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META-ANALYSIS

Interleukin-17 SNPs and serum levels increase ulcerative colitis risk: A meta-analysis

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Abstract

AIM: To investigate the associations of interleukin-17 (*IL-17*) genetic polymorphisms and serum levels with ulcerative colitis (UC) risk.

METHODS: Relevant articles were identified through a search of the following electronic databases, excluding language restriction: (1) the Cochrane Library Database (Issue 12, 2013); (2) Web of Science (1945-2013); (3) PubMed (1966-2013); (4) CINAHL (1982-2013); (5) EMBASE (1980-2013); and (6) the Chinese Biomedical Database (1982-2013). Meta-analysis was conducted using STATA 12.0 software. Crude odds ratios and standardized mean differences (SMDs) with corresponding 95% confidence intervals (CIs) were calculated. All of the included studies met all of the following five criteria: (1) the study design must be a clinical cohort or a case-control study; (2) the study must relate to the relationship between *IL-17A/F* genetic polymorphisms or serum IL-17 levels and the risk of UC; (3) all patients must meet the diagnostic criteria for UC; (4) the study must provide sufficient information about single nucleotide polymorphism frequencies or serum IL-17 levels; and (5) the genotype distribution of healthy controls must conform to the Hardy-Weinberg equilibrium (HWE). The Newcastle-Ottawa Scale (NOS) criteria were used to assess the methodological quality of the studies. The NOS criteria included three aspects: (1) subject selection: 0-4; (2) comparability of subjects: 0-2; and (3) clinical outcome: 0-3. NOS scores ranged from 0 to 9, with a score $\geqslant$ 7 indicating good quality.

RESULTS: Of the initial 177 articles, only 16 case-control studies met all of the inclusion criteria. A total of 1614 UC patients and 2863 healthy controls were included in this study. Fourteen studies were performed on Asian populations, and two studies on Caucasian populations. Results of the meta-analysis revealed that *IL-17A* and *IL-17F* genetic polymorphisms potentially increased UC risk under both allele and dominant models ($P < 0.001$ for all). The results also showed that UC patients had higher serum IL-17 levels than healthy controls (SMD = 5.95, 95%CI: 4.25-7.65, $P < 0.001$). Furthermore, serum IL-17 levels significantly correlated with the severity of UC (moderate *vs* mild: SMD = 2.59, 95%CI: 0.03-5.16, $P < 0.05$; severe *vs* mild: SMD = 7.09, 95%CI: 3.96-10.23, $P < 0.001$; severe *vs* moderate: SMD = 5.84, 95%CI: 5.09-6.59, $P < 0.001$). The NOS score was $\geqslant$ 5 for all of the included studies. Based on the sensitivity analysis, no single study influenced the overall pooled estimates. Neither the Begger's funnel plots nor Egger's test displayed strong statistical evidence for publication bias (*IL-17A/F* genetic polymorphisms: $t = -2.60$, $P = 0.019$; serum IL-17 levels: $t = -1.54$, $P = 0.141$).

CONCLUSION: The findings strongly suggest that *IL-17A/F* genetic polymorphisms and serum IL-17 levels contribute to the development and progression of UC.

Key words: Ulcerative colitis; Interleukin-17; Polymorphism; Serum; Meta-analysis

Core tip: This is the first meta-analysis focusing on the associations of interleukin-17 (*IL-17*) genetic polymorphisms and serum IL-17 levels with the risk of ulcerative colitis. The results of the study indicate that both *IL-17A/F* genetic polymorphisms and serum IL-17 levels may play a role in the development and progression of ulcerative colitis.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic relapsing intestinal inflammatory disorder of the colon. Although the disease has a variable distribution, it is limited to the distal bowel[1]. Clinically, UC affects the colon and rectum, involving the innermost mucosal lining and manifesting as a continuous area of inflammation without unaffected mucosal segments[2]. The most common symptoms of UC are abdominal discomfort and blood or pus present in diarrhea[3]. Although UC can occur in people of any age, it usually develops between the ages of 15 and 30 and is less common between the ages of 60 and 80[3]. It is estimated that the highest annual incidence of UC was 24.3 per 100000 people per year in Europe. Other parts of the world fared better with 6.3 per 100000 person-years in Asia and the Middle East, and 19.2 per 100000 person-years in North America[4]. In general, UC is a disease caused by a complex interaction of environmental, genetic, and immunoregulatory factors[5,6]. Environmental risk factors, such as infectious agents, drugs, diets, and stress, are crucial to UC susceptibility[7]. A dysregulated T helper (Th) cell response has been suggested to play a major role in causing chronic gut inflammation[8,9]. Furthermore, recent studies have also suggested that interleukin-17 (*IL-17*) genetic polymorphisms and serum levels may be associated with an increased risk of UC[10,11].

The *IL-17* family is generally regarded as a bridge system connecting innate and adaptive immunity[12]. Six related ligands (IL-17 A-F) and five receptors have been identified in this family[13]. Among them, IL-17A and IL-17F are the most researched cytokines responsible for the pathogenic activity of Th17 cells[14,15]. The most important role of IL-17 is induction and mediation of proinflammatory responses[16]. Previous studies have demonstrated a strong and independent association between IL-17 and the pathogenesis of multiple T-cell-mediated autoimmune diseases including rheumatoid arthritis, multiple sclerosis, and inflammatory bowel diseases[17,18]. In short, the dynamic equilibrium between pro-inflammatory and anti-inflammatory cytokines may be decisive in normal cells[19]. Although IL-17 stimulates the expression and production of proinflammatory cytokines in human cells, it may disrupt this equilibrium. As a result, proinflammatory cytokines are overexpressed, leading to facilitation of the pathologic lesions of the colonic mucosa, which is inevitably related to the severity of gut inflammation[20,21]. It has been hypothesized that *IL-17* is significantly associated with the development and progression of UC[22], with the majority of the studies focusing on the role of *IL-17A* and *IL-17F*[23]. Recently, however, some studies have also suggested that elevated serum IL-17 levels are associated with an increased UC risk[14,24]. Moreover, several studies on single nucleotide polymorphisms have suggested that there is a connection between UC susceptibility and the *IL-17* gene cluster[10,25]. Genetic polymorphisms in *IL-17A* and *IL-17F* may influence the expression of IL-17 *via* CXC chemokine induction and subsequent neutrophil recruitment, thus affecting UC susceptibility[26]. Recent evidence has proposed that genetic polymorphisms in *IL-17A* and *IL-17F* and serum IL-17 levels may be involved in the incidence of UC[14,24]. However, the results of these studies have been contradictory. Therefore, the aim of this meta-analysis was to evaluate the associations of *IL-17A/F* genetic polymorphisms and serum IL-17 levels with UC risk.

MATERIALS AND METHODS

Literature search

Without language restriction, the following databases were searched through August 1, 2013: PubMed, Web of Science, Google Scholar, Cochrane Library, CISCOM, CINAHL, EBSCO, and Chinese Biomedical Database. The following keywords and Medical Subject Headings terms were used for the search: ("SNP" or "mutation" or "genetic polymorphism" or "variation" or "polymorphism" or "single nucleotide polymorphism" or "variant") and ("ulcerative colitis" or "ulcer colitis" or "ulcerative colonitis" or "ulcer enterocolitis" or "UC") and ("interleukin-17" or "interleukin-17A" or "IL-17A" or "interleukin-17F" or "IL-17F"). A manual search was also performed to identify other potential articles.

Selection criteria

Studies had to meet all five of the following criteria in order to be included in the analysis: (1) the study design must be a clinical cohort or a case-control study; (2) the study must relate to the relationship between *IL-17A/F* genetic polymorphisms or serum IL-17 levels and risk of UC; (3) all patients must meet the UC diagnostic criteria; (4) the study must provide sufficient information about SNP frequencies or serum IL-17 levels; and (5) the genotype distribution of healthy controls must conform to the Hardy-Weinberg equilibrium (HWE). If a study did not

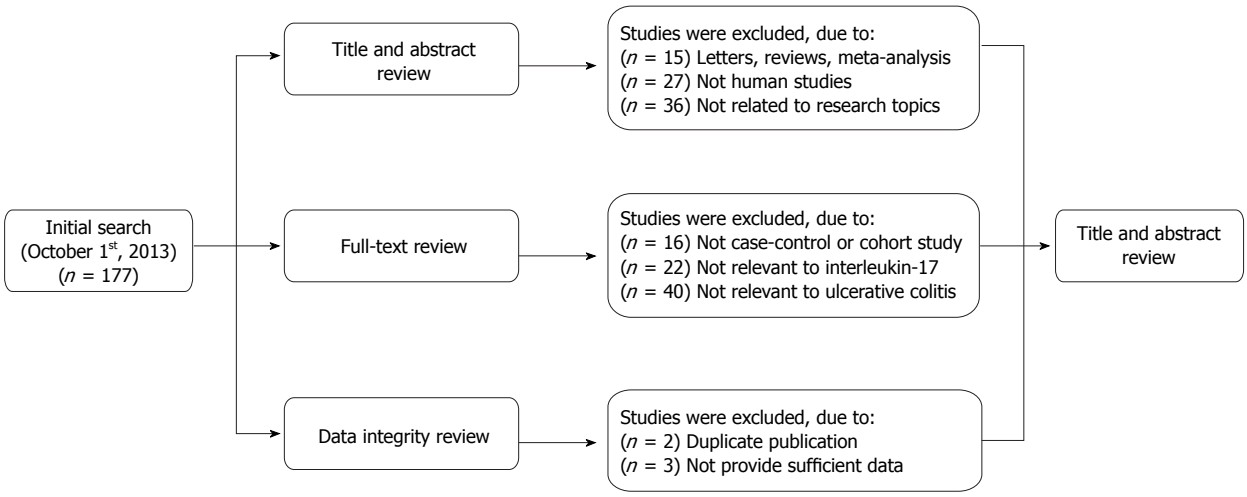


Figure 1 Flow chart of the literature search and study selection.

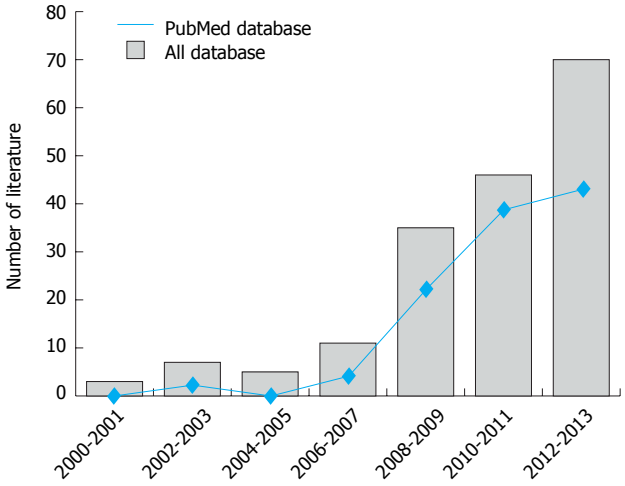


Figure 2 Distribution of the number of topic-related literatures in the electronic databases.

meet all of the inclusion criteria, it was excluded. In cases where authors published several studies using the same subjects, either the most recent or the largest sample size publication was included.

Data extraction

Two researchers systematically extracted all relevant data from all included studies using a standardized form, including: (1) publication language; (2) publication year; (3) first author's surname; (4) geographic location of the study; (5) study design; (6) sample size; (7) source of the subjects; (8) allele frequencies; (9) tissue sample source; (10) SNP genotyping method; (11) evidence of HWE in healthy controls; and (12) serum IL-17 levels.

Study quality assessment

Methodological qualities of the studies were independently assessed by two researchers according to the Newcastle-Ottawa Scale (NOS)[27]. The NOS included three criteria: (1) subject selection: 0-4; (2) comparability of subjects: 0-2; and (3) clinical outcome: 0-3. NOS scores ranged from 0 to 9, with a score $\geqslant 7$ indicating good quality.

Statistical analysis

The STATA version 12.0 software (Stata Corp, College Station, TX, United States) was used for analyses. Crude odds ratios (ORs) or standardized mean differences (SMDs), with their corresponding 95% confidence intervals (CIs), were used to evaluate the specified relationships. The Z test was used to estimate the statistical significance of the pooled data. The Cochran's Q-statistic and I^2 test were used to evaluate inter-study heterogeneity[28]. If the Q-test showed a $P < 0.05$ or I^2 test exhibited $> 50\%$, indicating the presence of significant heterogeneity, the random effects model was used; otherwise, the fixed-effects model was used. Subgroup and meta-regression analyses were performed to investigate potential sources of heterogeneity. Sensitivity analysis was performed to evaluate the influence of a single study on the overall estimate. Begger's funnel plots and Egger's linear regression tests were conducted to investigate the possibility of publication bias[29]. A P-value < 0.05 was considered statistically significant.

RESULTS

Characteristics of the included studies

An initial literature search identified 177 potential articles. Subsequent review of the titles and abstracts excluded 78 articles. Examination of the remaining studies' full texts and data integrity led to the exclusion of an additional 83 articles. Finally, 16 case-control studies, which met all the inclusion criteria, were included in the meta-analysis[10,14,26,30-42]. The study selection process is shown in Figure 1. The distribution of the number of topic-related publications in electronic databases for the last decade is shown in Figure 2. A total of 1614 UC patients and 2863 healthy controls were included in this meta-analysis. Overall, 14 studies were conducted on Asian populations

Table 1 Baseline characteristics and methodological quality of the included studies focused on *IL-17A/F* genetic polymorphisms

Ref.	Year	Country	Ethnicity	Number		Gender (M/F)		Age (yr)		Genotyping method	Gene type	NOS score
				Case	Control	Case	Control	Case	Control			
Yu *et al*[42]	2012	China	Asian	270	268	130/140	136/132	47.4 ± 14.1	47.1 ± 12.9	PCR-LDR	*IL-17A/F*	8
Hayashi *et al*[10]	2012	Japan	Asian	202	475	114/88	241/234	41.1 ± 14.3	59.4 ± 12.7	PCR-SSCP	*IL-17A*	8
Kim *et al*[41]	2011	South Korea	Asian	268	258	-	-	-	-	Direct sequencing	*IL-17A*	6
Chen[40]	2009	China	Asian	148	373	83/65	233/140	38.4 ± 12.9	37.9 ± 16.1	PCR-RFLP	*IL-17F*	8
Seiderer *et al*[26]	2008	Germany	Caucasian	216	967	110/106	609/358	42.6 ± 14.8	47.4 ± 11.3	PCR-RFLP	*IL-17F*	8
Arisawa *et al*[39]	2008	Japan	Asian	111	248	56/55	133/115	39.0 ± 14.3	46.6 ± 18.4	PCR-SSCP	*IL-17A/F*	7

F: Female; LDR: Ligase detection reaction; M: Male; NOS: Newcastle-Ottawa Scale; PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism; SSCP: Single-strand conformation polymorphism.

Table 2 Baseline characteristics and methodological quality of the included studies focused on serum interleukin-17 levels

Ref.	Year	Country	Ethnicity	Number		Gender (M/F)		Age (yr)		Detection method	NOS score
				Case	Control	Case	Control	Case	Control		
Ohman *et al*[14]	2013	China	Asian	99	10	70/29	4/6	32	48	ELISA	6
Liu[38]	2013	China	Asian	20	30	-	-	-	-	ELISA	7
Lin *et al*[37]	2012	China	Asian	50	50	22/28	25/25	38.0 ± 6.0	37.0 ± 5.0	ELISA	7
Chen[36]	2012	China	Asian	24	20	10/14	7/13	37.6 ± 9.4	38.9 ± 9.9	ELISA	7
Zhen *et al*[35]	2011	China	Asian	54	30	30/24	19/11	40.9 ± 8.3	50.6 ± 5.3	ELISA	7
Luo *et al*[34]	2011	China	Asian	24	30	14/10	17/13	-	-	ELISA	8
Xin *et al*[33]	2010	China	Asian	29	26	18/11	13/13	41.4 ± 9.6	32.0 ± 11.2	ELISA	6
He *et al*[32]	2010	China	Asian	25	10	12/13	-	-	-	ELISA	8
Rovedatti *et al*[31]	2009	United Kingdom	Caucasian	34	38	-	-	35.6 (14-53)	-	ELISA	8
Liang *et al*[30]	2005	China	Asian	40	30	28/12	19/11	41.5 ± 12.0	41.3 ± 12.0	ELISA	8

F: Female; M: Male; NOS: Newcastle-Ottawa Scale.

and two studies on Caucasian populations. Genotyping methods included polymerase chain reaction (PCR)-single-strand conformation polymorphism assays, PCR-ligase detection reactions, direct sequencing, and PCR-restriction fragment length polymorphism assays. The control genotype frequencies were all found to be within the HWE. Serum IL-17 levels were determined by ELISA assays in all of the studies. The NOS scores were ⩾ 5 for all the included studies. Tables 1 and 2 contain summaries of the study characteristics and methodological quality on *IL-17A/F* genetic polymorphisms and serum IL-17 levels, respectively.

Quantitative data synthesis

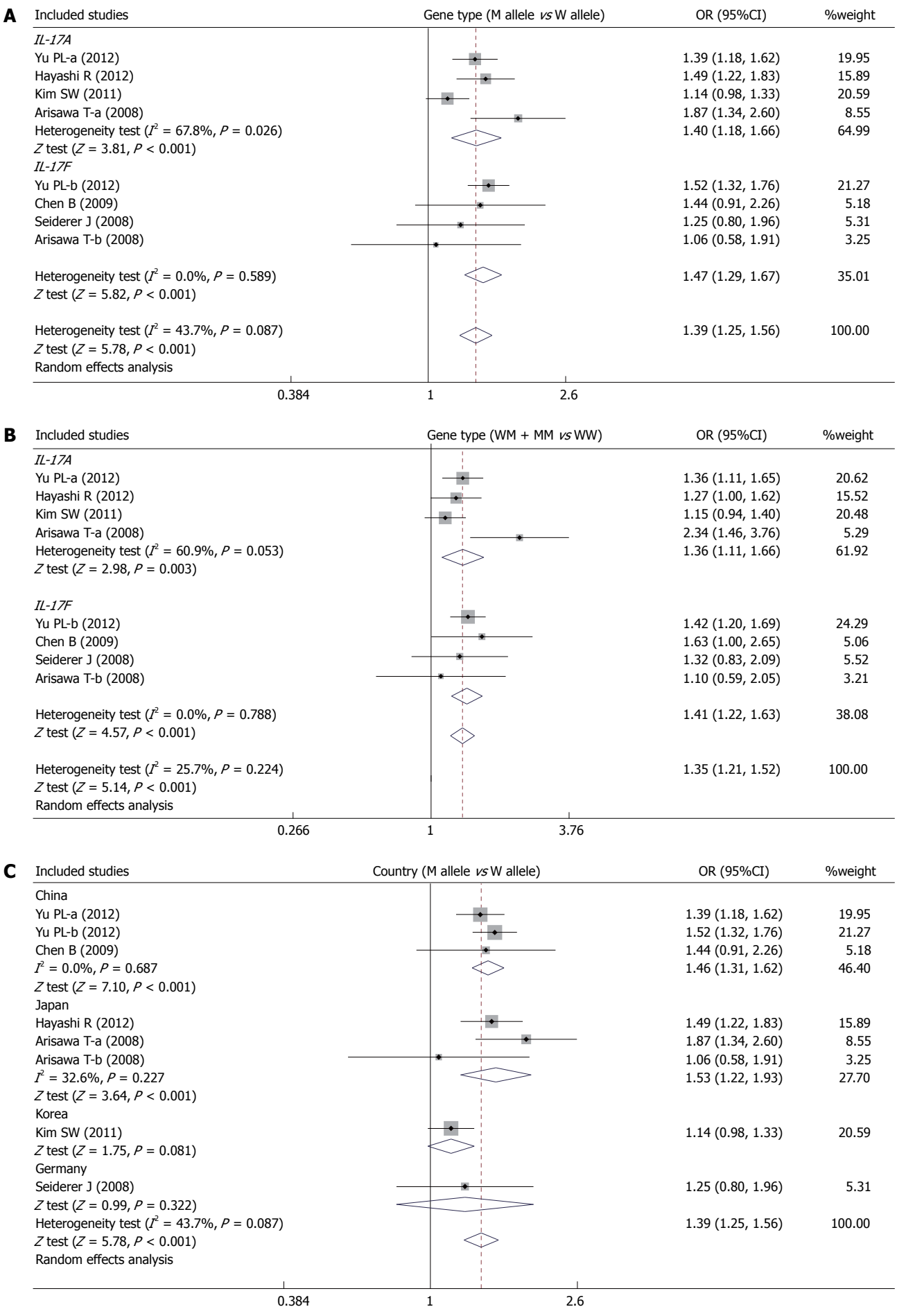
Six studies focused on the relationships between the *IL-17A/F* genetic polymorphisms and susceptibility to UC[10,26,39-42]. The random effects model was used due to the existence of significant heterogeneity among studies. The meta-analysis shows strong correlations between *IL-17A* (allele model: OR = 1.40, 95%CI: 1.18-1.66, $P < 0.001$; dominant model: OR = 1.36, 95%CI: 1.11-1.66, $P < 0.01$) and *IL-17F* (allele model: OR = 1.47, 95%CI: 1.29-1.67, $P < 0.001$; dominant model: OR = 1.41, 95%CI: 1.22-1.63, $P < 0.001$) genetic polymorphisms and an increase in UC risk (Figure 3A and B). A subgroup analysis by country suggests that there are associations between the *IL-17A/F* genetic polymorphisms and an increased risk of UC in Chinese and Japanese populations (Figure 3C and D), but not in Korean and German populations.

Ten studies reported differences in serum IL-17 levels between UC patients and healthy controls. Due to obvious heterogeneity, the random effects model was used to analyze the data. Our results demonstrate that UC patients have higher serum IL-17 levels than healthy controls (SMD = 5.95, 95%CI: 4.25-7.65, $P < 0.001$) (Figure 4A). Furthermore, serum IL-17 levels showed significant correlations with the severity of UC (moderate *vs* mild: SMD = 2.59, 95%CI: 0.03-5.16, $P < 0.05$; severe *vs* mild: SMD = 7.09, 95%CI: 3.96-10.23, $P < 0.001$; severe *vs* moderate: SMD = 5.84, 95%CI: 5.09-6.59, $P < 0.001$) (Figure 4B-D).

The sensitivity analysis results suggest that no single study influenced the overall pooled estimates (Figure 5). There was no evidence of obvious asymmetry in the Begger's funnel plots (Figure 6). An Egger's test also did not display strong statistical evidence for publication bias (*IL-17A/F* genetic polymorphisms: $t = -2.60$, $P = 0.019$; IL-17 serum levels: $t = -1.54$, $P = 0.141$).

DISCUSSION

IL-17, a relatively recently described cytokine, has been shown to act as a bridge between adaptive and innate


A
Included studies
Gene type (M allele vs W allele)
OR (95%CI)
%weight
IL-17A
Yu PL-a (2012) 1.39 (1.18, 1.62) 19.95
Hayashi R (2012) 1.49 (1.22, 1.83) 15.89
Kim SW (2011) 1.14 (0.98, 1.33) 20.59
Arisawa T-a (2008) 1.87 (1.34, 2.60) 8.55
Heterogeneity test (I^2 = 67.8%, P = 0.026) 1.40 (1.18, 1.66) 64.99
Z test (Z = 3.81, P < 0.001)
IL-17F
Yu PL-b (2012) 1.52 (1.32, 1.76) 21.27
Chen B (2009) 1.44 (0.91, 2.26) 5.18
Seiderer J (2008) 1.25 (0.80, 1.96) 5.31
Arisawa T-b (2008) 1.06 (0.58, 1.91) 3.25
Heterogeneity test (I^2 = 0.0%, P = 0.589) 1.47 (1.29, 1.67) 35.01
Z test (Z = 5.82, P < 0.001)
Heterogeneity test (I^2 = 43.7%, P = 0.087) 1.39 (1.25, 1.56) 100.00
Z test (Z = 5.78, P < 0.001)
Random effects analysis
0.384
1
2.6
B
Included studies
Gene type (WM + MM vs WW)
OR (95%CI)
%weight
IL-17A
Yu PL-a (2012) 1.36 (1.11, 1.65) 20.62
Hayashi R (2012) 1.27 (1.00, 1.62) 15.52
Kim SW (2011) 1.15 (0.94, 1.40) 20.48
Arisawa T-a (2008) 2.34 (1.46, 3.76) 5.29
Heterogeneity test (I^2 = 60.9%, P = 0.053) 1.36 (1.11, 1.66) 61.92
Z test (Z = 2.98, P = 0.003)
IL-17F
Yu PL-b (2012) 1.42 (1.20, 1.69) 24.29
Chen B (2009) 1.63 (1.00, 2.65) 5.06
Seiderer J (2008) 1.32 (0.83, 2.09) 5.52
Arisawa T-b (2008) 1.10 (0.59, 2.05) 3.21
Heterogeneity test (I^2 = 0.0%, P = 0.788) 1.41 (1.22, 1.63) 38.08
Z test (Z = 4.57, P < 0.001)
Heterogeneity test (I^2 = 25.7%, P = 0.224) 1.35 (1.21, 1.52) 100.00
Z test (Z = 5.14, P < 0.001)
Random effects analysis
0.266
1
3.76
C
Included studies
Country (M allele vs W allele)
OR (95%CI)
%weight
China
Yu PL-a (2012) 1.39 (1.18, 1.62) 19.95
Yu PL-b (2012) 1.52 (1.32, 1.76) 21.27
Chen B (2009) 1.44 (0.91, 2.26) 5.18
I^2 = 0.0%, P = 0.687 1.46 (1.31, 1.62) 46.40
Z test (Z = 7.10, P < 0.001)
Japan
Hayashi R (2012) 1.49 (1.22, 1.83) 15.89
Arisawa T-a (2008) 1.87 (1.34, 2.60) 8.55
Arisawa T-b (2008) 1.06 (0.58, 1.91) 3.25
I^2 = 32.6%, P = 0.227 1.53 (1.22, 1.93) 27.70
Z test (Z = 3.64, P < 0.001)
Korea
Kim SW (2011) 1.14 (0.98, 1.33) 20.59
Z test (Z = 1.75, P = 0.081)
Germany
Seiderer J (2008) 1.25 (0.80, 1.96) 5.31
Z test (Z = 0.99, P = 0.322)
Heterogeneity test (I^2 = 43.7%, P = 0.087) 1.39 (1.25, 1.56) 100.00
Z test (Z = 5.78, P < 0.001)
Random effects analysis
0.384
1
2.6

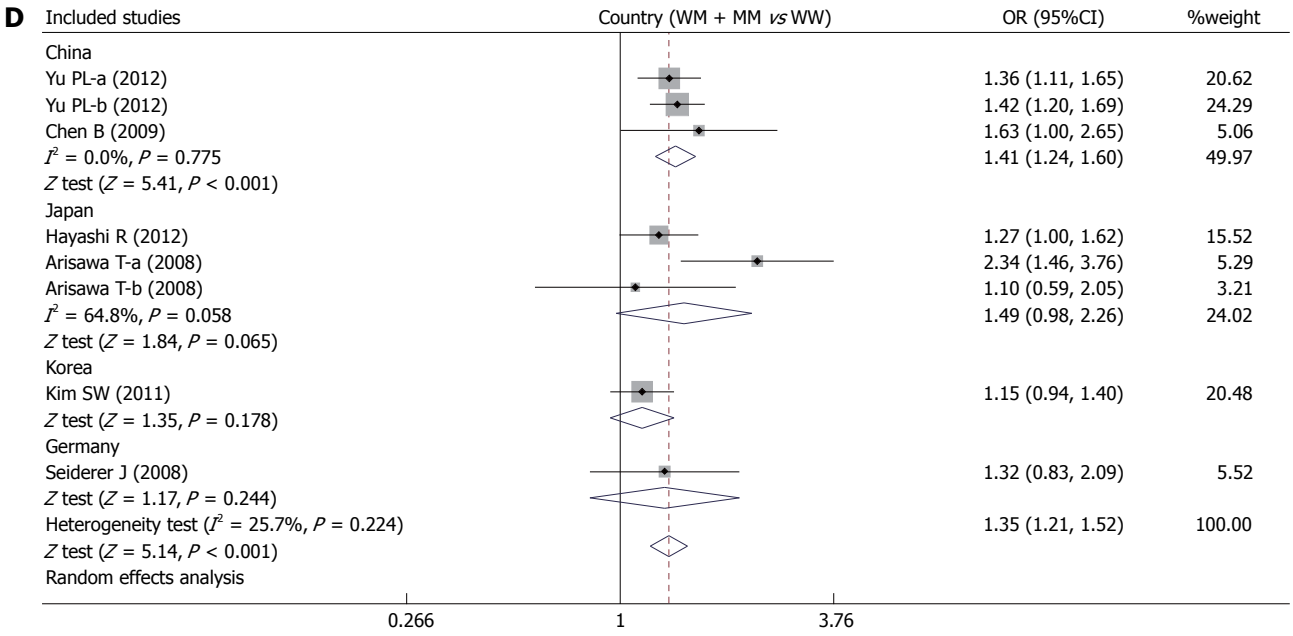


Figure 3 Forest plots of the relationship between *IL-17A/F* genetic polymorphisms and ulcerative colitis risk under the allele and dominant models.

immune systems[43]. Generally, IL-17 functions as a pro-inflammatory cytokine, which induces destruction of the pathogen's cellular matrix upon invasion of the immune system by extracellular pathogens[44]. Six members of the IL-17 family have been identified, including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F[45]. Of these, IL-17A and IL-17F, responsible for the pathogenic activity of Th17 cells, have been widely investigated. Recent studies have shown a potentially important role between *IL-17* polymorphisms and the risk of UC[39,41]. UC, an inflammatory disorder of the gastrointestinal tract, is a result of the dysregulation of the immunologic response to microbial flora in intestinal lumen[31]. IL-17 may stimulate cytokine and chemokine production in endothelial cells *via* macrophage activation, thereby leading to neutrophil recruitment and inflammation[46]. Consequently, IL-17 has been presumed to be a pleiotropic cytokine in an autocrine loop of the mucosal immune system during UC pathogenesis[14]. Several investigations have shown that IL-17 increased intercellular adhesion molecule-1 cell surface expression and upregulated the production of nitric oxide. Proinflammatory activities and effects of IL-17 on adhesion molecules suggest its importance in UC[47,48]. As members of the IL-17 family, IL-17A and IL-17F share similar functions, especially in terms of their ability to induce chemokine expression, which is important in neutrophil recruitment and activation. Consequently, IL-17A and IL-17F may also significantly correlate with the risk of UC[44,49].

The human *IL-17* gene was mapped to chromosome 2q31[50]. Several studies have indicated that the *IL-17A* G197A (rs2275913)[39] and *IL-17F* 7488 A>G (rs763780)[40] alleles, as well as serum IL-17 levels[24,51], are significantly linked to the development of UC. However, contradictory conclusions on the exact role of *IL-17* gene polymorphisms and expression in UC exist[52,53]. Potential explanations for the inconsistent results include ethnic differences, the various gene areas examined, and small sample sizes used in the studies. Thus, this meta-analysis aimed to provide a more comprehensive and reliable conclusion regarding the associations of *IL-17* gene polymorphisms and serum IL-17 levels with the risk of UC.

The results of this meta-analysis show that polymorphisms in both the *IL-17A* (G197A) and *IL-17F* (7488T/C) genes are associated with an increased incidence of UC and suggest that these polymorphisms may be significantly involved in the development of UC. Although the mechanism has yet to be identified, mutations in *IL-17A* and *IL-17F* may affect their activation and pro-inflammatory functions, which are necessary for the response to immune system invasion, resulting in cellular matrix destruction, colonic injuries, and thereby increasing susceptibility to UC[25,41]. Consistent with our study, Hayashi *et al*[10] have reported a significantly higher G197A (*IL-17A*) allele frequency in UC patients than in healthy controls, suggesting an increased risk of developing UC with homozygosity. A study conducted by Arisawa *et al*[39] revealed that both G197A (*IL-17A*) and 7488 A>G (*IL-17F*) alleles were independently and significantly associated with susceptibility to and pathophysiologic features of UC.

Additionally, IL-17 serum levels were significantly correlated with the severity of UC, suggesting serum IL-17 might be closely related to the inflammatory progress of this disease. A reasonable explanation for this correlation may be that *IL-17* mutations alter the stability of a larger number of related pro-inflammatory cytokines secreted into the serum of UC patients[54]. Consistent with these findings, Ajduković *et al*[47] revealed that the median serum

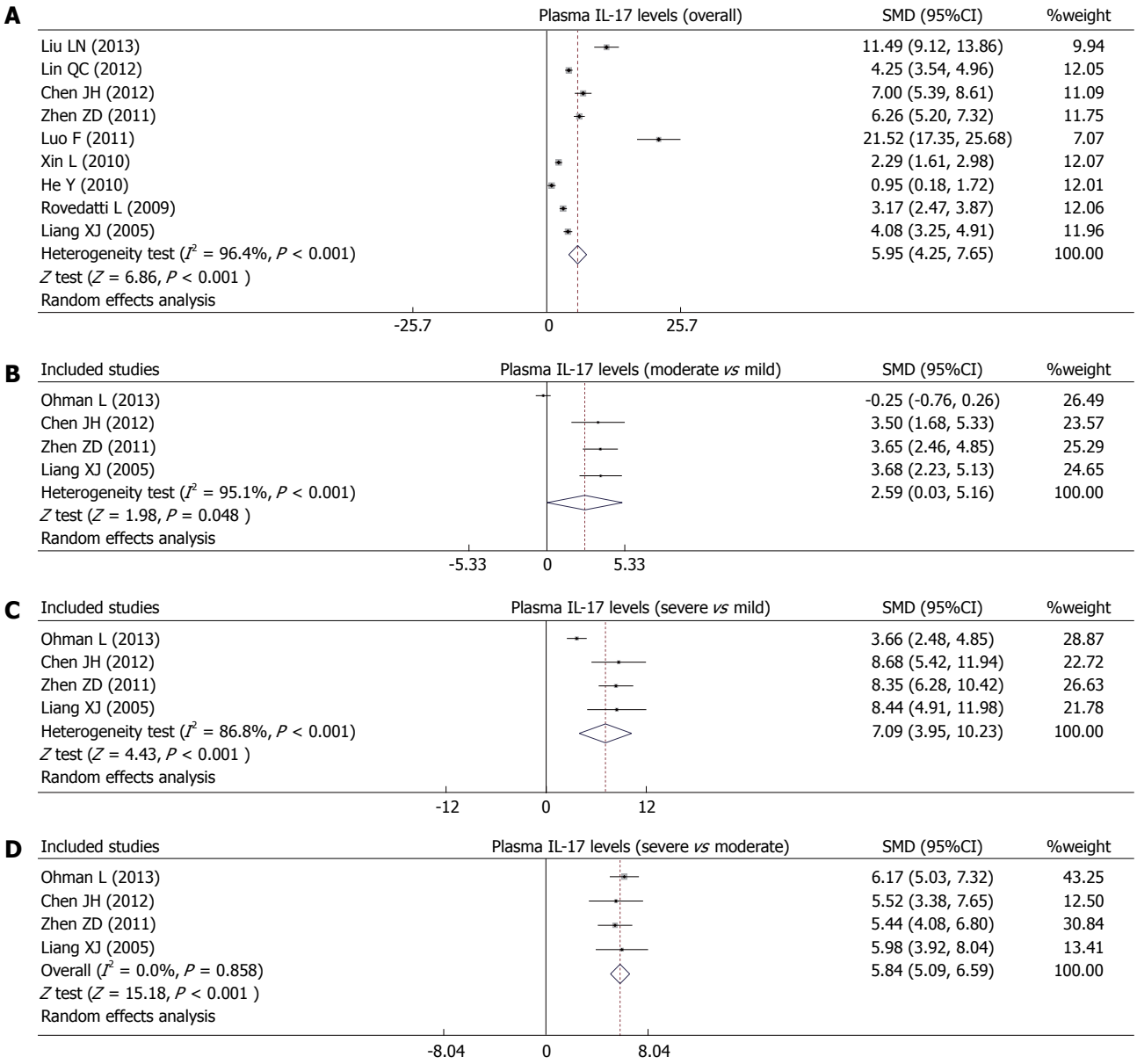
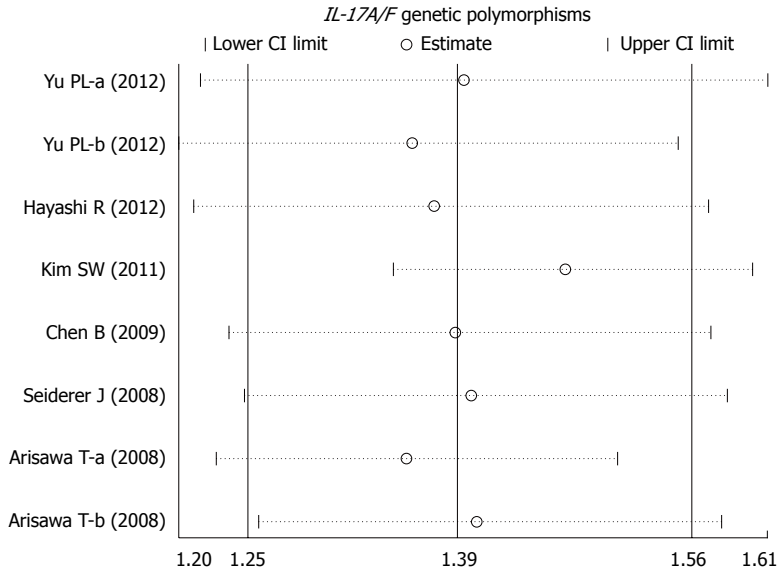


Figure 4 Forest plots of the relationship between serum interleukin-17 levels and ulcerative colitis risk under the allele and dominant models.



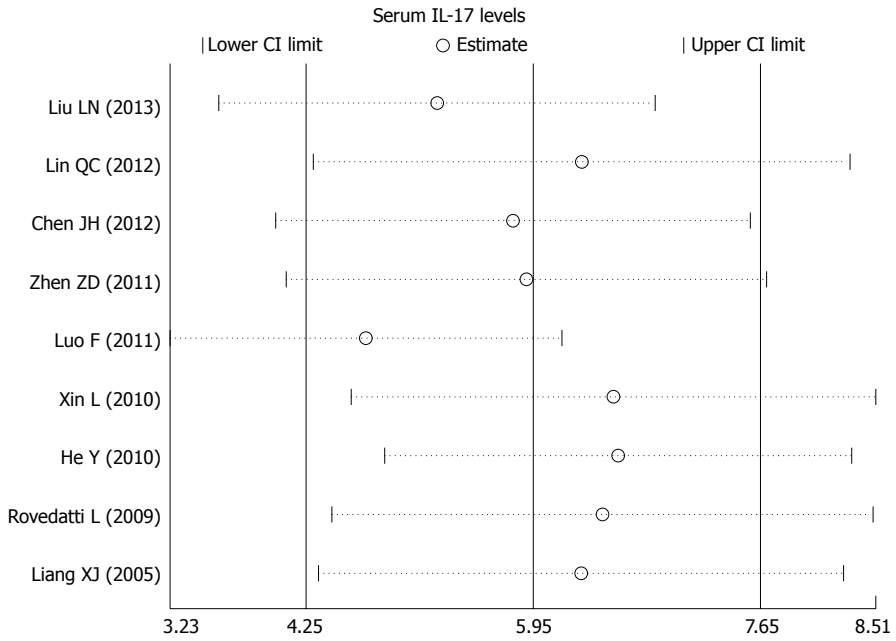


Figure 5 Sensitivity analyses of the summary odds ratio coefficients for the associations of interleukin-17/F polymorphisms and serum interleukin-17 levels with susceptibility to ulcerative colitis. Results were computed by omitting each study in turn. Meta-analysis random effects estimates (exponential form) were used. The two ends of the dotted lines represent the 95%CI.

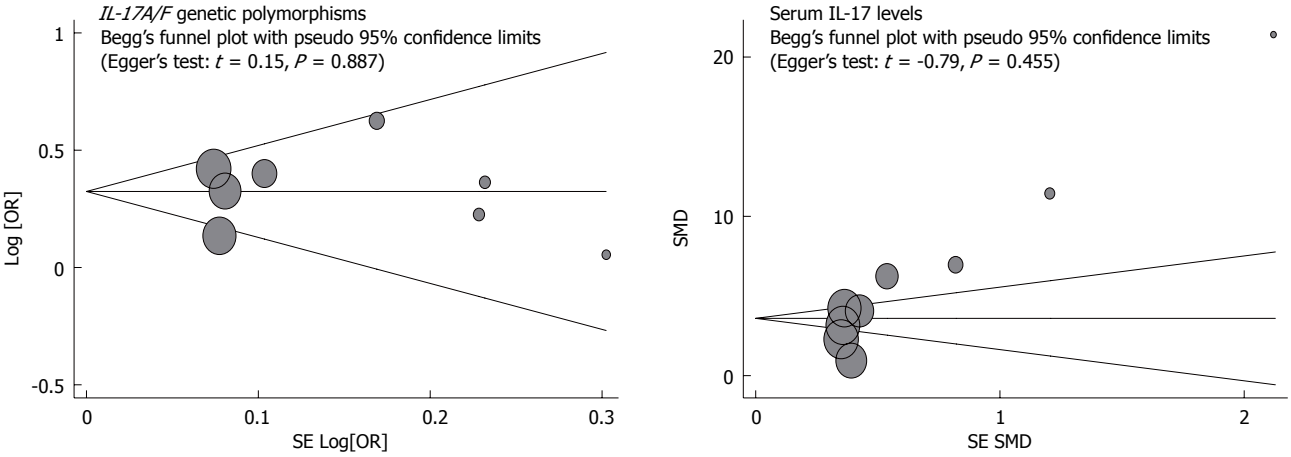


Figure 6 Begger's funnel plot of publication biases on the associations of interleukin-17/F polymorphisms and serum interleukin-17 levels with susceptibility to ulcerative colitis. Each point represents a separate study for the indicated association. Log (OR) refers to the natural logarithm of the odds ratio; Horizontal line indicates the mean magnitude of the effect. IL-17: Interleukin-17.

IL-17 concentration in patients with UC was significantly higher than that in controls. Ohman *et al*[14] also found that serum IL-17 levels in treatment-naive UC patients, measured at the onset of the disease, reflected the clinical disease severity, and thus, might be a valuable tool in the clinical management of newly diagnosed UC patients. Despite the relatively small sample sizes in the present study, a subgroup analysis by country suggests that *IL-17A/F* genetic polymorphisms are associated with an increased risk of UC in Chinese and Japanese populations, but not in Korean and German populations. Taken together, the findings are partially consistent with previous studies, which suggested that *IL-17A* and *IL-17F* gene polymorphisms, as well as serum IL-17 levels, contribute to an individual's susceptibility to UC and may be useful biomarkers in the detection and clinical management of UC.

As the first meta-analysis on the association of *IL-17* genetic polymorphisms and serum IL-17 levels with the risk of UC, our study has some limitations. First, the results lacked sufficient statistical power to assess associations between IL-17 and UC risk due to a relatively small sample size. In addition, a meta-analysis is a retrospective study that may lead to subject selection bias. Third, this meta-analysis failed to obtain the original data of included studies, potentially limiting further clinical assessment of importance of *IL-17* genetic polymorphisms and serum IL-17 levels in UC. Importantly, the inclusion criteria

of cases and controls were not always well defined in the included studies, thus potentially influencing the results.

In conclusion, the meta-analysis suggests a potential role of *IL-17A/F* polymorphisms and serum IL-17 levels in the development and progression of UC and they can thus potentially be used as biomarkers for early UC detection. However, due to limitations mentioned above, additional detailed studies are still necessary to confirm these findings.

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COMMENTS

Background

Ulcerative colitis (UC), a chronic relapsing intestinal inflammatory disorder of the colon, has a variable distribution, but is limited to the distal bowel. In short, UC is a disease caused by a complex interaction of environmental, genetic, and immunoregulatory factors.

Research frontiers

This is the first meta-analysis focused on the association between interleukin-17 (*IL-17*) genetic polymorphisms and serum IL-17 levels with respect to UC risk.

Innovations and breakthroughs

As the first reported meta-analysis, the results of this study suggest a potentially important role of IL-17A/F polymorphisms and serum IL-17 levels in the development and progression of UC.

Applications

IL-17A/F genetic polymorphisms and serum IL-17 levels could be useful biomarkers for early detection of UC.

Terminology

Crude odds ratios or standardized mean difference, with their 95% confidence intervals, were used to evaluate specified relationships. The *Z* test was used to estimate the statistical significance of pooled statistics. The Cochran's *Q*-statistic and I^2 test were used to evaluate potential heterogeneity among studies.

Peer review

This manuscript describes a meta-analysis of the association of IL-17 genetic polymorphisms and serum levels with UC risk. A significant association between *IL-17A/F* gene polymorphisms and serum IL-17 levels with the risk of UC has been found. This study selected appropriate methods for the literature search, data extraction, and quality assessment of the literature.

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