Hepatocellular Carcinoma Pattern after the Era of Direct-Acting Antiviral Agents: Does it Differ?

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Background and study aim: Hepatocellular carcinoma is one of the most frequent tumors worldwide. In Egypt, HCC represents the fourth most frequent tumor, with HCV as the leading risk factor for liver cancer development. This study compared tumor characteristics between cases with de novo HCV-induced HCC following DAAs and cases with de novo HCC without prior DAA treatment.

Patients and Methods: The current retrospective observational study was conducted on HCV patients with de novo HCC. 196 cases were enrolled in the study and separated into two groups. Group (A): included 79 chronic HCV patients who developed HCC after DAA treatment. Group (B): included 117 chronic HCV patients who developed HCC not preceded by any antiviral drugs. The two groups were compared together regarding their clinical presentation, laboratory data, and radiological findings.

Results: The current study showed male predominance in group A (81%) and group B (70.1%). Non-significant variances were observed in median AFP level, Child-Pugh class, FIB-4 score, or performance status between the two studied groups. Although BCLC staging showed a significantly more advanced HCC stage in patients of group A (P=0.002), non-significant variances were noticed among the two studied groups regarding the number, site, or size of hepatic focal lesions.

Conclusion: Chronic HCV patients who developed HCC following DAA treatment exhibited a more advanced HCC stage according to the BCLC staging and showed higher rates of lymph node metastasis in comparison to patients who had not received DAA treatment. Additional studies with larger sample sizes are still needed.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a globally frequent tumor, accounting for 90% of primary hepatic tumors and ranking as the second leading cause of cancer-related mortality worldwide [1]. In countries with a high hepatitis C virus (HCV) burden, HCV contributes to over 70% of chronic liver disease morbidity and mortality [2].

Liver cirrhosis, often caused by chronic viral hepatitis, is a major risk factor for HCC, with an annual incidence of about three to eight percent in HCV-infected cirrhotic patients [1]. In Egypt, HCC represents the fourth most common cancer, with HCV being the leading risk factor for its development [3].

The utilization of direct-acting antiviral agents (DAAs) in the treatment of HCV showed that higher sustained virologic response (SVR) rates than the previously used interferon-based regimens could be achieved with fewer adverse events [4, 5]. Nevertheless, the risk of HCC has not been eliminated, particularly in patients with advanced fibrosis [6].

Clinical observations on patients receiving DAAs resulted in a debate over the impact of DAAs on hepatocellular carcinoma development [4]. This research aimed to compare tumor characteristics among patients with de novo HCV-induced HCC following DAAs and patients who developed de novo HCC without prior DAA treatment.

PATIENTS AND METHODS

The current retrospective observational study was carried out on HCV patients with de novo hepatocellular carcinoma presented to the HCC clinic at our university hospital between January 2019 and January 2020. Patients with HCC due to other causes rather than HCV and patients who received previous treatment for HCC were excluded .

The total number of hepatocellular carcinoma cases who visited the hepatocellular carcinoma clinic was 382 cases; of which 196 patients had de novo HCC fulfilling the inclusion criteria were enrolled in the study and separated into two groups. Group (A): included 79 chronic hepatitis C virus patients who developed hepatocellular carcinoma following achieving SVR after DAA treatment according to National Committee for Control of Viral Hepatitis (NCCVH) guidelines [7]. Group (B): included 117 untreated chronic hepatitis C virus patients who developed HCC not preceded by any antiviral drugs because most of these patients were accidentally discovered to have HCV at the time of diagnosis of HCC, and some patients were known to have chronic HCV, but they refused to receive DAA treatment.

Diagnosis of HCC was confirmed by abdominal triphasic CT scan and/or Dynamic Magnetic Resonance Imaging with heavy T2 diffusion showing hepatic focal lesion (HFL) with criteria of hepatocellular carcinoma in the form of enhancement in the early arterial phase and washout in portal-venous and delayed phases compared to the rest of the liver [8].

The two studied groups were compared together in terms of the recorded demographic data, clinical findings, laboratory data, radiological findings detected by abdominal triphasic CT scan and/or Dynamic MRI, Child-Pugh Classification, Eastern Cooperative Oncology Group (ECOG) Performance status, and The Barcelona-Clinic Liver Cancer (BCLC) staging system.

Statistical methods*:*

The collected data was processed using SPSS 23, with analysis tailored to each parameter type.

Descriptive statistics: Mean, SD, and range for parametric information; Median and IQR for non-parametric data. Frequency and percentage for categorical information.

Analytical statistics: Student T-test for comparing two group means; Mann-Whitney U test for non-parametric variables; Chi-Square and Fisher's exact tests for qualitative variable relationships.

A P-value of $\leq$ 0.05 was considered statistically significant.

RESULTS

This retrospective study involved 196 de novo hepatocellular carcinoma patients meeting the inclusion criteria and divided into two groups. Group A included 79 patients who developed hepatocellular carcinoma following achieving SVR after DAA treatment according to NCCVH guidelines [7], while group B included 117 untreated chronic HCV patients who developed HCC without prior antiviral therapy.

Demographic characteristics, clinical presentation, and laboratory characteristics of the enrolled patients are illustrated in Tables 1, 2, and 3. A statistically insignificant variance was detected among group A and group B according to age, sex, residence, smoking, diabetes mellitus, or hypertension .

Regarding the clinical presentation shown in Table 2, abdominal pain, lower limb edema, and hepatic encephalopathy were significantly more common in group A. Non-significant variances were found among the two groups as regards their laboratory investigations, except

for total bilirubin (P<0.001) and INR (P<0.005), which were significantly higher in group A, while AST was significantly lower in group A (P<0.001) (Table 3).

Radiological findings detected by Triphasic CT were reported in Table 4 showing non-significant variance among the two studied groups except for abdominal lymphadenopathy which was significantly higher in group A (P=0.005). Although a statistically insignificant variance was reported among the two studied groups as regards the presence of malignant portal vein thrombosis (PVT) and tumor extension, patients of group A still showed higher rates of malignant PVT and tumor extension (27.8% and 26.6%, respectively) compared to patients of group B (13.7% and 16.2%, respectively). Only two patients in group B had extrahepatic tumor metastasis to lung.

Table 5 shows liver condition according to different scoring systems. According to BCLC staging: in group A, 26.5% of patients were stage C and 6.3% were stage D, while in group B, 12.8 percent of patients were stage C and 1.7 percent were stage D showing significant differences among both groups regarding BCLC staging (P=0.002). Other parameters such as FIB-4 score, ECOG performance status, and Child-Pugh class showed no statistically significant variance among both groups.

Table (1): Comparative analysis between Group A and Group B regarding demographic characteristics (n=196)

Characteristics		Group A (N=79)	Group B (N=117)	p-value
Age (years)		60.2±7.4	61.9±7.9	0.128
Sex	**Male**	64 (81.0%)	82 (70.1%)	0.085
	Female	15 (19.0%)	35 (29.9%)	
Residence	**Urban**	40 (50.6%)	66 (56.4%)	0.426
	Rural	39 (49.4%)	51 (43.6%)	
Smoking		34 (43.0%)	44 (37.6%)	0.446
DM		17 (21.5%)	33 (28.2%)	0.292
Hypertension		17 (21.5%)	24 (20.5%)	0.865

^Independent t-test. #Chi square test.

Table (2): Comparative analysis between Group A and Group B regarding clinical presentation (n=196)

Characteristics	Group A (N=79)	Group B (N=117)	p-value
Accidental discovery	72 (91.1%)	103 (88.0%)	0.491
Abdominal pain	26 (32.9%)	19 (16.2%)	**0.006***
Loss of weight	3 (3.8%)	1 (0.9%)	0.305
Bleeding tendency	7 (8.9%)	5 (4.3%)	0.230
Ascites	7 (8.9%)	5 (4.3%)	0.230
Lower limb edema	9 (11.4%)	1 (0.9%)	**0.001***

Jaundice	0 (0.0%)	2 (1.7%)	0.516
Hepatic encephalopathy	4 (5.1%)	0 (0.0%)	**0.025***

#Chi square test. §Fisher's Exact test. *Significant

Table (3): Comparative analysis between group A and group B regarding important laboratory findings (n=196)

Characteristics	Group A (N=79)	Group B (N=117)	p-value
ALT (IU/L)	41.8±47.7	50.1±28.6	0.128
AST (IU/L)	43.0±22.5	61.6±34.8	**0.001***
Albumin (gm/dL)	3.5±0.7	3.6±0.6	0.544
Total bilirubin (mg/dL)	1.4±1.0	1.1±0.6	**0.001***
INR	1.3±0.3	1.2±0.2	**0.005***
WBC (x103/mL)	5.9±2.2	6.3±2.6	0.308
Hemoglobin (gm/dL)	13.0±1.9	13.1±2.0	0.708
Platelets (x103/mL)	134.4±65.1	159.3±77.3	0.020
Creatinine (mg/dL)	1.0±0.3	0.9±0.2	0.073
AFP (ng/mL)	36.3 (7.5–364.0)	26.7 (6.5–282.8)	0.876

*Significant

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; AFP, α-fetoprotein

Table (4): Comparative analysis between Group A and Group B regarding important radiological findings by Triphasic CT

Characteristics		Group A (N=79)	Group B (N=117)	p-value
Liver size	Average	56 (70.9%)	68 (58.1%)	0.19
	Shrunken	4 (6.8%)	8 (6.8%)	
	Enlarged	19 (35.0%)	41 (35.0%)	
Liver parenchyma	Homogenous	4 (5.1%)	6 (5.1%)	0.999
	Coarse	75 (94.9%)	111 (94.9%)	
PVT	None	57 (72.2%)	101 (86.3%)	0.083
	Segmental	8 (10.1%)	4 (3.4%)	
	Right/Left PV	9 (11.4%)	8 (6.8%)	
	Main	5 (6.3%)	4 (3.4%)	
Splenomegaly	No	25 (31.6%)	48 (41.0%)	0.224
	Yes	54 (68.4%)	68 (58.1%)	
	Removed	0 (0.0%)	1 (0.9%)	
Ascites	No	60 (75.9%)	101 (86.3%)	0.276
	Minimal to mild	12 (15.2%)	11 (9.4%)	

	Moderate to severe	7 (8.9. %)	5(4.3%)	
Focal lesions number	One	50 (63.3%)	73 (62.4%)	0.085
	Two	14 (17.7%)	33 (28.2%)	
	Three	5 (6.3%)	6 (5.1%)	
	≥Four	10 (12.7%)	5 (4.3%)	
Focal lesions site	Right	51 (64.6%)	79 (67.5%)	0.868
	Left	18 (22.8%)	23 (19.7%)	
	Bilateral	10 (12.7%)	15 (12.8%)	
Tumor extension more than 50% of the total liver size		21 (26.6%)	19 (16.2%)	0.078
IHBR		2 (2.5%)	3 (2.6%)	0.999
HCC criteria		74 (93.7%)	110 (94.0%)	0.999
Extrahepatic Metastasis		0 (0.0%)	2 (1.7%)	0.516
Average focal lesion size (cm)		5.1±3.1	4.9±3.2	0.719
Lymph nodes metastasis		**20 (25.3%)**	**12 (10.3%)**	**0.005***

*Significant

HCC, hepatocellular carcinoma, PVT; portal vein thrombosis, IHBR; intrahepatic biliary radical dilation

Table (5): Comparative analysis between Group A and Group B regarding different scoring systems (n=196)

Characteristics		**Group A (N=79)**	**Group B (N=117)**	**p-value**
Fib4 score		4.1±2.5	4.5±3.0	0.34
Child-Pugh class	**A**	53 (67.1%)	91 (86.3.8%)	0.123
	B	21 (26.6%)	24 (20.5%)	
	C	5 (6.3%)	2 (1.7%)	
ECOG performance status	**0**	54 (68.3%)	101 (30.8%)	0.105
	1	20 (25.3%)	14 (11.9%)	
	2	5 (6.3%)	2 (1.7%)	
BCLC stage	**O**	17 (21.5%)	13 (11.1%)	**0.002***
	A	11 (13.9%)	24 (20.5%)	
	B	25 (31.6%)	63 (53.8%)	
	C	21 (26.5%)	15 (12.8%)	
	D	5 (6.3%)	2 (1.7%)	

*Significant

Fib4; Fibrosis 4 index, ECOG: Eastern Cooperative Oncology Group, BCLC; Barcelona Clinic Liver Cancer

DISCUSSION

Hepatitis C virus (HCV) represents a major global and national health concern, causing around 400,000 deaths annually, primarily due to hepatocellular carcinoma (HCC) and chronic liver disease [9]. Direct-acting antivirals (DAAs) are reported to be highly effective in many countries, including Egypt [10]. However, even though direct-acting antivirals resulted in high rates of SVR, the risk of hepatocellular carcinoma development persists due to underlying liver cirrhosis [6].

This study compared the clinical presentation, laboratory data, and radiological findings in patients with de novo Hepatocellular carcinoma presented to our university hospital's HCC clinic. Participants were divided into two groups: group A involved 79 patients who received DAAs according to NCCVH guidelines, and group B included 117 patients who had not received direct-acting antivirals before .

The current study showed a male predominance of 81% in group A and 70.1% in group B. Abdominal pain, lower limb edema and hepatic encephalopathy were significantly more frequent in group A in comparison to group B. Nevertheless, other non-significant variances have been observed among the two groups in general or abdominal examinations.

In addition, the current study reported no statistically significant variance in the median AFP level, Child-Pugh class, FIB-4 score, or ECOG Performance status among the two groups .

As regards the BCLC staging, the variance among the two studied groups was statistically significant (P=0.002). In group A, 21.5% of patients were stage Zero, 13.9% of patients were stage A, 31.6% of patients were stage B, 26.5% of patients were stage C and 6.3% of patients were stage D, while In-group B; 11.1% of patient were stage Zero, 20.5% of patients were stage A, 53.8% of patients were stage B, 12.8% of patients were stage C and 1.7% of patients were stage D. These results partially agree with the outcomes of the study conducted by El Fayoumie et al. in 2019 [11] which showed that in patients who developed HCC after DAA treatment, there were 5.9% of patients had stage Zero, 17.6% of patients had stage A, 13.7% of patients had stage B, 41.2% of patients had stage C and 21.6% of patients had stage D, while in HCC patients without DAA treatment, there were 7.4% of patients had stage Zero, 29.6% of patients had stage A, 24.1% of patients had stage B, 11.1% of patients had stage C and 27.8% of patients had stage D. The variance among the two groups was statistically significant (P=0.01).

Regarding PVT, cases of group A showed a higher rate of malignant PVT (27.8%) compared to group B (13.7%), but this variance was not statistically significant (P=0.083) which could be attributed to the smaller sample size of our study in comparison to the study conducted by Shiha et al. in 2020 [12] which showed that portal vein invasion was more common in patients who developed HCC before DAA treatment compared to those who developed HCC after DAA treatment (44.6% vs 7.3%, p<0.001).

Regarding lymphadenopathy, in group A, 25.3% of patients had abdominal lymphadenopathy mainly porta hepatis with malignant criteria by triphasic CT abdomen, while in group B, only 10.3% of patients had malignant abdominal lymphadenopathy, with a higher statistically significant difference in group A (p <0.005). This agrees with Abdelaziz et al, 2019 [13] who compared tumor aggression of HCV-related HCC patients in terms of the presence of lymph node metastasis and portal vein invasion which was reported in nine out of 89 patients (10.1%) in group I (DAA-treated patients) in comparison with eight out of 207 patients (3.9%) in group II patients (non-DAA treated patients), with a statistically significant variance among both groups (P=0.03). This could be due to the more aggressive pattern of hepatocellular carcinoma in patients who received DAAs in comparison to patients who had not received DAAs before.

On the other hand, a study at our university hospital, conducted between December 2017 and December 2018, examined 160 cirrhotic HCV patients with de novo HCC. Findings revealed that cases managed with Direct-Acting Antiviral agents had larger HCC lesions than untreated patients. Nevertheless, no differences were observed in BCLC staging or tumor aggressiveness among the two groups

[14]. This difference from our results, which reported a more advanced stage of HCC according to the BCLC staging and higher rates of lymph node metastasis compared to chronic HCV patients who developed HCC not preceded by DAA treatment, could be attributed to our longer period of follow-up after receiving the DAAs because the current study included patients who developed HCC up to 5 years after receiving DAA treatment while the previous study included patients who developed HCC one to three years after receiving DAA treatment.

CONCLUSION

Despite the advancement achieved in HCV treatment with DAAs, HCC remains a great risk for patients with liver cirrhosis. In our study, patients with chronic HCV who developed HCC following DAA treatment showed more advanced stages of HCC according to the BCLC staging and higher rates of lymph node metastasis compared to patients with chronic HCV who developed HCC not preceded by DAA treatment. Further studies with larger sample sizes are still required to stand on the effect of DAA treatment on the pattern of de novo HCC following DAA treatment.

List of abbreviations:

HCC: Hepatocellular carcinoma

HCV: Hepatitis C Virus

DAAs: Direct-acting antiviral agents

NCCVH: National Committee for Control of Viral Hepatitis

AFP: Alpha-FetoProtein

BCLC: Barcelona Clinic Liver Cancer

Fib4: Fibrosis 4 index

HFL: Hepatic Focal Lesion

ECOG: Eastern Cooperative Oncology Group

PVT: Portal Vein Thrombosis

WHO: World Health Organization

SVR: Sustained Virologic Response

Ethical approval:

This study was approved by the Research Ethics Committee (REC) of the Faculty of Medicine, Ain Shams University. The FMASU REC is organized and operated according to guidelines of the International Council on Harmonization (ICH) Anaesthesiology and the Islamic Organization for Medical Sciences (IOMS), the United States Office for Human Research Protections, and the United States Code of Federal Regulations and operates under Federal Wide Assurance No. FWA 000017585.

Authors' contributions:

AM made the data collection and contributed to writing. HA, IF, and HK were involved in manuscript writing and revision. EG made the final revision and paraphrasing .

Competing interests:

The authors declare that they have no competing interests to disclose.

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HIGHLIGHTS

- Despite the advancement achieved in HCV treatment with DAAs, HCC remains a great risk for patients with liver cirrhosis**.**
- The available clinical data on patients receiving DAAs resulted in a debate regarding the impact of DAAs on the development of HCC**.**
- Patients with chronic HCV who developed HCC following DAA treatment showed a more advanced stage of HCC according to the BCLC staging and higher rates of lymph node metastasis compared to patients with chronic HCV who developed HCC not preceded by DAA treatment**.**

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