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# Systematic review with meta-analysis: recurrence of hepatocellular carcinoma following direct-acting antiviral therapy

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## Summary

**Background:** Although studies suggest decreased incident hepatocellular carcinoma (HCC) after direct-acting antivirals (DAA), data are conflicting regarding HCC recurrence and aggressiveness in patients who have a history of HCC with complete response.

**Aim:** Characterize HCC recurrence patterns after DAA therapy.

**Methods:** Two reviewers searched MEDLINE and SCOPUS from January 2015 to December 2017 and identified studies evaluating HCC recurrence patterns following DAA therapy. A pooled estimate was calculated using the DerSimonian and Laird method for a random effects model. The study was conducted in accordance with PRISMA guidelines.

**Results:** Among 24 studies (n = 1820 patients), the proportion of patients with HCC recurrence following DAA therapy ranged from 0% to 59% (pooled estimate 24.4%; 95% CI: 18.4%-30.4%). Among 11 full text manuscripts, pooled HCC recurrence was 21.9% (95% CI: 16.2%-28.3%). Factors associated with recurrence included history of prior HCC recurrence and a shorter interval between HCC complete response and DAA initiation. Nine studies comparing DAA-treated and interferon-treated or untreated patients found similar recurrence among DAA-treated patients. Most (77.8%) patients with HCC recurrence were detected at an early tumour stage, of whom 64.7% received curative treatment. Study limitations included heterogeneous cohorts, potential misclassification of HCC absence prior to DAA, ascertainment bias for recurrence, and short durations of follow-up.

**Conclusions:** Current data suggest acceptable HCC recurrence rates after DAA therapy, particularly if DAA therapy is delayed at least 6 months after HCC complete response. However, data characterising HCC recurrence after DAA therapy are of limited quality, highlighting the need for high quality prospective studies.

Drs. Parikh and Singal are co-senior authors.

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## 1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide, with chronic hepatitis C (HCV) being the most common underlying etiology in the United States and Europe.[1] Liver transplantation, surgical resection, and local ablative therapy are potentially curative and associated with excellent long-term survival but are limited by tumour recurrence exceeding 50% at 5 years.[2]

Prior attempts at adjuvant pharmacologic therapy for HCC have failed to improve survival or reduce recurrence, with the exception of anti-viral therapy.[3] Interferon-based therapy was associated with a significant reduction in HCC incidence in patients with HCV-related cirrhosis as well as HCC recurrence after curative therapy.[4] The mechanism for reduction in HCC recurrence is unclear—whether related to sustained viral response (SVR) or direct interferon-related immune-mediated antitumour effect.[5] This debate has become more relevant to the introduction of direct acting antiviral (DAA) therapy, which has replaced interferon-based therapy for HCV.[6] Although studies have demonstrated improvements in fibrosis and portal hypertension as well as decreased risk of incident HCC in patients with HCV-related cirrhosis, some observational studies suggest an *increased* risk and aggressiveness of HCC recurrence after DAA therapy.[7-10]

This issue remains a topic of debate, leading to uncertainty if or when to treat HCV-infected patients with a history of HCC.[11,12] These data have created fear among patients receiving DAA therapy and prompted some providers to withhold HCV treatment from patients with a history of HCC. The European Medicine Agency's Pharmacovigilance Risk Assessment Committee has required high quality data evaluating this association. Given the lack of randomised data evaluating this association, we are forced to rely on cohort studies and indirect comparisons across studies. The aim of this systematic review is to characterize HCC recurrence patterns following DAA-based therapy.

## 2 | METHODS

### 2.1 | Literature search and study selection

We searched MEDLINE and SCOPUS databases from January 1, 2015 through December 1, 2017 using search terms: (liver ca$ or hepatocellular ca$ or hcc or hepatoma) and (hepatitis C or HCV) and (interferon-free or direct-acting antiviral or DAA). We also manually searched abstracts from the 2016 and 2017 American Association for the Study of Liver Diseases, European Association for the Study of the Liver, and International Liver Cancer Association annual conferences. Additional studies that may have been missed by the electronic search were identified through manual searching of reference lists from applicable studies and consultation with experts in the field. If the applicability of an article could not be determined by title or abstract alone, the full text was reviewed. Articles and abstracts were independently evaluated for possible inclusion by 2 authors (N.S. and A.S.) and any uncertainties were resolved through discussion with another reviewer (N.P.). The study was conducted in accordance with Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines.[13]

Studies were included for analysis if they evaluated HCC recurrence after DAA therapy in a cohort of patients with chronic HCV infection and a history of HCC with complete response. We included studies with complete response from surgical, local ablative, or locoregional therapies; however, we excluded cohorts focusing exclusively on post-transplant HCC recurrence and studies that included interferon-based regimens in combination with DAAs. Complete response in studies was typically defined using modified Response Evaluation Criteria in Solid Tumours (mRECIST), that is, disappearance of arterial enhancement in all HCC lesions. Studies may have been retrospective or prospective but were required to report the proportion of patients with recurrence after DAA therapy. Additional exclusion criteria included (1) non-English language, (2) nonhuman data, and (3) lack of original data. If publications reported data using the same cohort of patients, the study with more complete data was included.

### 2.2 | Data extraction

Two authors (N.S. and A.S.) independently reviewed and extracted required information from eligible studies using standardised forms. A third investigator (N.P.) was available to resolve any discrepancies between the sets of extracted data. The data extraction form included the following study design items: geographical location and date of study, study design (prospective vs retrospective), characteristics and size of study cohort, inclusion and exclusion criteria, HCC treatment regimen, median time from HCC treatment to DAA treatment, and duration of follow-up. In addition, the extraction form recorded the following primary data: proportion of patients with HCC recurrence and patterns of recurrence (ie, tumour burden and HCC-directed treatment). Two authors (N.S. and A.S.) independently assessed study quality using a modified checklist based upon a modified version of the Newcastle-Ottawa quality assessment scale, with discrepancies resolved by consensus.[14] Studies with <1 year of follow-up or loss to follow-up exceeding 5% were regarded as high risk of bias.

### 2.3 | Statistical analysis

The aim of this study was to characterize HCC recurrence patterns after DAA therapy. For each individual study, the proportion of patients with HCC recurrence with 95% confidence intervals was calculated. Estimates of effect were pooled using a binomial-normal model and the DerSimonian and Laird method for a random effects model. Heterogeneity was initially evaluated graphically by examination of forest plots and statistically by the inconsistency index ($I^2$), with values >50% consistent with the possibility of substantial heterogeneity.[15] Subgroup analyses were planned for HCC detection for predefined subsets of studies based on (i) prospective vs retrospective study design, (ii) study location, (iii) duration of follow-up (iv) timing of DAA initiation, and (v) availability of full text manuscripts. We assessed for presence of heterogeneity between subgroups, with statistical significance defined as $P < 0.05$. We also performed a subgroup analysis among studies reporting early HCC recurrence after DAA initiation. We performed univariate and multivariate meta-regression analyses to

evaluate the potential association between study-level covariates (study location, study design, sample size, proportion of patients with early HCC, timing of DAA initiation, and length of follow-up) and HCC recurrence. A secondary analysis among studies reporting relative recurrence rates between DAA-treated and untreated patients, in which we determined a pooled estimate for the relative risk of recurrence using a random effects model. Publication bias was evaluated graphically by funnel plot analysis. Analyses were performed using STATA 14.0 (StataCorp, College Station, TX, USA).

## 3 | RESULTS

### 3.1 | Literature search

Upon review of the 827 titles identified by the search strategy, 63 abstracts were further examined. Twenty-three publications underwent full-text review to determine their eligibility for the meta-analysis and 4 were excluded. The remaining 16 studies were selected after meeting all applicable inclusion criteria. Overall, 20 studies were excluded because they presented data on HCC occurrence but not recurrence, 11 had insufficient data for abstraction, 5 had overlapping cohorts, 4 exclusively characterised post-transplant HCC recurrence, and 7 studies were excluded for lack of original data (Figure S1). Finally, review of American Association for the Study of Liver Diseases, European Association for the Study of the Liver, and International Liver Cancer Association conference abstracts identified 7 additional studies and recursive literature searches identified 1 full-length manuscript and 2 letters to the editor that met inclusion criteria, producing a total of 26 studies.[16-39] The study by the ANRS collaborative study group included 2 distinct cohorts,[24] yielding a total of 27 cohorts. Two included studies reported relative HCC recurrence rates compared to interferon-treated or untreated patients but did not report absolute HCC recurrence rates,[40,41] yielding 24 studies with 25 cohorts characterising the primary outcome of absolute HCC recurrence rates after DAA initiation.

### 3.2 | Study characteristics

Characteristics of the 24 studies (ie, 25 cohorts) reporting the absolute proportion of patients with HCC recurrence after DAA therapy are described in Table 1. The majority of cohorts were retrospective (n = 19) and only available as abstracts or letters to the editor (n = 14). Thirteen cohorts were conducted in Europe, 10 in Asia, and 2 in the United States. Studies included a total of 1820 DAA-treated patients, although most cohorts (n = 19) included less than 100 patients, resulting in imprecise estimates for HCC recurrence with wide confidence intervals. Most patients had achieved HCC complete response after resection or ablation; however, 25%-50% of patients in some studies had received noncurative therapies, including transarterial chemoembolisation (TACE). Duration of follow-up to assess recurrence ranged from 3 to 36 months, although some studies defined recurrence from date of HCC treatment and others evaluated recurrence from date of DAA initiation. Although most studies only included single-arm cohorts, 7 of the studies included a comparator arm of interferon-treated and/or untreated patients. Two additional studies did not report the absolute proportion of patients with HCC recurrence but compared relative recurrence between DAA-treated patients and interferon-treated or untreated patients, yielding a total of 9 comparative studies (Table 2).

### 3.3 | HCC recurrence following DAA therapy

The pooled point estimate for HCC recurrence following DAA therapy was 25.1% (95% CI: 19.4%-31.2%); however, there was significant statistical heterogeneity ($I^2$ = 86%) (Figure 1). The proportion of patients with HCC recurrence varied widely between studies, ranging from 0% to 59% within 2 years (Table 1). In subgroup analyses, pooled estimates for HCC recurrence were similar between prospective and retrospective cohort studies (23.9% vs 25.6%, $P$ = 0.76), studies with duration of follow-up shorter or longer than 12 months (21.9% vs 27.6%, $P$ = 0.29), and studies in which HCC recurrence was assessed starting at DAA initiation vs other times (24.6% vs 26.0%, $P$ = 0.84). However, HCC recurrence was higher in studies conducted in the United States compared to Europe and Asia (43.3% vs 22.1% vs 28.9%, $P$ < 0.001). There continued to be significant heterogeneity, with $I^2$ values remaining greater than 70%, in all subgroup analyses. Among the 11 studies with data regarding "early" recurrence, the proportion with recurrence within 6 months ranged from 5% to 29%, with a pooled proportion of 10.3% (95% CI: 6.3%-14.4%; $I^2$ = 49%).

Among the 11 studies available as a full text manuscript, the pooled HCC recurrence rate was 21.9% (95% CI: 16.2%-28.3%), although there continued to be statistical heterogeneity with $I^2$ > 75%. In subgroup analyses, pooled estimates for HCC recurrence were similar between prospective and retrospective cohort studies (18.6% vs 22.9%), studies with duration of follow-up shorter or longer than 12 months (22.6% vs 22.0%), studies in which HCC recurrence was assessed starting at DAA initiation vs other times (22.7% vs 21.1%), and studies conducted in Europe and Asia (20.1% vs 25.7%). There was no association between HCC recurrence and study location, study design, sample size, the proportion of patients with early HCC, median time from HCC treatment to DAA initiation, or median length of follow-up in meta-regression analyses.

The most commonly reported factor associated with increased recurrence within included studies was the interval between HCC complete response and DAA initiation. Reig and colleagues found higher recurrence (41% vs 23%) in patients treated within 4 months of HCC complete response,[21] whereas Ogawa reported this association using a cut-off of 1 year (HR: 0.31, 95% CI: 0.10-0.77),[20] and Minimi et al. using a cut-off of 2 years (HR: 0.34).[42] Similarly, Kolly et al. found patients with a longer timeframe between HCC treatment and DAA therapy had significantly lower hazards of recurrence (HR: 0.91, 95% CI: 0.85-0.96).[31] A history of prior HCC recurrence was also associated with increased risk of HCC recurrence following DAA therapy (HR: 2.2-2.3), as reported by Minami, Cabibbo, and Ikeda.[17,18,42] Although many studies reported no difference in HCC

**TABLE 1** Characteristics of studies reporting HCC recurrence rates after DAA therapy

| Author year | Study location | Study design | Number DAA-HCC patients (% early) | AFP level prior to HCC treatment | Type of HCC treatment | Time from HCC treat to DAA | Follow-up Start | Follow-up Period | Recurrence (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| Bielen 2017[16,a] | Belgium | Retrospective | 41 (83%) | 46 ± 70 | Transplant 51% Resection 24% Ablation 22% TACE 3% | 12 months | End of DAA treatment | 32 months | 14.6 (5.6-29.2) |
| Cabibbo 2017[17,a] | Italy | Prospective | 143 (100%) | 18 ± 26 | Resection 36% Ablation 46% TACE 18% | 11 months | Start of DAA treatment | 8.7 months | 20.3 (14.0-27.8) |
| Ikeda 2017[18,a] | Japan | Retrospective | 177 (NR) | 17 (2-4730) | Resection 31% Ablation 46% TACE 20% Radiation 3% | 10.7 months | Start of DAA treatment | 20.7 months | 34.6 (27.9-41.7) |
| Nagata 2017[19,a] | Japan | Retrospective | 83 (100%) | NR | Resection or ablation | NR | HCC treatment | 27.6 months | 27.1 (18.2-36.9) |
| Ogawa 2017[20,a] | Japan | Prospective | 152 (95%) | 7 (5-16) | Resection 40% Ablation 32% TACE 15% Multimodal 12% Radiation 1% | 14.4 months | Start of DAA treatment | 17 months | 17.5 (11.9-23.9) |
| Reig 2017[21,a] | Spain | Retrospective | 77 (97%) | 10 (1-369) | Resection 36% Ablation 53% TACE 10% | 11.2 months | Start of DAA treatment | 8.2 months | 27.3 (17.7-38.6) |
| Virlogeux 2017[22,a] | France | Retrospective | 23 (91%) | 13 (2-170) | Resection 26% Ablation 61% Other 13% | 7.1 months | Start of DAA treatment | 35.7 months | 47.8 (26.8-69.4) |
| Conti 2016[23,a] | Italy | Retrospective | 59 (98%) | NR | Resection 32% Ablation 41% TACE 8% Multimodal 17% | 12.4 months | End of DAA treatment | 5.5 months | 28.8 (17.8-42.1) |
| ANRS 2016[24,a] | France | Retrospective | 189 (NR) | NR | NR | NR | Start of DAA treatment | 20.2 months | 12.7 (8.3-18.3) |
| ANRS 2016[24,a] | France | Retrospective | 13 (NR) | NR | NR | >3 months | Start of DAA treatment | 21.3 months | 7.6 (0.2-36.0) |
| Rinaldi 2016[25,a] | Italy | Retrospective | 15 (100%) | NR | Resection 14% Ablation 86% | 11.3 months | Start of DAA treatment | 2.8 months | 6.7 (0.2-32.0) |
| Zavaglia 2017[26] | Italy | Retrospective | 31 (84%) | 10 (2-278) | Resection 42% Ablation 19% TACE 13% Multimodal 26% | 19.3 months | Start of DAA treatment | 8 months | 3.2 (0-16.7) |
| Zeng 2016[27] | China | Retrospective | 10 (100%) | NR | Ablation 100% | NR | End of DAA treatment | 15 months | 0 (0-25.9) |
| Torres 2016[28] | USA | Prospective | 8 (NR) | 51 (6-7258) | Resection 50% Ablation 38% Proton therapy 12% | 7.5 months | Start of DAA treatment | 12 months | 0 (0-31.2) |
| Gheoghe 2017[29] | Romania | Retrospective | 20 (NR) | NR | NR | NR | DAA treatment | 6 months | 20.0 (5.7-43.7) |
| Granata 2017[30] | Italy | Prospective | 65 (83%) | NR | NR | 9 months | Start of DAA treatment | 18 months | 27.7 (17.3-40.2) |
| Kolly 2017[31] | Germany, Belgium, Switzerland | Retrospective | 56 (NR) | NR | Ablation, resection or TACE | NR | HCC treatment | 21 months | 1-year 19% 2-year 44% |
| Yasui 2017[32] | Japan | Retrospective | 46 (NR) | NR | NR | NR | End of DAA treatment | 6 months | 14.3 (5.4-28.5) |
| Minami 2017[33] | Japan | Retrospective | 163 (91%) | NR | Resection 14 Ablation 147 Radiotherapy 1 TACE 1 | 8 months | Start of DAA treatment | 14.5 months | 47.9 (40.0-55.8) |

(Continues)

**TABLE 1** (Continued)

| Author year | Study location | Study design | Number DAA-HCC patients (% early) | AFP level prior to HCC treatment | Type of HCC treatment | Time from HCC treat to DAA | Follow-up Start | Follow-up Period | Recurrence (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| Ohki 2017[34] | Japan | Retrospective | 20 (100%) | 13 (7-25) | Ablation 100% | 7.6 months | HCC treatment | 24 months | 35.0 (15.4-59.2) |
| Sangiovanni 2017[35] | Italy | Prospective | 101 (98%) | NR | Resection 28% Ablation 48% TACE 10% Multi-modality 14% | 12 months | Start of DAA treatment | 11.1 months | 32.7 (23.7-42.7) |
| Singal 2017[37] | USA | Retrospective | 207 (87%) | 16 (7-52) | Resection 19% Ablation 27% TACE 37% Multi-modality 16% | 7.2 months | HCC treatment | 22.7 months | 45.9 (39.0-52.9) |
| Urabe 2017[36] | Japan | Prospective | 63 (NR) | NR | NR | 24.3 months | Start of DAA treatment | 10.9 months | 38.5 (26.2-51.2) |
| Tokoro 2016[38] | Japan | Retrospective | 22 (NR) | NR | NR | NR | Start of DAA treatment | 16.2 months | 59.1 (36.4-79.3) |
| Tsuda 2016[39] | Japan | Retrospective | 36 (NR) | NR | NR | NR | Start of DAA treatment | 11.4 months | 25.0 (12.1-42.2) |

DAA, direct acting antiviral; HCC, hepatocellular carcinoma; NR, not reported; TACE, transarterial chemoembolisation.
[a]Available as full length manuscript.

recurrence by classic risk factors including degree of liver dysfunction, tumour burden, or alpha fetoprotein (AFP) levels, each was found to be associated with higher recurrence in 1 study. Conti described higher recurrence in those with increased liver stiffness (OR: 1.19, 95% CI: 1.01-1.39),[23] Ogawa and Cabibbo found higher recurrence in those with a history of multifocal HCC (HR: 2.34, 95% CI: 1.05-5.39)[20] and larger HCC lesions (HR: 2.73, 95% CI: 1.23-6.06)[17] respectively, Minami reported higher recurrence in those with AFP-L3 >15% (HR 3.08) or DCP >40 mAU/mL (HR: 2.0),[42] and Ogawa found higher recurrence in patients who underwent noncurative procedures such as TACE (HR: 2.31, 95% CI: 1.04-5.15).[20]

Nine studies compared HCC recurrence in DAA-treated (n = 947) patients to interferon-treated (n = 210) and/or untreated (n = 641) patients (Table 2).[22,24,30,32,34,37,40,41] Five studies reported no significant difference in HCC recurrence between DAA-treated and untreated patients in multivariable analyses, while 2 studies found significantly lower HCC recurrence among DAA-treated patients. Among the 5 studies reporting relative risk of recurrence with 95% confidence intervals, DAA-treated patients had a lower pooled recurrence risk than untreated patients (OR: 0.55, 95% CI: 0.25-0.85). All 3 studies comparing DAA-treated and interferon-treated patients reported no difference in HCC recurrence between the 2 groups; however, only unadjusted analyses were reported.

## 3.4 | HCC recurrence patterns

Patterns of HCC recurrence including tumour burden and HCC-directed treatment after DAA therapy are detailed in Table 3. The majority of patients (77.8%, 95% CI: 72.9-82.1) with HCC recurrence across studies were detected at an early stage, and two-thirds of those found at an early stage (64.7%, 95% CI: 57.9-71.2) received curative treatment with liver transplant, resection or ablation. Only 3 studies described response to HCC therapy.[18,21,37] Reig et al. reported that 32% of patients had tumour progression within 6 months of recurrence,[21] whereas Singal et al. reported 17% had progressive disease after HCC-directed therapy[37] and Ikeda et al. observed rapid tumour progression in only 5% of patients.[18]

## 3.5 | Quality assessment

Quality assessment of included studies is provided in Table 4. Most studies had appropriate representativeness of the cohort and exposure ascertainment. There was heterogeneity in cohorts with several studies including patients with nonearly stage HCC, high AFP levels, multiple prior HCC recurrences, or treatment with locoregional therapies who are all at higher risk of HCC recurrence than their counterparts. There was also heterogeneity in the length of time between HCC complete response and DAA initiation, which is associated with risk of HCC recurrence. However, some studies required patients to have HCC complete response for at least 3-6 months, other studies included patients who were treated immediately after HCC-directed treatment. Most studies ascertained HCC recurrence through medical records but only 7 excluded patients with any suspicious nodules prior to DAA initiation and only 5 included prospective surveillance protocols. There were an additional 11 studies that explicitly stated they required documented absence of HCC (but not suspicious nodules) on imaging prior to DAA initiation, and 8 retrospective studies reported a recommended surveillance protocol after HCC complete response but were regarded as medium risk of bias given potential for underuse of surveillance in clinical practice. Seven studies did not explicitly state they excluded HCC prior to DAA initiation and 12 studies did not describe their surveillance protocol after

**TABLE 2** Characteristics of studies with direct comparisons of HCC recurrence rates

| Author year | Study location | Study arms | Number of patients | Comparison of recurrence |
|---|---|---|---|---|
| Virlogeux 2017[22] | France | DAA-treated and untreated | 23/45 | 1.7 vs 4.2/100 person-months in DAA-treated and untreated patients (adjusted HR: 0.24, 95% CI: 0.10-0.55) |
| ANRS 2016[24] | France | DAA-treated and untreated | 189/78 | 0.73 vs 0.66/100 person-months in DAA-treated and untreated patients (adjusted HR: 1.04, 95% CI: 0.53-2.07) |
| ANRS 2016[24] | France | DAA-treated and untreated | 13/66 | 1.1. vs 1.7/100 person-months in DAA-treated and untreated patients (adjusted HR: 0.40, 95% CI: 0.05-3.03) |
| Granata 2017[30] | Italy | DAA-treated and untreated | 65/186 | Time to recurrence: 23.2 vs 23.0 months in DAA-treated and untreated patients |
| Yasui 2017[32] | Japan | DAA-treated and IFN-treated | 46/26 | Proportion: 14% vs 22% in DAA-treated and IFN-treated ($P = 0.50$) |
| Joko 2017[40] | Japan | DAA-treated and IFN-treated | 368/148 | No difference in early recurrence between DAA-treated and IFN-treated patients |
| Ohki 2017[34] | Japan | DAA-treated, IFN-treated, and untreated | 20/20/20 | 35% vs 55% vs 55% in DAA-treated, IFN-treated, and untreated patients ($P = 0.38$) |
| Singal 2017[37] | USA | DAA-treated and untreated | 207/127 | Proportion: 46% vs 50% in DAA-treated and untreated patients (adjusted OR: 0.80, 95% CI: 0.48-1.35) |
| Tanaka 2017[41] | Japan | DAA-treated, IFN-treated, and untreated | 16/16/119 | Lower recurrence in DAA-treated than untreated group (adjusted HR: 0.56, 95% CI: 0.26-0.97) |

DAA, direct acting antiviral; IFN, interferon.

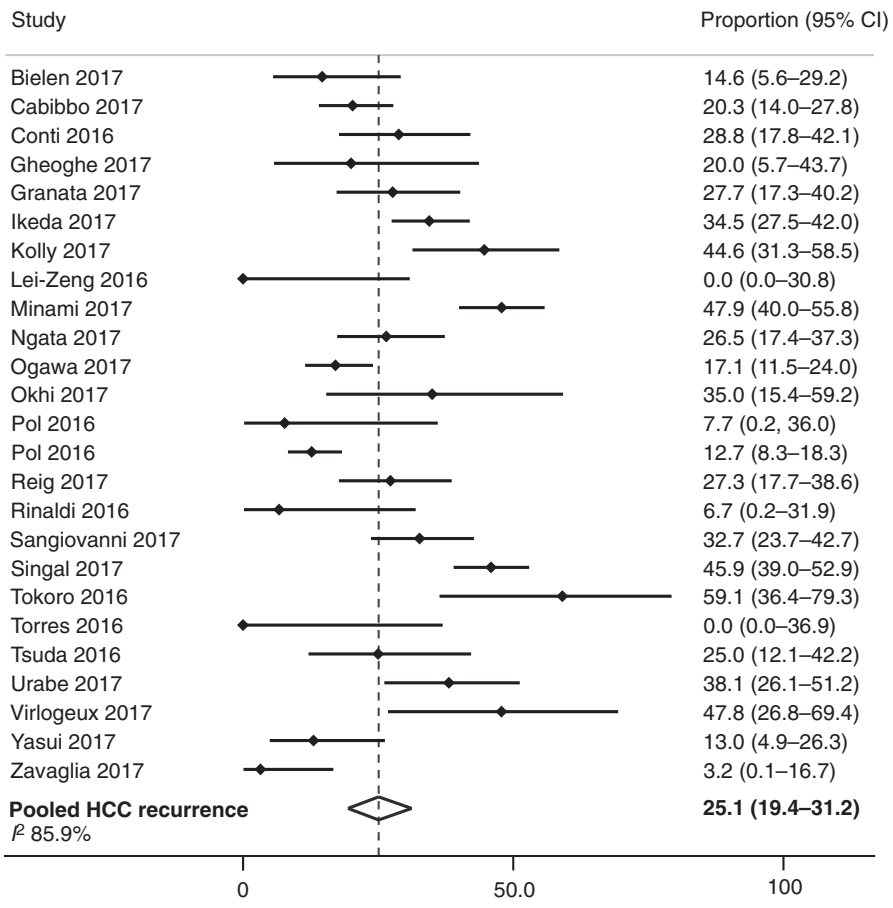


**FIGURE 1** Proportion of patients with recurrence of hepatocellular carcinoma following direct-acting antiviral therapy

HCC complete response so were regarded as having a high risk of bias. Most studies had short follow-up periods <1 year as well as high (>10%) or unknown loss to follow-up. Although comparative studies performed multivariable or propensity-score matched analyses, there were remaining issues with confounders including degree of liver dysfunction and immortal time bias.

**TABLE 3** Patterns of HCC recurrence after DAA therapy

| Author year | Number with HCC recurrence | Tumour burden at time of recurrence | HCC-directed treatment |
|---|---|---|---|
| Bielen 2017[16] | 6 | 33% BCLC A, 33% BCLC B, 17% BCLC C, 17% unknown | 17% resection<br>33% TACE and 50% supportive care |
| Cabibbo 2017[17] | 29 | 62% BCLC A, 21% BCLC B, 7% BCLC C, 10% BCLC D | 38% resection or ablation<br>45% TACE and 7% systemic therapy |
| Reig 2017[21] | 21 | 90% BCLC A, 10% BCLC B | 38% transplant, resection or ablation<br>19% TACE and 29% systemic therapy |
| Conti 2016[23] | 17 | 56% unifocal and 70% diameter <2 cm | Not reported |
| Rinaldi 2016[25] | 1 | 100% BCLC A | Patient treated with ablation |
| Granata 2017[30] | 18 | 76% monofocal, 12% multifocal, 12% advanced | Not reported |
| Yasui 2017[32] | 6 | 100% BCLC A | Not reported |
| Minami 2017[33] | 78 | 86% BCLC A, 13% BCLC B, 13% BCLC C | 85% resection or ablation<br>14% TACE and 1% supportive care |
| Ohki 2017[34] | 7 | 100% BCLC A | 86% ablation<br>14% TACE |
| Sangiovanni 2017[35] | 33 | 79% BCLC A, 6% BCLC B, 6% BCLC C, 9% unknown | 52% transplant, resection or ablation<br>42% TACE and 6% systemic therapy |
| Singal 2017[37] | 95 | 74% within Milan Criteria | 27% transplant, resection or ablation<br>54% TACE and 7% systemic therapy |
| Tokoro 2016[38] | 13 | Diameter 1.2 cm (0.7-2.0) | Not reported |
| Tsuda 2016[39] | 9 | 56% unifocal, 22% 2-3 nodules, 22% >3 nodules | Not reported |

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma.

## 4 | DISCUSSION

There is ongoing uncertainty about the potential risks and benefits of DAA therapy in patients with a history of HCC. In this comprehensive systematic review, we found a pooled estimate of 24.4% for HCC recurrence after DAA therapy, although this point estimate must be interpreted in the context of its wide confidence intervals, clinical heterogeneity within and between studies, and methodological limitations of current data. While there are few comparative studies with interferon-treated or untreated patients, these data suggest DAA-treated patients have similar if not lower recurrence than interferon-treated or untreated patients. Most patients with HCC recurrence across studies were found at an early stage and underwent curative treatments, suggesting recurrence following DAA therapy is not aggressive; however, few data characterised treatment response or post-recurrence prognosis. Current studies have notable limitations including risk for misclassification of HCC complete response prior to DAA initiation and ascertainment bias, precluding definitive conclusions about the risk of HCC recurrence and highlighting the need for higher quality data.

Providers and patients must weigh the potential for increased early HCC recurrence against demonstrated long-term benefits of DAA therapy. Patients treated for HCC are at risk for both early and late recurrence, with early recurrence typically related to intrinsic tumour factors, while late recurrence is associated with cirrhosis-related factors such as active viremia and degree of liver dysfunction.[43,44] It has been hypothesised that rapid decrease in HCV viral load with DAAs results in decreased immune surveillance of microscopic HCC tumour clones and hence an increased risk of early HCC recurrence.[21,45] Conversely, as seen with interferon-based therapies, successful treatment with DAAs can result in fibrosis regression and improvements in portal hypertension and liver dysfunction, shown to be the major driver of death in patients with HCC complete response and untreated HCV infection.[46] Further, DAA therapy may reduce risk of late HCC recurrence, by decreasing HCV viremia and improving liver function.[10,47] Unfortunately, current studies are limited by short durations of follow-up, precluding adequate characterisation of early vs late recurrence, highlighting a need for studies with longer durations of follow-up.

Identifying predictors for increased early recurrence may identify subgroups in whom DAA therapy should be avoided. Few predictors for early recurrence were consistently reported except history of prior HCC recurrence and the interval between HCC complete response and DAA initiation, with shorter intervals being associated with higher risk of recurrence. Delaying DAA therapy may allow for longer duration of immune surveillance of existing microscopic HCC clones. Delaying DAA treatment can also create a longer time to verify HCC complete response, thereby minimising the chance of misclassification bias. The sensitivity of 1-time CT or MRI for small HCC lesions is low, with sensitivities of only 40%-50% for subcentimeter lesions and 60%-70% for 1-2 cm lesions.[48] Given the lack of urgency for HCV therapy after HCC complete response, it appears prudent to wait at least 6 months after HCC complete response to initiate DAA

**TABLE 4** Quality assessment of studies by checklist

| Author year | Representative cohort | Ascertainment of exposure | Outcome not present at start | Assessment of outcome | Sufficient follow-up period | Adequacy of follow-up |
|---|---|---|---|---|---|---|
| Bielen 2017[16] | * | * | High | High | * | High |
| Cabibbo 2017[17] | * | * | * | * | High | Unknown |
| Ikeda 2017[18] | * | * | Medium | Medium | * | * |
| Ngata 2017[19] | * | * | High | Medium | * | Unknown |
| Ogawa 2017[20] | * | * | * | * | * | Unknown |
| Reig 2017[21] | * | * | * | Medium | High | * |
| Virlogeux 2017[22] | * | * | * | Medium | * | High |
| Conti 2016[23] | * | * | Medium | Medium | High | * |
| ANRS 2016[24] | * | * | Medium | High | * | Unknown |
| ANRS 2016[24] | * | * | Medium | High | * | Unknown |
| Rinaldi 2016[25] | * | * | * | Medium | High | Unknown |
| Zavaglia 2017[26] | * | * | * | High | High | High |
| Zeng 2016[27] | * | * | High | Medium | * | * |
| Torres 2016[28] | * | * | Medium | * | High | Unknown |
| Gheoghe 2017[29] | * | * | Medium | High | High | Unknown |
| Granata 2017[30] | * | * | * | * | * | Unknown |
| Kolly 2017[31] | * | * | High | High | * | Unknown |
| Yasui 2017[32] | High | * | High | High | High | Unknown |
| Minami 2017[33] | * | * | Medium | High | * | High |
| Ohki 2017[34] | * | * | High | High | * | Unknown |
| Sangiovanni 2017[35] | * | * | Medium | * | High | High |
| Singal 2017[37] | * | * | Medium | High | * | Unknown |
| Urabe 2017[36] | * | * | Medium | High | High | Unknown |
| Tokoro 2016[38] | * | * | High | Medium | * | Unknown |
| Tsuda 2016[39] | * | * | Medium | High | High | Unknown |

High, high risk of bias; Medium, intermediate risk of bias; *, low risk of bias.

therapy, which would typically allow for 2-3 interim multi-phase CT or MRI scans to confirm durable HCC response.

Notably, most studies to date are single-arm, retrospective cohort studies with clinical heterogeneity in tumour burden, HCC treatments leading to complete response, and follow-up periods. When interpreting the proportion of patients with HCC recurrence in these single arm studies, it is important to consider the natural history of HCC after complete response, in which many patients will have HCC recurrence independent of DAA therapy. HCC recurrence after complete response can vary substantially depending on which HCC-directed treatment received. While surgical resection and local ablative therapies are considered curative, recurrence rates approach 25%-35% within the first year and 50%-60% within 2 years.[44,49,50] Further, up to 25%-50% of patients in some studies received TACE, which is typically not curative and associated with a high risk of recurrence.[51] Further, patients with high-risk tumour characteristics (eg, multifocal HCC or elevated AFP) have higher recurrence rates than their counterparts; however, specific data regarding these risk factors and subgroup analyses were not reported in many studies.

In addition to concerns about clinical heterogeneity within study populations, we noted potential for misclassification and ascertainment biases. Several studies did not exclude patients with suspicious nodules prior to DAA treatment or included patients with HCC complete response for short periods of time. Therefore, it is likely some patients already had recurrent HCC at the time of DAA initiation, which would lead to an overestimation of post-DAA HCC recurrence. On the other hand, most studies did not include a standardised surveillance protocol to assess for HCC recurrence. Prior studies have demonstrated underuse of HCC surveillance in patients with cirrhosis and the same issue may plague post-treatment patients, leading to an underestimation of post-DAA recurrence.[52,53] These limitations highlight the need for high-quality prospective studies with strict inclusion criteria and a standardised surveillance protocol. Although comparative studies suggest recurrence rates among DAA-treated patients may be similar to interferon-treated and untreated patients, these analyses are limited by potential for confounders such as degree liver dysfunction. These studies can also be limited by immortal time bias, as patients with early recurrence would typically not receive DAA treatment and therefore would be over-represented in the untreated group. Given the high prevalence of limitations in study design, we propose minimum criteria for future studies in this area (Table 5).

**TABLE 5** Minimum reporting recommendations for future studies

1. Presence of cirrhosis and Child Pugh score at baseline
2. Baseline tumour burden and median AFP prior to HCC treatment
3. Number of prior HCC recurrences
4. Types of HCC treatment leading to complete response
5. Confirmation of HCC complete response immediately preceding DAA therapy
6. Time from HCC treatment to DAA initiation
7. Time from last HCC complete response assessment to HCC recurrence
8. HCC surveillance protocol and adherence
9. Tumour burden at time of recurrence, treatment of recurrence, and response to treatment
10. Predictors of HCC recurrence after DAA therapy

A prior systematic review comparing HCC occurrence and recurrence following interferon-and DAA-based therapy only included 10 studies characterising recurrence after DAA therapy,[54] whereas we identified 26 studies—including several recent prospective studies. Waziry and colleagues also included cohorts evaluating post-transplant recurrence, but we excluded these studies given post-transplant recurrence could be driven by a different mechanism. Finally, our study also characterised patterns of HCC recurrence and highlighted limitations of available data, which informed our recommendations for minimum reporting criteria.

Although our study provides a comprehensive summary of current literature, limitations of available data hindered our ability to make strong conclusions about the potential association between DAA therapy and HCC recurrence. In fact, only 3 studies did not have high risk of bias for at least 1 category of the Newcastle-Ottawa quality assessment scale. There was also significant heterogeneity between studies, including different patient selection criteria, timing of DAA therapy, and durations of follow-up. Second, an individual-level meta-analysis would be more powerful, but we did not have patient-level data to perform subgroup analyses by degree of tumour burden, type of HCC treatment, or time between HCC complete response and DAA initiation. Given most data were obtained from small single-centre cohorts, included studies may suffer from reporting bias. Factors associated with recurrence were based on descriptive review of included studies, with differential reporting and meta-analysis of these factors was not possible. In addition, we excluded non-English studies due to practical considerations, which may further bias the results.

In summary, there are conflicting data about the potential for increased HCC recurrence after DAA therapy; however, most studies have methodological limitations. Ongoing multi-centre retrospective and prospective studies should provide some insight into this controversial issue; we highlighted some suggested minimum reporting requirements to avoid the pitfalls of current studies. While awaiting these data, it is likely prudent to wait at least 6 months after HCC complete response before initiating DAA therapy.

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## AUTHORSHIP

*Guarantor of the article:* Amit G. Singal.

*Author contributions:* Neema Saraiya was involved in acquisition of data, interpretation of data, and critical revision of manuscript for important intellectual content. Adam Yopp, Nicole Rich, Neehar Parikh were involved in interpretation of data and critical revision of manuscript for important intellectual content. Mobolaji Odewole was involved in critical revision of manuscript for important intellectual content. Amit G. Singal was involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of manuscript for important intellectual content, and study supervision.

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## SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

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