Hepatocellular carcinoma recurrence after direct-acting antiviral therapy: an individual patient data meta-analysis

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HEPATOCELLULAR CARCINOMA RECURRENCE AFTER DIRECT-ACTING ANTIVIRAL THERAPY: AN INDIVIDUAL PATIENT DATA META-ANALYSIS.

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ABSTRACT

Objective

The benefit of direct-acting antivirals (DAAs) against hepatitis C virus (HCV) following successful treatment of early hepatocellular carcinoma (HCC) is a highly controversial topic despite the data reported from North America. This meta-analysis of individual patient data assesses the risk of HCC recurrence after DAAs.

Design

We pooled 977 consecutive patients from 21 published studies of HCV-related cirrhosis and HCC, who had achieved complete radiologic response after surgical or locoregional treatments and were subsequently treated with DAAs (DAA group). Risk of recurrence or death was expressed as HCC recurrence per 100 person-year (100PY) or death per 100PY. Propensity score matched patients from the ITA.LI.CA. cohort (n=328) served as DAA-unexposed controls (no-DAA group). Risk factors for HCC recurrence were identified by random effect Poisson.

Results

Recurrence rate and death risk per 100PY in DAA-treated patients was 20 (95%CI:13.9-29.8, I^2=74.6%) and 5.7 (95%CI:2.5-15.3, I^2=54.3), respectively. Heterogeneity among studies was high for both outcomes. Predictive factors of recurrence were logarithm of alpha-fetoprotein (RR=1.11[95%CI:1.03-1.19];p-value=0.01, per 1 log of ng/ml), history of HCC recurrence before DAA-initiation (RR=1.11[95%CI:1.07-1.16];p-value<0.001), ECOG-PS (2 vs 0, RR=4.35[95%CI:1.54-11.11] and 2 vs 1, RR=3.7[95%CI:1.3-11.11];p-value=0.01) and tumor burden prior to HCC treatment (multifocal vs. solitary nodule, RR=1.75[95%CI:1.25-2.43];p-value<0.001).

Relative risk between DAA-exposed and unexposed in propensity score matched patients (167 pairs) remains inconclusive, with no statistically significant differences (RR=0.64 [95%CI:0.37-1.1];p-value=0.1).

Conclusion

The effect of the DAA exposure on HCC recurrence risk was inconclusive in this study. Active surveillance is justified in this population for whom no effective adjuvant treatment is available.

INTRODUCTION

The first reports[1,2] about the potential increased risk of hepatocellular carcinoma (HCC) recurrence in patients with successfully treated HCC who subsequently received direct-acting antiviral (DAA) treatment triggered major interest in the topic. Almost all centres in the world published their experience or presented it at liver-oncology meetings. Furthermore, systematic reviews and cumulative meta-analyses addressed the issue[3–7], but while such approach yielded a suggestion for a reduced recurrence risk, the heterogeneity across studies prevented a robust message that would end the controversy. Indeed, despite applying statistical tools to decrease the rate of heterogeneity, this remained unacceptably high, ranging from 80.5%[3] to 96.7%[7]. Thus, the optimism about a reduction of recurrence risk by HCV therapy was not sustained by scientific evidence. In that sense, cohort studies included in the meta-analytic assessment suffer from patient heterogeneity at baseline, different follow-up time and different follow-up procedures to detect recurrence. The multicentre retrospective cohort studies by Singal et al[8,9] ~~done only in North America~~ suggested no increased recurrence and improved survival after DAA treatment ~~and improved survival~~ but only included patients from the U.S. and ~~then highlighting~~there remain a need for ~~systematic review of~~ international data given differences in patients characteristics and HCC practice patterns.

Since the controversy is still open, all guidelines about HCC[10] and antiviral therapy[11–14] describe the limitations of the current data. The unequivocal answer would be obtained through a randomized controlled trial (RCT) with allocation to treatment or no treatment and a homogeneous follow-up strategy. Such RCTs that would directly compare DAAs versus no-DAAs are considered not feasible, non-ethical or not-timely, or all at the same time. In that sense, long term survival of these patients is dictated by the HCC-recurrence or progression of the tumour, and by the development of complications due to progression of liver disease. The latter represents the one of

the drivers of death in HCV-viremic patients with successfully treated early HCC[2], and it has been showed that DAAs could improve overall survival through a reduction of the risk of hepatic decompensation[8,15]. Therefore, the acceptance of a RCT to assess the risk of HCC recurrence is precluded[15].

Because of this situation of uncertainty and unfeasibility to expect results from an RCT, we designed an international, multicentre study using individual data. This would overcome the limitations associated with the use of aggregate data as in prior meta-analyses, increasing the relevance of the statistical analysis and improving the estimates of effect size. The present meta-analysis using individual patient data (MIPD) aimed to: (1) assess the recurrence rate of HCC in DAA-treated patients after complete response; (2) identify risk factors for HCC recurrence after DAA treatment. Finally, we incorporated a propensity score analysis to assess the impact of DAA therapy as compared vs a DAA-unexposed control group derived from the Italian curated prospective database ITA.LI.CA.

MATERIALS AND METHODS

Meta-analysis using individual patient data (MIPD) of DAA-exposed patients.

The current MIPD was designed to pool the data of individuals from different studies evaluating the risk of HCC recurrence after DAA exposure in HCV-infected cirrhotic patients with previous successful treatment for HCC [16].

This study complied with the principles of the Declaration of Helsinki and its appendices, and local and national laws. It was approved by the Research Ethics Committee of the Hospital Clínic of Barcelona (HCB/2019/0030) and registered in PROSPERO database (CRD42020133457-https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=133457).

Studies were included in the qualitative analysis if they met all of the following criteria: a) data in English language with full-text accessibility/presentation or poster/oral presentation; b) target

population of the original paper was HCC patients who received DAAs after HCC treatment; c) the study had to assess the risk of developing HCC recurrence after DAA treatment; d) report HCC recurrence of patients; e) report the date of prior HCC treatment. A systematic search for records up to April 3, 2018 in PubMed Central/MEDLINE was performed with different combinations of keywords. The search details are reported in Supplementary Material.

A Data Transfer Protocol (DTP) was written according to the European regulation (General Data Protection Regulation (GDPR) 2016/679 of the European Parliament and of the Council of April 27, 2016 and approved by each cohort responsible. Centres were requested to provide baseline data and follow-up events and dates. The complete list of variables extracted from the included studies and the DTP document are reported in Supplementary Material.

The primary outcomes were - HCC recurrence rate, defined as the number of patients per 100 patient-year (100PY) who previously obtained HCC complete response (CR) and that developed HCC after DAA treatment, and - death rate per 100PY.

DAA-unexposed patients' cohort

Data from the 328 DAA-unexposed patients who acted as controls were obtained from the retrospective study of prospective ITA.LI.CA. database[17] enrolled from 2007 to 2015. They were HCV-related compensated cirrhotic patients with a first diagnosis of early HCC (BCLC 0/A), who had achieved CR after ablation or resection and who had not been treated with DAAs.

Statistical analysis

Quantitative variables were expressed as median and interquartile range [IQR:25th-75th percentiles]. Categorical variables were described as absolute frequencies and percentages (%).

For MIPD analysis of the DAA-exposed patients' cohort, pooled recurrences of HCC or death were expressed as number of events per 100PY. Rates and 95% confidence intervals (95%CI) were estimated by means of Poisson models using a random effects *one-stage* step approach and including as offset the logarithm of the radiological follow-up time. Heterogeneity was evaluated by means of the I^2 and the Q heterogeneity test. Values of I^2 around 25%, 50% and 75% were considered, respectively as: low, moderate and high levels of heterogeneity[18]. Q heterogeneity test was considered significant when p-values were <0.1. Sensitive analyses were conducted to explore the potential sources of heterogeneity and included assessment by subgroups, univariate or multivariate Poisson regression models and leave-one-out strategy, using the same *one-stage* random effects approach. Prognostic factors for recurrence were analysed using univariate and multivariate Poisson regression models, including in the multivariate analysis those variables with p-value<0.1 on the univariate testing.

Propensity score (PS) matching (PSM) was performed between the DAA-exposed and unexposed patients. Matching 1:1 was conducted using the greedy nearest neighbour approach with a caliper of 0.06 for the predicted probability. The balance between cohorts, before and after PSM was assessed by standardized mean differences (STD). STD>10% were considered unbalanced[19–21]. Details of PS model are described in supplementary materials.

The comparison of risk of recurrence between matched patients was performed by relative risks and their 95%CI, estimated using the same Poisson model but including also the DAA-unexposed group. A sensitivity survival analysis was conducted for overall survival using restricted mean survival time (RMST) methods since the proportional-hazards assumption did not hold[22]. The restricted time (tau) was established at the time of the last observed death.

The level of significance was set at the two-sided 5% level. All analyses were performed with SAS 9.4 software (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics

Initial search found 87 studies. After first assessment, 32 studies meeting the inclusion criteria were invited to participate. After first contact, 23 corresponding authors of each study sent the data, of which 21 were finally included[1,2,9,23–40]. Two full studies involving 67 patients were excluded because they did not fulfil the prespecified data requirements Thus, there were 977 DAA-treated patients: 12 retrospective and 9 prospective, including 12 full-length paper, 5 abstracts and 4 Letters to the Editor (Figure 1). The studies baseline characteristics are reported in Table 1, and the individual characteristics of the included patients are reported in Supplementary Table S1. Most of the DAA treated patients were male (63%), with a median age of 67.9 years, and Child-Pugh class A (88%). More than half (52.8 %) met Milan criteria, 38.6% had solitary HCC at tumour diagnosis, 7.1% had multifocal HCC and less than 0.5% of the cohort had extrahepatic spread or vascular invasion. Performance status (ECOG-PS) was 0 in 93.3% of the patients and the most frequent treatment was ablation (47.3%), followed by resection (31%) and chemoembolization (15.3%). Sustained virological response (SVR) rate in the studies ranged from 60% to 98.2%.

Table 1. Characteristics of included patients

	Males (%)	Child-Pugh (A/B/C,%)	ECOG-PS (0/1,%)	Extrahepatic Spread / Vascular Invasion (Yes,%)	Esophageal Varices / Ascites / AHT / HBV / DM / Alcohol consumption (Yes,%)	Images used for CR assessment (MR/CT/Others,%)	Radiological follow-up (Yes,%)	Waiting list for LT (Yes,%)	SVR (Yes,%)
Conti F. et al., 2016[37]	67.2	83 / 17 / 0	100 / 0	0 / 0	41.4 / 25.9 / 0 / 3.5 / 34.5 / 6.9	7 / 29 / 64	100	5.2	89.7
Minami T. et al., 2016 (L)[26]	59	98 / 2 / 0	100 / 0	0 / 0	10.3 / 0 / 15.1 / 0 / 21.9 / 50.7	25 / 75 / 0	100	0	91.8
ANRS, 2016[24]	80	83 / 17 / 0	89 / 11	0 / 0	20 / 20 / 20 / 0 / 10 / 90	60 / 30 / 10	100	10	80
Reig M. et al., 2016[1]	68.8	86 / 6 / 3	100 / 0	0 / 0	28.6 / 5.2 / 0 / 1.3 / 0 / 0	47 / 17 / 36	100	0	67.5
HEPADAT, 2017 (†)[28]	72.4	92 / 7 / 1	84 / 13	0 / 0	18.4 / 10.3 / 48.3 / 4.6 /	19 / 32 / 49	100	0	92

					24.1 / 31				
Zavaglia C. et al., 2017 (L)[33]	44.7	74 / 26 / 0	92 / 8	0 / 2.6	31.6 / 18.4 / 15.8 / 0 / 21.1 / 7.9	50 / 42 / 8	100	2.6	92.1
Kohla M. et al., 2017 (††)[40]	76.9	85 / 15 / 0	100 / 0	0 / 0	30.8 / 0 / 38.5 / 0 / 26.9 / 0	0 / 100 / 0	0	0	69.2
Villani R. et al., 2017 (*)[31]	100	80 / 20 / 0	100 / 0	0 / 0	0 / 0 / 40 / 0 / 60 / 0	40 / 60 / 0	100	0	60
Cavalletto L. et al., 2017 (*)[36]	58.3	75 / 25 / 0	25 / 58	0 / 0	83.3 / 33.3 / 25 / 0 / 25 / 41.7	33 / 58 / 8	100	8.3	83.3
Tsai PC. et al., 2017 (L)[30]	41.3	70 / 0 / 0	66 / 34	0 / 2.2	4.4 / 0 / 0 / 4.4 / 21.7 / 4.4	9 / 20 / 71	100	13	100
Nagata H. et al., 2017[27]	60	97 / 3 / 0	97 / 3	3.3 / 0	46.7 / 3.3 / 6.7 / 6.7 / 20 / 43.3	53 / 47 / 0	100	0	96.7
Kolly P. et al., 2017 (L)[23]	68.8	81 / 19 / 0	50 / 44	0 / 0	50 / 18.8 / 37.5 / 6.3 / 18.8 / 6.3	31 / 69 / 0	100	56.3	68.8
Calleja JL. et al., 2017[35]	50	63 / 13 / 0	100 / 0	0 / 0	37.5 / 12.5 / 50 / 0 / 25 / 0	75 / 13 / 13	100	25	87.5
El Kassas M. et al., 2017[39]	65.1	98 / 2 / 0	93 / 7	0 / 0	53.5 / 0 / 46.5 / 0 / 32.6 / 0	0 / 100 / 0	0	0	74.4
Cabibbo G. et al., 2017[2]	60.3	87 / 13 / 0	96 / 4	0 / 0	58.9 / 11.4 / 45.4 / 1.4 / 31.9 / 0	23 / 77 / 0	99.3	0	96.5
Masetti C. et al., 2018 (**)[24]	62.5	92 / 4 / 4	100 / 0	4.2 / 0	37.5 / 4.2 / 29.2 / 0 / 20.8 / 25	4 / 42 / 54	100	4.2	91.7
Toyoda H. et al., 2018[29]	52.8	96 / 4 / 0	100 / 0	0 / 0	27.1 / 2.9 / 47.1 / 0 / 57.1 / 27.1	100 / 0 / 0	100	0	95.7
Ashraf Omar A. et al., 2018[32]	89.5	87 / 13 / 0	79 / 21	0 / 0	0 / 0 / 2.6 / 0 / 23.7 / 0	74 / 26 / 0	100	2.6	94.7
Merchante N. et al, 2018[25]	87.5	88 / 6 / 6	75 / 25	0 / 0	0 / 0 / 0 / 0 / 0 / 0	38 / 31 / 31	0	0	93.8
Singal A. et al., 2019[9]	73.3	87 / 13 / 0	97 / 3	0 / 0	0 / 6.7 / 0 / 0 / 0 / 0	53 / 47 / 0	0	0	86.7
Degasperi E. et al., 2019[38]	58.9	89 / 11 / 0	100 / 0	0 / 0	46.4 / 14.3 / 41.1 / 3.6 / 14.3 / 21.4	18 / 68 / 14	94.6	0	98.2

*: Works presented on EASL2017; **: Works presented on EASL2018; †: Works presented on AASLD2017; ††: Works presented on ILCA2017; L: Letter to the Editor; AHT: Arterial Hypertension; HBV: Hepatitis B Virus; DM: Diabetes Mellitus; CR: Complete Response; MR: Magnetic Resonance; CT: Computed Tomography; LT: Liver Transplant; SVR: Sustained Virological Response; ECOG-PS: Eastern Cooperative Oncology Group Performance Status

Outcomes

The median follow-up of the whole cohort was 15 [IQR:9–22.6] months. During this period, 41.8% patients developed HCC recurrence and 12.9% have died. The characteristics of patients at HCC recurrence are reported in Supplementary Table S2.

The rate of decompensation was not analysed because up to 296 patients (>30%) did not have this data available. Indeed, the trigger for decompensation and its date were not reported in 31.9% of the patients.

HCC recurrence

The pooled HCC recurrence rate per 100PY was 20 (95%CI: 13.9-29.8). Heterogeneity among studies was very high for the main analysis (I^2 = 74.6%, 95%CI: 61.6%-83.3%; p-value<0.001) (Figure 2). Predictive factors of recurrence at multivariate analysis were logarithm of AFP (RR= 1.11 [95%CI: 1.03–1.19], per 1 log of ng/mg increase; p-value=0.01), number of previous HCC recurrence before DAA initiation (RR= 1.11 [95%CI: 1.07–1.16]; p-value<0.001), ECOG-PS (2 vs 0, RR = 4.35 [95%CI: 1.54–11.11] and 2 vs 1, RR = 3.7 [95%CI: 1.3–11.11]; p-value=0.01) and tumor burden of last HCC before DAA initiation (<=3 nodules and <=3cm vs. Solitary nodule, RR = 1.47 [95%CI: 1.2–1.85] and multifocal vs. solitary nodule, RR = 1.75 [95%CI: 1.25–2.43]; p-value<0.001)(Table 2).

Table 2. Prognostic baseline factors for HCC recurrence

		Univariate		**Multivariate**	
Parameter	**Contrast**	**RR (95%CI)**	**P-value**	**RR (95%CI)**	**P-value**
Age (Years)		2.56 (2.55-2.56)	<0.001		
Gender	Male vs. Female	1.22 (0.99-1.52)	0.06		
Weight		2.55 (2.55-2.56)	<0.001		
Height		2.69 (2.58-2.81)	0.6		
MELD score		1.79 (1.68-1.93)	<0.001		
Presence of HBV	Yes vs. No	1.12 (0.49-2.56)	0.8		
Presence of HIV	Yes vs. No	0.52 (0.08-3.26)	0.3		
Child-Pugh			<0.001		

	A vs. B	0.77 (0.56-1.05)			
	A vs. C	1.55 (0.21-11.28)			
	A vs. Non-Cirrhotic	2.08 (0.85-5.08)			
	B vs. C	2.02 (0.27-14.99)			
	B vs. Non-Cirrhotic	2.71 (1.06-6.9)			
	C vs. Non-Cirrhotic	1.34 (0.15-11.74)			
Total bilirubin (mg/dl)		2.25 (1.66-3.69)	0.4		
ALT (UI/L)		2.63 (2.63-2.64)	<0.001		
Log(AST, UI/L)		1.44 (1.43-1.46)	<0.001		
Alkaline phosphatase (UI/L)		2.7 (2.69-2.7)	<0.001		
Hemoglobin (g/dl)		2.54 (2.53-2.56)	<0.001		
Creatinine (mg/dl)		2.52 (2.44-2.62)	<0.001		
Prothrombin time (%)		2.56 (2.53-2.58)	<0.001		
Platelets ($x10^9$)		2.72 (2.72-2.72)	0.1		
Leucocyte ($x10^9$)		2.71 (2.69-2.74)	0.8		
Neutrophil ($x10^9$)		2.72 (2.71-2.72)	<0.001		
Number of previous HCC recurrence		1.86 (1.78-1.96)	<0.001	**1.11 (1.07-1.16)**	**<0.001**
Ascites	Yes vs. No	0.85 (0.57-1.28)	0.4		
Encephalopathy	Yes vs. No	0.86 (0.25-3.03)	0.8		
Esophageal varices	Yes vs. No	0.97 (0.76-1.23)	0.8		
ECOG-PS	1 vs. 0	1.1 (0.75-1.61)	<0.001	1.14 (0.78-1.64)	**0.01**
	2 vs. 0	3.7 (1.32-10)		**4.35 (1.54-11.11)**	
	2 vs. 1	3.33 (1.14-10)		**3.7 (1.3-11.11)**	
Log(AFP, ng/ml)		1.14 (1.05-1.41)	<0.001	**1.11 (1.03-1.19)**	**0.01**
Tumor burden of last treatment before DAA initiation	<=3 nodules and <=3cm vs. Solitary nodule	1.38 (1.12-1.72)	<0.001	**1.47 (1.2-1.85)**	**<0.001**
	Multifocal vs. Solitary nodule	1.72 (1.23-2.38)		**1.75 (1.25-2.43)**	
	Multifocal vs. <=3 nodules and <=3cm	0.81 (0.59-1.11)		0.84 (0.63-1.16)	

HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; HIV: human immunodeficiency virus; HCC: Hepatocellular carcinoma; ALT: Alanine aminotransferase; DAA: Direct Acting Antiviral agents; NE: Not estimable; 95%CI: 95% confidence interval; RR: Relative risk; ECOG-PS: Eastern Cooperative Oncology Group Performance Status

Additional exploratory multivariate regression models in the whole population were done but no model improved the high heterogeneity rate.

Details of multivariate regression models, as well as the leave-one-out analysis, and the stratified analyses are described in Supplementary Table S3.

A regression model was also done in the 377 patients with solitary nodules before starting DAA. The recurrence rate per 100PY in these patients was 16.5 (95%CI: 9.1–33.47). The rate per 100PY in these patients without prior history of recurrence was 13.7 (95%CI:6.2–35.9); Table 3.

Table 3. Regression models on patients with solitary nodules.

	Number of Events	**Number of Patients**	**Recurrence rate per 100PY (95%CI)**	**I^2 (95%CI)**	**heterogeneity test (p-value)**
Solitary nodule	134	377	16.54 (9.12-33.47)	38.5 (0.5-62)	0.04
Solitary nodule | without history previous recurrence	69	223	13.69 (6.16-35.94)	0 (0-100)	0.6
Solitary nodule | without history previous recurrence | treated with resection	20	63	13.7 (3.95-55.09)	0 (0-18.2)	>0.9
Solitary nodule | history of 1 previous recurrence	36	88	20.92 (7.9-71.42)	0 (0-97)	0.5
Solitary nodule | history of 1 previous recurrence | treated with resection	7	25	19.9 (5.8-145.88)	0 (0-30.2)	>0.9

95%CI: 95% confidence interval

The subgroup analysis of HCC recurrence per 100PY according to the time between the last CR registration and DAA initiation (>=3 moths vs >3 months; <=6 months vs >6 months and <=12 months vs >12 months) in the whole cohort and according to the baseline tumour burden is reported in Supplementary Table S4. We did not observe an impact of the time elapsed between CR registration and DAA treatment initiation.

Death

The pooled death rate per 100PY was 5.7 (95%CI: 2.5-15.3). Heterogeneity among studies was high [I^2= 54.25%, (95%CI: 26.87%-71.38%); p-value<0.01](Figure 3).

Risk factors for HCC recurrence in DAA-exposed and DAA-unexposed patients

Supplementary Table S5 shows the baseline characteristics of 1,305 HCV patients (977 DAA-exposed and 328 DAA-unexposed) who achieved complete radiological response after HCC treatment. The STD were more than 10% (and 20%) in 12 (and 7) out of 18 variables analysed in both cohorts. After matching 1 control (DAA-unexposed patient) for 1 DAA-exposed patient, 167 pairs were obtained (N=334). The control cohort represents the 50.1% of patients of the ITA.LI.CA. cohort[17]. Supplementary Table S6 describes the baseline characteristics of the matched cohort, where the STD was <10% in all variables.

All matched patients had single HCC or HCC within Milan Criteria (BCLC 0/A) treated by resection or ablation.

The recurrence rate per 100PY (95%CI) was 23.21 (95%CI: 16.23-33.19) in DAA-unexposed patients and 14.75 (95%CI: 9.78-22.24) in DAA-exposed patients [RR=0.64 (95%CI: 0.37 - 1.1); p-value=0.1].

The recurrence rate per 100PY (95%CI) in DAA-exposed patients with single HCC was 14.3 (95%CI: 10.5–19.6) and 15.9 (95%CI: 9.78–25.9) in Milan-in patients.

Overall survival in DAA-exposed and DAA-unexposed patients

Among 334 matched patients, the median follow-up was 27 [IQR: 16.5–39] months in DAA-unexposed patients and 29 [IQR: 17–51.1] months in DAA-exposed patients. Forty-five patients died during the follow-up, 13 DAA-exposed and 32 DAA-unexposed patients. The overall survival rate per 100PY (95%CI) in DAA-exposed patients was 3.4 (95%CI: 1.7–6.8) and 6.6 (95%CI: 4.2–10.4) in DAA-unexposed patients [RR=0.51 (95%CI: 0.22 - 1.8); p-value=0.11]. A sensitivity survival analysis using the RMST technique showed a RMST difference (95%CI) of 2.8 (95CI: -1.7 to 7.3) months, p=0.22. RMST (95%CI) values for the DAA-exposed and the DAA-unexposed were, respectively, 58.1 (95%CI: 55.5 – 60.65) and 55.3 (95%CI: 51.5 -59.0) months.

DISCUSSION

Meta-analysis of individual data involving all studies reported represents the best assessment to be in place in the absence of a randomized prospective trial. Unfortunately, even this MIPD of 977 DAA-exposed patients does not allow to deliver a conclusive message about the increase or decrease of the rate of HCC recurrence associated with the treatment of HCV with DAAs. Our evaluation disclosed a very high heterogeneity of the data source and this prevents any robust message. Studies suffer from the heterogeneity of the patients recruited, the length of follow-up time and strategy and time interval to detect and register recurrence. Thus, despite collecting almost 1000 patients around the world, we were deceived not to be able to provide clarity into the

controversy. However, these data offered relevant information about the clinical profile that may be associated with a higher recurrence risk and that should be carefully assessed in clinical practice in order to decide whether to treat HCV or not. Also, such parameters should be considered when new cohort studies are designed or reported. As detailed in the results, some of the parameters linked to a higher risk (such as increased AFP, tumour burden and multifocality) are not unexpected. A reduced sample size limits the predictive value of prior treatment with chemoembolization, but it may also be a surrogate of the higher tumour burden. Indeed, it has to be retained that the assessment of complete response by imaging after TACE may incur in overestimation and may miss viable tumour cells that will retain the risk of dissemination and recurrence. However, the role of impaired ECOG-PS meaning cancer-related symptoms is not usually included at the time of selecting variables for the predictive models. Indeed, it could be considered also as a surrogate of tumour burden as early HCC tends to be subclinical, while a more advanced tumour stage may be associated with symptoms. Old surgical series already included symptoms as a predictor of poorer survival despite similar tumour stage[2,41,42].

One relevant aspect is the finding of a significant interaction between the absence of DAA-induced SVR and history of recurrence before DAAs. The rate of SVR is somewhat lower in patients with HCC through a not well known mechanism[43]. Thus, failure to achieve SVR when using antiviral agents with high effectiveness may reflect the existence of subclinical malignant clones[44] that are involved in the mechanism of treatment failure.

Finally, the identification of history of recurrence as a predictor of higher risk confirmed prior studies[2,36,45] and is not unexpected. Recurrence reflects malignant spread and even if successful treatment has been in place, the emergence of new sites is highly likely. To avoid such confounder, we assessed if the strength of the data and homogeneity would increase if we excluded patients with prior recurrence. Unfortunately, the expectation was not fulfilled, and the model did not improve. Similar results were obtained when running different statistical models and also when stratifying

patients according to time elapsed between HCC treatment and DAA initiation. This latter aspect is critical as it challenges the proposals to wait to start DAAs for some months after HCC treatment in order to avoid increasing the risk of early recurrence.

Unlike the present MIPD, all the five previously published meta-analyses on aggregate data failed to explain the high level of variability in the risk of HCC recurrence and were unable to identify differences in baseline patients' characteristics that were significantly associated with the probability of HCC recurrence. The results of these meta-analyses of aggregate data may be affected by ecological bias. When a significant heterogeneity of baseline risk of HCC recurrence exists, more accurate treatment comparisons could be achieved only by a MIPD. Finally, the unavailability of individual data hampers the analysis of HCC recurrence as a time-dependent variable. It is recognized that the results of meta-analyses of time-to-event outcomes may be affected by censoring and by the duration of follow-up of individual studies. These limitations are particularly important when the follow-up duration across studies is heterogeneous.

The results of this MIPD are subjected to several limitations. First, we underline the potential limitation of the generalizability of these results to new populations and settings, particularly in patients with more advanced liver disease or more advanced HCC stage. However, the observational studies included in this MIPD were performed by individual data of patients treated in the real-world setting. Therefore, we are confident that clinicians could replicate these results in conventional clinical practice. Second, our primary endpoint was a radiology-based outcome and none of the studies blindly assessed HCC recurrence. Third, the accuracy of our MIPD could have been limited by the high level of clinical and statistical heterogeneity. However, we tried to control for these differences by using a random-effects model including the centre as a covariate. Fourth, lack of data on other potentially relevant risk factors for HCC recurrence, such as microscopic vascular invasion, histology grade, cancer and patient genomic portrait, may have affected our results.

The deceiving results of the MIPD prompted us to develop a collateral assessment through the use of the ITA.LI.CA. database[17]. We were able to compare the rate of HCC recurrence in our multicentre cohort of 977 DAA-exposed patients after successful treatment of HCC with a cohort of 328 DAA-unexposed patients that were matched through a propensity score (167 pairs). Such analysis exposed that the recurrence rate after DAA treatment in patients with early HCC stages was still high and not different from the rate in patients without DAA treatment. The risk is heterogeneous according to the baseline patients' profile, but it remains high. Nevertheless, the overall survival rate in such 167 pairs of patients did not show significant differences in mean survival (58.1 vs 55.3 in DAA-exposed and unexposed patients, respectively), which is a reflection of the complexity of the competing risk analysis in the setting of liver cancer. Unfortunately, the selected studies included in the study did not have data about cirrhosis complications to define the proportion of patients who improves/worse liver function and time-frame between DAA and liver function improvement/deterioration in each group and if it was related to HCV eradication in decompensated patients.

It is important to underline that the large multicentre studies by Singal et al[8,9] included only patients from United States (US), while the present study evaluated patients enrolled around the world (56.1% in Europe, 29.9% in Asia, 11% in Africa and 3% in North America). Therefore, these data may be more generalizable to cohorts across the globe given differences in HCC practice patterns. There may be differences in timing of DAA therapy after curative treatment receipt, availability of liver transplantation as destination therapy, and differences in surveillance utilization. Further, ~~and in that studies~~ nearly half of patients in ~~that~~ the U.S. ~~study~~ cohort had complete response from ~~TACE, TARE, SBRT~~locoregional therapy, raising increased concern about misclassification of complete response, whereas most patients in our analysis had complete response from traditional curative therapies, such as local ablation or resection. Thus, our analysis

could be useful to well describe the impact of DAAs at international level in patients with early HCC stage.

In summary, the results of our MIPD have shown that the comparison between different cohorts of distinct groups will not allow a valid assessment of outcomes as the heterogeneity exceeds any acceptable cut-off. This currently prevents the end of the controversy about the impact of DAA therapy on the risk of cancer progression in patients successfully treated for this neoplasm. However, at the same time we have shown that the risk of recurrence is 20/100PY in the whole population and 13.7/100PY in the subgroup of patients with the lowest clinical risk. Therefore, the risk of DAA-treated patients is not significantly different from that of untreated HCV patients, at least during the first two years. Longer follow-up studies should define if the recurrence risk is modified or not beyond this time limit and also confirm the finding observed in the survival analysis. Thus, active surveillance is fully justified in this population for whom no effective adjuvant treatment is available. Trials are ongoing in this realm and the current identified predictive factors for recurrence we have identified in the so-called real world provide relevant information to characterize patients included in such investigations.

FIGURE LEGEND

Figure 1. Flow chart of included patients in meta-analysis.

Figure 2. Forest plot of pooled effect for HCC recurrence per 100PY. Lines represent the 95%CI for HCC recurrence rate per 100PY of each study. Size of squares represent the weight of each study. Diamond represents the pooled effect.

Figure 3. Forest plot of pooled effect for Exitus per 100PY. Lines represent the 95%CI for HCC Exitus rate per 100PY of each study. Size of squares represent the weight of each study. Diamond represents the pooled effect.

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