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ORIGINAL ARTICLE

Risk of hepatocellular carcinoma occurrence after antiviral therapy for patients with chronic hepatitis C Infection: a systematic review and meta-analysis

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Abstract

Background and Aims The risk of hepatocellular carcinoma (HCC) occurrence following antiviral therapy in patients with chronic hepatitis C (CHC) remains unclear. The current study aims to compare: (1) the HCC occurrence rate following sustained virological response (SVR) versus non-response (NR); (2) the HCC occurrence rate following direct-acting antiviral (DAA) therapy versus interferon (IFN)-based therapy, and (3) the HCC occurrence rate in SVR patients with or without cirrhosis.

Methods A search was performed for articles published between January 2017 and July 2022. Studies were included if they assessed HCC occurrence rate in CHC patients following anti-HCV therapy. Random effects meta-analysis was used to synthesize the results from individual studies.

Results A total of 23 studies including 29,395 patients (IFN-based = 6, DAA = 17; prospective = 10, retrospective = 13) were included in the review. HCC occurrence was significantly lower in CHC with SVR (1.54 per 100 person-years (py, 95% CI 1.52, 1.57) than those in non-responders (7.80 py, 95% CI 7.61, 7.99). Stratified by HCV treatment regimens, HCC occurrence following SVR was 1.17 per 100 py (95% CI 1.11, 1.22) and 1.60 per 100 py (95% CI 1.58, 1.63) in IFN- and DAA treatment-based studies. HCC occurrence was 0.85 per 100 py (95% CI 0.85, 0.86) in the non-cirrhosis population and rose to 2.47 per 100 py (95% CI 2.42, 2.52) in the cirrhosis population. Further meta-regression analysis showed that treatment types were not associated with a higher HCC occurrence rate, while cirrhosis status was an important factor of HCC occurrence rate.

Conclusion HCC occurrence was significantly lower in the SVR population than in the NR population. HCC risk following SVR occurred three times more frequently in patients with cirrhosis than patients without cirrhosis. However, we found no significant difference in HCC occurrence risk following SVR between DAA and IFN therapies.

Clinical trial number CRD42023473033.

Keywords Hepatocellular carcinoma · Chronic hepatitis C virus · Sustained virological response · Direct-acting antiviral · Occurrence

Abbreviations

CHC	Hepatitis C
DAA	Direct-acting antiviral
G1	HCV genotype 1
G2	HCV genotype 2
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
IFN	Interferon
NR	Non-response
OR	Odds ratio
SVR	Sustained virological response

Gui-Ji Lv, Dong Ji, Lingxiang Yu and Hong-Yan Chen are the co-first authors and contributed equally.

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Extended author information available on the last page of the article

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Introduction

Primary liver cancer (PLC), mainly hepatocellular carcinoma (HCC), is the sixth most prevalent malignant tumor worldwide and ranks as the third leading cause of cancer-related mortality due to its poor prognosis [1, 2]. HCC is closely associated with hepatitis virus infection, particularly hepatitis C virus (HCV) [3]. The World Health Organization (WHO) estimated that cirrhosis or HCC caused 290,000 deaths among the HCV-infected population [2]. Achieving sustained virological response (SVR) early in HCV-infected patients can provide significant benefits [4–6]. A previous meta-analysis has demonstrated that SVR is associated with a reduced risk of HCC compared to non-response (NR) [7]. In the past 10 years, there is a paradigm shift from interferon (IFN)-based therapy to pan-oral direct-acting antiviral (DAA) as primary treatment regimens for chronic HCV infection [8, 9]. However, the risk of HCC after SVR with these regimens remains unclear. A study suggested an increased risk of HCC in patients with liver fibrosis/cirrhosis, even post-SVR [10]. To understand these associations, we conducted a systematic review and meta-analysis to compare the HCC occurrence rates between the SVR and NR populations. We also stratified our analysis by treatment regimens (DAA vs. IFN-based therapy) and cirrhosis status (non-cirrhosis vs. cirrhosis) post-SVR.

Materials and methods

Literature search

The PubMed, Embase, Ovid Medline, Cochrane databases, web of Science Core Collection, and CINAHL PLUS were searched by text and MeSH terms spanning from January 2017 to July 2022, using the terms hepatocellular carcinoma, HCC, hepatitis C, HCV, direct-acting antiviral, DAAs, sustained virological response, and SVR. The search process, along with inclusion and exclusion criteria, is illustrated (Fig. 1). This review adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and the review protocol was registered in PROSPERO (CRD42023473033). We used only previously published data, so approval from an ethics committee was not required.

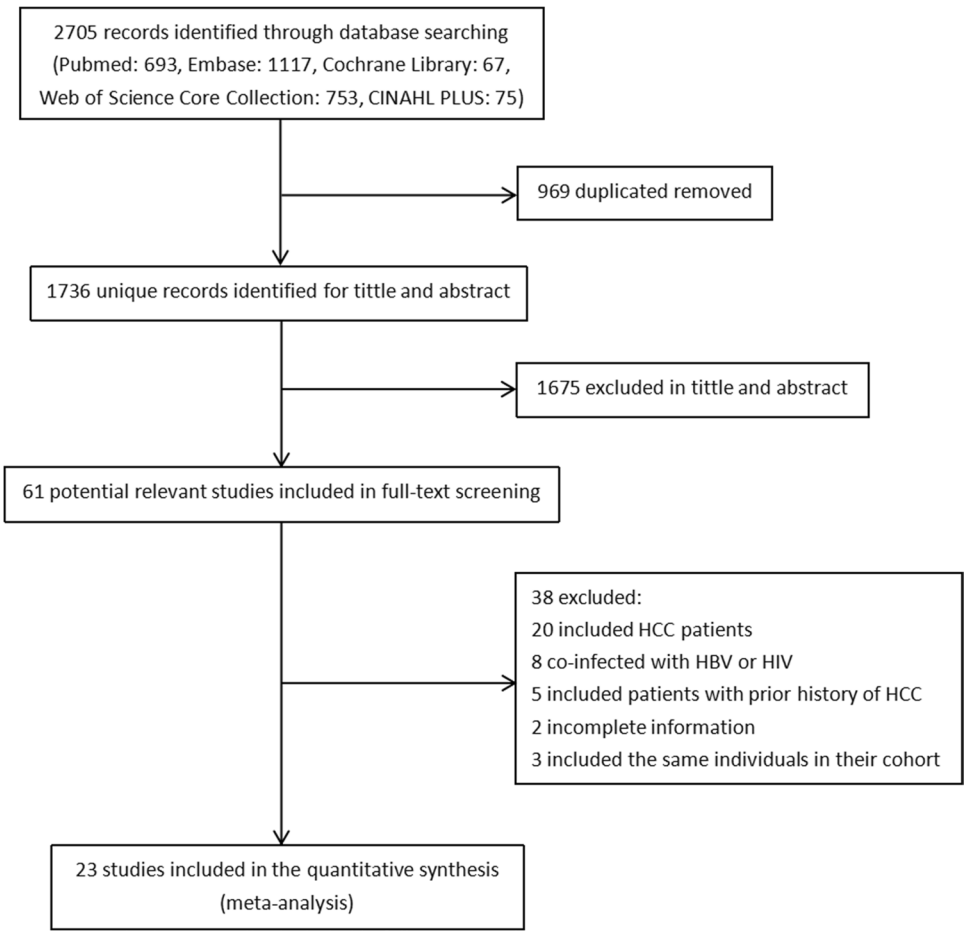


Fig. 1 Summary of record search and selection

Study selection

In this review, the primary outcome was the rate of HCC occurrence following anti-HCV therapy, in patients with different treatments with or without cirrhosis. Sustained virological response (SVR) was defined as undetectable serum HCV RNA for at least 12 weeks follow-up following the completion of anti-HCV therapy. This review mainly focused on retrospective and prospective cohort observational studies. Studies were included if they assessed HCC occurrence in HCV patients after anti-HCV therapy. Studies were excluded if they involved patients with a history of HCC and those co-infected with hepatitis B or human immunodeficiency virus, and not in English. Two authors (GJ. L. and D.J.) independently screened titles and abstracts to identify relevant studies. In case of incomplete or unclear data, two authors conducted joint assessments, and any disagreements were resolved through discussions or with the involvement of a third author (LX.Y.).

Data extraction and quality assessment

Data were extracted independently by two authors (GJ. L. and D.J.) using a standardized form. Extracted information included study design, study year (s), study population characteristics, location of study conducted, number of patients included, number of patients with SVR or NR, number of patients who developed HCC post-SVR or NR, type of anti-HCV treatment (DAA or IFN-based therapy), cirrhosis status (non-cirrhosis vs. cirrhosis), and duration of study follow-up. Studies with complete data were included in the meta-analysis. To assess the risk of bias, a method similar to the Cochrane Risk of Bias tool was used, evaluating study selection, compatibility, and outcomes, rated as low, high, or unclear. [11, 12].

Data synthesis and analysis

HCC occurrence rates, calculated as per 100 person-years (py), were reported using log transformation along with log standard error (SE) for both patients with SVR and NR [7, 13]. Pooled HCC incidence rates per 100 person-years were analyzed using a random effects model, stratified by HCV treatment regimens (DAA or IFN) and cirrhosis status of patients (non-cirrhosis or cirrhosis) post-SVR. Meta-regression analyses were conducted to identify the difference in occurrence rates between HCV therapy regimens and cirrhosis status, respectively. Sensitivity analyses were performed to estimate the HCC occurrence rate based on the risk of bias assessment. Heterogeneity between studies was evaluated using the Q statistic and I^2 statistic. All analyses were conducted by Stata (16.0, StataCorp LLC, College Station, Texas).

Results

The search strategy yielded 2705 records. After removing duplicates, 1736 titles or abstracts were screened, resulting in the selection of 61 publications for full-text review and assessment for inclusion. Ultimately, 23 studies met the inclusion criteria, consisting of 17 studies with DAA treatment [14–30] and 6 with IFN-based treatment (Fig. 1.) [31–36] Of these studies, 8 involved patients without cirrhosis, [14, 15, 18, 20–22, 24, 27] and 15 involved patients with cirrhosis [14, 15, 17, 18, 20–24, 26, 27, 31, 33, 34, 36]. Included studies comprised 13 retrospective and 10 prospective observational cohort studies. The total sample size was 29,395 and the average sample size was 1278 (range, 34–5,814, Table 1). Study details are displayed in Table 2.

Table 1 Summary of baseline on HCC occurrence

Group	Study baseline characteristics					Study outcome		
	Patients (studies), *n*	Age	Male, (%)	Genotype G1/G2/others, (%)	AFP, ng/ml	Treatment outcome, (%) SVR/NR	Follow-up, years	Post-SVR HCC rate, 100 py
HCV treatment								
DAA	25,638 (17)	64	50.3	78.1/21.8/0.1	7.2	95.3/4.7	2.9	1.6
IFN	3,757 (6)	56	49.7	62.8/28.4/9.8	10.1	59.5/40.5	4.3	1.2
Cirrhosis status								
Without cirrhosis	10,541 (8)	65	43.5	73.8/26.1/0.1	5.6	97.1/2.9	3.6	0.9
With cirrhosis	8,994 (15)	63	45.2	67.4/30.5/2.1	7.8	95.2/4.8	3.6	2.5

Table 2 Summary of study characteristics

Study	HCV treatment	Patients, *n*	Age	Male (%)	Genotype G1/G2/others (%)	AFP, ng/ml	Fibrosis/cirrhosis	follow-up duration (years)	HCC rate/100 py (95% CI) SVR/NR
Ampuero [14]	DAA	1054	57‡	65.4	NA	7.2	58.0%	4.1†	1.3/– (1.0,1.7)/–
Tamaki [15]	DAA	3823	67†	42.4	NA	1.6	26.2%	3.0†	1.3/– (1.1,1.5)/–
Joshita [16]	DAA	932	69†	41.2	69.3/30.3/0.4	4.1	26.2%	2.1†	1.4/– (0.9,2.0)/–
Kilany [17]	DAA	1630	55‡	72.7	0/0/100	7.8	100%	1.9‡	1.9/5.6 (1.5,2.5)/ (3.4,10.4)
Ide [18]	DAA	2552	64‡	39.3	78.1/21.8/0.1	10.0	25.4%	1.9‡	1.4/– (1.1,1.8)/–
Lusivika-Nzinga [19]	DAA	3045	59‡	76.7	NA	NA	18.1%	3.1†	2.6/8.7 (2.3,2.9)/ (7.0,10.9)
Abe [20]	DAA	1086	67†	47.1	67.4/31.9/0.7	4.0	17.6%	3.6†	1.0/– (0.7,1.4)/–
MawatariI [21]	DAA	1494	67‡	40.4	80.0/19.9/0.1	9.5	67.0%	4.0†	1.0/– (0.8,1.3)/–
Flisiak [22]	DAA	192	54‡	55.2	95.3/NA/NA	NA	57.3%	5.0‡	1.2/– (0.7,2.2)/-
Kozbial [23]	DAA	551	57‡	61.2	86.4/NA/NA	3.4	100%	1.3†	2.2/– (1.4,3.6)/-
Tanaka [24]	DAA	5814	64‡	42.3	69.7/NA/NA	NA	51.9%	2.9†	1.5/4.7 (1.3,1.7)/ (3.2,7.0)
Akuta [25]	DAA	958	64†	46.7	99.6/NA/NA	5.0	NA	1.1†	1.3/– (0.8,2.2)/–
Muzica [26]	DAA	479	60†	45.5	NA	9.3	100%	5.0‡	1.0/– (0.6,1.4)/–
Kumada [29]	DAA	567	72†	44.6	69.5/30.5/0	2.8	38.1%	3.6†	0.9/– (0.5,1.3)/–
Watanabe [28]	DAA	1212	65†	46.4	NA	10.6	5.1%	1.5†	1.9/3.5 (1.3,2.6)/ (1.0,11.9)
Yoo [29]	DAA	95	66‡	50.5	100/0/0	NA	89.0%	1.9†	2.9/– (1.2,6.6)/–
Nagaoki [30]	DAA	154	73†	37.7	100/0/0	16.9	54.5%	1.9†	2.4/– (1.2,4.9)/–
Lu [31]	IFN	50	63‡	44.0	56.0/26.0/18.0	23.6	NA	7.5†	2.9/– (1.6,5.2)/–
Tahata [32]	IFN	2121	58†	49.5	69.6/30.4/–	2.5	8.2%	3.5†	0.7/– (0.5,0.9)/–
Ji [33]	IFN	34	55‡	38.2	52.9/47.1/–	12.2	100%	3.4‡	4.3/– (1.9,9.7)/–
Nagaoki [34]	IFN	210	65†	45.2	65.2/NA/NA	7.2	100%	9.2†	1.7/2.9 (1.1,2.7)/ (2.0,4.4)
Ji [35]	IFN	757	50‡	44.1	71.5/26.4/2.1	NA	NA	4.0†	0.8/– (0.6,1.2)/–
Innes [36]	IFN	585	48‡	77.1	NA	10.1	100%	4.6‡	1.3/– (0.9,1.8)/–

†median

‡mean

NA not available

Summary of baseline characteristics

The included studies involved a total of 29,395 patients, with 25,638 receiving DAA and 3757 receiving IFN. Compared to DAA studies, IFN-based studies had a lower proportion of patients with HCV genotype 1 (62.8% vs. 78.1%, $p = 0.152$) and a higher proportion of patients with HCV genotype 2 (28.4% vs. 21.8%, p = 0.294). Patients treated with IFN were younger (mean age 56 vs. 64 years, p = 0.034), with higher level of alpha-fetoprotein (AFP) (10.1 vs. 7.2 ng/ml, $p = 0.298$) and longer follow-up (4.3 vs. 2.9 years, $p = 0.017$). SVR was achieved by 95.3% and 59.5% of patients treated with DAAs and IFN-based therapy, respectively (Table 1). DAA studies showed a broader geographical distribution (Europe = 4, Asia = 11, Oceania = 1 and Africa = 1) compared to IFN-based studies (Europe = 1, Asia = 5). Compared to patients without cirrhosis, a lesser proportion of patients with cirrhosis were of HCV genotype 1 (67.4% vs. 73.8%, $p = 0.315$) and a greater proportion of patients with cirrhosis were of genotype 2 (30.5% vs. 26.2%, $p = 0.718$). Patients with cirrhosis were younger (mean age 63 vs. 65 years, $p = 0.299$), with higher level of AFP (7.8 vs. 5.6 ng/ml, $p = 0.378$), and longer follow-up (3.6 vs. 3.6 years, $p = 0.717$) (Table 1). SVR was achieved by 95.2% of patients with cirrhosis and by 97.1% of patients with cirrhosis, and these studies exhibited a more diverse geographical distribution (Europe = 4, Asia = 9, Oceania = 1 and Africa = 1) compared to non-cirrhosis patients (Europe = 2, Asia = 6).

HCC occurrence following SVR.

Following HCV treatment, the HCC occurrence rate was 1.54/100 py (95% CI 1.52, 1.57) and 7.80/100 py (95% CI 7.61, 7.99) in the SVR population and NR population, respectively (Fig. 2A, B). Stratified by HCV treatment regimens, the occurrence rate of HCC following SVR was 1.60/100 py (95% CI 1.58, 1.63) and 1.17/100 py (95% CI 1.11, 1.22) in the DAA and IFN-based studies, respectively (Fig. 3A, B). Analysis stratified by cirrhosis group suggested that the occurrence rate of HCC following SVR was 0.85/100 py (95% CI 0.85, 0.86) and 2.47/100 py (95% CI 2.42, 2.52) in non-cirrhosis studies and cirrhosis studies, respectively (Fig. 4A, B). Heterogeneity between studies was significant both in treatment and cirrhosis status populations ($p < 0.001$ with I^2 exceeding 90%). Meta-regression showed that treatment types had no impact on the result of meta-analysis, but cirrhosis status could sufficiently explain the difference (Table 3). In sensitivity analysis, each study was evaluated for overall effect and no significant difference was found in the two groups' meta-analysis (therapy group: OR 0.41, 95% CI 0.25, 0.57; cirrhosis group: OR 0.31, 95% CI 0.09, 0.52).

Quality assessment.

The potential risk of bias was low for most studies (Table 4; Fig. 5). Small sample studies may increase the risk of bias (Fig. 5).

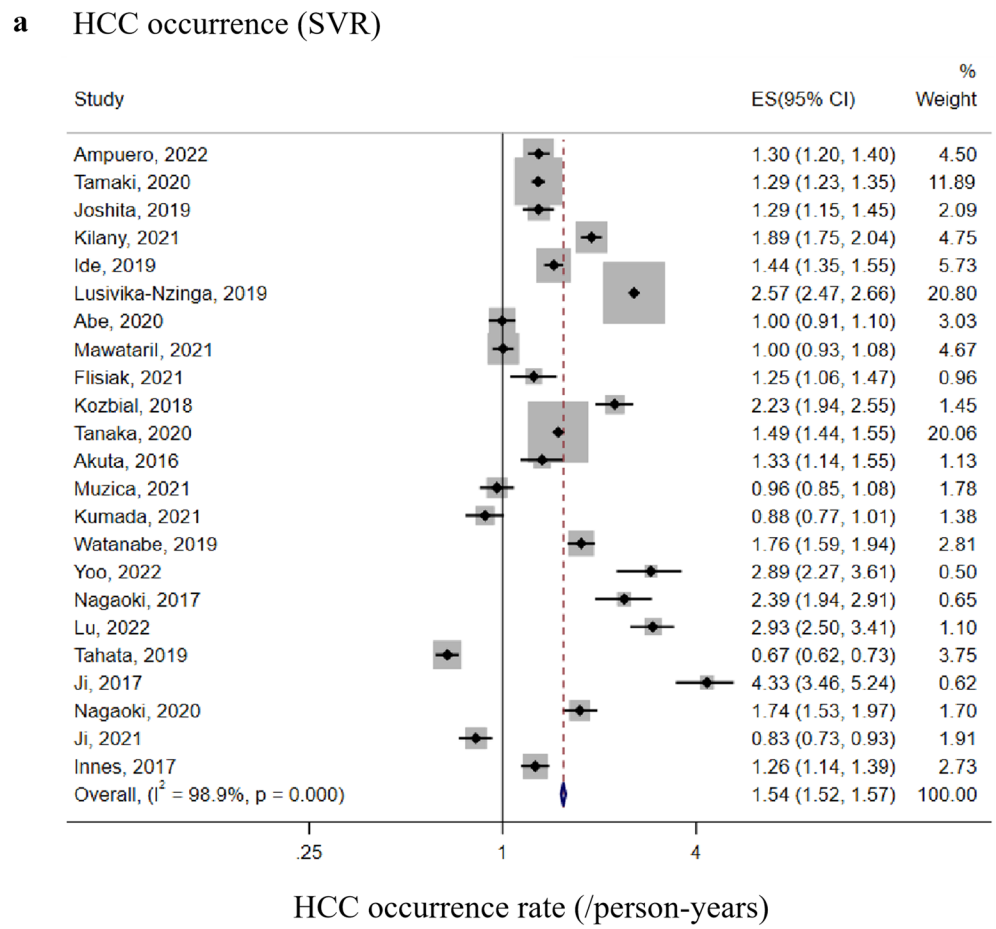
Discussion

Our systematic review and meta-analysis, incorporating evidence from 23 studies, assessed the risk of HCC development in HCV-infected patients who attain SVR or NR, stratified by regimens (DAA or IFN treatment) and cirrhosis status (cirrhosis or non-cirrhosis). Our analysis showed that the risk of HCC occurrence was significantly lower in those with SVR. Importantly, we found no substantial difference in HCC risk post-SVR between patients treated with DAAs or IFN-based therapy and the HCC occurrence risk occurred three times more frequently in patients with cirrhosis than patients without cirrhosis.

Patients in early stages of liver disease present better liver function and are more likely to respond to anti-HCV treatment than those with advanced liver disease [37]. Initiating IFN-based treatment in the early stages of liver fibrosis significantly enhances the likelihood of achieving SVR, while DAA treatment could achieve SVR regardless of the liver fibrosis stages. Our meta-analysis showed that the risk of post-SVR HCC occurred three times more frequently in the cirrhosis group than in the non-cirrhosis group. This underscores the significance of early treatment to increase the likelihood of achieving SVR. Given that patients with cirrhosis have threefold higher baseline risk for HCC development compared to patients without cirrhosis, earlier anti-HCV treatment should be performed in patients with advanced liver disease to prevent the development of HCC, resulting in a greater overall benefit.

Previous reviews have shown that SVR was a protective factor associated with the potential reversibility of fibrosis and cirrhosis, offering promising therapeutic prospects for patients with advancing fibrosis [38–40]. Our review provided evidence supporting a differential effect on the risk of HCC between cirrhosis and non-cirrhosis, and it was important to acknowledge that cirrhosis was a potential risk factor for HCC occurrence in HCV patients [41, 42]. When comparing DAA with IFN-based regimen, our review found no evidence to support a differential effect on the risk of developing HCC between the two regimens Therefore, when weighing the pros and cons of anti-HCV treatment, it is essential to take into account the association between SVR and the risk of HCC.

The older age in DAA-treated population versus IFN-based treated population, as indicated in our baseline characteristics, may offer an explanation for the observed



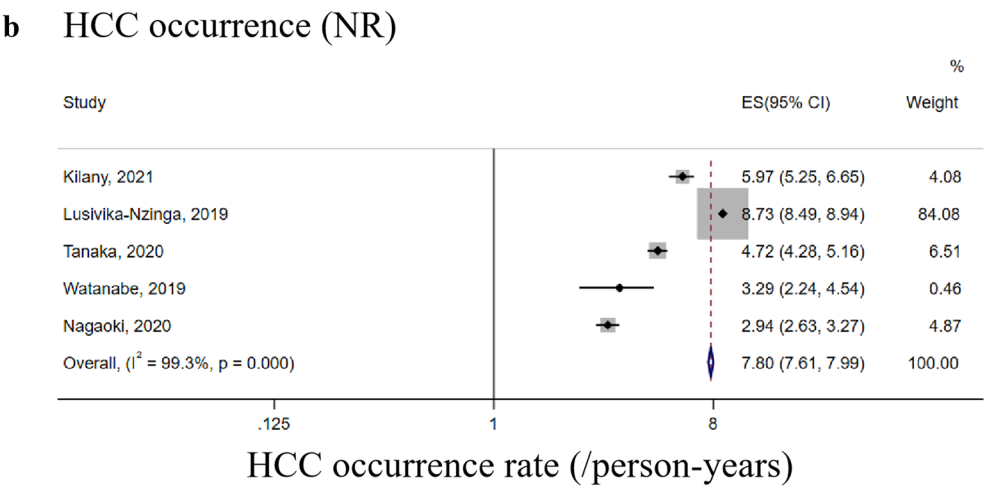


Fig. 2 HCC occurrence rate in SVR and NR patients. **a** HCC occurrence rate in SVR patients. **b** HCC occurrence rate in NR patients

association between DAA therapy and a seemingly higher risk of HCC in previous studies. Older age has been identified as one of the predictors for HCC occurrence [43]. Moreover, HCC incidence was also related to the duration of follow-up, with cases undiagnosed at baseline assessment more likely to be diagnosed as new-onset HCC cases after a short period of DAA treatment. A recent study showed that the risk of HCC, after the adjustment

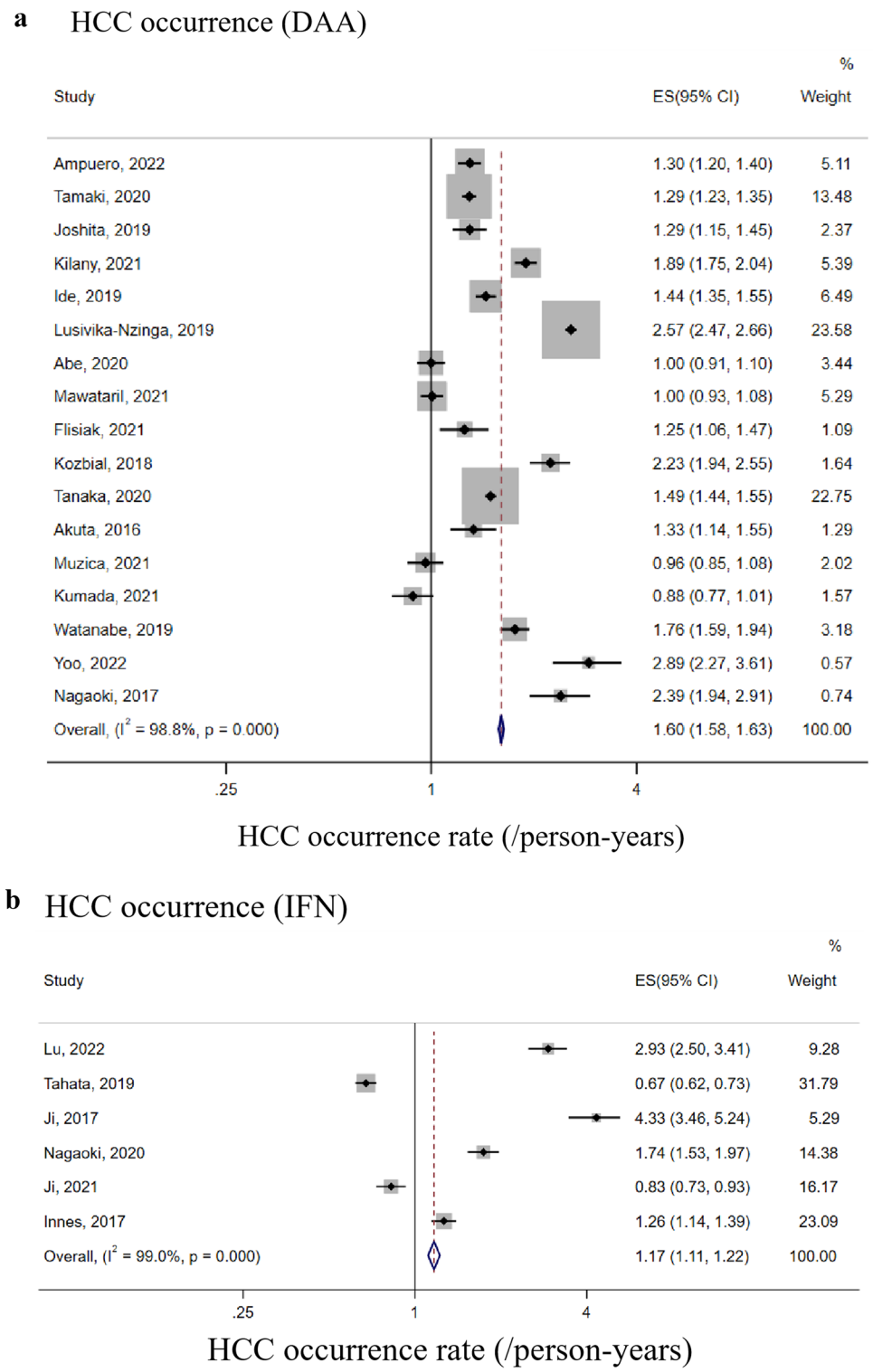


Fig. 3 HCC occurrence rate by DAA and IFN treatments in SVR patients. **a** HCC occurrence rate by DAA treatments in SVR patients. **b** HCC occurrence rate by IFN treatments in SVR patients

of age and follow-up duration, does not appear to be higher in patients treated with DAA [44]. Considering the elderly population and the limitations of IFN application, DAA therapy holds great promise in preventing liver disease progression and reducing the incidence of HCV-related HCC. Recent studies have also suggested that DAA-induced HCV clearance can improve the outcomes of patients at all stages of liver disease [7]. Our systematic review provides compelling evidence that DAA therapy reduces the risk of HCC by 70%, supporting its continued application. To enhance the relevant research, accelerating DAA therapy studies can provide more evidence-based

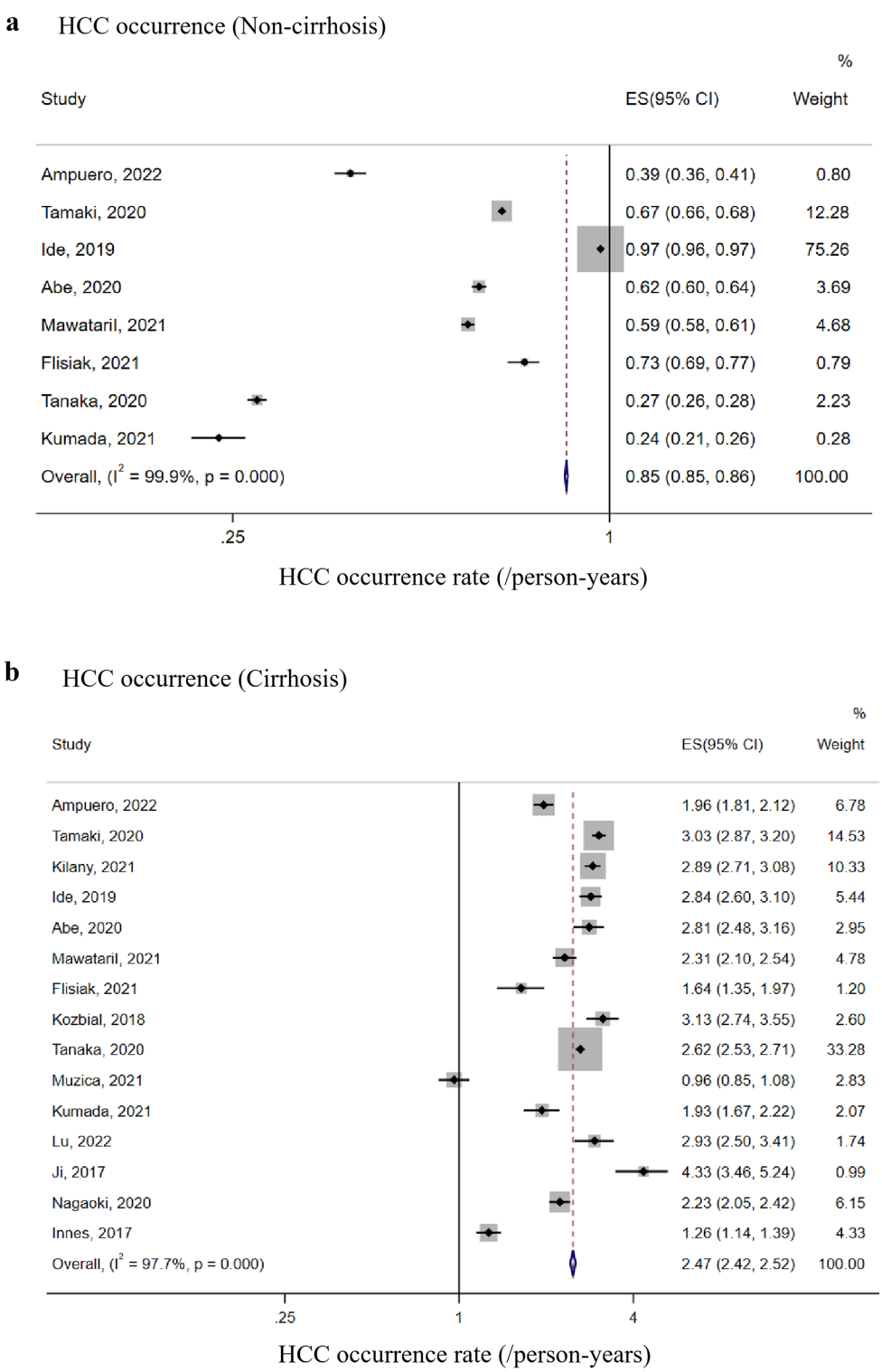


Fig. 4 HCC occurrence rate in SVR patients without cirrhosis and in SVR patients with cirrhosis. **a** HCC occurrence rate in SVR patients without cirrhosis. **b** HCC occurrence rate in SVR patients with cirrhosis

information for anti-HCV treatment to increase patients' confidence. Because of the convenient administration and high cure rate, DAA therapy may be more acceptable especially in the elderly and advanced liver disease populations and IFN could be considered for application in the other population [45, 46].

This study synthesized real-world observational data while effectively controlling for confounding factors, incorporating stratified analysis to enhance the accuracy of the assessment. Nonetheless, limitations exist. In this meta-analysis, studies from diverse regions were included, resulting in heterogeneity in HCC surveillance practices. The variation

Table 3 Meta-regression analysis for HCC occurrence

Variable	HCV treatment ($n=23$)			Variable	Cirrhosis status ($n=23$)		
	Adj R-squared (%)	95% CI	p value		Adj R-squared (%)	95% CI	p value
Treatment type	− 4.72	− 0.519, 0.413	0.815	Cirrhosis status	75.17	1.127, 1.899	0.000
Average follow-up, years	− 4.48	− 0.124, 0.092	0.764	Average follow− up, years	− 4.75	− 0.211, 0.226	0.944
Average age	− 4.92	− 0.030, 0.033	0.943	Average age	− 1.14	− 0.085, 0.035	0.395
AFP	35.20	− 0.016, 0.086	0.007	AFP	1.76	− 0.036, 0.124	0.263
G1	− 9.72	− 0.035, 0.025	0.735	G1	− 7.77	− 0.030, 0.018	0.610
G2	− 11.21	− 0.033, 0.034	0.968	G2	− 10.81	− 0.066, 0.075	0.893

Table 4 HCC occurrence after SVR: risk of bias assessment of studies

Study	Selection		Comparability		Outcome		
	Ascertainment of population	Ascertainment of SVR	Control group	Adjusted for potential confounding factors	Ascertainment of HCC occurrence	Follow-up duration	Assessment during follow-up
Ampuero, 2022	Low	Low	Unclear	Low	Low	Low	Low
Tamaki, 2020	Low	Low	High	Low	Low	Low	Low
Joshita, 2019	Low	Low	High	Low	Low	Low	Low
Kilany, 2021	Low	Low	Low	Low	Low	Low	Low
Ide, 2019	Low	Low	High	Low	Low	Low	Low
Lusivika-Nzinga, 2019	High	Low	Low	Low	Unclear	Low	Unclear
Abe, 2020	Low	Low	High	Low	Low	Low	Low
MawatariI, 2021	Low	Low	High	Low	Low	Low	Low
Flisiak, 2021	Low	Low	High	Low	Unclear	Low	Unclear
Kozbial, 2018	Low	Low	High	Low	Low	Low	Low
Tanaka, 2020	High	Low	Low	Low	Low	Low	Low
Akuta, 2016	Low	Low	High	Low	Low	Low	Low
Muzica, 2021	Low	Low	Unclear	Low	Low	Low	Low
Kumada, 2021	Low	Low	High	Low	Low	Low	Unclear
Watanabe, 2019	Low	Low	Low	Low	Low	Low	Low
Yoo, 2022	Low	Low	High	Low	Low	Low	Low
Nagaoki, 2017	Low	Low	Low	Low	Low	Low	Low
Lu, 2022	Low	Low	High	Low	Low	Low	Low
Tahata, 2019	Low	Low	High	Low	Low	Low	Low
Ji, 2017	Low	Low	High	Low	Low	Low	Low
Nagaoki, 2020	Low	Low	High	Low	Low	Low	Low
Ji, 2021	Low	Low	High	Low	Low	Low	Low
Innes, 2017	Low	Low	Unclear	Low	Low	Low	Unclear

in HCC detection time emerged as a potential source of bias, as different surveillance intervals could directly influence HCC occurrence rates. Early detection of HCC leads to higher occurrence rates. Additionally, variations in surveillance methods across different regions contribute to the heterogeneity, serving as another potential source of bias. The predominantly Asian representation in the IFN-based treatment studies potentially limited the generalizability of the findings to non-Asian populations. This discrepancy may artificially accentuate the antiviral effects in Western countries [1]. The retrospective design of most included studies may introduce selection bias, as studies with significant results are more likely to be included, making it challenging to eliminate publication bias. While randomized controlled trial is the most scientific method, the potential ethical concerns may limit their feasibility. Large prospective studies with long-term follow-up are crucial for future investigations. Included studies mainly focused on antiviral therapies

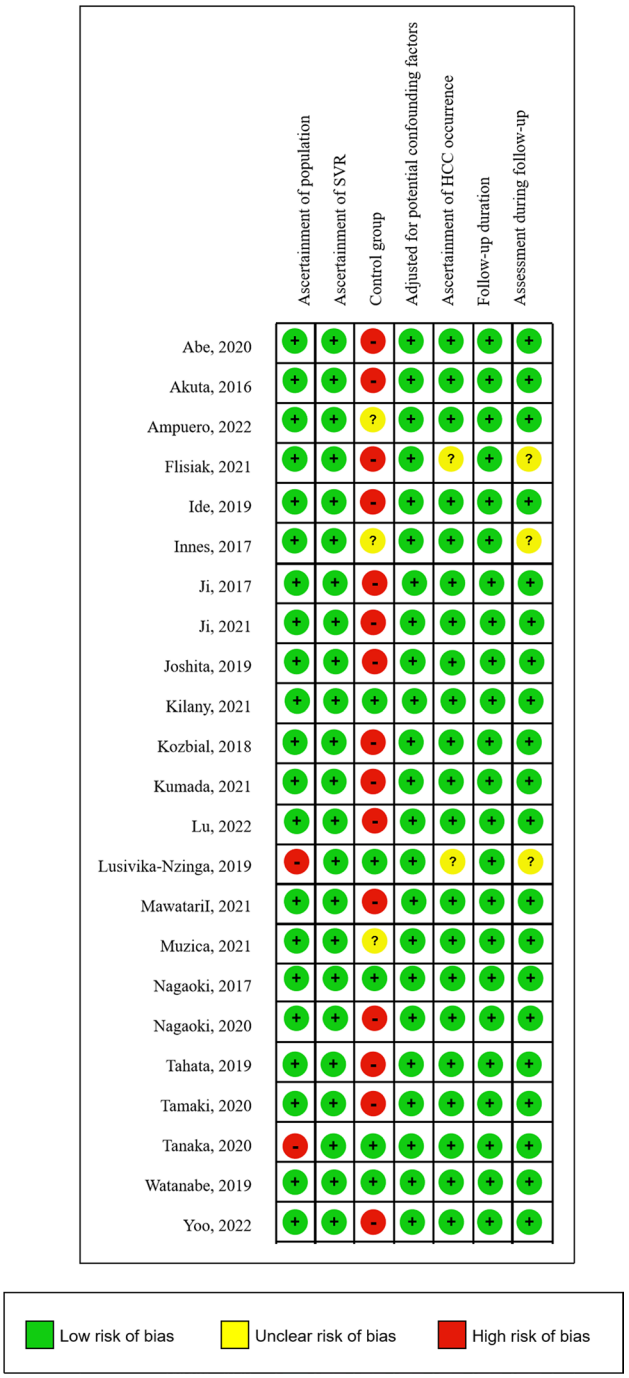


Fig. 5 Risk of bias summary: each risk of bias item for each included study

but overlooked precise fibrosis stages, so the HCC occurrence in this study was determined by comparing the non-cirrhosis to cirrhosis patients. Patients should be stratified by more precise fibrosis stages in future studies to identify the HCC occurrence risk of different fibrosis stages. Our meta-analysis underscores the critical role of HCC surveillance in post- SVR patients. Those with F3 fibrosis, particularly if they have HBV/HIV co-infection, other chronic liver diseases, or risk factors, should undergo regular monitoring for HCC. Notably, our findings suggest that fibrosis assessment should encompass patients with F0–2 fibrosis, as fibrosis emerges as a significant factor influencing HCC occurrence, emphasizing the importance of comprehensive surveillance practices in mitigating HCC risk.

Conclusion

In our present study, we revealed that achieving SVR after anti-HCV treatment is associated with a lower risk, and cirrhosis is associated with a higher risk of HCC occurrence in HCV-infected population. There was no significant difference in HCC occurrence risk following SVR between IFN-based treatment and DAA treatment. Our study addresses the concerns of physicians and patients in treatment options and provides evidence for revision of treatment guidelines, leading to a substantial reduction in the risk of HCC occurrence ultimately.

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Declarations

Conflict of interest Gui-Ji Lv, Dong Ji, Lingxiang Yu, Hong-Yan Chen, Jing Chen, Mengwen He, Wen-Chang Wang, Hong-Bo Wang, Christopher Tsang, Jianjun Wang, Ming-Lung Yu and George Lau declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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