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Research article

Inflammatory factor Interleukin-6 and its correlation with rheumatoid arthritis: A meta-analysis

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ABSTRACT

Introduction: at present, there are inconsistent research findings regarding the precise relationship between IL-6 gene polymorphisms (GPMs) and rheumatoid arthritis (RA). This work employed meta-analysis (MA) methodology to systematically evaluate the correlation between IL-6 GPMs and susceptibility to RA.

Material and methods: this study comprehensively searched multiple databases from inception to March 31, 2024. The search utilized keywords including "IL-6," "Interleukin-6," "Cytokines," "Autoimmune diseases," "Arthritis," "rheumatoid arthritis," "Inflammation," "genetic polymorphism," and "genetic variation." Included studies focused on patients diagnosed with rheumatoid arthritis (RA), with healthy individuals or those without RA-related diseases as controls. The study designs encompassed cohort studies and case-control studies. Genetic frequency distributions of IL-6 gene rs1800795 (G-174C), rs1800796 (G-572C), and rs1800797 (G-597A) polymorphic sites were statistically analyzed. Quality of included studies was assessed. The preliminary assessment of literature heterogeneity was conducted. Quantitative assessment of heterogeneity results was performed using the I^2 statistic in *RevMan5.3*. Publication bias (PB) assessment was conducted.

Result: the study included a total of 21 articles, comprising 9772 participants, with 4679 cases diagnosed with RA and 5093 individuals in the control (CT) group. The IL-6 gene allelic model (G *vs* C) exhibited a notable association with RA [OR = 0.66, 95%CI: 0.51–0.87, Z = 3.02, P = 0.003]. In Southeast Asian populations, IL-6 gene rs1800795 (G-174C) genotype (CC) demonstrated a considerable correlation with RA [OR = 15.23, 95%CI: 3.53–65.67, P = 0.00003]. IL-6 gene rs1800795 (G-174C) genotype (CG) was associated with RA [OR = 1.54, 95%CI: 1.10–2.17, Z = 2.48, P = 0.01], with only the Asian population showing an observable correlation [OR = 6.55, 95%CI: 1.28–33.45, P = 0.02]. Additionally, IL-6 rs1800795 (G-174C) genotype (GG) was associated with RA [OR = 0.66, 95%CI: 0.49–0.91, Z = 2.55, P = 0.01], with notable associations observed in the Asian [OR = 0.17, 95%CI: 0.03–0.83, P = 0.03] and mixed populations [OR = 1.29, 95%CI: 1.011.65, P = 0.04]. No correlation was found between rs1800796 (G-572C) and rs1800797 (G-597A) GPMs and RA (P > 0.05).

Conclusion: IL-6 gene rs1800795 (G-174C) allelic model and genotypes (CC, CG, GG) were all associated with susceptibility to RA, with the G allele model being susceptible in Southeast Asian populations, and genotypes (CG and GG) being susceptible in Asian populations. However, there was neglectable correlation between rs1800796 (G-572C) and rs1800797 (G-597A) GPMs and susceptibility to RA.

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1. Introduction

Rheumatoid arthritis (RA) is characterized by chronic arthritis, joint inflammation, and systemic inflammation, often leading to joint destruction and functional impairment. Its pathological features include progressive and persistent synovitis, resulting in cartilage and bone destruction, ultimately leading to joint deformity and functional impairment, greatly affecting patients' quality of life [1,2]. The disease typically manifests as symmetric, persistent joint swelling and pain, often accompanied by morning stiffness. RA has a wide age range of onset, but the peak onset age is between 30 and 50 years, with a markedly higher incidence rate in females than in males [3]. RA pathogenesis is not fully understood, with current research generally suggesting that genetics, environment, and infection are closely related factors [4,5]. One of the recent focuses of research is the relationship between single nucleotide polymorphisms (SNPs) and susceptibility to RA [6], with numerous studies implying a notable association between SNPs and the onset of RA [7,8].

The role of cytokines in RA pathogenesis has been receiving increasing attention. Cytokines are a class of small molecular glycoproteins distributed in the extracellular space, participating in immune responses and playing crucial roles in the pathophysiological processes of arthritis-related diseases such as RA [9]. In the onset and progression of RA, cytokines are involved in joint bone and cartilage destruction, promoting the occurrence of osteoporosis. Among them, cytokines like IL-6 are considered to be one of the more important contributing factors in the pathogenesis of RA [10]. IL-6 is capable of regulating immune responses, inflammatory reactions, and tissue repair processes [11]. Past studies indicated that IL-6 acts in the onset of RA by promoting the production of inflammatory mediators, stimulating joint destruction, and influencing immune regulation [12]. The genetic polymorphism (PM) of IL-6 has been suggested to be associated with susceptibility to RA and its clinical manifestations [13]. However, there are inconsistent research findings regarding the precise relationship between IL-6 gene polymorphisms (GPMs) and RA. Some studies have reported a correlation between IL-6 GPMs and an increased risk of RA [14,15], while others have failed to observe this association [16,17]. To better understand the relationship between IL-6 GPMs and RA, this work conducted a meta-analysis (MA) to comprehensively assess the results of existing research and provide more reliable evidence. Through a systematic review and quantitative synthesis of existing literature, the aim was to demonstrate the correlation between IL-6 GPMs and the risk of RA, thus providing references for further research and clinical practice.

2. Materials and methodologies

2.1. Search

A comprehensive literature search was implemented using a keyword search methodology to obtain all relevant studies on correlation between the inflammatory factor IL-6 SNPs and RA. Keywords included "IL-6," "Interleukin-6," "Cytokines," "Autoimmune diseases," "Arthritis," "rheumatoid arthritis," "Inflammation," "genetic polymorphism," and "genetic variation". The search utilized a combination of subject terms and their related expansion terms. Logical operators "or" and "and" were utilized to combine the keywords for joint searches, such as ((((IL-6) OR (Interleukin-6)) OR (Cytokines)) AND (Autoimmune diseases)) OR (Arthritis)) OR (rheumatoid arthritis)) AND (genetic polymorphism). A comprehensive search was conducted across CNKI, Wanfang, VIP, CBM, Google Scholar, Medline, Embase, PubMed, Cochrane Library, Nature, Web of Science, Springer, and Science Direct. The search period extended from inception to March 31, 2024, and tracking searches based on the references of retrieved articles were performed. During the search process, no language, ethnicity, or geographical restrictions were set to ensure the retrieval of the most comprehensive research literature possible.

2.2. Criteria

Inclusion criteria: i.) studies related to RA and IL-6 GPMs; ii.) all RA patients must meet the classification criteria and criteria for active RA established by the American College of Rheumatology (ACR), with no restriction on disease duration; iii.) the control (CT) group consisted of healthy individuals or those without RA-related diseases, while RA group comprised RA patients of any age, gender, or ethnicity; iv.) the exposure factor was IL-6 GPMs; v.) cohort studies and case-control studies; vi.) studies included IL-6 gene distribution proportions; vii.) observation indicators: distribution of SNP genetic models.

Exclusion criteria: i.) studies on other types of arthritis or immune diseases besides RA; ii.) studies where IL-6 GPM association with RA was not addressed in the original literature, or IL-6 GPM genotype frequencies and/or allele frequencies were not provided; iii.) studies lacking necessary data availability; iv.) non-randomized or non-case-control study designs; v.) reviews, individual case reports; vi.) literature focusing on animal subjects; vii.) duplicate publications.

2.3. Screening and data extraction

Two reviewers conducted literature screening independently. After keyword screening, *EndNote X9* was employed for literature management, and duplicate literature was removed. The two reviewers individually read the article titles and abstracts, preliminarily excluding literature that was clearly unrelated to IL-6 GPMs and RA association. If there were disagreements between the two reviewers regarding the inclusion of certain literature, a third-party expert could be consulted for judgment, and the submitter could be contacted to supplement missing data. The literature full text was read, and inclusion in the study was further determined based on the

full-text content.

Two reviewers independently conducted data extraction and cross-checked the extracted data to ensure accuracy. The extracted data included: year, author, country, ethnicity, sample size, age, gender, genotyping methods, genotypes, genotype frequencies in each group, and allele frequencies. The extracted data were organized in Excel.

2.4. Risk assessment of literature bias

The Newcastle-Ottawa Scale (NOS), a commonly utilized tool for assessing bias in observational studies, was employed. This tool aims to evaluate the quality of observational studies, including cohort and case-control studies. Two researchers independently assessed the risk of bias. The NOS consists of three aspects: selection of study subjects, comparability between the study group and CT group, and exposure or outcome assessment, each comprising multiple items. Evaluation criteria typically cover representativeness of study subjects, fairness of comparison between the study group and CT group, and accuracy of exposure or outcome assessment, among others. Based on the degree of compliance with each item, corresponding star ratings were assigned, and the scores were summed to obtain a total score. Each evaluator utilized the NOS to score each included study, with scores ranging 0–9 stars, where higher scores imply higher study quality, and studies with 6 or more stars are considered high quality. Evaluators utilized the NOS score to assess the quality of each study and determine whether to include it in the MA or systematic review. After independent scoring by the two evaluators, the results were cross-checked. In cases where there were discrepancies in scoring, evaluators resolved them through discussion or consulted a third-party expert to reach a consensus evaluation result.

2.5. Statistical methodologies

The included literature data were subjected to MA using *RevMan5.3*. Heterogeneity analysis: Initially, χ^2 test was employed to conduct a preliminary examination of literature heterogeneity, with $\alpha = 0.05$ and $P < 0.05$. Subsequently, I^2 statistic in *RevMan5.3* was utilized to quantitatively assess heterogeneity results. When $I^2<50$ %, a fixed-effects model (FEM) was utilized for MA. When $I^2>50$ %,

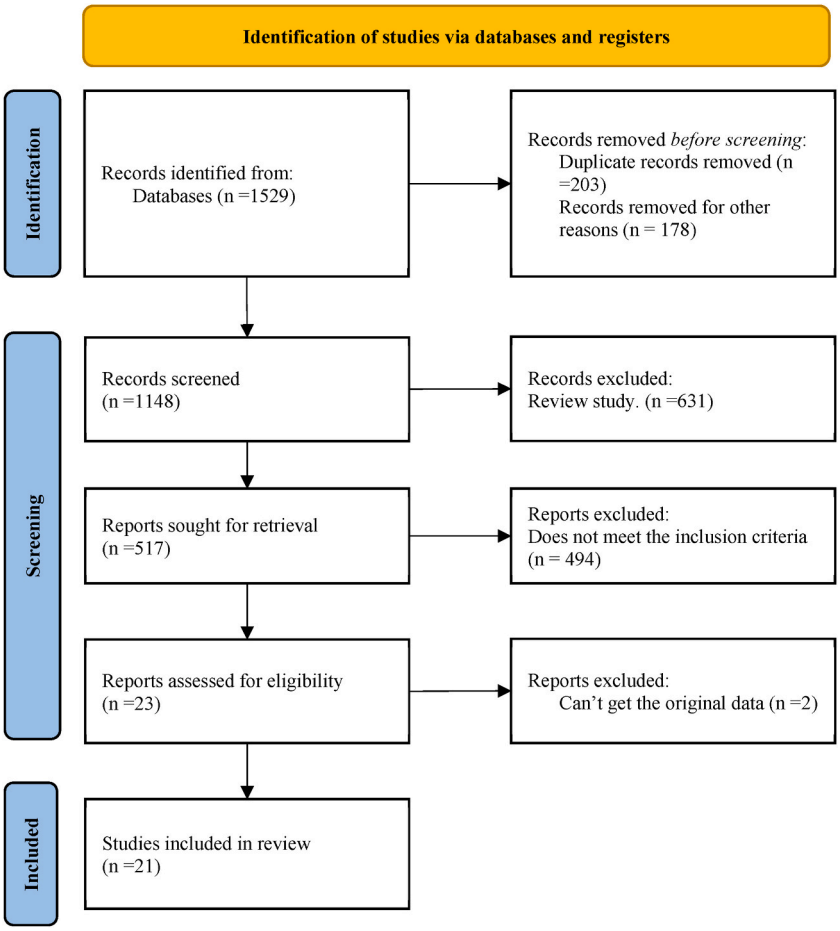

Fig. 1. Basic process of literature search.

a random-effects model (REM) was utilized for MA. Forest plots (FOPs) were generated, and *Z* values and *P* values were extracted from the results for determining the MA results, with all effect sizes expressed using 95 % confidence intervals (CI). $P < 0.05$ indicated statistically significant intergroup differences. Funnel plots (FUPs) were created using *RevMan5.3*, followed by Egger's linear regression test for quantitative assessment of publication bias (PB) using *STATA 10.0*. After that, if the 95%CI included 0 and the corresponding *P* value was greater than 0.10, it indicated no PB.

3. Results

3.1. Search results of literature

During the literature search, each keyword was entered separately into various online databases for searching, resulting in a total of 1529 articles retrieved. Initially, 203 duplicate articles were removed using *EndNote X9*, and an additional 178 reports, reviews, and commentaries were excluded. Further exclusions were made based on reading the titles and abstracts, resulting in the exclusion of 631 review articles. Additionally, 494 articles that did not address correlation between IL-6 GPMs and RA or failed to meet the inclusion criteria were excluded. This process left 23 articles remaining, but 2 of them could not be accessed to obtain original data through various channels. Finally, 21 articles were included for analysis. The literature search and screening process of this study are illustrated in Fig. 1.

3.2. Basic information included in the literature

Twenty-one articles [18–38] were selected. Basic information from the included literature was compiled and summarized in Table 1. In total, 9772 samples were included, with 4679 cases in RA group and 5093 cases in CT group.

3.3. Quality evaluation of included literature

All 23 articles included in this study were observational studies, and their quality was assessed. The evaluation results showed that the NOS scores of all articles were 6 or above, meeting the quality requirements (Table 2).

3.4. Correlation analysis between IL-6 gene rs1800795 (G-174C) and RA

A total of 15 articles included in the literature examined association between IL-6 gene rs1800795(G-174C) allelic model (G *vs* C) and RA (Fig. 2). Marked heterogeneity was observed in the statistical results of the SNP allelic model (G *vs* C) of IL-6 gene rs1800795(G-174C) in both RA and CT groups ($I^2 = 84$ %, $P < 0.00001$). Therefore, a REM was employed. Results indicated a considerable correlation between IL-6 gene rs1800795(G-174C) PM and RA [OR = 0.66, 95%CI: 0.51–0.87, Z = 3.02, $P = 0.003$]. To ensure the accuracy of this result, a sensitivity analysis (SA) was further conducted on the included literature.

The results in Fig. 3 demonstrated that the MA of IL-6 gene rs1800795(G-174C) allelic model (G vs C) and its correlation with RA remained considerable [combined effect: OR = 0.541, 95%CI: 0.388–0.754, P < 0.05], implying a stable correlation between IL-6 gene rs1800795(G-174C) PM and RA. This suggests good stability of the obtained result.

A funnel plot was utilized to analyze PB regarding correlation between IL-6 gene rs1800795(G-174C) allelic model (G *vs* C) and RA in the included literature. The results in Fig. 4 indicated a symmetric distribution of scatter points in the funnel plot, suggesting neglectable PB. Additionally, Egger's test was conducted to further analyze PB. The results revealed that $t = -0.60$, $P = 0.557$, implying neglectable PB in the included studies.

A total of 18 articles included in the literature examined correlation between IL-6 gene rs1800795(G-174C) genotype (CC) and RA (Fig. 5). Marked heterogeneity was observed in the statistical results of IL-6 rs1800795(G-174C) genotype (CC) between RA and CT groups ($I^2 = 50$ %, $P = 0.008$). Hence, a REM was employed for analysis. The results indicated no correlation between IL-6 gene rs1800795(G-174C) PM and RA [OR = 1.33, 95%CI: 0.97–1.83, Z = 1.78, $P = 0.07$].

To ensure the accuracy of this result, a SA was further conducted on the included literature. The results (Fig. 6) demonstrated that the MA of correlation between IL-6 gene rs1800795(G-174C) genotype (CC) and RA was conducted by sequentially excluding individual studies. The combined effect [OR = 0.083, 95%CI: 0.516–0.132, $P < 0.05$] indicated a notable correlation between IL-6 gene rs1800795(G-174C) genotype (CC) and RA, suggesting that this result exhibits a certain degree of heterogeneity.

A funnel plot was utilized to analyze PB regarding correlation between IL-6 gene rs1800795(G-174C) genotype (CC) and RA in the included literature. The results, as depicted in Fig. 7, revealed a symmetric distribution of scatter points in the funnel plot, but some studies were located in the narrow part of the funnel plot, implying the potential presence of PB. Additionally, Egger's test was conducted to further analyze PB. It indicated a considerable $t = -2.46$ with a corresponding $P = 0.028$, further suggesting the presence of PB in the included studies.

Based on different ethnicities, the groups were categorized into Asian, European, Caucasian, Southeast Asian, and mixed. MA revealed that among different ethnicities, only in the Southeast Asian population, IL-6 gene rs1800795(G-174C) genotype (CC) showed a marked correlation with RA [OR = 15.23, 95%CI: 3.53–65.67, $P = 0.00003$] (Table 3).

Incorporating a total of 19 articles, statistical analysis was conducted on correlation between IL-6 gene rs1800795(G-174C) genotype (CG) and RA (Fig. 8). The statistical results of IL-6 rs1800795(G-174C) genotype (CG) between RA and CT groups exhibited marked heterogeneity ($I^2 = 88$ %, $P < 0.00001$). Therefore, a REM was employed, revealing an association between IL-6 gene

Table 1
Basic information of included literature.

First author	Year	Country	Ethnicity	Number of cases: Total number of cases	RA group	CT group	Age: RA group	Age: CT group	Sex (male/female): RA group	Sex (male/female): CT group	GPM detection methods	Locus
Emonts M [18]	2011	Netherlands	Mixed	839	376	463	59.3±13.7	59.3±13.7	99/277	233/230	SBE	rs1800795(G-174C)
Arman A [19]	2012	Türkiye	Caucasus	425	178	247	53.12±12.7	54.3±11.8	29/149	87/160	PCR-RFLP	rs1800795(G-174C)
Chen J [20]	2021	China	Asia	1002	508	494	54.34 ±12.01	54.03±8.83	134/374	124/370	SBE	rs1800796(G-572C)
Dar SA [21]	2017	India	Southeast Asia	114	34	80	51.39±2.27	36±2.9	15/19	32/48	PCR-SSP	rs1800795(G-174C)
Li X [22]	2014	China	Asia	1550	752	798	52.3±16.3	52.1±17.1	398/354	431/367	PCR-RFLP	rs1800795(G-174C)
Li F [23]	2014	China	Asia	587	256	331	50.26 ±12.86	48.08 ±13.92	60/196	92/239	PCR-HRM	rs1800795(G-174C, rs1800796 (G-572C), rs1800797(G-597A)
Shafia S [24]	2014	India	Asia	350	150	200	Unreported	Unreported	19/131	27/173	PCR-RFLP	rs1800795(G-174C)
You CG [25]	2013	China	Asia	825	452	373	47.08 ±15.36	47.35 ±14.37	104/348	102/271	PCR-HRM	rs1800797(G-597A),rs1800796 (G-572C), rs1800795(G-174C)
Trajkov D [26]	2009	Macedonia	Europe	386	85	301	Unreported	Unreported	Unreported	Unreported	PCR-SSP	rs1800795(G-174C)
Palomino-Morales R [27]	2009	Spain	Europe	537	311	226	Unreported	Unreported	83/228	Unreported	TaqMan	rs1800795(G-174C)
Panoulas VF [28]	2009	England	Europe	805	383	422	Unreported	Unreported	Unreported	Unreported	Real-time PCR	rs1800795(G-174C)
Huang XZ [29]	2007	China	Asia	288	120	168	48.48 ±14.98	45.18±8.11	20/100	67/101	PCR-SSP	rs1800795(G-174C), rs1800796 (G-572C)
Pawlik A [30]	2005	Poland	Europe	203	98	105	48.5	Unreported	37/61	Unreported	PCR-RFLP	rs1800795(G-174C)
Pascual M [31]	2000	Spain	Europe	320	163	157	50.7±14	Unreported	Unreported	Unreported	PCR-RFLP	rs1800795(G-174C)
Dahlqvist SR [32]	2002	Sweden	Europe	440	257	183	62±12.9	Unreported	70/187	Unreported	PCR-SSP	rs1800795(G-174C)
Amr K [33]	2016	Egypt	Southeast Asia	198	99	99	Unreported	Unreported	9/90	41/58	PCR-SSP	rs1800795(G-174C), rs1800796 (G-572C)
Ad'hiah AH [34]	2018	Iraq	Southeast Asia	96	51	45	44.9±10.7	41.3±8.7	22/29	15/30	PCR-RFLP	rs1800796(G-572C),
Yucel B [35]	2020	Türkiye	Caucasus	145	49	96	52±12	Unreported	Unreported	Unreported	PCR-SSP	rs1800795(G-174C),
Nisar H [36]	2021	Pakistan	Southeast Asia	315	150	165	43.53 ±11.11	Unreported	31/119	Unreported	TaqMan	rs1800795(G-174C)
Zavaleta-Muñiz SA [37]	2016	Mexico	Mixed	239	137	102	50±9	48±10	2/135	6/96	PCR-RFLP	rs1800795(G-174C)
Melo TS [38]	1992	Brazil	Mixed	108	70	38	50.9±11.4	52.3±12.2	Unreported	Unreported	TaqMan	rs1800795(G-174C)

RA: rheumatoid arthritis; PCR: polymerase chain reaction; SBE: single base extension; RFLP: restriction fragment length polymorphism; SSP: sequence specific primers.

Table 2
Basic information of patients in the literature.

First author	Year	Selection of research population	Intergroup comparability	Measurement of exposure factors	NOS score (points)
Emonts M	2011	★★★	★★	★★★	8
Arman A	2012	★★★	★★	★★★	8
Chen J	2021	★★★	★★	★★★	8
Dar SA	2017	★★★	★★	★★★	8
Li X	2014	★★★	★★	★★★	8
Li F	2014	★★★	★★	★★★	8
Shafia S	2014	★★	★★	★★★	7
Zavaleta-Muñiz SA	2013	★★★	★★	★★★	8
You CG	2013	★★★	★★	★★	7
Trajkov D	2009	★★	★★	★★★	7
Palomino-Morales R	2009	★★	★★	★★	6
Panoulas VF	2009	★★	★★	★★	6
Huang XZ	2007	★★★	★★	★★★	8
Pawlik A	2005	★★★	★★	★★	7
Pascual M	2000	★★	★★	★★★	7
Dahlqvist SR	2002	★★	★★	★★★	7
Amr K	2016	★★	★★	★★★	7
Ad'hiah AH	2018	★★★	★★	★★★	8
Yucel B	2020	★★	★★	★★★	7
Nisar H	2021	★★	★★	★★★	7
Zavaleta-Muñiz SA	2016	★★★	★★	★★★	8
Melo TS	1992	★★	★★	★★★	7
Jahan T	2024	★★	★	★★★	6

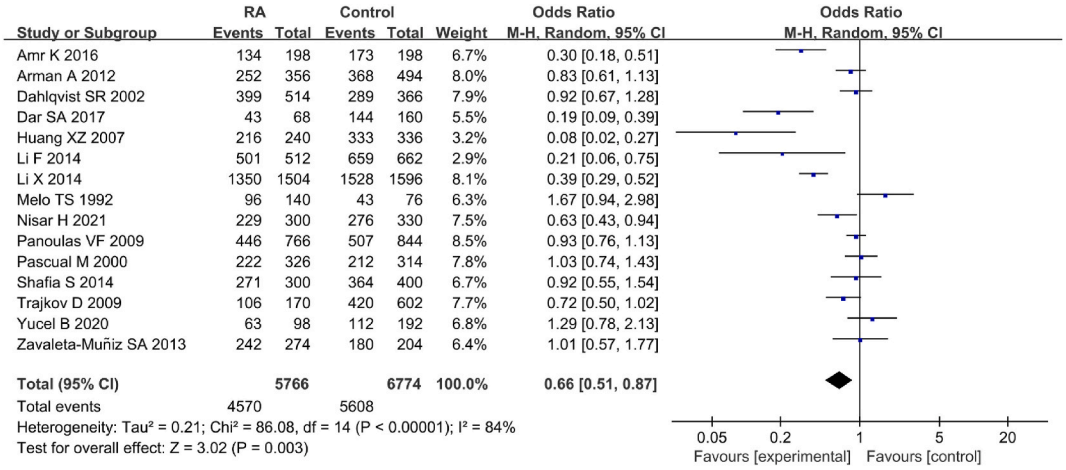

Fig. 2. FOP of allelic model (G *vs* C) and its correlation with RA.

rs1800795(G-174C) PM and RA [OR = 1.54, 95%CI: 1.10–2.17, Z = 2.48, $P = 0.01$].

To ensure the accuracy of this result, a SA was conducted by systematically excluding individual studies on correlation between IL-6 gene rs1800795(G-174C) genotype (CG) and RA (Fig. 9). The pooled effect size [OR = 0.371, 95%CI: 0.284–0.483, $P < 0.05$] remained substantial, implying a stable correlation between IL-6 gene rs1800795(G-174C) genotype (CG) and RA.

A funnel plot was employed to analyze the PB of correlation between IL-6 gene rs1800795(G-174C) genotype (CG) and RA (Fig. 10). The scatter plot distribution of the funnel plot appeared symmetric, but some studies were located outside the funnel, suggesting the potential presence of PB. Furthermore, Egger's test was conducted to further analyze the PB, yielding a result of $t = -2.69$, $P = 0.015$, further implying the existence of PB in the included studies.

Based on different ethnicities, including Asian, European, Caucasian, Southeast Asian, and mixed populations, MA revealed a considerable correlation between IL-6 gene rs1800795(G-174C) genotype (CG) and RA only in the Asian population [OR = 6.55, 95% CI: 1.28–33.45, $P = 0.02$] (Table 4).

Twenty studies were included in correlation analysis between IL-6 gene rs1800795(G-174C) genotype (GG) and RA (Fig. 11). Considerable heterogeneity was observed in the statistical results between RA and CT groups ($I^2 = 86$ %, $P < 0.00001$). Hence, a REM was applied for the analysis. The results revealed a notable correlation between IL-6 gene rs1800795(G-174C) PM and RA [OR = 0.66, 95%CI: 0.49–0.91, Z = 2.55, $P = 0.01$].

To ensure the accuracy of this result, a SA was conducted on the included studies. The results, as depicted in Fig. 12, indicated that

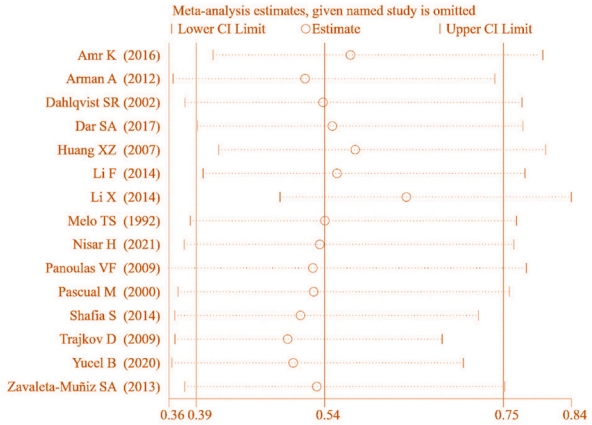

Fig. 3. SA of the allelic model and its correlation with RA.

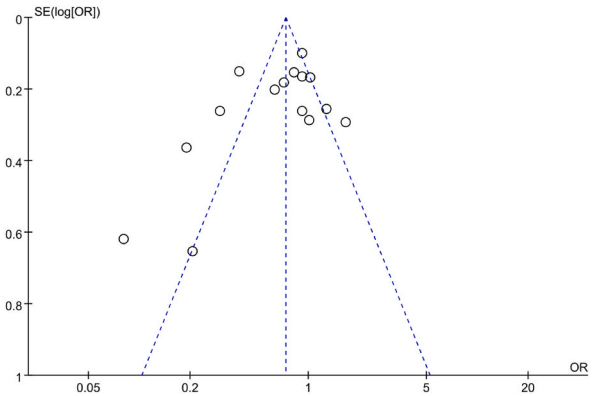

Fig. 4. FUP of association between the allelic model (G *vs* C) and RA.

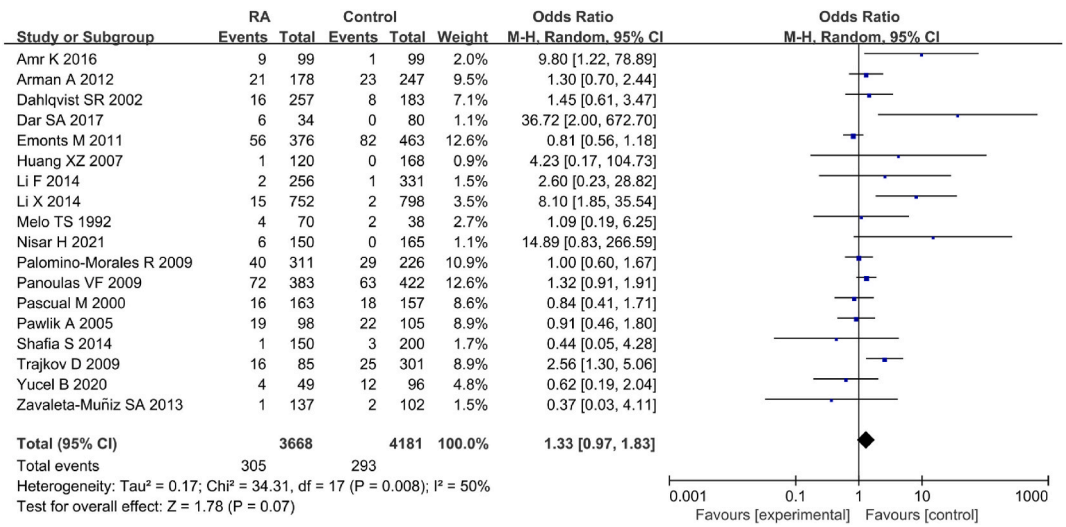

Fig. 5. FOP of correlation between IL-6 gene rs1800795(G-174C) genotype (CC) and RA.

upon sequentially excluding studies examining association between IL-6 gene rs1800795(G-174C) genotype (GG) and RA, the pooled effect size was [OR = 0.427, 95%CI:0.326–0.558, $P < 0.05$]. This suggests a stable correlation between IL-6 gene rs1800795(G-174C) genotype (GG) and RA.

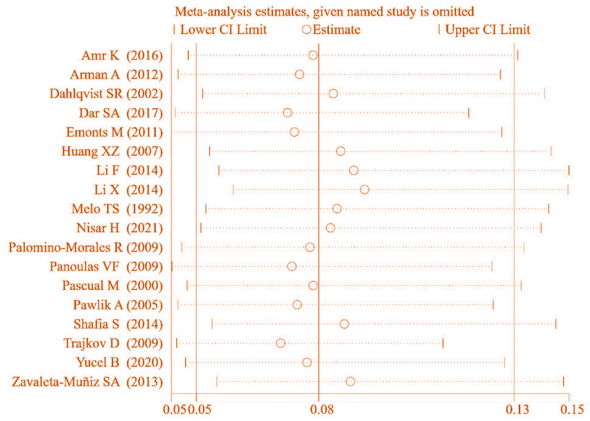

Fig. 6. SA of association between IL-6 gene rs1800795(G-174C) genotype (CC) and RA.

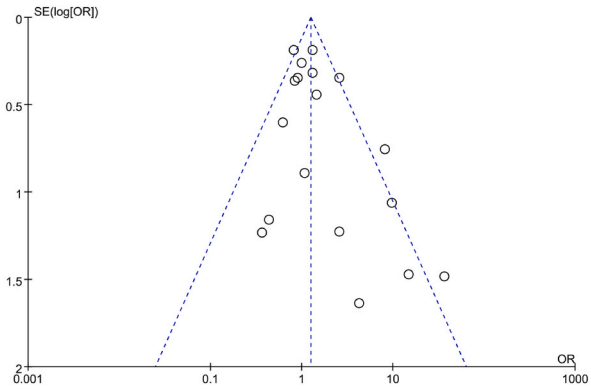

Fig. 7. FUP of correlation between IL-6 gene rs1800795(G-174C) genotype (CC) and RA.

Table 3
Correlation between IL-6 gene rs1800795(G-174C) genotype (CC) and RA across different ethnicities.

Ethnicity	Number of studies included	Sample size	RA group(n/total)	CG (n/total)	Heterogeneity (I^2)	OR [95%CI]	*P*
Asian	4	2775	19/1278	6/1497	34 %	2.85 [0.73, 11.04]	0.13
European	6	2691	1791297	165/1394	31 %	1.24 [0.92, 1.66]	0.16
Caucasian	2	570	25/227	35/343	14 %	1.08 [0.57,2.03]	0.82
Southeast Asian	3	627	21/283	1/344	0	15.23 [3.53,65.67]	0.0003
Mixed	3	1186	61/583	86/603	0	0.81 [0.57, 1.16]	0.25

A funnel plot was employed to assess PB regarding correlation between IL-6 gene rs1800795(G-174C) genotype (GG) and RA. In Fig. 13, the scatter distribution of the funnel plot appeared symmetrical, implying neglectable PB. Additionally, an Egger's test was conducted to further analyze PB. It revealed a $t = 1.05$ with a corresponding $P = 0.310$, further implying the absence of marked PB in the included studies.

Various ethnic groups were categorized into Asian, European, Caucasian, Southeast Asian, and mixed populations. MA revealed a notable correlation between IL-6 gene rs1800795(G-174C) genotype (GG) and RA in Asian populations [OR = 0.17, 95%CI: 0.03–0.83, $P = 0.03$]. Similarly, a marked correlation was observed in mixed populations [OR = 1.29, 95%CI: 1.01–1.65, $P = 0.04$] (Table 5).

3.5. Correlation analysis between IL-6 gene rs1800796 (G-572C) and RA

Seven studies were included in the analysis of IL-6 gene rs1800796(G-572C) allele model (G *vs* C) and its correlation with RA (Fig. 14). Notable heterogeneity was observed in the statistical results of the SNP allele model (G *vs* C) of IL-6 gene rs1800796(G-572C) between the RA and CT groups ($I^2 = 94$ %, $P < 0.00001$). Therefore, a REM was employed. Neglectable correlation existed between IL-6 gene rs1800796(G-572C) PM and RA [OR = 0.67, 95%CI: 0.52–1.25, Z = 1.42, $P = 0.15$].

To ensure the accuracy of this result, a SA was conducted on the included studies. The results in Fig. 15 demonstrated that the MA of

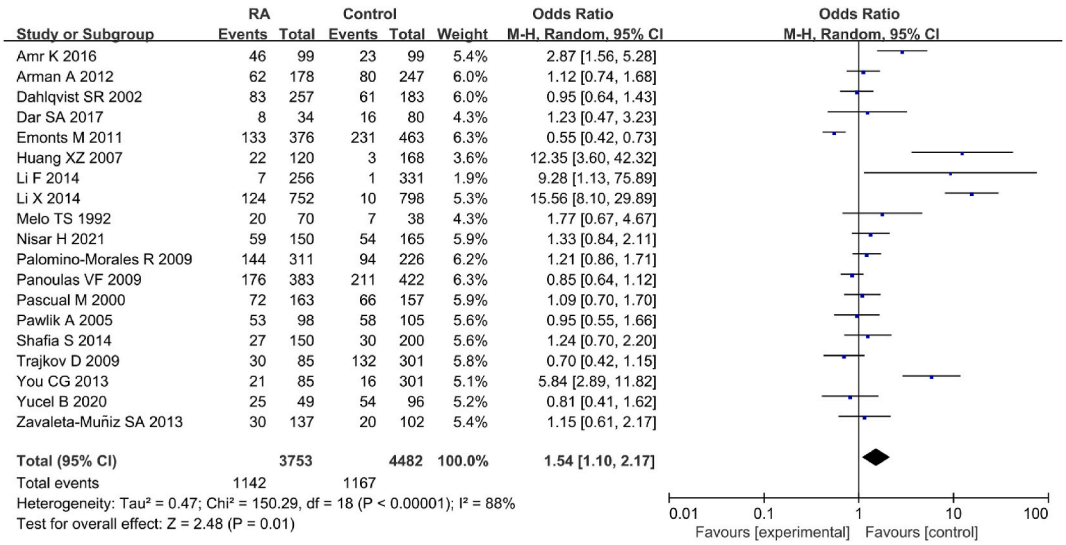

Fig. 8. FOP of correlation between IL-6 gene rs1800795(G-174C) genotype (CG) and RA.

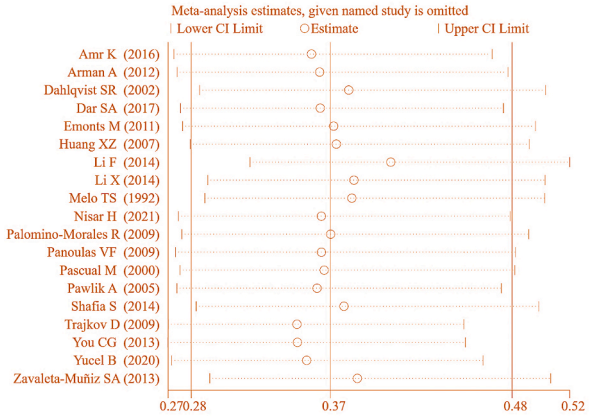

Fig. 9. SA of association between IL-6 gene rs1800795(G-174C) genotype (CG) and RA.

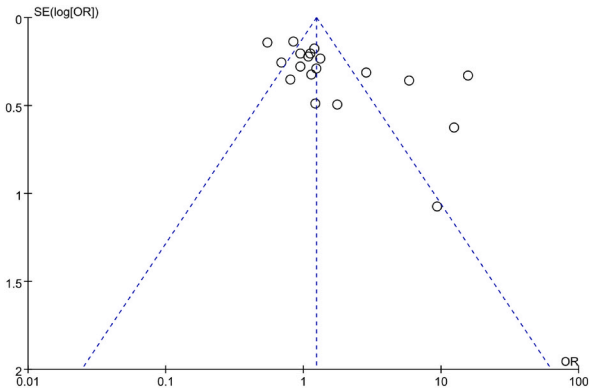

Fig. 10. FUP of correlation between IL-6 gene rs1800795(G-174C) genotype (CG) and RA.

correlation between IL-6 gene rs1800796(G-572C) allele model (G *vs* C) and RA, with one study removed at a time, yielded a combined effect [OR = 0.265, 95%CI: 0.156–0.450, $P < 0.05$]. This suggests a correlation between IL-6 gene rs1800796(G-572C) PM and RA. However, it was noted that this result exhibited some heterogeneity, warranting further analysis.

Table 4
Correlation between IL-6 gene rs1800795(G-174C) genotype (CG) and RA among different ethnicities.

Ethnicity	Number of studies included	Sample size	RA group(n/total)	CG (n/total)	Heterogeneity (I^2)	OR [95%CI]	*P*
Asian	4	2775	180/1278	44/1497	92 %	6.55 [1.28, 33.45]	0.02
European	**7**	3077	579/1382	638/1695	79 %	1.15 [0.81, 1.65]	0.43
Caucasian	2	570	87/227	134/343	0	1.03 [0.72,1.46]	0.88
Southeast Asian	3	627	113/283	93/344	54 %	1.72 [0.99,2.97]	0.05
Mixed	3	1186	183/583	258/603	77 %	0.94 [0.46, 1.90]	0.85

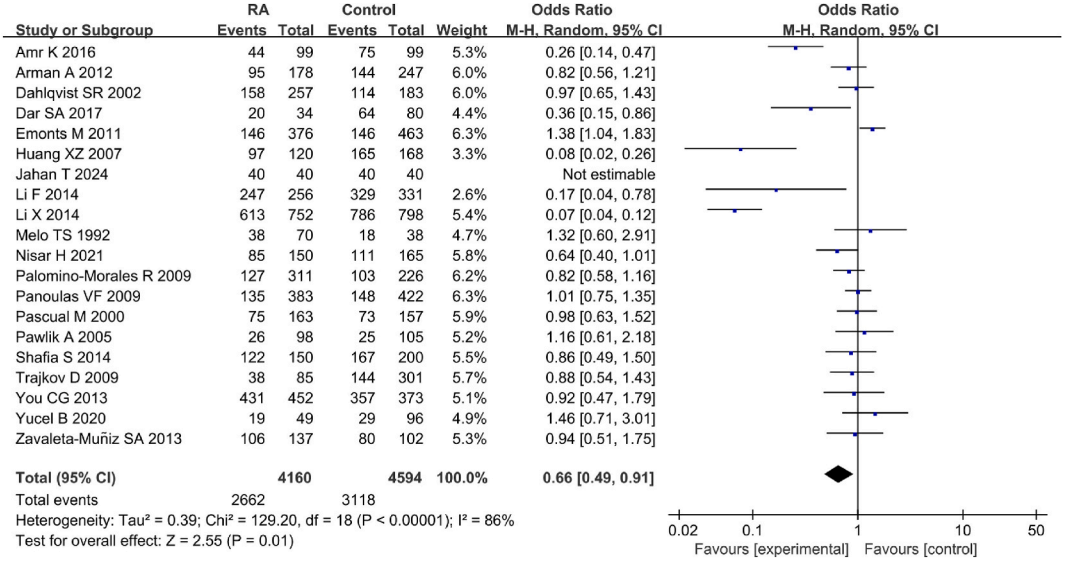

Fig. 11. FOP of correlation between IL-6 gene rs1800795(G-174C) genotype (GG) and RA.

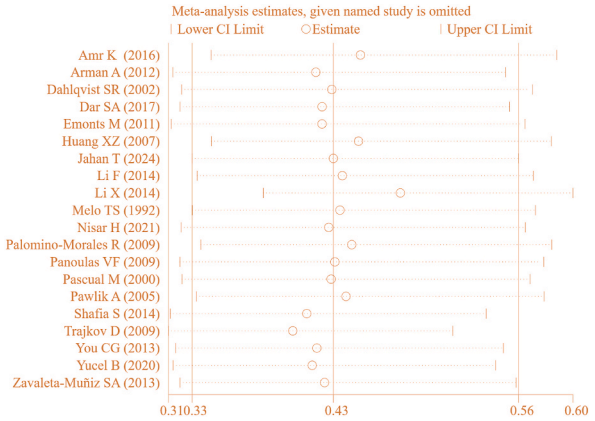

Fig. 12. SA of association between IL-6 gene rs1800795(G-174C) genotype (GG) and RA.

A funnel plot was utilized to analyze the PB regarding correlation between IL-6 gene rs1800796(G-572C) allele model (G *vs* C) and RA. The results, depicted in Fig. 16, indicated a symmetrical distribution of data points on the funnel plot, suggesting the absence of PB. Additionally, an Egger's test was conducted for further analysis of PB. The results revealed a $t = -1.02$ and a corresponding $P = 0.365$, further confirming the absence of PB in the included studies.

Eight studies were included in the analysis of correlation between IL-6 gene rs1800796(G-572C) genotype (CC) and RA (Fig. 17). The statistical results revealed considerable heterogeneity in the statistical outcomes between RA and CT groups ($I^2 = 74$ %, $P = 0.008$). Consequently, a REM was employed for the analysis. The findings indicated neglectable correlation between IL-6 gene rs1800796(G-572C) PM and RA [OR = 1.20, 95%CI: 0.80–1.78, Z = 0.89, $P = 0.37$].

To ensure the accuracy of these findings, a SA was conducted by sequentially excluding studies on correlation between IL-6 gene

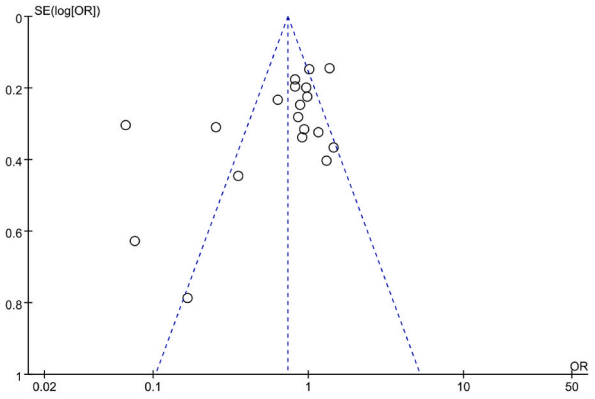

Fig. 13. FUP of correlation between IL-6 gene rs1800795(G-174C) genotype (GG) and RA.

Table 5
Correlation between IL-6 gene rs1800795(G-174C) genotype (GG) and RA across different ethnicities.

Ethnicity	Number of studies included	Sample size	RA group(n/total)	CG (n/total)	Heterogeneity (I^2)	OR [95%CI]	*P*
Asian	4	2775	1079/1278	1447/1497	93 %	0.17 [0.03, 0.83]	0.03
European	**7**	3516	990/1749	964/1767	0	0.95 [0.81, 1.11]	0.50
Caucasian	2	570	114/227	173/343	48 %	0.93 [0.66,1.31]	0.69
Southeast Asian	3	627	149/283	150/344	98 %	1.19 [0.07,20.23]	0.90
Mixed	3	1186	290/583	244/603	0	1.29 [1.01, 1.65]	0.04

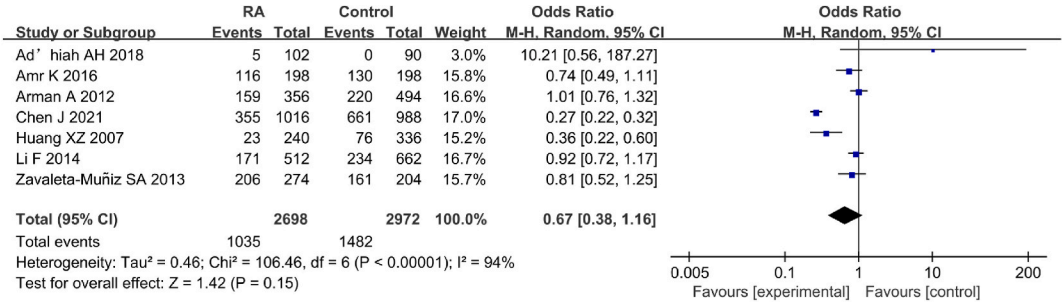

Fig. 14. FOP of association between the allele model (G *vs* C) and RA.

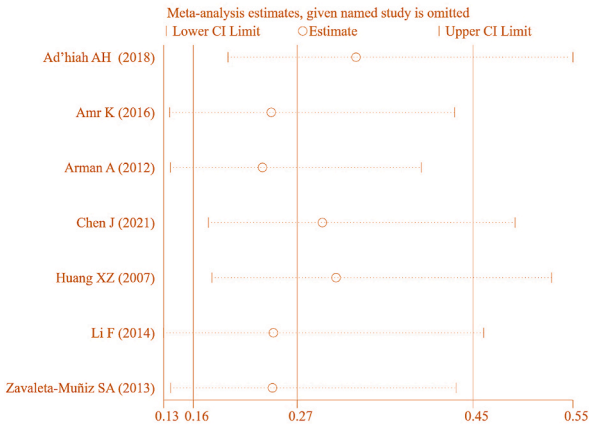

Fig. 15. SA of association between IL-6 gene rs1800796(G-572C) allele model (G *vs* C) and RA.

rs1800796(G-572C) genotype (CC) and RA (Fig. 18). The pooled effect size [OR = 0.233, 95%CI: 0.118–0.458, $P < 0.05$] suggested a considerable correlation between IL-6 gene rs1800796(G-572C) genotype (CC) and RA, implying some degree of heterogeneity in these results.

The PB regarding correlation between IL-6 gene rs1800796(G-572C) genotype (CC) and RA was assessed using a funnel plot (Fig. 19). Although the scatter distribution in the funnel plot appeared symmetrical, some studies were located outside the funnel plot, implying potential PB. Furthermore, Egger's test was employed to further analyze the PB. The results revealed a considerable Egger's regression intercept ($t = -5.13$, $P = 0.004$), implying the presence of PB in the included studies.

Eight studies were included in analysis of correlation between IL-6 gene rs1800796(G-572C) genotype (CG) and RA (Fig. 20). Great heterogeneity was observed in the statistical results of IL-6 rs1800796(G-572C) genotype (CG) between the RA and CT groups ($I^2 = 59$ %, $P = 0.02$). Hence, a REM was applied for the analysis. The results revealed neglectable correlation between IL-6 gene rs1800796(G-572C) PM and RA (OR = 0.97, 95%CI: 0.75–1.24, Z = 0.288, $P = 0.78$).

To ensure the accuracy of this result, a SA was conducted on the included literature (Fig. 21). Each study examining correlation between IL-6 gene rs1800796(G-572C) genotype (CG) and RA was sequentially excluded from the MA. The combined effect revealed a notable correlation between IL-6 gene rs1800796(G-572C) genotype (CG) and RA (OR = 0.335, 95%CI: 0.233–0.482, $P < 0.05$), implying a certain level of heterogeneity in this result.

The PB of the included literature on correlation between IL-6 gene rs1800796(G-572C) genotype (CG) and RA was assessed using a funnel plot (Fig. 22). The symmetrical distribution of data points in the funnel plot suggests the absence of considerable PB. Furthermore, an Egger's test was employed for further analysis of PB. The results revealed a $t = -1.46$ and a $P = 0.203$, implying neglectable PB in the included studies.

Eight studies analyzed correlation between IL-6 gene rs1800796(G-572C) genotype (GG) and RA (Fig. 23). The statistical analysis revealed neglectable heterogeneity in the statistical results between the RA and CT groups ($I^2 = 13$ %, $P = 0.33$). Hence, a FEM was employed for the analysis. The findings indicated neglectable correlation between IL-6 gene rs1800796(G-572C) PM and RA [OR = 0.87, 95%CI: 0.72–1.06, Z = 1.39, $P = 0.16$].

To ensure the accuracy of this result, further SA was conducted on the included literature, as depicted in Fig. 24. Each study examining correlation between IL-6 gene rs1800796(G-572C) genotype (GG) and RA was sequentially removed for MA. The combined effect yielded [OR = 0.148, 95%CI: 0.072–0.307, $P < 0.05$], implying a correlation between IL-6 gene rs1800796(G-572C) genotype (GG) and RA. This suggests a certain degree of heterogeneity in the results.

The PB regarding correlation between IL-6 gene rs1800796(G-572C) genotype (GG) and RA was analyzed using a funnel plot (Fig. 25). The symmetrical scatter distribution on the funnel plot indicates the absence of considerable PB. Furthermore, Egger's test was employed for further analysis of PB. The results revealed a $t = -0.49$ with a corresponding $P = 0.645$, suggesting neglectable PB in the included studies.

Different ethnic groups were categorized into four groups: Asian, Caucasian, Southeast Asian, and mixed. Only one study was available for the Caucasian and mixed groups and hence were not included in the analysis. MA revealed neglectable correlation between IL-6 gene rs1800796(G-572C) genotype (CC) and RA in both Asian and Southeast Asian populations ($P > 0.05$) (Table 6).

3.6. Correlation analysis between IL-6 gene rs1800797 (G-597A) and RA

Three studies analyzed correlation between IL-6 gene rs1800797(G-597A) genotype and RA (Table 7). The genotype GG of IL-6 rs1800797(G-597A) exhibited heterogeneity in both the RA and CT groups ($I^2 = 74$ %, $P = 0.02$), thus a REM was employed for the analysis. The results indicated neglectable association between IL-6 gene rs1800795(G-174C) PM and RA (OR = 0.57, 95%CI: 0.24–1.346, Z = 1.29, $P = 0.20$). Conversely, the genotype AA of IL-6 rs1800797(G-597A) showed no heterogeneity in the RA and CT groups ($I^2 = 0$ %, $P = 0.46$), therefore a FEM was utilized for the analysis. The findings revealed neglectable correlation between IL-6 gene rs1800795(G-174C) PM and RA (OR = 1.28, 95%CI: 0.73–12.23, Z = 0.87, $P = 0.38$).

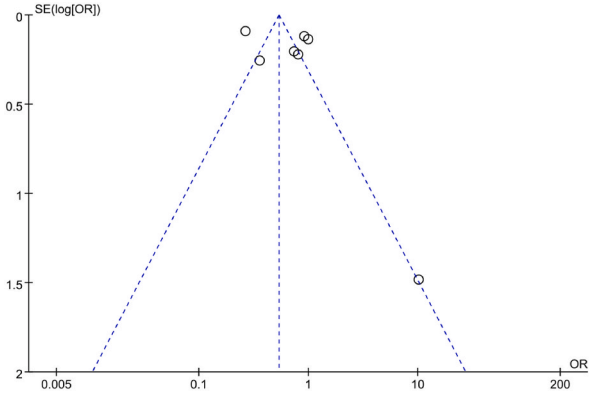

Fig. 16. FUP of association between the allele model (G *vs* C) and RA.

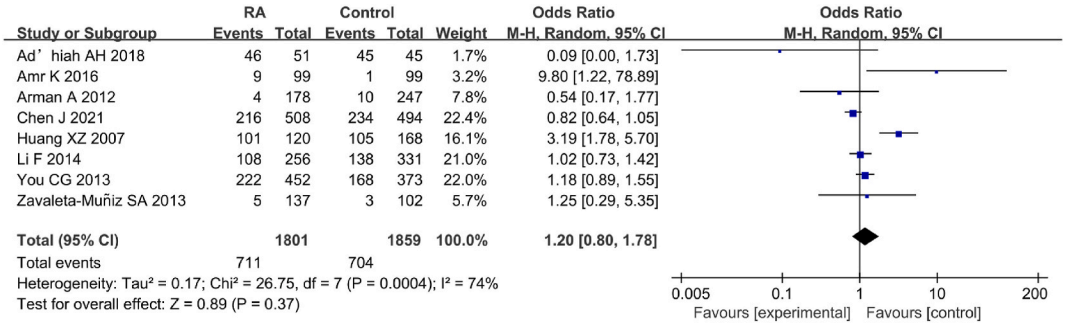

Fig. 17. FOP of correlation between IL-6 gene rs1800796(G-572C) genotype (CC) and RA.

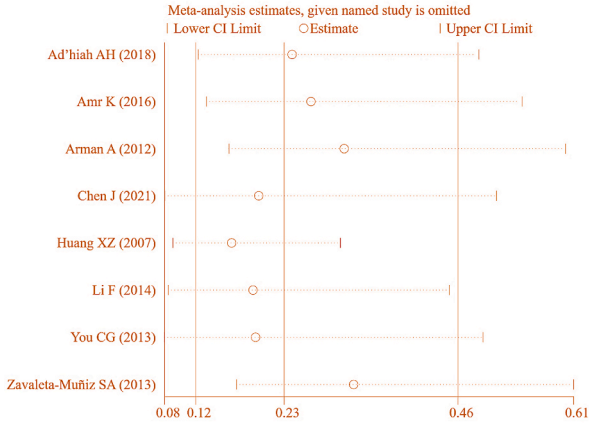

Fig. 18. SA of association between IL-6 gene rs1800796(G-572C) genotype (CC) and RA.

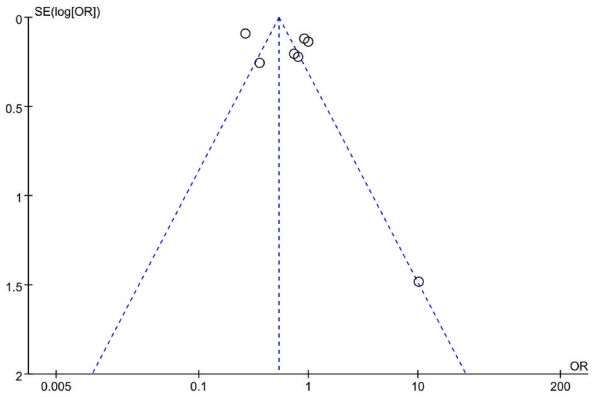

Fig. 19. FUP of correlation between IL-6 gene rs1800796(G-572C) genotype (CC) and RA.

4. Discussion

IL-6 regulates the onset and progression of arthritis through two distinct signaling pathways. The first pathway involves IL-6 binding to its membrane receptor, IL-6Rα, forming a complex. This complex subsequently influences tyrosine protein kinases 1 and 2, leading to the release of pro-inflammatory cytokines such as TNF-α and IL-17, which ultimately trigger arthritis. The second pathway involves IL-6 binding to the gp130 membrane protein, activating associated JAK family proteins. These JAK proteins then phosphorylate specific residues on gp130, activating downstream STAT proteins, particularly STAT3. Activated STAT3 translocates to the nucleus and regulates the expression of genes associated with inflammation and immune responses, including pro-inflammatory cytokines (*e.g.,* IL-1, TNF-α) and factors related to immune cell proliferation and differentiation. Researchers noted that IL-6 and its receptor significantly stimulate RANKL secretion in synovial tissue, promoting osteoclast maturation and contributing to joint damage.

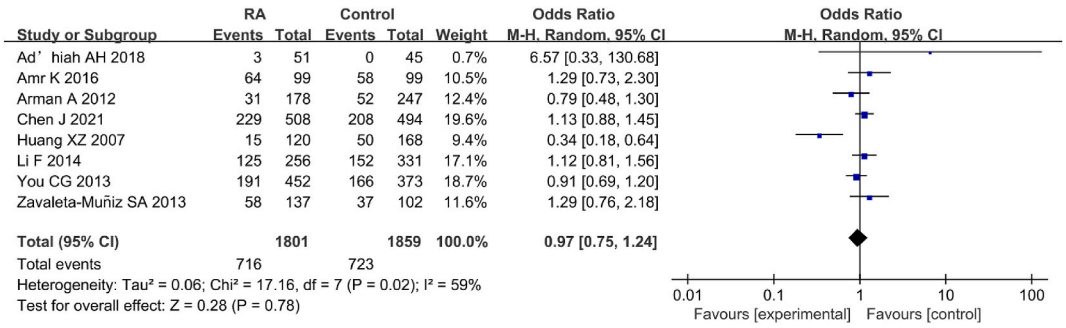

Fig. 20. FOP of correlation between IL-6 gene rs1800796(G-572C) genotype (CG) and RA.

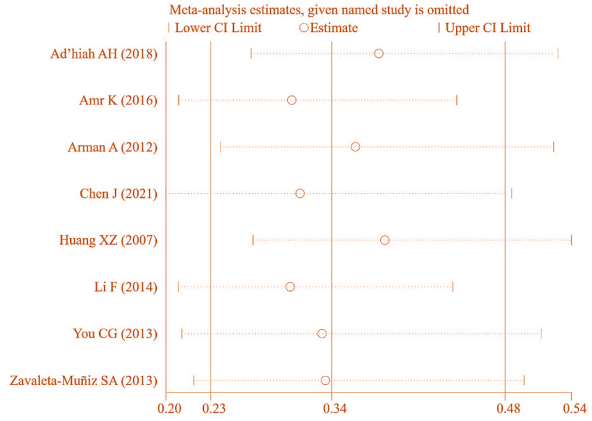

Fig. 21. SA of association between IL-6 gene rs1800796(G-572C) genotype (CG) and RA.

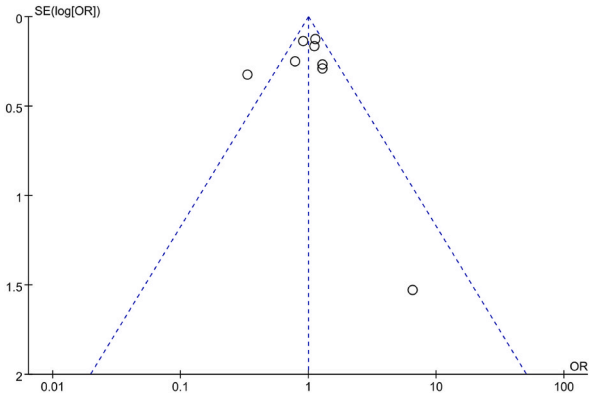

Fig. 22. FUP of correlation between IL-6 gene rs1800796(G-572C) genotype (CG) and RA.

Studies showed that serum IL-6 levels are elevated in RA patients, and its levels can reflect changes in the disease status of RA [39]. High levels of IL-6 can stimulate B lymphocytes to produce autoantibodies such as rheumatoid factors, thus enhancing the inflammatory response [40,41]. In RA, the synthesis and serum IL-6 are influenced by multiple factors, including PMs in the promoter or coding region of IL-6 gene [42]. IL-6 gene is on chromosome 7p21, and its genetic PMs may affect IL-6 expression levels, thereby influencing the proliferation and secretion of immune cells, leading to worsening of RA symptoms and related tissue damage [43]. Some studies indicated that specific PMs in IL-6 gene are related to susceptibility to RA in certain populations [44,45], and in patients with active RA, serum and synovial fluid levels of IL-6 are greatly elevated, positively correlating with disease activity and severity [46]. Therefore, PMs in IL-6 gene may influence the pathogenesis and clinical manifestations of RA. However, there is currently no consensus on the exact relationship between IL-6 GPMs and susceptibility to RA. Although some studies supported an association between IL-6 GPMs and RA, this correlation has not consistently been observed across different populations and studies, possibly due

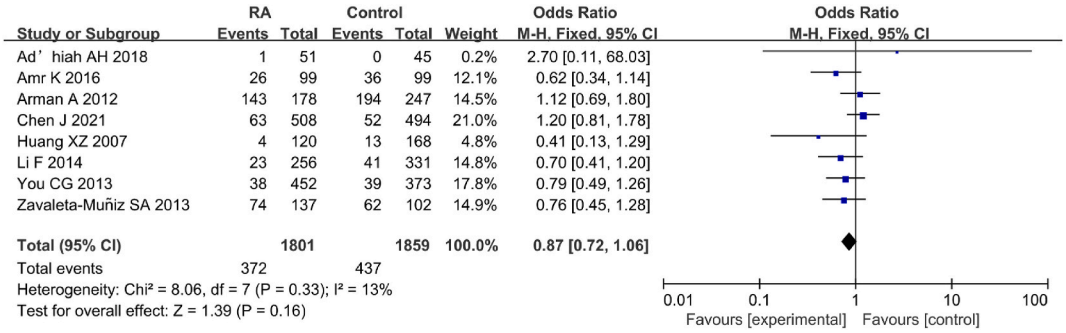

Fig. 23. FOP of correlation between IL-6 gene rs1800796(G-572C) genotype (GG) and RA.

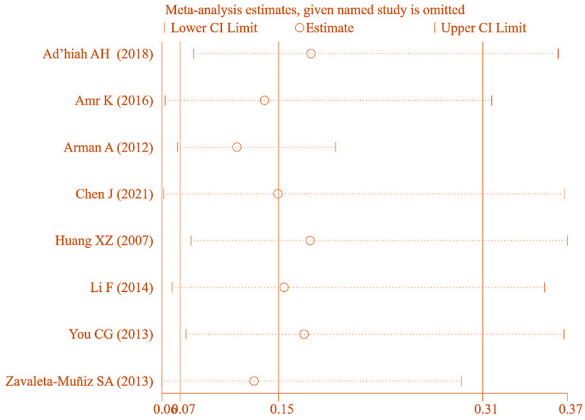

Fig. 24. SA of association between IL-6 gene rs1800796(G-572C) genotype (GG) and RA.

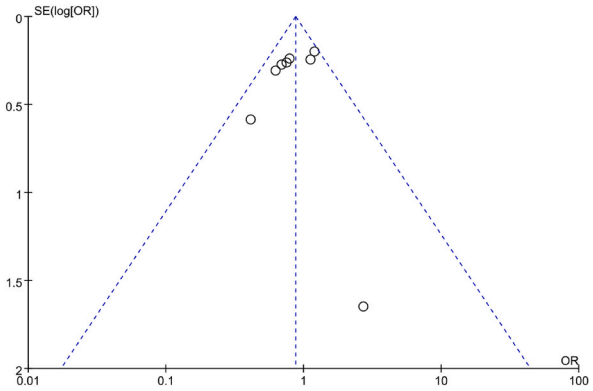

Fig. 25. FUP analysis of correlation between IL-6 gene rs1800796(G-572C) genotype (GG) and RA.

Table 6
Association between IL-6 gene rs1800796(G-572C) genotype (CC) and RA across different ethnicities.

Ethnicity	Number of studies included	Sample size	RA group (n/total)	CG (n/total)	Heterogeneity (I^2)	OR [95%CI]	*P*
CC							
Asian	4	2702	647/1336	645/1366	84 %	1.24 [0.83, 1.87]	0.30
Southeast Asian	2	294	55/150	46/144	85 %	1.07 [0.01,105.82]	0.98
CG							
Asian	4	2702	560/1336	576/1366	77 %	0.87 [0.62, 1.24]	0.45
Southeast Asian	2	294	67/150	58/144	10 %	1.47 [0.61,3.53]	0.38

Table 7
Correlation analysis between rs1800797 (G-597A) genotype and RA.

Genotype	Research included	RA group (n/total)	CG (n/total)	Weight/Heterogeneity	OR [95%CI]	*P*
GG						
	Arman A	97/178	133/247	47.0 %	1.03 [0.70, 1.51]	
	Li F	249/256	330/331	12.7 %	0.11 [0.01,0.88]	
	You CG	418/452	359/373	40.4 %	0.48 [0.25, 0.91]	
Merger effect				**74 %**	**0.57 [0.24,1.34]**	**0.20**
AA						
	Arman A	22/178	28/247	93.6 %	1.10 [0.61, 2.00]	
	Li F	2/256	1/331	3.9 %	2.60 [0.23,28.82]	
	You CG	3/452	0/373	2.5 %	0.48 [0.30,112.96]	
Merger effect				**0**	**1.28 [0.73,2.23]**	**0.38**

to population differences, variations in study design, and other unknown factors.

In this MA, a total of 21 studies were identified, comprising 9772 participants, with 4679 RA patients and 5093 controls. The focus was on the analysis of IL-6 GPMs rs1800795 (G-174C), rs1800796 (G-572C), and rs1800797 (G-597A) gene loci. The results showed a notable correlation between IL-6 gene rs1800795 (G-174C) PM (G vs C) and RA [OR = 0.66, 95%CI: 0.51–0.87, Z = 3.02, $P = 0.003$]. SA revealed a combined effect [OR = 0.541, 95%CI: 0.388–0.754, $P < 0.05$], implying the potential importance of IL-6 gene rs1800795 (G-174C) PM in the pathogenesis of RA. There was marked genetic PM at IL-6 gene rs1800795 (G-174C) locus in both RA patients and controls, and this PM was negatively correlated with the risk of RA occurrence. This suggests that individuals carrying specific alleles may be less susceptible to RA than others in certain circumstances. Additionally, it was found that only in the Southeast Asian population, IL-6 gene rs1800795 (G-174C) genotype (CC) was notably associated with RA [OR = 15.23, 95%CI: 3.53–65.67, $P = 0.00003$]. This finding indicates that individuals carrying IL-6 gene rs1800795 (G-174C) genotype (CC) are more likely to develop RA in the Southeast Asian population. This may imply a closer correlation between this genotype and the pathogenesis of RA in the Southeast Asian population compared to other ethnicities. The results indicated an association between IL-6 gene rs1800795 (G-174C) genotype (CG) and RA [OR = 1.54, 95%CI: 1.10–2.17, Z = 2.48, $P = 0.01$]. Interestingly, this correlation was found to be considerable only in the Asian population, where IL-6 gene rs1800795 (G-174C) genotype (CG) showed a strong correlation with RA [OR = 6.55, 95%CI: 1.28–33.45, $P = 0.02$]. This suggests a considerable difference in correlation of IL-6 gene rs1800795 (G-174C) genotype (CG) with RA among different ethnic groups. Particularly in the Asian population, individuals carrying IL-6 gene rs1800795 (G-174C) genotype (CG) are more susceptible to RA compared to other ethnicities. Zhang et al. (2022) [47] found in a Han Chinese population that the genotype distribution of IL-6 gene rs1800795 locus was GG > GC > CC, with the heterozygous GC and homozygous CC genotypes, as well as the frequency of the C allele, greatly higher in RA group than in CT group ($P < 0.05$). This finding, similar to the results of our study, supports association of rs1800795 with RA occurrence in Asian populations. However, researchers suggested that there is no correlation between IL-6 gene rs1800795 (G-174C) genotype and the occurrence of RA, further substantiating correlation of the rs1800795 (G-174C) genotype (CG) with RA in Asian populations [48–50]. Additionally, it was found that IL-6 gene rs1800795 (G-174C) genotype (GG) was associated with RA, with a notable correlation observed in the Asian population and also in the mixed population. The lack of correlation between IL-6 gene rs1800795 (G-174C) genotype (GG) and RA in other ethnicities (including European, Caucasian, and Southeast Asian populations) suggests that the genotype at IL-6 gene rs1800795 (G-174C) locus may have ethnicity-specific effects, leading to varying associations with RA among different ethnic groups.

The MA results indicated neglectable correlation between IL-6 gene rs1800796 (G-572C) and rs1800797 (G-597A) loci and the occurrence of RA. However, SA of multiple results suggests an association, which may be attributed to differences in study design, sample size, genotyping methods, characteristics of study subjects, and statistical methods. Therefore, further research is needed to explore correlation between IL-6 gene rs1800796 (G-572C) and rs1800797 (G-597A) loci and the occurrence of RA.

In summary, there is a notable correlation between IL-6 GPM rs1800795 (G-174C) and the occurrence of RA, while rs1800796 (G-572C) and rs1800797 (G-597A) show neglectable correlation with RA. Due to limitations in the included study data, this study did not identify associations between IL-6 GPMs and the clinical phenotype or serological markers of RA. Moreover, the correlation between IL-6 levels and factors such as comorbidities, disease duration, disease severity, body weight, and lifestyle has not been analyzed. These confounding variables may impact the development of RA. Future research should focus on expanding the sample size and further investigating the relationship between IL-6 GPMs and RA clinical phenotypes, serological markers, and relevant confounding factors. This will provide valuable insights for understanding the pathogenesis and treatment strategies of RA.

5. Conclusion

This study systematically evaluated correlation between IL-6 GPMs and susceptibility to RA using MA. Twenty-one articles were included, assessing the gene frequency distribution of IL-6 GPMs at rs1800795 (G-174C), rs1800796 (G-572C), and rs1800797 (G-597A) loci. The results revealed a notable correlation between the allelic model (G vs C) of IL-6 gene rs1800795 (G-174C) locus and RA. Among different ethnicities, notable correlations were observed between IL-6 gene rs1800795 (G-174C) genotype (GG) and RA in Asian and mixed populations, while the genotype (CC) in Southeast Asian populations was also related to RA. Neglectable correlations were found between rs1800796 (G-572C) and rs1800797 (G-597A) GPMs and RA. These findings are crucial for understanding the role of IL-6 gene in pathogenesis of RA, particularly with potential clinical implications in Asian populations.

CRediT authorship contribution statement

Xiaojuan Hao: Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Huani Zhao:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Linhui Zhu:** Writing – original draft, Visualization, Validation, Data curation. **Zhiteng Li:** Writing – review & editing, Writing – original draft, Validation, Formal analysis, Data curation, Conceptualization. **Jing Yang:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Qian Bai:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization.

Data availability statement

The data relevant to this study are available in accordance with applicable requirements.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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