Association between miR-499 rs3746444 polymorphism and the risk of ischemic stroke: A systematic review and meta-analysis

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Abstract. The aim of the present study was to explore the generic association between the miR-499 (rs3746444) polymorphism and the risk of ischemic stroke (IS). A systematic review and meta-analysis was performed, and odds ratios (ORs) and 95% confidence intervals (CIs) were used to quantitatively estimate the association. A total of 8 studies (involving 3,400 IS cases and 3,652 controls) were included in the present meta-analysis. The results of the allelic model (G allele vs. A allele) revealed a statistically significant association between the miR-499 (rs3746444) polymorphism and the risk of IS; the OR was 1.16 (95% CI, 1.00-1.34; P<0.05). Similarly, the results of the recessive model (GG vs. AG + AA), the heterozygote model (AG vs. AA) and the homozygote model (GG vs. AA) were statistically significant; the ORs were 1.36 (95% CI, 1.05-1.77; P<0.05), 1.11 (95% CI, 1.00-1.23; P<0.05) and 1.42 (95% CI, 1.09-1.86; P<0.05), respectively. However, the dominant model (GG + AG vs. AA) did not exhibit any significant differences; the OR was 1.16 (95% CI, 0.99-1.36; P>0.05). The results of the Q test indicated that the heterogeneity of the allelic model (I^2=63%, P=0.01), as well as that of the dominant model (I^2=60%, P=0.02), was relatively large. Subsequently, a sensitivity analysis was performed; the I^2 of each model then decreased to <50%. Notably, by sensitivity analysis, both the allelic model and the dominant model exhibited a statistically significant association between the miR-499 (rs3746444) polymorphism and the risk of IS. Egger's test did not reveal any publication bias for any of the models. On the whole, the present study demonstrates that the miR-499 (rs3746444) polymorphism may contribute to an increased risk of IS.

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Introduction

MicroRNAs (miRNAs or miRs) play important roles in gene regulation; more than half of human genes are known to be regulated by miRNAs. miRNAs are also involved in numerous pathological pathways/process, such as the inflammatory response (1,2) and cancer development (3,4), as well as in the formation/development of ischemic stroke (IS) (5-9).

Gene polymorphisms, including the Leu33Pro polymorphism (5), the apolipoprotein E gene polymorphism (among the Chinese population) (6,7), the Gly82Ser polymorphism (8) and the breast susceptibility gene 2 rs9534275 polymorphism (9), have been reported to be associated with an increased risk of IS. Several studies have assessed the association between the miR-499 (rs3746444) polymorphism and the risk of IS; however, the varying conclusions reached by the different studies are contradictory. Jeon *et al* (10) reported no difference in the allele frequencies of the miR-499 polymorphism between patients with IS and the controls; a previous meta-analysis (11) based on 3 studies reported a similar finding. On the contrary, Darabi *et al* (12) reported that the miR-499 A/G polymorphism was significantly associated with an increased risk of IS.

Thus, whether the miR-499 polymorphism increases the risk of IS remains controversial. The present study aimed to assess this association through a systematic review and meta-analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to quantitatively estimate the association in 5 models, including the allelic model (G allele vs. A allele), the dominant model (GG + AG vs. AA), the recessive model (GG vs. AG + AA), the heterozygote model (AG vs. AA) and the homozygote model (GG vs. AA).

Materials and methods

Inclusion and exclusion criteria. Studies were selected under the following considerations: i) Studies should use a case-control design; ii) the subjects should include both patients with IS and healthy controls; iii) there must be extractable data on allele frequencies and genotype frequencies; iv) the subjects/models studied should be human, instead of animals or cells.

Studies were excluded if any of the following conditions were met: i) Duplication studies; ii) case reports, letters, editorials, or reviews; iii) studies not written in the English language; iv) studies without extractable data on allele frequencies or genotype frequencies.

Databases and search strategy. A comprehensive literature search was performed using the PubMed, Embase, Science Direct and google scholar databases (from inception to June 15, 2020). The following terms were used to perform the literature search: rs3746444, miRNA-499, microRNA-499, miR-499; with a combination of stroke, ischemic, ischemia, ischemic stroke, cerebrovascular and cerebrovascular disease.

Data extraction. The data were extracted independently by 2 researchers using a predesigned data extraction form; the following information was extracted: i) Name of the first author; ii) year of publication; iii) country where the study was conducted; iv) the study design; v) sample size; vi) gene sequencing method; vii) P-values of Hardy-Weinberg equilibrium (HWE) of the control group. Most importantly, the frequencies of genotypes of the patients with IS and the controls were extracted.

Assessment of methodological quality. Two researchers used the Newcastle-Ottawa scale (13) to assess the quality of the included studies independently. For the Newcastle-Ottawa scale, a full score is 9; a score of 5-9 indicates a high methodological quality, whereas a score of 0-4 indicates poor quality. Any disagreement would be resolved by other authors following a comprehensive reassessment. Low-quality studies were excluded from the current meta-analysis.

Data synthesis and statistical analysis. Prior to the meta-analysis, the heterogeneity across studies was assessed by the Q test and the I^2 statistic. I^2 describes the percentage of variability caused by heterogeneity rather than by chance. An I^2 <50% indicates a small heterogeneity; consequently a fixed-effects model would be used to perform the meta-analysis, otherwise a random-effects model would be used, and a sensitivity analysis (13) would be performed in the case of a large heterogeneity. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to estimate the association between the miR-499 (rs3746444) polymorphism and the risk of IS. Egger's test (14) was used to determine whether there was a publication bias. The significance level was set as 0.05, two-tailed. All the analyses were performed using the open source R program (version 4.0.1).

Results

Study selection. A total of 187 studies were identified through initial database searching. A total of 65 duplicates were removed, and 122 records were reviewed for title and Abstract. In total, 103 irrelevant records and studies not written in the English language were further excluded. A total of 19 articles were full-text reviewed, and 11 records were further excluded due to ineligible study design or the lack of extractable data. The details of the study selection process are presented in Fig. 1.
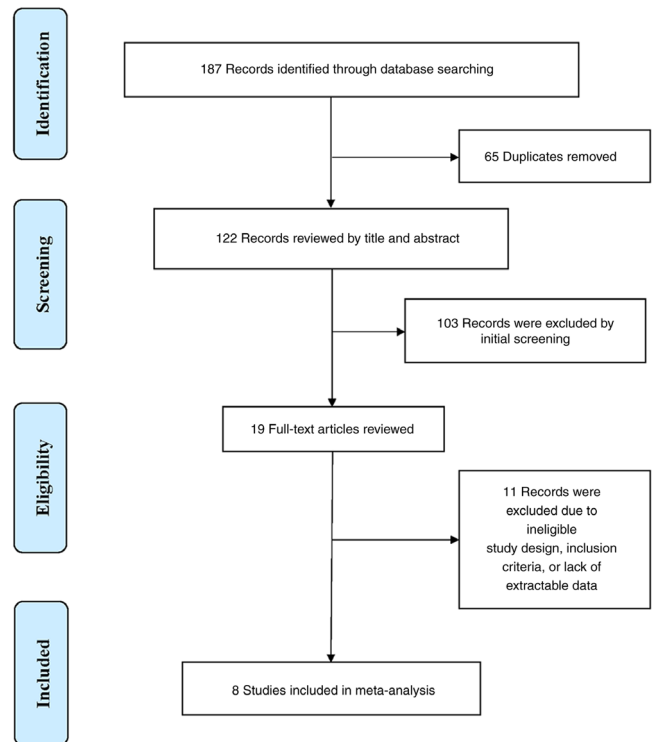

Figure 1. Flow chart of the study selection.

Characteristics of included studies. A total of 8 studies (10,12,15-20), involving 3,400 patients with IS and 3,652 controls, met the inclusion and exclusion criteria. The characteristics of the included studies are presented in Table I. A total of 5 studies were carried out in China, 2 in Korea and one in Iran. All studies were hospital-based studies, and used a case-control study design. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was the most popular method for genotype sequencing. The age and sex of the patients in the selected studies were matched between the patients with IS and the controls in each study. Only in 1 study, the P-value of HWE was <0.05.

Study quality assessment. The mean Newcastle-Ottawa score of the included studies was 7 (Table II); thus, the overall quality of the included studies was high.

Results of the allelic model. The results of the allelic model revealed a statistically significant association between the miR-499 (rs3746444) polymorphism and an increased risk of IS (Fig. 2); the OR was 1.16 (95% CI, 1.00-1.34). However, the I^2 was 63%, and there was a large heterogeneity across the included studies. A sensitivity analysis was further performed. It was found that after omitting the study of Zhu *et al*, 2020 (20), the I^2 decreased to 51.3% (data not shown). Moreover, the conclusion remained unaltered; the association between the miR-499 (rs3746444) polymorphism and the increased risk of IS was still significant; the OR was 1.19 (95% CI, 1.08-1.31; P<0.05) (data not shown).

Results of the dominant model. The results of the dominant model revealed a non-significant association between the miR-499 (rs3746444) polymorphism and the risk of IS (Fig. 3);

Table I. Characteristics of the included studies.

Author	Year	Country	Study design	Sample size Cases	Sample size Controls	Genotyping methods	P-value (HWE)	(Refs.)
Jeon *et al*	2013	Korea	Hospital-based	678	553	PCR-RFLP	0.740	(10)
Liu *et al*	2014	China	Hospital-based	296	391	PCR-RFLP	0.394	(16)
Huang *et al*	2015	China	Hospital-based	531	531	TaqMan	0.002	(15)
Luo *et al*	2017	China	Hospital-based	298	303	RT-PCR	0.447	(17)
Darabi *et al*	2019	Iran	Hospital-based	470	489	PCR-RFLP	0.061	(12)
Zhu *et al*	2018	China	Hospital-based	296	378	PCR-RFLP	0.512	(18)
Hong *et al*	2019	Korea	Hospital-based	264	455	PCR	0.999	(19)
Zhu *et al*	2020	China	Hospital-based	567	552	PCR-LDR	0.630	(20)

PCR, polymerase chain reaction; PCR-RFLP, PCR-restriction fragment length polymorphism; polymerase chain reaction-ligation detection reaction.
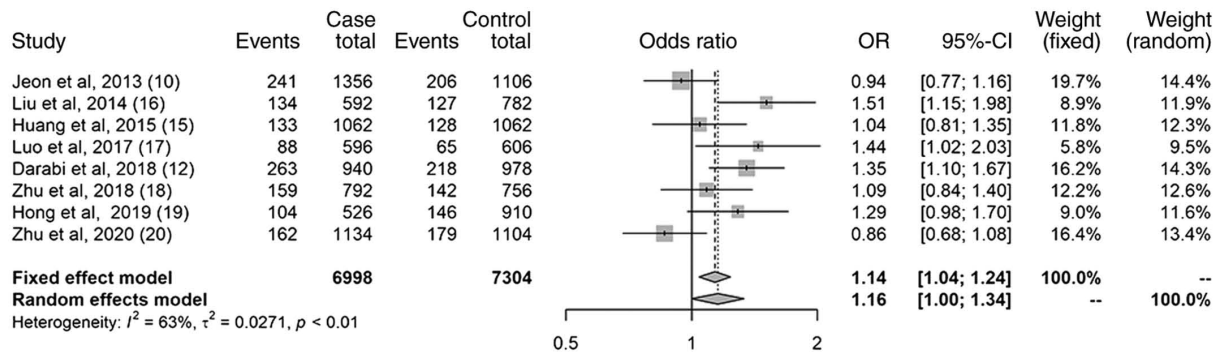

Figure 2. Forest plot of the allelic model.
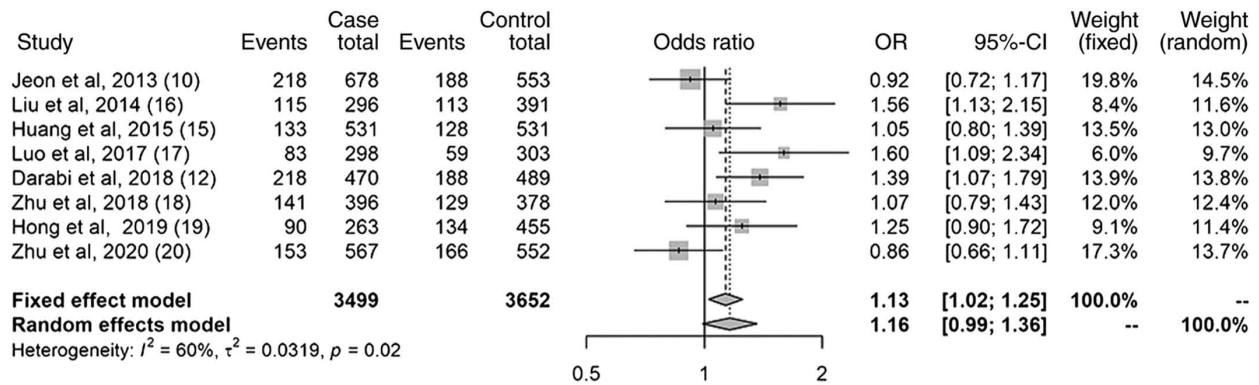
Figure 3. Forest plot of the dominant model.

the OR was 1.16 (95% CI, 0.99-1.36). The I^2 was 60%; a sensitivity analysis was subsequently performed. After omitting the study of Zhu *et al*, 2020 (20), the I^2 dropped to 50.9% (data not shown). Notably, the conclusion changed, and there was a statistically significant association between the miR-499 (rs3746444) polymorphism and the risk of IS; the OR was 1.19 (95% CI, 1.07-1.33) (data not shown).

Results of the recessive model. The results of the recessive model (Fig. 4) revealed a statistically significant association between the miR-499 (rs3746444) polymorphism and the increased risk of IS; the OR was 1.36 (95% CI, 1.05-1.77). The heterogeneity was small (I^2=4%).

Results of the heterozygote model. The results of the heterozygote model (Fig. 5) also revealed a statistically significant association between the miR-499 (rs3746444) polymorphism and the increased risk of IS; the OR was 1.11 (95% CI, 1.00-1.23). The I^2 was 50%; the heterogeneity was not large.

Results of the homozygote model. The results of the homozygote model (Fig. 6) revealed a statistically significant

Table II. Methodological quality of the studies by the Newcastle-Ottawa scale.

Score	Items	Jeon et al, 2013 (10)	Liu et al, 2014 (16)	Huang et al, 2015 (15)	Luo et al, 2017 (17)	Darabi et al, 2019 (12)	Zhu et al, 2018 (18)	Hong et al, 2019 (19)	Zhu et al, 2020 (20)
Selection.	Adequate definition of patient cases	1	1	1	1	1	1	1	1
	Representativeness of patient cases	1	1	1	1	1	1	1	1
	Selection of controls	0	0	0	0	0	0	0	0
	Definition of controls	1	1	1	1	1	1	1	1
Comparability	Control for important/additional factor	2	2	2	2	2	2	2	2
Exposure.	Ascertainment of exposure (blinding)	0	0	0	0	0	0	0	0
	Same ascertainment method for participants	1	1	1	1	1	1	1	1
	Non-response rate[a]	1	1	1	1	1	1	1	1
Total score[b]		7	7	7	7	7	7	7	7

Included studies, author, year (Refs.)

[a]When there was no significant difference in the response rate between both groups based on a Chi-squared test, 1 point was awarded. [b]Total score. was calculated by adding up the points awarded in each item.

Table III. Egger's test results.

Model	t value	P-value
Allele	0.818	0.440
Dominant	2.223	0.067
Recessive	-0.969	0.377
Heterozygous	2.124	0.053
Homozygous	-0.898	0.410

association between the miR-499 (rs3746444) polymorphism and the increased risk of IS; the OR was 1.42 (95% CI, 1.09-1.86). The heterogeneity was small (I^2=23%).

Publication bias. There was no publication bias for all the 5 models according to results of Eggers' test (Table III).

Discussion

The present meta-analysis aimed to determine whether the miR-499 (rs3746444) polymorphism had an influence on the risk of IS based on case-control studies. The main finding was that the miR-499 (rs3746444) polymorphism was associated with an increased risk of IS; the association was statistically significant in the allelic model, the recessive model, the heterozygote model and the homozygote model. Furthermore, by sensitivity analysis, the dominant model was found to be significant.

In a previous review article, Zou *et al* (21) concluded that the miR-499 (rs3746444) polymorphism may not be associated with a risk of IS in Asian populations. However, in the present study, neither the allelic model, dominant model, recessive model, homozygote model, or the heterozygote model were found to be significant in the study by Zou *et al*. However, as 3 Chinese articles were included in the review article by Zou *et al* (21), it is difficult for researchers who do not speak Chinese to repeat the results.

The present study attempted to explain why findings by the previous review article were contrary to those of the present study. Considering that the previous review article focused on a Chinese population, the present study performed a subgroup analysis in the meta-analysis, and studies were divided by ethnicity into subgroup 1 (studies based on Chinese population) and subgroup 2 (studies based on non-Chinese population). Subgroup analysis revealed that the homozygote model and the recessive model of subgroup 1 was indeed non-significant; however, the allelic model, the dominant model, and the heterozygote model still exhibited a significant association between the miR-499 (rs3746444) polymorphisms and the increased risk of IS. Notably, there was a tendency that the ORs of subgroup 2 were larger than those of subgroup 1. The results of subgroup analysis indicated that the association between the miR-499 (rs3746444) polymorphism and the risk of IS may vary for different ethnicities (data not shown). The relatively small sample size of the study by Zou *et al* (21) (there were only 4 studies if the 3 articles written in Chinese were not counted) may be another reason why non-significant results were found, and that is why an updated meta-analysis is of utmost importance.
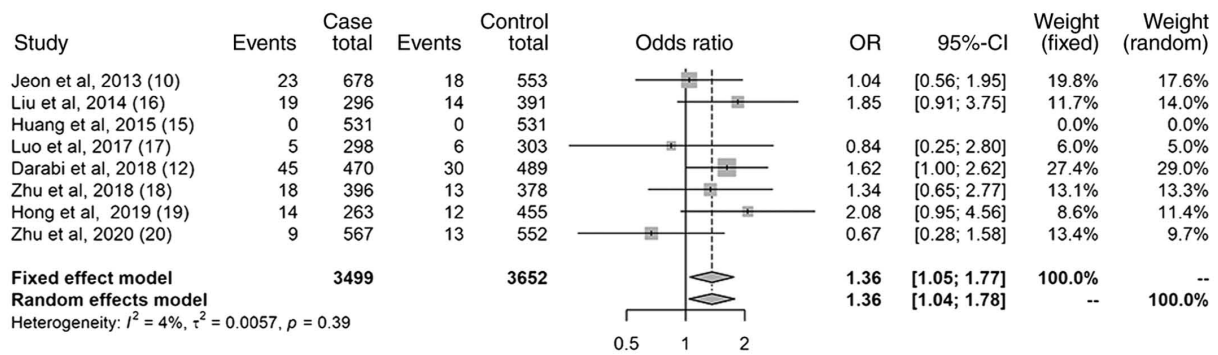
Study	Events	Case total	Events	Control total	Odds ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Jeon et al, 2013 (10)	23	678	18	553		1.04	[0.56; 1.95]	19.8%	17.6%
Liu et al, 2014 (16)	19	296	14	391		1.85	[0.91; 3.75]	11.7%	14.0%
Huang et al, 2015 (15)	0	531	0	531				0.0%	0.0%
Luo et al, 2017 (17)	5	298	6	303		0.84	[0.25; 2.80]	6.0%	5.0%
Darabi et al, 2018 (12)	45	470	30	489		1.62	[1.00; 2.62]	27.4%	29.0%
Zhu et al, 2018 (18)	18	396	13	378		1.34	[0.65; 2.77]	13.1%	13.3%
Hong et al, 2019 (19)	14	263	12	455		2.08	[0.95; 4.56]	8.6%	11.4%
Zhu et al, 2020 (20)	9	567	13	552		0.67	[0.28; 1.58]	13.4%	9.7%
Fixed effect model		3499		3652		1.36	[1.05; 1.77]	100.0%	--
Random effects model						1.36	[1.04; 1.78]	--	100.0%

Heterogeneity: $I^2 = 4\%$, $\tau^2 = 0.0057$, $p = 0.39$

Figure 4. Forest plot of the recessive model.

Study	Events	Case total	Events	Control total	Odds ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Jeon et al, 2013 (10)	195	655	170	535		0.91	[0.71; 1.17]	19.7%	15.0%
Liu et al, 2014 (16)	96	277	99	377		1.49	[1.06; 2.09]	8.2%	11.1%
Huang et al, 2015 (15)	133	531	128	531		1.05	[0.80; 1.39]	14.4%	13.5%
Luo et al, 2017 (17)	78	293	53	297		1.67	[1.13; 2.48]	5.8%	9.3%
Darabi et al, 2018 (12)	173	425	158	459		1.31	[1.00; 1.72]	13.5%	13.8%
Zhu et al, 2018 (18)	123	378	116	365		1.04	[0.76; 1.41]	11.9%	12.3%
Hong et al, 2019 (19)	76	249	122	443		1.16	[0.82; 1.63]	9.1%	11.0%
Zhu et al, 2020 (20)	144	558	153	539		0.88	[0.67; 1.15]	17.3%	14.1%
Fixed effect model		3366		3546		1.11	[1.00; 1.23]	100.0%	--
Random effects model						1.13	[0.97; 1.32]	--	100.0%

Heterogeneity: $I^2 = 50\%$, $\tau^2 = 0.0241$, $p = 0.05$

Figure 5. Forest plot of the heterozygote model.

Study	Events	Case total	Events	Control total	Odds ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Jeon et al, 2013 (10)	23	483	18	383		1.01	[0.54; 1.91]	20.7%	17.5%
Liu et al, 2014 (16)	19	200	14	292		2.08	[1.02; 4.26]	11.1%	14.6%
Huang et al, 2015 (15)	0	398	0	403				0.0%	0.0%
Luo et al, 2017 (17)	5	220	6	250		0.95	[0.28; 3.14]	5.9%	6.1%
Darabi et al, 2018 (12)	45	297	30	331		1.79	[1.10; 2.93]	26.0%	24.5%
Zhu et al, 2018 (18)	18	273	13	262		1.35	[0.65; 2.82]	13.4%	14.0%
Hong et al, 2019 (19)	14	187	12	333		2.16	[0.98; 4.78]	8.6%	12.4%
Zhu et al, 2020 (20)	9	423	13	399		0.65	[0.27; 1.53]	14.2%	10.9%
Fixed effect model		2481		2653		1.42	[1.09; 1.86]	100.0%	--
Random effects model						1.40	[1.03; 1.92]	--	100.0%

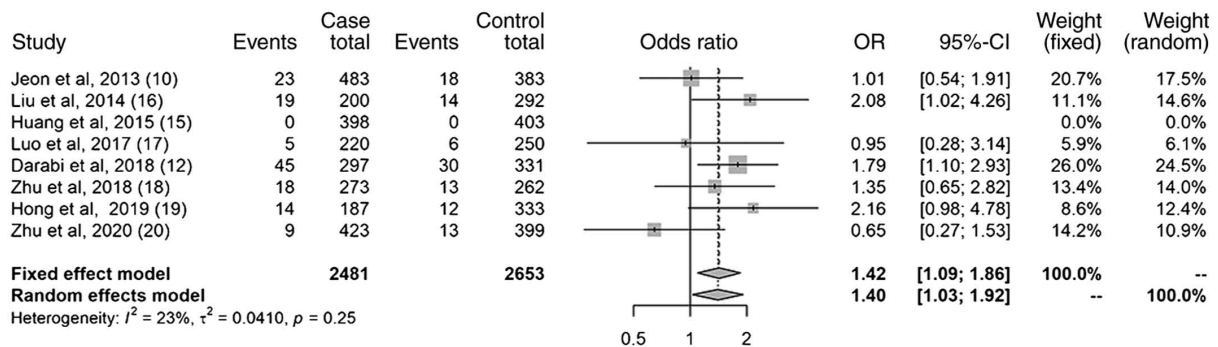Heterogeneity: $I^2 = 23\%$, $\tau^2 = 0.0410$, $p = 0.25$

Figure 6. Forest plot of the homozygote model.

The association between the miR-499 polymorphism and the increased risk of IS was understandable: It has been reported that hsa-miR-499 plays a role in cell apoptosis under ischemic conditions (22); the mechanisms involved may be that miR-499 inhibits cell apoptosis by suppressing the dephosphorylation of dynamin-related protein-1 (Drp1) that is mediated by calcineurin. miR-499 affects the regulation of C-reactive protein (CRP) (23), and C-reactive protein has been reported to be a cause of cerebral ischemia (24). Similarly, TNF-α (25), another general cause of cerebral ischemia, has been reported to be regulated by miR-499; both CRP and TNF-α are activated under conditions of stress (26). Furthermore, it has been reported that the thrombosis and inflammation pathways of the.

In conclusion, miR-circulation system can be influenced by the miR-499 (rs3746444) polymorphism; an A:U pair to a G:U mismatch of hsa-miR-499 precursor caused by miR-499

(rs3746444) (27,28) polymorphism can alter the function/expression of mature hsa-miR-499, and the regulation of its' target mRNAs. The miR-499 polymorphism is associated with a risk of IS, and the G allele increases the risk of IS.

There are two limitations to the current meta-analysis. On the one hand, all the included studies used a case-control design; there may thus be a selection bias, which could enhance or weaken the true association between miR-499 polymorphism and the risk of IS. On the other hand, subgroup analysis based on 8 studies was not sufficient; thus, whether the association between the miR-499 polymorphism and risk of IS is dependent on ethnicity remains a matter of debate.

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Availability of data and materials

The datasets used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Authors' contributions

KC designed the study. XHL and MLL performed the literature search and manuscript writing. RL extracted the data for the analysis. YPX performed the quality control of the extracted data. MZ and QRL performed the data analysis. WZ and TLZ interpreted the data and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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