ORIGINAL ARTICLE

Liver Cancer INTERNATIONAL   WILEY

Incidence of HCC recurrence after DAA treatment for HCV in a multicentre Italian cohort study

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Abstract

Background and aim: The present real-life multicentre, prospective study aims to investigate the effects of direct-acting antivirals (DAAs) in HCV patients with a previous successfully treated hepatocellular carcinoma (HCC), in terms of neoplastic recurrence and sustained virological response (SVR) rates.

Methods: From March 2015 to March 2017, all consecutive HCV patients with a previous successfully treated HCC who underwent DAA therapy were enrolled. Neoplastic recurrence was used as the primary outcome, whereas the secondary outcomes were patient characteristics predicting HCC recurrence. Cumulative probabilities of recurrence were extracted from time-to-event curves based on the Kaplan-Meier method. Hazard ratios with 95% confidence intervals were estimated using univariate and multivariate Cox regressions.

Results: A total of 101 patients were enrolled: 83% of them were in Child-Pugh class A, 88% had a history of HCC BCLC stage 0/A and 91.1% achieved SVR. The median time from the last successful HCC treatment to DAA start was 10.1 months [IQR: 5.6-16.7]. Thirty-one HCC recurrences were observed from DAA start (median follow-up: 31.7 months). The incidence rate of recurrence was 20.5/100 person-years. The 6-, 12- and 24-months HCC recurrence rates from the last HCC treatment were 1%, 8.9% and 25.6% respectively. DAA treatment failure, higher level of total bilirubin, higher BMI and higher level of AFP were significantly associated with higher risk of HCC recurrence in both univariate and Cox multivariate analysis.

Conclusions: Our data suggest that the achievement of SVR and the absence of well-known HCC risk factors reduce recurrence in patients who have taken DAAs.

1 | INTRODUCTION

Worldwide, 130-150 million people are estimated to be chronically infected with the hepatitis C virus (HCV). Cirrhosis develops in 10%-15% of patients with chronic HCV infection within 20 years, and in cirrhotic subjects, the risk of hepatocellular carcinoma (HCC) is estimated to be 3% to 7% per year.[1] Antiviral treatment of HCV infection has experienced a revolutionary advancement with the advent of direct-acting antivirals (DAAs), which can be administered in short, highly effective and well-tolerated interferon (IFN)-free schedules, including in patients with decompensated cirrhosis or with a history of HCC.[2] In the interferon era, many studies have shown that cirrhotic patients achieving sustained virological response (SVR) had a reduced HCC development risk, with annual incidence rates of 1.2%-1.4%[3]; unfortunately, solid data concerning the risk of recurrence of successfully treated HCC in patients who obtained SVR are poor.[4] After the introduction of the new antiviral drugs, a controversial issue has arisen concerning their possible role in increasing the risk of HCC development and recurrence.[5-14]

Recently, some prospective studies, including large cohorts of patients, demonstrated the absence of increased risk of HCC occurrence after successful DAA therapy.[9,15-18] On the other hand, it is not straightforward to draw conclusions on the risk of HCC recurrence after DAAs [12] since multiple risk factors are involved. In particular, in this special setting it is necessary to take into account (a) the neoplastic risk related to the cirrhosis (higher risk in decompensated disease); (b) the risk factors related to the characteristics of the primary HCC (site, numbers of nodules, vascular invasion, etc) and (c) the lack of well-designed studies because of small sample size, retrospective designs without a control group of untreated HCV patients (ie patients not treated with DAAs), and heterogeneity of enrolled patients.[19] Furthermore, several publications about HCV-infected patients with previously successfully treated HCC highlighted that DAA-treated cohorts are older and show more advanced chronic liver disease in comparison to cohorts of IFN-treated patients, leading to higher HCC recurrence rates and making any comparison with historical IFN-treated controls suboptimal.

In this scenario, the recurrence of HCC has been reported as early recurrence (before 12 months) and late recurrence (after 12 months), according to the time of reappearance. An early recurrence is considered to have the same characteristics as the primary tumour, so its risk factors are tumour-related, such as tumour size, number of nodules and direct intrahepatic dissemination. Necro-inflammatory activity from chronic hepatitis and the fibrosis burden lead to underlined persistent carcinogenesis, which can be related to late 'de novo' recurrence.

In light of all the aforementioned variables and of the limitations in the design of previous studies, it is very difficult to draw reliable conclusions. The present analysis of prospectively enrolled patients in a real-life multicentre study aims to investigate the effects of IFN-free DAA therapies on SVR rates and neoplastic recurrence in cirrhotic patients with HCV infection and a history of HCC who had achieved a complete radiological response after curative treatments or TACE.

> **Key points**
> - New direct-acting antivirals (DAAs) are short, highly effective and well-tolerated therapy, also in patients with decompensated cirrhosis or with a history of hepatocellular carcinoma (HCC).
> - DAAs treatment appears not to be associated with a major increased risk of HCC recurrence in our study.
> - DAAs treatment failure, levels of total bilirubin, BMI and levels of AFP can be used to stratify the risk of HCC recurrence

2 | PATIENTS AND METHODS

2.1 | Study design and patient population

From March 2015 to March 2017, an observational, prospective, real-life study collecting consecutive cirrhotic patients infected by different HCV genotypes treated with any of the DAA regimens and with a history of successfully treated HCC (complete radiological response after curative treatments or TACE) was conducted in six community and academic Italian centres.

The study was performed in accordance with the principles of the Declaration of Helsinki and its appendices. Approval was obtained from the Institutional Review Board and Ethics Committee.

Eligible patients were adults (≥18 years old) with chronic HCV infection, cirrhosis and a history of successfully treated HCC (complete radiological response achieved by ablation, surgical resection or chemoembolization). The previous HCC was diagnosed by pathology or by non-invasive criteria according to the European Association for the Study of the Liver (EASL)[20] guidelines. HCC was defined as successfully treated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (ie absence of residual tumour or complete necrosis evaluated with dynamic computed tomography (CT) or magnetic resonance imaging (MRI) performed 1 and 3 months after HCC treatments).[20,21] Patients were enrolled in the study according to the absence of non-characterized nodules on dynamic imaging (CT or MRI) before starting antiviral treatment (within

3 months) and at least one tumour status imaging assessment after the antiviral therapy.

Patients with any of the following features were excluded: absence of cirrhosis, active HCC, treated HCC but without a radiological complete response and/or the presence of 'non-characterized nodules' on imaging before starting DAAs, human immunodeficiency virus (HIV) or hepatitis B virus (HBV) coinfection, liver-transplant recipients, history of alcohol intake and iron or copper metabolism disorders.

The choice of antiviral schedule therapy was left to the clinician's discretion, in accordance with national and international guidelines. [22,23]

For each enrolled patient, demographic characteristics and clinical parameters at baseline were recorded: sex, body mass index (BMI), age, prior antiviral treatment, cirrhotic status and signs of portal hypertension, enlisting for orthotopic liver transplantation (OLT), presence of comorbidities and characteristics of HCC. In addition, the following biochemical parameters were registered: albumin, total bilirubin, creatinine, international normalized ratio (INR), blood count and alpha-1 fetoprotein (AFP).

2.2 | Follow-up and outcomes

The baseline characteristics, laboratory data and radiological tumour response were recorded in all patients before starting antiviral therapy. From a virological point of view, patients were followed up monthly for clinical and laboratory evaluation during antiviral treatment, and virological response was assessed by quantitative HCV-RNA at week 4, at the end of treatment and at 4 and 12 weeks after the end of treatment. Virological failures and early discontinuations of therapy because of adverse events were also registered. After the end of DAA treatment, the patients were followed up every 3 months, or with a different timing according to their clinical needs, for at least 12 months. From an oncological point of view, all patients underwent a periodic imaging follow-up for HCC recurrence detection according to the international guidelines,[20] including physical examination, laboratory evaluation and abdominal ultrasonography (US) every 3 months, in addition to dynamic CT or MRI every 6 months. HCC recurrence was diagnosed according to combined abnormal findings on US and on one of the additional dynamic imaging techniques. [20] HCC recurrences were treated, whenever possible, according to the Barcelona Clinic Liver Cancer (BCLC) schedule and EASL guidelines.[20]

Finally, we recorded the patients' status (alive/death) at the end of follow-up. Overall, the median follow-up from DAA start until the present analysis was 24.7 months (range: 12-36.9).

The assessment of neoplastic recurrence was the primary outcome in this study. The secondary outcomes were the baseline characteristics that could predict HCC recurrence, including the SVR, defined as the persistent absence of detectable serum HCV-RNA 12 weeks after the end of treatment.

2.3 | Statistical analysis

Baseline characteristics of patients were summarized using standard descriptive statistics and compared between groups (subjects with and without recurrence) using either the T test for independent samples, the Mann-Whitney U test, the chi-square test or the Fisher exact test.

Median follow-up was computed according to the reverse Kaplan-Meier technique using DAA initiation as a starting point. Recurrence incidence rates were calculated as per 100 person-years, and the corresponding 95% CIs were estimated assuming a Poisson distribution for the number of events. Cumulative probabilities of recurrence were extracted from time-to-event curves based on the Kaplan-Meier product limit method. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using univariate and multivariate Cox regressions. The proportional hazard assumption was tested using the method of Grambsch and Therneau.[24] In Cox models, SVR was not considered a time-dependent variable. For all statistical comparisons, a $P < .05$ was accepted as statistically significant. All analyses were performed using R version 3.4.1 (www.r-project.org).

3 | RESULTS

3.1 | Patients characteristics and follow-up

The baseline demographic, clinical and laboratory characteristics of the enrolled patients are summarized in Table 1.

There were 101 patients treated with DAAs in the defined time period. The majority of patients were male (65/101, 64.4%), and the mean age was 67.2 ± 7.8 years. The mean BMI was 25.8 ± 3 kg/m^2. Overall, the predominant HCV genotype was genotype 1 (89/101, 88.1%). All the enrolled patients had cirrhosis, mostly in a well-compensated stage (Child-Pugh class A in 81/101 patients), with a mean Model for End-stage Liver Disease (MELD) value of 7 [range: 5-11]). The presence of oesophageal varices was recorded in 37/101 patients (37.4%). Laboratory parameters for liver function at baseline are reported in Table 1. Moreover, 34 (33.7%) patients were diabetic. At the time of HCC, most of them showed an early or very early BCLC stage (88.3%), and most had a single nodule (74.2%). The median size of the main nodule was 2.6 cm (IQR: 2-3.5). Thirty-five percent of patients had a history of previous HCC recurrence before the antiviral treatment. The most frequent last successful treatment performed for HCC was a percutaneous ablation (70.3%). The median time from diagnosis of HCC to DAA treatment was 17.2 months [IQR: 10-36.8], whereas the median time from the last successful HCC treatment (ie after the diagnosis of HCC or, for patients with prior HCC recurrence, after the last HCC recurrence) to DAA initiation was 10.1 months [IQR: 5.6-16.7]. Overall, the reverse KM estimate of the median follow-up was 31.7 months [95% CI 30.0-34.9]. The 2-year survival rate in the overall population was 92.0% (95% CI 86.8% to 97.5%).

TABLE 1 Baseline characteristics of patients, overall and according to HCC recurrence

	Overall (n = 101)	No recurrence (n = 70)	Recurrence (n = 31)	P
Age, years (mean ± SD)	67.2 ± 7.8	68.4 ± 7.2	64.7 ± 8.5	**.032**
Male, n (%)	65 (64.4)	39 (55.7)	26 (83.9)	**.007**
BMI, mean ± SD	25.8 ± 3.01	25.4 ± 3.1	27.1 ± 2.5	**.015**
Genotype 1, n (%)	89 (88.1)	61 (87.1)	28 (90.3)	.342
HCV-RNA, IU/mL (median, IQR)	1 100 000 [406 389-2 341 000]	986 500 [396 975-2 857 620]	1 200 000 [370000-2329268]	.968
Child-Pugh A, n (%)	81 (83.5)	59 (86.8)	22 (75.9)	.234
MELD, median, IQR	7 [6-9]	6 [6-9]	7 [6-10]	.123
Oesophageal varices, n (%)	37 (37.4)	21 (30.9)	16 (51.6)	.072
Presence of diabetes, n (%)	34 (33.7)	24 (34.3)	10 (32.3)	1.000
Laboratory parameters				
Albumin (g/dL) (mean ± SD)	3.7 ± 0.5	3.7 ± 0.5	3.6 ± 0.6	.457
INR, mean ± SD	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.2	.435
Bilirubin (mg/dL) (mean ± SD)	1.1 ± 0.6	1.0 ± 0.5	1.3 ± 0.6	**.052**
Platelets count, median (IQR)	103 000 [72 000-151 000]	110 000 [80 250-158 000]	83 000 [55 000-133 000]	**.021**
AFP (ng/mL) (median, IQR)	9.8 [4.9-18]	10 [5-20]	9 [4.2-16.9]	.87
Characteristics of HCC before DAAs initiation[a]				
HCC morphology, n (%)				
Single nodule	75 (74.2)	54 (77.1)	21 (67.7)	.51
Two nodules	15 (15.5)	9 (13.2)	6 (20.7)	
Multiple nodules	11 (11.3)	7 (10.3)	4 (13.8)	
Tumour size, *cm* (median, IQR)	2.6 [2-3.5]	2.5 [1.9-3.3]	2.8 [2-3.6]	.276
BCLC stage, n (%)				
0	12 (12.1)	10 (14.5)	2 (6.7)	.664
A	77 (76.2)	52 (74.2)	25 (80.6)	
B	12 (12.1)	8 (11.6)	4 (13.3)	
Prior HCC recurrence, n (%)	30 (34.9)	21 (34.4)	9 (36)	1.000
Last HCC treatment, n (%)				
Surgery	9 (8.9)	7 (10)	2 (6.5)	.602
RFA	49 (48.5)	36 (51.4)	13 (41.9)	
Laser ablation	22 (21.8)	15 (21.4)	7 (22.6)	
TACE	14 (13.9)	7 (10)	7 (22.6)	
TACE + ablation	7 (6.9)	5 (7.1)	2 (6.5)	
Time from HCC diagnosis to DAAs, mo (median, IQR)	17.2 [10-36.8]	20.6 [10.2-40.9]	15.4 [8-34.1]	.129
Time from last HCC treatment to DAAs, mo (median, IQR)	10.1 [5.6-16.7]	10.8 [5.6-19.8]	8.7 [4.8-13.6]	.159
DAA schedule				
DAA combination, n (%)				
Sofosbuvir + ribavirin	7 (6.9)	5 (7.1)	2 (6.5)	n.a.
Simeprevir + sofosbuvir +ribavirin	12 (11.9)	6 (8.6)	6 (19.4)	
Paritaprevir/ritonavir + ombitasvir+dasabuvir + ribavirin	17 (16.8)	14 (20)	3 (9.7)	
Sofosbuvir + daclatasvir +ribavirin	4 (4)	2 (2.9)	2 (6.5)	
Sofosbuvir + ledipasvir+ribavirin	11 (10.9)	8 (11.4)	3 (9.7)	
Simeprevir + sofosbuvir	7 (6.9)	6 (8.6)	1 (3.2)	
Paritaprevir/ritonavir + ombitasvir+dasabuvir	13 (12.9)	9 (12.9)	4 (12.9)	
Sofosbuvir + ledipasvir	26 (25.7)	17 (24.3)	9 (29)	
Sofosbuvir + daclatasvir	4 (4)	3 (4.3)	1 (3.2)	

(Continues)

TABLE 1 (Continued)

	Overall (n = 101)	No recurrence (n = 70)	Recurrence (n = 31)	P
DAA 12-week treatment, n (%)	61 (61)	45 (65.2)	16 (51.6)	.268
SVR rate, n (%)	92 (91.1)	69 (98.6)	23 (74.2)	**<.001**
Treatment failure rate, n (%)	9 (8.9)	1 (1.4)	8 (25.8)	

[a]At the diagnosis of HCC or, for patients with prior HCC recurrence, at the last HCC recurrence.

The values in bold represent the statistically significant P values.

3.1.1 | Virological response to DAA and recurrence of HCC

A total of 92/101 (91.1%) patients achieved SVR. All nine patients showing a DAA treatment failure had HCV genotype 1. Most of them had a well-compensated liver disease (Child-Pugh class A in 8/9 patients) and a history of early HCC stage (BCLC A in 7/9 patients, BCLC B in 2/9 patients).

Out of the 101 enrolled patients, 31 (30.6%) were diagnosed with an HCC recurrence within the time of observation. The characteristics of patients showing an HCC recurrence are detailed in Table 2 and Table S1. At the time of HCC recurrence, most patients were at the very early/early BCLC stage (64.5%), and many were at the intermediate BCLC stage (25.8%). Only two patients (6.5%) were at the

TABLE 2 Characteristics of the 31 recurred patients at the time of HCC recurrence

BCLC stage	n (%)
0	3 (9.7)
A	17 (54.8)
B	8 (25.8)
C	2 (6.5)
D	1 (3.2)
Tumour size, cm (mean ± SD; [min-max])	4 ± 4.1 [1-20]
Time to recurrence from DAA initiation, months	median [min-max]
Overall	8.6 [0.1-17.7]
Only patients with recurrence during DAAs	1.9 [0.1-8.7]
Only patients with recurrence after DAAs	8.0 [0.9-13.0]
Time to recurrence from last HCC treatment, mo	Median [min-max]
Overall	17.0 [4.3-40]
Only patients with recurrence during DAAs	11.7 [4.3-19]
Only patients with recurrence after DAAs	19.1 [11.2-40]
Treatment of HCC at recurrence	n (%)
RFA	6 (19.4)
Laser ablation	8 (25.8)
TACE	8 (25.8)
TACE + ablation	4 (12.9)
Sorafenib	3 (9.7)
Best supportive care	1 (3.2)
Liver transplantation	1 (3.2)

advanced BCLC stage, whereas one patient (3.2%) was at the terminal stage. Some 75.9% of the patients were in Child-Pugh class A, and the median MELD score was 7 [range: 5-11]. The pattern of recurrence was heterogeneous: 28 patients developed intrahepatic growth with a nodular profile (single nodule: 21 patients; two nodules: 6 patients; multiple nodules: 4 patients), whereas three patients developed infiltrative HCC (2 with macro-vascular invasion and 1 with extrahepatic metastases). For details about these three patients, see supporting data.

Most of the patients who had HCC recurrence underwent thermal ablation (45.2%) or trans-arterial chemoembolization (TACE) (29%). The median time from HCC diagnosis to DAA treatment was 15.4 months in the recurrence group and 20.6 months in the non-recurrence group. The median time from the last successful HCC treatment to DAA initiation was 8.7 and 10.8 months respectively. During the follow-up, a total of 13 deaths (12.9%) were observed, 5 (7.1%) in the non-recurrence group and 8 (25.8%) in the recurrence group (P = .02). The causes of death were the following: cancer progression (two patients), hepatic failure (one patient), haemorrhage (two patients), infection (three patients), renal failure (one patient) and other causes unrelated to liver disease (in particular, two patients died because of cardiovascular disease, one patient died after a car accident and one patient died after hip fracture).

3.1.2 | Risk factors associated with HCC recurrence

Clinical findings of the patients divided according to HCC recurrence are found in Table 1. At baseline, patients with recurrence were younger (64.7 ± 8.5 vs 68.4 ± 7.2, P = .032), were more commonly male (83.9% vs 55.7%, P = .007) and had higher BMI (27.1 ± 2.5 vs 25.4 ± 3.1, P = .015). With respect to biochemical parameters, patients with recurrence showed higher levels of total bilirubin (1.3 ± 0.6 vs 1.0 ± 0.5, P = .052) and lower median platelet count (83 000 [IQR: 55 000; 133 000] vs 110 000 [IQR: 80 250; 158 000], P = .021). Child-Pugh class distribution did not differ between the two groups.

Among the patients with tumour recurrence, significantly more patients did not achieve SVR (n = 8/31; 25.8%) compared to the non-recurrence HCC group (n = 1/70; 1.4%) (P < .001). Although not statistically significant, more patients in the HCC recurrence group were previously treated with TACE (29.1% vs 17.1%, P = .602).

The results of the univariate and multivariate analysis comparing patients with and without HCC recurrence are summarized in Table 3. In univariate analysis, the following factors were associated

TABLE 3 Univariate and multivariate analysis for risk of recurrence

	Univariate		Multivariate	
	HR [95% CI]	*P*	HR [95% CI]	*P*
Age	0.95 [0.91-0.99]	**.018**	0.95 [0.89-1.01]	.098
Male sex	3.48 [1.33-9.07]	**.011**	1.13 [0.32-3.96]	.853
BMI	1.16 [1.02-1.31]	**.02**	1.2 [1.01-1.42]	**.036**
HCV-RNA	1.01 [0.83-1.24]	.908		
Child-Pugh A	1.75 [0.75-4.11]	.196		
MELD	1.15 [1-1.34]	**.057**	0.91 [0.69-1.2]	.515
Oesophageal varices	2.14 [1.06-4.32]	**.035**	1.75 [0.59-5.25]	.316
Albumin	0.7 [0.35-1.4]	.313		
INR	3.79 [0.28-51.91]	.318		
Total bilirubin	1.78 [1.06-3]	**.029**	2.54 [1.04-6.19]	**.041**
Platelets	0.99 [0.99-1[	**.042**	1 [0.99-1.01]	.725
AFP	1.02 [1.01-1.03]	**.002**	1.02 [1-1.03]	**.019**
Presence of diabetes	0.93 [0.44-1.98]	.857		
HCC morphology				
Single nodule	ref			
Two nodules	1.67 [0.67-4.18]	.275		
Multiple nodules	1.37 [0.47-4.04]	.564		
Mean tumour size	1.12 [1.01-1.23]	**.024**	1.08 [0.75-1.56]	.682
BCLC stage				
0	ref			
A	2.16 [0.51-9.15]	.295		
B	2.13 [0.39-11.62]	.384		
BCLC stage				
0/A	ref			
B	1.07 [0.37-3.07]			
Prior HCC recurrence before starting DAA	1.05 [0.46-2.37]	.912		
Last HCC treatment before starting DAA				
Surgery	ref			
RFA	1.48 [0.33-6.55]	.608		
Laser ablation	1.76 [0.37-8.48]	.481		
TACE	2.78 [0.58-13.39]	.203		
TACE + ablation	0.92 [0.13-6.51]	.931		
Last HCC treatment before starting DAA				
Surgery/RFA/Laser ablation (n = 77)	ref			
TACE/ TACE + ablation (n = 24)	1.29 [0.59-2.79]	.525		
Time from last HCC treatment to DAA initiation	0.97 [0.95-1.01]	.109		
Time from HCC diagnosis to DAA initiation	0.99 [0.98-1]	.168		
DAA treatment duration	1.01 [0.95-1.08]	.66		
SVR rate	0.16 [0.07-0.36]	**<.001**	0.18 [0.05-0.61]	**.006**

The values in bold represent the statistically significant *P* values.

with the risk of HCC recurrence: SVR, age, sex, BMI, MELD, presence of oesophageal varices, AFP level, total bilirubin value, platelet count and tumour size, whereas the multivariate analyses selected as independent risk factors of HCC recurrence only DAA treatment failure, higher BMI and higher AFP and total bilirubin levels. In particular, patients with SVR showed an 82% reduction in HCC risk (HR:

0.18, 95% CI: 0.05-0.61; Figure 1). BMI was significantly associated with HCC development, with a 20% increment in the hazard of recurrence for every unit increase in BMI (HR: 1.2, 95% CI: 1.01-1.42, $P = .036$; Figure 2). Finally, of the baseline laboratory parameters, AFP and total bilirubin remained significantly associated with the risk of recurrence in multivariate analysis (HR: 1.02, 95% CI: 1-1.03, $P = .019$; and HR: 2.54, 95% CI 1.04-6.19, $P = .041$ respectively). The significant association with HCC recurrence risk of age, sex, MELD,

presence of oesophageal varices, platelet count and tumour size found in univariate analysis disappeared in the multivariate model.

1.2.1 | Recurrence probabilities analysis and timing evaluation

The overall rate of HCC recurrence was 30.6%. The incidence rate of HCC recurrence in the overall population was 20.5 per 100 person-years (95% CI: 13.9-29), whereas in patients with and without prior history of HCC recurrences, the rates were 19.0 per 100 person-years
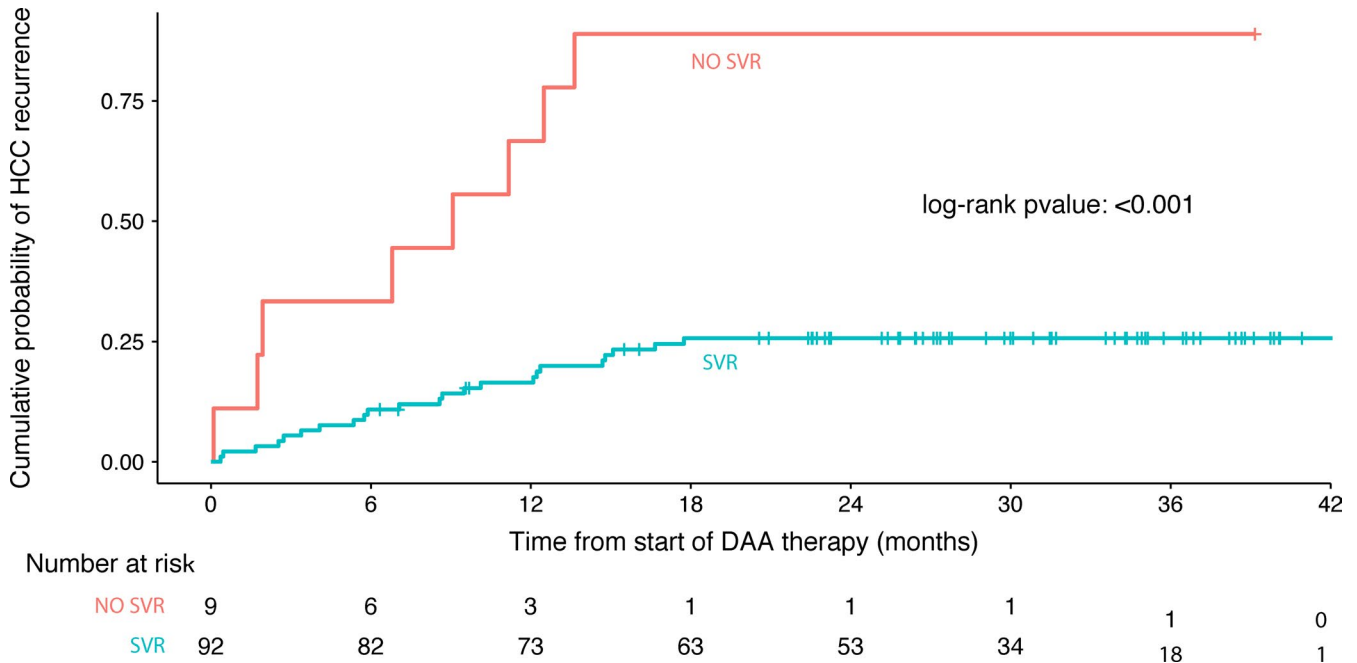

FIGURE 1 Cumulative probability of HCC recurrence according to SVR status
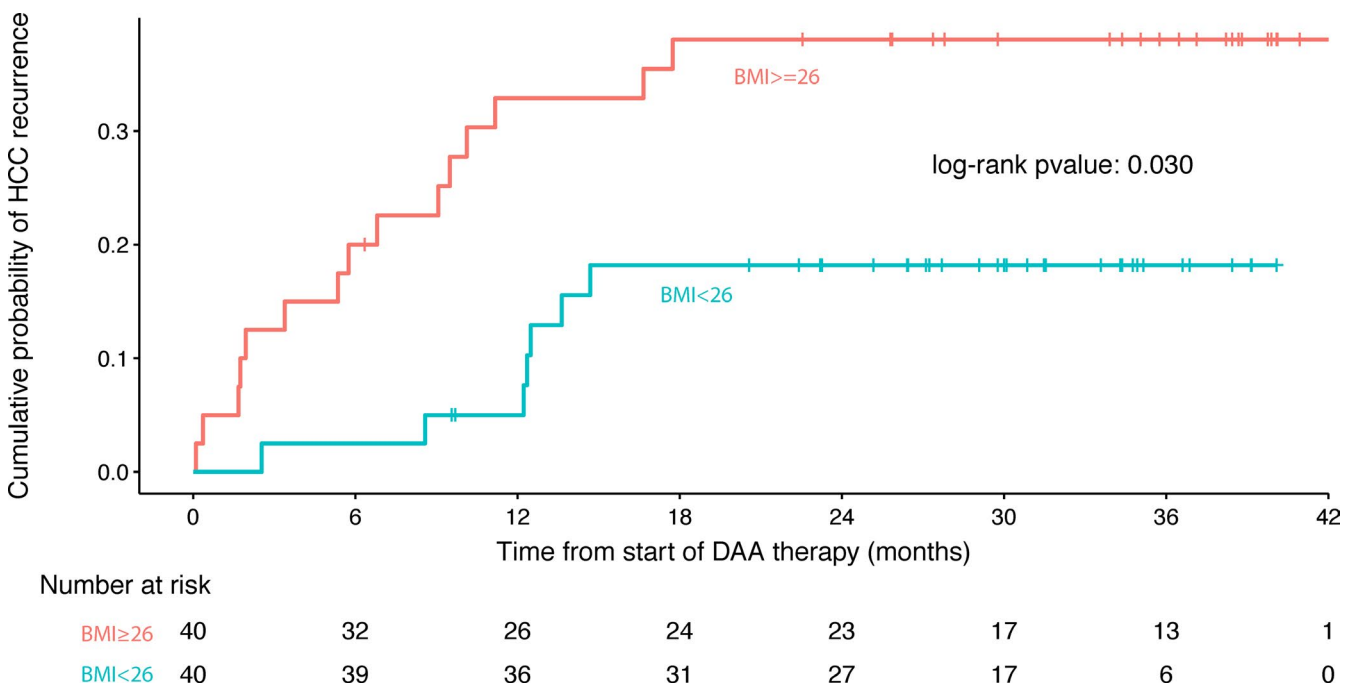

FIGURE 2 Cumulative probability of HCC recurrence according to BMI (≥ 26 vs < 26)

(95% CI: 8.7-36.1) and 18.1 per 100 person-years (95% CI: 10.6-32.4) respectively. By Kaplan-Meier analysis, the overall cumulative rates of HCC recurrence at 1 and 2 years were 21.2% and 32.6% respectively (Figure 3). The incidence rate of recurrence was 12.4 per 100 person-years (95% CI: 7.8-18.5) in SVR patients and 99.9 per 100 person-years (95% CI: 43.1-196.8) in patients without SVR ($P < .001$; Figure 1). The cumulative probability of recurrence at 1 year was 16.5% (95% CI: 8.5%-28.3%) for the SVR patients and 66.7% (95% CI: 16.0%-86.8%) in non-SVR patients at 1 year ($P < .01$), whereas it was 25.7% (95% CI: 16.0%-34.2%) for SVR and 88.9% (95% CI: 29.5%-98.2%) for non-SVR ($P < .001$) at 2 years of observation.

Using the time of last successful HCC treatment as baseline, the 6-, 12- and 24-months HCC cumulative recurrence probabilities were 1%, 8.9% and 25.6% in the whole population, respectively, whereas in patients with vs without prior history of HCC recurrences, the probabilities were 0%, 13.3% and 20.4% vs 1.8%, 7.1% and 25.7% respectively (Table 4). Conversely, using time of DAA initiation as baseline, the 6-, 12- and 24-months HCC cumulative recurrence probabilities were 12.9%, 21.0% and 32.6% in the whole population, respectively, whereas in patients with vs without prior history of HCC recurrences, these probabilities were 6.7%, 20.8% and 32.4% vs 14.3%, 21.5% and 29.3% respectively (Table 4).

Moreover, 9/31 patients showed early HCC recurrence within 12 months from the last HCC treatment. Among them, 8/9 (88.8%) showed HCC recurrence during the DAA treatment period. On the other hand, 22 patients showed late HCC recurrence after 12 months from the last HCC treatment, and only 2/22 (9.1%) of them showed HCC recurrence during the DAA treatment period. The comparison between patients with early vs late HCC recurrence showed no statistically significant difference (Table S2).

Additionally, we divided our population into two subgroups according to DAA initiation time from last HCC treatment (before and after 6 months). We found no statistically significant difference between the two subgroups (Table S3).

4 | DISCUSSION

The present real-life multicentre prospective study showed a cumulative rate of HCC recurrence of 20.5 per 100 person-years in a median observational follow-up of 31.7 months from DAA initiation. In particular, the 6-, 12- and 24-months HCC recurrence rates from the last HCC treatment were 1%, 8.9% and 25.6% respectively. These data are in contrast with first reports describing early, unexpected increases in HCC recurrence after HCV elimination with DAA therapy,[5,7] but they are in line with the few more recent papers countering the alarmist results initially observed.[9,16,25-28]

Of note, a useful benchmark for indirect comparisons of the benefit of HCV eradication by antiviral therapy has been recently provided by Cabibbo et al[29] They performed a meta-analysis of individual and aggregated data of untreated arms from 11 studies of HCV-related early HCC recurrence, in which the pooled estimate of the actuarial probability of 2-year recurrence was 47%. Comparing our results with these data, a beneficial effect of DAA treatment on HCC recurrence is clear (2-year recurrence rate: 25.6% vs 47%), probably because of the benefit of SVR on overall survival and hepatic decompensation, as recently highlighted by the same group.[28]

The authors are divided into two different scenarios: the first one raises doubts about a potentially increased risk of HCC recurrence after the use of DAAs,[5,7,12,30,31] and the second one suggests a reduction or at least a stability of this risk.[9,11,16,28,32,33] Our results showed a stability of the risk of HCC recurrence according to both evaluation times: time from the last successful HCC treatment and time from the antiviral therapy initiation. In fact, using time of
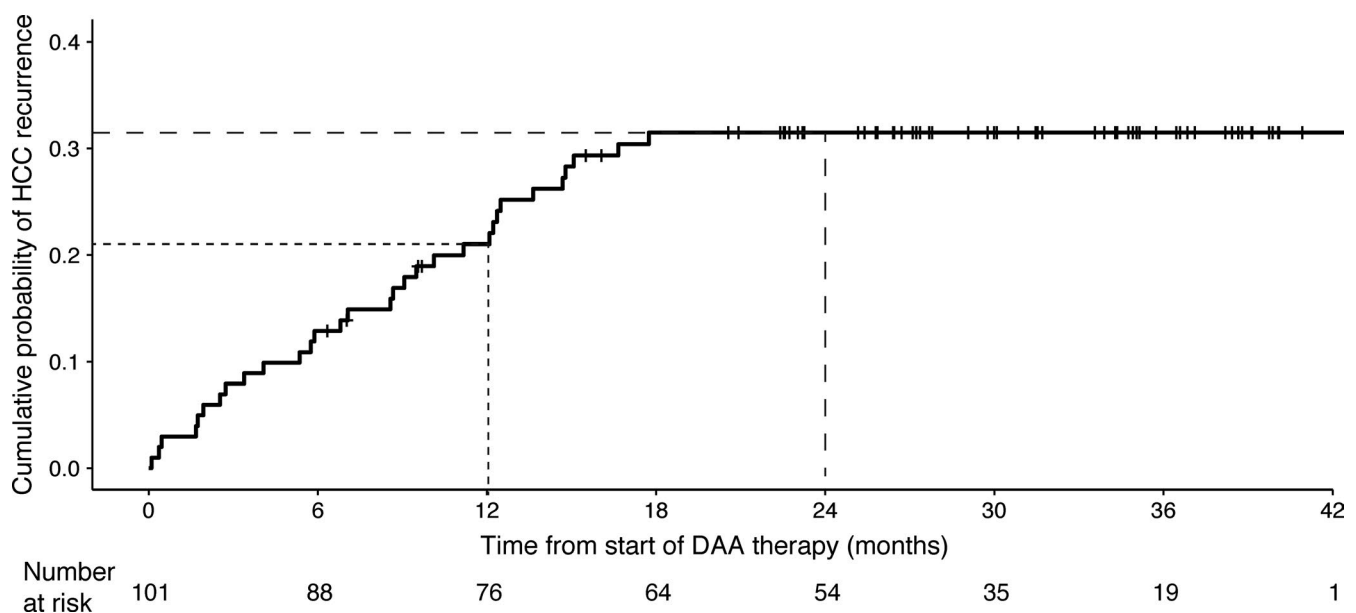

FIGURE 3 Cumulative probability of HCC recurrence in the overall population according to the time of DAAs initiation

TABLE 4 Recurrence probability and timing analysis

Incidence (per 100 person-years)	% (95% CI)
Overall (n = 101)	n =31; 20.5 [13.9-29.0]
Among patients with prior HCC recurrence	n = 9; 19.0 [8.7-36.1]
Among patients without prior HCC recurrence	n = 16; 18.1 [10.6-32.4]
Recurrence rates from DAA initiation (%)	Overall
6 mo	12.9 [6.1-19.2]
12 mo	21.2 [12.7-28.8]
24 mo	32.6 [22.3-41.4]
Among patients with prior HCC recurrence	
6 mo	6.7 [0-15.2]
12 mo	20.8 [4.5-34.3]
24 mo	32.4 [12.3-47.9]
Among patients without prior HCC recurrence	
6 mo	14.3 [4.6-23.0]
12 mo	21.5 [10-31.6]
24 mo	29.3 [16.1-40.5]
Recurrence rates from last HCC treatment (%)	Overall
6 mo	1 [0-2, 9]
12 mo	8.9 [3.2-14.3]
24 mo	25.6 [16.4-33.9]
Among patients with prior HCC recurrence	
6 mo	0 [0-0]
12 mo	13.3 [0.3-24.7]
24 mo	20.4 [4.4-33.8]
Among patients without prior HCC recurrence	
6 mo	1.8 [0-5.2]
12 mo	7.1 [0.1-13.6]
24 mo	25.7 [13.1-36.5]

last successful HCC treatment as baseline, the 6-, 12- and 24-months HCC cumulative recurrence probabilities in our population (1%, 8.9% and 25.6% respectively) were in line with the following rates reported by Shimizu et al reporting: 0%, 8.7% and 27.9%.[34] Using time of DAA initiation as baseline, the 6-, 12- and 24-months HCC cumulative recurrence probabilities in our population (12.9%, 21.2% and 32.6% respectively) were in line with several findings,[32,35-38] but lower than the rates found by Minami et al (38% at 1 year and 54.5% at 2 years)[33,39] and by Kolly et al (23% at 6 months and 42% at 1 year).[30] It has to be pointed out that all current published studies have several limitations, including study design (most of them are single-arm, retrospective cohort studies with clinical heterogeneity in tumour burden and patient selection), unstandardized definition of curative HCC treatments leading to complete response, absence of a consistent surveillance protocol to assess HCC recurrence, potential misclassification of HCC absence prior to DAA initiation, inadequate characterization of early vs late HCC recurrence, ascertainment bias for HCC recurrence, short duration of follow-up and absence of a well-defined timing of recurrence (several baseline starting points: HCC diagnosis, last HCC treatment, last radiological assessment,

DAA initiation, end of DAA therapy). These limitations highlight the need for high-quality prospective studies with strict and well-defined inclusion criteria and follow-up. In this scenario, the biggest strength of our study is the availability of different time points of the HCC history (HCC diagnosis, last successful HCC treatment, DAA initiation) for every single patient, allowing for an appropriate comparison to several published studies, using different starting points.

Several risk factors for HCC recurrence after DAA are consistently reported in the literature, such as history of previous HCC recurrence, antiviral treatment failure, previous HCC shape, higher AFP level, the use of non-curative procedures (such as TACE), the shorter interval between HCC complete response and DAA initiation being associated with higher risk of recurrence.[7,32-33,35,37,39,40] This study identified antiviral treatment failure (HR: 5.68) as an independent risk factor for HCC recurrence after DAA. In fact, we observed a rate of antiviral treatment failure of 25.8% in the recurrence group and of 1.4% in the non-recurrence group, in line with the data of Bielen et al (50% vs 5.7%).[31] Moreover, we showed that SVR was associated with an 82% reduction in the risk of HCC recurrence (HR: 0.18) in multivariate analyses. It is interesting to highlight that in

prospective studies the protective effect of SVR seems to be on the same order of magnitude (HCC risk reduction: 76% [18] vs 82%) in the contexts of both HCC occurrence and recurrence. In this context, the hypothesis of sequential events favouring HCC development after DAAs proposed by Faillaci et al [41] is supported. Indeed, in cirrhotic patients, DAAs induce an increase in already elevated circulating vascular endothelial growth factor, which further activates angio-poietin 2 (ANGPT2) expression in the liver of predisposed patients (those with severe fibrosis, extensive splanchnic collateralization and increased microvascular shear stress), acting as a trigger for carcino-genesis together with the antiviral treatment failure. Perhaps future studies focussing on the small group of patients showing DAA treat-ment failure could be helpful to characterize the clinical and biological risk factors of HCC recurrence for selecting the ones at real risk.

Our analysis also showed that higher BMI (HR 1.20) was inde-pendently associated with higher risk of HCC recurrence. Higher BMI as a risk factor for HCC recurrence has never been reported in the literature until now, at least in association with the HCC recurrence risk after DAA. It is well known that obesity is a risk factor for both HCC occurrence and recurrence,[42,43] and it has been suggested that the rising prevalence of obesity and metabolic diseases, includ-ing diabetes, is contributing considerably to the increasing burden of HCC in Western countries.[44,45] Our study did not show any as-sociation between diabetes and risk of HCC recurrence after DAA, even if diabetes is one of the most important factors associated with carcinogenesis and is recognized as a strong correlation with obesity and NASH.[46] We can speculate that our study failed in showing this association because of the impact of DAA on glucose metabolism. [47,48] Nevertheless, it is necessary to underline that obesity and metabolic features are weaker risk factors than the presence of HCV infection per se, and their association with HCC is coming to light in recent years according to the increasing incidence of metabolic-re-lated liver diseases and to the decrease in HCV-related liver disor-ders. Therefore, in the emerging setting of patients with a previous HCV infection, it is important to take into account the lifestyle- and metabolic-related HCC-risk factors, such as alcohol intake, obesity and diabetes.[45] Moreover our analysis showed that higher level of bilirubin (HR: 2.54) was independently associated with higher risk of HCC recurrence. It is well known that lower serum bilirubin lev-els correlate with better hepatic reserve. This is the substrate of the ALBI (Albumin-Bilirubin) score used very commonly in HCC patients because of its better correlation in terms of survival.[49] Additionally, the ALBI score showed also a correlation with HCC occurrence and recurrence.[50,51]

In addition to the increased risk of HCC recurrence after DAAs, additional alarming data have been published suggesting a more ag-gressive tumour pattern.[12,32,38,52,53] In our population, we did not observe such aggressiveness, in contrast to Reig (18.7% infiltra-tive pattern),[53] Calleja (23.8% untreatable tumours) [35] or Cabibbo (17% advanced/terminal BCLC stage).[32] In fact, at the time of HCC recurrence, only two patients (6.5%) showed an advanced BCLC stage, whereas one patient (3.2%) was at the terminal stage, all with an infiltrative pattern of HCC.

Our data seem to confirm that the HCC recurrence risk after DAA is associated with the neoplastic disease and the viral status, but not to the use of DAAs per se. HCC recurrence after a curative treatment is influenced by many factors related to tumour characteristics (tu-mour size, number of nodules, vascular invasion, AFP level, presence of satellite nodules), the presence of cirrhosis and the type of HCC treatment.[32,54] As suggested by several authors,[10-11,29,55] the rate of HCC recurrence may be related to the interval between HCC treatment and the initiation of the antiviral therapy, with a higher risk of recurrence during the first months after HCC treatment. It can be hypothesized that early HCC recurrence develops from invisible pre-existing HCC foci not detected at pre-DAA imaging, on which successful DAA therapy (achieving SVR) cannot have any impact. Our study is the first to demonstrate all of the data for a time-to-event analysis. The time interval between successful HCC treatment and the initiation of DAAs was shorter for patients with HCC recur-rence compared with those without recurrence (8.7 vs 10.8 months), even if not statistically significant. Similarly, the time between HCC diagnosis and the initiation of DAAs was shorter for patients with HCC recurrence compared with those without recurrence (15.4 vs 20.6 months).

Our study has some limitations. First, because of the different durations of antiviral therapy according to the schedule, there could have been a bias, especially when the recurrence of HCC was observed during the antiviral therapy. A second limitation includes factors related to the observational, real-life design of the study, including potential physician prescribing bias. One of the biggest strengths of this study was our ability to follow and analyse HCC recurrence after DAA exposure in a well-se-lected cohort of HCV cirrhotic patients from the moment of HCC diagnosis.

In conclusion, our prospective study failed to show any negative impact of DAA treatment on the incidence of HCC recurrence. The risk of HCC recurrence in our cohort was comparable and not higher than that observed in HCV-untreated patients. DAA treatment fail-ure, level of total bilirubin, BMI and level of AFP can be used to strat-ify the risk of HCC recurrence and the schedule of the surveillance protocol. Successful HCV therapy with DAAs is probably not likely to prevent per se early recurrence of HCC, but surely it improves liver function, decreasing the risk of death from end-stage liver disease. For all these reasons, we conclude that there is no need to hold back from DAA therapy in patients with a history of HCC after ascertain-ing that the tumour is fully controlled and a complete radiological re-sponse has been achieved.

CONFLICT OF INTEREST

AUTHORS' CONTRIBUTIONS

MG and FM involved in study concept and design. MG, FM, MG, LR, ASM, NC and AA involved in acquisition of data. DB and MG involved in analysis and interpretation of data. MG, AS and FM involved in drafting of the manuscript. GGDC, NC and FM performed critical revision of the manuscript for an important intellectual content. DB performed statistical analysis. FM and NC involved in study supervision.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.