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■■■ R E S E A R C H   A R T I C L E

Optimum initiation-time of direct-acting antivirals for hepatitis C after curative ablation of hepatocellular carcinoma improves neoplastic recurrence-free survival

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■■■ ABSTRACT   ■■■ ARTICLE INFO

Background: Early initiation of direct-acting antivirals (DAAs) after ablation of hepatocellular carcinoma (HCC) may boost the proliferation of the potentially present extra-lesion dormant neoplastic micro-nodules. **Aim:** We evaluated the performance of early initiation of DAAs therapy after curative ablation of HCC as a risk factor for early neoplastic recurrence in chronic hepatitis-C patients, aiming to select an optimum initiation time for DAAs therapy. **Materials and Methods:** This retrospective cohort study was conducted at hepatology unit at Tanta university Hospitals in the period from January 2016 to January 2020 on 142 naïve HCV patients who achieved SVR to DAAs therapy after complete ablation response of HCC. Post-ablation to DAAs-initiation elapsed time window were estimated. All patients were followed up regularly for 18 months from completion of DAAs therapy for the ascertainment of HCC recurrence. **Results:** HCC recurrence occurred in 27.5% of our patients, most of them (43.6%) in the first 6 months post-DAAs therapy with an incidence rate of 1 per100 persons-months. Post-ablation to DAAs-initiation time window had a significant performance as a risk factor for early HCC recurrence after DAAs therapy (AUROC:0.8887; CI:0.821-0.953; sig:0.000), the tenth month of post-ablation time was the most accurate cutoff value for ruling out HCC recurrence for values more than it (sensitivity: 97.4%, LR-:0.09). **Conclusions:** Early DAAs-initiation after curative HCC ablation seems to be a significant risk factor for early HCC recurrence; DAAs-initiation should be delayed after 10 months.

Keywords: Direct Acting Antivirals, Hepatocellular Carcinoma, Initiation Time, Risk Factor, Recurrence
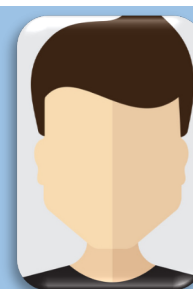
INTRODUCTION

Successful DAAs therapy for chronic hepatitis (CHC) has a beneficial effect in the prevention of cirrhosis progression and decompensation; accordingly, it may reduce the risk of HCC incidence, however, an extensive debate is still ongoing around the possible increase of HCC recurrence after curative ablation in CHC patients who received DAAs therapy even after the sustained virological response (SVR) (European Association for the Study of the Liver, 2018; El Kasssas et al., 2019; Saraiya et al., 2018; Reig et al., 2016). This debate encouraged many researchers to study the possible risk factors that may be linked to the increased HCC recurrence after DAAs therapy hoping to explain and introduce suitable solutions to mitigate this phenomenon, most of these risk factors were related to the degree of liver fibrosis, reserve liver function, tumor burden, alpha-fetoprotein (AFP) as well as the interval time from ablation to DAAs initiation (Colombo et al., 2018; Guarino et al., 2018; Reig et al., 2017; Baumert et al., 2017; Piscaglia, et al., 2017; Tampaki et al., 2018).

Early recurrence of HCC after DAAs therapy for CHC may be attributed to multiple explanations, mostly related to incomplete ablation or the potential presence of intrahepatic extra-lesion micro-metastasis (Sherman, 2008). DAAs

induced immune reconstitution by abrupt virus clearance seems to open a transitory immunosuppressive phase (Meissner et al., 2014; Serti et al., 2015; Chu et al., 2017; vanWilgenburg et al., 2016); accordingly, these dormant tumor micro-nodules or micro-metastasis might find an ideal condition to proliferate and become radiologically apparent. The equilibrium between both cancer cell proliferation and lysis may be achieved by changes in the immune system and/or angiogenesis and it seems to be the leading cause of this tumor mass dormancy (Teng et al., 2008; Sanduzzi-Zamparelli et al., 2019).

Based on these explanations, we hypothesized that early initiation of DAAs after ablation may boost the proliferation of these dormant neoplastic micro-nodules, so, the post-ablation to DAAs initiation elapsed time may share an important link to the possibility of HCC recurrence after starting of DAAs therapy. We focused in our study on this elapsed time parameter to evaluate its performance as a risk factor for early neoplastic recurrence after DAAs therapy for HCV aiming to select an optimum time to start DAAs therapy after curative ablation of HCC.

MATERIALS AND METHODS

Ethical consideration

We conducted this study in accordance with the declaration of Helsinki and our institutional ethics committee.

Study design

This was a retrospective cohort study that was conducted in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Statement (Collin et al., 2015).

Study setting and participants

This study was conducted at the hepatology unit at Tanta University Hospital (a tertiary hospital). We reviewed the registered data for all CHC patients (who were already received DAAs therapy after ablation of HCC with a complete response and who were followed up periodically at our outpatient clinic in the period from January 2016 to January 2020) for potential eligibility criteria (n=189).

In our study, we focused on the potential link between the post-ablation to DAAs-initiation elapsed time window and HCC recurrence, so, we tried to enhance our exclusion criteria to exclude other known risk factors for HCC recurrence;7 patients were excluded due to the combined HCV/HBV affection, 11 patients were excluded as they had previous HCV treatment experience, 4 patients were excluded due to failure of achievement of SVR to DAAs therapy, 4 patients were excluded as the HCC ablation modality were transarterial chemoembolisation (TACE), 6 patients were excluded due to unconfirmed complete ablation response immediately before DAAs- initiation, 2 patients were excluded as their pre-ablation criteria were not registered, 4 patients were excluded due to previous history of HCC recurrence, 12 patients were excluded due to irregular adherence to post-ablation follow up protocol and 3 patients were excluded due to the presence of non-characterized hepatic nodules immediately before DAAs-initiation. Therefore, the eligibility criteria were fulfilled in only 142 naïve HCV patients who achieved SVR to DAAs therapy after curative HCC ablation (surgical resection, radiofrequency ablation, microwave ablation or percutaneous ethanol injection) as illustrated in our study flowchart (Figure 1).

Data collection

The registered pre-ablation, post-ablation and post-DAAs follow-up data for each enrolled patient were thoroughly evaluated. The following participants' criteria were evaluated: demographic criteria (age and sex), pre-ablation laboratory criteria (alanine aminotransferase [ALT], aspartate aminotransferase [AST], s.albumin, s.bilirubin, prothrombin concentration [PC], s.creatinine, platelet count, hemoglobin, fibrosis-4 [FIB-4] score and Child-Pugh score), pre-ablation HCC criteria (volume, number and alpha-fetoprotein [AFP] level), post-ablation to DAAs-initiation elapsed time window.

The assessment of HCC ablation was done using either triphasic computed tomography (TCT) or dynamic magnetic resonance imaging (DMRI) and the complete ablation response was achieved when there were no radiological criteria for remained active neoplastic areas

within the previously ablated HCC (arterial hyper-enhancement with delayed washout) (European Association for the Study of the Liver, 2018), the last radiological assessment was done just before DAAs-initiation to rule out any HCC recurrence before the start of DAAs therapy. All our naïve HCV patients were treated in accordance with EASL recommendations on treatment of hepatitis C using either the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) once daily for 12 weeks or the combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks, the SVR was defined as undetectable HCV RNA in blood by a sensitive assay 12 weeks (SVR 12) or 24 weeks (SVR 24) after the treatment completion (European Association for the Study of the Liver, 2017).

Follow up and study endpoint

The registered post-DAAs follow up data were traced periodically every 3-6 months for 18 months after completion of DAAs therapy for the ascertainment of the recurrent HCC which was confirmed by using either TCT or DMRI and was defined by the reappearance of radiological criteria of active neoplastic lesions within or nearby the previously ablated mass (arterial hyper-enhancement with venous or delayed washout). The time of HCC recurrence was calculated from the registered date of ablation.

Statistical analysis

IBM SPSS; version 23 statistic software (IBM, NY, USA) was used for data summarization and statistical analysis. The mean (with standard deviation) was used for normally distributed quantitative data while the median (with minimum and maximum) was calculated for abnormally distributed quantitative data; qualitative data were cross-tabulated as frequency and relative frequency.

Cox-regression analysis was performed for the possible risk predictors for post-DAAs HCC recurrence. Candidate risk predictors in this analysis were post-ablation to DAAs-initiation elapsed time window, the pre-ablation reserve liver function using Child-Pugh score, pre-ablation HCC criteria (volume, number and AFP) and the pre-ablation degree of liver fibrosis using fibrosis-4 (FIB-4) score. Univariate Cox-

regression analysis was done first for each predictor, and then the best predictors were evaluated using the multivariate Cox-regression analysis by entering all predictors simultaneously with a stepwise backward strategy.

Receiver operating characteristic (ROC) curve was calculated for the post-ablation to DAAs-initiation elapsed time window and its area under the ROC curve (with their 95% confidence interval [CI]) was computed, two cutoff values were selected according to the clinical rule of the predictor, that is, to rule in or rule out the risk prediction of HCC recurrence. Sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR-) were calculated for each cutoff point.

The post-ablation to DAAs-initiation elapsed time window was graded using the ruling out cutoff value to two risk grades; low risk, and high-risk grades, the recurrence-free survival function was illustrated using Kaplan Meier method and analyzed using Log Rank test. P-values less than 0.05 were considered statistically significant**.**

RESULTS

The main evaluated participants' criteria are illustrated in table 1 including the demographic criteria (age and sex), pre-ablation reserve liver functions using Child-Pugh score, pre-ablation values of liver fibrosis using FIB-4 score, pre-ablation HCC criteria (tumor volume, number, AFP and treatment modality) and post-ablation to DAAs-initiation elapsed time window. The incidence rate of HCC recurrence was found to be 1 per 100 person-months with a total of 39 patients (27.5%). We missed outcome data for only 8 (5.6%) patients without an identified cause.

Table2 illustrated the Cox-regression analysis for our evaluated risk factors of post-DAAs HCC recurrence. Firstly the univariate Cox-regression analysis was done, the candidate risk factors in this analysis were patients' demographic criteria (age and Sex), reserve liver status; we used Child-Pugh score as a surrogate parameter for liver functions and FIB-4 score was used as a non-invasive score for liver fibrosis, criteria of HCC burden (tumor volume, number and AFP)

as well as post-ablation to DAAs-initiation elapsed time window (sig: 0.073, 0.967, 0.000, 0.000, 0.000, 0.536, 0.001 and 0.000 respectively). After that, multivariate Cox-regression analysis was done to identify the most independent significant risk factors of HCC recurrence and their respective hazard ratios (HR), these predictors were the Child-Pugh score (sig: 0.002, adjusted HR: 2.184 with CI: 1.346-3.542), HCC volume (sig:0.016, adjusted HR: 1.056 and CI: 1.010-1.103) and post-ablation to DAAs-initiation elapsed time window (sig: 0.000, adjusted HR: 0.506 and CI: 0.414-0.618).

Table3 of illustrated the Receiver operating characteristics (ROC) of the post-ablation to DAAs-initiation elapsed time window and its area under the ROC curve was computed (AUC: 0.887 with CI: 0.821-0.953) as illustrated in figure 2, two cutoff values were selected according to the clinical rule of the predictor; the 1st cutoff value was ≤4 months to rule in the risk prediction of HCC recurrence and it was selected in accordance to its highest specificity (98.1%) and the highest LR+ (17.17), the 2nd cutoff value was ≥10 months to rule out the risk prediction of HCC recurrence and it was selected in accordance to its highest sensitivity (97.4%) and the lowest LR- (0.09), this time window was graded using the ruling out cutoff value (10 months) to 2 grades; low risk initiation-time for periods ≥10 months, high risk initiation-time for periods <10 months, the recurrence free survival function between those different risk grades were illustrated using Kaplan Meier method and analyzed using Log Rank test showing pairewise significant difference (sig: 0.000 with an estimated mean of recurrence free survival: 36.4 months and 24.1 months for low risk and high risk initiation-time respectively) as illustrated in figure 3. As illustrated in table 4, the incidence rate of HCC recurrence was 1.8 per100 persons-months if DAAs initiated within the high-risk time window (<10 months) and 0.17/100 person-months if DAAs initiated within low-risk time window. At the same time, we found that 17 HCC recurrent cases (43.6%) occurred within 1st 6 months after DAAs completion, 12 (30.8%) cases occurred within the 2nd 6 months and 10 (25.6%) cases occurred within the 3rd 6 months.

DISCUSSION

We focused here in our study on the post-ablation to DAAs-initiation elapsed time window to evaluate its performance as a risk factor for early HCC recurrence after DAAs therapy for HCV hoping to appropriate selection of optimum starting time for DAAs therapy after curative ablation of HCC.

We found that the incidence rate of HCC recurrence was 1/100 persons-months, however, it ranges from 0.73 to 1.7/100 persons-months in other studies, (Virlogeux, et al. 2017; ANRS collaborative study group on hepatocellular carcinoma, 2016) at the same time, we found that total cases of HCC recurrence were 39 (27.5%) of patients within a median post-DAAs follow up time of 18 months most of them within the 1st 6 months. Saraiya et al. (2018) found a pooled HCC recurrence rate was 21.9% (95% CI: 16.2%-28.3%). El Kassas et al. (2018) found that HCC recurrence occurred in 37.7% of patients after a median post-DAAs follow-up period of 16 months. The variability between the results of these studies seems to be due to differences in study designs, differences in HCC ablation modalities, differences in follow up periods, geographic differences, and the wide variability in the timing of DAAs-initiation, however, the proximity of HCC recurrence in most patients of our study to the timing of DAAs completion could be attributed as an alarm that needed an explanation.

Early recurrence of HCC after DAAs therapy for CHC may be attributed to multiple explanations, mostly related to, incomplete ablation or the potential presence of extra-lesional micro-metastasis (Sherman, 2008). DAAs induced immune reconstitution by abrupt virus clearance seems to open a transitory immunosuppressive phase (Chu et al., 2017; vanWilgenburg et al., 2016; Waring et al., 2016; Villani et al., 2016). Accordingly, these dormant tumor micro-nodules or micro-metastasis might find an ideal condition to proliferate and become radiologically apparent. The equilibrium between both cancer cells proliferation and lysis may be achieved by changes in the immune system and/or angiogenesis and it seems to be the leading
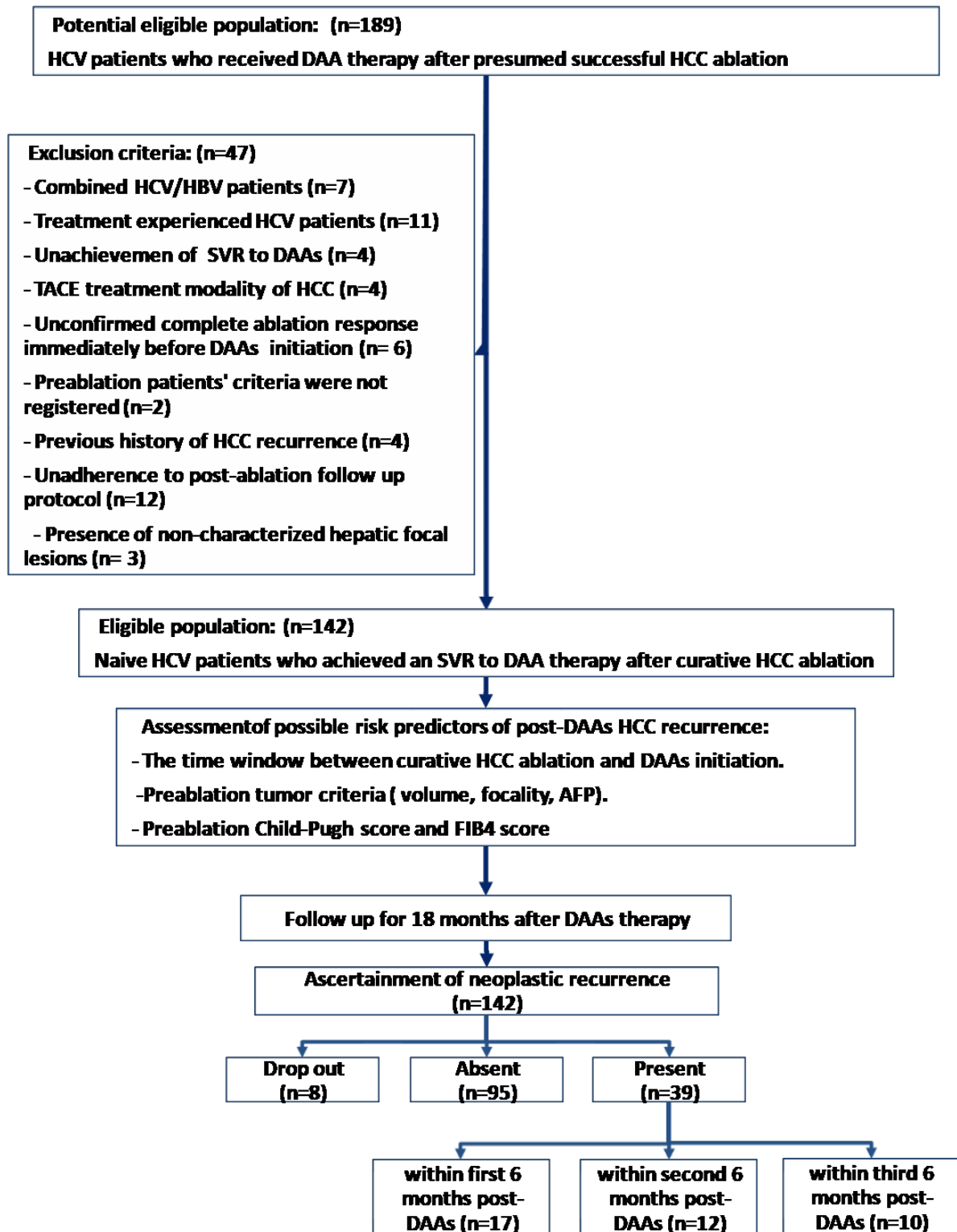
Potential eligible population: (n=189)

HCV patients who received DAA therapy after presumed successful HCC ablation

Exclusion criteria: (n=47)

- Combined HCV/HBV patients (n=7)

- Treatment experienced HCV patients (n=11)

- Unachievemen of SVR to DAAs (n=4)

- TACE treatment modality of HCC (n=4)

- Unconfirmed complete ablation response immediately before DAAs initiation (n= 6)

- Preablation patients' criteria were not registered (n=2)

- Previous history of HCC recurrence (n=4)

- Unadherence to post-ablation follow up protocol (n=12)

- Presence of non-characterized hepatic focal lesions (n= 3)

Eligible population: (n=142)

Naive HCV patients who achieved an SVR to DAA therapy after curative HCC ablation

Assessment of possible risk predictors of post-DAAs HCC recurrence:

- The time window between curative HCC ablation and DAAs initiation.

- Preablation tumor criteria (volume, focality, AFP).

- Preablation Child-Pugh score and FIB4 score

Follow up for 18 months after DAAs therapy

Ascertainment of neoplastic recurrence (n=142)

Drop out (n=8)

Absent (n=95)

Present (n=39)

within first 6 months post-DAAs (n=17)

within second 6 months post-DAAs (n=12)

within third 6 months post-DAAs (n=10)

Figure 1. Study participants' flowchart.

Table 1. Main participants' criteria

Participants' criteria		Value (n=142)		
Demographic criteria				
Age (years)		Mean (SD)	56.12	(7.917)
Sex	**Female**	Count (%)	47	(33.1%)
	Male	Count (%)	95	(66.9%)
Pre-ablation laboratory parameters				
ALT (IU/L)		Mean (SD)	52.26	(10.041)
AST (IU/L)		Mean (SD)	47.30	(7.656)
S. albumin (gm/dl)		Mean (SD)	3.23	(0.280)
S. bilirubin (mg/dl)		Mean (SD)	1.43	(0.256)
Prothrombin concentration (%)		Mean (SD)	69.72	(6.306)
Child-Pugh score	**A5**	Count (%)	17	(12%)
	A6	Count (%)	52	(36.6%)
	B7	Count (%)	55	(38.7%)
	B8	Count (%)	18	(12.7%)
FIB-4 score		Mean (SD)	2.49	(0.560)
Platelets (x10^3/mm^3)		Mean (SD)	150.42	(18.769)
Hemoglobin (g/dl)		Mean (SD)	11.65	(0.661)
S. creatinine (mg/dl)		Mean (SD)	1.07	(0.110)
Pre-ablation HCC criteria				
Number	**Unifocal**	Count (%)	76	(53.5%)
	Multifocal	Count (%)	66	(46.5)
Volume (CC^3)		Median (min-max)	27	(12-53)
AFP		Median (min-max)	41.5	(9-1471)
Treatment modality	**PEI**	Count (%)	12	(8.5%)
	RFA	Count (%)	52	(36.6%)
	MWA	Count (%)	70	(49.3)
	Surgical resection	Count (%)	8	(5.6%)
Post-ablation related criteria				
Post-ablation to DAAs-initiation elapsed time window (months)		Median (min-max)	9	(3-16)
HCC recurrence	**Incidence rate**	/100 persons-months	1	
	Total cases	Count (%)	39	(27.5%)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, FIB-4 score: fibrosis-4 score, HCC: hepatocellular carcinoma, AFP: alpha-fetoprotein, DAAs: direct antiviral agents, PEI: percutaneous ethanol injection, RFA: radiofrequency ablation, MWA: microwave ablation

Table 2. Cox-regression analysis for all studied risk factors of HCC recurrence

Participants' criteria	Univariate Cox-regression analysis				Multivariate Cox-regression analysis					
	B	SE	Wald	Sig.	B	SE	Wald	Sig.	Adjusted HR	
									value	95% CI
Demographic criteria										
Age	0.038	0.021	3.213	0.073						
Male gender	0.014	0.340	0.002	0.967						
Reserve liver status										
Child-Pugh score	1.094	0.213	26.504	0.000	0.781	0.247	10.017	0.002	2.184	1.346-3.542
FIB-4 score	1.197	0.264	20.505	0.000						
HCC burden										
HCC volume (CC^3)	0.12	0.021	32.307	0.000	0.054	0.023	5.793	0.016	1.056	1.010-1.103
HCC focality	0.198	0.320	0.382	0.536						
AFP (ng/ml)	0.002	0.000	12.088	0.001						
Post-ablation to DAAs-initiation elapsed time window										
Post-ablation to DAAs-initiation time window (months)	-0.721	0.091	63.056	0.000	-0.681	0.102	44.610	0.000	0.506	0.414-0.618

FIB-4 score: fibrosis-4 score, HCC: hepatocellular carcinoma, AFP: alpha fetoprotein, DAAs: direct antiviral agents, HR: hazard ratio, CI: confidence interval, sig: significance

Table 3. Receiver operating characteristics of the post-ablation to DAAs-initiation time window as a risk predictor of recurrence of hepatocellular carcinoma

	Clinical Rule	Cutoff	Sensitivity	Specificity	LR+	LR-	AUROC		
							Value	(95% CI)	Sig.
Post-ablation to DAAs-initiation time window (months)	**Rule out**	**≥10**	97.4%	27%	1.34	0.09	0.887	0.821-0.953	**0.000**
	Rule in	**≤4**	33.3%	98.1%	17.17	0.68			
LR+: positive Likelihood ratio, LR-: negative likelihood ratio, AUROC: Area Under Receiver Operating Characteristics Curve, Sig: significance, DAAs: direct antiviral agents									

Table 4. HCC recurrence in relation to study follow up time factors

Time factor			Value (n=39)
Post-ablation to DAAs-initiation elapsed time	High-risk initiation-time (<10 months)	Incidence rate	1.8/100 persons-months
	Low-risk initiation-time (≥10 months)	Incidence rate	0.17/100 persons-months
Post-DAAs follow-up time	Within 1st 6 months after DAAs	Count (%)	17(43.6%)
	Within 2nd 6 months after DAAs	Count (%)	12(30.8%)
	Within 3rd 6 months after DAAs	Count (%)	10(25.6%)
HCC: hepatocellular carcinoma, DAAs: direct antiviral agents			

cause of this tumor mass dormancy (Teng et al., 2008; Sanduzzi-Zamparelli et al., 2019). So, we could hypothesize that early initiation of DAAs after ablation may boost the proliferation of the potential dormant extra-lesional neoplastic micro-nodules so, the post-ablation to DAAs initiation elapsed time may share an important link to the possibility of HCC recurrence after starting of DAAs therapy.

The Cox-regression analysis of our results identified that the most independent significant risk factors for early HCC recurrence were the shorter post-ablation to DAAs-initiation time window, larger HCC volume, and higher Child-Pugh score. Multiple risk predictors for HCC recurrence after DAAs therapy were evaluated in many studies with variable results, most of these risk factors were related to the degree of liver fibrosis, reserve liver function, tumor burden (size and number), AFP as well as the elapsed time from ablation to start of DAAs therapy (Colombo et al., 2018; Guarino et al., 2018; Reig et al., 2017; Baumert et al., 2017; Piscaglia et al., 2017; Tampaki et al.,(2018).

We found that, the post-ablation to DAAs-initiation elapsed time window had an accurate and significant performance in risk prediction of HCC recurrence after DAAs therapy as described by its Receiver operating characteristics (AUC: 0.887; CI: 0.821-0.953; sig: 0.000), at the same time we tried to select a suitable starting time point for DAAs therapy through selecting two

cutoff values of this elapsed time window; the 1st cutoff value was found to be ≤4 months to rule in the risk prediction of HCC recurrence and it was selected in accordance to its highest specificity (98.1%) and the highest LR+ (17.17), the 2nd cutoff value was found to be ≥10 months to rule out the risk prediction of HCC recurrence and it was selected in accordance to its highest sensitivity (97.4%) and the lowest LR- (0.09), this time window was graded using the ruling out cutoff value to 2 grades; low risk time window for periods ≥10 months and high risk time window for periods < 10 months with a significant difference as regard the recurrence free survival distribution (sig: 0.000), the incidence rate of HCC recurrence was found to be 1.8/100 persons-months if DAAs-initiation was within the high risk time window while it was 0.17/100 persons-months if DAAs-initiation was within the low risk time window. These results were confirmed by that identified by many papers that found that shorter elapsed periods from ablation to DAAs-initiation were more significant than longer time post-ablation periods however with variable cutoff time points (Ogawa et al., 2018; Minami et al., 2016; Kolly et al., 2017; Bielen et al., 2017). However, El kassas et al., (2018) found that there was no significant difference in the rate of HCC recurrence between HCV patients who received DAAs within the first 3 months post-ablation time window and those who received it later in the time window (more than 6 months).
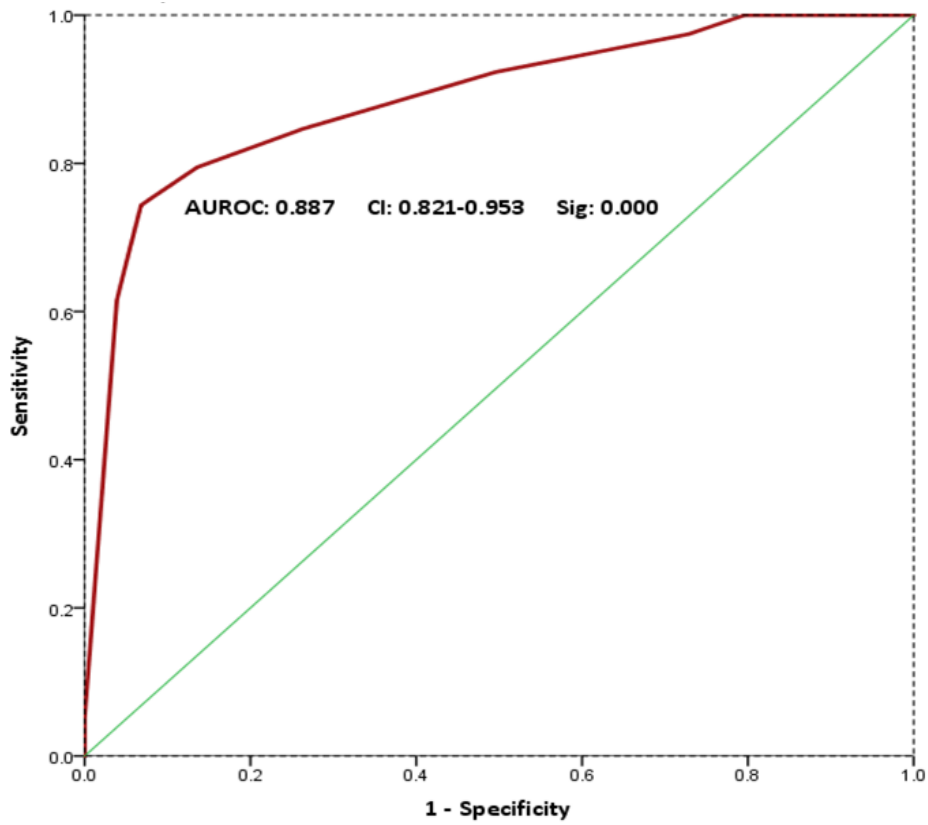
Figure 2. ROC curve for the post-ablation to DAAs-initiation time window in relation to HCC recurrence
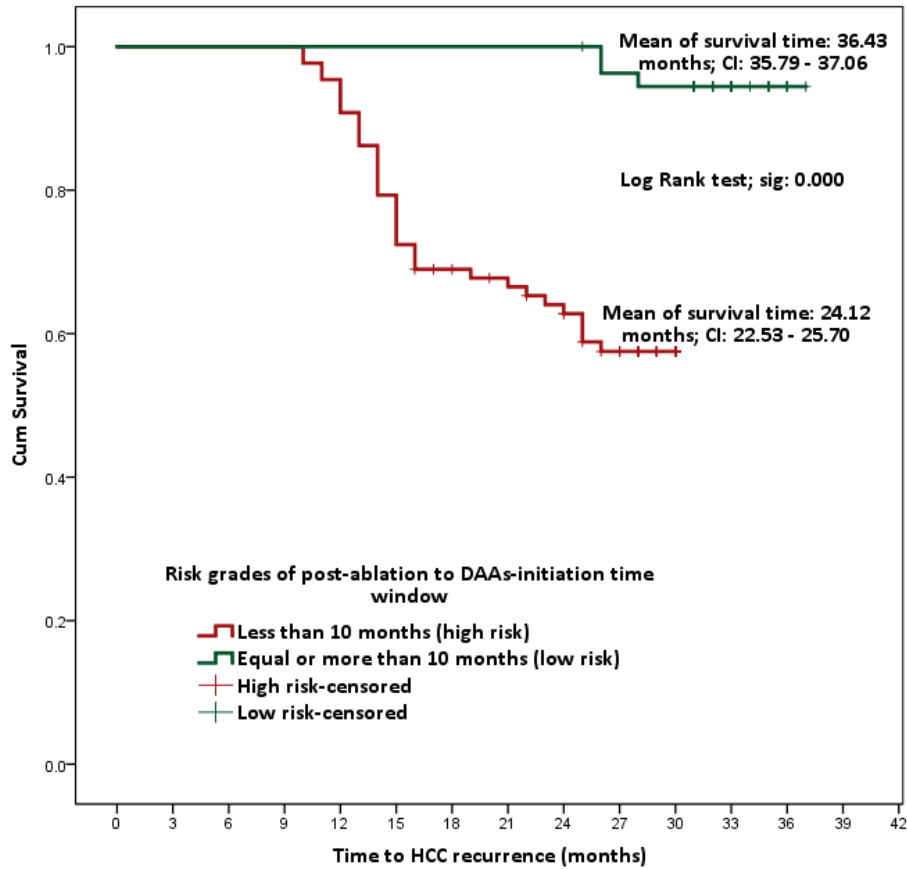

Figure 3. The Kaplan Meier of HCC recurrence-free survival function for the different risk grades of DAAs initiation-time

Based on these explanations, we could hypothesize that early initiation of DAAs after HCC ablation may boost the proliferation of potentially present extra-lesional dormant neoplastic micro-nodules so, the post-ablation to DAAs initiation elapsed time may share an important link to the possibility of HCC recurrence after starting of DAAs therapy

Our study has some limitations; the retrospective data collection is one of these limitations, however, we tried to enhance our participants' selection and exclusion criteria to focus on our research question. This study is a uni-centric study, which affects the external generalizability of our results, and at the same time, we couldn't identify some risk factors in most of the participants' criteria as diabetes mellitus related data and body mass index. Finally, we did not include the different patterns of HCC recurrences hoping to be included in other wider studies.

We could conclude that Early DAAs-initiation after curative HCC ablation seems to be an important significant risk factor for early HCC recurrence after DAAs therapy; DAAs initiation should be delayed after 10 months from curative HCC ablation to rule out the presence of post-ablation dormant neoplastic nodules and the potential post-DAAs HCC recurrence.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

FUND

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