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Original Article

Association of matrix metalloproteinase-1 -519A/G polymorphism with acute coronary syndrome: a meta-analysis

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Abstract: Matrix metalloproteinase-1 (MMP-1) has been demonstrated to play an important role in the development and progression of acute coronary syndrome (ACS). Recent studies have shown that MMP-1 -519A/G (rs1144393) polymorphism is associated with the susceptibility to ACS. However, published studies showed inconsistent results. Therefore, a meta-analysis of eligible studies reporting the association between -519A/G polymorphism and ACS was carried out. A systematic search was conducted using PubMed, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure and Chinese Wan Fang database. Six eligible studies involving 5670 subjects (2868 ACS patients and 2802 healthy controls) were included in this meta-analysis. Overall, this meta-analysis showed a significant association between the rs1144393 polymorphism and ACS (A vs. G: OR = 1.385, 95% CI = 1.019-1.882, *P* = 0.037; AA vs. AG/GG: OR = 1.547, 95% CI = 1.002-2.389, *P* = 0.049). Furthermore, subgroup analyses also displayed significant associations between MMP-1 rs1144393 polymorphism and susceptibility to acute myocardial infarction (AA/AG vs. GG: OR = 1.275, 95% CI = 1.016-1.600, *P* = 0.036) or unstable angina pectoris subjects (A vs. G: OR = 2.128, 95% CI = 1.696-2.670, *P* < 0.001; AA vs. GG: OR = 2.933, 95% CI = 1.339-6.421, *P* = 0.007; AA vs. AG/GG: OR = 2.477, 95% CI = 1.457-4.211, *P* = 0.001). But we found no significant association between the -519A/G polymorphism and ACS either in Asian or Caucasian. In conclusion, our meta-analysis suggests that MMP-1 -519A/G polymorphism was associated with the susceptibility to ACS. However, further large scale case-control studies with rigorous design should be conducted to confirm above conclusions in the future.

Keywords: Matrix metalloproteinase-1, acute coronary syndrome, gene polymorphism, rs1144393, meta-analysis

Introduction

Coronary heart disease (CHD) is one of major cause of morbidity and mortality worldwide [1]. Among different types of CHD, acute coronary syndrome (ACS), including unstable angina (UA) and acute myocardial infarction (AMI), is the most serious event and always results in sudden death or permanent disability in a large number of patients due to lack of methods for early prediction and diagnosis of ACS [2-4]. Therefore, there is a great need to discover novel biomarkers for early prediction and diagnosis of ACS.

It is now widely accepted that the development and rupture of vulnerable plaque is involved in the occurrence of ACS [5]. The typical vulnerable plaque usually consists of lipid-rich core and a thin fibrous cap that includes smooth muscle cells and extracellular matrix proteins [6]. Recent studies have reported that nearly 60% of matrix proteins (mainly type I and III collagens) could be degraded by matrix metalloproteinase-1 (MMP-1) and excessive expression of MMP-1 was found in the shoulder of the atherosclerotic plaque, suggesting MMP-1 may play a key role in the rupture of vulnerable plaque [7, 8].

The rs1144393 (-519A/G) polymorphism locates in the MMP-1 gene promoter. Recent study has suggested that haplotype of this polymorphism could increase the promoter activity

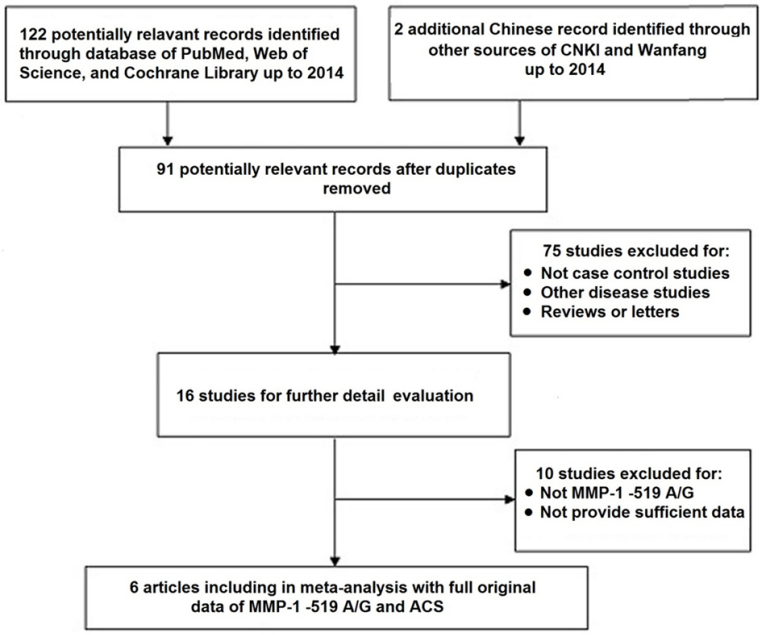

Figure 1. Flow diagram of the study selection process.

and gene expression of MMP-1 [9]. Meanwhile, the rs1144393 polymorphism was also reported to be associated with the risk of AMI or ACS [9-12]. However, two studies have suggested that none of the MMP-1 -519A/G polymorphism was associated with ACS [13, 14]. Considering these discrepancies in the results, we performed a meta-analysis of the available studies between MMP-1 -519A/G polymorphism and ACS to evaluate its contribution to the risk of ACS.

Materials and methods

Search strategy

Relevant papers published before November 1st, 2014 were identified through a search in PubMed, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) and Chinese Wan Fang database. The search strategy was the assemblage of ("genetic polymorphism" or "single nucleotide polymorphism" or "SNP" or "gene mutation" or "genetic variants") and ("coronary atherosclerosis" or "myocardial ischemia" or "acute coronary syndrome" or "coronary disease" or "myocardial infarction" or "ischemic heart disease") and ("matrix metalloproteinase-1" or "MMP-1"). Hand-searching of references and the related articles function in PubMed was performed to identify any additional studies. The full-text articles that potentially met criteria were then reviewed in duplicate to determine the inclusion in the analysis. Then all the authors further critically reviewed the studies upon which the 2 reviewers (Pengyu Jia and Nan Wu) disagreed. Either the inclusion or exclusion of a certain study was agreed upon by all the authors finally.

Eligibility criteria

References of retrieved articles were also screened. The major inclusion criteria were (i) assessment of the MMP-1 gene polymorphism and ACS risk; (ii) related case-control or cohort studies; (iii) sufficient data about allele frequency for calculating genotypic odds ratio (OR) with corresponding 95% confidence interval (95% CI) in cases and controls. The major exclusion standards were (i) overlapping data; (ii) case-only studies, review articles and reports based on pedigree data. The diagnosis of the ACS case group (either AMI or UA) was according to the result of coronary artery angiography supplemented by troponin blood test, clinical symptoms and ECG changes. All control subjects were judged to be free of ACS based on patient history, clinical examination and electrocardiography.

Data extraction

Data extraction was performed independently by two authors (Pengyu Jia and Xiaowen Zhang) using a standardized data extraction form: 1) author's name, year of publication; 2) patient characteristics of each group; 3) number of participants in case and control groups; 4) method of screening for ACS; 5) study type; 6) genotyping method; 7) the *P*-value of Hardy-Weinberg equilibrium (HWE) test in the control OR and 95% CI for association with ACS. Quality score assessment was performed using Newcastle-Ottawa Scale (NOS) as previous described [15]. Briefly, two authors (Pengyu Jia and Xiaowen Zhang) of this article independently assessed the qualities based on eight items and scored

Table 1. Main characteristics of studies included in the meta-analysis

Studies	Country	Ethnicity	Number (case/control)	Age, year (case/control)	Male% (case/control)	Hypertesion n% (case/control)	Study type	Primary outcome	Genotype method	NOS score	HWE test (control)
Han et al. (2008)a	China	Asian	222/191	58.47/52.4	74.32/48.17	55.41/43.98	Case-control study	ACS	PCR-RFLP	9	Yes
Pablo et al. (2009)	Spain	Caucasian	261/194	46.05/43.49	100/100	39/18	Case-control study	AMI	PCR-RFLP	9	Yes
Xu et al. (2013)	China	Asian	660/914	62/62	69/67	49/48	Case-control study	ACS	PCR-RFLP	9	Yes
Pearce et al. (2005)	England; Swedish	Caucasian	639/538; 387/387	62.9/63.8; 52.5/53	79/73; 82/82	42/49; 34/6	Case-control study	AMI	PCR-RFLP	9	Yes
Wang et al. (2010)	China	Asian	295/198	58.4/58.2	63.39/55.05	NA	Case-control study	ACS (AMI; UAP)	PCR-RFLP	9	Yes
Han et al. (2008)b	China	Asian	404/380	58.9/51.9	73.89/52.63	59.2/42.4	Case-control study	ACS (AMI; UAP)	PCR-RFLP	9	Yes

HWE: Hardy-Weinberg equilibrium; ACS: acute coronary syndrome, UAP: unstable angina pectoris, AMI: acute myocardial infarction; NA, not available. "a" and "b" indicate that the same author published different article.

Table 2. Main characteristics of studies included in the meta-analysis

Variable	Cases/controls (n)	OR b (95% CI) Ph value				
		Allele (A vs. G)	Homozygote (AA vs. GG)	Heterzygote (AG vs. GG)	Dominant (AA/AG vs. GG)	Recessive (AA vs. AG/GG)
All subjects	2868/2802	1.385 (1.019-1.882)	1.382 (0.895-2.135)	1.095 (0.905-1.326)a	1.189 (0.844-1.675)	1.547 (1.002-2.389)
		0.037*	0.145	0.350	0.323	0.049*
Primary outcome						
UAP	458/578	2.128 (1.696-2.670)a	2.933 (1.339-6.421)a	1.179 (0.525-2.648)a	2.074 (0.950-4.531)a	2.477 (1.457-4.211)
		0.000*	0.007*	0.690	0.062	0.001*
MI	1528/1697	1.502 (0.979-2.306)	1.421 (0.770-2.622)	1.269 (0.999-1.613)a	1.275 (1.016-1.600)a	1.640 (0.900-2.989)
		0.063	0.260	0.051	0.036*	0.106
Ethnicity						
Asian	1581/1683	1.632 (0.968-2.751)	2.005 (0.760-5.293)	0.907 (0.667-1.232)a	1.493 (0.728-3.062)	1.923 (0.993-3.722)
		0.066	0.160	0.530	0.274	0.052
Caucasian	1287/1119	1.039 (0.924-1.167)	1.146 (0.890-1.477)a	1.117 (0.687-1.819)	1.201 (0.952-1.515)a	0.983 (0.833-1.161)a
		0.525	0.290	0.655	0.122	0.84

Ph, *P* value for Cochran's Q test for between-study heterogeneity in each genetic comparison model. a: A fixed effects model was used when the *P* value for Cochran's Q test for heterogeneity was more than 0.1. Otherwise, a random effects model was used. *: $P < 0.05$.

the studies from zero to nine points. Studies with a score of seven stars or greater were considered to be of high quality. Disagreement was settled as described above.

Statistical analysis

We firstly tested the HWE for all included studies, because the results of transmission-disequilibrium analysis could be biased if there is deviation from HWE. The HWE was checked by applying a chi-square goodness-of-fit test. The strength of association was estimated as OR and corresponding 95% CI. Standard meta-analysis methods were applied. We performed primary analyses utilizing dominant models to maximize the number of studies included. Subsidiary analysis involved recessive genetic model, co-dominant model and allele contrast. OR with 95% CI in each case-control study was used to assess the strength of association. The between-study heterogeneity across all eligible comparisons was determined using the chi square -based Q statistic. Heterogeneity was considered significant at a *P*-value of < 0.10, which also was used to select the appropriate pooling method. A random effects model was performed when heterogeneity was present. Strength of agreement between reviewers regarding study selection was evaluated by NOS in agreement with HWE. Subgroup analyses were performed according to ethnicity (Asian and Caucasian) and primary outcome (AMI and UA). The Egger's linear regression test and funnel plot were utilized to assess publication bias. ($P < 0.05$ was considered representative of statistically significant publication bias). Sensitivity analysis was also performed for estimating the stability of the meta-analysis. First, studies that failed the HWE test were excluded. Another analysis was conducted by omitting one study at a time to examine its influence on the overall summary estimate. Data were analyzed using stata software, version 11.0 (STATA Corp., College Station, TX, USA). All *P*-values are two-tailed.

Results

Characteristics of included studies

124 potential eligible records were initially identified with literature search. After different levels of screening, 118 articles that were excluded, including 33 articles that were duplicated, 75 articles that were not about ACS, 10 articles that were not concerned with the rs1144393 (-519A/G) polymorphism. 6 studies in accordance with the inclusion criteria were finally included in this meta-analysis [9-14] (**Figure 1**).

The characteristics of the included studies are summarized in **Table 1**. A total of 5670 subjects including 2868 ACS patients and 2802 healthy controls were involved in this meta-analysis. The publication years of the involved studies ranged from 2005 to 2013. The HWE test was conducted on the genotype distribution of the controls in all studies and the controls were consistent with HWE in all the studies (**Table 1**).

Quantitative data synthesis

Overall, we found some associations between the MMP-1 rs1144393 polymorphism and ACS when we pooled all the data in the meta-analysis in allele contrast model (OR = 1.385, 95% CI = 1.019-1.882, $P = 0.037$) and recessive model (OR = 1.547, 95% CI = 1.002-2.389, $P = 0.049$) (**Figure 2A** and **2E**). We also performed subgroup analyses according to primary outcome or ethnicity. In the analyses, we found evidence of statistical significant association between the rs1144393 polymorphism and AMI subjects in dominant model (OR = 1.275, 95% CI = 1.016-1.600, $P = 0.036$), also, a remarkable association between the rs1144393 polymorphism and UA subjects in allele contrast model (OR = 2.128, 95% CI = 1.696-2.670, $P < 0.001$), homozygote (co-dominant) model (OR = 2.933, 95% CI = 1.339-6.421, $P = 0.007$) and recessive model (OR = 2.477, 95% CI = 1.457-4.211, $P = 0.001$). But we still found no significant associations between the polymorphism and ACS risk either Asian or Caucasian (**Table 2**). All above results indicate MMP-1 rs1144393 polymorphism was associated with the susceptibility to ACS.

Sensitivity analysis

A sensitivity analysis was performed by omitting one study at a time and calculating the pooled ORs for the remaining studies. The included studies were limited to those conforming to HWE and those with high NOS score (> 7). This procedure was used to ensure that no individual study was entirely responsible for the

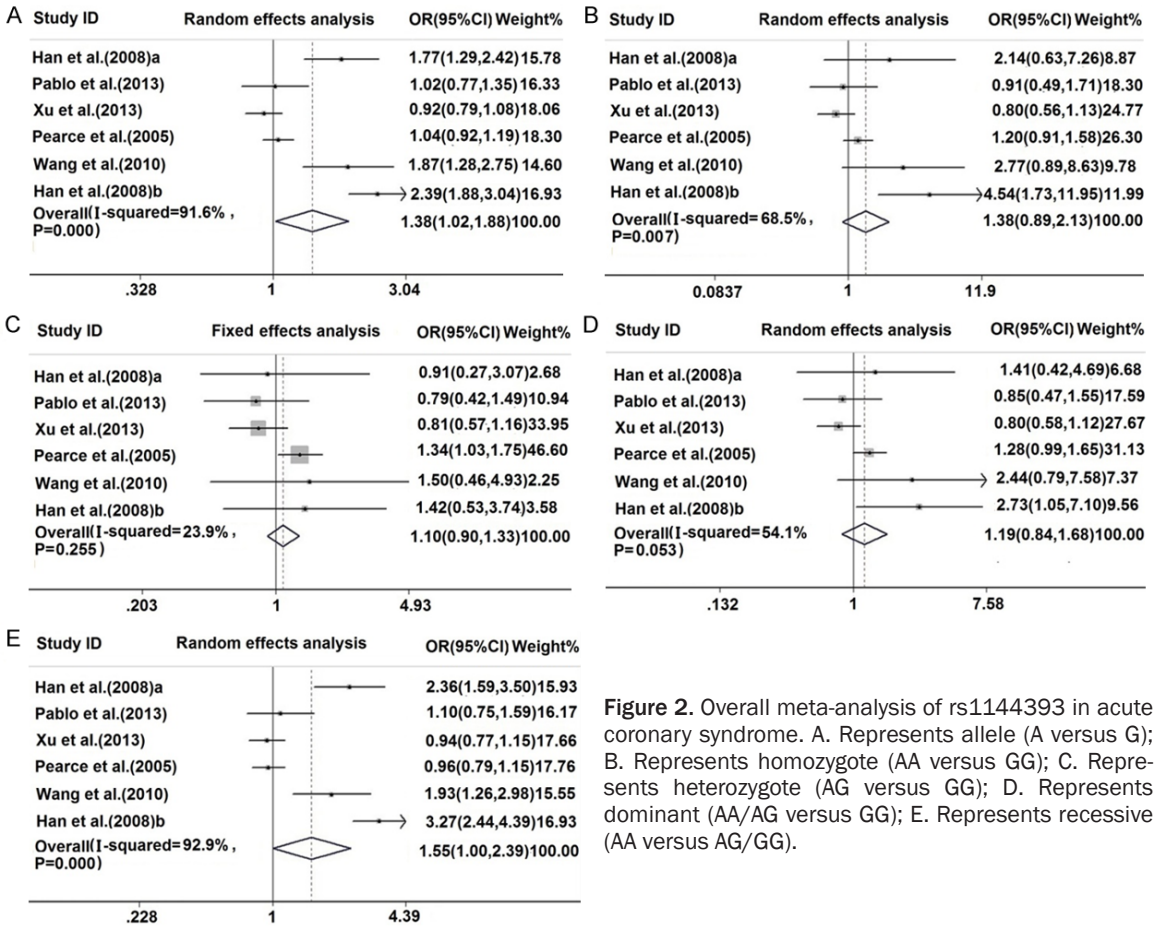

Figure 2. Overall meta-analysis of rs1144393 in acute coronary syndrome. A. Represents allele (A versus G); B. Represents homozygote (AA versus GG); C. Represents heterozygote (AG versus GG); D. Represents dominant (AA/AG versus GG); E. Represents recessive (AA versus AG/GG).

combined results of Allele (A vs. G), Homozygote (AA vs. GG), Heterozygote (AG vs. GG), Dominant (AA/AG vs GG), Recessive (AA vs. AG/GG) model for CHD, respectively (**Table 3**). The corresponding pooled ORs were not materially altered indicating that our results were robust.

Publication bias

Funnel plot and Egger's test were performed to determine whether the literature showed a publication bias based on dominant genetic model data. The funnel plots were symmetrical by visual inspection (**Figure 3**). Egger's test suggested no publication bias for some genetic models (P = 0.393, 95% CI: -0.911, 1.869 for allele model; P = 0.565, CI: -1.190, 1.884 for homozygote (co-dominant) model; P = 0.079, 95% CI: -0.149, 1.786 for dominant model; P = 0.968, 95% CI: -2.922, 3.012 for recessive model, respectively). However, Egger's test for the heterozygote (co-dominant) model suggested the presence of a potential publication bias (P = 0.01, 95% CI: 0.478, 1.880).

Discussions

MMP-1, one member of the MMPs family, is believed to be a major human interstitial collagenase, which is produced by several types of cells, especially endothelial cells in atherosclerotic plaques [7, 16]. MMP-1 can degrade collagens types I and III collagens that accounting for 60% of matrix proteins in fibrous cap of vulnerable plaque [7]. Previous study suggests that high MMP-1 levels in patients with coronary artery disease may be associated with plaque instability in coronary arteries [17]. Furthermore, MMP-1 serum levels is positively associated with non-calcified lesions, which have primarily been found in patients presenting with acute coronary syndrome and unstable angina [18-20]. Therefore, over-expression of MMP-1 will increase instability of vulnerable plaque and promote plaque rupture, and subsequently lead to onset of ACS.

MMP-1 -519A/G polymorphism has been demonstrated to increase the promoter activity and

Table 3. Sensitivity analysis

Study omitted	Cases/controls (n)	Crude OR 95% CI				
		Allele (A vs. G)	Homozygote (AA vs. GG)	Heterzygote (AG vs. GG)	Dominant (AA/AG vs. GG)	Recessive (AA vs. AG/GG)
Han et al. (2008)a	222/191	1.44 (0.93, 1.95)	1.92 (1.03, 2.80)	1.13 (0.94, 1.33)	1.42 (0.90, 1.95)	1.64 (0.78, 2.49)
Pablo et al. (2009)	261/194	1.59 (1.05, 2.13)	2.19 (1.21, 3.17)	1.16 (0.96, 1.36)	1.57 (0.99, 2.14)	1.89 (0.99, 2.79)
Xu et al. (2013)	660/914	1.61 (1.03, 2.20)	2.26 (1.11, 3.40)	1.26 (1.03, 1.49)	1.62 (1.02, 2.23)	1.92 (0.95, 2.89)
Pearce et al. (2005)	1026/925	1.59 (0.97, 2.22)	2.18 (0.89, 3.47)	0.90 (0.62, 1.18)	1.54 (0.80, 2.29)	1.92 (0.95, 2.89)
Wang et al. (2010)	295/198	1.42 (0.92, 1.93)	1.80 (0.94, 2.66)	1.12 (0.92, 1.31)	1.27 (0.80, 1.74)	1.72 (0.84, 2.60)
Han et al. (2008)b	404/380	1.29 (0.99, 1.59)	1.31 (0.83, 1.78)	1.12 (0.92, 1.31)	1.17 (0.78, 1.56)	1.43 (0.95, 1.91)

Abbreviation: OR, odds ratio; 95% CI, 95% confidence interval. "a" and "b" indicate that the same author published different article.

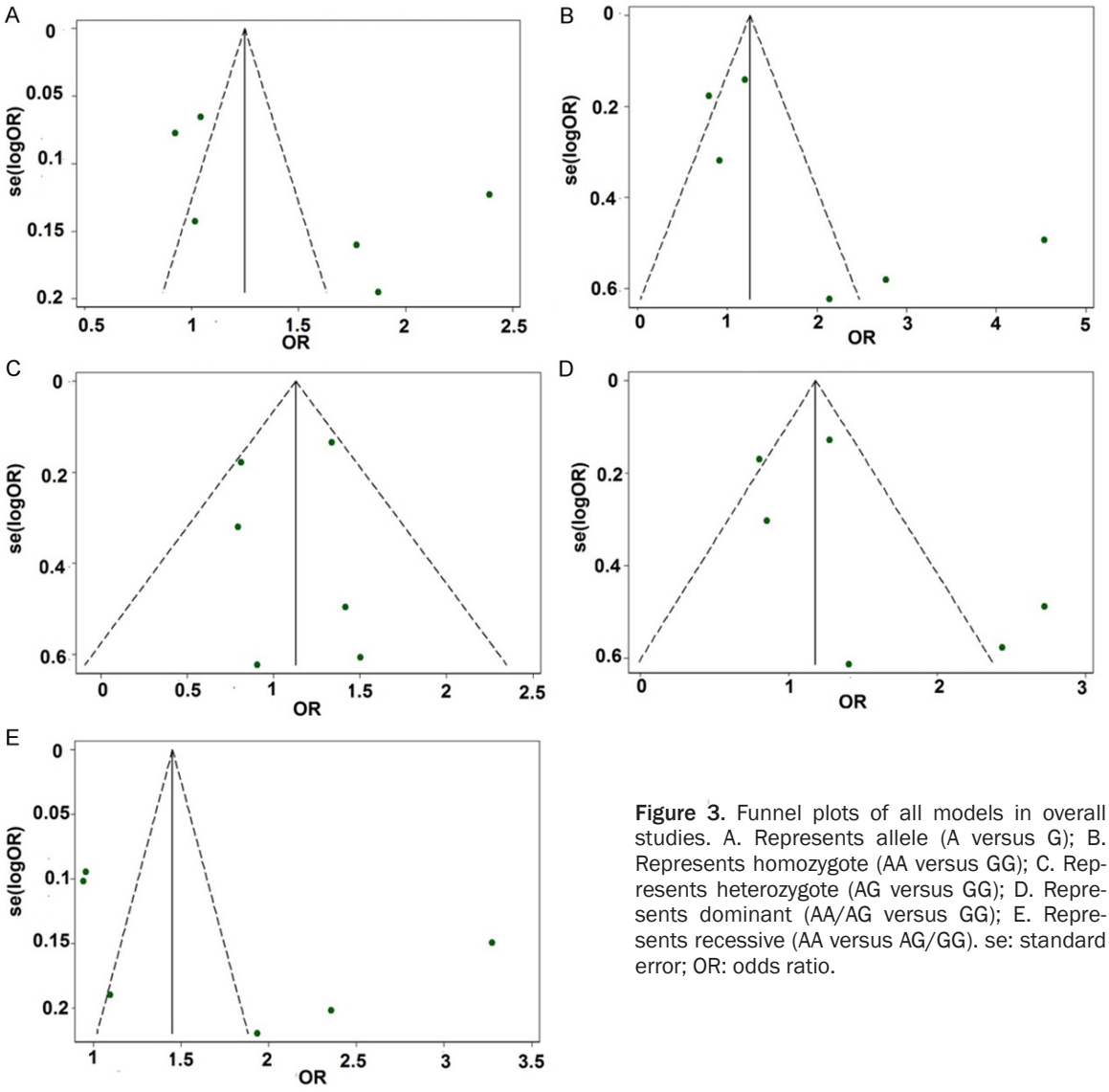

Figure 3. Funnel plots of all models in overall studies. A. Represents allele (A versus G); B. Represents homozygote (AA versus GG); C. Represents heterozygote (AG versus GG); D. Represents dominant (AA/AG versus GG); E. Represents recessive (AA versus AG/GG). se: standard error; OR: odds ratio.

gene expression of MMP-1 [9]. Meanwhile, several studies also confirmed -519A/G polymorphism of MMP-1 may influence the susceptibility to ACS [10-12]. However, Xu et al. and Román-García et al. found no relationship between -519A/G polymorphism and the risk of ACS [13, 14]. Based on these contradicted results, a meta-analysis should be a best way

to determine the association between -519A/G polymorphism and the susceptibility to ACS.

To our knowledge, our study was the first performed to pool published available studies to obtain estimates for association between -519A/G polymorphism and the susceptibility to ACS. This meta-analysis included with 5670 subjects including 2868 ACS patients and 2802 healthy controls from six independent studies. The results demonstrated that MMP-1 -519A/G polymorphism was associated with susceptibility to ACS under allele contrast model and recessive model. Meanwhile, sensitivity analysis indicated that no single study influenced the pooled OR qualitatively for MMP-1 -519A/G polymorphism. This data further enhance the reliability and stability of the meta-analysis results. Furthermore, a subgroup analysis of primary outcome also displayed a remarkable association between MMP-1 -519A/G polymorphism and the susceptibility to either AMI or UA under several genetic models. However, none of association was found by a subgroup analysis of ethnicity.

Similar to other meta-analyses, our study also has some limitations. Firstly, only 6 published studies with total 5670 subjects were included in the final meta-analysis. The sample size is still relatively small and may not provide sufficient statistical power to estimate the correlation between MMP-1 -519A/G polymorphism and the susceptibility to ACS. Therefore, more studies with larger sample size are still needed to accurately provide a more representative statistical analysis. Secondly, the Egger's test indicated a publication bias exists in heterozygote (co-dominant) model. Although a publication bias usually is not avoided in meta-analysis, it may possibly influence the reliability of our study results. Finally, coronary heart disease, especially ACS, is a complex disorder affected by multiple cardiovascular risk factors, such as smoking, diabetes and hypercholesterolaemia [21]. We were unable to adjust the meta-analysis to correct for these risk factors because some information is not uniformly reported and provided by authors.

In conclusion, our meta-analysis suggests that MMP-1 -519A/G polymorphism was associated with the susceptibility to ACS. However, further large scale case-control studies with rigorous design should be conducted to confirm above conclusions in the future. Despite of some limitations, this meta-analysis still gives us new insight into MMP-1 gene associated with the development and progression of ACS.

Disclosure of conflict of interest

None.

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