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## Hepatocellular Carcinoma Post Direct Anti Hepatitis C Viral Agents; Clinical Features

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**Abstract:****Background:**

Direct Anti Hepatitis C Viral Agents (DAAs) were introduced for Hepatitis C Virus (HCV) infection management, which resulted in high sustained virological response (SVR) in many countries and a low failure rate. However, hepatocellular carcinoma (HCC) post DAAs therapy is controversial; few studies related aggressive pattern HCC to DAAs. Therefore, we aimed to study the hepatocellular carcinoma relation to direct anti-hepatitis C viral drugs.

**Patients and Methods:** This observational cross-sectional study included 67 adults Egyptian HCC patients associated with HCV diagnosed at the Zagazig University Hospitals, who were divided into two groups according to DAAs treatment.

**Results:**

HCC is more common in male patients (77.6%) of all studied cases, and those are treated by DAAs (62.7%). The median age of HCC post-DAA was 63(48-83), while 58 (45-75) in HCC patients without DAA, with no significant difference  $p=0.053$ . HCC presented in the non-DAAs treated group, mainly decompensating by hematemesis (HM) (32%). While in the post-DAAs group, HCC was significantly diagnosed primarily with abdominal pain at 31%. There is no significant difference as regards the liver status with frequent liver cirrhosis in both groups, 14(56%) and 32(76.2%).

**Conclusion:** DAAs therapy of HCV added no specific pattern association for hepatocellular carcinoma.

**Keywords:** Liver cirrhosis; HCV; Direct Antiviral Drugs; hepatocellular carcinoma; focal lesion.

**Introduction**

Hepatitis C Virus (HCV) infection is a significant health problem in different countries. In Egypt, HCV infection is the most known cause of chronic liver diseases and Hepatocellular carcinoma (HCC) cases [1]. However, the mechanism and the pathogenesis of how HCV causes HCC are complex and not completely understood [2]. HCC, a leading cause of death worldwide, ranks 6th among cancers globally [3].

In the past, Pegylated Interferon and Ribavirin were used in the treatment of HCV, with several limitations of use, many complications, and unsatisfactory SVR [4]. A few years ago, Direct Anti Hepatitis C Viral Agents (DAAs) were introduced for HCV infection management, which resulted in high sustained virological response (SVR) in many countries and a low rate of failure [5].

HCC post-DAAs therapy is controversial. Although few studies related DAAs to HCC, others showed an aggressive pattern of HCC associated with DAAs therapy [6].

In the face of long-term follow-up deficiency, several worrying results have reported unpredictably high HCC incidence rates following DAAs therapy in liver cirrhosis patients. At first, these reports concerned HCC recurrence after curative measures done as ablation or hepatic resection [7].

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Investigators concluded that a suspected increase in the incidence of HCC-related cirrhosis in patients treated with DAAs compared to the IFN-treated patients who attained SVR was clarified by characteristics of patients as age, diabetes, and reduced liver function combined with lower screening protocols [8]. Therefore, we aimed to study the clinical features and the pattern of hepatocellular carcinoma related to direct anti-hepatitis C viral drugs.

**Patients and Methods****The study designs.**

The study was conducted at the Tropical, Internal medicine, and Oncology departments of Zagazig University Hospitals. This was an observational cross-sectional study [20] for patients diagnosed with HCC from Jan 2019 to Dec 2021 admitted to Zagazig University hospitals (HCC analyzed by history, clinical, laboratory, and radiological measures).

**Inclusion criteria**

The study's inclusion criteria were HCC patients post HCV, older than 18 years old.

**Exclusion criteria**

The exclusion criteria in our study were age less than 18 years old, recurrent HCC, HCC patients, post autoimmune, HBV liver diseases, and other known causes such as metabolic diseases. In addition, other malignancies than HCC and liver transplanted patients were excluded.

**Patients' assessment**

Whole history taking was detailed by the patients or their relatives about the time, period, type of medications taken, presenting symptoms of HCC, history, and family history. A complete examination, routine investigation, HCV PCR, HBV surface antigen,  $\alpha$  fetoprotein, abdominal ultrasound, Abdominal Triphasic CT, and MRI were evaluated to confirm HCC according to BCLC [18]. The screening program of HCC post-HCV therapy by DAAs is by abdominal US every six months  $\pm$   $\alpha$ -FP, irrespective of liver cirrhosis.

**Treatment of HCC**

The type of intervention, according to Barcelona Clinic Liver Cancer (BCLC) [18] of the patients was percutaneous ethanol injection (PEI), microwave ablation, Radiofrequency (RF), Transarterial chemoembolization (TACE), targeted therapy, supportive management and referral to liver resection or transplantation according to Milan criteria [19].

**Statistical analysis**

The collected data were computerized and statistically analyzed using the SPSS program (Statistical Package for Social Science) version 24 and NCSS 12, LLC, USA. Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were denoted as frequencies and relative percentages. The Chi-square test ( $\chi^2$ ) and Fisher exact were used to calculate the difference between qualitative variables as indicated. Quantitative data were stated as median and range. Mann-Whitney test was used to calculate the difference between quantitative variables in two groups for non-normally distributed variables. All statistical comparisons were two-tailed with a significance level of P-value  $\leq 0.05$ , indicating significance. P < 0.001 indicates a highly significant difference, while P > 0.05 indicates a non-significant difference.

**Results**

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**The patient Characteristics.**

The study demonstrates no significant difference between the two groups regards to age, sex, BMI, and diabetes Mellitus. HCC post-DAA recorded with triple therapy (59.2%) and dual therapy (40.8%), while HCC without DAAs group with no specific antiviral management represented 84% and post (PI/RBV) 16% (Tab 1).

**Clinical Features and Presentations.**

There was a difference between the two groups regarding the clinical presentation. HCC presented in 1<sup>st</sup> group mainly by hematemesis (32%), hepatic encephalopathy (24%), abdominal pain (20%), and ascites (16%). While in the post-DAA group, HCC was diagnosed mainly by abdominal pain (31%), followed by a symptomatic presentation diagnosed during routine follow-up 23.8%, ascites (16.7%), fatigue, and less commonly HM and HE (4.8%) for each (Tab 2).

**Laboratory parameters.**

There are no significant differences between the studied groups regards the most common laboratory elements. At the same time, there are substantial differences between the groups concerning AST p-value <0.001, Bilirubin 0.003, Albumin <0.001 and HB level 0.02, which reflect the hepatic decompensation in HCC without DAAs group (Tab 3).

**The liver status and focal lesions:**

There is no significant difference as regards the liver status with frequent liver cirrhosis in both groups, 14(56%) and 32(76.2%). Single HCC lesion is more frequent than multifocal lesions in DAAs-group (73.8%, 26.2%) or without the DAAs therapy group (52%, 48%), respectively. PVT presented no significant difference between the two groups, 28.6% of DAAs treated groups and 12% without DAAs therapy with no significant difference between them regarding meeting the Milan criteria for Liver transplantation (Tab 4).

**Management of HCC.**

Management of non-DAAs and DAAs group was by supportive measures (24%, 33%) or Sorafenib (4%, 4.8%). In comparison, intervention with Microwave (8%, 19%), TACE (4, 7.1%), and PEI (4%, 4.8%) have no significant difference between most of the intervention's procedures except with radiofrequency (4%, 31%) had a substantial difference between the studied groups (p value= 0.005) (Tab 4).

**Table 1 shows the studied population's general characteristics, features, and antiviral therapy.**

		<i>HCC without DAAs</i> N=25(37.3%)		<i>HCC after DAA</i> N=42 (62.7%)		<i>Total</i> N=67		<i>P</i>
<i>Age</i>		58 (45-75)		63 (48-83)		60 (45-83)		0.053
<i>Sex</i>	Female	6	24.0%	9	21.4%	15	22.4%	0.807
	Male	19	76.0%	33	78.6%	52	77.6%	
<i>Smoking</i>	No	16	64.0%	20	47.6%	36	53.7%	0.197
	Smoker	9	36.0%	22	52.4%	31	46.3%	

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<b>Diabetes Mellitus</b>	DM	14	56.0%	22	52.4%	36	53.7%	0.774
	NOT DM	11	44.0%	20	47.6%	31	46.3%	
<b>BMI</b>		28.5 (19.0-39.0)		28.0 (21.0-44.0)		28.0 (19.0-44.0)		0.815
<b>Antiviral</b>	Dual (SOV/DACLA)	-	-	17	40.5%	17	26.9%	
	Triple (SOV/DACLA/RIB)	-	-	25	59.2%	25	35.8%	
	PEG. Interferon (PI)	4	16%	-	-	4	6.0%	

*Quantitative variables were expressed as median (range) and compared using the Mann-Whitney U test. In contrast, qualitative variables were expressed as numbers and percentages and compared using the Chi-square X<sup>2</sup> test.*

**Table 2. The clinical presentations of the studied groups.**

		<i>HCC without DAAs</i> N=25		<i>HCC after DAA</i> N=42		<i>Total</i> N=67		<i>P</i>
<b>Presentation</b>	Asymptomatic	1	4.0%	10	23.8%	11	16.4%	0.02
	Fatigue	1	4.0%	6	14.3%	7	10.4%	0.09
	abdominal pain	5	20.0%	13	31.0%	18	26.9%	0.1
	Ascites	4	16%	7	16.7%	11	16.4%	0.4
	Hematemesis	8	32.0%	2	4.8%	10	14.9%	0.001

*Variables were expressed as numbers and percentages and compared using the Chi-square X<sup>2</sup> test.*

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Table 3. The laboratory data of the studied groups.

	Group		Total N=67	P
	HCC without DAAs N=25	HCC after DAA N=42		
<b>AFP</b>	110.0 (12.0-3024.0)	59.0 (4.0-3824.0)	85.0 (4.0-3824.0)	0.361
<b>PLT</b>	128 (74-298)	106 (45-356)	114 (45-356)	0.321
<b>Hb</b>	9.9±1.3	10.6±1.3	10.3±1.3	0.048
<b>AST</b>	80 (18-80)	55 (16-55)	61 (16-80)	<0.001
<b>ALT</b>	65 (14-228)	47 (15-228)	49 (14-228)	0.238
<b>Bilirubin</b>	1.87 (0.60-19.00)	1.30 (0.50-19.00)	1.45 (0.50-19.00)	0.003
<b>ALB</b>	2.73±0.56	3.36±0.61	3.12±0.66	<0.001
<b>INR</b>	1.3 (0.9-2.2)	1.3 (0.9-1.9)	1.3 (0.9-2.2)	0.763
<b>Creatinine</b>	1.00 (0.39-2.10)	1.10 (0.60-11.60)	1.10 (0.39-11.60)	0.162

Continuous variables are described as mean± SD for normally disturbed variables and compared using the Independent T-test and median (range) for nonnormally disturbed variables and compared using the Mann-Whitney test.

Table 4. the pattern of the HCC and the interventions applied to the studied groups.

		HCC without DAAs N=25		HCC after DAA N=42		Total n(%)		P Value
<b>Liver status</b>	Cirrhosis	14	56%	32	76.2%	46	64.2%	0.08
	Non-cirrhosis	11	44%	10	23.8%	21	35.2%	
<b>Child. p</b>	A	2	8%	12	29%	14	20.9%	0.1
	B	3	12%	7	17%	10	14.9%	0.2
	C	6	24%	13	31%	19	28.4%	0.3
<b>HCC Number</b>	Single	13	52.0%	31	73.8%	44	65.7%	0.069
	Multi	12	48.0%	11	26.2%	23	34.3%	
<b>PVT</b>	PVT	3	12.0%	12	28.6%	15	22.4%	0.116
	No PVT	22	88.0%	30	71.4%	52	77.6%	
<b>Milan C</b>	Within	16	64.0%	21	50%	37	55.2%	0.458
	Out	9	36.0%	21	50%	30	43.8%	
<b>Intervention</b>	Microwave	2	8.0%	8	19.0%	10	14.9%	0.2
	Supportive	6	24.0%	14	33.3%	20	29.9%	0.2
	PEI	1	4.0%	2	4.8%	2	3.0%	0.4
	Radiofrequency	1	4.0%	13	31.0%	13	19.4%	<b>0.005</b>
	Sorafenib	1	4.0%	2	4.8%	3	4.5%	0.4
	TACE	1	4.0%	3	7.1%	4	6.0%	0.3

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Variables were expressed as numbers and percentages and compared using the Chi-square X2 test.

**Discussion**

HCV infection is a leading cause of chronic liver disease and hepatocellular cancer (HCC). Hepatocellular carcinoma (HCC) is prevalent worldwide and in Egypt. Egypt ranks the third and 15<sup>th</sup> most populous in Africa and worldwide, respectively. [9]. Even though DAAs are associated with higher SVR, there is still debate concerning the relationship between DAAs and the development, recurrence, morphological, and clinical characteristics of de novo HCC [10, 11]. Our goal was to study the factors of HCC associated with direct antiviral treatments for hepatitis C infection.

The study enrolled 67 patients with HCC, divided into two groups according to DAAs therapy or not. Group I included 25 HCC patients not treated by DAAs, and group II included 42 patients previously treated by DAAs and gained SVR. All the patients were HCC naive. The studied population with HCC showed male predominance 77.6% with an age range of 45-83 years. Fatima et al. 2020 [6] recorded that 62% of the DAAs patients were men. Moreover, the DAAs group had more patients in the 40–60 age range, whereas the (Pegylated Interferon) PI group had more patients over 60. In our study, the HCC post-DAAs prevalence was 62.7%, while it was 37.7% in the group without DAAs (Table 1), which can be explained by the DAAs era for the treatment of HCV patients in Egypt in the last years.

There was no significant difference between the two groups regarding age, sex, BMI, and diabetes mellitus. El Fayoumie et al., 2020 [12] studied the Pattern of HCC after DAAs. They recorded that the HCC patients' mean age after DAAs treatment ( $59.1 \pm 7.4$  years) was older than the HCC patients who did not receive DAAs medication. Still, there was not a significant variance in sex distribution between the groups. HCC post-DAAs are recorded with triple therapy (59.2%) more than the dual therapy (40.8%), while HCC without DAAs group with no specific antiviral management represented 84% and with PI/RBV was 16% (Table 1).

There was a significant difference between the two groups regarding the clinical presentation. HCC presented in the first group mainly decompensating as hematemesis (HM) (32%) and hepatic encephalopathy (HE) (24%). While in the post-DAAs group, HCC was significantly diagnosed during routine follow-up at 23.8% and right hypochondria pain at 31%. However, Fatima et al. 2020 [6] showed no discernible difference between the HCC patterns in patients receiving DAAs or PI therapy at the initial presentation. Moreover, in our study, there were significant differences between the two groups regarding AST p-value <0.001, Bilirubin 0.003, Albumin <0.001 and HB level 0.02, which reflect a predominant liver failure in the HCC without DAAs group (Table 3). In coherence with Fatima et al., 2020[6], they discovered that liver fibrosis was significantly lower in HCC patients following DAAs treatment compared to those who did not receive DAAs treatment.

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In this study, there was no significant difference as regards the liver status with predominant liver cirrhosis in HCC post-DAAs group 32(76.2%) (Table 4). However, Tarao et al. 2019 [13] determined that liver cirrhosis played a significant role in the development of HCC in DAAs-treated individuals with no history of HCC, which contributes to the increasing prevalence of HCC in Egypt. In our study, the single HCC lesion is more frequent than multifocal lesions with or without DAAS therapy with no significant difference between the two groups, associated with PVT in 28.6% of DAAs-treated groups and 12% without DAAs therapy (no considerable difference  $p=0.116$ ). Furthermore, no significant difference was found between the two groups regarding the Milan criteria for Liver transplantation (Table 4). In contrast, Abdelaziz et al. [14] examined the differences in tumor behavior between the patients treated with or without DAAS for HCV-induced HCC. They concluded that DAAs-treated patients exhibited more aggressive HCC behavior based on portal vein thrombosis, malignant lymphadenopathy, and HCC imaging characteristics. Also, El Fayoumie et al. [12] examined the pattern alterations in the HCC following DAAs therapy and showed that the HCC following DAAs therapy might arise in less severe liver disease. Following DAAs therapy, infiltrative and multiple nodular HCC patterns were considerably more numerous than in HCC patients who did not get DAAs therapy.

The management of non-DAAS and DAAS groups was by supportive therapy in most cases of both groups (24%, 33%) or Sorafenib (4%, 4.8%), while the intervention with Microwave (8%, 19%), TACE (4, 7.1%), and PEI (4%, 4.8%) had no significant difference between the two groups. In comparison, RF (4%, 31%) had a significant difference ( $p$  value=0.005) (Table 4), which agrees with Abdelaziz et al., 2019 [14], who found that 30% of the HCC patients with DAAs treatment is more than HCC patients without DAAs treatment (15.5%), the best supportive therapy is the only option for management.

**Limitations**

The study is a descriptive cross-section with small numbers of patients, so risk factors cannot be assessed. Some causes of malignancy as occult HBV and Aflatoxin, were not excluded. The HCC management was recorded according to the data available, which had many biases according to the patient decision, cost, and the available options of HCC management.

**Conclusion:** DAAs therapy of HCV added no additional risk for hepatocellular carcinoma.

**Footnotes.****Ethical consideration**

Patients or their relatives gave consent to participate in this research.

The institutional review board of Zagazig university approved this study (2022/11/21 no: 10139).



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**Declaration of competing interest**

There are no conflicts of interest related to this study.

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All authors had direct exposure to the study data and read and agreed with the final text.

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