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Association between the interleukin-6 genetic polymorphism 174 G/C and thrombosis disorder risk

Meta-analysis of 10,549 cases and 19,316 controls

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Abstract

Studies investigating the association between interleukin-6 (*IL-6*) gene-174 G/C polymorphism (rs1800795) and thrombosis disorder risk reported conflicting results. The aim of our study was to assess the association between the *IL-6* gene 174 G/C polymorphisms and the risk of thrombosis disorders.

Thirty four case–control studies in 29 articles with 29,865 individuals were incorporated in this meta-analysis by searching the public databases including Medline, Embase, and ISI Web of Science databases as of June 1st, 2015. The odds ratio (OR) and 95% confidence interval (95%CI) were used to assess the strength of the association.

By pooling all studies, there was marginal association between and the risk of thrombotic disorders (1.09[0.97–1.22]), arterial thrombotic disorders (1.08[0.95–1.23]), and myocardial infarction (MI, 1.14[0.99–1.32]) under dominant genetic effect (C carriers vs GG). In subgroup analyses stratified by ethnicity, study scale, thrombotic category, and country, the results indicated that *IL-6* gene-174 G/C polymorphism was significantly associated with increased risk of thrombotic disorders given the conditional such as Asians, large sample-sized, MI, population-based, and Indian studies (C carriers vs GG: 1.39 [1.13–1.72] and C allele vs G allele: 1.36 [1.18–1.56] for Asian; C carriers vs GG: 1.15 [1.01–1.31] and C allele vs G allele: 1.12 [1.01–1.23] for large sample-sized studies; C allele vs G allele: 1.10 [1.03–1.18] for population-based studies; and C carriers vs GG: 1.40 [1.19–1.65] for Indian studies). We did not observe significant association between *IL-6*-174 G/C and the risk of Caucasians, small sample-sized studies, stroke and venous studies, and other country studies.

This meta-analysis suggests that *IL-6* gene-174 G/C polymorphism may be marginally associated with risk of thrombotic disorders, arterial disorders, MI especially for Asian, Indian, population-based, and large sample-sized studies. More studies with larger sample size and well-designed studies might be warranted.

Abbreviations: CI = confidence interval, CRP = C-reactive protein, HWE = Hardy–Weinberg equilibrium, IL-6 = interleukin-6, IS = ischemic stroke, MI = myocardial infarction, NOS = Newcastle–Ottawa Scale, OR = odds ratio.

Keywords: IL-6, meta-analysis, polymorphism, thrombosis disorders

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1. Introduction

Arterial and venous thrombotic disorders, including myocardial infarction (MI) and ischemic stroke (IS) which are common and frequently fatal events, are hypothesized to share some etiologic pathway. Despite recent advances in effective prevention and acute thrombotic disorders intervene is a vital strategy to reduce the overall burden of thrombotic disorders worldwide. Epidemiologic studies show the favored model and the polygenic foundation for the pathophysiologic mechanism of thrombotic disorders is an interaction between genetic/cultural background and identified risk factors.[1,2] Numerous genetic/congenital, acquired, and environmental risk factors can keep the balance in favor of coagulation, which exists between fibrinolytic and anticoagulant forces and procoagulant (clotting) forces, predisposing to the pathologic thrombi formation in arteries (e.g., MI, IS) and veins (e.g., deep venous thrombosis).[3] Subsequent thrombi may lead to detach and embolize to obstruct a distant blood vessel or block blood flow at the site of thrombi formation and define the risk of thrombotic disorders (e.g., pulmonary embolism, embolic stroke).[3]

Arterial, venous thrombotic disorders and system inflammation are 2 closely correlated entities, which measured by predisposing factors (such as genetic, acquired, and environmental factors) and

activity or quantity of natural anticoagulant molecules in human plasma and tested for specific human gene defects.[3] Interleukin-6 (IL-6) is a pleiotropic cytokine related with atherosclerosis and cardiovascular diseases which may also be a pivotal mediator in the inflammatory response to cerebral ischemia.[4] The human IL-6 gene is mapped to chromosome 7p21-24 region,[5] containing of 4 introns and 5 exons. Among the mutations described, the 174 G/C (namely rs1800795), polymorphism in the IL-6 promoter region was detected the association with tuberculosis,[6] Alzheimer disease,[7] and multiple sclerosis,[8] although other reports failed to confirm these relationships.[9,10]

A common single nucleotide polymorphism at position -174 (IL-6-174 G/C, namely rs1800795) of the IL-6 gene promoter is demonstrated to impact the adherence of the glucocorticoid receptor and then results in repressive transcriptional activation.[5,11] Recently, increasing studies reported the role of this polymorphism in the predisposition to thrombotic disorders including MI, IS, and venous thromboembolism.[2,4,12] However, the conclusions are rather inconsistent, partially caused by the relative statistics power which stems from small sample size and diverse origins of incorporated studies. To our best knowledge, there is no meta-analysis involving in the IL-6 gene-174 G/C polymorphism and the risk of whole thrombotic disorders available up to now. Therefore, we carried out the meta-analysis to explore the relationship between IL-6 gene-174 G/C polymorphism and the susceptibility to thrombotic disorders based on the eligible published papers.

2. Methods

2.1. Publication search

This study was with approval by the Ethics Committee of Huazhong University of Science and Technology and Shidong Hospital, thus we assessed the association between the IL-6 genetic polymorphism 174 G/C and thrombosis disorder risk using meat-analysis. All published literatures investigating the association between polymorphism of IL-6 gene and the risk of thrombotic disorders were systematically searched using several electronic databases (Pubmed, EBASE, and ISI Web of Science database) as of June 1, 2015 using the following search terms: "myocardial infarction" or "stroke or venous thrombosis," "pulmonary embolism" and "interleukin-6" or "IL-6" in combination with "polymorphism," "mutation" or "variant." Selection criteria in our meta-analysis incorporated: the association of 174 G/C polymorphism of IL-6 gene and risk of thrombotic disorders in English articles must be evaluated, detailed genotype frequency in participants (cases and controls) to assess odds ratios (ORs) and corresponding 95% confidence intervals (CIs), and studies with no deviation from Hardy–Weinberg equilibrium (HWE) in genotype distribution of the control subjects were included. For the exclusion criteria, we used as follows: without original data for the calculation of ORs and the corresponding 95% CIs in case and control studies; we incorporated only the largest or most recent studies when overlapping or repeat publications; and papers classified as reviews, abstracts, or case reports.

2.2. Data extraction

Two authors (HR and YY) independently extracted all potentially eligible reports and reached an agreement on all information. In case of disagreement, a 3rd author (YZ) would check these studies. The following information were collected and applied from the studies: 1st author, publication year,

ethnicity/race, thrombotic disorder category, source of control, genotyping approaches, total number of case and control participants, and genotype distributions in all subjects of cases and controls.

2.3. Statistical analysis

For each study, by using an Internet-based program (http://ihg2. helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl), we first examined whether the genotype distribution in controls was according to HWE. The strength of the association between the G/C polymorphism and thrombotic risk was measured by ORs and 95% CI. The statistical significance of summary OR was determined with Z-test. We first estimated the risk of with 3 models including recessive model (CC vs GG + GC) and dominant model (CC + GC vs GG) and then evaluated variant genotype CC and compared with the wild-type GG homozygote. We also estimated the risks of C allele versus G allele and GC versus GG.

A Chi-squared-based Q-statistic test was assessed to identify the statistical heterogeneity across studies (presence of heterogeneity was considered if $P < 0.10$). In the condition of absent of statistical heterogeneity (when the P-value is >0.10), a random-effect model was applied to the pooled OR of each study was calculated by the fixed-effects model (Mantel–Haenszel method); otherwise the fixed-effect model was selected (DerSimonian and Laird method). Z test was carried out to determine the statistical significance of pooled ORs.[13] In addition to overall analysis, subgroup evaluations were conducted according to ethnic group and thrombotic disorder category. Sensitivity analysis was performed through removing each study in turn to evaluate the stability of the results.[14]

Potential publication bias was analyzed by the funnel plot of the ORs versus their standard errors.[15] The Begg test and Egger test were also carried out to statistically observe the publication bias.[16,17] All statistical tests were analyzed by using the software STATA 12.0 (STATA Corporation, College Station, TX).

3. Results

As presented in Fig. 1, a total of 34 eligible and no overlap case–control reports in 29 research articles, assessing 10,549 cases and 19,316 controls were incorporated in our current meta-analysis, and there were 18 studies about MI[2,12,18–29] in 14
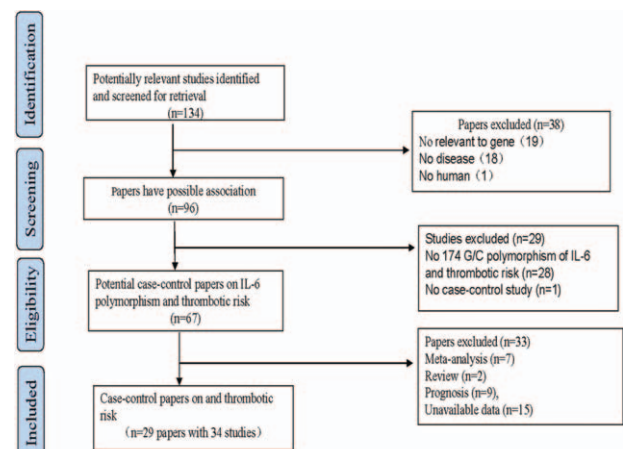
Figure 1. Flow diagram summarizing the search strategy for meta-analysis of 174 G/C polymorphism of interleukin-6 (IL-6) and the risk of thrombotic diseases.

Table 1

Characteristics of studies included in our meta-analysis.

| First author | Disease | Country | Ethnic origin | Year | Genotype | | | | | | MAF | HWE (controls) |
| | | | | | GG | | GC | | CC | | | |
					No. of cases	No. of controls	No. of cases	No. of controls	No. of cases	No. of controls		
Humphries	MI	UK	Caucasians	2001	40	827	95	1263	25	470	0.45	0.75
Georges (1)	MI	Sweden	Caucasians	2001	170	231	340	336	104	105	0.45	0.35
Georges (2)	MI	Germany	Caucasians	2001	45	47	109	97	32	28	0.47	0.06
Nauck	MI	Germany	Caucasians	2002	436	230	668	355	261	144	0.44	0.74
Bennet (1)	MI	Sweden	Caucasians	2003	210	278	402	500	200	235	0.49	0.73
Bennet (2)	MI	Sweden	Caucasians	2003	95	120	175	254	75	113	0.47	0.34
Licastro	MI	Italy	Caucasians	2004	35	46	88	44	15	7	0.43	0.25
Lieb	MI	Germany	Caucasians	2004	451	331	627	499	244	193	0.42	0.84
Kelberman (1)	MI	UK	Caucasians	2004	89	71	100	120	40	53	0.39	0.86
Kelberman (2)	MI	UK	Caucasians	2004	138	169	119	120	21	28	0.29	0.32
Rosner	MI	USA	Caucasians	2005	204	822	233	973	85	294	0.39	0.82
Chiappelli (1)	MI	UK	Caucasians	2005	35	101	88	81	15	22	0.43	0.35
Chiappelli (2)	MI	France	Caucasians	2005	36	26	24	25	6	2	0.27	0.17
Sie (1)	MI	Italy	Caucasians	2006	44	673	54	849	21	288	0.4	0.5
Sie (2)	MI	Italy	Caucasians	2006	29	1142	43	1505	17	556	0.43	0.12
Bennermo	MI	Sweden	Caucasians	2010	119	109	150	176	87	93	0.46	0.19
Coker	MI	Turkey	Caucasians	2011	102	141	56	81	9	13	0.22	0.76
Biswas	MI	India	Asian	2014	348	407	139	92	13	1	0.09	0.07
Revilla	IS	Spain	Caucasians	2002	27	37	40	39	15	6	0.43	0.83
Pola	IS	Italy	Caucasians	2003	56	28	48	58	15	47	0.33	0.55
Greisenegger	IS	Australia	Caucasians	2003	81	76	96	108	37	30	0.4	0.27
Flex	IS	Italy	Caucasians	2004	100	56	115	99	22	68	0.34	0.22
Karahan	IS	Turkey	Asians	2004	54	55	24	22	8	6	0.23	0.14
Chamorro	IS	Spain	Caucasians	2004	104	46	134	50	35	9	0.37	0.37
Balding	IS	Ireland	Caucasians	2004	33	123	60	198	12	68	0.4	0.93
Lalouschek	IS	Austria	Caucasians	2006	143	156	187	192	74	67	0.41	0.54
Banerjee	IS	India	Asians	2007	123	156	53	52	0	4	0.15	0.09
Tong	IS	China	Asians	2010	99	98	1	2	0	0	0.005	0.05
Chakraborty	IS	India	Asian	2013	57	73	35	39	8	8	0.26	0.38
Xuan	IS	China	Asian	2014	205	246	170	171	55	44	0.54	0.08
Pieroni	VTE	Brazil	Caucasians	2006	217	232	172	153	32	35	0.28	0.18
Vormittag	VTE	Australia	Caucasians	2006	72	50	126	48	35	24	0.42	0.05
Beckers	VTE	Netherland	Caucasians	2010	38	116	49	165	21	44	0.42	0.22
Matos	VTE	Brazil	Caucasians	2011	70	75	41	46	8	5	0.24	0.53

HWE = Hardy–Weinberg equilibrium, IL-6 = interleukin-6, IS = ischemic stroke, MAF = minimum allele frequency, MI = myocardial infarction, VTE = venous thromboembolism.

papers, 12 studies about IS[3,30–40] in 12 papers, and 4 studies about venous thrombosis in 4 papers.[41–44] Among the 29 papers regarding on *IL-6* and thrombosis disorders, 6 studies were conducted in Asian populations,[4,28,29,34,38–40] containing Chinese, India; 28 studies were conducted in Caucasians, including Italians, Germans, English, and so on; no study was assessed about the Africans. The controls in 6 studies were from hospitalized-based patients,[18,27,31–33,45] and 28 studies were from on healthy-based subjects. The detailed characteristics of the genotype distributions in case and control groups in this meta-analysis are presented in the Table 1 and Supplemental Table 1, http://links.lww.com/MD/B89.

We first analyzed the influence on the overall incidence of thrombotic disorders. Then subgroup analyses were performed on the types of thrombotic disorders, ethnicity, country, study design, etc. As shown in Tables 2 and 3, overall analyses showed that there were marginal associations between *IL-6 gene-174 G/C* polymorphism and risks of thrombotic disorders (OR [95% CI]: 1.09 [0.97–1.22] for C carriers vs GG, $P_{heterogeneity} < 0.01$; 1.05 [0.96–1.14] for C allele vs G allele, $P_{heterogeneity} < 0.01$).

Subgroup analyses according to types of thrombotic disorders showed that *IL-6 G/C* was significantly associated with risk of MI (1.14[0.99–1.32] for C carriers vs GG, $P_{heterogeneity} < 0.01$; 1.08 [0.99–1.18] for C allele vs G allele, $P_{heterogeneity} < 0.01$, Fig. 2), marginally associated with the risk of arterial thrombotic disorders (1.08[0.95–1.23] for C carriers vs GG, $P_{heterogeneity} < 0.01$), but not associated with IS (0.95[0.73–1.24] for C carriers vs GG, $P_{heterogeneity} < 0.01$) and venous thrombotic disorders (1.17[0.97–1.42] for C carriers vs GG, $P_{heterogeneity} = 0.99$).

When analyzing for ethnicity, *IL-6 gene-174 G/C* was suggested to be associated with risks for the thrombotic disorders for Asians (1.99 [0.82–3.09] for CC vs GG, $P_{heterogeneity} = 0.15$; 1.39 [1.13–1.72] for C carriers vs GG, $P_{heterogeneity} = 0.26$; 1.36 [1.18–1.56] for C allele vs G allele, $P_{heterogeneity} = 0.11$), but not for Caucasians (0.97 [0.85–1.09] for CC vs GC, $P_{heterogeneity} = 0.003$; 1.05 [0.93–1.18] for C carriers vs GG, $P_{heterogeneity} < 0.01$) (Supplemental Fig. 1, http://links.lww.com/MD/B89).

When analyzing by countries, we found that *IL-6 gene-174 G/C* was associated with risks of the thrombotic disorders for India (1.40 [1.19–1.65] for C carriers vs GG, $P_{heterogeneity} = 0.17$), but not associated with Sweden (1.03 [0.91–1.15] for C allele vs G allele, $P_{heterogeneity} = 0.12$), not for German (0.98 [0.87–1.10] for CC vs G carriers, $P_{heterogeneity} = 0.94$), Italians (0.67 [0.36–1.25] for CC vs CG, $P_{heterogeneity} < 0.01$), and reduce the risk of English

Table 2

Summary ORs and 95% CIs of the association rs1800795 polymorphism and thrombosis risk.

Indexes	No. of studies	CC vs GG OR (95%CI)	CC vs GC OR (95%CI)	CC vs G carriers OR (95%CI)	C carriers vs GG OR (95%CI)	C vs G OR (95%CI)
Total	34	1.03 (0.87–1.22)	0.97 (0.85–1.09)	0.99 (0.86–1.13)	1.09 (0.97–1.21)	1.05 (0.96–1.14)
Ethnicity						
Caucasians	28	0.99 (0.84–1.18)	0.95 (0.83–1.07)	0.96 (0.84–1.10)	1.05 (0.93–1.18)	1.01 (0.93–1.10)
Asians	6	1.99 (0.82–3.09)	1.03 (0.74–2.29)	1.48 (0.79–2.07)	1.39 (1.13–1.72)	1.3m 6 (1.18–1.56)
Country						
Sweden	4	1.05 (0.85–1.30)	1.03 (0.89–1.19)	1.04 (0.90–1.20)	1.03 (0.82–1.29)	1.03 (0.91–1.15)
English	4	1.00 (0.64–1.55)	0.81 (0.66–0.992)	0.85 (0.69–1.06)	1.31 (0.76–2.25)	1.09 (0.81–1.46)
India	3	1.88 (0.24–14.6)	1.40 (0.23–8.61)	1.73 (0.24–12.7)	1.40 (1.19–1.65)	1.40 (0.96–2.05)
Germany	3	0.97 (0.87–1.08)	0.99 (0.89–1.11)	0.98 (0.87–1.10)	0.99 (0.95–1.03)	0.90 (0.94–1.03)
Italy	5	0.63 (0.23–1.7)	0.67 (0.36–1.25)	0.64 (0.29–1.41)	0.84 (0.43–1.62)	0.80 (0.47–1.36)
Design						
HB	6	0.58 (0.28–1.20)	0.66 (0.41–1.07)	0.62 (0.35–1.11)	0.79 (0.52–1.19)	0.77 (0.53–1.10)
PB	28	1.12 (0.99–1.27)	1.04 (0.96–1.13)	1.06 (0.98–1.15)	1.15 (1.03–1.29)	1.10 (1.03–1.18)
Diseases						
MI	18	1.06 (0.93–1.21)	1.01 (0.92–1.11)	1.02 (0.94–1.11)	1.14 (0.99–1.32)	1.08 (0.99–1.18)
stroke	12	0.85 (0.48–1.50)	0.88 (0.58–1.33)	0.88 (0.54–1.42)	0.95 (0.73–1.24)	0.94 (0.73–1.22)
Venous Thrombosis	4	1.14 (0.83–1.58)	0.98 (0.58–1.67)	1.03 (0.76–1.40)	1.17 (0.97–1.42)	1.10 (0.95–1.28)
Arterial Thrombosis	30	1.02 (0.85–1.22)	0.97 (0.85–1.10)	0.98 (0.85–1.13)	1.08 (0.95–1.23)	1.04 (0.94–1.14)
Sample size						
≤400	25	0.98 (0.75–1.28)	0.90 (0.74–1.10)	0.93 (0.75–1.15)	1.05 (0.88–1.25)	1.01 (0.88–1.15)
>400	9	1.13 (0.97–1.31)	1.05 (0.95–1.16)	1.08 (0.96–1.21)	1.15 (1.01–1.31)	1.12 (1.01–1.23)
NOS score						
≥6	31	1.00 (0.84–1.19)	0.96 (0.84–1.08)	0.97 (0.84–1.11)	1.07 (0.95–1.19)	1.03 (0.94–1.12)
<6	3	1.68 (1.05–2.69)	1.24 (0.54–2.80)	1.36 (0.89–2.08)	1.37 (0.62–3.01)	1.30 (0.95–1.77)

95%CI = 95% confidence interval, HB = hospital-based case–control studies, NOS = Newcastle–Ottawa Scale, OR = odds ratio, PB = population-based case–control studies.

(0.81 [0.66–0.99] for CC vs CG, $P_{heterogeneity} = 0.84$). Detailed information is shown in Table 3.

Stratifying this meta-analysis by control source, the overall ORs for population-based studies and hospital-based studies were 1.15 (95%CI = 1.03–1.29 for C carriers vs GG, $P_{heterogeneity} < 0.01$) and 1.10 (95%CI = 1.03–1.18 for C allele vs G allele $P_{heterogeneity} < 0.01$), respectively. Further analyses for study scale and study design were performed. We found that *IL-6* gene-174 G/C was associated with the risks of thrombotic disorders with sample size more than 400 (1.15 [1.01–1.31] for C carriers vs

GG, $P_{heterogeneity} < 0.01$), but not associated with the risk of sample size less than 400 (0.90 [0.75–1.28] for CC vs GC, $P_{heterogeneity} < 0.01$). However, when subgroup analyses according to Newcastle–Ottawa Scale (NOS) score were performed, we found that CC was significantly associated with increased risk of thrombotic disorders with NOS less than 6 (1.68 [1.05–2.69] for CC vs GG, $P_{heterogeneity} = 0.80$), but no associated with the risk of NOS more than 6 (0.96 [0.84–1.08] for CC vs GC, $P_{heterogeneity} = 0.004$). Therefore, with different study designs, we also found statistically significant differences between the thrombotic case and control groups for association between GC status and thrombotic risk.

The above results suggested that the effect of 174 G/C on the risk of thrombotic disorders could be modulated by country/area, ethnicity, sample scale, and control subject resource. Details are showed in Table 3.

3.1. Sensitivity analyses and publication bias

Sensitivity analysis was conducted to assess the stability of the result by removing individually 1 study at a time, and then reanalysis was conducted. The results were not altered, which indicated that our results were reliable. Through applying asymmetry of funnel plots, the Begg test, and Egger test, we did not find publication bias for analyzing CC versus GG (Pbeg = 0.65, Pegger = 0.47), CC versus G carriers (Pbeg = 0.14, Pegger = 0.11), and C carrier versus GG ((Pbeg = 0.91, Pegger = 0.22) (shown in Table 3 and Fig. 3).

4. Discussion

Various genetic risk factors are known to increase the susceptibility to thrombotic disorders.[18] Increasing evidence reveals a "cross-talk" between the coagulation and inflammatory
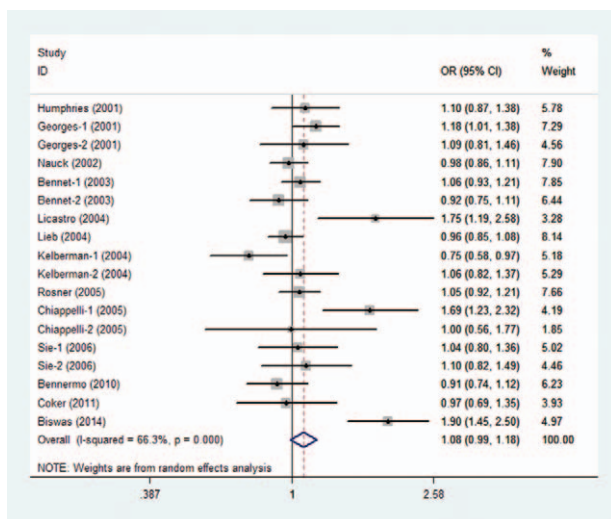
Figure 2. Forest plot of MI risk associated with the IL-6-174 G/C polymorphism in overall analysis (C carriers vs GG). IL-6 = interleukin-6, MI = myocardial infarction.

Table 3

Heterogeneity and publication bias test for meta-analysis of rs1800795 polymorphism and thrombosis risk.

Indexes	No. of studies	CC vs GG				CC vs GC				CC vs G carriers				C carriers vs GG				C vs G			
		P_{her}*	I^2, %†	Pbegg	Pegger	P_{her}	I^2, %	Pbegg	Pegger	P_{her}	I^2, %	Pbegg	Pegger	P_{her}	I^2, %	Pbegg	Pegger	P_{her}	I^2, %	Pbegg	Pegger
Total	34	<0.01	67.8	0.64	0.50	0.003	45.7	0.01	0.06	<0.01	58.9	0.26	0.15	<0.01	70.6	0.65	0.17	<0.001	74.7	0.01	0.78
Ethnicity																					
Caucasians	28	<0.01	69.3	0.68	0.52	0.003	48.0	0.001	0.07	<0.01	60.0	0.44	0.15	<0.01	71.2	0.28	0.15	<0.01	74.4	0.05	0.92
Asians	6	0.15	41.4	1.00	0.31	0.26	24.4	0.73	0.02	0.16	38.8	1.00	0.77	0.26	23.5	1.00	1.00	0.11	44.7	0.45	0.23
Country																					
Sweden	4	0.2	35.2	1.00	0.77	0.94	0	0.31	0.76	0.83	0	0.73	0.96	0.03	67	0.73	0.59	0.12	48.2	1.00	0.56
UK	4	0.077	56.2	0.73	0.26	0.835	0	0.73	0.557	0.932	0	0.308	0.154	<0.01	87.6	0.734	0.462	0.002	80.3	1.00	0.454
India	3	0.033	70.8	1.00	0.95	0.071	62.2	1.00	0.97	0.037	69.6	1.00	0.958	0.173	43	0.296	0.004	0.051	66.3	0.296	0.015
Germany	3	0.776	0	0.296	0.08	0.962	0	1.00	0.827	0.94	0	1.00	0.218	0.62	0	0.296	0.232	0.735	0	0.296	0.146
Italy	5	<0.01	91.7	0.806	0.8	0.001	79.8	0.806	0.975	<0.01	88.4	0.806	0.889	<0.01	90.4	0.806	0.818	<0.01	93.2	0.221	0.769
Design																					
HB	6	<0.01	88.5	1.00	0.61	0.001	75	0.45	0.80	<0.01	84.5	0.45	0.62	<0.01	86	0.71	0.65	<0.01	90.7	1.00	0.17
PB	28	0.05	32.8	0.83	0.60	0.45	1.00	0.02	0.11	0.35	8	0.12	0.18	<0.01	1.1	0.74	0.67	<0.01	54.5	0.49	0.09
Diseases																					
MI	18	0.08	33.5	0.20	0.70	0.71	0	0.41	0.04	0.67	0	0.41	0.15	0	74	0.30	0.09	<0.01	66.3	0.71	0.23
stroke	12	<0.01	58.6	0.59	0.03	<0.01	73.1	0.37	0.19	<0.01	82.6	0.86	0.3	<0.01	73.7	0.84	0.87	<0.01	85.4	0.09	0.27
VTE	4	0.68	0	0.73	0.50	0.07	58.2	1.00	0.47	0.22	32.6	0.74	0.36	0.56	0	1.00	0.31	0.99	0	0.73	0.57
Arterial	30	<0.01	71.2	0.02	0.61	<0.01	45.8	0.02	0.09	<0.01	61.8	0.24	0.11	<0.01	73.4	0.64	0.10	<0.01	77.6	0.01	0.76
Sample size																					
≤400	25	<0.01	71.6	0.92	0.44	0.002	52.0	0.75	0.29	<0.01	63.2	0.35	0.81	<0.01	72.3	0.92	0.25	<0.01	75.8	0.06	0.21
>400	9	0.10	40.5	0.92	0.44	0.48	0	0.75	0.29	0.24	22.7	0.35	0.81	0.03	66.3	0.92	0.25	<0.01	69.6	0.60	0.21
NOS score																					
≥6	31	<0.01	69.2	0.02	0.20	0.004	45.5	0.01	0.09	<0.01	60.9	0.11	0.13	<0.01	68.2	0.54	0.14	<0.01	75.1	0.002	0.75
<6	3	0.8	0	1.00	0.49	0.075	61.4	1.00	0.19	0.483	0	1.00	0.92	0.002	84.6	100	0.39	0.13	50.9	1.00	0.56

HB=hospital-based case-control studies, MI=myocardial infarction, NOS=Newcastle–Ottawa Scale, PB=population-based case-control studies, VTE=venous thromboembolism.

* P_{value} for heterogeneity, if $P<0.10$, random effects model was used, otherwise, fixed effects model was used. I^2 calculated by %.

† I^2 was the abbreviations of I^2 (%).
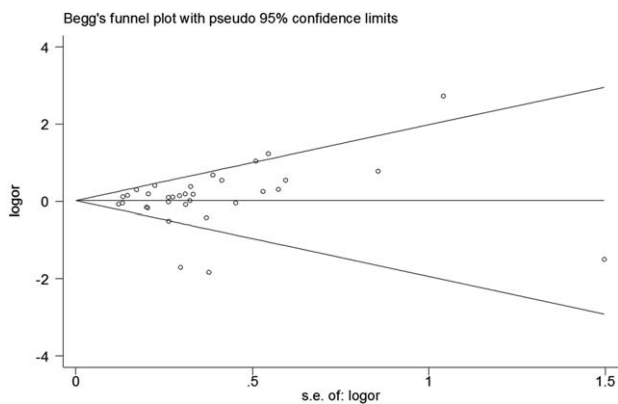
Figure 3. Begg funnel plot for publication bias test (CC vs GC). Each point represents a separate study for the indicated association. LogOR = natural logarithm of OR.

cascade.[46] In addition, variants in genes related to inflammation may predispose to thrombotic disorders. Recent reports reveal that the vessel wall is often unmarred, although venous thrombosis is accompanied by a low blood flow and shear rate.[46–49] Be independent of venous thromboembolism, arterial thrombotic diseases, including MI and stroke, have a correlation with platelet aggregation stem from the split of an atherosclerotic platelet at sites in the artery vessels where the shear stress is high, stimulating the formation of a blood clot and the subsequent obstruction of the blood vessel.[48,49] Inflammatory processes take a pivotal part in the pathogenesis of atherosclerosis.[47,50] The inflammatory cytokines perform a multitude of functions within the inflammatory pathway.[50] IL-6 is a pleiotropic inflammatory cytokine.[50] It plays an important part in the acute-phase response and inflammatory cascade, such as upregulation of acute-phase proteins like C-reactive protein,[50] which has been observed to be related to the risk of coronary heart disease. IL-6 is able to initiate coagulation through tissue factor and indirectly by the endothelium.[31] IL-6 was capable of engendering tissue factor on monocytes in vitro,[51] and was demonstrated to play a key role in the activation of coagulation[52] and the subsequent and potential thrombosis diseases in animal models.

According to Fishman the G/C polymorphism at position -174 of the gene IL-6 has the potential to influence the binding of the glucocorticoid receptor, and therefore it has ability to repress transcriptional activation.[5,11] It is significant that the alteration from a G to a C at position -174 causes a potential binding site for the transcription factor NF-1, a repressor of IL-6 gene expression.[11] The C allele and further the CC genotype create lower expression level of IL-6 after an inflammatory initiates when compared with the GG genotype.[11]

The present meta-analysis involved 34 case–control studies in 29 papers containing 29,865 individuals (including 10,549 cases and 19,316 controls) made us well understand the relationship between IL-6 gene-174 G/C and risk of thrombotic disorders. The results of this meta-analysis indicated that of IL-6 gene-174 G/C was marginally associated with increased risk of thrombotic disorders, especially for Asian, Indian, population based case-control studies, and large sample-sized studies. However, combined analyses suggested that there was no association between IL-6 gene-174 G/C and risk of thrombotic disorders for Caucasians. In addition, it should be acknowledged that there were no original studies for analyzing association between 174 G/

C and the risk of thrombotic disorders for Africans. Therefore, relationship between 174 G/C and risk of thrombotic disorders was required that the results should be demonstrated with great caution.

To get better understanding for our current study, we carried out the subgroup analysis stratified by control resource (hospital-based case–control studies or population-based case–control studies), because the selection bias may occur when controls were employed from different sources of participants, given that control participants selected from hospital-based case-control studies might be exposed in some risk factors (such as genetic factors and lifestyle), which can distort the reliability of the conclusions. Additionally, in the present meta-analysis, it has been mentioned that the larger sample-size study led to more statistical power and potential bias could be eventually decreased or avoided, compared with the small-scale investigation.

Alternatively, the stratified analysis indicated several interesting observations. First, although the ethnic background seems to have no obvious distortion on the heterogeneity of our meta-analysis, Asian population has significant association between the IL-6 gene-174 G/C polymorphism and thrombotic disorders for under the dominant model, whereas no significant result was observed in Caucasians in all the genetic models. In addition, our current analysis demonstrated that there was a significant relationship between the IL-6 gene-174 G/C polymorphism and thrombotic disorders for Indian subjects without significant heterogeneity using by all the genetic models. Such potential sources of heterogeneity in our present meta-analysis may incorporate diversities in the possible thrombotic disorder category, different bio-sample ascertainment, ethnic/area, or to varied methods of genotyping.

It was interesting that G allele frequency in IL-6 gene-174 G/C greatly varied according to ethnicity and geography, with the G allele frequency were 60% to 83% in Asians and while different 50.6% to 77.8% in Caucasians. Different susceptibilities exist from different ethnic subjects, which might lead to a common phenomenon that the distribution of a genetic allele greatly varied in different ethnicities. In our meta-analysis, we found that C allele of IL-6 gene-174 G/C was significantly associated with increased risk of thrombotic disorders for Asians, but not Caucasians. The G allele on the risk of thrombotic disorders for Caucasians should be studied to validate our results in the future.

Recently, genome-wide association studies, which does not contingently rely on previous information involving in candidate genes, have made great progress in exploring the potential genetic predisposition to thrombosis disorders containing ischemic heart disease, stroke, and venous thrombosis. The genome-wide association studies result from Coronary Artery Disease Genome-wide Replication and Meta-analysis (CARDIoGRAMplusC4D) indicates that among candidate gene reports studying the predisposition to thrombosis disorders only 19 loci showed the correlation at $P < 1 \times 10^{-6}$ in the combination of stage 1 and 2 analysis, with 13 of them having the genome-wide significance, namely APOB, ABCG5-ABCG8, FURIN-FES, FLT1, GUCY1A3, IL6R, KCNK5, LPL, PLG, TRIB1, SLC22A4-SLC22A5, TRIB1, VAMP5-VAMP8-GGCX, and ZEB2-AC074093.1.[53,54] NINDS Stroke Genetics Network (SiGN) and International Stroke Genetics Consortium (ISGC) confirmed a novel site (G allele at rs12122341) at 1p13.2 near TSPAN2 which was correlated with large artery atherosclerosis-related stroke, and their data also supported robust relationships with IS for 4 other loci which have been demonstrated in published studies, including HDAC9 for large artery atherosclerosis stroke, and

ZFHX3 and PITX2 for cardioembolic stroke.[55] Germain et al[56] reported that the common mutations left to be confirmed are not uniformly distributed across the genome and chromosome 20, itself, could attribute to 7% of the total genetic mutation for venous thrombosis. The findings emerged among different studies may be due to different genetic or culture backgrounds, and environmental factors.

Heterogeneity existed in overall analysis under the recessive model due to the differences in thrombotic disorder category, genetic backgrounds, and environmental exposures which existed among different ethnicities/cultures and in difference study groups. Another potential factor contributing to heterogeneity was minor allele frequencies difference between studies. Subsequently, sensitivity and subgroup analyses were explored to investigate the underlying causes. Our sensitivity analysis revealed that even after excluding studies with a small number of cases (n < 100), the results of our main meta-analysis remain unchanged.

As far as we know, the present meta-analysis involving 10,549 cases and 19,316 controls was the most comprehensive to date to investigate the relation between the IL-6-174 G/C polymorphism and thrombosis susceptibility. Our finding suggested that the IL-6-174 G/C polymorphism was not associated with the thrombosis risk both in Caucasian and Asian populations, which were in line with the conclusion of the previous meta-analysis by Kumar et al[57] and inconsistent with Jin et al's results.[58] Compared to the previous study, our meta-analysis has some potential strength. First, we had the largest sample size. Second, this meta-analysis incorporated all types of thrombosis disorders into pooled analysis, while the meta-analyses from Kumar and Jin et al only investigated MI/stroke susceptibility.

Our subgroup meta-analysis suggested that IL-6-174 G/C was not associated with the stroke risk, which is consistent with the study conducted by Kumar et al.[57] The pooled ORs were performed in our meta-analysis for allelic comparison (C vs G), dominant model (CC + GC vs GG), recessive model (CC vs GC + GG), homozygote comparison (CC vs GG), and heterozygote comparison (GC vs GG), respectively. The study out of HWE conducted by Tuttolomondo et al[59] were excluded in present meta-analysis. Deviation from HWE can be due to laboratory/genotyping errors, population stratification, selection bias in the choice of controls, and confounding factors unaccounted for.[60] It is suggested that the analysis without studies not conforming to HWE would be more valid.[61]

Prior published articles have revealed conflicting results regarding the association of the IL-6-174 G/C polymorphism with MI risks. Significant association between the IL-6-174 G/C polymorphism and MI development has been identified in the study by Jin et al.[58] Such discrepancy may be caused from different population, sample sizes, and stratification. As stroke analysis, we excluded studies in which HWE was absent in the controls as well.

In addition, our updated analysis incorporated more studies with a larger sample and subgroup analyses. Beside to exclusion to the studies departure from HWE and 5 analysis model for MI, noticeably, the previous meta-analysis[58] only contained published data from prior to 2011, involving 5429 cases and 4823 controls. Fewer studies were included in these meta-analyses compared with ours, probably due to insufficient attention in the search process or screening methods, which might lead selection bias. Moreover, small studies showed a risk factor for 174C allele. Small sample with limited subjects is usually accompanied with selection biases, and is powerless to deny or support an association.

When explaining the results, several limitations of the current meta-analysis should be acknowledged. First, we only studied 174 G/C polymorphism in IL-6 gene in present meta-analysis, thus, we cannot exclude the potential effect that other haplotypes or polymorphisms in IL-6 gene might also be implicated in the risk of thrombosis disorders. Second, all original studies were from Asians and Caucasians and data involving other ethnicities were limited; thus, our conclusion may not be applied to all ethnic groups and participants incorporating African American should be examined the relationship to consummate result in present the meta-analysis. Third, raw data were not listed by other life factors such as smoking, diet preference, and physical activities, because lack of sufficient information could be provided from the original papers, which prevents us from interpreting any interaction between IL-6-174 G/C and other factors on thrombosis disorders. Fourth, due to the study sample size for some subgroup and unpublished data (so-called "gray literature"), the current meta-analysis was limited to exclude the possibility of type I and type II errors and contribution to the power analysis.

To our best knowledge, this study is the first comprehensive meta-analysis till now to explore the correlation between the IL-6 gene-174 G/C polymorphism and over risk of thrombosis disorders. It provided evidence of the association between IL-6 gene - 174 G/C polymorphism and risk of thrombotic disorders, supporting the hypothesis that the IL-6-174 G/C polymorphism may be a predisposed marker for arterial thrombotic disorders including MI, Asians including Indian. However, additional larger and more case–control studies are required to confirm our conclusions. Since no study was conducted in an Africans, it is essential that larger and well-designed and multicentric studies incorporating African population should be carried out to further examine the association. Moreover, further studies investigating the effect of haplotypes and gene–environment interactions can ultimately provide a better and comprehensive finding of the associations between the IL-6 gene-174 G/C polymorphism and the risk of thrombotic disorders. Future analyses should be carried out in large-scale population studies and should examine the potential effect stratified by age and smoke status in different ethnicity and populations.

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