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Association of IL-27 gene rs153109 and rs17855750 polymorphisms with preeclampsia susceptibility and severity

Meta-analysis and trial sequential analysis

Fengzhen Wang, MD[a,*], Ersheng Wen, MS[b], Yuyang Huang, BA[c], Zhenyin Wen, BA[c], Ziyou Liu, MD[a]

Abstract

Background: The aim of this meta-analysis is to evaluate the association of interleukin-27 gene rs153109 and rs17855750 polymorphisms with preeclampsia susceptibility and severity.

Methods: Web of Science, PubMed, Embase, CBM, WanFang Data, CNKI, and VIP database were used for retrieving. After screening with our inclusion and exclusion criteria, data extraction and quantity evaluation were performed by 2 independent authors. Included case-control studies were used for meta-analysis by RevMan 5.4, and sensitivity analysis was carried out through 1-by-1 exclusion procedure. If heterogeneity exists, then random effects model was used; otherwise, fixed effect model was used. Publication bias analysis was performed using Begg test and Egger test. Trial sequential analysis was performed using trial sequential analysis 0.9.5.10 Beta.

Results: A total of 5 articles were included. The heterogeneity was high across most models during the meta-analysis. Meta-analysis results related to preeclampsia susceptibility showed that *P* values of all the models were higher than .05, while for meta-analysis results related to preeclampsia severity showed that *P* values of all the models were higher than .05 except for TT versus TG + GG and TT versus TG models of rs17855750 group. The sensitivity of the meta-analysis was high, and trial sequential analysis showed the possibility of false negative results. No obvious publication bias was found.

Conclusions: There is no obvious association between interleukin-27 gene rs153109 and rs17855750 polymorphisms and preeclampsia susceptibility or severity. However, more multi-center and large sample case-control studies are expected to be carried out to verify our conclusion in the future.

Abbreviations: IL-27 = interleukin-27, OR = odds ratio, SNP = single nucleotide polymorphism, TSA = trial sequential analysis.

Keywords: gene polymorphism, IL-27, meta-analysis, preeclampsia, severity, susceptibility, trial sequential analysis

1. Introduction

Preeclampsia is a major complication of pregnancy, involving multiple organs and systems.[1] It is mainly manifested by new onset hypertension and proteinuria in the pregnant woman.[2] Other symptoms can specifically manifest as maternal headache, vision impairment, and kidney malfunction, as well as coagulation and respiratory dysfunction.[3–6] Preeclampsia is thought to complicate 2% to 8% of pregnancies worldwide.[2] It not only puts the life of gravida in great danger, but prevents the placenta from exchanging nutrients, which influences the normal development of fetus, thus decreasing the survival rate, and increasing the deformity rate of the fetus.[7]

Interleukin-27 (IL-27) is a member of the Interleukin-6/Interleukin-12 family which regulates a variety of immunological responses.[8,9] As an inflammatory mediator, IL-27 can lead to the activation of a series of cells and influence the secretion of other inflammatory mediators such as Interleukin-1 beta, monocyte chemoattractant protein-1, tumor necrosis factor-α, and transforming growth factor-β.[10] Previous studies proved that by influencing the epithelial-mesenchymal transition process via a signal transducer and activator of transcription 1 dominant route, IL-27 may prevent trophoblast cell migration and invasion in preeclampsia patients.[11] Besides, plenty of studies have demonstrated that IL-27 can suppress Th1, Th2, Th9, and Th17 reactions.[9] The imbalance between regulatory T cells and Th17,

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[a] Heart Medical Centre, First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi, China, [b] Department of Physiology, Gannan Medical University, Ganzhou, Jiangxi, China, [c] School of Nursing, Gannan Medical University, Ganzhou, Jiangxi, China.

** Correspondence: Fengzhen Wang, Heart Medical Centre, First Affiliated Hospital of Gannan Medical University, Ganzhou 341000, Jiangxi, China (e-mail: zhenzi37w@163.com).*

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which is inhibited by IL-27, can reverse the maternal tolerance of preeclampsia.[12] Therefore, changes in IL-27 gene expression and serum concentration may influence a series of pathways and play a role in the occurrence and development of diseases.

DNA sequence polymorphism caused by double nucleotide variations in the genome is referred to as single nucleotide polymorphism, which is ideally suited genetic marker related to risks of diseases.[13] Studying the relationship between single nucleotide polymorphisms and disease characteristics can provide great help for basic research, gene diagnosis and gene therapy.[14] There are plenty of studies that assessed the relationship between IL-27 gene polymorphisms and disease characteristics. Many diseases have been proved to have the connection to IL-27 gene rs153109 and rs17855750 polymorphisms, such as colorectal cancer,[15,16] papillary thyroid carcinoma,[17] renal cell carcinoma,[18] bladder cancer[19] and allergic rhinitis.[20]

Recently, there have also been many case-control studies that evaluated the association of IL-27 gene rs153109 and rs17855750 polymorphisms with preeclampsia suspensibility and severity. However, the odds ratio (OR) values between different studies differ a lot, which means that the results obtained from different studies are not the same. And most of the original studies published before have no statistical significance so the strength of the evidence was low. Therefore, this meta-analysis and trial sequential analysis (TSA) were carried out in order to perform secondary research with a higher evidence level, in this way providing hints for basic research and clinical practice.

2. Methods

2.1. Study inclusion criteria

Case-control studies evaluating the relationship between preeclampsia susceptibility or severity and the IL-27 gene polymorphisms rs153109 and rs17855750 were included. Patients with preeclampsia who had been clinically diagnosed with the condition using specific diagnostic criteria made up the case group in the case-control study. Healthy individuals of any gender or race made up the control group. For studies assessing the influence on preeclampsia severity, there should be clear criteria for classifying patients as having mild or severe preeclampsia. Data of alleles frequencies of all genotypes in each group should be obtained.

2.2. Study exclusion criteria

The study will not be included if the original data is incomplete, and the corresponding author could not be contacted, or the entire data could not be obtained after contacting. Repeated publication or retrieved studies with the same data should then be ignored. The publication with the best quality and greatest sample size should be chosen when an author published more than 1 articles. In addition, if the subject is not a human, the study will not be included.

2.3. Retrieval strategy

Web of Science, PubMed, Embase, CBM, WanFang Data, CNKI and VIP database were used for retrieving. The retrieval time interval was from the date of database establishment to July 31, 2022. The retrieval was carried out by combining free words with subject words. The key words used include IL-27, IL-27, interleukin-27, preeclampsia, preeclampsia, polymorphisms, and variants. Taking PubMed as an example, the retrieval strategy is shown in Table 1.

2.4. Article screening and data extraction

Article screening and data extraction process were performed by 2 researchers independently. Cross examination was also performed after these, and disputes were handled by discussion with a third party. The title was initially reviewed to weed out items that seemed irrelevant while screening articles. The abstract and complete text were then read once more to see whether they could be finally included. If required, an email was sent to the author to get the crucial details that were left out of the original study. The fundamental information from each included study is recorded in the data extraction process, including the first author, publication year, country, number of cases and controls corresponding to each genotype.

2.5. Study quality evaluation

Two researchers independently assessed the overall characteristics of the included case-control studies using the Newcastle-Ottawa Scale principle.[21] Disputes were handled by discussion with a third party.

2.6. Statistical methods

RevMan 5.4 (RevMan, 11-13 Cavendish Square, London, UK) and Stata MP-17 (Stata, 4905 Lakeway Drive, College Station, TX) software were used for the meta-analysis, and TSA 0.9.5.10 Beta was used for trial sequential analysis. The test level of heterogeneity test was $\alpha = 0.10$. The random effects model was applied if the heterogeneity test result was $P < .10$, which indicated heterogeneity exists. The fixed effect model was applied if the heterogeneity test result was $P > .10$, which indicated that no heterogeneity exists. The test level of meta-analysis and TSA analysis was $\alpha = 0.05$. Begg test and Egger test were used to examine the publication bias, and the test level was $\alpha = 0.05$. The 95% confidence intervals of all the test were also recorded.

2.7. Institutional review board statement

Ethical approval is not applicable as data were derived from published articles.

3. Results

3.1. Article retrieving and quality evaluation results

Through the step-by-step search shown in Figure 1, a total of 5 articles from 2 countries were included in our meta-analysis.[12,22–25] There are 10 studies on gene polymorphism and susceptibility to preeclampsia, 5 of them are related to rs153109, and 5 of them are related to rs17855750. A total of 3923 people were included in the case group and 5033 in the control group. There are 6 studies on gene polymorphism and severity of preeclampsia, 3 of them are related to rs153109, and 3 of them are related to rs17855750. A total of 682 people were included in the severe group and 480 in the mild group. The results of study quality evaluation showed that the quality of the above-mentioned studies was high-scored,

Table 1

Retrieval strategy of PubMed.

#1	IL-27
#2	IL-27
#3	Interleukin-27
#4	#1 OR #2 OR #3
#5	"Preeclampsia"[Mesh]
#6	Preeclampsia
#7	Preeclampsia
#8	#5 OR #6 OR #7
#9	Polymorphism
#10	Variants
#11	#9 OR #10
#12	#4 AND #8 AND #11

IL-27 = Interleukin-27, OR = odds ratio.

and all of them met the criteria to be included in this meta-analysis. Tables 2 and 3 illustrate the fundamental characteristics of the original studies included in this meta-analysis.

3.2. Meta-analysis results of preeclampsia susceptibility

Meta-analysis of the relationship of IL-27 gene rs153109 and rs17855750 polymorphisms with preeclampsia susceptibility was carried out using the effect model selection procedures discussed before. The heterogeneity across different groups was high during meta-analysis, particularly for models related to rs153109. Table 4 shows all meta-analysis results related to preeclampsia susceptibility. Taking the allele models as examples, forest plots are shown in Figure 2. The evidence presented above demonstrates that the results of all models are not statistically significant. The IL-27 gene rs153109 and rs17855750 polymorphisms were not associated with susceptibility to preeclampsia.

3.3. Meta-analysis results of preeclampsia severity

Meta-analysis of the relationship of IL-27 gene rs153109 and rs17855750 polymorphisms with preeclampsia severity was

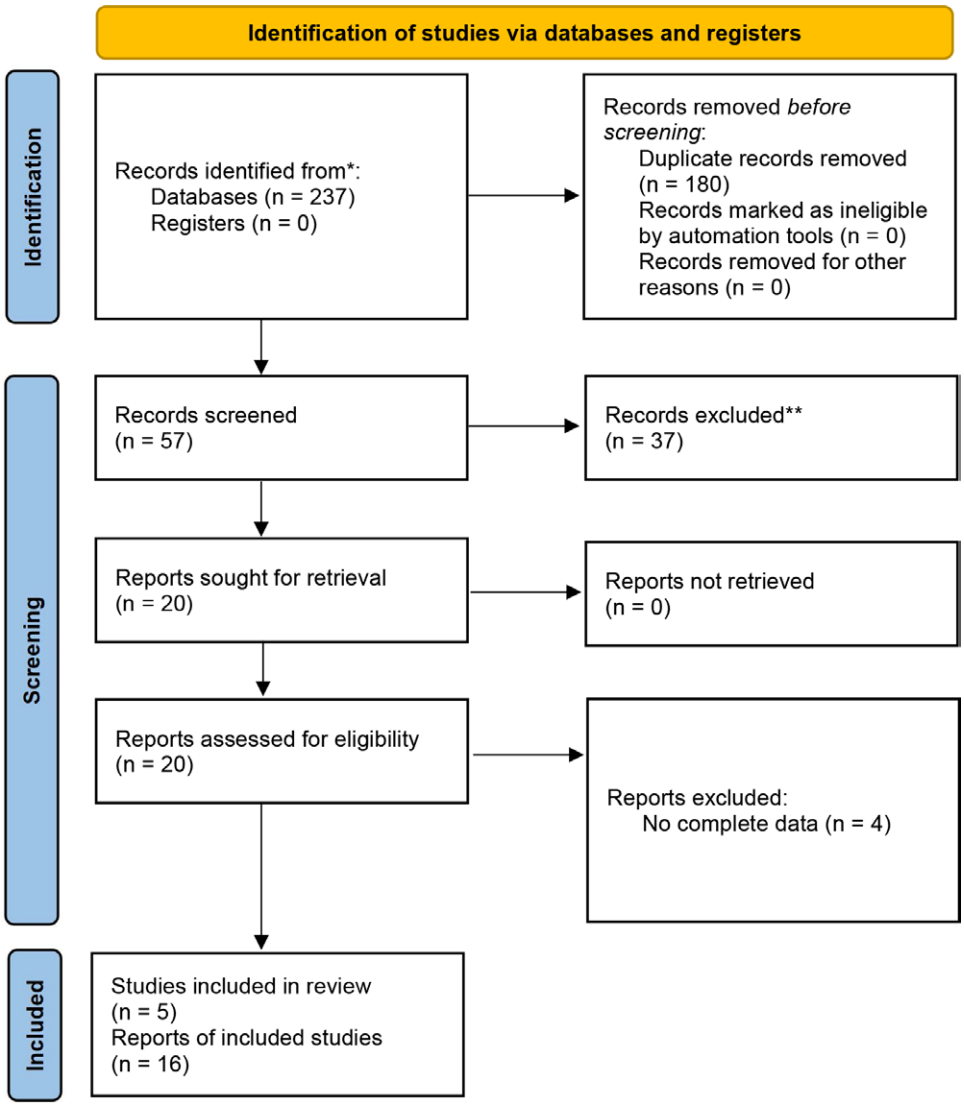

Figure 1. Article retrieving and selection process.

Table 2

Fundamental characteristics of the original studies related to rs153109.

				Case group			Control group				Severe group			Mild group		
First Author	Year	Country	Case/control	TT	TC	CC	TT	TC	CC	Severe/mild	TT	TC	CC	TT	TC	CC
Chen P	2016	China	1034/1240	405	431	198	467	608	165	172/40	80	72	20	16	20	4
Liu B	2016	China	212/451	96	92	24	162	210	79	/	/	/	/	/	/	/
Chen A	2020	China	342/457	128	154	60	178	217	62	/	/	/	/	/	/	/
Jahantigh D	2020	Iran	170/170	73	81	16	96	67	7	103/67	47	45	11	26	36	5
Aramesh A	2021	Iran	199/228	82	84	33	82	117	29	66/133	24	30	12	58	54	21

C=cytosine, T = thymine.

Table 3

Fundamental characteristics of the original studies related to rs17855750.

First Author	Year	Country	Case/control	Case group			Control group			Severe/mild	Severe group			Mild group		
				TT	TG	GG	TT	TG	GG		TT	TG	GG	TT	TG	GG
Chen P	2016	China	1014/1210	763	224	27	885	291	34	172/40	140	28	4	26	14	0
Liu B	2016	China	212/451	166	42	4	364	78	9	/	/	/	/	/	/	/
Chen A	2020	China	342/457	270	64	8	342	104	11	/	/	/	/	/	/	/
Jahantigh D	2020	Iran	170/170	62	89	19	79	84	7	103/67	38	52	13	24	37	6
Aramesh A	2021	Iran	228/199	106	80	42	99	59	41	66/133	38	15	13	61	44	28

G = guanine, T = thymine.

Table 4

Meta-analysis results related to preeclampsia susceptibility.

	rs153109			rs17855750		
	OR	95% CI	*P* value	OR	95% CI	*P* value
aa vs bb	0.84	0.55, 1.28	.42	0.91	0.67, 1.23	0.53
aa + ab vs bb	0.79	0.55, 1.13	.20	0.94	0.70, 1.27	0.70
aa vs ab + bb	1.03	0.81, 1.32	.80	1.02	0.89, 1.17	0.77
aa vs ab	1.11	0.88, 1.39	.37	1.02	0.89, 1.18	0.73
ab vs bb	0.74	0.53, 1.03	.07	0.95	0.70, 1.31	0.76
a vs b	0.95	0.78, 1.16	.63	0.97	0.81, 1.17	0.77

For rs153109, a represents T, b represents C; For rs17855750, a represents T, b represents G.
C = cytosine, CI = confidence interval, G = guanine, OR = odds ratio, T = thymine.

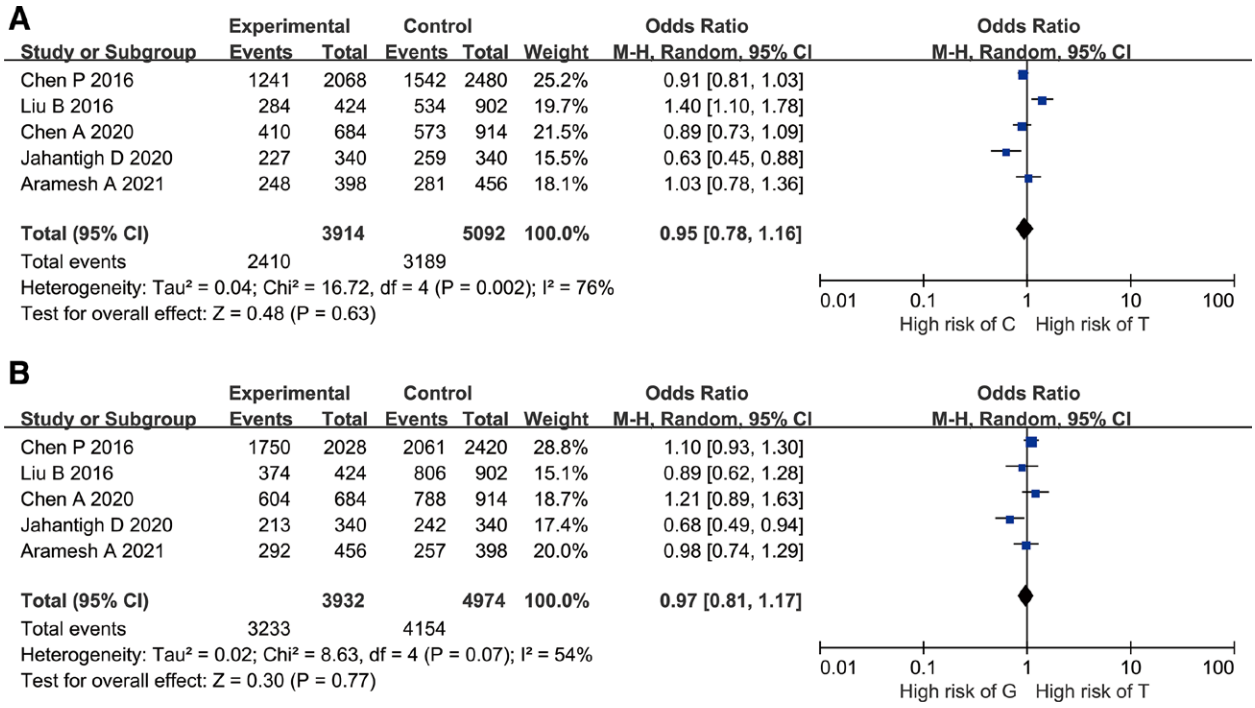

Figure 2. Forest plots of allele models about preeclampsia susceptibility. (A) rs153109; (B) rs17855750.

carried out using fixed effect model as the heterogeneity across all the groups was low. Table 5 shows all meta-analysis results related to preeclampsia severity. Taking the allele models as examples, forest plots are shown in Figure 3. The evidence presented above demonstrates that the results of all models are not statistically significant, except TT versus TG + GG and TT versus TG models of rs17855750. The IL-27 gene rs153109 and rs17855750 polymorphisms were weakly associated with severity to preeclampsia.

3.4. Sensitivity analysis results

Taking the allele models as examples, sensitivity analysis was carried out through 1-by-1 exclusion procedure. As for rs153109 polymorphism group about preeclampsia susceptibility, combined OR value reached the highest level 1.02 with P = .81 (excluded Jahantigh D 2020), and reached the lowest level 0.88 with P = .08 (excluded Liu B 2016). As for rs17855750 polymorphism group about preeclampsia

Table 5

Meta-analysis results related to preeclampsia severity.

	rs153109			rs17855750		
	OR	95% CI	*P* value	OR	95% CI	*P* value
aa vs bb	0.81	0.45, 1.48	.50	1.06	0.58, 1.94	.85
aa + ab vs bb	0.80	0.46, 1.39	.42	0.89	0.50, 1.58	.69
aa vs ab + bb	1.06	0.74, 1.53	.75	1.50	1.03, 2.20	.03
aa vs ab	1.13	0.77, 1.66	.54	1.67	1.11, 2.52	.01
ab vs bb	0.78	0.44, 1.39	.40	0.64	0.33, 1.23	.18
a vs b	0.98	0.75, 1.28	.87	1.22	0.92, 1.62	.17

For rs153109, a represents T, b represents C; For rs17855750, a represents T, b represents G.
C = cytosine, CI = confidence interval, G = guanine, OR = odds ratio, T = thymine.

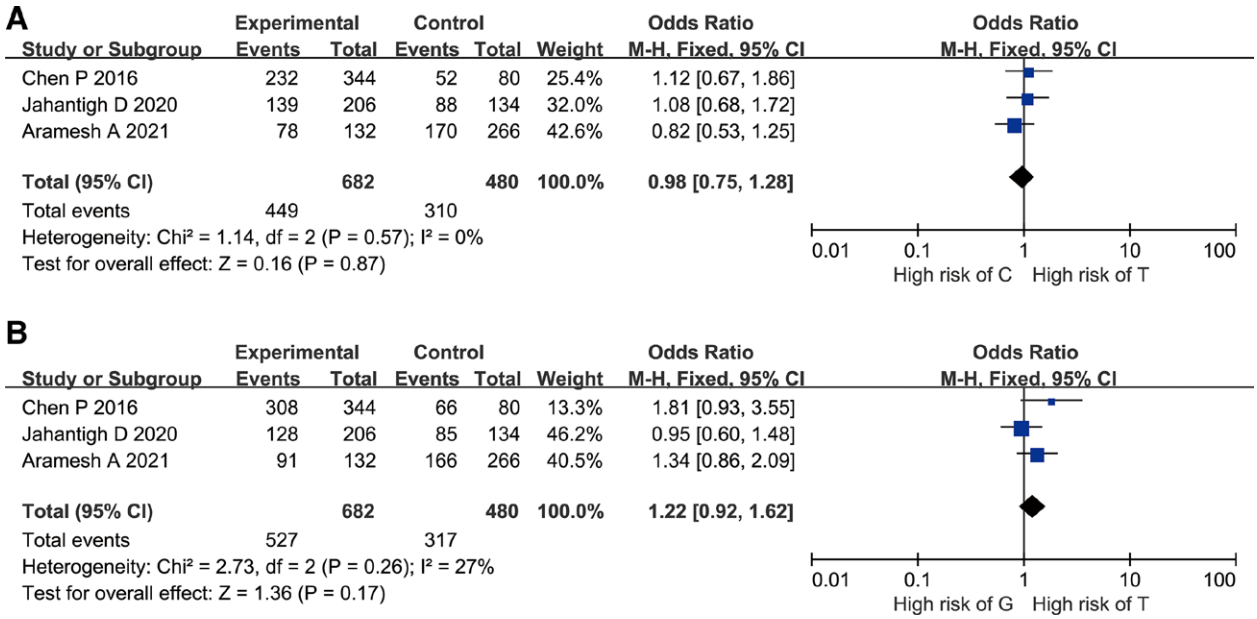

Figure 3. Forest plots of allele models about preeclampsia severity. (A) rs153109; (B) rs17855750.

susceptibility, combined OR value reached the highest level 1.06 with $P = .32$ (excluded Jahantigh D 2020), and reached the lowest level 0.92 with $P = .45$ (excluded Chen A 2020). This shows that the sensitivity of meta-analysis is high, the results are greatly affected by a single study, and the stability is low. The situation was similar considering the rs153109 and rs17855750 polymorphism groups about preeclampsia severity.

3.5. Publication bias analysis results

Taking the allele models as examples, publication bias analysis was carried out by Begg test and Egger test. The publication bias analysis results of each group are shown in Table 6. Funnel plots are shown in Figure 4. All the *P* values were higher than .05, which indicated no obvious publication bias, and that the reliability of meta-analysis results was less influenced by publication bias.

3.6. Trial sequential analysis results

Taking the allele models as examples, trial sequential analysis was carried out. As for rs153109 (Fig. 5A) and rs17855750 (Fig. 5B) polymorphism groups about preeclampsia susceptibility, the Z-curve did not cross the TSA boundary line and the accumulated data did not meet the required information size. This situation was the same as for rs153109 (Fig. 5C) and rs17855750 (Fig. 5D) polymorphism groups about preeclampsia severity. These suggested that there was a chance of false negative outcomes. Therefore, additional case-control studies are still required to further support the findings of this meta-analysis.

4. Discussion

In this meta-analysis, we investigated the association of IL-27 gene rs153109 and rs17855750 polymorphisms with preeclampsia susceptibility and severity. A total of 5 articles from multiple medical institutions were included. According to the results of meta-analysis, considering the impact of IL-27 gene rs153109 and rs17855750 polymorphisms to preeclampsia susceptibility, OR values of some of the models were higher than 1 while others were lower than that. Besides, *P* values in each model were higher than .05, which means that no statistical significance existed. These indicated that there was no association between IL-27 gene rs153109 and rs17855750 polymorphisms and preeclampsia susceptibility. Considering the impact of IL-27 gene rs153109 and rs17855750 polymorphisms on preeclampsia severity, although $P < .05$ in TT versus TG + GG and TT versus TG models of rs17855750 group, the association between the 2 can still not be confirmed as the OR value of volatility and high sensitivity. Therefore, there was no obvious relationship between the IL-27 gene rs153109 and rs17855750 polymorphisms with preeclampsia susceptibility and severity.

Table 6

Publication bias analysis *P* values of allele models.

	Susceptibility		Severity	
	rs153109	rs17855750	rs153109	rs17855750
Begg test	1.000	0.221	0.296	1.000
Egger test	0.935	0.325	0.309	0.476

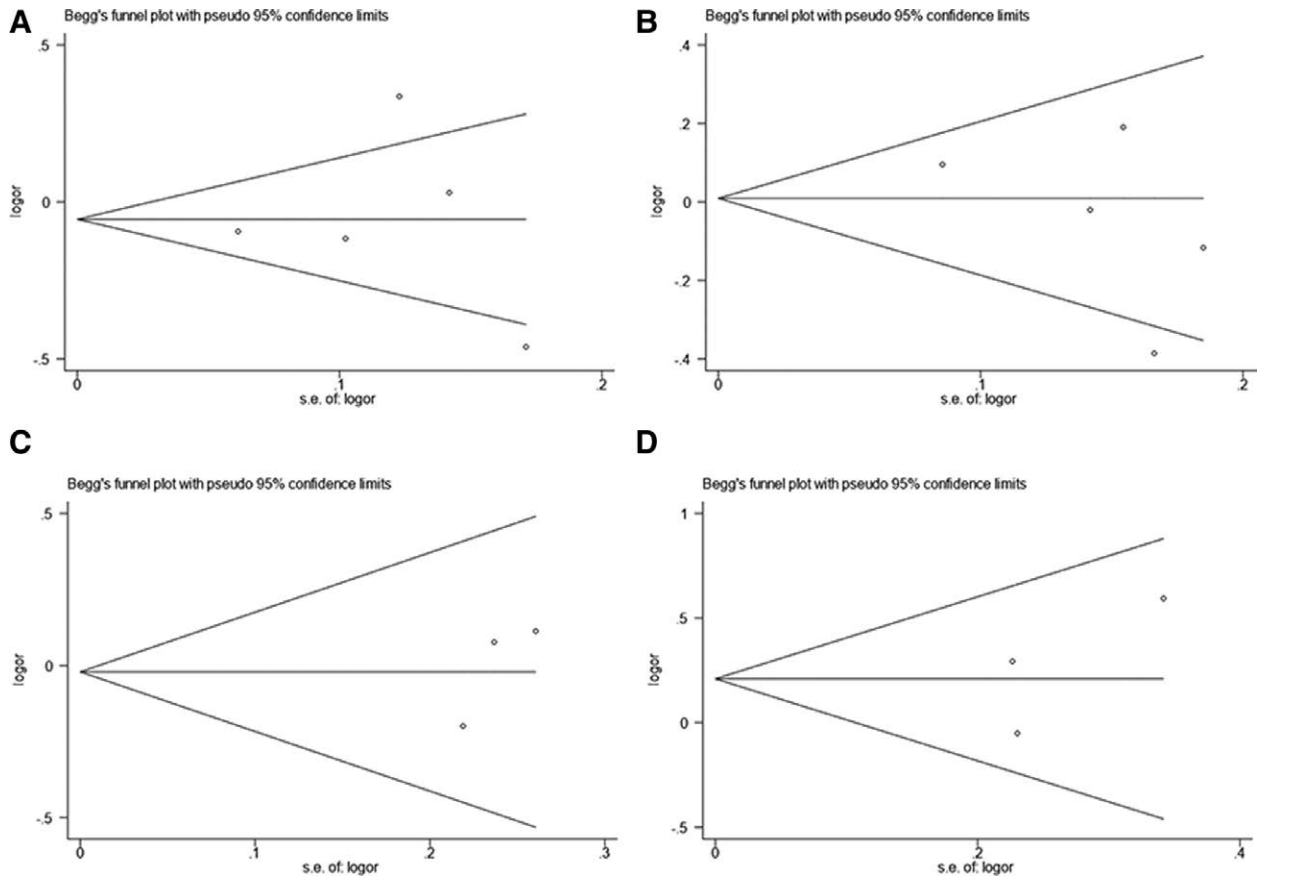

Figure 4. Funnel plots of publication bias analysis. (A) rs153109 and preeclampsia susceptibility; (B) rs17855750 and preeclampsia susceptibility; (C) rs153109 and preeclampsia severity; (D) rs17855750 and preeclampsia severity.

In order to verify the reliability of our conclusion, publication bias analysis and trial sequential analysis were performed. After Begg test and Egger test, no obvious publication bias was found as the *P* values of each group of allele models were higher than .05. This evidence proved that the original studies with negative and positive results were reasonably considered in the meta-analysis. This meta-analysis is less influenced by the publication bias and the conclusion is relatively reliable. Trial sequential analysis showed that the TSA boundary value or the required information size was not crossed by the Z-curve. This indicated that the number of participants included in the original studies we included in the meta-analysis was insufficient, and the results still had the possibility of false negatives.

It is likely that IL-27 gene rs153109 and rs17855750 polymorphisms are low-penetrance sites, which means that the polymorphisms of these sites may not be the key influencing factor of IL-27 gene expression.[26,27] However, although the IL-27 gene rs153109 and rs17855750 polymorphisms were found not associated with preeclampsia susceptibility and severity, some studies included suggest that the serum concentration of IL-27 may still show a significant difference between case and control groups.[25]

As a pregnancy related disease, the pathophysiology of preeclampsia is complex and not fully understood.[28] More and more studies regard that autoimmune, endocrine disorders and fetal diseases are related to the incidence and prognosis of preeclampsia, while it is associated with many processes such as immune dysregulation, endothelial dysfunction, and vasoconstriction.[29,30] Considering the immune mechanism, cytokine concentration directly affects endothelial function in pregnancy and plays a role in the occurrence of preeclampsia.[31] As a consequence, some studies believed that immune biomarkers like cytokines in peripheral blood can predict preeclampsia.[28,31–34] For example, it have been demonstrated that there is a decrease in secretion of IL-5 and IL-10 by blood monocytes and blood basophil count compared with normal pregnancy.[33] Besides, imbalance of IL-17 and IL-35 expressions in peripheral blood and placenta of preeclamptic pregnant women have been found.[34] IL-27 is widely considered as one of the most immune specific genes. Previous basic research based on rats demonstrated that preeclampsia group had noticeably greater levels of IL-27 mRNA expression in peripheral blood than control.[35] As for clinical studies, it was also observed that there was a significant difference in the serum level of IL-27 between participants in the case and control groups,[25,36] which may give evidence for biomarker selection for preeclampsia diagnosis.

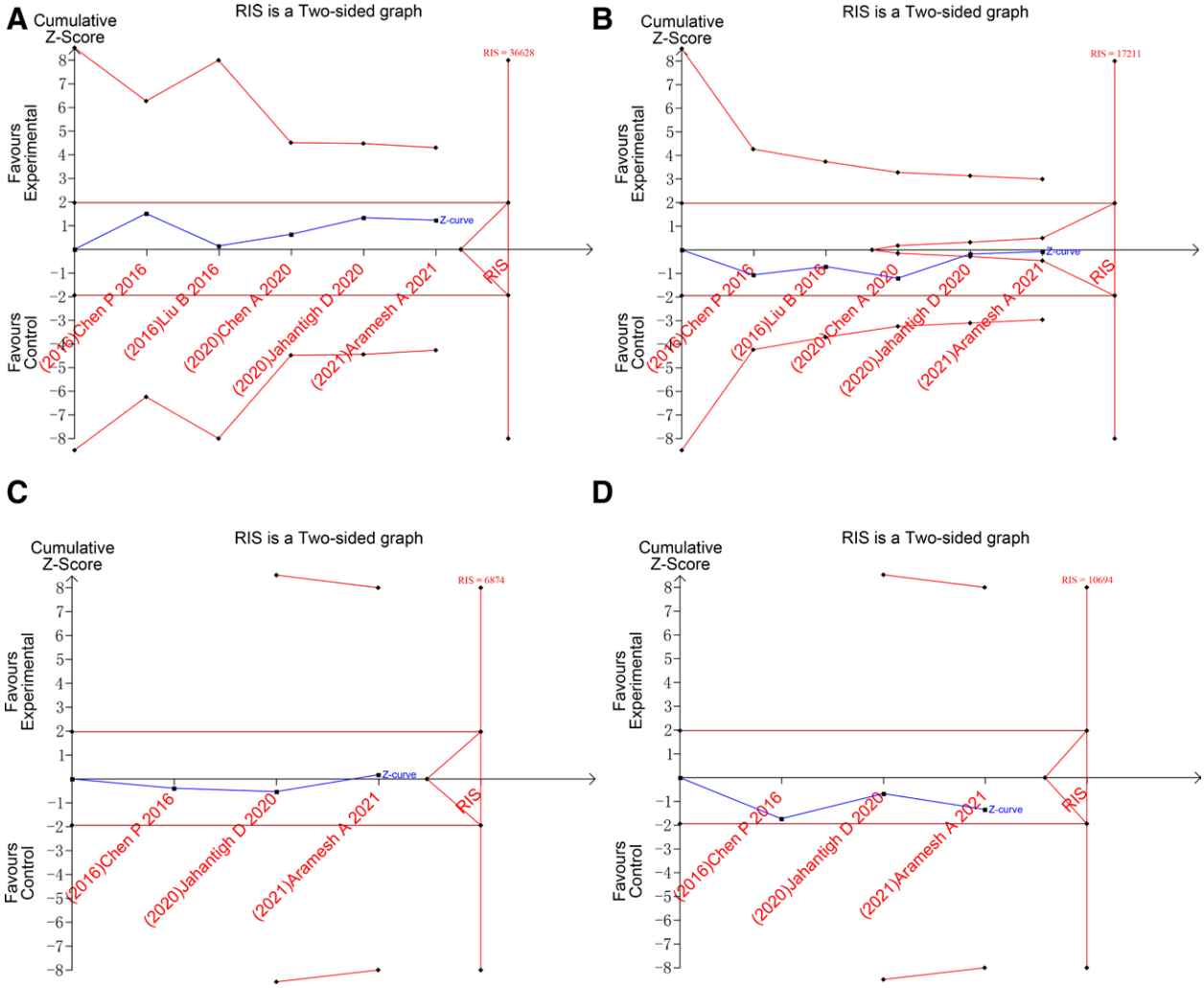

Figure 5. Trial sequential analysis results. (A) rs153109 and preeclampsia susceptibility; (B) rs17855750 and preeclampsia susceptibility; (C) rs153109 and preeclampsia severity; (D) rs17855750 and preeclampsia severity.

As the amount of included studies is limited, the limitations of this meta-analysis are obvious. The first one is the possibility of false negatives showed by trial sequential analysis. As a consequence, more multi-center and large sample case-control studies are expected to be carried out in order to provide reliable data support to meta-analysis which assesses the association of IL-27 gene rs153109 and rs17855750 polymorphisms with preeclampsia susceptibility and severity. Then, as the countries that the original studies carried out were limited to China and Iran, the subgroup analysis based on race cannot be performed. In this situation, heterogeneity can only be dealt with by applying random effects model. Besides, as the data of linkage between different polymorphism sites was not provided by original studies, it does not meet the requirement for meta-analysis based on haplotypes.

In conclusion, our meta-analysis indicates that there is no obvious association between IL-27 gene rs153109 and rs17855750 polymorphisms and preeclampsia susceptibility or severity. However, IL-27 might serve as serum indicators for determining the risk to preeclampsia. As the possibility of false negatives may still exist, more multi-center and large sample case-control studies are expected to be carried out to verify our conclusion in the future.

Author contributions

Conceptualization: Fengzhen Wang, Ersheng Wen, Ziyou Liu.
Data curation: Fengzhen Wang, Ersheng Wen, Yuyang Huang, Zhenyin Wen, Ziyou Liu.
Formal analysis: Fengzhen Wang, Ersheng Wen, Yuyang Huang, Zhenyin Wen, Ziyou Liu.
Funding acquisition: Fengzhen Wang, Ziyou Liu.
Investigation: Fengzhen Wang, Ersheng Wen, Yuyang Huang, Ziyou Liu.
Methodology: Fengzhen Wang, Ersheng Wen, Yuyang Huang, Ziyou Liu.
Project administration: Fengzhen Wang, Ersheng Wen, Yuyang Huang, Ziyou Liu.
Resources: Fengzhen Wang, Ersheng Wen, Yuyang Huang, Zhenyin Wen.
Software: Fengzhen Wang, Ersheng Wen, Yuyang Huang, Zhenyin Wen.
Supervision: Fengzhen Wang, Ersheng Wen, Yuyang Huang, Zhenyin Wen.
Validation: Fengzhen Wang, Ersheng Wen, Yuyang Huang, Zhenyin Wen, Ziyou Liu.
Visualization: Fengzhen Wang, Ersheng Wen, Zhenyin Wen, Ziyou Liu.
Writing – original draft: Fengzhen Wang, Ersheng Wen, Yuyang Huang, Zhenyin Wen, Ziyou Liu.
Writing – review & editing: Fengzhen Wang, Ziyou Liu.

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