Research Article

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Hepatic decompensation is the major driver of death in HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma

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Background & Aims: Assessment of long-term outcome is required in hepatitis C virus (HCV)-infected patients with cirrhosis, who have been successfully treated for Barcelona Clinic Liver Cancer (BCLC) stage A hepatocellular carcinoma (HCC). However, problems arise due to the lack of models accounting for early changes during follow-up. The aim of this study was to estimate the impact of early events (HCC recurrence or hepatic decompensation within 12 months of complete radiological response) on 5-year overall survival (OS) in a large cohort of patients with HCV and cirrhosis, successfully treated HCC.

Methods: A total of 328 consecutive Caucasian patients with HCV-related cirrhosis and BCLC stage 0/A HCC who had complete radiological response after curative resection or thermal ablation were prospectively recruited to this study. Primary endpoint of the study was 5-year OS. Independent baseline and time-dependent predictors of 5-year OS were identified by Cox model.

Results: The observed 5-year survival rate was 44%. The observed HCC early recurrence and early hepatic decompensation rate were 21% and 10%, respectively. Early hepatic decompensation (Hazard Ratio [HR] 7.52; 95% confidence intervals (CI): 1.23–13.48) and HCC early recurrence as time-dependent covariates (HR 2.50; 95%CI: 1.23–5.05), presence of esophageal varices at baseline (HR 1.66; 95% CI: 1.02–2.70) and age (HR 1.04; 95% CI: 1.02–1.07) were significantly associated with the 5-year OS.

Conclusion: Survival in HCV-infected patients with cirrhosis and successfully treated HCC is influenced by early hepatic decompensation. Our study indirectly suggests that direct-acting antiviral agents could improve OS of HCC patients through long-term preservation of liver function, resulting in a lower cirrhosis-related mortality and a greater change of receiving curative treatments.

Keywords: Hepatocellular carcinoma (HCC); Hepatitis C; Hepatic decompensation; Recurrences; Sustained virological response; Overall survival; Prognosis; Survival rate; Antiviral agents; Liver cirrhosis; Carcinoma, hepatocellular.

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Lay summary: Survival in hepatitis C virus (HCV) infected patients with cirrhosis and successfully treated hepatocellular carcinoma (HCC), is mainly influenced by early hepatic decompensation. HCV eradication after treatment with new direct-acting antiviral agents could improve overall survival of HCC patients through long-term preservation of liver function.

Introduction

The prognosis of patients with cirrhosis due to hepatitis C virus (HCV) is decided by the progression towards hepatic decompensation and hepatocellular carcinoma (HCC), the latter being the leading cause of mortality in patients with compensated cirrhosis.[1,2] Patients with cirrhosis due to HCV should be monitored for HCC regardless of HCV clearance. This would allow diagnosis of potentially curative early stage disease (Barcelona Clinic Liver Cancer [BCLC] stage 0 or A) using treatments, such as liver transplantation or, in most cases surgical resection or local ablation.[3–5]

Our group recently carried out a meta-analysis on the available data. It showed that despite the availability of potentially curative treatments, pooled estimates of the 2-year recurrence and 5-year survival rates in HCV cirrhotic patients with a BCLC A HCC cured with resection or ablation were both about 50%.[6] This figure underlines the urgent need for an effective adjuvant therapy for these patients. However, adjuvant strategies targeting HCC, such as the use of sorafenib, have failed to show a significant treatment effect on HCC recurrence and overall survival (OS).[7,8] Conversely, we recently provided evidence that sustained virological response (SVR) achieved by both IFN or direct-acting antiviral agents (DAAs) significantly reduced HCC recurrence in HCV-infected patients successfully treated for early HCC.[9] However, there are conflicting results for DAAs in this treatment context,[10–15] and therefore further evidence from prospective studies is needed.

Prognosis in patients with HCV and successfully treated BCLC stage A HCC results from a balance between two parameters: HCC recurrence and hepatic decompensation. However, there have been no studies to evaluate the different weight of these two time-dependent events on long-term survival. In successfully treated BCLC stage A HCC located in a cirrhotic liver, the clinical situation may change early after treatment, which is consistent with most other chronic diseases. Conceivably, the relative weight of prognostic predictors may change in the early phase of the disease, and estimates of prognosis should account for time-dependent changes.

The knowledge of the relative prognostic impact of HCC early recurrence and early hepatic decompensation may also assist in foreseeing the real prognostic outcome of DAAs in these patients. Based on the evidence obtained with interferon-based[1,2,16] and interferon-free[2,16–18] regimens, it can be assumed that SVR reduces the risk of decompensation/progression of HCV-related cirrhosis. The effect of DAAs on the risk of HCC recurrence, however, is currently a matter of debate.[10–14]

In this study, a survival analysis was performed using a time-dependent Cox model[19] and aimed to estimate the impact of early events (HCC recurrence or hepatic decompensation within 12 months of complete radiological response) on 5-year overall survival (OS) in a large cohort of patients with HCV and cirrhosis, successfully treated HCC.

Patients and methods

Patients

The Italian Liver Cancer (ITA.LI.CA) database currently contains data from 6,595 HCC patients consecutively diagnosed from 1987 to 2015 at 24 Italian medical institutions. Since 2007, the ITA.LI.CA database includes follow-up clinical and imaging data that were collected prospectively and updated every 2 years. After data collection and before statistical evaluation, the group coordinator (F.T.) examined the consistency of data sets. If clarifications or additional information were needed, the data were resubmitted to the relevant centre.

The presence of cirrhosis was assessed according to histological findings or clinical evidence, and liver function was evaluated using Child-Pugh[20] and model for end-stage liver disease (MELD) scores.[21] The presence of esophageal varices was assessed by upper-digestive endoscopy and were classified as absent, small, medium, or large.[22]

The diagnosis of HCC was made by ultrasound-guided biopsy or by non-invasive criteria according to the guidelines published at the time of patient inclusion. Performance status (PS) was scored as per the Eastern Cooperative Oncology Group.[23] HCC staging was assessed according to both the Milan criteria[24] and BCLC classification, and treatments were performed according to the BCLC schedule[3,5] unless the individual centre care providers chose different patient-tailored therapeutic options.[25] Patients with early tumors (BCLC stage A) were considered for resection, orthotopic liver transplantation (OLT), or ablation. Hepatic resection was not precluded for BCLC A patients with clinically significant portal hypertension (CSPH; defined as either splenomegaly, varices, or platelet count <100,000/ml but without ascites), because surgery may be proposed in strictly selected cases based on multidisciplinary evaluation of the patient.[25] TACE was performed in patients with intermediate stage (BCLC B) tumors (provided that radical therapies were not possible).[26] Starting July 2008, compensated patients with advanced HCC (BCLC C) and patients with an intermediate HCC who were not eligible for, or failed locoregional therapies were treated with sorafenib.

This retrospective study of prospectively collected data, included all no-SVR patients with HCV-related compensated cirrhosis and early HCC who achieved complete radiological response after curative treatment, consecutively observed since 2007.

Due to the poor efficacy and safety of pegylated interferon and ribavirin therapy (PegIFN + RBV) in patients with cirrhosis, only 142/371 patients underwent PegIFN + RBV before the diagnosis of HCC. Patients who achieved SVR (43/142) were not included in the study. The patient selection process is illustrated in Fig. 1.

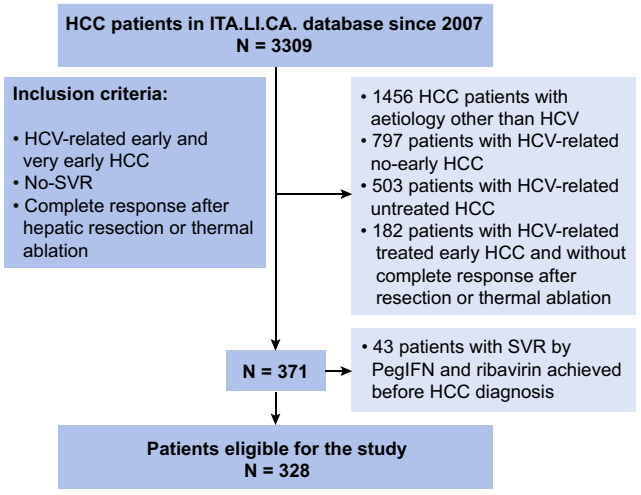

Fig. 1. Flow diagram of patient selection.

Complete radiological response was based on validated imaging criteria using multiphasic, contrast-enhanced computed tomography (CT) or magnetic resonance (MR) of the abdomen approximately 1 month after tumor resection or the last locoregional treatment (thermal ablation). Blood cell counts, serum chemistry, and serum α-fetoprotein (AFP) levels were measured by standard laboratory procedures. HCV markers were tested using commercial kits.

Outcomes

The primary endpoint of the study was the overall survival (OS), defined as the time from inclusion in the study (time of the first complete radiological response after resection or thermal ablation) to death (by any cause), OLT, or last visit. This study investigates the association between OS and two early events (HCC recurrence or hepatic decompensation within 1 year after complete radiological response) included as time-dependent first event variables, using time-dependent Cox model.

Follow-up

After the documented complete radiological response to the curative treatment of HCC, all patients were followed in dedicated outpatient clinics. The follow-up protocol included clinical assessment by physical examination, abdominal ultrasound scan, biochemistry every 3 months, and multiphasic CT or MRI every 6 months. HCC recurrence was diagnosed based on combined abnormal findings on ultrasonography and on one additional dynamic imaging technique confirming hypervascularisation in the arterial phase with washout in the portal venous or late venous phase. All ITA.LI.CA centres had high-quality and updated radiological facilities. Recurrences were defined as 'early' if they occurred within 1 year of complete radiological response, and 'late' if they occurred after 1 year. HCC recurrences were also classified as local or distant. 'Local' recurrence was defined as the development of tumor staining at the margin of the tumor or enlargement of the tumor on a follow-up spiral CT or MR. 'Distant' recurrence was defined as the appearance of another HCC distinct from the treated one.[27]

HCC recurrences were treated, whenever possible, as the naïve tumor (see above).

Hepatic decompensation was defined as the occurrence of portal hypertensive bleeding, hepatic encephalopathy, ascites, jaundice, or an increase in Child-Pugh score of at least two points with respect to baseline value.

Statistical analyses

Experienced medical personnel collected data. Continuous variables were expressed as means with standard deviations while categorical data were reported as counts and percentages. The Kaplan-Meier method was used to estimate time to recurrence, time to liver decompensation, and OS. Log-rank testing was used to assess the differences in survival. Potential prognostic variables were evaluated as predictors of OS. All baseline variables in Table 1 were evaluated by univariate analyses. Baseline variables with p values ≤ 0.10 in the univariate analyses were included in the final multivariate model. If early HCC recurrence or early hepatic decompensation were the first event to occur within one year after complete radiological response, they were included as time-dependent covariates in Cox regression.[18] 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 values ≤ 0.05 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.

Ethics

Management of the ITA.LI.CA database conforms to all Italian laws on privacy and 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

Table 1 shows the baseline characteristics of included patients. All the 328 patients included had a HCV-related BCLC A HCC and showed complete radiological response after curative resection or thermal ablation. The mean age was 69 ± 9.9 years and most patients were male (66%). The mean MELD score was 8.6 ± 2.3. Prevalence of esophageal varices was 38%. A single lesion was present in 86% of patients, two lesions in 12%, and three lesions in 3%. Thermal ablation was the most commonly used therapy (73%). Distribution of esophageal varices according to HCC treatment is shown in Table S1. When splitting patients according to the type of HCC treatment they received, those who underwent resection were significantly younger than those who underwent thermal ablation (64 *vs.* 71 years, p <0.001), had a lower MELD score (8.1 *vs.* 8.7, p = 0.03) and a lower prevalence of esophageal varices (25% *vs.* 43%, p = 0.002).

Table 1. Baseline characteristics of 328 HCV patients with early HCC who achieved a complete radiological response after curative treatment.

Patient characteristic	(n = 328)
Age (years)	69.4, 9.9
Male sex, n (%)	217 (66)
INR	1.12, 0.14
Total bilirubin (mg/dl)	1.0, 0.5
Albumin (g/dl)	3.7, 0.5
Platelets ($\times 10^3/\mu l$)	123, 53
Creatinine (mg/dl)	0.9, 0.5
MELD score	8.6, 2.3
Child-Pugh class, n (%)	
A	307 (94)
B	21 (6)
Esophageal varices, n (%)	
F0	204 (62)
F1	85 (26)
F2/F3	39 (12)
Performance status 0, n (%)	328 (100)
AFP, median [range] (ng/ml)*	22.9 [1–432]
Number of lesions, n (%)*	
1	281 (86)
2	38 (12)
3	9 (3)
Mean tumour size (cm)*	2.2, 0.8
BCLC staging, n (%)	
BCLC 0	12 (4)
BCLC A	316 (96)
Treatment, n (%)	
Thermal ablation	240 (73)
Surgical resection	88 (27)

Values are mean, SD.
HCV, hepatitis C virus; HCC, hepatocellular carcinoma; n, number; INR, international normalised ratio; MELD, model for end-stage liver disease; AFP, alpha fetoprotein.
* Data are related to the state before treatment of HCC.

Follow-up

The mean length of follow-up after complete radiological response was 32 months (median 27 months, range 3–95 months).

During the follow-up, HCC recurred in 142/328 (43.3%) patients, and most were late recurrences (79/142). The 1-, 3-, and 5-year recurrence rates were 21%, 55%, and 64% respectively (Table 2; Fig. S1). Local recurrences were significantly more frequent within the early time period (41%) compared to late (24%), while distant recurrences were more frequent within the late time period (76%) compared to early (59%; p = 0.028; Table S2). Treatment modalities of HCC recurrences are shown in Table 2. The majority of the patients underwent a second

Table 2. Follow-up of 328 patients HCV patients with early HCC who achieved a complete radiological response after curative treatment.

Follow-up parameter	(n = 328)
Recurrence during follow-up – no. (%)	142 (43)
Early (before 12 months)	63 (19)
Late (after 12 months)	79 (81)
Recurrence rates*	
1-year	21%
2-year	41%
3-year	55%
4-year	61%
5-year	64%
Treatment of recurrences – no. (%)	111 (78)
Resection	5 (3.5)
Thermal ablation	61 (43)
TACE	41 (28.3)
OLT	1 (0.7)
Sorafenib	3 (2)
Decompensation during follow-up – no. (%)	81 (25)
Decompensation rates*	
1-year	10%
2-year	21%
3-year	30%
4-year	36%
5-year	44%
Survival rates*	
1-year	97%
2-year	89%
3-year	79%
4-year	73%
5-year	63%
Deaths, no (%)	66 (20)
Cause of death – no. (%)	
Tumour progression	21 (32)
Liver failure	45 (68)

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; TACE, Transarterial chemoembolization; mo, months.
* According to Kaplan-Meier analysis.

course of thermal ablation (43%). HCC recurrence rates according to the treatment modality are show in Fig. S2 and in Table S3.

During the follow-up, 81/328 (25%) patients experienced hepatic decompensation. The 1-, 3-, and 5-year rates of hepatic decompensation are shown in Table 2 and Fig. S3. Decompensation rates according the treatment modality are show in Fig. S4 and in Table S4.

During the follow-up, 66/328 (20%) patients died. Survival rates at 1-, 3-, and 5-years are shown in Table 2 and Fig. S5.

First early events occurring within 12 months after complete radiological response

During the 1-year of follow-up 43/328 (13%) patients had an early HCC recurrence as a first event, while 31/328 (9.4%) had an early hepatic decompensation as a first event. The remaining 8% of HCC recurrences observed in the first year, occurred in patients who had previously developed an early hepatic decompensation. Two hundred fifty-four patients (77.4%) did not experience either early HCC recurrence or early hepatic decompensation during the first year of follow-up. Fig. 2 shows the long-term survival probability, stratified by the presence and type of the first early event.

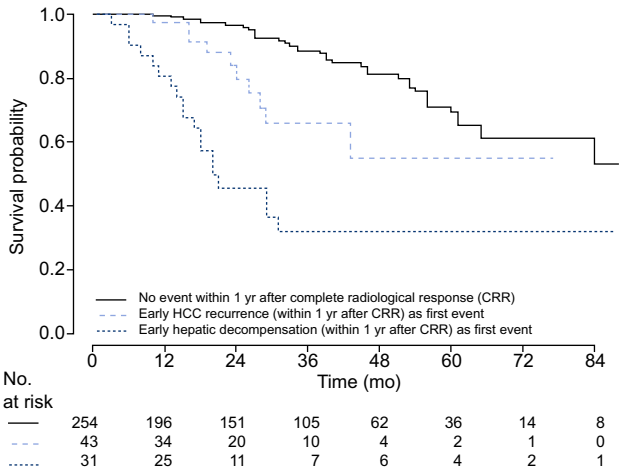

Fig. 2. Overall survival in 328 HCV patients with early HCC who achieved complete radiological response after curative treatment. Data is stratified according to first early event (within 1 year of follow-up).

Predictors of overall survival

Table 3 shows predictors of OS from the univariate analysis. The time-dependent Cox regression analysis showed that early hepatic decompensation (HR 7.52; 95% CI: 1.23–13.48; p <0.0001) and early HCC recurrence (HR 2.50; 95% CI: 1.23–5.05; p = 0.0110) were independent predictors of overall mortality, as well as age (HR 1.04; 95% CI: 1.02–1.07; p = 0.0013) and the presence of esophageal varices at baseline (HR 1.66; 95% CI: 1.02–2.70; p = 0.0427) (Table 3). Multivariate analysis accounting for site of recurrence as a first event was performed, and showed that early distant (but not early local) HCC recurrence was an independent predictor of mortality (Table S5).

Multivariate analyses performed on the subsets of patients treated with hepatic resection (Hazard Ratio [HR] 9.0; 95% CI: 2.4–33.9; p = 0.0011) or thermal ablation (HR 8.9; 95% CI: 4.6–17.5; p <0.0001) confirmed first event early hepatic decompensation as a significant predictor of mortality in both groups.

The estimated probabilities of 5-year mortality for hypothetical patients according to the factors that significantly predict mortality (*i.e.* early hepatic decompensation and early HCC recurrence as first event, and esophageal varices at baseline) are shown in Fig. 3. In the subgroup of patients with the most favourable covariates (the best class, *i.e.* no events within 1-year follow-up after complete radiological response and without esophageal varices at baseline), the 5-year mortality was 22%. For a patient with early hepatic decompensation as the first event and esophageal varices at baseline (the worst class) the 5-year mortality was 96%.

Discussion

This study included a large cohort of HCV-related BCLC A HCC patients with cirrhosis, who achieved complete radiological response after curative resection or thermal ablation, and prospectively assessed OS by a time-dependent multivariate Cox model. To the best of our knowledge, the model shows for the first time that the main risk factor for death during the follow-up was a hepatic decompensation as the first event within the first year of follow-up. In fact, it increased the risk for mortality of about 7.5

Table 3. Factors associated with 5-year mortality in 328 patients HCV patients with early HCC who achieved a complete radiological response after curative treatment.

	Univariable model			Multivariable model		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (years)*	1.02	0.99–1.05	0.077	1.04	1.02– 1.07	0.0013
Male sex, n (%)	0.95	0.57–1.57	0.831			
Albumin (g/dl)	0.61	0.39–0.99	0.046	0.90	0.49–1.63	0.719
INR	1.33	0.32–5.52	0.692			
Total bilirubin (mg/dl)	1.78	1.13–2.79	0.012	0.99	0.59–1.65	0.96
Platelets ($\times 10^3/\mu l$)	0.994	0.989–0.999	0.026	0.996	0.991–1.002	0.231
Creatinine (mg/dl)	0.92	0.51–1.64	0.769			
Esophageal varices	1.55	0.95–2.51	0.077	1.66	1.02–2.45	0.0427
Log (AFP) (ng/ml)	1.09	0.91–1.31	0.343			
More than 1 lesion	1.15	0.58–2.26	0.685			
Tumour size (cm)	1.07	0.80–1.45	0.626			
Type of HCC treatment°	0.64	0.35–1.18	0.150			
First event within 12 mo**						
First early recurrence	2.54	1.26–5.15	0.001	2.50	1.23–5.06	0.0110
First early decompensation	6.00	3.44–10.47	<0.001	7.52	4.19–13.48	<0.0001

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HR, Hazard Ratio; CI, Confidence Interval.
* Quantitative variable.
° Hepatic resection *vs.* thermal ablation.
** Included as time-dependent variable.

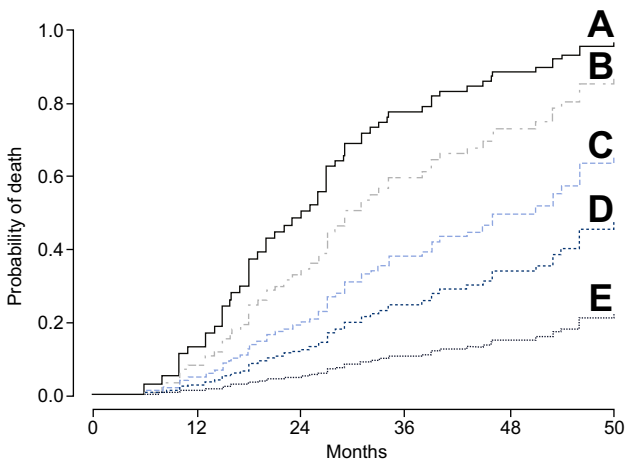

Fig. 3. Estimated probability of 5-year mortality for five hypothetical HCV patients with early HCC who achieved complete radiological response after curative treatment, according to predictors of mortality identified by the time-dependent Cox model. (A) Patient with early hepatic decompensation as first event and esophageal varices at baseline. (B) Patient with early hepatic decompensation as first event without esophageal varices at baseline. (C) Patient with early HCC recurrence as first event and esophageal varices at baseline. (D) Patient with early HCC recurrence as first event without esophageal varices at baseline. (E) Patient without early event and without esophageal varices at baseline.

times, a figure much higher than that obtained when early HCC recurrence was the first event (about 2.5 times).

Age and esophageal varices at baseline were additional independent predictors of OS and could refine the prognosis in these patients. This confirms the clinical utility of knowing whether esophageal varices are present. This study clearly shows that the key prognostic factors of successfully cured HCV-related BCLC A HCC change over time, and that two easily obtainable baseline characteristics and two time-dependent early predictors can be combined into a model that accurately estimates the long-term mortality of patients.

This result indicates that a time-dependent model, accounting for early changes during the course of the disease, is able to adequately express the complexity of interactions between tumor factors and degree of liver failure during follow-up.

In the subgroup of patients with the most favourable covariates (the best class, *i.e.* no event within first year of follow-up and without esophageal varices at baseline), the probability of 5-year death was 22%. Contrastingly, in patients with early hepatic decompensation as first event and the coexistence of esophageal varices at baseline (the worst class), the prognosis was very poor.

Despite many efforts to disentangle HCC recurrences caused by pre-treatment tumor cell dissemination from a second primary tumor, classification of recurrences still relies on disputed chronological criteria. In fact, there is no widely accepted definition of early and late HCC recurrences after curative treatment.[15,28–32]

Conventionally, early HCC recurrences are classified as tumor metastases of the primary tumor reflecting: a) incomplete ablation/resection, b) cell dedifferentiation and, c) microscopic vascular invasion. Conversely, later HCC recurrences fall into the domain of second tumors, related to the field cirrhosis risk and driven by the degree of liver cell inflammation and proliferation; therefore, they represent a potentially preventable event by antiviral therapy. In the absence of histological and molecular characterization of recurrences, this distinction appears very fragile.[15,28–32]

In this study, a time span of 1-year was adopted to define early and late events. According to the model, early distant HCC recurrence, but not early local recurrence, was significantly associated with mortality. This indicates that patients with early distant HCC recurrences have an underlying multifocal and more aggressive tumor than their counterparts, where early local HCC recurrences could be principally related to treatment failure.

It was also demonstrated that early HCC recurrence and early hepatic decompensation of underlying HCV-related cirrhosis are frequent events after curative resection or thermal ablation in HCV patients (21% and 10% at 1 year, respectively). Although

adjuvant therapy in HCC still represents an unmet medical need, current guidelines for HCC management do not endorse any adjuvant approach. A recent randomized controlled trial testing sorafenib as an adjuvant treatment after curative resection or thermal ablation, failed to show a benefit on recurrence-free and OS rates with respect to placebo.[7] Another way to control HCC recurrence could be to eliminate the boosting effect of HCV-induced inflammation on cancer initiation and progression.[33] Although, a number of studies have tried to assess the impact of DAA regimens on HCC recurrence, the results remain conflicting.[15] Two recent reports would indicate an unexpected increased risk of early HCC recurrence,[10,11] while others do not confirm this finding.[9,12–14] Within this debate, a large recent multicentre prospective study has shown that OS of Milan in HCC patients who underwent curative treatment was significantly improved in SVR patients compared to non-SVR.[2] Interestingly, the causes of death differed according to SVR: all SVR patients died from HCC progression, while patients without SVR mainly died from complications of liver failure. This result would suggest that the currently unproven effect of DAA treatment on the risk of HCC early recurrence could be overcome by the proven benefit on hepatic decompensation, leading to a longer survival. Conclusive evidence is needed.

Consistent with results from Nahon *et al.*[2], this study showed indirect evidence that, in HCV patients with early stage HCC who achieved a complete radiological response after curative treatment, HCV eradication can have an important role in the short- and long-term preservation of liver function, resulting in a lower cirrhosis-related mortality and in an increased chance of receiving curative treatments if HCC recurs. Moreover, the cure of the infection may curb the risk of late recurrences that are probably driven by the severity of underlying disease.

Finally, it can be speculated that a benefit of viral eradication also may be observed in intermediate and advanced stage of HCC patients, in whom anti-tumor treatments are often precluded due to the functional impairment of cirrhosis.

The retrospective nature of this study did not permit the exclusion of unintended biases, it also relied on the generalizability of its results. In addition, the cohort of analyzed Italian patients with early HCC ensuing in HCV-related and well-compensated cirrhosis, enrolled in expert centres, represented a combination of conditions not always present in real-world clinical practice.

In conclusion, this study suggests that, in HCV patients who undergo curative resection or thermal ablation of BCLC A HCC:

Early hepatic decompensation and early HCC recurrence, are both important risk factors for death, but the adverse impact of early decompensation is much more prominent.

Baseline esophageal varices further and independently increase 5-year mortality, indicating that their presence should be systematically considered for assessing prognosis.

This scenario would predict an important protective effect of DAA treatments that could prevent the progression of cirrhosis in most compensated patients. Nevertheless, prospective, large-scale, field-practice studies are needed to definitively prove the benefit of DAAs on survival of patients with HCV-related BCLC A HCC undergoing successful surgical resection or ablation.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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

Authors' contributions

G. Cabibbo, S. Petta, M. Barbara, S. Attardo and C. Cammà planned the study design, performed analyses and drafted the article. L. Bucci checked the data quality of the database. All the authors had full control of the study design, data analysis and interpretation, and preparation of article. The final draft article was approved by all the authors.

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Supplementary data

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