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Original Article

The association between three IL-6 polymorphisms and HBV-related liver diseases: a meta-analysis

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Abstract: Background: A quantity of case-control studies have been performed to address the association between the three interleukin-6 (IL-6) polymorphisms (-572G/C, -597G/A and -174G/C) and the risk of HBV related liver diseases. However, previous research results are inconsistent. We conducted this meta-analysis to clarify the correlation between these IL-6 polymorphisms and HBV related liver diseases. Methods: We searched in PubMed, EMBASE, Cochrane Library as well as Chinese databases including China National Knowledge Infrastructure (CNKI) and WanFang database for all the relevant studies up to April 15, 2015. The data were extracted by two independent authors. Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated. Results: A total of 10 studies consisting of 3879 cases and 2812 controls were included in this metaanalysis. For IL-6 polymorphism -572G/C, an association with increased chronic hepatitis B (CHB) risk was observed under in allelic, homozygous, heterozygous, dominant and recessive model. However, IL-6 polymorphisms (-572G/C) were not related to Inactive Carrier (IC), Liver Cirrhosis (LC) and Hepatocellular Carcinoma (HCC) risk in this study. We also found that IL-6 polymorphisms (-597G/A) were related to CHB in allelic, heterozygous, recessive model. For IL-6 polymorphism -174G/C, we did not find any association with CHB risk. Conclusion: The present meta-analysis indicated that IL-6 polymorphisms -572G/C and -597G/A significantly associate with CHB risk, but might not be significantly related to the progressive HBV such as LC and HCC. IL-6 polymorphisms -174G/C might not significantly associate with HBV related liver diseases.

Keywords: Interleukin-6, polymorphisms, hepatitis B virus, liver diseases, meta-analysis

Introduction

HBV infection is the most common cause of chronic liver disease around the world, the total number of HBV-infected population is 350 to 400 million and the number of deaths summed up to 250,000 [1], which continues to be a significant public health problem. The HBV-related liver disease contains self-limiting acute hepatitis, chronic hepatitis (CHB), fulminant hepatic failure (FHF), liver cirrhosis (LC) and hepatocellular carcinoma (HCC), the latter three are always considered to be the direct factors of HBV-infected patient's death. However, about 95% of HBV infection individuals can successfully clear HBV, and only 5-10% will develop CHB. Among the CHB individuals, 20-30% will develop liver cirrhosis and 5% further progress to hepatocellular carcinoma [2]. The mechanism for persistent and progressive HBV infection is still unclear, which could be affected by complex factors including virus subtype, host condition, environmental and genetic elements. The current mainstream idea is that host immune factors and genetic factors may play important roles in the process [3].

Interleukin-6 (IL-6) is a multifunctional potent pleiotropic inflammatory cytokine that is considered a key growth-promoting and anti-apoptotic factor [4]. It plays a central role in the regulation of immune response. Previous studies have found that serum level of IL6 was increased in HBV-infected patients [5-7]. So high IL-6 levels might reflect more active hepatic necroinflammation and be associated with the presentation and severity in chronic HBV infection.

A number of studied about single nucleotide polymorphisms (SNPs) identified in the IL-6 gene, especially within the non-coding promoter sequence, involving -572G/C, -597G/A, and -174G/C, has been shown to influence the transcription and expression of IL-6. Zhao et al.

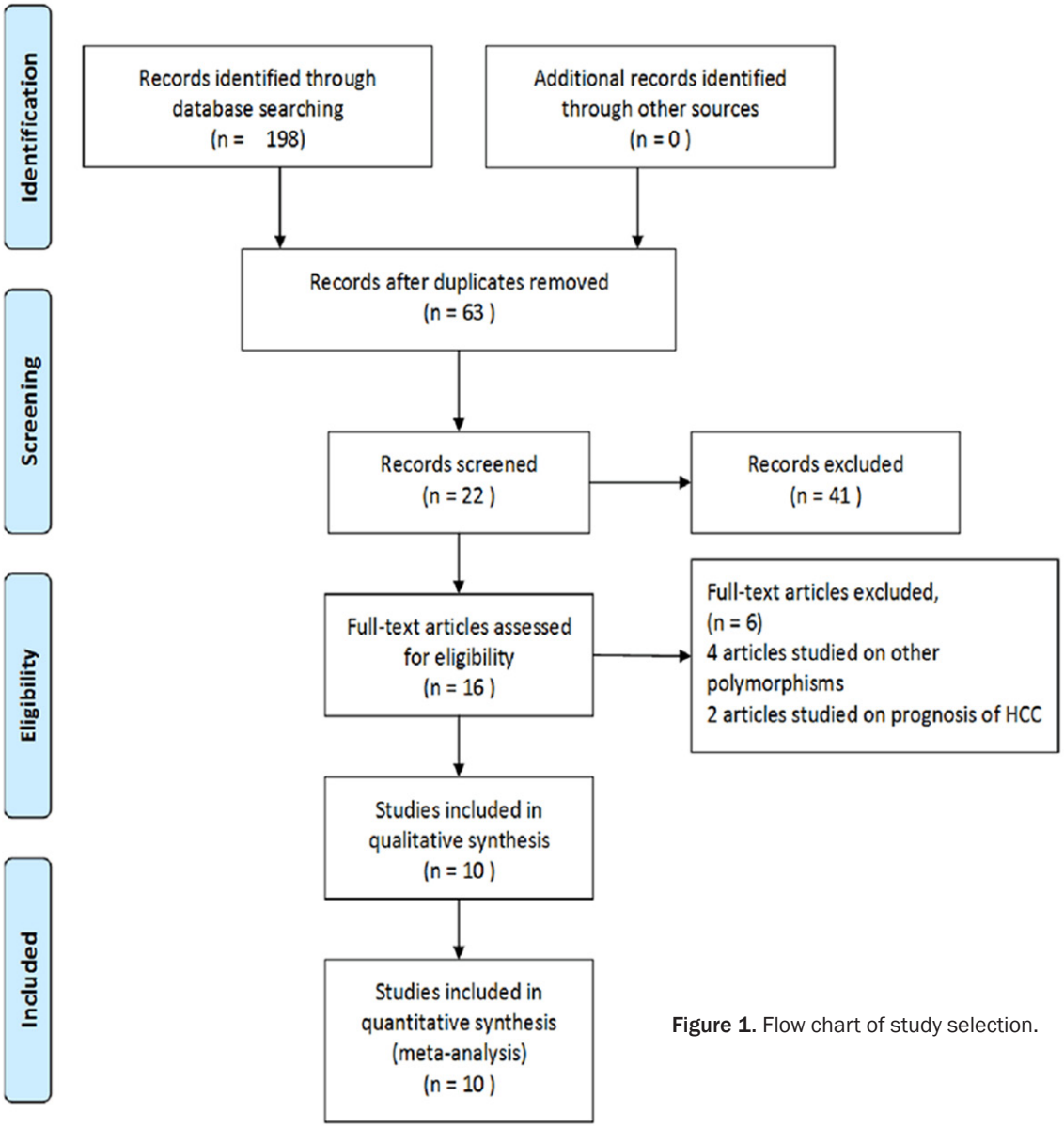


Figure 1. Flow chart of study selection.

have revealed four tag SNPs of IL-6 to be associated with susceptibility to chronic HBV infection in Chinese population [8]. Another study indicated that IL-6 (-572G/C) GC genotype shared a positive association with hepatitis among controls, and a negative association with cirrhosis and consequent HCC development among carriers in India [9]. However, in a Brazilian population, there are no significant differences in the polymorphism of IL-6 (-174G/C) between the chronic HBV-infected patient group and the self-limited infection group [10]. So far, large quantities of studies have confirmed the hypothesis that several IL-6 SNPs were potentially correlated with HBV infection risk, but the results were rather controversial and unconvincing, and no meta-analysis has examined the association between IL-6 polymorphism and HBV related liver diseases. Therefore, we have extensively reviewed literatures and conducted a meta-analysis to provide more credible evidence by systematically summarizing existed data.

Methods

Search strategy

We performed a systemic search in PubMed, EMBASE, Cochrane Library as well as Chinese

Table 1. Characteristics of studies included in the meta-analysis

SNPs	Study	Year	Country	Genotyping methods	Genotype distribution														HWE
					Controls			IC			CHB			LC			HCC			
-572G/C					GG	GC	CC	GG	GC	CC	GG	GC	CC	GG	GC	CC	GG	GC	CC	
	Saxena, R.	2014	India	PCR-RFLP	42	78	33	6	46	9	8	41	16	19	38	6	16	25	20	0.775
	Lu, Y.	2014	China	PCR-RFLP	16	96	100				7	78	134							0.279
	Tang, S.	2013	China	RT-PCR	11	78	176	1	7	17	11	87	194	6	46	101	7	51	90	0.53
	Liu, S.	2012	China	TaqMan	15	132	271				6	74	206				13	136	237	0.827
	Qiu, X. Q.	2011	China	TaqMan	13	105	241	23	107	210							12	110	259	0.71
	Dai, Y.	2009	China	PCR-RFLP	23	116	73				7	87	66							0.073
	Xing, P.	2007	China	PCR	8	54	38				7	59	45							0.062
	Park, B. L.	2003	Korea	PCR-RFLP	62	371	557				17	88	175	32	169	274	12	92	117	0.983
-597G/A					GG	GA	AA	GG	GA	AA	GG	GA	AA	GG	GA	AA	GG	GA	AA	
	Saxena, R.	2014	India	PCR-RFLP	75	55	8	18	45	1	47	15	2	40	18	3	28	26	5	0.614
	Lu, Y.	2014	China	PCR-RFLP	211	1	0				219	0	0							0.973
	Xing, P.	2007	China	PCR	99	1	0				109	2	0							0.960
-174G/C					GG	GC	CC	GG	GC	CC	GG	GC	CC	GG	GC	CC	GG	GC	CC	
	Ribeiro, C. S.	2007	Brazil	PCR	20	18	2				15	14	1							0.416
	Xing, P.	2007	China	PCR	98	2	0				107	4	0							0.920
	Chen, L.	2006	China	PCR	62	1	0	59	1	0	62	0	0							0.949

databases including China National Knowledge Infrastructure (CNKI) and WanFang database for all the relevant studies utilizing the following search terms: "interleukin-6" or "IL-6", "polymorphism" or "SNPs", "Hepatitis B virus" or "HBV" (the latest research was updated to April 15, 2015). We only utilized data from fully published papers and not from meetings or conference abstracts. Additionally, articles in the reference list were manually searched for potentially relevant studies. When more than one of the same patient population was included in several publications, only the most recent or complete study was used. Search and literature retrieval were completed independently by two of the authors (Lei Chang and Tian Lan). Disagreements of the search result were settled by discussion among all the authors.

Inclusion and exclusion criteria

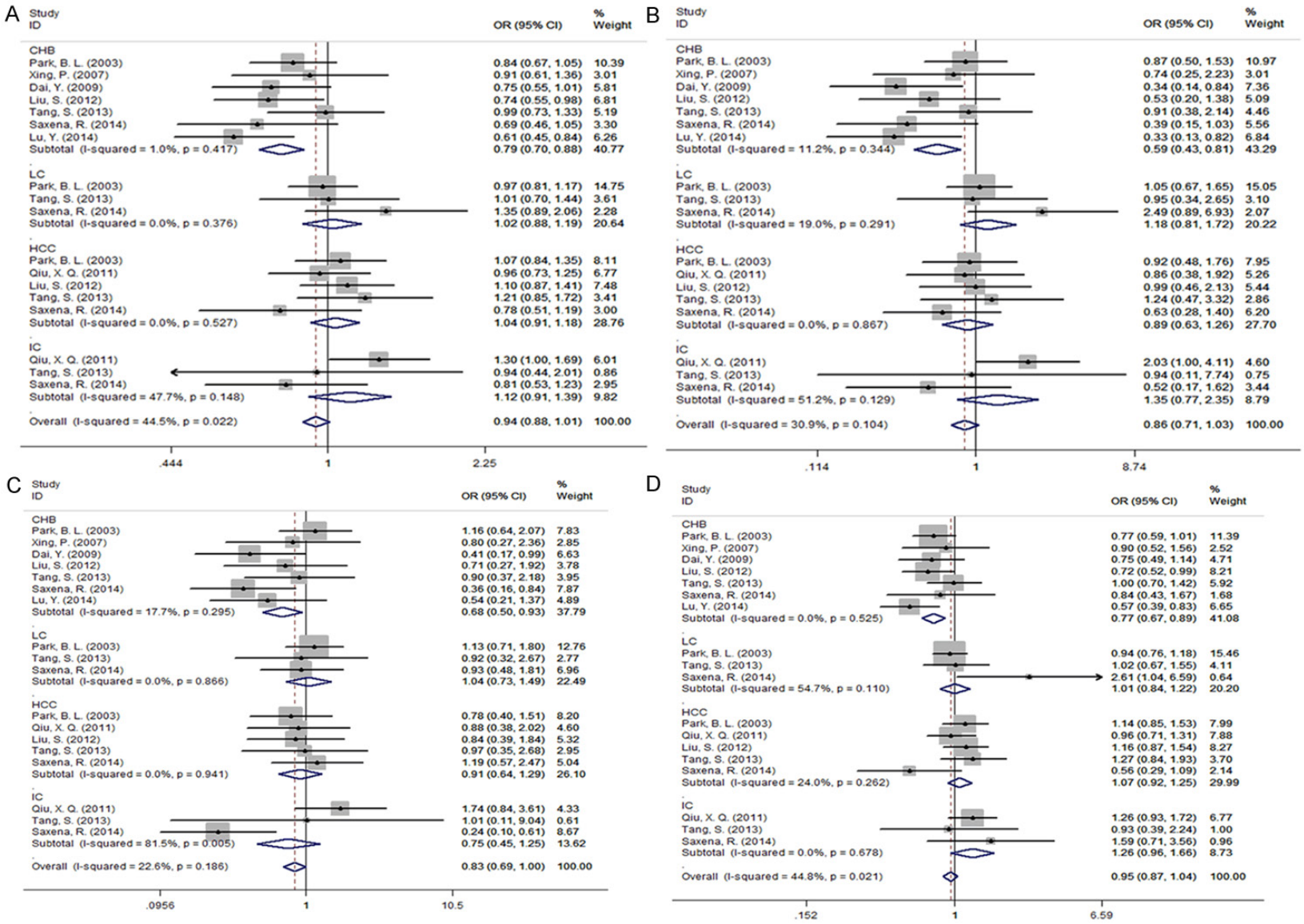
Studies were included in this meta-analysis if they met the following criteria: (1) the study assessed the association between HBV related disease and IL-6 polymorphisms (-572G/C, -597G/A and -174G/C); (2) chronic HBV infection cases included CHB, LC, HCC and IC (individuals who did not have any clinical symptoms and had persistently normal liver transaminase levels, serum albumin, and total serum bilirubin for at least 6 months); (3) case-control studies; (4) data in the studies were adequate to calculate odds ratio (OR) and 95% confidence interval (95% CI); (5) the genotype was tested in controls to ensure its fitting with the Hardy-Weinberg equilibrium (HWE). The major reasons for exclusion from our studies were: (1) family-based or sibling-based association studies; (2) the study without control group; (3) duplicated publication; (4) significant deviation of the genotype distribution in the control group from the HWE; (5) literature with insufficient data for evaluating OR and 95% CI.

Data extraction

Two investigators (Lei Chang and Yufeng Yuan) independently extracted the data from all eligible studies according to the inclusion and exclusion criteria above. The following information was collected from each study: author, year of publication, experimental method, ethnicity of research population, numbers of chronic HBV infection cases (including chronic hepatitis B, liver cirrhosis, hepatocellular carcinoma, and inactive carriers) and healthy controls, numbers of individual genotypes, distribution of haplotypes (-572/-597/-174), and the Hardy-Weinberg equilibrium (HWE) results.

Statistical analysis

We measure the strength of the association between IL-6 SNPs (-572G/C, -597G/A and -174G/C) and HBV related disease by pooled OR with its corresponding 95% CI. For -572G/C, the pooled ORs were estimated for allelic com-


A
Study ID
OR (95% CI)
% Weight
CHB
Park, B. L. (2003) 0.84 (0.67, 1.05) 10.39
Xing, P. (2007) 0.91 (0.61, 1.36) 3.01
Dai, Y. (2009) 0.75 (0.55, 1.01) 5.81
Liu, S. (2012) 0.74 (0.55, 0.98) 6.81
Tang, S. (2013) 0.99 (0.73, 1.33) 5.19
Saxena, R. (2014) 0.69 (0.46, 1.05) 3.30
Lu, Y. (2014) 0.61 (0.45, 0.84) 6.26
Subtotal (I-squared = 1.0%, p = 0.417) 0.79 (0.70, 0.88) 40.77
LC
Park, B. L. (2003) 0.97 (0.81, 1.17) 14.75
Tang, S. (2013) 1.01 (0.70, 1.44) 3.61
Saxena, R. (2014) 1.35 (0.89, 2.06) 2.28
Subtotal (I-squared = 0.0%, p = 0.376) 1.02 (0.88, 1.19) 20.64
HCC
Park, B. L. (2003) 1.07 (0.84, 1.35) 8.11
Qiu, X. Q. (2011) 0.96 (0.73, 1.25) 6.77
Liu, S. (2012) 1.10 (0.87, 1.41) 7.48
Tang, S. (2013) 1.21 (0.85, 1.72) 3.41
Saxena, R. (2014) 0.78 (0.51, 1.19) 3.00
Subtotal (I-squared = 0.0%, p = 0.527) 1.04 (0.91, 1.18) 28.76
IC
Qiu, X. Q. (2011) 1.30 (1.00, 1.69) 6.01
Tang, S. (2013) 0.94 (0.44, 2.01) 0.86
Saxena, R. (2014) 0.81 (0.53, 1.23) 2.95
Subtotal (I-squared = 47.7%, p = 0.148) 1.12 (0.91, 1.39) 9.82
Overall (I-squared = 44.5%, p = 0.022) 0.94 (0.88, 1.01) 100.00
.444
1
2.25
B
Study ID
OR (95% CI)
% Weight
CHB
Park, B. L. (2003) 0.87 (0.50, 1.53) 10.97
Xing, P. (2007) 0.74 (0.25, 2.23) 3.01
Dai, Y. (2009) 0.34 (0.14, 0.84) 7.36
Liu, S. (2012) 0.53 (0.20, 1.38) 5.09
Tang, S. (2013) 0.91 (0.38, 2.14) 4.46
Saxena, R. (2014) 0.39 (0.15, 1.03) 5.56
Lu, Y. (2014) 0.33 (0.13, 0.82) 6.84
Subtotal (I-squared = 11.2%, p = 0.344) 0.59 (0.43, 0.81) 43.29
LC
Park, B. L. (2003) 1.05 (0.67, 1.65) 15.05
Tang, S. (2013) 0.95 (0.34, 2.65) 3.10
Saxena, R. (2014) 2.49 (0.89, 6.93) 2.07
Subtotal (I-squared = 19.0%, p = 0.291) 1.18 (0.81, 1.72) 20.22
HCC
Park, B. L. (2003) 0.92 (0.48, 1.76) 7.95
Qiu, X. Q. (2011) 0.86 (0.38, 1.92) 5.26
Liu, S. (2012) 0.99 (0.46, 2.13) 5.44
Tang, S. (2013) 1.24 (0.47, 3.32) 2.86
Saxena, R. (2014) 0.63 (0.28, 1.40) 6.20
Subtotal (I-squared = 0.0%, p = 0.867) 0.89 (0.63, 1.26) 27.70
IC
Qiu, X. Q. (2011) 2.03 (1.00, 4.11) 4.60
Tang, S. (2013) 0.94 (0.11, 7.74) 0.75
Saxena, R. (2014) 0.52 (0.17, 1.62) 3.44
Subtotal (I-squared = 51.2%, p = 0.129) 1.35 (0.77, 2.35) 8.79
Overall (I-squared = 30.9%, p = 0.104) 0.86 (0.71, 1.03) 100.00
.114
1
8.74
C
Study ID
OR (95% CI)
% Weight
CHB
Park, B. L. (2003) 1.16 (0.64, 2.07) 7.83
Xing, P. (2007) 0.80 (0.27, 2.36) 2.85
Dai, Y. (2009) 0.41 (0.17, 0.99) 6.63
Liu, S. (2012) 0.71 (0.27, 1.92) 3.78
Tang, S. (2013) 0.90 (0.37, 2.18) 3.95
Saxena, R. (2014) 0.36 (0.16, 0.84) 7.87
Lu, Y. (2014) 0.54 (0.21, 1.37) 4.89
Subtotal (I-squared = 17.7%, p = 0.295) 0.68 (0.50, 0.93) 37.79
LC
Park, B. L. (2003) 1.13 (0.71, 1.80) 12.76
Tang, S. (2013) 0.92 (0.32, 2.67) 2.77
Saxena, R. (2014) 0.93 (0.48, 1.81) 6.96
Subtotal (I-squared = 0.0%, p = 0.866) 1.04 (0.73, 1.49) 22.49
HCC
Park, B. L. (2003) 0.78 (0.40, 1.51) 8.20
Qiu, X. Q. (2011) 0.88 (0.38, 2.02) 4.60
Liu, S. (2012) 0.84 (0.39, 1.84) 5.32
Tang, S. (2013) 0.97 (0.35, 2.68) 2.95
Saxena, R. (2014) 1.19 (0.57, 2.47) 5.04
Subtotal (I-squared = 0.0%, p = 0.941) 0.91 (0.64, 1.29) 26.10
IC
Qiu, X. Q. (2011) 1.74 (0.84, 3.61) 4.33
Tang, S. (2013) 1.01 (0.11, 9.04) 0.61
Saxena, R. (2014) 0.24 (0.10, 0.61) 8.67
Subtotal (I-squared = 81.5%, p = 0.005) 0.75 (0.45, 1.25) 13.62
Overall (I-squared = 22.6%, p = 0.186) 0.83 (0.69, 1.00) 100.00
.0956
1
10.5
D
Study ID
OR (95% CI)
% Weight
CHB
Park, B. L. (2003) 0.77 (0.59, 1.01) 11.39
Xing, P. (2007) 0.90 (0.52, 1.56) 2.52
Dai, Y. (2009) 0.75 (0.49, 1.14) 4.71
Liu, S. (2012) 0.72 (0.52, 0.99) 8.21
Tang, S. (2013) 1.00 (0.70, 1.42) 5.92
Saxena, R. (2014) 0.84 (0.43, 1.67) 1.68
Lu, Y. (2014) 0.57 (0.39, 0.83) 6.65
Subtotal (I-squared = 0.0%, p = 0.525) 0.77 (0.67, 0.89) 41.08
LC
Park, B. L. (2003) 0.94 (0.76, 1.18) 15.46
Tang, S. (2013) 1.02 (0.67, 1.55) 4.11
Saxena, R. (2014) 2.61 (1.04, 6.59) 0.64
Subtotal (I-squared = 54.7%, p = 0.110) 1.01 (0.84, 1.22) 20.20
HCC
Park, B. L. (2003) 1.14 (0.85, 1.53) 7.99
Qiu, X. Q. (2011) 0.96 (0.71, 1.31) 7.88
Liu, S. (2012) 1.16 (0.87, 1.54) 8.27
Tang, S. (2013) 1.27 (0.84, 1.93) 3.70
Saxena, R. (2014) 0.56 (0.29, 1.09) 2.14
Subtotal (I-squared = 24.0%, p = 0.262) 1.07 (0.92, 1.25) 29.99
IC
Qiu, X. Q. (2011) 1.26 (0.93, 1.72) 6.77
Tang, S. (2013) 0.93 (0.39, 2.24) 1.00
Saxena, R. (2014) 1.59 (0.71, 3.56) 0.96
Subtotal (I-squared = 0.0%, p = 0.678) 1.26 (0.96, 1.66) 8.73
Overall (I-squared = 44.8%, p = 0.021) 0.95 (0.87, 1.04) 100.00
.152
1
6.59

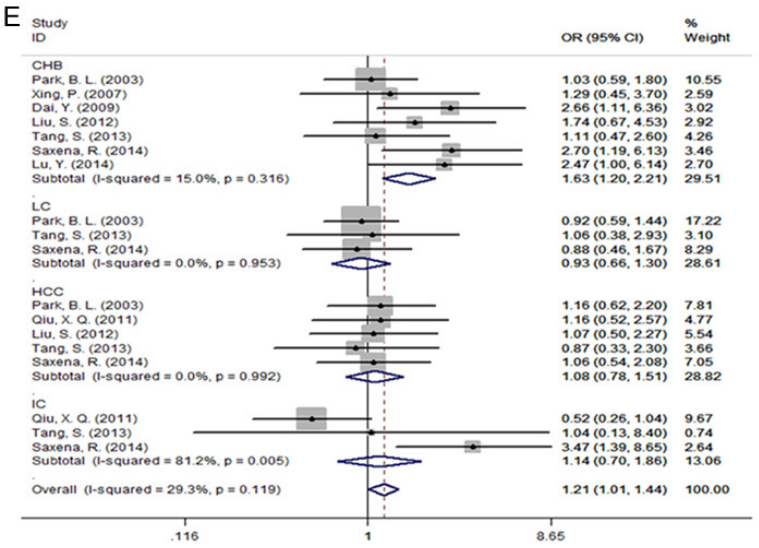


Figure 2. Forest plot of IL-6 -572G/C polymorphisms associated with hepatitis B virus related liver diseases risk for subgroup analysis of IC, CHB, LC, and HCC as compared with healthy control (HC). A: Allelic model, G vs C; B: Homozygous model, GG vs CC; C: Heterozygous modle, GG vs GC; D: Recessive model, GC + GG vs CC; E: Dominant model, GC + CC vs GG. The results indicated that IL-6 -572G/C exhibited the obvious association with CHB risk in all models.

Table 2. The meta-analysis results of association between IL-6 -572G/C polymorphisms and HBV-related liver diseases

SNPs	Contrast model	CHB						HCC					
		Test for heterogeneity		OR (95% CI)	P_A	Publication bias (Egger's test)		Test for heterogeneity		OR (95% CI)	P_A	Publication bias (Egger's test)	
		I^2 (%)	P			t	P	I^2 (%)	P			t	P
-572G/C	G vs C	1.0	0.417	0.786 (0.701-0.881)	0.000	-0.49	0.787	0.0	0.527	1.038 (0.915-1.178)	0.564	-1.41	0.539
	GG vs CC	11.2	0.344	0.587 (0.428-0.806)	0.001	-1.59	0.135	0.0	0.867	0.891 (0.628-1.623)	0.517	1.24	0.548
	GG vs GC	17.7	0.295	0.681 (0.497-0.934)	0.017	-2.37	0.105	0.00	0.941	0.911 (0.644-1.288)	0.598	0.50	0.775
	GG + GC vs CC	0.0	0.525	0.768 (0.666-0.886)	0.000	0.36	0.758	24.0	0.262	1.075 (0.922-1.253)	0.357	-1.96	0.334
	GC + CC vs GG	15.0	0.316	1.630 (1.202-2.210)	0.002	4.02	0.268	0.0	0.992	1.083 (0.777-1.508)	0.639	-1.25	0.148
SNPs	Contrast model	IC						LC					
		Test for heterogeneity		OR (95% CI)	P_A	Publication bias (Egger's test)		Test for heterogeneity		OR (95% CI)	P_A	Publication bias (Egger's test)	
		I^2 (%)	P			t	P	I^2 (%)	P			t	P
-572G/C	G vs C	47.7	0.148	1.121 (0.907-1.385)	0.291	-2.20	0.500	0.0	0.376	1.022 (0.880-1.187)	0.777	1.96	0.434
	GG vs CC	51.2	0.129	1.347 (0.773-2.349)	0.293	-2.38	0.515	19.0	0.291	1.181 (0.811-1.719)	0.385	2.29	0.594
	GG vs GC	81.5	0.005	0.752 (0.454-1.246)	0.269	-1.24	0.796	0.0	0.866	1.044 (0.730-1.494)	0.813	-0.84	0.395
	GG + GC vs CC	0.0	0.678	1.262 (0.960-1.659)	0.095	-0.02	0.992	54.7	0.110	1.011 (0.836-1.223)	0.907	3.80	0.287
	GC + CC vs GG	81.2	0.005	1.145 (0.704-1.861)	0.585	1.59	0.872	0.0	0.953	0.926 (0.657-1.304)	0.658	0.34	0.586

Table 3. The meta-analysis results of association between IL-6 -597G/A, -174G/C polymorphisms and CHB risk

SNPs	Contrast model	CHB					
		Test for heterogeneity		OR (95% CI)	P_A	Publication bias (Egger's test)	
		I^2 (%)	P			t	P
-597G/A	G vs A	0	0.570	1.887 (1.113-3.202)	0.019	3.54	0.175
	GG vs GA	0	0.521	2.209 (1.117-3.923)	0.021	3.17	0.195
	GA + AA vs GG	0	0.515	0.470 (0.257-0.861)	0.014	0.51	0.698
-174G/C	G vs C	0	0.630	0.992 (0.511-1.927)	0.982	0.85	0.552
	GG vs GC	0	0.644	0.920 (0.414-2.045)	0.838	0.23	0.853
	GC + CC vs GG	0	0.638	1.058 (0.482-2.324)	0.888	1.22	0.438

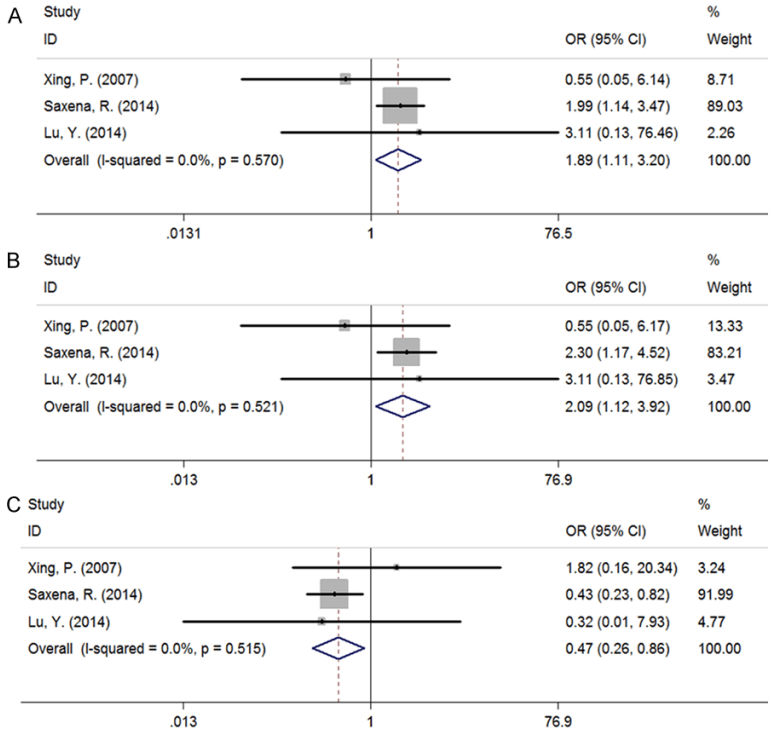


Figure 3. Forest plot of IL-6 -597G/A polymorphisms associated with CHB risk as compared with healthy control (HC). A: Allelic model, G vs A; B: Heterozygous model, GG vs GA; C: Dominant model, GA + AA vs GG; The results indicated that IL-6 -597G/A exhibited the obvious association with CHB risk in allelic, heterozygous, dominant model.

parison (G vs C), homozygote comparison (GG vs CC), heterozygote comparison (GG vs CC), dominant model (GG + GC vs CC), and recessive model (GC + CC vs GG) respectively. For -597G/A, because of fewer researches the pooled ORs were estimated only for allelic comparison (G vs A), heterozygote comparison (GG vs GA) and recessive model (GA + AA vs GG). For -174G/C, the pooled ORs were estimated only for allelic comparison (G vs C), heterozygote comparison (GG vs GC) and recessive model (GC + CC vs GG). The *P* value of the pooled OR was considered significant if less than 0.05, which was examined by Z test. Heterogeneity across studies was determined by Chi-square test based Q statistic test and I^2 statistic and the presence of heterogeneity was confirmed if the result was $P_Q < 0.05$ or $I^2 \geq 50\%$. In the condition of existence of heterogeneity, a random-effect model was utilized [11, 12]; otherwise the fixed-effect model was employed to pool the results [13]. Additionally, in order to evaluate the stability of results, a sensitivity analysis was conducted. Both Begg's test and Egger's test were performed to test whether publication bias existed or not. All the analyses that have been mentioned were completed by STATA v.12.0.

Results

Characteristics of included studies

As shown in the **Figure 1**, 198 articles were found with the search strategy and then 135 duplicates are removed. After reading the titles or the abstracts, 35 records with improper titles, 6 articles were master thesis also exclud-

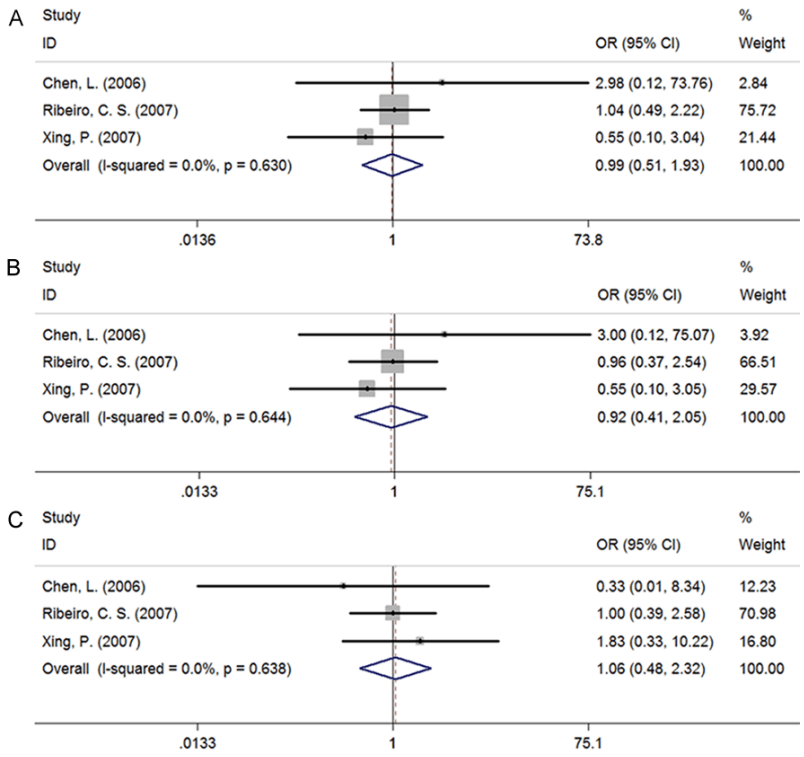


Figure 4. Forest plot of IL-6 -174G/C polymorphisms associated with CHB risk as compared with healthy control (HC). A: Allelic model, G vs C; B: Heterozygous model, GG vs GC; C: Dominant model, GC + CC vs GG; There was no any association between IL-6 -174G/C polymorphisms and CHB risk.

ed. Meanwhile, 2 articles based on the same population 4 articles studied on other polymorphisms. Eventually, 10 studies met the criteria were included in the meta-analysis of which 5 articles were in English and other 5 in Chinese [5, 9, 10, 14-20]. The characteristics of included articles were showed in **Table 1**. For -572G/C polymorphism of IL-6, we included 8 articles including 3727 cases and 2709 controls (for subgroup analysis of IC; 426 cases and 777 controls; for subgroup analysis of CHB: 1413 cases and 2350 controls; for subgroup analysis of LC: 691 cases and 1408 controls; for subgroup analysis of HCC: 1197 cases and 2185 controls). 3 articles about -597G/A consisting of 578 cases and 450 controls (for subgroup analysis of CHB: 394 cases and 450 controls; for other subgroups, as only one studies was included, the analysis result tended to be less reliable, of which detailed data were not showed in this study) and 3 articles of -174G/C involving 263 cases and 203 controls were included as well (for subgroup analysis of CHB: 203 cases and 203 controls; for other subgroups, as only one studies was included, the analysis result tended to be less reliable, of which detailed data were not showed in this study). All these studies were case-control study.

Quantitative synthesis

Table 2 showed the main meta-analysis results of relationships between IL-6 -572G/C polymorphisms and HBV related disease for all population. Subgroup analysis by disease showed that IL-6 -572G/C exhibited the obvious association with CHB risk in allelic (**Figure 2A**), homozygous (**Figure 2B**), heterozygous (**Figure 2C**), recessive (**Figure 2D**) and dominant model (**Figure 2E**) (G vs C: OR = 0.786, 95% CI 0.701-0.881, P_A = 0.000; GG vs CC: OR = 0.587, 95% CI 0.428-0.806, P_A = 0.001; GG vs GC: OR = 0.681, 95% CI 0.497-0.934, P_A = 0.017; GG+GC vs CC: OR = 0.768, 95% CI 0.666-0.886, P_A = 0.000; GC+CC vs GG: OR = 1.630, 95% CI 1.202-2.210, P_A = 0.002). However, there was no association between IL-6 -572G/C polymorphisms and IC (G vs C: OR = 1.121, 95% CI = 0.907-1.385, P_A = 0.291; GG vs CC: OR = 1.347, 95% CI = 0.773-2.349, P_A =0.293; GG vs GC: OR = 0.752, 95% CI = 0.454-1.246, P_A = 0.269; GG + GC vs CC: OR = 1.262, 95% CI = 0.960-1.659, P_A =0.095; GC + CC vs GG: OR = 1.145, 95% CI = 0.704-1.861, P_A = 0.585), LC (G vs C: OR = 1.022, 95% CI = 0.880-1.187, P_A = 0.777; GG vs CC: OR = 1.181, 95% CI = 0.811-1.719, P_A = 0.385; GG vs GC: OR = 1.044, 95% CI = 0.730-1.494, P_A = 0.813; GG + GC vs CC: OR = 1.011, 95% CI = 0.836-1.223, P_A = 0.907; GC + CC vs GG: OR= 0.926, 95% CI = 0.657-1.304, P_A = 0.658) and HCC (G vs C: OR = 1.038, 95% CI = 0.915-1.178, P_A = 0.564; GG vs CC: OR = 0.891, 95% CI = 0.628-1.623, P_A = 0.517; GG vs GC: OR = 0.911, 95% CI = 0.644-1.288, P_A = 0.598; GG + GC vs CC: OR = 1.075, 95% CI = 0.922-1.253, P_A = 0.357; GC + CC vs GG: OR = 1.083, 95% CI = 0.777-1.508, P_A = 0.639) (**Figure 2A-E**).

Table 3 showed the main meta-analysis results of relationships between IL-6 -597G/A, IL-6 -174G/C polymorphisms and CHB for all population. The results indicated that IL-6 -597G/A exhibited the obvious association with CHB risk in allelic (**Figure 3A**), heterozygous, (**Figure 3B**) dominant model (**Figure 3C**) (G vs A: OR = 1.887, 95% CI 1.113-3.202, P_A = 0.019; GG vs GA: OR = 2.209, 95% CI 1.117-3.923, P_A = 0.021; GA + AA vs GG: OR = 0.470, 95% CI 0.257-0.861, P_A = 0.014). As only one study of other models was included, the analysis result tended to be less reliable, of which detailed data were not showed in this study. Meanwhile, we did not find any association between IL-6 -174G/C polymorphisms and CHB risk (**Figure 4A-C**).

Publication bias and sensitivity analysis

The Begg's test and Egger's test were applied to assess the publication bias of included literature.The shapes of funnel plot were symmetrical, which have not implied the existence of publication bias. All the Egger's test results of three polymorphisms were demonstrated in **Tables 2** and **3**, all *P* values were greater than 0.05 and thus there was no obvious publication bias in the meta-analysis.

Sensitivity analysis was performed to evaluate the stability of the result. Each data set was omitted individually to investigate the impact of a single study on the pooled ORs. The exclusion of any single study did not alter the overall conclusion, indicating that results were reliable.

Discussion

Human IL-6 genes located on chromosome 7p21 and total length of 5 KB, including four introns and five exons, which composed of 184 amino acids encoding protein IL-6 [21]. IL-6 was considered to be the starting stage of an important factor, when the virus infection happened, IL-6 inducied a variety of cell synthesis and secretion of a variety of acute phase protein, and promoted T, B lymphocyte proliferation, differentiation and produced immune globulin. IL-6 played a very important role in virus infection of inflammation [22]. Current researchers found that transcription factor such as NF-κB, Fos/Jun and glucocorticoid receptors can combine with the IL-6 promoter sequences and then regulation of expression of IL-6 gene at the transcriptional level [23]. IL-6 promoter polymorphism could lead to interindividual differences in gene transcription and expression, which affects the susceptibility to HBV infections and the progression of HBV-related diseases.

In current meta-analysis, we have investigated the relationships between three interlenkin-6 polymorphisms and HBV-related diseases risk. The results demonstrated that -572G/C in the promoter region of IL-6 gene was associated with an increased risk of HBV infection in heterozygous and dominant model (GG vs GC: OR = 0.832, 95% CI = 0.694-0.999, P_A = 0.048; GC + CC vs GG: OR = 1.207, 95% CI = 1.014-1.437, P_A = 0.034). Furthermore, In the subgroup analysis by HBV-related disease, an significant risk was found among CHB in all genetic models(G vs C: OR = 0.768, 95% CI 0.701-0.881, P_A = 0.000; GG vs CC: OR = 0.587, 95% CI 0.428-0.806, P_A = 0.001; GG vs GC: OR = 0.681, 95% CI 0.497-0.934, P_A = 0.017; GG + GC vs CC: OR = 0.768, 95% CI 0.666-0.886, P_A = 0.000; GC + CC vs GG: OR = 1.630, 95% CI 1.202-2.210, P_A = 0.002), but no statistical association has been observed among other HBV-related diseases (LC, HCC and IC), indicating that the risk of HBV infection caused by -572G/C polymorphism may contribute to the difference of latter's distribution in CHB patients. Therefore, we can conclude that to some extent, the single nucleotide polymorphism of -572G/C in IL-6 promoter region is inclined to promote the development of CHB.

For -597G/A, a total of 3 case-control studies [9, 14, 19] were analyzed to provide a comprehensive assessment of the association between its polymorphism and CHB. We noticed that a significant correlation exists under the allelic, heterozygous, dominant model (G vs A: OR = 1.887, 95% CI 1.113-3.202, P_A = 0.019; GG vs GA: OR = 2.209, 95% CI 1.117-3.923, P_A = 0.021; GA + AA vs GG: OR = 0.470, 95% CI 0.257-0.861, P_A = 0.014). Simultaneously, there was no heterogeneity in the three genetic models, of which the result data possess a high centrality and credibility. Similarly, we have analyzed the data from three included studies [10, 14, 20] about the SNP of -174G/C in IL-6 promoter region and the result of meta-analysis illustrated that IL-6 -174G/C could not play a part in the susceptibility to CHB.

Nowadays, the number of studies about the association between the single nucleotide polymorphisms (-572G/C, -597G/A and -174G/C)

and HBV infection risk is not enough. And in today's era of evidence-based medicine, the system review or meta-analysis is insufficient. In addition, the research findings are conflicting and don't achieve a consensus, which makes this meta-analysis indispensable. Simultaneously, this is the first meta-analysis concerning the association between IL-6 Polymorphisms and HBV-related Diseases.

However, the shortcomings of this study should be taken into consideration. Firstly, due to lack of related data, the quantity of involved studies about the SNP of -597G/A and -174G/C was not adequate. Only three studies were included respectively, although there was no heterogeneity in the results. Secondly, a few of the study controls were not from healthy populations. Selection bias could have occurred, which may have confounded the results. Third, the meta-analysis contains no prospective study to confirm the correlation between three IL-6 polymorphisms and CHB risk, which can provide a higher reliability.

In general, our meta-analysis illuminated that the IL-6 -572G/C and IL-6 -597G/A might be associated with CHB risk, but the IL-6 -174G/C did not play a part in the susceptibility to CHB. Nevertheless, because of the aforementioned limitations, more evidence of prospective, multi-centric and multi-populational trials are needed to further explore the association between IL-6 polymorphisms and HBV infection risk.

Disclosure of conflict of interest

None.

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