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Is early recurrence of hepatocellular carcinoma in HCV cirrhotic patients affected by treatment with direct-acting antivirals? A prospective multicentre study

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Summary

Background: Data on HCV-related hepatocellular carcinoma (HCC) early recurrence in patients whose HCC was previously cured, and subsequently treated by direct-acting antivirals (DAAs), are equivocal.

Aim: To assess the risk of HCC early recurrence after DAAs exposure in a large prospective cohort of HCV-cirrhotic patients with previous successfully treated HCC, also looking for risk factors for cancer early recurrence.

Methods: We enrolled 143 consecutive patients with complete response after curative treatment of HCC, subsequently treated with DAAs and monitored by the web-based RESIST-HCV database. Clinical, biological, and virological data were collected. The primary endpoint was the probability of HCC early recurrence from DAA starting by Kaplan-Meier method.

Results: Eighty-six per cent of patients were in Child-Pugh class A and 76% of patients were BCLC A. Almost all patients (96%) achieved sustained virological response. Twenty-four HCC recurrences were observed, with nodular or infiltrative pattern in 83% and 17% of patients, respectively. The 6-, 12- and 18-month HCC recurrence rates were 12%, 26.6% and 29.1%, respectively. Main tumour size and history of prior HCC recurrence were independent risk factors for HCC recurrence by Cox multivariate model.

Conclusions: Probability of HCC early recurrence in patients who had HCC previously cured remains high, despite HCV eradication by DAAs. Risk was comparable but not higher to that reported in literature in DAA-untreated patients. Previous HCC recurrence and tumour size can be used to stratify the risk of HCC early recurrence. Further studies are needed to assess impact of DAAs on late recurrence and mortality.

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[a]See Appendix 1.

1 | INTRODUCTION

Direct-acting antivirals (DAAs) have revolutionised the treatment of hepatitis C virus (HCV) infection, with very high rates (>90%) of sustained virological response (SVR) and good safety profile, also in the advanced stages of disease.[1] However, data on the benefit of viral eradication after DAAs on disease progression and liver-related complications in cirrhotic patients are still limited.[2, 3] In this scenario, of interest is the clinical impact of SVR on the risk of hepatocellular carcinoma (HCC) recurrence. This is a controversial topic[4-15] where evidence is limited and sometime contrasting, because these limitations are the results of different issues. First, since current DAAs are the accepted standard of care even in patients with previously treated HCC, randomised controlled trials (RCTs) comparing DAAs to placebo are unethical and unfeasible. Second, the benchmark for indirect comparisons of the benefit of HCV eradication by DAAs on HCC recurrence risk has been recently provided by a meta-analysis.[16] However this last one showed that HCC early recurrence risk in HCV-untreated patients with early (Barcelona Clinic Liver Cancer stage 0 or A—BCLC 0/A) HCC stage, who achieved complete radiological response (CRR) after curative treatment, was extremely heterogeneous ranging between 0% and 12.5% at 6th month and 4.9%-62.5% at 12th month. Moreover, study-level and patient-level variables were not able to fully explain the great deal of heterogeneity of the reported HCC early recurrence rates. Therefore, the results of published studies remain inconsistent and the overall assessment of the HCV eradication on HCC recurrence risk is difficult to evaluate. Specifically, two small retrospective observational reports[4,5] suggested that treatment with DAAs could increase the risk of HCC early recurrence in HCV-related cirrhotic patients with previously cured HCC, while other studies did not confirm this harmful effect.[6-9]

The high clinical, biological and epidemiological heterogeneity of successfully treated HCC, and several methodological weaknesses of retrospective uncontrolled studies, could explain the heterogeneity and the discrepancy among the obtained results. In fact, evaluating the risk of HCC recurrences after DAAs, it is affected by several biases, as consequence of the high variability in available data as to: (1) the design of study, retrospective or prospective, (2) inclusion criteria, (3) baseline patients and tumour characteristics, (4) type of curative HCC treatment, (5) assessment of CRR, (6) HCC recurrence definition (early or late and local or distant), (7) time frames between tumour cure and DAA therapy and between last assessment of tumour response and DAA therapy and (8) history of prior successfully treated HCC recurrences before DAA therapy.

We aimed to assess the risk of HCC early recurrence after DAA therapy in a large prospective cohort of DAA-treated HCV-cirrhotic patients with previous successfully treated early HCC, also looking for factors affecting the risk of HCC early recurrence.

2 | METHODS

RESIST HCV (Rete Sicilia Selezione Terapia HCV) is a regional network, acknowledged by the Regional Health Authority, registering all consecutive patients with chronic HCV infection assessed for DAA treatment, encompassing 22 public hospitals and academic centres throughout Sicily. Recording of all patients in the RESIST HCV database has been mandatory since availability of DAAs in Italy (February 2015) to access to treatment if Italian Medicines Agency (AIFA) criteria were fulfilled. The RESIST HCV database registers individually disease features and staging (liver biopsy, liver stiffness values measurement by transient elastometry, platelets, oesophageal gastroscopy [EGS], liver ultrasonography [US], liver function tests, baseline virological evaluation [HCV genotype, viral load, HBV and HIV co-infection], DAA regimens [drug combination, use of ribavirin, time of treatment], adverse events occurring during treatment [AEs] and treatment outcome [SVR at 12-week after treatment]). Cirrhosis diagnosis is established if at least one of the following features is present: previous liver biopsy with stage 4 fibrosis by METAVIR score, oesophageal and/or gastric varices at EGS, liver stiffness measurement higher than 12 kPa at fibroscan, platelets less than 100×10^9/L. Functional class of cirrhosis was attributed by Child-Pugh and MELD score.

In this prospective cohort study, we analysed data from all consecutive HCV-infected cirrhotic patients, who had HCC previously cured, that were treated with DAAs.

The study included all patients with HCV infection and CRR after successfully treated HCC by ablation, resection or chemoembolization and treated by DAAs between February 2015 and December 2016. Follow-up ended in March 2017.

The inclusion criteria were: (1) HCC diagnosed by pathology or by non-invasive criteria according to European Association for the Study of the Liver (EASL) guidelines,[17] (2) HCC should have been treated before DAA exposure by resection, ablation or chemoembolization, (3) CRR (ie, absence of residual tumour or complete necrosis according to EASL criteria) (4) at least one radiological assessment before starting DAAs, and (5) treatment with an Interferon-free DAA combination.

Exclusion criteria were: (1) previous liver transplantation; (2) patients with treated HCC but without radiological complete response and/or presence of "non-characterized nodules" before starting DAAs.

2.1 | Follow-up of patients successfully treated for HCC

The follow-up protocol for HCC patients who achieve CRR included clinical assessment by physical examination, laboratory evaluation, and abdominal ultrasound scan every 3 months, and multiphasic 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.[17] HCC recurrences were treated, whenever possible, according to BCLC schedule and EASL guidelines.[17]

Before starting DAA therapy, all HCV-cirrhotic patients had a dynamic CT or MR that confirm CRR according EASL criteria. During DAA treatment, all patients were followed up monthly for clinical and laboratory evaluation (blood cell count, serum chemistries, and serum AFP). US scan was performed at month 3 of DAA therapy, and at any time when considered by clinical judgement. Dynamic CT or MR was performed at month 6 of DAA therapy or when a focal lesion was detected at US.

Virological response to therapy was assessed by quantitative HCV RNA detection, using real-time PCR with a limit of detection of 15 IU/mL. SVR-12 was defined as undetectable serum HCV RNA by sensitive qualitative polymerase chain reaction assay (Amplicor HCV v2.0; Roche Diagnostics, Indianapolis, IN), with a cut-off of <50 IU/mL, 12 weeks after cessation of therapy.

2.2 | Statistical analyses

Experienced medical personnel collected data. Continuous variables were expressed as means ± SDs while categorical data were reported as counts and percentages. The Kaplan-Meier method was used to estimate time to recurrence (TTR) from the inception point (ie, beginning of DAA treatment). Log-rank testing assessed differences in TTR. Potential variables were evaluated as predictors of HCC recurrence. All baseline variables reported in Table 1 were evaluated as potential risk factors for HCC early recurrences by univariate analysis. Variables with $P \leq .10$ by univariate analyses were included in the final multivariate Cox model.

Moreover, to avoid the effect of co-linearity with the single variables, MELD, BCLC and Child-Pugh scores 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%. The R Statistical Computing Environment (R Foundation for Statistical Computing, Vienna, Austria) was used to perform analyses and plot results.

The RESIST HCV regional network was founded by an unrestricted grant of MSD, Gilead, AbbVie and Bristol-Myers Squibb. This investigator-driven study was entirely founded by the involved hospitals, and was approved by the hospital's ethics committee.

3 | RESULTS

3.1 | Baseline features of patients

Table 1 shows the baseline characteristics of included patients. All the 143 included patients had a BCLC 0/A HCC who showed CRR after resection, thermal ablation or chemoembolization. The mean age was 70.4 ± 9 years and most patients were male (86%). Eighty-six per cent of the patients were in Child-Pugh class A,

TABLE 1 Characteristics of 143 HCV patients with early HCC who achieved a complete radiological response after HCC curative treatment, at the time of starting direct anti-viral agent therapy

	n = 143
Age (y)	70.4 ± 8.9
Male sex, n (%)	86 (60.1)
INR	1.12 ± 0.26
Total bilirubin (mg/dL)	1.1 ± 0.6
Albumin (g/dL)	3.7 ± 0.5
Platelets ($\times 10^3/\mu L$)	113 ± 64
Haemoglobin (g/dL)	13.3 ± 1.9
Creatinine (mg/dL)	0.9 ± 0.2
AST (IU/L)	83 ± 52
ALT (IU/L)	81 ± 63
AFP (ng/mL)	17.7 ± 26
Genotype (%)	
1a	9 (6.3)
1b	114 (79.7)
2	9 (6.3)
3	7 (4.9)
4	4 (2.8)
HCV-RNA (log_{10}) (IU/mL)	13.3 ± 1.7
MELD score	8.6 ± 2.5
Diabetes, n (%)	46 (32.2)
BMI	25.7 ± 4.2
Naïve for prior IFN-based therapy	59 (41.3)
Child-Pugh class, n (%)	
A	123 (86)
B	20 (14)
Oesophageal varices, n (%)	
F0	59 (41)
F1	69 (48)
F2/F3	15 (10)
Number of lesions, n (%)[a]	
1	114 (79.7)
2	23 (16.1)
3	6 (4.2)
Mean tumour size (cm)[a]	2.5 ± 0.98
BCLC staging, n (%)[a]	
BCLC 0	34 (24)
BCLC A	109 (76)
First HCC treatment before DAA therapy, n (%)	
Thermal ablation	66 (46.1)
Surgical resection	52 (36.4)
TACE	25 (17.5)

(Continues)

TABLE 1 (Continued)

	n = 143
History of prior HCC recurrences before DAA therapy, n (%)	
No	101 (70.6)
Yes	42 (29.4)
Last HCC treatment in patients with history of prior HCC recurrences before DAA therapy, n (%)	
Thermal ablation	18 (42.9)
Surgical resection	6 (14.3)
TACE	18 (42.9)
Median time from end of first HCC treatment to initiation of DAA therapy, months (range)	11 (1-126)
Median time from the last complete radiological response to initiation of DAA therapy, months (range)	1.7 (0.5-5.5)
DAA treatment duration, n (%)	
12-week	55 (38)
24-week	88 (62)
DAA combination, n (%)	
Ombitasvir/Paritaprevir/Ritonavir ±Dasabuvir±Ribavirin	16 (11.2)
Sofosbuvir/Daclatasvir±Ribavirin	18 (12.6)
Sofosbuvir/Ledipasvir± Ribavirin	85 (59.4)
Sofosbuvir/Simeprevir±Ribavirin	15 (10.5)
Sofosbuvir/Ribavirin	9 (6.3)

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; n, number; INR, International Normalised Ratio; ALT, Alanine transaminase; AST, aspartate transaminase; BMI, Body mass Index; IFN, Interferon; DAA, direct-acting antivirals; TACE, transarterial chemoembolization; MELD, model for end-stage liver disease; BCLC, Barcelona clinic liver cancer.
Values are mean ± SD.
[a]Data are related to the state before treatment of HCC.

58% had oesophageal varices, and the mean MELD score was 8.3 ± 2.5.

When HCC was diagnosed and treated, they corresponded to BCLC stage 0 in 34 cases and BCLC stage A in 109 cases. Single lesion was present in the 80% of patients, two lesions in 16%, and three lesions in 4%. Thermal ablation was the most common used therapy (46%). Forty-two patients (29.4%) have a history of prior HCC recurrences before starting DAA therapy, while 101 patients (70.6%) have maintained CRR between first HCC treatment and DAA therapy.

3.2 | Follow-up

The mean length of follow-up after DAA was 9.1 months (median 8.7 months, range 3-19 months). One hundred and thirty-eight patients achieved SVR-12 (96%), while five patients experienced a virological failure.

Hepatocellular carcinoma recurred in 29/143 (20.3%) patients. At the time of HCC recurrence most of patients was at early BCLC stage (62%) or intermediate BCLC stage (21%). Only two patients (7%) were at advanced BCLC stage, while three patients (10%) were at terminal stage. During follow-up, patients with HCC recurrence showed significantly higher AFP levels compared to those without recurrence ($P = .04$). Eighty-seven per cent of the patients were in Child-Pugh class A, and the mean MELD score was 8.9 ± 3.2 (Table 2).

The pattern of recurrence was heterogeneous: Twenty-eight patients developed intrahepatic growth; 24 patients had a nodular profile, while five patients (one of them with macro-vascular invasion) developed infiltrative HCC. None patient developed extrahepatic metastases. Treatment modalities of HCC recurrences are shown in Table 2. Most of the patients who had HCC recurrence underwent TACE (45%).

The 6-, 12- and 18-month HCC recurrence rates in the whole cohort were 12%, 26.6% and 29.1% respectively. The 6-, 12- and 18-month HCC recurrence rates in patients without prior history of HCC recurrences and in those with prior history of HCC recurrences were 9.2%, 20.9% and 24.2% and 18.5%, 39.7% and 39.7% respectively (Table 2 and Figure 1).

We did not find any significant difference ($P = .507$) of TTR between the subgroup of 101 successfully treated HCC patients, without prior history of HCC recurrence subsequently exposed to DAA, and 701 HCV-cirrhotic patients untreated for HCV pooled by meta-analysis,[16] with successfully treated HCC without prior history of HCC recurrence (Figure 2).

Similar results were observed when the 18-month HCC recurrence rate of 101 successfully treated HCC patients, without prior history of HCC recurrence, subsequently exposed to DAA, where compared to 226 HCV-cirrhotic patients with successfully treated HCC, without prior history of HCC recurrence, subsequently treated by IFN-based therapy, recalculated from the previous published meta-analysis by Singal et al[18] (Figure S1) ($P = .814$).

3.3 | Predictors of HCC recurrences

Table 3 shows predictors of HCC recurrence by univariate analysis. No significant differences were observed when patients were stratified according to baseline Child-Pugh class (class A, n = 123 patients; class B, n = 20 patients; $P = .153$) (Figure S2) and MELD score (≤8, n = 50 patients; >8, n = 93 patients; $P = .083$) (Figure S2). Main tumour size (HR 2.73; 95% CI 1.23-6.06; $P < .014$) and history of prior HCC recurrence (HR 2.22; 95% CI 1.02-4.83; $P = .043$) were independent predictors of HCC recurrence by multivariate Cox model (Table 3).

The discriminating ability of the model in predicting HCC recurrence was evaluated by time-dependent ROC curve values at 12 months (AUROC = 0.758) (Figure 3).

The estimated probability of HCC recurrence in the four hypothetical patients according to factors significantly predicting HCC recurrence by the Cox model (ie, tumour size and history of prior HCC recurrences) are shown in Figure 4. For a patient with the most favourable covariates (the best class, ie, tumour size <2.5 cm and without history of prior HCC recurrences), the 6-, 12-, and 18-month recurrence rates were 6.3%, 17% and 19.6% respectively. For a

TABLE 2 Follow-up of 143 HCV patients with successfully treated HCC, subsequently exposed to DAAs

	n = 143
Follow-up, range (mo)	8.7, 3-19
AFP, mean ± SD (ng/mL)	
Whole cohort (n=143)	17.9 ± 59.3
Patients with HCC recurrences (n=29)[a]	52.4 ± 124.8
Patients without HCC recurrences (n=114)[b]	9.1 ± 13.4
MELD score at the end of follow-up, mean ± SD	8.9 ± 3.2
Child-Pugh class at the end of follow up, n (%)	
A	125 (87.4)
B	18 (12.6)
Recurrence during follow-up, n (%)	29 (20.3)
During DAA therapy	13 (9.1)
After DAA therapy	16 (11.2)
Recurrence rate of the whole cohort (95%CI)[c]	
6-month	12 (6.1-17.6)
12-month	26.6 (17.2-34.9)
18-month	29.1 (18.6-38.3)
Recurrence rate of 101 patients naïve for HCC recurrences (95% CI)[c]	
6-month	9.2 (2.9-15.1)
12-month	20.9 (10.4-30.2)
18-month	24.2 (11.9-34.7)
Recurrence rate of 42 patients with prior history of HCC recurrences (95% CI)[c]	
6-month	18.5 (5.1-29.9)
12-month	39.7 (19.5-54.8)
18-month	39.7 (19.5-54.8)
Stage of HCC recurrences, n (%)	
BCLC A	18 (62)
BCLC B	6 (21)
BCLC C	2 (7)
BCLC D	3 (10)
Treatment of recurrences, n (%)	
Resection	2 (7)
Thermal ablation	9 (31)
TACE	13 (45)
Sorafenib	2 (7)
Supportive care	3 (10)
Deaths, n (%)	6 (4.2)
Cause of death, n (%)	
Liver failure	5 (83)
Lung neoplasm	1 (17)

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; DAAs, direct-acting antivirals; BCLC, Barcelona Clinic Liver Cancer; TACE, Transarterial chemoembolization.
[a]AFP levels at the time of HCC recurrence.
[b]AFP levels at the end of the follow-up.
[c]According Kaplan-Meier analysis.

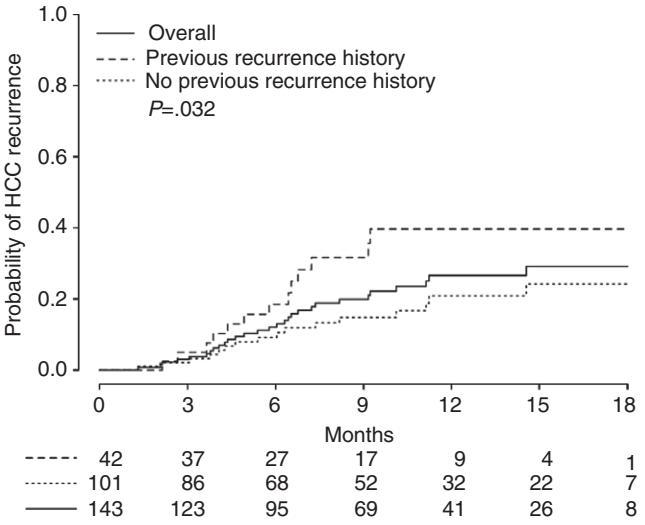

FIGURE 1 Time to HCC recurrence in the whole cohort of 143 HCV patients with early HCC who achieved a complete radiological response after HCC curative treatment, at the time of starting direct anti-viral agent therapy, and stratified according to history of prior HCC recurrences before DAA therapy

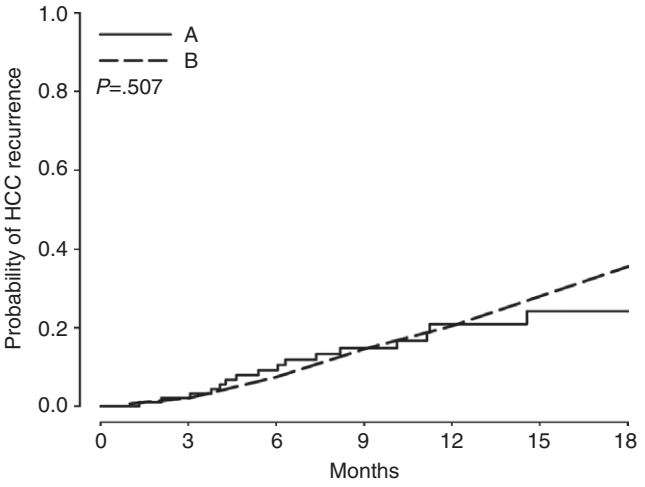

FIGURE 2 Time to recurrence in HCV-cirrhotic patients, with successfully treated HCC without prior history of HCC recurrence: A, 101 patients subsequently treated with DAA; B, 701 patients untreated for HCV[16]

patient with tumour size >2.5 cm and history of prior HCC recurrences (the worst class) the 6-, 12- and 18-month recurrence rates were 32.7%, 67.6% and 73.3% respectively (Figure 4).

4 | DISCUSSION

In this large prospective study, we found that 6-month and 1-year probability of HCC early recurrence after DAA therapy were 12% and 26.6% respectively. Previous history of HCC recurrence and tumour size were the only two independent risk factors for HCC early recurrence.

TABLE 3 Factors associated with HCC recurrence in 143 HCV patients with early HCC who achieved a complete radiological response after HCC curative treatment, subsequently exposed to DAAs

	Univariable model			Multivariable model		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Male sex	0.50	0.24-1.03	.062	0.5	0.24-1.10	.086
Age (y)	0.99	0.95-1.02	.436			
BMI	0.93	0.84-1.04	.215			
IFN-therapy naive	1.33	0.65-2.78	.441			
Oesophageal varices	1.83	0.77-4.36	.170			
Ascites	1.01	0.30-3.33	.992			
Viremia	1.00	1.00-1.00	.224			
AST	1.00	0.99-1.01	.821			
ALT	1.00	0.99-1.01	.867			
Alpha-fetoprotein	0.99	0.97-1.01	.494			
HB	0.99	0.83-1.20	.942			
INR	3.95	1.48-10.52	.006	2.6	0.2-36.3	.478
Albumin	0.74	0.35-1.60	.450			
Creatinine	2.65	0.51-13.71	.247			
Total bilirubin	1.47	0.94-2.31	.091	1.32	0.69-2.53	.402
Platelets	1.00	1.00-1.00	.269			
Glucose	0.99	0.97-1.01	.176			
Diabetes	0.82	0.36-1.85	.633			
Treatment (baseline: hepatic resection)						
Thermal ablation	1.12	0.45-2.78	.808			
TACE	1.75	0.69-4.43	.239			
Genotype $\neq$ 1b	0.39	0.12-1.31	.128			
24-week treatment	0.63	0.30-1.32	.222			
SVR	0.74	0.25-2.17	.578			
Time from complete response to DAA	0.99	0.97-1.01	.169			
Number of lesions	1.12	0.61-2.09	.708			
Main tumour size >2.5 cm	2.530	1.18-5.41	.017	2.73	1.23-6.06	.014
History of prior recurrence	2.19	1.05-4.58	.036	2.22	1.02-4.83	.043

HCV, hepatitis C virus, HCC, hepatocellular carcinoma; DAAs, direct-acting antivirals; INR, international normalised ratio; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; IFN, interferon; TACE, transarterial chemoembolization.

Several retrospective and prospective studies reported conflicting results about HCC recurrence rates after DAA therapy,[4-15] sometimes also raising doubts about an increase in HCC recurrence risk.[4,5]

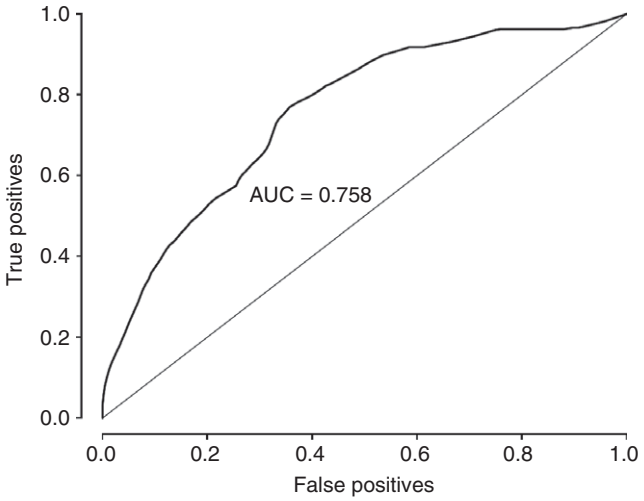

FIGURE 3 Receiver operating characteristic (ROC) curve and area under the ROC curve for predictors of HCC recurrence by Cox regression model (main tumour size >2.5 cm and history of prior HCC recurrences) at 12 months

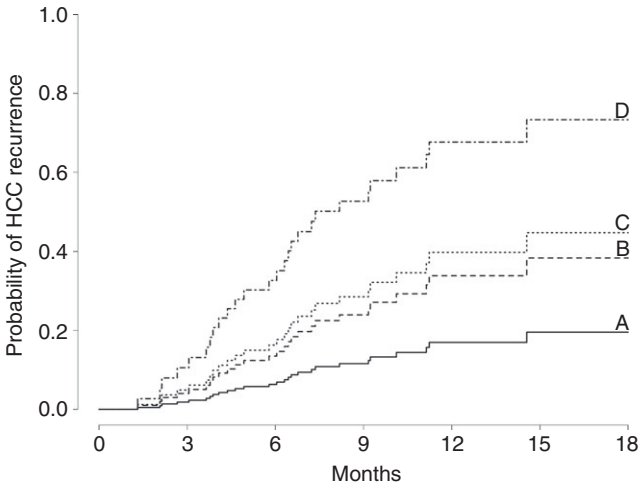

FIGURE 4 Estimated probability of HCC recurrences for 4 hypothetical HCV patients with early HCC who achieved a complete radiological response after HCC curative treatment after start DAA, according to factors significantly predicting mortality by the Cox model. A, Patient with tumour size <2.5 cm and without history of prior HCC recurrences; B, patient with tumour size <2.5 cm and with history of prior HCC recurrences; C, patient with tumour size >2.5 cm and without history of prior HCC recurrences; D, patient with tumour size >2.5 cm and history of prior HCC recurrences

This inconsistency among studies is not surprising when we take into account all potential biases among studies with different design, sample size, inclusion and diagnostic criteria, definition of HCC early recurrence, methods and timing of imaging follow-up, type of curative HCC treatment, time lag between tumour cure and start of DAA therapy, and between last assessment of tumour response and start of DAA therapy. The only large prospective study by Pol et al—similar to our results—did not show an increased risk of HCC recurrence during/after DAAs, using a "pseudo survival curve" rather than

Kaplan-Meier method.[6] Therefore, for the first time to the best of our knowledge, our study assessed HCC early recurrence after DAAs in a large prospective cohort, by actuarial method.

In this complex scenario, the HCC early recurrence rate observed in this study was comparable—and not increased—to that estimated both by meta-analyses, in 701 patients untreated for HCV,[16] and in 226 patients treated with IFN-based therapy (Figure S1). Our study also showed that 17% of the HCC recurrences had an infiltrative pattern, like data by Reig et al.[4] Furthermore, long-term prospective studies are necessary to better substantiate the benefit of SVR on liver decompensation and death. Consistently, we recently demonstrated that hepatic decompensation, not HCC early recurrence, is the major driver of death in patients untreated for HCV with successfully treated HCC.[19]

The association between tumour size and HCC early recurrence, observed in our study confirms previous observations from individual studies[20,21] and meta-analysis.[16] Moreover, it is biologically plausible that the risk of cancer recurrence is higher in patients who already experienced recurrence reflecting a higher biological aggressiveness of the tumour. In patients without previous history of HCC recurrence and tumour size <2.5 cm (best class) the 6-month risk of HCC recurrence is 6.3%, while those with previous history of HCC recurrence and tumour size >2.5 cm (worst class) the risk is 32.7%. Modelling timing of imaging after HCV eradication by DAAs according to these predictors may improve follow-up efficiency.

This study has some limitations. Although the number of included patients is large, suggesting robustness of the estimated recurrence rates, the follow-up is short with relatively small number of events. Therefore, the CIs of 6-month (95% CI, 6.1%-17.6%) and 1-year (95% CI, 17.2%-34.9%) HCC early recurrence rates remain wide. Another limitation is the indirect comparison between DAA exposed and unexposed patients. In fact, indirect comparison among DAA treated, IFN-based treated, and HCV untreated patients should be discouraged because the high variability in HCC early recurrence could be entirely related to different baseline risks of included patients, design and methodological quality of the studies. Unfortunately, RCTs comparing DAA treated vs untreated controls are unfeasible. Finally, although the discriminating ability of our model, as assessed by AUROC, was fair good, a level of accuracy sufficient to predict HCC early recurrence at individual patient level could not be reached. Lack of data on other potential risk factors, such as microscopic vascular invasion, histological grading and gene profiling,[22,23] also could affect the accuracy of the results.

In conclusion, our results obtained in patients with successfully treated HCV-related liver cancer underwent DAA-based anti-viral therapy, finally demonstrated that: (1) the risk of HCC early recurrence was comparable and not higher than that observed in DAA unexposed patients; (2) previous HCC recurrence and tumour size can be used to stratify the risk of HCC early recurrence, and the efficiency of imaging follow-up. HCC early recurrence rate remains high despite the achievement of SVR, highlighting the need for adjuvant therapy for preventing HCC recurrence. Long-term large prospective studies, aimed to prove the benefit of DAAs on survival are needed.

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Declaration of personal interests: None.

AUTHORSHIP

Guarantor of the article: Giuseppe Cabibbo.

Author's contribution: 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.

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

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APPENDIX 1

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APPENDIX 2

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