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Assessment of Incidence of Hepatocellular Carcinoma among Hepatitis C Patients Who Achieved Sustained Virological Response with Direct Acting Antiviral Agents (DAAs)

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ABSTRACT

Background: In terms of cancer mortality rates, hepatocellular carcinoma (HCC) ranks third. Direct-acting antiviral drugs (DAAs) had a profound impact on the treatment of hepatitis C virus (HCV).

Objective: Understanding HCC frequency among cured HCV cases and to evaluate direct acting antiviral agents (DAAs) impact on occurrence of hepatocellular carcinoma among chronic hepatitis C patients who received these drugs.

Subjects and methods: In a retrospective cross-sectional study we carried out this trial in Hepatitis Viruses' Treatment Unit, El-Ahrar Teaching Hospital, Egypt on 415 patients who received direct acting antiviral agents (DAAs) for treating chronic hepatitis C virus and achieved sustained virological response (SVR) between 2017 to 2022 where all file of cases fulfilled the inclusion as well as exclusion criteria.

Result: HCC was significant in older age, male, DM, HTN and patient from rural residence. Platelet and albumin significantly decreased after HCC, but alpha fetoprotein, bilirubin, ALT, AST, serum creatinine and APRI score significantly increased after HCC.

Conclusion: The incidence of HCC is highest among those who already have cirrhosis, and chronic hepatitis C is the leading risk factor of this condition. Direct anti-viral agents (DAAs) may play role in occurrence of hepatocellular carcinoma (HCC) in chronic hepatitis C patients who achieved sustained virological response (SVR).

Keywords: HCC, DAAs, Chronic hepatitis C patients, SVR, HCV.

INTRODUCTION

In terms of cancer mortality rates, hepatocellular carcinoma (HCC) ranks third. The prevalence of chronic hepatitis C (HCV) as the underlying cause of HCC is highest in patients with cirrhosis. Consistent monitoring for HCC may increase the number of cancer cases caught early enough for curative therapy [(1)].

In individuals with cirrhosis caused by HCV, the risk of getting HCC each year is between 2%-8%. Despite the availability of potentially curative treatments like liver resection (LR) and radiofrequency ablation (RFA), the cumulative recurrence rate of HCC is estimated to be over 70% over a period of 5 years [(2)].

The introduction of direct-acting antiviral drugs (DAAs) for the treatment of HCV has had a profound impact on the disease. Despite the fact that more than 90% of HCV patients can achieve a virological cure with current DAA regimens, many patients still run the risk of developing HCC even after achieving a virology management [(3)].

Multiple meta-analyses conducted over the past two decades have assessed SVR's ability to avoid hepatic decompensation and, thus, lowering the risk of HCC development and progression, reducing the requirement for liver transplantation, and increasing liver-related and overall survival in HCV cirrhotic cases [(4)].

Routine HCC surveillance should be performed every 6 months in patients with virologically cured HCV and cirrhosis, as recommended by current clinical guidelines [(5)]. Liver function in virologically treated HCV patients may improve, leading to increased longevity and the possibility of long-term follow-up [(6)].

In contrast, routine HCC surveillance may not be performed on patients with virologically cured HCV despite the fact that they are at risk for HCC. Patients may develop HCC while receiving DAA therapy, according to previous research. For this reason, it may be more difficult to detect cases of HCC through surveillances than it is to detect cases in other high-risk persons [(7)].

This study objective was understanding HCC frequency among cured HCV cases and to evaluate direct acting antiviral agents (DAAs) impact on occurrence of hepatocellular carcinoma among chronic hepatitis C patients who received these drugs.

SUBJECTS AND METHODS

In a retrospective cross-sectional study, we carried out this trial in Hepatitis Viruses' Treatment Unit, El-Ahrar Teaching Hospital, Egypt on 415 patients who received direct acting antiviral agents (DAAs) for treating chronic hepatitis C virus and achieved sustained virological response (SVR) between 2017 to 2022, where all file of patients fulfilled the inclusion and exclusion criteria.

Patients were classified into two groups:

Group I: Cases who had received DAAs and achieved sustained virological response and without HCC development during follow up period till their inclusion in the present study (N=300 including 168 male and 132 female).

Group II: Patients who received DAAs and achieved sustained virological response then developed HCC during their follow up period (N=115 including 87 male and 28 female), this group was compared according to history, laboratory, clinical and radiological data before and after development of HCC.

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Inclusion criteria:

- Age between 18 –75 years.
- Cases with clinically and laboratory-proven chronic hepatitis C who received DAAs (sofosbuvir and daclatasvir) according to the Egyptian guideline and obtained a sustained virological response (SVR).

Exclusion criteria:

- Transplantation of the liver prior to the introduction of DAAs.
- Preexisting history or diagnosis of HCC.

All participants were subjected to the following:

Full evaluation of patient medical records, including previous, present, and family history as well as any treatment with DAAs or non-DAAs, Review of patient files for their general and local abdominal examination, Review of patient files for their routine laboratory investigations including: Complete blood picture (CBC), liver function tests, prothrombin concentration (PT) and international randomization ratio (INR), kidney function tests, as well as serum alpha fetoprotein (AFP).

- APRI score: (AST/upper limit normal) x 100/platelet count: (when score is less than 0.5 it is negative predictive for cirrhosis, when score higher than 0.7 it indicates significant hepatic fibrosis, and when score is higher than 1 it is positive predictive for cirrhosis)
- Child- Pugh classification
- ***Imaging studies:*** Involved abdominal ultra-sonography (U/S), and tri-phasic computed tomography were performed to all cases.

Ethical approval:

This experiment was ethically approved by the Faculty of Medicine, Zagazig University's. After being fully informed, all participants provided written consent of treatment and of using their data in the researches later. The study was conducted out in line with the Helsinki Declaration.

Statistical analysis

The statistical software used was SPSS 23. (Statistical Package for the Social Sciences). Quantitative data were presented as mean and standard deviation and on comparing the 2 groups; independent student's t test (T) was used, while on comparing the same group at 2 different times, paired t-test was used. Qualitative data were presented as frequency and percentage and were compared by Pearson Chi-Square test. The threshold for statistical significance was set at P 0.05.

RESULTS

Table 1 shows that HCC was significantly more in older age, male, DM, HTN and patient from rural residence.

Table (1): Demographic and clinical data among the two studied groups

		Group I (N=300)	Group II (N=115)	P
Age		**56.69±13.09**	**61.66±8.42**	**0.00 ****
Sex	**Female (N=160)**	**132**	**28**	
		43.8%	**24.3%**	
	Male (N=255)	**168**	**87**	**0.00 ****
		56.2%	**75.7%**	
Residence	**Rural**	**199**	**113**	
		66.5%	**98.3%**	
	Urban	**101**	**2**	**0.00 ****
		33.4%	**1.7%**	
Smoking (N=135)	**No**	**195**	**85**	
		65.2%	**73.9%**	
	Yes	**105**	**30**	**0.085**
		34.8%	**26.1%**	
DM (N=96)	**No**	**246**	**64**	
		82.3%	**55.7%**	
	Yes	**54**	**51**	**0.00 ****
		17.7%	**44.3%**	
HTN (N=119)	**No**	**222**	**74**	
		74.2%	**64.3%**	
	Yes	**78**	**41**	**0.046 ***
		25.8%	**35.7%**	
History of bilharziasis (N=18)	**No**	**287**	**110**	
		96.0%	**95.7%**	
	Yes	**13**	**5**	**0.87**
		4.0%	**4.3%**	
HBV Co-infection (N=6)	**-VE**	**295**	**114**	
		98.3%	**99.1%**	
	+VE	**5**	**1**	**0.54**
		1.7%	**0.9%**	

Group I are patients without hepatocellular cancer and group 2 are patients with hepatocellular cancer, Data are presented as mean ± standard deviation or as frequency and percentage, **: Highly significant

Table 2 shows that moderate ascites and jaundice were significantly more among HCC group.

Table (2): Clinical examination among the two studied groups

		Group I (N=300)	Group II (N=115)	P
Ascites	**No**	**212**	**93**	
		70.6%	**80.9%**	
	Mild	**87**	**16**	**0.00****
		29.1%	**13.9%**	
	Moderate	**1**	**6**	
		0.3%	**5.2%**	
Jaundice	**No**	**216**	**94**	
		71.9%	**81.7%**	
	Yes	**84**	**21**	**0.00****
		28.1%	**18.3%**	
LL edema	**No**	**272**	**106**	
		90.6%	**92.2%**	
	Yes	**28**	**9**	**0.72**
		9.4%	**7.8%**	
Encephalopathy	**No**	**269**	**109**	
		90.0%	**94.8%**	
	grade 1	**6**	**3**	
		2.0%	**2.6%**	
	grade 2	**21**	**3**	**0.541**
		7.0%	**2.6%**	
	grade3	**3**	**0**	
		1.0%	**0.0%**	

Group I are patients without hepatocellular cancer and group 2 are patients with hepatocellular cancer, *: Significant, **: Highly significant

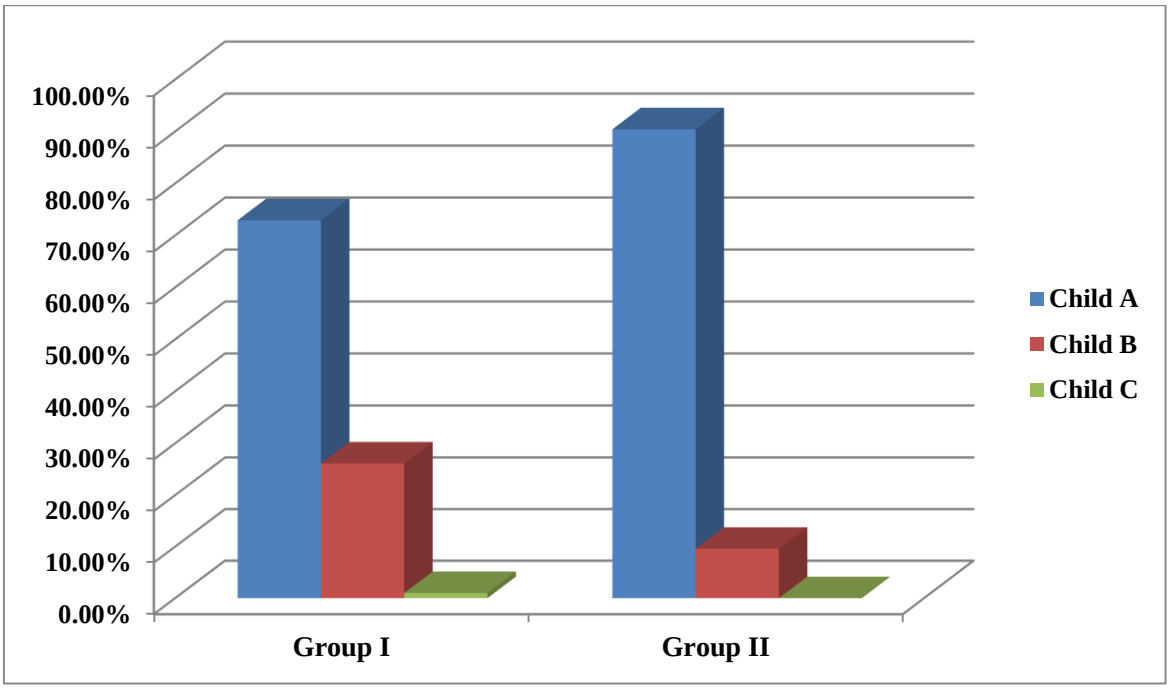
Table 3 shows that hemoglobin, platelet, AST and alpha fetoprotein were significantly higher among HCC group.

Table (3): Laboratory investigations among the two studied groups

	Group I (N=300)	Group II (N=115)	P
WBC thousands /cmm	**7.63±1.87**	**7.54±1.80**	**0.870**
Hemoglobin gm/dl	**9.18±1.74**	**11.41±1.09**	**0.00****
Platelet thousands/cmm	**137.56±33.12**	**163.4±40.5**	**0.015***
Alpha fetoprotein ng/ml	**100.14±24.3**	**264.75±65.9**	**0.025***
Total bilirubin mg/dl	**0.83±0.18**	**0.86±0.18**	**0.922**
Serum albumin gm/dl	**3.70±0.39**	**3.68±0.31**	**0.761**
ALT u/l	**28.65±6.61**	**29.45±7.01**	**0.854**
AST u/l	**33.98±8.01**	**41.47±10.12**	**0.007***
INR	**1.28±0.29**	**1.25±0.15**	**0.185**
Serum creatinine mg/dl	**0.98±0.2**	**0.98±0.23**	**0.992**
APRI score *	**0.77±0.18**	**0.71±0.16**	**0.215**

Group I are patients without hepatocellular cancer and group 2 are patients with hepatocellular cancer, Data are presented as mean ± standard deviation, **: Highly significant

Figure (1) shows that most of HCC patients were of Child A group. Frequency of HCC was 32% among Child-Pugh class A group (104 patient out of 323) while frequency in Child-Pugh class B was 12.4 (11 patient out of 89).



Group I are patients without hepatocellular cancer and group 2 are patients with hepatocellular cancer

Fig. (1): Bar chart shows Child-Pugh classification among HCC and non-HCC groups

Table 4 shows that cirrhotic liver was significantly more among HCC group.

Table (4): Radiological finding (Ultrasound and triphasic CT) among the two studied groups

		Group I (N=300)	Group II (N=115)	P
Liver	**Average size**	**68**	**0**	**0.00****
		22.8%	**0.0%**	
	Enlarged	**22**	**3**	
		7.0%	**2.6%**	
	Cirrhotic	**210**	**112**	
		70%	**97.4%**	
Splenic size by ultrasound	**Average**	**70**	**38**	**0.00****
		23.4%	**33.0%**	
	Mild	**197**	**77**	
		65.9%	**67.0%**	
	Moderate	**33**	**0**	
		10.7%	**0.0%**	
PV diameter (8-12mm)		**12.17±2.61**	**12.62±1.27**	**0.288**

Group I are patients without hepatocellular cancer and group 2 are patients with hepatocellular cancer, Data are presented as mean ± standard deviation or as frequency and percentage, **: Highly significant

Table 5 shows that ascites, jaundice and encephalopathy were significantly worsened after HCC.

Table (5): Clinical data before and after development of HCC

		Before HCC (N=115)	After HCC (N=115)	P
Ascites	**No (N=157)**	**93**	**64**	
		80.9%	**55.7%**	
	Mild (N=45)	**16**	**29**	**<0.01****
		13.9%	**25.2%**	
	Moderate (N=24)	**6**	**18**	
		5.2%	**15.7%**	
	Tense (N=4)	**0**	**4**	
		0.0%	**3.5%**	
Jaundice	**No (N=209)**	**115**	**94**	
		100.0%	**81.7%**	
	Yes (N=21)	**0**	**21**	**0.00****
		0.0%	**18.3%**	
LL edema	**No (N=197)**	**106**	**91**	
		92.2%	**79.1%**	
	Yes (N=33)	**9**	**24**	**0.004***
		7.8%	**20.9%**	
Encephalopathy	**No (N=193)**	**109**	**84**	
		94.8%	**73.0%**	
	grade 1 (N=5)	**3**	**2**	
		2.6%	**1.7%**	
	grade 2 (N=24)	**3**	**21**	**0.541**
		2.6%	**18.3%**	
	grade3 (N=8)	**0**	**8**	
		0.0%	**7.0%**	

**: Highly significant

Table 6 shows that cirrhotic liver and PV diameter significantly increased after HCC.

Table (6): Radiological finding (Ultrasound and triphasic CT) before and after development of HCC

		Before HCC (N=115)	After HCC (N=115)	P
Liver	**Average size**	**16**	**0**	
		13.9 %	**0.0%**	
	Enlarged	**2**	**3**	
		1.7%	**2.6%**	
	Cirrhotic	**97**	**112**	**0.001****
		84.3%	**97.4%**	
Splenic size by ultrasound	**Average**	**38**	**26**	
		33.0%	**22.6%**	
	Mild	**77**	**78**	**0.004***
		67.0%	**67.8%**	
	Moderate	**0**	**11**	
		0.0%	**9.6%**	
	Before HCC	**After HCC**		**P**
PV diameter (8-12) mm	**12.62±1.27**	**13.55±2.20**		**0.001****

Data are presented as mean ± standard deviation or as frequency and percentage, **: Highly significant

Table 7 shows that platelet and albumin significantly decreased after HCC, but alpha fetoprotein, bilirubin, ALT, AST, serum creatinine and APRI score significantly increased after HCC.

Table (7): Laboratory investigations before and after development of HCC

	Before HCC (N=115)	After HCC (N=115)	P
WBC (thousands/cmm)	**7.54±1.80**	**7.50±1.70**	**0.980**
Hemoglobin (gm/dl)	**11.41±1.09**	**11.15±1.91**	**0.126**
Platelet (thousands/cmm)	**163.4±39.8**	**152.22±37.91**	**0.035***
Alphafeto protein (ng/ml)	**64.75±16.11**	**251.84±60.91**	**<0.01****
Total bilirubin (mg/dl)	**0.86±0.18**	**1.15±0.26**	**0.035***
Serum albumin (gm/dl)	**3.68±0.31**	**3.41±0.49**	**<0.01****
ALT u/l	**29.45±7.21**	**35.40±11.8**	**0.011***
AST u/l	**41.47±10.21**	**52.75±12.74**	**0.019***
INR	**1.25±0.15**	**1.28±0.17**	**0.185**
Serum creatinine (mg/dl)	**0.98±0.23**	**1.10±0.24**	**0.011***
APRI score *	**0.71±0.16**	**1.21±0.28**	**<0.01****

Data are presented as mean ± standard deviation, *: Significant, **: Highly significant

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DISCUSSION

HCC is responsible for 75–85% of all occurrences of liver cancer. HCC is a severe public health issue in Egypt, accounting for 33.63 percent of male and 13.54 percent of female malignancies [8]. In actual medical practice, hepatitis C and B viruses, alcoholism, and non-alcoholic fatty liver disease are the leading causes of liver cancer. Cirrhosis caused by HCV and HBV is the leading risk factor for HCC worldwide. HBV is the primary driver of HCC in Southeast Asia and sub-Saharan Africa [9].

The development of oral drugs that directly inhibit the HCV replication cycle led to a significant advancement in HCV therapy in recent years. Direct-acting antivirals (DAAs) work by inhibiting the enzymes NS3/4A protease, NS5A RNA-dependent polymerase, and NS5B RNA-dependent polymerase found in the HCV genome. Compared to interferon-based regimens, the period of treatment is shorter, the drugs can be taken orally, and there are less adverse effects. Different DAAs have different therapeutic effects, genotypic effects, side events, and drug-drug interactions (DDIs), hence they are always prescribed in tandem with another DAA [10].

Our research shows that older individuals and men are more likely to be diagnosed with HCC. Consistent with the work of **Ogawa *et al.*** [11], we see that individuals with HCV in their denovo HCC were much older than those without the virus. In agreement with our results, the study of **Liu *et al.*** [12] found that male gender is an important predictor of HCC development in response to DAA medications. Our result also in agreement with **Shiha *et al.*** [13] who found that patients with HCC tended to be older (59 vs. 56 years old; P .001) and more likely to be male (75.2% vs. 51.3% in HCC patients, compared to patients without HCC). Also, our results were in accordance with other studies done by **Mawatari *et al.*** [14] who found that patients who eventually had HCC were older, more likely to be male, and more likely to have cirrhosis than those who did not.

In the present study we found that HCC was significantly more in diabetic (DM) and hypertensive (HTN) patients and these results were in agreement with **Hattori *et al.*** [15] who found that important risk factors for HCC included advanced age, male gender, diabetes, and hypertension. They were also similar to the results of **Hiramatsu *et al.*** [16] and **Garcia-Compean *et al.*** [17] who cleared that age, liver cirrhosis, being male, problems with glucose and lipid metabolism, and heavy alcohol consumption are all variables that increase the likelihood of developing HCC.

In the present study, moderate ascites and jaundice were significantly more among HCC group. These results were in agreement with **Carrat *et al.*** [18] who found that ascites and jaundice were more common in HCC patients compared to those without the disease, and similar to the result of **Hattori *et al.*** [15] who found that HCC patients were more likely to experience ascites and jaundice.

In the present study hemoglobin, platelet, AST and alpha fetoprotein were significantly higher among HCC group. These results were in agreement with **Shiha *et al.*** [13] who found that higher levels of AST and AFP were found at baseline in individuals with HCC (P =0.023 and less than 0.001, respectively). Also, in agreement with study of **Nahon *et al.*** [19] who reported that when comparing ALT, AST, and total bilirubin levels, the HCC group significantly deviated from the non-HCC group.

In the present study we found that platelet and albumin significantly decreased in patients who developed HCC, but alpha fetoprotein, bilirubin, ALT, AST, serum creatinine and APRI score significantly increased in patients who developed HCC. These results were also presented by **Yoo *et al.*** [20], who found that at the conclusion of treatment, all patients with elevated alpha fetoprotein (AFP) developed HCC. They performed a multivariate study on 574 HCV patients who were treated with DAA and found that alpha fetoprotein levels >9.5 ng/mL were the only independent early onset risk factor for HCC. Also, in

agreement with our study **Hagiwara *et al.*** [21] demonstrated that patients with HCC had significantly elevated alpha fetoprotein, bilirubin, AST, serum creatinine, and APRI score, although platelet and albumin levels decreased.

In the present study we found the frequency of HCC was (27. 7%) within (1-5) years, among 415 HCV patient received DAAs and achieved SVR 115 cases develop HCC. In comparison to other international studies, denovo HCC occurrence incidence rate ranged from zero to 7.4% (maximum follow up 18 months) by **Guarino *et al.*** [2]**.** These difference between the incidence of HCC and these international studies may be explained by the heterogeneity of cohort studies, short follow up (18 month compared to 48 months in our study), absence of control group in our study group. Our study may suggest higher rate of denovo HCC compared to other international study may be explained by different selection criteria.

Cohort studies of 22-500 patients treated with DAAs who did and did not reach SVR corroborated the relationship between DAA-induced SVR and lower HCC risk, with risk reductions of up to 75% after DAA-induced SVR [22]**,** and this was also proven in our study that we found the frequency of HCC was (27. 7%) within (1-5) years. Among 415 HCV patient received DAAs and achieved SVR 115 cases developed HCC.

Our study was different from another Egyptian study by **Lashen *et al.*** [8] who reported that the median age at diagnosis of denovo HCC in individuals was 72.0. Variations in patient selection and length of follow-up explain this.

In the present study we found that frequency of HCC was 32% among Child-Pugh class A group (104 patient out of 323) while frequency in Child-Pugh class B was 12.4 (11 patient out of 89). In agreement with our study **Conti *et al.*** [23] reported that DAA-induced SVR does not prevent HCC in the short-term, and that the vast majority of HCC patients belonged to the Child A group. While **Shiha *et al.*** [13] found that contrary to our findings, Child B patients had a greater HCC incidence than Child A patients.

We tried to find an explanation for increased number of HCC in Child A group of patients and by reviewing some of patient file we found that most of laboratory investigation and radiology evaluation of these patients was done outside the viral hepatitis treatment center, while most of patients later on developed decompensation (Ascites, jaundice or even hepatic encephalopathy) and some of them developed HCC after starting treatment with DAAs.

Although it would seem that severe cirrhosis would be connected to a higher incidence of HCC, this may not be the case. This may be due to the rigorous early screening programme for identification of HCC in our tertiary centre, which allows early diagnosis of tiny lesions.

In the present study we demonstrated that cirrhotic liver was significantly more among HCC group. Frequency of HCC was 33.7% among cirrhotic patients (112 patient out of 332) while frequency of HCC was 3.6% among non-cirrhotic patients (3 patient out of 80). This also was reported by **Roche *et al.*** [24] who found that after SVR, the yearly incidence of HCC was greater in patients with cirrhosis compared to patients without cirrhosis.

In our study we cleared that cirrhotic liver and PV diameter were significantly more common in patients who developed HCC. This result was in agreement with, **Roche *et al.*** [24] who found that Patients with HCC also showed a striking rise in cirrhosis of the liver and PV diameter.

In the present study we cleared that ascites, jaundice and encephalopathy were significantly worsened in patients who developed HCC. This result in agreement with **Ide *et al.*** [25]**,** who demonstrated that patients with HCC were more likely to experience ascites, jaundice, and encephalopathy. It is also in agreement with **Hagiwara *et al.*** [21] who found that patients with HCC were more likely to experience ascites, jaundice, and encephalopathy.

Conti and his colleagues [23] confirmed in patients previously treated for HCC that despite effective DAA treatment, a substantial chance of tumor recurrence persists. Tumor recurrence is common even after effective DAA treatment. Seventeen out of 59 patients (those with a history of HCC) developed recurrent HCC, while only nine out of 285 did not. Recurrence of HCC was associated with the severity of cirrhosis. The findings of our investigation were nearly corroborated by these findings.

Marrero *et al.* [26] provided evidence that effective DAA therapy reduces the risk of HCC by 71%, supporting the concept that treating HCV may be a preventive factor against HCC formation. T cell mediated response and improved immune surveillance of the virus-induced aggressive HCC tumor are triggered by the removal of HCV particles with DAA treatment. This is probably also linked to the diminished degree of liver fibrosis brought on by HCV therapy.

CONCLUSION

Chronic hepatitis C (HCV) is the most common underlying aetiology for HCC; yet, although inducing clearance of HCV infection, DAAs do not appear to diminish the development of HCC in long-term follow-up. All cirrhotic patients using DAAs should be carefully followed for HCC because the study did not find an elevated risk of HCC in those who achieved SVR from hepatitis C.

LIMITATION

Firstly, we did not have an untreated control group in our study, which is a major flaw. It would have been unacceptable for our screening outreach programme to send individuals home without treatment.

Second, all relapsers in the outreach programme were handled with second or even third courses of

treatment, so patients who did not achieve SVR were lost to follow-up.

Further studies with larger sample size are needed to establish our results.

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Competing interests: Nil.

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