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Achieving SVR in patients with hepatitis C-related HCC is associated with an improvement in overall survival: real word data

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Abstract

Aims: The optimal timing for DAA therapy initiation in patients with chronic hepatitis C (CHC) and HCC is still debated. The aim of our study was to provide real-world data on virological response and overall survival in patients with hepatitis C-related HCC.

Methods: Retrospectively, we included patients with HCV-related HCC between 2015 and 2020. The primary outcome was to compare the SVR rate in the patients with active or historical HCC who were treated with DAA therapy. The secondary outcome was to measure the overall survival of those patients.

Results: 98 patients were included, and the majority were cirrhotic with compensated liver disease. 71.4% received DAA therapy at the time of initial HCC diagnosis and 11.2% received HCV treatment at the time of HCC recurrence (Active HCC cohort). 17.3% had previously received HCC treatment, but there was no evidence of recurrence at the time of DAA (Historical HCC Cohort). The SVR rate was 81.6%, but decreased to 75.7% in patients with active HCC. The presence of active HCC and the number of HCC nodules were the only factors associated with not achieving SVR in the multivariate analysis. The median survival was higher in those who achieved SVR. Active HCC and failure to achieve SVR were the main factors associated with mortality.

Conclusions: Treating hepatitis C in patients with HCC is feasible with significant rates of SVR, even if SVR rates

decrease in patients with active HCC and these patients require more than one DAA therapy. Failure to achieve SVR is one of the main factors associated with mortality.

Keywords: Hepatitis C treatment, hepatocellular carcinoma, DAA therapy, sustained virological response, overall survival

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide[1]. Despite the introduction of oral direct-acting antivirals (DAAs) for hepatitis C virus (HCV) over the last 7 years, with high efficacy and tolerability, chronic HCV remains a major cause of HCC in cirrhotic patients[2].

Achieving a sustained virological response (SVR) after hepatitis C treatment results in an improvement in patient survival rates[3], with a reduction in the risk of liver decompensation, hepatic oncogenesis, and hospital admissions[4]. Recent data have also shown clinical improvements in patients with decompensated cirrhosis awaiting liver transplantation who were treated with oral DAAs. Overall, a quarter of patients were delisted due to an improvement in their liver function[5]. In a large European cohort, this improvement was maintained for a significant period of time. Moreover, patients who were delisted had a low risk of liver-related complications during long-term follow-up[6].

Early reports raised concerns about an adverse effect of the new DAA HCV treatments on the natural course of HCC, with unexpectedly higher rates of HCC incidence and recurrence in those who received antiviral therapy. They suggested that there was aggressive tumour behaviour, which implied oncogenic effects from DAA therapy[7]. However, these results were not corroborated in prospective studies, and the most recent meta-analysis reported that DAA therapy does not seem to significantly influence the HCC recurrence rate compared with non-treated patients[8] or those previously treated with an Interferon (IFN) regimen[9].

Additionally, HCV antiviral treatments reduce the risk of HCC recurrence among patients receiving curative HCC treatments such as liver transplantation, resection, and local ablation. However, the optimal timing for DAA therapy initiation in patients with active HCC is still debated[10]. Some authors recommend deferring DAA therapy for at least 4 to 6 months following potentially curative HCC treatment. There is also a lack of consensus as to whether to treat HCV in patients who are not candidates for HCC treatment due to their poor liver function and, as such, their possible competitive risk of mortality. Therefore, patients who could potentially improve their liver function after achieving SVR are at a disadvantage in possibly receiving HCC treatment.

The HCV treatment policy at King's College Hospital has allowed us to provide HCV therapy to all viraemic patients, including those with HCC. The aim of this retrospective study is to provide a real-life data analysis of HCV treatment, virological cure rates, and overall survival of patients with HCC (historical or active) and current HCV infection who were treated with DAA therapies.

MATERIALS AND METHODS

This was a retrospective cohort study from a prospective database of patients who were diagnosed with HCC and positive HCV RNA that were managed by a multidisciplinary team between January 2015 and January 2020 at King's College Hospital and followed up until either death, liver transplantation, or until September 2022. This database was matched with the national Hepatitis C register, so patients with HCC

were selected.

Patients treated with the DAAs over that period, either historical or active HCC, were included. A diagnosis of HCC was confirmed by biopsy or radiological criteria in accordance with European guidelines[11]. Patients were divided into two main groups: (1) **Historical HCC cohort:** HCC diagnosed and treated prior to 2015, and no evidence of active recurrence at the time of administering DAA therapy. Patients who had a liver transplant before 2015 for HCC and have active infection post-transplant were included in this group; (2) **Active HCC cohort:** DAA therapy at the time of active HCC. This group was further subdivided into those receiving DAAs at the time of initial HCC diagnosis (**Active HCC Index Cohort**) *vs.* those treated at the time of HCC recurrence (**Active HCC Recurrence Cohort**). Patients who were diagnosed with HCC during the DAA therapy were also included in the Active HCC cohort.

The diagnosis of cirrhosis was based on liver biopsy or transient elastography (> 12.5 kPa).

Patients with combined HCC-cholangiocarcinoma or fibrolamellar-HCC were excluded. Treatments for HCC were defined as curative-ablation, resection, or liver transplantation, or non-curative-transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT), stereotactic body radiation therapy (SBRT), or systemic therapy[8,12]. Active HCV infection was defined by confirmatory positive HCV RNA and SVR was defined as undetectable HCV RNA at 12 weeks after the end of treatment.

Baseline data were collected by reviewing clinical records, multidisciplinary team reports, and investigation results (blood tests, histopathology reports, radiological images). Blood test results were noted before and after HCV treatment, regardless of whether the patient achieved SVR. Alpha-fetoprotein measurements (AFP) were collected at the time of HCC diagnosis.

OUTCOMES

The main outcome of our study was to compare the SVR rate in the three HCC groups, as defined above. SVR was calculated based on intention-to-treat (ITT), and thus, all patients who initiated treatment were included.

Our secondary outcome was to measure the overall survival from the *time of HCV treatment* until death, liver transplant, or the patient's last clinic appointment. For the survival analysis, HCC was divided into historical HCC and active HCC cohorts. Overall survival was calculated for both cohorts, but specific analysis was separately carried out only for patients with cirrhosis and active HCC according to BCLC stage and type of treatment.

STATISTICAL ANALYSIS

Continuous variables were reported as mean and SD (median and IQR if appropriate), while categorical variables were expressed as numbers and percentages. Chi-square tests were used to test the difference in proportions of categorical variables between groups. Variables associated with SVR and non-SVR were compared using the chi-squared test, or the Fisher's exact test for categorical variables if appropriate, and the *t* -test or Mann-Whitney test for continuous variables.

Data analysis for SVR was presented by intention to treat (ITT). Univariate and multivariate modelling were performed for SVR and overall survival (OS). Univariable and multivariable Cox regression models were performed for OS. OS was calculated for both cohorts, but specific analysis according to SVR status, tumour

stage (BCLC stage 0/A *vs.* BCLC stage B/C), and tumour treatment (curative *vs.* non-curative) was only calculated in the active HCC cohort by a Kaplan-Meir. Patients in the historic HCC cohort were excluded from the Kaplan-Meir analysis as most of them achieved SVR. For the active HCC cohort, liver transplantation (dichotomy variable) was considered an independent variable (competitive variable) in the modelling. Analysis was performed using SPSS v.25 and a *P*-value < 0.05 was considered significant.

RESULTS

98 patients with HCC and active HCV were identified [Figure 1]. 83.7% were male, most of whom were white (74.2%) with a median age of 60 (IQR 55-64) years. 84.7% were cirrhotic with compensated liver function Child-Pugh A (72.3%) and MELD less than 15 (84.1%). 19.6% had type 2 diabetes, 15.5% had hypertension, and the same proportion tested positive for the hepatitis B core antibody. Demographic and clinic variables are summarised in Table 1.

Hepatitis C infection and treatment

The most common HCV genotype was 1 (45.9%), followed by genotype 3 (41.8%). More than half of patients had a history of failed IFN therapy and almost one-third of patients received more than one DAA therapy (28.6%). The most common initial DAA treatment was sofosbuvir/ledipasvir ± ribavirin (33 patients, 34.8%), followed by sofosbuvir/velpatasvir ± ribavirin (23 patients, 24.2%), sofosbuvir/daclastavir/ribavirin and ombitasvir/paritaprevir/ritonavir/dasabuvir ± ribavirin (14.7%). At the time of the second DAA therapy, sofosbuvir/velpatasvir ± ribavirin (11 patients, 39.3%) and sofosbuvir/velpatasvir/voxilaprevir (9 patients, 32.1%) were the most prescribed treatments.

Only two patients who had DAA failure to the second DAA therapy showed resistance associated with substitutions in the NS5A region.

HCC diagnosis and stage

71.4% of patients were treated with DAA therapy at the time of initial HCC diagnosis (Active HCC cohort), whereas 11.2% received HCV treatment at the time of HCC recurrence (Active HCC Recurrent cohort). 17.4% had a history of HCC but no evidence of recurrence at the time of DAA therapy (Historical cohort, Figure 1). The majority of patients displayed well-compensated liver function at the time of treatment (82.5% were BCLC stage 0/A, 10.3% BCLC stage B). 70.4% had one nodule at the time of diagnosis, and 52% of patients received a curative therapy, 44.9% received a non-curative therapy, and 3.1% received palliative care. The median number of HCC treatments was 2 (IQR 1-3). The median AFP at the time of the HCC diagnosis was 19 (IQR 9-113).

Demographic and clinical characteristics by group are summarised in Table 2. Patients with historical HCC were less likely to be cirrhotic at the time of hepatitis C treatment compared with the active HCC or active HCC recurrence cohorts (29.4% *vs.* 97.1% *vs.* 90.9%, respectively). All patients with historical HCC were classified as early stage (BCLC 0/A), so they received curative treatments (84.3% of which were liver transplants). Patients with active HCC recurrence had higher median HCC treatments in comparison with active HCC index cohort (4 *IQR* 3-4 *vs.* 2 *IQR* 1-2, $P < 0.001$).

One quarter of patients who were in the active HCC-index cohort and had an early-stage tumour ($n = 56$) underwent a liver transplant ($n = 14$) during the follow-up, compared with only 10% ($n = 1$) of patients who were in the active HCC-recurrence cohort.

Table 1. Demographic and clinical outcomes divided by SVR status

	Total (*n* = 98)	SVR (no 18)	SVR (yes 80)	*P*
Male *n* (%)	82 (83.7)	18 (100)	64 (80)	0.027
Female *n* (%)	16 (16.3)	0 (0)	16 (20)	
Age (years), median (IQR)	60 (55-64)	60.5 (57.8-64)	60 (55-64)	0.767
Race *n* (%)				
White	73 (74.5)	14 (93.3)	59 (85.5)	
Black African/Caribbean	3 (3.1)	1 (5.6)	2 (2.9)	
Asian	5 (5.1)	0	5 (7.2)	0.507
Mediterranean	3 (3.1)	0	3 (4.3)	
Presence of Cirrhosis%	83 (84.7)	17 (94.4)	66 (82.5)	0.180
Presence portal Hypertension (yes)	48 (49.0)	5 (31.3)	43 (60.6)	0.028
Child-Pugh A	60 (72.3)	13 (76.5)	47 (71.2)	
Child-Pugh B/C	23 (27.7)	4 (23.5)	19 (28.8)	0.446
MELD ≥ 15	10 (15.9)	0	10 (18.9)	0.153
Genotype				
1	45 (45.9)	7 (38.9)	38 (47.5)	
2	1 (1)	0	1 (1.3)	
3	41 (41.8)	11 (61.1)	30 (37.5)	
4	9 (9.2)	0	9 (11.3)	0.235
Unknown	2 (2.0)		2 (2.5)	
Previous HCV treatment (IFN)%	51 (53.7)	9 (52.2)	41 (53.2)	0.595
Number of Hepatitis C treatment				
One treatment (%)	70 (71.4)	7 (38.9)	63 (78.8)	
More than one (%)	28 (28.6)	11 (61.1)	17 (21.3)	0.002
Type initial DAAs				
Ledipasvir/Sofosbuvir ± RBV	30 (31.6)	5 (27.8)	25 (31.3)	
Sofosbuvir/Daclastavir ± RBV	14 (14.7)	0	14 (17.5)	
Sofosbuvir/Velpatasvir ± RBV	15 (15.8)	7 (38.9)	8 (10)	0.016
Ombitasvir/paritaprevir/ritonavir/dasabuvir ± RBV	12 (12.6)	2 (11.1)	10 (12.5)	
Comorbidities *n* (%)				
Hypertension	15 (15.3)	2 (11.1)	13 (16.5)	0.441
Type 2 diabetes	19 (19.4)	2 (11.1)	17 (21.3)	0.259
Obesity	7 (7.1)	1 (5.6)	6 (7.5)	0.615
Psychiatric disorders	7 (7.1)	0	7 (8.9)	0.226
COPD	8 (8.2)	3 (16.7)	5 (6.3)	0.164
HIV coinfection	4 (4.1)	1 (5.6)	3 (3.8)	0.566
HBV coinfection	1 (1)	0	1 (1.3)	0.814
Anti-hep B core positive	15 (15.3)	0	15 (18.8)	0.035
HCC%				
Active HCC index	70 (71.4)	17 (94.9)	53 (66.3)	
Historical HCC	17 (17.3)	1 (5.1)	16 (20.0)	
Active HCC recurrence	11 (11.2)	0	11 (13.8)	0.026
BCLC stage				
0/A	81 (82.7)	10 (55.6)	71 (88.8)	
B	10 (10.2)	5 (27.8)	5 (6.3)	
C	5 (5.1)	2 (11.1)	3 (3.8)	0.010
D	2 (2.0)	1 (5.6)	1 (1.3)	
N. nodules				
1	69 (70.4)	9 (50)	60 (77.9)	
2	15 (15.3)	3 (16.7)	12 (15)	0.005
≥ 3	11 (11.2)	6 (33.4)	5 (6.3)	
Type treatment				
Curative	51 (52)	5 (27.8)	46 (57.5)	
Non-curative	44 (44.9)	13 (72.2)	31 (38.8)	0.074
Best supportive care	3 (3.1)	0	3 (3.8)	
No. HCC therapies	2 (1-3)	2 (1-2)	2 (1-3)	0.403
Albumin g/L	39 (34.8-41.0)	39 (34.5-41.5)	39 (34.5-41.0)	0.816
Bilirubin umol/L	15 (11-27)	17 (11.5-27.5)	14 (11-27)	0.377
Platelets 10*9/L	120 (75.5-162.0)	125 (90.5-167.0)	115.5 (75-160)	0.266
INR (ratio)	1.14 (1.06-1.30)	1.11 (1.00-1.23)	1.16 (1.08-1.32)	0.109
AFP kIU/L (time of HCC diagnosis)	19 (9-113)	105 (12.5-424.0)	17 (8.0-85.5)	0.017

HCC: hepatocellular carcinoma; HCV: hepatitis C virus; DAAs: direct-acting antivirals; IFN: Interferon; AFP: alpha-fetoprotein measurements; BCLC: Barcelona clinic liver cancer; IQR: interquartile range; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; MELD: model for end stage liver disease.

Table 2. Demographic and clinical outcomes divided by HCC group

	Total (*n* = 98)	Historical HCC (17)	Active HCC index cohort (70)	Active HCC recurrence cohort (11)	*P*
Presence of cirrhotic% (yes)	83 (84.7)	5 (29.4)	68 (97.1)	10 (90.9)	0.693
Child-Pugh A					
Child-Pugh B/C	60 (72.3)	4 (23.5)	49 (70)	7 (63.6)	0.057
MELD ≥ 15	23 (27.7)	1 (5.9)	19 (27.1)	3 (27.3)	
	10 (12.0)	1 (5.9)	9 (12.9)	0	
Genotype					
1					
2	45 (45.9)	7 (41.2)	32 (45.7)	6 (54.5)	
3	1 (1)	0	1 (1.4)	0	0.654
4	41 (41.8)	6 (36.3)	30 (42.9)	5 (45.5)	
	9 (9.2)	3 (17.6)	6 (8.3)	0	
Previous HCV treatment (IFN)					
SVR rates (%)	50 (51.0)	11 (73.3)	34 (48.6)	5 (55.6)	0.216
Number of Hepatitis C treatment	70 (71.4)	16 (94.1)	53 (75.7)	11 (100)	0.037
One treatment (%)					
More than one (%)					
	70 (71.4)	16 (94.1)	45 (64.3)	9 (81.8)	0.037
	28 (28.6)	1 (5.9)	25 (35.7)	2 (18.2)	
HCC					
BCLC stage (%)					
0/A	81 (82.7)	16 (94.1)	56 (80)	8 (72.7)	
B	10 (10.2)	1 (5.9)	7 (10)	2 (18.2)	
C	5 (5.1)		5 (7.1)	1 (9.1)	0.092
D	2 (2.0)		2 (2.9)		
No. Tumours (%)					
1	69 (70.4)	11 (64.7)	49 (70)	9 (81.8)	
2	15 (15.3)	2 (11.8)	12 (17.1)	1 (9.1)	0.809
3+	11 (11.2)	3 (17.6)	7 (10)	1 (9.1)	
Type treatment					
Curative	51 (52.0)	17 (100)	29 (41.4)	5 (45.5)	
Non-Curative	44 (44.9)		38 (54.3)	6 (54.5)	<
BSC	3 (3.1)		3 (4.3)		0.001
No. HCC therapies *median (IQR)*	2 (1-3)	1 (1-2)	2 (1-2)	4 (3-4)	< 0.001

HCC: hepatocellular carcinoma; HCV: hepatitis C virus; IFN: Interferon; BCLC: Barcelona clinic liver cancer; IQR: interquartile range; MELD: model for end stage liver disease; BSC: best support care.

The median time from HCC diagnosis to the first DAA therapy was 41 months (IQR 30-73), 61 months (IQR 25-81), and 1 month (IQR negative-10) in historical HCC cohort, active HCC recurrence cohort, and active HCC index cohort, respectively.

Hepatitis C SVR

The overall SVR was 81.6% (80/98). By subgroups: 100% in patients in the active HCC recurrence cohort, 94.1% in patients with historical HCC, and 75.7% in patients in the active HCC index cohort (P = 0.005) [Figure 1].

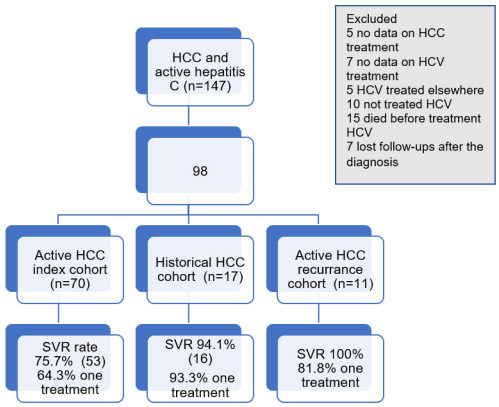

Figure 1. Flow chart of rate of ITT SVR stratified by HCC group and the rate of SVR with the first DAA therapy. ITT: intention-to-treat; SVR: sustained virological response; HCC: hepatocellular carcinoma; DAA: direct-acting antiviral.

SVR was achieved in 63.3% (62/98) of patients who received the first DAA therapy. Amongst those who received the second DAA therapy, 50% (14/28) achieved SVR. For those who received the third DAA therapy, 80% (4/5) achieved SVR. It is important to highlight that only 38.5% (4/13) of non-responders to a second DAA therapy received the third course [Figure 2].

Additionally, SVR was higher in females, as well as patients with early-stage tumours (BCLC 0/A), lower number of nodules, or receiving curative treatments [Table 1]. Furthermore, patients with higher AFP at the time of HCC diagnosis had the lowest SVR rate.

After adjusting for sex, age, presence of cirrhosis, number of HCV therapies, HCC stage, and type of HCC treatment, only the presence of active HCC at the time of HCV therapy (HR, 5.46: 95%CI: 1.25-23.82, $P = 0.024$) and the number of HCC nodules (2.19 95%CI: 1.08-4.41, $P = 0.029$) were factors associated with not achieving SVR in multivariate modelling [Table 3A].

After achieving SVR, there was no statistical improvement in liver function of patients (Child-Pugh A 58.8% *vs.* 63.7%, Child-Pugh B 23.8% *vs.* 18.8%, $P = 0.43$).

OVERALL SURVIVAL

Whole cohorts

The median survival for the historical HCC cohort was 82 (95%CI: 69-94) months and 62 (95%CI: 55-71) months for active HCC cohort (log-rank test $P = 0.02$).

The median survival of those who achieved SVR was 67 (95%CI: 59-75) months compared with 45 (95%CI: 29-61) months for those who did not achieve SVR (log Rank test $P = 0.02$).

Active HCC cohorts

Patients with active tumour who achieved SVR had a median survival of 67 (95%CI: 59-75) months compared with those who did not achieve SVR, 45 (95%CI: 30-62; log-rank test $P = 0.023$) months, as shown in Figure 3A.

A separate analysis of the early-stage tumour group (BCLC 0/A) showed that median survival was significantly higher in those who achieved SVR (72, 95%CI: 64-80 months), compared with those who did

Table 3. (A) multivariate analysis for non-SVR; (B) multivariate analysis for mortality

A (non-SVR)	**Multivariate Cox regression**		
	HR	**95%CI**	***P***
Male *vs.* Female	1.03	0.51-2.21	0.926
Age (years), median	-		
Presence of cirrhosis *vs.* no cirrhosis	3.61	0.44-29.41	0.231
Child-Pugh A *vs.* Child-Pugh B/C	-		
Number of Hepatitis C treatment One treatment *vs.* more than one	1.07	0.49-2.33	0.858
Active HCC *vs.* historical HCC (at the time of HCV treatment)	5.46	1.25-23.82	0.024
BCLC B/C *vs.* BCLC 0/A	1.11	1.08-4.41	0.817
N. HCC nodules more than 1 *vs.* 1	2.19	1.08-4.41	0.029
Type of treatment Curative *vs.* non-curative	-		
AFP (time of HCC diagnosis)	1.00	0.99-1.00	0.771
B (mortality)	**HR**	**95%CI**	***P***
Age (years), median (IQR)	0.97	0.920-1.018	0.210
Non-cirrhotic *vs.* cirrhotic	0.420	0.141-1.251	0.119
Child-Pugh B/C *vs.* Child-Pugh A	-		
Non-SVR *vs.* SVR	2.65	1.323-5.320	0.006
Number of hepatitis C treatment one *vs.* more than one	-		
Active HCC *vs.* Historical HCC	37.70	4.72-300.7	0.001
BCLC 0/A *vs.* B/C	0.612	0.190-1.972	0.411
Type treatment Non-curative *vs.* curative	1.580	0.761-3.282	0.220
AFP < 10 kiu/L *vs.* ≥ 10	0.954	0.452-2.013	0.901

SVR: sustained virological response; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; AFP: alpha-fetoprotein measurements; BCLC: Barcelona clinic liver cancer; CI: confidence interval; HR: hazard ratio.

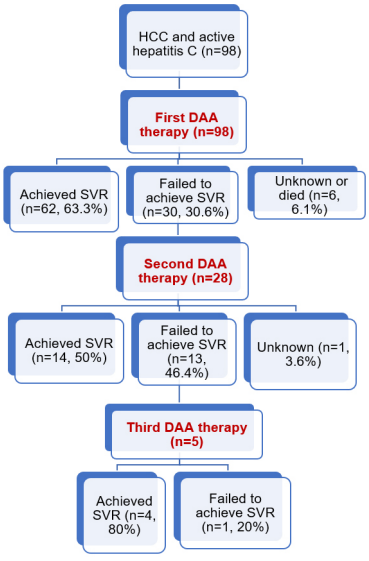

Figure 2. Flow chart of the number of hepatitis C treatments during the study.

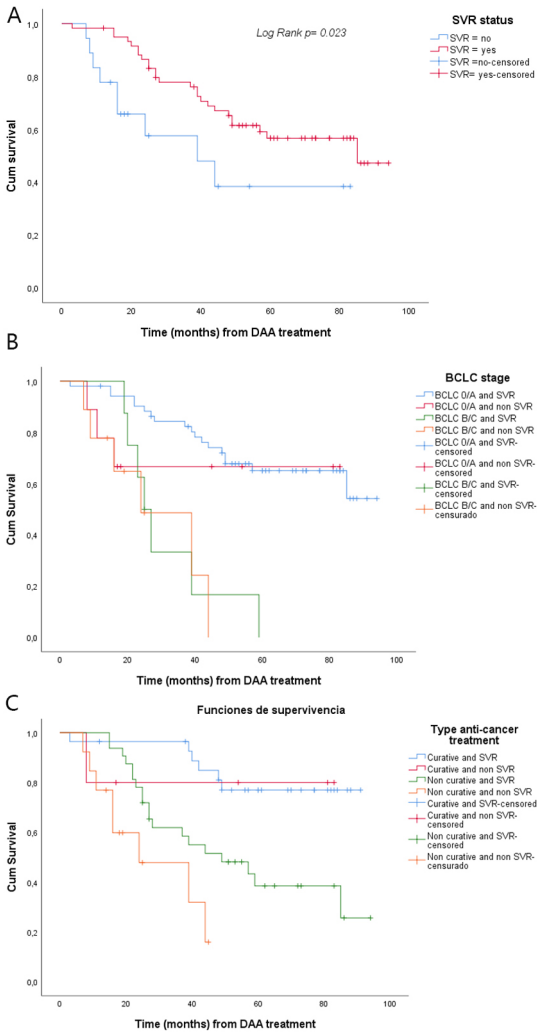

Figure 3. Median overall survival in the active HCC cohort. (A) according to SVR status; (B) according to BCLC staging; (C) according to HCC treatment. SVR: sustained virological response; HCC: hepatocellular carcinoma; BCLC: Barcelona clinic liver cancer.

not achieve SVR (58, 95%CI: 37-81 months; log-rank test $P = 0.051$). However, when we compared patients with curative HCC treatments who achieved SVR (78, 95%CI: 70-88 months) with those who did not achieve SVR (68, 95%CI: 41-94 months; log-rank test $P = 0.902$), the median difference did not reach statistical significance, but this reached the statistical significance in non-curative treatments [SVR (54, 95%CI: 43-66 months) *vs.* non-SVR (28, 95%CI: 20-37 months); log-rank test $P = 0.024$], as shown in Figure 3B and C.

In the multivariable Cox regression model, after being adjusted by sex, age, presence of cirrhosis, liver function, number of HCV therapies, HCC stage (BCLC system), and AFP at the time of tumour diagnosis, failure to achieve SVR (HR, 2.63) and active HCC (HR, 37.71) were associated with mortality in the whole cohort [Table 3B].

Thirty-eight patients died (38.8%) at the end of the follow-up, 32 of whom died due to tumour progression with hepatic failure.

DISCUSSION

Our study showed that antiviral treatment with new DAA therapies in patients with hepatitis C-related HCC is feasible and provides acceptable SVR rates of over 80%. As previously published, patients with a prior treated HCC are more likely to achieve high SVR rates in comparison with those with active HCC[13,14]. Indeed, a systematic review and meta-analysis showed an 18.8% SVR reduction in patients with active/residual HCC *vs.* inactive/ablated HCC[15]. It is also known that patients with HCC who had previously received a liver transplant have higher SVR rates than those who did not[10]. Our results are in accordance with these previous publications, and we showed a SVR of more than 94% in patients with historical HCC in comparison with 82.8% of SVR in patients with active HCC at the time of the HCV treatment. In our study, patients with a historical HCC had early-stage tumours, with 84.3% undergoing liver transplant as a modality of treatment.

In addition, our study showed that more than one-third of the patients with an active HCC (35.7%) received more than one DAA therapy. According to the literature, failure of DAA treatment in patients with HCC could be related to inadequate regimens (first-generation DAAs or viral resistance). However, in our cohort, initial DAA therapy failures were only seen in those receiving sofosvubir/ledipasvir/ribavirin (25.8%) or sofosvubir/velpatasvir/ ribavirin (38.9%). The latter is now considered to be the standard treatment for hepatitis C in patients with active HCC. It is important to mention that only two patients who had DAA failure to the second DAA therapy showed resistance associated with substitutions in the NS5A region. Furthermore, the treatment failure was not associated with a lack of adherence, as this was good in our cohort.

The mechanism of SVR reduction in HCC patients remains unclear but could be related to the impaired immunity of patients with HCC, a reduction in DAA delivery due to a reduced blood supply in the HCC lesions, or regional fibrosis caused by some HCC treatments[16]. Furthermore, the subverted cellular architecture of HCC foci may impair the bioavailability of DAAs which may already have a suboptimal drug delivery via the portal system[16]. In our study, the presence of active HCC and multiple nodules were the only factors associated with not achieving SVR.

The benefits of achieving SVR with hepatitis C antiviral therapy are well established. These benefits have been shown throughout each stage of fibrosis and also in patients with a history of HCC after curative treatment[17,18] and non-curative treatment[19]. A recently published multicentre USA retrospective study showed that the SVR is associated with a decreased risk of hepatic decompensation in patients with HCV-related HCC who receive non-curative therapies[19]. These findings were consistent in their subgroups according to liver function (Child-Pugh A) and in tumour stage (intermediate or advanced). However, in this study, the SVR occurred before the diagnosis of HCC, so the estimated benefits of HCV treatment and/or achievement of SVR in patients with active HCC may be overrated. Only 27.3% of the patients in their group with active HCV and HCC were treated with DAAs in their follow-up. In contrast, in our study, 82.7% of patients had active HCC at the time of DAA therapy and the survival rate was higher in those who achieved SVR. In our study, the survival benefit was noted in patients who had early-stage cancer and non-curative treatments.

Our study shows that having an active HCC and non-achieving SVR are the main factors associated with mortality. In the previously discussed multicentre study which included a large number of patients[19], SVR was also associated with improved survival, although the differences noted were not deemed to be of statistical significance. Previously published data showed that hepatic decompensation and tumour recurrence are the major drivers of death in patients who had successful treatment of early-stage HCC[20].

However, data for when these patients are treated with DAA therapy show significant improvements in the overall survival compared with those who were not treated[15].

One of the main reasons for treating hepatitis C in patients with active HCC, irrespective of tumour stage, was to improve liver function with the benefit of opening access to HCC treatment modalities including clinical studies. However, only 27.7% of the cirrhotic patients had a Child-Pugh score of B/C and only 15.9% of patients had a MELD of more than 15 prior to antiviral treatment. Despite the fact that there was a mild improvement in liver function after SVR in our study, this did not reach statistical significance.

Our study has some limitations, mainly due to its retrospective and observational nature. The number of patients included in the analysis is relatively small, and we believe that a higher number would have enabled us to obtain more powerful statistical results, as well as carrying out more specific subgroup analyses. However, it is difficult to increase the sample as the hepatitis C treatment strategies for patients with HCC vary in each centre in the UK. Moreover, our centre has aggressively treated hepatitis C across London, independent of the presence of liver cancer. Our centre is a tertiary referral centre for cancer patients who are to receive curative treatments in London and the South East of England. This means that there is the possibility that patients with advanced-stage tumours are not always referred to us but are instead treated locally, and we believe that this is the reason that our study includes a higher rate of patients with early-stage tumours.

In conclusion, our real-world data show that treating hepatitis C in patients with HCC is feasible with significant rates of SVR, even if SVR rates decrease in patients with active HCC and these patients require more than one DAA therapy to achieve SVR. Failure to achieve SVR is one of the major risk factors associated with mortality. Achieving SVR needs to be the goal in patients with HCC. However, further prospective studies are required in order to confirm these results.

DECLARATIONS

Authors' contributions

Provided the project concept and design: Ross PJ, Carey I, Agarwal K, Cannon M, Shah S
Reviewed patients and collected the initial data: Guerra-Veloz MF, Lok J, Mohamed A Interpreted and analysed the data: Guerra-Veloz MF, Mohamed A
Wrote the manuscript: Guerra-Veloz MF
Approved the final version of the manuscript: Guerra-Veloz MF, Shah S, Lok J, Mohamed A, Cannon M, Ross PJ, Carey I, Agarwal K

Availability of data and materials

The data and materials are available upon request.

Financial support and sponsorship

None.

Conflicts of interest

Guerra-Veloz MF, Shah S, Lok J, Mohamed A, Cannon M, and Carey I do not have any conflicts of interest. garwal K reports being on the advisory board, a consultant, and a speaker for Assembly Biosciences, Aligos, Arbutus, BMS, Gilead, Immunocore, Janssen, Merck, Sobi, Shinoigi, Novartis, Roche, and Vir, and receiving grants from Gilead, Abbott, and Roche.

Ethical approval and consent to participate

This project was part of a service evaluation and thus a UK NHS Research Ethics Committee review was not required. We guaranteed that the data were anonymised for the statistical analysis.

Consent for publication

Not applicable.

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