Association between interleukin-8 gene −251 A/T polymorphism and the risk of coronary artery disease
A meta-analysis

Quanfang Zhang, MMa, Zhexun Lian, PhDa, Wenzhong Zhang, MMa, Yan Cui, MMa, Wugang Wang, PhDb, Jun Wu, PhDc, Zuoyuan Chen, MMa, Wei Wang, MMd

Abstract
Background: The association between interleukin-8 (IL-8) gene polymorphism −251 A>T and susceptibility to coronary artery disease (CAD) has been investigated previously; however, results remain controversial. Thus, a meta-analysis was conducted to reassess the effects of this polymorphism on CAD risks.

Methods: The PubMed, Cochrane Library, China National Knowledge Infrastructure, and Wanfang databases were searched for relevant studies published up to December, 2018. The pooled odds ratios (OR) were calculated using STATA 13.0 software for allelic (A vs T) as well as homozygote (AA vs TT), heterozygote (AT vs TT), recessive (AA vs AT + TT), and dominant (AA + AT vs TT) genotype models, respectively.

Results: Ten case-control studies (3744 cases and 3660 controls) were included. Overall, a significant association of IL-8 gene −251 A>T polymorphism with an increased risk of CAD was only observed in the dominant genotype model (OR = 1.48), but not others. In the subgroup analysis, significantly increased risks were also found for Chinese (OR = 1.64), polymerase chain reaction-restriction fragment length polymorphism genotyping (OR = 1.61), acute coronary syndrome (ACS) type (OR = 1.92 for 3 datasets; OR = 1.88 for 4 datasets), high quality (OR = 1.64), and age/gender matching status (OR = 1.55) under the dominant model. Furthermore, significantly increased risks were also found for ACS type under allelic (OR = 1.32 for 3 datasets; OR = 1.27 for 4 datasets), homozygote (OR = 1.64 for 3 datasets; OR = 1.50 for 4 datasets), heterozygote (OR = 1.32 for 3 datasets; OR = 1.30 for 4 datasets), and recessive (OR = 1.40 for 3 datasets; OR = 1.28 for 4 datasets) models.

Conclusion: This meta-analysis suggests that Chinese patients carrying −251A allele of IL-8 may have an increased risk for the development of CAD, especially ACS.

Abbreviations: ACS = acute coronary syndrome, CAD = coronary artery disease, CI = confidence interval, CVD = cardiovascular disease, HWE = Hardy–Weinberg equilibrium, IHD = ischemic heart disease, IL-8 = interleukin-8, MI = myocardial infarction, NOS = Newcastle–Ottawa scale, OR = odds ratio, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, SNP = single nucleotide polymorphism.

Keywords: coronary artery disease, interleukin-8, meta-analysis, polymorphism

1. Introduction
Cardiovascular disease (CVD) is ranked as the first leading cause of death worldwide, with an estimated annual mortality of 23.3 million people by the year 2030.[1] Coronary artery disease (CAD) is the most common form of CVD, accounting for approximately one-third of all deaths.[2] Although diabetes mellitus, hypertension, dyslipidemia, smoking, alcohol...
consumption, and obesity have been demonstrated as main risk factors, several studies suggested that individuals may be genetically predisposed to developing CAD.[3–6] Thus, investigation of key genetic variants underlying CAD may be of significance to develop efficient strategies for predicting, preventing and treating CAD.

There is an increasing amount of evidence to indicate that inflammation plays important roles in the pathogenesis of CAD, specifically in the process of atherosclerosis.[7,8] Progressively increased inflammation may contribute to endothelial dysfunction and then facilitate the deposition of local lipid within the arterial wall, ultimately resulting in plaque formation and vascular stenosis followed by the development of CAD and even sudden death.[9] Interleukin-8 (IL-8) is an important pro-inflammatory mediator produced by macrophages and its level has been reported to be increased in patients with CAD.[10]

Elevated IL-8 in plasma was also proved to be an independent predictor for long-term all-cause mortality in patients with acute coronary syndrome (ACS) that include unstable angina and acute myocardial infarction (MI).[11] These findings imply genetic variants that cause the differences in the production of IL-8 levels may be associated with CAD susceptibility. This hypothesis has been implicated in recent studies: Zhang et al found the promoter region of IL-8 had a remarkable single nucleotide polymorphism (SNP) structure (IL-8 –251A/T, rs4073). IL-8 level was the highest among patients carrying the AA genotype, followed by AT and then TT genotype. IL-8 –251 A/T polymorphism was associated with increased susceptibility to ACS (odds ratio [OR] = 1.30, 95% confidence interval [CI]: 1.12–1.53; \( P = 0.004 \)).[12] The study of Zhang et al also showed patients with AT (OR = 1.59; 95% CI = 1.01–2.57; \( P = 0.04 \)) and AA (OR = 2.06, 95% CI = 1.21–3.52; \( P = 0.005 \)) genotypes were at an increased risk for developing CAD compared to those with the TT genotype.[13] However, subsequent research by Kaur et al[14] and Chang et al[15] suggested that the T allele may be a risk factor for CAD, while Yang et al.[16] Ren et al.[17] and Wang et al.[18] found no association of IL-8 –251 A/T polymorphism with CAD risks. These controversial conclusions may be partially attributed to small sample size of individual studies. Therefore, we aimed to re-evaluate the effects of IL-8 –251 A/T polymorphism on CAD risks by performing a meta-analysis that can synthesize data from all eligible case-control studies and may achieve a more convincing conclusion. To our knowledge, this related meta-analysis has not been reported previously.

2. Materials and methods

2.1. Search strategy

Articles were identified by an electronic search on PubMed, the Cochrane Library, the China National Knowledge Infrastructure (Chinese), and Wanfang (Chinese) databases using the following keywords interleukin-8 (OR IL-8) AND coronary artery disease (OR CAD OR coronary heart disease OR CHD OR myocardial infarction OR MI OR ischemic heart disease OR IHD OR acute coronary syndrome OR ACS OR angina OR atherosclerosis OR cardiovascular) AND single nucleotide polymorphism (OR SNP OR variation OR variant OR mutation). The searching time was up to December, 2018. Furthermore, additional relevant studies on this topic were identified by a hand search of references cited by retrieved articles. Searches were limited to papers published in the English and Chinese language. This search followed the Guidelines of the preferred reporting items for systematic review and meta-analysis statement.

2.2. Selection criteria

All the articles were eligible if they met the following inclusion criteria:

1. assessing the association between IL-8 –251A/T polymorphism and CAD;
2. being human case-control studies;
3. providing sufficient information on the genotypes or alleles for calculating the OR and its corresponding 95% CI; and
4. providing the genotype distribution of control groups conformed to the assumptions of the Hardy–Weinberg equilibrium (HWE).

Studies were excluded when they were

1. duplicated data;
2. meeting abstracts, case reports/series, review articles, and editorial comment; and
3. not meeting all of the inclusion criteria.

2.3. Data extraction

The following characteristics were extracted from the eligible studies: author’s name, year of publication, country of origin, type of CAD, genotyping method, the source of controls, sex and age matching, HWE test, sample size, genotype and allele frequencies of cases and controls. The quality of included studies was evaluated based on the Newcastle–Ottawa scale (NOS)[18] that assessed 3 aspects:

1. subject selection (0–4 points),
2. comparability of subject (0–2 points), and
3. clinical outcome (0–3 points).

A high-quality study was defined as a score of ≥7. Studies with NOS scores ≥6 were considered to be of high quality. Two authors independently reviewed, extracted, and assessed the quality of the data. All disagreements were discussed and resolved with consensus.

2.4. Statistical analysis

The analyses were conducted using the STATA software (version 13.0; STATA Corporation, College Station, TX). The overall strength of an association between –251 A/T polymorphism and CAD risk was determined by calculating the crude ORs with 95% CIs for allelic (A vs T) model as well as homozygote (AA vs TT), heterozygote (AT vs TT), recessive (AA vs AT + TT), and dominant (AA + AT vs TT) genotype models, respectively. The \( \chi^2 \)-test was used to measure the statistical significance of the pooled OR and \( P < .05 \) was considered to be statistically significant. Furthermore, the subgroup analysis was also performed according to ethnicity (Chinese or Indian), genotyping method (polymerase chain reaction-restriction fragment length polymorphism [PCR-RFLP] or others), type of CAD (CAD, ACS, or MI), study quality (low quality: quality score < 7; high quality: quality score ≥7), and the matching status of age and gender (yes or no). Heterogeneity among studies was assessed with the Cochran Q (Chi-squared) statistic and the \( I^2 \) statistic (\( P < .10 \) and \( I^2 > 50\% \) indicated evidence of heterogeneity). A random-effects
and only 1 (10%, 1/10) was in Indian. In addition, there were 8 studies conducted by PCR-RFLP[12,13,15,16,18-21] performed by amplification refractory mutation system-PCR[14] and only 1 used MassARRAY[17] to detect the SNPs. Of these included studies, 6 studies reported about overall CAD (in which 1 was also divided into ACS and non-ACS cases[21]), 1 about ACS (which included 2 datasets)[13] and 1 about MI (which was not reported to be acute or old).[18] Coronary angiography was the mainly used method to diagnose CAD, which was defined as more than 50% or 70% stenosis in at least 1 coronary artery. All of studies provided the distributions of genotype and conformed to HWE. The genotype distribution and allele frequencies in cases and controls are listed in Table 2. According to the NOS criteria, most of the included studies were considered to be of high methodological quality other than one that was performed in Indian[14] (Table 3).

3. Results

3.1. Characteristics of eligible studies

The flow diagram of study selection is shown in Figure 1. According to the inclusion and exclusion criteria, 10 case-control studies (including 3744 cases and 3660 controls) were eligible for this meta-analysis[12-21] (Table 1). The selected papers were published between 2010 and 2018. Most of the included studies (90%, 9/10) were performed in the Chinese population[12,13,15-21].

### Table 1

| Author | Year | Country | Genotype method | Control source | Sample size | Sample size | Matching | Type | P_HWE | Language |
|--------|------|---------|-----------------|----------------|-------------|-------------|----------|------|--------|----------|
| Kaur N | 2018 | India   | ARMS-PCR        | PB             | 500         | 500         | No       | CAD  | Yes    | English  |
| Zhang RJ | 2017 | China   | PCR-RFLP        | PB             | 217         | 245         | Age      | CAD  | Yes    | English  |
| Yang HT | 2015 | China   | PCR-RFLP        | PB             | 410         | 410         | Age      | CAD  | Yes    | English  |
| Ren B  | 2015 | China   | MassARRAY       | PB             | 325         | 342         | Age, gender | CAD  | Yes    | English  |
| Wang S  | 2015 | China   | PCR-RFLP        | PB             | 260         | 285         | Age, gender | MI   | Yes    | English  |
| Zhang X  | 2011 | China   | PCR-RFLP        | PB             | 675/360     | 636/360     | Age, gender | ACS  | Yes    | English  |
| Zhang Y  | 2018 | China   | PCR-RFLP        | PB             | 349         | 365         | Age, gender | CAD  | Yes    | Chinese  |
| Zhang BH | 2010 | China   | PCR-RFLP        | PB             | 268         | 205         | Age, gender | CAD  | Yes    | Chinese  |
| Zhang JH | 2015 | China   | PCR-RFLP        | PB             | 136         | 122         | Age, gender | CAD  | Yes    | Chinese  |
| Hou HJ  | 2012 | China   | PCR-RFLP        | PB             | 244         | 170         | Age, gender | CAD (ACS) | Yes    | Chinese  |

ACS = acute coronary syndrome, ARMS-PCR = amplification refractory mutation system-polymerase chain reaction, CAD = coronary artery disease, HWE = Hardy-Weinberg equilibrium, MI = myocardial infarction, PB = population-based, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.
3.3. Publication bias
The evaluation of publication bias for AA + AT vs TT model using the Egger test indicated that the publication bias was nonsignificant \((P = .370)\). Also, no obvious asymmetry was observed in the funnel plot (Fig. 3). These results revealed no evidence of publication bias.

3.4. Sensitivity analyses
As presented in Figure 4, although each study was successively removed, the overall results did not alter obviously, which indicated the high stability of the meta-analysis results.

4. Discussion
On the basis of 10 case–control studies, our meta-analysis revealed IL-8 –251A/T polymorphism was significantly associated with the susceptibility of ACS. Patients with A allele or AA, AT and AA + AT genotypes had a significantly increased risk of developing ACS. Furthermore, the AA + AT genotype was also associated with an increased risk of CAD in overall analysis and this association was consistently significant in subgroups of Chinese, PCR-RFLP genotyping, high quality, and age/gender matching status.

The IL-8 gene, located on chromosome 4q12–21, is composed of 4 exons, 3 introns, and a proximal promoter region.\[22\] Although several polymorphisms had been reported in these genomic structures of IL-8 gene, including +781C/T, +353A/T, +678T/C, +1633C/T, -251A/T, and +394 T/G,\[23–25\] only -251A/T\[12–21\] and +394 T/G\[25\] polymorphisms were studied to investigate their associations with CAD. Also, -251A/T polymorphism in the promoter region was shown to be related to the expression alteration of IL-8, with AA genotype contributing to a significantly increased level of IL-8 compared with that of the AT or TT genotype.\[12,26\] Moreover, higher IL-8 mRNA levels were also reported in patients with the TA genotype compared with the TT genotype.\[27\] Thus, -251A/T polymorphism may be a biomarker associated with a serial of inflammatory diseases, which had been demonstrated in cancer,\[28\] Alzheimer’s disease,\[29\] and CAD.\[12,13,19\] In line with these studies, we also found AA + AT genotype was associated with an increased risk of overall CAD and all genetic models including mutant A-251 conferred susceptibility to ACS risk. This finding was also consistent with the fact that the cytokine related immune activity (exhibiting elevated level of IL-8, IL-18, IL-1β, IL-16, etc) was higher in the ACS patients compared with stable angina and normal controls.\[30–32\]

### Table 2
**IL-8 –251A/T polymorphisms genotype and allele distribution in cases and controls.**

| Author    | Sample size (cases/controls) | Genotype of cases (N) | Genotype of control (N) | Allele of cases (N) | Allele of control (N) |
|-----------|------------------------------|------------------------|-------------------------|---------------------|-----------------------|
| Kaur N    | 500/500                      | AA 148 AT 195 TT 157   | AA 199 AT 225 TT 76    | A 491 T 509        | A 623 T 377          |
| Zhang RJ  | 217/245                      | AA 69 AT 101 TT 47    | AA 57 AT 108 TT 80    | A 239 T 195        | A 222 T 268          |
| Yang HT   | 410/410                      | AA 114 AT 178 TT 118  | AA 105 AT 171 TT 134  | A 406 T 414        | A 381 T 439          |
| Ren B     | 325/342                      | AA 93 AT 147 TT 85    | AA 85 AT 149 TT 108   | A 333 T 317        | A 319 T 365          |
| Wang S    | 260/285                      | AA 75 AT 113 TT 72    | AA 77 AT 119 TT 89    | A 263 T 257        | A 273 T 297          |
| Zhang X   | 675/636                      | AA 123 AT 320 TT 232  | AA 80 AT 292 TT 264   | A 566 T 784        | A 452 T 850          |
| Zhang X   | 360/360                      | AA 76 AT 176 TT 108   | AA 58 AT 159 TT 143   | A 328 T 392        | A 275 T 445          |
| Yang Y    | 349/385                      | AA 79 AT 163 TT 107   | AA 56 AT 159 TT 170   | A 321 T 377        | A 271 T 499          |
| Zhang BH  | 268/285                      | AA 43 AT 126 TT 99    | AA 39 AT 103 TT 63    | A 212 T 324        | A 181 T 299          |
| Zhang JH  | 136/122                      | AA 32 AT 49 TT 55     | AA 41 AT 60 TT 21     | A 113 T 159        | A 142 T 102          |
| Hou HJ    | 244/170                      | AA 41 AT 130 TT 73    | AA 21 AT 85 TT 64     | A 212 T 276        | A 127 T 213          |

OR = 1.40, 95% CI = 1.12–1.75, \(P = .047\) for 3 datasets; OR = 1.28, 95% CI = 1.01–1.63, \(P = .040\) for 4 datasets) models.

### Table 3
**Quality of included studies was evaluated based on the Newcastle–Ottawa Scale (NOS).**

| Study | Adequate definition of patient cases (score) | Representativeness of patients cases (score) | Selection of controls (score) | Definition of controls (score) | Control for important factor or additional factor (score) | Ascertainment of exposure (blinding) (score) | Same method of ascertainment for participants (score) | Non-response rate (score) | Total score |
|-------|---------------------------------------------|---------------------------------------------|-------------------------------|--------------------------------|----------------------------------------------------------|---------------------------------------------|-----------------------------------------------|--------------------------|-------------|
| Kaur N| 1                                           | 1                                           | 1                             | 1                              | 0                                                        | 0                                            | 1                                             | 1                        | 6           |
| Zhang RJ | 1                                           | 1                                           | 1                             | 1                              | 1                                                        | 0                                            | 1                                             | 1                        | 7           |
| Yang HT | 1                                           | 1                                           | 1                             | 1                              | 1                                                        | 0                                            | 1                                             | 1                        | 7           |
| Ren B | 1                                           | 1                                           | 1                             | 1                              | 2                                                        | 0                                            | 1                                             | 1                        | 8           |
| Wang S | 1                                           | 1                                           | 1                             | 1                              | 2                                                        | 0                                            | 1                                             | 1                        | 8           |
| Zhang X | 1                                           | 1                                           | 1                             | 1                              | 2                                                        | 0                                            | 1                                             | 1                        | 8           |
| Chang Y | 1                                           | 1                                           | 1                             | 1                              | 2                                                        | 0                                            | 1                                             | 1                        | 8           |
| Zhang BH | 1                                           | 1                                           | 1                             | 1                              | 2                                                        | 0                                            | 1                                             | 1                        | 8           |
| Zheng JH | 1                                           | 1                                           | 1                             | 1                              | 2                                                        | 0                                            | 1                                             | 1                        | 8           |
| Hou HJ | 1                                           | 1                                           | 1                             | 1                              | 2                                                        | 0                                            | 1                                             | 1                        | 8           |
| Table 4 | Meta-analysis results. |
|--------|------------------------|
| **Comparison** | **Association** | **Heterogeneity** |
| | OR (95% CI) | P-value | Model | P-value | I² (%) |
| **Allelic (A vs T)** | | | | | |
| Overall | 1.08 (0.87–1.33) | .498 | R | .000 | 90.0 |
| Ethnicity | | | | | |
| China (n = 11) | 1.17 (1.00–1.36) | .051 | R | .000 | 78.5 |
| Others (n = 1) | 0.58 (0.49 – 0.70) | .000 | R | – | – |
| Genotyping method | | | | | |
| PCR-RFLP (n = 10) | 1.16 (0.98–1.38) | .091 | R | .000 | 80.7 |
| Others (n = 2) | 0.84 (0.61–1.70) | .619 | R | .000 | 96.1 |
| **Type of CAD** | | | | | |
| CAD (n = 8) | 0.99 (0.82–1.21) | .858 | R | .000 | 92.1 |
| ACS* (n = 3) | 1.32 (1.17–1.48) | .000 | F | 404 | 0.0 |
| MI (n = 1) | 0.88 (0.75–1.04) | .376 | R | – | – |
| ACS* (n = 4) | 1.27 (1.13–1.42) | .008 | F | 342 | 10.1 |
| **Study quality** | | | | | |
| Score ≥ 7 (n = 11) | 1.17 (1.00–1.36) | .051 | R | .000 | 78.5 |
| Score < 7 (n = 1) | 0.58 (0.49–0.70) | .000 | R | – | – |
| Age and gender matching status (yes or no) | | | | | |
| No (n = 3) | 0.99 (0.57–1.71) | .961 | R | .000 | 95.2 |
| Yes (n = 9) | 1.14 (0.94–1.37) | .181 | R | .000 | 61.7 |
| **Homozygote (AA vs TT)** | | | | | |
| Overall | 1.14 (0.77–1.69) | .510 | R | .000 | 88.7 |
| Ethnicity | | | | | |
| China (n = 11) | 1.32 (0.99–1.77) | .060 | R | .000 | 75.7 |
| Others (n = 1) | 0.36 (0.26–0.51) | .000 | R | – | – |
| Genotyping method | | | | | |
| PCR-RFLP (n = 10) | 1.31 (0.95–1.82) | .105 | R | .000 | 95.9 |
| Others (n = 2) | 0.70 (0.19–2.65) | .604 | R | .000 | 78.1 |
| **Type of CAD** | | | | | |
| CAD (n = 8) | 1.06 (0.61–1.85) | .353 | R | .000 | 91.3 |
| ACS* (n = 3) | 0.84 (0.28–2.13) | .332 | F | 332 | 9.2 |
| MI (n = 1) | 1.20 (0.77–1.88) | .413 | R | – | – |
| ACS* (n = 4) | 1.50 (1.18–1.92) | .001 | F | 305 | 17.2 |
| **Study quality** | | | | | |
| Score ≥ 7 (n = 11) | 1.32 (0.99–1.77) | .060 | R | .000 | 75.7 |
| Score < 7 (n = 1) | 0.36 (0.26–0.51) | .000 | R | – | – |
| Age and gender matching status (yes or no) | | | | | |
| No (n = 3) | 0.96 (0.35–2.66) | .938 | R | .000 | 94.9 |
| Yes (n = 9) | 1.26 (0.88–1.80) | .205 | R | .000 | 79.2 |
| **Heterozygote (AT vs TT)** | | | | | |
| Overall | 1.04 (0.79–1.37) | .802 | R | .000 | 84.3 |
| Ethnicity | | | | | |
| China (n = 11) | 1.18 (0.97–1.43) | .107 | R | .001 | 65.1 |
| Others (n = 1) | 0.42 (0.30–0.59) | .000 | R | – | – |
| Genotyping method | | | | | |
| PCR-RFLP (n = 10) | 1.16 (0.94–1.44) | .554 | R | .001 | 68.6 |
| Others (n = 2) | 0.72 (0.25–2.19) | .176 | R | .000 | 94.7 |
| **Type of CAD** | | | | | |
| CAD (n = 8) | 0.84 (0.63–1.10) | .749 | R | .000 | 87.7 |
| ACS* (n = 3) | 1.32 (1.10–1.50) | .002 | F | 734 | 0.0 |
| MI (n = 1) | 1.17 (0.78–1.76) | .436 | R | – | – |
| ACS* (n = 4) | 1.30 (1.10–1.53) | .002 | F | 826 | 0.0 |
| **Study quality** | | | | | |
| Score ≥ 7 (n = 11) | 1.18 (0.97–1.43) | .107 | R | .001 | 65.1 |
| Score < 7 (n = 1) | 0.42 (0.30–0.59) | .000 | R | – | – |
| Age and gender matching status (yes or no) | | | | | |
| No (n = 3) | 0.92 (0.41–2.03) | .830 | R | .000 | 0.000 |
| Yes (n = 9) | 1.13 (0.89–1.44) | .313 | R | .000 | 0.001 |
| **Recessive (AA vs AT + TT)** | | | | | |
| Overall | 1.14 (0.91–1.42) | .262 | R | .000 | 73.8 |
| Ethnicity | | | | | |
| China (n = 11) | 0.64 (0.49–0.83) | .027 | R | .016 | 54.4 |
| Others (n = 1) | 1.23 (1.03–1.48) | .001 | R | – | – |
| Genotyping method | | | | | |
| PCR-RFLP (n = 10) | 1.23 (1.00–1.52) | .051 | R | .009 | 58.8 |
| Others (n = 2) | 0.87 (0.46–1.64) | .684 | R | .003 | 88.3 |
| **Type of CAD** | | | | | |
| CAD (n = 8) | 1.11 (0.81–1.51) | .515 | R | .000 | 80.3 |
| ACS* (n = 3) | 1.40 (0.12–1.75) | .047 | F | 227 | 32.5 |
| MI (n = 1) | 1.10 (0.75–1.58) | .830 | R | – | – |
| ACS* (n = 4) | 1.28 (1.01–1.63) | .040 | F | 245 | 27.8 |
| **Study quality** | | | | | |
| Score ≥ 7 (n = 11) | 0.64 (0.49–0.83) | .027 | R | .016 | 54.4 |
| Score < 7 (n = 1) | 1.23 (1.03–1.48) | .001 | R | – | – |
| Age and gender matching status (yes or no) | | | | | |
| No (n = 3) | 1.01 (0.61–1.68) | .963 | R | .000 | 0.001 |
| Yes (n = 9) | 1.21 (0.96–1.52) | .103 | R | .000 | 0.009 |

(continued)
| Comparison                      | Association | Heterogeneity |
|--------------------------------|-------------|---------------|
|                                | OR (95% CI) | P-value       | Model | P-value | f (%) |
| Dominant (AA + AT vs TT)       |             |               |       |         |      |
| Overall                        | 1.48 (1.08–2.02) | .015 | R   | .000 | 90.0 |
| Ethnicity                      |             |               |       |         |      |
| China (n = 11)                 | 1.64 (1.29–2.08) | .000 | R   | .000 | 80.2 |
| Others (n = 1)                 | 0.57 (0.42–0.77) | .000 | R   | –   | –    |
| Genotyping method              |             |               |       |         |      |
| PCR-RFLP (n = 10)              | 1.61 (1.24–2.10) | .000 | R   | .000 | 82.2 |
| Others (n = 2)                 | 1.03 (0.82–1.32) | .963 | R   | .000 | 96.3 |
| Type of CAD                    |             |               |       |         |      |
| CAD (n = 8)                    | 1.33 (0.84–2.09) | .223 | R   | .000 | 92.0 |
| ACS (n = 3)                    | 1.92 (1.63–2.57) | .000 | F   | .169 | 43.8 |
| MI (n = 1)                     | 1.80 (1.25–2.58) | .001 | R   | –   | –    |
| ACS † (n = 4)                  | 1.88 (1.58–2.24) | .000 | F   | .300 | 18.2 |
| Study quality                  |             |               |       |         |      |
| Score ≥7 (n = 11)              | 1.64 (1.29–2.08) | .000 | R   | .000 | 80.2 |
| Score <7 (n = 1)               | 0.57 (0.42–0.77) | .000 | R   | –   | –    |
| Age and gender matching status (yes or no) |             |               |       |         |      |
| No (n = 3)                     | 1.34 (0.56–3.17) | .511 | R   | –   | –    |
| Yes (n = 8)                    | 1.55 (1.16–2.06) | .003 | R   | .000 | 0.00 |

Bold indicated the P-values to be significant by meta-analysis of at least 2 studies.

ACS = acute coronary syndrome, CAD = coronary artery disease, CI = confidence interval, F = fixed-effects model, MI = myocardial infarction, OR = odds ratios, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, R = random-effects model.

∗Analysis with 3 datasets, not including the study of Wang et al due to no specific description of it as acute MI.
†Including the study of Wang et al by hypothesis of it as acute MI.

Figure 2. Forest plots of the association of IL-8 gene –251 A > T polymorphism with an increased risk of CAD under the dominant genotype model (AA + AT vs TT). Squares indicate OR; horizontal lines indicate 95% CI; hollow diamond indicates the pooled OR and its 95% CI. CAD = coronary artery disease, CI = confidence intervals, OR = odds ratio.
Although the mechanism remains unclear, it is supposed the higher IL-8 may contribute to the development and progression of CAD via the following potential mechanisms:

(1) cholesterol efflux: Chen et al used the human IL-8-neutralizing antibody to demonstrate that IL-8 may inhibit cholesterol efflux and promote lipid accumulation, leading to the development of atherosclerosis[33];

(2) angiogenesis: Kyriakakis et al reported that antigen-activated invariant natural killer T cells could release IL-8 and then up-regulate the expression of surface IL-8 receptors (C-X-C motif chemokine receptor 2 and vascular endothelial growth factor receptor 2) to promote endothelial cell migration and sprouting, influencing the stability of atherosclerotic plaques[34]; and

(3) apoptosis: IL-8 is involved in the initiation and amplification of acute inflammatory reactions and then induces injured apoptosis of endothelial cells.[33]

There are several limitations in this meta-analysis. First, CAD is a multifactorial disease, which may be influenced by interactions between gene-gene as well as gene-environment. However, unadjusted ORs estimates were only used in this study due to the lack of the link between compounding factors (ie, diabetes mellitus, hypertension, dyslipidemia, smoking, alcohol consumption, and obesity) and genotype distribution in the original data of the eligible studies. Second, the number of cases and controls in some specific subgroups was relatively small, which may not provide sufficient statistical power to estimate the correlation between the IL-8 gene polymorphisms and the susceptibility to CAD. Third, only 2 Asian countries were included in the analysis and most of the data (90%) were from China. Fourth, only English or Chinese published studies were included in this meta-analysis. Non-significant or negative findings in other language may be missed.

In conclusion, this meta-analysis provides robust evidence that Chinese patients carrying -251A allele of IL-8 may have an increased risk for the development of CAD, especially ACS.

**Author contributions**

Conceptualization: Quanfang Zhang.

Data curation: Quanfang Zhang, Zhexun Lian.

Formal analysis: Quanfang Zhang, Zhexun Lian.

Investigation: Wugang Wang, Wei Wang.

Methodology: Wugang Wang, Zuoyuan Chen.

Software: Yan Cui.

Validation: Wenzhong Zhang.

Visualization: Jun Wu.

Writing – original draft: Quanfang Zhang.

Writing – review and editing: Quanfang Zhang.

**References**

[1] Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.

[2] Yang ZJ, Liu J, Ge JP, et al. Prevalence of cardiovascular disease risk factor in the Chinese population: the 2007–2008 China National Diabetes and Metabolic Disorders Study. Eur Heart J 2012;33:213–20.

[3] Wang P, Dong P, Yang X. ANRIL rs2383207 polymorphism and coronary artery disease (CAD) risk: a meta-analysis with observational studies. Cell Mol Biol (Noisy-le-grand) 2016;62:6–10.

[4] Xie L, Li YM. Lipoprotein lipase (LPL) polymorphism and the risk of coronary artery disease: a meta-analysis. Int J Environ Res Public Health 2017;14:84.

[5] Zhang MM, Chang XW, Hao XQ, et al. Association between matrix metalloproteinase 9 C-1562T polymorphism and the risk of coronary artery disease: an update systematic review and meta-analysis. Oncotarget 2018;9:9468–79.

[6] Bao MH, Luo HQ, Ju X, et al. Meta-analysis for the association between polymorphisms in interleukin-17A and risk of coronary artery disease. Int J Environ Res Public Health 2016;13:660.

[7] Teague H, Mehta NN. The link between inflammatory disorders and coronary heart disease: a look at recent studies and novel drugs in development. Curr Atheroscler Rep 2016;18:3.

[8] Moreira DM, Da SR, Vieira JL, et al. Role of vascular inflammation in coronary artery disease: potential of anti-inflammatory drugs in the prevention of atherothrombosis. Inflammation and anti-inflammatory drugs in coronary artery disease. Am J Cardiovasc Drugs 2015;15:1–1.

[9] Gimbrone MA Jr, Garcia-Garcia M. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res 2016;118:620–36.

[10] Danisiewicz A, Skodzinski J, Hudzik B, et al. Effects of trimetazidine on interleukin-2 and interleukin-8 concentrations in patients with coronary artery disease. Can J Physiol Pharmacol 2017;95:759–62.

[11] Causuoglu E, Marmur JD, Yanamadala S, et al. Elevated baseline plasma IL-8 levels are an independent predictor of long-term all-cause mortality
in patients with acute coronary syndrome. Atherosclerosis 2015;242:589–94.

[12] Zhang X, Zhang BH, Zhang M, et al. Interleukin-8 gene polymorphism is associated with acute coronary artery disease susceptibility in a Chinese Han population. Cytokine 2011;56:188–91.

[13] Zhang RJ, Li XD, Zhang SW, et al. IL-8 -251A/T polymorphism contributes to coronary artery disease susceptibility in a Chinese population. Genet Mol Res 2017;16.

[14] Kaur N, Singh J, Reddy S. Association of IL-8-251 A/T rs4073 and IL-10 rs1800872-592C/A polymorphisms and coronary artery disease in North Indian population. Biochem Genet 2017;57:129–46.

[15] Chang YZB, Tong FN, Cheng MH, et al. The correlation of IL-8 rs4073 single nucleotide polymorphism and coronary artery disease complicated with type 2 diabetes mellitus. Clin J Med Off 2018;46:528–33.

[16] Yang HT, Wang SL, Yan LJ, et al. Association of interleukin gene polymorphisms with the risk of coronary artery disease. Genet Mol Res 2015;14:12489.

[17] Ren B, She Q. Study on the association between IL-1β, IL-8 and IL-10 gene polymorphisms and risk of coronary artery disease. Int J Clin Exp Med 2015;8:7937.

[18] Wang S, Dai YX, Chen LL, et al. Effect of IL-1β, IL-8, and IL-10 polymorphisms on the development of myocardial infarction. Genet Mol Res 2015;14:12016–21.

[19] Zheng J, Ning G, Chen J, et al. Analysis between IL-8 polymorphism and the risk of blood stasis syndrome with coronary artery disease. China J Tradit Chin Med Pharm 2015;30:3286–9.

[20] Zhang B, Han Y, Zhang X, et al. Correlation between Interleukin 8 gene -251A/T polymorphism and coronary heart disease in Northern Chinese Han population. Chin J Pract Intern Med 2010;30:1030–1.

[21] Hou H, Gong H, Zhao H, et al. Relationship between IL-8-251A/T single nucleotide polymorphism and plasma level with coronary heart disease susceptibility. Chin J Arterioscler 2012;20:261–4.

[22] Mukaida N, Shroo M, Matsushima K. Genomic structure of the human monocyte-derived neutrophil chemotactic factor IL-8. J Immunol 1989;143:1366–71.

[23] Meng Z, Fang T, Kai W, et al. Association of polymorphisms interterleukin-8gene with cancer risk: a meta-analysis of 22 case-control studies. Onco Targets Ther 2016;9:3727–37.

[24] Wang JL, Nong LG, Wei YS, et al. Association of interleukin-8 gene polymorphisms with the risk of hepatocellular carcinoma. Mol Biol Rep 2014;41:1483–9.

[25] Zhang X, Zhang B, Liang Z, et al. Association of interleukin-8 +394T/G with acute coronary syndrome in a Han population in Northern China. Chin Heart J 2012;24:442–5.

[26] Petch W, Taka-Aki N, Boyd JL, et al. AA genotype of IL-8 -251A/T is associated with low PaO2/FiO2 in critically ill patients and with increased IL-8 expression. Respiratory 2012;17:1253–60.

[27] Andia DC, de Oliveira NF, Letra AM, et al. Interleukin-8 gene promoter polymorphism (rs4075) may contribute to chronic periodontitis. J Periodontal 2011;82:493–9.

[28] Gao P, Zhao H, You J, et al. Association between interleukin-8 -251A/T polymorphism and risk of lung cancer: a meta-analysis. Cancer Invest 2014;32:518.

[29] Qin B, Li L, Wang S, et al. Interleukin-8 gene polymorphism -251T>A contributes to Alzheimer’s disease susceptibility. Medicine 2016;95:e5039.

[30] Tsakas DN, Chalikias GK, Tentes IK, et al. Interleukin-8 is increased in the membrane of circulating erythrocytes in patients with acute coronary syndrome. Eur Heart J 2008;29:2713.

[31] Yan W, Wen S, Wang L, et al. Comparison of cytokine expressions in acute myocardial infarction and stable angina stages of coronary artery disease. Int J Clin Exp Med 2015;8:18082–9.

[32] Sun H, Zhang J, Zheng Y, et al. Expressions and clinical significance of factors related to acute coronary syndrome. J Biol Regul Homeost Agents 2018;32:299–305.

[33] Yandong C, Zheng W, Lijun Z. Interleukin 8 inhibition enhanced cholesterol efflux in acetylated low-density lipoprotein-stimulated THP-1 macrophages. J Investig Med 2014;62:615–20.

[34] Kyriakakis E, Cavallari M, Pfaff D, et al. IL-8-mediated angiogenic responses of endothelial cells to lipid antigen activation of iNKT cells depend on EGFR transactivation. J Leukoc Biol 2011;90:929–39.

[35] Li S, Sun Y, Zhong L, et al. The suppression of ox-LDL-induced inflammatory cytokine release and apoptosis of HCAECs by long non-coding RNA-MALAT1 via regulating microRNA-155/SOCS1 pathway. Nutr Metab Cardiovasc Dis 2018;28:1175–87.