



Genetic association between inflammatory genes (IL-1 α , CD14, LGALS2, PSMA6) and risk of ischemic stroke: A meta-analysis



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ABSTRACT

Background: Sequence variations in genes involved in inflammatory system are known to contribute to the risk of cerebrovascular diseases (CVD) including stroke. Very few number of studies have been published in the context of the association between Interleukin-1 α (IL-1 α), CD14 cell surface glycoprotein (CD14), Galectin-2-encoding gene (LGALS2) and proteasome subunit type 6 (PSMA6) gene polymorphisms with susceptibility to ischemic stroke (IS).

Objective: The present meta-analysis aimed to provide a comprehensive account of the association between IL-1 α (-C889T and -C511T), CD14 (-C159T), LGALS2 (-C3279T) and PSMA6 (-C8G) gene polymorphisms and susceptibility to IS.

Methods: A literature search for eligible genetic studies published before August 31, 2015 was conducted in the PubMed, Medline, EMBASE, OVID, and Google Scholar databases. Fixed or random effects models were used to estimate the Pooled Odds ratio (OR) and 95% confidence interval (CI) using RevMan 5.3 software.

Results: Total 21 studies were included in our meta-analysis. No significant association was observed between IL-1 α (-C889T) [OR = 1.18, 95% CI: 0.67–2.08, P = 0.58], IL-1 α (-C511T) [OR = 0.95, 95% CI: 0.66–1.37, P = 0.77], LGALS2(-C2379T) [OR = 0.29, 95% CI: 0.02–4.26, P = 0.37] and CD14 (-C260T) [OR = 0.93, 95% CI: 0.77–1.11, P = 0.42] gene polymorphisms and risk of IS. However, protective level of association was observed between PSMA6 (-C8G) gene polymorphism and susceptibility to IS under the recessive model [OR = 0.25, 95% CI: 0.08–0.72, P = 0.01].

Conclusion: Our meta-analysis shows that IL-1 α (-C889T and -C511T), CD14 (-C159T), LGALS2 (-C3279T) and gene polymorphisms are not significantly associated with the risk of IS while PSMA6 (-C8G) gene polymorphism may play a protective role with the susceptibility of IS. Further prospective large epidemiological studies are needed to confirm these findings in different populations.

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Contents

1.	Introduction	22
2.	Materials and methods	22
2.1.	Identification of relevant studies	22
3.	Inclusion and exclusion criteria	22
4.	Data extraction	22
5.	Quality assessment	22
6.	Statistical analysis	22
7.	Results	23
7.1.	IL-1 α gene polymorphism with the susceptibility of IS	23
7.2.	PSMA6 gene polymorphism with the susceptibility of IS	26
7.3.	LGALS2 gene polymorphism with the susceptibility of IS	26
7.4.	CD14 gene polymorphism with the susceptibility of IS	27
8.	Discussion	27

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Funding source	28
Conflict of interest	28
Acknowledgement	29
References	29

1. Introduction

Stroke is among the leading causes of death in the world and a common cause of disability (Feigin et al., 2009; Bevan and Markus, 2011). Its incidence is rising with increasing life expectancy, although about 20% of strokes occur before the age of 65. Ischemic stroke (IS) is a heterogeneous multi-factorial, polygenic, complex disease resulting from the combination of vascular, environmental and genetic factors (Kim et al., 2012). Inflammation and genetics are both prominent mechanisms in the pathogenesis of ischemic stroke (Jin et al., 2010). Candidate genes, stroke susceptible alleles and their association with stroke pathogenesis have been intensively studied in the last few years (Carr et al., 2002; Hansson, 2005; Takashima et al., 2007).

Numerous epidemiological studies in twins and families have revealed that the genetic factors in addition to other risk factors are involved in the predisposition of stroke. Recent findings have suggested that variations in the pro and anti-inflammatory cytokine genes may be associated with the risk of stroke. The genes encoding interleukin-1 α (IL-1 α), CD14 cell surface glycoprotein (CD14), galectin-2-encoding gene (LGALS2) and proteasome subunit type 6 (PSMA6), all of which are involved in the inflammatory mechanisms, were reported to be involved in the pathogenesis of cerebrovascular diseases (Takashima et al., 2007; Ozaki et al., 2006; Um et al., 2003; Wright et al., 1990; DeGraba, 2004).

CD14 is a receptor for bacterial lipopolysaccharide (LPS, endotoxin), and it mediates cell activation by LPS, while IL-1 α acts as a proinflammatory cytokine which contributes to atherogenesis. Increased activity of PSMA6 activates the nuclear factor KB (NF-KB). (NF-KB) is a central transcription factor that regulates the expression of the genes of adhesion molecules and cytokines which are involved in atherogenesis. LGALS2 gene C3279T is encoded by galectin-2 which is thought to reduce the transcriptional level of galectin-2, and also play a role in protection against myocardial infarction. The single nucleotide polymorphisms (SNPs) present in the genes CD14 (-C260T), IL-1 α (-C511T, -C889T), LGALS2 (-C3279T) and PSMA6 (-C8G) respectively, were found to be associated with increased risk of cardiovascular diseases in different populations, but limited studies have been published so far examining these SNPs and their association with susceptibility for IS.

Since a single study may not prove to be sufficient in providing reliable conclusions because of the presence of small amounts of subjects and weight age of statistical and clinical heterogeneities, therefore, we carried out this meta-analysis, which combines the eligible published literatures based on quantitative synthesis to obtain a more convincing assessment of the association between these inflammatory gene polymorphisms and risk of IS.

2. Materials and methods

2.1. Identification of relevant studies

A literature search for eligible candidate gene studies published before August 31, 2015 was conducted in the PubMed, Medline, EMBASE, OVID and Google Scholar databases. The following combinations of main keywords were used: ('Interleukin-1 alpha' or 'IL-1 α ' or 'IL1F1') and ('CD14 cell surface glycoprotein' or 'CD14') and ('Galectin-2-encoding gene' or 'LGALS2' or 'HL14') and ('proteasome subunit type 6' or 'PSMA6') and ('ischemic stroke' or 'cerebral infarction' or

'IS') and ('genetic polymorphism' or 'single nucleotide polymorphisms' or 'SNP'). Fixed or random effects models were used to estimate the Pooled Odds ratio (OR) and 95% confidence interval (CI). Begg's funnel plot was used to assess the publication bias in the studies. Meta-analysis was carried out by using RevMan 5.3 software.

3. Inclusion and exclusion criteria

To be included in the analysis, eligible studies have to meet the following criteria: (1) case-control studies on the association between the IL-1 α (-C889T or -C511T); CD14 (-C260T); LGALS2 (-C3279T); PSMA6 (-C8G) genetic polymorphisms and susceptibility to IS; (2) all patients in the candidate studies meet the diagnostic criteria for IS; (3) studies with sufficient available data to calculate ORs with corresponding 95% CIs. The major reasons for excluding studies were: (1) not a case-control study; (2) duplicate publications with overlapping subjects from the same study; and (3) no available data reported. This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (Moher et al., 2009). No author was contacted regarding the missing information that was required for the meta-analysis to avoid the risk of retrieval bias.

4. Data extraction

According to the PRISMA guidelines, two investigators independently SM and PK checked each full-text report for eligibility and extracted the following data from eligible studies: surname of first author, year of publication, country of origin, ethnicity, definition and number of case and control, age, sex ratio, genotyping method and genotype frequency, etc. Disagreements were solved by discussion between all authors until consensus was reached.

5. Quality assessment

We also evaluated the methodological quality of every study which is included in our analysis using a quality assessment scale developed for genetic association studies (Attia et al., 2003) which was modified by us to increase the relevance of our study. This scale took into account both traditional epidemiological considerations and genetic issues. The scores ranged from 0 (worst) to 16 (best). Details of the scale are presented in Table 1. Two authors independently assessed the quality of included studies. Discrepancies over quality scores were resolved by discussion among all the authors and subsequent consensus was reached.

6. Statistical analysis

Genotype distributions in the controls were tested for confirmation to Hardy-Weinberg equilibrium (HWE) using the chi-square test. The association between the inflammatory genetic polymorphisms and susceptibility to IS was assessed by the pooled OR with their corresponding 95% CI under two genetic models, including dominant and recessive models. Taking into consideration possible heterogeneity between-study, a statistical test for heterogeneity was first conducted using Cochran's Q statistic and I² metric (Higgins et al., 2003). We considered the presence of significant heterogeneity at the 10% level of significance and values of I² exceeding 50% as an indicator of significant heterogeneity. When no heterogeneity was

Table 1
Scale for quality assessment.

Criteria	Score
<i>Representativeness of cases</i>	
Selected from any population disease registry or multiple center sites	2
Selected from any cardiology/neurology	1
Not described	0
<i>Source of controls</i>	
Population or neighbor based	3
Hospital based	2
Healthy volunteers with total description	1
Healthy volunteers without total description	0.5
Not described	0
<i>Matching of controls</i>	
Age & sex match	2
Smoking, hypertensive, diabetics	1
Not matched	0
<i>Ascertainment of IS</i>	
Adequate confirmation	2
Diagnosis of IS by patient medical record	1
Not described	0
<i>Ascertainment of controls</i>	
Stroke free status by using appropriate QVSS or CT/MRI	1
Not described	0
<i>Genotyping</i>	
Genotyping done under blinded conditions	1
Unblinded or not mentioned	0
<i>Genotyping method</i>	
DNA sequencing/multiplex PCR	2
PCR-RFLP	1
Others	0
<i>HWE</i>	
Allelic frequency in accordance HWE	2
Not HWE but followed statistics to adjust confounding	1
Not checked	0
<i>Association assessment</i>	
Appropriate statistics and examining confounders and effect modifiers	1
Inappropriate statistics used	0
Total score	16

found with $P < 0.10$ or I^2 , 50%, a fixed-effect model was used to estimate the pooled ORs and 95% CIs. Otherwise, a random-effect model was applied. Begg's funnel plot was used to assess the potential for publication bias.

7. Results

A total of 99 published articles were identified by using the pre-specified search strategy. Fig. 1 depicts a flow chart of both the retrieved and excluded studies with their reasons for exclusion. Out of 99 retrieved articles, 42 studies were excluded due to its irrelevancy to our interest and 9 studies were excluded as they were in duplicate records. Keeping the inclusion criteria in mind, 21 case-control studies were included in our meta-analysis. Studies were carried out in two major ethnic populations; 9 studies were in Asian and the other 11 studies were in Caucasian population. The publication years of the included studies ranged from 2000 to 2013. 17 studies in this meta-analysis had controls in HWE. The quality scores of all included studies were moderately high. Out of 21 studies, 8 studies had hospital based and 13 studies had population based source of controls. Begg's funnel plot suggested significant publication bias in the studies (Fig. 3). Table 2 gives a summary of the characteristics and methodological quality of all the included studies.

7.1. IL-1 α gene polymorphism with the susceptibility of IS

For C889T, six case-control studies with a total of 2809 IS patients and 2854 controls showed a non-significant association with susceptibility to IS under dominant [TT + TC vs. CC: OR = 1.18, 95% CI: 0.67–2.08, $P = 0.58$], and recessive models [TT vs. CC + TC: OR = 1.15, 95% CI: 0.82–1.62, $P = 0.43$] (Fig. 2).

For C511T, 10 case-control studies with a total of 2718 IS patients and 2748 controls showed a non-significant association with susceptibility to IS under dominant [TT + TC vs. CC: OR = 0.95, 95% CI: 0.66–1.37, $P = 0.77$] and recessive models [TT vs. CC + TC: OR = 1.17, 95% CI: 0.88–1.54, $P = 0.28$] (Fig. 2).

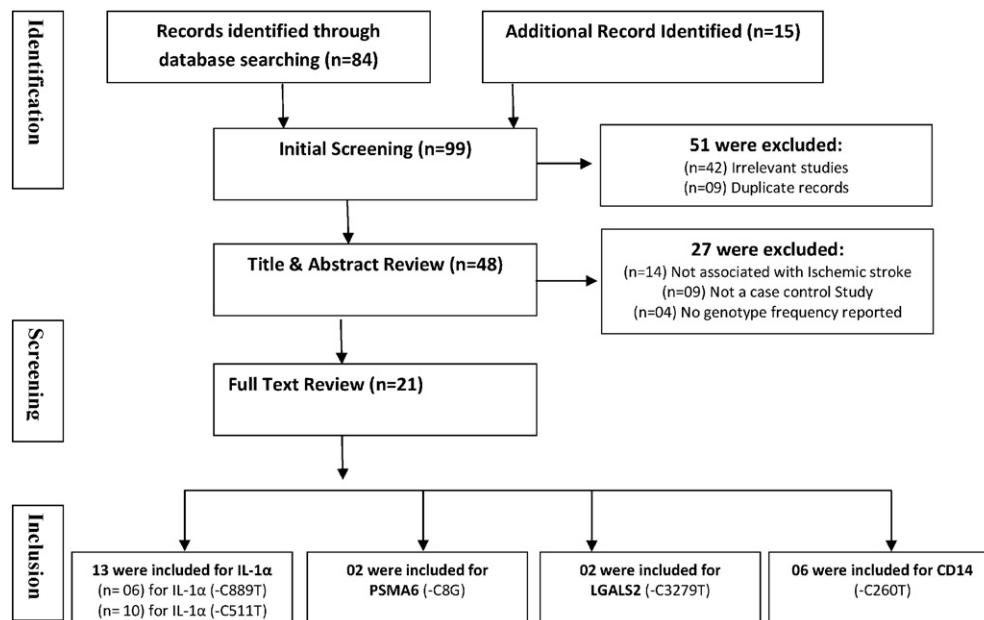


Fig. 1. Flow diagram of the selection of studies and specific reasons for exclusion from the present meta-analysis.

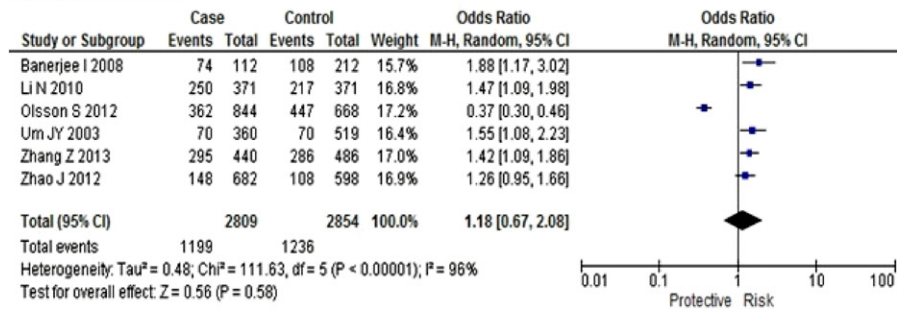
Table 2Characteristic of studies included in the meta-analysis of the association of TNF- α gene polymorphism with the risk of ischemic stroke.

S. no	Author, year	Origin	Ethnicity	Sample size case(N)/ control(N)	Gene polymorphism	Variant	PCR-method	Matching criteria	M/F Case M/F Control M/F	Age Case/ control	HWE	Source of control	Quality score
1.	Banerjee I, 2008 (Banerjee et al., 2008)	India	Asian	112/212	IL-1 α PSMA6	C889T 8C/G	PCR-RFLP	Age–sex and geography	72/40 143/69	58.6 \pm 14.2 57.4 \pm 8.8	Yes	HB	10
2.	Olsson S, 2012 (Olsson et al., 2012)	Sweden	Caucasian	844/668	IL-1 α	C889T C511T	NA	Age–sex	554/290 392/276	59 (51–64) 58 (50–64)	Yes	PB	12
3.	Li N, 2010(Li et al., 2010)	China	Asian	371/371	IL-1 α	C889T C511T	PCR-RFLP	NA	230/141 247/124	63.88 \pm 7.36 62.87 \pm 7.57	Yes	PB	12
4.	Zhao J, 2012 (Zhao et al., 2012)	China	Asian	682/598	IL-1 α	C889T	PCR-RFLP	Age–sex	403/279 336/262	62.09 \pm 9.43 61.84 \pm 10.12	Yes	HB	13
5.	Zhang Z, 2013 (Zhang et al., 2013)	China	Asian	440/486	IL-1 α	C889T C511T	PCR-sequencing	Age–sex	291/149 314/172	66.6 \pm 8.4 66.1 \pm 5.2	Yes	HB	13
6.	Zee RYL, 2008 (Zee et al., 2008)	USA	Caucasian	258/258	IL-1 α	C511T	ABI fluorescence-based allelic discrimination	Age–smoking	Geography	62.1 \pm 0.5 61.7 \pm 0.5	Yes	PB	11
7.	Um JY, 2003 (Um et al., 2003)	Korea	Asian	360/519	IL-1 α	C889T	PCR-RFLP	Age–sex	177/183 250/269	61.0 \pm 14.5 62.2 \pm 9.8	Yes	HB	10
8.	Lai J, 2006	China	Asian	112/95	IL-1 α	C511T	PCR-RFLP	Geography	72/40 60/35	56.9 \pm 13.1 57.4 \pm 10.0	Yes	PB	11
9.	Dziedzic T, 2005 (a)	Poland	Caucasian	122/227	IL-1 α	C511T	PCR-RFLP	Age–sex	66/56 123/104	63.2 \pm 12.4 62.8 \pm 12.4	Yes	HB	12
10.	Dziedzic T, 2005 (b)	Poland	Caucasian	221/219	IL-1 α	C511T	PCR-RFLP	Age–sex	91/130 94/125	70.4 \pm 13.1 69.2 \pm 13.0	Yes	HB	12
11.	Rubattu S, 2005	Italy	Caucasian	115/180	IL-1 α	C511T	PCR-RFLP	Age	51/64 98/82	35.95 \pm 8.12 34.7 \pm 6.9	Yes	PB	12
12.	Lacoviello L, 2005	Italy	Caucasian	134/134	IL-1 α	C511T	DNA sequencing	Age–sex	69/65 65/65	35 \pm 7 35 \pm 8	Yes	PB	15
13.	Seripa D, 2003	Italy	Caucasian	101/110	IL-1 α	C511T	PCR-RFLP	Age	51/50 60/50	65.8 \pm 10.4 63.7 \pm 14.0	Yes	PB	12
14.	Freilinger T, 2009 (Freilinger et al., 2009)	Germany	Caucasian	601/736	PSMA6 LGALS2	8C/G C3279T	MALDI-TOF mass spectrometry	Age–sex	377/– 447/–	64/– 62/–	Yes	HB	10
15.	Szolnoki Z, 2009 (Szolnoki et al., 2009)	Hungary	Caucasian	385/303	LGALS2	C3279T	PCR-RFLP	NA	222/163 201/102	67.4 \pm 13.65 57.4 \pm 14.3	Yes	HB	9
16.	Lin TM, 2008 (Lin et al., 2008)	Taiwan	Asian	450/450	CD14	C260T	PCR-RFLP	Age–sex	248/202 252/198	64.2 \pm 12.7 63.2 \pm 12.3	No	PB	10
17.	Lichy C, 2002 (Lichy et al., 2002)	Germany	Caucasian	151/149	CD14	C260T	PCR-RFLP	Age–sex	107/44 109/40	59.7 \pm 10.8 58.1 \pm 10.1	No	PB	10
18.	Zee RYL, 2002 (Zee et al., 2002)	USA	Caucasian	338/338	CD14	C260T	PCR-FRLP	Age–smoking	NA	61.0 \pm 8.3 60.5 \pm 8.2	Yes	HB	11
19.	Ito D, 2000 (Ito et al., 2000)	Japan	Asian	235/309	CD14	C260T	PCR-RFLP	Age–sex	183/52 238/71	58.3 \pm 7.8 58. \pm 64.4	No	HB	9
20.	Kis Z, 2007 (Kis et al., 2007)	Hungary	Caucasian	59/52	CD14	C260T	Nested PCR	NA	38/21 26/26	52.8 50.4	No	HB	8
21.	Park MH, 2006	Korea	Asian	125/125	CD14	C260T	PCR-RFLP	Age–sex	63/62 63/62	66.74 \pm 7.69 66.84 \pm 7.86	Yes	HB	13

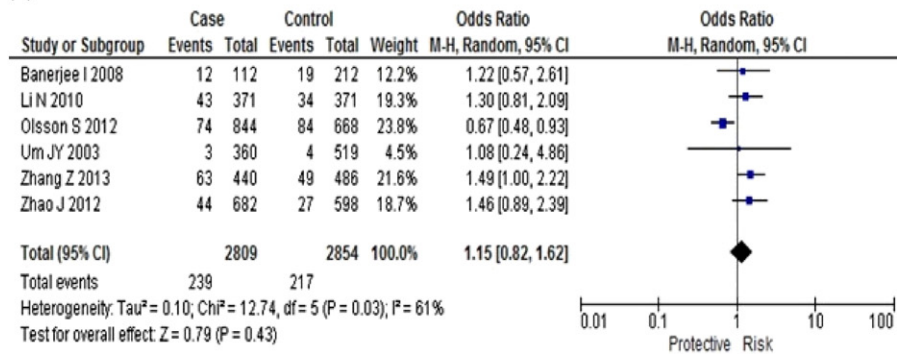
Abbreviations: PCR – polymerase chain reaction; RFLP – restriction fragment length polymorphism; M – male; F – female; NA – not available; PB – population based; HB – hospital based; MALDI-TOF – matrix assisted laser desorption ionization-time of flight; and HWE – Hardy Weinberg equilibrium.

1. IL1α- C889T

(a)Dominant Model

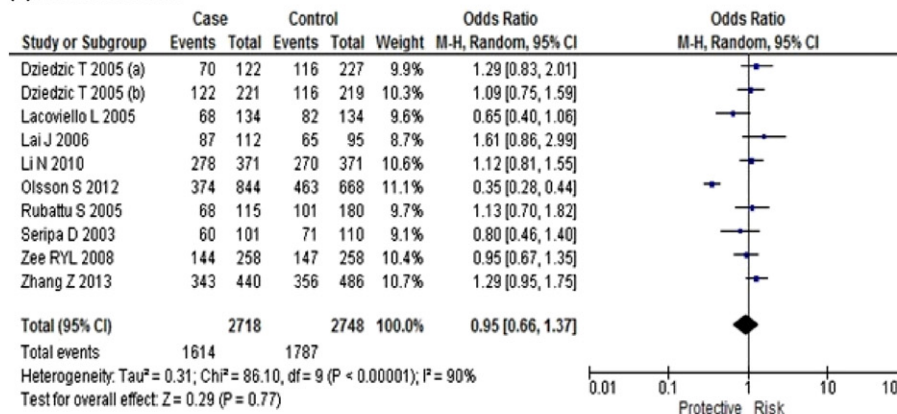


(b)Recessive Model



2. IL1α-C511T

(a)Dominant Model



(b)Recessive Model

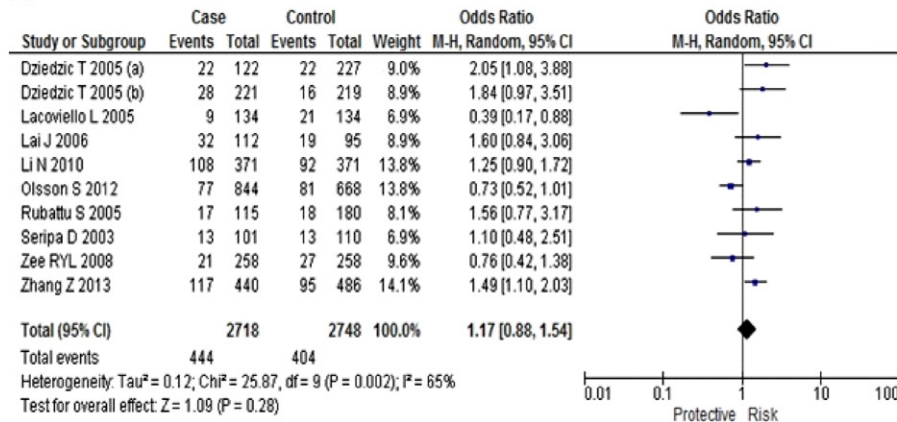
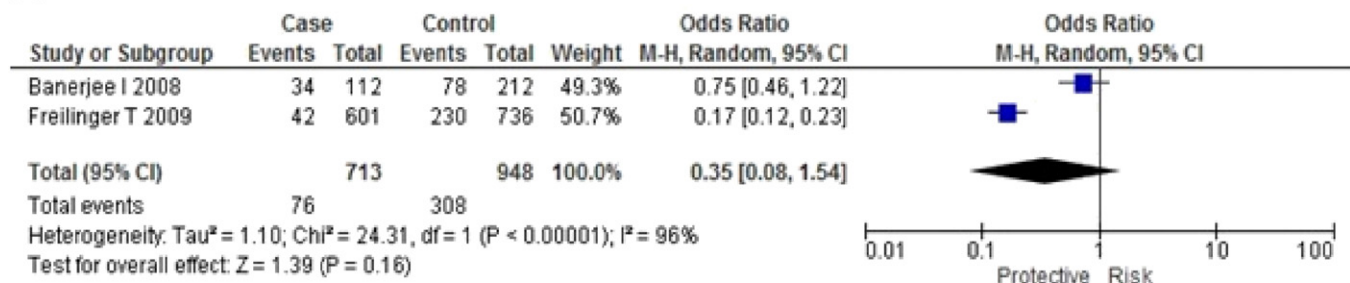


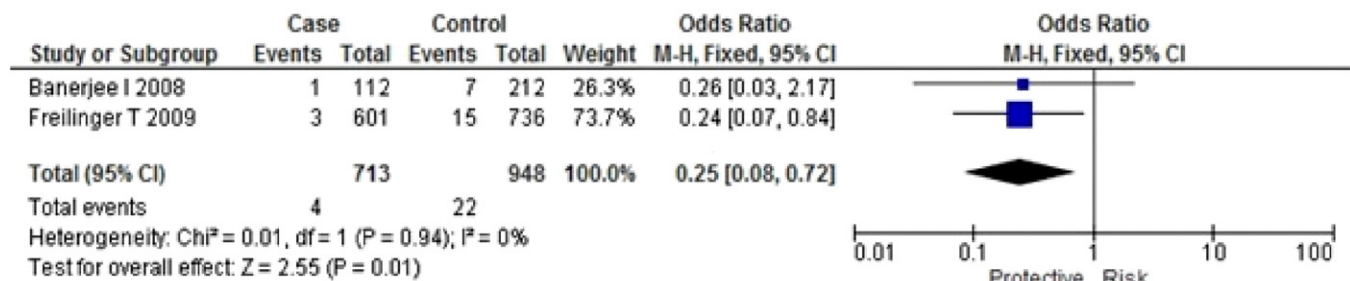
Fig. 2. Forest plot for the association between (1) IL1α-C889T, (2) IL1α-C511T, (3) PSMA6-C8G, (4) LGALS2-C3279T and (5) CD14-C260T gene polymorphisms and IS risk under (A) dominant model, (B) recessive model.

3. PSMA6- C8G

(a) Dominant Model

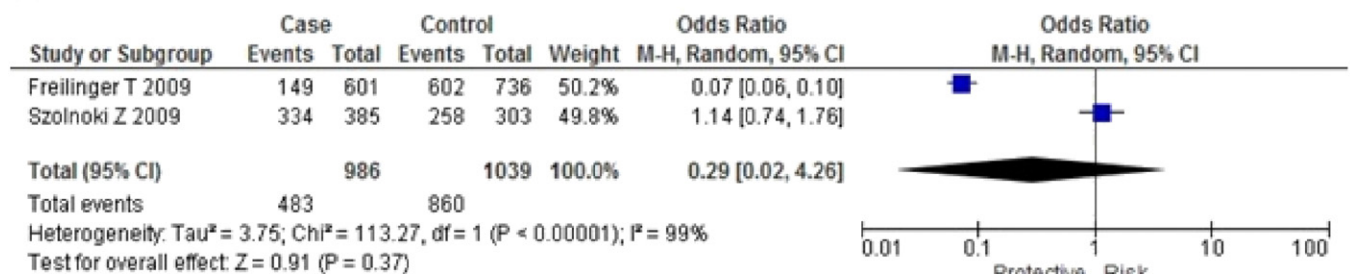


(b) Recessive Model



4. LGALS2- C3279T

(a) Dominant Model



(b) Recessive Model

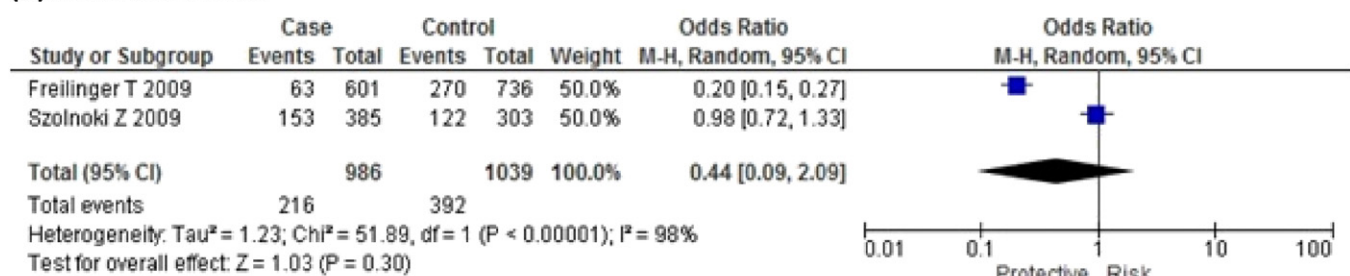


Fig. 2 (continued).

7.2. PSMA6 gene polymorphism with the susceptibility of IS

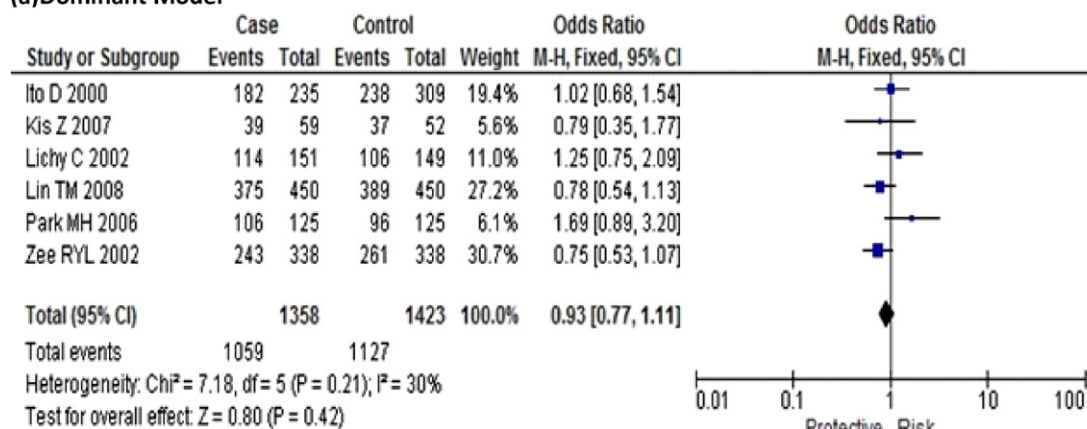
For PSMA6-C8G genetic polymorphism, two case-control studies with a total of 713 IS patients and 948 controls showed a non-significant association with susceptibility to IS under dominant model [GG + GC vs. CC: OR = 0.35, 95% CI: 0.08–1.54, P = 0.16] and a protective level of association with the recessive model [GG vs. CC + GC: OR = 0.25, 95% CI: 0.08–0.72, P = 0.01] (Fig. 2).

7.3. LGALS2 gene polymorphism with the susceptibility of IS

For LGALS2-C2379T genetic polymorphism, two case-control studies with a total of 986 IS patients and 1039 controls showed a non-significant association with susceptibility to IS under dominant [TT + CT vs. CC: OR = 0.29, 95% CI: 0.02–4.26, P = 0.37] and recessive models [TT vs. CC + TC: OR = 0.44, 95% CI: 0.09–2.09, P = 0.30] (Fig. 2).

5. CD14- C260T

(a) Dominant Model



(b) Recessive Model

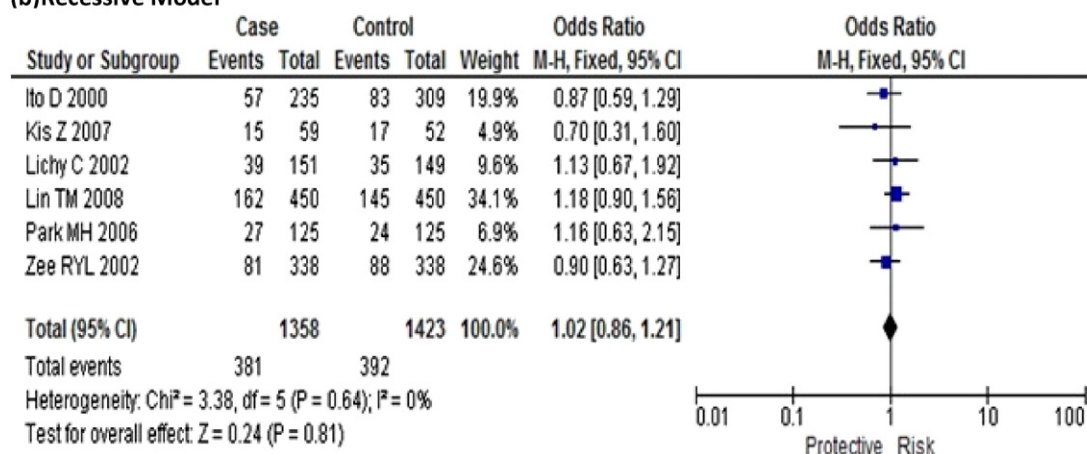


Fig. 2 (continued).

7.4. CD14 gene polymorphism with the susceptibility of IS

For CD14-C260T genetic polymorphism, six case-control studies with a total of 1358 IS patients and 1423 controls showed a non-significant association with susceptibility to IS under dominant [TT + TC vs. CC: OR = 0.93, 95% CI: 0.77–1.11, $P = 0.42$] and recessive models [TT vs. CC + TC: OR = 1.02, 95% CI: 0.86–1.21, $P = 0.81$] (Fig. 2).

8. Discussion

In our comprehensive meta-analysis, five SNPs of four genes involving 21 studies with 6216 IS cases and 6539 controls were analyzed. Our findings suggest that the variants in the inflammatory genes did not show any significant association with the risk of IS. No significant association was observed under both dominant and recessive models of IL-1 α (-C889T and -C511T), CD14 (-C159T), LGALS2 (-C3279T) and dominant model of PSMA6 (-C8G) gene polymorphisms with the risk of IS. However, the recessive model of PSMA6 (-C8G) gene polymorphism showed a protective level of association with susceptibility to IS. Our findings are consistent with the recently published meta-analysis of IL-1 α showing no significant association with the risk of IS for C511T, however Zou et al. (2015) concluded that IL-1 α (-C889T) was found to be associated with the risk of IS (Zou et al., 2015). Previous meta-analysis by Ye et al. (2012) also showed no association for IL-1 α (C889T and C511T) with the risk of IS in overall population. But, T allele

of IL-1 α C511T showed a 1.97 fold risk of IS in Polish population compared with the control group. It may be possible that the effect of IL-1 α C511T polymorphism on IS risk might be modified by age or other unknown factors (Ye et al., 2012). Meta-analysis published by Pu et al. (2013) suggested that CD14 (-C260T) polymorphism is a risk factor of coronary heart disease (CHD), especially in East Asians (Pu et al., 2013).

Our meta-analysis is the first meta-analysis to report the association of inflammatory gene polymorphisms with the risk of IS to the best of our knowledge. Overall findings did not observe any significant association between IL-1 α (-C889T and -C511T), CD14 (-C159T), LGALS2 (-C3279T) and PSMA6 (-C8G) gene polymorphisms and risk of IS. The present meta-analysis must be interpreted with caution because of certain limitations. First, the studies included in meta-analysis were varied in ethnicity, age and environmental factors. Second, the use of different methodologies for genotyping method, selection of controls and matching criteria may lead to heterogeneity. Therefore, more credible evidences are required to illustrate solid conclusions on the association between inflammatory gene polymorphisms and risk of IS.

In summary, our meta-analysis shows that IL-1 α (-C889T and -C511T), CD14 (-C159T), LGALS2 (-C3279T) and gene polymorphisms are not significantly associated with the risk of IS while PSMA6 (-C8G) gene polymorphism may play a protective role with the susceptibility of IS. Further prospective large epidemiological studies are needed to confirm these findings.

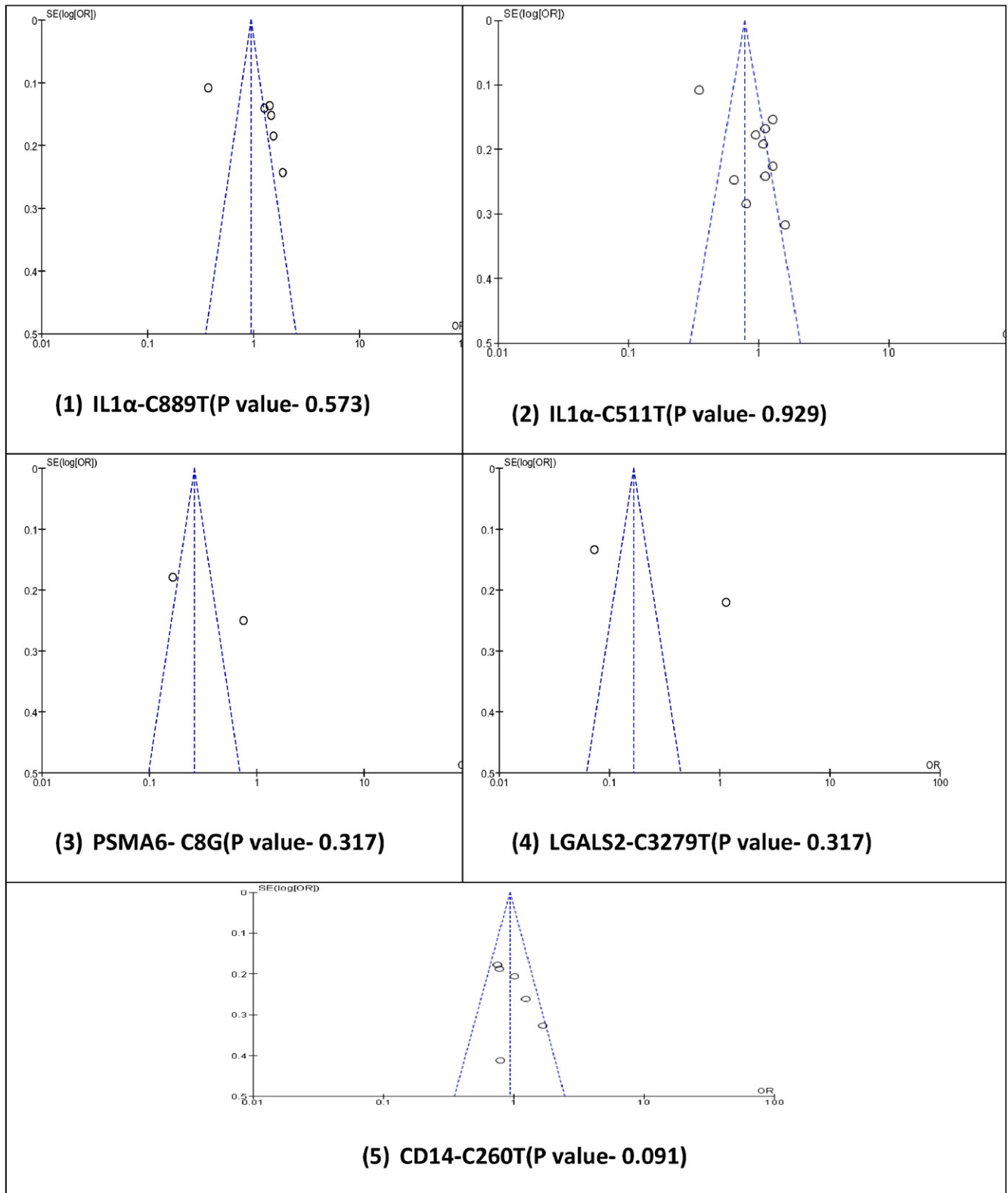


Fig. 3. Begg's funnel plot for assessing publication bias for (1) IL1 α -C889T, (2) IL1 α -C511T, (3) PSMA6- C8G, (4) LGALS2-C3279T and (5) CD14-C260T gene polymorphisms.

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Conflict of interest

No potential conflict of interest.

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