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Frequency of Hepatocellular Carcinoma in HCV Patients Treated with Direct-Acting Antiviral Drugs

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a serious disease that affects people all over the world. It is the second most common cause of cancer mortality in men and the sixth in women.

Objective: The aim was to study frequency of Hepatocellular carcinoma in HCV patients treated with direct-acting antiviral drugs. **Patients and Methods:** The present work was performed on 90 patients. The patients were selected from Oncology Center Mansoura University (OCMU) and specialized medical hospital Mansoura University. The 90 patients were divided into 3 groups: Group 1: 30 HCV-related HCC patients received DAAs previously and in SVR within 2 years of HCC diagnosis. Group 2: 30 HCV-related HCC patients without a previous history of exposure to DAAs. Group 3: 30 patients with chronic HCV (CLD= chronic liver diseases) treated by DAAs without developing HCC within 2 years of treatment and in SVR in addition to a control group of 10 normal persons.

Results: BMI was found significantly lower in group 1 compared to group 2 patients. Ascites is more frequent among group 2 than group 1 (43.3% versus 30%, respectively) without statistically significant difference between them. Diabetes history shows statistically significant higher frequency among group 2 than group 3 (53.3% versus 23.3%, respectively).

Conclusion: Male gender was predominant among HCC patients even exposed to DAA or not in comparison to group 3 (CLD successfully treated with DAA). A significant increase in HCC patient groups whatever exposed to DAA or not in comparison to HCV CLD patients with SVR as regards ALT, AST, Total bilirubin, INR and AFP, while albumin and Hb levels noticed to be significantly decreased in HCC patients groups in comparison to HCV CLD patients with SVR.

Keywords: Hepatocellular carcinoma, HCV patients, Direct-acting antiviral drugs.

INTRODUCTION

Infection with the hepatitis C virus (HCV) is a significant public health issue in Egypt. Hepatocellular carcinoma (HCC) is a serious disease that affects people all over the world. It is the second most common cause of cancer mortality in men and the sixth in women [(1)]. HCC is the second most common malignancy in males and accounts for 13% of all malignancies in Egypt. In Egypt, HCC cases accounted for more than 90% of all cases [(1, 2)]. Direct acting antivirals (DAAs) have made significant advancements in the treatment of HCV in recent years, with exceptional outcomes reaching more than 90% sustained virological response (SVR). This outstanding accomplishment constitutes a significant hepatology advance [(3)].

SVR following interferon-based treatments for chronic HCV reduces mortality from all causes, including HCC. The impact of DAAs on the development of HCC and its recurrence following effective therapy has been discussed in a number of recent researches and reports [(4)]. Moreover, various DAAs impact based SVR on HCC recurrence following curative treatment for early HCC have produced contentious results (resection, local ablation, chemoembolization or liver transplantation). While a French research including 189 patients found a 12% HCC recurrence rate following DAAs treatment with a median follow-up of 20 months [(5)], two further studies involving a combined total of 140 patients reported a 25-30% HCC recurrence at 6 months following DAAs treatment [(3, 6)].

The aim was to study frequency of Hepatocellular carcinoma in HCV patients treated with direct-acting antiviral drugs.

PATIENTS AND METHODS

The present work was performed on 90 patients, 58 males (64%) and 32 females (36%), with age ranged from 47 to 67 years. The patients were selected from Oncology Center Mansoura University (OCMU) and specialized medical hospital Mansoura University.

The 90 patients were divided into 3 groups: *Group 1*: 30 HCV-related HCC patients received DAAs previously and in SVR within 2 years of HCC diagnosis. ***Group 2:*** 30 HCV-related HCC patients without a previous history of exposure to DAAs. ***Group 3:*** 30 patients with chronic HCV (CLD= chronic liver diseases) treated by DAAs without developing HCC within 2 years of treatment and in SVR. In addition to a control group of 10 normal persons with matched age and sex.

Inclusion Criteria:

- Patients with HCV-related HCC or patients with HCV without HCC aged up to 70 years.
- Both genders are eligible.

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Exclusion Criteria:

- Unfit patients because of associated co-morbidities and poor performance.
- Patients with chronic hepatitis B virus (HBV) or any other identifiable cause for chronic hepatitis other than HCV.
- Any associated malignancies.
- patients with previous history of cancer.
- HCC patients with previous history of treatment by chemotherapy, radiotherapy or surgically were excluded.

Investigational Plan:

All patients were subjected to the following:

1- Detailed history taking pre and after treatment with DAA including epidemiologic, radiologic, as well as protocols of DAA used.
2- Physical examination in addition to routine systemic examination.
3- laboratory investigations Fasting venous blood samples were collected from all patients for routine workup, including:
   a. Complete blood count (CBC).
   b. Chemistry profile: ALT, AST, Serum bilirubin, serum albumin, prothrombin concentration and INR, AFP, anti-HCV titer, HBsAg, and HBc-Ab, serum creatinine and serum uric acid, using commercially available assays.
4- Ultrasound, CT scan or MRI.
5- Fibroscan.

Diagnosis of HCC: All HCC patients were on top of HCV cirrhosis and HCC diagnosis was made upon the presence of hepatic focal lesions diagnosed by abdominal ultrasound and confirmed by computed tomography (CT) and/or magnetic resonance imaging according to European Association of the Study of the Liver (EASL) guidelines [(7)]. Tumor-node-metastasis (TNM) staging system was used to determine the stage of tumors (TNM I, II, III, or IV) on the basis of their status of metastasis (yes or no), distant metastasis (yes or no) and tumor size (≤5 cm or >5 cm [(8)].

Liver disease severity in HCC patients was assessed by Child- Pugh: The Child-Turcotte-Pugh (CTP) classification has been used to stratify patients with cirrhosis [(9)].

Ethical consent:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Mansoura University, Written informed consent was taken from all participants. The study was conducted according to the Declaration of Helsinki.

Statistical analysis

The machine was supplied with data, and IBM SPSS Corp.'s 2013. release was used to analyse it. Version 22.0 of IBM SPSS Statistics for Windows. IBM Inc., Armonk, New York. Number and percentage were used to describe qualitative data. After confirming normality with the Kolmogrov-Smirnov test, quantitative data were reported using the median (minimum and maximum) and interquartile range for non-parametric data and the mean and standard deviation for parametric data. Chi-Square test for two or more group comparisons When more than 25% of the cells in tables (>2*2) have a count of less than 5, the Monte Carlo test is used to correct the Chi-Square test. Two independent groups were compared using a student t-test. More than two independent groups were compared using the One Way ANOVA test, and pair-wise comparisons were found using the Post Hoc Tukey test. Two independent groups were compared using the Mann-Whitney U test. The Mann Whitney U test was used to identify pair-wise comparisons when comparing more than two independent groups using the Kruskal Wallis test. P value less than 0.05 was regarded as significant.

RESULTS

From demographic data analysis, we found no significant difference between the studied groups as regard age. However, male gender was predominant among HCC patients even exposed to DAA or not in comparison to group 3 (successfully treated with DAA), p value (0.009& 0.002, respectively). Interestingly, BMI was found significantly lower in group 1 compared to group 2 patients, p value (0.037) **(Table 1)**.

Table (1): Demographic characteristics of the studied groups.

	Group 1 n=30	Group 2 n=30	Group 3 n=30	Test of significance	Within group significance
Age/years mean±SD	59.13±6.26	61.33±6.82	57.73±12.47	F=1.23 P=0.298	P1=0.345 P2=0.547 P3=0.124
Sex N(%)					P1=0.542
Male	22(73.3)	24(80.0)	12(40)	χ^2=12.03	*P2=0.009**
Female	8(26.7)	6(20.0)	18(60)	p=0.002*	*P3=0.002**
BMI (Kg/m2) mean±SD	30.98±3.60	32.73±3.44	32.37±2.46		*P1=0.037**
median (IQR)	30 (28-34.25)	33 (29.7-34.2)	32 (31-34)	F=2.48 P=0.089	P2=0.098 P3=0.659

F:One Way ANOVA test, χ^2=Chi-Square test, P1=difference between group 1& 2, P2= difference between group1 & 3, P3=difference between group 2&3 *statistically significant (p<0.05).

Table (2) illustrates that for Ascites and presence of diabetes. Ascites is more frequent among group 2 than group 1 (43.3% versus 30%, respectively) without statistically significant difference between them. A statistically significant difference is detected between group 1 & 3 and between group 1& 2. Diabetes history shows statistically significant higher frequency among group 2 than group 3 (53.3% versus 23.3%, respectively).

Table (2): Comparison of ascites and diabetes between studied groups.

	Group 1 n=30	Group 2 n=30	Group 3 n=30	Test of significance	Within group significance
Ascites n(%)					P1=0.284
-ve	21(70)	17(56.7)	30(100)	χ2MC=16.0	*P2=0.001**
+ve	9(30.0)	13(43.3)	0	*p<0.001**	*P3<0.001**
Diabetes n(%)					P1=0.067
-ve	21(70)	14(46.7)	23(76.7)	χ2MC=6.49	P2=0.559
+ve	9(30)	16(53.3)	7(23.3)	*P=0.039**	*P3=0.017**

χ2MC=Monte Carlo test, P1=difference between group 1& 2, P2= difference between group1 & 3, *statistically significant (p<0.05).

Table (3) shows comparison between studied groups as regards laboratory findings with the following paired comparison;

Between group 1& 2; there was statistically significant difference as regards hemoglobin level and platelet count with higher mean values among group 1 than group 2.

Between group 1& 3; Mean values of ALT, AST, T. Bilirubin, INR and AFP were significantly higher in group 1 than group 3, while mean values of albumin and hemoglobin were significantly lower in group 1 than group 3.

Between group 2& 3; mean values of ALT, AST, T. bilirubin, INR and AFP were significantly higher among group 2 than group 3, while there were lower levels of albumin, platelets count and hemoglobin among group 2 than group 3.

Table (3): Laboratory findings among studied groups.

	Group 1 n=30	Group 2 n=30	Group 3 n=30	Test of significance	Within group significance
ALT (U/L) mean±SD	61.47±14.47	63.70±12.99	51.60±6.23	F=11.25 *P<0.001**	P1=0.802 *P2<0.001** *P3<0.001**
AST (U/L) mean±SD	67.63±14.83	65.47±13.52	53.83±10.84	F=9.53 *P<0.001**	P1=0.526 *P2<0.001** *P3=0.001**
Albumin (g/dL) mean±SD	3.25±0.49	3.27±0.42	4.02±0.233	F=3.83 *P<0.001**	P1=0.871 *P2<0.001** *P3<0.001**
T.Bilirubin (mg/dL) mean±SD	1.277±0.25	1.270±0.22	1.05±0.117	F=11.96 *P<0.001**	P1=0.900 *P2<0.001** *P3<0.001**
HB (g/dL) mean±SD	9.87±0.977	9.17±1.72	10.93±0.84	F=15.34 *P<0.001**	*P1=0.032** *P2=0.001** *P3<0.001**
PLT x10^3/cmm mean±SD	103.50±24.72	86.47±19.66	108.43±20.62	F=6.15 *P=0.003**	*P1=0.01** P2=0.455 *P3=0.001**
INR mean±SD	1.713±0.205	1.690±0.266	1.483±0.132	F=11.06 *P<0.001**	P1=0.666 *P2=0.001** *P3=0.001**
AFP (ng\mL) median (min-max) (IQR)	23.90 (2.1-15000) (6-292.5)	29.5 (1.8-96848) (8-695)	6 (3-28) (4-7.25)	KW χ2= 28.62 *P<0.001**	P1=0.524 *P2<0.001** *P3<0.001**

Median, (min-max), (IQR): non-parametric test.

F:One Way ANOVA test, KWχ2=:Kruskal Wallis test P1=difference between group 1& 2, P2= difference between group1 & 3,, P3=difference between group 2&3 *statistically significant (p<0.05).

Table (4) illustrates that there was statistically significant difference between studied groups as regards Child score (p=0.016). Child score distribution as follows; Child score C was detected among 6.7% of group 2. Child score B was found in 23.3% and 20% of groups 1 and 2 respectively .

Table (4): Child-Pugh classification among studied groups

	Group 1 n=30 n (%)	Group 2 n=30 n (%)	Group 3 n=30 n (%)	Test of significance	Within group significance
Child score					
A	23(76.7)	22(73.3)	30(100)	χ2 MC=12.14	*P1<0.001**
B	7(23.3)	6(20)	0	*P=0.016**	*P2<0.001**
C	0	2(6.7)	0		*P3<0.001**

χ2MC=Monte Carlo test, P1=difference between group 1& 2, P2= difference between group1 & 3.
*statistically significant (p<0.05).

DISCUSSION

In the present work, from demographic data analysis, we found no significant difference between the studied groups as regards age. However, male gender was predominant among HCC patients whether exposed to DAA or not in comparison to group 3 (CLD successfully treated with DAA), p value (0.009& 0.002, respectively).Interestingly, BMI was found significantly lower in group 1 compared to group 2 patients, p value (0.037).

In our study, laboratory data analysis among the studied groups, revealed that a significant increase in HCC patients groups whatever exposed to DAA or not in comparison to HCV CLD patients with SVR as regards ALT, AST, Total bilirubin, INR and AFP, while albumin and Hb levels noticed to be significantly decreased in HCC patients groups in comparison to HCV CLD patients with SVR. Also, as regards to the platelets count, it was found to be significantly lower in HCC patients exposed previously to DAA in comparison to the other studied patient groups.

Our study finding, as noticed here the fibrosis stage by fibroscan among the studied group, showed significant increase in HCC patient groups whatever exposed to DAA or not in comparison to HCV CLD patients with SVR P<0.001.while no significant differences in tumour size was detected between the 2 HCC groups.

Although With IFN-based therapies, a decreased risk of HCC formation has been seen in several long-term follow-up investigations. With an efficiency up to 90% compared to IFN-based regimens, the emergence of an efficient therapy with direct-acting antivirals (DAAs) for HCV infection has significantly boosted the likelihood of viral eradication. Because to the excellent current safety profile, many patients who were previously ineligible for IFN-based therapy, such as elderly patients and those with severe cirrhosis, are now using DAAs extensively. Contrary to predictions, numerous investigations revealed concerns over the persistence of HCC risk in cirrhotic patients after DAA treatment [(10-11)].

Several research and publications have implications on the impact of DAAs on HCC incidence and HCC recurrence following effective treatment, while other studies have raised concerns regarding an unanticipated hepatocellular carcinoma (HCC) occurrence rate after DAA therapy [(11, 4)].

Moreover, various DAAs impact based SVR on HCC recurrence following curative treatment for early HCC have produced contentious results (resection, local ablation, chemoembolization or liver transplantation). But a French research on 189 patients found that after receiving DAAs, HCC recurrence rates were 12% with a median follow-up of 20 months [(5)].

After six months following DAA therapy, three more trials with a combined total of 140 patients found a 25–30% HCC recurrence [(4, 6)].

Moreover, tumors that developed after administration of DAA therapies were noted as being more aggressive and involving several metastatic sites [(12, 13)].

Many large cohort studies that found that the sustained virological response (SVR) was linked to a lower risk of HCC without the presence of more aggressive phenotypes came to opposite results [(14)].

A persistent risk of tumor growth persists, especially in patients with cirrhosis, despite the fact that the incidence of HCC was decreased in patients with SVR compared to non-responders [(15)].

This is the rationale for the EASL guidelines' recommendation that all patients with advanced fibrosis and cirrhosis undergo post-SVR monitoring [(7)].

CONCLUSION

Male gender was predominant among HCC patients whether exposed to DAA or not in comparison to group 3 (CLD successfully treated with DAA). A significant increase in HCC patients groups whatever exposed to DAA or not in comparison to HCV CLD patients with SVR as regards ALT, AST, Total bilirubin, INR and AFP, while albumin and Hb levels noticed to be significantly decreased in HCC patients groups in comparison to HCV CLD patients with SVR.

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