Medical Journal of
Viral Hepatitis (MJVH)

Original Article

Hepatocellular carcinoma before and after the era of direct-acting antiviral therapy for chronic hepatitis C: Dose the story differ?

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Abstract

Background. *Hepatitis C virus (HCV) infection is a leading cause of liver cancer globally. Treating chronic HCV with direct-acting antivirals (DAAs) in cirrhotic patients has raised concerns about their effect on HCC development and progression.* ***Objective:*** *To compare the characteristics of de novo HCC in chronic HCV cirrhotic patients who achieved sustained virological response (SVR) with DAAs therapy, with that of HCC which developed in chronic HCV cirrhotic patients who did not receive DAAs or PEG interferon-based treatments.* ***Methods*** *The study included 200 chronic HCV cirrhotic patients divided into two groups: group 1 with 100 patients who developed de novo HCC post-SVR following DAAs, and group 2 with 100 HCV-related HCC patients who developed HCC without prior antiviral therapy. Non-invasive HCC diagnosis was based on EASL guidelines. Baseline demographic, clinical, and laboratory data were collected. The Child-Turcotte-Pugh (CTP) score, class, and Barcelona Clinic Liver Cancer (BCLC) staging system were determined (stages 0/A as early stages, while BCLC stages B/C/D as late stages of HCC). The types of DAAs used for chronic HCV treatment were also recorded.* ***Results.*** *Post-DAAs HCC was diagnosed approximately 4.3 years post-SVR, characterized by multifocal or diffuse infiltration compared to HCV-related HCC. The tumor diameter in post-DAAs HCC was larger versus in HCV-related HCC (p= 0.002). Linear regression analysis indicated that DAAs therapy was a significant predictor of a larger tumor diameter. Malignant portal vein thrombosis (PVT) was more prevalent in post-DAAs HCC compared to HCV-related HCC (p= 0.001). CTP score was significantly lower in post-DAAs HCC compared to HCV-related HCC (p< .001). Post-DAAs HCC was diagnosed at later BCLC stages than HCV-related HCC. The serum AFP level was insignificantly higher in post-DAAs HCC than in HCV-related HCC. Platelets were significantly higher in post-DAAs HCC than in HCV-related HCC (p= 0.001). ALT levels were significantly lower in post-DAAs HCC compared to HCV-related HCC (p=0.02).* ***Conclusion*** *Post-DAAs HCC had larger size, a more diffuse pattern, and a higher rate of malignant PVT compared to HCV-related HCC. It was diagnosed at later BCLC stages but had lower CTP scores, lower ALT levels, and higher platelet counts.*

Introduction

Hepatitis C virus infection (HCV) is considered one of leading cause of chronic liver disease in many countries, including Egypt[1,2]. The risk of HCC development in HCV-related liver cirrhosis is 2% to 8% per year[3]. In Egypt, HCC is responsible for 33.63% and 13.54% of all cancers in males and females, respectively[4]. The introduction of direct-acting antiviral agents (DAAs) has revolutionized treatment options for patients with advanced liver disease[5]. These new regimens offer high efficacy, safety, and have few contraindications, making them suitable for patients who cannot be treated with interferon. Furthermore, by utilizing various combination treatment options, a success rate of over 95% in achieving sustained virologic response (SVR) can be attained, irrespective of the HCV genotype or the severity of fibrosis[6]. The debate over the evidence supporting HCC recurrence after DAAs therapy continues[7]. Some studies have shown an increased risk of HCC occurrence or recurrence in cirrhotic patients after DAA treatment[8,9], while others have not found evidence to support these findings[10-12]. This study aimed to compare the clinical, radiological, and laboratory characteristics of HCC in patients who achieved SVR after DAAs treatment with that of HCC which developed in chronic HCV cirrhotic patients who did not receive DAAs or pegylated (PEG) interferon-based treatment.

Materials and Methods

This single center retrospective study included 200 adult HCV cirrhotic patients who developed HCC. The patient records were collected from the early detection of hepatocellular carcinoma outpatient clinic at Specialized Medical Hospital, Mansoura University between December 2016 and April 2019. The patients were divided into two groups; group 1 consisted of 100 cirrhotic patients with SVR following DAAs treatment for chronic HCV infection who later developed HCC, and group 2 included 100 chronic HCV cirrhotic patients who developed HCC before the era of DAAs and did not receive PEG interferon-based treatment due to various contraindications.

Doi: 10.21608/mjvh.2024.350728
Keywords: Hepatocellular carcinoma, Chronic hepatitis C, Direct acting antivirals
Received: 24-2-2024
Accepted: 10-5-2024
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Exclusion criteria

Patients with a history of previous PEG Interferon treatment for chronic HCV, previous treatment for HCC, other malignancies, combined HCV and HBV infection, and those who did not achieve SVR, were excluded from the study. Baseline demographic, clinical, laboratory, and radiological data were recorded for all enrolled patients. The diagnosis of liver cirrhosis was established using a combination of clinical, laboratory, imaging, endoscopic findings, and liver biopsy when available. Liver imaging studies, including abdominal ultrasound and contrast-enhanced computed tomography/ magnetic resonance imaging (CT/MRI), were performed, along with serum alpha-fetoprotein (AFP) level measurements. Hepatocellular carcinoma (HCC) was diagnosed following the EASL guidelines for non-invasive HCC diagnosis in cirrhotic patients[13]. Extra-hepatic metastasis was defined as radiological evidence of malignant spread to lymph nodes, lungs, suprarenal glands, bones, or spine. The Child-Turcotte-Pugh (CTP) score and class[14,15], BCLC stage[16], and types of DAAs used for chronic HCV treatment were documented.

Ethical Research approval

The study was conducted with approval from the Institutional Research Board (IRB) at the Faculty of Medicine, Mansoura University (Proposal code: R.23.11.2372). Written informed consent was obtained from all participants prior to their enrollment in the study.

Statistical analysis

Data analysis was performed by SPSS software, version 25 (SPSS Inc., PASW statistics for windows version 25. Chicago: SPSS Inc.). Qualitative data were described using number and percent. Quantitative data were described using median (interquartile range) for non-normally distributed data and mean± standard deviation for normally distributed data. Significance of the results was judged at the (≤0.05) level. Chi-Square test was used to compare qualitative data. Mann Whitney U test was used to compare de-novo post-DAAs HCC with HCV related HCC for non-normally distributed data. Student t test was used to compare between de-novo post-DAAs HCC & HCV related HCC for normally distributed data. Multiple linear regression analysis was used to assess the predictors of HCC characteristics in enrolled patients.

Results

The study included 220 eligible patients. Twenty patients were excluded: 10 patients had a previous history of PEG Interferon treatment, 5 patients had a history of previous treatment for HCC, two patients had combined HCV and HBV infection, two patients did not achieve SVR, and one patient had other malignancies. **Table 1** displays demographic, clinical, laboratory, and radiological data of the enrolled patients. There were no significant differences between the studied groups in terms of age, gender, presence of diabetes mellitus, extra-hepatic metastasis, and AFP levels. Compared to HCV related HCC, post-DAAs HCC had a significantly larger diameter, **figure 1** and a higher incidence of malignant portal vein thrombosis. Post-DAAs HCC was diagnosed as a single nodule in 49% of cases, 2 nodules in 40% of cases, and multifocal or diffuses infiltration in 11% of cases. In contrast, HCV related HCC was diagnosed as a single nodule in 40% of cases, 2 nodules in 57% of cases, and multifocal or diffuse infiltration in 3% of cases, **figure 2**. At the time of HCC diagnosis, the CTP score was significantly lower in post-DAAs HCC compared with HCV related HCC cases (6.78 ±1.74 versus 7.74 ± 2.20 points). In post-DAAs HCC, 54% of the cases were CTP class A, 39% were CTP class B, and 7% were CTP class C. In HCV related HCC, 35% of the cases were CTP class A, 44% were CTP class B, and 21% were CTP class C. Furthermore, post-DAAs HCC was diagnosed at an advanced BCLC stages in 82% of cases, a significantly higher percentage than HCV related HCC which was diagnosed at an advanced BCLC stages in 65% of cases, **figure 3**. The study revealed a significantly higher platelet count (PLC) in post-DAAs HCC patients compared with HCV related HCC patients. Additionally, the ALT level was significantly lower in post-DAAs HCC patients compared with HCV related HCC patients, while there was no significant difference in AST levels between the two groups. In group I, 87% of the cases had previously received Sofosbuvir (SOF) 400 mg with Daclatasvir (DAC) 60 mg daily for 84 days, while 13% received Sofosbuvir 400 mg with Ledipasvir (LED) 90 mg daily for 84 days. Post-DAAs HCC developed on average of 4.3 years after achieving SVR. **Table 2** shows the results of regression analysis for predictors of HCC characteristics. The analysis indicated that DAA therapy was a significant predictor of larger tumor diameter, younger age was a significant predictor of advanced BCLC stage, presence of DM was a significant predictor of lower serum AFP level, higher PLC at the time of HCC diagnosis was associated with advanced BCLC stage, while lower PLC was linked to higher serum AFP level. However, gender was not a significant predictor of tumor characteristics or BCLC stage.

Table 1. Comparison of demographic, clinical, laboratory and radiological data of the enrolled patients

	Group I (Post-DAAs HCC) n=100	**Group II (HCV related HCC) n=100**	**P value**
Age/years	62.12±7.41	60.67±9.17	0.22
Gender: (*Male/Female*)	77/23(77/23%)	75/25(75/25%)	0.741
DM: *Yes/No*	40/60 (40/60%)	29/71(29/71%)	0.10
HCC diameter in cm	6.7(4.0-10.0)	4.5 (3-7)	0.002*
Malignant PVT	54(54.0%)	27(27.0%)	0.001*
HCC number (*One/Two/Three or diffuse*)	49/40/11(49/40/11%)	40/57/3(40/57/3%)	0.015
Extra-hepatic metastasis	9 (9%)	8 (8%)	0.75
CTP score (points)	6.78±1.74	7.74±2.20	<.001*

CTP class: A/B/C	54/39/7(54/39/7%)	35/44/21(35/44/21%)	0.003*
BCLC: A/B/C/D	18/20/54/8(18/20/54/8%)	35/17/27/21(35/17/27/21%)	0.001*
AFP (ng/ml) median(range)	214.5(18.05-2000)	105(11-1250)	0.23
PLC (10^9/L) median(range)	104.5(72250-157500)	96(63.25-141.75)	0.001*
ALT(IU/l) median(range)	36 (23.5-55)	47.5(30.25-71.5)	0.02*
AST(IU/l) median(range)	55 (32.75-97)	70 (45-103)	<0.19
DAA(SOF+DAC/SOF+LED)	87/13%	No	
Post DAAs duration in years	4.3 ± 2.09	No	

***DM**: diabetes mellitus; **PVT**: portal vein thrombosis; **CTP**: Child Turcotte Pugh; **BCLC**: Barcelona Clinic Liver Cancer; **AFP**: Alfa Fetoprotein; **PLC**: platelets; **ALT**: Alanine aminotransferase; **AST**: Aspartate aminotransferase; **DAAs**: direct-acting antivirals.*

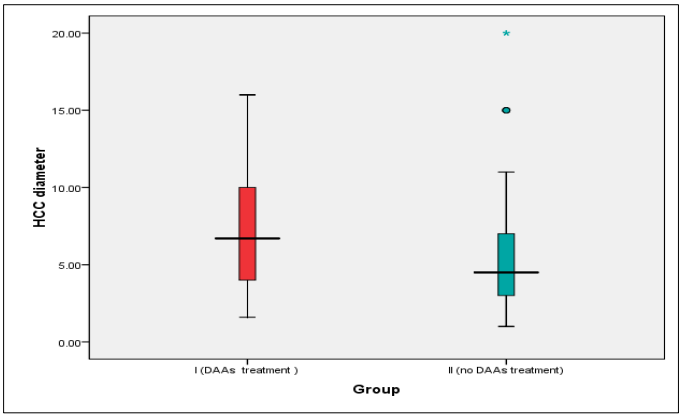

Figure 1. Comparison of median HCC diameter in both groups.

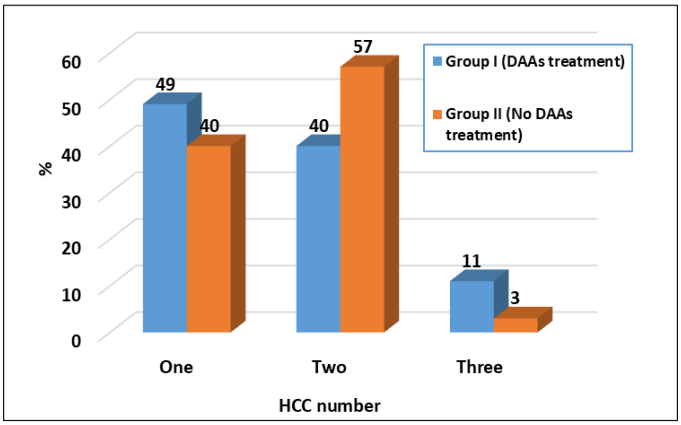

Figure 2. Comparison of HCC number in both groups

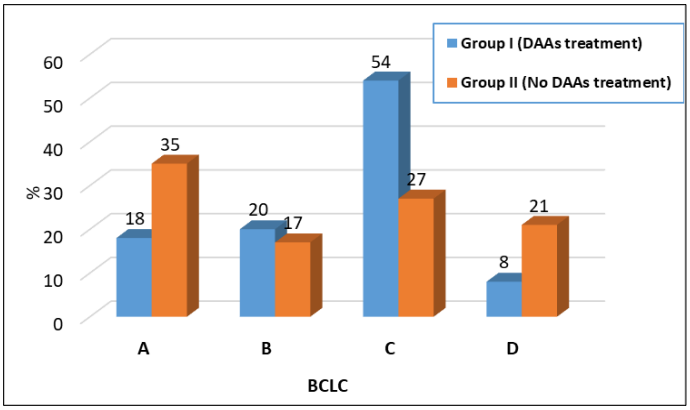

Figure 3. Comparison of BCLC stages in both groups.

Table 2. Regression analysis for predictors of HCC characteristics in study patients.

	HCC diameter in cm			HCC number			Serum AFP level			BCLC stage		
	B	**t**	**P value**	**B**	**t**	**P value**	**B**	**t**	**P value**	**β**	**t**	**P value**
(Constant)	8.877	3.003	.003	1.610	11.709	.001*	134.9	1.77	0.08	-48.24	-0.02	0.982
DAAs (Yes/No)	-.194	-2.776	.006*	.008	.115	.909	-.129	-1.791	.075	0.119	1.65	0.101
Age in years	-.100	-1.397	.164	-.075	-1.032	.303	.084	1.164	.246	-.178	-2.441	.016*
Gender (*male/female*)	.000	.001	.999	-.037	-.519	.605	.018	.251	.802	.084	1.164	.246
DM (Yes/No)	.067	.931	.353	-.082	-1.127	.261	.182	2.504	.013*	.018	.251	.802
PLC (10^9/L)	.180	1.607	.110	.044	.608	.544	-.178	-2.441	.016*	.182	2.504	.013*
Adjusted R Square	0.033			0.015			0.011			0.041		
Prediction equation	**HCC size** = 8.87-.194× Studied groups			No significant predictors			**AFP**= 134.9+0.182×DM-0.178×PLC			**BCLC** = - 48.24×.178× Age+0.182×PLC		

***DAAs**: direct-acting antivirals; **DM**: diabetes mellitus; **PLC**: platelets.*

Discussion

Several studies had shown that DAAs did not increase the risk of developing new cases of HCC in patients with chronic HCV-related cirrhosis[17]. Additionally, these studies had found that achieving SVR with DAAs did not provide protection against HCC[8]. The question is whether de novo post-DAA HCC in chronic HCV cirrhotic patients differs from HCC in untreated chronic HCV cirrhotic patients. This study found no significant differences in age, gender, or presence of diabetes mellitus between the HCV related HCC and post-DAAs HCC. This is consistent with the findings of Brozzetti et al., who reported no significant differences in age, gender, or presence of diabetes mellitus between post-DAAs and HCV related HCC[18]. However, the study by Ohama et al. found that patients who developed HCC after receiving DAAs were older than those who developed HCC before receiving DAAs[19]. Our study found that de novo post-DAAs HCC occurred at an average age of 62 years with a higher prevalence in males, after an average period of 4.3 years post-SVR. This contrasts with the findings of Lockart et al.'s meta-analysis, which indicated a decrease in HCC risk with each additional year of follow-up after DAAs induced SVR in cirrhotic patients[20]. Conti et al. found that DAAs did not offer immediate protection against the development of new HCC in cirrhotic patients who achieved SVR [8]. The findings of our study were in line with several other studies, including a Japanese study, which reported HCC incidence rates of 6.6% and 7% within 2 years of follow-up in cirrhotic patients treated with DAAs[9,21,22]. Additionally, a study by El Fayoumie et al. found that HCC could develop up to 4 years after achieving SVR with DAAs[23]. The study revealed that de novo post-DAAs HCC was diagnosed with multinodular or diffuse infiltrative lesions more frequently than HCV related HCC. Additionally, post-DAAs HCC had a significantly larger tumor diameter at presentation (6.7 cm versus 4.5 cm). The diameter of post-DAAs HCC in our study ranged from 4 to 10 cm, with a median diameter of 6.7 cm. This finding is consistent with a study by Toyoda et al, which reported a range of 3.6 to 10 cm and a median diameter of 7.9 cm for post-DAAs HCC in patients with neglected surveillance [24]. In our study, linear regression analysis predicted that DAA therapy was a significant factor in larger tumor diameter for HCC. This contrasts with the findings of Brozzetti et al., who reported median tumor diameters of 2.6 cm and 2.56 cm in post-DAA HCC and pre-DAA HCC, respectively, in elderly patients. This discrepancy may be attributed to differences in patient surveillance protocols[18]. Our study found that post-DAAs HCC was diagnosed as a single nodule in 49% of cases and with 2 nodules in 40% of cases. Similarly, Toyoda et al. reported that post-DAAs HCC was monofocal in 39.5% of cases[24]. However, in our study, multinodular or diffuse infiltrative lesions were found in 11% of cases, while Toyoda et al. found multifocal lesions in 60.5% of their cases[24]. This study revealed a higher prevalence of malignant portal vein thrombosis (PVT) in post-DAAs HCC compared with HCV related HCC (54% vs. 27%). This finding aligns with El Fayoumie et al., who found malignant PVT in 54% of post-DAAs HCC and 25% of pre-DAAs HCC cases[23]. Additionally, Abdelaziz et al. reported a significantly increased incidence of PVT in post-DAAs HCC[25]. The study revealed that patients with post-DAAs HCC had a better liver functional status compared to HCV related HCC, with significantly lower CTP scores in post-DAAs HCC (6.78 versus 7.74 points). In post-DAAs HCC cases, 54% were classified as CTP class A, 39% as CTP class B, and 7% as CTP class C. This finding is consistent with previous studies by El fayoumie et al[23] and Brozzetti et al[18], which also showed that post-DAAs HCC occurred in patients with better liver functional status. Furthermore, the study found that ALT levels were significantly lower in post-DAAs HCC compared with HCV related HCC, while there was no significant difference in AST levels between both groups. This is in line with previous research that reported better serum bilirubin, serum albumin, and AST levels in post-DAAs HCC compared with pre-DAAs HCC patients[26]. In addition, Ohama et al. study found that post-DAA HCC patients had lower levels of AST and ALT, improved prothrombin time, and a lower albumin-bilirubin grade compared with pre-DAA HCC patients[19]. This improvement in liver function and transaminase levels could be attributed to the successful viral eradication achieved through DAA therapy. This study revealed that post-DAAs HCC was diagnosed at an early BCLC stages in 18% of cases and at late BCLC stages in 82% of cases, while HCV related HCC was diagnosed at an early BCLC stages in 35% of cases and at late BCLC stages in 65% of cases, indicating a worse overall BCLC stages at presentation for post-DAAs HCC. This finding is consistent with a study by El fayoumie et al.,

which reported that post-DAAs HCC patients had BCLC stage A in 17.6% of cases and late BCLC stages in 82.4% of cases, while pre-DAAs HCC patients had BCLC stage A in 29.6% of cases and late BCLC stages in 70.4% of cases[23]. However, Brozzetti et al. found that de novo post-DAA HCC was diagnosed at early BCLC stages in 41.9% of cases and at late BCLC stages in 58.1% of cases[18]. In contrast, Ohama et al. reported no significant differences in BCLC stages between post-DAA HCC and pre-DAA HCC patients[19].The variations in the outcomes could be due to the implementation of surveillance for HCC in cirrhotic patients following SVR, leading to the early detection of newly developed HCC after DAAs treatment. Our study found that the serum AFP level was slightly higher in post-DAAs HCC compared to HCV related HCC. Previous researches have also shown a significant increase in serum AFP levels in post-DAAs HCC compared to pre-DAAs HCC[23,25]. In contrast, Ohama et al reported lower serum AFP level in post-DAAs HCC[19]. The study found that platelets level was significantly higher in patients with post-DAAs HCC compared to HCV related HCC. This is consistent with previous studies that also reported higher platelet levels in post-DAAs versus pre-DAAs HCC[18, 23]. This could be due to the enhanced liver function following viral clearance. A previous study found a strong inverse relationship between platelet levels and MELD score in HCV-related HCC[27]. The present study found that higher platelet level at the time of HCC diagnosis was a significant predictor of advanced BCLC stages. This is consistent with a previous study that showed a larger diameter of HCV-related HCC in patients with normal platelet levels compared to those with low platelet levels[27]. That study also reported a significant positive correlation between platelet levels and BCLC stage[27]. Our study found that post-DAAs HCC presented with more aggressive criteria compared to HCV related HCC. It raises the question of whether these differences were due to a change in the tumor's biological behavior or a shift in patient and healthcare provider behavior leading to reduced surveillance for HCC in cirrhotic patients after viral eradication. Reig et al. supported the idea that the sudden resolution of chronic inflammation caused by hepatitis C could disrupt the immune system's ability to resist the progression of liver cancer[28]. The second possibility was supported by Im et al. who found that patients diagnosed with HCC through surveillance had early BCLC stages, while those who were not surveyed had late BCLC stages[29]. The study had limitations such as small sample size and being a single-center study with historical controls who were not treated with antiviral therapies. It is recommended that patients with chronic HCV cirrhosis who achieve SVR; undergo HCC surveillance to improve survival by enabling early diagnosis of HCC, and application of curative therapies. Additionally, exploring molecular subtypes of HCC in pre- and post-DAAs HCC through immune-histochemical tests is recommended.

Conclusion

Post-DAAs HCC was characterized by larger tumor diameter, more diffuse pattern, a higher percentage of malignant portal vein thrombosis, and later BCLC stages at diagnosis; compared to HCV related HCC. However, it was associated with a lower Child-Turcotte-Pugh score, lower ALT levels, and higher platelet counts.

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