HCC Incidence in DAAs-Treated and Untreated Egyptian HCV-Infected Patients

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Background and study aim: It was initially presumed that SVR after DAAs would be associated with a reduction in incidence of new or recurrent HCC. However, suggesting that DAAs may increase the risk of HCC recurrence created uncertainty in the field. This was followed by publication of number of studies in various populations looking at both new and recurrent HCC.The aim of this article is t study the incidence rate of HCC in DAAs-treated patients who have achieved SVR12 and those who haven't been treated.

Patients and Methods: 416 patients were randomly-selected for prospective follow-up screening for the incidence of HCC (by abdominal U/S and AFP) at a 6-months interval for a completed 12 months duration on 1st, 2nd and 3rd screening sessions. They were distributed 132, 112 and 162 patients in groups I (SOF-treated), II (Qurevo-treated) and III (DAAs-ineligible cirrhotic patients). The DAAs-treated patients were selected from those who had achieved SVR12. Patients who didn't attend the 3 screening sessions were excluded from the prospective analysis.

Results: 297 patients completed the 3 screening sessions, distributed 100, 97 and 100 in groups I, II and III respectively. The total incidence of HCC at the 3 screening sessions was significantly-higher among Group III 30% (30/100 patients) versus 19% (19/100 patients) in Group I and 1.03% (1/97 patients) in Group II.

Conclusion: The HCC incidence was significantly lower in DAAs-treated patients who achieved SVR12. The incidence of HCC was significantly higher in patients with advanced stages of cirrhosis.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most frequent primary neoplasm of hepatocytes. It is the fifth most common malignancy in men and the seventh in women world-wide, with more than million new cases diagnosed annually. HCC is the second leading cause of cancer-related mortality in the world **[1]**.

Chronic HCV infection accounts for about one-third of the total HCC incidence rates and one-fifth of HCC-related deaths **[2]**.

In Egypt, HCC incidence has almost doubled (from 4% to 7.2%) over the last decade. This doubling may be rationalized by the marked increase in HCV infections that emerged over the same duration **[3]**.

DAAs has revolutionized the treatment of HCV in the last few years. The cure rate has increased to more than 95% compared to previous results of IFN-based regimens, which usually didn't exceed 50% **[4]**.

Cirrhosis and fibrosis are the primary risk factors for the development of HCC among HCV-infected persons yet, other factors e.g. old age, male gender, diabetes, obesity, smoking, HCV genotype 3, heavy alcohol use and HBV co-infection are basic co-morbids for HCC risk **[5]**.

Because of the reduced HCC incidence in HCV-infected patients

who achieved SVR after interferon-based therapy, it has been postulated that successful DAAs therapy will result in marvelous reductions in HCC incidence among HCV-infected patients due to its associated higher SVR rates **[6]**.

Unexpectedly, some recent studies have reported high incidence rates of HCC following DAAs therapy **[7,8]** while others have found no increased rates or risk of HCC incidence or recurrence following DAAs treatment **[9,10,11]**. Conclusions from these studies have been complicated by methodological limitations, such as the lack of appropriate control groups, and limited follow-up time **[12]**.

Initially, DAAs were condemned to accelerate the onset of HCC in patients with liver cirrhosis. However, the annual risk of HCC in HCV-related cirrhotic patients is approximately 2-8% **[13]**.

This prospective study aimed at discriminating whether DAAs increases or decreases the risk of HCC incidence in patients with HCV-related cirrhosis. Our plan was to include a reasonable number of patients who were treated by Sofosbuvir-based regimens, and a matched number of patients treated by Qurevo (as an alternative non-sofosbuvir-based DAAs that's available in Egypt), in addition to another comparable number of cirrhotic patients of matched age, sex, BMI, diabetes mellitus prevalence and degree of hepatic cirrhosis (estimated by FIB4).

PATIENTS AND METHODS

After taking permission from the National Committee for Control of Viral Hepatitis (NCCVH), we checked the files of the DAAs-treated patients at Shebin Elkom Hospital of Hepatology, Gastroenterology and Infectious Diseases. 300 patients were selected from those who have achieved SVR12 after receiving the therapeutic course of SOF/DCV±RVN for 12 weeks (Group I=165 patients) and Qurevo for 12 weeks (Group II=135 patients). The Date of PCR test that concluded SVR12 is at least 6 months ago i.e. patients have ended the treatment course at least 9 months ago. We started to call the 300 patients by telephone to inform them to attend at the outpatient clinic on a pre-scheduled time for a follow-up visit. Another 175 patients (Group III) of those with frequent admission to the inpatient wards or attending the outpatient clinic of tropical medicine department, at Menoufia University Hospital with decompensated or compensated HCV-related cirrhosis who are DAAs-ineligible because they had one or more of the followings: total serum bilirubin > 3 mg/dl, serum albumin < 2.8 g/dl, INR ≥ 1.7 and/or Platelet count < 50000/mm^3. Patients with HBV- or HIV co-infection were excluded from the study.

Within January to May 2017 the 1st screening session was carried out. On the 1st screening session, a total number of 416 out of the pre-called 475 patients responded to our calls and attended at the pre-defined date for screening. They were distributed as 132, 112 and 172 patients in groups I, II and III respectively **(Table 1)**. Twelve out of 416 patients (2.88%) had AFP> 200 ng/dl and 18/416 patients (4.32%) had HFLs on abdominal U/S examination. Triphasic CT was done for the 18 patients and 13 of them were confirmed to have HCC (3.13% of the totally-included 416 patients). The 13 cases were distributed as 2/132 patients (1.5%) in group I and 11/172 patients (6.4%) in group III. The remaining 5 patients who were not proved to have HCC by triphasic CT were excluded after being given the appropriate medical advice.

The next step after exclusion of these 13 cases, was primary statistical analysis of data of the remaining 403 cases. We tried to match age, sex, BMI and diabetes mellitus prevalence of the included patients as well the stage of cirrhosis. We used the FIB-4 score as a low-cost and broadly-approved tool for staging liver cirrhosis. There was a high statistically-significant difference between the studied groups regarding the distribution of patients' FIB-4 scores ($p<0.001$). Most patients in group III had a FIB-4 > 3.25 (correlating with > F3 stage of cirrhosis in Metavir score). In addition, we couldn't include a parallel number of patients with FIB-4 scores < 1.4 (correlating with < F3 stage of cirrhosis in Metavir score) in group III because of treatment eligibility for such stages of cirrhosis. So, we excluded some patients at the two extremes of FIB-4 distribution (the least and the highest) to decrease the statistical gap between the included groups regarding the cirrhosis stage. Then, we had 361 cases of matched age, sex, BMI, diabetes prevalence and FIB-4 score ($p=0.203$), distributed as 126, 98 and 137 patients in groups I, II and III respectively.

On the 2nd screening session (6 months later), only 297 patients attended at the pre-defined dates of screening. They were distributed as 100, 97 and 100 patients in groups I, II and III respectively. 17 patients were confirmed to have HCC by triphasic CT (8 & 9 patients in groups I & II respectively). They were discarded from the study after giving them the appropriate referral. Then, we had a remaining number of 280 patients for the 3rd screening session.

Another 6 months later, the 3rd screening session was done and all the 280 patients attended at the pre-defined dates and 33 of them were confirmed to have HCC (11, 1 & 21 in groups I, II & III respectively).

All the included patients were subjected to the followings in every screening session:

I- Thorough History Taking.

II- Full general and local abdominal examination.

III- Laboratory Investigations including: Complete blood picture (CBC), Liver profile (ALT, AST, albumin, total bilirubin & direct bilirubin, prothrombin time and INR), Renal function tests (blood urea and serum creatinine), random blood glucose level, Alpha feto-protein (AFP).

IV- Abdominal Ultrasonography with stress on the presence of hepatic focal lesions.

V- Triphasic CT abdomen and pelvis to confirm diagnosis of HCC for cases with AFP> 200 ng/dL and/ or when abdominal Ultrasonography showed a focal hepatic lesion.

Because our plan was to carry up a prospective screening for the annual incidence rate of HCC study in comparable numbers of DAAs-treated and untreated patients, the end point of the study for any included patient is the development of HCC or completing the 3 screening sessions. So, data and results of patients who didn't meet these rules will be discarded from the prospective analysis.

RESULTS

Cross-sectional analysis

On the 1st screening session; there was a high statistically-significant difference between the studied groups regarding incidence of HCC. Thirteen out of 416 patients were confirmed to have HCC (3.13%). The 13 cases were distributed as two out of 132 patients (1.5%) in group I and 11/172 patients (6.4%) in group III. There were no HCC cases in group II.

On the 2nd screening session, there was a statistically-significant difference between the studied groups regarding HCC incidence (p=0.012). Seventeen out of 297 patients (5.7%) were confirmed to have HCC, distributed as eight out of 100 patients (8%) in group I and nine out of 100 patients (9%) in group III. No HCC cases in group II.

On the 3rd screening session, there was a high statistically-significant difference between the studied groups regarding incidence of HCC (p< 0.001). Thirty three out of 280 patients (11.79%) were confirmed to have HCC, distributed as 11/92 patients (11.96%) in group I and 1/97 patients (1.03%) in group II and 21/91 patients (23.08%) in group III.

Prospective analysis

After excluding the patients who didn't complete a 12 months follow-up duration of the study, we had 297 patients, distributed 100, 97 & 100 in groups I, II & III respectively. There ages ranged 23-75 years old, consisting of 155 females (52.19%) and 142 males (47.81%). There was a statistically-insignificant difference between the three groups regarding age and sex distribution, diabetes prevalence and BMI**.**

Group I included 100 patients; 65 of them were easy-to-treat and were treated by SOF/DCV (subgroup Ia) while the remaining 35 patients were difficult-to-treat and were treated by SOF/DCV/RBV (subgroup Ib). On the 2nd screening session (n=100), we had 4/65 confirmed HCC cases in subgroup Ia (6.15%) and 4/35 confirmed HCC cases in subgroup Ib (11.43%) with a statistically-insignificant difference between both subgroups. On the 3rd screening session (n=92), we had 3/61 confirmed HCC cases in subgroup Ia (4.92%) and 8/31 confirmed HCC cases in subgroup Ib (25.81%) and there was a statistically-significant difference between both subgroups (p=0.0037).

Concerning FIB4 index there was a high statistically-significant difference between the studied groups at the 1st screening session. In Group I; 5/100 patients had FIB4-score less than 1.4, 37/100 patients had FIB4-score 1.4-3.25 while 58/100 patients had FIB4-score > 3.25. In Group II: 31/97 patients had FIB4-score 1.4-3.25

while 66/97 patients had FIB4-score > 3.25. Group III; 2/100 patients had FIB4-score 1.4-3.25 while 98/100 patients had FIB4-score > 3.25.

There was a high statistically-significant difference between the studied groups regarding Child-Turcott-Pugh classification (CTP-Classification) at the 1st screening session. In Group I; 94/100 patients (94%) were CTP-Class A while, 6/100 (6%) patients were CTP-Class B. In Group II; All patients (97/97) were CTP-class A. While in Group III 21/100 patients (21%) were CTP-Class A while, 60/100 patients (60%) were CTP-Class B and 19/100 patients (19%) were CTP-Class C.

There was a high statistically-significant difference between the studied groups regarding AFP levels at the 1st, 2nd and 3rd screening sessions of the present study.

Comparing demographic and clinical criteria of patients with and without HCC at the 2nd screening session, there was a high statistically-significant difference regarding abdominal U/S, FIB4, SGPT, SGOT and AFP and a statistically-significant difference for the incidence of variceal bleeding, WBCs, PLT, S. Albumin, S. Bilirubin and INR.

Comparing demographic and clinical criteria of patient with and without HCC at the 3rd screening session; there was a high statistically-significant difference regarding liver U/S, FIB4, PLT, SGOT, SGPT and AFP and there is statistically-significant difference regarding farmer occupation, hepatic encephalopathy, variceal bleeding, random blood sugar, HB%, S. Albumin and INR. Incidence of DM is higher in patients developed HCC.

Table (1): Inclusion flowchart throughout the study.

	Group I	Group II	Group III	Total
Pre-screening we called → 475	165	135	175	475
1st session: Only 416 patients attended	132	112	172	416
After exclusion of 13 HCC cases → remaining 403	130	112	161	403
2nd session: 64 patients didn't attend →	100	97	100	297
3rd session: 280 patients attended →	92	97	91	280

Table (2): FIB-4 distribution of the studied groups.

	Group I	Group II	Group III	X^2	P-value
FIB-4 after exclusion of HCC cases at the 1st screening session					
<1.4	13	9	5	22.179	0.0002
1.4-3.25	32	41	27		
>3.25	85	62	129		
Total	**130**	**112**	**161**	**403**	
FIB-4 after exclusion of 42 cases to decrease the statistical gap					
<1.4	9	6	5	5.944	0.203
1.4-3.25	32	30	27		
>3.25	85	62	١٠٥		
Total	**126**	**98**	**137**	**361**	
FIB-4 of patients who had completed the 3 screening sessions					
<1.4	5	0	0	51.709	<0.001
1.4-3.25	37	31	2		
>3.25	58	66	98		
Total	**100**	**97**	**100**	**297**	

Table (3): Demographic data of the studied groups.

	GROUP I (N=100)			Group II (N=97)			Group III (N=100)			Anova	P-value
Age											
Range	25	-	72	25	-	75	23	-	73	22.881	> 0.05
X ±SD	50.4	±	11.38	49.845	±	11.45	59.01	±	9.166		
BMI											
Range	16.9	-	32	17.5	-	30	17.2	-	31	0.250	0.779
X ±SD	22.886	±	3.223	22.716	±	2.291	22.570	±	3.771		

	GROUP I (N=100)		Group II (N=97)		Group III (N=100)		Total (N=297)		X^2	P-value
	N	%	N	%	N	%	N	%		
Sex										
Female	53	53.00	56	57.73	46	46.00	155	52.19	2.76	0.252
Male	47	47.00	41	42.27	54	54.00	142	47.81		
Diabetes										
Diabetic	19	19.00	13	13.40	26	26.00	58	19.53	4.99	0.082
Non-diabetic	81	81.00	84	86.60	74	74.00	239	80.47		
Smoking										
Smoker	12	12.00	16	16.49	9	9.00	37	12.46	2.565	0.277
Non-smoker	88	88.00	81	13.51	91	91.00	260	87.54		

Table (4): Triphasic CT-confirmed HCC incidence of the studied groups.

CT HCC		GROUP I (N=100)		Group II (N=97)		Group III (N=100)		Total (N=297)		X^2	P-value
		N	%	N	%	N	%	N	%		
1st session	**No HCC**	130	98.49	112	100	161	93.61	403	96.87	10.819	0.005
	HCC	2	1.51	0	0	11	6.39	13	3.13		
2nd session	**No HCC**	92	92.00	97	100.00	91	91.00	280	94.28	8.838	0.012*
	HCC	8	8.00	0	0.00	9	9.00	17	5.72		
3rd session	**No HCC**	81	88.04	96	98.97	70	76.92	247	88.21	21.953	<0.001*
	HCC	11	11.96	1	1.03	21	23.08	33	11.79		
P-value	**1st-2nd**	0.012*		1.000		0.006*					
	1st-3rd	0.001*		1.000		<0.001*					
	2nd – 3rd	0.500		1.000		0.014*					

Table (5): Multivariate analysis of HCC and Non-HCC patients.

	Non-HCC (N=247)			HCC (N=33)			Anova	P-value
Age	51.684	±	11.564	59.576	±	8.467	3.784	<0.001*
RBG mg/dL	103.785	±	9.991	99.485	±	18.635	2.049	0.041*
HbA1c %	7.400	±	0.479	7.750	±	0.212	1.016	0.317
Body mass index	22.838	±	3.126	21.952	±	2.700	1.553	0.122
FIB4	0.487	±	0.457	2.327	±	1.447	15.213	<0.001*
Hb %	11.147	±	1.191	10.639	±	1.204	2.295	0.022*
WBCs ($X10^3/mm^3$**)**	5.904	±	1.832	5.882	±	2.116	0.063	0.950
PLT ($X10^3/mm^3$**)**	162.279	±	66.548	88.879	±	36.214	6.208	<0.001*
S.Albumin (g/dL**)**	3.504	±	0.718	3.174	±	0.564	2.531	0.012*
T. Bilirubin (g/dL**)**	1.149	±	1.020	1.337	±	1.037	0.994	0.321
SGOT (IU/mL**)**	41.704	±	18.760	58.636	±	34.472	4.315	<0.001*
SGPT (IU/mL**)**	35.449	±	15.571	47.333	±	24.710	3.799	<0.001*
INR %	1.252	±	0.252	1.404	±	0.256	3.242	0.001*
S. Creatinine (mg/dL**)**	1.937	±	1.075	1.573	±	0.552	1.910	0.057
Alpha Feto-Protein (ng/dL**)**	17.021	±	46.553	480.075	±	512.237	13.940	<0.001*

		Non-HCC		HCC		Total		X^2	P-value
		N (247)	%	N (33)	%	N(280)	%		
Sex	**Female**	140	56.68	9	27.27	149	53.21	10.112	0.001*
	Male	107	43.32	24	72.73	131	46.79		
Occupation	**Non-Farmer**	147	59.51	13	39.39	160	57.14	4.812	0.028*
	Farmer	100	40.49	20	60.61	120	42.86		

DISCUSSION

Over the past two decades, multiple meta-analyses were made to evaluate the role of SVR in preventing hepatic decompensation and HCC occurrence in patients with HCV-related cirrhosis. Studies from the interferon-era definitely agreed that HCV eradication reduces but does not eliminate the risk of HCC so long cirrhosis has already been developed **[14].**

However, the impact of SVR of a DAAs-based regimen on liver cancer occurrence and recurrence seems to be controversial. This is due to the possibility of including patients with more advanced stages of cirrhosis and decompensation in DAAs-based regimens. By the end of 2016, this topic had become of particular interest because of the publication of two papers from Spain and Italy that suggested a potential increase in the occurrence and recurrence rates of HCC in patients who were treated with DAAs. More than 100 papers have been published later on this topic with a wide range of controversies. These controversies could be rationalized by the heterogeneity of the included populations, variabilities of the inclusion and exclusion criteria of different studies, the study duration and the screening interval **[15].**

The promising Egyptian dream of HCV eradication was abruptly interrupted by an unexpected high incidence of HCC among treated cases. Whether it is a treatment-related complication or the well-recognized cirrhosis-related complication, HCC was repeatedly-investigated in different studies to rationalize this relationship.

On the 1st screening session, there was a statistically-significant difference between the studied groups regarding incidence of HCC diagnosed by triphasic CT (p= 0.005) with higher incidence of HCC in group III (6.4%) versus (3.13%) in group I and 0% in group II. On the 2nd screening session, only 297 patients attended, and there was a statistically-significant difference between the studied groups regarding HCC incidence confirmed by triphasic CT (p= 0.012) **(Table 4).** The incidence rate of HCC was also higher in group III (9%) versus (8%) in group I and 0% in group II. On the 3rd screening session, there was a high statistically-significant difference between the studied groups regarding incidence of HCC diagnosed by triphasic CT (p< 0.001) **(Table 4).** The HCC incidence rate was obviously-high in group III (23.08%) versus 11.96% in group I and 1.03% in group II. This obviously-denotes that untreated chronic HCV-

infected patients are at higher risk of HCC development.

Prospective analysis of the annual incidence rate of HCC in patients who have been followed in our study for a completed 12 months duration, the HCC incidence rate was 19% in group I (19/100 patients), 1.03% in group II (1/97 patients) and 30% in group III (30/100 patients). There was a high statistically-significant difference between the studied groups regarding the annual incidence rate of HCC (P< 0.0001). This clearly indicated that DAAs-treated patients who have achieved SVR were at decreased risk of HCC incidence than untreated.

The reported rates of HCC incidence in DAAs-treated patients are variable world-wide. The designs of different studies, the ethnic composition of the included patients, the inclusion and exclusion criteria are widely-variable. Here we will discuss some of them.

Ravi et al reported a 6-months HCC incidence rate of 9.1% (6/66 patients developed HCC within 6 months after completing successful DAA therapy) that is almost near to our reported annual incidence rate of HCC within treated groups (10.15% in groups I&II together) **[15].**

Also, **Waziry et al** concluded that "DAAs was not associated with a higher incidence rate of HCC" (RR 0.68; 95% CI 0.18-2.55, *P* =0.55) in a large metanalysis of 32 study including 11.523 patients **[9].**

Ioannou et al. performed a study of a mean follow-up of 6.1 years in 62.354 treated patients. 3271 incident cases of HCC were diagnosed. They reported that the incidence of HCC was highest in patients with cirrhosis and treatment failure (3.25 per 100 patient-years), followed by cirrhosis and SVR (1.97), followed by those without cirrhosis and treatment failure (0.87) and followed by those without cirrhosis and SVR (0.24) **[16].**

Kanwal et al. reported a significantly-reduced HCC risk in patients with SVR compared to those without (0.90 vs 3.45 HCC/100 person-years). Also, they concluded a 76% reduction in the incidence rate of HCC in existence of DAAs-induced SVR in that study **[17].**

In disagreement with our results, **Conti et al.** concluded that "a DAAs-induced SVR does not reduce the short-term occurrence of HCC" **[18].** This is because HCC was detected in 9/285 patients (3.16%) during the 24-week post-treatment follow-up. All of them were cirrhotic and 91% of them achieved SVR. Though considered high by Conti et al; this rate looks much lower than the one reported in our study in successfully-treated patients (10.15% in groups I&II together). This could be rationalized by the fact that all the included patients in Conti et al study were cirrhotic while our study included lower number of patients with advanced cirrhosis (35 patients; subgroup Ib). Though the incidence rate of HCC in treated groups in our study which is more than the reported rate in **Conti et al** study (3.16%), our reported rate is much lower when compared with that of the untreated group (group III) in our study (30%). Also, the reported rate by Conti et al. is at 24 weeks after SVR achievement while our reported rate is more than 1 year after development of SVR **[18]**.

Cardoso et al reported an increased rate of HCC incidence in patients with hepatitis C associated cirrhosis that underwent successful IFN-free antiviral therapy, at their institution. They included 54 patients that were treated with sofosbuvir and ledipasvir for 24 weeks in 2015. After a median follow-up of 12.0 months (IQR 9.4–12.5 months), since viral suppression, 7.4% were diagnosed with HCC. They considered this rate high because they compared it with the previously reported rates in IFN-treated patients (1.2-1.4%) **[8].**

Group I included 100 patients; 65 of them (65%) were classified easy-to-treat and were treated by SOF/DCV (subgroup Ia) while the remaining 35 patients were difficult-to-treat and were treated by SOF/DCV/RBV (subgroup Ib). On the 2nd screening session, we had 4 confirmed HCC cases in each subgroup and there was a statistically-insignificant difference between both subgroups (p= 0.354). But on the 3rd screening session we had 3/46 patients in subgroup Ia (6.52%) and 8/46 patients in subgroup Ib (17.39%) and there was a statistically-significant difference between the two subgroups regarding incidence of HCC (p=0.004). Difficult to treat patients have more advanced stages of cirrhosis roughly estimated to be more that F3 (Peg-IFN treatment experienced, Total bilirubin ≥ 1.2 mg/dl, Serum Albumin 2.8 – 3.5 g/dl, INR 1.2 – 1.7 and Platelet count 50000-150000 mm^3 according to NCCVH guidelines. This may force us to take the alternate hypothesis which is "HCC is the sibling of cirrhosis" rather than null hypothesis of "HCC is the sibling of DAAs-therapy".

The least HCC incidence rate in our study was that of group II (1.03%). Qurevo should not be used in patients with advanced liver failure and a Child-Pugh score of C. Patients with a history of hepatic decompensation including patients with a Child-Pugh score of B can be considered for treatment under close monitoring in experienced hepatologic centers **[19].**

Kanawl et al. concluded that "Patients with cirrhosis had a higher annual incidence of HCC after achieving SVR than those without (1.82 vs 0.34/100 person/years)". Moreover, the HCC incidence rate remained high in cirrhotic patients who achieved of SVR (annual incidence 0.9%)" **[17].**

Again, the so-reported "high" rate of HCC incidence in the study of **Conti et al.** could be rationalized by the fact that all the included patients in Conti et al study were cirrhotic while our study included lower number of patients with advanced cirrhosis (35 patients; subgroup Ib) **[18].**

Univariate analysis of patients with and without HCC at the 1st screening session, there was a high statistically-significant difference regarding SGPT, SGOT, AFP and FIB4 while there was a statistically-significant difference regarding the incidence of variceal bleeding, PLT, S. albumin, S. bilirubin and INR. On the 3rd screening session; there was a high statistically-significant difference regarding liver U/S, FIB4, PLT, SGOT, SGPT and AFP and there is statistically significance regarding farmer occupation, hepatic encephalopathy, variceal bleeding, random blood sugar, HB%, S. Albumin and INR. Incidence of DM is higher in patients developed HCC. FIB4 and Fibro-test are the most useful to use next to transient elastography to stage hepatic cirrhosis **[20].** There was a high statistically-significant difference between the studied groups regarding FIB4-score at the 1st screening session **(Table 2)**. We tried at the 1st screening session to exclude patients at the extremes of FIB4-scores between the three groups to nullify the effect of variation of cirrhosis stage. On the 1st screening session; we had 9 patients in group III with FIB4-score < 1.4. Six patients were refusing DAAs-therapy for non-medical believes and we succeeded to persuade 4 of them to seek DAAs-treatment after discussing its promising results and safety in a psycho-social approach but we failed to persuade the remaining one. The 3 other cases were not treatment-eligible because of advanced cardiac diseases.

There was a high statistically-significant difference between the studied groups regarding Child-Pugh score classes at the 1st screening session. In Group I; 94/100 patients (94%) were CTP-Class A while, 6/100 (6%) patients were CTP-Class B. In Group II; All patients (97/97) were CTP-class A. While in Group III 21/100 patients (21%) were CTP-Class A while, 60/100 patients (60%) were CTP-Class B and 19/100 patients (19%) were CTP-Class C. This is in disagreement with **Mettke et al.** who reported a statistically-insignificant difference between the studied groups regarding the severity of liver disease indicated by Child-Pugh-Scores **[21]**. This could be rationalized by the fact that the control group in that study included peg-IFN-treated patients whose liver functions are fully-compensated with earlier stages of cirrhosis (proved by liver biopsy) while the control group in our study included decompensated patients.

CONCLUSION

The annual incidence rate of HCC is higher in untreated HCV-infected patients than in those who have been successfully treated with DAAs. HCC incidence is related to the severity of cirrhosis rather than the treatment regimen.

List of Abbreviations:
Hepatitis C Virus (HCV), Hepatitis B Virus (HBV),Child-Turcott-Pugh (CTP), Direct Acting Antivirals (DAAs), Daclatasvir (DCV), Interferon (IFN), Enzyme linked immunosorbent assay (ELISA), Hepatocellular carcinoma (HCC), Fibrosis score based on 4 factors (FIB-4), Ribavirin (RVN), Sofosbuvir (SOF), Sustained virologic response 12 weeks after end of treatment (SVR12), National Committee for Control of Viral Hepatitis (NCCVH)

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Ethical consideration

This study was carried out in conformity with the Declaration of Helsinki. An informed consent was provided by all participants, and, the study protocol was notarized by the Ethics Committee of the Faculty of Medicine, Menoufia University and NCCVH.

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