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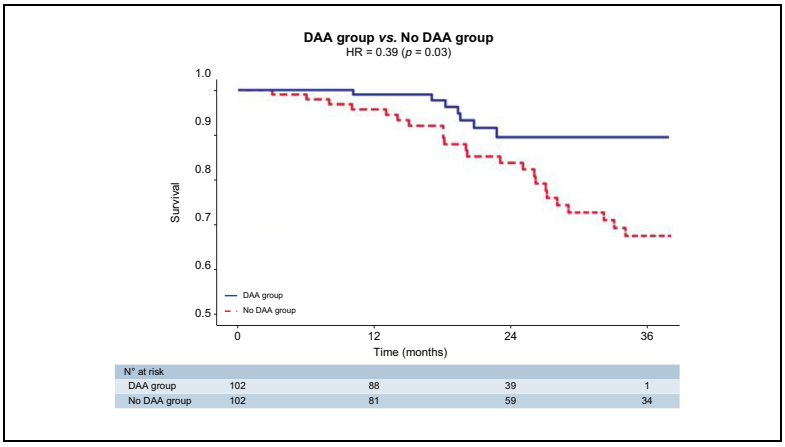
Graphical abstract



Highlights

- DAAs improve survival in patients with HCV-related early HCC that has been successfully treated.
- The improvement in survival seems to be caused by a reduction in hepatic decompensation.
- DAAs did not impact on HCC recurrence.

Authors

Giuseppe Cabibbo, Ciro Celsa, Vincenza Calvaruso, ..., Antonio Craxì, Vito Di Marco, Calogero Cammà

Correspondence

calogero.camma@unipa.it
(C. Cammà)

Lay summary

We aimed to determine whether direct-acting antivirals (DAAs) significantly improve overall survival in patients with hepatitis C virus-related compensated cirrhosis and a first diagnosis of hepatocellular carcinoma (HCC) which has been successfully treated with curative resection or ablation. Using propensity-score matched patients, we found that DAAs improved overall survival and reduced the risk of hepatic decompensation. However, the risk of HCC recurrence was not significantly reduced.

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

Giuseppe Cabibbo[1,†], Ciro Celsa[1,†], Vincenza Calvaruso[1], Salvatore Petta[1], Irene Cacciola[2], Maria Rita Cannavò[3], Salvatore Madonia[4], Margherita Rossi[1], Bianca Magro[1], Francesca Rini[1], Marco Distefano[5], Licia Larocca[6], Tullio Prestileo[7], Giuseppe Malizia[8], Gaetano Bertino[9], Francesco Benanti[10], Anna Licata[11], Ignazio Scalisi[12], Giovanni Mazzola[13], Maria Antonietta Di Rosolini[14], Giuseppe Alaimo[15], Alfonso Averna[16], Fabio Cartabellotta[17], Nicola Alessi[1], Salvatore Guastella[1], Maurizio Russello[3], Gaetano Scifo[5], Giovanni Squadrito[2], Giovanni Raimondo[2], Franco Trevisani[18], Antonio Craxì[1], Vito Di Marco[1], Calogero Cammà[1,*], on behalf of Rete Sicilia Selezione Terapia – HCV (RESIST-HCV) and Italian Liver Cancer (ITA.LI.CA.) Group

[1]*Section of Gastroenterology and Hepatology, Dipartimento di Promozione della Salute, Materno Infantile, Medicina Interna e Specialistica di Eccellenza (PROMISE), University of Palermo, Italy;* [2]*UOC Epatologia Clinica e Biomolecolare; AOUP G. Martino, Dipartimento di Medicina Interna e Sperimentale, University of Messina, Italy;* [3]*UOS Epatologia, ARNAS Garibaldi-Nesima, Catania, Italy;* [4]*UOC Medicina Interna, AO Villa Sofia-Cervello, Palermo, Italy;* [5]*UOC Malattie Infettive, Ospedale Umberto I, Siracusa, Italy;* [6]*UOC Malattie Infettive, AOUP G. Rodolico, Catania, Italy ;* [7]*UOC Malattie Infettive, ARNAS Civico-Di Cristina-Benefratelli, Palermo, Italy;* [8]*UOC Gastroenterologia, AO Villa Sofia-Cervello, Palermo, Italy;* [9]*UOC Medicina Interna, AOUP G. Rodolico, Catania, Italy;* [10]*UOC Malattie Infettive, ARNAS Garibaldi-Nesima, Catania, Italy;* [11]*UOC Medicina Interna, AOUP Paolo Giaccone, Palermo, Italy;* [12]*UOC Medicina Interna, Ospedale di Mazzara del Vallo, ASP, Trapani, Italy;* [13]*UOC Malattie Infettive, Azienda Ospedaliera Universitaria Paolo Giaccone, Palermo, Italy;* [14]*UOC Malattie Infettive, Ospedale di Modica; ASP Ragusa, Italy;* [15]*UOC Medicina Interna, Ospedale di Agrigento, ASP Agrigento, Italy;* [16]*UOC Malattie Infettive, Ospedale di Caltanissetta, ASP Caltanissetta, Italy;* [17]*UOC Medicina Interna, Ospedale Buccheri La Ferla, Palermo, Italy;* [18]*Semeiotica Medica, Dipartimento di Scienze Mediche e Chirurgiche, Alma Mater Studiorum - University of Bologna, Italy*

Background & Aims: The effectiveness of direct-acting antivirals (DAAs) against hepatitis C virus (HCV), following 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 prospectively enrolled 163 consecutive patients with HCV-related cirrhosis and a first diagnosis of early Barcelona Clinic Liver Cancer stage 0/A HCC, who had achieved a complete radiologic response after curative resection or ablation and were subsequently treated with DAAs. DAA-untreated patients from the 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 the 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 the DAA group compared to the No DAA group (hazard ratio [HR] 0.39; 95% CI 0.17–0.91; $p = 0.03$). HCC recurrence was not significantly different between the 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 the DAA group compared with the No DAA group (HR 0.32; 95% CI 0.13–0.84; $p = 0.02$). In the DAA group, sustained virologic response was a significant predictor of OS (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 who had been successfully treated for early HCC, DAAs significantly improved OS compared with No DAA treatment.

Lay summary: We aimed to determine whether direct-acting antivirals (DAAs) significantly improve overall survival in patients with hepatitis C virus-related compensated cirrhosis and a first diagnosis of hepatocellular carcinoma (HCC) which has been successfully treated with curative resection or ablation. Using propensity-score matched patients, we found that DAAs improved overall survival and reduced the risk of hepatic decompensation. However, the risk of HCC recurrence was not significantly reduced.

Keywords: Hepatitis C virus (HCV); Hepatocellular carcinoma (HCC); Direct-acting antiviral (DAA); Overall survival; Prognosis; Survival rate; Liver cirrhosis.
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* Corresponding author. Address: Sezione di Gastroenterologia, Dipartimento Biomedico di Medicina Interna e Specialistica, University of Palermo, Piazza delle Cliniche 2, 90127 Palermo, Italy.
E-mail address: calogero.camma@unipa.it (C. Cammà).
† These authors equally contributed to this work.

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 HCC (*i.e.* Barcelona Clinic Liver Cancer [BCLC] stage 0/A).[2]

Unfortunately, hepatic decompensation of underlying cirrhosis, the major driver of death, and tumour 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 of 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 studies[10–13] and 2 meta-analyses[14,15] 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, randomized controlled trials (RCTs) comparing DAAs to No DAAs are not feasible, ethical or 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 whether DAAs prolong overall survival in patients with HCV-related compensated cirrhosis and a first diagnosis of early HCC (without history of HCC recurrence before DAA treatment) who had achieved a complete radiologic response after curative resection or ablation. We used an appropriately matched control group of patients who had not received DAAs for this comparison. 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: i) 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] ii) HCC should have been treated before DAA exposure by resection or ablation; iii) CRR (*i.e.*, the absence of residual tumour or complete necrosis evaluated with dynamic computed tomography [CT] or magnetic resonance imaging [MRI] performed 1 month after HCC treatment, according to EASL criteria[19]); iv) at least 1 dynamic CT/MRI assessment not later than 6 months before starting DAAs; v) treatment with DAA regimens. The exclusion criteria were: i) treated HCC without CRR; ii) presence of "non-characterized nodules" before starting DAA treatment; iii) history of HCC recurrence before DAA treatment; iv) previous OLT; v) coinfection with hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV); vi) addiction to intravenous drugs.

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

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 a 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 patients with HCC 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 techniques.[19] HCC recurrences were treated, whenever possible, according to BCLC schedule and EASL guidelines.[19] During DAA treatment, 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 necessary 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 matching[16] and inverse probability of treatment weighting (IPTW) using propensity score. 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 2 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 propensity score), starting follow-up from DAA initiation for DAA-exposed patients and from a comparable index time for DAA-unexposed patients. Index time was obtained by 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 ± SD 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, alanine aminotransferase (ALT), platelets, international normalized ratio, total bilirubin, albumin, creatinine, MELD score, Child-Pugh class, oesophageal varices, alpha-fetoprotein, number of HCC lesions, size of main tumour lesion, HCC treatment) in order to provide a one-to-one match between DAA and No DAA groups. The nearest neighbour with a caliper of width equal to 0.2 of the SD of the logit of the propensity score was used.[23] Standardized mean difference (SMD) was used to compare the balance between DAA and No DAA groups, with a value more than 0.10 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. IPTW using propensity score, following the approach proposed by Xie and Liu,[25] enabled the inclusion of all study subjects in the analysis. More details are shown in Figs. 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 ≤0.10 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, $p \leq 0.05$ were considered statistically significant. All p values were 2-tailed, and all 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 tumour diagnosis. The HCC treatment received by the majority of 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 3 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 had significantly more advanced liver disease in terms of ALT levels, liver function (Child-Pugh class), portal hypertension (oesophageal varices) and tumour burden (mean size of main tumour lesion) compared to patients who had not received DAAs (see Table 1 and Fig. S1).

As shown in Table 2 and Fig. 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

The outcomes observed during follow-up of the DAA group (n = 102) and No DAA group (n = 102) after propensity score matching are shown (Table 3). 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 Fig. 1. The DAA group had a significantly higher survival rate than the No DAA group (hazard ratio [HR] 0.39; 95% 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, 4 other models were performed using DAA as a time-dependent covariate or starting follow-up from DAA initiation in the 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 Table S2 and Fig. S4).

HCC recurred in 28 of 102 patients in the DAA group (27.5%) and in 38 of 102 (37.3%) patients in the 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 Fig. 2. In the DAA group, HCC recurrence rate was lower than in the No DAA group, but the 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 the DAA group and 14 of 102 (13.7%) patients in the No DAA group experienced hepatic decompensation. The 6-, 12-, 24- and 36-month actuarial rates of hepatic decompensation are shown in Table 3 and Fig. 3. The DAA group had a significantly lower decompensation rate than the No DAA group (HR 0.32; 95% CI 0.13–0.84; $p = 0.02$).

Table 1. Baseline characteristics of 163 patients treated with DAAs and 328 patients who did not receive DAAs.

	DAA (n = 163)	No DAA (n = 328)	*p* value	SMD
Age (yr)	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/m^2)	25.7 ± 3.7	25.2 ± 3.5	0.144	0.054
Diabetes, n (%)	46 (28.2)	n.a.	–	–
ALT (IU/L)	72.61 ± 36.02	58.27 ± 36.88	<0.001	0.732
Platelets (10^3/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 (%)			0.001	0.307
A	137 (84)	307 (93.6)		
B	26 (16)	21 (6.4)		
Oesophageal varices, n (%)			<0.001	0.509
F0	65 (39.9)	205 (62.5)		
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 tumour lesion (cm)[a]	2.68 ± 0.49	2.23 ± 0.81	<0.001	0.835
HCC treatment before DAA therapy, n (%)			0.003	0.292
Thermal ablation	97 (59.5)	240 (73.2)		
Surgical resection	66 (40.5)	88 (26.8)		

Comparison performed before propensity score matching. Values are mean ± SD or numbers (%). The *t* test for continuous variables and the chi-square test for categorical variables were used to compare them between DAA and No DAA groups.
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BMI, body mass index; DAA, direct-acting antivirals; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease; n.a., not available; 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 and 102 patients who did not receive DAAs after propensity score matching.

	DAA	No DAA	*p* value	SMD
Number of patients	102	102		
Age (yr)	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/m^2)	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 (10^{ny}/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 (%)			1.000	0.031
A	90 (88.2)	91 (89.2)		
B	12 (11.8)	11 (10.8)		
Oesophageal varices, n (%)			0.889	0.039
Absent	48 (47.1)	50 (49)		
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 tumour 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

Comparison performed after propensity score matching. Values are mean ± SD or numbers (%). The *t* test for continuous variables and the chi-square test for categorical variables were used to compare them between DAA and No DAA groups.
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BMI, body mass index; DAA, direct-acting antivirals; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease; 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 and 102 patients who did not receive DAAs after propensity score matching.

	DAA n = 102	No DAA n = 102	Hazard Ratio (95% CI)
Follow–up, mean, range (months)	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) $p = 0.03$
6-month	100 (100–100)	99 (97–100)	
n at risk	*101*	*101*	
12-month	99 (97–100)	95 (90–99)	
n at risk	*88*	*81*	
24-month	90 (83–96)	83 (75–92)	
n at risk	*39*	*59*	
36-month	90 (83–97)	66 (60–77)	
n at risk	*1*	*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) $p = 0.15$
6-month	6 (1–10)	9 (3–14)	
n at risk	*99*	*93*	
12-month	15 (8–22)	20 (11–27)	
n at risk	*74*	*64*	
24-month	27 (16–36)	40 (28–50)	
n at risk	*33*	*33*	
36-month	70 (22–88)	57 (40–65)	
n at risk	*1*	*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)	n.a.	
Hepatic decompensation during follow–up, n (%)	6 (5.9)	14 (13.7)	
Hepatic decompensation rate (95% CI)[a]			0.32 (0.13–0.84) $p = 0.02$
6–month	0	2 (0–5)	
n at risk	*101*	*101*	
12–month	1 (0–3)	10 (4–15)	
n at risk	*86*	*72*	
24–month	6 (0–11)	18 (8–25)	
n at risk	*36*	*50*	
36–month	21 (0–35)	32 (24–41)	
n at risk	*1*	*27*	

The Kaplan-Meier method was used to assess overall survival, HCC recurrence and hepatic decompensation rates. Log-rank test was used to compare the outcome distributions between DAA and No DAA groups.
Hazard ratios were obtained using Cox proportional hazard regression analyses.
DAA, direct-acting antivirals; HCC, hepatocellular carcinoma.
[a] According to Kaplan-Meier analysis.

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

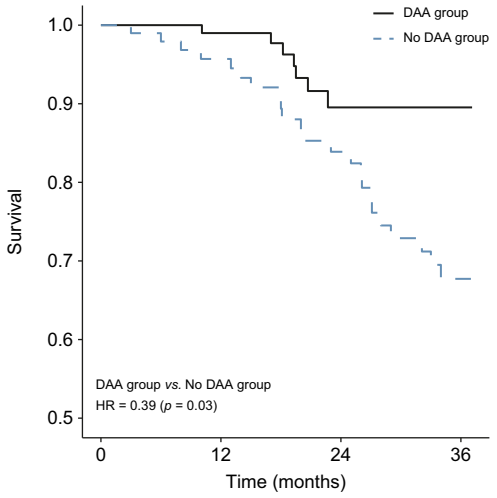
Predictors of outcomes (mortality, HCC recurrence, hepatic decompensation) in the cohort of 102 DAA-treated patients are shown in Table 4. SVR was the only variable associated with a decrease in mortality (HR 0.02; 95% CI 0.00–0.19; p <0.001). It is noteworthy that SVR was independently associated with 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 shown in Table S3. The presence of oesophageal varices at baseline was not significantly associated with long-term outcomes.

Discussion

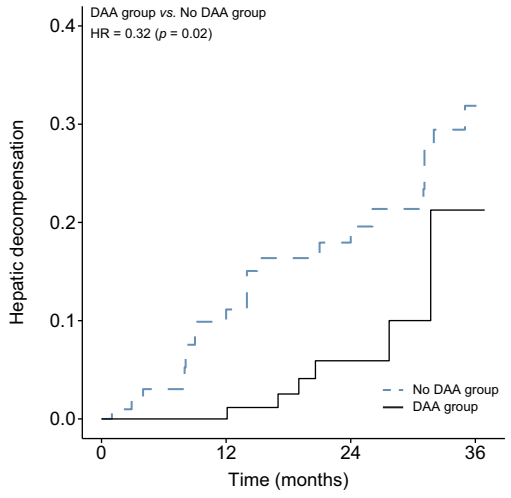
This prospective real-world multicentre observational study involved a cohort of patients with HCV-related cirrhosis who had received treatment with DAAs after curative resection or ablation of early HCC. According to methods for comparative effectiveness, we used our observational data to emulate a 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



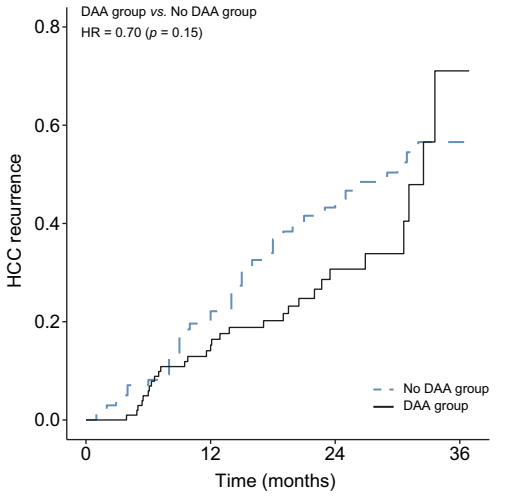
N° at risk				
DAA group	102	88	39	1
No DAA group	102	81	59	34

Fig. 1. Overall survival after complete radiological response in 102 patients treated with DAAs and 102 patients who did not receive DAAs. Comparison performed 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. DAAs, direct-acting antivirals; HCC, hepatocellular carcinoma.



N° at risk				
No DAA group	102	72	50	27
DAA group	102	86	36	1

Fig. 3. Cumulative incidence of hepatic decompensation after complete radiological response of 102 patients treated with DAAs and 102 patients who did not receive DAAs. Comparison performed 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. DAAs, direct-acting antivirals.



N° at risk				
No DAA group	102	64	33	17
DAA group	102	74	33	1

Fig. 2. Cumulative incidence of HCC recurrence after complete radiological response of 102 patients treated with DAAs and 102 patients who did not receive DAAs. Comparison performed 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. DAAs, direct-acting antivirals; HCC, hepatocellular carcinoma.

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 tumour 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 a previous meta-analysis of DAA-unexposed patients with compensated cirrhosis,[4] suggesting 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 to the recurrence rate in the No DAA group, still remains high (27%). This finding is consistent with the results of 2 recently 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 reliably identify patients at higher risk of HCC recurrence 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 tumour 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 of 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 the multifactorial mechanism behind the observed reduction in mortality associated with DAAs is outside the scope of the present study. We can speculate that DAAs improve OS through

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.

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

Independent risk factors for mortality, HCC recurrence and hepatic decompensation were analysed using Cox proportional hazard regression analyses.
DAAs, direct-acting antivirals; HR, hazard ratio; HCC, hepatocellular carcinoma; INR, international normalized ratio; SVR, sustained virologic response.
* SVR was the only variable associated with a decrease in mortality.
** After adjustment for sex, INR and HCC treatment.
*** After adjustment for age, sex, INR and total bilirubin.

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 tumour progression or death.[7] Although waitlisted patients had more advanced liver disease (half had Child-Pugh B or C cirrhosis) compared to our cohort of compensated cirrhotic patients, these results add further evidence that DAAs also reduce the risk of decompensating events 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] This evidence lends 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 also be 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, the issue of survivor treatment selection bias in observational studies, such as immortal and time-lag biases, must be considered as this was a non-randomised study.[20,21,36,37] The effectiveness of DAAs was also confirmed when DAA treatment was assessed as a time-dependent covariate, mitigating misclassified immortal-time bias. Regarding the time-lag bias[20] (*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, whether starting follow-up from DAA initiation or from CRR, 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 ruled out. Whatever efforts were made to control for confounding and survivor treatment selection bias, "bias-zero" observational studies of drug effects do not exist, leaving RCTs as 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 trial[5] (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 did not receive 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 a 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]

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Conflict of interest

Marco Distefano: participated in advisory board for Abbvie. Gaetano Scifo: participated in advisory board for Abbvie. Vincenza Calvaruso: participated in advisory board for Abbvie. Salvatore Petta: advisory board and/or speaker for Abbvie, Gilead, MSD, Intercept. Vito Di Marco: research support from Abbvie, BMS, Gilead, Merck/MSD. Participated in advisory boards for Abbvie, BMS; MSD/Merck. Antonio Craxì: Research support from Abbvie, BMS, Gilead, Merck/MSD, Intercept, provided consultancy, speakers bureau and participated in advisory boards for Abbvie, BMS, Gilead, MSD/Merck. Giovanni Raimondo: Participated in advisory boards for Abbvie, BMS, Gilead, MSD/Merck. Calogero Cammà: participated in advisory board for MSD/Merck. The other authors have no disclosures to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All the authors had full control of the study design, data analysis and interpretation, and preparation of article. All authors were involved in planning the analysis and drafting the article. All authors approved the final version of the manuscript.

Acknowledgments

MEMBERS OF THE RESIST-HCV GROUP

PALERMO A.O.U.P. Paolo Giaccone, Palermo: U.O.C. di Gastroenterologia e Epatologia (A. Craxì, V. Di Marco, C. Cammà, G. Cabibbo, V. Calvaruso, S. Petta, C. Celsa, B. Magro, M. Rossi, F. Rini, E. Conte); U.O.C. di Malattie Infettive (P. Colletti, G. Mazzola), U.O.C. di Medicina Interna (A. Licata, L. Giannitrapani). ARNAS Civico-Di Cristina-Benefratelli, Palermo: U.O.C. di Malattie Infettive (S. Corrao, T. Prestileo, F. Di Lorenzo, R. Fecarotta, P. Sanfilippo) A.O. Villa Sofia-Cervello, Palermo: U.O.C. di Medicina Interna (S. Madonia) U.O.C. di Gastroenterologia (F. Tinè, G. Malizia, F. Latteri, M. Maida). Ospedale Buccheri La Ferla, Palermo U. O.C. di Medicina Interna (F. Cartabellotta, R. Vassallo) MESSINA A.U.O.P G Martino, Messina. U.O.C. di Epatologia Clinica e Biomolecolare (I. Cacciola; G. Caccamo, S. Maimone, C. Saitta, G. Squadrito, G. Raimondo) A.O. Papardo Piemonte, Messina. U.O.C. Malattie Infettive (L. Mondello, A. Smedile). CATANIA A. O.U.P. Vittorio Emanuele, Catania: U.O.C. di Medicina Interna e d'Urgenza (G. Bertino, A.L. Ardiri) U.O.C. di Malattie Infettive (A. Montineri, L. N. Larocca), ARNAS Garibaldi- Nesima, Catania. U.S.C. di Malattie Infettive (B. Cacopardo, F. Benanti), U.S.D. di Epatologia (M. Russello, R. Benigno, M. R. Cannavò, A. Bellia) A.O. Cannizzaro, Catania U.O.C. Malattie Infettive (C. Iacobello). RAGUSA ASP di Ragusa, U.O.C. di Malattie Infettive Ospedale di Modica (A. Davì, M. A. Di Rosolini) U.O.C. Medicina Interna Ospedale di Comiso (A. Digiacomo, G. Fuduli). SIRACUSA ASP di Siracusa, U.O.C. Malattie Infettive Ospedale di Siracusa (G. Scifo, M. Distefano). TRAPANI ASP di Trapani. U.O.C. Malattie Infettive Ospedale di Trapani (V. Portelli, F. Savalli) U.O.C. Medicina Interna Ospedale di Catelvetrano (I. Scalici, G. Gioia). AGRIGENTO ASP di Agrigento. U.O.C. Medicina Interna Ospedale di Agrigento (A. Magro, G. Alaimo). CALTANISSETTA ASP di Caltanissetta, U.O.C. Malattie Infettive Ospedale di Caltanissetta (A. Salvo, A. Averna, F. Lomonaco, U. Quattrocchi). ENNA ASP di Enna; U.O.C. Malattie Infettive Ospedale di Enna (L. Guarneri, F. Maffeo). The RESIST-HCV is funded by unrestricted grants from Gilead, Italy; Merck Sharp & Dohme (MSD), Italy; Abbvie, Italy and Bristol-Myers Squibb (BMS), Italy.

MEMBERS OF THE ITA.LI.CA GROUP

Franco Trevisani, Francesca Garuti, Andrea Neri, Maurizio Biselli, Paolo Caraceni, Marco Domenicali, Annagiulia Gramenzi, **Marco Zoli**, Donatella Magalotti, **Fabio Piscaglia**, Alessandro Granito, Francesco Tovoli, Luca Ielasi, Giulia Negrini, Lucia Napoli, **Davide Festi**, Giovanni Marasco, Federico Ravaioli, Carla Serra (Department of Medical and Surgical Sciences, Alma Mater Studiorum – University of Bologna, Bologna, Italy); **Fabio Farinati**, Filippo Marafatto, Giulia Peserico, Caterina Pozzan (Gastroenterology Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy); **Edoardo Giovanni Giannini**, Matteo Brunacci, Alessandro Moscatelli, Gaia Pellegatta, (Gastroenterology Unit, Department Internal Medicine, Policlinico San Martino, University of Genoa, Genoa, Italy); **Eugenio Caturelli**, Paola Roselli, Valentina Lauria, Giorgio Pelecca, Giorgia Ghittoni (Gastroenterology Unit, Belcolle Hospital, Viterbo, Italy); **Calogero Cammà**, Giuseppe Cabibbo, Salvatore Petta, Margherita Rossi, Teresa Li Vigni, Ciro Celsa (Department of Internal and Specialized Medicine (DI.BI.M.I.S.), section of Gastroenterology, Biomedical, University of Palermo, Palermo, Italy); **Filomena Morisco**, Maria Guarino, Anna Vitiello, Anna Sessa (Gastroenterology Unit, Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy); **Rodolfo Sacco**, Valeria Mismas (Division of Gastroenterology and Metabolic Diseases, University Hospital of Pisa, Pisa, Italy); **Gian Ludovico Rapaccini**, Nicoletta de Matthaeis (Division of Internal Medicine and Gastroenterology, Complesso Integrato Columbus, Università Cattolica del Sacro Cuore, Rome, Italy); **Antonio Gasbarrini**, Francesca Romana Ponziani (Division of Internal Medicine, Gastroenterology, Hepatology - Fondazione Policlinico Universitario A. Gemelli IRCCS -Università Cattolica del Sacro Cuore, Roma, Italy); **Gianluca Svegliati Baroni**, Alessio Ortolani (Division of Gastroenterology, Polytechnic University of Marche, Ancona, Italy); **Francesco Giuseppe Foschi**, Vittoria Bevilacqua, Giorgio Ercolani, Erica Fiorini, A. Casadei Gardini, Fabio Conti, Alberto Borghi, Federica Mirici Cappa (Department of Internal Medicine, Ospedale per gli Infermi di Faenza, Faenza, Italy); **Gabriele Missale**, Andrea Olivani, Elisabetta Biasini (Division of Infectious Diseases and Hepatology, Parma University Hospital, Parma, Italy); **Alberto Masotto**, Fabiana Marchetti, Matteo Valerio (Gastroenterology Unit, Ospedale Sacro Cuore Don Calabria, Negrar, Italy); **Roberto Virdone**, Maria Rosa Barcellona, Maria Grazia Bavetta (Division of Internal Medicine 2, Ospedali Riuniti Villa Sofia Cervello, Palermo, Italy); **Fabio Marra**, Sami Aburas, Gabriele Dragoni, Claudia Campani (Department of Clinical and Experimental Medicine, Internal Medicine and Hepatology, University of Firenze, Firenze, Italy); **Gerardo Nardone** (Internal Medicine Unit, University of Salerno, Salerno); **Giovanni Raimondo**, Carlo Saitta e Maria Stella Franzè (Department of Clinical and Experimental Medicine, Division of Clinical and Molecular Hepatology, University Hospital of Messina, Messina); **Rita Golfieri**, Alberta Cappelli,Cristina Mosconi, Matteo Renzulli (Department of Dygestive Diseases and Internal Medicine, Bologna Hospital and University Agency, Radiology Unit, Bologna).

Supplementary data

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Author names in bold designate shared co-first authorship

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