Clinicoepidemiologic Study of Hepatocellular Carcinoma among HCV Induced Compensated Cirrhotic Patients who Achieved Sustained Virologic Response with Direct Acting Antiviral Drugs.

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Background and study aim: Hepatocellular carcinoma (HCC) is a major complication of hepatitis C virus (HCV) induced liver cirrhosis. Cirrhotic patients who achieved sustained virologic response (SVR) after DAAs remain at risk of HCC.

Patients and Methods: This cross-sectional study, carried out at hepatitis viruses' treatment unit affiliated to Al Ahrar teaching hospital in Sharkia governorate, Egypt in the period between 2017 and 2022 on 440 HCV induced compensated cirrhotic patients who received DAAs for treating HCV and had achieved SVR.

Results: By the end of the study, 110 out of 440 (25 %) patients developed de novo HCC. Risk factors for HCC were old age, male gender, rural residence, and diabetes mellitus. Clinical, laboratory and radiologic features of this type of HCC were similar to those of HCC in general.

Conclusion: Frequency of HCC is still high among DAAs treated HCV induced compensated cirrhotic patients with SVR and the 6 monthly follow up by AFP and pelviabdominal ultrasound in these patients is mandatory.

INTRODUCTION

Hepatocellular carcinoma (HCC) comes in the third rank among cancer mortality rates. HCV induced liver cirrhosis is a condition that may be complicated by hepatocellular carcinogenesis. Early detection of HCC depends on patient's adherence to the 6 monthly follow up by alpha fetoprotein (AFP) and pelvi abdominal ultrasound **[1].** In HCV induced liver cirrhotic patients, the each-year risk of development of HCC is between 2% and 8% **[2].**

The introduction of direct-acting antiviral drugs (DAAs) generated a new era in the treatment of HCV with more than 90% sustained virologic response (SVR) and a limited side effect profile during treatment **[3].** Multiple meta-analyses were conducted over the past years to assess the relationship between SVR and the risk of hepatocellular carcinogenesis and hence improving the liver related and the overall survival of HCV induced liver cirrhotic patients and reducing the need for liver transplantation **[4].**

As recommended by the current guidelines, HCC surveillance by follow up AFP measurement and liver ultrasonography should be performed every 6 months in cirrhotic patients with SVR **[5].** Improvement of liver functions in DAAs treated HCV induced liver cirrhotic patients is assumed to increase the patient's longevity and

hence the need for more follow up HCC surveillance visits **[4].** The main goal of routine HCC surveillance is to detect HCC at earlier stages where locoregional ablation, resection and liver transplantation may be curative for HCC while lack of adherence to routine HCC surveillance is accused for late detection of HCC at stages where curative therapies would not be of benefit **[5].** The objective of this follow up 5 year study is to determine epidemiology and clinical features of HCC among DAAs treated HCV induced liver cirrhotic patients with SVR.

PATIENTS AND METHODS

After application of the predetermined inclusion and exclusion criteria, 440 patients met the condition to join and complete this prospective cross-sectional study which was carried out at hepatitis viruses' treatment unit affiliated to Al Ahrar teaching hospital in Sharkia governorate, Egypt in the period between 2017 and 2022. By the start of the study, all patients were HCV induced Child Pugh class A cirrhotic who received direct acting antiviral drugs (DAAs) for treating HCV and had achieved sustained virologic response (SVR). Files and data of these patients were the responsibility of one investigator from whom the mother table data were collected.

All files of patients at the start and at the end of the study fulfilled the inclusion and exclusion criteria. By the end of the study, patients were classified into two groups; group I which included patients who developed HCC during the study period (N=110) and group II which included patients who did not develop HCC during the study period (N=330). Using the appropriate statistical methods, both groups were compared as regard clinical, laboratory and radiologic data. Clinical, laboratory and radiologic data of group I patients were compared at diagnosis of HCC, at the start of the study and at the end of the study.

This study included patients 18-75 years old who were DAAs (sofosbuvir and daclatasvir with or without ribavirin for 3 or 6 months according to Egyptian guidelines) treated HCV induced Child Pugh class A cirrhotic patients with SVR during the study period. Patients who developed liver cirrhosis related events other than HCC were still included in the study even if these events resulted in death during the study period eg ascites, hepatic encephalopathy, GIT bleeding, LCF, SBP and HRS. Data about these patients were collected from the inward department and the ICU affiliated to hepatitis viruses' treatment unit in Al Ahrar teaching hospital.

Patients with following criteria were excluded from the study :

•Less than 18 years and more than 75 years age

•Positive HCV RNA PCR at the start of or during the study period.

•Non cirrhotic patients (by imaging studies(

•Patients who received interferon for HCV treatment

•Patients who developed HCC before documentation of SVR (during or within 3 months after finishing DAAs treatment(

•Patients who had HCC at the start of the study

•Patients who had HCC and received ablative treatment before starting DAAS treatment

•Child Pugh classes B and C liver cirrhotic patients at the start of the study.

•Patient who died during the study period from non-liver related causes (eg, Covid-19 pandemic, stroke and malignancies other than HCC.(

•Patients who did not come for the 6 monthly follow up and failed to reach by telephone

All patients were subjected to full evaluation of their medical files including their past, present and family histories as well as their antiviral treatment. From patient files, clinical, laboratory and radiologic data during the period of DAAs treatment were collected. At the start of the study, clinical, laboratory and radiologic data of all patients were collected, and all patients proved to be Child Pugh class A liver cirrhotic with no radiologic nor laboratory evidence of HCC.

All patients were subjected to follow up every 6 months by laboratory and radiologic investigations. Laboratory investigations included complete blood picture (CBC), liver function tests (LFT), prothrombin time and concentration, international normalized ratio (PT and INR), kidney function tests (KFT) as well as serum alpha fetoprotein (AFP). Radiologic investigations included pelviabdominal ultrasound and triphasic CT liver with contrast was resorted for confirmation of the diagnosis of HCC or when there was sonographic suspicion in cases of heterogenous liver .

Patients who developed HCC were subjected to monthly follow up by CBC, LFT, KFT and pelviabdominal ultrasonography until the end of the study or death.

All data were collected, tabulated, and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA.(

RESULTS

Study participants

This study comprised 440 patients. By the end of the study, patients were classified into two groups; group I which included patients who developed HCC during the study period (N=110) and group II which included patients who did not develop HCC during the study period (N=330). Analysis of the demographic and clinical data among both groups showed that there were statistically significant differences as regard age, sex, residence and DM. As HCC cases showed higher mean values of age, and 76.36% were male, 98.18% rural residence and 53.63% diabetic patients in Table 1.

Comparing both groups at the start of the study

At the start of the study, laboratory investigations of both groups showed that there were no statistically significant differences as regard all laboratory investigations between both groups at the start of the study except for AFP that showed high significant difference with slightly higher values in HCC group in Table 2. The radiologic findings of both groups at the start of the study showed that there was no statistically significant difference when comparing radiologic findings of both groups at the start of the study in Table 3.

Cases with HCC (group 1) throughout the study

Comparing laboratory investigations of group I patients throughout the study showed that there were statistically significant differences as regard all laboratory investigations when comparing group 1 patients at the start of the study versus at diagnosis of HCC and at diagnosis of HCC versus at the end of the study in Table 4.

Comparing radiologic findings of group I patients throughout the study showed that apart from the non-significant difference of liver size, there were significant differences as regard splenic size, ascites, liver focal lesions, portal vein thrombosis and abdominal lymph node enlargement when comparing HCC patients at the start of the study versus at diagnosis of HCC and at diagnosis of HCC versus at the end of the study in Table 5.

Non-HCC patients (Group II) at the start and at the end of the study

Comparing laboratory investigations of group II at the start and at the end of the study showed that there was no statistically significant difference when comparing laboratory investigations of Group II patients at the start and at the end of the study in Table 6.

Comparing radiologic findings of group II patients at the start and at the end of the study showed that there was no statistically significant difference when comparing radiological findings of group II patients at the start and at the end of the study in Table 7.

Table 1. Demographic and clinical data among both groups.

		Group I (N=110)	Group II (N=330)	t	P
Age (years)		61.66±8.42	56.69±13.09	3.775	<0.001*
Sex	**Female**	26	142	13.30	<0.001*
		23.63%	43.04%		
	Male	84	188		
		76.36%	56.96%		
Residence	**Rural**	108	219	254.6	<0.001*
		98.18%	66.39%		
	Urban	2	111		
		1.82%	33.63%		
Diabetes Mellitus (N=123)	**No**	51	266	31.29	<0.001*
		46.36%	80.60%		

	Yes	59	64		
		53.63%	19.40%		
Hypertension (N=129)	**No**	69	242	3.99	0.046*
		62.72%	73.33%		
	Yes	41	88		
		37.27%	26.66%		
		99.1%	95.45%		

Table 2. Laboratory investigations of both groups at the start of the study:

	Group I (N=110)	**Group II (N=330)**	**t test**	**P value**
WBCs (x10^3/mm3) Mean±SD	6.5±2.168	6.20±2.94	0.958	0.338
Hb (g/dl) Mean±SD	12.61±1.72	13.35±2.02	1.02	0.213
Platelet's count (x10^3/mm3)	125.45±47.66	152.76±100.69	2.04	0.066
Total Bilirubin (mg/dl)	1.10±0.24	1.18±0.39	2.027	0.063
Serum Albumin (g/dl)	4.17±0.47	4.19±0.54	0.381	0.703
ALT (IU/L)	28.90±8.00	30.21±7.17	1.60	0.108
AST (IU/L)	44.27±9.55	49.22±8.85	2.06	0.062
INR	1.27±0.17	1.28±0.162	0.550	0.582
Serum creatinine (mg/dl)	1.11±0.22	0.99±0.264	0.461	0.642
AFP (ng/mL) Median IQR	24 (17-30)	16 (8-19)	Z test 10.125	<0.001*

WBCs (white blood cells), **ALT** (alanine transaminase), **AST** (aspartate aminotransferase), **INR** (The international normalized ratio), **AFP** (Alpha-fetoprotein).

Table 3. Radiologic findings of both groups at the start of the study:

		Group I (N=110)	**Group II (N=330)**	**P value**
Liver size	**Average**	50	211	0.319
		45.45 %	63.93%	
	Enlarged	50	83	
		45.45 %	25.15%	
	Shrunken	10	36	
		9.09%	10.90%	
Splenic size	**Average**	40	122	0.909
		36.36%	36.96%	
	Enlarged	70	208	
		63.63%	63.03%	
Ascites	**No**	110	330	-
		100%	100%	
	Yes	0	0	
		0%	0%	
Liver focal lesion(s)	**No**	110	330	-
		100%	100%	
	Yes	0	0	

		0%	0%	
Number of focal lesion(s)	**Single**	0	0	-
		0%	0%	
	Multiple	0	0	
		0%	0%	
Portal vein thrombus	**No**	110	330	-
		100%	100%	
	Yes	0	0	
		0%	0%	
Abdominal lymph node enlargement	**No**	110	330	-
		100%	100%	
	Yes	0	0	
		0%	0%	

Table 4. Comparing laboratory investigations of group I patients throughout the study:

	At the start of the study	**At diagnosis of HCC**	**At the end of the study**	**P value**
WBCs ($x10^3$/mm3) Mean±SD	6.50 ± 2.16	7.67±2.88	14.74 ±6.00	P1<0.001* P2<0.001*
Hb (g/dl) Mean±SD	12.61±1.72	11.34±2.07	8.93±1.21	P1<0.001* P2<0.001*
Platelet's count ($x10^3$/mm3)	125.45±47.66	130.27±57.50	153.72±85.69	P1=0.004* P2<0.001*
Total Bilirubin (mg/dl)	1.10±0.24	2.87±0.97	14.08±8.01	P1<0.001* P2<0.001*
Serum Albumin (g/dl)	4.17±0.47	3.10±0.60	2.90±0.61	P1=0.038* P2<0.001*
ALT (IU/L)	28.90±8.00	94.90±20.243	78.63±16.97	P1<0.001* P2<0.001*
AST (IU/L)	44.27±9.55	124.72±27.67	101.54±19.14	P1<0.001* P2<0.001*
INR	1.27±0.17	1.62±0.18	2.37±0.45	P1<0.001* P2<0.001*
Serum creatinine (mg/dl)	1.11±0.22	1.25±0.197	2.26±0.764	P1<0.001* P2<0.001*
AFP (ng/mL) Median IQR	24 (17-30)	270 (90-1190)	390 (200-2078)	P1<0.001* P2<0.001*

WBCs (white blood cells), **ALT** (alanine transaminase), **AST** (aspartate aminotransferase), **INR** (The international normalized ratio), **AFP** (Alpha-fetoprotein).
McNemar test.
P1= at the start of the study versus at diagnosis of HCC.
P2= at diagnosis of HCC versus at the end of the study.

Table 5. Comparing radiologic findings of group I patients throughout the study:

			At the start of the study	At diagnosis of HCC	At the end of the study	P value
Liver size	**Average**	N	20	10	0	P1=0.127 P2=0.232
		%	18.2%	9.1%	0%	
	Enlarged	N	80	100	110	
		%	72.7%	90.9%	100%	
	Shrunken	N	10	0	0	
		%	9.1%	0%	0%	
Splenic size	**Average**	N	40	30	20	P1<0.001* P2<0.001*
		%	36.4	27.3%	18.2%	
	Enlarged	N	70	80	90	
		%	63.6%	72.7%	81.8%	
Ascites	**No**	N	110	70	0	P1<0.001* P2<0.001*
		%	100%	63.6%	0%	
	Yes	N	0	40	110	
		%	0%	36.4%	100%	
Liver focal lesion(s)	**No**	N	110	0	0	P1<0.001* P2<0.001*
		%	100%	0%	0%	
	Yes	N	0	110	110	
		%	0%	100%	100%	
Number of focal lesion(s)	**Single**	N	0	80	20	P1<0.001* P2<0.001*
		%	0%	72.7%	18.2%	
	Multiple	N	0	30	90	
		%	0%	27.3%	81.8%	
Portal vein thrombus	**No**	N	110	50	30	P1<0.001* P2<0.001*
		%	100%	45.5%	27.3	
	Yes	N	0	60	80	
		%	0%	54.5%	72.7	
Abdominal lymph node enlargement	**No**	N	110	20	10	P1<0.001* P2<0.001*
		%	100%	18.2%	9.1%	
	Yes	N	0	90	100	
		%	0%	81.8%	90.9%	

McNemar test.
P1= at the start of the study versus at diagnosis of HCC.
P2= at diagnosis of HCC versus at the end of the study.

Table 6. Comparing laboratory investigations of group II at the start and at the end of the study:

	At the start of the study	At the end of the study	P value
WBCs (x10^3/mm3) Mean±SD	6.20± 2.94	6.06±2.77	0.386
Hb (g/dl) Mean±SD	13.35±2.02	13.25±1.97	0.406
Platelet's count (x10^3/mm3)	152.76±100.69	149.19±103.9	0.518
Total Bilirubin (mg/dl)	1.189±0.392	1.25±0.53	0.064
Serum Albumin (g/dl)	4.19±0.54	4.13±0.56	0.0725
ALT (IU/L)	30.2±7.17	30.95±7.82	0.122
AST (IU/L)	49.22±8.85	50.03±9.09	0.193
INR	1.28±0.16	1.302±0.196	0.099

Serum creatinine (mg/dl)	0.992±0.264	1.02±0.24	0.115
AFP (ng/mL) **Median** **IQR**	 16 (8-19)	 15 (8-0)	 0.114

WBCs (white blood cells), **ALT** (alanine transaminase), **AST** (aspartate aminotransferase), **INR** (The international normalized ratio), **AFP** (Alpha-fetoprotein).

Table 7. Comparing radiologic findings of group II patients at the start and at the end of the study:

			At the start of the study	At the end of the study	P value
Liver size	**Average**	N	211	202	0.327
		%	63.9%	62.12%	
	Enlarged	N	83	80	
		%	25.2%	24.24%	
	Shrunken	N	36	45	
		%	10.9%	13.63%	
Splenic size	**Average**	N	122	119	0.427
		%	37.0%	36.1%	
	Enlarged	N	208	211	
		%	63.0%	63.9%	
Ascites	**No**	N	330	320	0.572
		%	100%	97.0%	
	Yes	N	0	10	
		%	0%	3.0%	
Liver focal lesion(s)	**No**	N	330	330	-
		%	100%	100%	
	Yes	N	0	0	
		%	0%	0%	
Number of focal lesion(s)	**Single**	N	0	0	-
		%	0%	0%	
	Multiple	N	0	0	
		%	0%	0%	
Portal vein thrombus	**No**	N	330	330	-
		%	100%	100%	
	Yes	N	0	0	
		%	0%	0%	
Abdominal lymph node enlargement	**No**	N	330	330	-
		%	100%	100%	
	Yes	N	0	0	
		%	0%	0%	

DISCUSSION

Hepatocellular carcinoma (HCC) is considered to be the most common form of primary liver cancer. HCC which evolves on top of cirrhosis is the 6th amongst most diagnosed types of cancer and the 3rd amongst cancer related deaths **[1].** In 2023, it was estimated that the incidence rate was tripled in the past 4 decades by the North American Association of Central Cancer Registries **[6].**

The most important leading factor for HCC is liver cirrhosis. The reported incidence of HCC is about 3-8 % per year in chronic HCV cirrhotic patients **[2].** The 5-year risk for HCC development in cirrhotic patients is approximately 30 % with the highest risk among chronic HCV cirrhotic patients **[7].**

Direct-acting antiviral agents (DAAs) showed improved eradication of HCV infection even in advanced liver disease with a good safety profile and a sustained virologic response (SVR) rate exceeding 95 % in clinical practice **[3].** So, they are the recommended treatment for patients with HCV infection **[8].**

However, the impact of achieving SVR in patients treated with DAAs therapy on the incidence of HCC is still a matter of debate **[4].** Several studies reported unexpected high HCC occurrence or recurrence in cirrhotic patients following DAAs therapy whereby others have not supported this observation **[9, 10].**

Incidence of HCC in patients with chronic hepatitis C after interferon (IFN) treatment was 5.6% (6 months after completion of IFN treatment) **[29].**

Before the era of HCV treatment, Hospital surveys in Egypt revealed a general rise in the relative frequency of all liver-related malignancies (> 95% as HCC) from about 4% in 1993 to 7.3% in 2003 **[30].**

The aim of the present study was to determine the epidemiology and clinical features of HCC among direct acting antiviral drugs (DAAs) treated hepatitis C virus induced liver cirrhotic patients with sustained virologic response.

In the present study, the incidence of de novo HCC in HCV induced liver cirrhotic patients post DAAs therapy was 25 % within a period of 5 years of follow up. Among 440 HCV induced liver cirrhotic patients who received DAAs and achieved SVR, 110 patients developed HCC.

Multiple studies suggested that cirrhotic patients who achieved SVR after DAA regimens may be more susceptible to develop HCC **[9]** while others reported that DAA regimens were associated with markedly decreased risk of HCC **[11].**

In harmony with the results of this study, Conti et al. reported that DAA regimens did not reduce the incidence of HCC after 1 year of achieving SVR (5.1 % was the incidence of occurrence of HCC) and concluded that achievement of SVR may not reduce HCC occurrence and close monitoring of all cirrhotic patients during and after antiviral therapy is a must **[9].** Also, Cardoso et al. found the incidence of HCC occurrence 7.4 % after following up for 1 year **[12].**

However, another study by Shiha et al. found the incidence of HCC was 2.9 % after 1 year. Their results showed regression of fibrosis and consequently decreased incidence of HCC supporting the beneficial effect of therapy on improving liver impairment **[13].**

Another 2 studies confirmed the reduced incidence of HCC; in a prospective study by Carrat et al., the incidence was 2.7 % per year **[11]** and in a retrospective study by Li et al., it was 2.1 % per year **[14].** The difference may be due to shorter follow up period and different genotypes of HCV were included in their studies.

With the increasing number of patients with HCV cure, it became very important to identify the value of ongoing surveillance for HCC as this issue provoked a wide debate **[5].**

In the present study, there were statistically significant differences as regard age, sex, residence and DM. This is in agreement with Ogawa et al. who found that most patients aged 75-84 years were at high risk for HCC development **[15].** Also, Shiha et al. declared that patients with HCC were significantly older with predominance of male gender when compared to patients without HCC **[13].**

The results of this study are in harmony with Luna-Cuadros et al. who found a number of factors including diabetes mellitus (T2DM contributes to fibrosis progression after DAA therapy, which is a risk of HCC) that has been associated with progression to HCC after cure of HCV infection **[16].**

As regard the significant risk of rural residence in this study, it is in agreement with Abd-Elsalam et al. who declared that about 26 % of the population work in agriculture in Egypt with high level of pesticides exposure making them at high risk for developing HCC mostly among rural males who are exposed to other risk factors as HBV and HCV infections **[17].**

At the start of this study, comparison of laboratory and radiologic investigations between both groups showed no statistically significant differences except for AFP and liver size that showed a highly significant difference between both groups of the study. This is in agreement with Shiha et al. who demonstrated that higher levels of AFP were found at baseline in HCC patients **[13].** Also, another study by Yoo et al. found that patients with elevated AFP developed HCC at the end of treatment declaring that AFP

more than 9.5 ng/mL was an early onset risk factor for developing HCC **[18].** Similarly, Kumada et al. reported that AFP more than 5.0 ng/mL might be associated with HCC development within 10 years after achieving SVR **[19].** Also, Leal et al. found an association between high AFP level before DAA and prediction of HCC development **[20].**

However, in contrast, Mawatari et al. demonstrated that AFP level before DAA therapy was not associated with the development of HCC explaining their results by multiple causes of AFP levels elevation before treatment such as reflection of liver regeneration, fibrosis, inflammation and microscopic HCC **[21].**

In the current study, analysis of HCC cases (Group I) throughout the stages of this study showed statistically significant differences as regard all laboratory investigations and clinical findings when comparing them at the start, at diagnosis of HCC and at the end of the study. Similar results were obtained by Cabibbo et al. and Dawood et al. who found that HCC patients had lower hemoglobin and serum albumin levels and higher ALT, AST, AFP, serum bilirubin, platelet count, PT and INR **[22, 23].** These results reflect malignant anorexia, GIT blood loss, malignant invasion on hepatocytes, disturbed synthetic and excretory liver functions along with secretions released by HCC cells.

There is significant progressive hepatic decompensation in this study when comparing the results of clinical findings and laboratory investigations at diagnosis of HCC with those at the end of the study. This is in agreement with Marie et al. who found significant hepatic decompensation during the course of HCC with features including ascites, jaundice, hepatic encephalopathy and hematemesis **[24].**

This study demonstrated that there was no statistically significant difference when comparing laboratory investigations and radiological findings of non-HCC patients (Group II) at the start and at the end of the study. This is similar to results of Carrat et al. who found that DAAs therapy was not associated with decompensated cirrhosis and even it resulted in decrease of mortality and HCC incidence [11]. This finding is also consistent with another study by Johnson et al. that reported improvement of liver function and survival after achievement of SVR **[25].** Moreover, Hassan et al. evaluated the laboratory and radiologic data of patients before DAAs treatment, 3 and 12 months after the end of treatment and found a significant improvement in the level of AFP, AST, ALT, serum albumin, and INR, while there were no significant changes in other laboratory parameters **[26].**

The hypothesis that DAAs treatment can maintain the compensated state of liver cirrhosis was studied by Nahon et al. who found that DAAs therapy was associated with a decrease in all-cause mortality and HCC and was not associated with occurrence of hepatic decompensation **[27].** Moreover, Pereira et al. demonstrated that the risk of liver decompensation after DAAs therapy was associated with a pretreatment history of decompensation, impaired liver synthetic capacity and baseline significant portal hypertension **[28].**

CONCLUSIONS

Chronic hepatitis C (HCV) is considered the most common cause for HCC; yet, despite inducing clearance of HCV infection, DAAs do not appear to diminish the development of HCC in long-term follow up. All cirrhotic patients who were treated by DAAs should be carefully followed up for HCC because the study did not find a decreased risk of HCC in those who achieved SVR from hepatitis C.

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HIGHLIGHTS

- Chronic hepatitis C (HCV) is considered the most common cause for HCC; yet, despite inducing clearance of HCV infection, DAAs do not appear to diminish the development of HCC in long-term follow up.
- All cirrhotic patients who were treated by DAAs should be carefully followed up for HCC because the study did not find a decreased risk of HCC in those who achieved SVR from hepatitis C.

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