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Absence of Viral Replication Is Associated With Improved Outcome in Anti-HCV-Positive Patients With Hepatocellular Carcinoma

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Abbreviations: 95% CI, 95% confidence internal; DAAs, direct-acting antivirals; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; ITA.LI.CA, ITAlian LIver CAncer; MELD, Model of End-Stage Liver Disease; PSM, propensity score matching; SVR, sustained virological response.

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ABSTRACT

Background and Aims: Presence of active hepatitis C virus (HCV) infection may influence the outcome of patients treated for hepatocellular carcinoma (HCC), although this issue has never been adequately assessed in a large series of patients. The aim of this study was to evaluate whether the presence of active HCV affects the survival of patients treated for HCC.

Methods: This study assessed the outcome of 3123 anti-HCV-positive patients with HCC, subdivided according to the presence of active HCV infection or previous sustained virological response (SVR). Comparisons were also carried out after propensity score matching (PSM) considering demographic, clinical and oncological characteristics.

Results: The median overall survival from HCC treatment was longer in patients with SVR than in those with active HCV infection both before ($n = 2118$: 61.0 months [95% confidence internal (CI): 56.5–65.5] vs. $n = 1005$: 51.0 months [95% CI: 43.4–58.6]; $p = 0.003$) and after PSM ($n = 1285$: 60.0 months [95% CI: 55.3–64.7] vs. $n = 926$: 54.0 months [95% CI: 46.7–61.3]; $p = 0.030$). Active HCV infection was associated with a greater risk of mortality (hazard ratio: 1.22–1.27, $p = 0.001$) independently of liver- and tumour-related variables, and modality of HCC treatment. Death due to liver failure was more common in patients with active HCV infection (24.5% vs. 17.1%; $p = 0.001$), while non-liver-related causes of death were more common in patients with SVR (25.0% vs. 17.0%; $p = 0.001$).

Conclusions: SVR is associated with a better outcome in patients undergoing HCC treatment, thus suggesting that these patients may benefit from antiviral therapy for HCV independently of cure of HCC.

1 | Introduction

Hepatitis C virus (HCV) infection represents the most common aetiological factor for hepatocellular carcinoma (HCC) in the Western world, despite a decrease in HCV-related HCCs recently observed both in Europe and in the US, and a further decrease expected in the next 10 years [1–3]. One of the main reasons behind this epidemiological change is the advent of direct-acting antivirals (DAAs) for the treatment of HCV, which allowed us to cure from infection an unprecedented proportion of patients [4].

At the population level, secondary prevention by means of eradication of HCV infection would lead to a great benefit in the context of global liver disease outcomes, preventing further spread of infection also targeting selected populations and eventually decreasing the overall burden of liver disease [5–8]. In patients with chronic liver disease, successful treatment with DAA proved to be able to decrease the rate of development of HCC and, despite some initial controversial results, also to reduce the rate of recurrence following radical treatment of this tumour [9–12]. In these latter patients, successful DAA treatment was also able to improve their prognosis by decreasing the rate of liver disease decompensation [13–15].

Taken together, these data provided compelling evidence that the cure of HCV infection is highly beneficial for HCC patients, and current guidelines recommend the eradication of HCV infection to improve the prognosis of patients with cured HCC [16]. This notwithstanding, the evidence supporting the antiviral treatment of HCV patients with treated HCC is provided only by one retrospective study carried out in the US, showing that in a series of 797 patients with a complete tumour response achieved with various treatments, successful DAA treatment was associated with a significant improvement of overall survival [17].

However, to the best of our knowledge, there are no confirmatory studies demonstrating, in large populations including all HCC stages treated with either curative or non-curative therapies, comprising systemic treatment, that the absence of viral replication is associated with improved prognosis. Therefore, this study aimed to assess, in a large population with HCV-related HCC, whether the absence of active infection is associated with a better outcome in patients undergoing various oncological treatments.

2 | Patients and Methods

The ITAlian LIver CAncer (ITA.LI.CA) database has been collecting data prospectively of patients diagnosed and treated for HCC in Italy since 1987. The database is updated biennially, with the last update conducted in December 2022 [2]. The use of the ITA.LI.CA database for scientific research was

Summary

- Whether the presence of active hepatitis C virus (HCV) infection might influence the outcome of patients treated for hepatocellular carcinoma (HCC) has not been assessed in a large series of patients undergoing various oncological therapies.
- In this study, we have shown that in patients with HCV–related HCC, the absence of viral replication is associated with improved survival, independently of liver- and tumour-related variables, and modality of HCC treatment and with a lower risk of liver-related mortality.
- On the basis of these results, we feel that the antiviral treatment for HCV should be considered in all patients with HCC independently of the modality of treatment of the tumour, as abolishing viral replication might improve the overall patients' outcome.

approved by the Institutional Review Board of the ITA.LI.CA Coordinating Centre (approval number 99/2012/O/Oss), and the study was conducted following the ethical guidelines of the 1975 Declaration of Helsinki.

For this study, data on patients with chronic liver disease associated with anti-HCV positivity were gathered from the ITA.LI.CA database, considering the period January 2011–December 2022, recruited by 24 centres. This period was selected as the antiviral therapy, with DAAs becoming commercially available in Italy in 2016, and this allowed us to include patients accrued in a time-span of at least 5 years preceding and following that date, resulting in a large sample size with a meaningful duration of follow-up. Patients were categorised into two groups based on whether the HCC diagnosis was made in patients with active HCV infection or in those with sustained virological response (SVR), regardless of the type of antiviral treatment received. The number of patients *per* year is shown in Figure S1.

Patients presenting with concurrent factors for chronic liver disease, such as hepatitis B virus infection, human immunodeficiency virus infection, excessive alcohol intake and hereditary or acquired liver storage disorders, were excluded from the analysis.

The diagnosis of cirrhosis was formulated on clinical and laboratory data, complemented by instrumental evidence or, when available, based on liver histology [18]. Liver function was evaluated using the Model of End-Stage Liver Disease (MELD) score and the Child–Turcotte–Pugh classification [19, 20]. The fibrosis-4 (FIB-4) score was calculated using the standard formula: age (years)$\times$AST (U/L)/[platelets (10^9/L)$\times\sqrt{}$ALT (U/L)]. The overall health status of patients was assessed using the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) [21]. The presence and size of oesophageal varices were assessed by means of endoscopy.

The diagnosis of HCC was made following the recommendations of the Italian consensus for the management of patients with HCC valid at the time of inclusion [22]. Additionally, the modality of HCC detection (i.e., under surveillance, incidental or symptomatic) and tumour characteristics were recorded. HCCs were classified according to the Milan criteria [23].

The initial, main treatment strategies were categorised into surgical interventions (liver transplantation and liver resection), ablative procedures (radiofrequency ablation, ethanol injection and other ablative treatments), trans-arterial procedures (trans-arterial chemoembolisation, trans-arterial embolisation and trans-arterial radioembolisation), systemic therapy and best supportive care.

Oncological response of HCC to treatment was assessed using the key metrics according to the Response Evaluation Criteria in Solid Tumours guidelines [24].

The duration of survival was calculated starting from the first HCC treatment to either the date of death or the latest follow-up data available, or the end of the study, whichever occurred first. Additionally, information on the causes for death was collected.

2.1 | Statistical Analysis

The median and interquartile range (IQR) were used for continuous variables, and frequency and proportion were used for categorical variables. The Kruskal–Wallis or Mann–Whitney tests were used, when appropriate, to compare continuous variables. Pearson's χ^2-test and Spearman's rank correlation were applied to analyse the relationship between nominal variables and continuous variables.

Patient survival was analysed by the Kaplan–Maier curves and compared with the log-rank test and reported as median and 95% confidence internal (95% CI). The Cox proportional hazard model was adjusted for death-related risk factors identified by statistical analysis. Two models were constructed (Model 1: MELD score; Model 2: Child–Turcotte–Pugh score) to adjust the multivariate Cox analysis given the collinearity of these variables.

A secondary analysis was conducted after the adjustment of baseline differences using propensity score matching (PSM). Initially, covariates or factors to be included in the PSM model were identified through univariate analysis, with a significant difference (threshold $p \leq 0.05$ for inclusion) between patients with active infection and those with SVR (1:2 ratio). The PSM estimation utilised a logistic regression model, with a calliper width of 0.2 deemed appropriate.

The IBM SPSS Statistics, Release Version 25.0 (SPSS Inc., 2017, Chicago, IL, USA, www.spss.com) and R (the R project, R version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria) were used for the statistical analysis.

3 | Results

3.1 | Main Characteristics of the Study Patients

The main demographic and clinical features of the 3123 study patients, subdivided according to the presence of HCV viremia, are summarised in Table 1. Overall 1005 patients had active

TABLE 1 | Main characteristics of the study cohort.

Characteristics	Active HCV infection ($n=1005$)	SVR ($n=2118$)	p
Gender, male	718 (71.4)	1492 (70.4)	0.566
Age, years	68.4 (56.7–76.8)	70.0 (58.9–76.6)	0.024
Body mass index, kg/m^2	24.6 (22.5–27.0)	25.0 (22.8–27.6)	0.006
ECOG performance status, score			
0–1	932 (92.7)	2018 (95.3)	0.004
≥2	73 (7.3)	100 (4.7)	
Alanine aminotransferase, $n\times$ULN	1.5 (1.0–2.4)	1.0 (1.0–2.0)	<0.001
Platelet count, $\times10^9$/L	113 (76–167)	122 (83–180)	0.001
Model for End-stage Liver Disease, score	9 (8–11)	8 (7–11)	0.036
Child–Turcotte–Pugh, class			
A	735 (73.1)	1617 (76.3)	0.003
B	238 (23.7)	470 (22.2)	
C	32 (3.2)	31 (1.5)	
Oesophageal varices[a]			
Absent	426 (52.3)	834 (50.9)	0.508
Present	388 (47.7)	804 (49.1)	

Note: Data are shown as the absolute value and percentage or median and interquartile range.
Abbreviations: ECOG-PS, performance status according to the Eastern Cooperative Oncology Group; SVR, sustained virological response; ULN, upper limit of normal.
[a]The total numbers of patients who underwent oesophagogastroduodenoscopy were 814/1005 (81.0%) patients with active HCV infection and 1638/2118 (77.3%) patients with SVR.

HCV infection, while 2118 patients were diagnosed with HCC after SVR. The majority of patients had cirrhosis with no difference between patients with active infection and those with SVR ($n=904$, 90.0% vs. $n=1909$, 90.1%; $p=0.971$). Elevated aminotransferases (ALT 1.5×upper limit of normal, IQR: 1.0–2.4 vs. 1.0×upper limit of normal, IQR: 1.0–2.0; $p<0.0001$) and more advanced liver disease (MELD score: 9, IQR: 8–11 vs. 8, IQR: 7–11; $p=0.036$; Child–Turcotte–Pugh score ≥ B7: $n=270$, 26.9% vs. $n=501$, 23.7%; $p=0.003$) were more common in patients with active HCV infection. The FIB-4 was higher in patients with active HCV infection compared to those with SVR (4.9, IQR 3.0–8.4 vs. 3.9, IQR 2.6–6.7; $p<0.001$). Lastly, patients with active HCV infection had a lower platelet count (113.0×10^9/L, IQR: 76–167 vs. 122×10^9/L, IQR: 83–180; $p=0.001$), while the prevalence of oesophageal varices was similar in both groups ($n=426$, 52.3% vs. $n=834$, 50.9%; $p=0.508$).

3.2 | Characteristics and Management of HCC

Overall, HCC was diagnosed mainly in the course of surveillance ($n=2005$, 64.2%); while diagnosis during surveillance was more frequent in patients with SVR ($n=1436$, 67.8% vs. $n=569$, 56.6%), both incidental diagnosis ($n=540$, 25.4% vs. $n=346$, 34.4%) and diagnosis due to symptoms ($n=142$, 6.7% vs. $n=90$, 9.0%; $p<0.0001$) were more frequent in patients with active HCV infection.

Table 2 shows the main characteristics of HCC subdivided according to viral status. HCC was more frequently uni-nodular ($n=1250$, 59.0% vs. $n=552$, 51.9%; $p<0.0001$) and less frequently diffuse/infiltrating ($n=60$, 2.8% vs. $n=43$, 4.3%; $p=0.002$) in patients with SVR, while macro-vascular invasion ($n=283$, 13.5% vs. $n=126$, 12.6%) and extra-hepatic spread ($n=101$, 4.7% vs. $n=42$, 4.2%) were not different between the two groups. Patients with SVR were more frequently Milan-in ($n=1241$, 58.6% vs. $n=543$, 53.1%, $p=0.004$) and had lower serum α-fetoprotein (12.0 ng/mL, 4.8–81.7 vs. 16.3 ng/mL, IQR 6.8–87.1, $p<0.0001$).

Table S1 shows the principal modality of HCC treatment. In the whole cohort, the most frequent initial treatments for HCC were those potentially curative ($n=2010$, 64.4%), with a more frequent use of resection in patients with SVR ($n=458$, 21.6% vs. $n=178$, 17.7%; $p=0.011$) and of liver transplantation in patients with active HCV infection ($n=88$, 8.8% vs. $n=135$, 6.4%; $p=0.016$). Local ablation as well as palliative treatments with a benefit on patient survival (trans-arterial and systemic therapies) were similarly represented in the two groups. Few patients received the best supportive care alone in both groups, but their prevalence was higher in those with active HCV infection ($n=59$, 5.9% vs. $n=74$, 3.5%; $p=0.002$).

3.3 | Overall Outcomes and Survival

The median overall survival from HCC treatment in the whole population was 58.0 months (95% CI: 54.4–61.6), with a significantly longer survival in patients with SVR (61.0 months, 95% CI: 56.5–65.5 vs. 51.0 months, 95% CI: 43.4–58.6; $p=0.003$; Figure 1A).

TABLE 2 | Modality of diagnosis, main characteristics and staging of hepatocellular carcinoma.

Characteristic	Active infection ($n=1005$)	SVR ($n=2118$)	p
Modality of tumour diagnosis			
Surveillance	569 (56.6)	1436 (67.8)	<0.0001
Incidental	346 (34.4)	540 (25.4)	
Symptomatic	90 (9.0)	142 (6.7)	
Gross pathology			
Uni-nodular	522 (51.9)	1250 (59.0)	<0.0001
Oligo-nodular (2–3 nodules)	218 (21.6)	444 (21.0)	
Multi-nodular (>3 nodules)	265 (26.4)	424 (20.0)	
Diffuse/infiltrating type	43 (4.3)	60 (2.8)	0.0412
Massive type	12 (1.2)	29 (1.4)	0.740
Median maximum diameter, cm	2.5 (1.7–4.0)	2.5 (1.6–4.0)	0.076
Median α-fetoprotein level, ng/mL	16.3 (6.8–87.1)	12.0 (4.8–81.7)	<0.0001
Macro-vascular invasion, present	126 (12.6)	283 (13.5)	0.112
Extra-hepatic spread, present	42 (4.2)	101 (4.7)	0.462

Note: Data are shown as the absolute value and percentage or median and interquartile range.
Abbreviation: SVR, sustained virological response.

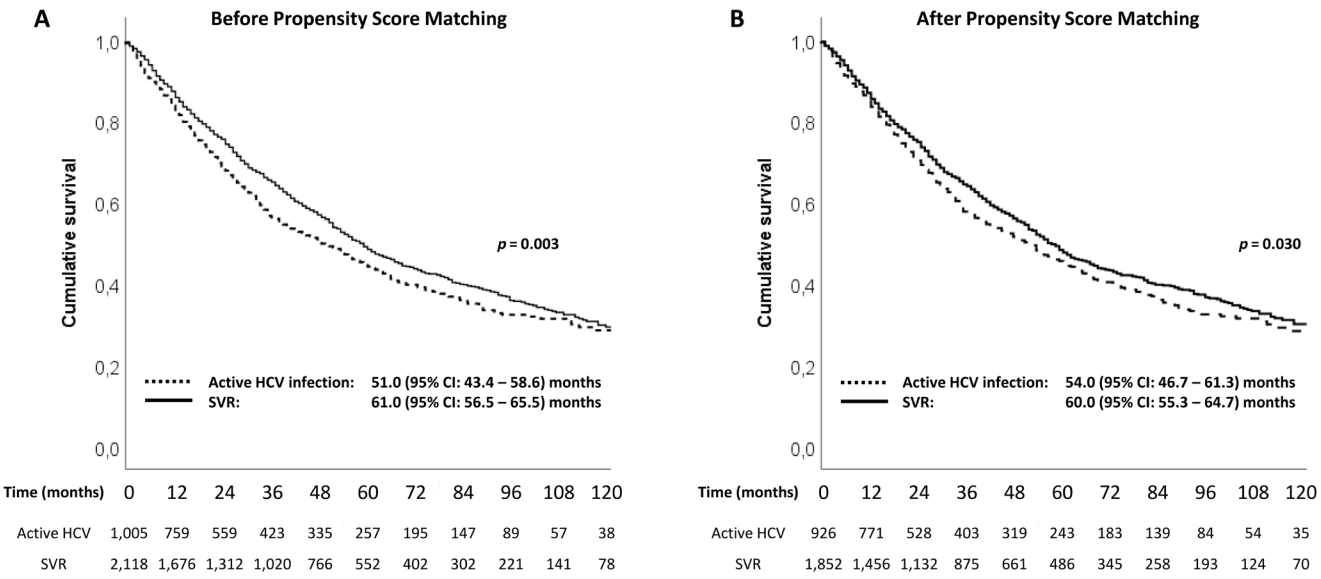

FIGURE 1 | Kaplan–Meier survival curves of patients according to viral status, before (A) and after (B) propensity score matching (PSM).

PSM included 926 patients with active HCV infection and 1852 patients with SVR whose general characteristics are reported in Table S1. The propensity score distributions before and after matching for patients with active infection and SVR are shown in Figure S2. After PSM, the median overall survival was 58.0 months (95% CI: 54.2–61.8) and was significantly longer in patients with SVR (60.0 months, 95% CI: 55.3–64.7 vs. 54.0 months, 95% CI: 46.7–61.3; $p=0.030$, Figure 1B).

Overall, the leading cause of death was HCC progression (49.7%), followed by liver failure (19.6%). Death due to HCC progression occurred without difference in patients with active HCV infection and in those with SVR ($n=263$, 50.8% vs. $n=487$, 49.1%; $p=0.548$), while more patients with active HCV infection died of liver failure ($n=127$, 24.5% vs. $n=169$, 17.1%; $p=0.001$). No significant difference was observed in bleeding-related deaths ($n=20$, 3.9% vs. $n=39$, 3.9%; $p=0.943$), death due to renal failure ($n=8$, 1.2% vs. $n=16$, 1.6%; $p=0.917$) and infection ($n=10$, 1.9% vs. $n=32$, 3.2%; $p=0.145$). Notably, non-liver-related causes of death were more prevalent in patients with SVR ($n=248$, 25.0% vs. $n=88$, 17.0%; $p=0.001$).

Oncological response was described in 2375 patients (76.1%), while 399 patients (12.8%) died before undergoing reassessment imaging, and in 349 patients (11.2%), response details were missing. Tumour progression was slightly, but significantly, more frequent in patients with active HCV infection ($n = 141$, 18.9% vs. $n = 251$, 15.4%; $p = 0.032$), while no difference was observed between the two groups in objective response ($n = 430$, 57.7% vs. $n = 995$, 61.1%, $p = 0.845$) and stable disease rates ($n = 174$, 23.4% vs. $n = 384$, 23.6%, $p = 0.424$; Figure 2A).

In patients with progressive disease, active HCV infection was associated with a lower median survival compared to SVR (11.0 months, 95% CI: 8.5–13.5 vs. 16.0 months, 95% CI: 12.6–19.4, $p = 0.016$; Figure 2B), while median survival was similar in the two groups, both considering patients with stable disease (38.0 months, 95% CI: 30.6–45.4 vs. 47.0 months, 95% CI: 40.0–54.0, $p = 0.768$; Figure 2C) and objective response (82.0 months, 95% CI: 66.9–97.1 vs. 86.0 months, 95% CI: 73.8–98.2, $p = 0.414$; Figure 2D).

Table 3 reports the results of the multivariate analysis, showing that using either model, male gender, higher ECOG-PS, higher MELD score [Model 1] or Child–Turcotte–Pugh score [Model 2], diagnosis due to symptoms, Milan-out stage, absence of active oncological treatment and active HCV infection were independently associated with a greater risk of mortality.

3.4 | Survival According to Different Main Treatments

When patients were categorised according to the different main treatments of HCC, liver transplantation was associated with the longest median overall survival, with no difference between the two groups (median not reached; Figure 3A). Among resected patients, the median overall survival was significantly shorter in patients with active HCV infection (82.0 months, 95% CI: 62.8–101.2 vs. 101.0 months, 95% CI: 82.0–120.0; $p = 0.040$; Figure 3B), while no survival differences were observed in patients treated with ablative therapies (68.0 months, 95% CI: 56.7–79.3 vs. 67.9 months, 95% CI: 61.3–74.7; $p = 0.433$; Figure 3C). Among patients undergoing transarterial therapies, the median overall survival was significantly shorter in those with active HCV infection (32.0 months, 95% CI: 26.6–37.4 vs. 39.0 months, 95% CI: 32.9–45.1; $p = 0.046$; Figure 3D). Lastly, viral status did not affect the life expectancy of patients treated with systemic therapy (13.0 months, 95% CI: 9.5–16.5 vs. 13.0 months, 95% CI: 10.6–15.4; $p = 0.334$; Figure 3E), while active HCV infection was associated with a shorter survival in patients treated with the best supportive care (5.0 months, 95% CI: 3.5–6.5 vs. 6.0 months, 95% CI: 3.8–8.3; $p = 0.055$; Figure 3F). When patients were categorised into those receiving non-surgical therapies and those who underwent surgical interventions, patients with active HCV

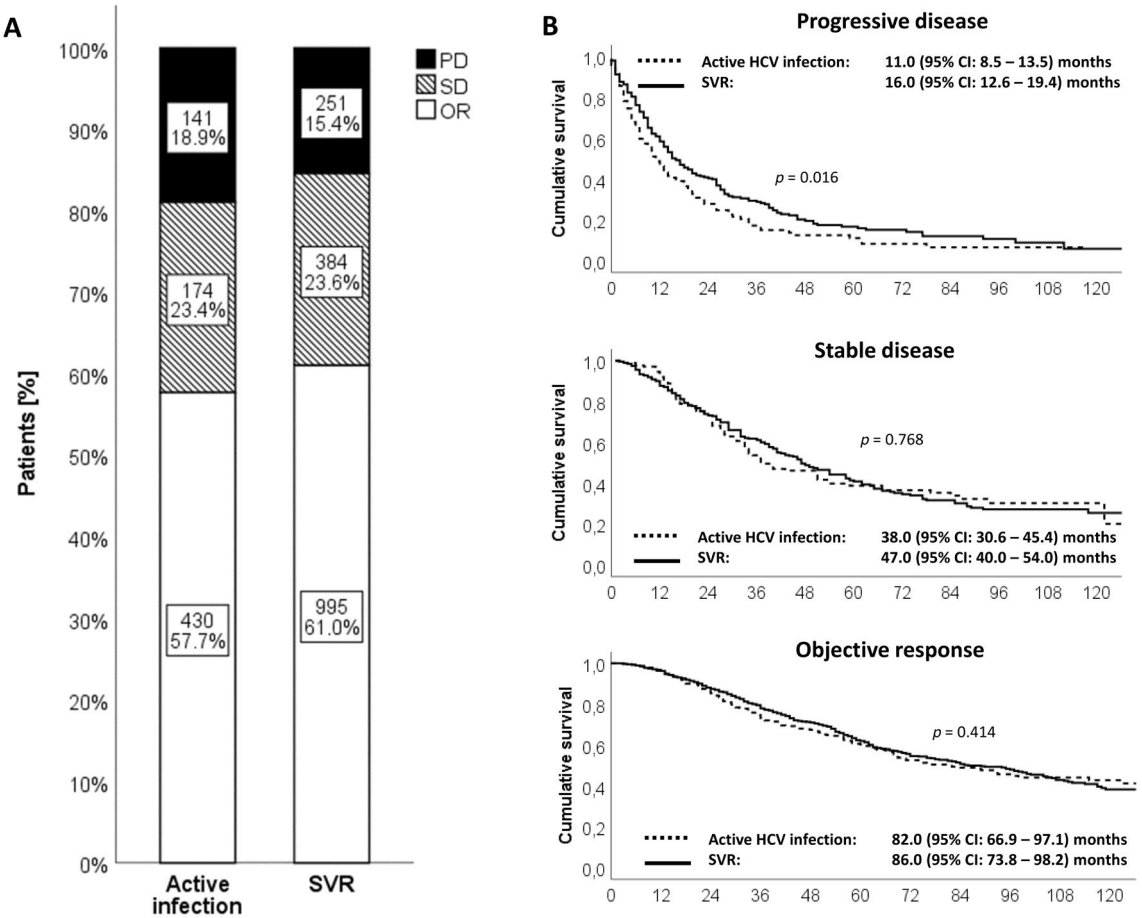

FIGURE 2 | (A) Proportion and number of patients with progressive disease (PD), stable disease (SD) and objective response (OR) according to viral status. (B) Kaplan–Meier survival curves of patients with PD, SD and OR according to viral status.

TABLE 3 | Univariate and multivariate Cox regression analyses of predictors of mortality.

	Univariate analysis	Multivariate analysis		Multivariate analysis		
		Model 1[a]		Model 2[a]		
Variable	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Gender (Female = ref)	1.11 (0.99–1.24)	0.062	1.17 (1.02–1.33)	0.023	1.23 (1.08–1.40)	0.002
Age (+1 year)	1.01 (1.01–1.02)	< 0.0001	1.00 (0.99–1.01)	0.241	1.01 (1.00–1.01)	0.051
ECOG-PS (+1 point)	1.74 (1.62–1.87)	< 0.0001	1.30 (1.19–1.42)	< 0.0001	1.24 (1.13–1.36)	< 0.0001
HCV status (active infection = ref)	0.85 (0.76–0.95)	0.003	0.79 (0.70–0.89)	< 0.0001	0.82 (0.73–0.93)	0.001
MELD score (+1 point)	1.06 (1.05–1.07)	< 0.0001	1.05 (1.04–1.06)	< 0.0001		
Child–Turcotte–Pugh score (+1 point)	1.09 (1.05–1.13)	< 0.0001			1.28 (1.22–1.34)	< 0.0001
Modality of diagnosis (surveillance = ref)						
Incidental	1.29 (1.13–1.48)		0.90 (0.77–1.05)	0.198	0.87 (0.74–1.01)	0.071
Symptomatic	3.44 (2.91–4.06)		1.53 (1.25–1.87)	< 0.0001	1.32 (1.08–1.61)	0.008
Milan criteria (OUT = ref)	0.43 (0.39–0.48)	< 0.0001	0.63 (0.55–0.72)	< 0.0001	0.62 (0.54–0.71)	< 0.0001
Main treatments (BSC = ref)						
Systemic therapies	0.40 (0.32–0.50)	< 0.0001	0.65 (0.50–0.85)	0.001	0.70 (0.54–0.91)	0.008
Trans-arterial therapies	0.15 (0.12–0.19)	< 0.0001	0.30 (0.23–0.39)	< 0.0001	0.32 (0.24–0.41)	< 0.0001
Ablative therapies	0.08 (0.07–0.10)	< 0.0001	0.18 (0.14–0.23)	< 0.0001	0.20 (0.16–0.27)	< 0.0001
Liver resection	0.06 (0.05–0.08)	< 0.0001	0.14 (0.11–0.19)	< 0.0001	0.17 (0.13–0.23)	< 0.0001
Liver transplantation	0.03 (0.02–0.04)	< 0.0001	0.05 (0.03–0.07)	< 0.0001	0.05 (0.03–0.07)	< 0.0001

Abbreviations: ECOG-PS, performance status according to the Eastern Cooperative Oncology Group; HRs, hazard ratios; MELD, Model for End-stage Liver Disease.
[a]Model 1: including MELD score. Model 2: including the Child–Turcotte–Pugh classification.

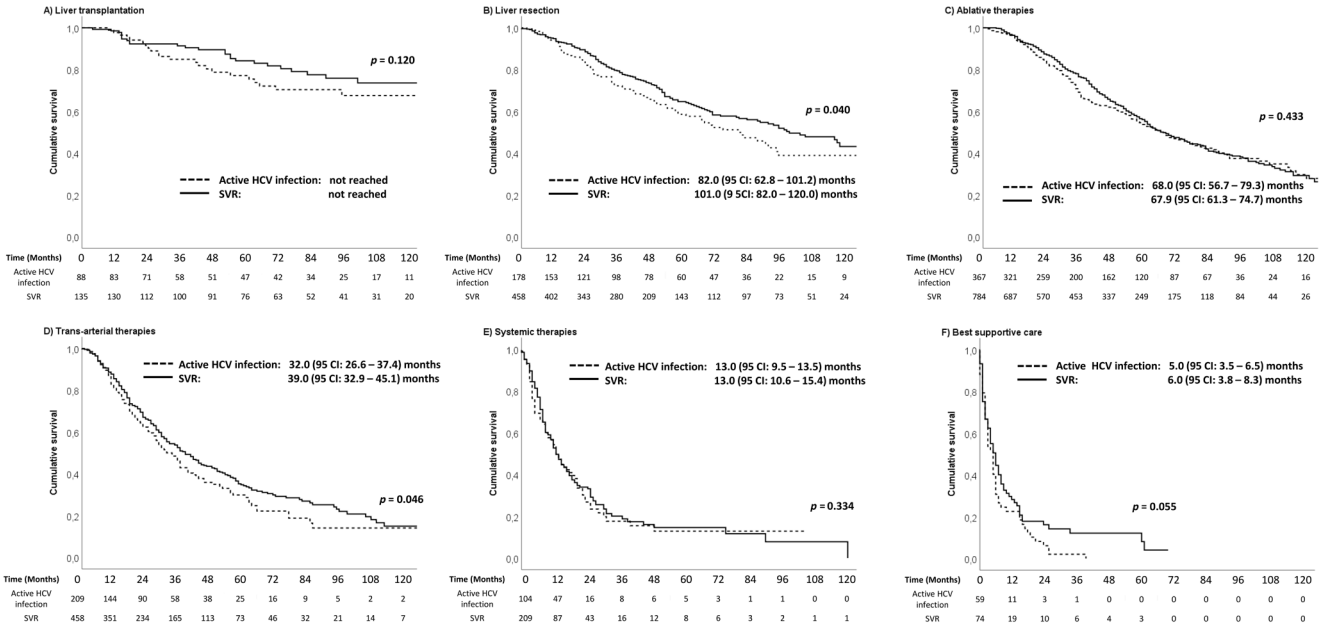

FIGURE 3 | Kaplan–Meier survival curves of all patients according to viral status per main treatment (A: liver transplantation; B: liver resection; C: ablative therapies; D: trans-arterial therapies; E: systemic therapies; F: best supportive care).

infection had shorter survival in both groups (non-surgical therapies: 37.0 months, 95% CI: 31.8–42.2 vs. 49.0 months, 95% CI: 44.7–53.3; $p = 0.044$; Figure S3A; surgical therapies: 98.0 months, 95% CI: 61.7–134.3 vs. 134.0 months, 95% CI: 105.7–162.3; $p = 0.031$; Figure S3B).

Table S3 details demographic, clinical and oncological characteristics of the patients according to the main HCC treatment and viral status. No difference between patients with active HCV infection and those with SVR was observed for all demographic, clinical and oncological characteristics in patients treated with the same modality, except liver transplantation. Namely, transplanted patients with SVR were significantly older (57.4 years, IQR 52.4–61.4 vs. 54.3 years, IQR 50.3–58.6) and more frequently Milan-in ($n = 94$, 69.6% vs. $n = 48$, 54.5%).

4 | Discussion

The introduction of DAAs for the treatment of chronic HCV infection truly represented a *watershed moment* in the history of clinical hepatology, as emphasised by the editorial article that accompanied the first studies providing seminal evidence of the efficacy of these drugs [4]. The subsequent availability of DAAs in clinical practice led to a dramatic decrease in the indication to liver transplantation for patients with HCV-related liver failure, as in patients with advanced liver disease viral clearance can improve liver function to a point where transplantation is no more required or may be deferred [25]. In fact, in patients with compensated advanced chronic liver disease, the eradication of HCV infection—however obtained—is associated with the improvement of liver function and clinical manifestations of portal hypertension, leading to a marked reduction in the risk of liver decompensation, death due to liver failure and of HCC development [9, 11, 13, 14, 26].

A recent retrospective study carried out in HCV patients with HCC who had a complete response to various oncological treatments showed that DAA treatment was associated with a reduced mortality compared to patients who did not receive antiviral therapy, supporting the concept that viral clearance is associated with an improved outcome even in patients with a history of HCC [17]. The authors surmised that the absence of viral replication, with its positive reflex on liver dysfunction, may also benefit patients undergoing non-curative therapies for HCC, thus calling for further studies on this issue [17].

Therefore, in order to shed further light on this issue, we compared the outcome of various oncological treatments in patients with active or cleared HCV infection in a large population of anti-HCV-positive patients with HCC. Patients with concurrent factors for chronic liver disease such as hepatitis B virus infection and alcohol abuse were excluded from the study cohort to avoid potential confounders and to be able to assess the relative role played by active HCV infection on the overall outcome of patients. We observed that patients with SVR were older, had a higher body mass index and had a more preserved liver function. In these patients, HCC was diagnosed more commonly during surveillance and was therefore more frequently within the Milan criteria as compared to patients with active HCV infection. Alpha-fetoprotein was higher in patients with active HCV infection, a finding that can be related to both more advanced tumour stage and greater necro-inflammatory activity [27]. Therefore, to avoid potential confounders affecting the overall outcome, we also carried out a comparison after adjustment with PSM. Noteworthy, before PSM, we observed a survival advantage of 10 months in favour of patients with SVR, and this advantage persisted, though reduced to 6 months, in the PSM cohorts. This benefit may be related to the combination of the intrinsic positive prognostic effect, testified by the significantly better outcomes of liver resection, intra-arterial therapies and best supportive care, and a greater access to potentially curative treatments, provided by a more preserved liver function in patients with SVR. Considering treatment distribution, these patients had a significantly higher access rate to hepatic resection than those with active infection. This disadvantage was partially compensated by a more liberal use of liver transplantation in the group with active infection, where expanded criteria (Milan-out) were more often adopted. Moreover, more patients with active HCV infection were considered manageable only with the best supportive care. These data show, at least for the main curative therapies, that in clinical practice, physicians tend to treat patients according to the principle of transplant benefit, as patients with active HCV infection, who were younger and with a more deranged liver function, more frequently received liver transplantation as a means to cure both the underlying liver disease and HCC, while patients with SVR who were older and with compensated liver disease more frequently underwent resection. Noteworthy, we also observed that active HCV infection had a role on the overall survival independently of clinical and oncological stages and HCC treatment.

A finding that further confirmed a role of active HCV infection on the outcome was identified when survival was analysed according to oncological treatments. Patients with active HCV infection who underwent treatments potentially responsible for a loss of liver function, such as resection and transarterial therapies, showed a significantly shorter survival than patients with SVR, indicating that the absence of the ongoing necro-inflammatory activity due to active infection has a key prognostic role when therapies reducing the functional liver volume are used. Lastly, a further stratification of patients into those who received surgical or non-surgical treatments highlighted how the presence of SVR is associated with a significant, median survival advantage of 1 year (non-surgical therapies) and 3 years (surgical therapies) as compared to patients with HCV active infection. One might also speculate that other factors besides active HCV infection were responsible for these findings, although when we assessed patients' outcome according to various treatments for HCC, PSM adjustment became redundant, as all the main clinical and oncological variables were not differently distributed between patients with active infection or SVR for each treatment apart liver transplantation where, expectedly, patients with SVR were older and more frequently had Milan-in tumours.

Lastly, the finding that active HCV infection was associated with a greater mortality from liver failure while more patients with SVR died from non-liver-related causes, and that HCC progression was responsible for death in a similar measure in both

patient groups, emphasises the role of preserving liver function on the outcome of HCC treatment. Despite patients of the two groups benefitted from a similar access to treatments with curative and palliative intention—leading to an equal distribution of death due to tumour progression—SVR extended the liver disease–related survival, thus increasing non-liver-related death rates. These findings align with those by Singal et al. who observed that in patients with successfully treated HCC death due to liver failure was more frequent in patients with active HCV infection than in those who obtained SVR to DAAs, while death due to HCC progression was similar in both groups [17].

This study has limitations that do not allow us to draw subtler conclusions regarding the actual effect on active HCV infection on the overall outcome of patients. Indeed, controversies still exist regarding the potential influence of the ongoing viral replication in response to oncological treatments, and our study was unable to provide a direct response to this clinical question, but it provided evidence that the presence of ongoing viral replication has an independent detrimental effect on patients' prognosis, even after adjustment for confounding factors. This effect was observed despite similar rates of objective response and stable disease between patients with active and cleared HCV infection, while we found a greater proportion of progressive disease in the former group. This *datum* may not easily be contextualised as patients underwent different treatments, and analyses for each treatment reduced sample size to an extent not allowing meaningful comparisons. However, considering that among patients with progressive disease, those with active HCV infection had a shorter survival than those with SVR, it can be surmised that active infection may be a prognostic determinant even in patients with an HCC not completely treated. Another drawback is inherent to the retrospective nature of the study, as viral categorisation was carried out at the time of treatment of HCC and, therefore, although it is likely that most patients undergoing curative treatment for HCC were subsequently treated with DAAs, the effect of this strategy on patients' outcome was not captured by the database; furthermore, patients were categorised according to the initial, main treatment for HCC received, and this analysis does not take into account potential subsequent treatments. Lastly, our results are limited by retrospective data analysis, which may introduce potential selection biases. While we feel that the most appropriate modality of providing a response to the relevant clinical query addressed in our study would be to perform a randomised study, we also acknowledge that such a study—due to the widespread availability of DAA treatment leading to, at least in the Western world, a residual population of HCV-RNA-positive among patients with HCC—unlikely will be performed for both practical and ethical reasons.

In conclusion, we observed that the absence of viral replication is beneficial in patients with anti-HCV-positive HCC. Patients who had obtained an SVR to previous antiviral therapy had an overall survival benefit of at least 6 months as compared to patients with active HCV infection, and this benefit exceeded 1 year when patients were treated with liver resection. When considering clinical and oncological characteristics, and access to various treatments for HCC, the absence of viral replication was independently associated with the risk of death. Overall, these findings would suggest that patients with HCV-related HCC benefit from antiviral therapy independently of the cure of HCC.

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Conflicts of Interest

Edoardo G. Giannini. AstraZeneca, Roche: speaking and teaching; Ipsen: consultancy. Franco Trevisani. AbbVie, Astra Zeneca, Gilead, MSD, Roche: research grants; EISAI, Roche: advisory board. Filippo Pelizzaro. MSD advisory board. Andrea Pasta, Maria Corina Plaz Torres, Giulia Pieri, Giuseppe Cabibbo, Angelo Sangiovanni, Fabio Piscaglia, Claudia Campani, Gabriele Missale, Gianpaolo Vidili, Giorgia Ghittoni, Filippo Pelizzaro, Francesco Giuseppe Foschi, Filomena Morisco, Valentina Santi, Gianluca Svegliati-Baroni, Francesco Azzaroli, Carlo Saitta, Maurizia Rossana Brunetto, Rodolfo Sacco, Antonio Gasbarrini, Sara Boninsegna, Gerardo Nardone, Andrea Martini, Andrea Mega, David Sacerdoti, Daniela Magalotti, Alessandro Vitale, Laura Bucci: nothing to declare.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

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