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REVIEW ARTICLE

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MicroRNAs as potential biomarkers for the diagnosis of glioma: A systematic review and meta-analysis

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Glioma is the most common central nervous system tumor and associated with poor prognosis. Identifying effective diagnostic biomarkers for glioma is particularly important in order to guide optimizing treatment. MicroRNAs (miRNAs) have drawn much attention because of their diagnostic value in diverse cancers, including glioma. We summarized studies to identify the potential diagnostic values of miRNAs in glioma patients. We included articles reporting miRNAs for differentiation of glioma patients from controls. We calculated sensitivities, specificities, and area under the curves (AUC) of individual miRNA and miRNA panels. We found that overall sensitivity, specificity, and AUC of miRNAs in diagnosis of glioma were 85% (95% confidence interval [CI]: 0.81-0.89), 90% (95% CI 0.85-0.93), and 93% (95% CI 0.91-0.95), respectively. Meta-regression analysis showed that the detection of miRNAs expression in cerebrospinal fluid (CSF) and brain tissue largely improved the diagnostic accuracy. Likewise, panels of multiple miRNAs could enhance the pooled sensitivity. Moreover, AUC of miR-21 was 0.88, with 86% sensitivity and 94% specificity. This study demonstrated that miRNAs could function as potential diagnosis markers in glioma. Detection of miRNAs in CSF and brain tissue displays high accuracy in the diagnosis of glioma.

KEYWORDS
biomarker, diagnosis, glioma, meta-analysis, miRNAs

1 | INTRODUCTION

Glioma is the dominant type of nervous system cancer and is associated with a poor prognosis.[1] The most prevalent glioma in adults is glioblastoma (6.34/100 000), which can evolve rapidly over several weeks or months.[2] Patients with glioblastoma have an average survival time of only approximately 15 months, despite receiving surgical, radiotherapy, and chemotherapy treatment.[3] Thus, early

Abbreviations: AUC, area under the curve; CI, confidence interval; CSF, cerebrospinal fluid; DOR, diagnostic odds ratio; FN, false negative; FP, false positive; miRNAs, microRNAs; NLR, negative likelihood ratio; PLR, positive likelihood ratio; SROC, summary receiver operator characteristic; TN, true negative; TP, true positive.

Qian Zhou and Jing Liu contributed equally to this work.

diagnostic markers and new therapies for glioma are urgently needed.

Molecular profiling of cancer has attracted a large amount of attention because of its clinical value in diagnosis, prognosis, and treatment of patients.[4] Thus, finding useful molecular markers to guide clinicians in optimizing treatment of glioma patients is important. miRNAs are a class of small non-coding RNA with 19-22 nucleotides. miRNAs have been found to be closely related to cancers because of the alterations in target binding sites of miRNAs and the miRNA processing machinery in tumor cells.[5] Recently, expression of miRNA in glioma has been extensively examined. Many studies have shown that some miRNAs are correlated with the diagnosis and prognosis of gliomas. For example, miR-301a is highly expressed in glioma serum exosomes and can be a diagnostic and prognostic indicator for glioma.[6] However, only two meta-analyses have studied the accuracy of diverse miRNAs for the diagnosis of glioma.[7] Ma et al[8] analyzed only the expression of miRNAs in blood samples. However, Akers et al[9] reported that miRNAs in CSF could serve as biomarkers for glioma. Moreover, new studies of miRNAs have been done since the publication of the meta-analyses of Qu et al[7] 4 years ago. Therefore, we carried out a meta-analysis to identify the potential diagnostic values of miRNAs in glioma patients.

2 | MATERIALS AND METHODS

2.1 | Search strategy

We carefully searched literature databases (PubMed, EMBASE, Cochrane Library, and Web of Science) to identify relevant studies published through June 13, 2018. The searches typically included 3 key terms "glioma," "miRNA," and "diagnosis." We searched PubMed using the following strategy: ((((("MicroRNAs"[Mesh]) OR ((((((((((((((((MicroRNA[Title/Abstract]) OR miRNAs[Title/Abstract]) OR Micro RNA[Title/Abstract]) OR RNA, Micro[Title/Abstract]) OR miRNA[Title/Abstract]) OR Primary MicroRNA[Title/Abstract]) OR MicroRNA, Primary[Title/Abstract]) OR Primary miRNA[Title/Abstract]) OR miRNA, Primary[Title/Abstract]) OR pri-miRNA[Title/Abstract]) OR pri miRNA[Title/Abstract]) OR RNA, Small Temporal[Title/Abstract]) OR Temporal RNA, Small[Title/Abstract]) OR stRNA[Title/Abstract]) OR Small Temporal RNA[Title/Abstract]) OR pre-miRNA [Title/Abstract]) OR pre miRNA[Title/Abstract])))) AND ((("Glioma" [Mesh]) OR ((((((((((((((((((Gliomas[Title/Abstract]) OR Glial Cell Tumors [Title/Abstract]) OR Glial Cell Tumor[Title/Abstract]) OR Tumor, Glial Cell[Title/Abstract]) OR Tumors, Glial Cell[Title/Abstract]) OR Mixed Glioma[Title/Abstract]) OR Glioma, Mixed[Title/Abstract]) OR Gliomas, Mixed[Title/Abstract]) OR Mixed Gliomas[Title/Abstract]) OR Malignant Glioma[Title/Abstract]) OR Glioma, Malignant[Title/Abstract]) OR Gliomas, Malignant[Title/Abstract]) OR Malignant Gliomas[Title/Abstract]) OR glioblastoma[Title/Abstract]) OR anaplastic astrocytoma[Title/Abstract]) OR diffuse astrocytoma[Title/Abstract]) OR anaplastic oligodendroglioma[Title/Abstract]) OR oligodendroglioma[Title/Abstract])))) AND ((("Diagnosis"[Mesh]) OR ((((((((((Diagnoses[Title/Abstract]) OR (Diagnoses[Title/Abstract] AND Examinations[Title/Abstract])) OR (Examinations[Title/Abstract] AND Diagnoses[Title/Abstract])) OR Postmortem Diagnosis[Title/Abstract]) OR Diagnoses, Postmortem[Title/Abstract]) OR Diagnosis, Postmortem[Title/Abstract]) OR Postmortem Diagnoses[Title/Abstract]) OR Antemortem Diagnosis[Title/Abstract]) OR Antemortem Diagnoses[Title/Abstract]) OR Diagnoses, Antemortem[Title/Abstract]) OR Diagnosis, Antemortem[Title/Abstract]))).

2.2 | Eligibility criteria and quality assessment

Studies were considered eligible if they met the following criteria: (i) diagnostic capacity of miRNA for glioma was provided; (ii) all patients with glioma were diagnosed by the gold standard test (histological examinations); (iii) FP, TP, FN and TN were provided to construct the 2×2 contingency table. Articles were excluded based on the following criteria: (i) written in a language other than English; (ii) not conducted on humans; (iii) reviews, letters, and meeting records; (iv) glioma and miRNAs were not studied; (v) studies focusing on gene polymorphisms; (vi) sample cases were from a database; and (vii) studies with insufficient data.

We assessed the quality of diagnostic studies based on the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria.[10] It consists of 4 key domains: patient selection, index test, reference standard, flow and timing and judge bias and applicability. Each is assessed in terms of risk of bias, and the first 3 domains were assessed with respect to applicability. Each item is answered with "yes," "no," or "unclear." The answer of "yes" means low risk of bias, whereas "no" or "unclear" means the opposite.

2.3 | Data extraction

Two reviewers (Zhou and Liu) independently extracted the data from the included studies using a standardized form. Data extraction included the following items: last name of the first author, publication year; study population and regions; false and true positives and negatives, and sample numbers.

2.4 | Statistical analysis

We extracted the number of TP, FP, FN, and TN of each study to calculate the pooled sensitivity, specificity, PLR, NLR, DOR, and corresponding 95% CI. We also tested the pooled diagnostic value of miRNAs through the SROC curve and the area under the SROC curve (AUC). In the present study, Deeks' funnel plot was also conducted to test publication bias. We assessed heterogeneity among the studies using the chi-squared and I^2 tests. If $P < .1$ or $I^2 > 50\%$, heterogeneity was defined as significant. We also conducted meta-regression, subgroup and sensitivity analyses to identify potential sources of heterogeneity. We carried out all analyses using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, London, UK) and Stata 12.0 (StataCorp, College Station, TX, USA), and a value of $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Study characteristics

We searched 1592 records in PubMed, EMBASE, and the Cochrane Library. Of these, 269 duplicate studies were excluded. We excluded 569 records after reading the titles and 500 records after reviewing the abstracts. Subsequently, we assessed the remaining 254 full-text articles and excluded 226 studies based on the exclusion criteria, including 30 meetings, and 196 without clinical data to make a 2×2 contingency table. In total, 28 studies were ultimately included in this study.[6,9,11–36] A flowchart of the selection process for this study is presented in Figure 1.

In total, 28 articles (ranging from years 2009 to 2018) reported 51 studies, including 2528 glioma patients and 2563 controls comprising healthy controls and patients with other diseases (Table 1). Among the 51 studies, 34 studies reported a single miRNA, whereas 17 studies discussed panel of miRNAs (Table S1). The diagnostic values of single miRNA (miR-128, miR-125b, and miR-221) were conducted in 2 studies, whereas single miRNA (miR-222) and a panel of miRNAs (miR-15b and miR-21) were reported in 3 studies. As single miRNA (miR-21) was reported by 4 studies, we conducted a meta-analysis of miR-21. Among the 51 studies analyzed, 39 studies detected miRNA in blood, 6 studies detected miRNA in CSF and 6 studies researched brain tissue. Of the 51 studies, 22 studies were conducted in Caucasian populations, and the remaining 29 studies focused on Asian populations.

3.2 | Quality assessment

Quality assessment results of all studies included in this meta-analysis are shown in Figure S1A,B.

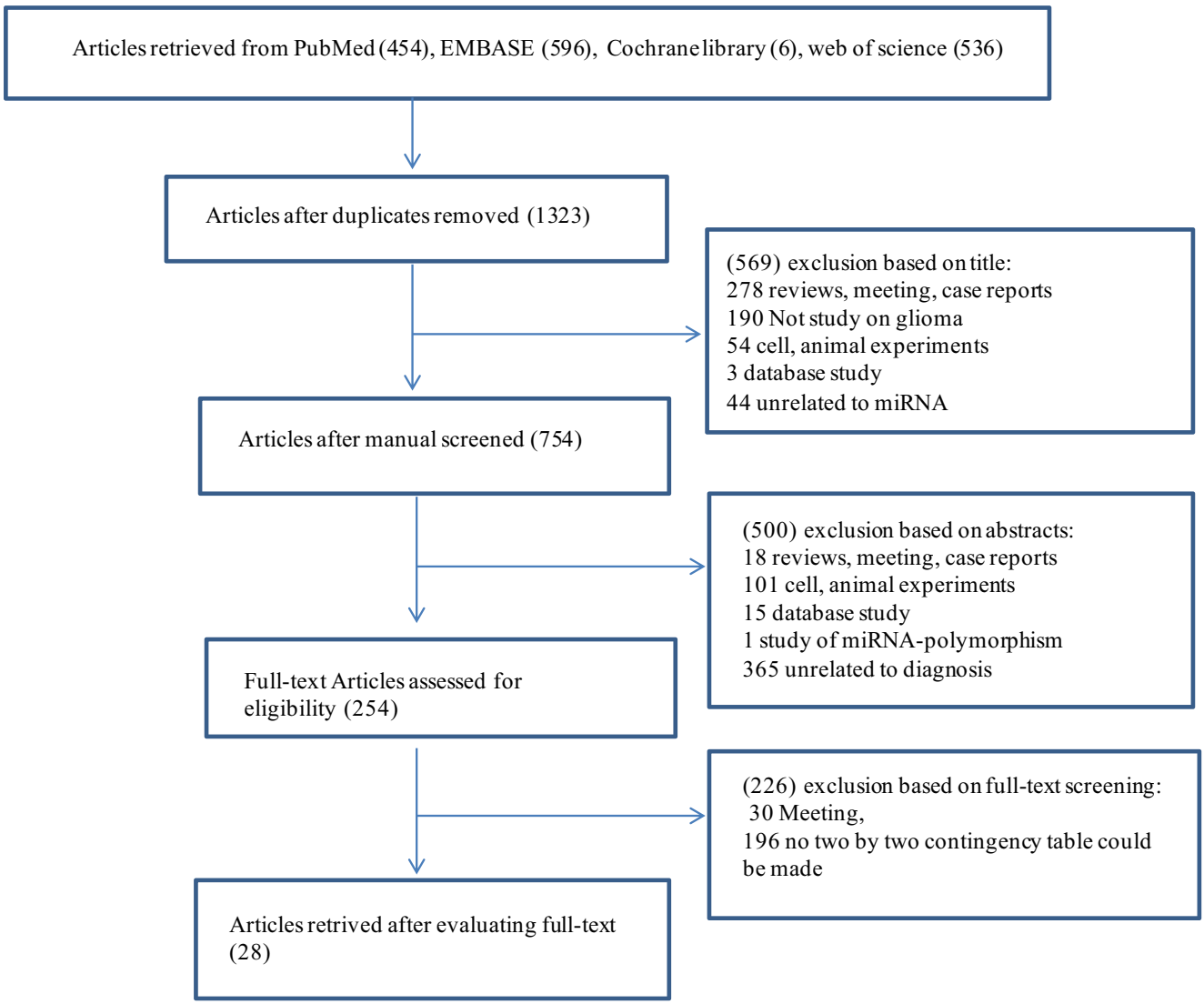

FIGURE 1 Flow diagram of the study selection for the present meta-analysis

TABLE 1 Characteristics of studies included in the present meta-analysis

First author	Publish year	Ethnicity	Cancer type	Controls	Patients/controls	miRNAS	Detected sample
Wang[26]	2012	Asian	GBM	Controls	10/10	miR-21 (up), miR-128, miR-342-3p (down)	Plasma
Nass[19]	2009	Caucasian	Glioma	Non-glioma	15/237	miR-9*, mir-92b, miR-124, miR-219-5p (up)	FT
D'Urso[14]	2015	Caucasian	Glioma	Non-glioma	30/82	miR-15b, miR-21 (up)	Plasma
Chen[13]	2017	Asian	GBM	Healthy controls	70/30	miR-203 (down)	Serum
Huang[15]	2017	Asian	Glioma	Healthy controls	100/50	miR-376a, miR-376b, miR-376c (up),	Serum
Zhao[34]	2016	Asian	Glioma	Healthy controls	118/84	miR-451a (down)	Serum
Xu[30]	2017	Asian	Glioma	Healthy controls	47/45	miR-17, miR-130a, miR-10b (up)	Plasma
Lai[16]	2015	Asian	Glioma	Healthy controls	126/40	miR-210 (up)	Serum
Lan[6]	2018	Asian	Glioma	Healthy controls	60/43	miR-301a (up)	Serum exosome
Li[17]	2016	Asian	Glioma	Healthy controls	60/43	miR-125b, miR-221, miR-222 (up)	FT
Xiao[29]	2016	Asian	Glioma	Healthy controls	112/54	miR-182 (up)	Plasma
Tang[25]	2017	Asian	Glioma	Healthy controls	74/74	miR-122 (down)	Plasma
Baraniskin[12]	2012	Caucasian	Glioma	Non-glioma	10/40	miR-15b, miR-21 (up)	CSF
Manterola[18]	2014	Caucasian	GBM	Healthy controls	25/25	miR-320, miR-574-3p (up)	Serum exosome
Zhi[35]	2015	Asian	Astrocytoma	Controls	90/110	miR-15b-5p,16-5p, 19a-9p, 19b-3p, 20a-5p, 106a-5p, 130a-3p, 181b-5p, 208a-3p	Serum
Akers[9]	2017	Caucasian	GBM	Non-cancer	28/32	miR-21, 218-5p, 193b-3p, 331-3p, 374a-5p, 548c-3p, 520f-3p, 27b-3p, 30b-3p	CSF
Akers[11]	2013	Caucasian	GBM	Non-cancer	28/28	miR-21 (up)	CSF exosome
Santangelo[22]	2018	Caucasian	GBM	Healthy controls	44/30	miR-21, miR-222, miR-124-3P (up)	Serum
Shao[23]	2015	Asian	Glioma	Healthy controls	70/70	miR-454-3p (up)	Plasma
Wei[27]	2016	Asian	Glioma	Healthy controls	33/33	miR-125b (down)	Serum
Yang[31]	2013	Asian	Astrocytoma	Healthy controls	133/80	miR-15b, 23a, 133a, 150, 197, 497, 548b-5p (down)	Serum
Yue[32]	2016	Asian	Glioma	Healthy controls	64/45	miR-205 (down)	Serum
Zhang[33]	2016	Asian	Glioma	Healthy controls	64/45	miR-221, miR-222 ()	Plasma
Roth[21]	2011	Caucasian	GBM	Healthy controls	20/20	180 miRNAs	Blood
Sun[24]	2015	Asian	Glioma	Healthy controls	153/51	miR-128 (down)	Serum
Wu[28]	2015	Asian	Glioma	Healthy controls	83/69	miR-29 (down)	Serum
Regazzo[20]	2016	Caucasian	GBM	Healthy controls	15/10	miR-497, miR-125b (down)	Serum
Manterola[18]	2014	Caucasian	GBM	Healthy controls	75/55	RNU61, miR-320, mir-574-4p (up)	Serum exosome
Gozé[36]	2018	Caucasian	Oligodendroglioma (5) and astrocytoma (10)	Healthy controls	15/15	miR-93, miR-593-3p (down), miR-454 (up)	Blood

CSF, cerebrospinal fluid; FT, frozen tissue; GBM, glioblastoma.

3.3 | Diagnosis

Sensitivity and specificity of miRNAs in diagnosing glioma are shown in Figure 2A,B. From forest plots of pooled data (51 studies from 28 articles), we found significant heterogeneity and used a mixed-effects model in the present meta-analysis. Diagnostic accuracy, sensitivity, and specificity of all miRNAs are summarized in Table S2. Pooled estimates of overall miRNA for diagnosis of glioma were as follows: sensitivity, 0.85 (95% CI: 0.81-0.89); specificity, 0.90 (95% CI: 0.85-0.93); PLR, 8.2 (95% CI: 5.5-12.3); NLR, 0.16 (95% CI: 0.12-

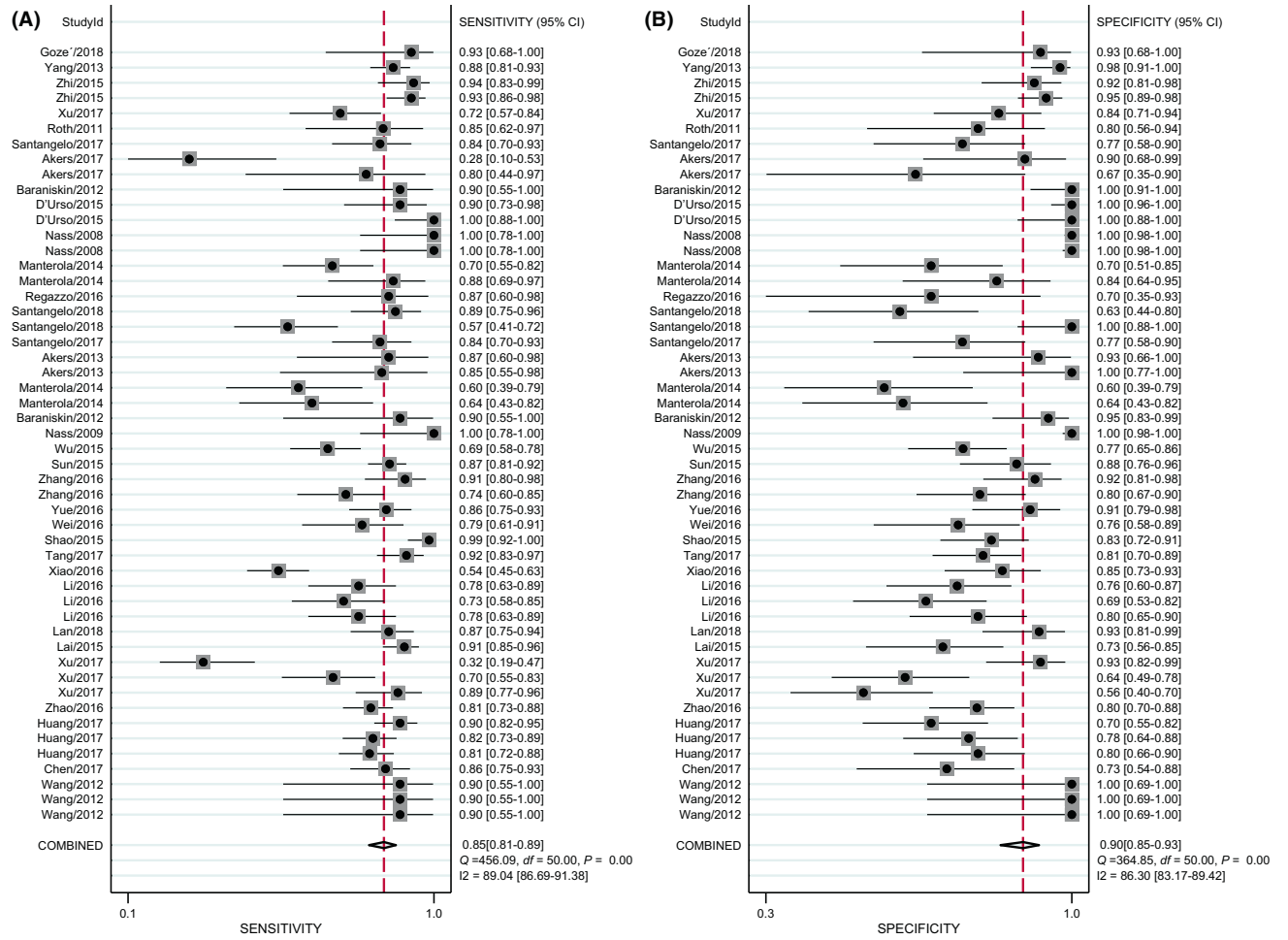

FIGURE 2 Forest plots for studies on overall microRNAs (miRNAs) used in the diagnosis of glioma among 51 studies included in the present meta-analysis A, Sensitivity; B, Specificity

0.22); and DOR, 50 (95% CI: 27-92). Moreover, we plotted the SROC curve to evaluate diagnostic accuracy (Figure 3). AUC was 0.93 (95% CI: 0.91-0.95), suggesting an outstanding diagnostic accuracy of overall miRNAs. To find the heterogeneity between studies, we carried out subgroup analyses based on ethnicity, miRNA profiling and detected sample (Figure 4). Sensitivity, specificity, PLR, NLR, DOR, and AUC of single miRNAs and miRNA panels was 0.83, 0.85, 5.4, 0.20, 27, 0.90; 0.90, 0.95, 19.8, 0.11, 185, 0.97, respectively (Figure S2A,B). Compared with Asians, miRNAs have a higher overall diagnostic accuracy in Caucasians, with sensitivity of 0.84 versus 0.87, specificity of 0.84 versus 0.96, LR of 5.3 versus 20.1, NLR of 0.19 versus 0.13, DOR of 28 versus 151, and AUC of 0.91 versus 0.96, respectively (Figure S2C,D). In detected samples of blood, results were 0.84 for sensitivity, 0.85 for specificity, 5.8 for PLR, 0.18 for NLR, 31 for DOR, and 0.92 for AUC (Figure 3C). In the CSF and brain tissue samples, sensitivity, specificity, PLR, NLR, DOR, and AUC was 0.89, 0.98, 39.3, 0.11, 358, and 0.98, suggesting that miRNA in CSF and brain tissue rather than in blood has a higher diagnostic accuracy (Figure 3D). The diagnostic value of miR-21 was as follows: sensitivity, 0.86 (95% CI: 0.75-0.93); specificity, 0.94 (95% CI: 0.68-0.99); PLR, 14.8 (95% CI: 2.1-103.7); NLR, 0.15 (95% CI: 0.08-0.28); and DOR, 99 (95% CI: 11-920). The AUC was 0.88 (95% CI: 0.85-0.91) (Figure 3B).

3.4 | Sensitivity analysis, meta-regression analysis, and publication bias

For sensitivity analysis, goodness of fit and bivariate normality showed that random effects bivariate model is suitable (Figure S3A,B). Influence analysis identified that studies of Xu et al, Shao et al, Nass et al, Santangelo et al, D'Urso et al and Akers et al were the most dominant studies in weight (Figure S3C). Outlier detection implied that studies of Xu et al, Nass et al, D'Urso et al, and Akers et al may be the reason for heterogeneity (Figure S3D). After excluding 5 outlier studies, the I^2 value for heterogeneity decreased 7.8% for sensitivity and 5.46% for specificity (Figure S4). We read those studies again and conducted meta-regression analysis on the bias of ethnicity, miRNAs, and detected sample. We found that sensitivity was influenced by ethnicity, miRNAs and detected sample, whereas specificity was affected only by detected sample. The miRNA detected in CSF or tissue shows a higher sensitivity and specificity in the diagnosis of glioma. Moreover, funnel

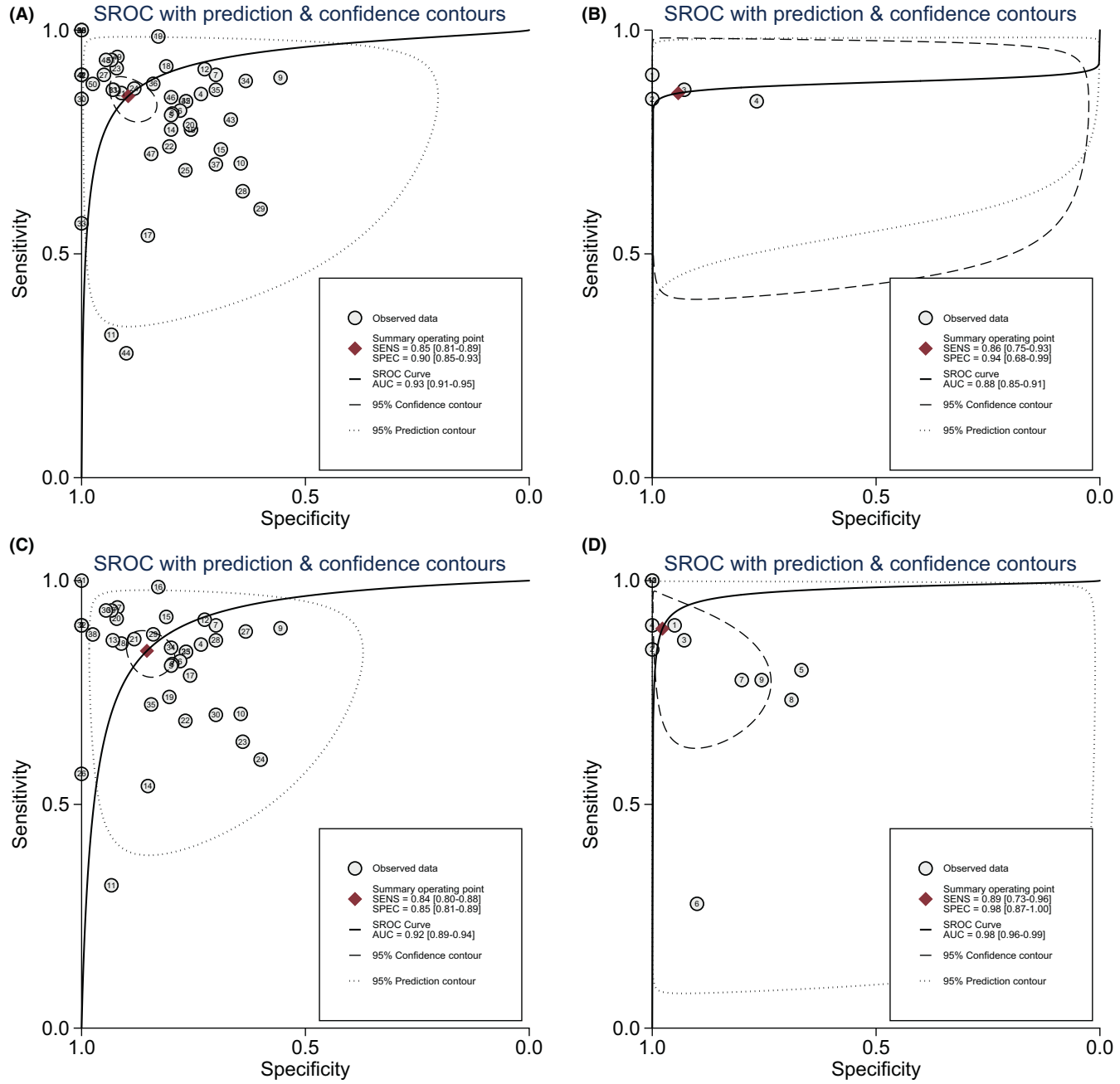

FIGURE 3 Summary receiver operator characteristic (SROC) curves based on microRNAs (miRNAs). A, All miRNAs, B, miRNA-21, C, miRNAs detected in blood samples, and D, miRNAs detected in cerebrospinal fluid and brain tissue. AUC, area under the curve; SENS, sensitivity; SPEC, specificity

plot showed no significant publication bias in the present meta-analysis (Figure S5).

4 | DISCUSSION

This meta-analysis of 28 articles including 2528 glioma patients and 2563 controls showed that miRNAs maintained high sensitivity (0.85) and specificity (0.90) in glioma diagnosis. Pooled PLR was 8.2, indicating that the probability of glioma increased by 8.2-fold with positive miRNAs testing. Moreover, NLR was 0.16, implying that the probability of glioma increased by 84% when the studied miRNAs were negative. Although a DOR of 1 suggests miRNAs failed to differentiate glioma and control, the DOR of 50 in our study showed that miRNAs are outstanding biomarkers in glioma diagnosis.

There were only 2 meta-analyses investigating the diagnostic accuracy of diverse miRNAs in glioma patients. In a meta-analysis from 2015, including 11 articles published between 2011 and 2015, Qu et al showed that the sensitivity, specificity, PLR, NLR, DOR, and AUC of overall miRNAs were 0.87, 0.87, 6.6, 0.15, 45, and 0.93,

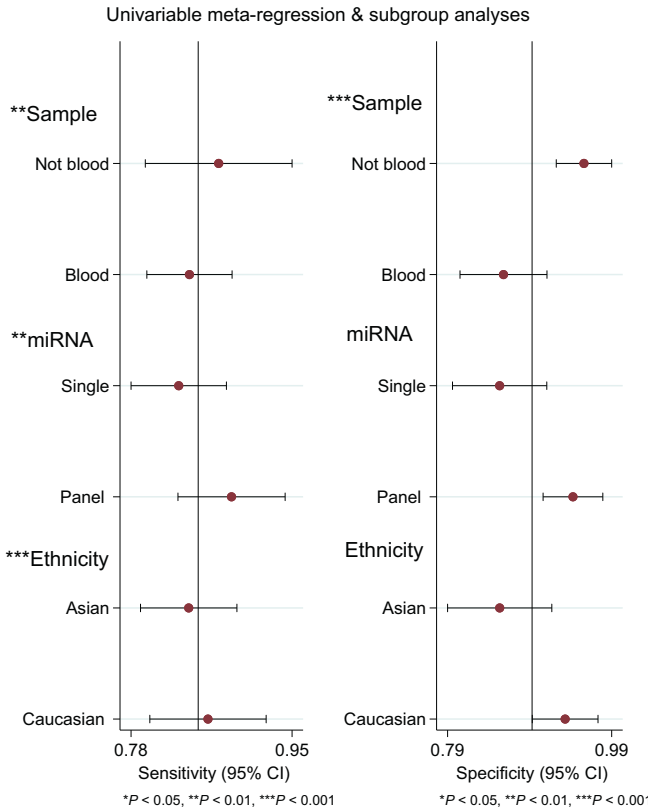

FIGURE 4 Univariable meta-regression and subgroup analyses for sensitivity and specificity of microRNAs (miRNAs) for diagnosis of glioma

which were similar to our results. However, the investigators carried out only subgroup analyses of miRNA profiling to explore the sources of heterogeneity. According to our meta-regression analysis, miRNA profiling would influence sensitivity rather than specificity. The researchers did not assess the heterogeneity of the source of the detected sample, which would have an influence on sensitivity and specificity. Moreover, Qu et al did not conduct subgroup analyses of ethnicity. In our study, Caucasians showed higher diagnostic value of miRNA than Asians, implying that expression difference of miRNA in different ethnicities may also influence diagnostic value of miRNAs. Furthermore, their article was published 3 years ago and many new studies of miRNAs have since been done. In another meta-analysis, including studies published before February 2017, sensitivity, specificity, PLR, NLR, DOR, and AUC of overall miRNAs were as follows: 0.87, 0.86, 6.39, 0.15, 41.91, and 0.93. However, their findings were biased because they only studied miRNAs detected in blood samples. According to our meta-regression analysis, we conducted subgroup analyses on detected samples, finding that the sources of detected sample in CSF and tissue have a higher sensitivity, specificity, and AUC than in blood (sensitivity, 0.89 vs 0.84; specificity, 0.98 vs 0.85; AUC, 0.98 vs 0.92). We guess that the blood-brain barrier restricts the passage of tumor miRNAs into the bloodstream and that this may be a reason for the diagnostic difference.

Several limitations in this meta-analysis should be emphasized. First, remarkable heterogeneity was observed in this study. However, the results of subgroup analysis found that detected sample

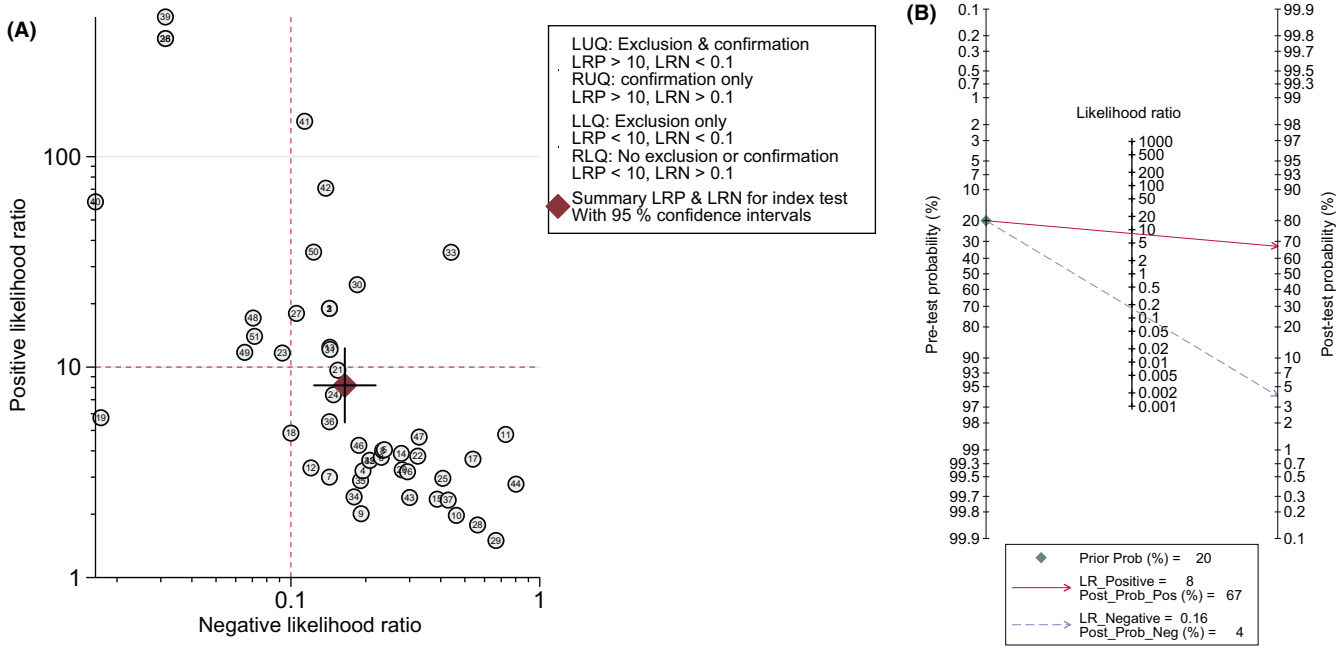

FIGURE 5 Assessment of the clinical applicability of microRNAs (miRNAs) for diagnosis. A, Summary of positive likelihood ratio and negative likelihood ratio for diagnosis of glioma. B, Fagan nomogram of the miRNA tests for diagnosis of glioma. LLQ, left lower quadrant; LRN, likelihood ratio negative; LRP, likelihood ratio positive; LUQ, left upper quadrant; RLQ, right lower quadrant; RUQ, right upper quadrant

could only partly explain the source of heterogeneity. Several different cut-off values were used in the included studies, which may have contributed to the heterogeneity. Second, after using the Quality Assessment of Diagnostic Accuracy Studies, we found that all studies enrolled in this meta-analysis were retrospective case-control studies. Moreover, all of the index test results were interpreted with knowledge of the results of the reference standard and used thresholds were not pre-specified (Figure S1). Third, studies with positive results are more likely to be published, which can amplify the overall diagnostic accuracy. Finally, we only included studies written in English, which may have affected our findings.

Helping clinical decision-making is the most important value of biomarkers. Likelihood ratios and post-test probabilities are helpful for clinicians because they supply information about the likelihood that a patient with a positive or negative test actually has glioma or not. We also summarized positive likelihood ratios and negative likelihood ratios to judge the clinical applicability of miRNAs for diagnosis (Figure 5A). PLR >10 and NLR <0.1 represent a high diagnostic accuracy.[37] We found that the miRNAs of the articles of Zhang et al, Zhi et al, D'Urso et al, Nass et al and Gozé et al had high diagnostic accuracy and clinical applicability. Hence, single miRNAs (miRNA-222) and a panel of miRNAs, such as (miRNA-93, miRNA-590-3p, miRNA-454); (miRNA-15b, miRNA-21); (miR-9*, miR-92b); (miRNA-124, miRNA-219-5p); (miRNA-15b-5p, miRNA-16-5p, miRNA-19a-9p, miRNA-19b-3p, miRNA-20a-5p, miRNA-106a-5p, miRNA-130a-3p, miRNA-181b-5p, miRNA-208a-3p) may be promising miRNAs and deserve future research. When the pretest probability was set at 20%, the post-test probability for a positive test result was 67%. When the negative likelihood ratio was set at 0.16, the post-test probability reduced to 4% for a negative test result (Figure 5B).

Our study indicated that miRNAs could be potential diagnostic biomarkers for glioma. Additionally, subgroup analysis indicated that miRNAs in CSF and tissues may improve the diagnostic accuracy. Also, panels of multiple miRNAs could discriminate patients with glioma more accurately than a single miRNA. However, large-sized and good-quality studies should be conducted to verify our results and confirm the clinical value of miRNAs in glioma patients.

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CONFLICTS OF INTEREST

Authors declare no conflicts of interest for this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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