

The influence of interleukin 28B polymorphisms on the risk of hepatocellular carcinoma among patients with HBV or HCV infection

An updated meta-analysis

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Abstract

Single nucleotide polymorphisms (SNPs) of the interleukin 28B (IL28B) gene has proven to be associated with the clinical outcome of patients with chronic hepatitis virus B or C (HBV or HCV) infections. However, whether IL28B SNPs have an influence on the risk of hepatocellular carcinoma (HCC) among patients with HBV or HCV infection remains controversial. Therefore, this study aims to determine the association between IL28B polymorphisms and the risk of HCC in individuals with HBV or HCV infection.

PubMed, EMBASE, and Chinese National Knowledge Infrastructure (CNKI) databases were used to identify studies meeting the selection requirements using the terms “interleukin 28B”, “IFN-lambda-3”, “IFNL3”, “single nucleotide polymorphisms”, “SNPs”, “hepatocellular carcinoma”, “HCC”, “liver cancer”.

A total of 24 eligible original studies (1 cohort study and 23 case-control studies) involved 20238 individuals (HCC group = 8725 vs control group = 11,513) were included. Both IL28B rs12979860 CC and rs8099917 TT genotypes were significantly associated with a decreased risk of HCC among patients with HBV or HCV infection (OR=0.71, 95% CI=0.57–0.88; OR=0.82, 95% CI=0.72–0.94, respectively). Egger test and Begg test revealed no publication bias ($P > .05$). Sensitivity analyses suggested the robustness of the results in this meta-analysis.

Both IL28B rs12979860 CC and rs8099917 TT genotypes are protective factors for the development of HCC among patients with HBV or HCV infection. Future prospective studies examining the impact of IL28B polymorphisms on the risk of HCC and investigating the underlying mechanism for the protective role of IL28B polymorphisms in HCC development are warranted.

Abbreviations: HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, IL28B = interleukin 28B, SNP = single nucleotide polymorphism.

Keywords: hepatitis B, hepatitis C, hepatocellular carcinoma, interleukin 28B

1. Introduction

Hepatocellular carcinoma (HCC) constitutes more than 90% of cases of primary liver cancer, which represents the fifth most

common cancer globally and the third most common cause of cancer-related mortality.^[1,2] Both hepatitis B virus and hepatitis C virus are believed to be major causes of chronic hepatitis and liver cirrhosis, which are at high risk for progressing to HCC. Clinical outcome of HBV or HCV infection is generally separated into spontaneous recovery, chronic hepatitis, liver cirrhosis, and HCC.^[3–5] Only a fraction of patients with chronic HBV or HCV infection, however, progress to HCC during their lifetime. The underlying mechanism responsible for the difference in clinical outcome between individuals is far from clear. A potential explanation for this discrepancy may be at least partly due to host genetic factors,^[6] and studies investigating these factors have provided some clues for this discrepancy.

Recent studies have demonstrated that 2 single nucleotide polymorphisms (SNPs) of IL28B rs12979860 and rs8099917, are involved in the diversity of immune responses to HCV infection.^[7] Similarly, IL28B polymorphisms may also play a critical role in the natural history of chronic HBV infection.^[8–10] Mechanistic studies suggest that Interferon- λ 3 (IFN- λ 3) encoded by the interleukin 28B (IL28B) gene has been involved in the defense mechanisms against several viruses including HBV and HCV.^[11–13] Moreover, it has been claimed that IL28B genotype could serve as a prognostic factor for patients with HBV or HCV infection, especially for those who received interferon treatment.^[14]

The potential association between IL28B polymorphisms and the risk of HCC development among individuals with chronic

Editor: Giovanni Tarantino.

This study is funded by the Science and Technology Department of Jilin Province (Grant no. 20160414036GH).

The authors have no conflicts of interests to disclose.

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How to cite this article: Qin S, Wang J, Zhou C, Xu Y, Zhang Y, Wang X, Wang S. The influence of interleukin 28B polymorphisms on the risk of hepatocellular carcinoma among patients with HBV or HCV infection. *Medicine* 2019;98:38 (e17275).

Received: 31 October 2018 / Received in final form: 14 June 2019 / Accepted: 28 August 2019

<http://dx.doi.org/10.1097/MD.00000000000017275>

HBV or HCV infection, however, has not yet to be determined, although IL28B SNPs have been shown to link to the clinical prognosis of HBV or HCV infected subjects.^[2,3,15,16] Several studies examining the association of IL28B rs12979860 polymorphism with the risk of HCC found that IL28B rs12979860 CC genotype may be a protective factor for HCC among subjects with HBV or HCV infection, particularly for those who accept IFN treatment but fail to achieve sustained virology response (SVR).^[2,17,18] A similar association between IL28B rs8099917 TT genotype and a decreased risk of HCC have also been observed in patients with chronic HCV genotype 1 infection and treatment based on IFN plus ribavirin.^[9,19] These studies regarding the impact of IL28 polymorphisms on the risk of HCC, however, have not yet to draw a consistent conclusion, because of the heterogeneity in patient ethnicity, the different underlying cause for HCC, and limited sample size. Therefore, this study aimed to determine the association between IL28B rs12979860 and rs8099917 polymorphisms and the risk of HCC among individuals with HBV or HCV infection.

2. Methods

2.1. Literature search strategy and study selection

PubMed, EMBASE, and Chinese National Knowledge Infrastructure (CNKI) databases were searched for relevant articles published up to October 2018. The search strategy were: (((((cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinoma*[Title/Abstract] OR malignanc*[Title/Abstract] AND ((liver[Title/Abstract] OR hepatic[Title/Abstract] OR hepatocellular[Title/Abstract])) OR (((hepatocarcinoma[Title/Abstract] OR "liver cell carcinoma*" [Title/Abstract] OR hepatoma[Title/Abstract]) AND ((((((IFN-lambda-3*[Title/Abstract] OR IFNL3* [Title/Abstract] OR Interferon lambda-3* [Title/Abstract] OR interleukin 28B* [Title/Abstract] OR IL-28B* [Title/Abstract] OR IL28B* [Title/Abstract])) OR "IL28B protein, human" [Supplementary Concept])). Also, we identified the literature cited by the articles retrieved from the databases.

Studies were included and excluded following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.^[20] Also, this meta-analysis was performed according to the statement of the meta-analysis of Observational Studies in Epidemiology, because of the observational design of included studies.^[21] No ethical approval and patient consent are required because all analyses were based on previously published studies.

2.2. Study selection criteria

Two researchers independently inspected all articles identified in the search. Any disagreements on the eligibility of studies were resolved by discussion. Eligible studies met the following criteria:

- (1) observational studies (cohort, nested case-control, or case-control studies);
- (2) patients who were divided into an HCC group and a non-HCC group, with or without HBV/HCV infection;
- (3) the incidence of HCC was compared with the IL28B rs12979860 CC genotype vs the CT/TT genotypes combined, or with the rs8099917 TT genotype vs the TG/GG genotypes combined; and
- (4) adequate information was provided to calculate the odds ratio with 95% confidence intervals.

Studies that met any of the following criteria were excluded:

- (1) the study was not designed to address the critical question (HCC);
- (2) the article was not original (including reviews, letters, and editorials); and
- (3) abstracts, conference proceedings, unpublished reports, reviews, and overlapping findings.

2.3. Data extraction and quality assessment

Data extraction was conducted by 1 researcher using predefined forms and was then checked independently for accuracy by another researcher. The following information was extracted: first author, publication year, ethnicity, and geographical area of the study subjects, number of total cases, genotype frequency of IL28B in all cases, number of HCC cases, and genotype frequency of IL28B in HCC cases.

Two researchers assessed the quality of included studies independently using the Newcastle–Ottawa quality assessment scale. Each study could be awarded to a maximum of 9 scores by evaluating its 3 aspects (selection, comparability, and outcome). A study with 7 or more scores was considered to be of high quality. Any disagreements on the results of data extraction and quality assessment were resolved by discussion.

2.4. Statistical analysis

Statistical analyses were performed using Stata version 12.0 software programs (StataCorp LP in College Station, TX). The statistical significance level was set at $P < .05$ under the 2-sided test unless otherwise specified. The association between IL28B SNPs and HCC was analyzed based on the ORs with 95% CIs (CC vs CT/TT for rs12979860, TT vs TG/GG for rs8099917). The statistical heterogeneity among the studies was assessed with I^2 -statistics ($I^2 > 75.0\%$ representing substantial heterogeneity, $50.0\% \leq I^2 \leq 75.0\%$ representing moderate heterogeneity, $I^2 < 50\%$ representing low heterogeneity) and Cochran's Q statistic ($P < .10$ suggesting statistical significance).^[22] Random-effects model was used to estimate pooled ORs whether or not heterogeneity between studies exists. The significance of the pooled ORs was determined using the Z test, and $P < .05$ was defined as statistically significant.

Sensitivity analyses were conducted by sequential omission of individual studies to check the stability of the pooled results. Publication bias was evaluated using Egger test and Begg test.^[23,24]

3. Results

3.1. Characteristics of included studies

Initially, 158 citations and 358 citations were identified from PubMed and EMBASE, respectively. According to the eligibility criteria, a total of 28 citations were thought to be potentially relevant after reviewing titles and abstracts. Six citations were further excluded after reading the full text carefully. Two studies were found to be eligible for inclusion in the process of hand search. Thus, 24 studies evaluating IL28B rs12979860 and rs8099917 were ultimately included in this meta-analysis, in which 18 studies evaluated the IL28B rs12979860 genotype CC vs CT/TT,^[1,2,7,8,17–19,23,25–33] and 15 studies evaluated the IL28B rs8099917 genotype TT vs TG/GG^[1,7,9,17,19,23,26,30,32,34–39] (Fig. 1).

The basic characteristics of the studies are presented in Tables 1 and 2. Overall, 24 studies included in this meta-analysis involved

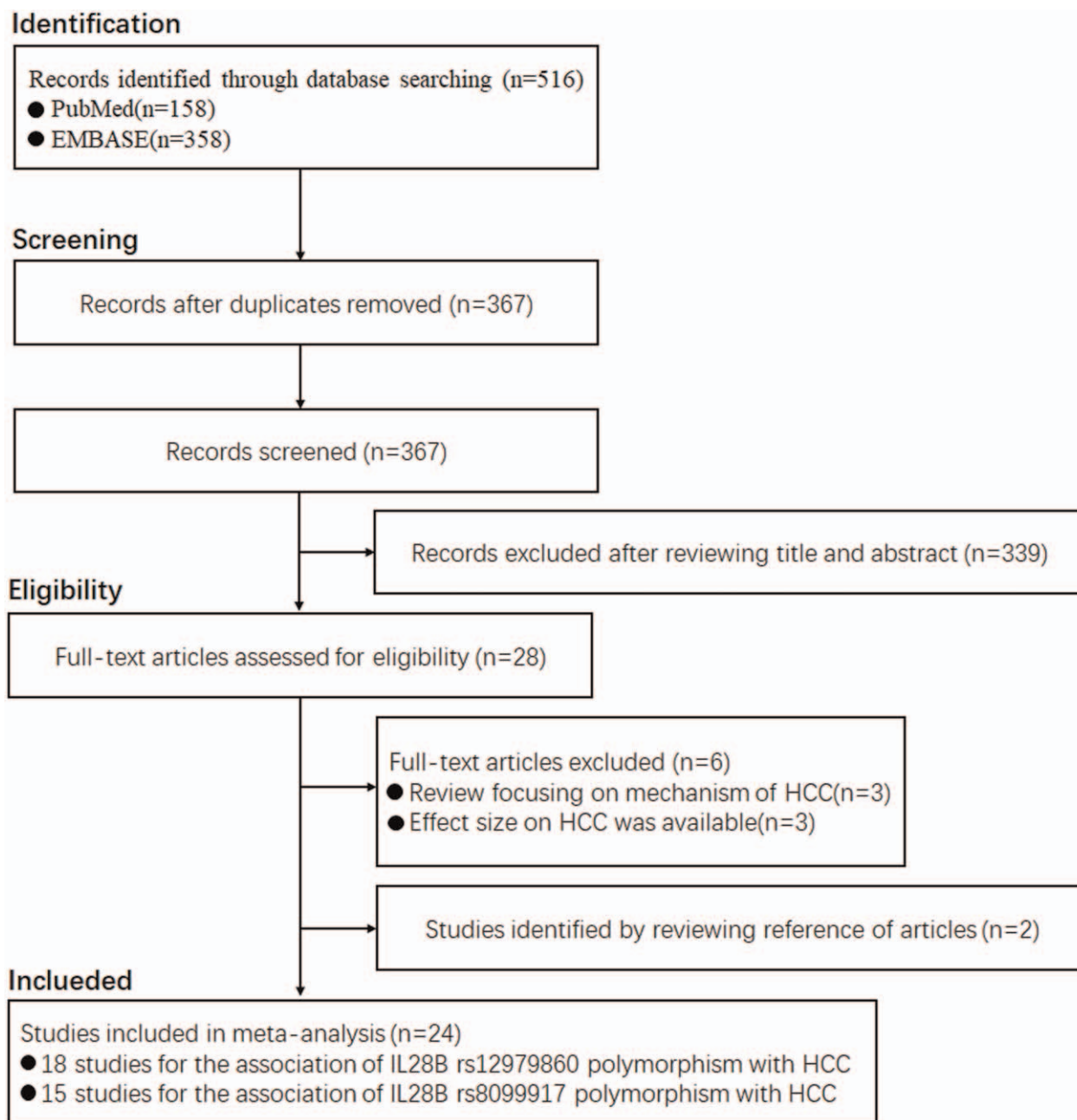


Figure 1. Included and excluded studies: the PRISMA flow diagram.

20238 individuals (HCC group = 8725 vs control group = 11513) for the association of HCC incidence with IL28B rs12979860 and rs8099917, respectively. Among all the eligible studies, there are 23 case-control studies and 1 cohort study. As for quality assessment, 19 (79%) studies were found to be of high quality, indicating the quality of included studies was generally good (Table 3).

3.2. The influence of IL28B rs12979860 polymorphism on the risk of HCC among patients with HBV or HCV infection

Eighteen studies examining the association between the IL28B rs12979860 polymorphism and the risk of HCC were included in this meta-analysis. Random-effects model was used for calculating pooled OR. The pooled result suggested that the IL28B

rs12979860 CC genotype is significantly associated with a decreased risk of HCC compared with the IL28B rs12979860 CT/TT genotype (OR = 0.71, 95% CI=0.57–0.88; Fig. 2, Table 4). The heterogeneity test showed that $I^2=73.7%$ (Cochran Q test, $P<.01$). Both Egger test and Begg test suggested no publication bias in the meta-analysis of the association between the IL28B rs12979860 polymorphism and the risk of HCC ($P=.072$, .198, respectively) (Fig. 4, Table 4).

3.3. The influence of IL28B rs8099917 polymorphism on the risk of HCC among patients with HBV or HCV infection

Fifteen studies reporting data on the association between the IL28B rs8099917 polymorphism and the risk of HCC were

Table 1
Characteristics of the included studies examining the association of IL28B rs12979860 polymorphism with the risk of HCC.

References	Region or country	Study design	Underlying cause	All patients	Genotype for all patients		HCC	Genotype for HCC patients	
					CC	CT/TT		CC	CT/TT
Chang, K.C. et al. 2017 ^[33]	Taiwan	Case-control	HCV	800	585	215	100	46	54
Marwa, K.L. et al. 2016 ^[39]	Egypt	Case-control	HCV	153	52	101	34	3	31
De Re, V. et al. 2016 ^[25]	Italy	Case-control	HCV	937	331	606	175	56	119
Lee, M.H. et al. 2016 ^[26]	Taiwan	Case-control	HCV	994	863	131	480	411	69
Moreira, J.P. et al. 2016 ^[23]	Brazil	Case-control	HCV	109	34	75	59	18	41
de la Fuente, S. et al. 2016 ^[8]	Spain	Case-control	HCV	311	117	194	100	35	65
Al-Qahtani, A. et al. 2015 ^[11]	Saudi Arabia	Case-control	HCV	678	238	440	160	53	107
Chang, K.C. et al. 2015 ^[2]	Taiwan	Case-control	HCV	1118	967	151	108	80	28
Shi, X. et al. 2015 ^[27]	China	Case-control	HBV	154	131	23	24	18	6
Akkiz, H. et al. 2014 ^[28]	Turkey	Case-control	HBV/HCV	395	172	223	187	80	107
Kimkong, I. et al. 2014 ^[7]	Thailand	Case-control	HBV	375	328	47	83	72	11
Agundez, J.A. et al. 2012 ^[29]	Spain	Case-control	HCV	231	89	142	134	52	82
Bochud, P.Y. et al. 2012 ^[30]	Swiss and French	Case-control	HCV	2335	794	1541	1915	651	1264
Chen, J. et al. 2012 ^[17]	China	Case-control	HBV	697	616	81	356	306	50
Eurich, D. et al. 2012 ^[31]	German	Case-control	HCV	167	48	119	61	13	48
Ren, S. et al. 2012 ^[32]	China	Case-control	HBV	239	177	62	154	115	39
Wang, Y. et al. 2012 ^[39]	China	Case-control	HBV/HCV	588	177	411	298	97	201
Fabris, C. et al. 2011 ^[18]	Italy	Case-control	HCV	256	102	154	85	23	62

included in the meta-analysis. Random-effects model was used for the calculation of pooled OR. The pooled result suggested that IL28B rs8099917 TT genotype is significantly linked to a decreased risk of HCC compared with IL28B rs8099917 GT/GG genotype (OR = 0.82, 95% CI = 0.72–0.94) (Fig. 3, Table 4). The heterogeneity test showed that $I^2 = 13.1\%$ (Cochran Q test, $P = .307$). Both Egger test and Begg test suggested no publication bias in the meta-analysis of the association between the IL28B rs8099917 polymorphism and the risk of HCC ($P = .268, .843$, respectively) (Fig. 4, Table 4).

3.4. Sensitivity analysis

A sensitivity analysis was conducted by sequentially omitting each study to determine the influence of individual study on the overall results of this meta-analysis (Fig. 5). The omission of any single study had no significant effects on either comparison model

of the IL28B rs12979860 or rs8099917 polymorphism, suggesting the robustness for the results in this meta-analysis.

4. Discussion

HCC is the fifth most common cancer worldwide and the third most common cause of cancer mortality.^[1,2] The carcinogenesis and progression of HCC is a complex multistep process that involves multiple genetic and epigenetic events.^[40–43] HBV or HCV is believed to be major causes of chronic hepatitis and liver cirrhosis, which are at high risk of progressing to HCC. Generally, the inflammation induced by chronic HBV or HCV infection is regarded as the driving force in the progression of HCC.^[1,44–46] An increasing number of studies suggested that IL28B polymorphisms play a vital role in the clinical outcome of chronic HBV or HCV infection owing to the association of IL28B polymorphisms with the response to IFN treatment in patients with HBV or HCV infection.

Table 2
Characteristics of the included studies examining the association of IL28B rs8099917 polymorphism with the risk of HCC.

Reference	Region or country	Study design	Underlying cause	All patients	Genotype for all patients		HCC	Genotype for HCC patients	
					TT	TG/GG		TT	TG/GG
Chang, K.C. et al. 2017 ^[33]	Taiwan	Case-control	HCV	800	585	215	100	73	27
Lee, M.H. et al. 2016 ^[26]	Taiwan	Case-control	HCV	997	883	114	481	419	62
Moreira, J.P. et al. 2016 ^[23]	Brazil	Case-control	HCV	109	64	45	59	34	25
Al-Qahtani, A. et al. 2015 ^[11]	Saudi Arabia	Case-control	HCV	678	436	242	160	103	57
Kimkong, I. et al. 2014 ^[7]	Thailand	Case-control	HBV	375	331	44	83	72	11
Asahina, Y. et al. 2014 ^[9]	Japan	Cohort study	HCV	792	588	204	53	30	23
Ma, N. et al. 2013 ^[34]	China	Case-control	HBV	792	712	80	308	270	38
Bochud, P.Y. et al. 2012 ^[30]	Swiss and French	Case-control	HCV	2335	1284	1051	1915	1053	862
Chen, J. et al. 2012 ^[17]	China	Case-control	HBV	697	623	74	356	312	44
Hagiwara, S. et al. 2012 ^[35]	Japan	Case-control	HCV	55	40	15	8	6	2
Ren, S. et al. 2012 ^[32]	China	Case-control	HBV	239	197	42	154	127	27
Wang, Y. et al. 2012 ^[39]	China	Case-control	HBV/HCV	607	538	69	299	255	44
Miura, M. et al. 2012 ^[36]	Japan	Case-control	HCV	228	162	66	68	47	21
Joshita, S. et al. 2011 ^[37]	Japan	Case-control	HCV	511	365	146	69	51	18
Jiao, X.L. et al. 2011 ^[38]	China	Case-control	HBV	486	434	52	99	87	12

Table 3
Methodological quality of studies included in the final analysis based on the Newcastle–Ottawa Scale for assessing the quality of (a) case-control studies; (b) cohort studies.

Study	Selection				Comparability	Exposure			
	Adequate definition of patient cases	Representativeness of patients cases	Selection of controls	Definition of controls		Control for important factor or additional factor	Ascertainment of exposure	Same method of ascertainment for participants	Non-response rate
(a)									
Chang, K.C. ^[33]	1	1	0	1	2	1	1	1	8
Marwa, K.L. ^[39]	1	1	0	1	2	1	1	1	8
De la Fuente, S. ^[8]	1	1	0	1	2	1	1	1	8
Al-Qahtani, A. ^[1]	1	0	0	1	1	1	1	1	6
Chang, K.C. ^[2]	1	1	0	1	2	1	1	1	8
Shi, X. ^[27]	1	1	0	1	1	1	1	1	7
Akkiz, H. ^[28]	1	0	0	1	2	1	1	1	7
Kimkong, I. ^[7]	1	0	0	1	2	1	1	1	7
Agundez, J.A. ^[29]	1	1	0	1	2	1	1	1	7
Bochud, P.Y. ^[30]	1	1	0	1	2	1	1	1	8
Chen, J. ^[17]	1	0	0	1	2	1	1	1	8
Eurich, D. ^[31]	1	1	0	1	1	1	1	1	7
REN.S. ^[32]	1	1	0	1	0	1	1	1	6
Wang, Y. ^[39]	1	1	0	1	1	1	1	1	7
Fabris, C. ^[18]	1	1	0	1	2	0	1	1	7
Lee, M.H. ^[26]	1	1	0	1	2	1	1	1	8
Moreira, J.P. ^[23]	1	0	0	1	1	1	1	1	6
Ma, N. ^[34]	1	0	0	1	0	1	1	1	5
Hagiwara, S. ^[35]	1	1	0	1	2	1	1	1	8
Miura, M. ^[36]	1	0	0	1	2	1	1	1	7
Joshita, S. ^[37]	1	1	0	1	1	1	1	1	7
Jiao X.L. ^[38]	1	1	0	1	2	1	1	1	8
De Re, V. ^[25]	1	0	1	1	0	1	1	1	6
(b)									
Study	Selection			Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Exposure		Total Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure				Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Asahina, Y. ^[9]	1	1	1	1	2	1	0	0	7

Moreover, IL28B rs12979860 and rs8099917 polymorphisms are linked to liver fibrosis staging and a higher risk of progressing to HCC development in patients with HBV or HCV infection. Recent studies have focused on the association of IL28B polymorphisms with the occurrence of HCC during the process of chronic HBV or HCV infection. However, the precise role of IL28B polymorphisms in hepatocarcinogenesis is not entirely clear, and the possible association between the IL28B polymorphisms and the risk of HCC remains controversial.

Several studies have investigated the impact of the IL28B rs12979860 SNPs (genotype CC vs CT/TT) on the occurrence of HCC. However, different conclusions on the association were reached. The results from 2 separate studies showed that IL28B CC genotype was associated with a decreased incidence of HCC in patients with chronic HBV and HCV infection among individuals with HBV or HCV infection,^[2,17,18] whereas no significant difference in the incidence of HCC was observed between genotypes CC and CT/TT in other studies.^[19,28–32] Similarly, evidence from studies focusing on the relationship of IL28B rs8099917 SNPs (genotype TT vs TG/GG) with the risk of HCC reflected a similar trend. A lower

incidence of HCC has also been observed among patients with the IL 28B rs8099917 TT genotype compared with the IL28B non-TT genotype.^[19] In contrast, several studies presented the opposite conclusion that there is no significant difference in the risk of HCC between the different genotypes.^[17,30,32,34–37] Totally, studies examining the association between the risk of HCC and IL28B polymorphism have shown inconsistent conclusion.

In this meta-analysis, we searched for studies focusing on the association between SNPs of the IL28B gene (rs12979860 and rs8099917) and the occurrence of HCC owing to various etiologies. IL28B rs12979860 gene polymorphism is associated with the incidence of HCC. The IL28B rs12979860 CC genotype was associated with a significant decrease in the incidence of HCC compared with the CT/TT genotype (OR=0.71, 95% CI=0.57–0.88). Similarly, the IL28B rs8099917 TT genotype was associated with a significant decrease in the incidence of HCC compared with the GT/GG genotype (OR=0.82, 95% CI=0.72–0.94). In brief, IL28B rs12979860 CC and rs8099917 TT genotypes could be considered as protective factors for HCC in patients with HBV or HCV infection.

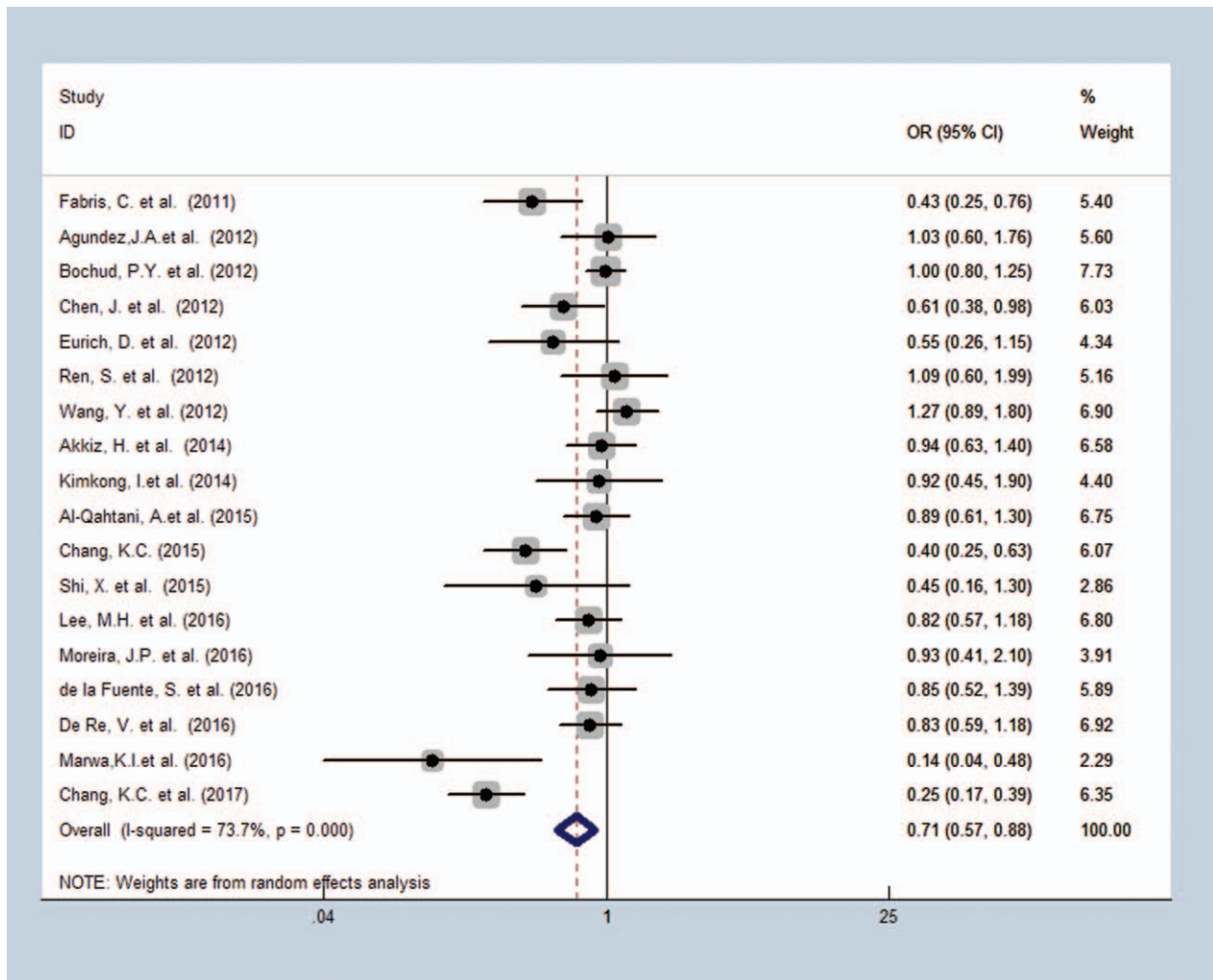


Figure 2. The influence of IL28B rs12979860 polymorphism (genotype CC vs CT/TT) on the risk of HCC among patients with HBV or HCV infection. The squares represent the risk estimate for each study. The sizes of the squares reflect the weight assigned to the study. Bars represent 95% confidence intervals. The diamond represents the summary effect, with width representing 95% confidence interval. CI = confidence interval, OR = odds ratio.

The potential molecular mechanisms underlying the effects of the IL28B polymorphisms on the risk of HCC remain unclear. Shi et al reported that the IL28B rs12979860 non-CC genotype results in lower IL28A/B mRNA and IL28B protein levels compared with the T-alleles. Furthermore, reduced IL28B expression tends to be associated with more active and advanced stages of liver disease.^[11] IL28B polymorphisms are strongly associated with HCV clearance and the response of HCV patients to IFN treatment.^[47] Peg-IFN plus ribavirin decrease the occurrence of HCC in HBV- or HCV-infected patients who

achieve a sustained virological response and have not yet progressed to cirrhosis.^[31] A nested case-control study in Taiwan reported that unfavorable genotype IL28B genotypes (rs12979860 CT/TT and rs8099917 GT/GG) were associated with spontaneous HCV RNA clearance, and variants associated with less likelihood of spontaneous HCV RNA clearance were associated with increased risk for HCC in patients infected by HCV genotype 1.^[26] Thus, the impact of IL28B SNPs on the risk of HCC may be indirect and primarily influenced by the effect of IFN treatment in HCV patients. However, a large-scale,

Table 4
Summary of the influence of IL28B polymorphisms on the risk of HCC.

IL28B Polymorphism	Number of studies	Odds ratio (OR)		Model	Heterogeneity			Egger test		Begg test
		OR (95% CI)	P		Q	I ² (%)	P	P	P	
rs12979860	18	0.71 (0.57–0.88)	.002	R	64.7	73.7%	<.01	.072	.198	
rs8099917	15	0.82 (0.72–0.94)	.005	R	16.1	13.1%	.307	.268	.843	

CI = confidence interval, R = random-effects model.

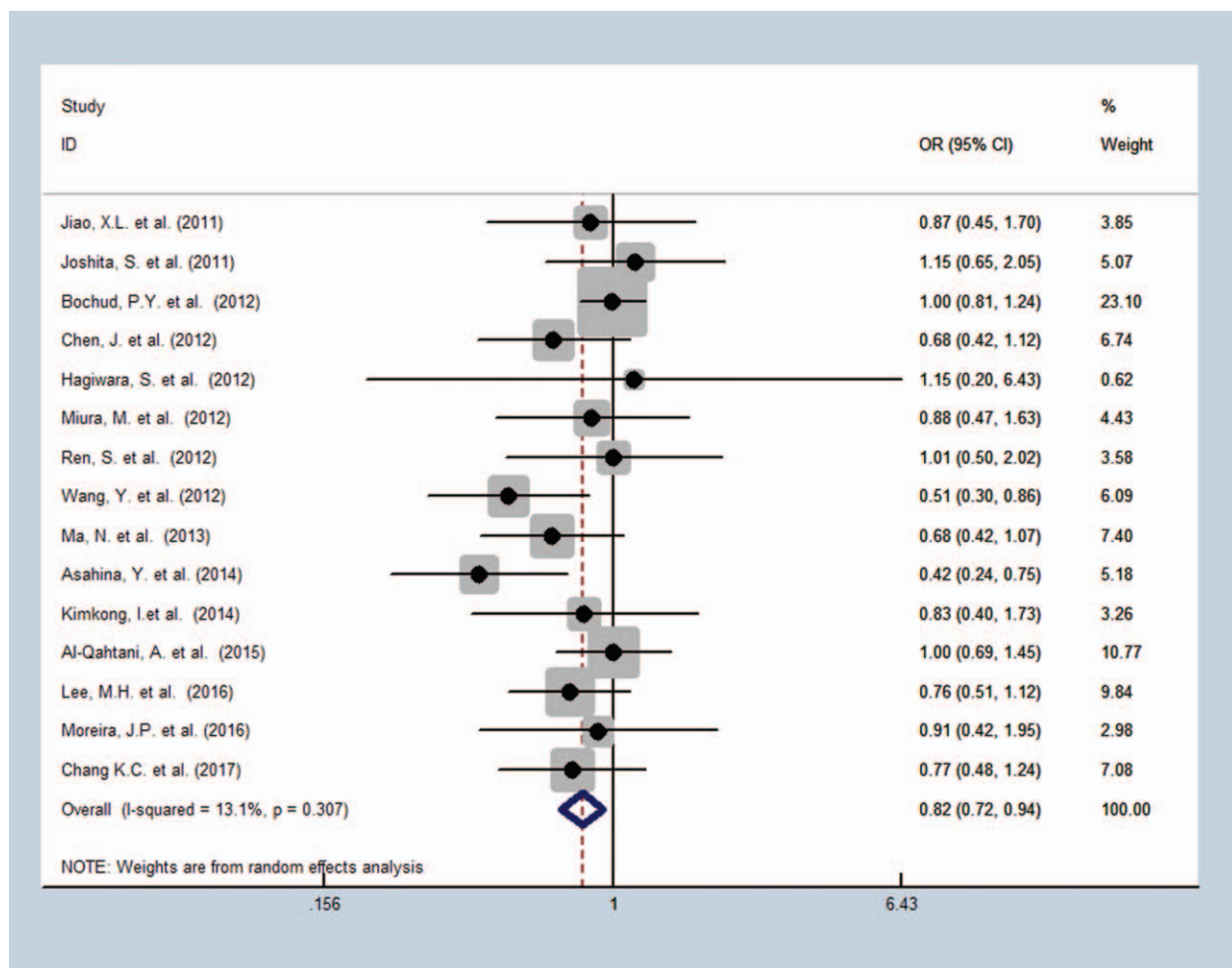


Figure 3. The influence of IL28B rs8099917 polymorphism (genotype TT vs TG/GG) on the risk of HCC among patients with HBV or HCV infection.

long-term cohort study reported a significantly higher incidence of HCC in non-TT patients among non-SVRs, indicating that the impact of non-TT on the risk of HCC was not fully explained by the poor virological response rates observed in non-TT patients.

Similarly, controversy regarding the effect of IL28B SNPs on hepatitis B infection has persisted for a long time.^[10,48] A systematic review has provided evidence that there is no direct association between common IL28B polymorphisms and the spontaneous clearance rate of hepatitis B surface antigen (HBsAg).^[8,49] However, recent studies have reported that IL28B polymorphisms are associated with a higher chance of HBsAg seroclearance during the natural history of chronic B infection. Several studies have demonstrated that IL28B SNPs (rs12979860 and rs8099917) are significantly associated with the risk of chronic hepatitis B infection and the risk of HCC.^[7] Hence, the impact of IL28B SNPs on the risk of HCC may be partly influenced by the IFN treatment effect in HBV patients.

This study has some limitations. Statistical heterogeneity was observed in the model of IL28B rs12979860 for the risk of HCC. The heterogeneity may be caused by discrepancies in clinical characteristics between the different studies,

including but not limited to the variation in fibrosis staging and the genotype of HCV or HBV. Although the limitations exist, the sensitivity analysis showed that the omission of any individual study had no significant impact on the final results for either the IL28B rs12979860 or the rs8099917 SNP model, suggesting the robustness for the pooled results in our meta-analysis. Also, methodological differences, such as dissimilarities in the selection of controls, treatment options, follow-up time, or diagnostic criteria for HCC also contribute to heterogeneity.

This meta-analysis has strengths, although there are limitations.^[50-52] First, this meta-analysis was performed using a comprehensive search of multiple databases and thus, included adequate numbers of original studies. Second, a proper sensitivity analysis was carried to confirm the robustness of the results of this meta-analysis.

In conclusion, both IL28B rs12979860 CC and rs8099917 TT genotypes are protective factors for the development of HCC among patients with HBV or HCV infection. Future prospective studies examining the impact of IL28B polymorphisms on the risk of HCC and investigating the underlying mechanism for the protective role of IL28B polymorphisms in HCC development are warranted.

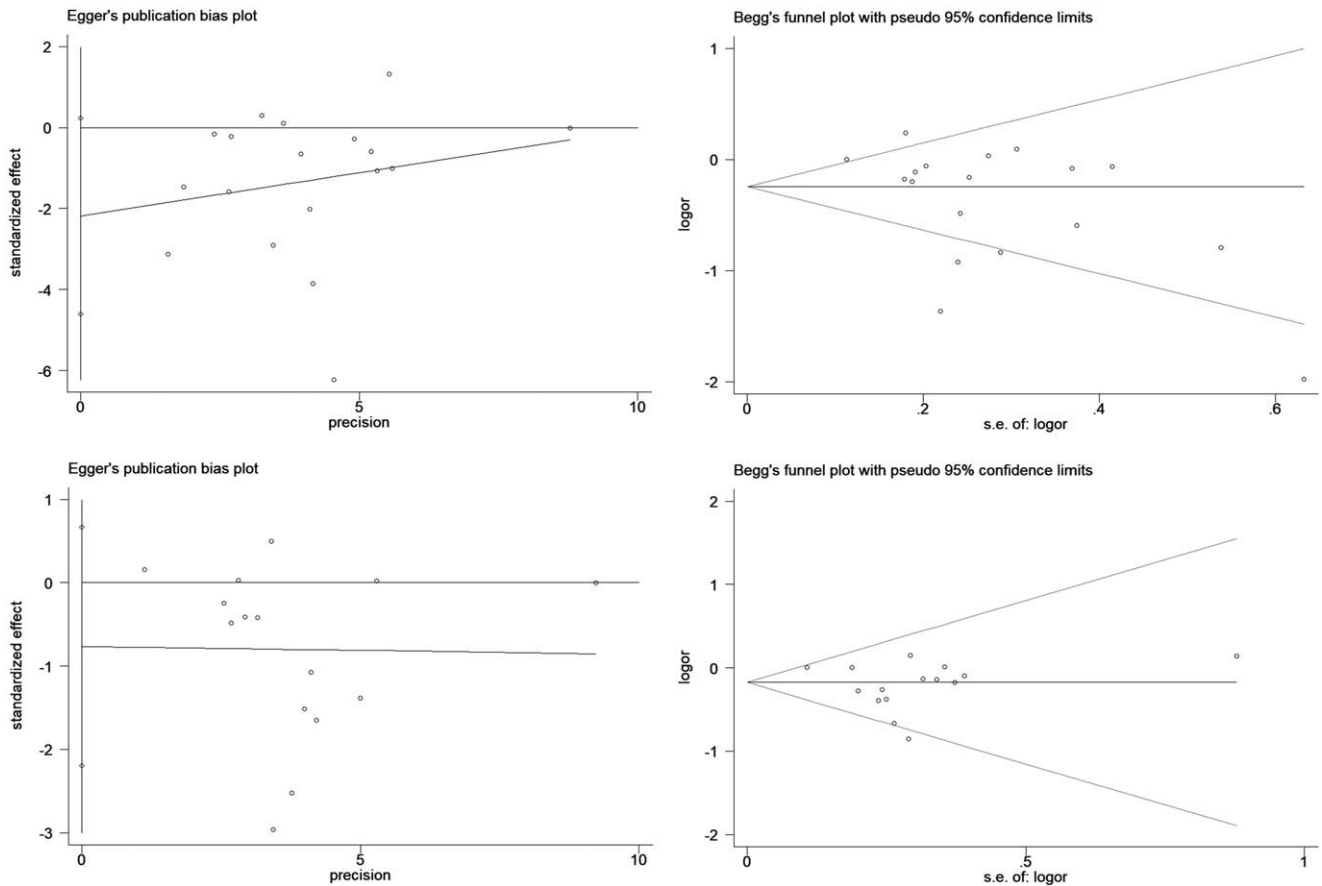


Figure 4. Egger test and Begg test for the evaluation of publication bias of 18 studies on the association of IL28B rs12979860 polymorphism with the risk of HCC (A, B), and 15 of studies on the association of IL28B rs8099917 polymorphism with the risk of HCC (C, D).

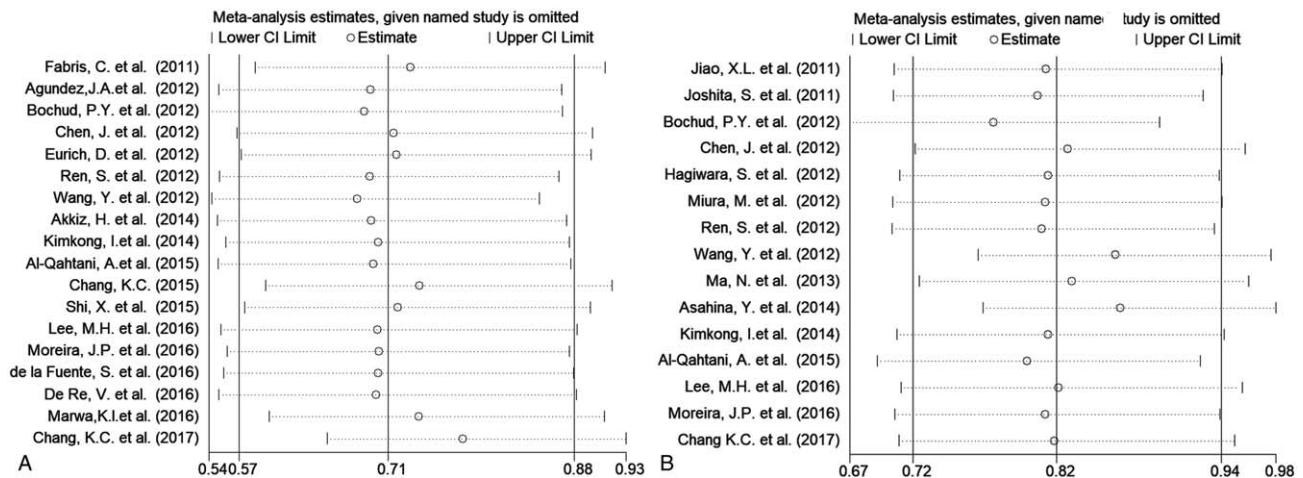


Figure 5. Sensitivity analysis for the association of IL28B rs12979860 (A) and IL28B rs8099917 (B) polymorphisms with the risk of HCC among patients with HBV or HCV infection.

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Visualization: Song Wang.
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