RESEARCH ARTICLE

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Prospective Comparison of Hepatocellular Carcinoma Behavior and Survival of Patients who Did or Did not Receive HCV Direct-Acting Antivirals

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Abstract

Background & Aims: The safety and efficacy of hepatitis C (HCV) direct-acting antivirals (DAAs) have been established in several real-world trials; however, some reports have claimed an association between DAAs and hepatocellular carcinoma (HCC) occurrence or aggressive behavior. We aimed to prospectively examine differences in de-novo HCC tumor behavior and overall survival (OS) in DAAs-treated versus HCV-untreated patients as measured by BCLC progression during a two-year follow-up period. **Methods:** This multicenter cohort study recruited 523 patients with de-novo HCV-related HCC. After exclusion criteria were applied, 353 patients were placed into; Group 1, including 236 patients without a history of DAAs therapy, and Group 2 including 117 patients with de-novo HCC developed after receiving DAAs. Patients were then stratified in each group according to BCLC staging (Liver, 2018). All patients received standard of care management and were followed until death or a maximum of 2 years. **Results:** No statistically significant differences were observed between the two groups regarding tumor characteristics (number and size of lesions) and criteria for aggressiveness upon presentation. Among all BCLC stages, DAAs treated patients showed significantly lower baseline Fib4 values than DAA untreated patients in BCLC-0 stage (4.1 vs 7.7, p 0.019). No statistically significant differences were evident in HCC progression in the different BCLC stages at 12 and 24 months follow up periods (p 0.0718 and 0.279 respectively). Significantly better survival was recorded in Group 1 compared to Group 2 patients for BCLC stages C and D (p = 0.003 and 0.01, respectively). **Conclusion:** HCC may develop at an earlier stage of liver disease after DAAs therapy. No defensive role was found for DAAs treatment in delaying HCC progression that occurs after viral eradication.

Keywords: HCC- HCV- Egypt- DAAs- occurrence

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Introduction

Globally, hepatocellular carcinoma (HCC) is the fifth and seventh most common cancer in men and women, respectively, and represents the second leading cause of cancer-related deaths (Sung et al., 2021). The annual risk for the development of HCC is 3%–5% in patients with chronic liver diseases (Lok et al., 2009). Despite the improvements in the overall survival because of the advances in the used interventions, the survival of patients diagnosed with HCC still represent a major concern (Ahmad et al., 2020). In Egypt, liver cancer is the most common cancer and the most common cause of cancer related death in both men and women (Sung et al., 2021).

Chronic hepatitis C infection is the leading cause of HCC (Yang et al., 2017). Treatment of the infection was complex, and interferon was considered too risky. Patients with advanced fibrosis and cirrhosis were restricted from the management of chronic HCV infection before the introduction of direct-acting antivirals (DAAs). DAAs offered sustained virologic response (SVR) rates for HCV patients, even those with advanced and decompensated cirrhosis (Elbaz et al., 2022). This progress was soon followed by debates over fundamental issues related to HCC in the context of DAA therapy. The first debate was the impact of DAAs on the incidence and recurrence of HCC. Several studies reported an alarming increased incidence of de-novo and recurrent HCC lesions (Conti et al., 2016; Kozbial et al., 2016); however, other studies recorded lower incidence rates of HCC in DAA-treated patients (Li et al., 2018; Carrat et al., 2019; Ide et al., 2019). Data regarding DAA-induced SVR are still conflicting and inconclusive (El Kassas et al., 2019). However, a Cochrane systematic review concluded that sufficient

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evidence is lacking to support high incidental rates of HCC in cirrhotic patients treated with DAAs (Jakobsen et al., 2017). Also, a recent meta-analysis indicated that the effect of DAA exposure on the risk of HCC recurrence remains inconclusive (Sapena et al., 2022).

A variety of factors underlying de-novo HCC in DAA-treated patients might explain the heterogeneity of results in previous studies. Methodologies used comparisons between treated and untreated patients (Li et al., 2018; Mettke et al., 2018), interferon-based and interferon-free regimens (Nagaoki et al., 2017; Nagata et al., 2017; Finkelmeier et al., 2018; Li et al., 2018), SVR achievers, and non-SVR patients (Kanwal et al., 2017; Calvaruso et al., 2018; Ioannou et al., 2018), cirrhotic and non-cirrhotic patients (Kanwal et al., 2017; Ioannou et al., 2018; Ogawa et al., 2018), and Child-Pugh score (Romano et al., 2018). Other variables included platelet counts (Conti et al., 2016), male sex, diabetes mellitus, liver stiffness, and Fib-4 (Degasperi et al., 2019). Generally, incidence of de-novo HCC ranged between 2.7% and 5.54% (Conti et al., 2016; Calvaruso et al., 2018; Finkelmeier et al., 2018; Ogawa et al., 2018; Degasperi et al., 2019; Buonomo et al., 2020).

The second debatable issue was the aggressive behavior of HCC in DAA-treated patients. HCC occurred in less advanced liver disease after DAA treatment in a recent study. A more infiltrative pattern was observed with multiple nodules at presentation (El Fayoumie et al., 2020). A higher percentage of portal vein thrombosis and malignant lymphadenopathy was present in DAA-treated patients (Abdelaziz et al., 2019). Similarly, Brozzetti (2021) demonstrated more aggressive, multinodular, and larger HCC lesions in patients after DAA treatment. This finding was expected to impact overall survival (OS). Indeed, no DAA-HCC patients completed five-year follow-up. Three-year OS was 76% in DAA-HCC patients versus 88.93% in control HCC subjects (Brozzetti et al., 2021). Conversely, other studies found a higher survival rate in SVR achievers who developed de-novo HCC lesions during surveillance, despite similar recurrence rates after curative HCC management (Toyoda et al., 2021). Tumors were more extensive in patients that received DAA treatment, but no difference in survival was reported in another study (Montasser et al., 2021).

Thus, conflicting results dominate studies related to the de-novo incidence of HCC in DAA-treated patients. Hence, we looked at the issues from a different viewpoint. We examined differences in de-novo tumor behavior in DAA-treated versus HCV-untreated patients as measured by BCLC staging, Child-Pugh score, and MELD Na score during a two-year follow-up period and assessed OS. We believe that this point of view has not been previously reported to the best of our knowledge.

Materials and Methods

Study design:

This multicenter prospective cohort study recruited 523 successive patients with de-novo HCV related HCC. Patients visited HCC outpatient clinics at Helwan and El-Minia University hospitals from December 2017 to December 2018. One hundred and seventy patients were excluded due to the presence of one or more exclusion criteria. The remaining 353 patients were then placed into study groups based on previous DAA exposure:

1- Group 1: 236 patients who were naive to DAAs.

2- Group 2: 117 patients who received DAAs for chronic HCV before developing HCC with SVR.

We confirmed diagnoses of HCC using EASL-EORTC guidelines (Liver, 2012). Patients were then classified according to BCLC staging into five subgroups (0, A, B, C, and D) (Liver, 2018). All patients received standard of care management according to their BCLC stage and were followed until death or a maximum of 2 years.

Exclusion criteria

We reduced bias that could affect study results by excluding patients that had a history of one or more of the following criteria:

i. Received INF therapy for chronic HCV infection.

ii. Infected with hepatitis B virus or any other cause of cirrhosis.

iii. Prior non-HCC malignancy without complete remission in the last five years.

iv. HCC developed after a liver transplant.

v. Received DAA therapy after curative treatment of HCC.

Methodology

Patients' baseline assessment

We assessed baseline demographic data, including age, gender, and diabetic status. Complete blood work (CBC), serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), albumin, total and direct bilirubin, INR, serum creatinine, and AFP level data were collected. Triphasic abdominal CT (Toshiba scanner Aquillion prime model TSX-303A) was uniformly performed for all patients to diagnose HCC by typical vascular patterns and assess tumor extent.

Tumor characteristics, including site and size of focal lesions, were recorded along with scores for tumor invasiveness, including portal vein thrombosis, lymph node enlargement, and extrahepatic spread. We assessed three main scores: Child-Pugh, MELD Na, and Fib-4. The FIB4 index was calculated as FIB-4 = (age x AST) / (platelet count [10^9/L] x $\sqrt{}$ALT) for all patients to assess the degree of fibrosis (Vallet-Pichard et al., 2007). Different treatment modalities were recorded in each group.

Follow-up schedule

Patients were followed up every three months until death or two years by abdominal ultrasonography (US) (Toshiba model USDI-A500A or Fukada Denish – 4500 with a transducer probe 3.5 MHZ.), CT scan, or MRI examination. All patients submitted to routine laboratory tests for liver function, CBC, kidney function, and AFP every three months regardless of HCC treatment. The same radiologist assessed all imaging exams. Changes in Child-Pugh and MELD Na scores during the two-year follow-up were recorded, and at the end of the second year the changes in Child-Pugh and MELD Na scores were calculated for survived patients only (Δ CTP and Δ MELD Na). This delta was not recorded in BCLC C

and D patients due to high mortality associated with advanced disease stages. Patients lost to follow-up for six months were contacted by phone, and inaccessible patients were excluded. In addition, we assessed BCLC stage progression during follow-up and looked for significance in changes among stages at 1- and 2-year intervals (progression was considered positive if BCLC stage advancement by one or more stages or death of the patient before these intervals). Finally, Cox regression analysis model and Kaplan–Meyer curves were plotted for two-year survival starting from time of de novo HCC diagnosis.

Statistical analysis

Data were statistically described in terms of means ± standard deviation (± SD), median and inter quartile ranges, or frequencies (number of cases) and percentages as appropriate. Numerical data were assessed for normality using Kolmogorov–Smirnov tests. Parametric numerical variables between study groups were analyzed using Student t-tests for independent samples. Comparison of non-parametric numerical variables used Mann-Whitney test and Kruskal–Wallis tests. Chi-square ($\chi 2$) tests were used for comparing categorical data; exact tests were used instead when the expected frequency was less than five. Cox regression analysis model and Kaplan–Meyer curves were used for survival data analysis. Two-sided p-values less than 0.05 were considered statistically significant. All statistical calculations used IBM Statistical Package for the Social Science (SPSS), IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Results

This case-cohort study included 353 patients who developed de-novo HCC. They were divided into Group 1, which included 236 patients with de-novo HCV-related HCC without a history of DAA therapy, and Group 2 included 117 patients with de-novo HCC discovered after receiving DAAs with SVR. We excluded 35 and 13 patients who dropped out from the study due to loss of follow-up for more than six months.

Study patients were predominantly male with a mean age of about 60 years in both groups. The difference was not statistically significant. Similarly, no statistically significant differences were observed between patient groups for tumor characteristics (number and site of

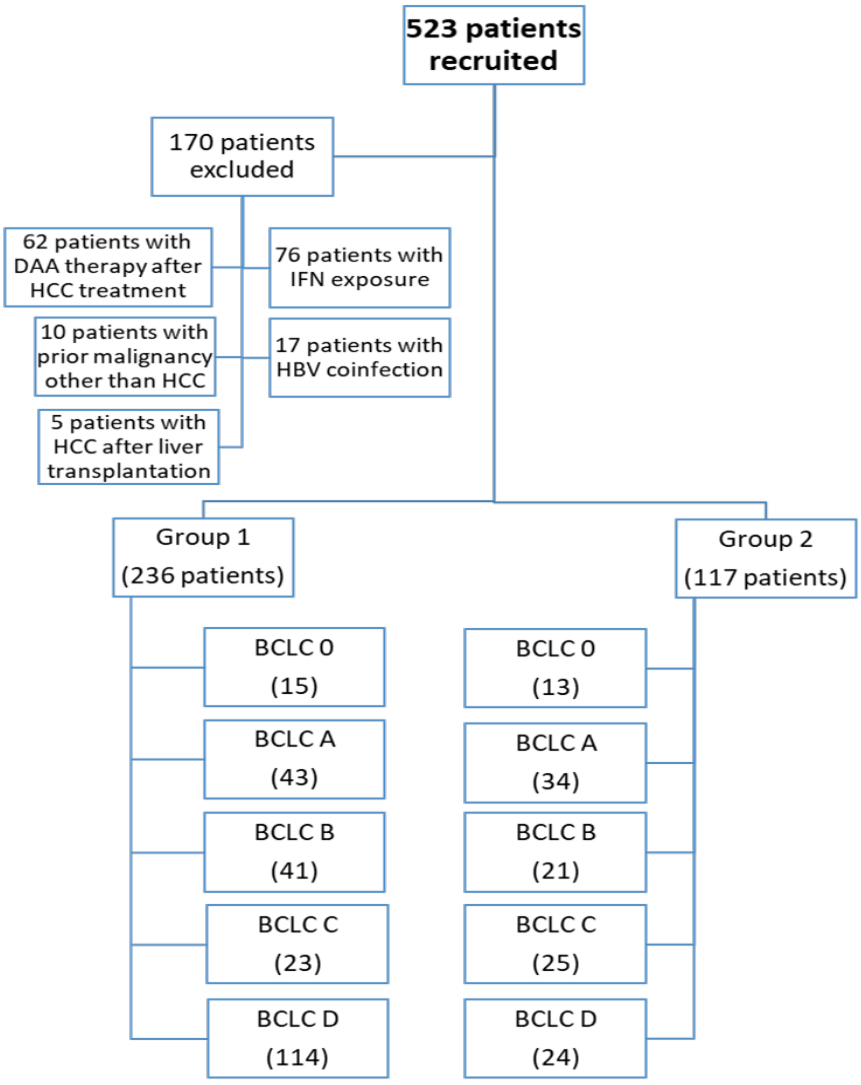

Figure 1. Flowchart of the Study

Table 1. Baseline Characteristics of Study Groups

	Group 1 (N = 201)	Group 2 (N = 104)	p value
Age (years) (mean ± SD)	60.2±7.4	60.4±6.6	0.769
Gender: Male/female (%)	78.6/21.4	73.1/26.9	0.279
Diabetes mellitus (%)	32	43	0.048
Number of focal lesions: (%)			0.422
Single	45.8	52.9	
Two	9	9.6	
Multiple	45.3	37.5	
Focal lesion site: (%)			0.221
Caudate lobe	1	1	
Left lobe	7	9.6	
Right lobe	64.2	72.1	
Both lobes	27.9	17.3	
PVT (yes) (%)	27.4	26.9	0.935
LN involvement (%)	5	2.9	0.392
Extrahepatic spread (%)	2.5	1.9	0.755
Ascites (%)	53.7	40.4	0.027
AFP (ng/ml) (%)			0.471
0–200	60.7	67.3	
201–1000	15.4	14.4	
>1000	23.9	18.3	
Hemoglobin (mean ± SD)	12.2±1.7	12.7±2.1	0.019
Platelets (median/IQR)	108/ (74-150.5)	118/ (88-178.5)	0.096
ALT (median/IQR)	47/ (34-65)	33/ (24-47)	<0.001
AST (median/IQR)	61/ (48-89)	45/ (35-62.8)	<0.001
T. bilirubin (median/IQR)	1.6/ (1-2.6)	1.2/ (0.8-1.9)	0.003
D. bilirubin (median/IQR)	0.7/ (0.4-1.6)	0.5/ (0.3-1)	0.001
Albumin (median/IQR)	3.1/ (2.7-3.7)	3.4/ (3.1-3.9)	<0.001
INR (median/IQR)	1.3/ (1.2-1.6)	1.3/ (1.2-1.5)	0.16
Serum creatinine (median/IQR)	0.9/ (0.8-1.1)	0.9/ (0.7-1.1)	0.669
Child Pugh score (median/IQR)	7/ (6-10)	6/ (5-8)	0.001
MELD Na score (median/IQR)	12/ (9-17)	11/ (9-14.8)	0.068
Fib-4 (median/IQR)	5.2/ (3.5-8.3)	4.2/ (2.4-6.1)	<0.001
Treatment modalities for HCC*			
Resection	2	2	
RFA	35	16	
MWA	6	11	
PEI	7	1	
TACE	42	35	
Sorafenib	3	3	
BSC	110	37	
HCC interval "months"			
(median/IQR)	16/(8-25)		
(minimum/maximum)	2/38		

*three patients in Group 1 underwent RFA and TACE and another patient underwent MWA plus PEI while in Group 2, only one patient underwent MWA plus TACE at baseline

lesions) and criteria for aggressiveness (portal vein thrombosis [PVT], lymph node involvement, and presence of extrahepatic spread) (Table 1). Group 1 (DAA-naïve patients) included a higher percentage of BCLC D and HCV-untreated subjects (Figure 1). Associated generally poorer laboratory data were significantly more frequent in these patients. Laboratory data included hemoglobin, liver enzymes, serum bilirubin and albumin, and INR

Table 2. Subgroup Analysis of Some Baseline Characteristics (CTP, MELD Na and Fib-4)

		CTP (median/IQR)	MELD Na (median/IQR)	FIB-4 (median/IQR)
BCLC 0	Group 1 (13)	5/(5-6)	12/(9.5-13)	7.7/(3.8-10)
	Group 2 (12)	5/(5-6)	10.5/(8-11)	4.1/(2-6.6)
	p value	0.853	0.121	0.019*
BCLC A	Group 1 (39)	6/(5-6)	10/(8-12)	5.3/(3.6-7.7)
	Group 2 (32)	6/(5-6)	9/(8-12)	4.6/(2.5-6)
	p value	0.446	0.538	0.094
BCLC B	Group 1 (36)	5/(5-6)	8/(7-11)	4.2/(2.3-5.5)
	Group 2 (19)	6/(5-7)	10/(8-13)	3.9/(2.4-6.1)
	p value	0.142	0.073	0.901
BCLC C	Group 1 (17)	6/(6-8)	11/(7.5-15.5)	3.6/(2.4-9.9)
	Group 2 (21)	7/(6-8)	13/(10.5-16)	3.1/(2.6-5.5)
	p value	0.536	0.19	0.628
BCLC D	Group 1 (96)	10/(8-11)	17/(13-21.8)	5.8/(3.8-8.5)
	Group 2 (20)	10/(8.3-10)	17.5/(13.5-19.8)	4.7/(2-7)
	p value	0.512	0.918	0.142

and also the presence of ascites. Median time from DAA treatment to HCC diagnosis for group 2 patients was 16 months with minimum and maximum of 2 and 38 months respectively (Table 1).

We also assessed three scores that reflect the hepatic reserve status of patients and severity of fibrosis. The DAA-naïve group showed higher Child-Pugh, MELD Na, and Fib-4 scores (p 0.001, 0.068, and $p < 0.001$ respectively) (Table 1). Subgroup analysis by BCLC class was examined for these three scores between groups. No further statistically significant differences were observed, apart from Fib-4 in BCLC 0 patients (p 0.019) (Table 2).

During the two-year follow-up at 6-months intervals, relative change was statistically significant for Child-Pugh score (Δ CTP) for BCLC B patients only (p 0.047) and in MELD Na score (Δ MELD Na) for BCLC 0 patients only (p 0.013). Significant differences were observed for Child-Pugh score in BCLC 0 patients at 24-month follow-up ($p = 0.041$) and MELD Na at 6-months in BCLC C patients (p 0.049). p-values at 12-, 18- and 24 months for BCLC C and D patients were not calculated due to high mortality in both groups and lowered sample size (Table 3).

Table 4 shows BCLC stage progression during the follow-up period. No significant differences were observed between groups at 1- and 2-year intervals (Table 4).

COX regression analysis for survival showed better

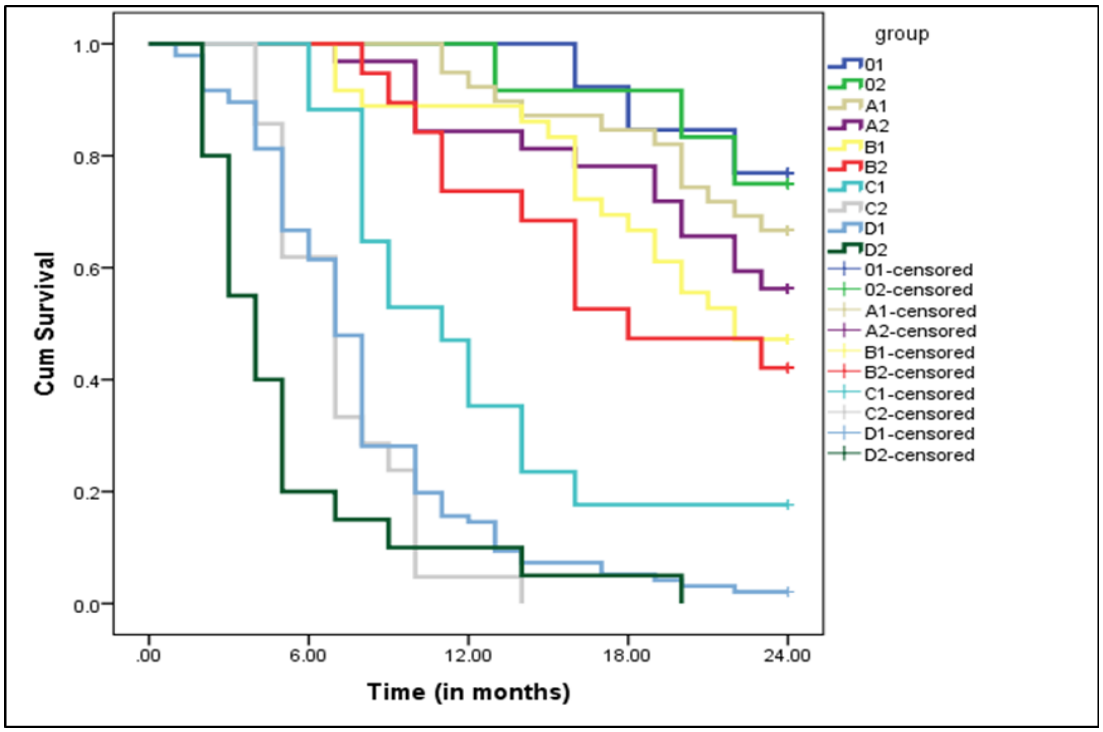

Figure 2. Kaplan-Meyer Curve for 24-Month Survival

Table 3. Six-Month Interval Follow-up and Delta Changes

		6 months		12 months		18 months		24 months		Δ CTP in 2 y	Δ MELD Na in 2 y
		CTP	MELD Na	CTP	MELD Na	CTP	MELD Na	CTP	MELD Na		
BCLC 0	G-1 (13)	6/(5-8)	11/(8-13)	7/(6-8)	13/(9-16)	8/(6-9)	11/(10-13)	8(6.8-9.8)	11(9.8-19.3)	-0.5(-3.3-11)	2.5(1-3.8)
	G-2 (12)	5.5/(5-7)	9/(7.3-11)	6/(5-7.8)	10.5/(8.3-16.3)	7/(5-7)	13/(10-17)	6.5(5-8)	9.5(8.8-13.5)	0.5(-0.5-2)	1(0-1.3)
	p value	0.234	0.171	0.331	0.477	0.077	0.74	0.041	0.36	0.675	0.013
BCLC A	G-1 (39)	6/(5-8)	11/(8-15)	7/(5.5-9)	12/(8-17)	7/(6-9)	14/(10-17.5)	8(6.8-9.3)	14(9.8-16.5)	3.5(0-5.3)	2(0-4)
	G-2 (32)	6/(5-7.8)	11/(9-14)	6/(5-8)	12/(9-17)	7/(5.5-9.5)	13/(9.5-19.5)	6.5(5-9)	13(9.8-17.3)	2(-1-6.3)	0.5(0-3.3)
	p value	0.425	0.63	0.118	0.967	0.498	0.813	0.176	0.811	0.692	0.144
BCLC B	G-1 (36)	6/(5-7.8)	10/(8-13)	7/(5-9.8)	11/(9-16.5)	7/(5-10)	10/(8-16.5)	7(5-8.5)	11(8.5-15.5)	3(1-6.5)	1(0-3.5)
	G-2 (19)	6/(5-9)	12/(9-16)	7.5/(5.8-9)	12.5/(9-16)	9/(5-10)	15/(9.8-20.5)	8(5-9)	12(6-13)	0(-2-2)	0(0-2)
	p value	1	0.163	0.913	0.801	0.589	0.138	0.471	0.678	0.047	0.42
BCLC C	G-1 (17)	10/(8.3-12)	19/(13.5-20.8)								
	G-2 (21)	10/(10-11)	22/(18.5-24)								
	p value	0.639	0.049								
BCLC D	G-1 (96)	12/(11-12.5)	22/(19-26.5)								
	G-2 (20)	10.5/(9.3-11)	20/(18.3-23.3)								
	p value	0.091	0.318								

Table 4. BCLC Stage Progression

BCLC progression	Group 1 (N = 201)	Group 2 (N = 104)	p value
At 12 months (%)			0.718
No progression	30.8	28.8	
Progression	69.2	71.2	
At 24 months (%)			0.279
No progression	14.4	19.2	
Progression	85.6	80.8	

survival rates in Group 1 patients with significant values in BCLC stages C and D (p = 0.003 and 0.010, respectively) while in BCLC stages 0, A and B, p values were 0.915, 0.34 and 0.539 respectively (table 5). Also, Kaplan-Meyer curves for 24-month survival showed significantly better survival in Group 1 than Group 2 patients for BCLC stages C and D (p = 0.001 and 0.004, respectively). Survival was also numerically better for other BCLC stages in Group 1 patients, but differences were not statistically significant (p = 0.914, 0.329, and 0.527 for BCLC stages 0, A, and B, respectively) (Figure 2).

Table 5. COX Regression Analysis for Survival

	Group	HR	95% CI	P value
BCLC 0	I	Ref.		
	II	1.091	0.22-5.41	0.915
BCLC A	I	Ref.		
	II	1.444	0.68-3.07	0.34
BCLC B	I	Ref.		
	II	1.263	0.6-2.66	0.539
BCLC C	I	Ref.		
	II	3.104	1.45-6.28	0.003*
BCLC D	I	Ref.		
	II	1.914	1.17-3.13	0.010*

Discussion

Significant controversy developed in studies of the incidence of de-novo and recurrent HCC in patients who received DAAs. However, few studies discussed tumor behavior itself within follow-up periods and instead focused on tumor characteristics on diagnosis only. We targeted the impact of DAAs on hepatic reserve and BCLC progression for de-novo HCC patients within a 2-year follow-up period. We planned our study to highlight the altered natural history of HCC in post-DAA patients and examine its responsiveness to treatment through dynamic changes in BCLC staging. The study also assessed changes in hepatic reserve as represented by Child-Pugh and MELD Na scores.

Nowadays, the success of DAAs, as evidenced by the achievement of SVR, improves the quality of life, enhances liver function, and reduces risks of hepatic decompensation and portal hypertension (Deterding et al., 2015; Younossi et al., 2015; Cheung et al., 2016; Foster et al., 2016; Mandorfer et al., 2016). These accepted responses are not applicable if DAA patients later develop de-novo HCC lesions. BCLC-0 patients showed a statistically significant difference in dynamic changes in MELD-Na score in favor of DAA-treated patients. Untreated patients showed worse progression in hepatic reserve (Δ MELD-Na change 2.5 in untreated patients versus 1 in DAA-treated patients). Similarly, Δ change in CTP was -0.5 vs. 0.5; this difference was not statistically significant. Further, Δ CTP was significantly better in BCLC B patients in DAA treated patients (3 vs 0 in G1 and G2 respectively, p 0.047). Otherwise, MELD-Na was significantly higher in the first follow up period after 6 months in BCLC-C patients who were DAA treated than untreated patients (22 vs 19, p 0.049). These results highlight a limited benefit of DAA to enhance hepatic reserve only for early BCLC stages. This benefit declines or even reverses in later BCLC stages. Thus, the role of surveillance for the early detection of HCC lesions is crucial for maximum benefit and enhancement of hepatic reserve. All patients in our study who received DAA therapy were confirmed to have been without HCC at the time of their HCV management, and de-novo lesions developed thereafter. Interestingly, Reig (2021) mentioned that if DAAs are administered at an irreversible time point, possible benefits to liver function could be reduced; the time needed to recover liver function could be longer than the time needed for HCC progression (Reig and Cabibbo, 2021). Using different timing, Ochi (2021) provided HCV management using DAAs after HCC treatment and found a protective role against deteriorating hepatic reserve with significant improvement in recurrence and survival (Ochi et al., 2021).

We noted that DAA-HCC patients showed less advanced hepatic fibrosis (median Fib-4 4.1 vs 7.7, p 0.019). At 1 and 2 years follow up period, BCLC progression rates were not significantly different between the two studied groups. However, survival rates in late BCLC stages (C and D) were better in DAA untreated patients. It seems that DAAs had no benefit for slowing or preventing BCLC progression. Toyoda (2021) compared DAA patients versus persistent HCV patients and found that HCC lesions were less advanced and showed less frequent worsening of liver functions in SVR patients. Liver function improved between initial HCC diagnosis and recurrence in these patients but declined in controls. SVR patients thus received more frequent curative treatment for recurrence (Toyoda et al., 2021). Montasser (2021) reported that tumor size in DAA-treated patients was statistically larger than in patients without a history of such treatment (p = 0.03), but types of intervention, BCLC stage, and survival had no impact (Montasser et al., 2021). The incidence of HCC after DAA administration and its biological behavior is also expected to impact survival. SVR reduced the risk of five-year all-cause and liver-specific mortality (Dang et al., 2020) and provided higher OS rates (Kamp et al., 2019; Kamp et al., 2020; Ochi et al., 2021). Kamp (2019) showed that HCV positive and negative patients had similar survival rates (20.7 vs. 17.4 months, p = 0.022), but SVR positive patients had better survival rates than SVR negative patients (75.6 months vs. 26.7 months) (Kamp et al., 2019). Conversely, Fouad

(2021) showed much more aggressive tumor behavior in DAA patients. Incidence rates for multiple focal lesions, large lesions of more than 5 cm, and PVT were statistically higher than in untreated subjects (53% vs 25% for multiplicity of focal lesions; 39% vs 33% for lesions >5 cm; 45% vs 21.7% for PVT, all with $p < 0.001$) (Fouad et al., 2021). In addition, Brozzetti (2021) indicated that HCC related death was higher in DAA-treated patients while cirrhosis-related death was higher in a historical group ($p = 0.0288$). Also, none of the DAA group completed the 5-year follow-up (Brozzetti et al., 2021). El Fayoumie (2020) reported a statistically more infiltrative pattern (41.2% vs 1.9%), PVT (45.1 vs 25.9%), regional lymph node metastases (27.5% vs 7.4%) and limited treatment options (30% vs 15.5%) in DAA-treated patients. Fib-4 was lower in HCC-DAAs patients (4.8 ± 3.53) than in controls (6.53 ± 4.78). Moreover, nine percent of HCC patients who received DAA therapy had surprisingly low Fib-4 scores, <1.5 (El Fayoumie et al., 2020). Desai (2019) reported that HCC developed F0-F2 hepatic fibrosis after DAA therapy (Desai et al., 2019). These alarming results may necessitate changing protocols for HCC surveillance after DAA therapy along with a revision of HCC pathogenesis in the DAA era; hepatic fibrosis is no longer considered the sole cause with increasingly reported HCC on top of less advanced fibrosis.

Our study has some limitations. We were not able to analyze the causes of mortality–whether liver decompensation-related or HCC related. Also, we could not determine the time interval between DAA therapy and the development of de-novo HCC lesions. Fib-4 was initially assessed, but we did not follow Fib-4 changes during the 2-year follow-up. Our study groups did not initially exhibit comparable baseline characteristics (higher Child-Pugh, MELD Na, and Fib-4 scores in the DAA untreated group). Our national program for HCV management, adopted by the National Committee for Control of Viral Hepatitis, allows cirrhotic patients up to Child-Pugh B7 or B8 to receive DAA therapy. Thus, the DAA group included a lower percentage of BCLC D patients. However, subgroup analysis of patients based on BCLC staging reduced the possible bias that could lead to misinterpretations. Patient groups were almost homogenous, without statistically significant differences apart for Fib-4 score in BCLC-0 patients.

HCC may develop at an earlier stage of liver disease after DAA therapy. DAA treatment led to preservation of hepatic function in early HCC stages (BCLC 0). No defensive role was found for DAA treatment in prevention of HCC progression according to BCLC staging.

Author Contribution Statement

The study was designed by MEK, AHE and EK. HS and DO collected study data and oversaw participant visits. Data analysis and interpretation were done by MEK and TE. HS, DO and TE wrote the Article. All authors contributed to the reviewing and editing of the article and approved the final version. The decision to submit the article for publication was made by all study authors.

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Clinical trial registration

The study was registered on the clinicaltrials.gov website on June 27, 2017, with registration number NCT03200171.

Ethical issues

The study was approved by the Research Ethics Committee of the General Organization for Teaching Hospitals and Institutes (serial number ITH00107), in July 2017. A written informed consent was obtained from each patient included in the study. The study protocol and conduction conform to the ethical guidelines of the 1975 Declaration of Helsinki.

Conflict of interest

None related to the current work.

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