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Original Article

Impact of Direct-Acting Antivirals on Recurrence of Hepatocellular Carcinoma after Curative Treatment

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Abstract

Background: The contradictory findings of most of the research on the impact of Direct-Acting Antivirals (DAAs) on HCV-related HCC have sparked debate and controversy. As a result, the picture remains hazy for the time being, with significant heterogeneity.

Aim: To study the effect of DAAs on the recurrence of HCC in patients with chronic hepatitis C virus infection and a previous history of cured HCC.

Patients and Methods: 128 patients with chronic HCV infection with prior history of treated HCC by ablation or resection among them 63 patients received DAAs compared with 65 who did not receive DAAs and followed for at least one-year duration

Results: SVR was achieved in 90.47% in DAAs exposed patients with the recurrence of HCC in patients who received DAAs (34.29%) but when compared with a patient who did not receive DAAs, no statistically significant difference in the recurrence rate (34.29% vs 24.62%) with increased liver tissue stiffness, advanced child score and use of DAAs were independent risk factors of HCC recurrence.

Conclusion: DAAs do not increase the recurrence of HCC after curative treatment but also do not decrease it, further studies with longer follow-up duration are needed to assess the impact of DAAs on the recurrence of HCC.

Keywords: HCV, DAAs, HCC

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Introduction

In Egypt, hepatocellular carcinoma (HCC) is the most prevalent cancer in males, the second most prevalent cancer in women, and the most prevalent cancer overall .[1] According to Egyptian research, HBV and HBV/HCV infection are losing their relevance, accounting for only 25% and 15%, respectively, while Hepatitis C virus (HCV) infection is becoming increasingly significant in the etiology of liver cancer, accounting for 40–50% of cases. [2, 3] HCC may occur at an average 3.5% annual rate on top of cirrhosis. Hence the importance of HCV viremia eradication as a feasible strategy to slow or prevent disease progression, hepatic sequelae, and HCC in individuals with chronic hepatitis C (CHC) .[1] Numerous strong direct-acting antivirals (DAAs) have been given the go-ahead by the U.S. Food and Drug Administration since 2011 for the treatment of chronic HCV infection. Regardless of the stage of

liver fibrosis, the introduction of these new DAAs allowed for SVR rates to reach over 90% in treated patients. This has increased hopes for a significant decrease in the incidence of HCC and even a decrease in recurrent HCC in patients who previously had liver cancer and underwent successful surgical or ablative treatment of the neoplastic lesions.[2, 3]

However, a substantial risk of tumor recurrence (28%) has been seen in individuals with full remission following curative HCC therapy who received antiviral treatment for chronic HCV infection using DAAs. With an anticipated low probability of HCC recurrence (4-5%), those individuals exhibited positive prognostic characteristics. [4] After HCC remission, a different research found that 29% of patients experienced an early HCC recurrence within 6 months of DAAs treatment. [5]

The major ANRS research from France, which was published in 2016, on the other hand, found no evidence of an aggressive or rapid pattern of HCC recurrence. Neoplastic recurrence was discovered in 7.7% of cirrhotic patients who got DAAs, compared to (47%) of recurrences in those who did not get DAAs, among 79 cirrhotic patients who had previously had treatment for HCC. HCC recurrence was discovered in 12.7% of individuals treated with DAAs versus 20.5% of untreated patients in a second cohort of the same research. [6]

The contradictory findings of all of the aforementioned research on DAAs' effects on HCV-related HCC have sparked debate and controversy. Consequently, the image is still hazy for the time being, with significant heterogeneity.

Aim of the work

The purpose of this study is to find out how direct-acting antiviral drugs affects the recurrence of hepatocellular carcinoma in individuals with chronic hepatitis C virus infection and a history of treated hepatocellular carcinoma.

Patients and methods

Technical design:

This is a cohort study conducted at Sohag University hospitals. from January 2018 to December 2020.

Ethical Consideration:

The study protocol was approved by the Ethics Committee of Sohag Faculty of Medicine. Informed written consent was obtained from all participants.

Target population:

(128 patients) with chronic HCV infection who have previously been treated for HCC via ablation or resection among them, 63 patients received DAAs and 65 did not receive DAAs and followed for at least one-year duration.

Inclusion criteria:

1. Both male and female patients with an age equal to or above 18 years old.
2. Patients with HCC who achieved complete treatment response [absence of a residual tumor or complete necrosis, as well as the absence of non-characterized nodules (nodules detected as lesion < 10 mm irrespective of their dynamic pattern) at imaging, confirmed before starting DAAs] according to EASL(2018) guidelines for the management of HCC. [7] [8]

Exclusion criteria:

1. Be under the age of 18.
2. Patients with a coexisting other viral infection affecting the liver like HBV infection and HIV infection
3. Patients with Child-Pugh class (C).
4. Less than a year has passed since treatment.
5. Previous liver transplantation history.
6. Patients treated for HCC who do not get a radiologic full response or who have nodules that are not defined.

Methods:

1. Clinical assessment:

A. Complete history taking.

B. Thorough clinical examination.

2. Laboratory assessment:

Peripheral venous blood samples were obtained from each participant in the appropriate vacutainers provided, the following was done:

- Complete blood count.
- Liver function tests (prothrombin time (PT), prothrombin concentration (PC), and internati-

onal normalized ratio (INR), as well as serum bilirubin "total, direct, and indirect," ALT, AST, total proteins, and serum albumin.

- Kidney function tests (urea and creatinine). (Both liver and renal functions were assayed using a Beckman CX4 chemistry analyzer(NY, USA).
- Random blood sugar and HBA1C if the patient had abnormal blood sugar tests or is known to be diabetic
- Viral hepatitis markers: (HBsAg), using ARCHITECT HBsAg kit (i2000 SR, Abbott, Sligo, Ireland); (HCVAb), using ARCHITECT Anti-HCV kit (i2000 SR, Abbott, Wiesbaden, Germany).
- Real-time polymerase chain reaction (PCR), Cobas Ampliprep, Cobas Taqman 48, Roche) with a limit of detection (LOD) of 15 IU/ml for quantitative HCV-RNA detection.Alpha-fetoprotein (AFP), using ARCHITECT AFP kit (i1000 SR, Abbott, Sligo, Ireland).

3. Radiological assessment:

A- Abdominal ultrasonography (US), was done on all patients using a 3.5-5 MHz convex transducer (C3-7EP probe Medison-Sonoace 8000SE, Seoul, South Korea). The following data were recorded: The extent of the right lobe in the mid-clavicular line was used to calculate liver size. Normally, it is 12±3 cm .[9] liver echogenicity and hepatic focal lesions (HFL): fine, coarse, or heterogeneous echo pattern and HFLs (number, size, sites)**.** Portal vein (PV) diameter and patency: The normal PV is up to 13 mm in diameter. It was measured between the inner margins of the echogenic walls of the vessel during quiet respiration .[10] Splenic size: measured along its longest axis from the upper to the lower pole in a coronal plane. Normally, it is up to 12 cm**.**

B-Fibroscan, Patients' liver stiffness was assessed using the transient elastography device (Fibroscan) made by the French company Echosens. Through intercostal spaces, measurements were taken on the right lobe of the liver while the patient was resting supine with the right arm at its maximum abduction. Ten successful acquisitions were done on each patient, and the results were expressed in Kilo Pascals (kPa).

Following cut-off values were utilised for classification: F0/F1/F2 10.2 kPa; F3 > 10.2 kPa; and F4 > 16.3 kPa .[11] When all three of the following conditions were satisfied—ten successful measures, an IQR that was less than 30% of the median value, and a success rate of higher than 60%—transient elastography was deemed to be trustworthy. Of all valid measures, liver stiffness was regarded as the median. An XL probe was used when the BMI was high (>30 kg/m2). [11]

C- CT scan of the abdomen with contrast for patients with HCC. When nodular lesions are contrast-enhanced in the arterial phase and rapidly fade out in the porto-venous phase, HCC is diagnosed. In high-risk individuals in the US, every suspected HCC lesion should be investigated, In accordance to the American Association for the Study of Liver Disease (AASLD), Furthermore, lesions with typical HCC characteristics were discovered, and the diagnosis of HCC was confirmed using a multidetector CT scan or dynamic MRI with contrast. A nodule more than 2 cm in size and compatible with HCC after one dynamic assessment can be diagnosed with HCC without a liver biopsy. [12]

4. Assessment of severity of liver cirrhosis:

A) Child-Turcotte-Pugh (CTP) classification: (Table 1). [13]

Table (1): Child-Turcotte-Pugh classification for severity of cirrhosis

	1	2	3
Bilirubin (mg/dL)	<2	2-3	>3
Albumen (g/dL)	>3.5	2.8-3.5	<2.8
International normalized ratio (INR)	<1.7	1.7-2.3	>2.3
Ascites	None	Controlled	Poorly controlled
Encephalopathy	None	Controlled	Poorly controlled

Child-Turcotte-Pugh class obtained by adding the score for each parameter (total points):
Class A = 5-6 points.
Class B = 7-9 points**.**
Class C = 10-15 points

B) Model for end-stage liver disease (MELD score): it is based on serum creatinine (mg/dl), total bilirubin (mg/dl), and INR. It is calculated according to the following formula [14]:
MELD = 3.78 × loge (total bilirubin) + 11.2 × loge (INR) + 9.57 × loge (serum creatinine) + 6.43 .

5. Patients with HCC cycle:
Diagnosis of HCC: When a suspected focal lesion was detected during routine abdominal ultrasound examination and or elevated AFP>20 ng/ml the patient was directly prepared for triphasic CT abdomen or dynamic MRI study and HCC diagnosed by arterial enhancement and early washout in the delayed phase .[15]
Staging of HCC: Barcelona Clinic Liver Cancer classification (BCLC) used for HCC staging. [16]

Intervention for HCC patients:
Patients with BCLC stages 0 and A received surgical resection or local ablation procedures; they had a maximum of three cancerous lesions, the largest of which was < 5 cm in diameter. Our center offered the following local ablative procedures: Percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), microwave ablation (MWA), or surgical resection. Following the ablative procedure, patients underwent dynamic CT and ultrasound imaging to monitor tumor response one and three months following the ablative intervention. Patients were seen for follow-up imaging every three to six months to continue confirming complete radiological response until death or loss to follow-up after a senior radiologist had confirmed full radiological response following modified RECIST criteria using these imaging modalities at both the first and third month visits. Patients were sent back to National HCV Therapy Centers to be evaluated for DAAs treatment acceptability following HCC's full radiological response (6 months after curative HCC treatment). The patient received a free three- or six-month DAA regimen if their clinical indicators were within the national HCV treatment recommendations. To determine if an SVR12 had occurred, these patients' viral loads were evaluated at the end of their DAAs therapy period (EOT) and 12 weeks after treatment. Following the initiation of DAAs, patients were then evaluated by triphasic CT abdomen every three months for at least a year.

Patterns of HCC recurrence:
We classified recurrent lesions into either new intrahepatic lesions (NIH) or intrahepatic growth (IHG). Then each lesion was subgrouped according to number to solitary or multiple and according to the pattern of recurrence to nodular or infiltrative lesions, taking into consideration the status of the portal vein (patent or thrombosed) and the presence or absence of extrahepatic metastasis (NEH).

6. Antiviral treatment:
According to the Egyptian national treatment protocol .[17] and AASLD 2018 .[18] recommendations for the treatment of genotype 4 chronic hepatitis C infection, all DAAs groups underwent a 12- or 24-week course of one of different DAAs regimens. Treatment comprised the following:

- Sofosbuvir, Daclatasvir ± Ribavirin,
- Sofosbuvir, Ledipasvir ± Ribavirin

7. Patients' evaluation and follow-up:

Before starting antiviral therapy, all of the patients were assessed. Medical history and examinations were obtained. All patients underwent laboratory (hematological, biochemical, and virological testing) and radiological evaluations, including abdominal ultrasound, Fibro Scan, and triphasic MSCT, as required. Patients were then started on their antiviral regimen and tested every 4 weeks until the end of treatment, then After 12 weeks of SVR12 evaluation, each patient was re-evaluated every 6 months with hematological, biochemical, and abdominal ultrasound testing until at least one year after the end of treatment.

Results:

The Basic characteristics of those patients were listed in **Table (2);** 128 patients (95 male and 33 female) were included in this group with an agerange (59.90±7.36), among them 63 patients treated with DAAs and 65 patients not received DAAs. Different all-oral regimens were administered to the DAAs-exposed group for either three or six months.

Table(2): Basic characteristics of patients with chronic HCV infection with prior history of treated HCC

Variable	Summary statistic
Age/year	
Mean ± SD	59.90±7.36
Median (range)	59.5 (43:80)
Gender	
Male	95 (74.22%)
Female	33 (25.78%)
Use of DAAs	
No	65 (50.78%)
Yes	63 (49.22%)
DAAs Regimens	
S+D+R 12 w	45 (71.43%)
S+D 24 w	7 (11.11%)
S+L+R 12 w	6 (9.52%)
S+L 24 w	5 (7.94%)

DAAs: Direct-acting antiviral drugs; S+D+R 12 w Sofosbuvir+Daclatasivir+Ribavirin for the 12-week duration; S+D 24 W: Sofosbuvir+Daclatasivir for 24 weeks duration; S+L+R 12 w Sososbuvir+Ledipasivir for the 12-week duration; S+L 24 w Sofosbuvir+Ledipasivir for 24 weeks duration; O/P/R+R 12 w Paritaprevir/Ritonavir/Ombitasvir +Ribavirin for 12 weeks duration

The sociodemographic variables, smoking status, comorbid illness, and BMI were summarized in **Table (3).** There were no statistically significant differences between the studied groups.

A comparison between Patients with previous HCC who received DAAs and those who did not receive them regarding Child classification, MELD score, and BCLC classification was listed in **Table (3)**. There were no statistically significant differences among the studied groups.

The DAAs-exposed and non-exposed groups were similar in terms of the number of hepatic focal lesions but patients who were exposed to DAAs had lesions more in the RT lobe and smaller in size in comparison with DAAs non-exposed patients. The majority of patients in both groups got radiofrequency ablation **Table (3).**

Table (3): Characteristics of patients with chronic HCV infection with prior history of treated HCC

Variable	No DAAs N=65	DAAs N=63	P-value
Age/year			
Mean ± SD	59.66±8.64	60.14±5.81	0.71
Median (range)	58 (43:80)	60 (49:75)	
Gender			
Male	47 (72.31%)	48 (76.19%)	0.62
Female	18 (27.69%)	15 (23.81%)	
Smoking			
No	40 (61.54%)	33 (52.38%)	0.30
Yes	25 (38.46%)	30 (47.62%)	
Hypertension			
No	49 (75.38%)	52 (82.54%)	0.32
Yes	16 (24.62%)	11 (17.46%)	
DM			
No	49 (75.38%)	44 (69.84%)	0.48
Yes	16 (24.62%)	19 (30.16%)	
Child			
A	56 (86.15%)	58 (92.06%)	0.28
B	9 (13.85%)	5 (7.94%)	
MELD			
Mean ± SD	9.29±2.57	9.79±2.40	0.17
Median (range)	8 (6:18)	10 (6:16)	
BCLC			
0	**4 (6.15%)**	**9 (14.29%)**	**0.18**
A	**61 (93.85%)**	**53 (84.13%)**	
B	**0**	**1 (1.59%)**	
Esophageal varices			
No	**43 (66.15%)**	**40 (63.49%)**	**0.75**
Yes	**22 (33.85%)**	**23 (36.51%)**	
HFL number			
Solitary	**57 (87.69%)**	**50 (79.37%)**	**0.20**
Multiple	**8 (12.31%)**	**13 (20.63%)**	
HFL size (largest diameter in cm)	**3.51±0.87**	**2.91±0.84**	**0.002**
Mean ± SD	**3.5 (1.2:5)**	**3 (1.2:5)**	
Median (range)			
Treatment of HCC			
Surgical resection	**5 (7.69%)**	**6 (9.52%)**	
RFA	**50 (76.92%)**	**49 (77.78%)**	**0.95**
MWA	**8 (12.31%)**	**6 (9.52%)**	
PEI	**2 (3.08%)**	**2 (3.17%)**	

DAAs: Direct-acting antiviral drugs ,DM: diabetes mellitus; BMI: body mass index,BCLC: Barcelona clinic of liver cancer,MELD: Model for end stage liver disease ,HFL: hepatic focal lesion; RFA: radiofrequency ablation; MWA: microwave ablation; PEI: percutaneous ethanol injection;

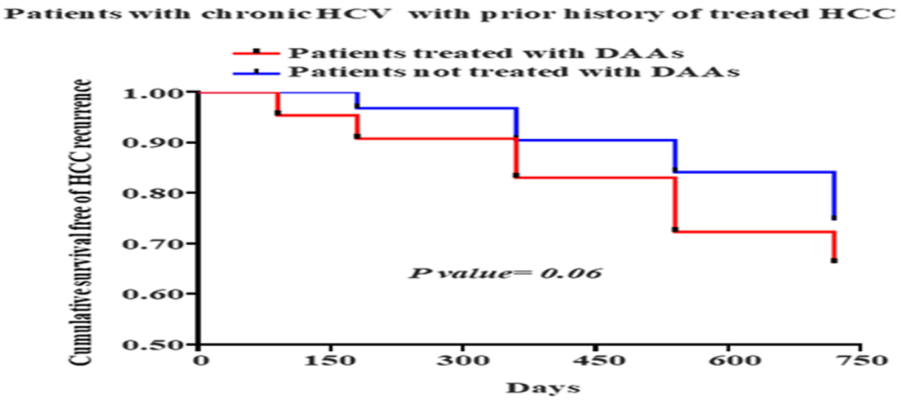
The sustained virological response was achieved in (**90.47%**) of cirrhotic patients with a history of cured HCC **Table (4).**

In comparing the recurrence of HCC after a median follows of 24 months between DAAs exposed and non-exposed patients there was no significant statistical difference (P = 0.2) **Table (4)**, also by Kaplan-Meier survival estimates per 100, there was no significant statistical difference (P = 0.06) **(Table 4**, **Figure 1)**.

Table(4): Outcome of patients with chronic HCV infection with prior history of treated HCC

Variable	No DAAs N=65	DAAs N=63	P-value
SVR			
No		6 (9.53%)	
Yes		57 (90.47%)	
Recurrence			
No	49 (75.38%)	41 (65.08%)	0.20
Yes	16 (24.62%)	22 (34.92%)	
Pattern of recurrence			
No reccurence	49 (75.38%)	41 (65.08%)	
NIH (one nodule)	9 (13.85%)	7 (11.11%)	
NIH (≤3 nodule≤3 cm)	2 (3.08%)	2 (3.17%)	
NIH (One nodule+NEH)	0	2 (3.17%)	0.64
NIH (≤3nodules≤3cm+PV)	0	1 (1.59%)	
Multiple+PVT	1 (1.54%)	2 (3.17%)	
IHG	3 (4.62%)	5 (7.94%)	
NIH(Infiltraative)+NEH	0	1 (1.59%)	
NIH (Infiltrative)	1 (1.54%)	2 (3.17%)	
Death			
No	63 (96.92%)	59 (93.65%)	0.44
Yes	2 (3.08%)	4 (6.35%)	
Cause of death			
No	63 (96.92%)	59 (93.65%)	0.33
Hepatic decompensation	1 (1.54%)	2 (3.17%)	
Hematemesis	1 (1.54%)	0	
Lung metastasis	0	2 (3.17%)	

DAAs: Direct-acting antiviral drugs , SVR,Sustained virological response; IHG, intrahepatic growth; EHG,extra-hepatic growth; NIH, new intrahepatic lesion; NEH, new extra-hepatic lesion and/or vascular invasion;PVT,portal vein thrombosis



Figure(1): Relation of type of treatment on recurrence-free survival

Regarding patterns of recurrent lesions, we divided recurrent lesions into either denovo (new intrahepatic; NIH) or local recurrence (intrahepatic growth; IHG), then according to number to solitary or multiple and according to patterns of recurrent lesions to nodular or infiltrative, also portal vein thrombosis (PVT) and extrahepatic metastases (NEH) were included, Our results according to this classification showed that patients who were exposed to DAAs (22 cases) NIH (17), IHG (5),19 lesions had nodular pattern vs 3 infiltrative lesions, PVT present in 3 cases, and NEH in one case when compared with that non-exposed to DAAs (16 cases), NIH .[13] IHG (3), 15 lesions had nodular patterns vs one

lesion had infiltrative behavior, one case had PVT with no extrahepatic metastasis, despite DAAs exposed patients lesions were more in number, extrahepatic spread, and PVT but the P-value was non-significant **Table (4).**

Univariate Cox regression analysis revealed that female gender, prolonged PT, AFP, DM, increased liver stiffness as measured by fibroscan, increased Child classification, and use of DAAs were significantly associated with increased recurrence of HCC as summarized in **Table (5)**

Table(5): Univariate cox regression analysis of factors affecting the recurrence of HCC

Variable	HR (95% CI)	P-value
Age/years	0.98 (0.94:1.03)	0.41
Female vs. male	0.43 (0.17:1.10)	0.08
Urban vs. rural	0.74 (0.36:1.52)	0.41
Smoker vs. none	1.58 (0.84:2.99)	0.16
Hypertension vs. none	1.06 (0.50:2.23)	0.89
DM vs. none	1.65 (0.85:3.18)	0.14
BMI	1.01 (0.95:1.09)	0.70
WBCs (10^3/µl)	1.08 (0.94:1.24)	0.28
HB (g/dl)	1.15 (0.94:1.41)	0.17
Platelets (10^3/µl)	0.998 (0.992:1.003)	0.44
Albumin (g/dl)	0.83 (0.39:1.78)	0.63
Total bilirubin (mg/dl)	1.09 (0.54:2.18)	0.81
PT (seconds)	1.18 (0.998:1.38)	0.052
PC (%)	0.99 (0.97:1.01)	0.15
INR	2.18 (0.57:8.41)	0.26
ALT (IU/L)	1.00 (0.99:1.01)	0.46
AST (IU/L)	1.00 (0.997:1.01)	0.27
Creatinine (mg/dl)	1.17 (0.34:4.00)	0.81
PCR (IU/ml)	1.00 (1.00:1.00)	0.20
AFP (ng/ml)	1.0002 (1.00:1.0004)	0.045
Fibroscan (kpa)	1.04 (1.02:1.06)	<0.0001
Splenomegaly vs. none	1.15 (0.60:2.19)	0.66
Ascites vs. none	1.52 (0.47:4.93)	0.49
Child B vs. child A	3.55 (1.67:7.56)	0.001
MELD	1.08 (0.96:1.21)	0.21
Multiple vs solitary	1.58 (0.72:3.46)	0.25
Rt lobe vs Lt lobe Both vs. Rt.lobe	1.07 (0.53:2.14) 1.06 (0.32:3.54)	0.86 0.92
HFL size (largest diameter in cm)	1.05 (0.74:1.49)	0.78
RFA vs. surgical MWA vs. surgical PEI vs. surgical	1.18 (0.36:3.87) 0.77 (0.15:3.80) 0 (0:0)	0.78 0.75 1.00
DAAs vs. none	1.81 (0.95:3.45)	0.07

WBCs: white blood cells; HB: hemoglobin; PLT: platelets; ALT: alanine aminotransferase; AST: aspartate aminotransferase; PT: prothrombin time; PC: prothrombin concentration; INR: international normalized ratio; PCR: Polymerase chain reaction; AFP: α-fetoprotein; HFL: hepatic focal lesion; RFA: radiofrequency ablation; MWA: microwave ablation; PEI: percutaneous ethanol injection; HR: Hazard ratio; CI 95%: 95% confidence interval, DAAs:direct acting antivirals

Multivariate and final Cox regression analysis confirmed that only increased liver stiffness by fibroscan (HR (95% CI) 1.05 (1.03:1.08, P = <0.0001), Child score (HR (95% CI) 5.72 (2.5:12.88) P = <0.0001 and use of DAAs (HR (95% CI) 2.45 (1.25:4.81) P =.01 were independent predictors for recurrence of HCC in patients with

HCV-related liver cirrhosis with history of curred HCC who treated with DAAs **Tables (6-7).**

Table(6): Multivariate cox regression analysis of factors affecting the recurrence of HCC

Variable	HR (95% CI)	P-value
Female vs. male	0.56 (0.21:1.49)	0.25
Oral vs. none	1.47 (0.64:3.39)	0.36
Insulin vs. none	2.21 (0.84:5.87)	0.11
PT (seconds)	0.99 (0.80:1.21)	0.89
Fibroscan (kpa)	1.05 (1.03:1.08)	<0.0001
Child B vs. child A	5.36 (1.91:15.04)	0.001
DAAs vs. none	2.49 (1.19:5.24)	0.02

PT; prothrombin time, DAAs: direct acting ativirals.

Table(7): Final multivariate cox regression analysis of factors affecting the recurrence of HCC

Variable	HR (95% CI)	P-value
Fibroscan (kpa)	1.05 (1.03:1.08)	**<0.0001**
Child B vs. child A	5.72 (2.5:12.88)	**<0.0001**
DAAs vs. none	2.45 (1.25:4.81)	0.01

DAAs: direct acting antivirals

A total of six (6) patients died: 4 exposed to DAAs (2 died from liver failure, one of them achieved complete response and another developed recurrence and tumor progression with deterioration of liver function, and 2 in recurrent populations died from lung neoplasm) while in the non-exposed group, 2 died (one developed recurrence died from liver failure and one did not develop recurrence who died after a massive attack of hematemesis) with no statistical significance in overall survival between two groups **(Figure 2).**

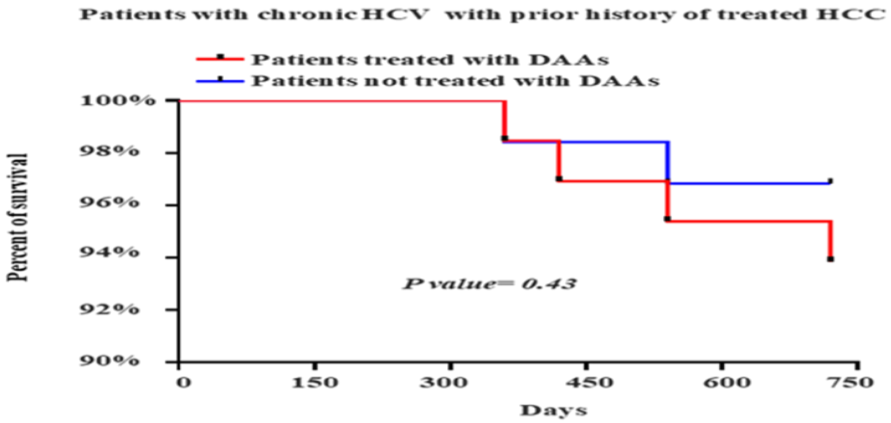


Figure (2): Relation between the type of treatment and overall survival

Discussion

In our study, SVR was achieved in 57 patients of 63 who received DAAs (90.47%). This is in agreement with an Egyptian study that reported that SVR was achieved in 89.2% of patients with chronic HCV and previous history of HCC. [19]

A meta-analysis was conducted to examine the impact of HCC on SVR, and the authors found that

patients with HCC had lower SVR rates than patients without HCC, with the drop in SVR being greater in patients with active or residual HCC. [20]

In the current study, the recurrence of HCC was detected in 22 out of 63 patients who received DAAs [34.29%]. Without a control group, it's difficult to tell if these findings are alarming despite the unexpectedly high recurrence rate of HCC. Because of this, we compared those patients with 65 patients with a history of cured HCC but not received DAAs, with similar background characteristics and equal follow-up duration. This comparison showed no statistically significant difference in the recurrence rate (34.29% vs. 24.62%) between the two groups.

Our results showed that the recurrence rate of HCC after DAAs per 100 PY was (22.51 in DAAs exposed vs. 13.50 in non-exposed patients (P-value =0.06). However, our analysis did not have enough statistical significance to determine if the recurrence of HCC was higher than that of non-exposed individuals to DAAs.

Our results were similar to those that conducted a retrospective case-control study comparing patients with cured HCC and exposed to DAAs with patients with cured HCC and not exposed to DAAs. The recurrent lesion in the exposed group was 41% vs. 35% in the non-exposed group with no significant statistical difference (P=0.79) .[21]

More than one study has found that DAA exposure increases the risk of HCC recurrence. [4] [5] [19] [22]

An unusually high rate of tumor recurrence and pattern of tumor recurrence following DAA therapy was observed by Reig et al .[4] in a Spanish multicentre study. This study included 58 people who obtained DAAs treatment (median duration between HCC intervention and the beginning of DAAs 11.2 months), and who had a complete radiological response after either curative (ablation, resection) or palliative (chemoembolization) treatment of HCC. 27.6% of patients experienced a radiological tumor recurrence after a mean follow-up of 5.7 months. The findings confirmed the original data and revealed that HCC recurrence with rapid tumor growth and a more aggressive course was associated with an increased proportion of patients with prolonged follow-up time .[23] In contrast, the modalities of treatment used in our study included only curative ones and a fixed 6-month interval between HCC intervention and the start of DAAs was used to eliminate the risk of HCC recurrence associated with a variation in this interval.

Furthermore, Reig's study did not contain a control arm. Instead, they used the STORM trial, which was double-blind and placebo-controlled that tested the efficacy of sorafenib to prevent the recurrence of HCC after surgical resection or ablation. [24] In addition, the STORM trial excluded patients with small HCCs if histology did not reveal a profile associated with a high risk of recurrence, and the follow-up period of Reig's study treated patients was not as long as in the STORM trial. In contrast, our study included a matched control arm with the same period of follow-up.

Conti identified a similar result, with HCC recurrence following DAAs treatment (28.8%) with 5.5 months median follow-up. Patients' age and severity of fibrosis were seen as correlated with strong recurrence risk. The authors concluded that patients who were previously treated for HCC still have a high risk of tumor recurrence, despite DAAs .[5]

Researchers in Egypt studied two groups of HCC patients who had only received curative care. With a recurrence rate of 37.7% for the first group receiving DAA therapy, compared to a recurrence rate of 25.4% for the second group not receiving DAA treatment. According to the authors, DAAs may raise the risk of HCC recurrence. [19]

The authors concluded that 77% of patients treated with DAAs for HCC were disease-free six months later. The time between HCC intervention and the initiation of antiviral medication was linked to recurrence. [22]

A meta-analysis used data from 1820 patients, The recurrence in HCC was 21.9%. HCC recurrence was linked with a history of HCC recurrence before treatment by DAAs therapy and a brief interval between the HCC response and the beginning of DAAs. Acceptable HCC levels were identified after treatment with the DAAs, particularly if treatment with the DAAs had been delayed six months after complete HCC response .[25]

Another meta-analysis that used pooled data from 977 patients from 21 studies reported that the

recurrence rate of HCC after DAAs per 100 PY was .[20] with no significant difference between the DAAs-exposed and DAAs-unexposed groups .[26]
In contrast, many other studies support the concept that DAAs do not affect HCC recurrence; In a study conducted by. [27] The researchers concluded that DAAs therapy did not raise the risk of HCC recurrence. In 16.5% of patients (median follow-up of 17 months), HCC recurrence occurred.

A French meta-analysis **(ANRS study)**, analyzed three prospective cohorts. 267 patients with a history of HCC who completed curative treatment made up the initial cohort, known as HEPATHER. When it came to them, the recurrence rate was 12.6% for those who received DAAs and 20.5% for those who did not. The second was the CirVir cohort, which had 79 individuals with a history of HCC. The third group was the ANRS CUPILT cohort, which consisted of 314 individuals who underwent liver transplants and had prior histories of HCC; all of these patients received DAA treatment. Only 7 individuals, or 2.22%, in each of the two groups, experienced HCC recurrence. [28]
Regarding patterns of HCC recurrence in our study the first impression looks aggressive, but when compared with non-exposed DAAs, we lacked the statistical ability to demonstrate if this was higher than the patients with this feature in the DAAs non-exposed recurring population. Our results are similar to results obtained from Reig, where out of 16 recurrent cases 3 cases had IHG and nodular pattern in 10 cases while 3 cases had infiltrative lesions with extrahepatic metastasis in 2 lesions and PVT in one case. [4]
In a comparative study, the authors concluded that DAAs do not affect the pattern of recurrence when compared with DAAs in non-exposed HCC patients with the same background characteristics .[21]
In contrast, aggressive behavior of HCC was detected in a comparative study that studied the behavior of recurrent HCC after DAAs treatment in comparison with non-DAAs treated HCC patients who were followed for the same time. The authors concluded that recurrent HCC attitude was more aggressive in DAAs-treated patients in terms of portal vein thrombosis, extrahepatic lymph node metastasis, and HCC radiological characteristics, which affected the treatment modality and response .[29] The different results of this study and ours could be explained by that the size of HCC lesions in patients who received DAAs was larger than those in our study (4.2 ± 2.5 vs 2.91±0.84) also, in the study by Abdelaziz et al they used old regimens of DAAs as (IFN/SOF/RBV and SOF/RBV) which not included in our study and most of the cases who developed PVT and lymph node metastasis associated with those regimens.
In addressing risk factors affecting the recurrence of HCC, our study showed that fibroscan, Child score, and use of DAAs were independent risk factors for HCC recurrence, Our findings were in agreement with [19] who reported that exposure to DAAs, Child-pugh score and presence of gastroesophageal varices were predictors of HCC recurrence. [5] Also reported that increased liver stiffness was a predictor of HCC recurrence. This may support the theory that advanced liver fibrosis is associated with less effective immunosurveillance. If this immunosurveillance is further reduced after DAAs therapy, it may be possible for liver cancer to grow .[30]
In our study, there was no significant difference between DAAs exposed and DAAs non-exposed in the number of cases and causes of death. The main cause of death in the two groups was hepatic decompensation. These results were similar to those reported by Cabbibo et al who mentioned that the main cause of death in patients who developed HCC recurrence was liver failure. [31]
Although there was no significant difference in HCC recurrence between the two groups in our cohort, the recurrence rate in DAAs exposed patients was higher than expected. The main challenge now is to identify a mechanism(s) that would justify why cancer recurrence occurs at a higher rate than expected. Indeed, all experts in the field predicted that curing HCV would minimize the recurrence of HCC.
The high recurrence rate of HCC after DAAs could be explained by different hypotheses:
An immunological mechanism explained by the sudden drop in viral HCV load caused by DAAs affecting anti-tumoral immune control allowing tumor cells to re-emerge and encouraging tumor recurrence .[32] Immune distortion can encourage the

growth of precancerous lesions already present. It is established that HCV infection induces an intrahepatic immune response that triggers a rise in IFN-stimulated gene expression and natural killer cell activation. Some data show that DAAs—induced clearance of the HCV is correlated with failure of the IFN immune activation, supported by decreased CXCL10 and CXCL11 levels, with normalization of the phenotype and function of natural killer cells. (33)

Reduced levels of microRNA 122 (miR-122) in HCV patients who underwent DAAs treatment after SVR is one of the most popular explanations. (34) MiR-122 is considered one of the most active miRNAs in hepatic tissue and has inhibitory effects on the development of chronic HCV .(35) By interacting with target genes involved in cell proliferation, migration, differentiation, apoptosis, and angiogenesis, MiR-122 inhibits the growth of HCC and functions as a tumor suppressor, So, decreased level of miR-122 in patients receiving DAAs may lead to a higher risk of HCC recurrence .(36)

Strength of our work: Our prospective study included a comparison between a relatively large number of DAAs exposed and non-exposed HCC-cured patients in our locality. Moreover, we decided on a fixed time for all patients to start DAAs therapy after achieving complete radiological response, All other recently published research on this topic report recurrence in DAAs-exposed groups following their HCC full radiological response after various median numbers of months. We also focused on patients with HCC who only received curative treatment such as surgical resection or percutaneous intervention and who underwent (PEI, RFA, and MWA) with exclusions of patients TACE and other palliative treatment options for HCC. Lastly, We included not only patients with liver cirrhosis but also those with advanced fibrosis measured by Fibroscan with a median follow-up period of 24 months.

Limitations of our work: The small number of participants, and Lack genotype testing, genotype testing have an impact on the response to therapy and possible occurrence and recurrence of HCC. We did not test for genotype because it is expensive and most of the Egyptian population is genotype 4. Lastly, the absence of liver biopsy for the assessment of the degree of liver fibrosis Instead we used non-invasive methods such as FIB 4 and fibroscan which were recommended by different guidelines.

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