

Original research

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 HCV following successful treatment of hepatocellular carcinoma (HCC) remains controversial. This meta-analysis of individual patient data assessed HCC recurrence risk following DAA administration.

Design We pooled the data of 977 consecutive patients from 21 studies of HCV-related cirrhosis and HCC, who achieved complete radiological response after surgical/locoregional treatments and received DAAs (DAA group). Recurrence or death risk was expressed as HCC recurrence or death per 100 person-years (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 using random-effects Poisson.

Results Recurrence rate and death risk per 100PY in DAA-treated patients were 20 (95% CI 13.9 to 29.8, $I^2=74.6%$) and 5.7 (2.5 to 15.3, $I^2=54.3%$), respectively. Predictive factors for recurrence were alpha-fetoprotein logarithm (relative risk (RR)=1.11, 95% CI 1.03 to 1.19; $p=0.01$, per 1 log of ng/mL), HCC recurrence history pre-DAA initiation (RR=1.11, 95% CI 1.07 to 1.16; $p<0.001$), performance status (2 vs 0, RR=4.35, 95% CI 1.54 to 11.11; 2 vs 1, RR=3.7, 95% CI 1.3 to 11.11; $p=0.01$) and tumour burden pre-HCC treatment (multifocal vs solitary nodule, RR=1.75, 95% CI 1.25 to 2.43; $p<0.001$). No significant difference was observed in RR between the DAA-exposed and DAA-unexposed groups in propensity score-matched patients (RR=0.64, 95% CI 0.37 to 1.1; $p=0.1$).

Significance of this study

What is already known on this subject?

- Eradication of HCV with direct antiviral agents (DAA) does not eliminate the risk of developing HCC recurrence after effective therapy.
- Multicentre retrospective cohort studies from North America have suggested no increase in HCC recurrence and improved survival after DAA treatment.
- However, these studies solely comprised patients from the USA; there remains a need for international data given differences in patient characteristics and HCC practice patterns.

Conclusion Effects of DAA exposure on HCC recurrence risk remain inconclusive. Active clinical and radiological follow-up of patients with HCC after HCV eradication with DAA is justified.

INTRODUCTION

Seminal reports^{1,2} on 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. The majority of centres worldwide reported on this topical issue, and various systematic reviews

Significance of this study

What are the new findings?

- ▶ The study of a worldwide cohort (56.1% from Europe, 29.9% from Asia, 11% from Africa and 3% from North America) disclosed an HCC recurrence risk of 20/100 person-years (100PY) in the whole population, while it is of $\approx 27\text{--}30/100\text{PY}$ in the subgroup of patients with the highest clinical risk (baseline multifocal tumour burden and presence of previous recurrence, respectively).
- ▶ There is a non-negligible risk even for patients with the lowest level (13.7 in 100PY).
- ▶ The HCC recurrence rate per 100PY (95% CI) was 23.21 (16.23 to 33.19) in DAA-unexposed patients and 14.75 (9.78 to 22.24) in DAA-exposed patients (RR=0.64, 95% CI 0.37 to 1.1; $p=0.1$).
- ▶ The overall survival rate per 100PY (95% CI) in DAA-exposed patients was 3.4 (1.7 to 6.8) and 6.6 (4.2 to 10.4) in DAA-unexposed patients (RR=0.51, 95% CI 0.22 to 1.8; $p=0.11$).
- ▶ Sensitivity survival analysis revealed a restricted mean survival time difference (95% CI) of 2.8 (−1.7 to 7.3) months, $p=0.22$.

How might it impact on clinical practice in the foreseeable future?

- ▶ Active clinical and radiological follow-up of HCC recurrence is justified in patients with HCC after eradication of HCV with DAA given that HCC recurrence remains clinically significant.
- ▶ DAA treatment does not necessarily translate to an overall improvement in survival, as it remains unclear if deaths were due to HCC recurrence/progression, hepatic decompensation or a combination of both.
- ▶ Expected benefit of DAA treatment is dependent on patients' clinical profile and prior history of HCC recurrence.

and cumulative meta-analyses have been published.^{3–7} Although suggestions to reduce recurrence risk have been proposed, heterogeneity across studies has precluded resolution of the controversy regarding this issue. Indeed, despite application of statistical tools, heterogeneity across studies remains unacceptably high, ranging from 80.5%³ to 96.7%.⁷ Thus, conclusions regarding the reduced recurrence risk following HCV therapy have not been supported by scientific evidence. In this regard, cohort studies included in meta-analyses are underscored by patient heterogeneity at baseline, different follow-up times and different follow-up procedures for detecting recurrence. Multi-centre retrospective cohort studies conducted by Singal *et al*^{8,9} suggested that recurrence was not increased and survival was improved after DAA treatment; however, these studies only included patients from the USA. As such, there remains a critical need for international data given the differences in patient characteristics and HCC practice patterns.

Given the remaining controversies in the literature, guidelines on HCC^{10,11} and antiviral therapy^{12–14} are underscored by limitations of currently available data. To address these limitations, randomised controlled trials (RCTs) with allocation of treatment or no treatment groups and homogeneous follow-up strategies are required. Nevertheless, RCTs directly comparing groups treated or untreated with DAAs are considered unfeasible, unethical and/or non-timely. In this regard, long-term survival of these patients is dictated by HCC recurrence or tumour progression and development of complications due to progression of liver disease. The

latter is a major driver of death in HCV-viraemic patients with successfully treated early stage HCC.² DAA treatment has been demonstrated to improve overall survival by reducing the risk of hepatic decompensation,^{8,15} thereby precluding RCTs to assess the risk of HCC recurrence.¹⁵

Due to the low feasibility of performing RCTs to address this issue, we designed an international, multicentre study using individual data. This approach overcomes the limitations associated with the use of aggregate data as in prior meta-analyses, thereby 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 assess the recurrence rate of HCC in DAA-treated patients after complete response and identify risk factors for HCC recurrence after DAA treatment. We incorporated a propensity score (PS) analysis to assess the impact of DAA therapy relative to that in the DAA-unexposed control group derived from the Italian curated prospective database ITA.LI.CA (Italian Liver Cancer Group).

MATERIALS AND METHODS

Meta-analysis using individual patient data of DAA-exposed patients

The current MIPD pooled data on individuals from different studies that evaluated the risk of HCC recurrence after DAA exposure in HCV-infected patients with cirrhosis and a previously successful treatment for HCC.¹⁶ This study was registered in the 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: (1) data in English language with full-text accessibility/presentation or poster/oral presentation; (2) target population of the original paper was patients with HCC who received DAAs after HCC treatment; (3) the study assessed the risk of developing HCC recurrence after DAA treatment; (4) HCC recurrence of patients was reported; (5) dates of prior HCC treatment were reported. A systematic search for records up to 3 April 2018 in PubMed Central/MEDLINE was performed with different combinations of keywords. The search details are reported in online supplemental material.

A Data Transfer Protocol (DTP) was written according to the European regulations (General Data Protection Regulation 2016/679 of the European Parliament and Council of 27 April 2016) and was 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 online supplemental material 2 and 3.

The primary outcomes were: (1) HCC recurrence rate, defined as the number of patients per 100 patient-years (100PY) who previously obtained HCC complete response (CR) and developed HCC after DAA treatment; (2) death rate per 100PY. Two expert reviewers performed an independent assessment of selected studies in the systematic search (GC and MR). Any discrepancies were resolved by discussion with a third expert reviewer (JB).

DAA-unexposed patient cohort

Data from 328 DAA-unexposed control patients were obtained from the retrospective study of the prospective ITA.LI.CA database¹⁷ enrolled from 2007 to 2015. Control patients were HCV-related compensated patients with cirrhosis and 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 are expressed as median and IQR (25th–75th percentiles). Categorical variables are presented as absolute frequencies and percentages (%). For MIPD analysis of the DAA-exposed patient cohort, pooled recurrences of HCC or death are expressed as number of events per 100PY. Rates and 95% CIs were estimated with Poisson models using a random effects one-stage step approach (ie, including individual patient data directly in the model) and including the logarithm of radiological follow-up time as offset. Heterogeneity was evaluated using the I^2 and Q heterogeneity test. I^2 values of 25%, 50%, and 75% were considered low, moderate and high levels of heterogeneity, respectively.¹⁸ Q heterogeneity test was considered significant when p values were <0.1 . Sensitivity analyses were conducted to explore 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. Variables with p value <0.1 in the univariate analysis were included in multivariate analysis.

Propensity score matching (PSM) was performed for DAA-exposed and DAA-unexposed patients. Matching 1:1 was conducted using the greedy nearest neighbour approach, which produced the smallest within-pair difference among all available pairs within a treated unit, with a calliper (ie, imposed restriction to matched-pairs distance) of 0.06 for the predicted probability. The balance between cohorts before and after PSM was assessed using standardised mean differences (STD). $STD >10\%$ was considered unbalanced.^{19–21} Details of the PS model are provided in the online supplemental material.

Comparison of recurrence risk between matched patients was performed using relative risks and their 95% CIs estimated using the same Poisson model including 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 was not met.²² The restricted follow-up time used for the RMST model was established at the time of the last observed death. The level of significance was set at 5% (two-sided). All statistical analyses were performed using SAS V.9.4 software (SAS Institute, Cary, North Carolina, USA). This manuscript did not have patient and public involvement.

RESULTS

Baseline characteristics

The initial search identified 87 eligible studies. Following the initial assessment, 32 studies that met the inclusion criteria were invited to participate. After first contact, 23 corresponding authors of the relevant studies provided the data. In total, 21 studies were included in the final analysis.^{1 2 9 23–40} Two full studies involving 67 patients were excluded because they did not fulfil the prespecified data requirements. Thus, the analysis comprised 977 DAA-treated patients from 12 retrospective and 9 prospective studies, including 13 full-length papers, 4 abstracts and 4 Letters to the Editor (figure 1). Characteristics of the included studies are presented in table 1. Individual characteristics of the included patients are presented in online supplemental table S1. Most of the DAA-treated patients were male (63%), with a median age of 67.9 (IQR 60–76) years and Child-Pugh class A (88%). More than half of the cohort (52.8%) met the

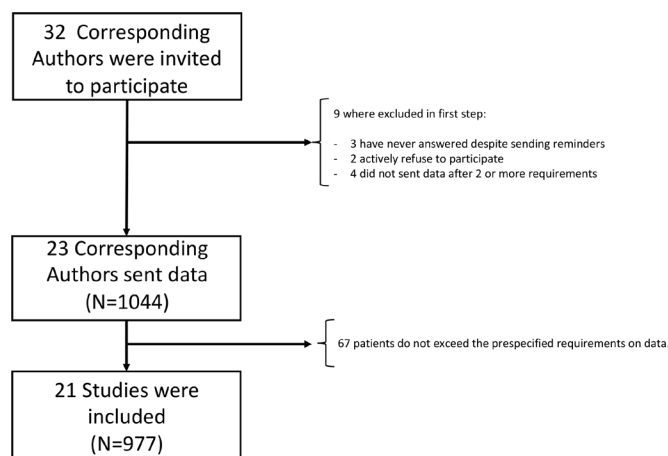


Figure 1 Flow chart of patients included in meta-analysis.

Milan criteria, 38.6% had solitary HCC at tumour diagnosis, 7.1% had multifocal HCC and $<0.5\%$ had extrahepatic spread or vascular invasion. Eastern Cooperative Oncology Group performance status (ECOG-PS) was 0 in 93.3% of the patients. The most frequent treatment was ablation (47.3%), followed by resection (31%) and chemoembolisation (15.3%). Sustained virological response (SVR) rate in the studies ranged from 60% to 98.2%.

Outcomes

The median follow-up time for the whole cohort was 15 (IQR 9–22.6) months. During this period, 41.8% patients developed HCC recurrence, and 12.9% died. The characteristics of patients with HCC recurrence are presented in online supplemental table S2. The rate of decompensation was not analysed due to the unavailability of data from up to 296 patients ($>30\%$). Indeed, the triggers and dates of decompensation were not reported for 31.9% of the patients.

HCC recurrence

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

Additional exploratory multivariate regression models for the whole population were performed; however, none of the models improved the high heterogeneity rate. Details of multivariate regression models, leave-one-out analysis and stratified analyses are provided in online supplemental table S3. A regression model was conducted for the 377 patients with solitary nodules before starting DAA. The recurrence rate per 100PY in these patients (ie, patients with solitary nodules) was 16.5 (95% CI 9.1 to 33.47). The recurrence rate per 100PY in patients with solitary nodules and without prior history of recurrence was 13.7 (95% CI 6.2 to 35.9) (table 3).

Table 1 Characteristics of included patients

Study	Males (%)	Child-Pugh (A/B/C, %)	ECOG-PS (0/1, %)	Extrahepatic spread/vascular invasion (yes, %)	Oesophageal varices/ascites/AHT/ HBV/DM/alcohol consumption (yes, %)	Imaging used for CR assessment (MR/CT/others, %)	Radiological follow-up (yes, %)	Waiting list for LT (yes, %)	SVR (yes, %)
Conti <i>et al</i> ³⁸	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 <i>et al</i> (L) ²⁷	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 ³⁵	80	83/17/0	89/11	0/0	20/20/20/0/10/90	60/30/10	100	10	80
Reig <i>et al</i> 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 ²⁹	72.4	92/7/1	84/13	0/0	18.4/10.3/48.3/4.6/24.1/31	19/32/49	100	0	92
Zavaglia <i>et al</i> (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 <i>et al</i> ^{23*}	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 <i>et al</i> ^{32†}	100	80/20/0	100/0	0/0	0/0/40/0/60/0	40/60/0	100	0	60
Cavalletto <i>et al</i> ^{37‡}	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 <i>et al</i> (L) ³¹	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 <i>et al</i> ²⁸	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 <i>et al</i> (L) ²⁴	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 <i>et al</i> ²⁶	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 <i>et al</i> ⁴⁰	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 <i>et al</i> 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 <i>et al</i> ^{25‡}	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 <i>et al</i> ²⁰	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
Abdelaziz AO. <i>et al</i> ³⁴	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 <i>et al</i> ²⁶	87.5	88/6/6	75/25	0/0	0/0/0/0/0/0	38/31/31	0	0	93.8
Degasperi <i>et al</i> ³⁹	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
Singal <i>et al</i> ⁶	73.3	87/13/0	97/3	0/0	0/6.7/0/0/0/0	53/47/0	0	0	86.7

*Study presented on ILCA2017.

†Study presented on EASL2017.

‡Study presented on EASL2018.

AHT, arterial hypertension; CR, complete response; DM, diabetes mellitus; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; L, Letter to the Editor; LT, liver transplant; SVR, sustained virological response.

Subgroup analyses of HCC recurrence per 100PY according to the time between the last CR registration and DAA initiation (≤ 3 months vs > 3 months, ≤ 6 months vs > 6 months and ≤ 12 months vs > 12 months) in the whole cohort and according to baseline tumour burden are presented in online supplemental table S4. No significant impact of time elapsed between CR registration and DAA treatment initiation was noted.

Death rate

The pooled death rate per 100PY was 5.7 (95% CI 2.5 to 15.3). Heterogeneity among studies was high ($I^2=54.25\%$, 95% CI 26.87% to 71.38%; $p<0.01$) (figure 3).

HCC recurrence in DAA-exposed and DAA-unexposed patients

The baseline characteristics of 1305 HCV-patients (977 DAA-exposed and 328 DAA-unexposed) who achieved complete radiological response after HCC treatment are presented in online supplemental table S5. STD exceeded 10% and 20% in 12 and 7 of 18 variables analysed in both cohorts, respectively. After 1:1 matching of control (DAA-unexposed) patients to DAA-exposed patients, 167 pairs were obtained ($n=334$). The control cohort comprised 50.1% of patients in the ITA.LI.CA. cohort.¹⁷ Online supplemental table S6 presents the baseline characteristics of the matched cohort, in which STD was $<10\%$ for all variables.

All matched patients had single HCC or HCC within Milan Criteria (BCLC 0/A) treated with resection or ablation. Recurrence rate per 100 was 23.21 (95% CI 16.23- 33.19) in DAA-unexposed patients and 14.75 (95% CI 9.78 to 22.24) in DAA-exposed patients (RR=0.64, 95% CI 0.37 to 1.1; $p=0.1$). The recurrence rate per 100PY in DAA-exposed patients with single HCC was 14.3 (95% CI 10.5 to 19.6) and 15.9 (95% CI 9.78 to 25.9) in Milan Criteria in-patients.

Overall survival in DAA-exposed and DAA-unexposed patients

Among 334 matched patients, the median follow-up time was 27 (IQR 16.5–39) months in DAA-unexposed patients and 29 (IQR 17–51.1) months in DAA-exposed patients. Among these patients, 45 died during follow-up (13 DAA-exposed and 32 DAA-unexposed patients). The overall survival rate per 100PY was 3.4 (95% CI 1.7 to 6.8) and 6.6 (95% CI 4.2 to 10.4) in DAA-exposed and DAA-unexposed patients, respectively (RR=0.51, 95% CI 0.22 to 1.8; $p=0.11$). Sensitivity survival analysis using the RMST technique revealed an RMST difference of 2.8 (95 CI –1.7 to 7.3) months ($p=0.22$). RMST values for DAA-exposed and DAA-unexposed groups were 58.1 (95% CI 55.5 to 60.65) and 55.3 (95% CI 51.5 to 59.0) months, respectively.

DISCUSSION

This MIPD of 977 DAA-exposed patients examined the rate of HCC recurrence associated with the treatment of HCV using DAAs. Our meta-analysis revealed high heterogeneity of data sources, which precluded definitive conclusions from being drawn. The majority of studies were underscored by heterogeneity in the patient sample, length of follow-up time and strategy and time interval of detecting and registering recurrence. Thus, despite collecting data from almost 1000 patients from diverse countries, we were unable to resolve the controversy surrounding the benefit of DAA treatment against HCV following successful treatment of HCC. Nevertheless, these data provided relevant information regarding clinical profiles that may be associated with a higher recurrence risk and that should be carefully assessed in clinical practice when deciding on treatment for HCV. These parameters should be considered when new cohort studies are designed or reported. As detailed in the results, several parameters linked to a higher risk (such

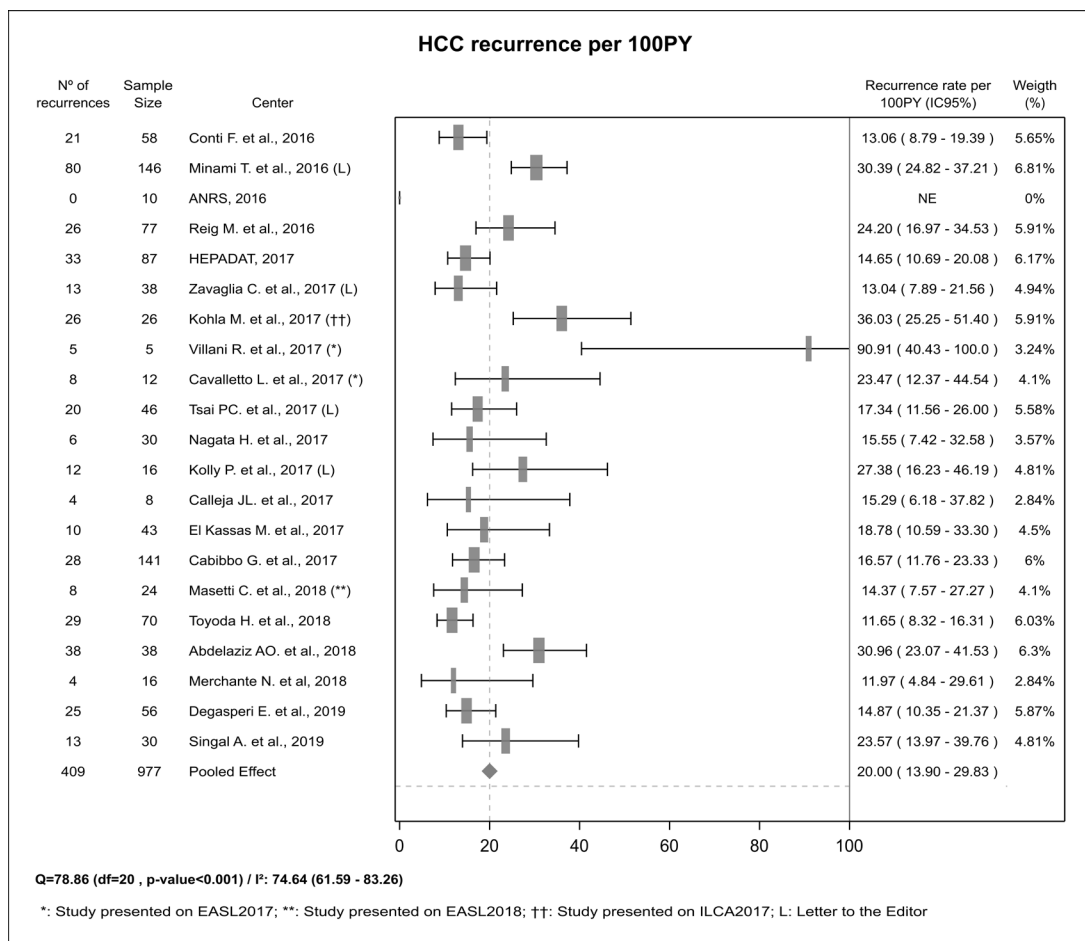


Figure 2 Forest plot of pooled effect for hepatocellular carcinoma (HCC) recurrence rate per 100 person-years (100PY). Lines represent the 95% CI for HCC recurrence rate per 100PY for each study. Size of squares represents the weight of each study. Diamond represents the pooled effect.

as increased AFP, tumour burden and multifocality) were not unexpected.⁴¹ The small sample size limits the predictive value of prior treatment with chemoembolisation, but this may serve as a surrogate of higher tumour burden. Indeed, assessment of complete response by imaging after TACE may lead to overestimation and overlook viable tumour cells that retain the risk of dissemination and recurrence. However, the role of impaired ECOG-PS indicative of cancer-related symptoms was not typically included when selecting variables for the predictive models. This measure could be considered a surrogate of tumour burden given that early HCC tends to be subclinical, whereas a more advanced tumour stage may be associated with symptoms. Prior surgical series have indicated that symptoms act as a predictor of poorer survival despite similar tumour stage.^{2,42,43}

The rate of SVR was lower in patients with HCC, although the underlying mechanism remains unclear.⁴⁴ Thus, failure to achieve SVR during treatment with highly effective antiviral agents may reflect the existence of subclinical malignant clones⁴⁵ that underpin treatment failure. Furthermore, the identification of recurrence history as a predictor of higher risk confirmed prior studies.^{2,37,46} Recurrence reflects malignant spread, and the emergence of new sites is highly likely despite successful treatment. To avoid these confounders, we assessed whether the strength of the data and homogeneity would increase if patients with prior recurrence were excluded. Nevertheless, this approach did not improve the model. Similar results were obtained with different statistical models and also when stratifying patients according to time elapsed between HCC treatment

and DAA initiation. The latter aspect is critical, as it challenges the proposal to delay commencement of DAA treatment for several months after HCC treatment in order to avoid increasing the risk of early recurrence.

In contrast to the present MIPD, all five previously published meta-analyses on aggregate data failed to explain the high level of variability in the risk of HCC recurrence. Indeed, previous meta-analyses were unable to identify differences in patients' baseline 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. Accurate treatment comparisons can only be achieved using an MIPD if there is significant heterogeneity in baseline risk of HCC recurrence. Additionally, the unavailability of individual data hampers the analysis of HCC recurrence as a time-dependent variable. The results of meta-analyses of time-to-event outcomes may be affected by censoring and duration of follow-up of individual studies. These limitations are particularly consequential when the follow-up duration across studies is heterogeneous.

This MIPD has several limitations. First, the generalisability of our results to other populations and settings, particularly patients with more advanced liver disease or HCC stage, may be limited. Nevertheless, the observational studies included in this MIPD were based on individual data of patients treated in real-world settings. Therefore, we are confident that the results may be replicated by clinicians conventional clinical practice. Second, our primary endpoint was a radiology-based outcome, and none of the studies blindly assessed HCC recurrence. Third, the

Table 2 Prognostic baseline factors for HCC recurrence

Parameter	Contrast	Univariate		Multivariate	
		RR (95% CI)	P value	RR (95% CI)	P value
Age (increase of 10 years)*		0.89 (0.81 to 0.97)	0.01		
Gender*	Male vs female	1.22 (0.99 to 1.52)	0.06		
BMI (kg/m ²)*		1 (0.99 to 1.01)	0.7		
MELD score*		1.26 (0.88 to 1.8)	0.2		
Presence of HBV*	Yes vs no	1.12 (0.49 to 2.56)	0.7		
Presence of HIV*	Yes vs no	0.52 (0.08 to 3.26)	0.3		
ALBI score*					
	ALBI 2 vs ALBI 1	0.7 (0.53 to 0.91)	0.01		
	ALBI 3 vs ALBI 1	0.45 (0.11 to 1.86)	0.3		
	ALBI 3 vs ALBI 2	0.65 (0.16 to 2.73)	0.5		
Cirrhosis*	Yes vs no	0.47 (0 to 111.8)	0.3		
Child-Pugh*			<0.001		
	A vs B	0.77 (0.56 to 1.05)			
	A vs C	1.55 (0.21 to 11.28)			
	A vs non-cirrhotic	2.08 (0.85 to 5.08)			
	B vs C	2.02 (0.27 to 14.99)			
	B vs non-cirrhotic	2.71 (1.06 to 6.9)			
	C vs non-cirrhotic	1.34 (0.15 to 11.74)			
Total bilirubin (increase of 10 mg/dL)*		1.12 (0.95 to 1.33)	0.2		
ALT (increase of 10 UI/L)*		0.99 (0.98 to 1.01)	0.6		
AST (increase of 1 log UI/L)*		1.01 (0.85 to 1.21)	0.9		
Alkaline phosphatase (increase of 10 UI/L)†		1 (1 to 1.01)	0.14		
Haemoglobin (increase of 10 g/dL)*		1 (0.97 to 1.04)	0.9		
Creatinine (increase of 10 mg/dL)*		1.03 (0.95 to 1.12)	0.4		
Prothrombin time (increase of 10%)*		0.98 (0.95 to 1.01)	0.13		
Platelets (increase of 100×10 ⁹)*		0.99 (0.96 to 1.02)	0.4		
Leucocyte (increase of 100×10 ⁹)‡		0.99 (0.99 to 1)	0.07		
Neutrophil (increase of 100×10 ⁹)‡		0.99 (0.97 to 1)	0.14		
Number of previous HCC recurrence*		1.1 (1.06 to 1.14)	<0.001	1.11 (1.07 to 1.16)	<0.001
Ascites*	Yes vs no	0.85 (0.57 to 1.28)	0.4		
Encephalopathy§	Yes vs no	0.86 (0.25 to 3.03)	0.8		
Oesophageal varices‡	Yes vs no	0.97 (0.76 to 1.23)	0.8		
ECOG-PS*	1 vs 0	1.1 (0.75 to 1.61)	<0.001	1.14 (0.78 to 1.64)	0.01
	2 vs 0	3.7 (1.32 to 10)		4.35 (1.54 to 11.11)	
	2 vs 1	3.33 (1.14 to 10)		3.7 (1.3 to 11.11)	
ECOG-PS (increase of 1 class, ref. ECOG-PS=0)*		1.27 (0.94 to 1.71)	0.12		
AFP (increase of 1 log ng/mL)*		1.12 (1.04 to 1.2)	0.003	1.11 (1.03 to 1.19)	0.01
Tumour burden at last HCC treatment before DAA initiation*	≤3 nodules and ≤3 cm vs solitary nodule	1.38 (1.12 to 1.72)	<0.001	1.47 (1.2 to 1.85)	<0.001
	Multifocal vs solitary nodule	1.72 (1.23 to 2.38)		1.75 (1.25 to 2.43)	
	Multifocal vs ≤3 nodules and ≤3 cm	0.81 (0.59 to 1.11)		0.84 (0.63 to 1.16)	
Tumour burden at last HCC treatment before DAA initiation (increase of 1 class, ref. 'solitary nodule')*		1.33 (1.15 to 1.54)	<0.001		

The rate of missingness was <10%*, 10%–20%‡, >20–30§ or >30%†, as specified.

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DAA, direct-acting antiviral agents; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NE, not estimable; RR, relative risk.

accuracy of our MIPD may have been limited by the high level of clinical and statistical heterogeneity. However, we attempted 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 portraits may have affected our results.

The limited results of the MIPD prompted us to develop an additional assessment using the ITA.LI.CA. database.¹⁷ We compared the rate of HCC recurrence between our multicentre

cohort of 977 DAA-exposed patients after successful treatment of HCC and a cohort of 328 DAA-unexposed patients that were matched through a PS, yielding 167 pairs. Our analysis revealed that the recurrence rate after DAA treatment in patients with early HCC stages was high and did not significantly differ to that of DAA-unexposed patients. Although the risk was heterogeneous based on patients' baseline profiles, it remained high. No significant between-group difference in mean overall survival rate was noted among the 167 pairs of patients (58.1 vs 55.3 in DAA-exposed and unexposed patients, respectively),

Table 3 Regression models for 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 to 33.47)	38.5 (0.5 to 62)	0.04
Solitary nodule without history of previous recurrence	69	223	13.69 (6.16 to 35.94)	0 (0 to 100)	0.6
Solitary nodule without history of previous recurrence and treated with resection	20	63	13.7 (3.95 to 55.09)	0 (0 to 18.2)	>0.9
Solitary nodule with history of one previous recurrence	36	88	20.92 (7.9 to 71.42)	0 (0 to 97)	0.5
Solitary nodule with history of one previous recurrence and treated with resection	7	25	19.9 (5.8 to 145.88)	0 (0 to 30.2)	>0.9

100PY, 100 person-years.

which reflects the complexity of the competing risk analysis in the setting of liver cancer.⁴⁷ The studies included in the meta-analysis lacked data regarding cirrhosis complications. Therefore, we were unable to define the proportion of patients whose liver function improved or worsened, timeframe between DAA and liver function improvement/deterioration in each group, and the relationship to HCV eradication in decompensated patients.

Previous large multicentre studies by Singal *et al*^{8,9} only included patients from the USA. In contrast, the present study evaluated patients from multiple countries (56.1% from Europe, 29.9% from Asia, 11% from Africa and 3% from North America). Therefore, our data may be more generalisable given the differences in factors such as HCC practice patterns worldwide, timing of DAA therapy after receiving curative treatment,

availability of liver transplantation as destination therapy and surveillance utilisation. Furthermore, nearly half of the patients in the American cohorts^{8,9} had complete response from locoregional therapy, which raises concern regarding misclassification of complete response. In contrast, most patients in our analysis had complete response from traditional curative therapies, such as local ablation or resection. Thus, our analysis provides insight into the impact of DAA treatment on patients with early HCC stage in diverse settings.

In conclusion, this MIPD demonstrated that a comparison of different cohorts from distinct patient groups did not entail a valid assessment of outcomes, as the heterogeneity exceeded an acceptable cut-off. Nevertheless, we demonstrated that the risk of recurrence was 20/100PY in the whole population and

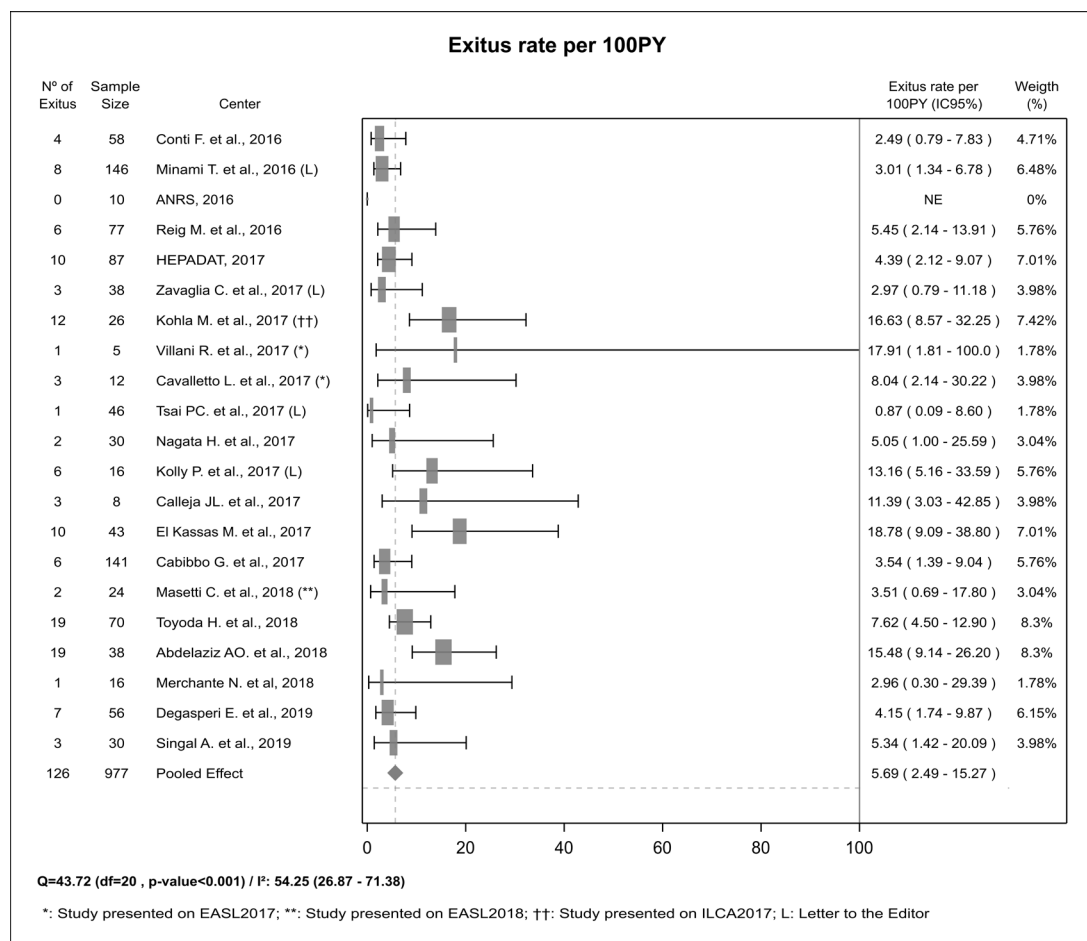


Figure 3 Forest plot of pooled effect for death rate per 100 person-years (100PY). Lines represent the 95% CI for hepatocellular carcinoma death rate per 100PY for each study. Size of squares represents the weight of each study. Diamond represents the pooled effect.

13.7/100PY in the subgroup of patients with the lowest clinical risk. Therefore, the HCC recurrence risk for DAA-treated patients is not significantly different to that of patients with untreated HCV, at least during the first 2 years. Studies with longer follow-up time should define if the recurrence risk is modified beyond this time frame and confirm the findings observed in the survival analysis. Our findings suggest that active clinical and radiological follow-up is fully justified in this population for whom no effective adjuvant treatment is available. The predictive factors for recurrence identified herein provide relevant information for characterising patients in real-world settings.

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