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Study of Frequency of Hepatocellular Carcinoma Development after Direct Acting Antiviral Therapy in Hepatitis C Virus Patients

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the fourth most prevalent cancer in Egypt. The use of direct-acting antivirals (DAAs) has come under attention recently due to concerns about increased HCC risk.

Objective: The aim of the current work was to determine the frequency of HCC after treatment of hepatitis C virus (HCV) by DAAs.

Patients and Methods: This retrospective cohort study included a total of 69 Egyptian patients with HCV. It was performed from the registered patients' records, Faculty of Medicine, Zagazig University Hospitals. Patients were treated using direct-acting antivirals (DAAs) and had sustained virological response after twelve weeks (SVR 12), a follow-up over the course of subsequent six months to detect HCC occurrence. Abdominal ultrasound screening and **s**erum alpha-fetoprotein level after completion of DAAs treatment was done every three months. Any suspicious lesion in the liver was further confirmed by Triphasic CT Scan.

Results: HCC incidence was 10.4%. Cases with a Child-Pugh score A were not more likely to develop HCC after completing treatment, and SVR12 was not associated with an increased risk of HCC, though, the patients with a Child-Pugh score B were at high risk (P = 0.0001). Treatment with SOF+DAC for 24 weeks was associated with a risk of HCC incidence (p 0.0001). Prolonged prothrombin time and the incidence of an unfavorable effect of DAAs (fatigue and gastrointestinal troubles) emerged as HCC development independent risk factors in a multivariate analysis with OR (CI) of 16.8 (10.2-78.6), 15 (1.16-73.7), 19 (1.48-46.6) respectively.

Conclusion: HCC following DAAs treatment still occurs in certain patients, especially with advanced liver cirrhosis. Prolonged prothrombin time and DAAs-related side effects are independent risk factors for HCC.

Keywords: Direct Acting Antivirals (DAA), Hepatitis C Virus (HCV), Hepatocellular Carcinoma (HCC).

INTRODUCTION

Worldwide, hepatocellular carcinoma (HCC) is the second largest cause of mortality from cancer [(1)]. HCC is the fourth most prevalent cancer in Egypt [(2)]. In the past, it was believed that the hepatitis B virus (HBV) was the major cause of the HCC epidemic in Egypt. However, research in 2013 has shown that the hepatitis C virus (HCV) is more directly associated with the current wave of cases. Seventy-five percent of HCC cases in Egypt were found in rural areas, and 45.7% of the patients were between the ages of 51 and 60 [(3)].

Because hepatocellular carcinoma typically occurs as a result of persistent liver disease, the prognosis is affected not only by the size of the tumor but also by the liver dysfunction severity. HCC patients are usually diagnosed at a late stage when there are fewer treatment choices available, and the median survival time is about a year [(4)]. When detected early, HCC can be cured with curative therapy, the 5-year survival rate is close seventy percent. However, until a liver transplant is performed, there is a considerable chance of recurrence, and there is always the potential of hepatic decompensation [(5)].

For a long time, HCV treatment plans that included interferon (IFN) were considered the gold standard option, with about fifty to sixty percent of eligible patients having a durable virological response (SVR). Regardless of the severity of liver disease, IFN-induced SVR has been linked to a roughly 4-fold reduction in HCC risk [(6)].

As a result, the widespread use of modern direct-acting antivirals (DAA) has resulted in SVR rates of greater than ninety percent among HCV patients [(7)]. Early research showed that DAA-treated patient cohorts experienced higher than predicted rates of hepatocellular carcinoma [(8)]. However, when accounting for potential confounding factors, the elevated risk for HCC associated with DAA treatment was either abolished or reversed in the bigger trials [(9, 10)].

The study was aimed for determining the frequency of development of HCC after treating HCV with DAAs.

PATIENTS AND METHODS

This retrospective cohort study included a total of 69 Egyptian patients with HCV. It was performed from the registered patients' records, Faculty of Medicine, Zagazig University Hospitals. Patients were treated using direct-acting antivirals (DAAs) and then observed for the development of HCC after the medication was finished. This study was conducted between October 2019 to June 2020.

Inclusion criteria:

Both genders aged from 18 to 70 years who had Sustained virologic response (SVR) 12 to be achieved by HCV-positive patients who had treatment of DAAs for 12 or 24 weeks following national guideline treatment regimens were included.

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Exclusion criteria:
Patients who were less than eighteen or over seventy years, who did not reach SVR12 after receiving a full course of direct-acting antiviral therapy, and patients who had been coinfected with HBV or HIV as well as pregnant were excluded from the trial.

The study was conducted as the following:
1. Patient assessment:
Revision of the medical records of the studied patients for:

- Full history taking including name, age, sex, occupation, residence, complaint, past medical history, and family history.
- General and Local examination
- **Investigations:** Complete Blood Count (CBC), Liver function tests, prothrombin time, international normalized ratio (INR), fasting plasma sugar, hemoglobin A1c, blood urea nitrogen (BUN) as well as serum creatinine, abdominal ultrasound, and abdominal MRI and CT scan with dynamic imaging.

2. Direct-acting antivirals therapy:
The DAAs treatment regimen was received for 12 or 24 weeks according to the national guideline treatment regimens as the following:

- Forty-eight patients were treated by combined sofosbuvir tablets (400 mg/day) and daclatasvir tablets (60mg/day). Forty-two of them were given 12-week courses of treatment, while six were given 24-week courses. Adverse effects which occurred with this combination: Fatigue (15 patients), Headache (8 patients), itching (5 patients), GIT trouble (4 patients), anemia (10 patients), thrombocytopenia (5 patients), hyperbilirubinemia (6 patients).
- Thirty-three patients were treated by combined sofosbuvir tablets (400 mg/day) and daclatasvir tablets (60 mg/day) and ribavirin tablets (1000 mg/day) for 12 weeks. Adverse effects which occurred with this combination: Fatigue (9 patients), Headache (6 patients), itching (8 patients), GIT trouble (2 patients), anemia (15 patients), thrombocytopenia (8 patients), hyperbilirubinemia (4 patients).
- Fifteen patients were treated by combining sofosbuvir tablets (400 mg/day) and simeprevir tablets (150 mg/day) for 12 weeks. Adverse effects which occurred with this combination: Fatigue (2 patients), Headache (1 patient), itching (4 patients), GIT trouble (4 patients), and anemia (3 patients).

3. Follow up during and after antiviral therapy:

- Patients underwent clinical follow-up, laboratory tests (CBC, alanine aminotransferase, serum bilirubin, serum albumin, prothrombin time, INR, serum creatinine), and abdominal ultrasounds monthly throughout the course of treatment and again 12 weeks after treatment completion.
- Baseline HCV quantitative PCR was performed before starting therapy, at 4th week of treatment, at Treatment Completion, and 12 Weeks Post-Treatment. The definition of a sustained virological response is an HCV RNA level below the detection threshold 12 weeks after therapy has ended.

The follow-up to detect HCC:
All HCV patients had undergone a screening abdominal ultrasonography and serum alpha-fetoprotein levels every three months following the end of DAAs treatment for six months. A Triphasic CT Scan of the abdomen with iv contrast was used to confirm the diagnosis.

***Ethical Consideration*:**
This study was ethically approved by Zagazig University's Research Ethics Committee (ZU- IRB #9798/19-9-2022). Written informed consent of all the participants was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis
Statistical Package for the Social Services was used to examine the data. The numerical data was represented by means, medians, ranges, and confidence intervals. The credibility of the data was demonstrated with the use of statistics like frequency and percentage. In statistical analysis, the student's t-test (T) was used to compare two groups whose means and/or variances were quantitatively different. Coefficient of Determination (r) and Pearson were used to test whether or not the qualitative data were linearly independent then the Chi-Square test was applied. A P value of less than 0.05 was determined to be statistically significant.

RESULTS
Table 1 shows that the ages of patients were ranging from 28 to 70 years. The gender of the studied patients was 36.5% females and 63.5% males.

Table (1): Demographics (n=96):

Variables			
Age (year)	**Mean ±SD** **Median(range)**	53.69±11.42 28-70	
Gender		**n.**	**%**
	Females	35	36.5
	Males	61	63.5

Significant associations were found between the occurrence of HCC and patients' age, diabetes mellitus, and Child-Pugh score B with a P value of 0.034, 0.014, and 0.0001 respectively (**Table 2**).

Table (2): Relation of demographic, clinical characteristics, and hepatocellular carcinoma in studied patients (n=96):

	HCC n.10		**Non-HCC n.86**		**Test of sig**	**p-value**
	No.	**%**	**No.**	**%**		
Age (year) Mean ±SD	60.9±4.4		52.9±11.7		2.2	0.034*
Sex						
Female	2	5.7	33	94.3	f [a]	0.32
Male	8	13.1	53	86.9		
Diabetes mellitus						
Yes	8	20.5	31	79.5	f [a]	0.014*
No	2	3.5	55	96.5		
Hypertension						
Yes	3	13.0	20	87.0	f [a]	0.699
No	7	9.6	66	90.4		
Child-Pugh Score						
Class B	10	76.9	3	23.1	f [a]	0.0001*
Class A	0	.0	83	100.0		

HCC: hepatocellular carcinoma, Non HCC: non hepatocellular carcinoma
Mean ±SD: t-test of significant, a: fisher exact test.

Occurrence of HCC was significantly correlated with patients' laboratory findings (Hg, T.bil, ALT, AST, ALP, PT, INR, Alfa fetoprotein, FIB-4 Index, and APRI**)** with a P value of 0.0001 except WBCs and blood urea (P value 0.99) (**Table 3**).

Table (3): Relation of laboratory finding and hepatocellular carcinoma in studied patients (n=96):

	HCC (n.10)		Non-HCC n.86		Number	p-value
	No.	%	No.	%		
WBCs (n 4 – 11 x10^3/ul)						
Abnormal	1	9.1	10	90.9	11	0.99
Normal	9	10.6	76	89.4	85	
Hb (n 11.5 – 15.5 g/dl)						
Abnormal	10	25.0	30	75.0	40	0.0001*
Normal	0	.0	56	100.0	56	
Plt (n 150 – 450 x10^3ul)						
Abnormal	10	76.9	3	23.1	13	0.0001*
Normal	0	.0	83	100.0	83	
T.bil (n up to – 1.2mg/dl)						
Abnormal	10	27.8	26	72.2	36	0.0001*
Normal	0	.0	60	100.0	60	
D.bil (n up to – 0.3mg/dl)						
Abnormal	10	17.5	47	82.5	57	0.01*
Normal	0	.0	39	100.0	39	
ALT (n up to – 33U/L)						
Abnormal	8	61.5	5	38.5	13	0.0001*
Normal	2	2.4	81	97.6	83	
AST (n up to – 32U/L)						
Abnormal	10	71.4	4	28.6	14	0.0001*
Normal	0	.0	82	100.0	82	
ALP (n 40 – 145 U/L)						
Abnormal	10	90.9	1	9.1	11	0.0001*
Normal	0	.0	85	100.0	85	
PT (n 11 – 15.5 Sec).						
Abnormal	7	77.8	2	22.2	9	0.0001*
Normal	3	3.4	84	96.6	87	
INR (n 0.8 – 1.2)						
Abnormal	9	31.0	20	69.0	29	0.0001*
Normal	1	1.5	66	98.5	67	
T. protein (n 6.6 – 8.7g/dl)						
Abnormal	6	25.0	18	75.0	24	0.014*
Normal	4	5.6	68	94.4	72	
S. albumin (n 3.97 – 4.94 g/dl)						
Abnormal	10	12.8	68	87.2	78	0.2
Normal	0	.0	18	100.0	18	
BUN (n 6 – 20 mg/dl)						
Abnormal	1	9.1	10	90.9	11	0.99
Normal	9	10.6	76	89.4	85	

	HCC (n.10)		Non-HCC n.86		Number	p-value
	No.	%	No.	%		
Creatinine (n 0.7– 1.2 mg/dl)						
Abnormal	4	44.4	5	55.6	9	0.01*
Normal	6	6.9	81	93.1	87	
Alfa fetoprotein Median(range)	590(480-1200)		18(7-33)		u [a] 14.9	0.0001*
FIB-4 Index Mean ±SD Median(range) points Approximate fibrosis stage: Ishak <4- 6 points Approximate fibrosis stage: Ishak 4- 6	4±0.94 4.1(2.7-5.36) 0 10(100.0)		1.37±0.59 1.3(0.41-3.26) 85(98.8%) 1(1.2%)		u [a] 5.1	0.0001*
APRI Mean ±SD Median(range) Unable to determine fibrosis Significant fibrosis	1.59±0.46 1.4(1.1 - 2.3) 0.0 10(100.0%)		0.39±0.14 0.4(0.2-0.8) 84(97.7%) 2(2.3%)		u [a] 5.3	0.0001*

a: Mann-Whitney test, WBC: white blood cells, Hg: hemoglobin, Plt: platelet, T.bil: total bilirubin, D.bil: direct bilirubin, ALT: alanin transaminase, AST: aspartate transaminase, S. Albumin: serum albumin, ALP: alkaline phosphatase, PT: prothrombin time, INR: international normalized ratio, T. protein: total protein, Urea, Cr: creatinine, FIB-4 Index: fibrosis-4 index, Alfa fetoprotein: AFP, APRI: AST to PLT Ratio Index.

Table 4 displays the connection between HCC and DAAs medication for HCV which showed that significant association between the occurrence of HCC and SOF+DAC therapy for 24 weeks of HCV patients with a P value of 0.0001.

Table (4): Relation of therapy of Hepatitis C virus (DAA therapy) and hepatocellular carcinoma in studied patients (n=96):

	HCC n.10		Non-HCC n.86		Number	χ^2	p-value
	No.	%	No.	%			
DAA therapy of hepatitis C virus:							
SOF+DAC 12 week	0	0.0	42	100.0	42		
SOF+DAC 24 week	6	100.0	0	0.0	6	56 [a]	0.0001*
SOF+DAC+RBV 12week	4	12.1	29	87.9	33		
SOF+SIM 12week	0	0.0	15	100.0	15		

a: χ^2 Chi square test, SOF+DAC: sofosbuvir plus daclatasvir, SOF+DAC+RBV: sofosbuvir plus daclatasvir plus ribavirin, SOF+SIM: sofosbuvir plus simeprevir

There was a significant association between the occurrence of HCC and adverse effects of DAAs which include fatigue, headache, itching, and GIT trouble with a P value of 0.0001, 0.0001, 0.0001, and 0.01 respectively (**Table 5**).

Table (5): Researching the link between hepatocellular cancer and the side effect of treating the hepatitis C virus with direct acting antivirals(n=96):

	HCC n.10		Non-HCC n.86		N	p-value
	No.	%	No.	%		
Fatigue	8	80.0	18	20.9	26	0.0001*
Headache	10	100.0	8	9.3	18	0.0001*
Itching	10	100.0	7	8.1	17	0.0001*
GIT troubles	4	40.0	6	7	10	0.01*

Univariate analysis showed in **Table 6** that independent risk factors for HCC development include diabetes mellitus with OR 7.1 (1.42-35.5 CI), abnormal laboratory data as prolonged prothrombin time, prolonged INR, low total serum protein, high creatinine, FIB-4 Index with OR of 98, 29.7, 5.7, 10.8, 88.4 (13.9-87.6, 3.5-48.8, 1.4-22.2, 2.3-51, 3.39-245.3 CI) respectively, fatigue and Gastrointestinal troubles as adverse effects of DAAs with OR of 15.1, 8.89 (2.9-77.5, 1.9-40.3 CI)) respectively.

Table (6): Univariate Logistic regression for predictors for hepatocellular carcinoma

Predictors	Sig.	Exp(B)	95% C.I.for EXP(B)	
			Lower	Upper
Age (year)	0.043	1.1	1.002	1.17
Diabetes mellitus	.017	7.1	1.42	35.5
Prolonged prothrombin time	.0001	98	13.9	87.6
Prolonged INR	.002	29.7	3.5	48.8
Low Total protein	.013	5.7	1.4	22.2
High creatinine	.003	10.8	2.3	51
FIB-4 Index	.012	88.4	3.39	245.3
Fatigue (adverse effect of treatment)	.001	15.1	2.9	77.5
GIT troubles (adverse effect of treatment)	.005	8.89	1.9	40.3
HCV treatment (DAAs): **SOF+DAC 24weeks** **SOF+DAC+RBV 12 weeks (reference)**	0.9	1.04	0.27	4

Exp(B): odds ratio (OR), C.I: confidence level. P<0.05: Significant, INR: international normalized ratio, FIB-4 Index: fibrosis-4 index, SOF+DAC: sofosbuvir plus daclatasvir, SOF+DAC+RBV: sofosbuvir plus

Multivariate analysis in **Table 7** disclosed that independent risk factors for HCC development include prolonged prothrombin time, the occurrence of an adverse effect of DAAs as fatigue, and Gastrointestinal troubles with OR of 16.8, 15, 19 (10.2-78.6, 1.16-73.7, 1.48-46.6 CI) respectively.

Table (7): Multivariate Logistic regression for predictors for hepatocellular carcinoma

Predictors	Sig.	Exp(B)	95% C.I.for EXP(B)	
			Lower	Upper
Prolonged prothrombin time	0.0001	16 .8	10.2	78.6
Fatigue (adverse effect of treatment)	0.038	15	1.16	73.7
GIT troubles (adverse effect of treatment)	0.024	19	1.48	46.6

Exp(B): odds ratio (OR), C.I: confidence level.

DISCUSSION

Significant advancements in knowledge of molecular virology, life cycle, and pathophysiology of HCV ushered in the age of direct-acting antiviral (DAA) treatment in 2011. One can choose from a variety of DAA regimens as an oral, interferon-free treatment for cirrhosis [(11)].

Once DAAs are widely used, it is projected that the incidence of HCV-related HCC will drop dramatically, However, direct-acting antiviral-treated individuals with cirrhosis and Hepatitis C had a higher risk of developing hepatocellular carcinoma [(12)].

Up to 2020 there were relatively few studies conducted on Egyptian patients, wherein various common HCV genotypes were detected and wherein other treatment protocols are followed [(13)].

Our results demonstrated that patients' age was ranging from 28 to 70 years with a mean of 53.69±11.42years old. The gender of the studied patients was 36.5% females and 63.5% males.

Consistent with our findings**, Abdelaziz *et al.*** [(14)] demonstrated that Patients' average age was 57.76 ± 6.516 when they enrolled in the trial. Most of the cases analyzed in this study were men. Also, **El-shaarawy *et al.*** [(15)] demonstrated that male patients constituted major of those studied. **Watanabe *et al.*** [(16)] indicated that there was a total of 562 men and 650 women included in the study population. Cases median age who began treatment was between 65.30 and 65.40 years old. The size of their sample may explain the discrepancy.

The HCC development incidence in our study after DAAs treatment was 10.4% after 24 months of follow-up. This coincides with a retrospective study, by **Tani *et al.*** [(17)] who revealed that the cumulative incidence of HCC over a period of 12 months was 1.88 percent, and over 36 months it was 6.00 percent. Also, **Watanabe *et al.*** [(18)] found HCC incidence rates of 1.9% in the first year and 4.1% in the second year.

There was a decreased risk of death and HCC among those who were treated with DAAs, as per the findings of a French multicenter prospective cohort research **Carrat *et al.*** [(10)]. Cases were followed for 33.4 months, with 7344 receiving DAA therapy and 2551 receiving placebo. In addition to reducing the risk of HCC (adjusted HR = 0.66, 95% CI: 0.46-0.91), the probability of dying from any cause was reduced in those who took DAAs.

According to results from prospective research conducted by **Romano *et al.*** [(19)]**,** the risk of HCC in patients with HCV-related cirrhosis who were given DAAs decreased from 0.97 per 100 Person-Years (PY) to 0.04 per 100 PY in the second year of follow-up (95 percent CI: 0.73-1.26).

The varying rates of HCC reported among studies can be traced back to variables including DAAs utilized, fibrosis severity, and length of follow-up.

We found that a patient's age, diabetes mellitus status, and Child-Pugh score were all significantly linked to hepatocellular carcinoma development. We found that WBCs, BUN, and albumin did not significantly differ from one another, but that hemoglobin, thrombocytopenia, liver function tests, creatinine, AFP, FIB-4, and APRI did.

In agreement with our study, **Conti *et al.*** [(20)] stated that the significant difference in essential synthetic liver functions between DAA-treated and non-treated persons may be an indicator of HCC risk and predict poorer outcomes for these patients. Also, **Kim *et al.*** [(21)] discovered that age, non-SVR, and advanced liver disease are related to an elevated risk of HCC incidence and recurrence in DAA-treated individuals.

the research that included patients treated with DAAs, by **Kanwal *et al.*** [(22)] revealed that The risk of getting HCC is increased by 4.7-fold in those with cirrhosis and a high FIB-4 score compared to those without cirrhosis (adjusted HR = 4.73; 95 percent CI: 3.34-6.68).

High Child-Pugh scores in individuals with decompensated cirrhosis had been linked to an increased risk of HCC [(20)]. In addition, high levels of AFP (> 5.4 ng/mL) were significantly linked with HCC in people who were given DAAs for their condition, according to a study comparing IFN-based and DAAs for the developing as well as progression of HCC [(23)].

Most of the publications we reviewed supported the conclusions of prior studies from the IFN era, which found that older age, non-SVR, liver fibrosis, and elevated AFP levels post-treatment are substantial risk factors for the development of HCC[(24)].

El-shaarawy *et al.* [(15)] revealed that HCC cases often had a substantially more advanced age at diagnosis than their healthy counterparts. In comparison to the non-HCC group, the HCC group had considerably higher serum levels of ALT, AST, and AFP. Overall, the HCC group had lower serum albumin levels than the non-HCC group.

The current study found a significant (p0.05) correlation between the use of SOF+DAC for 24 weeks in the treatment of HCV and the development of HCC.

No significant increase in HCC risk was seen between those treated with DAAs and those not treated

with DAAs, according to a prospective, multicenter French investigation using ANRS cohorts[25].

Using DAAs was correlated with HCC development among our cases ($p<0.05$). All patients who received SOF+DAC for 24 weeks developed HCC and After 12 weeks of treatment with SOF+DAC+RBV, 12.1% of patients developed HCC. However, no patients who were given SOF+DAC for 12 weeks or SOF+SIM for 12 weeks were diagnosed with HCC.

Concerning HCC incidence in the **Essawy *et al.*** [26] study, after an average of 18 weeks of treatment with DAAs, 6.5% of patients in the SOF/DAC/RIB group developed HCC.

Biochemical data showed that all patients in the SOF+DAC 24 weeks group and 4 patients in the SOF+DAC+RBV 12 weeks group had the most advanced liver disease, It explains why the four treatment groups in this study had such different rates of hepatocellular carcinoma progression. Patients in the SOF+DAC 24-week and SOF+DAC+RBV 12-week groups had older mean ages than those in the other therapy groups. Six patients in the SOF+DAC 24-week group and four patients in the SOF+DAC+RBV 12-week group had their cirrhosis verified to be the primary cause of their HCC.

A potentially novel observation in our study on Egyptian HCV genotype 4 patients**,** the treatment plan for each of the four subtypes were described and it did appropriately depict the progression of HCC in the difficult-to-treat subtype rather than the easy-to-treat subtype.

We demonstrated that independent risk factors for the development of HCC include diabetes mellitus with OR 7.1 (1.42-35.5 CI), abnormal laboratory data as prolonged prothrombin time, prolonged INR, low total serum protein, high creatinine, FIB-4 Index with OR of 98, 29.7, 5.7, 10.8, 88.4 (13.9-87.6, 3.5-48.8, 1.4-22.2, 2.3-51, 3.39-245.3 CI) respectively, fatigue and Gastrointestinal troubles as adverse effects of DAAs with OR of 15.1, 8.89 (2.9-77.5, 1.9-40.3 CI)) respectively.

In agreement with our study, **Watanabe *et al.*** [16] revealed that sex, WBC, PLT, ALT, AST, T.Bil, Albumin, PT, AFP, and HbA1c were all potential predictors of HCC development.

In the current study, multivariate analysis showed that independent risk factors for the development of HCC include prolonged prothrombin time, the occurrence of an adverse effect DAAs as fatigue, and Gastrointestinal troubles with OR of 16.8, 15, 19 (10.2-78.6, 1.16-73.7, 1.48-46.6 CI) respectively.

Watanabe *et al.* [16] exhibited that a multivariate analysis was performed, taking into account both baseline and treatment conditions, we found that post-treatment AFP (HR = 1.11; 95% CI, 1.054-1.172; P 0.001), the FIB-4 index (HR = 1.09; 95% CI, 1.021-1.178; P = 0.011) were each independent factors for HCC emergence. Post-treatment sex, AST, prothrombin time, AFP, and AFP were included in the multivariate analysis, as well as pre-treatment FIB-4 index, pre-treatment albumin, and pre-treatment total cholesterol.

Buonomo *et al.* [28] showed that Multivariate time-to-event analysis showed no factors to be significantly linked with the probability of HCC.

The study's limitations involve that: sample size was small, no control groups, and a short length of follow-up.

CONCLUSION

HCC following DAAs treatment still occurs in certain patients, especially with advanced liver cirrhosis.

The probability of developing HCC after achieving SVR12 from HCV with DAAs treatment was not uncommon and mainly in patients with a Child-Pugh score B. Patients treated for 24 weeks with a combination of SOF and DAC tablets had a higher risk of developing HCC. In addition to the prolonged prothrombin time, the occurrence of adverse events from DAAs therapy were independent risk factors of HCC development. Extra caution is warranted for cases who had these risk factors.

RECOMMENDATIONS

To better understand the long-term risk of HCC incidence and the risk factors affecting it, more research is needed with larger patient numbers and longer durations of follow-up.

Cases who had end-stage liver disease should be carefully selected for antiviral medication and intensive monitoring.

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