Systematic Review and Meta-Analysis

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Interleukin-6 gene polymorphisms and susceptibility to liver diseases

A meta-analysis

Xuehan Wang, PhD[a,*], Zhenghui Yan, MS[a], Qingjian Ye, MM[b,*]

Abstract

Background: Several studies have explored the associations between interleukin-6 (IL-6) gene polymorphisms and the susceptibility to liver diseases, however, results remain ambiguous. The goal of this study was to conduct a meta-analysis to provide more credible evidence.

Methods: Studies identified in the PubMed, Cochrane Library, and EMBASE databases were used to perform a meta-analysis via the STATA software. Pooled odds ratios (OR) were calculated under fixed- and random-effects models to estimate the potential genetic associations.

Results: Twenty-five case-control studies involving 5813 cases and 5298 controls were included in this meta-analysis. Overall, the pooled results suggested that rs1800795 polymorphism was significantly associated with the risk of liver diseases in heterozygote (GC vs CC; OR = 1.57) and dominant (GG+GC vs CC: OR = 1.47) models; rs1800796 polymorphism was significantly associated with the susceptibility to liver diseases in heterozygote (GG vs GC; OR = 0.58) and recessive (GG vs GC+CC: OR = 0.68) models; rs1800797 polymorphism was significantly associated with genetic predisposition to liver diseases in homozygote (GG vs AA: OR = 1.63), heterozygote (GA vs AA; OR = 1.53) and dominant (GG + GA vs AA: OR = 1.61) models. A similar conclusion was found in the HBV, HCV, HCC, NASH and alcoholic liver disease of all ethnic populations for rs1800795; HBV and Asian subgroups for rs1800796; HCV and non-Asian subgroups for rs1800797. However, IL-6 rs2069837 and rs2066992 polymorphisms did not exhibit significant associations with the risk of liver diseases under any genetic models.

Conclusion: This meta-analysis suggests that patients carrying G (rs1800795), C (rs1800796) or G (rs1800797) allele or genotypes of IL-6 may be more likely to suffer from liver diseases, which was ethnic-dependent.

Abbreviations: CI = confidence interval, HBV = hepatitis B virus, HC = healthy, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HIV = human immunodeficiency virus-type 1, IF = infection resolved, IL-6 = interleukin-6, LC = liver cirrhosis, NASH = nonalcoholic steatohepatitis, NOS = New-castle–Ottawa Scale, OR = odds ratio, PRISMA = Preferred Reporting Items for Systematic Review and Meta-analysis, SNP = single nucleotide polymorphism, STAT3 = signal transducer and activator of transcription 3.

Keywords: genetic variation, hepatitis B virus, hepatitis C virus, interleukin-6, liver diseases, transformation

1. Introduction

The liver is one of the key organs of the body, which performs many pivotal functions essential for human life, including carbohydrate, protein and fat metabolism,[1] immune response against pathogens[2] as well as detoxification of xenobiotic.[3] The consequence of hepatic impairments, including viral hepatitis, alcoholic or nonalcoholic steatohepatitis (NASH), drug-induced liver injury, autoimmune hepatitis, fatty liver, liver cirrhosis (LC) and liver cancer, may be serious and even lethal.[4] Thus, it is vital to understand the etiology of liver diseases for developing efficiently predictive, preventive and therapeutic strategies.

Despite the pathogenesis remains unclear, increasing evidence has suggested liver diseases are of an inflammatory nature.[5] Interleukin-6 (IL-6) is an important inflammatory cytokine and may play a central role for the development and progression of liver diseases. Serum IL-6 concentration was detected to be significantly higher in alcoholic or non-alcoholic cirrhosis and toxic hepatitis when compared to controls.[6] Higher level of IL-6 was observed to be produced in CD4(+) T cells from acute-on-

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chronic hepatitis B virus (HBV) liver failure patients.[7] Higher level of IL-6 was significantly associated with advanced liver fibrosis in human immunodeficiency virus-type 1 (HIV)-infected patients [adjusted odds ratio (OR)=11.78, 95% confidence interval (CI): 1.17–118.19, $P=.036$].[8] High plasma IL-6 was also suggested as a biomarker for poor prognosis of patients with hepatocellular carcinoma (HCC).[9] IL-6 promoted HCC cell proliferation and migration by activating signal transducer and activator of transcription 3 (STAT3) signaling pathway.[10] These findings imply any factor that influences the expression of IL-6 may be an underlying contributor for the development of liver diseases.

Recently, some scholars have found genetic mutations in the IL-6 gene could alter its expression, with genotype CC carriers of rs1800796 showing higher level of IL-6 mRNA compared with genotype CG/GG carriers.[11,12] Therefore, this IL-6 single nucleotide polymorphism (SNP) may be a possible risk factor to contribute to the susceptibility to liver diseases. This hypothesis has been validated as follows: genotyping of IL-6 rs1800796 SNP showed a significant increase in GC genotypes, but reduction in GG genotype in HBV infection group compared with controls. A direct positive correlation was also detected between HBV and the presence of GC genotype and C allele.[13] Riazalhosseini et al also observed the frequency of allele G of rs1800796 was higher among healthy controls than that among chronic HBV patients (0.303 vs 0.258) and GC+CC genotype was associated with a protection mechanism against HBV infection (OR=0.40, 95% CI: 0.34–0.48).[14] However, inconsistent conclusions were also reported, with no significant associations of rs1800796 polymorphism with HBV infection,[15] hepatitis C virus (HCV) infection,[16] LC and HCC.[15,17] Furthermore, there were also studies to investigate the associations between the risk of liver diseases and other polymorphisms in IL-6, including rs1800795, rs1800797,[13,16] rs2066992,[18,19] and rs2069837[14,18,20] and the controversial outcomes were also present in them. These equivocal results may be attributed to small sample size and limited statistical power of each individual study.

The goal of this study was to conduct a meta-analysis to comprehensively estimate the associations of IL-6 polymorphisms and genetic predisposition to all liver diseases.

2. Materials and methods

2.1. Literature search

Our study was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) standard.[21] PubMed, the Cochrane Library and EMBASE databases were searched for papers published before February, 2019 using the keywords: interleukin-6 (OR IL-6) AND polymorphism (OR SNP OR variant OR mutation) AND liver diseases (OR hepatitis OR liver cirrhosis OR hepatocellular carcinoma OR liver injury OR fatty liver). The publication language was restricted to English. Furthermore, potentially eligible literatures were supplemented through manually mining bibliographies of relevant studies.

2.2. Inclusion and exclusion criteria

Studies were included if they satisfied the following criteria:

(1) human genotyping;
(2) case-control design;
(3) healthy (HC) or infection resolved (IF) controls;
(4) evaluation of the associations between IL-6 polymorphisms and liver diseases in more than 2 articles; and
(5) providing adequate data to calculate the OR and its corresponding 95%CI.

Studies having the following characteristics were excluded:

(1) repeated studies;
(2) animal studies, reviews, case reports, series, meeting abstracts, as well as comment;
(3) the data of genotype frequency were unavailable;
(4) studies that investigated the therapy response; and
(5) some controls showing HBV positive or having other liver diseases.

2.3. Data extraction and quality assessment

Two investigators independently extracted the data from each eligible study, including first author's name, year of publication, country, ethnicity, liver disease type, genotyping method, number of cases and controls, source of control, and frequency of genotypes. If articles included more than 1 disease type, each group was considered as an independent dataset. The quality of individual studies was also assessed independently by two authors using the New-castle–Ottawa Scale (NOS) system[22] that includes 3 aspects: selection (0–4 points), comparability (0–2 points) and exposure (0–3 points). The NOS ranges from zero (worst) to 9 stars (best). Studies scored more than 7 stars were considered to be of high quality. Any disagreements in data extraction and quality assessment were resolved by the involvement of a third part.

2.4. Statistical analysis

STATA software (version 13.0; STATA Corporation, USA) was used for this meta-analysis. The associations between IL-6 polymorphisms (rs1800795, rs1800796, rs1800797, rs2066992, and rs2069837) and the risk of liver diseases were estimated based on pooled ORs and 95%CI under various genetic models. P value of Cochran's Q-statistic >0.1 or I^2 value $<50\%$ indicated the absence of heterogeneity among studies and thus of a fixed-effect model was utilized in the association test; otherwise ($P<.10$ or $I^2>50$), a random-effect model was chosen. The significance of the pooled ORs was determined by the Z test, and $P<.05$ was considered statistically significant. Potential publication bias was evaluated using the Egger linear regression test. If there was evidence of publication bias ($P<.05$), trim and fill method was used to adjust for the effect of publication bias.[23] Sensitivity analysis was performed to evaluate the stability of the results by omitting each study at a time.

3. Results

3.1. Study characteristics

The search strategy retrieved 1035 relevant papers. Based on the inclusion and exclusion criteria (Fig. 1), 25 case-control studies including 5813 cases and 5298 controls were finally included for this meta-analysis.[12–16,18–20,24–40] Among these 25 studies published between 2005 and 2018, 17 of them with 20 datasets investigated the associations between rs1800795 polymorphism of IL-6 gene and liver diseases (including 1 for autoimmune

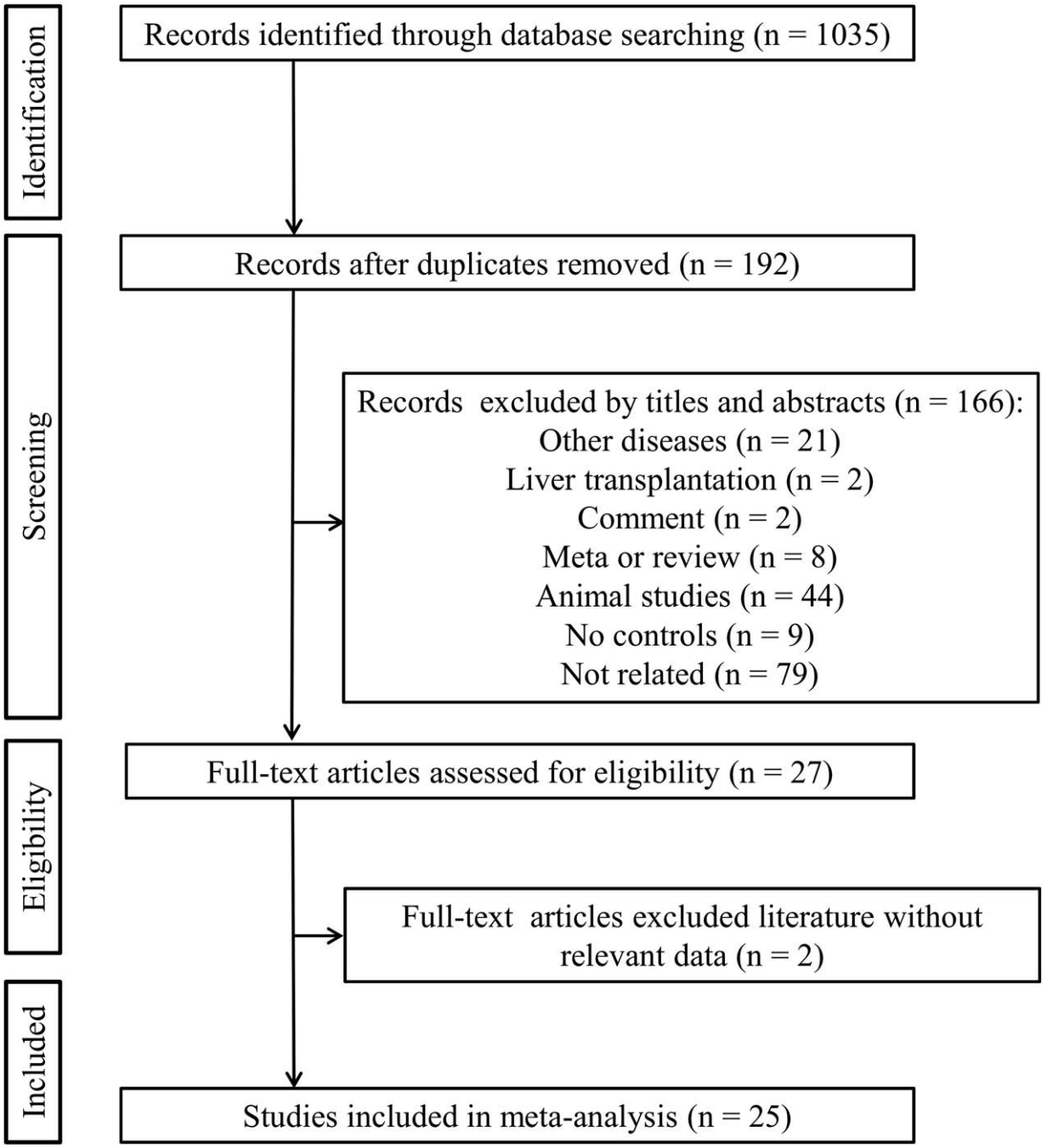

Figure 1. Flow diagram of the study selection process.

hepatitis, 3 for HBV infection, 4 for NASH, 4 for HCV infection, 3 for LC, 1 for HEV infection, 2 for HCC and 2 for alcoholic liver disease), 8 studies with 16 datasets involved rs1800796 (including 6 for HBV infection, 2 for HCV infection, 1 for HIV infection, 3 for LC, 3 for HCC and 1 for LC/HCC), 5 studies with 8 datasets analyzed rs1800797 (including 3 for HBV infection, 1 for HCV infection, 2 for LC and 2 for HCC), 4 studies with 5 datasets explored rs2069837 (including 2 for HBV infection, 1 for anti-tuberculosis drug-induced hepatitis, 1 for LC-HCC and 1 for HCC) and 3 studies with 4 datasets surveyed rs2066992 (including 2 for HBV infection, 1 for anti-tuberculosis drug-induced hepatitis and 1 for LC-HCC). According to the NOS, all the included studies were of high quality. The detailed characteristics of included studies are listed in Table 1.

3.2. Meta-analysis

The meta-analysis results of the correlations between five IL-6 polymorphisms and vulnerability to liver diseases in all genetic models are shown in Table 2. The pooled results suggested that rs1800795 polymorphism was significantly associated with the risk of liver diseases in heterozygote (GC vs CC: OR = 1.57, 95%

Table 1

Characteristics of studies included in this meta-analysis.

First author	Year	Country/ethnicity	Liver disease	Genotyping method	SNP	Source of control		Cases	Controls	NOS
Yousefi A	2018	Iran/Asian	Autoimmune hepatitis	PCR-SSP	rs1800795	PB	HC	57	140	9
El-Maadawy EA	2019	Egypt/non-Asian	HBV	MS-PCR	rs1800795; rs1800796; rs1800797	PB	HC	108	102	7
Riazalhosseini B	2018	Malaysia/Asian	HBV LC-HCC	MassARRAY	rs2069837; rs1800796; rs2066992	PB	HC + IF	423 103	623 97	7
Kurbatova IV	2017	Russia/non-Asian	NASH	PCR-PDRF	rs1800795	HB	HC	126	116	8
Bocsan IC	2017	Romania/non-Asian	NASH	PCR-RFLP	rs1800795	PB	HC	66	30	9
Motawi T	2017	Egypt/non-Asian	HCV LC	PCR-RFLP	rs1800795	HB	HC	85 65	100	7
Attar M	2016	Iran/Asian	HBV-hepatitis	PCR-SSP	rs1800795	PB	HC	297	368	7
Zhang G	2015	China/Asian	HBV; HCV; HIV	Taq PCR	rs1800796	PB	HC	566 184 183	618	8
Zheng X	2015	China/Asian	HCC	PCR-RFLP	rs2069837	PB	HC	226	220	8
Wang J	2015	China/Asian	Anti-tuberculosis drug-induced hepatitis	TaqMan	rs2066992; rs2069837; rs1524107	HB	Pulmonary tuberculosis	89	356	9
Lu Y	2014	China/Asian	HBV	DNA sequencing	rs1800796; rs1800797	HB	IF	219	212	9
Saxena R	2014	India/Asian	LC; HCC; HBV	PCR-RFLP	rs1800796; rs1800797	HB	HC	63 61 126	153	7
Tarragô AM	2014	Brazil/non-Asian	HCV	PCR-RFLP	rs1800795	PB	HC	69	47	8
Devi SG	2014	India/Asian	HEV	PCR-RFLP	rs1800795	PB	HC	222	376	9
Cengiz M	2014	Turkey/non-Asian	NASH	PCR-RFLP	rs1800795		HC	38	38	
Zhao XM	2013	China/Asian	HBV	SNaPshot reaction	rs2066992; rs2069837; rs2069852	HB	IF	501	301	9
Tang S	2013	China/Asian	HBV; LC; HCC	Taq PCR	rs1800796	PB	HC	330 153 148	265	8
Giannitrapani L	2011	Italy/non-Asian	LC; HCC	PCR-RFLP	rs1800795	HB	HC	95 105	98	9
Cussigh A	2011	Italy/non-Asian	HCV	PCR-RFLP	rs1800797; rs1800796; rs1800795	PB	HC	424	344	7
Falleti E	2009	Italy/non-Asian	LC HCC	PCR-RFLP	rs1800797 rs1800796; rs1800795	PB	HC	153 66	236	7
Carulli L	2009	Italy/non-Asian	NASH	PCR-RFLP	rs1800795	PB	HC	114	79	7
Marcos M	2009	Spain/non-Asian	ALD	PCR-RFLP	rs1800795	PB	HC	95	259	7
Gleeson D	2008	United Kingdom/non-Asian	ALD	PCR-RFLP	rs1800795	PB	HC	223	79	7
Ribeiro, CSS	2007	Brasil/non-Asian	HBV	PCR-RFLP	rs1800795	PB	IF	30	41	8
Minton EJ	2005	United Kingdom/non-Asian	HCV	TaqMan	rs1800795	HB	HCV-negative	253	44	7

ALD = alcoholic liver disease, HB = hospital-based, HBV = hepatitis B virus, HC = healthy control, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HEV = hepatitis E virus, HIV = Human immunodeficiency virus-type 1, IF = infection resolved, LC = liver cirrhosis, MS = mutagenically separated, NASH = nonalcoholic steatohepatitis, NOS = New-castle–Ottawa Scale, PB = population-based, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, SSP = sequence-specific amplification.

CI = 1.32–1.88, $P < .0001$) (Fig. 2A) and dominant (GG + GC vs CC: OR = 1.47, 95% CI = 1.14–1.91, $P < .0001$) (Fig. 2B) models; rs1800796 polymorphism was significantly associated with the susceptibility to liver diseases in heterozygote (GG vs GC: OR = 0.58, 95% CI = 0.39–0.85, $P = .006$) (Fig. 3A) and recessive (GG vs GC+CC: OR = 0.68, 95% CI = 0.50–0.91, $P = .009$) (Fig. 3B) models; rs1800797 polymorphism was significantly associated with genetic predisposition to liver diseases in homozygote (GG vs AA: OR = 1.63, 95% CI = 1.17–2.27, $P = .004$) (Fig. 4A), heterozygote (GA vs AA: OR = 1.53, 95% CI = 1.09–2.14, $P = .013$) (Fig. 4B) and dominant (GG + GA vs AA: OR = 1.61, 95% CI = 1.17–2.22, $P = .003$) (Fig. 4C) models. However, IL-6 rs2069837 and rs2066992 polymorphisms did not exhibit significant associations with liver disease risk in any genetic model.

Due to the presence of significant heterogeneity in some overall analysis (Table 2), subgroup analyses were conducted based on liver disease type and ethnicity. For rs1800795 polymorphism, only a significant association was observed for patients with HBV [G vs C: OR = 1.75, 95% CI = 1.13–2.72, $P = .012$; GG vs CC: OR = 2.98, 95% CI = 1.63–5.45, $P < .001$; GC vs CC: OR = 2.08, 95% CI = 1.15–3.77, $P = .016$; GG+GC vs CC: OR = 2.54, 95% CI = 1.37–4.71, $P = .003$; GG vs GC+CC: OR = 1.91, 95% CI = 1.03–3.56, $P = .041$], NASH (GC vs CC: OR = 1.60, 95% CI = 1.03–2.49, $P = .038$), HCV (GC vs CC: OR = 1.58, 95% CI = 1.04–2.42, $P = .034$), HCC (GC vs CC: OR = 3.11, 95% CI = 1.24–7.79, $P = .015$) and alcoholic liver disease [GC vs CC: OR = 1.51, 95% CI = 1.03–2.21, $P = .036$; GG vs GC+CC: OR = 1.47, 95% CI = 1.03–2.10, $P = .036$] (Table 3). For rs1800796 polymorphism, only a significant association was detected for patients with HBV [G vs C: OR = 0.74, 95% CI = 0.65–0.85, $P < .001$; GG vs CC: OR = 0.56, 95% CI = 0.42–0.74, $P < .001$; GC vs GC: OR = 0.42, 95% CI = 0.20–0.87, $P = .020$; GG vs GC + CC: OR = 0.46, 95% CI = 0.29–0.73, $P = .001$] (Table 4). For rs1800797 polymorphism, no significant association was detected for most of liver disease patients other than HCV (Table 5), but only 1 literature was included for HCV and this result remained inconclusive. In both of Asian and non-Asian

Table 2

Overall meta-analysis results.

Comparison	Qualified studies	Test of association			Test of heterogeneity	
		OR (95%CI)	*P* value	Model	*P* value	I^2 (%)
rs1800795 (G > C)						
Allelic (G vs C)	20	1.19 (0.98–1.44)	.076	R	.000	74.9
Homozygote (GG vs CC)		1.36 (0.95–1.94)	.091	R	.000	64.2
Heterozygote (GG vs GC)		0.98 (0.75–1.29)	.889	R	.000	73.6
Heterozygote (GC vs CC)		1.57 (1.32–1.88)	.000	F	.136	28.0
Dominant (GG+GC vs CC)		1.47 (1.14–1.91)	.000	R	.021	45.0
Recessive (GG vs GC+CC)		1.16 (0.89–1.52)	.276	R	.000	77.2
rs1800796 (G > C)						
Allelic (G vs C)	16	0.91 (0.80–1.04)	.147	R	.001	62.2
Homozygote (GG vs CC)		0.85 (0.62–1.15)	.293	R	.006	53.2
Heterozygote (GG vs GC)		0.58 (0.39–0.85)	.006	R	.000	80.3
Heterozygote (GC vs CC)		1.37 (1.00–1.86)	.050	R	.000	83.7
Dominant (GG+GC vs CC)		1.08 (0.87–1.35)	.496	R	.000	71.5
Recessive (GG vs GC+CC)		0.68 (0.50–0.91)	.009	R	.000	69.6
rs1800797 (G >A)						
Allelic (G vs A)	8	1.10 (0.83–1.45)	.511	R	.001	70.1
Homozygote (GG vs AA)		1.63 (1.17–2.27)	.004	F	.132	38.9
Heterozygote (GG vs GA)		1.01 (0.65–1.55)	.973	R	.001	72.7
Heterozygote (GA vs AA)		1.53 (1.09–2.14)	.013	F	.620	0.0
Dominant (GG+GA vs AA)		1.61 (1.17–2.22)	.003	F	.613	0.0
Recessive (GG vs GA+AA)		1.08 (0.71–1.63)	.731	R	.001	72.8
rs2069837 (G > A)						
Allelic (G vs A)	5	1.12 (0.98–1.23)	.085	F	.519	0.0
Homozygote (GG vs AA)		1.46 (0.58–3.69)	.420	R	.053	60.9
Heterozygote (GG vs GA)		1.20 (0.48–2.99)	.702	R	.063	58.9
Heterozygote (GA vs AA)		1.11 (0.95–1.31)	.188	F	.390	2.9
Dominant (GG+GA vs AA)		1.13 (0.97–1.32)	.124	F	.425	0.0
Recessive (GG vs GA+AA)		1.33 (0.55–3.23)	.526	R	.064	58.6
rs2066992(G > T)						
Allelic (G vs T)	4	0.94 (0.83–1.07)	.338	F	.191	36.8
Homozygote (GG vs TT)		0.85 (0.63–1.14)	.273	R	.105	51.2
Heterozygote (GG vs GT)		0.95 (0.72–1.25)	.720	F	.497	0.0
Heterozygote (GT vs TT)		0.91 (0.77–1.09)	.309	F	.234	29.7
Dominant (GG+GT vs TT)		0.91 (0.77–1.07)	.261	F	.114	49.7
Recessive (GG vs GT+TT)		0.89 (0.68–1.15)	.364	F	.328	12.8

F = fixed-effects model, OR = odds ratios, CI, confidence interval, R = random-effects model.

population, a significant increased risk to develop liver diseases can be observed in G allelic carriers of rs1800795 polymorphism; G allele (OR = 0.87, 95% CI = 0.77–0.99, *P* = .037) or GG genotype (GG vs CC: OR = 0.77, 95% CI = 0.59–1.00, *P* = .046; GG vs GC: OR = 0.51, 95% CI = 0.30–0.85, *P* = .009; GG vs GC +CC: OR = 0.62, 95% CI = 0.45–0.85, *P* = .003) of rs1800796 polymorphism was related with the lower risk of liver diseases only in Asian population, but contrast results for the non-Asian (GC vs CC: OR = 1.76, 95% CI = 1.11–2.79, *P* = .017; GG vs GC +CC: OR = 1.85, 95% CI = 1.20–2.88, *P* = .006); rs1800797 polymorphism was significantly associated with the susceptibility to liver diseases only in non-Asian population (GG vs AA: OR = 1.75, 95% CI = 1.21–2.53, *P* = .003; GA vs AA: OR = 1.72, 95% CI = 1.19–2.49, *P* = .004; GG+GA vs AA: OR = 1.76, 95% CI = 1.24–2.51, *P* = .002) (Table 6).

3.3. Publication bias and sensitivity analysis

Egger linear regression test was performed to investigate the potential publication bias for significant results in overall meta-analysis. The results showed the intercept did not pass through the origin (that is, asymmetry) in association analysis of rs1800796 under heterozygote model (GG vs GC) (Fig. 5A), indicating the presence of publication bias (*P* = .017). Subsequently, trim and fill method was used to further adjust for the publication bias (Fig. 5B). The results showed the association remained significant after correcting the publication bias (OR = 0.76, 95% CI = 0.64–0.90, *P* = .001), implying our results were statistically robust. No obvious asymmetry was observed in the evaluation of publication bias for rs1800795 (GC vs CC: *P* = 0.072; GG+GC vs CC: *P* = .182) and rs1800797 (GG vs AA: *P* = .242; GA vs AA: OR = 1.53, *P* = .316; GG + GA vs AA: *P* = .321), suggesting no evidence of publication bias.

As shown in Figure 6, the omission of any single study did not significantly affect the pooled ORs or 95% CIs, indicating our results may be reliable.

4. Discussion

In this study, we performed a meta-analysis to investigate the associations of IL-6 SNPs with liver diseases. Our findings showed that IL-6 rs1800795 and rs1800796 polymorphisms may be potential genetic factors for the development of liver diseases. Patients with G allele or GG, GC and GG+GC genotypes of

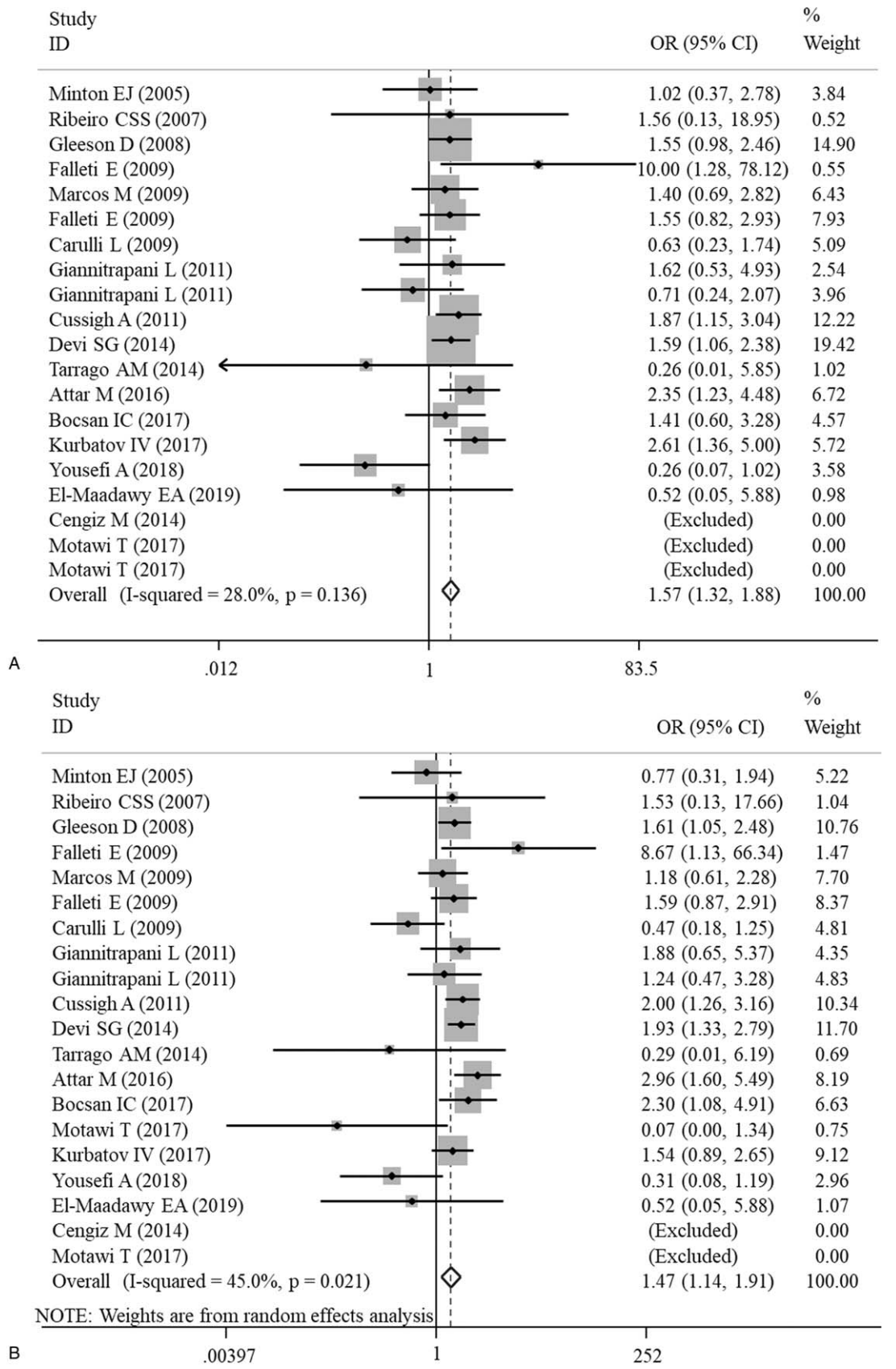

Figure 2. Forest plots of the association of IL-6 gene rs1800795 polymorphism with an increased risk of liver diseases under heterozygote (GC vs CC) and dominant (GG+GC vs CC) models. A, heterozygote; B, dominant. CI = confidence intervals; OR = odds ratio.

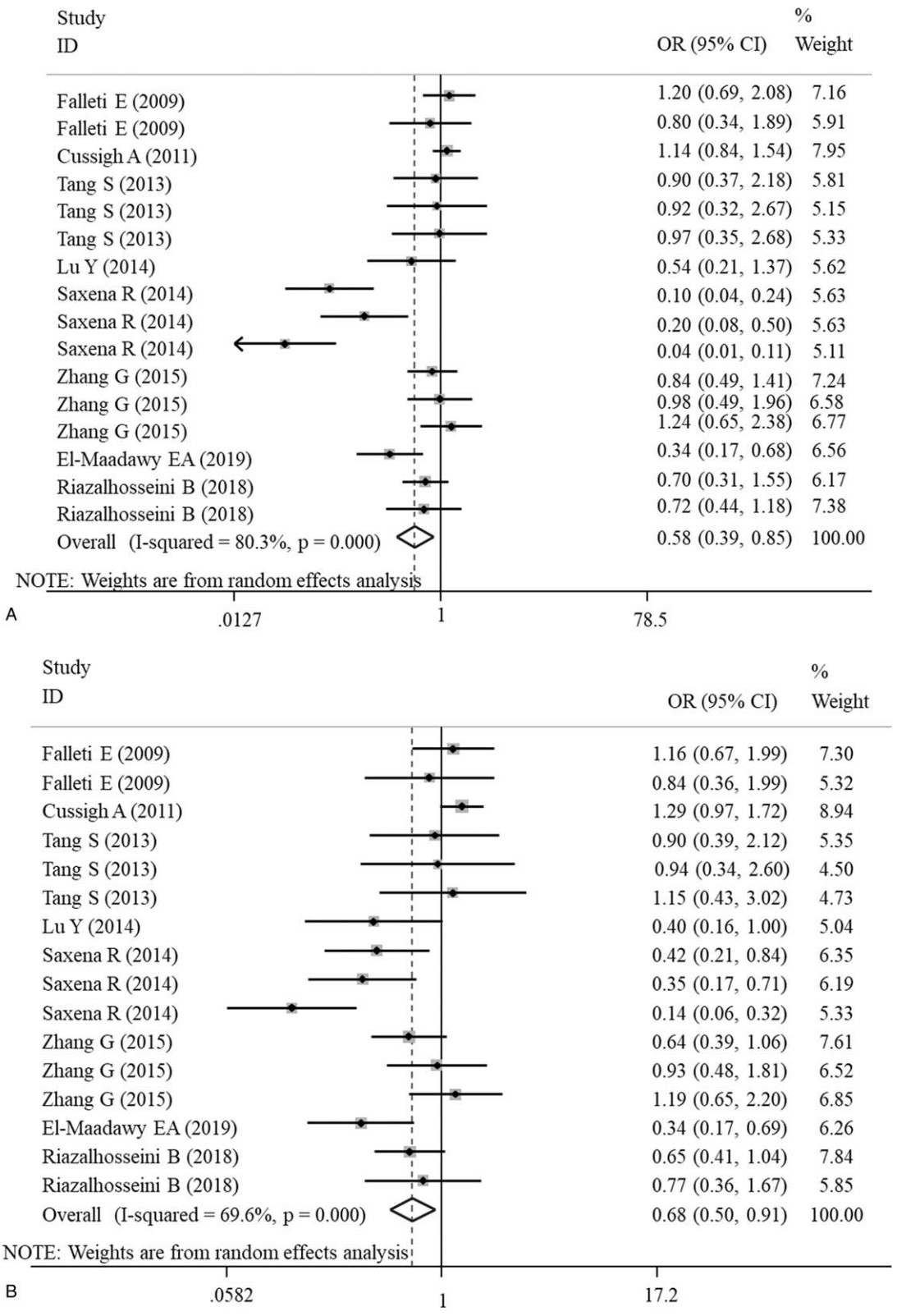

Figure 3. Forest plots of the association of IL-6 gene rs1800796 polymorphism with an increased risk of liver diseases under heterozygote (GC vs CC) and recessive (GG vs GC+CC) models. A, heterozygote; B, recessive. CI = confidence intervals; OR = odds ratio.

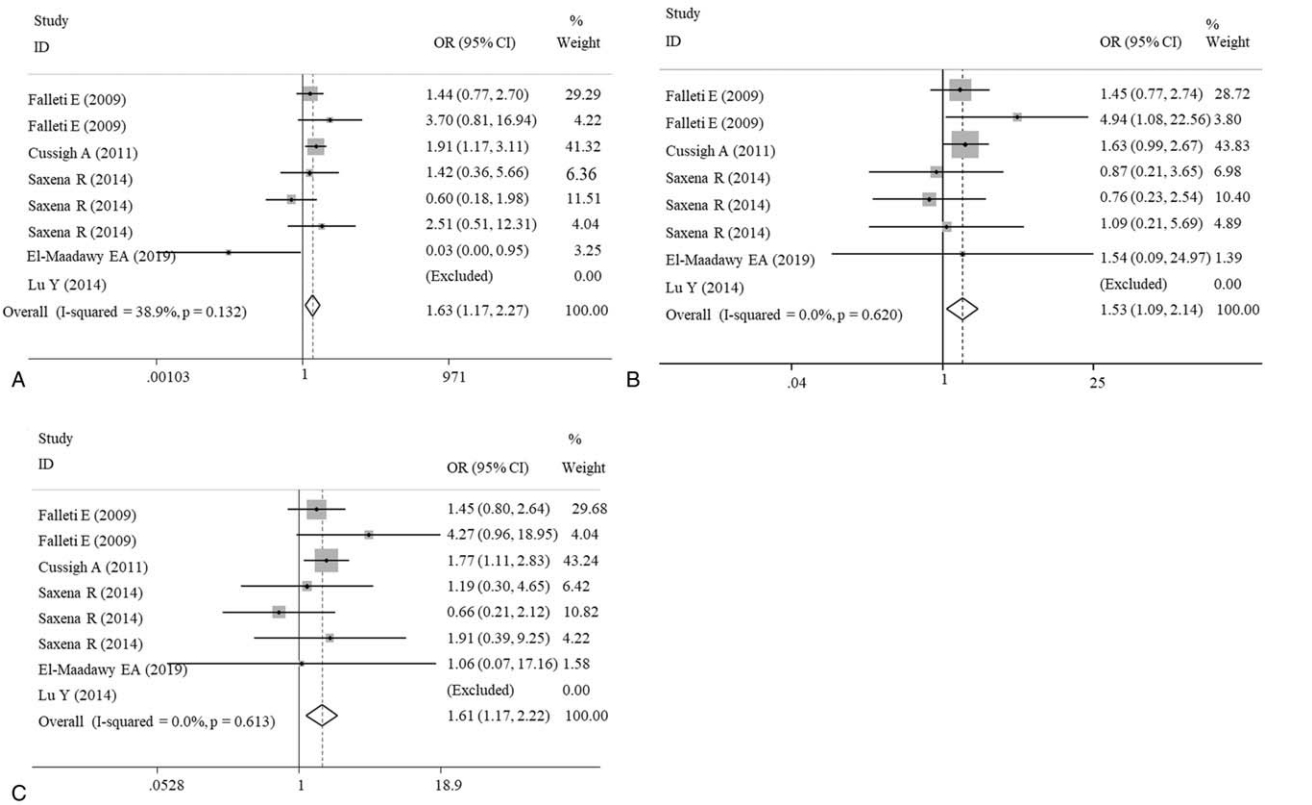

Figure 4. Forest plots of the association of IL-6 gene rs1800797 polymorphism with an increased risk of liver diseases under homozygote (GG vs AA), heterozygote (GA vs AA) and dominant (GG+GA vs AA) models. A, homozygote; B, heterozygote; C, dominant. CI = confidence intervals; OR = odds ratio.

rs1800795 had significantly increased risks for developing liver diseases in all ethnic populations, especially HBV, HCV, HCC, NASH and alcoholic liver disease subgroups. On the contrary, G allele, GG or GC genotypes of rs1800796 may be significant protective factors for the development of liver diseases, especially HBV and Asian population. Although the overall and ethnic meta-analysis showed people carrying the GG, GA or GG+GA genotypes of rs1800797 had a higher risk of suffering liver diseases in non-Asian population, subgroup analysis seemed to show no significant association between this polymorphism and various subtypes of liver diseases except HCV identified in one article. For IL-6 rs2069837 and rs2066992 polymorphisms, we did not find any association with liver disease risk, although this was the first meta-analysis study to investigate them in liver diseases.

Previously, there have 2 meta studies to explore the associations between IL-6 polymorphisms and liver diseases,[41,42] but they were obviously different from our study:

(1) only the HBV-related liver diseases or HCC were analyzed in the study of Chang et al[42] and Liu et al,[41] but not all types of liver diseases as reported in our study;
(2) Chinese papers were included in these studies, but not in our study;
(3) articles with HBV carriers as controls were included, which were excluded in our study; and
(4) these 2 meta-analyses only searched the published papers up to 2015.

The differences in these 4 aspects may contribute to the slight deviation of our results from them. For example, the significant associations between IL-6 rs1800795 polymorphism and risk of HCC under homozygote model (CC vs GG: OR = 0.36; 95% CI = 0.16–0.85) and recessive model (GG+CG vs CC: OR = 2.82; 95% CI = 1.26–6.28) identified by Liu et al[41] were not observed in our study, but only significant under heterozygote model (GC vs CC: OR = 3.11, 95% CI = 1.24–7.79); significant associations between IL-6 rs1800797 polymorphism and the risk of HBV under allelic (G vs A: OR = 1.89; 95% CI = 1.11–3.20), heterozygote (GG vs GA: OR = 2.21; 95% CI = 1.12–3.92) and recessive (GA + AA vs GG: OR = 0.47; 95% CI = 0.26–0.86) models identified by Chang et al,[42] were not shown in our study, but we found some novel conclusions, including significant associations with HBV, HCV, NASH, and alcoholic liver disease of rs1800795.

rs1800795 polymorphism is located at the 174 base pair upstream of IL-6 gene promoter and variation from G to C at this region was reported to reduce this gene's transcription rate and lead to the lower production of IL-6.[43,44] A recent study even found IL-6 mRNA expression was especially higher in the GC than in the GG and CC cases.[45] It had been demonstrated hepatitis B core antigen transfection increased the expression and secretion of IL-6 through activating extracellular signal-related kinase, p38 mitogen-activated protein kinase and nuclear factor-kappa B in hepatocytes.[46] Subsequently, HBV-IL-6 activated the transcription and translation of angiogenin and vascular endothelial growth factor genes via the STAT3 pathway and

Table 3

Subgroup analysis for rs1800795.

Comparison	Qualified studies	OR (95%CI)	*P* value
Autoimmune hepatitis			
Allelic (G vs C)	1	1.06 (0.67–1.67)	.816
Homozygote (GG vs CC)		0.42 (0.10–1.72)	.227
Heterozygote (GG vs GC)		1.62 (0.84–3.14)	.150
Heterozygote (GC vs CC)		0.26 (0.07–1.02)	.054
Dominant (GG+GC vs CC)		0.31 (0.08–1.19)	.088
Recessive (GG vs GC+CC)		1.45 (0.76–2.77)	.257
HBV			
Allelic (G vs C)	3	1.75 (1.13–2.72)	**.012**
Homozygote (GG vs CC)		2.98 (1.63–5.45)	**.000**
Heterozygote (GG vs GC)		1.06 (0.50–2.29)	.874
Heterozygote (GC vs CC)		2.08 (1.15–3.77)	**.016**
Dominant (GG+GC vs CC)		2.54 (1.37–4.71)	**.003**
Recessive (GG vs GC+CC)		1.91 (1.03–3.56)	**.041**
NASH	4		
Allelic (G vs C)		1.03 (0.62–1.73)	.897
Homozygote (GG vs CC)		1.01 (0.30–3.45)	.983
Heterozygote (GG vs GC)		0.89 (0.35–2.25)	.802
Heterozygote (GC vs CC)		1.60 (1.03–2.49)	**.038**
Dominant (GG+GC vs CC)		1.36 (0.92–2.02)	.126
Recessive (GG vs GC+CC)		1.02 (0.42–2.43)	.974
HCV	4		
Allelic (G vs C)		0.76 (0.37–1.57)	.461
Homozygote (GG vs CC)		0.64 (0.17–2.44)	.517
Heterozygote (GG vs GC)		0.71 (0.32–1.55)	.386
Heterozygote (GC vs CC)		1.58 (1.04–2.42)	**.034**
Dominant (GG+GC vs CC)		0.81 (0.27–2.46)	.709
Recessive (GG vs GC+CC)		0.68 (0.29–1.60)	.381
LC	3		
Allelic (G vs C)		0.88 (0.33–2.35)	.800
Homozygote (GG vs CC)		1.63 (0.95–2.78)	.074
Heterozygote (GG vs GC)		0.63 (0.15–2.75)	.543
Heterozygote (GC vs CC)		1.27 (0.74–2.19)	.385
Dominant (GG+GC vs CC)		1.48 (0.89–2.48)	.132
Recessive (GG vs GC+CC)		0.70 (0.18–2.66)	.597
HEV	1		
Allelic (G vs C)		1.81 (1.43–2.29)	.000
Homozygote (GG vs CC)		2.69 (1.72–4.21)	.000
Heterozygote (GG vs GC)		1.69 (1.12–2.56)	.012
Heterozygote (GC vs CC)		1.59 (1.06–2.38)	.024
Dominant (GG+GC vs CC)		1.93 (1.33–2.79)	.000
Recessive (GG vs GC+CC)		2.08 (1.42–3.03)	.000
HCC	2		
Allelic (G vs C)		1.31 (0.96–1.80)	.091
Homozygote (GG vs CC)		2.25 (0.30–17.04)	.432
Heterozygote (GG vs GC)		0.98 (0.58–1.64)	.930
Heterozygote (GC vs CC)		3.11 (1.24–7.79)	**.015**
Dominant (GG+GC vs CC)		3.19 (0.71–14.36)	.130
Recessive (GG vs GC+CC)		1.15 (0.77–1.71)	.502
ALD	2		
Allelic (G vs C)		1.12 (0.75–1.68)	.590
Homozygote (GG vs CC)		1.35 (0.75–2.43)	.311
Heterozygote (GG vs GC)		0.87 (0.54–1.42)	.584
Heterozygote (GC vs CC)		1.51 (1.03–2.21)	**.036**
Dominant (GG+GC vs CC)		1.47 (1.03–2.10)	**.036**
Recessive (GG vs GC+CC)		1.04 (0.61–1.76)	.896

Bold indicates the significance in at least 2 datasets.

ALD = alcoholic liver disease, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HEV = hepatitis E virus, LC = liver cirrhosis, NASH = nonalcoholic steatohepatitis.

ultimately promoted HCC cell proliferation.[10,47] Furthermore, activation of IL6/STAT3 pathway also could support HBV replication to further deteriorate HBV-related carcinogenesis.[48] HCV infection was also proved to play important roles in the development of liver diseases by IL-6/STAT3 pathway.[49] IL-6

Table 4

Subgroup analysis for rs1800796.

Comparison	Qualified studies	OR (95%CI)	*P* value
HBV			
Allelic (G vs C)	6	0.74 (0.65–0.85)	**.000**
Homozygote (GG vs CC)		0.56 (0.42–0.74)	**.000**
Heterozygote (GG vs GC)		0.42 (0.20–0.87)	**.020**
Heterozygote (GC vs CC)		1.06 (0.67–1.65)	.818
Dominant (GG+GC vs CC)		0.82 (0.63–1.07)	.134
Recessive (GG vs GC+CC)		0.46 (0.29–0.73)	**.001**
LC/HCC	1		
Allelic (G vs C)		1.03 (0.75–1.42)	.844
Homozygote (GG vs CC)		0.85 (0.38–1.89)	.692
Heterozygote (GG vs GC)		0.70 (0.32–1.56)	.380
Heterozygote (GC vs CC)		1.22 (0.79–1.88)	.377
Dominant (GG+GC vs CC)		1.15 (0.75–1.74)	.522
Recessive (GG vs GC+CC)		0.77 (0.36–1.67)	.514
HCV	2		
Allelic (G vs C)		1.14 (0.80–1.62)	.487
Homozygote (GG vs CC)		1.43 (0.62–3.30)	.396
Heterozygote (GG vs GC)		1.11 (0.84–1.46)	.467
Heterozygote (GC vs CC)		1.29 (0.65–2.57)	.472
Dominant (GG+GC vs CC)		1.33 (0.63–2.84)	.456
Recessive (GG vs GC+CC)		1.23 (0.94–1.60)	.128
HIV	1		
Allelic (G vs C)		1.02 (0.78–1.33)	.914
Homozygote (GG vs CC)		1.16 (0.62–2.18)	.635
Heterozygote (GG vs GC)		1.24 (0.65–2.38)	.512
Heterozygote (GC vs CC)		0.94 (0.66–1.33)	.716
Dominant (GG+GC vs CC)		0.97 (0.70–1.36)	.870
Recessive (GG vs GC+CC)		1.19 (0.65–2.20)	.570
LC	3		
Allelic (G vs C)		1.09 (0.85–1.39)	.522
Homozygote (GG vs CC)		1.38 (0.58–3.26)	.463
Heterozygote (GG vs GC)		0.48 (0.10–2.33)	.364
Heterozygote (GC vs CC)		2.40 (0.18–32.91)	.512
Dominant (GG+GC vs CC)		1.73 (0.36–8.28)	.493
Recessive (GG vs GC+CC)		0.77 (0.39–1.52)	.453
HCC	3		
Allelic (G vs C)		0.95 (0.66–1.38)	.791
Homozygote (GG vs CC)		0.84 (0.46–1.54)	.571
Heterozygote (GG vs GC)		0.53 (0.20–1.42)	.207
Heterozygote (GC vs CC)		2.27 (0.72–7.13)	.162
Dominant (GG+GC vs CC)		1.30 (0.91–1.85)	.153
Recessive (GG vs GC+CC)		0.66 (0.32–1.37)	.265

Bold indicates the significance in at least 2 datasets.

HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HEV = hepatitis E virus, HIV = Human immunodeficiency virus-type 1, LC = liver cirrhosis, NASH = nonalcoholic steatohepatitis.

Table 5

Subgroup analysis for rs1800797.

Comparison	Qualified studies	OR (95%CI)	*P* value
HBV			
Allelic (G vs A)	3	1.14 (0.35–3.73)	.826
Homozygote (GG vs AA)		1.40 (0.38–5.15)	.610
Heterozygote (GG vs GA)		0.51 (0.01–22.62)	.728
Heterozygote (GA vs AA)		1.19 (0.28–4.98)	.812
Dominant (GG+GA vs AA)		1.68 (0.43–6.50)	.455
Recessive (GG vs GA + AA)		0.51 (0.01–23.10)	.731
LC	2		
Allelic (G vs A)		1.19 (0.93–1.52)	.173
Homozygote (GG vs AA)		1.44 (0.81–2.55)	.211
Heterozygote (GG vs GA)		1.18 (0.74–1.88)	.480
Heterozygote (GA vs AA)		1.34 (0.78–4.54)	.321
Dominant (GG+GA vs AA)		1.40 (0.81–2.43)	.227
Recessive (GG vs GA + AA)		1.20 (0.84–1.73)	.309
HCC	2		
Allelic (G vs A)		0.96 (0.64–1.43)	.826
Homozygote (GG vs AA)		1.43 (0.59–3.46)	.427
Heterozygote (GG vs GA)		0.77 (0.50–1.19)	.235
Heterozygote (GA vs AA)		1.88 (0.78–4.54)	.163
Dominant (GG+GA vs AA)		1.64 (0.70–3.87)	.255
Recessive (GG vs GA + AA)		0.84 (0.55–1.27)	.405
HCV	1		
Allelic (G vs A)		1.32 (1.06–1.63)	.013
Homozygote (GG vs AA)		1.91 (1.17–3.11)	.010
Heterozygote (GG vs GA)		1.17 (0.87–1.59)	.302
Heterozygote (GA vs AA)		1.63 (0.99–2.67)	.055
Dominant (GG+GA vs AA)		1.77 (1.11–2.83)	.017
Recessive (GG vs GA + AA)		1.29 (0.97–1.72)	.077

HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, LC = liver cirrhosis.

Table 6

Ethnicity-based subgroup meta-analysis.

Comparison	Qualified studies	Test of association			Test of heterogeneity	
		OR (95%CI)	*P* value	Model	*P* value	I^2 (%)
rs1800795 (G > C)						
Non-Asian	17					
Allelic (G vs C)		1.12 (0.90–1.39)	.320	R	*.000*	*72.4*
Homozygote (GG vs CC)		1.23 (0.84–1.78)	.288	R	*.005*	*55.1*
Heterozygote (GG vs GC)		0.86 (0.63–1.19)	.369	R	*.000*	*73.3*
Heterozygote (GC vs CC)		1.56 (1.27–1.93)	**.000**	F	*.365*	*8.0*
Dominant (GG+GC vs CC)		1.42 (1.09–1.85)	**.010**	F	*.131*	*29.9*
Recessive (GG vs GC+CC)		1.05 (0.77–1.43)	.764	R	*.000*	*77.0*
Asian	3					
Allelic (G vs C)		1.59 (1.23–2.05)	**.000**	F	*.112*	*54.4*
Homozygote (GG vs CC)		2.07 (0.93–4.59)	.075	R	*.027*	*72.4*
Heterozygote (GG vs GC)		1.57 (1.23–1.99)	**.000**	F	*.877*	*0.0*
Heterozygote (GC vs CC)		1.60 (1.15–2.22)	**.005**	R	*.018*	*75.2*
Dominant (GG+GC vs CC)		1.55 (0.68–3.53)	.301	R	*.012*	*77.5*
Recessive (GG vs GC+CC)		1.80 (1.44–2.26)	**.000**	F	*.591*	*0.0*
rs1800796 (G > C)						
Non-Asian						
Allelic (G vs C)	4	1.02 (0.70–1.47)	.937	R	*.033*	*65.6*
Homozygote (GG vs CC)		1.59 (0.78–3.26)	.204	F	*.343*	*10.1*
Heterozygote (GG vs GC)		0.82 (0.49–1.40)	.473	R	*.016*	*71.1*
Heterozygote (GC vs CC)		1.76 (1.11–2.79)	**.017**	F	*.692*	*0.0*
Dominant (GG+GC vs CC)		1.85 (1.20–2.88)	**.006**	F	*.646*	*0.0*
Recessive (GG vs GC+CC)		0.86 (0.49–1.50)	.587	R	*.007*	*75.4*
Asian						
Allelic (G vs C)	12	0.87 (0.77–0.99)	**.037**	R	*.022*	*50.8*
Homozygote (GG vs CC)		0.77 (0.59–1.00)	**.046**	F	*.140*	*31.4*
Heterozygote (GG vs GC)		0.51 (0.30–0.85)	**.009**	R	*.000*	*81.0*
Heterozygote (GC vs CC)		1.35 (0.97–1.89)	.077	R	*.000*	*86.9*
Dominant (GG+GC vs CC)		1.02 (0.82–1.27)	.837	R	*.000*	*73.2*
Recessive (GG vs GC+CC)		0.62 (0.45–0.85)	**.003**	R	*.007*	*57.3*
rs1800797 (G >A)						
Non-Asian						
Allelic (G vs A)	4	1.00 (0.69–1.44)	.991	R	*.001*	*80.9*
Homozygote (GG vs AA)		1.75 (1.21–2.53)	**.003**	F	*.080*	*55.6*
Heterozygote (GG vs GA)		0.71 (0.37–1.36)	.300	R	*.000*	*83.3*
Heterozygote (GA vs AA)		1.72 (1.19–2.49)	**.004**	F	*.536*	*0.0*
Dominant (GG+GA vs AA)		1.76 (1.24–2.51)	**.002**	F	*.595*	*0.0*
Recessive (GG vs GA+AA)		0.80 (0.43–1.51)	.496	R	*.000*	*83.6*
Asian						
Allelic (G vs A)	4	1.30 (0.78–2.18)	.318	R	*.067*	*58.1*
Homozygote (GG vs AA)		1.19 (0.55–2.56)	.658	F	*.337*	*8.0*
Heterozygote (GG vs GA)		1.46 (0.83–2.55)	.191	F	*.133*	*46.4*
Heterozygote (GA vs AA)		0.87 (0.39–1.93)	.726	F	*.554*	*0.0*
Dominant (GG+GA vs AA)		1.07 (0.50–2.28)	.868	R	*.000*	*0.0*
Recessive (GG vs GA+AA)		1.44 (0.80–2.60)	.230	F	*.085*	*54.7*

CI = confidence interval, F = fixed-effects model, OR = odds ratios, R = random-effects model.

level, which activated downstream immune and oxidative stress signaling to exacerbate inflammation infiltration, was also found to be increased in patients with NASH[50] and alcoholic liver injury.[51] Accordingly, we believe patients carrying GC genotype of rs1800795 may have higher risks to suffer HBV, HCV infection, HCC, NASH and alcoholic liver disease, which was confirmed in our study.

rs1800796 polymorphism (-572 G/C) is also located within the promoter region of IL-6 gene. The individuals harboring -572GG or GC genotype was observed to have significantly lower IL-6 levels than those harboring the -572CC genotype.[52] Also, CD14 (+) monocytes from subjects carrying the rs1800796C allele were shown to produce more IL-6 in response to in vitro HBV core antigen stimulation than those carrying G allele.[12] Thus, rs1800796 C allelic or genotype (CC or GC) polymorphism may be associated with an increased risk to HBV infection, which was confirmed in both of our study involving 1772 cases and 1973 controls and the study of Chang et al[42] involving 426 cases and 777 controls. However, this conclusion seemed to be only suitable to the Asian population. In the non-Asian group, GC and GG+GC genotype were risk factors for the development of liver diseases, which was in line with some studies showing the mRNA expressions of IL-6 was higher in the rs1800796 GG genotype compare with others.[45,53]

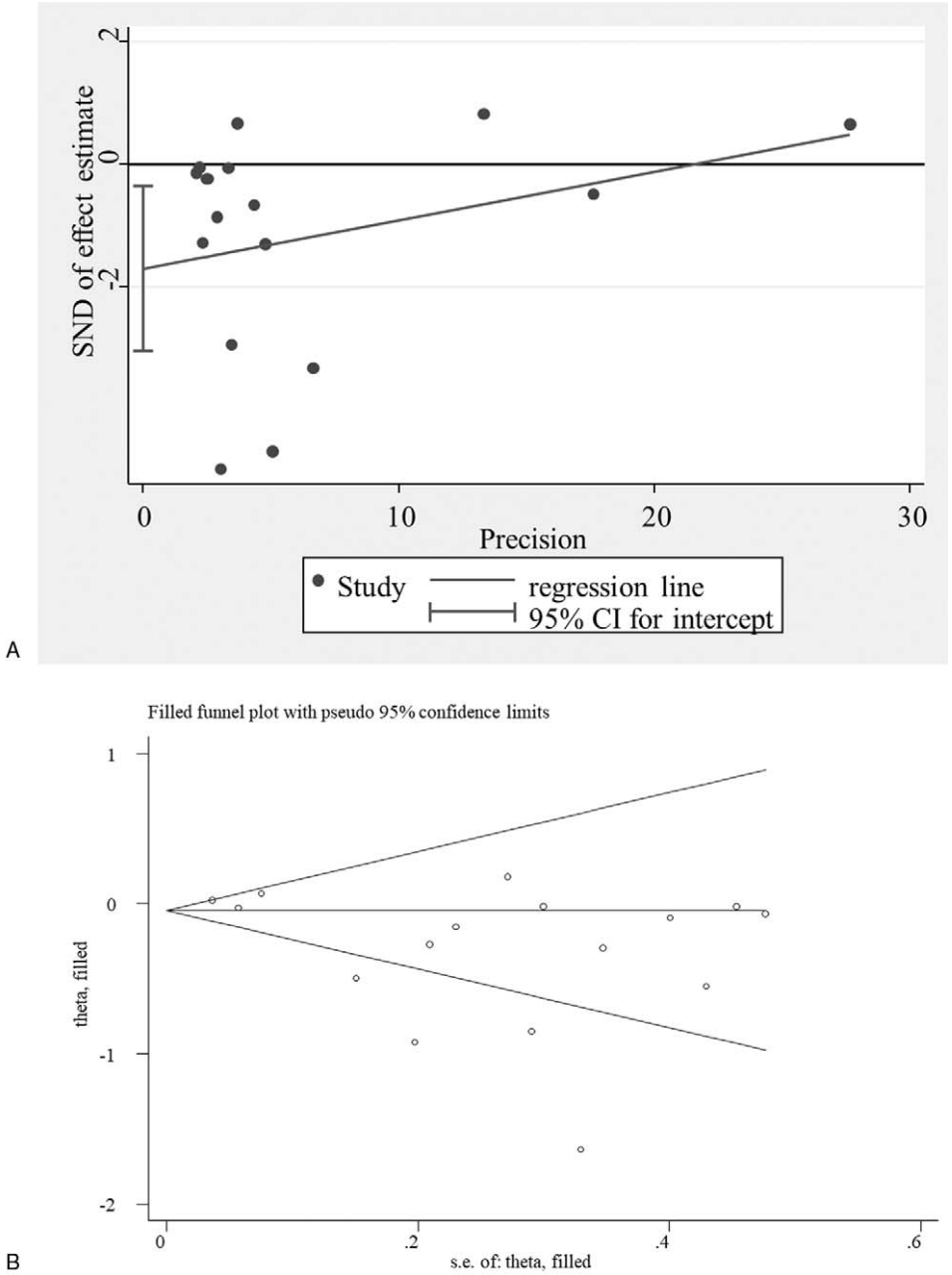

Figure 5. Potential publication bias. A, Egger funnel plot for the assessment of rs1800795 polymorphism (GG+GC vs CC); Trim and fill for adjusting publication bias. CI = confidence intervals, SND = standard normal deviation.

rs1800797 (-579 G/A) is also another polymorphism located within the promoter region of IL-6 gene. Our overall, non-Asian subgroup analysis and the study of Chang et al,[42] showed GG and GA genotype may be risk factors for liver diseases, indicating patients with these genotypes may have higher IL-6 levels. However, recent studies on lung cancer or obesity revealed IL-6 expression level was increased in an A allelic dose-dependent manner (that is, the highest for AA),[54,55] which may be attributed to the dual-function of IL-6[56] or disease difference.

There are several limitations in this meta-analysis. First, the number of studies in some liver disease subtypes was relatively small and thus statistical power may be still sufficient to estimate the correlation between the IL-6 gene polymorphisms with them. Second, articles in languages other than English were not included in this meta-analysis. Third, although the meta-analysis only included case-control designed studies, several studies did not report whether they were age and sex matched, which may influence the creditability of conclusions. Fourth, although there were studies to indicate a linkage disequilibrium between some SNPs of IL-6 (such as rs1800796-rs1800797,[13] rs1800796-rs2066992,[14] rs2069837-rs17147230,[20] rs2069837-rs1524107-rs2066992,[19] rs17147230-rs2066992-rs2069837-rs2069852,[18] rs1800796-rs1800797,[13] and rs1800795-rs1800797[17]) and haplotypes were calculated for more effective markers for prediction the risk of liver diseases, no meta-analysis was conducted for these haplotypes because no same haplotypes

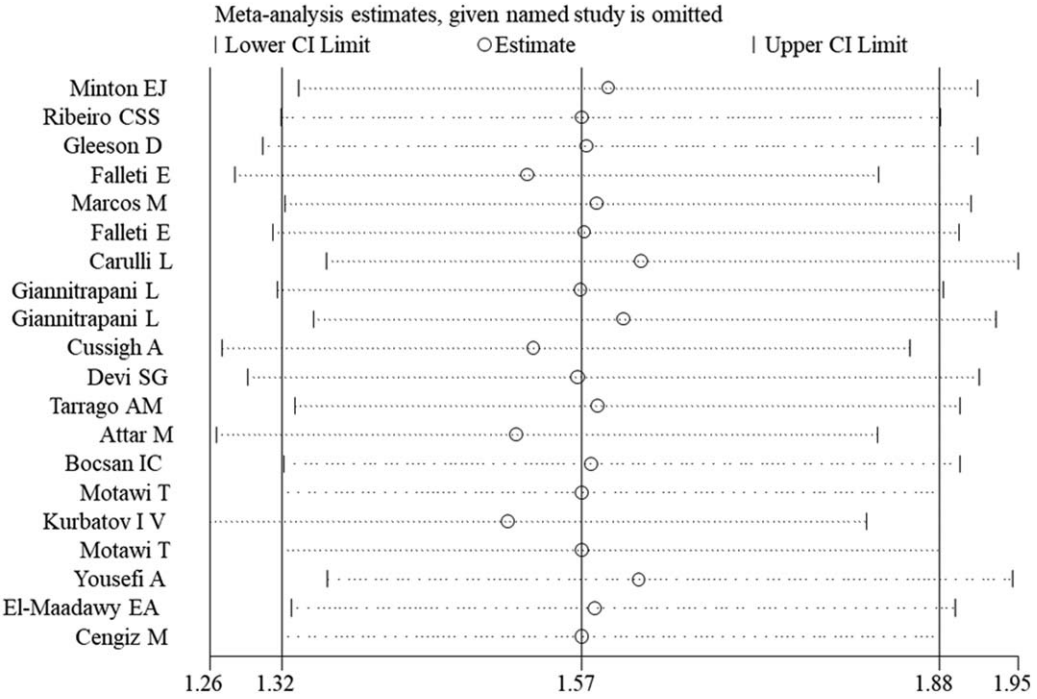

Figure 6. Sensitivity analysis for the assessment of result stability for rs1800795 polymorphism (GC vs CC). CI = confidence intervals.

were reported. Fifth, the association between IL-6 level and IL-6 gene polymorphisms could not be evaluated to reveal the function mechanisms due to the lack of the related data.

In conclusion, our meta-analysis of 25 studies revealed that IL-6 rs1800795 (all ethnic populations) and rs1800797 (non-Asian) polymorphisms may be associated with an increased risk of liver diseases, while rs1800796 polymorphism was associated with a decreased susceptibility factor for liver diseases in Asian population. The absence of a relationship between IL-6 rs2069837 and rs2066992 polymorphisms and the risk of liver diseases was demonstrated. A similar conclusion was found in the HBV, HCV, HCC, NASH and alcoholic liver disease population for rs1800795; HBV subgroup for rs1800796; and HCV subgroup for rs1800797.

Author contributions

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