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Viral Hepatitis

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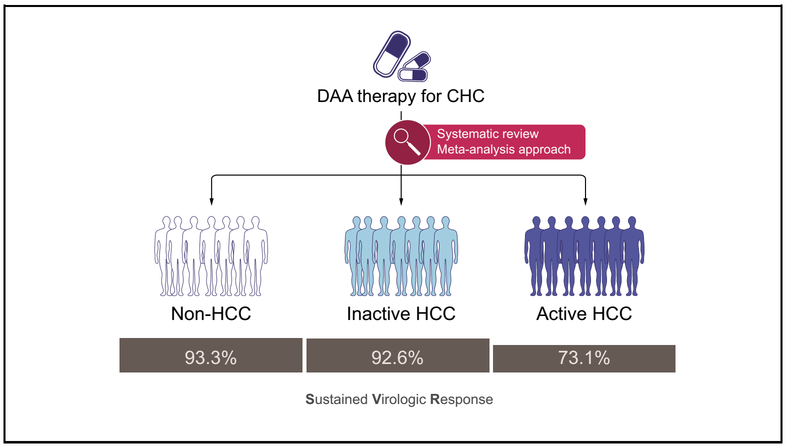
Sustained virologic response to direct-acting antiviral therapy in patients with chronic hepatitis C and hepatocellular carcinoma: A systematic review and meta-analysis

Graphical abstract



Highlights

- The present study summarizes the SVR rate in patients with/without liver cancer treated with all oral DAAs.
- The cure rate was lower in patients with liver cancer, especially those with active cancer.
- Additional controlled studies are needed to study the impact of liver cancer on HCV cure rate in DAA-treated patients.

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Lay summary

There are now medications (direct-acting antivirals or "DAAs) that can "cure hepatitis C virus, but patients with hepatitis C and liver cancer may be less likely to achieve cure than those without liver cancer. However, patients with liver cancer are also more likely to have advanced liver disease and risk factors that can decrease cure rates, so better controlled studies are needed to confirm these findings.

http://dx.doi.org/10.1016/j.jhep.2019.04.017
 J. Hepatol. 2019, 71, 473–485

JOURNAL OF HEPATOLOGY

Sustained virologic response to direct-acting antiviral therapy in patients with chronic hepatitis C and hepatocellular carcinoma: A systematic review and meta-analysis

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Background & Aims: The effect of hepatocellular carcinoma (HCC) on the response to interferon-free direct-acting antiviral (DAA) therapy in patients with chronic hepatitis C (CHC) infection remains unclear. Using a systematic review and meta-analysis approach, we aimed to investigate the effect of DAA therapy on sustained virologic response (SVR) among patients with CHC and either active, inactive or no HCC.

Methods: PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials were searched from 1/1/2013 to 9/24/2018. The pooled SVR rates were computed using DerSimonian-Laird random-effects models.

Results: We included 49 studies from 15 countries, comprised of 3,341 patients with HCC and 35,701 without HCC. Overall, the pooled SVR was lower in patients with HCC than in those without HCC (89.6%, 95% CI 86.8–92.1%, $I^2 = 79.1\%$ *vs.* 93.3%, 95% CI 91.9–94.7%, $I^2 = 95.0\%$, $p = 0.0012$), translating to a 4.8% (95% CI 0.2–7.4%) SVR reduction by meta-regression analysis. The largest SVR reduction (18.8%) occurred in patients with active/residual HCC *vs.* inactive/ablated HCC (SVR 73.1% *vs.* 92.6%, $p = 0.002$). Meanwhile, patients with HCC who received a prior liver transplant had higher SVR rates than those who did not ($p < 0.001$). Regarding specific DAA regimens, patients with HCC treated with ledipasvir/sofosbuvir had lower SVR rates than patients without HCC (92.6%, n = 884 *vs.* 97.8%, n = 13,141, $p = 0.026$), but heterogeneity was high ($I^2 = 84.7\%$, $p < 0.001$). The SVR rate was similar in patients with/without HCC who were treated with ombitasvir/paritaprevir/ritonavi r ± dasabuvir (n = 101) (97.2% *vs.* 94.8%, $p = 0.79$), or daclatasvir/asunaprevir (91.7% *vs.* 89.8%, $p = 0.66$).

Conclusion: Overall, SVR rates were lower in patients with HCC, especially with active HCC, compared to those without HCC, though heterogeneity was high. Continued efforts are needed to aggressively screen, diagnose, and treat HCC to ensure higher CHC cure rates.

Keywords: Asian; Non-Asian; Liver transplant; Real-world analysis; HCC treatment.
Received 23 July 2018; received in revised form 31 March 2019; accepted 25 April 2019; available online 13 May 2019

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Lay summary: There are now medications (direct-acting antivirals or "DAAs") that can "cure" hepatitis C virus, but patients with hepatitis C and liver cancer may be less likely to achieve cure than those without liver cancer. However, patients with liver cancer are also more likely to have advanced liver disease and risk factors that can decrease cure rates, so better controlled studies are needed to confirm these findings.

Introduction

Chronic hepatitis C virus (HCV) infection affected an estimated 71.1 million patients worldwide in 2015 and is a leading cause of liver cirrhosis and hepatocellular carcinoma (HCC).[1] Among patients who have undergone treatment with curative intent for HCC, early hepatic decompensation and HCC recurrence were the major drivers of mortality.[2] In recent studies of chronic hepatitis B-related HCC, antiviral therapy was shown to significantly reduce overall long-term mortality even in patients with very advanced HCC or decompensated cirrhosis, including those who were only receiving palliative treatment for HCC.[3–6] Prior to the advent of interferon (IFN)-free direct-acting antiviral (DAA) therapy, patients with HCV-related HCC were often excluded from anti-HCV therapy as they tended to be older and had multiple non-liver and liver comorbidities, many of which rendered them unsuitable candidates for IFN-based therapy. Since 2014, many of these patients with HCC became treatment candidates for their chronic hepatitis C (CHC), despite the presence of advanced liver disease and comorbidities, as DAA therapy is not only highly efficacious but well tolerated.[7] Individual real-world studies to date have included patients with HCC from both the East and West, and some have reported significantly lower cure rates.[8–14] However, most studies had small sample sizes and heterogeneous patient demographic and clinical characteristics.

Therefore, we performed a systematic review and meta-analysis to evaluate the effect of HCC on cure rates in DAA-treated patients with CHC, taking into account various viral, host and tumor factors.

Materials and methods

Search strategy and selection criteria

This study was performed based on a pre-defined and registered protocol (PROSPERO: CRD42017079155). We searched PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials for relevant studies published from January 1, 2013 to September 24, 2018 without language restrictions. The search strategy, developed by a medical librarian (MBB), included ("direct-acting antiviral" OR "DAA") AND ("hepatocellular carcinoma" OR "HCC" OR "carcinoma, hepatocellular" OR "liver cancer" OR "liver neoplasms") AND ("hepatitis C" OR "hepatitis C antibodies" OR "hepatitis C antigens" OR "hepacivirus") (further details in supplementary information). We also manually searched the reference lists of included articles and relevant systematic reviews for additional appropriate studies to include in this analysis. In addition, we contacted authors of relevant studies to clarify inclusion/exclusion criteria and/or for additional aggregate data as needed for data analysis, including subgroup analyses.

Three independent reviewers (FPJ, MTW and BW) screened the titles and abstracts for eligibility using a pre-planned list of inclusion/exclusion criteria. Eligible studies were original research studies published as full articles, which included at least 10 adult (≥18 years) patients with HCV-related HCC who were treated with IFN-free DAAs and reported SVRs separately for patients with HCC. We did not include articles that only recruited patients without HCC. SVRs may be measured 12 or 24 weeks after the end-of-treatment. We excluded studies that included >5% of patients co-infected with hepatitis B or human immunodeficiency virus, or if we did not have sufficient data to calculate SVRs. If there were multiple reports from the same cohort, the most recent report or the most complete one including subgroup data was selected.

Data extraction

Three reviewers (FPJ, MTW and BW) screened the full texts according to the inclusion/exclusion criteria and extracted data separately, with discrepancies resolved by consensus with 2 other investigators (YHY and MHN). Following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement for reporting meta-analyses of observational studies,[15] we developed a case report form to abstract the following information from each study: The first author's name, year of publication, study design, study type, study country, scale of study (single *vs.* multicenter), patient demographics including age, gender, study location (Asia *vs.* outside Asia), severity of liver disease (non-cirrhosis *vs.* cirrhosis and compensated cirrhosis *vs.* decompensated cirrhosis), prior history of HCV treatment (treatment naïve *vs.* treatment experienced), tumor status (active tumor *vs.* inactive tumor), non-transplant tumor treatment prior to DAA therapy (radiofrequency ablation [RFA]/surgical resection/transarterial chemoembolization [TACE]/others), liver transplantation for tumor prior to antiviral therapy (HCC non-LT *vs.* HCC/LT), HCV genotype (GT) and DAA regimens. Treatment outcomes were determined by SVR (SVR at 12 or 24 weeks after completion of therapy). For studies with outcomes for both SVR 12 and 24, we extracted the former data. Intention-to-treat analyses were favored over modified intention-to-treat or per-protocol analyses for studies that provided both measures. If relevant data were not readily accessible, authors were contacted for additional data and/or for clarification. We reported this systematic review and meta-analysis in accordance with the PRISMA statement.[16,17]

Quality assessment

The quality of included studies was appraised by 2 authors independently using the modified Newcastle-Ottawa scale (NOS), which was used for observational studies in the meta-analysis.[18] In this scale, observational studies were scored across 3 categories: Selection (up to 4 points), comparability (up to 2 points), and exposure or outcome of study participants (up to 3 points). Studies with a cumulative score ≥7, 4–6, and <4 were considered as high, fair, and low quality, respectively. Disagreements in the above procedures were resolved by joint re-evaluation of the full text with a third investigator (MHN or YHY).

Statistical analyses

The primary outcome of this study was the pooled SVR rate in patients with or without HCC, pooled SVR rate by regimen and/or GT, and overall SVR by study location (Asia *vs.* outside

Asia). We performed a meta-analysis of proportion to compute the pooled estimates by using a random-effects model (DerSimonian-Laird Method). Given that the SVR rates in many studies were very high and close to 100%, we employed the Freeman-Tukey double arcsine transformation to transform the pooled estimates and stabilize the variance.[19] All 95% CIs were estimated using the Wilson score method. Heterogeneity across the included studies was assessed using Cochran Q-statistics and I^2 statistics, with I^2 statistics <50%, 50–75%, and >75% considered as mild, moderate, and severe heterogeneity, respectively. We conducted subgroup analyses to determine the source of heterogeneity. In addition, we performed random-effects meta-regression to examine whether the heterogeneity could be explained by the variables in subgroup analyses. To determine the difference in SVR (and corresponding 95% CI) between the pooled estimates of 2 subgroups, we back-transformed the output of meta-regression and computed the difference between intercept and estimate of relevant variable. As this is a meta-analysis of studies of proportion data, we used the method described by Peters *et al.* to evaluate for publication bias.[20] All statistical analyses were conducted using the *meta* and *ggplot2* packages in R(3.3.2).[21,22] The threshold of statistical significance was set as a 2-tail p value below 0.05.

For further details regarding the materials used, please refer to the CTAT table and supplementary information.

Results

Of the 6,249 citations identified from PubMed, Embase, Web of Science, Cochrane Databases, and an additional 44 studies identified via manual bibliography review, 49 full-text studies, comprising 3,341 patients with HCC and 35,701 without HCC were included in the final analysis (Fig. 1).[8–12,23–66] We also contacted authors and obtained further detailed data from 1,070 patients with HCC and 8,714 without HCC in 20 studies.[12,23–25,27–29,31,34,35,37,39,46,47,50,53,58–61] The included studies were conducted in 15 countries: Japan (18), USA (7), Italy (6), Egypt (3), France (3), China (2), Spain (2), and 1 each from United Kingdom, Germany, Switzerland, Romania, Belgium, Australia, Canada, and Poland.

A summary of study characteristics is shown in Table 1. Regarding the quality of studies, 35 were considered high quality with cumulative NOS score of 7 points or greater,[8,9,11,12,23–25,27–33,35–40,42–44,46,47,49,53,54,56,58–60,62–64] and the remaining 14 studies had fair quality (4–6 points) (Table S1).[10,26,34,41,45,48,50–52,55,57,61,65,66]

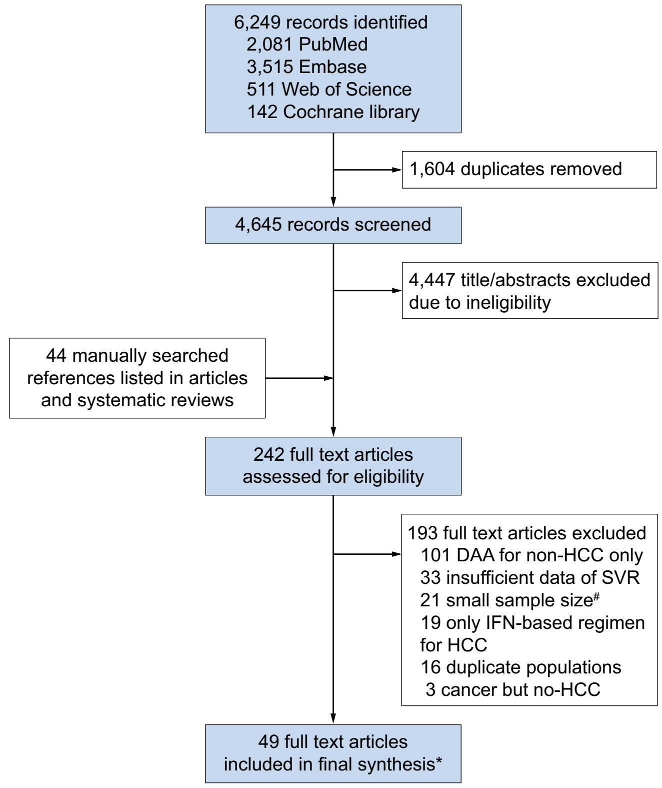

Fig. 1. Flow chart of the study screening and selection for inclusion in the meta-analysis. #<10 Patients with HCC in all IFN-free DAA regimens. *Japan (18), USA (7), Italy (6), France (3), Egypt (3), Spain (2), China (2), Germany (1), Switzerland (1), Romania (1), Belgium (1), Australia (1), UK (1), Canada (1), Poland (1). DAA, direct-acting antiviral; IFN, interferon; HCC, hepatocellular carcinoma; SVR, sustained virologic response.

Comparison of pooled SVR rates for all patients with or without HCC, overall and by DAA regimen

The overall SVR rate for all 39,042 patients included in the 49 studies was 91.8% (95% CI 90.5–93.0%) (Fig. 2, Table S2). The overall SVR rate among patients with HCC (n = 3,341) was lower than in those without HCC (n = 35,701) (89.6%, 95% CI 86.8–92.1% *vs.* 93.3%, 95% CI 91.9–94.7%, p = 0.0012). On meta-regression analysis, patients with HCC had a 4.8% (95% CI 0.2–7.4%) reduction in SVR rate compared to those without HCC. Publication bias analysis showed no significant bias in either the HCC group (p = 0.17), or the non-HCC group (p = 0.109).

In stratified analyses by DAA regimen, SVRs in patients with HCC treated with any sofosbuvir (SOF)-based regimen (n = 1,694) were lower than SVRs of patients without HCC treated with SOF-based regimens (n = 26,355) (86.7%, 95% CI 82.1–90.8% *vs.* 94.6%, 95% CI 92.7–96.2%, p <0.0001).[8–10,12,25,34–44,46,47,50,53–55,59,61–65] The same trend was noted for those treated with ledipasvir/sofosbuvir (LDV/SOF) (92.6%, 95% CI 85.9–97.5% [n = 884 HCC] *vs.* 97.8%, 95% CI 95.0–99.6% [n = 13,141 non-HCC], p = 0.026) (Table S2, Fig. S2),[8,25,34–38,47,53,55] corresponding to a 9.2% (95% CI 3.0–13.2%) and 6.4% (95% CI −1.7 to 12.5%) reduction in SVR on meta-regression analyses, respectively.

In contrast, SVR rates were similar in patients with or without HCC who received ombitasvir/paritaprevir/ritonavir ± dasabuvir (3D/2D) (97.2%, 95% CI 92.2–99.9% [n = 101 HCC], *vs.* 94.8%, 95% CI 92.3–96.9% [n = 5,438 non-HCC], p = 0.79)[8,46,58–60] or daclatasvir/asunaprevir (DCV/ASV) (91.7%, 95% CI 88.4–94.5% [n = 584 HCC] *vs.* 89.8%, 95% CI 87.7–91.7% [n = 2,997 non-HCC], p = 0.66) (Fig. 3, Figs. S3 and S4, Table S2).[23–32]

Comparison of pooled SVR rates for patients with inactive HCC or no HCC, overall and by DAA regimen

The overall SVR rate among patients with inactive HCC was 92.0% (95% CI 89.4–94.3%), which was still lower than that of patients without HCC (94.5%, 95% CI 93.0–95.9%, p = 0.0111) (Fig. S5).[9,11,23–42,46–53,57–58,60–64,66] The presence of inactive HCC was associated with a 3.6% (95% CI 0.9–6.1%) reduction in SVR rate on meta-regression analysis. The pooled SVR rate with SOF-based regimens was also lower in those with inactive HCC

Table 1. Eligible studies listed by region (Asia then non-Asia) and by country within each region in the order of decreasing number of studies.

Ref.	Country/area	Genotype	Regimen	SVR 12 or 24	SVR in HCC patient (n/N, %)	SVR in non-HCC patients (n/N, %)	Subgroup analysis Included*
23	Japan	GT1b	DCV/ASV	SVR 12	96/111, 86.5%	469/540, 86.9%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; TE *vs.* TN; LC *vs.* non-LC; LT *vs.* non-LT; Active *vs.* inactive
24	Japan	GT1b	DCV/ASV	SVR 12	55/59, 93.2%	235/262, 89.7%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; TE *vs.* TN; LC *vs.* non-LC; LT *vs.* non-LT; Active *vs.* inactive
25	Japan	GT1/2	DCV/ASV LDV/SOF ± RBV SOF + RBV	SVR 24	143/167, 85.6%	943/1022, 92.3%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT
26	Japan	GT1	DCV/ASV	SVR 12	12/12, 100%	106/111, 95.5%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; Active *vs.* inactive
27	Japan	GT1	DCV/ASV	SVR 12	83/91, 91.2%	473/550, 86.0%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LC *vs.* non-LC; LT *vs.* non-LT; Active *vs.* inactive
28	Japan	GT1	DCV/ASV LDV/SOF ± RBV	SVR 12	15/16, 93.8%	83/85, 97.6%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; Active *vs.* inactive
29	Japan	GT1b	DCV/ASV	SVR 24	22/22, 100%	116/123, 94.3%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LC *vs.* non-LC; LT *vs.* non-LT; Active *vs.* inactive; LT/surgical resection/local ablation *vs.* TACE/others
30	Japan	GT1b	DCV/ASV	SVR 12	28/30, 93.3%	152/176, 86.4%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; Active *vs.* inactive
31	Japan	GT1	DCV/ASV	SVR 12	107/120, 89.2%	448/509, 88.0%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LC *vs.* non-LC; LT *vs.* non-LT; Active *vs.* inactive
32	Japan	GT1	DCV/ASV	SVR 24	27/34, 79.4%	79/86, 91.9%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; Active *vs.* inactive
33	Japan	GT1/2	DCV/ASV LDV/SOF ± RBV 2D ± RBV SOF + RBV	SVR 24	76/83, 91.6%	646/669, 96.6%	LT *vs.* non-LT; LT/surgical resection/local ablation *vs.* TACE/others
34	Japan	GT1/2	DCV/ASV LDV/SOF ± RBV SOF + RBV	SVR 12	23/27, 85.2%	–	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; LC *vs.* non-LC; Active *vs.* inactive; LT/surgical resection/local ablation *vs.* TACE/others
35	Japan	GT1b	LDV/SOF ± RBV	SVR 12	84/88, 95.5%	679/684, 99.3%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; TE *vs.* TN; LC *vs.* non-LC; Active *vs.* inactive
36	Japan	GT1	LDV/SOF ± RBV	SVR 12	41/43, 95.3%	195/197, 99.0%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT;
37	Japan	GT1	LDV/SOF ± RBV	SVR 12	41/46, 89.1%	473/484, 97.7%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; LC *vs.* non-LC; Active *vs.* inactive
38	Japan	GT1	LDV/SOF	SVR 12	152/159, 95.6%	1286/1302, 98.8%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; Active *vs.* inactive
39	Japan	GT2	SOF + RBV	SVR 12	19/20, 95%	408/426, 95.8%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; TE *vs.* TN; LC *vs.* non-LC; Active *vs.* inactive
40	Japan	GT2	SOF + RBV	SVR 12	23/29, 79.3%	137/153, 89.5%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; Active *vs.* inactive
41	Mainland China	GT1b	SOF/DCV + RBV	SVR 12	10/10, 100%	20/21, 95.2%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; TE *vs.* TN; LC *vs.* non-LC; Active *vs.* inactive; LT/surgical resection/local ablation *vs.* TACE/others

(*continued on next page*)

Table 1 (*continued*)

Ref.	Country/area	Genotype	Regimen	SVR 12 or 24	SVR in HCC patient (n/N, %)	SVR in non-HCC patients (n/N, %)	Subgroup analysis Included*
42	Taiwan	GT1/2/3/6	SOF/DCV + RBV	SVR 12#	20/20, 100%	99/104, 95.2%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; Active *vs.* inactive
8	USA	GT1/2/3/4	LDV/SOF ± RBV 2D/3D ± RBV SOF ± RBV	SVR£	439/553, 79.4%	13851/15200, 91.1%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; TE *vs.* TN; LC *vs.* non-LC; LT/surgical resection/local ablation *vs.* TACE/others
9	USA	GT1/2/3/other	LDV/SOF ± RBV SOF + RBV SOF/SMV ± RBV 3D ± RBV	SVR 12	106/135, 78.5%	251/284, 88.4%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LC *vs.* non-LC; Active *vs.* inactive
43	USA	GT1/2/3/4	SOF + RBV	SVR 12	30/43, 69.8%	–	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; LC *vs.* non-LC; Active *vs.* inactive
44	USA	GT1	SOF/SMV ± RBV	SVR 12	10/16, 62.5%	146/183, 79.8%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV;
10	USA	GT1/2/3/4	LDV/SOF ± RBV SOF + RBV SOF + SMV ± RBV	SVR 12	14/21, 66.7%	–	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; Active *vs.* inactive
12	USA	GT1/2/3/6	LDV/SOF ± RBV SOF + SMV ± RBV SOF + RBV SOF/DCV	SVR 12	14/17, 82.4%	88/93, 94.6%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT
45	USA	GT1/2/3/4/6	LDV/SOF ± RBV SOF/SMV ± RBV SOF/DCV ± RBV 2D/3D ± RBV SOF + RBV	SVR 12	48/62, 77.4%	–	LT *vs.* non-LT
46	Italy	GT1/2/3/4	LDV/SOF ± RBV SOF/SMV ± RBV SOF/DCV ± RBV 2D/3D ± RBV SOF + RBV	SVR 12	78/85, 91.8%	437/471, 92.8%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; Active *vs.* inactive
47	Italy	GT1b	LDV/SOF ± RBV	SVR 12	23/23, 100%	389/401, 97.0%	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; LC *vs.* non-LC; Active *vs.* inactive
48	Italy	GT1/2/4	LDV/SOF ± RBV SOF/SMV ± RBV SOF/DCV ± RBV 2D/3D ± RBV SOF + RBV	SVR 12	26/31, 83.9%	–	LT *vs.* non-LT
49	Italy	GT1/2/3	LDV/SOF ± RBV SOF/SMV ± RBV SOF/DCV ± RBV 2D/3D ± RBV SOF + RBV	SVR 12	138/143, 96.5%	–	–
11	Italy	GT1/2/3/4	LDV/SOF ± RBV SOF/SMV ± RBV SOF/DCV ± RBV SOF + RBV VIEKIRAX ± EXVIERA	SVR 12	153/161, 95.0%	1679/1766, 95.1%	LT *vs.* non-LT; LC *vs.* non-LC; Active *vs.* inactive
55	Italy	GT1/2/3/4	LDV/SOF ± RBV SOF/SMV ± RBV SOF/DCV ± RBV SOF + RBV	SVR 12	29/30, 96.7%	–	LT *vs.* non-LT; LC *vs.* non-LC
50	France	GT1/2/3/4/6	LDV/SOF ± RBV SOF/SMV ± RBV SOF/DCV ± RBV 2D/3D ± RBV SOF + RBV	SVR 12	22/23, 95.6%	–	SOF-based *vs.* 2D/3D *vs.* DCV/ASV; LT *vs.* non-LT; LC *vs.* non-LC; Active *vs.* inactive
51	France	GT1/2/3	LDV/SOF ± RBV SOF/DCV ± RBV 3D ± RBV SOF + RBV	SVR 12	19/22, 86.4%	–	LC *vs.* non-LC; Active *vs.* inactive

(*continued on next page*)

Table 1 (*continued*)

Ref.	Country/area	Genotype	Regimen	SVR 12 or 24	SVR in HCC patient (n/N, %)	SVR in non-HCC patients (n/N, %)	Subgroup analysis Included*
52	France	GT1/others	LDV/SOF ± RBV SOF/SMV ± RBV SOF/DCV ± RBV SMV/DCV 3D ± RBV SOF + RBV	SVR 12[&]	248/256, 96.9%	–	LT *vs.* non-LT; Active *vs.* inactive; LT/surgical resection/ local ablation *vs.* TACE/others
53	Germany	GT1/4	LDV/SOF ± RBV	SVR 12	20/20, 100%	31/31, 100%	SOF-based *vs.* 2D/3D *vs.* DCV/ ASV; LT *vs.* non-LT; Active *vs.* inactive
54	UK	GT1/3/others	LDV/SOF ± RBV SOF/DCV ± RBV	SVR 24	18/29, 62.1%		SOF-based *vs.* 2D/3D *vs.* DCV/ ASV; LC *vs.* non-LC
56	Spain	GT1/3/4/5	LDV/SOF ± RBV SOF/SMV ± RBV SOF/DCV ± RBV SMV/DCV + RBV 2D/3D ± RBVSOF + RBV	SVR 12	101/116, 87.1%	102/122, 83.6%	LT *vs.* non-LT; LC *vs.* non-LC; Active *vs.* inactive
57	Spain	GT1/3/4	LDV/SOF ± RBV SOF/SMV ± RBV SOF/DCV ± RBV SMV/DCV 3D ± RBV	SVR 12	39/40, 97.5%	–	LT *vs.* non-LT; Active *vs.* inactive
58	Australia	GT1	3D ± RBV	SVR 12	30/31, 96.8%	399/420, 95%	SOF-based *vs.* 2D/3D *vs.* DCV/ ASV; LT *vs.* non-LT; Active *vs.* inactive
59	Belgium	GT1/2/3/4/5	SOF/SMV ± RBV SOF/DCV ± RBV3D ± RBV	SVR 12	36/43, 83.7%	509/536, 95.0%	SOF-based *vs.* 2D/3D *vs.* DCV/ ASV
60	Romania	GT1b	3D ± RBV	SVR 12	12/14, 85.7%	1987/2056, 96.6%	SOF-based *vs.* 2D/3D *vs.* DCV/ ASV; LT *vs.* non-LT; LC *vs.* non-LC; Active *vs.* inactive
61	Switzerland Germany Belgium	GT1/2/3/4	LDV/SOF ± RBV SOF/SMV ± RBV SOF/DCV ± RBV SOF + RBV	SVR 12	40/47, 85.1%	–	SOF-based *vs.* 2D/3D *vs.* DCV/ ASV; LT *vs.* non-LT; Active *vs.* inactive
62	Egypt	GT4	SOF/SMV ± RBV	SVR 12	18/20, 90%	5821/6191, 94.0%	SOF-based *vs.* 2D/3D *vs.* DCV/ ASV; Active *vs.* inactive
63	Egypt	NA	LDV/SOF ± RBV SOF/SMV ± RBV SOF/DCV ± RBV SOF + RBV	SVR 12	41/53, 77.4%	–	SOF-based *vs.* 2D/3D *vs.* DCV/ ASV; LT *vs.* non-LT; LC *vs.* non-LC; Active *vs.* inactive; LT/surgical resection/local ablation *vs.* TACE/others
64	Egypt	GT4	SOF/SMV SOF/DCV ± RBV SOF + RBV	SVR 12	40/62, 64.5%	–	SOF-based *vs.* 2D/3D *vs.* DCV/ ASV; LT *vs.* non-LT; LC *vs.* non-LC; Active *vs.* inactive
65	Canada	GT1/2/3/4/6	LDV/SOF ± RBV SOF/SMV ± RBV SOF/DCV ± RBV SOF + RBV	SVR 12	32/39, 82.1%	56/66, 84.8%	SOF-based *vs.* 2D/3D *vs.* DCV/ ASV; LT *vs.* non-LT; LC *vs.* non-LC; Active *vs.* inactive
66	Poland	NA	NA	SVR 12	18/19, 94.7%	–	LT *vs.* non-LT; Active *vs.* inactive; LT/surgical resection/ local ablation *vs.* TACE/others

2D, paritaprevir/ritonavir/ombitasvir; 3D, paritaprevir/ritonavir/ombitasvir + dasabuvir; ASV, asunaprevir; DCV, daclatasvir; GT1/2/3, genotype 1/2/3; HCC, hepatocellular carcinoma; IFN, interferon; LC, liver cirrhosis; LDV, ledipasvir; LT, liver transplant; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment experience; TN, treatment naïve; VEL, velpatasvir.

[£]SVR based on viral load >12 weeks after the end-of-treatment, if no viral load test was available >12 weeks, defined SVR by a viral load performed 4–12 weeks post-treatment

[#]Patients treated with SOF/RBV, LDV/SOF, and VEL/SOF were not included in analysis due to more than 5% co-infection with HBV or HIV.

[&]Patients in HEPATHER cohort were not included in analysis due to 17 patients treated with IFN-based regimen and cannot get sufficient data to calculate SVR in IFN-free regimen.

*Depending on available data, included studies may contribute data to one or both comparison arm.

than in patients without HCC (90.1%, 95% CI 85.0–94.3 *vs.* 96.4%, 95% CI 94.8–97.7, $p = 0.0009$),[9,25,34–42,46–47,50,53,61–64] as it was in those treated with LDV/SOF (93.3%, 95% CI 87.1–97.8% *vs.* 98.4%, 95% CI 97.4–99.2%, $p = 0.0047$) (Fig. S6),[25,34–38,47,53] corresponding to a 7.9% and 5.5% reduction in SVR on meta-regression analyses, respectively.

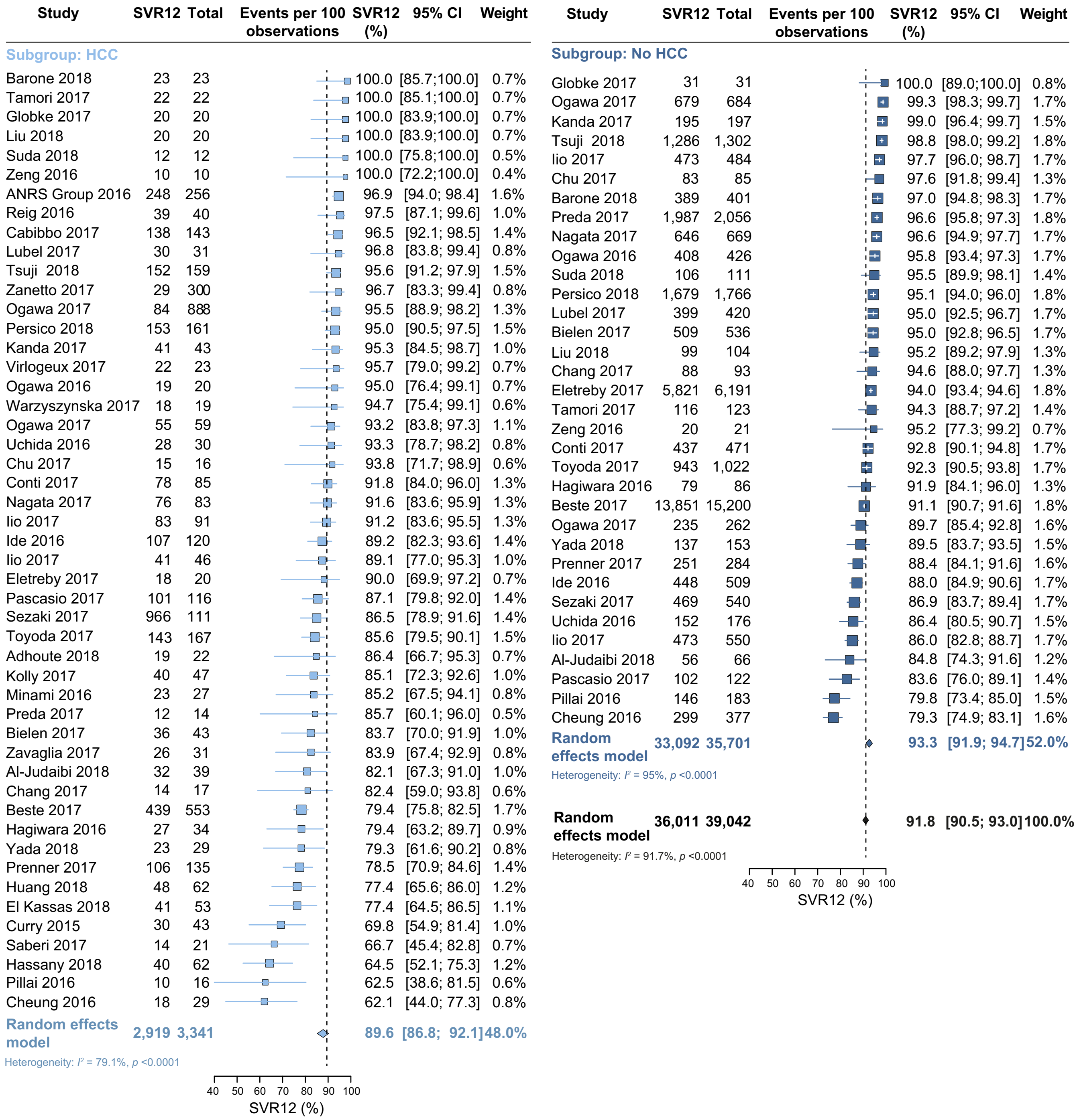

Fig. 2. The pooled SVR rates for all patients with or without HCC. The dotted vertical line and the diamond represent the summary effect (random effects model), with outer edges representing the 95% CI. The overall SVR rate in patients with HCC (n = 3,341) was lower than in those without HCC (n = 35,701) (89.6%, 95% CI 86.8–92.1 *vs.* 93.3%, 95% CI 91.9–94.7%, $p = 0.0012$). HCC, hepatocellular carcinoma; SVR, sustained virologic response; SVR12, SVR at week 12.

Comparison of pooled SVR rates of GT1-infected patients with or without HCC, overall and by DAA regimens

Among GT1-infected patients treated with any DAA regimen, the decrease in the pooled overall SVR rates between patients with HCC (n = 1,703) and without HCC (n = 21,310) was modest but statistically significant (92.1%, 95% CI 89.3–94.6% *vs.* 94.2%, 95% CI 92.1–96.0%, $p = 0.044$) (Fig. 3, Table S2).[8,10,12,23–32,34–38,41,44,46–47,53,55,59–61] For GT1-infected patients treated with a SOF-based regimen, there was a significant reduction of 6.8% (95% CI −1.8–12.8%) in SVR rate between patients with HCC (n = 911) and those without HCC (n = 13,233) (90.8%, 95% CI 84.4–95.8%, *vs.* 96.4%, 95% CI 93.5–98.5%, $p = 0.017$).[8,10,12,25,34–38,41,44,47,53,55] For the subgroup of LDV/SOF-treated patients, there was also a significant SVR reduction of 7.7% (95% CI −0.2 to 14.2%) in patients with HCC (n = 736) compared to those without HCC (n = 12,853) (91.3%, 95% CI 83.1–97.2% *vs.* 98.1%, 95% CI 95.7–99.7%, $p = 0.016$).[8,25,28,34–38,47,53] Conversely, there were no significant differences between GT1-infected patients with or without HCC who were treated with 2D/3D[8,58,60] or DCV/ASV,[23–32] with a small sample size of n = 87 for the

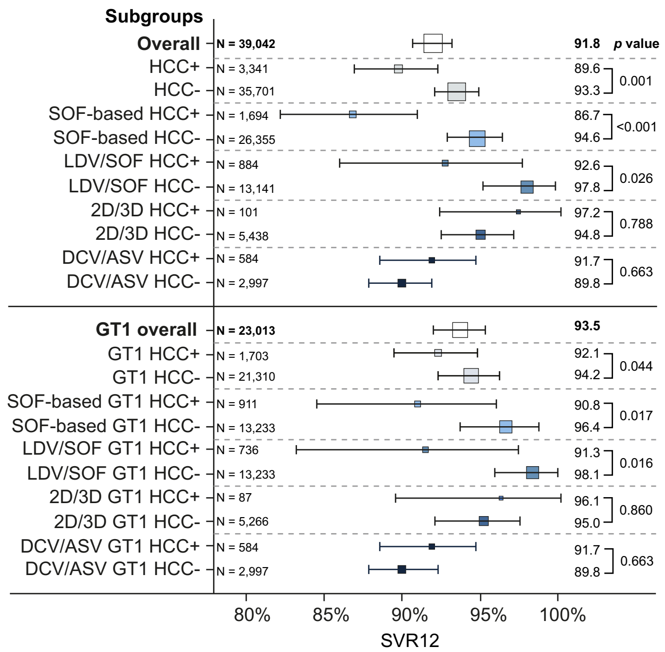

Fig. 3. SVR rates of DAAs for overall HCV population and HCV genotype 1-infected patients, by presence of HCC. Horizontal bars represent 95% CI and the sizes of box represent relative sample size. Levels of significance: 2-tailed *p* value (threshold: 0.05) was determined by meta-regression. 2D, ombitasvir/paritaprevir/ritonavir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; ASV, asunaprevir; DCV, daclatasvir; DAA, direct-acting antiviral; GT1, genotype 1; HCC, hepatocellular carcinoma; LDV, ledipasvir; SOF, sofosbuvir; SVR, sustained virologic response.

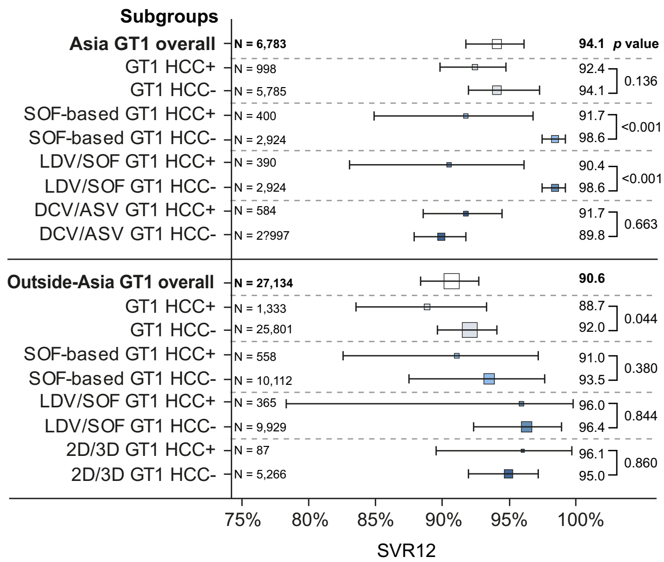

Fig. 4. SVR rates of DAAs in HCV genotype 1-infected patients in Asia and outside Asia, by presence of HCC. Horizontal bars represent 95% CI and the sizes of box represent relative sample size. Levels of significance: 2-tailed *p* value (threshold: 0.05) was determined by meta-regression. 2D, ombitasvir/paritaprevir/ritonavir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; ASV, asunaprevir; DCV, daclatasvir; DAA, direct-acting antiviral; GT1, genotype 1; HCC, hepatocellular carcinoma; LDV, ledipasvir; SOF, sofosbuvir; SVR, sustained virologic response.

2D/3D group and data without stratification by resistance-associated variants for the DCV/ASV group (Fig. 3, Table S2).

Comparison of pooled SVR rates of GT1-infected patients with or without HCC, by study location and DAA regimen

For analysis of patients from Asia, there were a total of 20 studies (18 from Japan and 2 from Taiwan and Mainland China), comprising 998 GT1-infected patients with HCC and 5,785 without HCC. There was no significant difference in SVR rates between GT1-infected patients with or without HCC in Asia (92.4%, 95% CI 89.7–94.8% *vs.* 94.1%, 95% CI 91.9–97.4%, $p = 0.136$) (Fig. 4).[23–32,34–38,41] However, SOF-treated, GT1-infected, Asian patients with HCC (n = 400) had lower SVR rates than their counterparts without HCC (n = 2,924) (91.7%, 95% CI 84.6–96.9% *vs.* 98.6%, 95% CI 97.6–99.4%, $p < 0.001$).[25,34–38,41] A similar difference in SVR rates was also seen in the LDV/SOF subgroup (90.4%, 95% CI 82.7–96.2% [n = 390 HCC], *vs.* 98.6%, 95% CI 97.6–99.4% [n = 2,924 non-HCC], $p < 0.001$) (Fig. S7).[25,28,34–38] While DCV/ASV-treated, GT1-infected, Asian patients with HCC had a similar SVR rate (91.7%, 95% CI 88.4–94.5% [n = 584]) to those without HCC (89.8%, 95% CI 87.7–91.7% [n = 2,997], $p = 0.66$) (Fig. 4, Table S3).[23–32]

Analysis of studies from outside Asian countries included 29 studies (7 from the USA, 6 from Italy, 3 from Egypt, 3 from France, 2 from Spain, 1 each from the other 8 countries represented in this study) and a total of 1,333 GT1-infected patients with HCC and 25,801 without HCC. SVRs trended lower in patients with HCC compared to those without HCC (88.7%, 95% CI 83.2–93.3% *vs.* 92.0%, 95% CI 89.5–94.1%, $p = 0.103$) (Fig. 4, Table S3).[8,9,43,44,46,47,49,50,53–56,58–61] Patients with or without HCC treated with any SOF-based or LDV/SOF regimens had similar pooled SVR rates, but with high accompanying heterogeneity (Fig. S8).

In addition, GT2-infected patients with HCC who were treated with SOF + RBV had a lower SVR rate than patients without HCC in the overall population (81.4%, 95% CI 70.6–90.4% [n = 125 HCC], *vs.* 92.8%, 95% CI 87.2–96.9% [n = 2,743 non-HCC], $p = 0.016$), with a 12.9% (95% CI −3.5 to 26.6%) reduction in SVR rate (Fig. S9).[8,25,39,40,46]

Subgroup analysis for patients with HCC

By DAA regimen

Among 3,341 patients with HCC, there were 2,381 HCC (all GTs) and 1,629 GT1-infected patients with sufficient data to estimate pooled SVR rates by DAA regimen. The pooled SVR rate for patients with HCC of any GTs was significantly lower for SOF-based regimens (86.8%, 95% CI 82.2–90.8%, n = 1,696)[8–10,12,25,34–44,46–47,50,53–55,59,61–65] when compared to 2D/3D (97.2%, 95% CI 92.2–99.9%, n = 101)[8,46,58,60] and DCV/ASV (91.7%, 95% CI 88.4–94.5%, n = 584) ($p = 0.011$) (Fig. 5, Fig. S10).[23–32] However, SVR rates were similar among GT1-infected patients treated with different DAA regimens ($p = 0.365$) (Fig. S11).

By history of LT

Compared to patients with HCC without a prior history of LT (n = 2,496),[8,11,12,23–43,45–48,50,55–58,60–62,64–66] patients with HCC who received an LT (n = 401) achieved a higher SVR rate (96.7%, 95% CI 94.1–98.7% *vs.* 90.3%, 95% CI 87.3–93.0%, $p < 0.001$) (Fig. S12, Table S4).[8,52,53] As all patients with HCC and a history of prior LT were from outside Asia, we performed further sub-analysis by LT history for patients outside Asia only and found that the difference in SVRs of patients with HCC by LT history (n = 401) *vs.* non-LT (n = 1,309) was even more evident: 96.7%, 95% CI 94.1–98.7% *vs.* 87.7%, 95% CI 82.3–92.4%, $p < 0.001$ (Fig. 5, Fig. S13, Table S4), corresponding to a

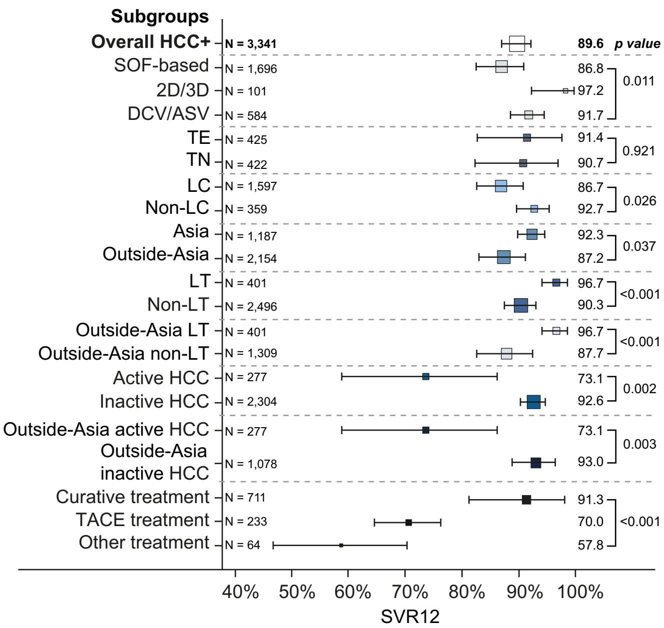

Fig. 5. Subgroup analyses of SVR rates in patients with HCV-related HCC. Horizontal bars represent 95% CI and the sizes of box represent relative sample size. Levels of significance: 2-tailed *p* value (threshold: 0.05) was determined by meta-regression. 2D, ombitasvir/paritaprevir/ritonavir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; ASV, asunaprevir; DCV, daclatasvir; HCC, hepatocellular carcinoma; LC, liver cirrhosis; SOF, sofosbuvir; TACE, transarterial chemoembolization; TE, treatment experienced; TN, treatment naïve.

9.8% (95% CI −3.4 to 17.4%) increase in SVR rate on meta-regression analysis.[8,11,12,43,45–48,50,52,53,55–58,60–62,64–66]

By active vs. inactive status of HCC

Overall, patients with active HCC (viable tumor on imaging, n = 277)[9,10,43,56,65] at the time of DAA treatment had significantly lower SVRs than those with inactive HCC (absence of residual tumor/complete necrosis, n = 2,304) (73.1%, 95% CI 57.9–86.0% *vs.* 92.6%, 95% CI 90.2–94.7%, *p* = 0.002) (Fig. 5, Fig. S14, Table S4).[9,11,23–42,46–53,57–58,60–64,66] Meta-regression analysis showed that an 18.8% (95% CI 7.3–31.8%) reduction in SVR rate was associated with the presence of active HCC. Since all patients with active HCC were from studies outside Asia, we performed additional sub-analysis to include only patients from studies outside Asia and found similar results (n = 277, 73.1%, 95% CI 57.9–86.0% *vs.* n = 1,078, 93.0%, 95% CI 88.7–96.5%, *p* = 0.003) (Fig. 6, Table S4), and with even higher SVR reduction of 19.5% (95% CI 4.2–36.0) in the presence of active HCC.[9–11,43,46–53,56–58,60–66]

By study location

Patients with HCC from Asia (n = 1,187) had significantly higher SVRs than patients with HCC not from Asia (n = 2,154) overall (92.3%, 95% CI 89.7–94.6% *vs.* 87.2%, 95% CI 82.7–91.1%, *P* = 0.037), but not in further sub-analysis of GT1-infected patients only (n = 998 in Asia and n = 680 not in Asia) (Fig. 5, Fig. S15, Table S4).[8,23–32,34–39,41,44,46,47,53,55,58–61]

By history of prior treatment failure

Patients with HCC without prior treatment histories (n = 422) and those with prior treatment failures (n = 425) had similar SVR rates (90.7%, 95% CI 82.0–97.0% *vs.* 91.4%, 95% CI 82.4–97.7%, *p* = 0.92) (Fig. 5, Table S4).[8,23,24,35,39,41] Similar findings were seen in further sub-analyses of GT1-infected patients only (94.8%, 95% CI 88.8–98.9%, n = 93 no prior treatment history *vs.* 92.8%, 95% CI 85.0–98.2%, n = 175 treatment failures, *p* = 0.59) (Fig. S13).[23,24,35,41]

By presence of cirrhosis

There was a lower pooled SVR rate in patients with HCC and cirrhosis (n = 1,597) than in those without cirrhosis (n = 359) (86.7%, 95% CI 82.3–90.7% *vs.* 92.7%, 95% CI 89.5–95.4%, *p* = 0.026) (Fig. S16).[8,9,11,23,24,27,29,31,34,35,37,39,41,43,45,47,50,51,54–56,60,63–65] In the subgroup analysis of GT1-infected patients with HCC who were further stratified by DAA regimen in addition to cirrhosis, there were no statistically significant differences between DCV/ASV-treated GT1-infected patients with HCC, with or without cirrhosis (n = 277, 89.3%, 95% CI 84.9–93.1% *vs.* n = 118, 93.5%, 95% CI 87.9–97.7%, *p* = 0.26, respectively), or between SOF-treated GT1-infected patients with HCC, with or without cirrhosis (n = 157, 95.4%, 95% CI 88.4–99.6% *vs.* n = 45, 95.8%, 95% CI 86.9–100%, *p* = 0.904, respectively) (Fig. S15, Table S4).

By HCC treatment modality prior to DAA treatment

Comparing prior treatment modalities, patients with HCC treated with LT/surgical resection/local ablation achieved a higher SVR rate than patients who received TACE or other modalities (n = 711, 91.3%, 95% CI 80.9–98.2% *vs.* n = 223, 70.0%, 95% CI 63.8–75.8% *vs.* n = 64, 57.8%, 95% CI 45.5–69.7%, *p* = 0.0002, respectively) (Fig. 5, Tables S4, 5).[8,29,33,34,41,52,63,66]

By treatment duration for patients treated with SOF-based regimens

Overall, there was no significant difference in the SVR rates between SOF-based regimens prescribed for 12 and 24 weeks (n = 391, 91.4%, 95% CI 83.4–97.4% *vs.* n = 38, 92.2%, 95% CI 85.0–97.6%, *p* = 0.71, respectively) (Table S6).[10,25,28,34–37,39,41,44,47,53,62]

Discussion

In this study, we pooled 49 articles (3,341 patients with HCC and 35,701 without HCC) and compared the pooled SVR rates in patients with or without HCC. To determine the source of heterogeneity and obtain more clinically relevant data, we categorized patients by several viral and host factors (*e.g.* HCV GT, HCC activity, prior HCV treatment status, presence of cirrhosis) as well as types of DAA treatment and study location to assess predictors for the lower SVR rates seen in patients with HCC (89.6%, 95% CI 86.8–92.1%) compared to those without HCC (93.3%, 95% CI 91.9–94.7%, *p* = 0.0012), and even in patients with inactive HCC. Except for those with active HCC, the overall cure rate with DAA treatment in patients with HCC was high, including those with cirrhosis and prior treatment failure.

Overall, patients with HCC who received SOF-based and LDV/SOF regimens experienced lower SVR rates compared to patients without HCC, with a 9.2% and 6.4% SVR reduction, respectively. Patients with HCC were more to have cirrhosis and those with cirrhosis in our study had lower SVR rates (86.7%, 95% CI 82.3–90.7% *vs.* 92.7%, 95% CI 89.5–95.4%, *p* = 0.026). Even among those without cirrhosis, patients with HCC may have had more advanced liver disease with poorer hepatic function. There were no significant SVR differences between patients with or without HCC treated with 2D/3D or

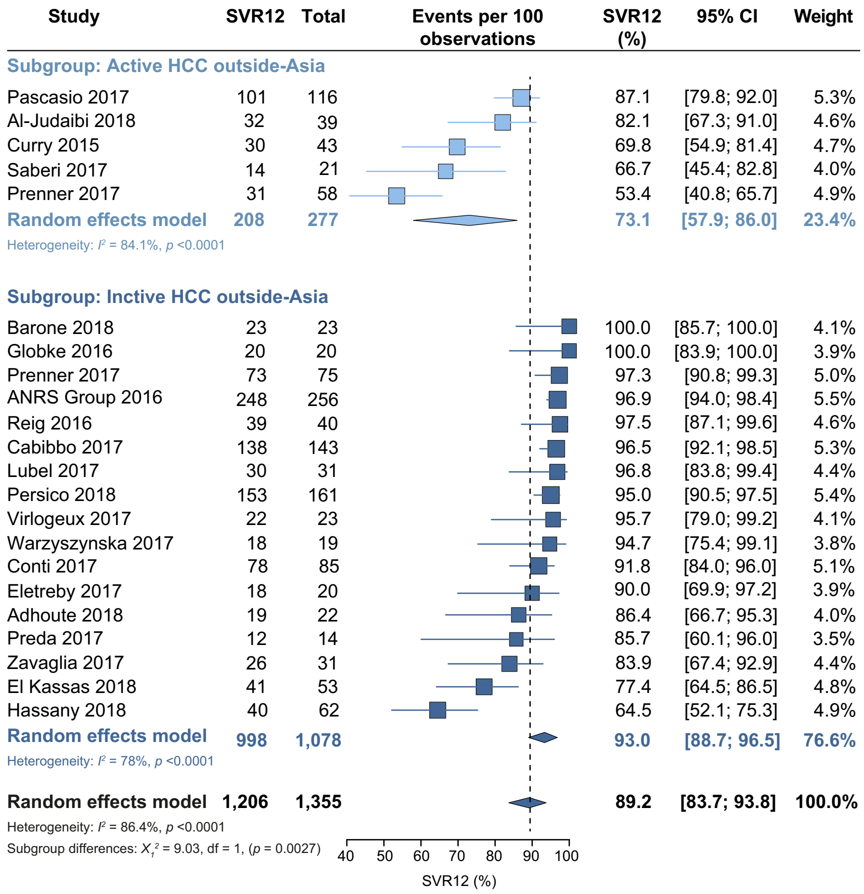

Fig. 6. Subgroup analysis of SVR rates in DAA-treated patients with active versus inactive HCC outside Asia. The dotted vertical line and the diamond represent the summary effect (random effects model), with outer edges represent the 95% CI. Patients with active HCC had lower SVRs than patients with inactive HCC (73.1%, 95% CI 57.9–86.0 *vs.* 93.0%, 95% CI 88.7–96.5, $p = 0.0027$). DAA, direct-acting antiviral; IFN, interferon; HCC, hepatocellular carcinoma; SVR, sustained virologic response; SVR12, SVR at 12 weeks.

DCV/ASV regimens. However, the 2D/3D regimen was used in only 101 patients with HCC from studies outside Asia, limiting comparability among the different DAA regimens. In addition, the 2D/3D regimen may have been avoided in patients with HCC and more severe liver disease, and this selection bias towards SOF-based patients with more severe liver disease may have had a greater impact on SVRs than the presence of HCC.[8–10,54,56] In the case of DCV/ASV, the presence of baseline resistance-associated variants, a major predictor for SVR for this regimen,[13,23,24,27,30–31] was not controlled in the analysis of SVRs in the majority of the downstream studies of this meta-analysis.[23,24,27,30,31] Therefore, conclusions regarding the effect of specific DAA regimens on the SVRs of patients with HCC require additional investigations.

With regards to treatment duration, there was a trend for higher SVR in GT1-infected patients treated with LDV/SOF for 24 weeks compared to 12 weeks (Table S6).[10,25,28,34–37,47,53] Indeed, a recent study showed that a 12-week treatment regimen with LDV/SOF alone may be suboptimal for GT1-infected patients with cirrhosis.[47] Larger studies are needed to determine the superiority of 24 weeks over 12 weeks of DAAs in the treatment of patients with HCC.

Another important finding of our study was that the overall SVR rate with all oral DAA treatments in patients with active HCC was significantly lower than in those whose HCC had been treated (no residual or active HCC). Specifically, patients with active HCC had a 18.8% reduction in SVR rate compared to patients with inactive HCC. The mechanism of lower SVR rates in patients with active HCC is not completely clear. HCC may function as a reservoir for HCV replication, or lead to distortion of liver architecture and alter liver inflammation, decrease drug delivery of DAAs, or lead to the development of resistant strains in HCC.[67,68] In fact, it has been suggested that HCC should be suspected in high-risk patients who fail to achieve SVRs with DAA therapy, as HCC diagnosis tends to follow shortly afterwards, *i.e.* these patients already harboured HCC that served as a reservoir for re-infection.[69,70]

Among patients with HCC who have undergone treatment for HCC, those with curative treatments (LT/surgical resection/local ablation) prior to DAA therapy were also found to have a higher SVR rate than those with only palliative treatments such as TACE and other regimens (sorafenib or Y-90 radioembolization) subgroups. This finding lends further support to the notion that residual tumor might contribute to the lower SVR rate observed in patients with HCC. Another reason may be that patients with HCC often have cirrhosis and thus may have impaired innate and adaptive immune responses due to reduced cytotoxicity of natural killer cells and T cell exhaustion,[71] leading to suboptimal SVRs in DAA-treated patients. This mechanism is partially in doubt due to the results observed in patients with HCC who received LT from studies (presumably tumor free and no cirrhosis). In fact, they had a 7.3% (95% CI −3.2 to 12.9%) increase in SVR compared to non-LT patients with HCC (mostly cirrhotic, some not tumor free), in spite of immunosuppression use in post-LT patients. As a result, the optimal timing of HCV treatment for patients with HCC awaiting LT is still unresolved. A recent study showed that the threshold model for end-stage liver disease score to treat non-HCC pre-LT patients with HCV infection is 23–27,[72] while treatment after LT is cost-effective in patients with HCC and HCV-related cirrhosis.[73] The latter may avoid late relapse that has been reported to occur after LT.[74]

Our study had several strengths: 1) it is the first meta-analysis investigating the impact of HCC on the SVRs of DAA-treated HCV-infected patients; 2) it involved a large number of patients; and 3) a meta-regression was performed to further determine how the pre-planned variables affected the pooled estimates.

Our study had some limitations. First, there was a moderate to high heterogeneity in the analysis of the overall cohort, but we performed subgroup analyses and meta-regression to determine the source of the heterogeneity. Second, due to insufficient data, we could not perform sub-analysis of SVRs in patients with HCC, with compensated and decompensated cirrhosis. Third, the sample size of patients with HCC treated with the 2D/3D regimen was small, and type 2 errors could not be excluded. Fourth, due to limited access to more optimal DAA regimens, some of the included patients received suboptimal therapy such as SOF + RBV for GT1, GT3 and GT4.[9,43,54,56,62–64] Several pan-genotypic DAAs, such as SOF/velpatasvir, grazoprevir/ruzasvir/uprifosbuvir, and glecaprevir/pibrentasvir, were not included in our study due to a lack of primary data.[75–79] Fifth, due to insufficient data, we could not perform sub-analysis of the time interval between HCC treatment and DAA treatment (more than 6 months *vs.* less than 6 months). Sixth, we included studies with HCC cases only and those with HCC and non-HCC cases, but no studies with only non-HCC cases, because of concerns that studies that include only non-HCC cases may select for patients with less advanced disease and may add additional heterogeneity to our findings. At the end, our study design still provided more than 30,000 non-HCC cases for comparison analyses to support the study conclusion. Seventh, we chose to report our meta-regression results for the between-group differences; however, we also performed subgroup analyses to help determine the sensitivity of our findings and found that the p values for the meta-regression and subgroup analyses were similar. Nevertheless, it is important to note that we may have inadvertently introduced ecological fallacy,[80] such that our group conclusions may not be applicable to all individuals, so further studies with individual patient level data may be warranted. Finally, there were significant differences in practice patterns in real-world settings, which may lead to patient selection bias, as well as the impact of baseline characteristics on effectiveness, in the primary studies included in this meta-analysis. Almost all patients with active HCC were from studies outside of Asia because patients with decompensated cirrhosis and untreated HCC are not approved for DAA treatment in Japan, where much of the Asian data originated.[81] This reimbursement policy may be the reason for the more similar SVR rates between patients with or without HCC from Asia. Data for LT patients were also mostly from studies outside Asia, due to better availability of LT in these regions. Therefore, we performed many subgroup analyses by region (Asia *vs.* outside Asia) to avoid some of the confounding effects of these selection biases.

In conclusion, SVR rates were lower in patients with HCC compared to those without HCC overall and especially in those with active HCC. HCC treatment should be considered prior to DAA therapy whenever possible. Patients with HCC who underwent LT achieved a higher SVR rate, but the optimal timing of HCV treatment for patients with HCC awaiting LT will have to be individualized. For some DAAs, differences in SVR rates between patients with and without HCC require additional investigation, especially as antiviral therapy of CHC is a rapidly evolving field, and the new wave of DAAs are achieving even higher SVR rates.

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

Yee Hui Yeo, Mike Tzuhen Wei, Eiichi Ogawa, Masaru Enomoto, Dong Hyun Lee, Etsuko Iio, Wenjun Wang, Bin Wei, Tatsuya Ide, Michelle B Bass, Carmen Monica Preda, Fabio Conti, Rob Bielen, Hitomi Sezaki, Michele Barone, Po-sung Chu, Victor Virlogeux, Dennis Eurich, Takanori Kanai, Shuangsuo Dang, Zongfang Li, Akihiro Tamori: None to disclose. Fanpu Ji: Speaker Gilead Sciences, MSD and Ascletis. John Lubel: Research support (Institutional support only) Abbvie, BMS, MSD; consulting/advisory board Gilead Sciences, Abbvie, Bayer, BMS; speaker Gilead Sciences, Abbvie, Bayer, BMS, Roche, Janssen; travel to international meetings by Bayer Tatsuya Minami; speaker's bureau MSD and Gilead Sciences. Philippe Kolly: Conference fee and travel cost reimbursement Gilead Sciences. Jean-François Dufour: Advisory committees Abbvie, Bayer, BMS, Falk, Genfit, Gilead Science, Intercept, Lilly, Merck, Novartis; speaking and teaching Abbvie, Bayer, BMS, Genfit, Gilead Science, Novartis; unrestricted research grant Bayer. Fabien Zoulim: Consultant for Abbvie and Gilead Sciences. Pietro Andreone: Grant/research support MSD, Abbvie, Gilead Sciences, BMS; advisory board MSD, Gilead Sciences, Abbvie, BMS, INTERCEPT. Ramsey C. Cheung: Grant/research support Gilead Sciences. Norihiro Furusyo: Grant/research support MSD, Gilead Sciences, BMS, Janssen Pharmaceuticals; speaker's bureau Gilead Sciences, MSD, BMS; advisory board Gilead Sciences, Abbvie, BMS. Yasuhito Tanaka: Grant/research support BMS, Gilead Sciences, GSK, Chugai Pharmaceuticals and Janssen Pharmaceuticals; speaker's bureau BMS, MSD, Gilead Sciences. Hidenori Toyoda: Speaker's bureau AbbVie, Gilead Sciences, MSD, Bayer Pharmaceuticals. Mindie Nguyen: Grant/research support Gilead Sciences, Janssen; advisory board member or consultant Gilead Sciences, Janssen.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contribution

All authors: Data contribution, data interpretation, and critical review of the manuscript for important content. FPJ, MTW, BW, YHY, MBB: Literature search and data extraction. FPJ, YHY, EO, ME, DHL, WJW, MB, SSD, ZFL, AT: Study quality assessment. FPJ, YHY, MTW, MHN: Study design and data analysis. FPJ, YHY, MHN: Drafting of the manuscript. MTW, MB, LH, RC: Critical revision of the paper. MHN: Study conception and study supervision.

Acknowledgment

We would like to thank Dr. Guido Schwarzer, PhD for his kind guidance with the R-programming for our meta-regression analysis.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.04.017.

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Author names in bold designate shared co-first authorship

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