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Recurrence of Hepatocellular Carcinoma in Hepatitis (C) Virus Related Cirrhosis Treated with Direct Acting Antiviral Therapy

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the fifth most common malignancy in the world. Its appearance is mainly linked to the presence of liver cirrhosis, hepatitis viruses (HCV and HBV) are major etiological factors of chronic hepatitis and fibrosis. The infection with HCV is still risk factor for HCC.

Objective: The aim of this work was to estimate recurrence rate of HCC in patients with HCV related cirrhosis after direct-acting antivirals (DAAs) in (Sharkia Governorate).

Patients and Methods: This prospective cohort study was conducted in Tropical Medicine Department, Zagazig University Hospitals, during the period between December 2017 and May 2018. This study included 120 patients with cirrhosis caused by chronic HCV infection. Group A: included 60 patients with HCC treated with different modality of intervention (ethanol alcohol injection, radiofrequency ablation and trans-arterial chemo-embolisation) showing complete radiologic response and had HCV related cirrhosis and treated with DAAs. While Group B: included 60 patients with HCV related cirrhosis without development of HCC and treated with DAAs.

Results: There was no significant difference between the two groups regarding age, sex or any other demographic data. Incidence of HCC was 33% in group A while 30% in group B 6 months after DAAs.

Conclusion: Recurrence of hepatocellular carcinoma in hepatitis (C) virus related cirrhosis treated with direct acting antiviral therapy was common.

Keywords: Cirrhosis, Direct Acting Antiviral Therapy, Hepatitis (C) Virus, Hepatocellular Carcinoma.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy in the world and the third cause of the cancer related mortality**.** Its appearance is mainly linked to the presence of liver cirrhosis, hepatitis viruses (HCV and HBV) are major etiological factors of chronic hepatitis and fibrosis [(1)]**.**

The HCV infection is still risk factor for HCC. The HCV virus, unlike the HBV virus, does not integrate into the genome and its oncogenic power seems to be related primarily to the effect of chronic inflammation with the progressive development of fibrosis and cirrhosis**.** The average time between infection and the development of cirrhosis is about 20-30 years; a variable proportion of patients with HCV cirrhosis develop HCC with wide range of annual incidence of between 1-8% [(2)]**.**

Other factors identified, which are associated with increased risk of HCC, include the duration of fibrosis, age, sex, platelet counts and level of HCV-RNA [(3)]**.** However, some HCV viral components may have direct oncogenic effect; viral proteins can induce deregulation of the host cells, the DNA mutations of the infected cells and cause immune-mediated oxidative stress [(4)]**.**

New antiviral therapy such as the direct-acting antivirals (DAA) treatments have shown high effectiveness with sustained virologic response (SVR) rates above 90%. Such therapies stop the necroinflammatory activity and so prevent the progression of fibrosis to cirrhosis and may reduce the risk of HCC [(5)]**.**

Accumulating clinical experience of DAA-based treatment has suggested that post-SVR HCC recurrence may be more frequent compared to interferon based treatment. In a small series of HCC patients who achieved a SVR by oral DAAs after HCC treatment cancer recurrence rates of approximately 30% within 6 months were reported; these rates are alarmingly high [(6)]**.**

The aim of this work was to estimate recurrence rate of HCC in patients with HCV related cirrhosis after DAAs in (Sharkia Governorate).

PATIENTS AND METHODS

This prospective cohort study was conducted in Tropical Medicine Department, Zagazig University Hospitals, during the period between December 2017 and May 2018. This study included 120 patients with cirrhosis caused by chronic HCV infection. Cirrhosis was diagnosed by history, clinical examination, laboratory and radiological investigations [(7)]. Chronic HCV infected patients were defined as positive HCV RNA for more than 6 months.

All patients were divided into 2 groups:

Group A: included 60 patients with confirmed HCC. Diagnosis of HCC was based on the radiological criteria according to EASL [(8)]**.** They were treated with different modalities of intervention (alcohol injection, radiofrequency ablation and trans-arterial chemo-embolisation) according to the stage of the HCC based on the AASLD guidelines [(9)]. Patients who had complete radiologic response were included and treated with DAAs sofosbuvir (400 mg/ day), daclatasvir (90

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mg/ day) and ribavirin (800-1200 mg/day) for 12 weeks [(10)].

Group B: included 60 patients with HCV related cirrhosis without evidence of HCC and treated with DAAs sofosbuvir (400 mg/day), daclatasvir (90 mg/day) and ribavirin (800-1200 mg/day) for 12 weeks.

Inclusion Criteria:

Group (A) include: Patients with HCC due to chronic HCV and showed complete radiological response to the intervention, and treatment with an oral DAAs combination for 12 weeks.

Group (B) include: Patients with HCV related cirrhosis whatever the stage of cirrhosis, no past history of HCC, and treated with oral DAAs combination for 12 weeks.

Exclusion criteria:

Co-infection with HBV, patient with untreated HCC, and patient with co-morbidity such as renal failure, cardiac disease, extra-hepatic cancer.

All patients were subjected to:

1. **Full history and clinical examination.**
2. **Laboratory investigations:** Complete blood picture (CBC), liver function tests (LFTs), kidney function tests (KFTs), prothrombin time and international normalized ratio (INR), viral markers: HCV antibodies and HBsAg, PCR for HCV RNA, alpha-fetoprotein (AFP)
3. **Radiological investigations:**
   - **Abdominal Ultrasonography(US):**

     The real time machine was used. The patients were examined while fasting for 6 hours at least; scanning was done by the same examiner to visualize different organs in deep inspiration. Cirrhotic patients were determined from the coarse nodular appearance and shrunken size with prominent caudate lobe. The spleen was evaluated for its diameter at mid axillary line, more than 13 cm suggested to be enlarged. If a focal lesion was seen, a Tri-phasic computerized tomography was done.
   - **Tri-phasic abdominal CT:**

     Tri-phasic abdominal CT is a standardized procedure for the detection and characterization of HCC. Tri-phasic CT technique was developed to image the entire liver in arterial, portal and delayed phases. HCC has hyper enhancement in arterial phase with rapid washout in both portal and delayed phases[(9)].

Primary outcome:

Follow up of the patients was done for 6 months to detect recurrence of HCC in group (A) and HCC development in group (B) after treatment with oral DAAs. Follow up of the patients was done every two months and up to 6 months duration. The follow up included evaluation of the patients regarding: (i) History and clinical examination. (ii) Laboratory investigations: CBC, LFTs, KFTs, HCV PCR and serum AFP were done at end of treatment then after 2, 4 and 6 months. (iii) Conventional abdominal U/S: if focal lesions were detected a contrast enhanced CT was done to detect HCC based on AASLD criteria (early arterial hypervascularization and portal washout) [(9)].

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA). Continuous quantitative variables were expressed as the mean ± SD and median (range), and categorical qualitative variables were expressed as absolute frequencies (number) and relative frequencies (percentage). Continuous data were checked for normality by using Shapiro Wilk test and were compared by Mann-Whitney U test. Categorical data were compared using Chi-square test or Fisher's exact test when appropriate. Disease Free Survival (DFS) was calculated as the time from start of DAAs to recurrence/occurrence of hepatic focal lesion or the most recent follow-up contact in which patients didn't have recurrence/occurrence (censored). These time-to-event distributions were estimated using the method of Kaplan-Meier plot, and compared using two-sided exact log-rank test. All tests were two sided. P value < 0.05 was considered significant.

RESULTS

Table (1) shows that there was significant difference between both groups as regard residence. No other significant difference was found between the two groups regarding demographic data with male predominance.

Table (1): Comparison between group A and group B regarding demographic data

Demographic data	Group A(N=60)		Group B (N=60)		p-value
	No.	%	No.	%	
Sex					
Male	40	66.7%	38	63.3%	0.702
Female	20	33.3%	22	36.7%	
Age (years)					
Mean ± SD	55.58 ± 4.11		53.96 ± 5.07		0.079
Median (Range)	55 (48 – 65)		54 (45 – 65)		
Occupation					
Farmer	20	33.3%	16	26.7%	0.859
Housewife	20	33.3%	22	36.7%	
Teacher	8	13.3%	10	16.7%	
Worker	12	20%	12	20%	
Residence					
Rural	30	50%	42	70%	0.025
Urban	30	50%	18	30%	
Special habits					
No	38	63.3%	44	73.3%	0.651
Cigarette	12	20%	8	13.3%	
Goza	6	10%	4	6.7%	
Ex-smoker	4	6.7%	4	6.7%	

Table (2) shows no significant difference between group A and B regarding sonographic findings before DAAs.

Table (2): Comparison between group A and group B regarding sonographic findings before DAAs

Sonographic findings before DAAs	Group A (N=60)		Group B (N=60)		p-value
	No.	%	No.	%	
Liver size					
Average size	8	13.3%	6	10%	0.368
Shrunken	44	73.3%	50	83.3%	
Enlarged	8	13.3%	4	6.7%	
Spleen size					
Not enlarged	28	46.7%	30	50%	0.715
Splenomegaly	32	53.3%	30	50%	
Ascites					
Absent	40	66.7%	38	63.3%	0.702
Mild ascites	20	33.3%	22	36.7%	

Table (3) shows no significant difference between group A and B regarding sonographic findings 6 months after DAAs.

Table (3): Comparison between group A and group B regarding sonographic findings six months after DAAs

Sonographic findings 6 months after DAAs	Group A (N=50)		Group B (N=48)		p-value
	No.	%	No.	%	
Liver size					
Average size	4	8%	6	12.5%	0.018
Shrunken	34	68%	40	83.3%	
Enlarged	12	24%	2	4.2%	
Spleen size					
Not enlarged	20	40%	22	45.8%	0.560
Spleenomegally	30	60%	26	54.2%	
Ascites					
Absent	40	80%	42	87.5%	0.066
Mild	10	20%	6	12.5%	

Table (4) shows no significant difference between group A and B regarding patient related variables.

Table (4): Comparison between group A and group B regarding patient related variables

Patient related variables	Group A (N=60)		Group B (N=60)		p-value
	No.	%	No.	%	
Degree of cirrhosis					
CTP score 5	42	70%	42	70%	1.000
CTP score 6	18	30%	18	30%	
Child A	60	100%	60	100%	1.000
Performance status					
PS	60	100%	60	100%	1.000
Intervention method					
N/A	0	0%	60	100%	1.000
Alcohol	39	65%	0	0%	
Radiofrequency	21	35%	0	0%	

CTP Child Turrcott Pough score, PS performance status, N/A no ablation.

Table (5) illustrates comparison between group A and B regarding HCC incidence: - Group A showed recurrence rate of 33.3% and Group B showed occurrence rate of 30% (18 cases).

Table (5): HCC incidence in studied patients

HCC incidence	Group A (N=60)	Group B (N=60)	P
2 months after DAAs	6 (10%)	6 (10%)	1.0
4 months after DAAs	4 (6.7%)	6 (10%)	0.5
6 months after DAAs	10 (16.7%)	6 (10%)	0.3
Total	20 (33.4%)	18 (30%)	0.7

Table (6): shows no significant difference between group A and group B regarding viral related variables**.**

Table (6): Comparison between group A and group B regarding viral related variables

Viral related variables	Group A		Group B		p-value
	No.	%	No.	%	
Duration of illness (years)	(N=12)		(N=10)		
Mean ± SD	7 ± 2.82		6.10 ± 2.92		0.380
Median (Range)	7.50 (3 – 10)		6.50 (3 – 10)		
PCR before DAAs	(N=60)		(N=60)		
Negative PCR	0	0%	0	0%	1.000
Positive PCR	60	100%	60	100%	
HCV-RNA ($x10^6$)	(N=60)		(N=60)		
Mean ± SD	2.6660 ± 2.9493		5.2912 ± 6.2060		0.009
PCR 2 months after DAAs	(N=60)		(N=60)		
Negative PCR	52	86.7%	50	83.3%	0.609
Positive PCR	8	13.3%	10	16.7%	
HCV-RNA ($x10^6$)	(N=8)		(N=10)		
Mean ± SD	0.0059 ± 0.0069		0.0118 ± 0.0206		0.721
PCR 4 months after DAAs	(N=54)		(N=54)		
Negative PCR	49	90.7%	50	92.6%	1.000
Positive PCR	5	9.3%	4	7.4%	
HCV-RNA ($x10^6$)	(N=5)		(N=4)		
Mean ± SD	0.0112 ± 0.0109		0.0013 ± 0.0002		0.137
PCR 6 months after DAAs	(N=50)		(N=48)		
Negative PCR	46	92%	45	93.8%	1.000
Positive PCR	4	8%	3	6.2%	
HCV-RNA ($x10^6$)	(N=4)		(N=3)		
Mean ± SD	0.0032 ± 0.0030		0.0046 ± 0.0054		1.000
Viral response	(N=60)		(N=60)		
Non-SVR	8	13.3%	10	16.7%	0.609
SVR	52	86.7%	50	83.3%	

Table (7): shows no significant difference between group A and group B regarding incidence of HCC.

Table (7): Comparison between group A and group B regarding incidence of HCC

		Group A (N=60)		Group B (N=60)		p-value
		No.	%	No.	%	
HCC recurrence/ occurrence		40	66.7%	42	70%	0.695
	Present	20	33.3%	18	30%	
Disease Free Survival	Mean DFS (months)	5.46 months		5.40 months		0.773
	(95%CI)	(5.14 – 5.79)		(5.06 – 5.73)		
	2 months DFS	90%		90%		
	4 months DFS	83.3%		80%		
	6 months DFS	66.7%		70%		

Table (8): shows no significant difference between group A and group B regarding new focal lesion characteristics after 6 months of DAAs.

Table (8): Comparison between group A and group B regarding new focal lesion characteristics after 6 months of DAAs

New focal lesion characteristics	Group A		Group B		p-value
	No.	%	No.	%	
Sonographic findings					
New focal lesion	(N=50)		(N=48)		
Absent	40	80%	42	87.5%	0.315
Present	10	20%	6	12.5%	
Number	(N=10)		(N=6)		
Single	6	60%	2	33.3%	0.608
Multiple	4	40%	4	66.7%	
Affected lobe					
Right lobe	8	80%	4	66.7%	0.099
Left lobe	2	20%	0	0%	
Both lobes	0	0%	2	33.3%	
Affected segment					
Segment IV	2	20%	0	0%	0.362
Segment V	2	20%	2	33.3%	
Segment VIII	2	20%	0	0%	
More than one	4	40%	4	66.7%	
Size (cm)					
Mean ± SD	3.10 ± 0.90		3.50 ± 0.77		0.377
Median (Range)	3 (2 – 4.5)		4 (2.50 – 4)		
Associated LN+					
Absent	10	100%	6	100%	1.000
Triphasic CT findings					
New focal lesion	(N=50)		(N=48)		
Absent	40	80%	42	87.5%	0.315
Present	10	20%	6	12.5%	
Number	(N=10)		(N=6)		
Single	6	60%	2	33.3%	0.608
Multiple	4	40%	4	66.7%	
Affected lobe					
Right lobe	8	80%	4	66.7%	0.099
Left lobe	2	20%	0	0%	
Both lobes	0	0%	2	33.3%	
Affected segment					
Segment IV	2	20%	0	0%	0.362
Segment V	2	20%	2	33.3%	
Segment VIII	2	20%	0	0%	
More than one	4	40%	4	66.7%	
Size (cm)					
Mean ± SD	3.10 ± 0.90		3.50 ± 0.77		0.377
Median (Range)	3 (2 – 4.5)		4 (2.50 – 4)		
Associated LN+					
Absent	10	100%	6	100%	1.000
BCLC					
Stage A	10	100%	6	100%	1.000

LN lymph nodes

Figure (1) illustrates the cummulative incidence of HCC after DAAs.

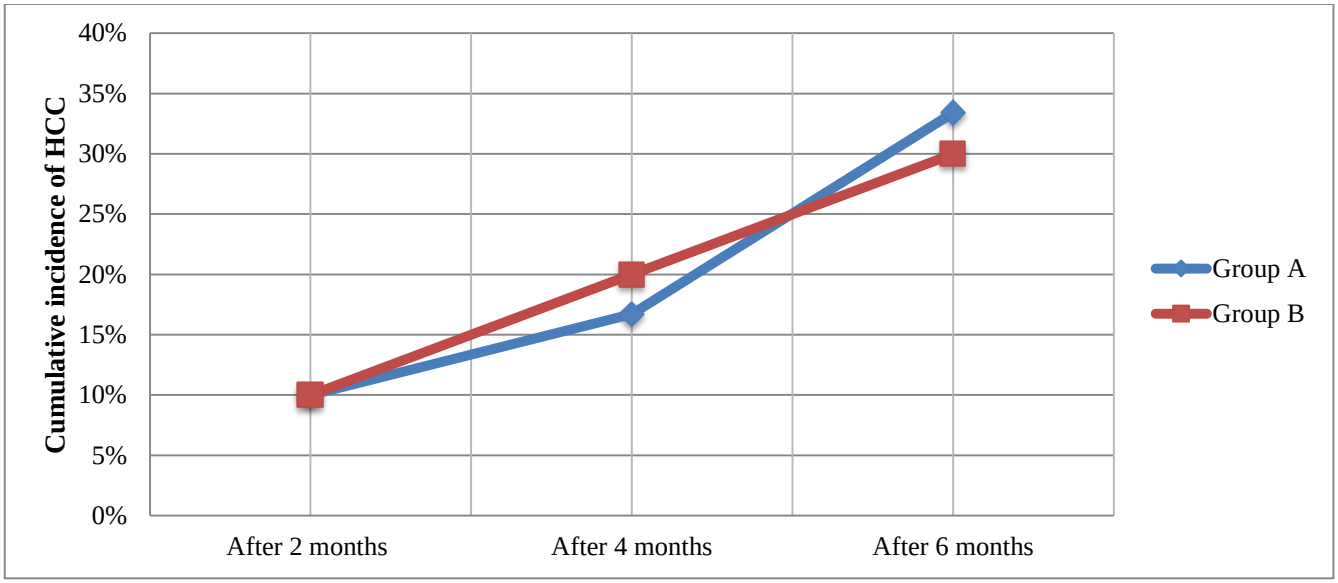

Figure (1): Cumulative incidence of HCC in studied patients

DISCUSSION

Demographic features of both studied groups showed that most of our patients were males (40 in group A and 38 in group B) with average age between 48-65 years. This is consistent with **El-Zayadi *et al.*** [11] who reported male to female ratio was 4:1 in Egyptian patients with HCC. This may be due to effect of hormones on HCC.

In this study incidence of HCC in both groups was significantly higher among patients with positive history of smoking. This was consistent with **Petrick *et al.*** [12] who reported high rate of HCC among heavy smokers than non-smokers and this was in contrary to **Hara et al.** [13] who reported minor effect of smoking on HCC incidence who attributed this to short duration of follow up the cases.

In the present study, the recurrence rate of HCC after treatment with DAAs was about 33%. Such high rate was consisted with what was reported by **Reig *et al.*** [14] who showed that the recurrence of HCC, after complete cure of HCC and treatment with DAAs, was about 28%. However, lower rates were reported in **Singal *et al.*** [15]**.** Such conflicting results have been explained by many possibilities including the difference in the demography of the patients. For example the mean age in our cohort of patients was about 56 years, while in **Reig *et al.*** [14] it was about 66 years. Also, there may be increased comorbidities in the group of patients with high recurrence. The screening status for HCC prior to starting DAA is not known, so, it might be poor screening.

The liver decompensation is an important determinant factor for the occurrence of HCC after DAAs, as in **Nahon *et al.*** [16], who compared the new occurrence of HCC among chronic HCV patients who showed SVR after interferon therapy and those treated by DAA. They found that patients who have been treated by DAA have more advanced liver disease, severe portal hypertension and more comorbidities [16]. Also, they reported that poor HCC surveillance before treatment and the presence of occult carcinoma before DAAs may represent a risk for high HCC incidence. High recurrence rate was reported by **Conti *et al.*** [6], they found that the recurrence rate of HCC was 29% among patients with past history of HCC and 8% new incidence of HCC among cirrhotic patients. They also, showed that HCC patients have advanced liver disease when compared to those without HCC [6]. This difference in the recurrence rate among these studies may be due to the selection of cases in the study who were older and cirrhotic in our study but not in others or no exclusion of occult carcinoma due to poor surveillance before treatment with DAAs.

CONCLUSION

Recurrence of hepatocellular carcinoma in hepatitis (C) virus related cirrhosis treated with direct acting antiviral therapy was common.

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Author contribution: Authors contributed equally in the study.

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