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RESEARCH ARTICLE

Association of polymorphisms in interleukin-18 and interleukin-28B genes with outcomes of hepatitis B virus infections: a meta-analysis

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Abstract Several polymorphisms in the interleukin-18 (*IL-18*) and nterleukin-28B (*IL-28B*) genes have been reported to influence hepatitis B virus (HBV) infection. However, the published findings have been conflicting. We conducted meta-analyses of randomized, controlled trials to address the association of IL-18 or IL-28B polymorphisms and the outcomes of HBV infection. Weipu, Wanfang, CNKI, MEDLINE, PubMed, EMBASE, and Cochrane Library databases were employed to search for citations using the MeSH terms as "interleukin-18"/"interleukin-28B" AND "HBV" AND "gene" AND "polymorphism" without any restriction in language and publication year. Meta-analysis was conducted by RevMan 5.0 software. The results showed that the IL28B rs8099917 AA genotype (AA vs AC+CC: odds ratio (OR)=0.63, 95 % confidence interval (CI)=0.46–0.87) was associated with a decreased risk of hepatocellular carcinoma (HCC). Carriage of IL28B rs12979860 CC genotype was associated with an increased risk for developing liver cirrhosis among patients with HBV infection (CC vs CT+TT: OR=1.39, 95 % CI=1.04–1.85). Further well-designed large studies are warranted to confirm the mechanisms by which these are involved in these outcomes of HBV infection.

Keywords Meta-analysis · HBV · IL-18 · IL-28B · Polymorphisms

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Introduction

Hepatitis B is an infectious disease resulting in an estimated 350 million chronically infected patients [1, 2]. The incidence rates of hepatitis B virus (HBV) infection have a markedly diverse regional distribution. It is very prevalent in developing Asian-Pacific countries [3]. In addition, chronic HBV infection (CHB) is a major cause of cirrhosis (LC) and primary hepatocellular carcinoma (HCC) worldwide and is among the top ten causes of death [4]. HBV is transmitted parenterally by contaminated blood or other body fluids through blood vessels, skin, or mucous membranes [5]. The natural history of HBV infection varies from spontaneous recovery post-infection, to chronic asymptomatic carrier, to decompensated cirrhosis, and HCC; the latter are associated with a high mortality rate and heavy economic burden [6, 7].

Recent studies suggest that certain cytokines, including interleukin (IL)-28, IL-29, and IL-12, control the host response and could play an important role in determining HBV infection outcome [8–10]. TaqMan single-nucleotide polymorphism (SNP) Genotyping Assays were used for the detection of the reference single nucleotide polymorphisms near the *IL-28B* gene on chromosome 19, rs12979860, rs12980275, and rs8099917 [11, 12]. Increasing evidence shows that genetic variants of IL-28B play a functional role during HBV infection. However, results derived from individually underpowered studies are conflicting. For example, the genotype and allele frequencies of the three SNPs in IL-28B

(rs12979860, rs12980275, and rs8099917) were reported to be strongly associated with the serum ALT levels and HBV viral loads [13]. Conversely, Peng et al. [14] found that IL-28B rs12979860 polymorphism has no association with spontaneous HBV clearance and HBV-related disease progression.

The published record suggests that IL-18 plays a role in mouse models of HBV replication and vaccinia virus infection [15–17]. Many SNPs in the *IL-18* gene region were predicted to be involved in clearing HBV, such as –607C/A and –137G/C in the IL-18 promoter regions [17], 148G/C [18] and 105A/C [19] in regulatory gene sequences, etc. The two SNPs (rs187238 and rs1946518) in the promoter region of the *IL-18* gene have been repeatedly found to be associated with the *IL-18* gene promoter transcription activity [20, 21].

Given the lack of previous meta-analyses in this area, our main objective was to assess the association between *IL-18* and *IL-28B* gene polymorphisms and the outcomes of hepatitis B infection by summarizing the results of published cohort and case–control studies.

Research design and methods

Search strategy

We searched the following databases to identify pertinent studies that examined the association between *IL-18* and *IL-28B* gene polymorphisms and hepatitis B: MEDLINE (1966 to March 2013), EMBASE (1980 to March 2013), Cochrane Central Register of Controlled Trials (1991 to March 2013), Chinese National Knowledge Infrastructure, Chinese WanFang database, and Chinese WeiPu database. The search strategy was based on a combination of ("interleukin-18" OR "interleukin 18" OR "IL-18" OR "IL18") AND "HBV" AND "gene" AND "polymorphism"/("interleukin-28B" OR "interleukin 28B" OR "IL-28B" OR "IL28B" OR "interferon lambda 3" OR "IFN lambda 3") AND "HBV" AND "gene" AND "polymorphism" without any restriction in language and publication year. References of retrieved articles were also screened. We reviewed titles for relevance from this search and examined all subject headings and abstracts. The scope notes in MEDLINE and EMBASE were also examined to ensure the correct subject headings were used based on their definitions; other subject headings were included based on previous indexing and the inclusion of keywords based on synonyms used in the scope notes.

Inclusion criteria

To ensure the maximum possible objectivity, the quality of each study was independently assessed by the same two authors (Dong and Xing). When discrepancies arose, a third party (Xia) was consulted. The major inclusion criteria were (a) evaluation of the *IL-18* or *IL-28B* gene polymorphisms and the outcomes of HBV infection and (b) provided relative risk (RR) or odds ratio (OR) estimates and their 95 % confidence intervals (CI) or sufficient data to calculate these estimates. The major reasons for exclusion of studies were (a) overlapping data, (b) case report studies, and (c) review articles. The Jadad scale for quality was then applied to included studies [22].

Data extraction

Two independent investigators (Zhou and Bai) performed the data extraction. Information included the authors, year of publication, demographic variables (number of subjects, age and gender), and illness variables (diagnosis and duration of illness) from every selected study and were recorded by using a data recording form. No patients received any treatments before sampling, and co-infections were excluded. After extraction, data were reviewed and compared by the two independent

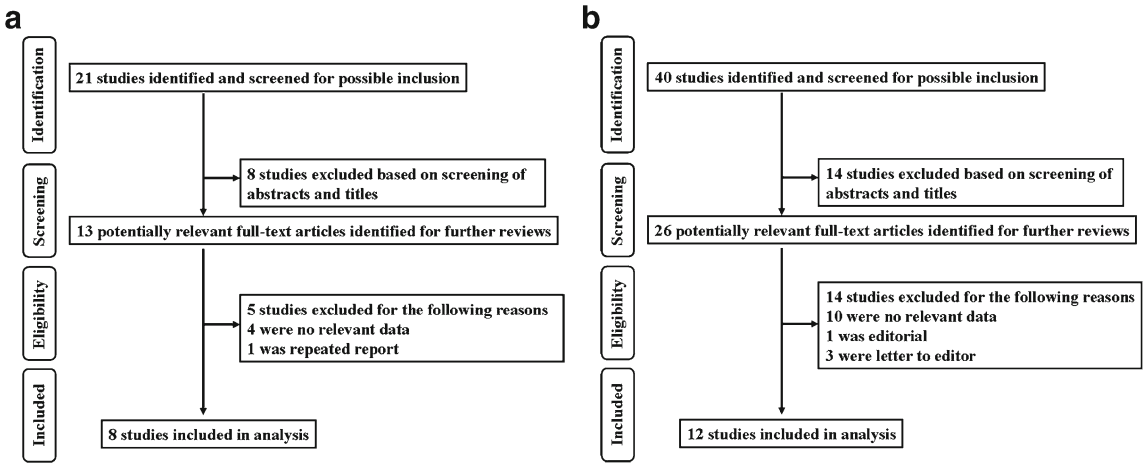

Fig. 1 Flow diagram of identifying potential studies in our meta-analysis. **a** Records relating to the *IL-18* gene polymorphisms and the outcomes of HBV infection. **b** Records relating to *IL-28B* gene and the outcomes of HBV infection

Table 1 Characteristics of case–control studies for interleukin-18 gene polymorphisms with the outcomes of Hepatitis B virus infection included in the meta-analysis

First author	Year	Country	Polymorphisms	Chronic HBV infection	Self-limited HBV infection	Liver cirrhosis	Hepatocellular carcinoma	Health control	Methods studied
Kim [18]	2009	South Korea	rs1946519, rs187238, rs360721, and rs549908	637			93		PCR
Hirankarn [26]	2007	Thailand	rs187238 and rs1946518	140				140	PCR-SSP
Cheong [27]	2010	South Korea	rs1946519, rs187238, rs360721, and rs549908	730	320				PCR
Zhang [28]	2005	China	rs187238 and rs1946518	231				300	PCR-SSP
Migita [29]	2009	Japan	rs187238 and rs1946518	62		52	47		PCR
Chen [30]	2012	China	rs187238 and rs1946518				228	300	PCR-SSP
Li [31]	2012	China	rs1946518 and rs574424	501				301	PCR
Gao [32]	2010	China	rs187238 and rs1946518	328				193	PCR

investigators. Disagreements between the two extractors were resolved by consensus among the investigators. Additional information concerning a specific study was obtained by direct questioning of the principal investigator (Xia).

Statistical analysis

The meta-analysis was performed using Review Manager Version 5.0 for Windows (Cochrane Collaboration, http://www.cc-ims.net/RevMan). Cochran's Chi-square (χ^2)-based Q-statistic test was applied to assess between-study heterogeneity. The inter-study heterogeneity in terms of degree of association was tested using the Cochran's Q-statistic [23]. If $P<0.10$, the heterogeneity was considered significant, which was further explored by using I^2 statistic. I^2 is expressed as the percentage of between-study variability that is attributable to genuine variation rather than sample error [24]. If there was heterogeneity among studies, we used a random-effect (RE) model to pool the ORs; otherwise, a fixed-effect (FE) model was selected [25].

Results

Literature retrieved

The selected study characteristics are listed in Tables 1 and 2. Briefly, we found that 21 articles met the keyword selection for

Table 2 Characteristics of case–control studies for interleukin-28B gene polymorphisms with the outcomes of hepatitis B virus infection included in the meta-analysis

First author	Year	Country	Polymorphisms	Chronic HBV infection	Self-limited HBV infection	Liver cirrhosis	Hepatocellular carcinoma	Health control	Methods studied
Chen [33]	2012	China	rs12979860, rs12980275, and rs8099917.	393		406	406	244	PCR
Li [33]	2011	China	rs12979860, rs12980275, and rs8099917.	203	203			203	Pyrosequencing
Ren [35]	2012	China	rs12979860, rs12980275, and rs8099917.	86	43		154	47	PCR
Martin [36]	2010	USA	rs12979860	226	384				
Peng [14]	2012	China	rs12979860	264	226	387			MALDI-TOF MS
Martín-Carbonero [37]	2012	Spain	rs12979860	49	49				PCR
Wang [38]	2012	China	rs12979860, rs8099917, rs4803223, and rs12972991				300	310	MALDI-TOF MS
Jiao [39]	2011	China	rs8099917		143	100	99	144	PCR
Fabris [41]	2011	Italy	rs12979860	57		75		344	PCR

Table 3 Characteristics of case–control studies for interleukin-28 gene polymorphisms with HBeAg seroconversion included in the meta-analysis

First author	Year	Country	Polymorphisms	HBeAg		Methods studied
				Positive	Negative	
Peng [14]	2012	China	rs12979860	202	449	PCR
Dunford [41]	2012	Viet Nam	rs12979860	87	127	PCR
Holmes [42]	2013	Australia	rs12979860	60	36	PCR
Lee [43]	2013	China	rs12979860, rs8099917, rs10853728, and rs8105790	48	67	PCR

IL-18. After initially screening titles and abstracts, the full texts of 13 were reviewed by detailed evaluation. Finally, eight studies met the criteria for inclusion (Fig. 1a) [18, 26–32]. The basic characteristics of each study for IL-18 included in our meta-analysis are summarized in Table 1. Our initial search strategy retrieved a total of 40 citations for IL-28B. After the titles and abstracts were screened, 28 articles were excluded because they were laboratory studies, review articles, or irrelevant to the current study. We identified 12 potentially relevant articles concerning IL-28B in relation to outcomes of HBV infections (Fig. 1b) [13, 14, 33–42]. The basic characteristics of each study for IL-28B included in our meta-analysis are summarized in Table 2. The studies on the relationship between the IL-28B polymorphisms and HBeAg seroclearance is summarized in Table 3. Pooled IL-18 or IL-28B genotype frequencies and the outcomes of HBV infection are summarized in Fig. 2.

Association between the IL-18 polymorphism and the HBV infection

There was no evidence for an association between the HBV infections and the variant genotypes of IL-18. The results are shown in Fig. 3. Based on the χ^2 and I^2 analyses (χ^2=8.35, df=2 (P=0.02); I^2=76 %), a RE approach was used to summary estimate the IL-18 rs187238 and the RR of HBV infection in CHB patients and healthy controls. No association between the IL-18 rs187238 and the HBV infection was observed in our meta-analysis of the three studies (GG vs GC+CC: OR=1.16, 95 % CI=0.69–1.97) (Fig. 3a). The pooled data also demonstrated that IL18 rs1946518 was not associated with an increased risk of HBV infection in CHB patients and healthy controls (AA vs CA+CC: OR=1.35, 95 % CI=0.91–2.01) by estimating a RE approach (χ^2=10.09, df=3 (P=0.02); I^2=70 %) (Fig. 3b).

Association between the IL-28B rs8099917 polymorphism and the HBV infection

IL-28B rs8099917 was not found to be associated with an increased risk of hepatitis B infection in CHB patients and healthy controls. The patients with IL-28B rs8099917 AA genotype showed lower risk of hepatitis B than the patients with IL-28B rs8099917 AC/CC genotype (OR=0.86, 95 % CI=0.59–1.26). However, the results were not statistically significant (P=0.44) (Fig. 4a). For estimating the risk of HCC with IL-28B rs8099917, we compared the healthy control group and HCC group and found that the IL-28B rs8099917 AA genotype showed a lower risk compared with AC/CC (OR=0.63, 95 % CI=0.46–0.87) (Fig. 4b). No relationship was observed between IL-28B rs8099917 and HBV self-limited infection (OR=0.70, 95 % CI=0.44–1.10) (Fig. 4c).

Association between the IL-28B rs12979860 polymorphism and the HBV infection

A RE approach was used to estimate IL-28B rs12979860 polymorphism and the RR of CHB in CHB patients and healthy controls or HCC in HCC patients and healthy controls, accruing to the χ^2 and I^2 analyses for CHB (χ^2=7.11, df=3 (P=0.07); I^2=58 %) and HCC (χ^2=8.76, df=2 (P=0.01); I^2=77 %). As shown in Fig. 5a, b, we found no association between the IL-28B rs12979860 polymorphism and CHB (OR=0.81, 95 % CI=0.50–1.32) or HCC (OR=0.83, 95 % CI=0.42–1.61) compared with HC. We also failed to find any increased frequency

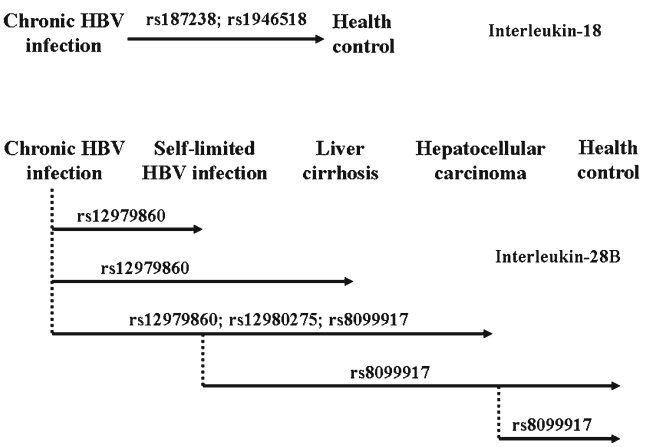

Fig. 2 IL-18 or IL-28B polymorphisms and the outcomes of HBV infection were pooled in this study

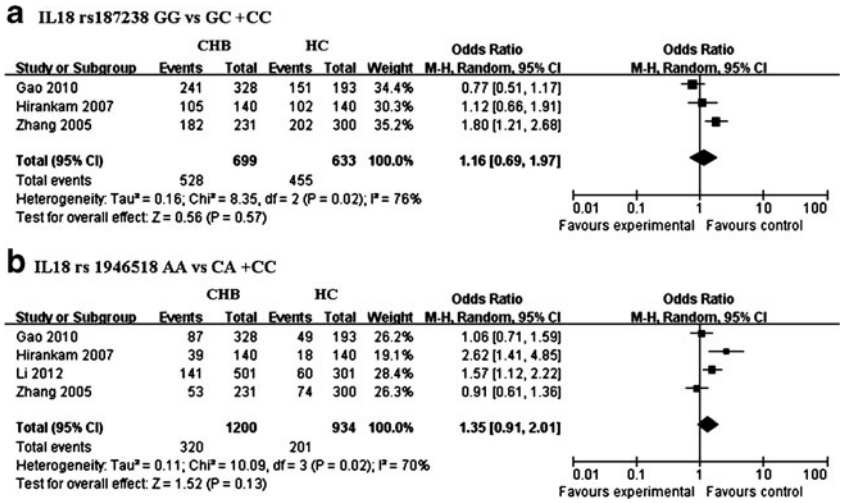

Fig. 3 Forrest plots for association between IL-18 polymorphisms and HBV infection. **a** OR on HBV infection associated with IL-18 rs187238 for the GG genotype compared with the GC+CC genotype. **b** OR on HBV infection associated with IL-18 rs 1946518 for the AA genotype compared with the CA+CC genotype

for IL-28B rs12979860 polymorphism in CHB patients compared to self-limited HBV infection patients (OR=1.01, 95 % CI=0.80–1.28) (Fig. 5c). However, we found significant effect of IL-28B rs12979860 on the risk of developing liver cirrhosis (CC vs CT+TT: OR=1.39, 95 % CI=1.04–1.85) (Fig. 5d). A FE approach was used to estimate IL-28B rs12979860 polymorphism and the RR of self-limited HBV infection (χ^2=5.91, *df*=3 (*P*=0.21); I^2=32 %) or LC (χ^2=3.64, *df*=2 (*P*=0.16); I^2=45 %). Furthermore, we found that the IL-28B rs12979860 polymorphism was not associated with HBeAg seroclearance (CC vs CT+TT: OR=1.39, 95 % CI=0.94–2.04) (Fig. 5e).

No association between the IL-28B 12980275 polymorphism and the HBV infection For IL-28B rs12980275, we found no association between that polymorphism and HBV infection (AA vs AG+GG: OR=0.89, 95 % CI=0.63–1.25) (Fig. 6), with no evidence of between-study heterogeneity (χ^2=0.66, *df*=2 (*P*=0.72); I^2=0 %).

Bias diagnostics

The publication bias of the individual studies was evaluated by funnel plot. No visual publication bias was found in the funnel plot for each study (Fig. 7).

Discussion

To the best of our knowledge, this is the first meta-analysis on the association between the *IL-18* or *IL-28B* gene polymorphism and the risk of the outcomes of HBV infection. Our

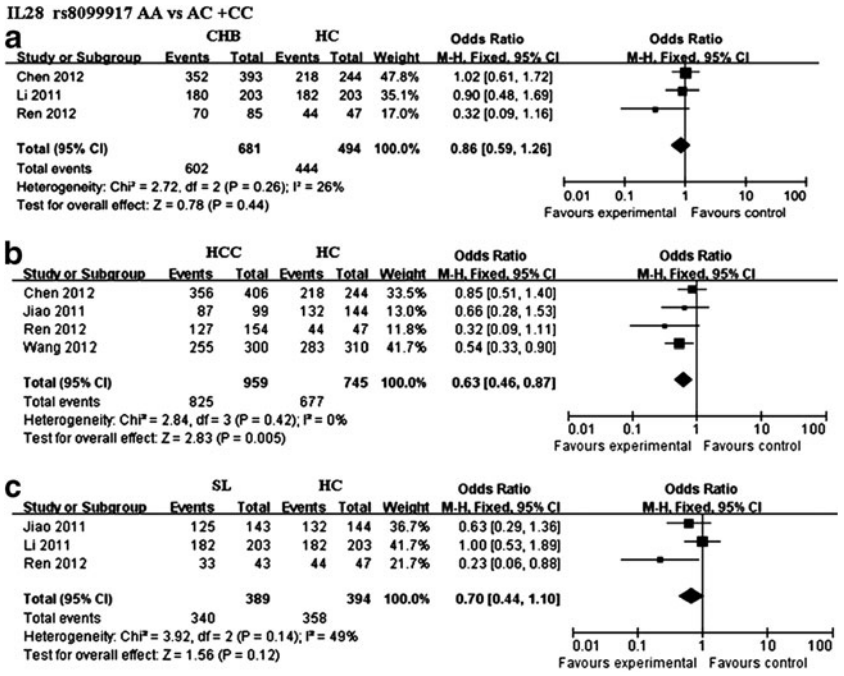

Fig. 4 Forrest plots for association between IL-28B rs8099917 AA polymorphism and the outcomes of HBV infection. **a** CHB vs HC; **b** HCC vs HC; and **c** SL vs HC

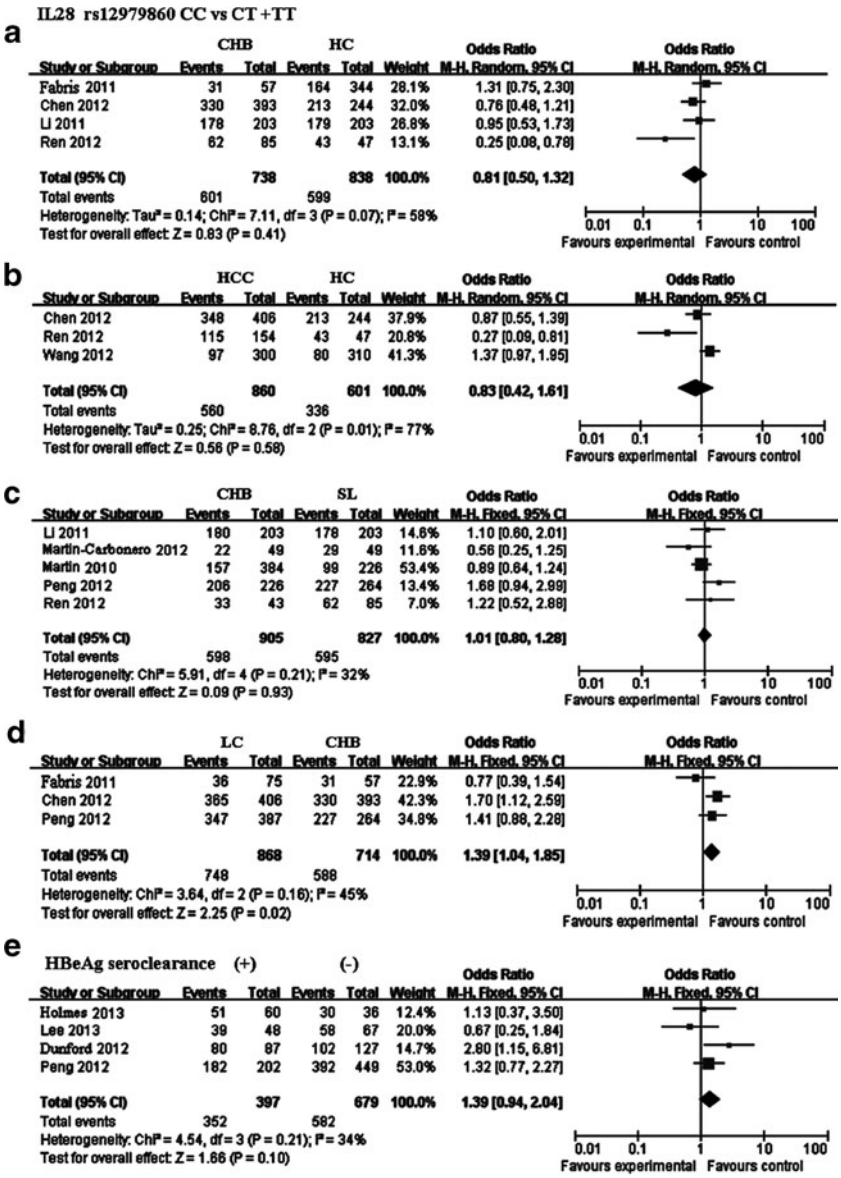

Fig. 5 Forrest plots for association between IL-28B rs12979860 CC polymorphism and the outcomes of HBV infection. **a** CHB vs HC; **b** HCC vs HC; **c** CHB vs SL; **d** LC vs CHB; and **e** OR on HBeAg seroclearance with IL28B rs12979860 CC compared with CT+TT

study combined the data from diverse studies that reveal inconsistent results on the same problem by using Meta-analysis.

As noted in the introduction, many SNPs in the *IL-18* gene region have been predicted to be involved in the clearance HBV [17–19]. Previous report by Zhang et al. [28] found no significant relationship between polymorphism at position IL-18 rs1946518 and disease susceptibility. However, they reported that C allele at position IL-18 rs187238 plays a protective role in the development of HBV infection [28]. Hirankarn et al. [26] found that A/A genotype at position of >607 in *IL-18* gene (rs1946518) can be used as a new genetic marker in Thai population for predicting chronic hepatitis B development. Li et al. [31] found that genotype AA and the allele A of the IL-18 at position rs1946518 are closely associated with the resistance to chronic hepatitis B. In the current study, we performed a meta-analysis to examine the association between the SNPs in

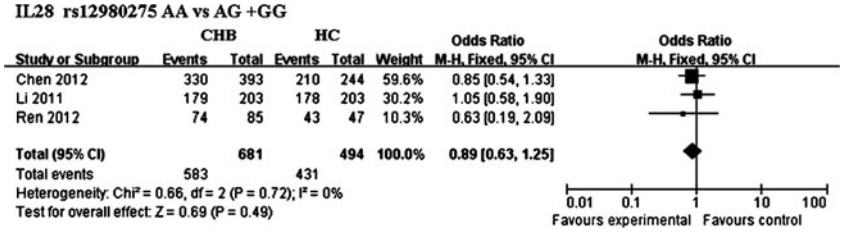

Fig. 6 Forrest plots for association between IL-28B rs12980275 AA polymorphism and the HBV infection

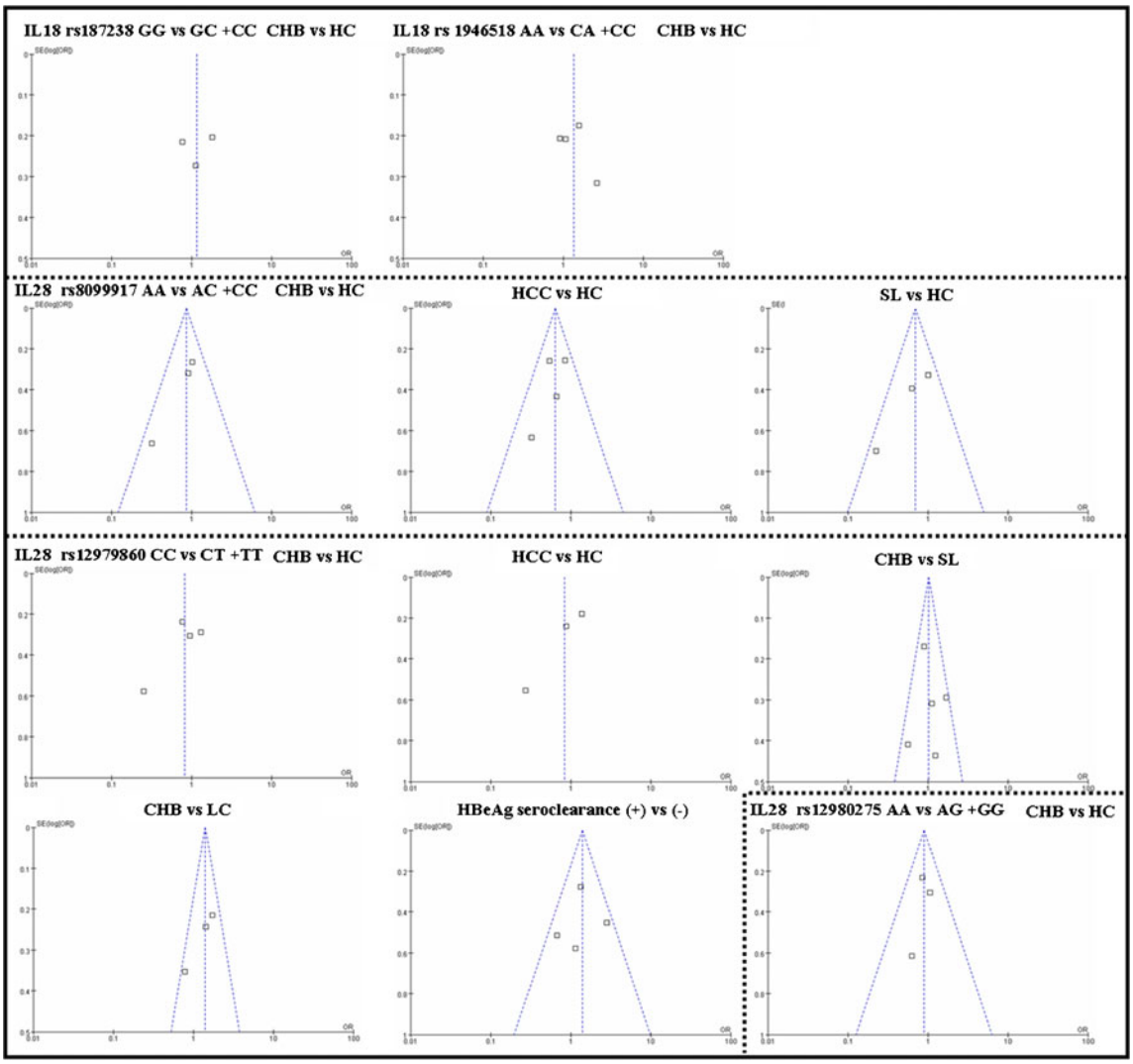

Fig. 7 Funnel plot analysis to examine publication bias

IL-18 gene region because of a larger size sample and provided explanations for the inconsistencies observed in previous studies. According to our findings, both IL-18 rs187238 and rs1946518 showed no effects on HBV infection. The HBV affectability of IL-18 rs1946518 played different roles in different population [32].

We found that genotype AA of IL-28B rs8099917 was not associated with the risk of CHB which supports the study of Chen et al [33], Li et al. [13], and Ren et al. [34]. In their studies, they also did not find the IL-28B rs8099917 and the risk of CHB. Furthermore, we estimated the relationship between genotype AA of IL-28B rs8099917 and the HBV self-limited infection. Consistent with the study of Jiao et al. [38], they also failed to find the IL-28B rs8099917 SNP had a correlation with the outcome of HBV infection. Ren et al. [34] did not find the significant differences in genotype distributions of the IL-28B rs8099917 among HBV self-limited infections and healthy control groups. However, Li et al. [13] provided indirect evidence for IL-28B rs8099917 and HBV clearance that an increase in IL-28B expression was detected in patients with the AA genotype compared with the CA/CC genotypes.

Li et al. [13] analyzed the potential role of IL-28B in the course of HBV infection and found no notable association with persistent HBV infection for IL-28B rs12979860. Chen et al. [33] also found no significant difference of frequency in IL-28B (rs12979860) between CHB and healthy control. However, Ren et al. [34] found rs12979860 in the *IL-28B* gene might be a candidate risk factor for CHB. Possible explanations for this difference are a lack of data, and ethnicity diversity. Our study provided a more believable result. We confirmed IL-28B rs12979860 polymorphism did not show any associations with the HBV outcome except cirrhosis based on our combined relatively large numbers of studies. In our study, comparing HBV-related cirrhosis patients with CHB patients, IL-28B rs12979860 CC genotype is a risk factor for

CHB transformed to liver cirrhosis. Consistent with previous studies, CHB patients who progress to liver cirrhosis showed a significant different frequency in IL-28B rs12979860 [14, 33]. The predictive value of IL-28B has been recently documented also in the different scenario of HBeAg positive patients with CHB from North Europe and Asia [43]. Consistent with our study, previous studies showed that IL-28B rs12979860 polymorphism had no association with clearance of hepatitis B e antigen [14, 40, 41].

In the study of Li et al. [13], no significant differences were observed in IL-28B rs12980275 genotype or allele frequencies among chronically HBV-infected, self-limited and healthy subjects. Recent experimental evidence is emerging suggesting that IL-28B rs12980275 AA genotype has no predictive effect of increasing susceptibility of CHB and healthy control [33]. In our study, we have a consistent result with previous studies that no associations were found between IL-28B rs12980275 genotype and HBV infection.

In conclusion, this study provides evidence of a positive association between HCC and IL-28B rs8099917 AA genotype. A second potentially interesting finding of our work was that carriage of IL-28B rs12979860 CC genotype enhances the risk for developing liver cirrhosis among patients with HBV infection. These genotypes might affect the outcome of HBV infection through regulation of IL-28B activation and production. Conversely, no other genotype polymorphisms of IL-18 and IL-28B could affect the outcomes of chronic infection. The value of the current meta-analysis compensates for the individual lack of precision of most studies, a problem alleviated by pooling. However, certain potential limitations exist in our meta-analysis. Some studies included in this meta-analysis were hospital-based case–control studies. In this instance, the hospital-based controls may not be representative of the general population. No publication bias was found in our meta-analysis, because the only studies published in English and Chinese were included. Furthermore, we were unable to perform further subgroup analyses for different ethnic populations due to a limited number of published studies available to be included. Ethnic diversity and HBV genotype may complicate the outcome of infection. Although, we performed this meta-analysis in an attempt to resolve the effects of IL-18 or IL-28B polymorphisms on the outcome of HBV infection, further well-designed large studies, particularly referring to gene-ethnic group and gene-HBV genotype interactions are warranted to confirm the real contribution of these polymorphisms to the outcome of HBV infection.

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Conflicts of interest None

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