RECURRENCE RATE OF HEPATOCELLULAR CARCINOMA AFTER TREATMENT OF CHRONIC HEPATITIS C PATIENTS WITH DIRECT ACTING ANTIVIRALS: RANDOMIZED CONTROLLED PHASE 3 TRIAL. PRELIMINARY RESULTS

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ABSTRACT:

Background: *There is a controversy regarding the appropriate use of direct acting antivirals (DAAs) in treatment of chronic hepatitis C virus (HCV) in patients with hepatocellular carcinoma (HCC) who were treated radically. Some studies published in 2016 showed increased aggressiveness and rates of HCC recurrence after curative treatment of HCC in HCV patients treated by DAAs who achieved sustained virological response (SVR). On the other hand, the ANRS study, did not show any increased risk of HCC recurrence in the same population of patients. This led to the conduction of this trial to shed some light on this debate.*

Aim of work: *Assess the recurrence rate of HCC in HCV infected patients who received curative treatment for HCC and achieved radiological complete response (rCR) with and without administration of DAAs and assess the effect of the timing of its administration.*

Patients and methods: *Open labeled, prospective, randomized, controlled, phase 3 study in which patients with HCV and prior history of treated HCC who achieved rCR were randomized to receive DAAs or not. Patients in the arm receiving DAAs are further subdivided into 2 groups, one receiving DAAs within 6 months, and the other after 6 months. Primary end point is recurrence rate of HCC in the two main randomized arms. Secondary end point is identification of predictive factors of HCC recurrence in chronic HCV patients treated with DAAs and achieved SVR.*

Results: *Eighty patients with rCR of HCC after curative treatment who met the inclusion criteria were randomly assigned in the 2 arms, 40 to DAAs based treatment arm and 40 to be kept on follow up. Interim Analysis showed that the 2-year HCC recurrence rate was lower in DAA treated arm 39.1% versus 42.6% in non DAA treated patients, however it is not statistically significant (P = 0.7223). Post DAA*

liver decompensation (P = 0.0212), SVR 12 (P = 0.0193) and ascites (P = 0.0238) were independent predictors of HCC recurrence.

Conclusion: *The interim analysis of our study demonstrated that the risk of HCC early recurrence was comparable and not higher than that observed in DAA unexposed patients, and Post DAA liver decompensation, SVR 12 and ascites can be used to stratify the risk of HCC early recurrence, and the efficiency of imaging follow-up. Final analysis of this long-term prospective randomized controlled trial*

(RCT) is expected to be published within 1 year, aims to assess the impact of DAAs on survival after longer follow up.

Key words: *HCC, Hepatitis C, DAAs, Recurrence*

INTRODUCTION:

Hepatocellular carcinoma (HCC) is a universal health problem that contributes significantly to the global burden of disease and mortality, due to its high incidence and extremely high death rate [1]. Worldwide, HCC is the sixth most commonly diagnosed cancer and the third leading cause of cancer-related death, after lung, and colorectal cancer [2].

In Egypt, HCC represents the most commonly diagnosed cancer, and the most common cause of cancer related mortality as well, with about 27 895 new case and 26 523 death in 2020 [3]. Therefore, the health authorities consider HCC as the most challenging health problem in Egypt [4].

HCC is more likely to develop in cirrhotic liver, the 5-year cumulative risk of developing HCC in cirrhotic patients ranges between 5 and 30% and the prevalence of cirrhosis among patients with HCC is 85–95% [5]. Regarding infectious risk factors Hepatitis C virus (HCV) and hepatitis B virus (HBV) increase HCC risk by 20-fold [6].

In 2016, WHO adopted a global hepatitis strategy to eliminate viral hepatitis as a public health threat by 2030, with ambitious targets: a 90% reduction in incident cases of hepatitis B and C and a 65% reduction in mortality. To reach these targets, 80% of treatment-eligible individuals with chronic HBV and HCV need access to care [7]. However, only 12 of 194 countries were on track to meet the 2030 WHO elimination targets in June, 2018 [8].

HCV infection is a major health problem, with an estimated 71 million people chronically infected worldwide and approximately 399,000 deaths in 2016, mostly due to progression to cirrhosis and HCC [8]. Egypt has the highest known prevalence rate of HCV globally, with an estimated 14.7% of the total population seropositive for HCV [9].

The success of DAAs against hepatitis C is a major breakthrough in Hepatology. Till now, there are very few data on the benefits of DAA-based antiviral therapy in patients who have already developed HCC, since this specific population have not been included in the pivotal trials [10].

A significant debate about the impact of DAA on the development of HCC. Among 11 studies examining HCC occurrence after DAA exposure, the de novo incidence rate ranged from 0 to 7.4% (maximum follow-up: 18 months), and among 18 studies regarding HCC recurrence, the rate ranged from 0 to 54.4% (maximum "not well-defined" follow up: 32 months). However, there are major difficulties in interpreting these data and reconciling the results of the included studies. These difficulties include heterogeneous cohorts, potential misclassifications of HCC prior to DAA therapy, the absence of an adequate control group, short follow-up times and different kinds of follow-up[11].

Treatment of HCV in patients with HCC has the potential to eliminate hepatic inflammation, stabilize liver function and reduce the risk of decompensated cirrhosis[12]. However, there are several issues relevant to DAA therapy among patients with HCC. First, initial data suggested a potential increased risk of HCC recurrence [10,13–17], although subsequent studies did not support these findings[18–25]. Second, in response to the controversy around HCC recurrence risk, the timing of DAA therapy in relation to HCC management became a point of debate[26–28]. Third, the DAA response among

patients with HCC is relevant, since it was reported in several studies that the sustained virological response (SVR) to DAA therapy was impaired in HCV-related HCC patients, compared to the non-HCC population[29&30].

PATIENTS AND METHODS:

Patients:

This study was carried out at Ain Shams University Hospitals, Cairo, Egypt. HCC patients with The Barcelona-Clinic Liver Cancer (BCLC) stages 0 and A were treated through surgical resection, local ablation procedures, and trans arterial chemoembolization (TACE). These patients had a maximum of three cancerous lesions, with the largest lesion being less than 5 cm in diameter. Additional inclusion criteria were confirmed HCV viremia by Polymerase chain reaction (PCR) for more than 6 months, an age of 18 years or older, a Child-Pugh score "A" or early “B7”, and confirmation of radiological complete response (rCR) after HCC treatment.

Response after loco-regional treatment of HCC will be assessed by modified Response Evaluation Criteria in Solid Tumors (mRECIST)[31] Assessment for HCC following the American Association for the Study of Liver Diseases and Journal of the National Cancer Institute (AASLD-JNCI) Guidelines[32]. Radiological complete response should be confirmed by a senior radiologist.

Local ablative procedures available at our center included the following: radiofrequency ablation (RFA), microwave ablation (MWA), percutaneous ethanol injection (PEI).

Key exclusion criteria were patients who underwent HCC treatment but without rCR before randomization, or below 18 years old, or with advanced liver condition, or patients with HBV or HIV co-infection, or patients with prior history of liver transplantation, or pregnancy and lactation, or patients with other malignancies other than HCC.

All patients provided written informed consent for participation. The study protocol obtained ethical approval by the Institutional Review Board for Human Subject Research at the faculty of Medicine, Ain Shams University, which is organized and operated according to the International Conference on Harmonization Guidelines on Good Clinical Practice and the Declaration of Helsinki. This study was registered with ClinicalTrials.gov no.: NCT03551444.

Study Design and Treatments:

Open labeled, interventional, randomized, controlled, prospective, phase 3 study. Patients were randomly assigned in a 1:1 ratio to receive DAAs (Arm 1) or be on follow up without DAA treatment (Arm 2). Then second randomization was done in Arm 1 into 2 subgroups in a 1:1 ration to receive DAAs within 6 months from HCC treatment (Arm 1A) or after more than 6 months (Arm 1B). Patients were stratified according to age (<65 vs. ≥65 years), Child-Pugh score, ascites, and HCC treatment procedure.

The baseline characteristics (i.e., at the time of HCC treatment), laboratory and radiologic tumor response were registered in all patients before randomization and during the follow-up according to the clinical practice policy. Evaluation of each patient by at least one tumor status assessment after randomization.

Before randomization, all patients had a dynamic magnetic resonance (MRI) or triphasic computed tomography (CT) to confirm rCR according to European Association for the Study of the Liver (EASL) criteria[33] and to exclude recurrence of HCC.

Our follow up protocol included clinical assessment by physical examination, laboratory evaluation, and multiphasic CT or

MRI every 3 months. However, we changed our follow up plan to be every 6 months since April 2020 due to COVID-19, with regular follow up for any new symptoms either by phone or WhatsApp, for continued confirmation of rCR until recurrence or death or loss to follow-up.

In the DAA administration arm; Antiviral therapy and treatment duration (12/24 weeks) will be indicated in each patient according to the severity of liver disease, in accordance with the EASL recommendations on treatment of hepatitis C 2018[34]. HCV-RNA quantification was assessed by real-time PCR, with a limit of detection (LOD) of15 IU/mL.

During antiviral treatment, follow-up of the patients was monthly by clinical and laboratory evaluation (blood cell count, serum chemistries, and serum alpha feto-protein (AFP)). Virological response to DAA-based treatment will be assessed by quantitative HCV-RNA at the end of treatment (EOT) and at 4 and 12 weeks after the EOT, to confirm SVR. SVR12 is defined as undetectable HCV-RNA at week 12 after the EOT. Virological failures and early discontinuations of therapy due to adverse events was also registered. Also, ultra-sound scan was performed at week 12 after DAA EOT, and at any time when considered by clinical judgement. Dynamic CT or MR was performed at week 24 of DAA EOT or when a focal lesion was detected at US.

HCC recurrence was diagnosed through multidisciplinary team including intervene-tional radiologist, hepatologist, and oncologist. HCC recurrence was treated, whenever possible, according to the BCLC schedule[35] and EASL guidelines[33].

End Points and Assessments:

The primary end point was 2-year recurrence rate (RR). 2-year Recurrence rate was defined as the percentage of patients that developed locoregional recurrence or distant recurrence at 24 months from randomization.

The secondary end points were overall survival and the identification of predictive factors of HCC recurrence in chronic HCV patients treated with DAAs and achieved SVR.

Statistics:

Analysis of data was carried out using SPSS 21 for Windows 2012 (SPSS Inc., Chicago, Illinois, USA). A description of variables is presented as follows:

(1) Numerical variables were described in the form of mean, Standard deviation (SD), median, 25^{th} and $75t^{h}$ percentiles.

(2) Categorical variables were described in the form of numbers and percent.

Numerical data were not normally distributed. Accordingly, nonparametric tests were used for comparison. This was carried out using the Mann–Whitney U-test when comparing between two groups of independent variables. The Kruskal–Wallis test was used when comparing between more than two groups of independent variables. Results were expressed in the form of P values.

Comparison between categorical variables was carried out using Chi-squared ($\chi 2$). Fisher exact test was used instead of the $\chi 2$-test when one expected cell or more were up to 5.

For all analyses, $P \leq .05$ were considered statistically significant. All P values were two-tailed and all confidence intervals (CIs) were 95%.

An interim analysis of recurrence rate was planned when approximately 45 events had occurred. Potential variables were evaluated as predictors of HCC recurrence. All baseline characteristics reported were evaluated as potential risk factors for HCC early recurrences by univariate analysis.

RESULTS

Baseline features of patients

Between December 2016, and January 2019, 146 BCLC stage 0 or A HCC patients were screened for study inclusion in Ain Shams University Hospitals, Cairo, Egypt. Of these, 66 patients were excluded: 12 patients didn't achieve radiological complete response, and 14 patients received DAAs before HCC treatment. Also, three patients were treated previously with liver transplantation, and six had second malignancy other than HCC (CLL, NHL, and breast cancer). At the time of screening; 11 patients were advanced liver disease; child B8 or more, and 2 of them developed hepatic encephalopathy later on. Nine patients were HBV co infected, while two were HIV that was discovered incidentally during screening. one female was pregnant, and two were CKD on dialysis. Furthermore, one patient died before randomization and five requested consent withdrawal due to their remote residency.

Therefore 80 patients with rCR of HCC after resection, ablation, or chemoembolization, and met our previously mentioned inclusion criteria were randomly assigned in 2 arms, 40 to DAA based treatment arm and 40 to be kept on follow up. Then we randomized Arm 1 into 2 subgroups; Subgroup 1A: Administration of DAAs within 6 months from HCC treatment, and Subgroup 1B: Administration of DAAs after more than 6 months as shown in diagram 1.

Baseline characteristics were homogenous in both arms as demonstrated in table 1. No patients in our cohort were alcoholic or had a history of alcoholism.

The median age was 60 years and most patients were males (62.5%). 96.2% of the patients were Child-Pugh class A. Only five patients received prior interferon-based treatment. 81.2% of patients presented with single lesion, with median size of treated hepatic focal lesions were 2.8 cm. There were only 5 patients had a history of prior HCC recurrence. Ablative therapy was the most common used therapy (71.3%).

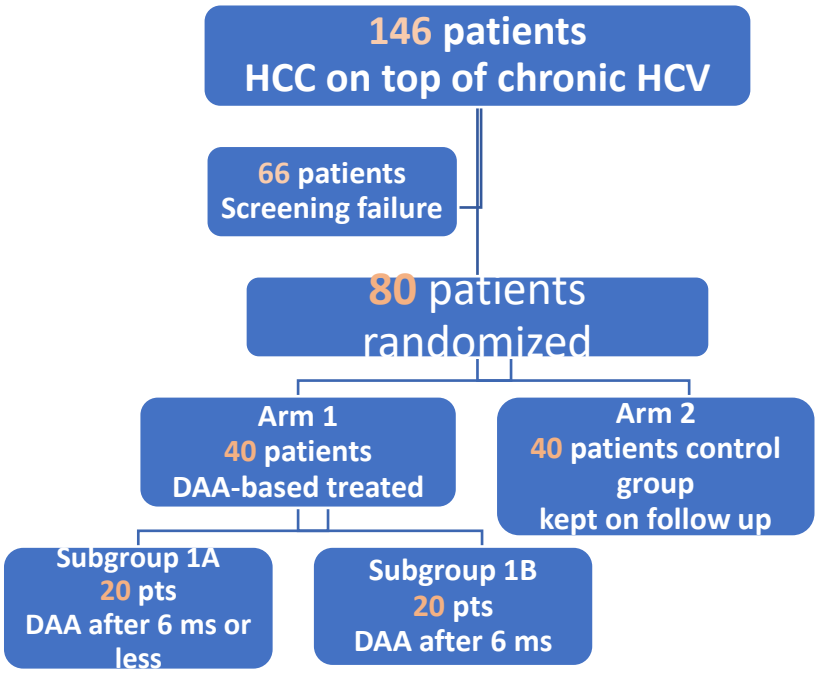

Diagram 1: study profile

Table 1: Baseline characteristics, at the time of HCC complete radiological response between the two arms

Baseline characteristic # (%)	DAA-treated (N=40)	Non DAA-treated (N=40)	P-value
Age			
<65	29 (72.5%)	31 (77.5%)	0.6078
≥65	11 (27.5%)	9 (22.5%)	
Sex			
Male	30 (75.0%)	20 (50.0%)	**0.0217**
Female	10 (25.0%)	20 (50.0%)	
Residency			
Rural	13 (32.5%)	29 (72.5%)	**0.0005**
Urban	27 (67.5%)	11 (28.2%)	
Hypertension	13 (37.1%)	8 (25.0%)	0.2881
Diabetes	13 (37.1%)	11 (34.4%)	0.8148
Child-Pugh score			
5	17 (42.5%)	23 (57.5%)	0.2784
6	22 (55.0%)	15 (37.5%)	
7	1 (2.5%)	2 (5.0%)	
Number of HFL			
Single	33 (82.5%)	32 (80.0%)	0.7759
Multiple	7 (17.5%)	8 (20.0%)	
HFL lobe			
Left	14 (35.0%)	12 (30.0%)	
Right	25 (62.5%)	27 (67.5%)	
Both	1 (2.5%)	1 (2.5%)	
Largest of HFL in cm, Median (Interquartile range)	2.65 (2.05 to 3.15)	2.95 (2.5 to 3.1)	0.1671
Previous antiviral treatment	5 (12.5%)	0 (0.0%)	0.054
Prior HCC recurrence	2 (5.0%)	3 (7.5%)	0.3654
HCC treatment type			
Surgery	2 (5.0%)	3 (7.5%)	
Ablation			
RFA	23 (57.5%)	16 (40.0%)	**0.0147**
PEI	4 (10.0%)	2 (5.0%)	
MWA	3 (7.5%)	9 (22.5%)	
TACE	8 (20.0%)	10 (25.0%)	
Ascites			
No	32 (82.1%)	31 (77.5%)	**0.0150**
Mild	6 (15.8%)	6 (15.0%)	
Moderate	2 (5.1%)	3 (7.5%)	
Baseline AFP Median (Interquartile range)	17.85 (8.2 to 38.4)	11.5 (6.3 to 35.0)	0.8883
Post DAAs Liver decompensation	11 (27.5%)	9 (22.5%)	0.6078

The DAA-treated patients received different all-oral regimens for either 12-or 24-weeks duration. SVR12 was confirmed in 85% of them as shown in Table 2.

Table 2: DAA treatment regimens and SVR12 proportions in the DAA-treated arm (N = 40)

DAA regimen	Duration of treatment (wks)	No of patients (%)	% EOT	%SVR 12
SOF/DCV/RBV	12 24	20 (50%) 5 (12.5%)	90% 100%	95% 100%
SOF/LDV+/-RBV	24	4 (10%)	100%	100%
SOF/RBV	24	5 (12.5%)	80%	60%
SOF/SMV+/-RBV	12	6 15%)	100%	50%
Total		40	92.5%	85%

SOF=Sofobuvir, DCV=Daclatasvir, RBV=Ribavirin, LDV=Ledipasvir, SMV=Simeprevir

HCC Recurrence rate

At the time of interim analysis, 56.2% of the cohort developed HCC recurrence, and 25% of them died. Median follow up was 32 and 27 months in Arm 1 and 2 respectively. Censoring was done for only one patient in arm 1A since he lost follow up.

The 2-year HCC recurrence rate was lower in DAA treated arm 39.1% versus 42.6% in non DAA treated patients, however it is not statistically significant (P = 0.7223).

However, median recurrence free survival (RFS) and overall survival (OS) are not reached yet, that are expected to be released within the next year, together with the analysis of the impact of timing of DAAs after HCC curative treatment (Arm 1A vs 1B).

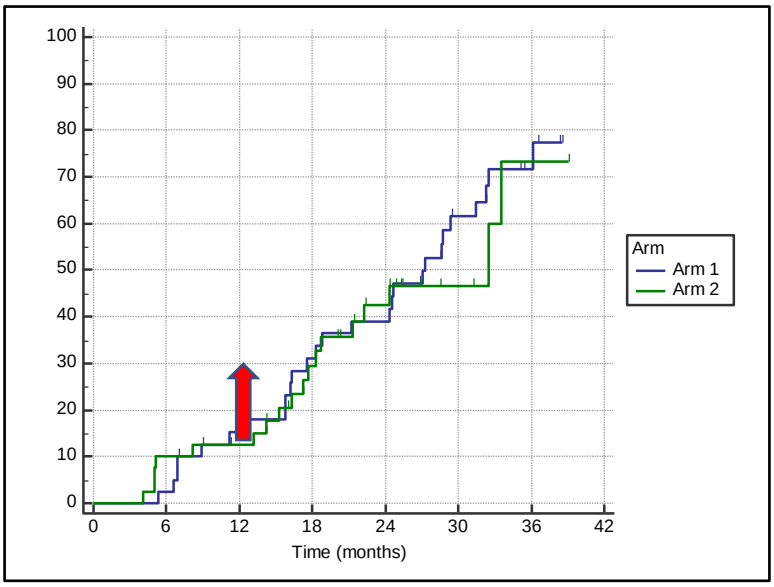

Diagram 2: 2-year Recurrence Rate: Arm 1 vs. Arm 2

Predictors of HCC recurrence:

Table 3 shows predictors of recurrence free survival. Post DAA liver decompensation, SVR 12 and ascites were independent predictors of HCC recurrence.

However, no significant differences were observed when patients were stratified according to baseline age, diabetes, Child-Pugh class, number of hepatic focal lesion (HFL), and HCC treatment procedure.

Table 3: Predictor factors of HCC recurrence free survival

Predictor factor	Median RFS	95% Confidence Interval	P-value
Age			
<65	29.4	24.3 to 32.5	0.2665
≥65	17.6	16.2 to 28.6	
Sex			
Female	28.7	22.3 to 36.1	0.2968
Male	24.7	17.3 to 32.3	
Residency			
Rural	24.6	17.6 to 36.1	0.7218
Urban	28.7	21.2 to 32.5	
Hypertension			0.1891
No	29.4	24.3 to 36.1	
Yes	18.7	15.8 to 31.4	
Diabetes			0.2945
No	28.6	22.3 to 33.5	
Yes	18.3	15.3 to 31.4	
Child-Pugh score			
5	24.3	17.6 to 31.4	0.2368
6	28.7	24.3 to 36.1	
7	18.3	5.1 to 18.3	
Number of HFL			
Multiple	18.3	5.3 to 18.8	0.6391
Single	28.6	24.3 to 32.5	
Prior HCC recurrence	2 (5.0%)	3 (7.5%)	0.3654
HCC treatment type			
Surgery	24.3	18.3 to 29.3	
Ablation			
RFA	31.4	18.3 to 33.5	0.6419
PEI	21.2	6.9 to 24.7	
MWA	24.3	17.7 to 27.2	
TACE	18.8	13.2 to 29.4	
Ascites			
Mild	16.3	5.1 to 24.7	**0.0238**
No	31.4	24.6 to 33.5	
SVR 12			
No	15.767	5.3 to 31.4	**0.0193**
Yes	28.733	24.3 to 36.1	
Post DAA Liver Decompensation			
No	32.3	21.2 to 33.5	**0.0212**
Yes	22.3	15.3 to 28.6	

DISCUSSION:

There has been extensive debate about the potential benefit of DAA therapy in patients with a history of HCC, primarily related to concerns about the risk of HCC recurrence.

Of these patients, those with previous HCC were noted to have higher Child-Pugh scores, increased rates of liver stiffness and portal hypertension, and decreased platelet counts than those with no history of HCC. It has been suggested earlier that rapid changes to the immune surveillance system and/or antitumor response following DAA treatment could be the reason for the apparent increase in HCC recurrence[18].

An observational study by Villani et al supported this idea through demonstration

that DAA administration induces an early increase in serum vascular endothelial growth factor (VEGF), and a change in the inflammatory pattern, coinciding with HCV clearance. This may alter the balance between inflammatory and anti-inflammatory processes and modify the antitumor surveillance of the host. Fortunately, such modifications return reverse to normal after the end of treatment[36].

On the other hand, HCC treatments such as surgical resection and local ablative therapies are potentially curative, they are limited by high risk of recurrence and 5-year mortality approaches 50%. Prior attempts to identify adjuvant therapies to reduce HCC recurrence, such as the STORM Trial evaluating sorafenib after resection or ablation, largely failed [37]. Cabbibo and colleagues demonstrated that hepatic decompensation was a stronger driver of mortality than HCC recurrence in patients with complete response to HCC therapy emphasizing the importance of DAAs in these group of patients [38].

Several retrospective and prospective studies reported conflicting results about HCC recurrence rates after DAA therapy [10,13,18,19,21,39–45]. The conflicting data may be due to the heterogeneity and discrepancies among the obtained results. The causes of the variability in the available data can be summarized as follows: (1) different study designs: retrospective, prospective, or case-control studies or meta-analyses; (2) different study settings: single-center, multi-center or real-world, nationwide or international studies; (3) inclusion and exclusion criteria; (4) basic information about the subject, such as gender, age, BMI, genotype of HCV virus; (5) tumor characteristics, including the diameter, number, whether the tumor has metastasis and the number of HCC recurrences; (6) risk factors such as alcohol abuse and diabetes; (7) interval between curative treatment and DAA therapy; (8) type of curative HCC treatment; (9) lack of a control group or inconsistent inclusion time between the control and experimental groups; (10) use of other medications before DAA treatment; (11) inconsistent follow-up time [46]. Compared with the interferon group, patients in the DAA treatment group were older and had more advanced liver cirrhosis. These are independent risk factors that affect HCC recurrence, this can explain the high risk of HCC recur in DAA group [25]

Additionally, the follow-up start time differed among the studies. Some started from the initiation of DAA therapy, some started from the end of DAA therapy, and some started from the HCC complete response. The significant variability in the timing of follow-up is a major area of potential bias [46].

Therefore, designing more scientific and rational clinical trials, as well as more detailed subgroup analysis to obtain less bias between different groups, was warranted.

Our study was a prospective randomized controlled trial study investigating the effects of DAA therapy on the recurrence rate after curative HCC treatment. we found that 2-year probability of HCC recurrence after DAA therapy were 39.1% compared to 42.6% in non DAA treated patients. In line with the large prospective study conducted with Cabibbo and his colleagues that 6-month and 1-year probability of HCC early recurrence after DAA therapy were 12% and 26.6% respectively [47].

However, the only two independent risk factors for HCC early recurrence as reported by Cabibbo et al.[47], were previous history of HCC recurrence and tumor size, while in our study we found that SVR 12 and ascites were the two independent risk factors for HCC recurrence.

Comparing with other studies, Reig and

his colleagues initially focused on HCV patients who had achieved complete radiologic response (no identifiable tumors on imaging) after treatment for HCC with ablation, resection, or chemoembolization and subsequently underwent all-oral DAA therapy. Patients with a history of interferon therapy or with non-characterized nodules (<10-mm, radiographically detectable lesions) were excluded. In this study, the authors noted HCC recurrence at a median of 5.7 months, with half of these recurrences characterized as multinodular and 20% having infiltrative or extrahepatic lesions[10].

Further studies continued to question the role of HCV therapy on HCC recurrence. A meta-analysis of 11 studies of adjuvant therapy with interferon compared to DAA agents showed accelerated HCC recurrence at 6 months in the latter group [48]. More specifically, between 0% and 12.5% of untreated patients experienced HCC recurrence at 6 months, which was significantly less than the rate found in patients who received DAA therapy (>28%). Patients with HCC recurrences were also noted to be younger (56 vs 73 years) and more frequently treatment-experienced (88.2% vs 61.9%) [48].

Nevertheless, some studies have suggested that there may be insufficient evidence for such a claim. The European studies that postulated an association between HCC recurrence and DAA therapy were noted to be mostly observational and were not randomized controlled trials, which thereby allowed for possible confounding variables [15].

This study has some limitations. The follow-up is relatively short with quite small number of events. Therefore, more follow up is needed for the final analysis.

Conclusion:

The interim analysis of our study demonstrated that the risk of HCC early recurrence was comparable and not higher than that observed in DAA unexposed patients, and Post DAA liver decompensate-ion, SVR 12 and ascites can be used to stratify the risk of HCC early recurrence, and the efficiency of imaging follow-up. Final analysis of this long-term prospective RCT, is expected to be published within 1 year, and aims to assess the impact of DAAs on survival after longer follow up.

Conflicts of interest:

The authors declare no personal conflict of interest, and no funding was received to conduct this study.

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