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

Victor Sapena,[1] Marco Enea,[2] Ferran Torres,[3,4] Ciro Celsa,[2,5] Jose Rios,[3,4] Giacomo Emanuele Maria Rizzo,[2] Pierre Nahon,[6] Zoe Mariño,[7] Ryosuke Tateishi,[8] Tatsuya Minami,[8] Angelo Sangiovanni,[9,10] Xavier Forns,[7] Hidenori Toyoda,[11] Stefano Brillanti,[12] Fabio Conti,[12] Elisabetta Degasperi,[9,10] Ming-Lung Yu,[13,14] Pei-Chien Tsai,[13] Kevin Jean,[15,16] Mohamed El Kassas,[17] Hend Ibrahim Shousha,[18] Ashraf Omar,[18] Claudio Zavaglia,[19] Hiroko Nagata,[20] Mina Nakagawa,[21,22] Yasuhiro Asahina,[23] Amit G Singal,[24] Caitlin Murphy,[24] Mohamed Kohla,[25] Chiara Masetti,[26] Jean-François Dufour,[27,28] Nicolas Merchante,[29] Luisa Cavalletto,[30] liliana LC chemello,[30] Stanislas POL,[31] Javier Crespo,[32,33] Jose Luis Calleja,[34,35] Rosanna Villani,[36] Gaetano Serviddio,[36] Alberto Zanetto,[37] Sarah Shalaby,[37] Francesco Paolo Russo,[37] Rob Bielen,[38,39] Franco Trevisani,[40] Calogero Cammà,[2] Jordi Bruix,[1] Giuseppe Cabibbo,[2] Maria Reig[1]

Correspondence to:

Dr Maria Reig, Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit, Hospital Clínic de Barcelona, IDIBAPS, Universidad de Barcelona, CIBEREHD, Hospital Clinic de Barcelona, Barcelona, Catalunya, Spain; MREIG1@clinic.cat and

Dr Giuseppe Cabibbo, Section of Gastroenterology and Hepatology, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, PROMISE, University of Palermo, Palermo, Italy; giuseppe.cabibbo78@gmail.com

---

VS and ME contributed equally.

FT and CC contributed equally.

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, I2=74.6%) and 5.7 (2.5 to 15.3, I2=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).

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 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. Multicentre 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. database[17] 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 I2 and Q heterogeneity test. I2 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 prob- ability. 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 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 (I2=74.6%, 95% CI 61.6% to 83.3%; p<0.001) (figure 2). Predictive factors of recurrence in multi- variate 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).

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 (I2=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 radio- logical 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 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 clones[45] 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 prob- ability 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 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), 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. There- fore, 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 world- wide, 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 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.

AUTHOR AFFILIATIONS

1 Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit, Hospital Clínic de Barcelona, IDIBAPS, Universidad de Barcelona, CIBEREHD, Hospital Clinic de Barcelona, Barcelona, Spain

2 Department of Health Promotion, Mother & Child Care, Internal Medicine & Medical Specialties, PROMISE, Gastroenterology & Hepatology Unit, University of Palermo, Palermo, Sicilia, Italy

3 Biostatistics and Data Management Core Facility, IDIBAPS, Hospital Clinic Barcelona, Barcelona, Spain

4 Biostatistics Unit, Faculty of Medicine, Universitat Autònoma de Barcelona, Bellaterra, Barcelona, Spain

5 Department of Surgical, Oncological and Oral Sciences (Di.Chir.On.S.), University of Palermo, Palermo, Sicilia, Italy

6 AP-HP, Hôpital Jean Verdier, Service d'Hépatologie, Bondy; Université Paris 13, Sorbonne Paris Cité, "Equipe labellisée Ligue Contre le Cancer", F-93206 Saint- Denis; Inserm, UMR-1162, "Génomique fonctionnelle des tumeurs solides", F-75000, Bondy, France

7 Liver Unit, Hospital Clinic de Barcelona, IDIBAPS, University of Barcelona, CIBEREHD, Barcelona, Spain

8 Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

9 Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Maggiore Hospital, University of Milan, Milan, Italy

10 CRC "A.M. and A. Migliavacca" Center for Liver Disease, Milan, Italy

11 Gastroenterology, Ogaki Municipal Hospital, Ogaki, Gifu, Japan

12 Department of Medical and Surgical Sciences (DIMEC), Research Centre for the Study of Hepatitis, University of Bologna, Bologna, Italy

13 Hepatobiliary Division, Department of Internal Medicine and Hepatitis, Center Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

14 Faculty of Internal Medicine and Hepatitis Research Center, School of Medicine, College of Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

15 Laboratoire MESuRS (EA 4628), Conservatoire National Des Arts et Métiers, Paris, France

16 Unité PACRI, Institut Pasteur, Conservatoire National des Arts et Métiers, Paris, France

17 Endemic Medicine, Faculty of Medicine, Helwan University, Cairo, Egypt

18 Endemic Medicine and Hepato-Gastroenterology, Faculty of Medicine, Cairo University, Cairo, Egypt

19 Department of Hepatology and Gastroenterology, Liver Unit, Niguarda Hospital, Milano, Lombardia, Italy

20 Gastroenterology and Hepatology, Tokyo Medical and Dental University, Bunkyo- ku, Tokyo, Japan

21 Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan

22 Institute of Education, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan

23 Department of Gastroenterology and Hepatology, Liver Disease Control, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan

24 Division of Digestive and Liver Diseases, UT Southwestern Medical Center, Dallas, Texas, USA

25 Hepatology, National Liver Institute, Shebin El-Kom, Egypt

26 Liver and Transplant Unit, Policlinico Tor Vergata, Rome, Italy

27 Hepatology, Department of Clinical Research, University Clinic for Visceral Surgery and Medicine Inselspital, Bern, Switzerland

28 Hepatology, Department of Clinical Research, University of Bern, Bern, Switzerland

29 Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario de Valme, Seville, Spain

30 Department of Medicine-DIMED, Padua University, University Hospital, Clinica Medica 5, Refering Center for Liver Diseases, Padova, Italy

31 l'Agence de recherche ANRS (France REcherche Nord&Sud Sida-HIV Hépatites), Paris, France

32 Gastroenterology and Hepatology Service, Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain

33 Facultad de Medicina, Universidad de Cantabria, Santander, Cantabria, Spain

34 Gastroenterology and Hepatology, IDIPHIM, Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda, Spain

35 (CIBEREHD), Instituto de Salud Carlos III, Centro de Investigacion Biomedica en Red Enfermedades Hepaticas y Digestivas, Madrid, Spain

36 Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy

37 Gastroenterology/Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology Unit, University of Padova, Padova, Italy

38 Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Limburg, Belgium

39 Department of Gastro-Enterology and Hepatology, Ziekenhuis Oost-Limburg, Genk, Limburg, Belgium

40 Department of Medical and Surgical Sciences, Semeiotics Unit, Alma Mater Studiorum—University of Bologna, Bologna, Italy

Contributors conceptualisation

MR, FT, CC, GC, JB. Investigation: VS, MR, CC, GC, JB, VS, FT, all authors and collaborators. Supervision: MR, JB, FT, CC, GC. Statistical analysis: VS, FT, JR, ME. Writing—original draft: VS, GC, MR. Writing—review and editing: MR, JB, CC, all authors and collaborators. Approval of the final version of the manuscript to be published: MR, GC.

Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

VS: travel funding from Bayer. FT: DSMB fees from Basilea Pharmaceutica International and ROVI; educational fees from Janssen and Ferrer. PN: consults for AbbVie, AstraZeneca, Bayer, BMS, Eisai, Gilead, Ipsen, Roche. He received grants from AbbVie and BMS. ZM: speaker fees and consultancy for Gilead and AbbVie. RT: personal fees from Merk Sharp & Dorme, Giliad Sciences and AbbVie GK. TM: personal fees from Merk Sharp & Dorme, Giliad Sciences and AbbVie GK. XF: consultancy fees for AbbVie and Gilead Sciences. HT: speaker fees from AbbVie, Gildead, MSD and Bayer. SB: consultancy fees and educational grants from: Gilead Sciences, MSD, Intercept. ED: advisory board from AbbVie; speaking and teaching from Gilead, MSD, AbbVie. M-LY: research grant from Abbott, BMS, Gilead and Merck; consultant of AbbVie, Abbott, BMS, Gilead, Merck and Roche; speaker of AbbVie, Abbott, BMS, Gilead and Merck. YA: donation-funded department funded by Toray Industries Inc., Gilead Sciences, AbbVie GK and Fuji Rebio Inc. AS: has received research funding from AbbVie and Gilead. He has served as a consultant for Wako Diagnostics, Glycotest, Exact Sciences, Roche, GRAIL, Genentech, Bayer, Eisai, Exelixis, AstraZeneca, BMS and TARGET Pharmasolutions. MK: lecture fees from Abott and AstraZeneca. J-FD: advisory committees: AbbVie, Bayer, Bristol-Myers Squibb, Falk, Genfit, Genkyotex, Gilead

Sciences, HepaRegenix, Intercept, Lilly, Merck, Novartis. Speaking and teaching: Bayer, Bristol-Myers Squibb, Intercept, Genfit, Gilead Sciences, Novartis, Roche. NM: research founding, lecture fees, advisory committees and travel grants from MSD. Lecture fees, advisory committees and travel grants from AbbVie and Gilead. SP: consulting and lecturing fees from Janssen, Gilead, MSD, AbbVie, Biotest, Shinogui, Viiv and grants from Bristol-Myers Squibb, Gilead, Roche and MSD, without relation to this manuscript. JC: grants and research support from Gilead Sciences, AbbVie, MSD, Shionogi and Intercept Pharmaceuticals (all outside the submitted work). Is a speaker for Gilead Sciences and AbbVie. JLC: reports grant support and/or consultancy and lecture fees from AbbVie, Gilead Sciences, Bristol- Myers Squibb, Janssen and MSD. RV: research grant from AbbVie. GS: consultancy fees and lecture fees from Gilead and AbbVie. FPR: lecture fees AbbVie, Gilead, MSD, Biotest; travel funds AbbVie, Biotest, Kedrion; research funds AbbVie, Gilead, MSD. RB: research grants from MSD, AbbVie and Gilead. JR: educational grants from Amgen, Grüenenthal Pharma, Boehringer Ingelheim España, Janssen-Cilag, Ferrer International, Lilly, Merck Sharp & Dohme and Roche Farma. FT: consultancy fees from AstraZeneca, Bayer, BMS, Eisai and Sirtex. Lecture fees from AlfaSigma and Bayer. Research grants from Bayer. CC: consultancy fees from Bayer, EISAI, MSD, Gilead, ABV. JB: consultancy fees from Arqule, Bayer, Novartis, BMS, BTG- Biocompatibles, Eisai, Kowa, Terumo, Gilead, Bio-Alliance/Onxeo, Roche, AbbVie, Merck, Sirtex, Ipsen, Astra-Medimmune, Incyte, Quirem, Adaptimmune, Lilly, Basilea, Nerviano. Research grants from Bayer and BTG. Educational grants from Bayer and BTG. Lecture fees from Bayer, BTG-Biocompatibles, Eisai, Terumo, Sirtex, Ipsen. GC: consultancy fees from Bayer, Ipsen. MR: consultancy fees from Bayer, BMS, Roche, Ipsen, AstraZeneca and Lilly. Lecture fees from Bayer, BMS, Gilead, Lilly and Roche. Research grants from Bayer and Ipsen.

Patient consent for publication

Not required.

Ethics approval

This study complied with the principles of the Declaration of Helsinki and its later amendments, and local and national laws. It was approved by the Research Ethics Committee of the Hospital Clinic of Barcelona (HCB/2019/0030).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Supplemental material

REFERENCES

1. Reig M, Mariño Z, Perelló C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol 2016;65:719–26.
2. Cabibbo G, Petta S, Calvaruso V, et al. Is early recurrence of hepatocellular carcinoma in HCV cirrhotic patients affected by treatment with direct-acting antivirals? A prospective multicentre study. Aliment Pharmacol Ther 2017;46:688–95.
3. Waziry R, Hajarizadeh B, Grebely J, et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: a systematic review, meta-analyses, and meta-regression. J Hepatol 2017;67:1204–12.
4. Saraiya N, Yopp AC, Rich NE, et al. Systematic review with meta-analysis: recurrence of hepatocellular carcinoma following direct-acting antiviral therapy. Aliment Pharmacol Ther 2018;48:127–37.
5. Manthravadi S, Paleti S, Pandya P. Impact of sustained viral response postcurative therapy of hepatitis C-related hepatocellular carcinoma: a systematic review and meta-analysis. Int J Cancer 2017;140:1042–9.
6. Singh S, Nautiyal A, Loke YK. Oral direct-acting antivirals and the incidence or recurrence of hepatocellular carcinoma: a systematic review and meta-analysis. Frontline Gastroenterol 2018;9:262–70.
7. Huang P, Liu M, Zang F, et al. The development of hepatocellular carcinoma in HCV-infected patients treated with DAA: a comprehensive analysis. Carcinogenesis 2018;39:1497–505.
8. Singal AG, Rich NE, Mehta N, et al. Direct-Acting antiviral therapy for hepatitis C virus infection is associated with increased survival in patients with a history of hepatocellular carcinoma. Gastroenterology 2019;157:1253–63.
9. Singal AG, Rich NE, Mehta N, et al. Direct-Acting antiviral therapy not associated with recurrence of hepatocellular carcinoma in a multicenter North American cohort study. Gastroenterology 2019;156:1683–92.
10. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.
11. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. Hepatology 2018;68:723–50.
12. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. J Hepatol 2018;69:461–511.
13. Ghany MG, Morgan TR, AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C guidance 2019 update: American association for the study of liver Diseases-Infectious diseases Society of America recommendations for testing, managing, and treating hepatitis C virus infection. Hepatology 2020;71:686–721.

14. Singal AG, Lim JK, Kanwal F. AGA clinical practice update on interaction between oral direct-acting antivirals for chronic hepatitis C infection and hepatocellular carcinoma: expert review. Gastroenterology 2019;156:2149–57.
15. Cabibbo G, Celsa C, Calvaruso V, et al. Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients. J Hepatol 2019;71:265–73.
16. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1–9.
17. Cabibbo G, Petta S, Barbara M, et al. Hepatic decompensation is the major driver of death in HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma. J Hepatol 2017;67:65–71.
18. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
19. Torres F, Ríos J, Saez-Peñataro J, et al. Is propensity score analysis a valid surrogate of randomization for the avoidance of allocation bias? Semin Liver Dis 2017;37:275–86.
20. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. Stat Med 2008;27:2037–49.
21. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083–107.
22. Royston P, Parmar MKB. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. Stat Med 2011;30:2409–21.
23. Kohla M, Omar Y, Assem M. Early recurrence of hepatocellular after successful therapy with direct acting antiviral agents for chronic hepatitis C: an observational study. ILCA Annu Conf 2017;2017:47.
24. Kolly P, Waidmann O, Vermehren J, et al. Hepatocellular carcinoma recurrence after direct antiviral agent treatment: a European multicentre study. J Hepatol 2017;67:876–8.
25. Masetti C, Lionetti R, Lupo M, et al. Lack of reduction of serum alphafetoprotein during treatment with direct antiviral agents predicts hepatocellular carcinoma development in a large cohort of patients with HCV-related cirrhosis. J Hepatol 2018;68:S533.
26. Merchante N, Rodríguez-Arrondo F, Revollo B, et al. Hepatocellular carcinoma after sustained virological response with interferon-free regimens in HIV/hepatitis C virus- coinfected patients. AIDS 2018;32:1423–30.
27. Minami T, Tateishi R, Nakagomi R, et al. The impact of direct-acting antivirals on early tumor recurrence after radiofrequency ablation in hepatitis C-related hepatocellular carcinoma. J Hepatol 2016;65:1272–3.
28. Nagata H, Nakagawa M, Asahina Y, et al. Effect of interferon-based and -free therapy on early occurrence and recurrence of hepatocellular carcinoma in chronic hepatitis C. J Hepatol 2017;67:933–9.

29. HEPADAT. Undefined/non-malignant hepatic nodules are associated with early occurrence of HCC in DAA-treated patients with HCV-related cirrhosis. J Hepatol 2020;73:593–602.
30. Toyoda H, Kumada T, Tada T, et al. Impact of previously cured hepatocellular carcinoma (HCC) on new development of HCC after eradication of hepatitis C infection with non-interferon-based treatments. Aliment Pharmacol Ther 2018;48:664–70.
31. Tsai P-C, Huang C-F, Yu M-L. Unexpected early tumor recurrence in patients with hepatitis C virus-related hepatocellular carcinoma undergoing interferon-free therapy: issue of the interval between HCC treatment and antiviral therapy. J Hepatol 2017;66:464.
32. Villani R, Facciorusso A, Bellanti F, et al. DAAs increase serum VEGF level: a rationale for tumour risk recurrence during anti-HCV treatment. J Hepatol 2017;66:S735.
33. Zavaglia C, Okolicsanyi S, Cesarini L, et al. Is the risk of neoplastic recurrence increased after prescribing direct-acting antivirals for HCV patients whose HCC was previously cured? J Hepatol 2017;66:236–7.
34. Abdelaziz AO, Nabil MM, Abdelmaksoud AH, et al. De-novo versus recurrent hepatocellular carcinoma following direct-acting antiviral therapy for hepatitis C virus. Eur J Gastroenterol Hepatol 2018;30:39–43.
35. ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts). Electronic address: stanislas.pol@aphp.fr. Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: data from three ANRS cohorts. J Hepatol 2016;65:734–40.
36. Calleja JL, Crespo J, Rincón D, et al. Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: results from a Spanish real-world cohort. J Hepatol 2017;66:1138–48.
37. Cavalletto L, Aliberti C, Romano A, et al. Relapse after direct-acting antivirals (DAAs) in cirrhotic patients with hepatitis C is highly related to development of liver cancer. J Hepatol 2017;66:S536.
38. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016;65:727–33.
39. Degasperi E, D'Ambrosio R, Iavarone M, et al. Factors associated with increased risk of de novo or recurrent hepatocellular carcinoma in patients with cirrhosis treated with direct-acting antivirals for HCV infection. Clin Gastroenterol Hepatol 2019;17:1183–91.
40. El Kassas M, Funk AL, Salaheldin M, et al. Increased recurrence rates of hepatocellular carcinoma after DAA therapy in a hepatitis C-infected Egyptian cohort: a comparative analysis. J Viral Hepat 2018;25:623–30.
41. Gerbes A, Zoulim F, Tilg H, et al. Gut roundtable meeting paper: selected recent advances in hepatocellular carcinoma. Gut 2018;67:380–8.
42. Tang ZY, MC W, S.S X. Primary liver cancer. China Academic Publishers, 1989.
43. Tang ZY. Subclinical hepatocellular carcinoma. China Academic Publishers, 1985.

44. Prenner SB, VanWagner LB, Flamm SL, et al. Hepatocellular carcinoma decreases the chance of successful hepatitis C virus therapy with direct-acting antivirals. J Hepatol 2017;66:1173–81.
45. Sosa MS, Bragado P, Aguirre-Ghiso JA. Mechanisms of disseminated cancer cell dormancy: an awakening field. Nat Rev Cancer 2014;14:611–22.
46. Nishibatake Kinoshita M, Minami T, Tateishi R, et al. Impact of direct-acting antivirals on early recurrence of HCV-related HCC: comparison with interferon-based therapy. J Hepatol 2019;70:78–86.
47. Reig M, Cabibbo G. Antiviral therapy in the palliative setting of HCC (BCLC B and C). J Hepatol 2021;100.

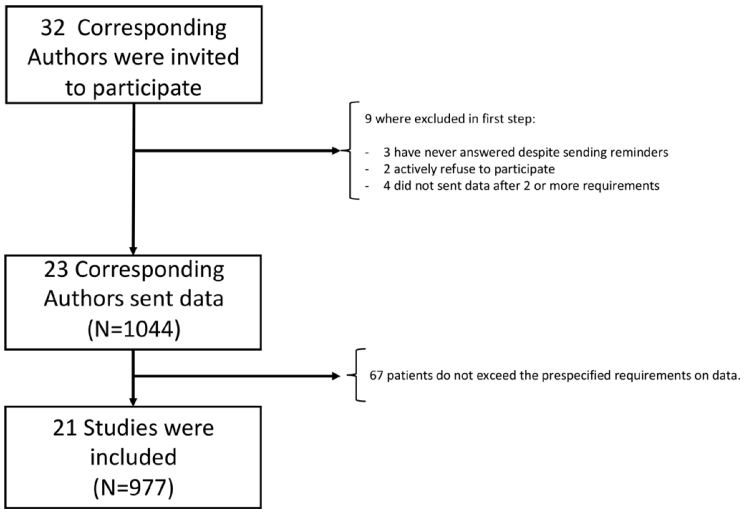

Figure 1 Flow chart of patients included in meta-analysis.

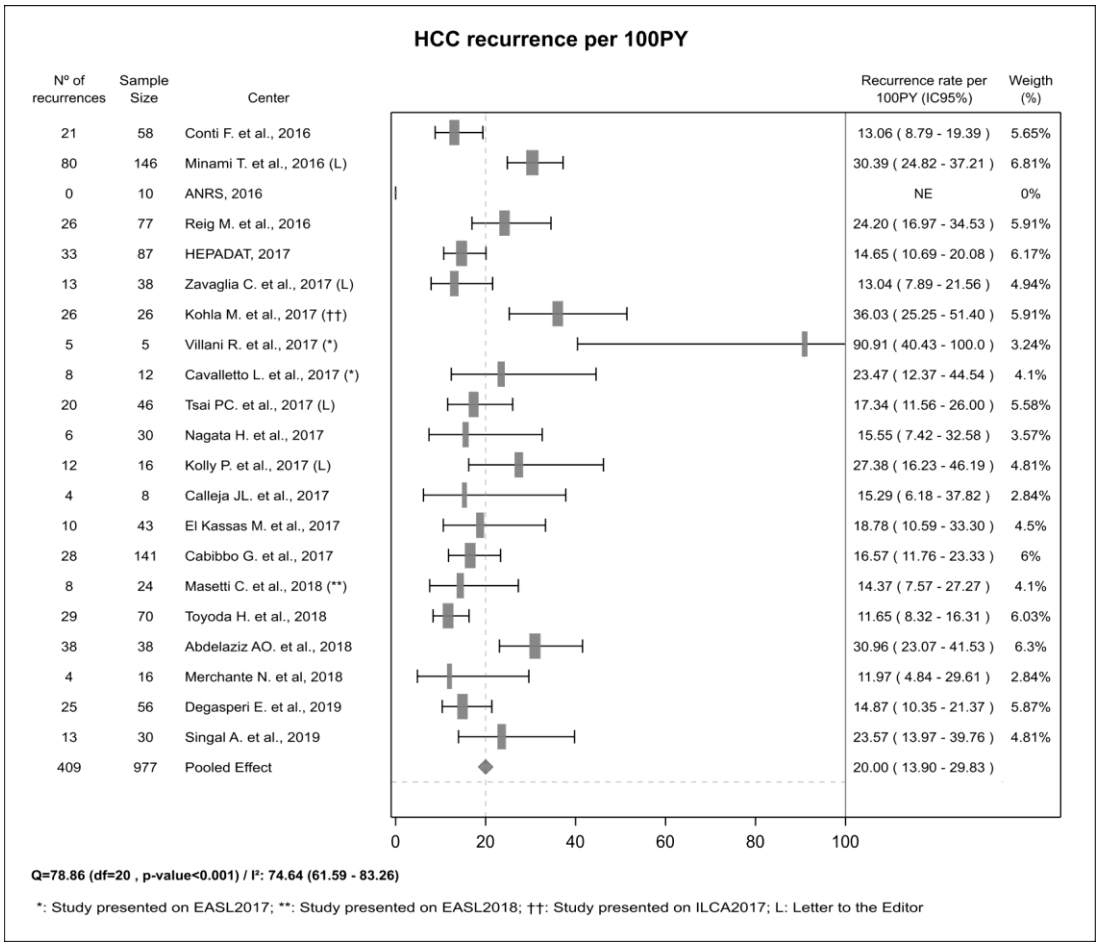

Figure 2 Forest plot of pooled effect for hepatocellular carcinoma (HCC) recurrence rate per 100 person-years (100PY). Lines represent the 95% CI for HCC recurrence rate per 100PY for each study. Size of squares represents the weight of each study. Diamond represents the pooled effect.

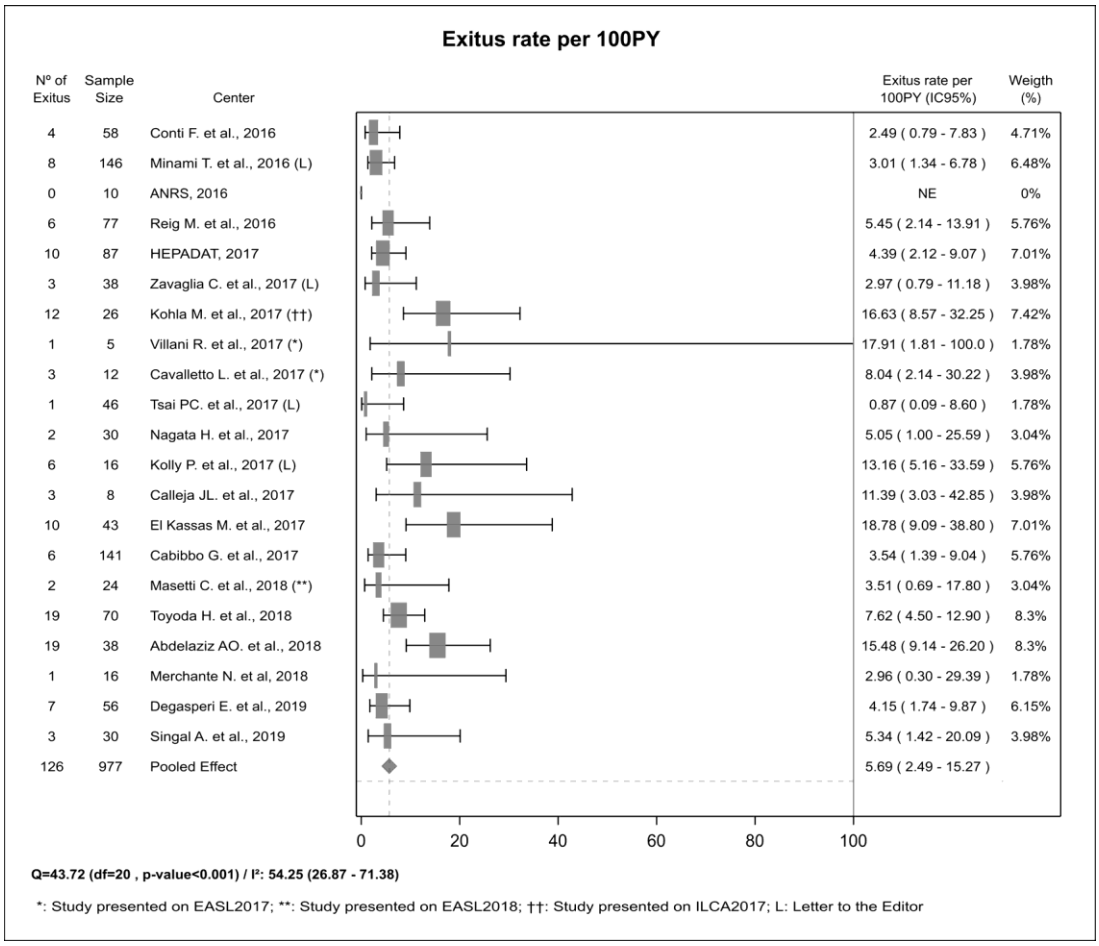

Figure 3 Forest plot of pooled effect for death rate per 100 person-years (100PY). Lines represent the 95% CI for hepatocellular carcinoma death rate per 100PY for each study. Size of squares represents the weight of each study. Diamond represents the pooled effect.

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 *et al*[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 *et al* (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 *et al*[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 *et al* (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 *et al*[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 *et al*[32]†	100	80/20/0	100/0	0/0	0/0/40/0/60/0	40/60/0	100	0	60
Cavalletto *et a*[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 *et al*(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 *et al*[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 *et al* (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 *et al*[36]	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 *et al*[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 *et al*[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 *et al*[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 *et al*[30]	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. *et al*[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 *et al*[26]	87.5	88/6/6	75/25	0/0	0/0/0/0/0/0	38/31/31	0	0	93.8
Degasperi *et al*[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 *et al*[9]	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.

Table 2 Prognostic baseline factors for HCC recurrence

		Univariate		Multivariate	
Parameter	**Contrast**	**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 DAAinitiation*	≤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.

Table 3 Regression models for patients with solitary nodules

	Number ofevents	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 andtreated 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 andtreated with resection	7	25	19.9 (5.8 to 145.88)	0 (0 to 30.2)	>0.9

100PY, 100 person-years.