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Gene polymorphisms in the interleukins gene and the risk of acute pancreatitis: A meta-analysis

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ABSTRACT

Single nucleotide polymorphisms (SNPs) within the interleukins (IL) gene may affect the risk of acute pancreatitis. Many epidemiological studies have reported an association between the IL gene and acute pancreatitis risk, but the results remain inconsistent. Given the controversial available data, we carried out a meta-analysis to systematically evaluate and clarify the association between IL gene polymorphisms and AP. A systematic search of studies for this association was obtained from the PubMed, EMBASE, Web of Science and Chinese National Knowledge Infrastructure (CNKI) databases until June 1, 2017. We also searched the references of the included studies to identify additional studies. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were used to pool the effect size. Stata12.0 was used for whole statistical analysis. Fifteen studies that contained 3371 AP cases and 3506 controls were included in final combination. Overall, a significant association was found between the IL-8-251 T/A (rs4073) polymorphism, the IL-10-1082 A/G (rs1800896) polymorphism and the AP risk in four genetic models (homozygote model, recessive model, dominant model, allele model). Meanwhile, individuals with IL-1β + 3954 C/T (rs1143634, (homozygote model, recessive model)), IL-1β -511 C/T (rs16944, (dominant model)) and IL-6-634C/G (rs1800796, (allele model)) polymorphism were associated with an increased risk of AP. No evidence of an association was found between IL and 10-592 C/A (rs1800872) and IL-10-819 C/T (rs1800871) polymorphism and AP risk.

1. Introduction

Acute pancreatitis (AP), a common necrotizing inflammatory disease, has become one of most common reasons for hospital admission associated with a gastrointestinal condition around the world [1]. The annual incidence of AP ranges from 13 to 45 per 100 000 people [2]. AP was the second highest cause of the total length of hospital stay, the largest benefactor to aggregate costs, and the fifth primary cause of in hospital mortality [3]. Gallstones, alcohol, hypertriglyceridemia and drug use are considered to be the most common risk factors for AP. Polymorphisms and mutations in some genes are involved in the occurrence of AP [1]. Meanwhile, it is well-known that inflammation plays a vital role in the pathological process of AP [4,5], indicating that inflammatory cytokines are candidates to act as risk factors for AP.

Interleukins (ILs), a group of cytokines, were firstly seen to be expressed in leukocytes, in which they play a crucially important role in nearly all aspects of immune regulation and the inflammatory response. According to the responding cell type, IL possess both pro- and/or anti-inflammatory effects [6]. IL abnormalities could result in numerous complicated diseases, including ulcerative colitis [7], gastric cancer [8] and bladder cancer [9]. Meanwhile, a large number of studies have illustrated that dysfunction of inflammatory cytokines might be important in accelerating the physiological and pathological process of AP [10–13]. Plasma IL levels are primarily regulated at a transcriptional level [14–19]. Many studies have demonstrated that SNPs occurring in the IL promoter region may have an influence on its transcription and secretion [14–19]. Thus, IL polymorphism may play a role in the pathological development of AP.

Although, several epidemiological studies have reported on the associations between IL gene polymorphisms and the risk of AP development in diverse population, the results have been inconclusive due to selection bias, limited sample size, single case-control studies and

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genotyping methods. Therefore, to better illustrate the relationship between IL gene polymorphism and the risk of AP, we performed a systematic review and an updated meta-analysis by pooling the latest and most convincing evidence.

2. Methods

2.1. Search strategy

Electronic databases including PubMed, Web of Science, EMBASE, China National Knowledge Infrastructure, CBMdisc and Google Scholar were systematically reviewed independently by two investigators (Zhu XL and Tu M) for potential eligible studies published prior to June 1, 2017. The following keywords were used either alone or in combination: ("interleukins"[MeSH Terms] OR "interleukins"[All Fields] OR "interleukin"[All Fields]) AND (("polymorphism, genetic"[MeSH Terms] OR ("polymorphism"[All Fields] AND "genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields]) OR ("mutation"[MeSH Terms] OR "mutation"[All Fields]) OR variant [All Fields] OR variation[All Fields] OR ("genotype"[MeSH Terms] OR "genotype"[All Fields])) AND ("pancreatic diseases"[MeSH Terms] OR ("pancreatic"[All Fields] AND "diseases"[All Fields]) OR "pancreatic diseases"[All Fields]).

Then the reference lists of the retrieved articles and recent reviews were screened for additional studies to prevent the loss of important data.

2.2. Inclusion and exclusion criteria

The included studies must were required to fulfil the following inclusion criteria to be involved in this meta-analysis. They needed to (a) follow a case-control design, (b) evaluate the association between IL polymorphisms and AP risk, (c) contain enough detailed genotype frequencies to obtain an estimated odds ratio (OR) with 95% CI, and (d) focus only on human data. Studies were excluded from further analysis if they: (a) contained insufficient genotype data, (b) were duplicated of publications or (c) were case reports, conference articles, reviews or comments.

2.3. Data extraction

All of the data from the eligible studies were extracted independently by two reviewers(Zhu XL and Tu M). The following data were included: name of the first author, year of publication, study population, ethnicity, genotype frequency of each SNP, source of control, sample size of cases and controls, Hardy-Winberg equilibrium. Different ethnicity descents were categorized as Asian and Caucasian. Eligible studies were defined as hospital-based (HB) and population-based (PB) according to the control source. If some disagreements were met during the period, inconsistencies were discussed and resolved by a third investigator (Li Qiang), Hardy-Winberg equilibrium (HWE) was chosen to assess the quality of selected studies.

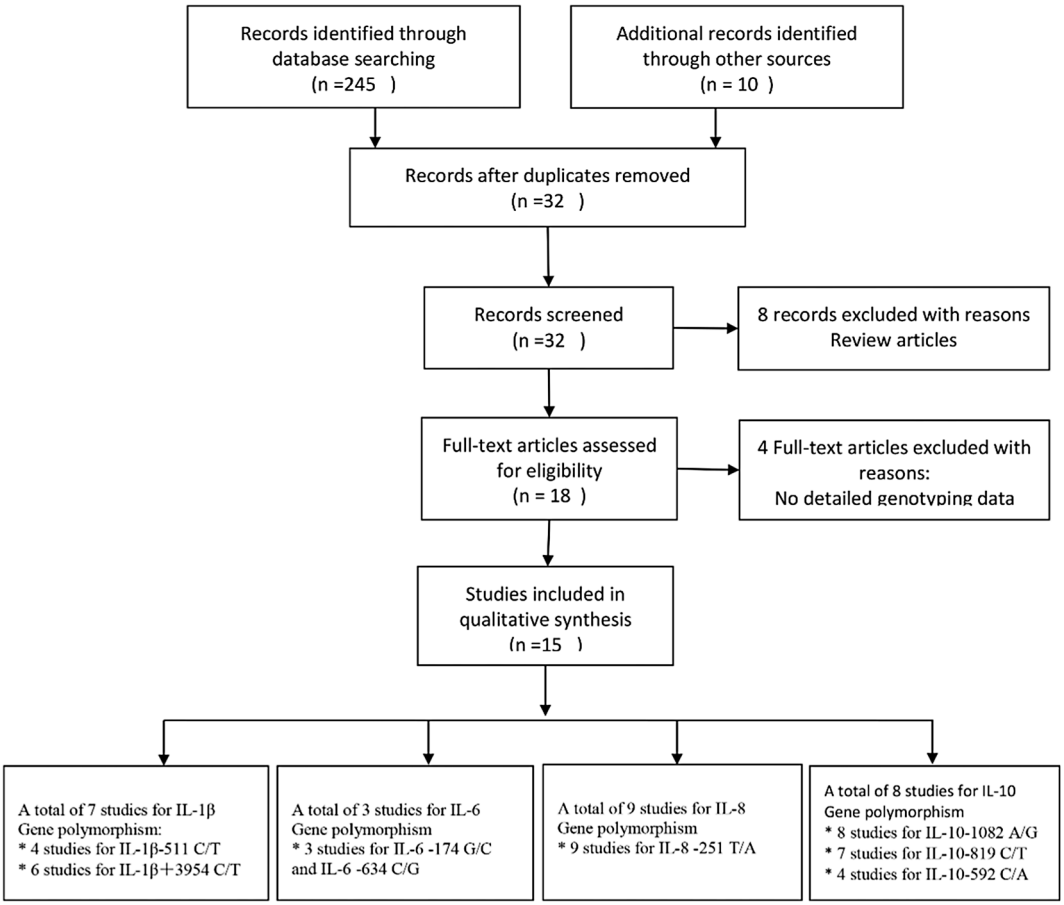

Fig. 1. Flow chart of the selection of studies.

Table 1
Characteristics of studies included in this meta-analysis (IL-1β).

Position	First author	Year	Ethnicity	Source of controls	case_CC	case_CT	case_TT	Control_CC	Control_CT	Control_TT	P value of HWE
IL-1β -511 C/T	Chen	2007	Asian	Population based	13	46	15	22	40	16	0.78
	Li	2015	Asian	Population based	50	81	45	56	78	42	0.15
	Chi	2015	Asian	Population based	82	125	65	93	123	56	0.19
	Bao	2015	Asian	Population based	105	155	75	118	149	68	0.09
IL-1β + 3954 C/T	Zhang	2005	Asian	Population based	189	26	0	98	18	0	0.36
	Li	2015	Asian	Population based	121	41	14	133	34	9	0.002
	Bao	2015	Asian	Population based	212	99	23	222	95	18	0.07
	Chi	2015	Asian	Population based	167	78	27	183	75	14	0.09
	Powell	2001	European	Population based	118	66	6	57	40	5	0.55
	Smithies	2000	European	Population based	72	40	2	115	53	2	0.13

Table 2
Characteristics of studies included in this meta-analysis (IL-6).

Position	First author	Year	Ethnicity	Source of controls	case_GG	case_GC	case_CC	control_GG	control_GC	control_CC	P value of HWE
IL-6-174 G/C	Chen	2007	Asian	Population based	72	2	0	77	1	0	0.95
	Bao	2015	Asian	Population based	202	109	24	213	106	16	0.55
	Chi	2015	Asian	Population based	159	94	19	173	88	11	0.96
IL-6-634 G/C	Chen	2007	Asian	Population based	38	36	0	46	32	0	0.02
	Bao	2015	Asian	Population based	163	126	46	176	122	37	0.02
	Chi	2015	Asian	Population based	136	106	30	149	101	23	0.32

Table 3
Characteristics of studies included in this meta-analysis (IL-8).

Position	First author	Year	Ethnicity	Source of controls	case_TT	case_TA	case_AA	control_TT	control_TA	control_AA	P value of HWE
IL-8-251 T/A	Hofner	2006	European	Population based	23	45	24	82	84	34	0.12
	Li	2007	Asian	Population based	31	32	8	38	30	2	0.17
	Chen	2008	Asian	Population based	41	54	6	43	64	13	0.13
	Cao	2010	Asian	Population based	48	56	15	115	110	11	0.02
	Tang	2010	Asian	Population based	54	54	12	72	56	4	0.07
	Anilir	2017	Asian	Population based	61	93	22	31	59	10	0.01
	Li	2015	Asian	Population based	37	77	62	53	74	49	0.03
	Bao	2015	Asian	Population based	84	144	106	108	139	88	0.002
	Yang	2016	Asian	Population based	73	136	106	121	194	61	0.25

Table 4
Characteristics of studies included in this meta-analysis (IL-10).

Position	First author	Year	Ethnicity	Source of controls	case_AA	case_AG	case_GG	control_AA	control_AG	control_GG	P value of HWE
IL-10-1082 A/G											
	Zhang	2005	Asian	Population based	156	59	0	79	37	0	0.04
	Sargen	2000	European	Population based							N/A
	Li	2015	asina	Population based	84	67	25	91	65	20	0.11
	Bao	2015	Asian	Population based	163	123	49	176	118	41	0.003
	Cai	2015	Asian	Population based	92	113	35	116	105	19	0.47
	Jia	2015	Asian	Population based	106	114	35	128	108	19	0.56
	Jiang	2015	Asian	Population based	69	85	28	130	112	20	0.53
	Jiang	2016	Asian	Population based	78	93	29	103	75	22	0.14
IL-10-819 C/T					case_CC	case_CT	case_TT	control_CC	control_CT	control_TT	
	Sargen	2000	European	Population based							N/A
	Li	2015	asina	Population based	59	80	37	66	76	34	0.15
	Bao	2015	Asian	Population based	115	149	71	123	144	68	0.03
	Cai	2015	Asian	Population based	85	109	46	93	106	41	0.2
	Jia	2015	Asian	Population based	108	112	35	116	105	34	0.19
	Jiang	2015	Asian	Population based	63	84	35	99	112	51	0.06
	Jiang	2016	Asian	Population based	67	90	43	73	86	41	0.09
IL-10-592 C/A					case_CC	case_CA	case_AA	control_CC	control_CA	control_AA	
	Sargen	2000	European	Population based							N/A
	Cai	2015	Asian	Population based	87	117	36	95	113	32	0.86
	Jia	2015	Asian	Population based	95	119	41	106	114	35	0.62
	Jiang	2016	Asian	Population based	71	98	31	77	94	29	0.97

Table 5
Meta-analysis results of association between ILs polymorphism and AP.

Position	Allelic model		Recessive model		Dominant model		Homozygote model	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
IL-1b + 3954 C/T	1.155(0.997–1.338)	0.054	1.473(1.011–2.146)	0.044	1.125(0.946–1.338)	0.184	1.516(1.036–2.219)	0.032
IL-1b -511 C/T	1.143(0.999–1.308)	0.051	1.135(0.904–1.426)	0.275	1.230(1.002–1.509)	0.047	1.277(0.982–1.662)	0.068
IL-6-174 G/C	1.222(1.009–1.479)	0.041	1.638(0.998–2.687)	0.051	1.197(0.951–1.507)	0.126	1.702(1.030–2.813)	0.038
IL-6-634 C/G	1.184(1.003–1.397)	0.046	1.308(0.913–1.873)	0.143	1.201(0.971–1.486)	0.091	1.376(0.947–2.000)	0.094
IL-8-251 T/A	1.355(1.162–1.580)	< 0.001	1.728(1.249–2.392)	0.001	1.396 (1.201–1.623)	< 0.001	1.992(1.400–2.836)	< 0.001
IL-10-1082 A/G	1.291(1.165–1.432)	< 0.001	1.584(1.260–1.993)	< 0.001	1.330(1.154–1.532)	< 0.001	1.787(1.405–2.274)	< 0.001
IL-10-819 C/T	1.078(0.973–1.194)	0.152	1.065(0.881–1.286)	0.516	1.142(0.980–1.330)	0.089	1.143(0.927–1.410)	0.21
IL-10-592 C/A	1.078(0.936–1.242)	0.295	1.148(0.853–1.546)	0.363	1.165(0.938–1.446)	0.168	1.236(0.895–1.708)	0.199

2.4. Statistical analysis

Whole statistical analyses were calculated with STATA software (Stata Corp, USA). If *P* is lower than 0.05, *P* value was considered as statistically significant. The strength of the association between ILs polymorphism and the risk of AP were measured by odds ratio (OR) with 95% confidence intervals (95% CI). Allelic (X vs. x), homozygote (XX vs. xx), recessive (XX vs. Xx + xx) and dominant (XX + Xx vs. xx) genetic models were assessed by pooled ORs and 95% CI respectively. If needed, subgroup analyses would be conducted to explore the influence of confounding factors such as ethnicities, source of control and so on. Heterogeneity test was performed by chi-square based Q test and Thompson and Higgins classification index (I^2) to check the statistical heterogeneity[20]. The four intervals consist of low heterogeneity (0–25%), moderate heterogeneity (25–50%), large heterogeneity (50–75%) and extreme heterogeneity (75–100%). Significant heterogeneity was drawn when $I^2 > 50\%$. The fixed-effects model (Mantel-Haenszel's method) and random-effects model (DerSimonian and Laird's

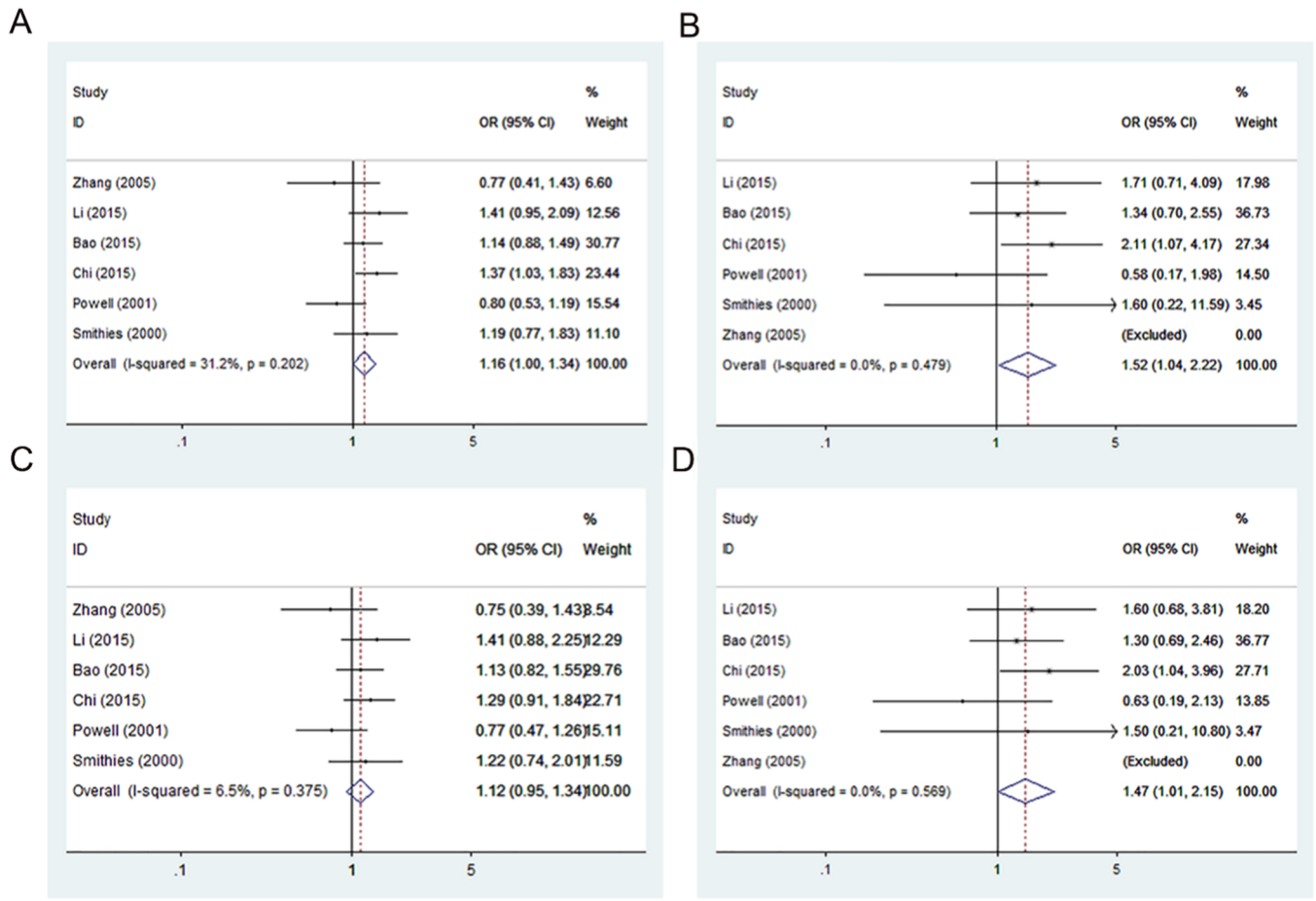

Fig. 2. Forest plots of IL-1β + 3954 C/T polymorphism and AP risk in different genetic model. A. Allele model (T vs. C); B. Dominant model (TC/TT vs. CC); C. Recessive model (TT vs. TC/TT); D. Homozygote model (TT vs. CC).

method) (DerSimonian and Laird, 1986) were performed to pool the data based on I^2 values. Fixed effects model was used when $I^2 < 50\%$, or else, the random-effects model was applied [21].

The results consistency was assessed by sensitivity test (based on Leave-one-out method), publication bias was detected with Egger's linear regression test and Begg's funnel plot and a $P < 0.05$ mean significance [22].

3. Results

3.1. Characteristics of eligible studies

Screening flow program of exclusion and inclusion was demonstrated using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram and shown in Fig. 1. A total of 255 potential eligible studies were identified by literature searching. After reviewing the titles, 223 articles were excluded because of duplication of publications. The remaining 32 articles seemed eligible. Of these, additional 18 articles were ruled out through abstract and full text reading, leaving 15 articles to be selected in our meta-analysis [23–37]. 4 studies included IL-1β-511 C/T. IL-1β + 3954 C/T was involved in 6 studies. IL-6-174 G/C and IL-6-634 C/G was included in 3 studies. 9 studies were related to IL-8-251 T/A. 8 studies for IL-10-1082 A/G, 7 studies for IL-10-819 C/T, and 4 studies for IL-10-92 C/A. Characteristics of each included studies and HWE/Chi-square values of the selected polymorphisms can be seen in Table 1–4. Meta-analysis results of association between ILs polymorphism and AP were showed in Table 5.

3.2. Association between the ILs polymorphism and risk of AP

3.2.1. IL-1β

The heterogeneity analysis indicated no heterogeneity in the analyzed genetic models among the studies of IL-1β. The fixed effects model showed a significant association between IL and 1β + 3954 C/T polymorphism and AP risk in Recessive model (TT vs. TC/TT: OR = 1.473, 95% CI: 1.011-2.146), Homozygote model (TT vs. CC: OR = 1.516, 95% CI: 1.036–2.219), and Dominant model (TC/CC vs. CC: OR = 1.230, 95% CI: 1.002-1.509) of IL-1β-511 C/T. Other genetic models of IL-1β + 3954 C/T (allelic model T vs. C: OR = 1.155, 95% CI: 0.997-1.338 and dominant model TC/CC vs. TT: OR = 1.125, 95% CI: 0.946-1.338) and IL-1β-511 C/T (Recessive model TT vs. TC/TT: OR = 1.135, 95% CI: 0.904-1.426, Homozygote model TT vs. CC: OR = 1.277, 95% CI: 0.982-1.662, allelic model T vs. C: OR = 1.143, 95% CI: 0.999-1.308) revealed no significant association with AP risk (Figs. 2, 3).

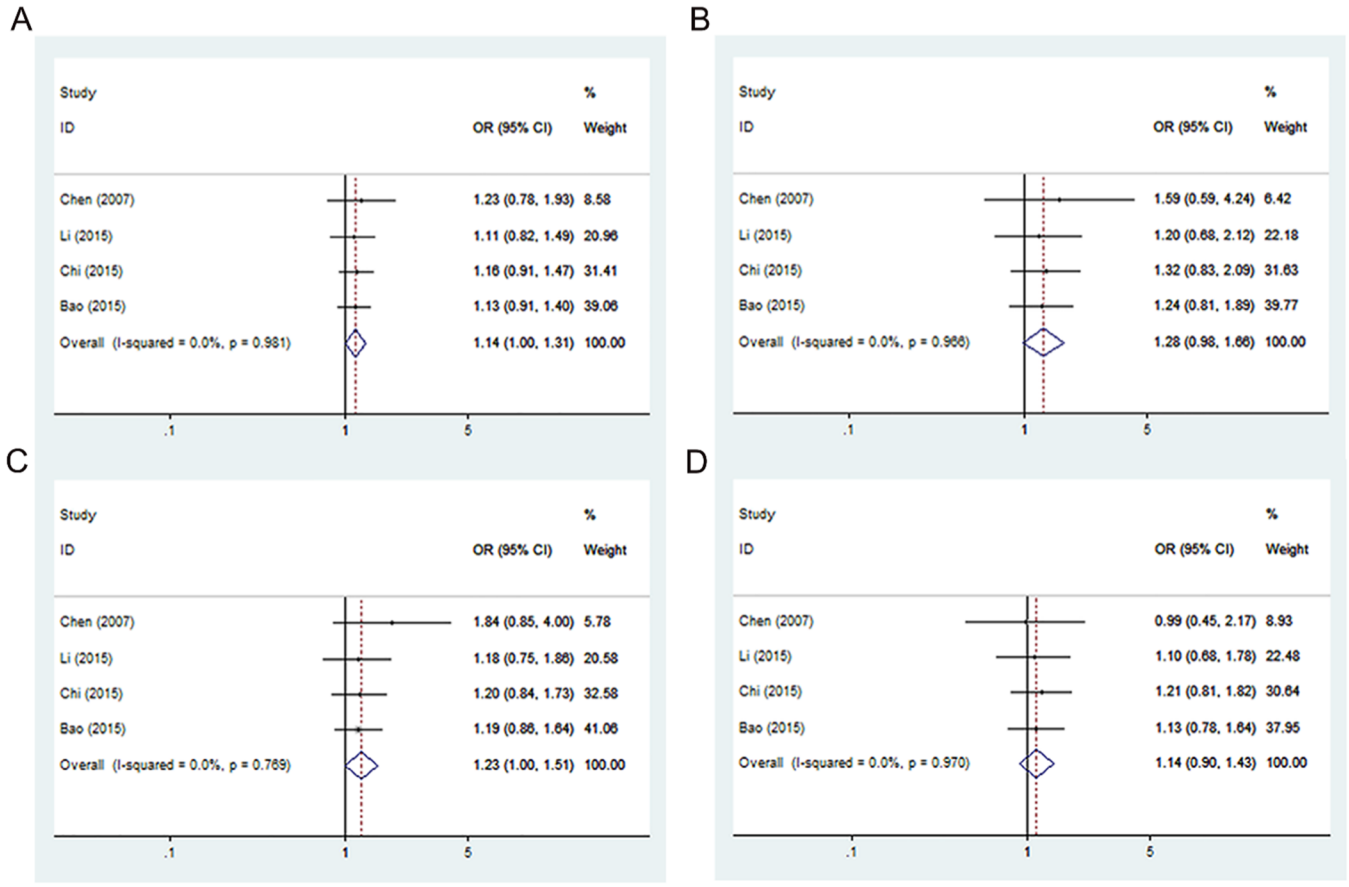

Fig. 3. Forest plots of IL-1β-511 C/T polymorphism and AP risk in different genetic model. A. Allele model (T vs. C); B. Dominant model (TC/TT vs. CC); C. Recessive model (TT vs. TC/TT); D. Homozygote model (TT vs. CC).

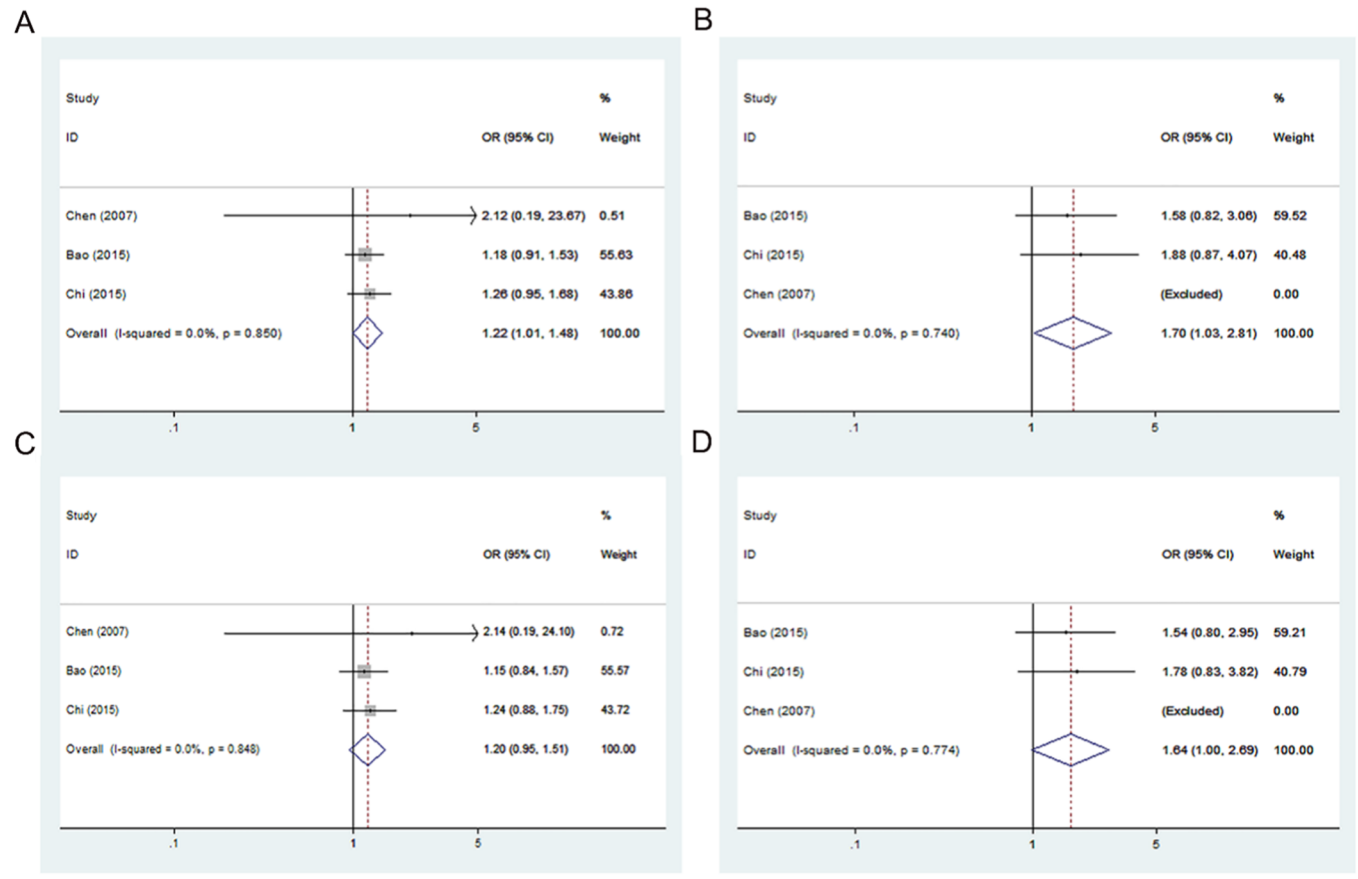

Fig. 4. Forest plots of IL-6–174 G/C polymorphism and AP risk in different genetic model. A. Allele model (C vs. G); B. Dominant model (GC/CC vs. GG); C. Recessive model (CC vs. GC/CC); D. Homozygote model (CC vs. GG).

3.2.2. Il-6

Three articles were selected to investigate the association of IL-6-174 G/C and IL-6-634 C/G polymorphism and AP risk. No significant heterogeneity was shown in all genetic models of IL-6-174 G/C and IL-6-634 C/G. A significantly increased risk of AP was obversed in allelic model (C vs. G: OR = 1.222, 95% CI: 1.009-1.479) and homozygote model (CC vs.GG: OR = 1.702, 95% CI: 1.030-2.813) of IL-6-174 G/C polymorphism, and in allelic model(G vs. C: OR = 1.184, 95% CI: 1.003-1.397) of IL-6-634 C/G polymorphism. No significant association was found in recessive model (CC vs. GC/CC: OR = 1.638, 95% CI: 0.998-2.687) and dominant model (GC/CC vs. AA: OR = 1.197, 95% CI: 0.951-1.507) of IL-6-174 G/C polymorphism, and in recessive model (GG vs. GC/GG: OR = 1.308, 95% CI: 0.913-1.873), dominant model (GC/GG vs. CC: OR = 1.201, 95% CI: 0.971-1.486) and homozygote model (GG vs. CC: OR = 1.376, 95% CI: 0.947-2.000) of IL-6-634 C/G polymorphism(Figs. 4, 5).

3.2.3. Il-8

Nine articles exploring the association between IL and 8-251 T/A polymorphism and AP risk were enrolled in the study. Because there was significant heterogeneity in allelic model (A vs. T: $P_Q = 0.035$, $I_2 = 51.7\%$), homozygote model (AA vs. TT: $P_Q = 0.027$, $I_2 = 53.8\%$) and recessive model (AA vs. AT/AA: $P_Q = 0.015$, $I_2 = 58.0\%$), but not in the dominant model (AT/AA vs. TT: $P_Q = 0.252$, $I_2 = 21.4\%$), random effects model was used for allelic model, homozygote model and recessive model and fixed effects model was chosen to analyze the data of dominant model. Pooled data indicated that significant association was identified in homozygote model (AA vs. TT: OR = 1.992, 95% CI: 1.400–2.836), dominant model (AT/AA vs. TT: OR = 1.396, 95% CI: 1.201-1.623), allelic model (A vs. T: OR = 1.355, 95% CI: 1.162–1.580) and recessive model (AA vs. AT/AA: OR = 1.728, 95% CI: 1.249–2.392) (Fig. 6).

3.2.4. Il-10

We firstly analyzed the association between IL and 10-1082 A/G polymorphism and the AP risk. No heterogeneity was identified by Q-test and *I*-squared statistic in all genetic model, therefore fixed effects model was implemented. Overall, results revealed that significant association was found between IL and 10-1082 A/G polymorphism and AP risk in all of the genetic models(GG vs. AA: OR = 1.787, 95% CI: 1.405–2.274; AG/GG vs. AA: OR = 1.330, 95% CI: 1.154-1.532; GG vs. AG/GG: OR = 1.584, 95% CI: 1.260–1.993; G vs. A: OR = 1.291, 95% CI: 1.165-1.432). (Fig. 7)

Seven enrolled studies of IL-10-819 C/T polymorphism was combined. Based on heterogeneity (I^2), the fixed effects model was used. Pool results showed no significant association between IL and 10-819

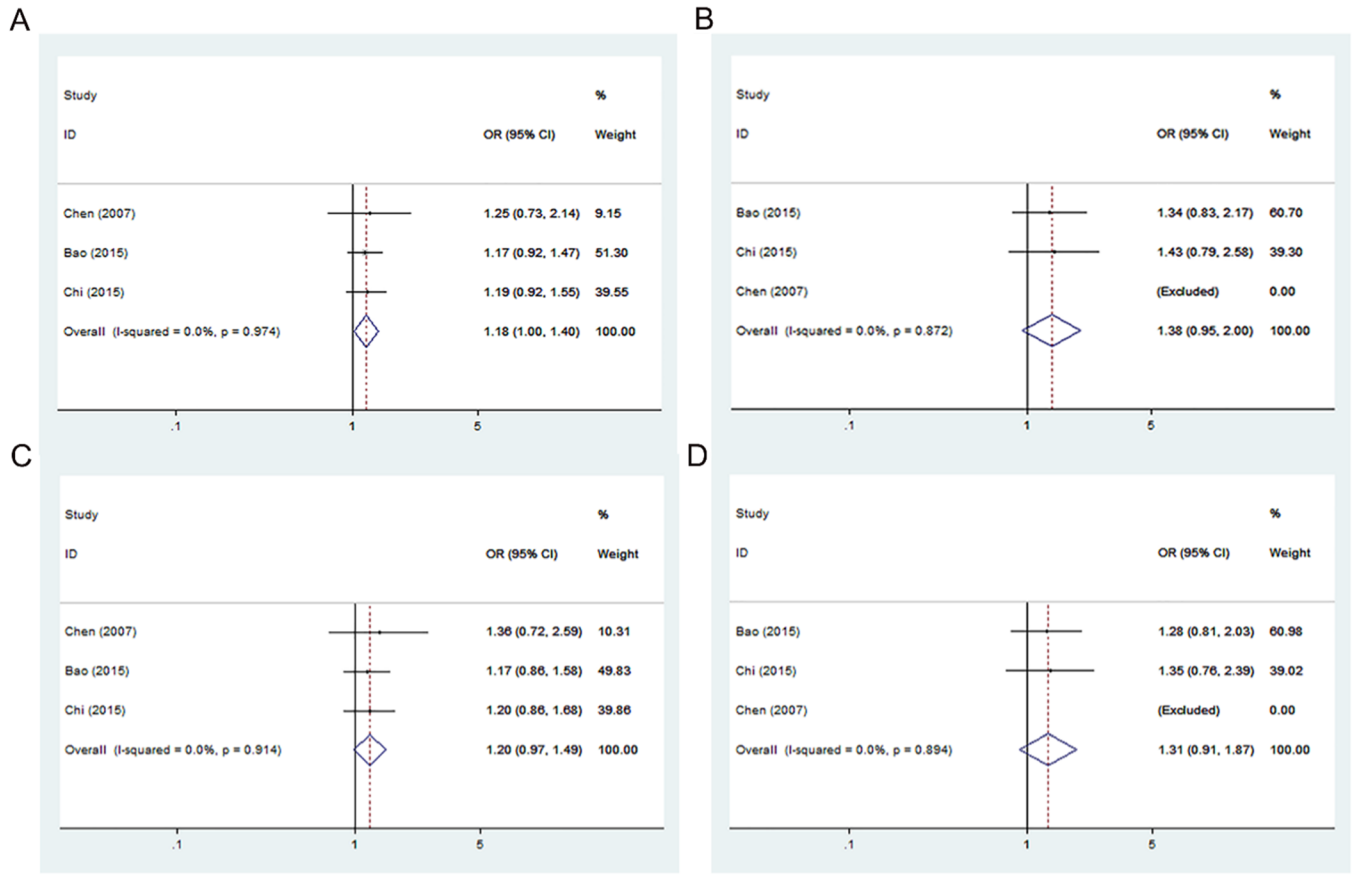

Fig. 5. Forest plots of IL-6-634 C/G polymorphism and AP risk in different genetic model. A. Allele model (G vs. C); B. Dominant model (GC/GG vs. CC); C. Recessive model (GG vs. GC/GG); D. Homozygote model (GG vs. CC).

C/T polymorphism and AP risk in four genetic models (TT vs. CC: OR = 1.143, 95% CI: 0.927-1.410; CT/TT vs. CC: OR = 1.142, 95% CI: 0.980-1.330; TT vs. TC/TT: OR = 1.065; 95% CI: 0.881-1.286; T vs. C: OR = 1.078, 95% CI: 0.973-1.194).(Fig. S1)

For IL-10-592 C/A polymorphism, data from four articles was pooled. The fixed effects model was used and results indicated no significant association in any genetic model (AA vs. CC: OR = 1.236, 95% CI: 0.895–1.708; AC/AA vs. CC: OR = 1.165, 95% CI: 0.938-1.446; AA vs. AC/AA: OR = 1.148; 95% CI: 0.853–1.546; A vs. C: OR = 1.078, 95% CI: 0.936–1.242) (Fig. S2)

3.3. Sensitivity analysis

Sensitivity analyses was conducted to reveal the effect of individual data on the outcomes by sequential removal of individual studies in each genetic model. There was no single study which affected the pooled ORs significantly. This result might validated the robustness of the current results (Figure not shown).

3.4. Publication bias

Possible publication bias of enrolled articles was tested by Begg's funnel plot and Egger's test. No publication bias for the association between IL and 8-251 T/A (Fig. S3) and IL-10-1082 A/G (Fig. S4) polymorphism and AP risk was identified. We didn't perform Begg's funnel plot and Egger's test for other ILs due to the limited number of included studies.

4. Discussion

This meta-analysis enrolled 15 studies with 3371 AP cases to assess the relationship between polymorphism of ILs(IL-1β, IL-6, IL-8, IL-10) and AP risk. Compared with a previous meta-analysis [38], new evidence was found for the association between ILs polymorphism and AP risk.

AP is an inflammatory disorder of pancreas, and can cause serious dysfunction and failure of other organs [39]. Inflammatory cytokines are major signaling molecules and play a vital role in the onset and development in the inflammatory processes of AP. ILs, an important member of inflammatory cytokines including IL-1β, IL-6, IL-8, IL-10 *etc.*, play a key role in promoting progression of AP. It has been reported that polymorphism of ILs could regulate the activation of macrophages, monocytes, and lymphocytes [40]. Several studies have investigated the relationship between ILs polymorphism and AP risk.

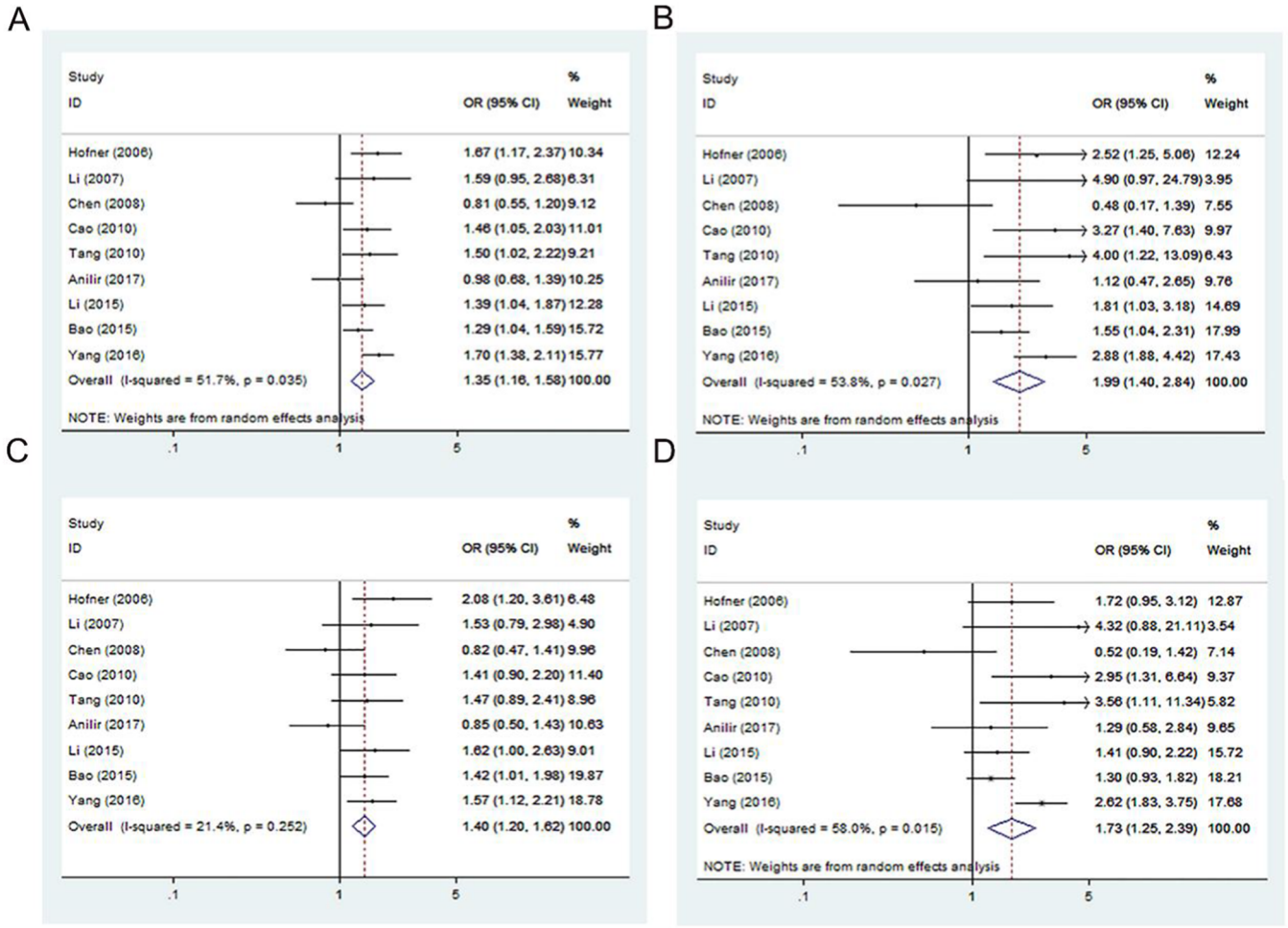

Fig. 6. Forest plots of IL-8-251 T/A polymorphism and AP risk in different genetic model. A. Allele model (A vs. T); B. Dominant model (AT/AA vs. TT); C. Recessive model (AA vs. AT/AA); D. Homozygote model (AA vs. TT).

However, their conclusions were inconclusive. In this study, we performed a meta analysis and draw a conclusion in which ILs were related to the development of AP. The results revealed significant association with AP risk in IL-1β + 3954 C/T (Recessive model and Homozygote model), IL-1β-511 C/T (Dominant model), IL-6-174 G/C(allelic model and Homozygote model), IL-6-634 C/G(allelic model), IL-10-1082 A/G(allelic model, Homozygote model, allelic model, Dominant model, Recessive model). In addition, combined results indicated that polymorphisms of IL-10-819 C/T and IL-10-592 C/A were not associated with the development of AP in all of the genetic models. Additional eligible articles were investigated, and pooled data confirmed that there was a significant association between IL and 8–251 T/A(allelic model, Homozygote model, Recessive model, Dominant model) and AP risk. Although there was no significant association between IL and 1β-511 C/T(Dominant model, allelic model), IL-1β + 3954 C/T (Recessive model, Homozygote model and allelic model), IL-6-174 G/C (Dominant model, Recessive model), IL-6-634 C/G(Dominant model, Recessive model, Homozygote model), and all genetic models of IL-10-819 C/T, IL-10-592 C/A and AP risk, our results suggested that the evidence supporting the association was increased and tendency started to change. Much more eligible article needed be enrolled for further analyze.

Notably, some limitations should be pointed out and the results should be interpreted with caution. Firstly, the number of articles included in our study is relatively small, which might introduced a series of bias and relatively high heterogeneity. Secondly, insufficient data was taken for subgroup analysis for the heterogeneity in IL-8-251 T/A. Finally, AP as a complex disease was influenced by various factors including genetic and environmental factors, among which the role of SNPs might be limited.

In conclusion, our results indicated that IL-1β-511 C/T, IL-1b + 3954 C/T, IL-8-251 T/A, IL-10-1082 A/G polymorphism are associated with increased risk of AP. What's more, IL-10-819 C/T and IL-10-592 C/A showed insignificant risk. Well designed studies with larger sample sizes and ethnically diversity are needed to validate the results identified in our meta-analysis.

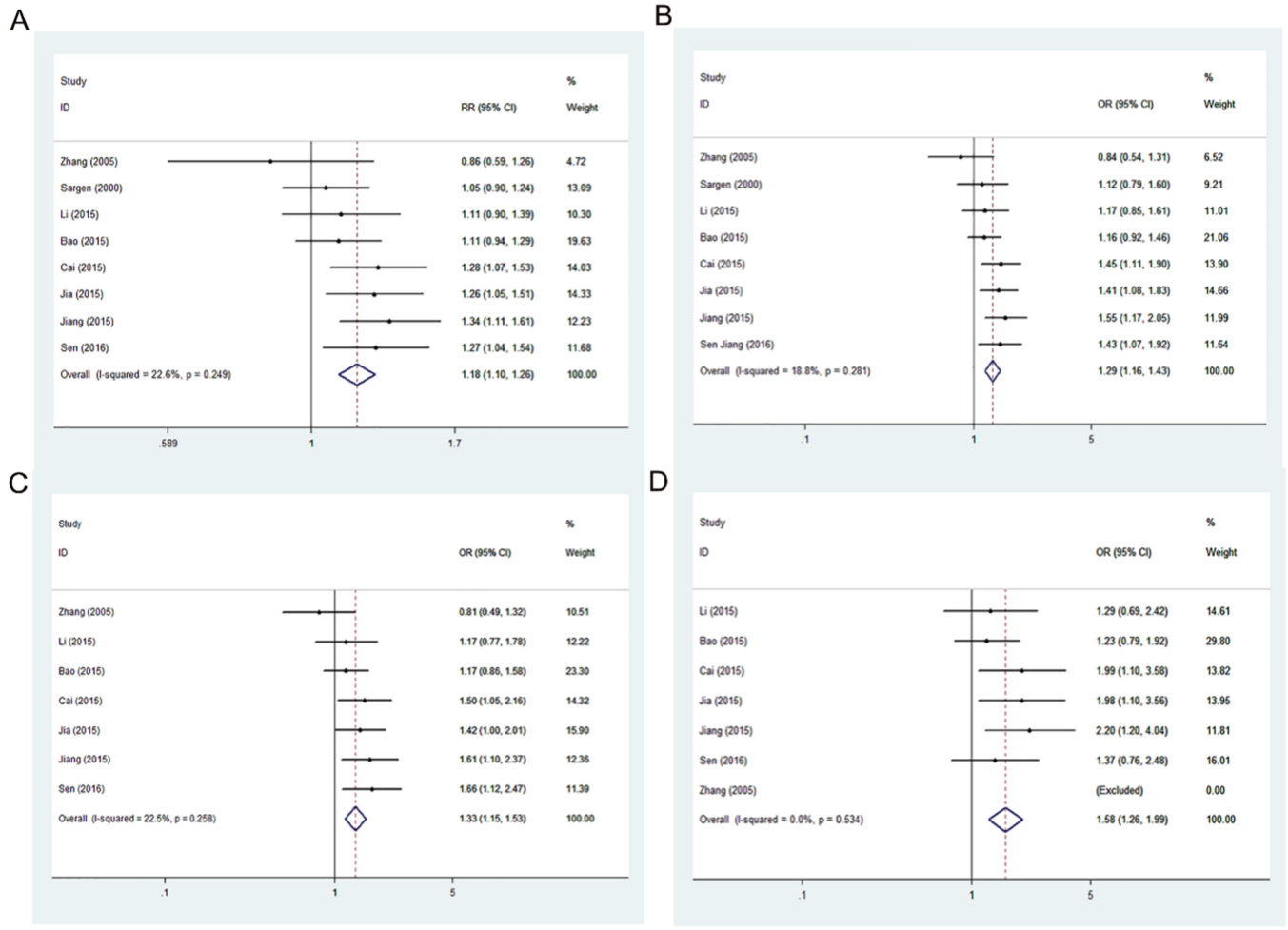

Fig. 7. Forest plots of IL-10-1082 A/G polymorphism and AP risk in different genetic model. A. Allele model (G vs. A); B. Dominant model (AG/GG vs. AA); C. Recessive model (GG vs. AG/GG); D. Homozygote model (GG vs. AA).

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Conflicts of interest

No.

Author contribution statement

LQ and MY conceived and designed the study strategy. TM and SCY were responsible for acquisition of data: statistical analysis and interpretation of data; and drafting or revision of the manuscript. PYP was responsible for reference collection and data management. ZXL wrote the manuscript and prepared the tables and figures. YLD and HDY were responsible for study supervision. All authors reviewed the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2018.12.003.

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