	
Transarterial chemoembolization	12 (43)	16 (42)	
Sorafenib	2 (7)	2 (5)	
Supportive care	2 (7)	NA	
Hepatic decompensation during follow-up, n (%)	6 (5.9)	14 (13.7)	
Hepatic decompensation rate (95% CI)^a			0.32 (0.13-0.84) <i>p=0.02</i>
6-month <i>N at risk</i>	0 101	2 (0-5) 101	
12-month <i>N at risk</i>	1 (0-3) 86	10 (4-15) 72	
24-month <i>N at risk</i>	6 (0-11) 36	18 (8-25) 50	
36-month <i>N at risk</i>	21 (0-35) 1	32 (24-41) 27	

Notes: The Kaplan-Meier method was used to assess overall survival, HCC recurrence and hepatic decompensation rates. Log-rank test was used to compare the outcomes distributions between DAA and No DAA groups.

DAA, direct-acting antivirals; CI, Confidence Interval; HCC, hepatocellular carcinoma.

a According to Kaplan-Meier analysis

Table 4. Predictors of mortality, HCC recurrence and hepatic decompensation of 102 propensity-score-matched patients treated with DAAs after previous successful treatment of early HCC.

Univariate model for mortality *			
	HR	95% CI	p value
SVR	0.02	0.00-0.19	<0.001
Multivariate model for HCC recurrence**			
	HR	95% CI	p value
SVR	0.25	0.11-0.57	<0.001
Multivariate model for hepatic decompensation***			
	HR	95% CI	p value
SVR	0.12	0.02-0.38	0.02

Notes: Independent risk factors for mortality, HCC recurrence and hepatic decompensation were analysed using Cox proportional hazard regression analyses.

HR, Hazard Ratio; CI, Confidence Interval; HCC, hepatocellular carcinoma; SVR, sustained virologic response; INR, International Normalised Ratio.

*SVR was the only variable associated with a decrease of mortality.

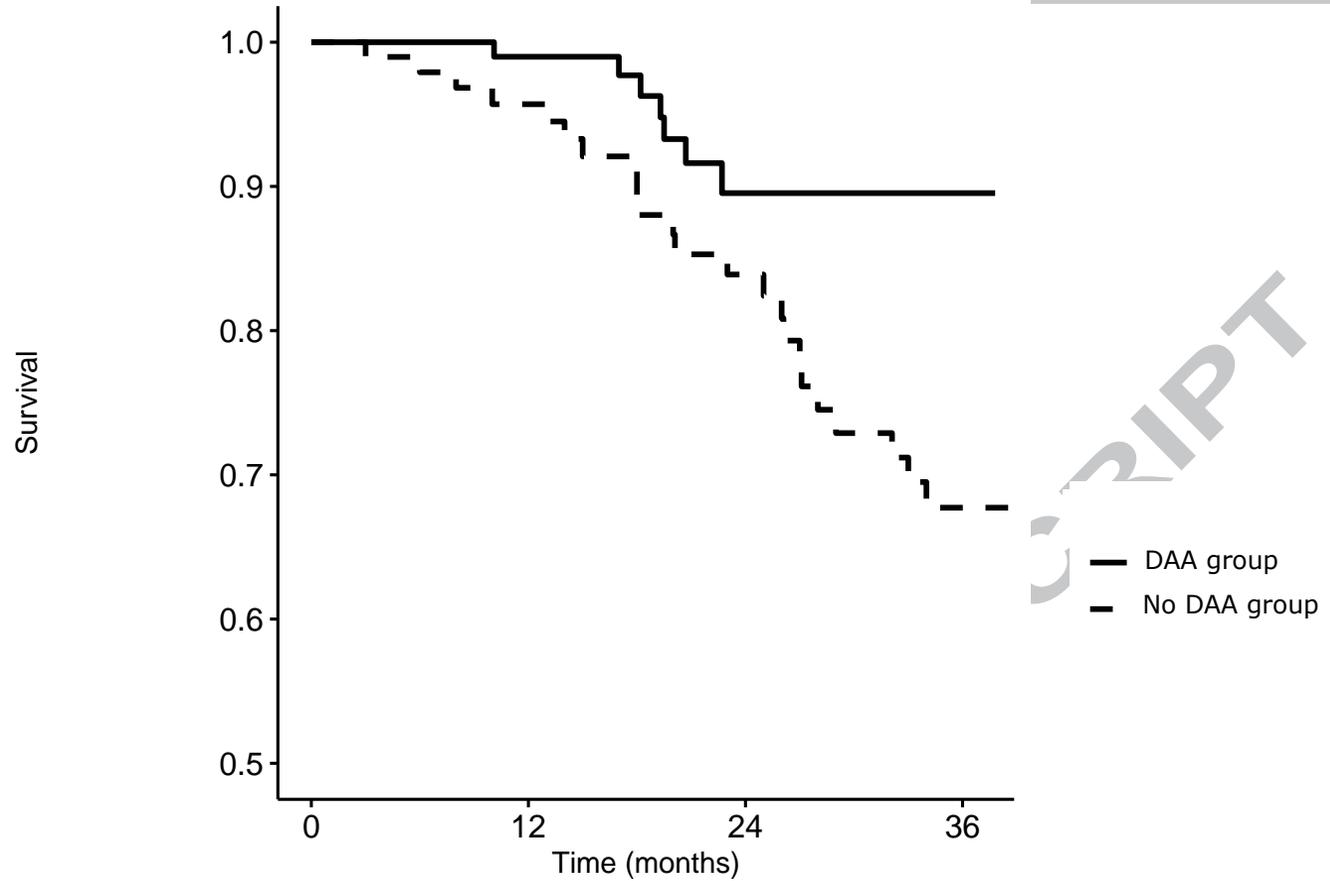
**After adjustment for sex, INR and HCC treatment.

***After adjustment for age, sex, INR and total bilirubin.

Highlights:

- **DAAs improve survival in patients with HCV-related successfully treated early HCC.**
- **Improvement of survival seems due to reduction in hepatic decompensation.**
- **DAAs don't impact on HCC recurrence.**

DAA group vs No DAA group
HR=0.39 (p=0.03)



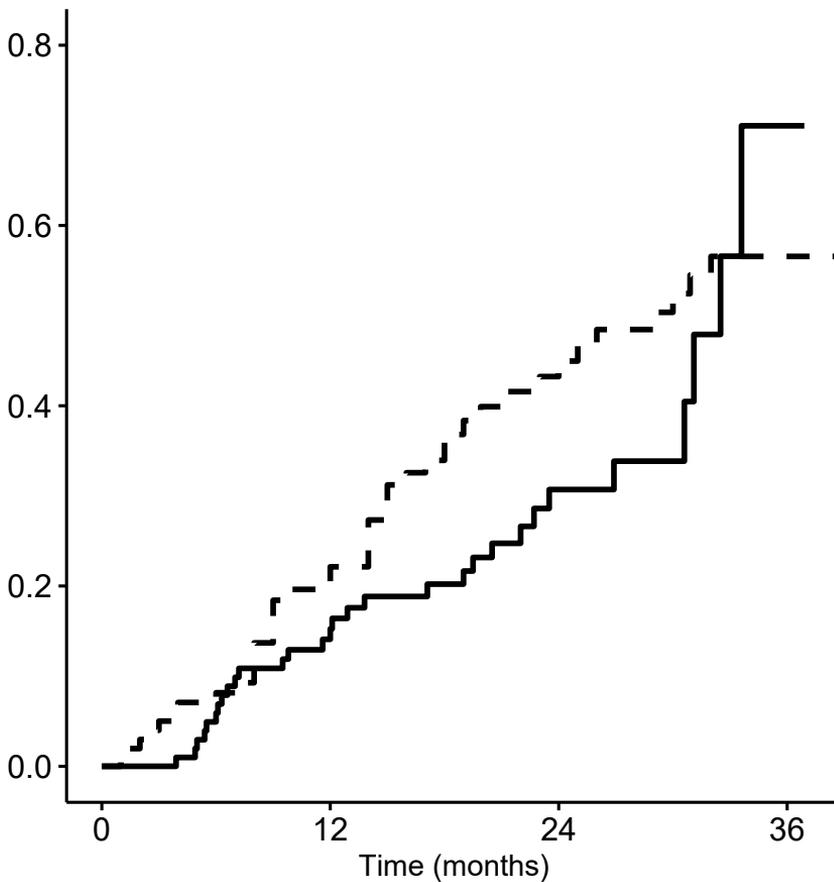
Number at risk

DAA group	102	88	39	1
No DAA group	102	81	59	34

DAA group vs No DAA group
HR=0.70 (p=0.15)



HCC Recurrence



Number at risk

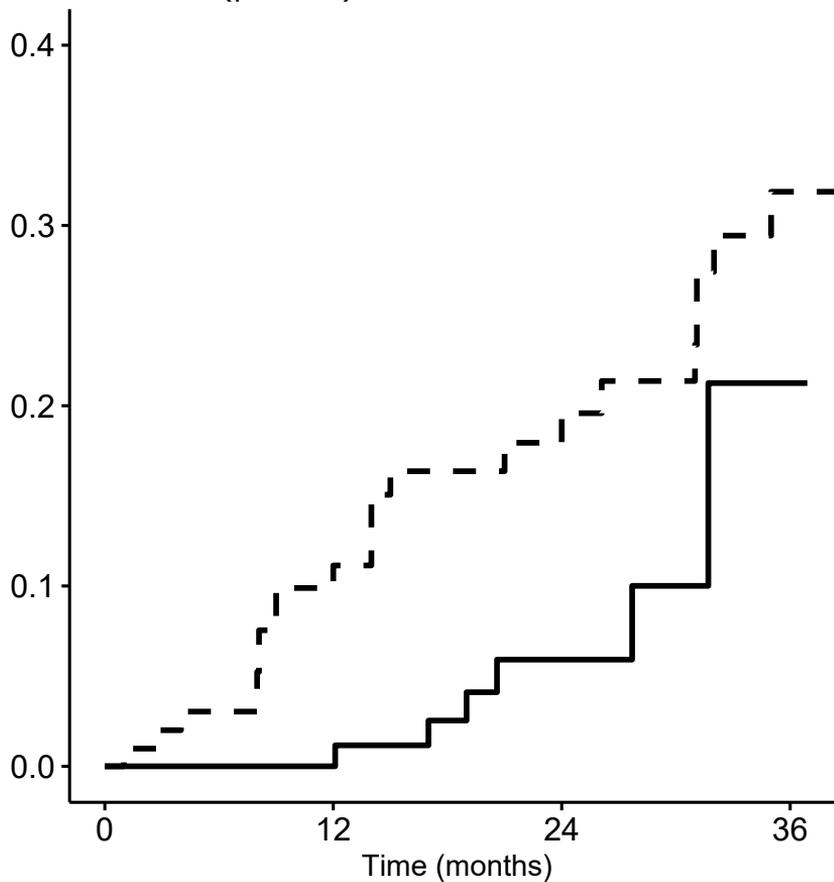
No DAA group	102	64	33	17
DAA group	102	74	33	1

DAA group vs No DAA group

HR=0.32 (p=0.02)



Hepatic decompensation

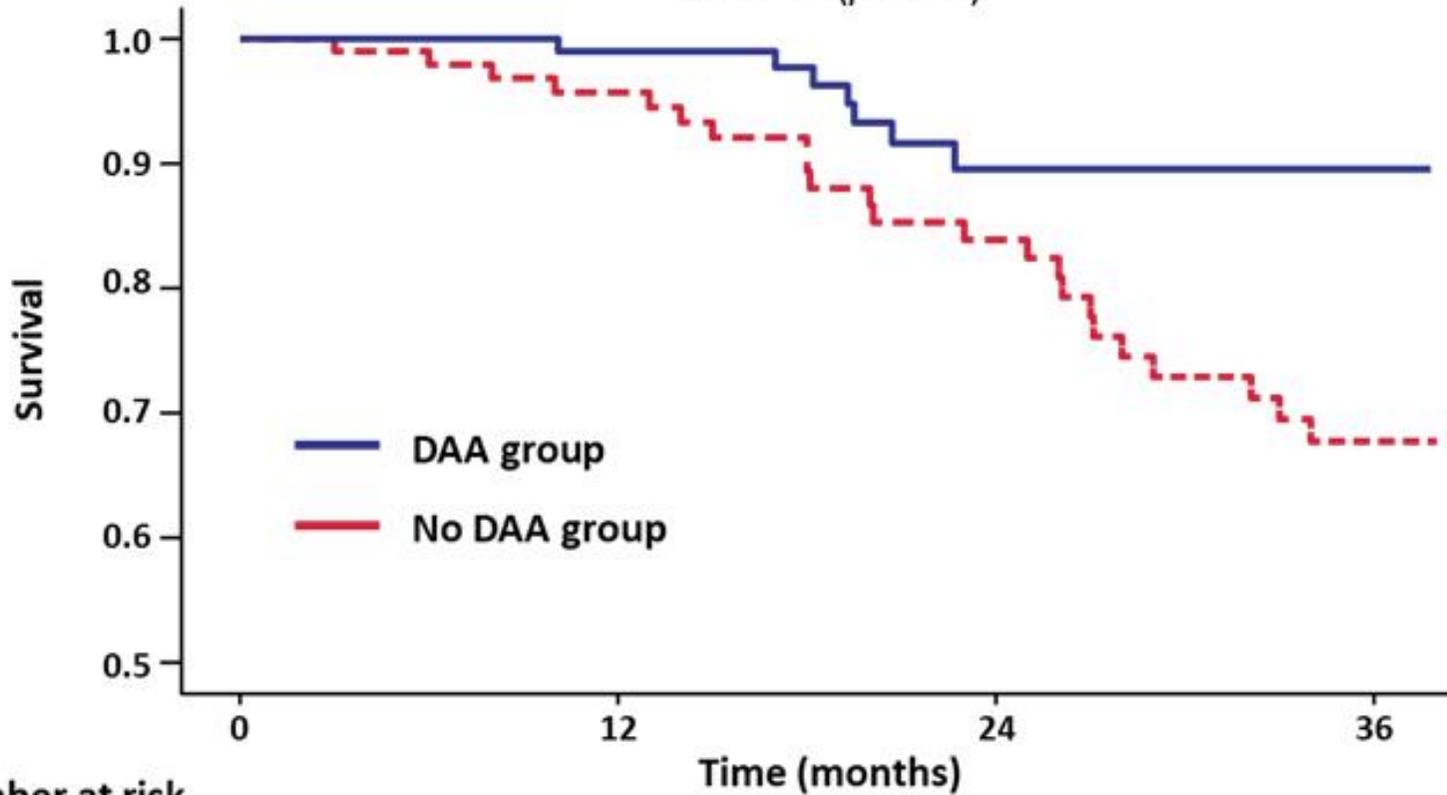


Number at risk

No DAA group	102	72	50	27
DAA group	102	86	36	1

DAA group vs no DAA group

HR=0.39 ($p=0.03$)



Number at risk

DAA group 102

No DAA group 102

102

102

88

81

39

59

1

34