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RESEARCH ARTICLE

New incidence or recurrence hepatocellular carcinoma (HCC) in genotype 4 hepatitis C virus treated with sofosbuvir/daclatasvir with or without ribavirin [version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Background: Several studies have resulted in controversial data about the recurrence or new incidence of hepatocellular carcinoma (HCC) in patients with hepatitis C who were treated with direct-acting antivirals (DAAs).

Aim: This observational study aimed to assess the occurrence rate of HCC in patients who developed a sustained virological response (SVR).

METHOD: A six-month prospective study was done at the National Hepatology and Tropical Medicine Research Institute [NHTMRI] in Cairo, Egypt on 150 chronic hepatitis C (CHC) patients treated with sofosbuvir and daclatasvir with or without ribavirin. Patients were assigned into two groups according to their laboratory values to either receive sofosbuvir/daclatasvir and ribavirin (S/D/R) or receive only sofosbuvir/daclatasvir (S/D). The main outcome measure was the occurrence of HCC.

Results: SVR-12 was 100%. 8.5% of patients developed HCC in the S/D/R group, while 0% in the S/D group.

Conclusion: New incidence or recurrence of HCC may occur in CHC genotype 4 cirrhotic patients receiving sofosbuvir/daclatasvir and ribavirin (difficult to treat) although achieving SVR. The cause of HCC development in this study is cirrhosis, not the administered DAAs.

Keywords

Chronic hepatitis C, Direct-acting antivirals, Hepatocellular carcinoma, Hepatitis c virus, Sofosbuvir.

Open Peer Review

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Introduction

Hepatitis C virus (HCV) is a major public medical condition. A quarter of infected patients have cirrhosis and associated complications, such as hepatocellular carcinoma. Treatment aims to remove the virus and prevent the development of cirrhosis and its complications. The treatment target for HCV has been identified in terms of a sustained virologic response (SVR), which is the absence of detectable levels of viral RNA in the blood 24 weeks after the end of the drug course.¹

The prevalence of hepatitis C virus (HCV) infection is the highest in the world in Egypt. It became clear that HCV infection was widespread among Egyptians and that it was the main cause of liver disease in the region. Before the HCV epidemic became evident, schistosomiasis was Egypt's most significant public health issue.²

Worldwide, 180 million people develop chronic HCV infections. While genotype 1 accounts for approximately 48% of HCV infections, the distribution of the seven genotypes varies geographically. Genotype 4 infections are around 20% of all HCV infections worldwide but accounts for nearly 93% of all HCV cases in Egypt.³

Globally, hepatocellular carcinoma (HCC) is known to be a severe malignancy with an approximate incidence of 5.6%. The second most common cause of all cancer-related deaths is also considered. Infection with HCV, studies have indicated that in approximately 30% of patients with chronic hepatitis C, the liver progresses towards cirrhosis of the liver. HCV functions as carcinogenic by many causes, direct viral oncogenic effects, or chronic inflammation and fibrosis.⁴

The pegylated interferon routine has long been a lonely potent regulation of chronic hepatitis C with moderate efficacy. The first appearance of boceprevir and telaprevir protease inhibitors was considered a significant breakthrough, but the potency of both drugs was limited to genotype 1. Currently, direct antiviral drugs have started a new era to effective control of HCV, undoubtedly following the approval by the FDA of medication that have further lead to a complete removal of HCV.⁵

Evaluation of HCC prevalence and hazard factors following a sustained virological response (SVR) is necessary to give priority to HCC surveillance patients during the DAA period. Evidence is especially restricted on the HCC risk of presenting SVR among people with superior fibrosis to support the most effective SVR follow-up for HCC.⁶

Patients with HCV-associated cirrhosis who have been treated with DAAs do not tend to minimize the occurrence of HCC over a limited time. Cirrhotic patients must also be closely monitored during and after antiviral therapy by applying or persevering with HCC monitoring, regardless of HCV infection treatment.⁷

Berge et al. reported one of the above-mentioned mechanisms of HCC induced by DAAs. As they cause a rapid decrease in HCV RNA levels leading to a fast decline in natural killer cells (NK) activity.⁸

The study aimed to examine new-onset or relapse of HCC in patients receiving Sofosbuvir and Daclatasvir both with and without Ribavirin.

Ethical approval

The study protocol was accepted by the Ethics Committee of the National Hepatology and Tropical Medicine Research Institute [NHTMRI 6-2017], approval date: 18/2/2017 in Cairo, Egypt. This research was reported on [ClinicalTrials.gov](https://www.clinicaltrials.gov) with ID number: NCT03247296. This research was performed following the criteria set out in the Norms of Good Clinical Practice and the Helsinki Declaration. Before enrollment, all patients have been informed of the study methodology and they signed detailed written consent.

Methods

This observational study was a six-month observational Prospective study that included 150 adults to detect HCC occurrence in HCV patients treated with SOF, DAC with or without RIB. Patients were recruited from the outpatient clinic of the National Hepatology and Tropical Medicine Research Institute (NHTMRI), Cairo, Egypt.

The study was performed on those who implemented the criteria of inclusion of the National Committee for Control of Viral Hepatitis, Ministry of Health and Population (MOHP), Egypt, and included male and female patients aged 18 to 75 years old, easy to treat group [treatment-naïve patients with PCR positive serum HCV RNA, total serum bilirubin ≤ 1.2 mg/dL, albumin ≥ 3.5 g/dL, INR ≤ 1.2 , and platelet count $\geq 150,000/\text{mm}^3$]. And difficult-to-treat group [interferon treatment-experienced, total serum bilirubin < 1.2 mg/dL, serum albumin < 3.5 g/dL, INR > 1.2 , and/or platelet count $< 150,000/\text{mm}^3$]. For an ethical reason, there was no control group for this study because it was immoral

to allocate an infected group without care. Also excluded were individuals with inadequately managed diabetes mellitus (HbA1c >9 %), total serum bilirubin, serum albumin, INR, platelet count > 3 mg/dL, >2.8 g/dL, ≥ 1.7 , and <50,000/mm³ respectively. co-infection with HIV, HBV, any chronic liver disease other than hepatitis C, poorly controlled hypothyroidism, hepatocellular carcinoma with exception of 4 weeks after treatment with no proof of dynamic imaging activity (CT or MRI), extra-hepatic malignancy except after two years of disease-free interval, patients with Child's Paugh C.

Patients' demographics, laboratory test results, and abdominal ultrasounds reports were collected. Verbally communicated information, *via* phone or directly from the patients, about the drug side effects were included. Medical records were screened for evidence of medication error and interaction occurrence taking into consideration that all the medication orders were handwritten. 150 patients were allocated into two groups according to their physical examination and lab parameters: difficult-to-treat group taking sofosbuvir/daclatasvir/ribavirin (S/D/R) and easy-to-treat group taking sofosbuvir/daclatasvir (S/D). **Figure 1** shows the methodology and primary results in a graphical image.

Lab parameters of the study participants were tested three times. At baseline, all participants were subjected to medical assessment, lab tests as well as quantitative HCV-RNA, fasting blood sugar levels or HbA1C if diabetes present as comorbidity, serum creatinine, CBC, AST, ALT, concentration of prothrombin or INR, total bilirubin, serum albumin, a test of pregnancy (childbearing aged females), alfa fetoprotein (AFP) as an HCC biomarker. Any participants who were men >40 years old, or women >50 years old underwent abdominal ultrasonography and electrocardiogram before start of the treatment.

Virological response to treatment was evaluated using quantitative HCV RNA assessment, by PCR. Laboratory tests for the participants including, serum creatinine, ALT, AST, CBC, HbA1C if diabetic, INR, serum total bilirubin, albumin, AFP. Abdominal ultrasonography was repeated and any suspected focal lesion of the liver was examined with a triphasic

Figure 1. Represents a graphical abstract to that visually shows the primary findings of the study.

CT scan or MRI to investigate the occurrence or the recurrence of HCC at the antiviral treatment end (12 weeks from the start) and SVR 12 (24 weeks from the start).

Statistical analysis

Enrolment was dependent on the clinical need for medication rather than on statistical factors.

Data were obtained, reviewed, and entered, processed, and statistically analyzed using SPSS Version 21 (RRID: SCR_002865); an open-access alternative is JASP (RRID:SCR_015823). The statistical significance of the difference between the two-study mean sample was analyzed by Mann–Whitney's U-test. For categorical results, a Chi-squared test was used. For the analysis of repeated measurements, the Kruskal–Wallis test was implemented to determine the statistical significance of the discrepancy between more than two study group means. The Dunn test was chosen as a *post hoc* test. P-values of less than 0.05 were considered statistically significant. A Kaplan–Meier estimator was used to determine the occurrence rate or recurrence of HCC, the log-rank (Mantel–Cox) test was used to test the difference between classes.

The sample size was estimated considering a 10% improvement in AFP between treatment groups as clinically significant. Assuming a standard deviation of 42, a total of 65 patients will be expected to detect a 10% improvement in AFP with a power of 80% at a significance level of 0.05. However, despite the possible drop-out or lack of follow-up, a total of 150 patients were enrolled.

Results

Participant characteristics

The current prospective research included 150 treatment-naïve chronic hepatitis C patients. Out of 150 patients, 145 accomplished the 12 weeks of protocol regimen with no reported clinically significant side effects. Four patients were eliminated from the study due to non-compliance and one patient died of non-medication-related cause in the (S/D/R) group. There remained 71 patients (30 males and 41 females) with mean age 53 ± 11.17 in the S/D/R group and 74 patients (29 males and 45 females) with mean age 46.1 ± 12.6 in the S/D group. Ribavirin dose modification was done for two patients who suffered from low hemoglobin (9.5 and 9 g/dL respectively for the two patients) during the treatment course. The study participants were assessed at end of treatment (EOT) and SVR12 after cessation of therapy. Basic demographic data and biochemical parameters are shown in [Table 1](#).

HCC incidence

Six patients (three males and three females) from the S/D/R group were diagnosed with HCC although all of them achieved sustained virological response (SVR-12). All with a single HCC lesion detected by triphasic CT scan. Four (66.66%) patients were diagnosed with HCC at the EOT followup, while two (33.33%) patients were diagnosed at the SVR12 follow up. All six patients were cirrhotic from the beginning of the study. The two patients who were diagnosed with HCC at SVR12 follow-up had a history of treated HCC before the start of the study. As all the six patients were cirrhotic, and cirrhosis plays a vital role in developing HCC, cirrhosis and different DAA regimens against HCC development were evaluated using the Chi-squared test to evaluate either the resulted HCC was a consequence of cirrhosis or the used DAA regimens *P*-value was >0.05 for the DAA regimens, on the other hand, *P*-value was <0.05 for the relation of cirrhosis with HCC. Using Kaplan–Meier analysis ([Figure 2](#)), the cumulative rate of HCC at SVR12 was 30% for the cirrhotic patients who received S/D/R, $P<0.001$ by log-rank test.

Biochemical lab values of HCC patients

As the great deviation in HCC patients' lab values, they were studied separately as shown in [Table 2](#). Analysis and comparison of the biochemical values (baseline, EOT, and SVR12) revealed that values of bilirubin, platelet, and INR were significantly different from the baseline with (*P*-value <0.05)

The child score and AFP levels of those patients were significantly different (*P*-values <0.05).

Response

- Sustained virological response (SVR):

All 145 patients who completed the study achieved SVR, including six patients diagnosed with HCC.

- Biochemical lab values

Table 1. Baseline demographics and biochemical parameters of the studied groups.

Parameter	(S/D/R) GP (N = 71)	(S/D) GP (N = 74)
Age [mean $\pm$ SD] years	53 $\pm$ 11.17	46.1 $\pm$ 12.6*
Males [N (%)]	30 (42)	29 (39)
Child score [median (Q1, Q3)]	5 (5,6)	5 (5,5)*
ALT [median (Q1, Q3)]	50 (33,69)	43 (29.75,65)
AST [median (Q1, Q3)]	50 (34,81)	41 (25,54)*
BIL [median (Q1, Q3)]	0.8 (0.6,1.6)	0.6 (0.4,0.8)*
ALB [median (Q1, Q3)]	3.7 (3.3,4.1)	4.25 (3.9,4.7)*
WBCs [median (Q1, Q3)]	5.8 (4.4,7.3)	6.65 (5.2,8.23)*
HgB [median (Q1, Q3)]	13 (11.7,14.4)	13.9 (12.5,15.3)*
PLT [median (Q1, Q3)]	132 (106,163)	222.5 (174,257)*
INR [median (Q1, Q3)]	1.2 (1.075,1.3)	1.04 (1,1.13)*
AFP [median (Q1, Q3)]	7.2 (3.3,15)	3.75 (2.47,5.3)*
SCr [median (Q1, Q3)]	0.9 (0.8,1.1)	0.8 (0.6,1)*
Cirrhosis [N (%)]	20 (29)	2 (2.7)*
History of HCC [N (%)]	3 (4)	0 (0)
Diabetic [N (%)]	23 (33)	13 (17.3)
Glycated HgB [median (Q1, Q3)]	6.2 (5.9,7.35)	7 (6.6,7.75)
Hypertensive [N (%)]	15 (21)	13 (17.3)

(S/D/R): Sofosbuvir/Daclatasvir/Ribavirin, (S/D): Sofosbuvir/Daclatasvir, N: Number, ALT: Alanine Transaminase, AST: Aspartate Amino-transferase, BIL: Bilirubin, ALB: Albumin, WBCs: White Blood cells, HgB: Hemoglobin, PLT: Platelet, INR: International Normalized Ratio, AFP: Alpha Feto protein, SCr: Serum Creatinine.

Chi square test was used to assess the statistical significance of the difference categorical data.

Mann-Whitney's U-test was used to assess the statistical significance of the difference between the two study groups, * means significance when the *P* less than 0.05.

Figure 2. Represents risk percentage of developing new incidence or recurrence of HCC between cirrhotic and non-cirrhotic patients in SDR group percentage of risk was analysed using Kaplan Meier estimator test. And the difference between the two groups was evaluated using Log-rank (Mantel-Cox) test *P* value < 0.05 (significant difference)

Laboratory data of the two groups excluding the patients who developed HCC. at EOT and SVR12 weeks, follow-up was collected and statistically analyzed as shown in Table 3.

At the EOT follow-up, the S/D group showed significantly lower values than the S/D/R group in child score, bilirubin, INR, and AFP with *P*-values <0.05. On the contrary, the S/D/R group showed significantly lower values than the S/D group in albumin, WBCs, hemoglobin, platelet, and glycated hemoglobin levels with *P*-values <0.05. The previous results changed at SVR12 follow up as the S/D group keeps its place in significantly lower values than S/D/R group in bilirubin and AFP with *P*-values <0.05 in both. On the other hand, the S/D/R group showed significantly lower values in albumin, WBCs, hemoglobin, platelets, and INR, with *p* values <0.05.

Table 2. HCC patients biochemical parameters at the baseline, 12 weeks, and 24 weeks follow up.

Parameter	BASAL	EOT	SVR12
Child score [median (Q1, Q3)]	6 (5,6)	8 (7,9.25)	10 (10,10)*
ALT [median (Q1, Q3)]	49.5 (28.5,54.25)	90 (35.75,99.25)	75 (70,80)
AST [median (Q1, Q3)]	51.5 (42,61)	85 (39.25,99.25)	85 (50,120)
BIL [median (Q1, Q3)]	0.87 (0.8,1.3)	1.95 (1.75,2.1)	1.55 (1.1,2)*
ALB [median (Q1, Q3)]	3.4 (3.03,3.8)	3.4 (3.17,3.5)	2.7 (2.5,2.9)
WBCs [median (Q1, Q3)]	5.3 (3.8,8.2)	7.9 (4.4,10)	6.25 (3.8,8.7)
HgB [median (Q1, Q3)]	12.15 (10.8,13.6)	9.65 (9,11.25)	11.6 (11,12.2)
PLT [median (Q1, Q3)]	113.5 (88.8,130)	82 (68.75,96.25)	75 (70,80)
INR [median (Q1, Q3)]	1.2 (1.1,1.5)	1.8 (1,2)	2.8 (2.5,3)*
AFP [median (Q1, Q3)]	8.9 (3.45,20)	875 (40.5,925)	1100 (1000,1200)*
SCr [median (Q1, Q3)]	1 (0.79,1.27)	1 (1,1.4)	1.1 (1,1.2)
Glycated HgB [median (Q1, Q3)]	6 (6,8.6)	8 (8,8)	NA

EOT: end of treatment, SVR12: week 24 follow up, ALT: Alanine Transaminase, AST: Aspartate Aminotransferase, BIL: Bilirubin, ALB: Albumin, WBCs: White Blood cells, HgB: Hemoglobin, PLT: Platelet, INR: International Normalized Ratio, AFP: Alpha Feto protein, SCr: Serum Creatinine, NA: Not Applicable.

Repeated measures Kruskal wallas test was used to assess the statistical significance of the difference between the study groups, * means significance when the *P* less than 0.05.

Table 3. Biochemical parameters of patients in the two groups after 12 and 24 weeks follow up.

Parameter	EOT follow-up		SVR12 follow-up	
	GP S/D/R (N = 65)	GP S/D (N = 74)	GP S/D/R (N = 65)	GP S/D (N = 74)
Child score [median (Q1, Q3)]	5 (5,6)	5 (5,5)*	5 (5,5)	5 (5,5)
ALT [median (Q1, Q3)]	19 (13.5,28)	22 (14.75,30)	20 (12,26.5)	20 (12,25)
AST [median (Q1, Q3)]	27 (17,32)	24 (19,30)	25 (16.5,30)	20 (17,26)
BIL [median (Q1, Q3)]	0.7 (0.5,0.9)	0.6 (0.49,0.7)*	0.7 (0.6,0.8)	0.5 (0.5,0.69)*
ALB [median (Q1, Q3)]	3.8 (3.5,4)	4 (3.8,4.03)*	3.9 (3.7,4)	4 (3.8,4.2)
WBCs [median (Q1, Q3)]	5.2 (4.5,6)	5.9 (5,7)*	5 (4.5,5.6)	5.5 (4.8,6)*
HgB [median (Q1, Q3)]	12 (11,13)	13 (11.75,14.4)*	12.4 (12,14)	13 (12,14.73)
PLT [median (Q1, Q3)]	160 (130,210)	220 (181.8,269.3)*	190 (160,241.5)	228.5 (200,280.3)*
INR [median (Q1, Q3)]	1 (1,1.1)	1 (1,1)	1 (1,1.1)	1 (1,1)*
AFP [median (Q1, Q3)]	4 (3,8)	3 (2,4)*	4 (3,8)	3 (2,3.05)*
SCr [median (Q1, Q3)]	0.9 (0.8,1)	0.8 (0.77,0.9)	0.9 (0.8,1)	0.8 (0.8,1)
Glycated HgB [median (Q1, Q3)]	5.85 (5.58,6)	6.5 (5.65,7)*		

(S/D/R): Sofosbuvir/Daclatasvir/Ribavirin, (S/D): Sofosbuvir/Daclatasvir, EOT: end of treatment, SVR12: week 24 follow up, N: Number, ALT: Alanine Transaminase, AST: Aspartate Aminotransferase, BIL: Bilirubin, ALB: Albumin, WBCs: White Blood cells, HgB: Hemoglobin, PLT: Platelet, INR: International Normalized Ratio, AFP: Alpha Feto protein, SCr: Serum Creatinine.

Mann-Whitney's U-test was used to assess the statistical significance of the difference between the two study groups, * means significance when the *P* less than 0.05.

Discussion

Direct-acting antivirals (DAA) have effectively produced a new HCV-eradication era. The involvement of DAAs in developing HCC in these patients is still questionable.⁹ More than one study has documented different findings of the relationship between therapy by the DAAs and emerging HCC.¹⁰ The findings of those studies were as follows, the previous one from Barcelona stated the HCC relapse in 27.6% of the studied patients after a median follow-up of 5.7 months. While they achieved sustained virological response and had a negative residual HCC before treatment.¹¹

The rates of 28.8% of HCC recurrence and 3.16% of HCC incidence were the result of an Italian study that included 59 patients with HCC history and 295 patients negative for HCC.⁷ Another research from France¹² which included 6000 patients who were treated with interferon (IFN)-free regimens had rebutted both Spanish¹¹ and Italian reports. Researchers found no raise in the development of HCC and an approximately low risk of recurrence of HCC.¹³

Concerning HCC incidence in the current study, six patients out of 71 from the SOF/DAC/RIB group had developed HCC with an incidence rate of 8.5% in a mean time 18 weeks from starting the DAAs treatment. These results came in agreement with those reported by Conti *et al.* who reported HCC incidence of 7.6% in DAA-treated patients.⁷

On the other hand, Calvaruso *et al.* found that the incidence of HCC was only 3.5% and this contrary can be attributed to different DAAs regimens used in both studies.¹⁴

In the present study, the explanation of different outcomes in developing hepatocellular carcinoma between the two groups is that patients in the S/D/R group had more advanced liver disease as shown by their biochemical data. The mean age of patients in the S/D/R group was 53 years old, which was significantly different from those in the S/D group. It is confirmed by the statistical analysis of this study results that the cirrhosis of the six patients is the main cause of their HCC development. This study's point of strength is the regimen detailing in the two groups and accurately illustrating the HCC development in the difficult-to-treat group patients, not the easy-to-treat group which can be a unique finding in Egyptian genotype 4 patients.

Upon studying the follow-up parameters of the patients who developed HCC in the current study it was found that there was an increase in Child scores, ALT, AST, bilirubin, WBCs, INR, and AFP values while there was a decrease in albumin, hemoglobin, and platelets levels, those results came in agreement with those detected by Rewisha *et al.*¹³

Concerning the virological response, patients in this study achieved 100% SVR which is greater than the percentages of both Mann *et al.* (84.9%) and Pariente *et al.* (91.1%); this difference in results may be attributed to the genotype difference of the patients and their response to the Sof/Dac regimen.^{15,16}

Concerning the biochemical parameters of the patients in the two groups, the comparison resulted in significantly lower values in SOF/DAC group than SOF/DAC/RIB group in child score, bilirubin, INR, and AFP with P values <0.05. On the contrary, the SOF/DAC/RIB group showed significantly lower values than the SOF/DAC group in albumin, WBCs, hemoglobin, platelet, and glycated hemoglobin levels with P values <0.05. Those biochemical values were comparable to those reported by Welzel *et al.* but, the bilirubin values between the two groups were equal. The drop in hemoglobin levels can be attributed to the fact that Ribavirin resulted in hemolytic anemia through direct oxidative damage followed by a decreased lifespan of the RBC.^{17,18}

A significant outcome of this research was the discovery of reduced AFP levels following treatment with DAAs; similar to those observed by Stine *et al.* and, as a result of their findings, they proposed a future study that AFP could be considered as a biomarker for the probability of SVR and indicated that AFP should be collected earlier than planned during therapy (e.g. week 4) rather than a viral load.¹⁸

Serum creatinine didn't show any significant change between groups which confirming the safe use of sofosbuvir-based regimens on kidney function and consequently their use in patients with chronic kidney disease patients as mentioned by Sise *et al.*¹⁹

It's worth mentioning a case reported by Ahmed M. who reported that harvoni (which also contains sofosbuvir) induced kidney function deterioration in a patient with normal kidney function, which keeps monitoring kidney functions while treating HCV patients an important issue.²⁰

Conclusion

After analyzing the data resulted in this study, we concluded that DAAs don't raise the risk of developing new incidence or recurrence HCC. The developing HCC risk is increased with cirrhosis. So close monitoring of cirrhotic patients receiving DAAs is required. Other different studies from different geographical areas reported conflicting conclusions about the relation of incidence or recurrence of HCC after DAAs treatment although the SVR achievement in some of those patients. So the close monitoring of patients who will be assigned to the difficult-to-treat group is becoming mandatory.

Funding

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Declarations

Informed consent

This study was conducted in accordance with the principles outlined in the Good Clinical Practice standard and the Declaration of Helsinki. Prior to participation, all patients were informed about the study protocol and they signed written informed consent.

Dual publication

No, the results/data/figures in this manuscript have not been published elsewhere nor are they under consideration from any of the contributing authors by another publisher.

Data availability

Underlying data

Dryad: Underlying data for New incidence or recurrence hepatocellular carcinoma (HCC) in genotype 4 hepatitis C virus treated with sofosbuvir/daclatasvir with or without ribavirin.

Project data, <https://doi.org/10.5061/dryad.x0k6djhk9>. This project contains the following underlying data:

- Data file 1: Demographic data of the S/D group
- Data file 2: Demographic data of the S/D group
- Data file 3: Basal data of the S/D group
- Data file 4: Basal data of the S/D/R group
- Data file 5: Basal data of the HCC patients
- Data file 6: Comorbidities of the S/D/R group
- Data file 7: Comorbiditis of the S/D group
- Data file 8: Diabetic patients of the S/D group with their basal glycated values
- Data file 9: Diabetic patients of the S/D/R group with their basal glycated values
- Data file 10: EOT glycated Hgb value for both groups
- Data file 11: EOT data for S/D group
- Data file 12: EOT data for S/D/R group
- Data file 13: EOT data for HCC patients
- Data file 14: SVR 12 data for S/D group
- Data file 15: SVR 12 data for S/D/R group
- Data file 16: SVR 12 data for HCC patients
- Readme file

Extended data

Zenodo: Protocol, ethics approvals, informed consent, inclusion and exclusion criteria, <https://doi.org/10.5281/zenodo.5534899>.

This project contains the following:

- Data file 1: plain form of data collection sheet
- Data file 2: trial protocol
- Data file 3: Informed consent
- Data file 4: Ethics committee approval of the NHTMRI
- Data file 5: enrollment method with inclusion and exclusion criteria

Reporting guidelines

Zenodo: STROBE checklist for 'New incidence or recurrence hepatocellular carcinoma (HCC) in genotype 4 hepatitis C virus treated with sofosbuvir/daclatasvir with or without ribavirin', <https://doi.org/10.5281/zenodo.5534899>.

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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Chia-Yen Dai

Department of Internal Medicine, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Essawy *et al.* have reported the retrospective study to assess the occurrence rate of HCC in patients with genotype 4 hepatitis C virus treated with sofosbuvir/daclatasvir with or without ribavirin developing a sustained virological response (SVR). With SVR-12 of 100%, the authors concluded that the cause of HCC development in this study is cirrhosis, not the administered DAAs. Some concerns are raised:

- The present study enrolled 150 patients treated by sofosbuvir/daclatasvir with or without ribavirin and got 100% of SVR-12. The case number is small. Without a control group, the results of the current study seem to be untested. It is recommended to enroll an untreated or treatment failure group (even if the SVR indeed is very high).
- It is difficult to make sure the occurrence of the HCC is new with the exclusion of the pre-existing HCC before and during treatment. Also, the follow-up period is quite short.
- Can the authors provide the patients' characteristics more in detail such as the HCV viral load and the fibrosis status (ex. The FIB-4 scores)?

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My areas of expertise are the natural course, treatment, and outcome of hepatitis and HCC.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 20 December 2021

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Asmaa Gomaa

Hepatology and Gastroenterology Department, National Liver Institute, Menoufia University, Menoufia, Egypt

The authors performed an observational study including 150 HCV patients treated with SOF, DAC with or without RIB for 12 weeks and followed for 12 weeks to detect HCC occurrence or recurrence.

The authors stated "The study aimed to examine new-onset or relapse of HCC in patients receiving Sofosbuvir and Daclatasvir both with and without Ribavirin". We can not combine the incidence of new cases with the recurrence. The recurrence of HCC is not considered a relapse.

The authors need to separate patients with no history of HCC from patients with previous HCC.

There are few typo errors. eg, recurrence of HCC is not a relapse.

I can approve this manuscript for indexing if the authors can make the required changes.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Viral hepatitis and HCC

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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