

Frequency of Hepatocellular Carcinoma in Cirrhotic Patients after Chronic Hepatitis C Infection Treatment with Direct-Acting Antivirals

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Background and study aim: Hepatocellular carcinoma (HCC) is the 4th most common cancer in Egypt and is the 2nd leading cause of cancer-related death in both men and women. The aim of this study is to determine the frequency of HCC in cirrhotic patients admitted in Al-Ahrar Teaching hospital especially after hepatitis C virus (HCV) treatment with new direct-acting antivirals (DAAs).

Patients and Methods: This study included 107 patients with liver cirrhosis admitted to Al-Ahrar Teaching hospital. All patients undergo complete blood count, liver functions, kidney functions, coagulation profiles, serology for viral hepatitis, serum alpha-fetoprotein, abdominal ultrasound, and tri-phasic computed tomography.

Results: HCC was diagnosed in about 9 % of cirrhotic patients in this study. The etiology of cirrhosis was HCV (66.4 %), non-viral causes (23.3 %), and HBV (9.3 %). There was no statistically significant difference between HCC and non-HCC patients as regard viral markers and HCV treatment. According to Barcelona-Clinic Liver Cancer staging, 80 % of patients among HCC group was stage D while 20 % of patients were Stage A - C.

Conclusion: HCC is prevalent in cirrhotic patient admitted in Al-Ahrar Teaching Hospital. HCV treatment with DAAs does not raise the risk of HCC occurrence in cirrhotic HCV patients.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the 5th most common malignancy and the 3rd leading cause of cancer related death. Nearly three-quarters of all hepatic malignancies are HCC [1]. In Egypt, the incidence of HCC has increased. According to Egyptian studies, the rate of HCC cases has increased from 4% in 1993 to 7.3 % in 2003 [2]. The incidence of HCC is increased to 19.7% of the total cancer cases in 2018. The 2018 incidence data were collected from Aswan, Damietta, and Minya Cancer Registries [3]. This rising incidence of HCC may be due to the increased frequency of HCV and its complications, advances in screening programs and diagnostic methods [4].

One of the most fatal cancers is hepatocellular carcinoma, with a high rate of recurrence and metastasis after surgical resection [5]. HCC has a significant death rate, particularly in people with late diagnosis due to the lack of symptoms in the early stages and lack of screening programmes particularly in developing countries [6].

Hepatocellular carcinoma is most commonly caused by hepatitis B virus (HBV) and C virus (HCV), but chronic alcohol intake, metabolic disorders (such as diabetes and obesity), and ageing can all play a role in the development of HCC. HBV and/or HCV infections cause about 80% of HCC cases, especially if liver cirrhosis occurs [7]. Chronic hepatitis occurs in 60 - 80% of patients with HCV infection, and 10 - 20% of them

will develop cirrhosis within 20 - 30 years. HCC can occur in 1 - 5% of cirrhotic patients [8].

Cirrhosis and HCC mortality continues to be a major concern in Egypt. Patients infected with HCV have a seventeen-fold greater chance of developing HCC [9]. Egypt was one of the highest HCV prevalence rates, with 14.7 % of the population infected. [10]. The use of direct-acting antivirals (DAAs) to treat HCV has raised hopes for a considerable reduction in the rate of HCC development [11]. However, the impact of DAA treatment on the incidence of HCC occurrence in cirrhotic patients is a debate [12].

The aim of this study is to determine frequency and possible risk factors for HCC occurrence in cirrhotic patients admitted in Al-Ahrar Teaching hospital especially after new DAAs have been used to treat HCV.

PATIENTS AND METHODS

Study design: It is a cross-sectional study.

Study settings: This study was conducted on patients admitted to Al-Ahrar Teaching hospital under supervision of Tropical Medicine Department, Zagazig University Hospitals, in the period between March 2020 to September 2020.

Study patients: This study included 107 patients with liver cirrhosis admitted to Al-Ahrar Teaching hospital.

Inclusion criteria:

Patients with liver cirrhosis (cirrhosis diagnosis based on clinical, biochemical, and imaging studies)

Exclusion criteria:

Patients who had any cancer other than HCC or had metastatic liver disease will be excluded from the study.

Patient assessment: All patients were subjected to

- Thorough history taking (including if patients received HCV or HBV treatment and type of it)
- Complete physical examination
- Child-Pugh scoring.
- Laboratory studies included Complete Blood Count, liver functions, kidney functions, coagulation profiles, serology for viral hepatitis, serum alpha-fetoprotein (AFP), antinuclear antibodies, anti-smooth

muscle antibodies, anti-liver kidney microsomal antibodies, serum iron, serum ferritin, serum ceruloplasmin and urinary copper.

- Abdominal ultrasonography (US) (GE P5): The US used to detect liver size, surface, echogenicity, hepatic veins, and measurement of portal vein. Hepatic focal lesions' number, location, and size are all determined. Also used to assess size, texture of spleen and the presence of ascites
- Tri-phasic Computed Tomography (GE Multislice CT 64): It was used for patients with hepatic focal lesions in ultrasonography. The hallmark for HCC diagnosis is arterial hypervascularity with intra-lesion contrast washout on venous, portal, and delayed phase images [13].
- HCC patients are classified according to Barcelona-Clinic Liver Cancer (BCLC) classification of HCC [14].

Statistical Analysis

The collected data was tabulated and statistically analyzed using SPSS 26.0 for windows (SPSS Inc., Chicago, IL, USA). Independent samples Student's t-test, Mann-Whitney U test, and Chi-square test were used for data analysis. P-value <0.05 was considered statistically significant.

RESULTS:

This study included 107 cirrhotic patients 70 male patients (65.4%) and 37 female patients (34.6%). These patients are classified according to CT findings into 97 patients (90.7%) without HCC and 10 patients (9.3%) with HCC. Non-HCC patients included 64 males and 33 females whose age ranged from 40-80 years with mean of age 59.6 ± 7.48 years. HCC patients included 6 males and 4 females whose age ranged from 50-62 with mean of age 57.57 ± 5.13 years. There was no statistically significant difference between the studied patients as regard demographic data (**Table 1**). According to Child Pugh classification among HCC & non-HCC patients, 85.6 % of non-HCC patients was child B and all HCC patients was child C (**Table 2**).

The etiology of cirrhosis was HCV in 66.4 % of patients, non-viral cause in 23.3 % of patients then HBV in 9.3 % of patients. In HCC patients, 6 patients were HCV positive, 1 patient HBV positive and 3 patients due to non-viral. There was no statistically significant difference

between HCC and non-HCC patients as regard cause of cirrhosis (**Table 3**).

The study included 56 HCV positive patients received HCV treatment with DAAs. 39 patients received sofosbuvir/daclatasvir and ribavirin for 3 months, and 11 patients received sofosbuvir and ribavirin for 6 months, and other remaining patients take either sofosbuvir/ledipasvir or sofosbuvir/simeprevir. HCC diagnosed in 4 patients of cirrhotic patients treated with DAAs and in 2 patients of cirrhotic HCV does not receive treatment. There was no statistically significant difference between HCC and non-HCC patients as regard HCV treatment with DAAs (**Table 4 – Figure 1**).

Regarding clinical picture, there was statistically significant difference between HCC and non-HCC patients as regard abdominal pain,

tenderness, fever, weight loss, wasting and weakness (**Figure 2**).

Regarding laboratory data, **Table 5** showed a statistically significant difference between HCC and non-HCC patients as regard total bilirubin, serum albumin, AST, and INR ($P < 0.05$) and a high statistically significant difference as regard AFP ng/ml ($P < 0.001$).

All HCC patients showed multiple hepatic focal lesions with variable size in both ultrasound and CT studies. Portal vein thrombosis detected in 8 patients with HCC in doppler ultrasound study. According to BCLC staging, 80 % of HCC patients was stage D (Ps > 2 or Child Pugh A-B) and treated by symptomatic drugs while 20 % of patients were Stage A - C (intermediate - stage B, Multinodular, PS 0) and treated by chemoembolization.

Table (1): Demographic data among HCC and non- HCC patients.

Variables		Total n = 107	Non- HCC n= 97	HCC n = 10	P value
		N (%)	N (%)	N (%)	
Sex	Male	70 (65.4)	64 (66)	6 (60)	0.693* (NS)
	Female	37 (34.6)	33 (34)	4 (40)	
Age					0.483† (NS)
Mean±SD		59.47 ± 7.35	59.6 ± 7.48	57.57 ± 5.13	
Median (IQR)		60 (52.5-64)	60 (52.5–65)	60 (54–61.5)	

NS= non-Significant

* Chi square test

†Mann Whitney test

Table (2): Child Pugh classification among HCC & non-HCC group.

	Non-HCC n=97	HCC n=10		P
	N (%)	N (%)		
Child A	0 (0)	0	(0)	0.001* (HS)
Child B	83 (85.6)	0	(0)	
Child C	14 (14.4)	10	(100)	

HS= highly significant

* Chi square test

Table (3): Cause of cirrhosis among HCC and non-HCC patients.

Variables		Total n = 107	Non- HCC n = 97	HCC n = 10	P
		N (%)	N (%)	N (%)	
Cause of cirrhosis	Non-viral	25 (23.3)	22 (22.7)	3 (30)	0.787* (NS)
	HCV +ve	71 (66.4)	65 (67.01)	6 (60)	
	HBV +ve	10 (9.3)	9 (9.3)	1 (10)	
	HCV & HBV +ve	1 (0.9)	1 (1.03)	0(0)	

NS= non-Significant

* Chi square test

Table (4): Comparison between HCC and non-HCC patients with HCV positive as regard HCV treatment with DAAs.

Variables		Total n= 71	Non- HCC n= 65	HCC n= 6	P
		N (%)	N (%)	N (%)	
HCV treatment	Yes	56 (78.9)	52 (80)	4 (66.7)	0.44* (NS)
	No	15 (21.1)	13 (20)	2 (33.3)	

NS= non-Significant

* Chi square test

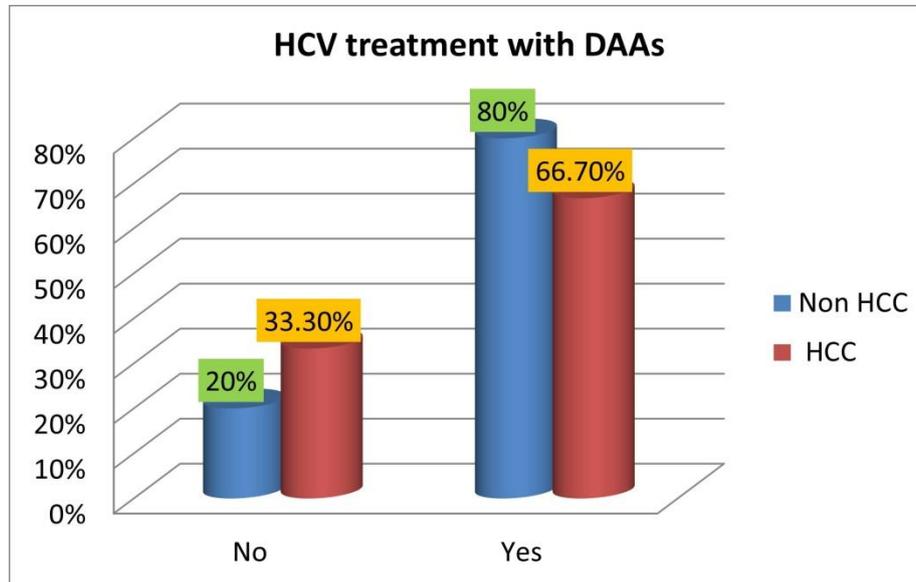


Figure 1: Bar charts showing HCV treatment among HCC and non- HCC patients. HCV treatment with DAAs was received in 80 % of patients without HCC and in 66.7 % of HCC patients and there was no statistically significant difference between HCC and non-HCC patients as regard HCV treatment.

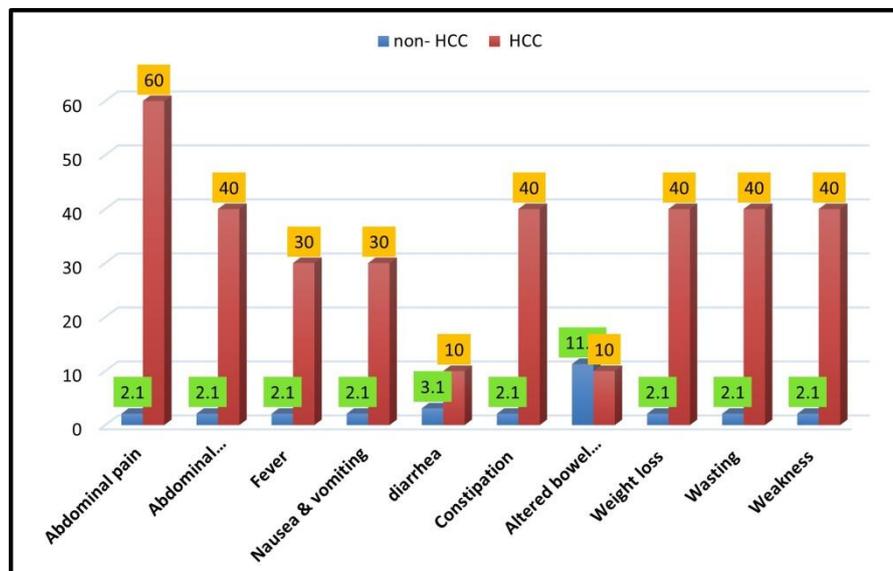


Figure 2: Bar charts showing different clinical parameters among HCC and non- HCC patients. Abdominal pain present in 60 % of HCC patients. Abdominal tenderness, weight loss, weakness and wasting in 40 % of HCC patients. Fever, nausea and vomiting in 30% of HCC p

Table (5): Liver function and AFP among HCC and non-HCC patients.

Liver function	Total n = 107	Non-HCC n = 97	HCC n = 10	P
	Mean±SD	Mean±SD	Mean±SD	
T. Bilirubin (mg/dl)	2.72 ± 2.62	2.50 ± 2.36	5.93 ± 4.10	0.002* (S)
AST(U/L)	8.0 ± 112.0	8.0 ± 112.0	55.0 ± 112.0	0.002* (S)
ALT(U/L)	39.97 ± 21.29	39.12 ± 20.97	52.14 ± 23.84	0.108* (NS)
AFP ng/ml	44.77 ± 142.1	8.64 ± 16.10	363.43 ± 227.69	<0.001* (HS)
Albumin(gm/dl)	2.79 ± 0.49	2.82 ± 0.48	2.35 ± 0.39	0.014* (S)
INR	1.60 ± 0.46	1.56 ± 0.42	2.26 ± 0.55	0.001* (S)
AFP ng/ml	44.77 ± 142.1	8.64 ± 16.10	363.43 ± 227.69	<0.001**

S=Statistically significant

HS= highly significant

* Mann Whitney test

DISCUSSION

Hepatocellular carcinoma is a serious public health problem in Egypt and most patients diagnosed at end stage of disease where surgery or effective local ablative therapies is impossible, and treatment of these patients is symptomatic [15]. Most HCC patients are due to chronic HCV infection, chronic HBV infection and alcohol. Its pathogenesis varies, but most cases evolve because of cirrhosis and depending on the underlying etiological factor [16]. The aim of this study is to determine frequency and possible risk factors for HCC occurrence in cirrhotic patients admitted in Al-Ahrar Teaching hospital especially after new DAAs have been used to treat HCV.

This cross-sectional study included 107 patients with liver cirrhosis admitted to Al-Ahrar Teaching Hospital in the period from March 2020 to September 2020. Diagnosis of cirrhosis in these patients based on clinical findings, biochemical data, and imaging studies. They are classified according to CT findings into 97 patients without HCC and 10 patients with HCC.

This study showed that 60% of patients with HCC are male, and their age ranged from 50 - 62 years. These results consistent with Zamzam, 2019, Pande et al. 2012, and Kuman et al. 2008 who explained that males are more liable to get infection with HBV or HCV, consume alcoholic beverages, smoke cigarettes, and have a higher level of iron in their bodies. Males also may be at greater risk due to androgenic hormones and increased genetic predisposition. Female sex hormones may have a protective effect [15,17,18].

According to Child Pugh classification, 100% of HCC patients were class C, while 83% of non-HCC patients were class B and 14% were class C. There was high statistically significant difference between HCC and non-HCC patients as regard Child Pugh classification ($p < 0.001$). Advanced liver cirrhosis is the main risk factor for HCC development and present in 90 % of HCC diagnosed patients as it causes carcinogenic changes in hepatocytes [19].

In this study, 67% of non-HCC patients were HCV positive, 9.3% were HBV positive, and 1% were both HCV & HBV positive, while in HCC patients; 60% were HCV positive and 10% were HBV positive. There was no statistically significant difference between HCC and non-HCC patients as regard both HCV and HBV infection. In consistency with these results, Anwar et al., 2008 found that HCV in Egypt was the primary factor related to the most HCC cases. Egypt before HCV treatment had the highest rates of HCV infection worldwide [20]. Similarly, Zamzam, 2019 found that 91.3% of HCC patients tested positive for HCV and 6.5 % tested positive for HBV [15]. On the contrary, Ferenci et al, 2010 reported that HCV cirrhosis is the main risk factor for HCC with 2 % to 8 % annual incidence, but there were no HCC patients positive for HBV [21].

There is a major debate regarding the relationship between using DAAs for HCV treatment in cirrhotic patients and the development of HCC. Many experts proposed a link between DAA usage and the development of HCC, while others insisted that DAA use

protects against the development of HCC [11]. In the present study, DAAs for HCV treatment was received in 80 % of HCV positive cirrhotic patients without HCC and in 66.7 % of HCC patients with cirrhotic HCV and there was no statistically significant difference between HCC and non-HCC patients as regard HCV treatment with DAAs. So, based on our findings, DAAs do not raise the risk of HCC development in cirrhotic patients and may reduce the incidence of HCC occurrence with mass treatment of HCV positive patients. This is in consistent with **Calvaruso et al. 2018** who found that only 78 patients (3.4 %) out of 2249 cirrhotic patients developed HCC after treatment with DAAs over a 14-month period and risk of HCC is greatly reduced [22]. In contrast, **Conti et al. 2016** demonstrated increased recurrence rate of HCC in 59 patients treated with DAAs (28.8%) during six months after treatment [11]. This difference may be due to small sample size.

This study included 25 patients developed cirrhosis due to non-viral cause. Because they were obese patients with type 2 diabetes, negative for Wilson disease, hemochromatosis, autoimmune hepatitis, and with normal hepatic veins doppler, the cirrhosis in these patients was mostly attributable to NASH. HCC diagnosed in 12 % of cirrhotic patient related to NASH. These results consistent with, **Bertot et al. 2017** who found that 12% of NASH patients developed HCC [23]. In patients with NASH-related cirrhosis, the annual incidence rate for HCC detection is about 2.4 % - 12.8 % [24]. Metabolic syndrome and insulin resistance are risk factors for HCC occurrence in NASH, as they generate chronic inflammation, alterations in serum cytokines, and changed gut microbiota and bile composition [25]. In contrast, **Sanyal et al. 2010** found that NASH accounted for 59 % of HCC cases, with a cumulative incidence rate of 0.3% after a 6-year follow up [26].

The clinical presentations of HCC in our patients were similar to those seen in other studies [27]. Patients often present with constitutional symptoms like anorexia, weight loss and fever. Many patients complain of abdominal pain and tenderness which may be acute if there is hemorrhage into the tumor (**Figure 2**). This emphasized that the development of HCC is an important cause of sudden worsening of clinical condition in compensated cirrhotic patients [28].

This study showed statistically significant difference as regard total bilirubin, AST, and INR ($P<0.05$) and high statistically significant difference as regard AFP ng/ml ($P<0.001$) between patients with HCC and non-HCC patients. As regard albumin, there was a statistically significant difference ($P<0.05$) where albumin had significant reduced level in the HCC patients. Lower levels of albumin were associated with higher levels of bilirubin due to liver parenchymal damage caused by tumor growth. Similarly, **Carr and Guerra, 2017** found that there is lower levels of albumin and higher levels of AFP, especially in tumors > 5 cm in diameter [29]. In contrast, **Mobarak et al., 2015** found higher level of albumin in HCC patients, they attribute that to increased synthetic function of malignant hepatocyte to compensate deficiencies in liver function due to cirrhosis [30].

According to BCLC staging, 80 % of our HCC patients were stage D ($Ps >2$ or Child Pugh A-B) and treated by symptomatic drugs, while 20 % of HCC patients were Stage A-C (intermediate - stage B - Multinodular, PS 0) and treated by chemoembolization. This suggested that HCC patients had a late diagnosis and were no longer candidates for curative treatments such as radiofrequency ablation, liver transplantation, or liver resection. These findings highlight the importance of strong adherence to routine screening and surveillance program for cirrhotic individuals to detect liver cancer early, while it is still treatable.

Finally, HCC diagnosed in about 9 % of cirrhotic patients in our study. The main risk factor for HCC development is cirrhosis caused by chronic HCV infection and NASH. This study has some limitations; it was a cross sectional study which limited to the available data in medical charts, small sample size, and there was no follow-up, thus the long-term results cannot be obtained. These points need to be in mind in future studies.

CONCLUSIONS:

HCC is prevalent in cirrhotic patient admitted in AL-Ahrar Teaching Hospital. Frequency of HCC increase with advanced cirrhosis, HCC suspected in cirrhotic patients when sudden deterioration occurs in absence of other causes especially infection and GIT bleeding. Chronic HCV infection and NASH are major risk factors for development of HCC. In cirrhotic HCV patients,

HCV therapy with DAAs does not raise the risk of HCC occurrence.

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Conflicts of interest: None.

Ethical consideration

Permission and official approval to carry out the study was obtained. All patients signed a written informed consent before inclusion into this study and the institutional ethical committee at Zagazig University, Faculty of Medicine approved the study (ZU-IRB #5836/15-2-2020). The study protocol conforms with the ethical guidelines of the 1975 Declaration of Helsinki.

HIGHLIGHTS:

- Hepatocellular carcinoma is a serious public health problem in Egypt and most patients diagnosed at end stage of disease where surgery or effective local ablative therapies is impossible, and treatment of these patients is symptomatic.
- There is a major debate regarding the relationship between using DAAs for HCV treatment in cirrhotic patients and the development of HCC. Many experts proposed a link between DAA usage and the development of HCC, while others insisted that DAA use protects against the development of HCC.
- This study was conducted on 107 cirrhotic patients admitted in Al-Ahrar Teaching hospital. HCC diagnosed in about 9 % of cirrhotic patients in our study. The main risk factor for HCC development is cirrhosis caused by chronic HCV infection and NASH.
- Most of HCC patients in this study was stage D according to Barcelona-Clinic Liver Cancer classification and not candidate for curative therapies and treated with palliative treatment. These findings highlight the importance of strong adherence to routine screening and surveillance program for cirrhotic individuals to detect liver cancer early, while it is still treatable.

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