# Effect of circulating miR-126 levels on intracranial aneurysms and their predictive value for the rupture of aneurysms: A systematic review and meta-analysis

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Received March 17, 2023; Accepted June 30, 2023

DOI: 10.3892/etm.2023.12110

**Abstract.** Intracranial aneurysm (IA) is a common cerebrovascular disease with a high risk of rupture. At present, the mechanisms underlying the formation and rupture of IAs is not clinically clear. MicroRNAs (miRNAs/miRs) are involved in the development of IAs. The present study aimed to determine the efficacy of circulating miRNA-126 (miR-126) levels as potential biomarkers for predicting aneurysmal ruptures. The present study searched comparative articles involving circulating miR-126 levels and intracranial aneurysms through electronic databases from 1980 to February, 2023. Collected variables included the first author's name, covered study period, publication year, total number of patients and age, and number of males. We collected information about the expression levels of circulating miR-126 in serum. Three articles met the eligibility criteria. The total number of patients was 379 [226 with IA rupture and 153 with non-rupture or/+ controls (healthy)]. The circulating miR-126 can be used as a biomarker for predicting aneurysmal rupture. Interestingly, an aneurysmal size >10 mm was associated with an IA rupture.

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*Key words:* aneurysm, microRNA-126, aneurysmal rupture, biomarker, hemorrhage

## Introduction

Intracranial aneurysm (IA) is a common cerebrovascular disease, and its rupture may lead to massive intracranial and subarachnoid hemorrhage (1). Therefore, patients who are at a high risk of aneurysm rupture need to be diagnosed at an early stage in order for this to be prevented or actively treated and to reduce severe complications.

However, even with different diagnostic procedures available for identifying and predicting the aneurysmal rupture (2,3), the majority of these patients have no evident clinical symptoms before the rupture occurs, and 16-65% consequently develop ischemia (2,4-6).

At present, the mechanisms responsible for the formation and rupture of IA are not yet clinically clear. Research has indicated that microRNAs (miRNAs/miRs) play a key role in processing the majority of proteins, can be identified in biological fluids, and may be potential early biomarkers for various cerebrovascular diseases (7,8).

It has been demonstrated that miRNAs are involved in the development of IAs (9). Although reports exist of protein biomarkers in IAs, including tumor necrosis factor receptor (TNFR)-1 and S100B (10,11), studies on circulating miRNAs as biomarkers for ruptured IAs are limited.

The present meta-analysis aimed to identify the circulating miRNA-126 (miR-126) in ruptured IAs and evaluate their potential function as biomarkers for predicting aneurysmal rupture.

## Data and methods

*Literature research strategy*. The present study searched the comparative articles involving circulating miR-126 levels and IAs through electronic databases, including the Cochrane

Library, MEDLINE (1980 to February, 2023), PubMed (1980 to February, 2023) and Embase (1980 to February, 2023). The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were applied for establishing the study protocol and design. The keywords 'aneurysm and genes', 'microRNA' or 'miRNA' or 'miR-126', and 'intracranial aneurysm and miR-126' were used in the MeSH list.

*Selection of studies*. Two of the authors (GF and VEG) independently extracted data from the included articles, following the guidelines for the epidemiology of meta-analysis. The following essential information was obtained: The main authors, year of publication, total case number in the IA rupture and non-rupture or/+ controls (healthy individuals) groups, study type, outcome indicator, etc. The extracted data were input into a designed, standardized table according to the Cochrane Handbook. The flow of the study selection process is depicted in Fig. 1. When there is disagreement, another author with authority has the final say.

*Inclusion and exclusion criteria*. If an article satisfied the following population, intervention, comparison, outcomes and study (PICOS) design criteria, it was considered for inclusion in the present meta-analysis: i) Population: Limited to patients with IA rupture and non-rupture or/+ controls (healthy individuals); ii) intervention: The use of the expression levels of circulating miR-126 at the IA rupture and non-rupture or/+ controls (healthy individuals); iii) comparison: The expression levels of circulating miR-126 were compared between patients with IA rupture and non-rupture or/+ controls (healthy individuals); iv) The detailed data of these articles are presented in Table I. To avoid publication bias, the final aim was to collect a homogeneous pool of manuscripts, including articles that compare only two modalities: The expression levels of circulating miR-126 between patients with IA rupture and non-rupture or/+ controls (healthy individuals).

All prospective and retrospective studies that evaluated at least one of the two modalities were included. Editorials, reviews, case reports and articles focusing on the pediatric population, unrelated outcomes, co-morbidities, experimental techniques, or one of the two modalities from that article pool were excluded. In addition, in the case of mixed or unclear results, the data were included in either the IA rupture, the non-rupture, or/+ controls (healthy individuals) group. In addition, to determine the association with levels of circulating miR-126 between patients with IA rupture and non-rupture or/+ controls (healthy individuals), information about the patient's age was collected. A body mass index (BMI) >22 kg/m$^2$, smoking, aneurysm location (anterior or posterior circulation); aneurysm size (<5, 5-10 and >10 mm); and the expression levels of circulating miR-126 >5 were detected in different time periods from 3 to 14 days. The expression levels of circulating miR-126 reported by the included articles were assessed after the IA rupture or in non-rupture or/+ controls (healthy individuals). Additionally, to decrease the risk of bias in the included articles, a quality assessment tool [the Newcastle-Ottawa Scale (NOS)] was used (Table II) (12).

*Procedure for determining circulating miR-126 levels. As previously described (*14-16), plasma was selected at a range of time points (1, 3, 7 and 14 days post-event) from each patient with IA rupture and from each patient with non-rupture or/+ controls (healthy individuals) (fasting state). All plasma samples were extracted from ethylene-diamine-tetra-acetic acid (EDTA) tubes and centrifuged as previously described (14-16). The serum miR-126 levels were examined using reverse transcription-quantitative PCR (RT-qPCR). Fasting venous blood (5 ml) was drawn from subjects [in the research group (RG)] on the first day after admission and 1 week after surgery, and in [the control group (CG)] during the morning physical examination], and then centrifuged for 10 min at 1,500 x g and 4˚C. The supernatant was obtained in the refrigerator at -80˚C for preservation. Total RNA in serum (200 $\mu$l) was extracted using TRIzol reagent, and the concentration and purity of the RNA solution were examined using a Narodrop spectrophotometer. The OD260/OD280 was between 1.8 and 2.1. The total RNA was applied as a template, and cDNA was synthesized by reverse transcription. The total reaction system of RT-qPCR was 20 $\mu$l, including template cDNA (1 $\mu$l), Taq polymerase (0.2 $\mu$l), forward primer and reverse primer (each 1 $\mu$l), 2X SYBR-Green mix (1 $\mu$l), 20 mmol/l dNTPs (1 $\mu$l). Finally, the RNase-free water was supplemented to 20 $\mu$l. The reaction conditions were 95˚C for 2 min, 95˚C for 15 sec, 60˚C for 30 sec, and 70˚C for 10 sec, for a total of 40 cycles. The forward primer of miR-126 was 5'-ACACTCCAGCTGGGTCGTACCGTGAGTAAT-3', and the reverse primer was 5'-CTCAACTGGTGTCGTGGA GTCGGCAATTCAGTTGAGCGCATTAT-3'. The forward primer of internal reference gene U6 was 5'-CTCGCTTCG GCAGCACA-3', and the reverse primer was 3'-AACGCT TCACGAATTTGCGT-5'. The results were represented by the relative quantitative method and calculated using the $2^{-\Delta\Delta Ct}$ method. The RT-qPCR protocol does not correspond to any analysis performed during the present study (14-16). The RT-qPCR protocol described herein is related to the included articles which constitute the article pool of the present meta-analysis. Thus, this protocol is described herein in order to present the procedure for determining circulating miR-126 levels used in the included articles.

*Evaluation of the risk of bias*. The Cochrane Collaboration tool was used to assess the risk of bias and was used by two authors (GF and VEG) for each study (13). The evaluation included random sequence generation, allocation concealment, the blinding of participants and assessors, the blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. The assessment results were classified into three levels: Low risk, high risk and unclear risk. A third author was designated to arbitrate any disagreements.

*Statistical analysis and assessment of heterogeneity*. All analyses were carried out using Review Manager Software (RevMan), version 5.4. Heterogeneity across trials was identified using $I^2$ statistics; considering $I^2$ >50% as high heterogeneity, a meta-analysis was conducted using a random-effect model according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0). Otherwise, the fixed-effect model was performed. The

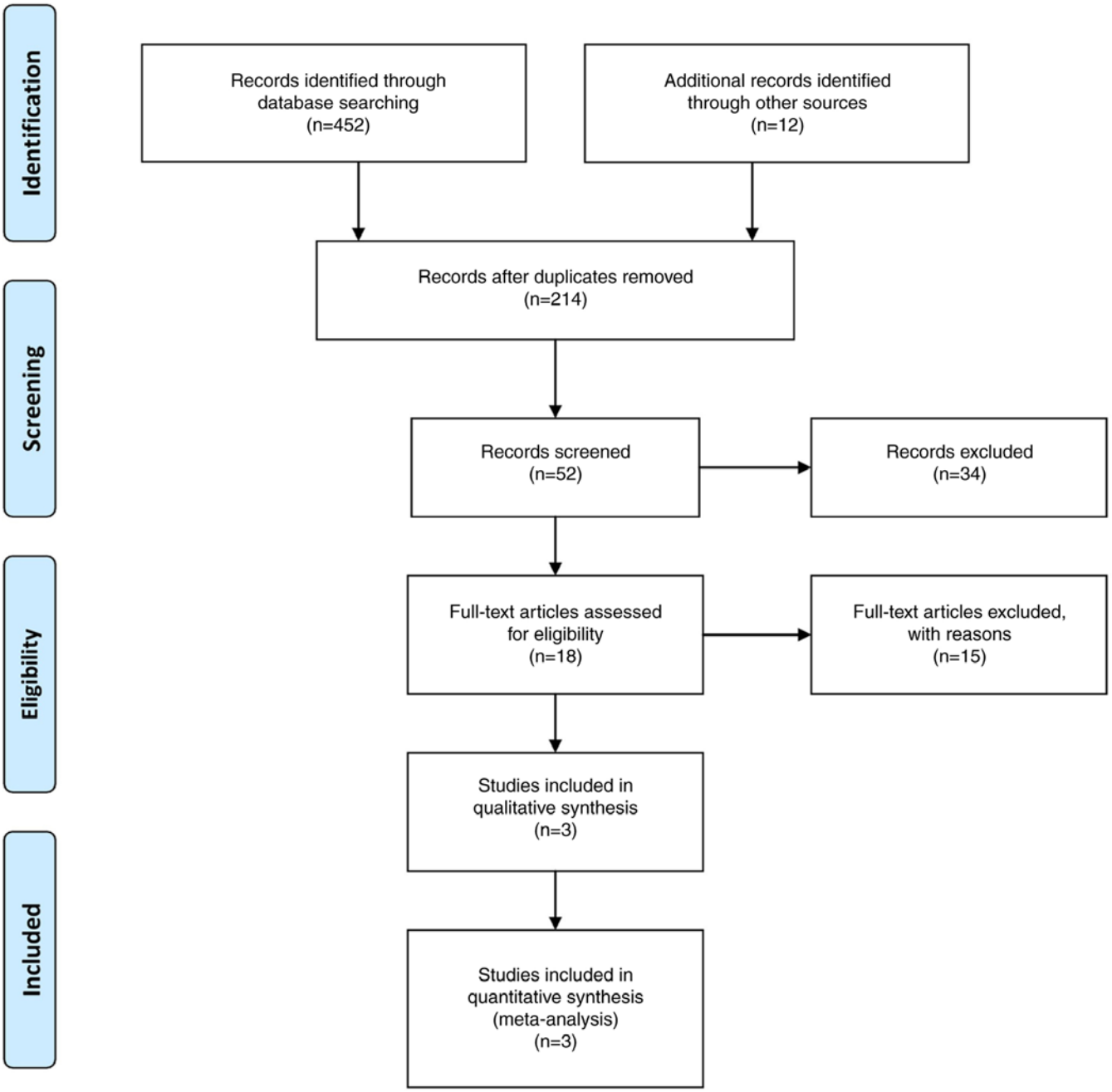


Figure 1. Flow chart of the study selection process.

continuous outcomes were expressed as a weighted mean difference with 95% confidence intervals (CIs). For discontinuous variables, odds ratios (OR) with 95% CIs were applied for the assessment. A P-value <0.05 was considered to indicate a statistically significant difference.

## Results

*Included studies*. In total, three articles (14-16) fulfilled the eligibility requirements. The total number of patients was 379 [226 with IA rupture and 153 with non-rupture or/+ controls (healthy individuals)]. The study sample was based on three studies (Table I). Of these three studies, two were retrospective and one was prospective.

*Epidemiological and clinical features*. The mean age of the patients was 52.1 (52.7 years for the IA rupture sample and 51.5 years for the non-rupture or/+ controls (healthy individuals sample). The male-to-female ratio was 1:1.9 (Table I).

*Age*. Information regarding age was available in three articles (14-16). No significant difference in age was observed between the patients with IA rupture and the non-rupture or/+ controls (healthy individuals) (OR, 1.14; 95% CI, -0.60 to 2.88; and P=0.20), but with heterogeneity (P=0.03 and $I^2$=70%) (Fig. 2A). For testing the sensitivity, the 'leave out one' model was used and one study was removed at a time (Table III). No heterogeneity (P=0.49 and $I^2$=0%) was achieved only after removing the article by Wu *et al* (14); again, no statistically

Table I. Design and baseline characteristics of the trials included in the present meta-analysis.

| Author, year | Sample size | | Mean age (mean ± SD) | | No. of males | | BMI ($kg/m^2$) >22 | | Smoking | | Location: Anterior circulation | Location: Posterior circulation | Size: <5 mm | | Size: 5-10 mm | | Size: >10 mm | | miR-126 expression >5 | | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Exp | Cont | Exp | Cont | Exp | Cont | Exp | Cont | Exp | Cont | Exp | Cont | Exp | Cont | Exp | Cont | Exp | Cont | Exp | Cont | |
| Yang *et al*, 2020 | 79 | 23 | 53.6±4.9 | 52.8±4 | 30 | 11 | 39 | 5 | 43 | 7 | 58 | 12 | 39 | 17 | 23 | 4 | 17 | 2 | 80 | 23 | (16) |
| Wu *et al*, 2021 | 62 | 47 | 54.3±5.1 | 51.4±4.7 | 23 | 22 | NR | NR | 25 | 19 | 26 | 0 | 32 | 0 | 26 | 0 | 4 | 0 | 19 | 8 | (14) |
| Luo *et al*, 2022 | 85 | 83 | 50.3±3.9 | 50.3±3.9 | 45 | 42 | 42 | 40 | NR | NR | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 | 33 | 22 | (15) |

Exp, experimental group; Cont, control group; miR, microRNA; NR, not reported; BMI, body mass index; SD, standard deviation.

significant difference was found (OR, 0.21; 95% CI, -0.80 to 1.22; P=0.68) (Fig. 2B). When examining the funnel plot of the same parameter, it was found that the study results without the study by Wu *et al* (14) displayed better dispersion, with a low publication bias (Fig. 2C and D).

*BMI >22(kg/m$^2$).* As regards information on BMI, it was available in two articles (15,16). No significant difference was found between the groups (OR, 1.76; 95% CI, 0.55 to 5.67; P=0.34), but with heterogeneity (P=0.06 and I2=72%) (Table III and Fig. S1).

*Smoking.* Information regarding smoking was available in two articles (14,16). No significant difference was found between the IA rupture and non-rupture or/+ control (healthy) groups (OR, 1.57; 95% CI, 0.59 to 4.19; P=0.37), but with heterogeneity (P=0.12 and I2=60%) (Table III and Fig. S2).

*Location*

*Anterior circulation.* As regards anterior circulation, information was available in two articles (14,16). No significant difference was found between groups (OR, 9.99; 95% CI, 0.41-243.1; P=0.16) and with no heterogeneity (P<0.05 and I2=79%) (Table III and Fig. S3).

*Posterior circulation.* Information regarding posterior circulation was available in two articles (14,16). Again, no significant difference was found between the IA rupture and non-rupture or/+ control (healthy) groups (OR, 3.09; 95% CI, 0.04 to 256.6; P=0.57), but with heterogeneity (P<0.05 and I2=93%) (Table III and Fig. S4).

*Aneurysm size*

*<5 mm.* As regards an aneurysm size <5 mm, information was available in two articles (14,16). No significant difference was found between groups (OR, 5.03; 95% CI, 0.02 to 1310.1; P=0.57) with no heterogeneity (P<0.05 and I2=93%) (Table III and Fig. S5).

*5-10 mm.* Information regarding an aneurysm size 5-10 mm was available in two articles (14,16). No significant difference was found between the IA rupture and non-rupture or/+ control (healthy) groups (OR, 9.11; 95% CI, 0.29 to 290.4; P=0.21), but with heterogeneity (P<0.05 and I2=81%) (Table III and Fig. S6).

*>10 mm.* As regards an aneurysm size >10 mm, information was available in two articles (14,16) and this demonstrated a statistically significant result (OR, 3.52; 95% CI, 0.90 to 13.8; P<0.05), with no heterogeneity (P=0.58; I2=0%) (Table III and Fig. 3). An aneurysm size >10 mm was found in 21 of 141 (14.8%) patients diagnosed with an IA ruptured aneurysm and in 2 of 70 (2.8%) non-rupture or/+ control (healthy) patients. When examining the funnel plot of the same parameter, no publication bias was found.

*miR-126 expression >5.* Information regarding miR-126 expression was available in three articles (14-16) and this demonstrated a statistical result (OR, 1.88; 95% CI, 1.10-3.21; P<0.05) with no heterogeneity (P=0.73 and I2=0%) (Table III and Fig. 4). A miR-126 expression >5 was found in 132 of 226 (58.4%) patients diagnosed with IA ruptured aneurysms and in 53 of 153 (34.6%) non-rupture or/+ controls (healthy) patients.

Table II. Newcastle-Ottawa Scale (NOS) quality assessment of final article pool.

| | | Newcastle-Ottawa Scale | | | | |
|---|---|---|---|---|---|---|
| Author, year | Study design | Selection | Comparability | Exposure | Total scores | (Refs.) |
| Yang *et al*, 2020 | Prosp | 3 | 3 | 3 | 9 | (16) |
| Wu *et al*, 2021 | Prosp | 3 | 3 | 3 | 9 | (14) |
| Luo *et al*, 2022 | Retro | 3 | 2 | 2 | 7 | (15) |

Retro, retrospective; prosp, prospective.

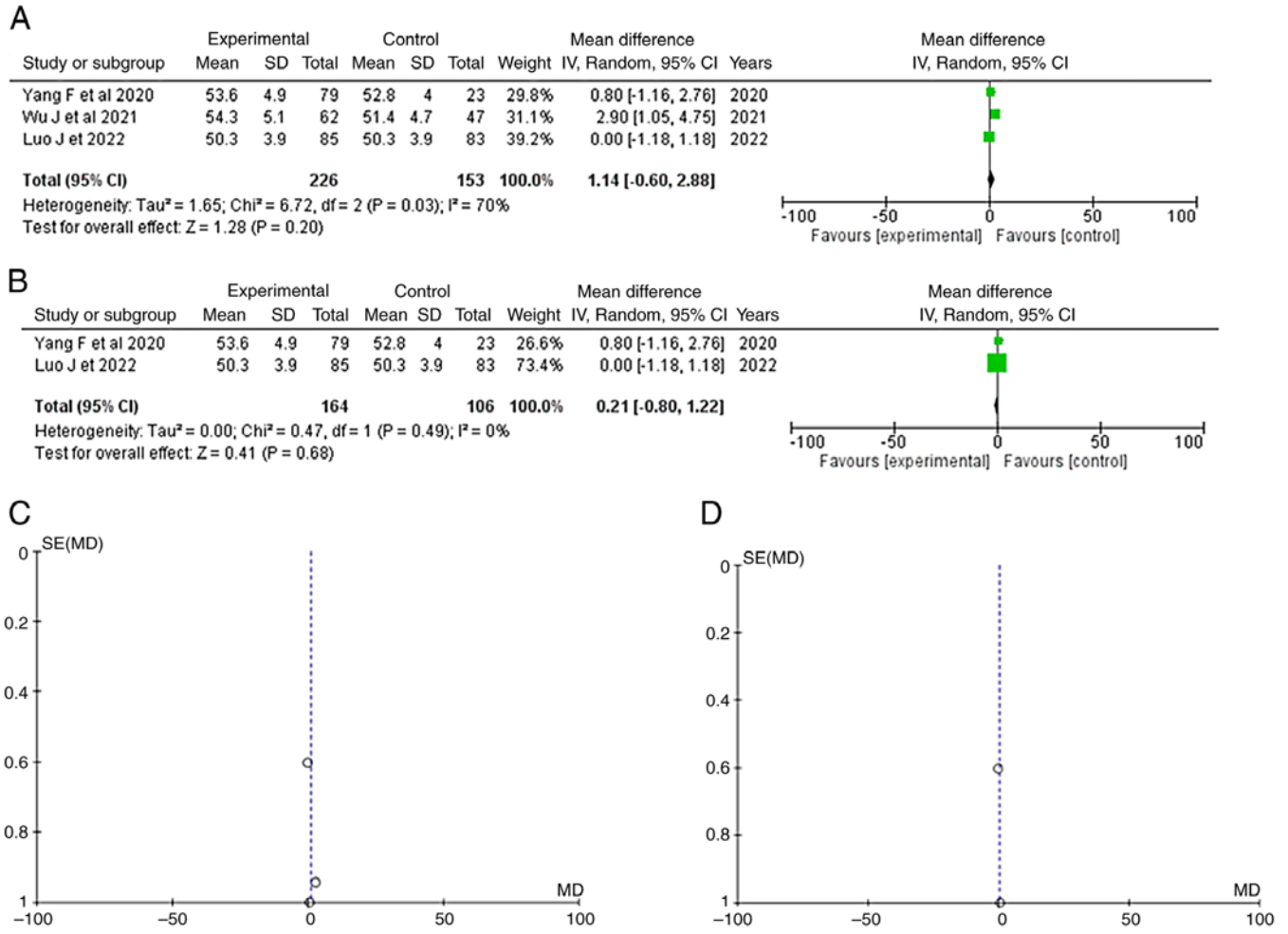


Figure 2. (A) Forest plot for age: The results demonstrate no statistically significant difference groups (OR, 1.14; 95% CI, -0.60 to 2.88; P=0.20). (B) Forest plot for age without the study by Wu *et al* (14). The results again demonstrate no statistically significant difference (OR, 0.21; 95% CI, -0.80 to 1.22; P=0.68). (C and D) Funnel plots of the age between groups, with (left) or without (right) Wu *et al* (14), and with (left) heterogeneity (P=0.03 and $I^2$=70%) or without (right) heterogeneity (P=0.49 and $I^2$=0 %). The studies depicted are as follows: Wu *et al* (14), Luo *et al* (15) and Yang *et al* (16). $I^2$, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval; P, P-value; OR, odds ratio.

When examining the funnel plot of the same parameter, no publication bias was found.

## Discussion

The present study suggests that the circulating miR-126 levels may be used as a biomarker for predicting aneurysmal rupture. More precisely, a *miR-126 expression* >5 was the only statistically significant parameter related to IA bleeding compared with non-rupture or/+ control (healthy) patients. Of note, an aneurysmal size >10 mm was also associated with an IA rupture.

miRNAs constitute a varied class of small (18-25 nucleotides in length) non-coding RNA molecules (17). miRNAs balance numerous genes, various biological pathways and regulatory networks inside cells by unifying various regulatory

Table III. Parameters for the results of the meta-analysis.

| | | | Groups | | Overall effect | | | Heterogeneity | |
|---|---|---|---|---|---|---|---|---|---|
| Parameter | 'Leave out one' model | Trial, n=3 | Exper | Control | Effect estimate | 95% CI | P-value | $I^2$ (%) | P-value |
| Age (years) | - | 3 | 226 | 153 | 1.14 | (-0.60-2.88) | 0.20 | 70 | <0.05 |
| | Yang *et al*, 2020 (16) | 2 | 147 | 130 | 1.36 | (-1.48-4.20) | 0.35 | 85 | <0.05 |
| | Wu *et al*, 2021 (14) | 2 | 164 | 106 | 0.21 | (-0.80-1.22) | 0.68 | 0 | 0.49 |
| | Luo *et al*, 2022 (15) | 2 | 141 | 70 | 1.88 | (-0.18-3.93) | 0.07 | 57 | 0.13 |
| Sex (male) | - | 3 | 98 | 75 | 0.85 | (056-1.30) | 0.46 | 0 | 0.52 |
| BMI ($kg/m^2$) >22 | | 2 | 81 | 45 | 1.76 | (0.55-5.67) | 0.34 | 72 | 0.06 |
| Alcohol use | | 2 | 43 | 37 | 0.88 | (0.51-1.52) | 0.64 | 0 | 0.33 |
| Smoking | | 2 | 68 | 26 | 1.57 | (0.59-4.19) | 0.37 | 60 | 0.12 |
| Location | | | | | | | | | |
| Anterior circulation | | 2 | 84 | 12 | 9.99 | (0.41-243.1) | 0.16 | 79 | <0.05 |
| Posterior circulation | | 2 | 38 | 11 | 3.09 | (0.04-256.6) | 0.62 | 89 | <0.05 |
| Size | | | | | | | | | |
| <5 mm | | 2 | 71 | 17 | 5.03 | (0.02-1310.1) | 0.57 | 93 | <0.05 |
| 5-10 mm | - | 2 | 49 | 4 | 9.11 | (0.29-290.4) | 0.21 | 81 | 0.02 |
| >10 mm | - | 2 | 21 | 2 | 3.52 | (0.90-13.85) | <0.05 | 0 | 0.58 |
| miR-126 | | 3 | 132 | 53 | 1.88 | (1.10-3.21) | <0.05 | 0 | 0.73 |

Exper, experimental; miR, microRNA; BMI, body mass index; $I^2$, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

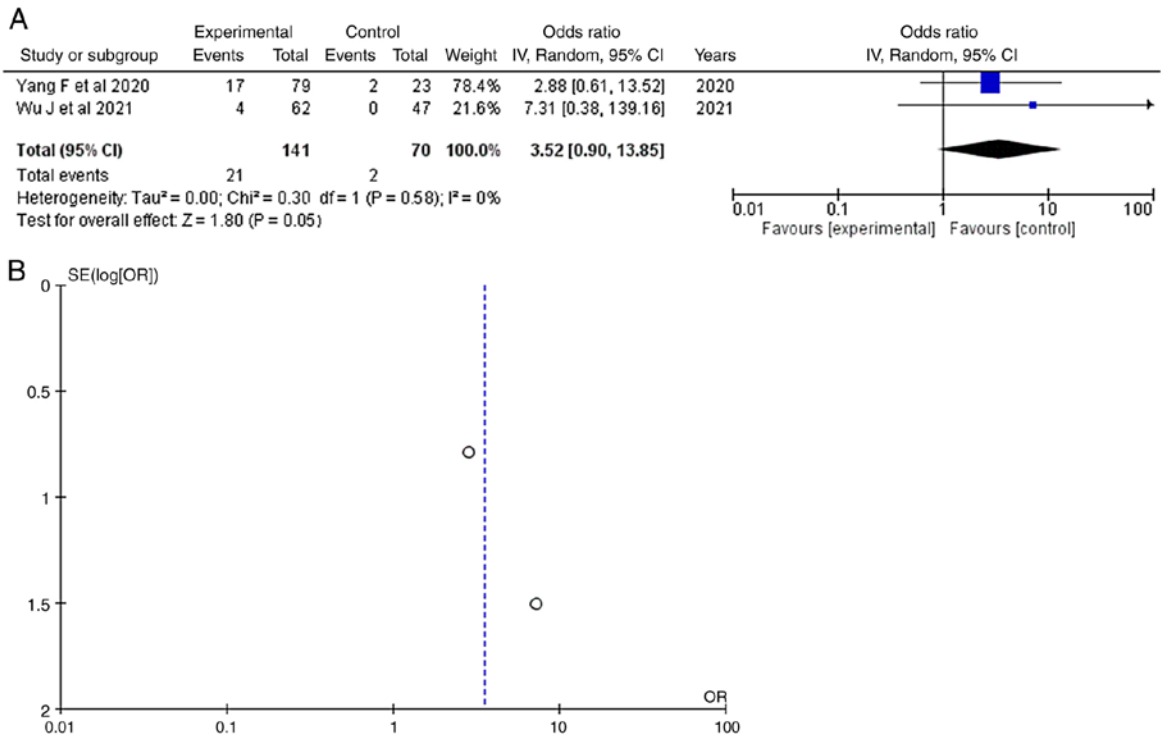


Figure 3. (A) Forest plot for an aneurism size >10 mm: The results demonstrated a statistically significant results (OR, 3.52; 95% CI, 0.90 to 13.85; P<0.05). (B) Funnel plot of the same parameter, demonstrating no heterogeneity (P=0.58 and $I^2$=0%). The studies depicted are as follows: Wu *et al* (14) and Yang *et al* (16). $I^2$, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval; P, P-value; OR, odds ratio.

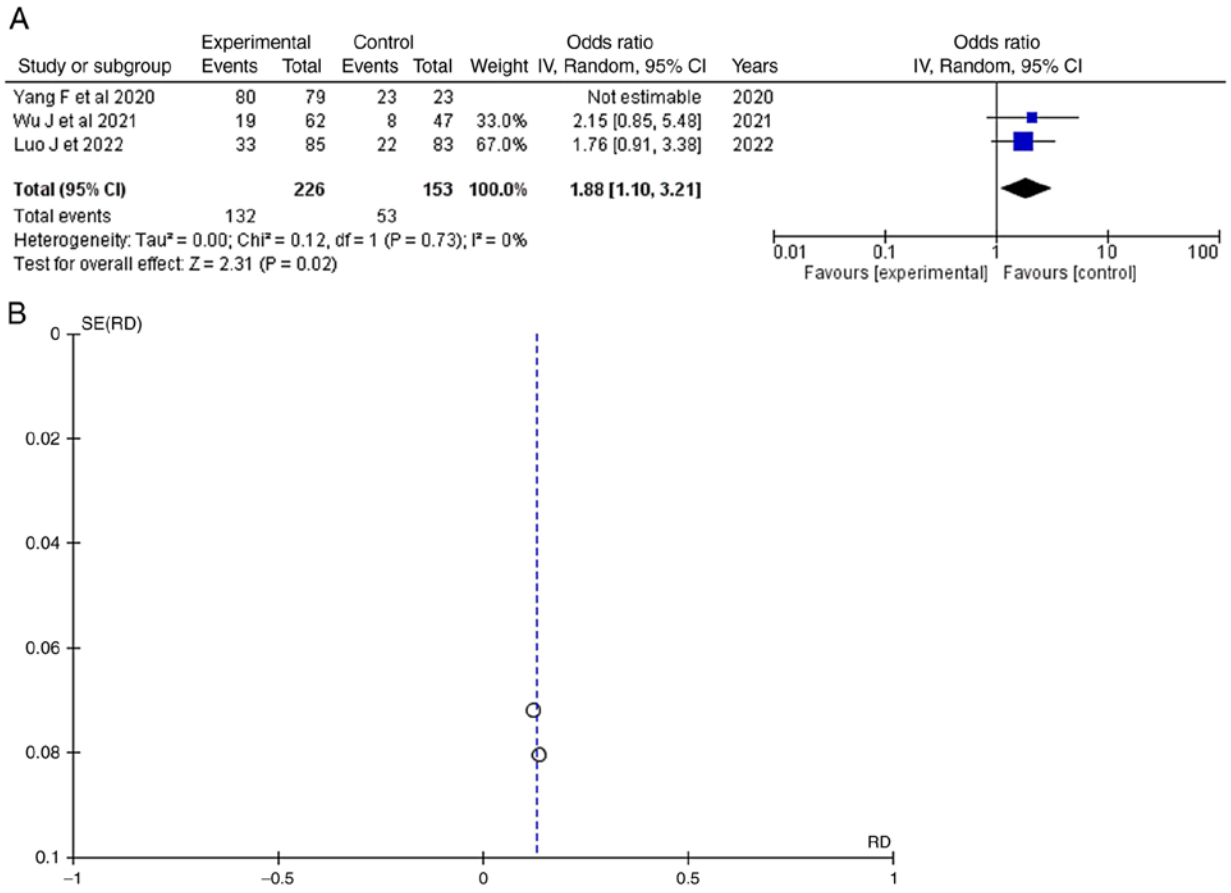


Figure 4. (A) Forest plot for miR-126 expression >5: The results demonstrated a statistically significant result (OR, 1.88; 95% CI, 1.10 to 3.21; P<0.05). (B) Funnel plot of the same parameter, demonstrating no heterogeneity (P=0.73 and $I^2$=0%). The studies depicted are as follows: Wu *et al* (14), Luo *et al* (15) and Yang *et al* (16). $I^2$, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval; P, P-value; OR, odds ratio.

mechanisms, whether in a type of transcriptional input or by their operating regulatory output on different pathways (18). Defects in miRNA regulation may often impair cellular and biological activity and, ultimately, contribute to disease progression. Since miRNAs are involved in disease evolution, circulating miRNAs have potential diagnostic value (19). The miR-126 gene is located on human chromosome 9 and is mostly expressed in vascular endothelial cells. Mature miR-126 controls the propagation of vascular endothelial cells (20). In the present study, the expression of serum miR-126 was higher in patients with IA rupture compared with non-rupture or/+ control (healthy) patients.

Circulating miR-126 levels have been formerly established to be increased in the serum of patients with unruptured IAs compared to healthy controls (16). However, further analysis has indicated that levels of circulating miR-126 can be increased in several pathways, such as erythroblastic leukemia viral oncogene homolog signaling and mitogen-activated protein kinase signaling pathways, which are related to IA, but have higher levels in ruptured IAs compared with unruptured IAs. Thus, the present meta-analysis included a miR-126 level of expression >5 to evaluate its potential role as a biomarker for predicting aneurysmal ruptures.

The underlying mechanisms responsible for the creation, enlargement and rupture of IAs are complex. It is considered that under conditions of continuous hemodynamic pressure, the cerebral artery walls turn fragile and becomes unable to resist these types of pressure, and structural modifications and pathological development are conducted in these walls. Therefore, intimal hyperplasia and the appearance of blood clots serve to distinguish the barriers of unruptured aneurysms (21).

Some researchers have reported that larger aneurysms are significantly associated with an increased risk of rupture (22). Although the difference in size between the ruptured and unruptured aneurysms decreases with an increasing age, the mean size of all ruptured aneurysms is significantly larger than the mean size of unruptured aneurysms (23). However, although size is one of the strongest predictors, small aneurysms often rupture (24,25). In the present meta-analysis, an aneurysmal size >10 mm was associated with an IA rupture.

The present study has several limitations however, which should be mentioned. The expression levels of circulating miR-126 were detected over a different time period of 3-14 days, and the value of miR-126 in the prognosis of patients remains uncertain. In addition, the possible association between aneurysm size and other parameters such as C-protein, and the association between miR-126 and varying degrees of severity of vasospasm and the small sample size constitute the main limitation of the present study.

In conclusion, the present study proposes that the circulating miR-126 levels may be used as biomarkers for predicting aneurysmal ruptures. The change in the circulating levels of miR-126 in plasma between patients with IA bleeding and non-rupture or/+ controls (healthy) may have a marked effect on IA ruptures. Furthermore, an aneurysmal size >10 mm in patients with unruptured aneurysms is associated with a high risk of bleeding and may thus help physicians confirm the level of therapy accordingly. Future studies are required to examine the circulating levels of miR-126, which were recognized in the present study as a potential biomarker for IA rupture. These levels may be relevant as a diagnostic tool in clinical practice for distinguishing between patients with severe and mild vasospasm.

**Acknowledgements**

Not applicable.

**Funding**

No funding was received.

**Availability of data and materials**

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

**Authors' contributions**

GF and VEG conceptualized the study. VEG, PS, GF, NM, PP, KP, DAS and NT analyzed the data, and wrote and prepared the draft of the manuscript. VEG and GF provided critical revisions. All authors contributed to manuscript revision, and have read and approved the final version of the manuscript. VEG and GF confirm the authenticity of all the raw data.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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