Meta-Analysis of Observational Studies in Epidemiology

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Treatment of chronic hepatitis C regiments containing with recombinant interferon in patients with sustained virological response predicts risk of hepatocellular carcinoma

A meta-analysis

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Abstract

Given that evidence supporting chronic hepatitis C (CHC) infection developed chance for hepatocellular carcinoma (HCC) following antiviral agents therapy is controversial. We conducted a meta-analysis to examine the risk.

We evaluated 20 retrospective and prospective cohort studies published up to 31 December 2017 which investigated the association between sustained virological response (SVR) and incidence of HCC patients treated with monotherapy interferon (IFN) or IFN plus ribavirin (RBV) therapy. The primary outcome of the study was the cumulative incidence of HCC. Odds ratio (OR) was used to evaluate the index of effect size for the association between SVR and treatment with IFN alone or IFN/RBV in CHC patients.

SVR patients demonstrated a lower incidence of HCC compared to non-SVR patients. Non-SVR patients had greater odds of HCC incidence compared to SVR patients in the treatment of IFN plus RBV (pooled OR = 7.405, 95% CI = 4.689 to 11.694, $P < .001$). Non-SVR patients had greater odds of HCC incidence compared to SVR patients in the treatment of IFN monotherapy (pooled OR = 4.135, 95% CI = 3.009 to 5.682, $P < .001$). Lack of SVR to IFN therapy was significantly associated with greater risk of HCC incidence (pooled OR = 5.035, 95% CI = 3.915 to 6.474, $P < .001$).

SVR could be as a predictor of HCC in CHC patients treated with IFN or IFN plus RBV, and have important implications during HCC screening, whereby patients who fail to achieve SVR need to be screened more rigorously.

Abbreviations: CHC = chronic hepatitis C, DAA = direct-acting antivirals, HAI = histology activity index, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, I2 = inconsistency index, IFN = Interferon, IR = incomplete response, NR = nonresponse, OR = odds ratio, Peg-interferon = pegylated interferon, PR = partial response, RBV = ribavirin, RCTs = randomized controlled trials, SVR = sustained virologic response, SVR = sustained virological response, TVR = transient virological response.

Keywords: chronic hepatitis C, direct-acting antiviral agents, hepatitis C virus infection, hepatocellular arcinoma, peg-interferon, ribavirin, sustained virological response

1. Introduction

Hepatitis C virus (HCV) infection is a major health concern, with approximately 71 million people infected worldwide and it was estimated that in 2016, approximately 399,000 people died from HCV infection, mostly from cirrhosis and hepatocellular carcinoma (HCC).[1] Chronic hepatitis C (CHC) infection can progress to liver fibrosis, cirrhosis, and HCC, which is currently the seventh most common malignancy, and the third cause of cancer-related deaths worldwide.[2] Necro-inflammation plays an important role in hepatic carcinogenesis, and the occurrence of HCC has been shown to be associated with the degree and severity of liver fibrosis and cirrhosis.[3,4] The goal of CHC

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The datasets generated during and/or analyzed during the current study are publicly available.

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treatment is virus elimination as well as prevention of HCC. Interferon (IFN) therapy has been shown to reduce inflammation and necrosis scores, prevent progression to HCC, and achieve viral clearance in CHC patients.[4,5]

A combination of pegylated interferon α (peg-IFNα) and a nucleos(t)ide analog has been used successfully to reduce viral load, and improve inflammation and fibrosis in the liver.[6,7] As previous studies reported CHC patients are treated with a combination of peg-IFNα along with ribavirin (RBV), which has been shown to arrest disease progression. IFN therapy was reported to be associated with a reduction in the incidence of HCC, especially in patients who achieve a sustained virological response (SVR).[8–10] SVR is defined as aviremia at 24 weeks after completion of antiviral therapy.[10,11] CHC patients on IFN therapy who achieved SVR have been shown to have a negligible risk of relapse.[12]

Patients who achieved SVR or a transient virologic response (TVR) also had a lower incidence rate of HCC within 5 years after the end of treatment compared to patients who did not achieve SVR.[13] A number of other studies validated these findings, and reported that SVR was significantly associated with a reduced risk of HCC. Particularly, patients with cirrhosis composed of life-threatening complications which may occur HCC even after SVR.[13–18]

Currently, HCV direct-acting antiviral (DAA) agents are the milestone for the standard treatment of CHC infection.[19,20] Although the present results have been already confirmed that the The present results have been already confirmed that HCV patients who undergoing the DAA treatment can decrease all-cause mortality and liver-related adverse effects, including end-stage liver disease and HCC.[20] However, therapy cost and access has served as a major barrier to low and middle-income countries in real-life clinical practice.[21] Although current studies showed that CHC-related cirrhosis patients who received DAA treatment to eliminate HCV and achieving SVR, but need further long-term follow-up study to evaluate the risk of HCC.[20]

A previous meta-regression analysis showed that a higher SVR rate was a predictor of the efficacy of antiviral therapy in preventing HCC occurrence in CHC patients.[6] However, the risk of developing HCC can persist in some patients with HCV-related cirrhosis who achieve SVR after completion of IFN therapy.[10] Additionally, there was no significant difference in the mean interval from the time of completion of IFN therapy until the detection of HCC between SVR and non-SVR HCC patients.[22]

Based on the available data, it is clear that the link between SVR and the risk of HCC is not fully understood. This meta-analysis aimed to investigate the association between SVR and risk of HCC in CHC patients treated with IFN-based antiviral regimens (IFN alone or IFN plus RBV).

2. Methodology

2.1. Study selection

We performed a comprehensive literature search of the PubMed, Cochrane, and Embase databases using the following combinations of search terms: (interferon OR ribavirin) AND (hepatocellular carcinoma OR cirrhosis) AND hepatitis C, (interferon OR ribavirin) AND (hepatocellular carcinoma OR HCC) AND (hepatitis C). Studies published up to March, 2015 were identified.

The inclusion criteria for this meta-analysis were: all randomized controlled trials (RCTs) or 2-arm prospective studies; retrospective studies, studies evaluating patients with hepatitis C virus infection, studies in which patients were treated with IFN therapy: peg-IFN or peg-IFN and RBV, studies in which virological response was measured, and studies that reported the incidence of HCC in patients who achieved SVR and those who did not. Exclusion criteria were reviews, letters, comments, editorials, case reports, proceedings, and personal communications; studies designed for Hepatitis B infection; studies that did not publish in English; and studies with no quantitative primary outcome.

Data collected from the studies included treatment details, patient demographics, duration of treatment, virologic response, and presence of cirrhosis. Data extraction was performed by 2 independent reviewers, and a third reviewer was consulted for resolution of disagreement. In case the information on study design or data or outcomes was ambiguous, we would contact the original authors by email for clarification. We further updated the references of the relevant studies between April 2015 and July 2019 which complied with the inclusion criteria through hand searching. This study was approved by the institutional review board of the Chung Shan Medical University Hospital, Taichung, Taiwan (CSMUH No: CS18193). Raw patient data and private information were neither required nor used in the present review, and therefore informed consent from study subjects was waived.

2.2. Data analysis

The primary outcome of the study was the cumulative incidence of HCC. Odds ratio (OR) was used to evaluate the index of effect size for the association between SVR and treatment with IFN alone or IFN/RBV in CHC patients. It was interpreted as the ratio of the odds of HCC development in patients without SVR (non-SVR) to the odds of HCC in patients with SVR; an OR greater than 1 indicated that non-SVR patients had a higher risk of HCC than SVR patients on interferon therapy. The DerSimonian and Laird random-effects model was used to determine pooled estimates of OR and 95% confidence interval (95% CI). A 2-sided P value $< .05$ was considered statistically significant.

The Cochran Q and I2 statistics were calculated to indicate the presence of heterogeneity across studies. For the Q statistics, a P value $< .10$ was considered statistically significant for heterogeneity. I2 statistics were defined as the percentage of the observed between-study variability which occurred due to heterogeneity rather than by chance; heterogeneity was assessed as follows: no heterogeneity (I2 = 0%– 25%), moderate heterogeneity (I2 = 25%–50%), large heterogeneity (I2 = 50%–75%), and extreme heterogeneity (I2 = 75%–100%).

Subgroup analysis was performed according to the treatment regimens (i.e., IFN plus RBV, IFN alone, or other). "Other" means that the patients were treated with IFN alone or IFN plus RBV, but the subgroup data (IFN alone or IFN plus RBV) were not reported. We also performed additional subgroup analyses according to the country of studies and according to follow-up durations. Sensitivity analysis was carried out for the outcomes using the leave one-out approach. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

2.3. Quality assessment

Quality evaluation of the included studies was performed as previously described[23] using 6 sources of bias related to study

participation, study attrition, measurement of prognostic factors, measurement of and controlling for confounding variables, measurement of outcomes, and analysis approaches. The quality of included studies was independently appraised by 2 reviewers. Disagreements were resolved by a third reviewer.

3. Results

Based on the search terms, and the inclusion and exclusion criteria, this meta-analysis identified a total of 389 studies, of which 336 were excluded for nonrelevance. Nonrelevance criteria included reviews, letters, comments, editorials, case reports; proceedings, personal communications, studies designed for Hepatitis B infection, studies that did not include IFN therapy, studies not designed to evaluate SVR and incidence of HCC. We removed duplicate studies when searching (n=4). Of the remaining 49 studies, 29 were excluded because they did not include a comparison of outcomes between the SVR and non-SVR groups (n=15), absence of IFN response data at the virologic level (n=5), studies focusing on post HCC IFN therapy (n=3), and studies reporting HCC incidence which could not be pooled with other studies (n=6) (Fig. 1).

Of the 20 studies that were included, 4 studies were prospective studies[13,15,24,25] and16 were retrospective studies.[4,11,16,17,22,26–36] Treatment regimens in 5 of the included studies consisted of combination therapy with peg-IFN and

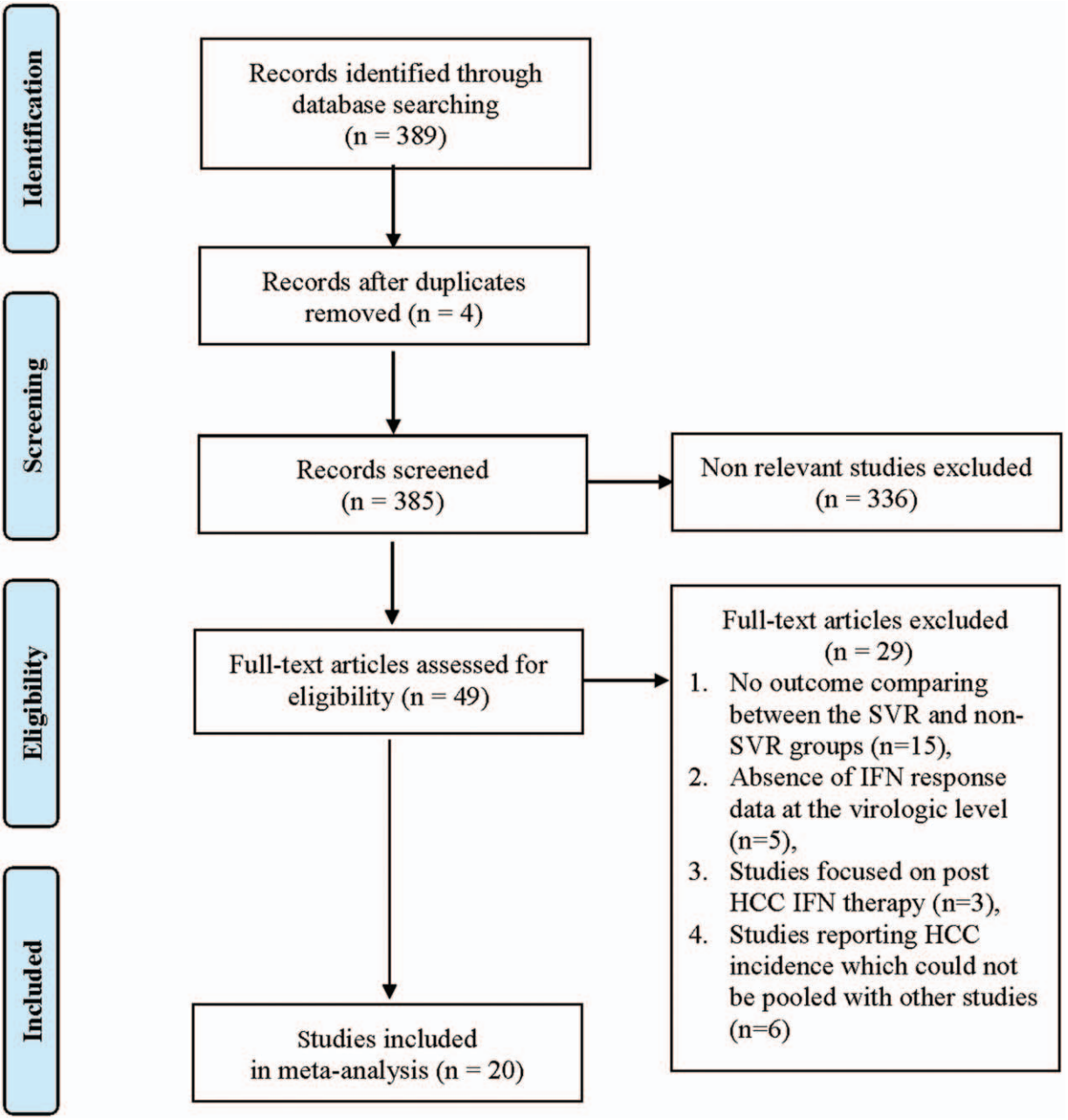


Figure 1. Flow diagram of study selection. ALT=alanine aminotransferase, HCC=hepatocellular carcinoma, IFN=Interferon, SVR=sustained virological response.

RBV.[4,11,24,26–28,31,33,34] The duration of treatment was at least 24 weeks in most of the included studies, and the total number of enrolled patients in each study ranged from 130 to 1654. The mean or median age ranged from 46.9 to 63.7 years, the proportion of male patients ranged from 37.6% to 73.4%, and the mean or median follow-up duration ranged from 34.6 months to 10.7 years (Table 1). The Knodell Histological Activity Index score (HAI score, denoted as scoring of necro-inflammatory activity in chronic hepatitis based on histological examination by pathologist), and percentage of patients with cirrhosis are also listed in Table 1. It is important to note that not all the included studies provided the number of incident cases of HCC. We therefore entered data as event rates and total sample size with the Comprehensive Meta-Analysis software, and the number of events was then generated by the software. As a result, there might be a difference in the HCC event number between what we presented and the actual event number.

3.1. Meta-analysis

Forest plots were used to determine the predictive effect of SVR on the incidence of HCC in patients receiving IFN therapy (Fig. 2). In 5 of the included studies where patients were treated with IFN plus RBV, the pooled odds ratio was 7.405 (95% CI= 4.689 to 11.694; $P<.001$), without heterogeneity between studies (Q=0.81, $P=.937$, I2=0%). In 10 of the studies where patients were treated with IFN monotherapy, there was no evidence supporting heterogeneity between studies (Q=7.51, $P=.585$, I2=0%). The pooled results showed that non-SVR patients had greater odds of HCC incidence compared to SVR patients (pooled OR=4.135, 95% CI=3.009 to 5.682, $P<.001$). There was extreme heterogeneity across 5 studies where patients were treated with other IFN-related therapeutic regimens (Q=31.43, $P<.001$, I2=87.3%). Lack of SVR to IFN therapy was significantly associated with greater risk of HCC incidence (pooled OR=5.035, 95% CI=3.915 to 6.474, $P<.001$).

Results of sensitivity analyses showed that regardless of subgroups regarding treatment regimen, the direction and magnitude of this association did not change considerably when individual study removed one at a time (Fig. 3).

Subgroup analysis was performed based on the country where the study was conducted (Fig. 4). The results demonstrated that regardless of country, non-SVR patients had greater odds of HCC occurrence compared to SVR patients (Asian countries: pooled OR=5.697, 95% CI=3.870 to 8.385, $P<.001$; Non-Asian countries: pooled OR=3.842, 95% CI=2.182 to 6.763, $P<.001$) (Fig. 4). Furthermore, the pooled results were consistent across subgroups defined according to follow-up duration (<10 years: pooled OR=6.365, 95% CI=4.395 to 9.218, $P<.001$; ≥10 years: pooled OR=4.915, 95% CI=2.933 to 8.234, $P<.001$) (Fig. 5).

Quality assessment was performed using 6 sources of bias which could have impacted the quality of the studies. The data showed that all the included studies were of moderate-to-high quality (Fig. 6).

4. Discussion

In this meta-analysis, we evaluated the data extracted from 20 studies to investigate the predictive value of SVR on risk of HCC in CHC patients treated with IFN therapy. Our analysis showed that CHC patients who achieved SVR after IFN or IFN plus RBV therapy had a lower risk of HCC compared to patients who failed to achieve SVR, suggesting that SVR may predict HCC risk in this group of patients.

IFN has been shown to reverse CHC-mediated inflammatory and regenerative processes in the liver.[37] Normalization of aminotransferase levels after IFN therapy was associated with decreased HCC incidence, even in patients who failed to clear HCV RNA from the serum,[31] and IFNα and IFNβ were shown to have a similar efficacy at reducing the incidence of HCC.[24] These studies were consistent with a meta-analysis of 3 RCTs and 6 prospective cohort studies which reported that single-course IFN therapy suppressed inflammation and fibrosis and significantly reduced the incidence of HCC even in virologic non-responders.[38] Importantly, it has been reported that although some cirrhotic CHC patients who achieved SVR with IFN therapy developed HCC, none of the patients with histological regression of cirrhosis developed HCC.[39] Even though, the actual mechanisms of HCV infection on hepatocarcinogenesis are currently not fully understood, similarly hepatitis B virus related to HCC, it is assumed that the hepatic inflammation and injury attributed frequently to host immune response and possibly provides the hepatocarcinogenesis.[40] These results suggested that the preventive effect of IFN therapy on hepatocarcinogenesis might associate with its anti-inflammatory effects.[40]

Although it would be interesting to understand if SVR reduces the risk of HCC regardless of the degree of liver fibrosis, we could not do this analysis because we did not have patient-level data for the degree of liver fibrosis. However, this issue has been described in 3 of our included studies that evaluated the incidence of HCC in cirrhotic versus noncirrhotic patients who achieved SVR. Patients who achieved SVR were shown to have a significantly lower risk of progression from a noncirrhotic to a cirrhotic state compared to patients who did not achieve SVR.[17] Among patients who achieved SVR, the 5-year cumulative incidence of HCC in non-cirrhotic patients was 1.7%, and cirrhosis patients was 18.9%.[13] This was consistent with another study that showed a significantly lower HCC incidence rate in noncirrhotic patients who achieved SVR compared to cirrhotic patients (0.09% vs 2.67%).[29]

A previous study suggested that the reduced incidence of HCC and improved survival rates in SVR patients after IFN therapy were strongly correlated with virus eradication.[29] Recent studies have shown that high SVR rates can predict a low risk of HCC occurrence in CHC patients treated with antiviral therapy.[11,13,15–17,30,32,35,36] A meta-analysis on CHC patients showed IFN therapy can reduce the 3- and 5-year cumulative incidence of HCC and SVR in these patients was a predictor of superior preventive efficacy.[6] Another meta-analysis study showed that although the effect of antiviral therapy on reduced risk of HCC was unrelated to virologic response, the effect was more pronounced among patients who achieved SVR compared to those who did not.[14] Additionally, although IFN monotherapy reduced the risk of HCC among patients aged under 60 years old, suppression of HCC by IFN among patients aged over 60 years old was only observed among those patients who achieved SVR.[34] Previous studies on the impact of TVR have also been shown to correlate with a lower cumulative incidence rate of HCC when compared with nonresponders.[13,26,27] Patients who achieved SVR or TVR had significantly lower rates of HCC incidence compared to those who did not show a virologic response to IFN monotherapy,[11,26–28] or to peg-IFN

Table 1

Study characteristics including treatment details, HAI-Kondell score, and proportion of cirrhosis.

Study name, year	Study design	Treatment details	Treatment duration	Group of virologic response	No. of patients	Mean age (yr)	Male (%)	HAI score	Cirrhosis (%)	Mean follow-up duration	References
Kashiwagi, 2003	Prospective	Natural IFNα (74.1%), or natural IFNβ (25.9%)	20 wk	SVR	66	55.7	66.7	9.9 (4.7)	13.7	5.7 yr	[24]
				Non-SVR	194						
Shiratoni, 2005	Prospective	IFNα-2a (n=157), or natural IFNα (n=114)	39 wk	SVR	64	Median: 57	37.6			Median: 6.8 yr	[25]
				Non-SVR	207						
Dohmen, 2013	Prospective	peg-IFN + RBV	24–72 wk	SVR	285	55.5	48.5			Median: 56 mo	[15]
				TVR	116						
				NVR	73						
Ogawa, 2013	Prospective	peg-IFNα-2b + RBV	47 (24–48) wk	SVR	557	Median: 58	49.2		14.8	Median: 3.6 yr	[13]
				TVR	304						
				NVR	152						
Imai, 1998	Retrospective	Recombinant IFNα-2a (n=149), or recombinant IFNα-2b (n=94)	6 mo	SVR	151	<60 yr: 71% ≥60 yr: 29%	67.0	<10: n=254, ≥10: n=165		Median: 47.6 mo	[11]
				Relapse	120						
				NR	148						
Kasahara, 1998	Retrospective	Recombinant IFNα-2a, recombinant IFNα-2b, natural IFNβ, or natural IFNα	24–52 wk	SR	313	52.9	67.4	9.0 (3.4)		38.9 mo	[27]
				TR	304		66.4	8.9 (3.6)		36.6 mo	
				NR	405		67.9	9.6 (3.6)		36.9 mo	
Tanaka, 2000	Retrospective	Human lymphoblastoid IFN, recombinant IFNα-2a, or recombinant IFNα-2b	6 mo	SR	175	51.7	69.0			59.6 mo	[26]
				TR	165					57.3 mo	
				NR	254					55.5 mo	
Takimoto, 2002	Retrospective	IFN-α (natural or recombinant) or natural IFN-β	8–24 wk	SVR	201	51.3	58.4			54.8 mo	[4]
				IR	95						
				NR	356						
				Non-SVR	194						
Yu, 2005	Retrospective	Recombinant IFNα-2a (n=40), IFNα-2b (n=102), or lymphoblastoid IFNα-n1 (n=72)	24 wk	SVR	64	46.5	53.1	4.21 (2.31)		6.81 yr	[28]
				Non-SVR	136		50.7	4.10 (2.59)			
Yu, 2006	Retrospective	IFNα only (n=297) or IFNα + RBV (n=760)	20–48 wk	SVR	715	46.9	60.5		15.6	5.18 yr	[29]
				Non-SVR	342						
Hung, 2006	Retrospective	INFα-2b + RBV	24 or 48 wk	SVR	73	56.1	57.5	6.8 (2.5)		Median: 37 mo	[30]
				Non-SVR	59		45.8	6.9 (2.6)			
Ikeda, 2006	Retrospective	Natural or recombinant IFNα (n=1238), natural IFNβ (n=386), or both (n=30)	24 wk	SVR	606	Median: 50	67.1			Median: 10.7 yr	[31]
				BR	266						
				NR	782						
Arase, 2007	Retrospective	IFNα, IFNβ, or IFN + RBV	Median 165 d	SVR	140	63.7	59.3	9.3 (3.4)		7.0 yr	[32]
				Non-SVR	360		46.7	9.8 (2.7)		7.7 yr	
Kobayashi, 2007	Retrospective	Natural IFNα, recombinant IFNα-2a, recombinant IFNα-2b, IFN-β, or recombinant IFNα-2b + RBV	24–48 wk	SVR	373	51.0	62.7			Median: 66 mo	[22]
				Non-SVR	751		59.9				
Bruno, 2007	Retrospective	IFN only	1 yr	SVR	124	54.7	73.4			96.1 mo	[33]
				non-SVR	759		61.7				
Imai, 2010	Retrospective	Human lymphoblastoid IFN, recombinant IFNα2a, or recombinant IFNα2b	6 mo	SVR, nonaged	134	48.0	67.8	<10: n=257, ≧10: n=153			[34]
				Non-SVR, nonaged	276						
				SVR, aged	41	63.5	54.4	<10: n=84 ≧10: n=74			
				Non-SVR, aged	117						
Cardoso, 2010	Retrospective	peg-IFN + RBV (82%), peg-IFN monotherapy (7%), conventional IFN with or without RBV (11%)		SVR	103	55.0	70.0		53	Median: 3.5 yr	[32]
				Non-SVR	204		66.0		61		
Velosa, 2011	Retrospective	IFN only or IFN + RBV	43 wk 38 wk	SVR	39	51.8	77.0			7.1 yr	[35]
				Non-SVR	91		68.0			6.2 yr	

(*continued*)

Table 1

(continued).

Study name, year	Study design	Treatment details	Treatment duration	Group of virologic response	No. of patients	Mean age (yr)	Male (%)	HAI score	Cirrhosis (%)	Mean follow-up duration	References
Harada, 2014	Retrospective	peg-IFNα2b + RBV	24–72 wk	SVR	454	56.7	67.0			36.2 mo	[16]
				Relapse	191						
				NR	164						
Moon, 2015	Retrospective	Peg-IFNα + RBV	24 or 48 wk	SVR	300	50.9	47.0		9.7	Median: 37.0 mo median: 34.6 mo	[17]
				Non-SVR	163		49.1		32.5		

BR = breakthrough response, HAI = histology activity index, IFN = interferon, IR = incomplete response, NR = nonresponse, NVR = nonvirological response, peg-IFN = pegylated interferon, PR = partial response, RBV = ribavirin, SVR = sustained virological response, TR = transient response, TVR = transient virological response.

plus RBV therapy.[13,15,16,41] A recent study reported that the risk of developing HCC in patients with HCV-related cirrhosis who achieve SVR can persist for up to 8 years.[42] In this study, we used the data extracted from the included studies to do a subgroup analysis for risk identification based on <10 years and ≧10 years, and found that the pooled results were consistent across subgroups defined according to follow-up duration.

Addition of DAA therapy to peg-IFN plus RBV therapy was associated with higher SVR rates, and virological cures were observed after 12 weeks of DAA treatment even in cirrhotic patients who were previously nonresponders.[43,44] The current DAA-based IFN-free regimens were also shown to achieve very high rates of SVR and less adverse effect events.[19,20,44] The recent studies reported an unexpectedly high rate of tumor recurrence coinciding with HCV clearance after DAA therapy,[45,46] and this was attributed to the significant difference in the kinetics of viral suppression between DAA-treated patients and patients treated with IFN-based regimes. Rapid viral clearance after DAA therapy is accompanied by a reduction in inflammation signals, leading to abrogation of immune-mediated inhibition of tumor progression.[46] The slower viral suppression seen with IFN-based therapies may be associated with IFN-mediated modulation of the immune system and promotion of antitumor immunity.[40] But, recent meta-analysis studies found no evidence for differential HCC occurrence or recurrence risk following SVR from DAA therapy compared with IFN-based therapy among CHC patients with cirrhosis.[47] Hence, DAA and IFN-based therapy associated with SVR and the risk of HCC require further investigation.

Although the current standard of care for CHC did not consist of peg-IFN plus RBV,[20,44] our study provided exclusive information which SVR could help to predict HCC risk in CHC patients with cirrhosis. Our meta-analysis included only 5 studies that used this regimen, while the rest of the studies used IFN monotherapy. Data from our present meta-analysis, which compared the pooled OR of HCC between the SVR and non-SVR

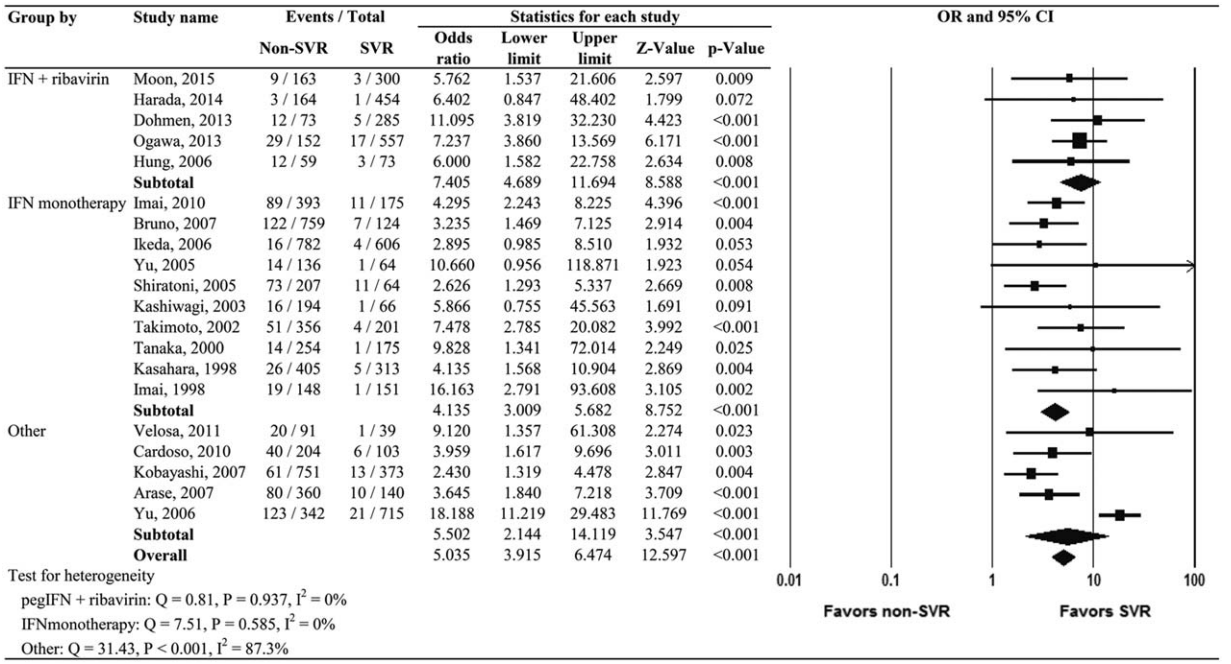
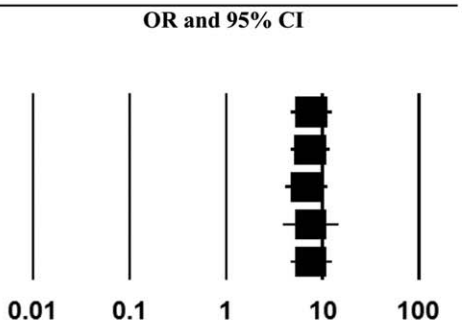


Figure 2. Forest plots to determine the effect of sustained virological response on incidence of hepatocellular carcinoma. 95% CI = 95% confidence interval, IFN = interferon, OR = odds ratio.

IFN + ribavirin

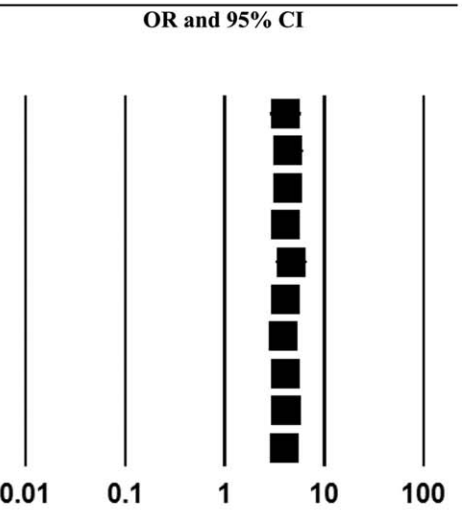
Study name	Statistics with study removed				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Moon, 2015	7.661	4.708	12.468	8.195	0.000
Harada, 2014	7.463	4.669	11.930	8.399	0.000
Dohmen, 2013	6.761	4.078	11.211	7.407	0.000
Ogawa, 2013	7.598	3.906	14.779	5.973	0.000
Hung, 2006	7.615	4.682	12.386	8.181	0.000



A

IFN monotherapy

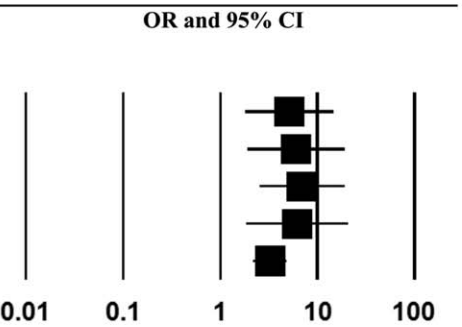
Study name	Statistics with study removed				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Imai, 2010	4.086	2.838	5.883	7.569	0.000
Bruno, 2007	4.336	3.064	6.136	8.280	0.000
Ikeda, 2006	4.278	3.067	5.966	8.563	0.000
Yu, 2005	4.066	2.951	5.604	8.574	0.000
Shiratoni, 2005	4.635	3.248	6.615	8.453	0.000
Kashiwagi, 2003	4.100	2.972	5.656	8.594	0.000
Takimoto, 2002	3.861	2.760	5.402	7.887	0.000
Tanaka, 2000	4.042	2.930	5.578	8.502	0.000
Kasahara, 1998	4.135	2.954	5.789	8.269	0.000
Imai, 1998	3.948	2.858	5.455	8.328	0.000



B

Other

Study name	Statistics with study removed				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Velosa, 2011	5.119	1.806	14.511	3.072	0.002
Cardoso, 2010	5.998	1.898	18.951	3.052	0.002
Kobayashi, 2007	6.977	2.545	19.128	3.775	0.000
Arase, 2007	6.186	1.869	20.471	2.984	0.003
Yu, 2006	3.249	2.184	4.833	5.815	0.000



C

Figure 3. Sensitivity-analysis for the effect of sustained virological response on incidence of hepatocellular carcinoma. (A) IFN + ribavirin; (B) IFN monotherapy; (C) other. 95% CI = 95% confidence interval, IFN = interferon, OR = odds ratio.

groups from 20 studies, showed that non-SVR patients had greater odds of HCC incidence compared to SVR. This effect is likely due to a combination of decreased inflammation and necrosis, and virus eradication, factors that modulate the progression of liver disease in CHC patients.[8,31] It will be interesting to investigate differences between IFN monotherapy regimens and IFN plus RBV regimens on SVR rates and rates of HCC incidence. The role of IFN therapy in CHC patients on hepatocarcinogenesis remains pivotal.

We performed a subgroup analysis based on the country where the study was conducted. The Asia region included Japan,[4,11,13,15,16,22,24–27,31,32,34] Taiwan,[28–30] and Korea.[17]

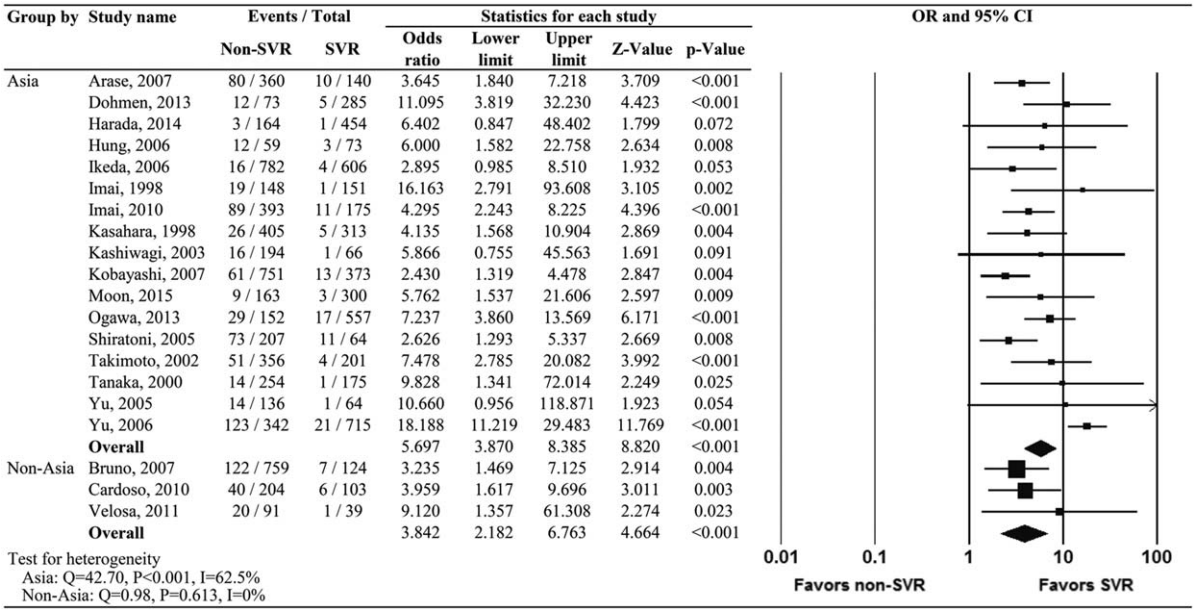


Figure 4. Subgroup analysis to evaluate the effect of sustained virological response on incidence of hepatocellular carcinoma according to the countries where studies were conducted. 95% CI = 95% confidence interval, IFN = interferon, OR = odds ratio.

The non-Asia region included France,[35] Italy,[33] and Portugal.[36] Our analysis showed that regardless of country, patients who failed to achieve SVR had greater odds of HCC occurrence compared to SVR patients. A number of the studies included in our meta-analysis compared survival/mortality rates in the SVR and non-SVR groups. Lack of SVR was shown to increase the risk of liver-related mortality in CHC patients who were treated with IFN therapy.[25,26,32,33,36] A prospective study investigating the association between mortality and virologic response to peg-IFNα and RBV reported that patients with SVR or TVR had a significantly lower mortality rate, and lower rates of decompensated liver disease and HCC compared to non-responders.[41] SVR and TVR were also shown to correlate with decreased mortality rates in chronic HCV patients treated with peg-IFNα plus RBV therapy,[13,29,35] suggesting that virologic response was a predictor of liver-related mortality. However, the heterogeneity of the data in the included studies made it a challenge to pool the survival data for this analysis. Sensitivity

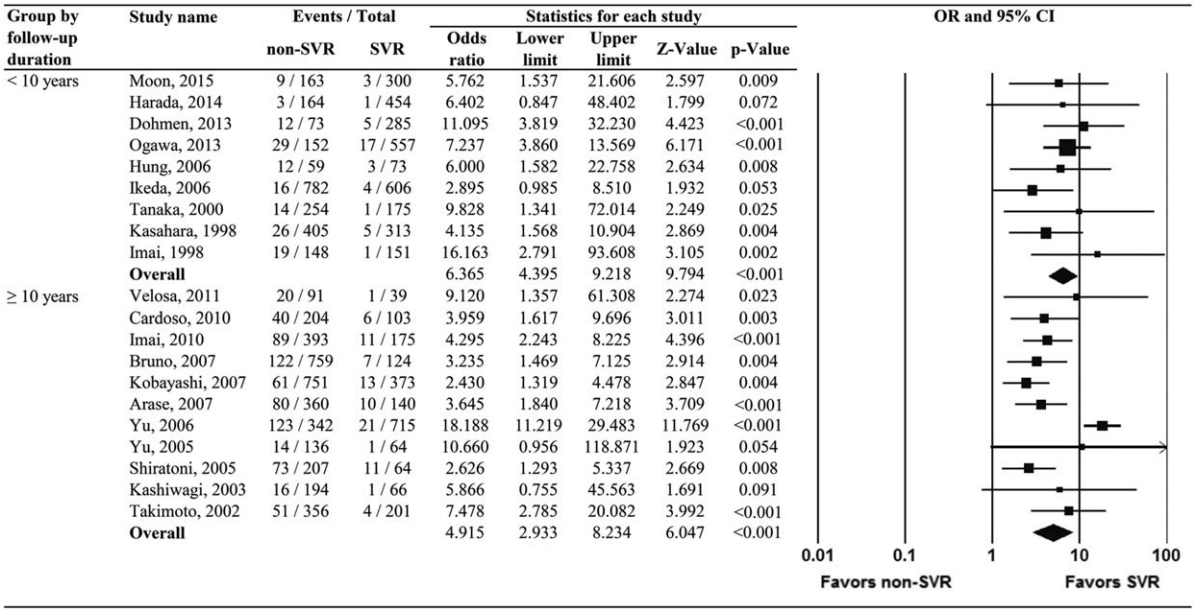


Figure 5. Subgroup analysis to evaluate the effect of sustained virological response on incidence of hepatocellular carcinoma according to follow-up duration. 95% CI = 95% confidence interval, IFN = interferon, OR = odds ratio.

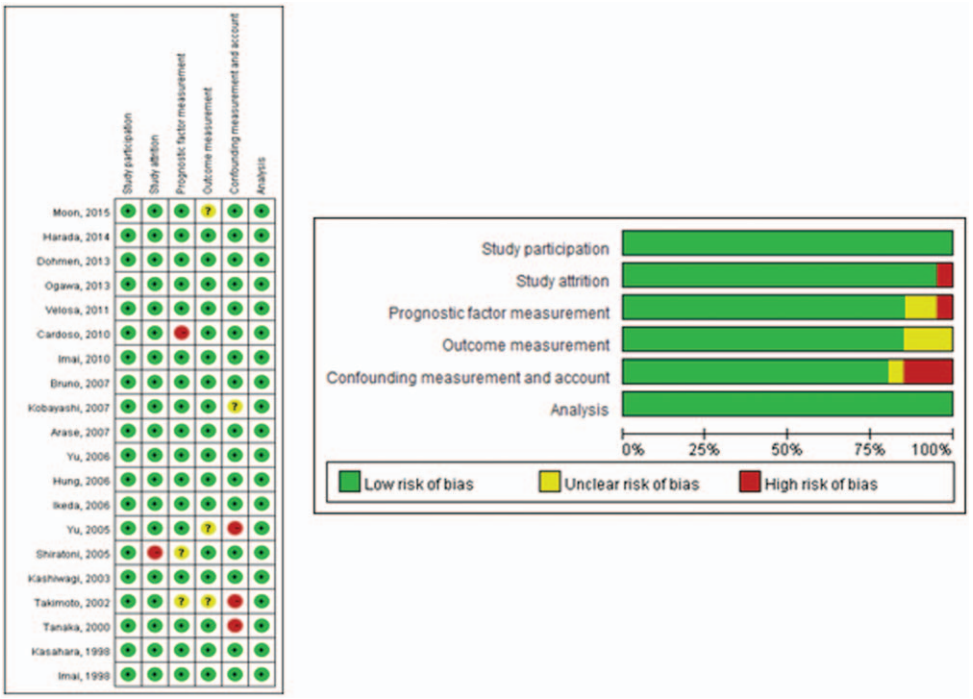


Figure 6. Quality assessment.

analyses for the outcomes using the leave–one-out approach showed that no single study had a significant impact on the pooled results.

Eventhough IFN-free DAA therapy of CHC became mainstream, it seems does not alter the short-term risk for HCC in patients with liver cirrhosis.[20,47] This meta-analysis notably focused on the incidence of HCC in patients who achieved SVR compared with the patients who did not achieve SVR after IFN therapy. Despite the strengths, there are several limitations associated with our study. First, this meta-analysis was that most of the included studies were retrospective. Only 4 prospective studies were included in the analysis. More well-designed prospective studies are needed to confirm our findings. Secondary, the response rates to IFN-based therapy vary significantly between the different HCV genotypes,[48,49] we did not have enough information to perform a subanalysis based on HCV genotype, since only one of our included studies provided genotype information.[30] Also, the results in some subgroups require cautious interpretation due to the heterogeneity observed across the studies included. Another important limitation was the lack of subgroup analysis of important HCC-related factors such as cirrhosis and age due to insufficient data. In future studies, it will be preferable to perform meta-analysis of individual patient data rather than aggregate-level data.

Finally, we did not include the studies published in non-English language.

5. Conclusion

Our data showed a significant correlation between SVR to IFN therapy and reduced incidence of HCC, and suggested that SVR could be as a predictor of HCC in CHC patients treated with IFN or IFN + RBV. These results have important implications for the decision-making process during HCC screening. CHC patients who fail to achieve SVR after IFN therapy are at high risk for progressing to HCC, and require rigorous follow-up, while patients who achieve SVR would require less frequent screening.

Author contributions

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Writing – review & editing: Yuan-Ti Lee.

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