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Improved survival of patients with hepatocellular carcinoma and compensated HCV-related cirrhosis who attained SVR

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Lists of abbreviations

AASLD American Association for the Study of Liver Diseases

BCLC Barcelona Clinic for Liver Cancer

DAAs Direct antiviral agents

EASL European Association for the Study of the Liver

ESLD End-stage liver disease

IFN Interferon

HCC Hepatocellular carcinoma

HCV Hepatitis C virus

MELD Model for End-Stage Liver Disease

OS Overall survival

RECIST Response Evaluation Criteria In Solid Tumors

SVR Sustained virological response

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ABSTRACT

Background

Few studies examined the outcome of patients with HCV-related cirrhosis who developed hepatocellular carcinoma (HCC). The relative weight as determinant of death for cancer versus end-stage-liver-disease (ESLD) and the benefit of HCV eradication remain undefined. This multicenter, retrospective analysis evaluates overall survival (OS), rate of decompensation and tumor recurrence in compensated HCC patients treated with IFN according to HCV status since HCC diagnosis.

Methods

Two groups of patients with HCV-related cirrhosis and HCC were followed since HCC diagnosis: (i) compensated cirrhotics with prior sustained virologic response (SVR) on IFN-based regimens (N=19); (ii) compensated cirrhotics without SVR (viremic) (N=156).

Results

Over a median follow-up of 3.0 years since the onset of HCC, OS was longer for HCC patients with SVR than for viremic patients (Log-rank P=0.004). The 5-year OS rate was 65.9% in patients with SVR versus 31.9% in viremic patients. Similar trends were reported for hepatic decompensation (Log-rank P=0.01) and tumor recurrence (Log-rank P=0.01). These findings were confirmed at multivariable and propensity score analysis. At propensity analysis, 0/19 compensated patients with SVR died for ESLD versus 7/19 (37%) viremic patients (p=0.004). HCC mortality was similar in the two groups.

Conclusions

HCC patients with prior SVR and compensated cirrhosis at the time of tumor diagnosis have prolonged OS than viremic patients. Given the lack of cirrhosis progression, no SVR patient ultimately died for ESLD while this condition appears the main cause of death among viremic patients.

Keywords: HCC; HCV; interferon; sustained virological response; survival

Key Points Box

- Studies on the long-term outcome of patients who developed HCC after anti-HCV therapy are lacking.
- HCC patients with SVR and compensated cirrhosis at diagnosis have prolonged OS than viremic patients.
- ESLD is the main cause of death in viremic patients; SVR patients do not die from it.
- This analysis represents a reference for further studies using DAA therapy, which are mandatory.

INTRODUCTION

Patients with HCV-related cirrhosis are priority candidates for antiviral treatment, since they have an expected high rate of progression to liver decompensation, hepatocellular carcinoma (HCC), and eventually to death.[1]

The achievement of sustained virological response (SVR) after anti-viral treatment results in improved clinical outcomes, including reduced risk of liver events and HCC development, compared with lack of response.[2–5] A recent prospective study by Bruno et al., with a median follow-up of 9.6 years, evaluated 1802 patients with HCV-related cirrhosis.6 Compensated patients with SVR on an interferon (IFN)-based regimen had a survival rate similar to that of the age- and gender-matched general population. These benefits attributable to SVR strongly suggest that eradicative treatment of HCV should be administered to patients with compensated HCV cirrhosis as early as possible, given also the recent introduction of IFN-free regimens based on direct antiviral agents (DAA) which allow SVR in the wide majority of patients.[2,6–8] At the same time, the study confirmed that SVR is associated with lower, but not negligible, risk of HCC occurrence,6 in line with other studies.[9–12]

To our knowledge, prospective studies with a follow-up allowing proper analysis of the outcome of patients who developed HCC after anti-HCV therapy – also in correlation with SVR or surrounding disease status - are lacking. In addition, an important clinical question still remains unanswered:[13] do patients who developed HCC benefit of HCV eradication by reducing, as a cause of death, the competing risk of cirrhosis progression that ultimately leads to end-stage-liver-disease (ESLD) independently from anti-HCC treatment?

The present retrospective analysis of a prospectively defined cohort assessed, in the group of cirrhotic patients reported by Bruno et al.[6] who had developed HCC during surveillance follow-up, overall survival (OS), rate of decompensation and HCC recurrence according to previous response to interferon (IFN)-based regimens, since HCC diagnosis.

Because treatment of cirrhosis with DAA has now become the standard of care, such information can assist in assessing priority for the vast allocation of financial and healthcare resources devoted to these patients.[6,14]

PATIENTS AND METHODS

Patients

Surveillance data from three independent cohorts of Italian patients with HCV-related cirrhosis who were followed in tertiary liver centers were considered.[6] In brief, the first cohort (Milan-1) included consecutive patients with either compensated (Child-Pugh class A5-A6 according to [15]) or decompensated (Child-Pugh B7-B9) HCV-related cirrhosis treated at three liver centers (San Paolo Hospital [Milan, Italy], Fatebenefratelli Hospital [Milan, Italy] and San Gerardo Hospital [Monza, Italy]) in the Milan area between 1989 and 1992. The second cohort (Milan-2) included consecutive compensated cirrhosis patients (Child-Pugh class A5-A6) enrolled at the Liver Unit Fondazione IRCCS Ca'Granda, Ospedale Maggiore (Milan, Italy) in 1997. The third cohort (Palermo) included all

cirrhotic HCV patients (Child-Pugh class A5-A6) enrolled at the Liver Unit of the University of Palermo who started IFN-based antiviral therapy from 2001 to 2009.

Among subjects enrolled in the above-mentioned cohorts, the present study analyzes only patients with compensated cirrhosis at study entry, who received IFN-based therapy and had later developed HCC during surveillance follow-up. Figure 1 displays the flow-chart of the study.

The diagnosis of cirrhosis (F4 METAVIR, F5-6 Ishak) was either made by liver biopsy or according to clinical criteria. Anti-HCV antibodies, HCV RNA (including genotype) and liver function were assessed according to the practice of each center at the time of patients' observation. HCC diagnosis and treatment (either with a curative intent or not), including the assessment of efficacy for recurrence of HCC were performed according to clinical guidelines available at the time of patients' evaluation, such as the Barcelona Conference and those issued by the American Association for the Study of Liver Diseases (AASLD). IFN mono-therapy or IFN (pegylated or not) in combination with ribavirin was administered according to the standard practice of each center at the time of evaluation.[6]

All patients underwent a follow-up program based on abdominal US every 6 months. Until 2001, patients with a newly-detected liver focal lesion underwent computed-tomography and US-guided fine-needle biopsy, and after 2001 diagnosis of HCC was in accordance with the European Association for the Study of the Liver (EASL) 2001 and the American Association for the Study of Liver Diseases 2005 criteria and subsequent updates.[16–19]

Surveillance, treatment and outcome at the time of HCC development

After HCC diagnosis, in all patients nodules and tumor-related complications were evaluated by a multidisciplinary team with management changing in line with updating of clinical guidelines when available and according to the specific expertise of each single Center (e.g., Centers with experienced surgeons would likely prefer surgery over locoregional treatments, and vice-versa, especially in BCLC very early HCC). Moreover, treatment selection took into account also other factors such as tumor site.

After the initiation of HCC treatment, each patient underwent radiological re-evaluation at 1 and 3 months to assess the efficacy of therapy, according to the EASL criteria for radiological response after 2001 and modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria for HCC in more recent years.[20] Only patients free of disease after the 3-month assessment (considered as complete responders) were considered for late recurrence.

Patients' vital status and cause of death were recorded during surveillance. We defined the causes of death when attributed to ESLD in absence of HCC as follows: liver failure in Child class CP-C or more, hepato-renal syndrome (HRS), spontaneous bacterial peritonitis with or without sepsis and hepatic encephalopathy. For progression of HCC, we considered BCLC terminal stage D in palliative treatment. For patients lost to follow-up, vital status was updated in 2015 by phone call or in case of non-response from residential town hall vital statistics registry offices.

Data collection and analysis were already approved by all local Institutional Review Committees (Milan 1, Milan 2 and Palermo) at enrolment for the above-mentioned purposes. All patients had signed an informed consent for the use of their personal data for research purposes.

Statistical analysis

Two groups of patients were considered: (i) IFN-based treated patients with compensated cirrhosis at the time of HCC diagnosis who had prior achieved SVR; (ii) IFN-based treated patients who failed to achieve SVR with compensated cirrhosis at the time of HCC diagnosis (viremic). Difference in the distribution of patients characteristics between the two groups was assessed by Fisher's Exact test.

The main study outcome was OS, calculated from the date of HCC diagnosis to last contact or death. OS curves were plotted using the Kaplan-Meier method and difference in survival between groups was compared with the Log-rank test. Other outcomes were the development of hepatic decompensation and HCC recurrence; these outcomes were also evaluated by Kaplan-Meier analysis. We used Cox proportional hazards regression models to identify characteristics at the time of development of HCC associated with overall mortality, development of hepatic decompensation and HCC recurrence. Multivariable models were constructed, in which factors that did not satisfy the criteria ($p<0.10$) were removed in a step-down phase.

As further confirmatory analysis, patients with SVR at the time of HCC diagnosis were matched using propensity score for demographic and clinical characteristics (age, gender, HCV genotype, albumin blood level, Model for End-Stage Liver Disease (MELD) score, gastro-esophageal varices, tumor size, Barcelona-Clinic Liver Cancer [BCLC] criteria) with an equal number of viremic patients. Fisher's exact test was used to assess differences in the distribution of characteristics between the two groups.

All analyses were two-tailed and p-values <0.05 were considered significant. All analyses were performed with the SAS software (version 9.2, Cary, NC).

RESULTS

Patients

We identified 175 IFN-based treated patients with cirrhosis who developed an HCC during scheduled surveillance follow-up and were compensated at the time of HCC diagnosis. Of these, 156 had previously failed to achieve SVR after IFN-based therapy, and 19 had prior achieved SVR (Figure 1).

Patients characteristics at HCC diagnosis in the overall population and stratified according to SVR status are presented in table 1. The groups differed in terms of HCV genotype ($p=0.0006$), duration of previous IFN treatment ($P=0.008$), serum albumin ($P=0.03$) level, diabetes ($P=0.045$) and type of HCC therapy ($P=0.02$).

Overall survival

The median observation time was 3.0 years (range 0.1-24.1). Over this follow-up 125 patients (71.4%) patients died; 47 patients (26.9%) were still alive at the end of observation while three patients (1.7%) were lost-to-follow-up. OS was significantly longer for patients with prior SVR than for viremic patients (Log-rank $P=0.004$) (Figure 2).

The 5-year OS rate was 65.9% (95% CI, 38.9-83.1%) in patients with SVR and 31.9% (24.2-39.8%) in viremic patients. Corresponding figures at 10 years were 56.5% and 16.5%, respectively.

At univariable analysis, viremic status, older age, class of Child-Pugh score, high serum bilirubin, low serum albumin, unmet Milan criteria, increased number and size of liver lesions, BCLC stage and palliative treatment (none or sorafenib-only) were associated with increased mortality, while orthotopic liver transplantation (OLT) was associated with reduced mortality (Table 2). At multivariable analysis, B class of Child (HR=3.17, 95% CI 1.72-5.86), low albumin (≤3.5 g/l) (HR=1.67, 95% CI 1.08-2.57), unmet Milan criteria (HR=2.71, 95% CI 1.70-4.32), and palliative treatment for HCC (HR=4.25, 95% CI 1.94-9.29) were independent predictors of mortality, while previous SVR (HR=0.41, 95% CI 0.19-0.90) and OLT (HR=0.13, 95% CI 0.04-0.50) remained associated with reduced mortality) (Table 2).

Hepatic decompensation

Information about hepatic decompensation after the diagnosis of HCC was available for 165/175 patients: 98 developed decompensation. The cumulative incidence of decompensation was significantly higher among viremic patients than SVR patients (Log-rank P=0.01) (Figure 2). The 5-year cumulative rate of decompensation was 35.6% (95% CI 17.5-63.7%) in patients with SVR and 64.2% (95% CI 55.5-72.7%) in viremic patients.

At univariable analysis, absence of SVR, increasing age, low albumin, MELD≥10, Milan criteria, ≥3 hepatic lesions, intermediate to end-stage BCLC and palliative treatment were associated with increased risk of decompensation while OLT was protective (Table 2). At multivariate analysis, SVR (HR=0.35, 95% CI 0.15-0.84), low albumin level (HR=1.81, 95% CI 1.17-2.80), unmet Milan criteria (HR=2.40, 95% CI 1.44-4.00) and OLT (HR=0.05, 95% CI 0.01-0.39) were independent predictors of decompensation (Table 2).

Tumor recurrence

Tumor recurrence was evaluated among 119 compensated patients with HCC who received treatment with a curative intent, including surgery (n=20), trans-arterial chemoembolization (n=38), percutaneous ethanol injection (n=13) or radio-frequency thermal ablation (n=48) and available information on tumor recurrence.

Time to recurrence was similar for all treatment subtypes (data not shown, P=0.32) but was significantly longer for SVR patients (Log-rank P=0.01) (Figure 2). At univariable analysis, factors associated with increased recurrence were lack of SVR, HCV genotype 1, presence of gastroesophageal varices, ≥3 hepatic lesions and intermediate to end-stage BCLC. At multivariable analysis, genotype 1 (HR=2.39, 95% CI 1.34-4.27), ≥3 hepatic lesions (HR=2.87, 95% CI 1.29-6.37) remained independent predictor of recurrence. After adjustment for these factors, the association with previous achievement of SVR was lost (HR=0.69, 95% CI 0.32-1.50).

Propensity score analyses

The 19 patients with SVR and compensated cirrhosis at the time of HCC diagnosis were matched with 19 viremic patients. None of the characteristics evaluated differed between the two groups (Table S1). Patients with SVR had a significantly longer OS than viremic patients (Log-rank P=0.049) (Figure S1). In addition, causes of death differed significantly between the two groups: 6 patients

with SVR ultimately died of HCC compared with 4 viremic patients (Log-rank P=0.75) while patients with SVR died for ESLD versus 7/19 (37%) matched viremic patients (p=0.004) (Figure S2).

Patients with SVR had also lower rate of decompensation and tumor recurrence than viremic patients but the difference was not significant (Figure S1).

DISCUSSION

This large retrospective analysis of a prospectively-defined cohort, conducted in Italian reference liver centers shows that patients treated with IFN with prior SVR and compensated cirrhosis have prolonged OS after the development of HCC compared with those without SVR. Remarkably, in our study two out of three compensated patients who previously attained SVR were alive five years after the development of HCC, while this figure dropped to one out of three in compensated patients who failed to achieve SVR at the time of IFN-based therapy. This advantage is still evident ten years after HCC diagnosis, as the majority of compensated patients with prior SVR were still alive.

A previous meta-analysis of patients who have undergone surgical resection/ablation of HCC and a retrospective cohort study of a pooled population of patients with and without SVR have suggested similar outcomes.[21,22] However, to our knowledge the prolonged OS associated with SVR in HCV patients who developed HCC is supported here by the analysis of a prospective cohort for the first time.

Although the low rate of SVR reported in our study - which was expected in the pre-DAA era – should be taken into account, the prolonged OS associated with SVR achievement was confirmed at both univariable and multivariable analysis. In addition, we performed a propensity score analysis in order to account for the worsened clinical conditions observed in still viremic patients, as compared with SVR patients. The results of the propensity analysis confirmed those reported in the main analysis. Remarkably, the propensity analysis showed that the ultimate cause of death significantly differs between viremic and SVR patients. As a matter of fact, none of patients with SVR died from ESLD, while this latter was the main cause of death in those who failed to achieve SVR. This evidence is in line with a previous analysis which indicated that the onset of HCC in viremic patients, as well as those of portal hypertension–related complications, quickly accelerates the course of liver disease course to its final stage.[23]

More favorable outcomes were also reported in terms of incidence of hepatic decompensation and time to recurrence, which were improved in the SVR group compared with the viremic group. However, the benefit on time to recurrence associated with SVR was lost at the multivariable analysis. This could be due to the limited statistical power for this outcome, with only 16 SVR patients included for this analysis, and also to the noted correlation between HCV genotype and SVR. In a multivariate model unadjusted for HCV genotype, the association with SVR remained statistically significant (HR=0.46; 95% CI 0.22-0.98; P=0.04) after adjustment for other confounders (center, number of lesions and BCLC).

We must also point out that we had sparse information on tumor recurrence and therefore definite conclusions cannot be made. With respect to recurrence, some recent notes of cautions derived from the results of a small retrospective study which reported a high rate of HCC recurrence after

DAA treatment.[24] However, this study was at least partially flawed by a number of methodological and statistical concerns, and its findings were not confirmed in a large analysis of three prospective studies.[25-27] Prospective studies on this issue, potentially using new antiviral therapies, may provide more grounded results. Moreover, data on patients with more advanced HCC stages were lacking in our study, since they did not receive IFN-based treatment.

The prolonged OS in eradicated patients is easily justified by the lack of the competing risk of death attributable to concurrent liver disease progression. On the other hand, HCC itself may have a relatively-indolent course, while eradication of HCV infection might play a major role in ensuring the best possible clinical outcomes, because multiple anti-tumor procedures can be offered over time to patients with well-preserved liver function provided by the attainment of SVR. By this way the best possible management of HCC could be ensured. Given the favorable efficacy/safety ratio of new antiviral therapies and their widespread use in clinical practice, we presume that this advantage will soon much improve, although specific studies on this issue appear warranted. However, interferon might have played a role in reducing HCC mortality due to its anti-proliferative effect.[28]

Limitations of the study

This study is not without its limitations. The most important weakness is the small – but reliable - number of patients who achieved SVR, as expected in the pre-DAA era. In addition, the group of SVR patients included subjects who were treated before the occurrence of HCC. Accordingly, patients overall presented more favorable characteristics when compared with those who did not achieve SVR (e.g. lower Child Pugh class and MELD scores, less advanced tumor burden and higher rates of curative treatment) and who were likely to have a shorter duration of infection and less portal hypertension.

We also acknowledge an intrinsic selection bias originated by the use of IFN-based regimens, which have excluded the sickest patients or those with poorest conditions from, treatment.

Last, since IFN-based therapy was successful only in a limited number of patients, with more favorable characteristics, we may not be sure that our findings could fully apply to patients responding to the more recent DAA-based regimens.

Other limitations inherent to any observational retrospective study, such as poor reporting of data (e.g., specific data on portal hypertension were not complete and hence this parameter was not considered; data on MELD scores were incomplete), should be also taken into account.

Conclusions

Despite the above-mentioned intrinsic and unavoidable limitations, our data show that HCC patients with prior IFN-based achieved SVR and compensated cirrhosis at the time of tumor diagnosis have prolonged OS than viremic patients. Moreover, ESLD appears to be the main cause of death among viremic patients, whereas patients with SVR do not die from this condition.

In the next future, due to the widespread use of effective DAA treatments, the ratio of HCC will increase in SVR patients compared with those with virological failure. These patients will be similar to our 19 subjects, and therefore the information provided by our study might represent a reference standard for this population. It is true that the patients enrolled in our cohort were treated with IFN-

based regimens. However, given that the biological meaning of SVR is independent from the actual treatment required to attain this goal,[12] we feel that our data may have a role also in the current DAA era. Indeed, in this illness in which two diseases concur, the virological eradication does cure cirrhosis, thus contributing to improve outcome of HCC patients, especially those with BCLC very early and early HCC and well-compensated cirrhosis. On the other hand, our data cannot be immediately transferred to patients with more advanced HCC or marginally-compensated/decompensated cirrhosis.

Because patients in this study were treated years before HCC development and the benefits of HCV therapy are not immediate, new data using dedicated studies on DAA therapy which may support our suggestion appear mandatory. Noteworthy, the present study might represent a key reference for further studies in this setting.

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Authors' contributions

Study design: SB, VDM, PM, AC, MC

Experiments and procedures: MI, LR, AC, GC, SR, VC, AA

Data analysis and interpretation: SB, IS, LG, PM

Manuscript drafting: SB, LG

Manuscript editing: All

Approval of final draft: All

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Figure legends

Figure 1. Study flowchart.
Figure 2. Overall survival (A), time to decompensation (B) and time to HCC recurrence (C) after HCC among 175 compensated cirrhotic patients according to viremic status.

Table 1. Patients characteristics at the time of development of hepatocellular carcinoma

		Total	Viremic	SVR	P-value Fisher exact test
All patients		175	156	19	
Center					
	Milan 1	52	45	7	
	Milan 2	47	42	5	
	Palermo	76	69	7	0.75
Sex					
	Male	126	111	15	
	Female	49	45	4	0.59
Age					
	<60	37	35	2	
	60-69	82	72	10	
	70+	56	49	7	0.51
HCV genotype					
	1	138	130	8	
	Non-1	36	26	10	**0.0006**
IFN duration					
	≤6 months	56	51	1	
	>6 months	115	97	18	**0.008**
Class of Child					
	A	144	126	18	
	B	18	18	0	0.23
Serum bilirubin (mg/dl)					
	Mean±SD	1.2±0.8	1.2±0.9	0.9±0.4	
	Low (<1.2 mg/dl)	101	88	13	
	High (≥1.2 mg/dl)	56	51	5	0.60

Serum albumin (g/l)				
Mean±SD	3.7±0.6	3.7±0.6	4.1±0.5	
Low (≤3.5 g/l)	53	51	2	
High (>3.5 g/l)	103	87	16	**0.03**
Prothrombin time (INR)				
Mean±SD	1.1±0.3	1.1±0.3	1.1±0.1	
Low (≤1.2)	133	119	14	
High (>1.2)	22	19	3	0.71
Creatinine (mg/dl)				
Mean±SD	0.9±0.2	0.9±0.2	0.9±0.2	
Low (<1.2 mg/dl)	139	123	16	
High (≥1.2 mg/dl)	12	10	2	0.64
MELD score				
6-7	67	59	8	
8-9	51	45	6	
10+	32	29	3	1.00
Esophageal varices				
Absent	94	82	12	
Present	80	73	7	0.47
Diabetes				
Absent	132	114	18	
Present	26	26	0	**0.045**

Table 1 (cont). Patients characteristics at the time of development of hepatocellular carcinoma

	Total	Viremic	SVR	P-value Fisher exact test
Interval IFN-HCC				
<5 years	67	63	4	
5-10 years	68	59	9	
≥10 years	38	32	6	0.21
Milan criteria				
Met	135	120	15	
Unmet	39	35	4	1.00
Number of lesions				
1	118	103	15	
2	34	32	2	
3 or more	22	20	2	0.61
Tumor size				
<20mm	41	36	5	
20-29mm	72	67	5	
≥30mm	57	48	9	0.27
BCLC				
Very early	37	32	5	
Early	105	93	12	
Intermediate	16	16	0	
Advanced	9	9	0	
End-stage	1	0	1	0.10
HCC therapy				
None	19	18	1	
Surgery	22	15	7	
TACE	47	45	2	

PEI	13	10	3	
RFTA	54	50	4	
OLT	13	12	1	
Sorafenib	6	5	1	**0.02**

* Information missing for few subjects (HCV genotype for 1 patient, duration of antiviral treatment for 8 patients, class of child for 13 patients, bilirubin for 18 patients, albumin for 19 patients, INR for 20 patients, creatinin for 24 patients, MELD score for 25 patients, varices for 1 patient, diabetes for 17 patients,interval between IFN and HCC for 2 patients, Milan criteria for 1 patient, number of lesions for 1 patient, tumor size for 5 patients, BCLC for 7 patients, HCC therapy for 1 patient).

BCLC: Barcelona-Clinic Liver Cancer criteria; MELD: Model for End-Stage Liver Disease; TACE: Transarterial chemoembolization; PEI: Percutaneous ethanol injection; RFTA: radio-frequency thermal ablation; OLT: Orthotopic liver transplantation

Table 2. Factors associated with overall mortality, hepatic decompensation and tumor recurrence in respectively 175, 165 and 119 patients with HCV-related cirrhosis

		OVERALL MORTALITY				HEPATIC DECOMPENSATION*				TUMOUR RECURRENCE**			
Variable	**Exposure**	**Univariable analysis**		**Multivariable analysis**		**Univariable analysis**		**Multivariable analysis**		**Univariable analysis**		**Multivariable analysis**	
		HR (95% CI)	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Status at HCC	SVR vs. viremic	**0.34 (0.16-0.73)**	**0.006**	**0.41 (0.19-0.90)**	**0.03**	**0.37 (0.16-0.84)**	**0.02**	**0.35 (0.15-0.84)**	**0.02**	**0.40 (0.19-0.84)**	**0.02**		
Center	Milan-2 vs .Milan 1	0.88 (0.56-1.37)	0.56			0.87 (0.52-1.47)	0.60			**2.41 (1.35-4.31)**	**0.003**	**3.27 (1.69-6.34)**	**.0004**
	Palermo vs. Milan 1	1.14 (0.74-1.74)	0.56			1.18 (0.73-1.89)	0.51			**2.04 (1.13-3.70)**	**0.02**	**2.12 (1.10-4.11)**	**0.03**
Sex	Female vs. Male	1.27 (0.87-1.86)	0.21			1.36 (0.89-2.08)	0.16			0.73 (0.46-1.16)	0.18		
Age	60-69 vs. <60	1.57 (0.96-2.56)	0.07			**1.86 (1.01-3.39)**	**0.04**			0.71 (0.38-1.33)	0.29		
	70+ vs. <60	**1.75 (1.03-2.97)**	**0.04**			**2.44 (1.31-4.55)**	**0.005**			0.69 (0.36-1.33)	0.27		
IFN duration	≥6 vs. <6 months	1.17 (0.80-1.71)	0.43			1.43 (0.91-2.24)	0.12			0.91 (0.57-1.45)	0.69		
HCV genotype	Type 1 vs. Non-1	1.34 (0.86-2.09)	0.20			1.31 (0.79-2.19)	0.30			**1.83 (1.08-3.11)**	**0.02**	**2.39 (1.34-4.27)**	**0.003**
Class of Child	Child B vs. Child A	**2.62 (1.53-4.48)**	**0.0004**	**3.17 (1.72-5.86)**	**.0002**	1.76 (0.94-3.32)	0.08			2.15 (0.92-5.05)	0.08		
Bilirubin	≥1.2 vs. <1.2 mg/dl	1.46 (0.99-2.15	0.05			1.49 (0.97-2.27)	0.07			1.27 (0.79-2.03)	0.32		
Albumin	≤3.5 vs. >3.5 g/l	**1.77 (1.20-2.61)**	**0.004**	**1.67 (1.08-2.57)**	**0.02**	**1.95 (1.28-2.98)**	**0.002**	**1.81 (1.17-2.80)**	**0.008**	0.72 (0.44-1.18)	0.19		
INR	> 1.2 vs. ≤1.2	0.93 (0.53-1.64)	0.81			1.01 (0.56-1.82)	0.98			1.01 (0.56-1.80)	0.98		
Creatinine	≥1.2 vs. <1.2 mg/dl	1.17 (0.59-2.32)	0.65			1.70 (0.85-3.40)	0.13			0.91 (0.40-2.10)	0.83		

MELD score	8-9 vs. 6-7	1.21 (0.78-1.88)	0.39			1.50 (0.92-2.43)	0.11	1.23 (0.76-1.99)	0.39	0.93 (0.55-1.54)	0.77		
	10+ vs. 6-7	1.43 (0.88-2.34)	0.16			**1.80 (1.05-3.10)**	**0.03**	1.58 (0.92-2.74)	0.09	1.12 (0.63-2.01)	0.71		
Varices	Present vs. Absent	0.81 (0.56-1.16)	0.24			0.86 (0.57-1.29)	0.46			**1.76 (1.13-2.74)**	**0.01**		
Diabetes	Yes vs. no	1.13 (0.69-1.86)	0.63			1.13 (0.65-1.98)	0.67			1.26 (0.68-2.33)	0.46		
Interval IFN	5-9 vs. <5 years	0.93 (0.65-1.35)	0.71			1.26 (0.80-2.00)	0.32			1.01 (0.61-1.69)	0.94		
To HCC	≥10 vs. <5 years	1.24 (0.83-1.85)	0.29			1.08 (0.62-1.88)	0.80			1.15 (0.65-2.01)	0.64		
Milan Criteria	Unmet vs. met	**3.78 (2.50-5.70)**	**<.0001**	**2.71 (1.70-4.32)**	**<.0001**	**2.67 (1.70-4.19)**	**<.0001**	**2.40 (1.44-4.00)**	**.0008**	1.29 (0.66-2.51)	0.45		
Lesions	2 vs. 1	1.27 (0.81-1.98)	0.29			1.19 (0.71-1.99)	0.51			1.00 (0.56-1.80)	0.99		
	3 or more vs. 1	**2.59 (1.54-4.33)**	**0.0003**			**2.35 (1.37-4.04)**	**0.002**			**2.70 (1.32-5.50)**	**0.006**	**2.87 (1.29-6.37)**	**0.01**
Tumor size	20-29 vs. <20mm	0.90 (0.57-1.42)	0.65			0.73(0.45-1.20)	0.21			1.31 (0.77-2.22)	0.32		
	≥30 vs. <20 mm	**1.77 (1.12-2.82)**	**0.02**			1.08 (0.65-1.80)	0.76			1.29 (0.72-2.30)	0.39		
BCLC	≥ Interm. vs. ≤ early	**4.03 (2.57-6.35)**	**<.0001**			**3.02 (1.79-5.10)**	**<.0001**			**2.60 (1.03-6.60)**	**0.04**	2.29 (0.87-6.01)	0.09
HCC therapy	Ablative† vs. surgery	**1.74 (0.92-3.28)**	**0.09**	**1.44 (0.75-2.75)**	**0.28**	1.26 (0.69-2.27)	0.45	1.00 (0.54-1.84)	0.99	-			
	Palliative vs. surgery	**7.76 (3.76-16.0)**	**<.0001**	**4.25 (1.94-9.29)**	**.0003**	**2.91 (1.40-6.02)**	**0.004**	1.33 (0.68-2.60)	0.48				
	OLT vs. surgery	**0.26 (0.07-0.92)**	**0.04**	**0.13 (0.04-0.50)**	**0.003**	**0.08 (0.01-0.58)**	**0.01**	**0.05 (0.01-0.39)**	**0.004**	-			

Hazards Ratios (HR) and 95% confidence intervals (CI) obtained from univariable and multivariable Cox proportional Hazards regression model. In the multivariable model, all factors presented the table were fitted simultaneously.

† Ablative interstitial therapies include transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI) or radio-frequency thermal ablation (RFTA).

* Hepatic decompensation was evaluated among 165 patients with compensated cirrhosis at the time of development of HCC;

** Tumor recurrence was evaluated among 119 patients with compensated cirrhosis at the time of development of HCC who underwent curative treatment.