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Original Article

Association between IL-1β +3954C/T polymorphism and acute coronary syndrome risk: a meta-analysis

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Abstract: Objectives: Numerous studies have shown that the IL-1β +3954C/T polymorphism (rs1143634) is associated with acute coronary syndrome (ACS). However, the results are controversial. Here, meta-analysis was designed to further precisely evaluate the association between IL-1β +3954C/T and ACS. Methods: Relevant studies were searched from electronic databases (Embase, PubMed, Cochrane and Web of Science). Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were utilized with fixed effect model or random effect model. Sensitivity analysis and publication bias are also been presented. Results: Ten eligible studies with 2467 cases and 2416 controls are included. The pooled results showed that the IL-1β +3954C/T was associated with risk of ACS in the allelic comparison (T versus C: OR=1.12, 95% CI 1.01-1.23, I^2=0%, P_H=0.485) and dominant model (TC+TT versus CC: OR=1.14, 95% CI 1.01-1.28, I^2=0%, PH=0.898). Ethnic subgroup analysis showed similar results in Caucasian populations: an allelic comparison (T versus C: OR=1.14, 95% CI 1.03-1.27, I^2=0%, PH=0.698), homozygote model (TT versus CC: OR=1.32, 95% CI 1.02-1.72, I^2=0%, PH=0.689) and dominant model (TC+TT versus CC: OR=1.15, 95% CI 1.01-1.31, I^2=0%, PH=0.865). Similar results were also observed in subgroup analyses of high-quality studies and PCR-RFLP (restriction fragment length polymorphism) data. Conclusions: The meta-analysis suggests that IL-1β +3954C/T is associated with ACS susceptibility, especially among Caucasian populations.

Keywords: Acute coronary syndrome, IL-1β, polymorphism, meta-analysis

Introduction

Acute coronary syndrome (ACS), including unstable angina and non-ST and ST segment elevation myocardial infarction, is a common clinical syndrome of atherosclerotic progression in the coronary plaque [1]. Inflammation plays vital roles in pathogenesis and progression of atherosclerosis leading to ACS [2]. Hansson [3] suggested that local inflammation in the coronary artery wall may be involved in the pathogenesis of ACS. Notably, inflammation seems to influence all stages of atherosclerotic development, such as oxidative injury [4], cell proliferation, and plaque evolution and instability [5, 6].

The pro-inflammatory cytokine interleukin-1 beta (IL-1β) is involved in activating an inflammatory cascade, which could promote atherogenesisby the chemotactic and hemostatic properties of endothelial and smooth muscle cells in the vessel wall [7-10]. IL-1β plays an important role in atherosclerotic inflammation. Expression of IL-1β is elevated in the myocardium early after injury [11, 12]. Kirii [13] reported that IL-1β deficient mice with ApoE gene knockout had reduced atherosclerosis. Many studies show that the serum IL-1β level in ACS patients is significantly higher than in the controls [14, 15]. A single nucleotide polymorphism (SNP) has been determined in exon 5 at position +3954C/T in the IL-1β gene. The T allele of IL-1β +3954C/T is associated with a higher level of IL-1β [16] and the polymorphism resulting in IL-1β overproduction may increase susceptibility to atherosclerosis [17]. Recently, association between IL-1β +3954C/T and ACS has been extensively studied. However, previous literature about the associations between the IL-1β +3954C/T and risk of ACS remain inconsistent [18-27]. Thus, meta-analysis was performed to clarify the association between IL-1β +3954C/T and ACS.

Table 1. Quality evaluation tabulation

Criteria	Score
1. Source of control	
Population-based	3
Hospital-based	2
Blood donors or volunteers	1
No described	0
2. Source of cases	
ACS diagnosed according to acknowledged criteria	1
Mentioned the diagnosed criteria but no specially described	0
3. Hardy-Weinberg equilibrium in controls	
Hardy-Weinberg equilibrium	1
Hardy-Weinberg disequilibrium	0
4. Case-control match	
Gender and age matching	1
Gender and age no matching	0
5. Sample size	
> 300	2
200-300	1
< 200	0
6. Genotyping methods	
Detecting samples by different methods	2
Detecting samples by the same method	1
No describing the genotyping methods	0

Materials and methods

Search strategy

A systematic search was performed in PubMed, Cochrane, Embase (Excerpta Medica Database) and Web of Science. The systematic search included articles published up to June 15, 2018. The following search terms were combined: "(SNP or SNPs or "single nucleotide polymorphism" or polymorphism or "genetic polymorphism" or mutation or variant or variation)", "("acute coronary syndrome" or ACS or "myocardial infarction" or "unstable angina" or "ischemic heart disease" or "coronary disease" or "myocardial ischemia" or "coronary atherosclerosis")" and "(IL-1β or "interleukin-1 beta" or "IL-1 beta" or IL-1B)". Language and publication year were not restricted. Finally, 613 articles were retrieved using the aforementioned terms.

Inclusion and exclusion criteria

Eligible articles conformed to the following inclusion criteria: (i) assessed ACS as the outcome of study; (ii) assessed the association between ACS and IL-1β +3954C/T (rs1143634); (iii) presented genotype data of cases and controls with risk of ACS sufficient to calculate odds ratios (ORs) and 95% confidence interval (CIs); (iv) used a case-control design for human. Exclusion criteria included: (i) deficient genotype frequency; (ii) duplicate literatures; (iii) published as a letter, comment, or review; (iv) evaluated other IL-1β SNPs and not rs1143634; (v) case-only study; (vi) not a human study. Two investigators separately selected potential literature according to these criteria. When divergences appeared, the third investigator made the final decision.

Data extraction

Information from all eligible literature was extracted by two authors independently. The third author handled any divergences until agreement among all authors was unanimous. The following data were collected: name of first author, ethnicity of subjects, Hardy-Winberg equilibrium (HWE), sample size, genotyping method, genotype distributions in cases and controls and the quality of study. Ethnicity was classified as Asian or Caucasian. Requests were sent to corresponding authors for additional data when the primary data could not be obtained from relevant articles.

Quality score assessment

The quality of eligible literature was accessed by two authors separately according to predetermined criteria (**Table 1**) which were adjusted and revised from previous articles [28, 29] and the Newcastle-Ottawa Scale (NOS). The adjusted criteria contained many items, such as the source of controls, the source of cases, case-control matching, sample size, genotyping method and the HWE in controls. Two authors separately graded all included studies and any divergence was assessed by the third author. Scores ranged from zero to ten. A study quality score ≥6 indicated "high quality", while a study quality score < 6 indicated "low quality" [30].

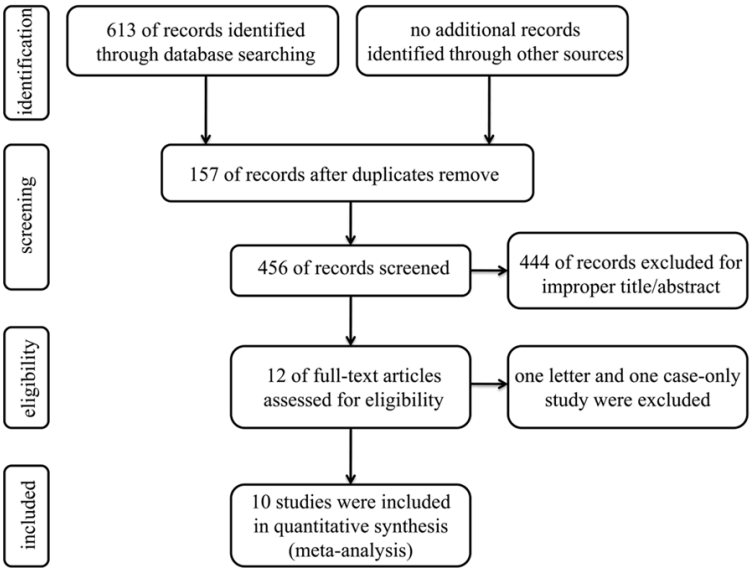

Figure 1. Flow chart of study selection.

Statistical methods

The meta-analysis was performed according to the PRISMA checklist and followed these guidelines [31]. The control group in each included study was assessed for HWE by a Chi-square test, and a group was considered to be in Hardy-Weinberg disequilibrium at $P < 0.05$. ORs and 95% CIs were calculated to assess the strength of the association between IL-1β +3954C/T and ACS risk. Pooled ORs were used to assess allelic comparison (T versus C), a heterozygote model (TC versus CC), a homozygote model (TT versus CC), a dominant model (TT+TC versus CC) and a recessive model (TT versus TC+CC). Heterogeneity was assessed by the Q statistic (significant value at $P < 0.1$) and the I^2 statistic ($I^2 > 50\%$ indicating a significant inconsistency) [32]. When heterogeneity existed, a random effect model (the DerSimonian and Laird method) was used to evaluate the pooled ORs and 95% CIs, otherwise, a fixed effect model (Mantel-Haenszel method) was performed to assess the pooled ORs and 95% CIs. Sensitivity analysis was performed by examining the effect of omitting individual studies. Begg's funnel plot and Egger's test were carried out to check for the publication bias ($P < 0.05$ suggested a significant bias). STATA software (version 12.0; StataCorp, College Station, Texas, USA) was used to perform all the tests in our meta-analysis, with two-sided *P*-values.

Results

Characteristics of studies

A total of 613 studies were identified from the PubMed, Cochrane, Embase and Web of Science databases. The flow diagram in **Figure 1** shows the literature screening process. A total of 601 articles were excluded, including 157 articles presenting repeated findings and 444 irrelevant articles. A total of 12 full-text articles were identified. Then 2 studies were excluded, among which, one was letter [33] and the other was not a case-control study [34]. Eventually, 10 eligible case-control publications, all conforming to the inclusion criteria, were included in our meta-analysis.

Ten studies included in our meta-analysis included 2467 cases and 2416 controls [18-27]. **Table 2** shows the main features of each study. Two studies were based on Asian populations [19, 22], while the other studies were based on Caucasian populations [18, 20, 21, 23-27]. The results of the HWE tests for genotypic distribution in controls are summarized in **Table 2**. Quality scores for included articles ranged from 4 to 8, with 80% (8 of 10) of the studies being of high quality (score ≥6).

Meta-analysis results

The pooled results show that a significantly increased risk of ACS susceptibility was observed in the allelic comparison (T versus C: OR=1.12, 95% CI 1.01-1.23, I^2=0%, P_H=0.485) and dominant model (TC+TT versus CC: OR=1.14, 95% CI 1.01-1.28, I^2=0%, PH=0.898) (**Figure 2**). No statistically significant association between ACS susceptibility and IL-1β +3954C/T was found in the recessive model (TT versus TC+CC: OR=1.15, 95% CI 0.91-1.45, I^2=14.7%, PH=0.308), homozygote model (TT versus CC: OR=1.20, 95% CI 0.95-1.52, I^2=13.4%, P_H=0.319) or heterozygote model (TC versus CC: OR=1.12, 95% CI 0.99-1.27, I^2=0%, PH=0.976) (**Figure 3**).

Table 2. Characteristics of the studies included in meta-analysis

First author	Year	Genotyping method	Ethnicity	Case			Control			HWE *p*-value	Quality
				CC	CT	TT	CC	CT	TT		
Wang	2015	PCR-RFLP	Asian	191	53	16	218	52	15	< 0.05	7
Zeybek	2011	PCR-RFLP	Caucasian	79	46	18	140	54	19	< 0.05	5
Latella	2009	Non-RFLP	Caucasian	247	140	22	240	129	22	0.401	9
Coker	2011	PCR-RFLP	Caucasian	86	68	13	136	84	15	0.677	7
Iacoviello	2005	Non-RFLP	Caucasian	244	140	14	258	130	14	0.630	7
Stein	2009	Non-RFLP	Caucasian	30	18	6	29	19	2	0.607	6
Zee	2008	Non-RFLP	Caucasian	188	130	23	198	123	20	0.877	6
Tulyakova	2005	PCR-RFLP	Caucasian	167	105	34	144	86	15	0.654	6
Daraei	2017	PCR-RFLP	Asian	64	46	7	62	41	17	0.025	5
Soylu	2008	PCR-RFLP	Caucasian	157	93	14	69	41	7	0.783	7

HWE=Hardy-Weinberg equilibrium.

Subgroup analysis

Subgroup analysis by ethnicity showed similar effects in Caucasian populations. There was a significant risk of ACS susceptibility in the allelic comparison (T versus C: OR=1.14, 95% CI 1.03-1.27, I^2=0%, PH=0.698), homozygote model (TT versus CC: OR=1.32, 95% CI 1.02-1.72, I^2=0%, PH=0.689) and dominant model (TC+TT versus CC: OR=1.15, 95% CI 1.01-1.31, I^2=0%, PH=0.865). Nevertheless, no significant association was observed in the recessive model (TT versus TC+CC: OR=1.26, 95% CI 0.98-1.63, I^2=0%, PH=0.694) or heterozygote model (TC versus CC: OR=1.12, 95% CI 0.98-1.28, I^2=0%, PH=0.917) (**Table 3**). However, no significant results were found in Asian populations (T versus C: OR=0.98, 95% CI 0.76-1.26, I^2=61.6%, PH=0.107; TC versus CC: OR=1.13, 95% CI 0.81-1.59, I^2=0%, PH=0.848; TT versus CC: OR=0.73, 95% CI 0.24-2.16, I^2=70.1%, PH=0.067; TC+TT versus CC: OR=1.06, 95% CI 0.78-1.44, I^2=0%, PH=0.386; TT versus TC+CC: OR=0.70, 95% CI 0.23-2.09, I^2=71.5%, PH=0.061) (**Table 3**).

Then, another subgroup analysis was performed to investigate the effect of study quality. Among the high-quality studies, there was a positive association in the allelic comparison (T versus C: OR=1.12, 95% CI 1.01-1.24, I^2=0%, PH=0.919), but, there was no evidence of a significant link in the other genetic models (TC versus CC: OR=1.11, 95% CI 0.97-1.26, I^2=0%, PH=0.993; TT versus CC: OR=1.26, 95% CI 0.97-1.65, I^2=0%, PH=0.754; TC+TT versus CC: OR=1.13, 95% CI 0.99-1.28, I^2=0%, PH=0.989; TT versus TC+CC: OR=1.23, 95% CI 0.95-1.59, I^2=0%, PH=0.723). No significant effects were observed in the low-quality studies (T versus C: OR=1.06, 95% CI 0.56-2.01, I^2=83.0%, PH=0.015; TT versus CC: OR=0.85, 95% CI 0.21-3.47, I^2=82.6%, PH=0.017; TT versus TC+CC: OR=0.78, 95% CI 0.21-2.90, I^2=81.0%, PH=0.022; TC+TT versus CC: OR=1.19, 95% CI 0.69-2.07, I^2=63.0%, PH=0.100; TC versus CC: OR=1.31, 95% CI 0.91-1.87, I^2=0%, PH=0.376) (**Table 3**).

When stratifying findings by genotyping method, several significant results were detected in the PCR-RFLP subgroup (T versus C: OR=1.15, 95% CI 1.01-1.32, I^2=33.3%, PH=0.186), but there was no statistically significant association in the heterozygote model, homozygote model, recessive model or dominant model (TC versus CC: OR=1.16, 95% CI 0.97-1.39, I^2=0%, PH=0.834; TT versus CC: OR=1.25, 95% CI 0.92-1.70, I^2=42.4%, PH=0.122; TT versus TC+CC: OR=1.18, 95% CI 0.87-1.60, I^2=42.7%, PH=0.121; TC+TT versus CC: OR=1.18, 95% CI 1.00-1.39, I^2=0%, PH=0.602). No significant association was observed in the Non-RFLP subgroup (**Table 3**).

Sensitivity analysis

The influence of individual studies on the pooled ORs for IL-1β +3954C/T were assessed by sensitivity analysis in each genetic model. Consistently, the pooled estimate remained no significant change when any single study was omitted at a time from each meta-analysis. The sensitivity analysis in heterozygote model (TC versus CC)was showed in **Figure 4**.

Publication bias

Publication bias of the literature was analyzed by Funnel plot and Egger's test. The result

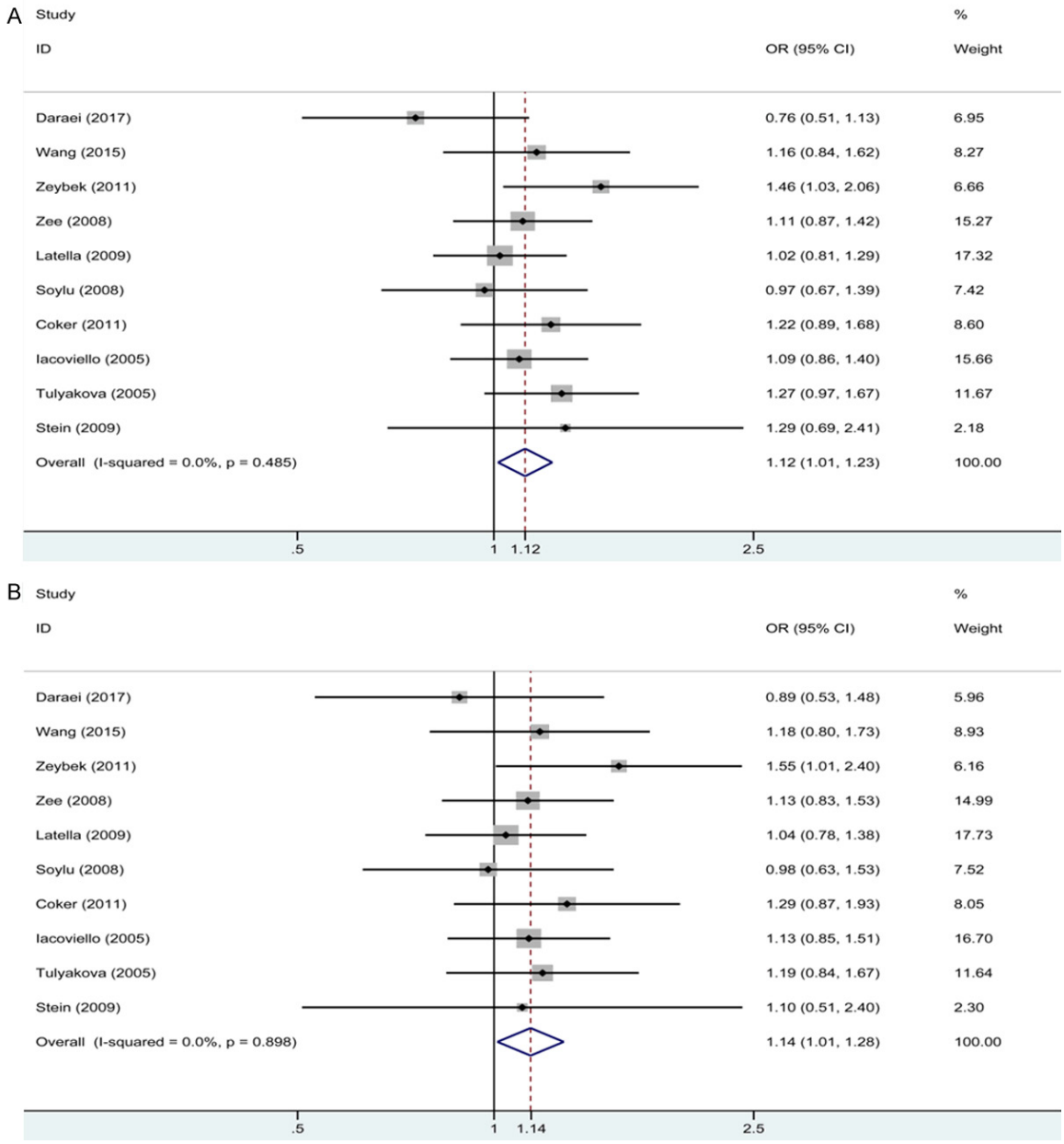

Figure 2. A: Forest plot for the allelic comparison of IL-1β +3954C/T in the overall comparison (T versus C), fixed effect model; B: Forest plot for the dominant model of IL-1β +3954C/T in the overall comparison (TC+TT versus CC), fixed effect model. The size of the black squares represents the weight of the study in the meta-analysis. The rhombus represents the combined OR. OR=Odds ratio.

shows no significant publication bias in all genetic models. **Figure 5** shows the Begg's funnel plot in dominant model (TC+TT versus CC, P=0.952). Information concerning the Egger's funnel plot is listed in **Table 4**.

Discussion

Meta-analysis showed that the IL-1β +3954C/T polymorphism significantly increased ACS susceptibility in the allelic comparison and dominant model. Heterogeneity was not observed in all genetic models. In the subgroup analysis according to the quality of the studies and genotyping method, the results for the PCR-RFLP subgroup and high-quality study subgroup were consistent with the pooled results. However, no association was observed in the low-quality studies and Non-RFLP subgroup, which was different from the pooled results.

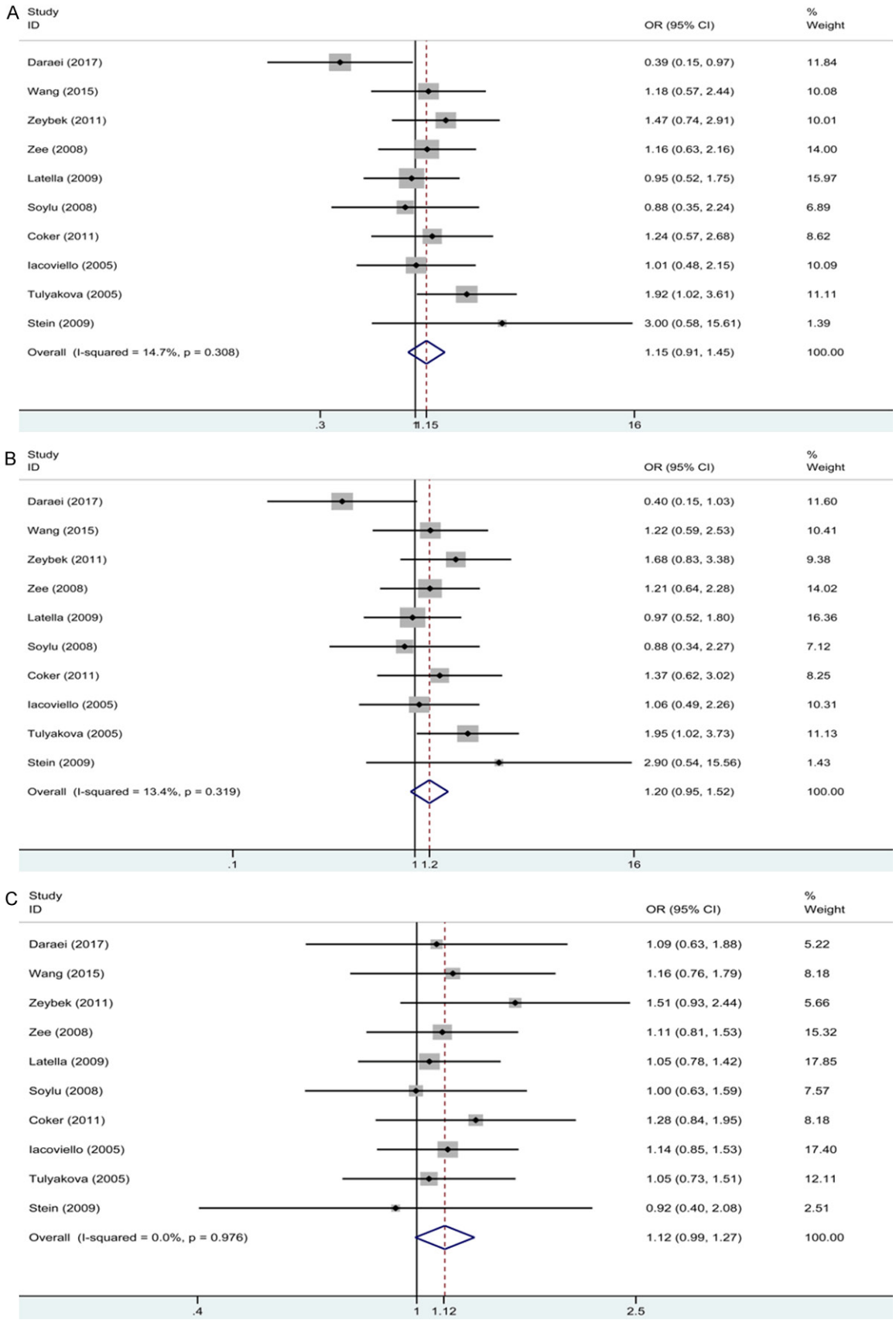
A
Study ID
OR (95% CI)
% Weight
Daraei (2017) 0.39 (0.15, 0.97) 11.84
Wang (2015) 1.18 (0.57, 2.44) 10.08
Zeybek (2011) 1.47 (0.74, 2.91) 10.01
Zee (2008) 1.16 (0.63, 2.16) 14.00
Latella (2009) 0.95 (0.52, 1.75) 15.97
Soylu (2008) 0.88 (0.35, 2.24) 6.89
Coker (2011) 1.24 (0.57, 2.68) 8.62
Iacoviello (2005) 1.01 (0.48, 2.15) 10.09
Tulyakova (2005) 1.92 (1.02, 3.61) 11.11
Stein (2009) 3.00 (0.58, 15.61) 1.39
Overall (I-squared = 14.7%, p = 0.308) 1.15 (0.91, 1.45) 100.00
.3
1 1.15
16
B
Study ID
OR (95% CI)
% Weight
Daraei (2017) 0.40 (0.15, 1.03) 11.60
Wang (2015) 1.22 (0.59, 2.53) 10.41
Zeybek (2011) 1.68 (0.83, 3.38) 9.38
Zee (2008) 1.21 (0.64, 2.28) 14.02
Latella (2009) 0.97 (0.52, 1.80) 16.36
Soylu (2008) 0.88 (0.34, 2.27) 7.12
Coker (2011) 1.37 (0.62, 3.02) 8.25
Iacoviello (2005) 1.06 (0.49, 2.26) 10.31
Tulyakova (2005) 1.95 (1.02, 3.73) 11.13
Stein (2009) 2.90 (0.54, 15.56) 1.43
Overall (I-squared = 13.4%, p = 0.319) 1.20 (0.95, 1.52) 100.00
.1
1 1.2
16
C
Study ID
OR (95% CI)
% Weight
Daraei (2017) 1.09 (0.63, 1.88) 5.22
Wang (2015) 1.16 (0.76, 1.79) 8.18
Zeybek (2011) 1.51 (0.93, 2.44) 5.66
Zee (2008) 1.11 (0.81, 1.53) 15.32
Latella (2009) 1.05 (0.78, 1.42) 17.85
Soylu (2008) 1.00 (0.63, 1.59) 7.57
Coker (2011) 1.28 (0.84, 1.95) 8.18
Iacoviello (2005) 1.14 (0.85, 1.53) 17.40
Tulyakova (2005) 1.05 (0.73, 1.51) 12.11
Stein (2009) 0.92 (0.40, 2.08) 2.51
Overall (I-squared = 0.0%, p = 0.976) 1.12 (0.99, 1.27) 100.00
.4
1 1.12
2.5

Figure 3. A: Forest plot for the recessive model of IL-1β +3954C/T in the overall comparison (TT versus TC+CC), fixed effect model; B: Forest plot for the homozygote model in the overall comparison (TT versus CC), fixed effect model; C: Forest plot for the heterozygote model of IL-1β +3954C/T in the overall comparison (TC versus CC), fixed effect model. The size of the black square represents the weight of the study in the meta-analysis. The rhombus represents the combined OR. OR=Odds ratio.

Table 3. Summary of polled ORs in the meta-analysis

Subgroup	Genetic model	Number of Study	OR (95% CI)	I^2	P_H
Overall	T vs C	10	1.12 (1.01-1.23)	0%	0.485
	TC vs CC	10	1.12 (0.99-1.27)	0%	0.976
	TT vs CC	10	1.20 (0.95-1.52)	13.4%	0.319
	TC+TT vs CC	10	1.14 (1.01-1.28)	0%	0.898
	TT vs TC+CC	10	1.15 (0.91-1.45)	14.7%	0.308
Caucasian	T vs C	8	1.14 (1.03-1.27)	0%	0.698
	TC vs CC	8	1.12 (0.98-1.28)	0%	0.917
	TT vs CC	8	1.32 (1.02-1.72)	0%	0.689
	TC+TT vs CC	8	1.15 (1.01-1.31)	0%	0.865
	TT vs TC+CC	8	1.26 (0.98-1.63)	0%	0.694
Asian	T vs C	2	0.98 (0.76-1.26)	61.6%	0.107
	TC vs CC	2	1.13 (0.81-1.59)	0%	0.848
	TT vs CC	2	0.73 (0.24-2.16)	70.1%	0.067
	TC+TT vs CC	2	1.06 (0.78-1.44)	0%	0.386
	TT vs TC+CC	2	0.70 (0.23-2.09)	71.5%	0.061
High quality	T vs C	8	1.12 (1.01-1.24)	0%	0.919
	TC vs CC	8	1.11 (0.97-1.26)	0%	0.993
	TT vs CC	8	1.26 (0.97-1.65)	0%	0.754
	TC+TT vs CC	8	1.13 (0.99-1.28)	0%	0.989
	TT vs TC+CC	8	1.23 (0.95-1.59)	0%	0.723
Low quality	T vs C	2	1.06 (0.56-2.01)	83.0%	0.015
	TC vs CC	2	1.31 (0.91-1.87)	0%	0.376
	TT vs CC	2	0.85 (0.21-3.47)	82.6%	0.017
	TC+TT vs CC	2	1.19 (0.69-2.07)	63.0%	0.100
	TT vs TC+CC	2	0.78 (0.21-2.90)	81.0%	0.022
PCR-RFLP	T vs C	6	1.15 (1.01-1.32)	33.3%	0.186
	TC vs CC	6	1.16 (0.97-1.39)	0%	0.834
	TT vs CC	6	1.25 (0.92-1.70)	42.4%	0.122
	TC+TT vs CC	6	1.18 (1.00-1.39)	0%	0.602
	TT vs TC+CC	6	1.18 (0.87-1.60)	42.7%	0.121
Non-RFLP	T vs C	4	1.08 (0.94-1.24)	0%	0.904
	TC vs CC	4	1.09 (0.92-1.30)	0%	0.956
	TT vs CC	4	1.14 (0.79-1.65)	0%	0.678
	TC+TT vs CC	4	1.10 (0.93-1.29)	0%	0.978
	TT vs TC+CC	4	1.11 (0.77-1.59)	0%	0.634

P_H=*p*-value of Q test for heterogeneity, OR=odds ratio, vs=versus, CI=confidence interval.

These differences may be due to the smaller sample size in these low quality studies and the non-RFLP subgroup which may obscure any potential association.

Inflammation plays a vital role in ACS. Substantial research has proved that inflammation make important contributions to the pathogenesis of atherosclerosis and the vulnerability of coronary artery plaques [35]. Infiltration of inflammatory cells can make atherosclerotic plaque unstable and increases the risk of complications of atherosclerosis [36]. IL-1β acting as a crucial inflammatory cytokineand plays a crucial role in inflammatory reactions and atherosclerosis. Lee [37] found that IL-1β may be directly involved in plaque destabilization by the stimulation of matrix metalloproteinases. Many studies involving animal models or *ex vivo* human samples have proved that IL-1β participates in atherothrombosis [13, 38]. In human, patients with acute coronary events have a higher local cardiac production of IL-1β [39]. Numerous studies have also shown that expression of IL-1β is elevated in ACS patients [14, 15]. In addition, inflammatory responses show a high inter-individual difference and have been linked to single-nucleotide genetic polymorphisms in the IL-1β gene [39-41]. IL-1β +3954C/T is a coding synonymous variant located in exon 5 of IL-1β gene. IL-1β +3954C/T with the transition from C to T leading to increase the production of IL-1β protein [42]. Moreover, *in vitro* experiments suggest that IL-1β +3954C/T could lead to overexpression of IL-1β in monocytes [16]. Indeed, numerous studies show that IL-1β +3954C/T play an important role in inflammatory diseases due to elevated expression of IL-1β [43, 44]. Therefore, IL-1β +3954C/T may increase IL-1β expression, which might worsen inflammation and finally increase the risk of ACS.

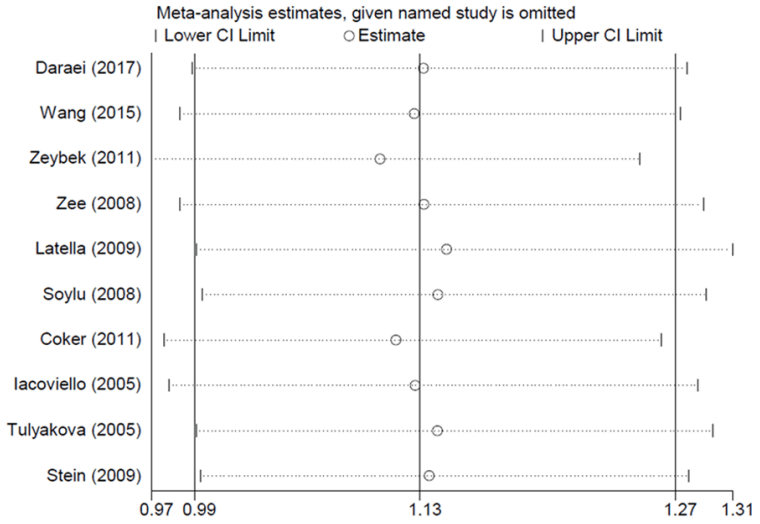

Figure 4. Sensitivity analysis for IL-1β +3954C/T in the heterozygote model (TC versus CC).

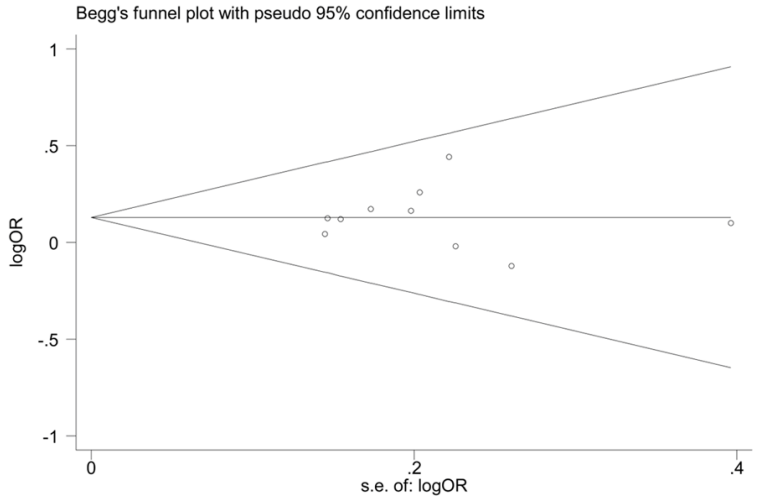

Figure 5. Begg's funnel plot showing publication bias analysis for IL-1β +3954C/T (TC+TT versus CC).

In the meta-analysis, the relationship between IL-1β +3954C/T and ACS was investigated. A positive association was observed in the allelic comparison and dominant model, which was consistent with previous studies [18, 20]. ACS is a myocardial ischemic state including myocardial infarction (MI). Tulyakova [18] found significant differences in IL-1β +3954C/T polymorphism distribution between MI patients and controls, moreover, frequencies of the T allele and TT genotype in the MI group were significantly higher than in the control group. In addition, Zeybek [20] also indicated that T allele of IL-1β +3954C/T was related to an increased risk of MI and CC genotype of IL-1β +3954C/T has protective effect against myocardial infarction. The both above studies support our conclusion that T allele of IL-1β +3954C/T polymorphism significantly increases ACS risk. However, no significant association between IL-1β +3954C/T and ACS was found in a recessive model, homozygote model or heterozygote model, which was coincident with the findings of previous studies [19, 21-27]. A subgroup analysis by ethnicity revealed that Caucasian populations have a significant risk of ACS susceptibility in the allelic comparison, homozygote model and dominant model. Some studies reached the same conclusion in Caucasian populations [18, 20]. Caucasians with TT genotype of IL-1β +3953 showed higher C-reactive protein (CRP) levels in ACS [45]. Furthermore, Caucasians carrying the T allele of IL-1β +3954C/T showed a higher level of CRP [46]. CRP is a marker of arterial inflammation and numerous studies have proven that CRP is present in atherosclerotic plaques and plays a vital role in promoting atherogenesis [47, 48]. Thus, IL-1β +3954C/T may increase the risk of ACS in Caucasians by elevating the level of inflammatory factors, such as CRP. No significant results were observed in Asian populations. Wang has come to the same conclusion in Chinese population [19]. However, Daraei has even reached the opposite conclusion that the TT genotype of the IL-1β +3954C/T polymorphism was related to a significant MI-protective effect in an Asian population [22]. ACS is a multi-factorial disease. Therefore, IL-1β +3954C/T polymorphisms may have diverse effects on the individual with different genetic background and living environment.

Table 4. Egger's funnel plot

IL-1β +3954C/T	95% CI	$P_{egger's\ test}$
T versus C	-3.057-3.183	0.964
TC versus CC	-1.534-1.697	0.910
TT versus CC	-4.049-3.307	0.822
TC+TT versus CC	-2.050-2.163	0.952
TT versus TC+CC	-4.006-3.424	0.861

$P_{Egger'test}$ is the *p*-value of Egger's test.

In the meta-analysis, a much larger total sample size was utilized than in previous studies to estimate the effect of the IL-1β +3954C/T polymorphism in ACS. There was no heterogeneity in the pooled results. Therefore, the consequences are more credible than previous studies. However, this meta-analysis has some limitations. First, ACS is a multi-factorial disease and many factors were not clear in the included studies, such as smoking, blood pressure, glucose levels and serum lipid levels. Therefore, a more precise analysis to assess the association between IL-1β +3954C/T and ACS could not be performed by adjusting these factors. Second, the relationship between IL-1β +3954C/T and ACS in Asian populations was performed with only two studies which were deviated from Hardy-Weinberg disequilibrium. So it may lead to unreliable results for these Asian populations. Third, although a systematic search was performed to access as much of the relevant literature as possible, it is possible that some studies were missed. Thus, in conclusion, meta-analysis proves that IL-1β +3954C/T is associated with ACS susceptibility, especially among Caucasian populations.

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Disclosure of conflict of interest

None.

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