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Diagnostic and Prognostic Value of Circulating microRNAs in Adult Brain Tumors: Systematic Review and Meta-Analysis

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ABSTRACT

Background and aim: Diagnosis and prognosis of brain tumors remains a clinical challenge, and noninvasive biomarkers can play a key role in improving the diagnosis and management of these patients. This study aimed to evaluate the diagnostic and predictive value of circulating microRNAs (miRNAs) in adult brain tumors.

Method: present systematic review and meta-analysis included studies from international databases, PubMed, Scopus, Web of Science, and Embase, from January 1, 2015 to November 23, 2025, using keywords aligned with the study objective. Studies included measurements of peripheral miRNAs in patients with brain tumors and healthy controls. Data included AUC, sensitivity, specificity, and information on miRNA type, sample source, and tumor type were collected. Study quality was assessed using the QUADAS-2 tool, and meta-analysis was performed with random and fixed-effects models. The statistical analysis was performed with Stata/MP.v17 as fixed effect models.

Result: A total of 15 studies with 1093 (case) and 753 (control) participants were included in the analysis. The meta-analysis showed that miRNAs had high diagnostic accuracy (AUC=0.84, sensitivity=0.81, specificity=0.80). Subgroup analysis showed that serum samples had higher AUC than plasma and exosomes (serum AUC=0.87).

Conclusion: Circulating miRNAs, especially in serum samples, are reliable diagnostic and predictive markers for brain tumors.

Introduction

Brain tumors pose a serious and challenging public health challenge; they have a significant prevalence across all age groups (1). According to available statistics, the overall 5-year incidence rate of primary brain and central nervous system tumors in the United States is 26.05 cases per 100,000 person-years; Of this, the incidence rate in children aged 0-14 years was approximately 5.51 per 100,000 and in adults over 40 years was 47.62 per 100,000 (2). Statistics have shown that the incidence of malignant brain tumors worldwide is estimated at approximately 4.25 per 100,000 person-years (3). According to global data, there were approximately 47,600 new cases of brain and central nervous system tumors in children worldwide, which is a rate of 1.8 per 100,000 person-years (4).

Studies have shown that the 5-year survival rate for all primary brain tumors in adults in the United States is about 54%, while in children (0-19 years) the rate has been reported to be about 77% (5).

Based on evidence, early diagnosis and prediction of disease progression play a vital role in improving treatment outcomes and increasing patient survival (6). Despite significant advances in brain imaging techniques such as MRI, fMRI, PET, and CT, as well as histopathology evaluations, there are still significant limitations in the diagnosis and prognosis of brain tumors (7-9). Studies have shown that biomarkers are accurate, non-invasive, and feel reliable (10).

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MicroRNAs (miRNAs), as short non-coding RNA molecules, have attracted attention as potential markers in the diagnosis and prognosis of brain tumors due to their key role in regulating gene expression and cellular pathways related to proliferation, apoptosis, and cell migration.

In this regard, circulating miRNAs (11) have attracted special attention as a new type of non-invasive biomarker, because changes in their levels in the blood are associated with the presence of a tumor, disease severity, and response to treatment, and can be a suitable alternative to current invasive and limited methods (12-14).

The findings of studies on the diagnostic and prognostic role of miRNAs in brain tumors are highly contradictory. In addition, differences in patient age, tumor types, measurement methods, and study design have prevented strong evidence from being provided. A comprehensive and systematic review of this data can help identify reliable miRNAs for both early diagnosis and disease progression prediction, leading to improved clinical decision-making and the design of targeted therapies. By simultaneously assessing the diagnostic and prognostic value of circulating miRNAs, this study could play a key role in identifying valid biomarkers and guiding future research to develop non-invasive tools and personalize brain tumor treatment. Therefore, the aim of present study was to evaluate diagnostic and prognostic value of circulating miRNAs in adult and pediatric brain tumors.

Method

Search and study selection

A systematic search was conducted in international databases, PubMed, Scopus, Web of Science, and Embase, from January 1, 2015 to November 23, 2025, using keywords aligned with the study objective. All retrieved articles were entered into End.Note.X8 software. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed at each stage.

PubMed search strategy: (((((("Brain Neoplasms"[Mesh]) OR "Glioma"[Mesh]) OR "Medulloblastoma"[Mesh]) OR ("Brain Neoplasms/diagnosis"[Mesh] OR "Brain Neoplasms/diagnostic imaging"[Mesh] OR "Brain Neoplasms/prevention and control"[Mesh])) AND ("Diagnosis"[Mesh] OR "Early Diagnosis"[Mesh])) AND "MicroRNAs"[Mesh]) OR "Circulating MicroRNA"[Mesh]) OR ("Circulating MicroRNA/administration and dosage"[Mesh] OR "Circulating MicroRNA/adverse effects"[Mesh] OR "Circulating MicroRNA/analysis"[Mesh] OR "Circulating MicroRNA/classification"[Mesh] OR "Circulating MicroRNA/standards"[Mesh] OR "Circulating MicroRNA/therapeutic use"[Mesh]).

Searches were also conducted in other databases using keywords similar to Mesh keywords. Google Scholar was searched for additional searches with the keywords " Brain Neoplasms", " brain tumor", " diagnosis" , " Circulating MicroRNA" , " MicroRNA" , " prognostic value".

Eligibility criteria

Inclusion Criteria: Inclusion criteria were based on the PICO strategy (Table 1), All human studies, and English language. Cohort studies, cross-sectional studies, case-control studies, were also assessed in the included study.

Table 1. PICO process in selecting studies

PICO strategy	
patient/population (P)	Adult patients (≥18 years) and pediatric patients (<18 years) diagnosed with primary or secondary brain tumor
intervention (I)	Circulating miRNAs
comparison (C)	healthy controls
outcomes (O)	diagnostic accuracy, sensitivity, specificity, Area Under the Curve (AUC).

Exclusion Criteria: case reports, incomplete or atypical data reporting, any type of review studies, laboratory studies, animal studies, letters to the editor, conference papers, studies without full text.

Data extraction

Two independent, blinded authors extracted the data from the studies based on a pre-designed table, and if there was any disagreement, it was resolved through discussion and review by the third author, and a consensus was reached in recording the data.

The columns of the table were: study name (first author), year of publication, study design, number of participants, mean age, gender of participants, Sample type and source, and Cancer Type.

Quality assessment

In the present study, QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) was used to assess the quality and risk of bias in diagnostic studies. This tool has four main domains: Patient Selection, Index Test, Reference Standard, Flow and Timing. Each area is assessed with one of three options (Low risk, High risk, and Unclear risk) (15).

Statistical analysis

The statistical analysis was performed with Stata/MP. v17 as fixed effect models. For diagnostic data, sensitivity, specificity, were calculated. For prognostic data, hazard ratio (HR) with 95% confidence intervals were extracted. Heterogeneity between studies was examined using I^2 and Cochran's Q test, and in case of high heterogeneity, a random effects model was used. Publication bias was assessed with funnel plots and Egger's test.

Result

254 articles were found by systematic literature review that matched the search strategy. A total of 197 articles were screened and articles that did not meet the inclusion criteria were excluded (n=135). The full texts of 62 articles were reviewed by two independent, blinded authors and subjected to screening for inclusion and exclusion criteria; only fifteen articles met the inclusion criteria, which were selected for review in the present study (Figure 1).

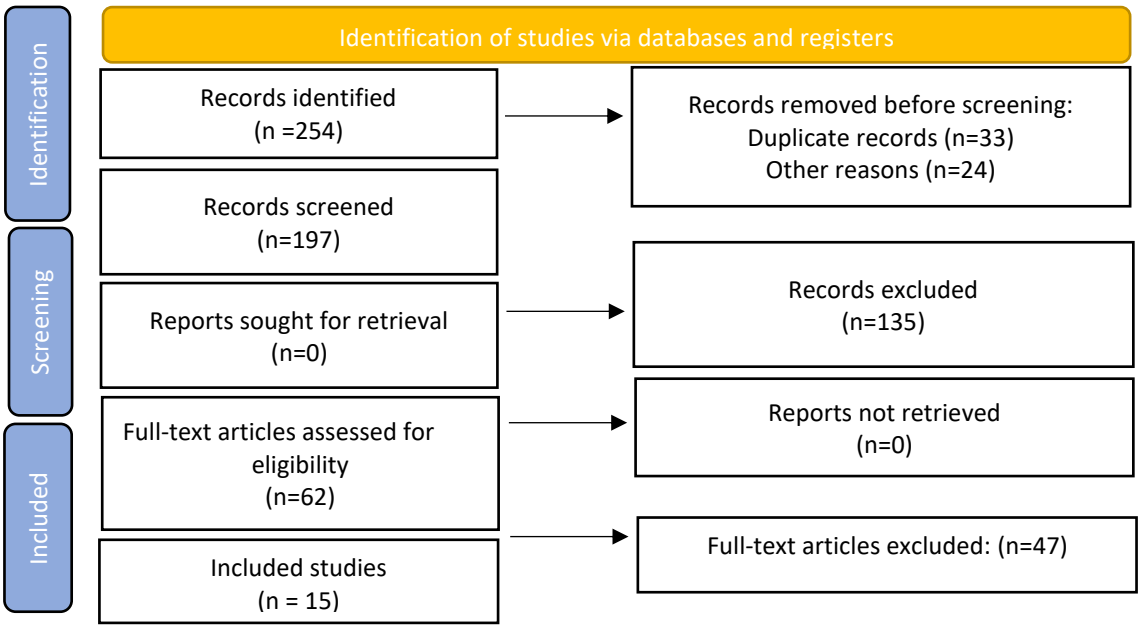

Figure 1. Flowchart of PRISMA.2020 and selection of studies

Characteristics of included studies

The sample size in the adult brain tumor group is 1093 people and in the healthy volunteer group was 753. The samples studied included serum (11 studies), plasma (2 studies), and exosome-rich serum (2 studies). The most frequently examined microRNAs included miR-21, miR-125b, miR-376 family, miR-221/222, miR-214, miR-145-5p, miR-182, miR-193b, miR-205, miR-301a, miR-15b, miR-23a, miR-133a, miR-150, miR-197, miR-497 and miR-548b-5p (Table 2).

Bias assessment

All studies included specific patients and had clear inclusion and exclusion criteria. Most studies did not fully report details of blinding, detection thresholds, or how miRNAs were measured. The diagnosis of cancer was often made by pathology or MRI. Some studies did not fully report all patients and sampling times (Table 3).

Table 2. Main characteristics of the included studies.

No.	Study	Number of participants		Type of miRNA	Type of Cancer	**Sample source**
		Case	Control			
1	Ali et al., 2025 (16)	25	20	miR-29a, miR-106a, and miR-200a	Glioblastoma	Serum
2	Ozdogan et al., 2020 (17)	39	40	miR-221	Glioblastoma	Serum
3	Wang et al., 2019 (18)	100	100	miR-214	Non-Glioblastoma	Serum
4	Swellam et al., 2019 (19)	20	20	miR-221, miR-222	Glioblastoma	Serum
5	Zhang et al., 2019 (20)	117	50	miR-145-5p	Glioblastoma	Serum
6	Zhu et al., 2019 (21)	122	68	miR-193b	Non-Glioblastoma	Serum
7	Lan et al., 2018 (22)	91	50	miR-210	Non-Glioblastoma	Serum

8	Santangelo et al., 2018 (23)	44	30	miR-21, miR-124-3p	Non-Glioblastoma	Exo-Serum
9	Xu et al., 2017 (24)	47	45	miR-10b, miR-17, miR-130a	Non-Glioblastoma	Plasma
10	Huang et al., 2017 (25)	100	50	miR-376a, miR-376b, miR-376c	Non-Glioblastoma	Serum
11	Lan et al., 2017 (26)	60	43	miR-301a	Non-Glioblastoma	Exo-Serum
12	Yue et al., 2016 (27)	64	45	miR-205	Non-Glioblastoma	Serum
13	Xiao et al., 2016 (28)	112	54	miR-182	Non-Glioblastoma	Plasma
14	Yang et al., 2016 (29)	122	123	miR-15b, miR-23a, miR-133a, miR-150, miR-197, miR-497, miR-548b-5p	Non-Glioblastoma	Serum
15	Regazzo et al., 2016 (30)	30	15	miR-497	Glioblastoma	Serum

Table 3. bias assessment

Study	Patient Selection (Risk of Bias / Applicability)	Index Test (Risk of Bias / Applicability)	Reference Standard (Risk of Bias / Applicability)	Flow & Timing (Risk of Bias)
Ali et al., 2025 (16)	□ / □	□ / □	□ / □	□
Ozdogan et al., 2020 (17)	□ / □	□ / □	□ / □	□
Wang et al., 2019 (18)	□ / □	□ / □	□ / □	□
Swellam et al., 2019	□ / □	□ / □	□ / □	□
Zhang et al., 2019	□ / □	□ / □	□ / □	□
Zhu et al., 2019	□ / □	□ / □	□ / □	□
Lan et al., 2018	□ / □	□ / □	□ / □	□
Santangelo et al., 2018	□ / □	□ / □	□ / □	□
Xu et al., 2017	□ / □	□ / □	□ / □	□
Huang et al., 2017	□ / □	□ / □	□ / □	□
Lan et al., 2017	□ / □	□ / □	□ / □	□
Yue et al., 2016	□ / □	□ / □	□ / □	□
Xiao et al., 2016	□ / □	□ / □	□ / □	□
Yang et al., 2016	□ / □	□ / □	□ / □	□
Regazzo et al., 2016	□ / □	□ / □	□ / □	□

□ Low; □ Unclear; ■ High

AUC

A fixed-effects model with the Inverse-variance method was used due to very low heterogeneity between studies (I^2=2.42%). The AUC value for circulating microRNAs was 0.84 (95% confidence interval: 0.81-0.87) (Figure 2), indicating a high diagnostic performance of these biomarkers for differentiating brain tumor patients from controls. The weight of each study in calculating the AUC was determined based on sample size and precision of estimates; the homogeneity test (Q=22.55, df=22, P=0.43) also showed that the studies were consistent and homogeneous in terms of AUC performance.

Sensitivity

A random-effects model with the DerSimonian–Laird method was used because heterogeneity between studies was moderately high (I^2 = 50.04%, tau^2=0.0064), indicating significant variation in reported sensitivity between studies. The sensitivity for circulating microRNAs was 0.81 (95% confidence interval: 0.77-0.86) (Figure 3), indicating that these biomarkers are able to identify approximately 81% of true brain tumor patients in comparison with health control. The homogeneity test (Q=44.03, df=22, P=0.0035) showed that heterogeneity between studies was significant, so the use of a random effects model was appropriate and necessary.

Specificity

Random-effects model with DerSimonian–Laird method was used because heterogeneity between studies was significant (I^2=64.05%, tau^2=0.0113). The specificity for circulating microRNAs was 0.80 (95% confidence interval: 0.75-0.86) (Figure 4), indicating that these biomarkers are able to identify approximately 80% of healthy individuals compared to patients. The homogeneity test (Q=61.19, df=22, P<0.001) showed that heterogeneity between studies

was significant, so using a random effects model to calculate the cumulative characteristic was appropriate and necessary.

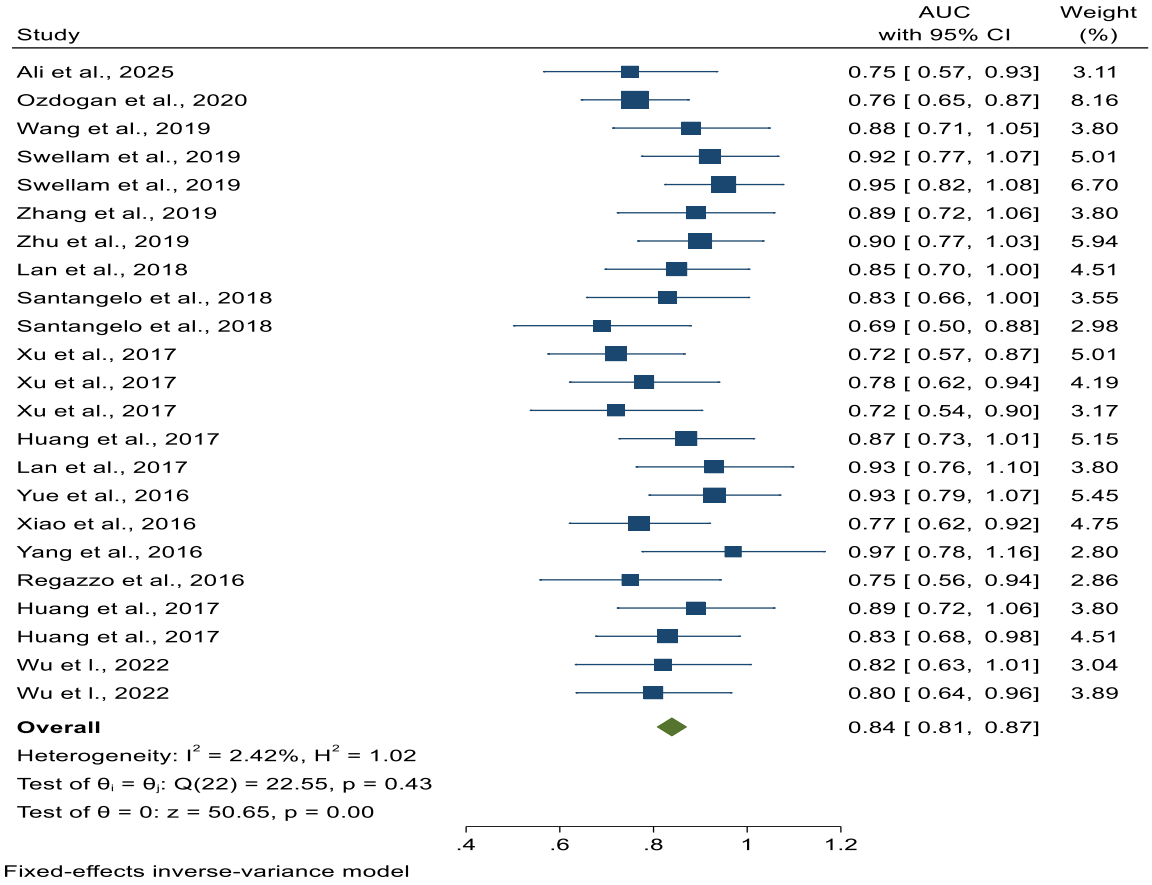

Figure 2. forest plot showed AUC of circulating microRNAs for diagnosing patients with brain tumors.

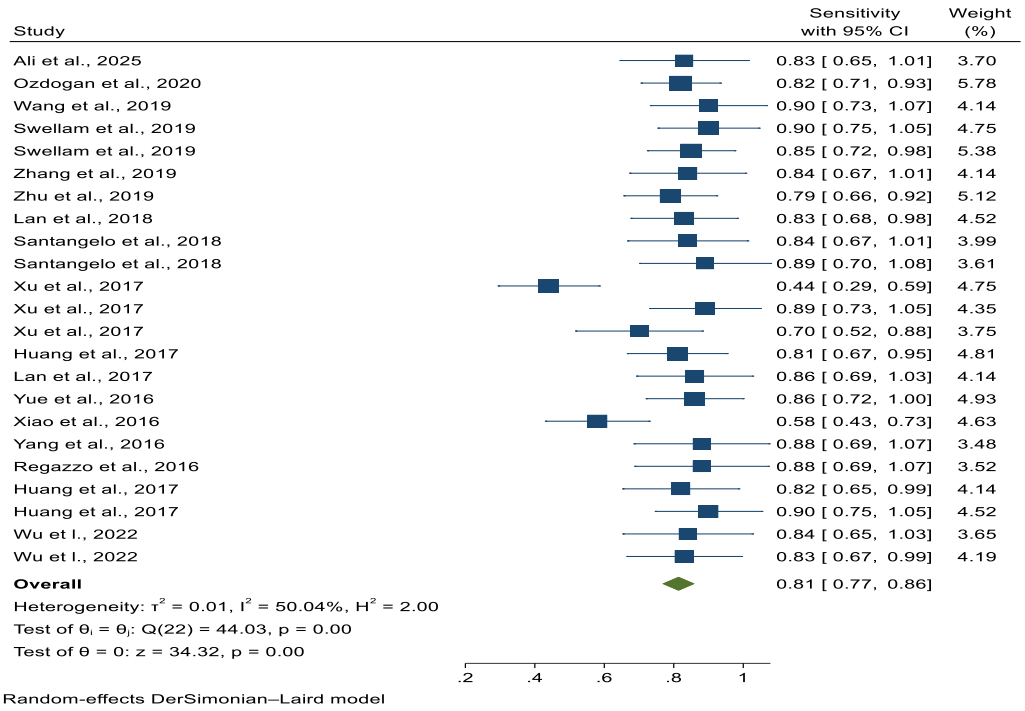

Figure 3. forest plot showed sensitivity of circulating microRNAs for diagnosing patients with brain tumors.

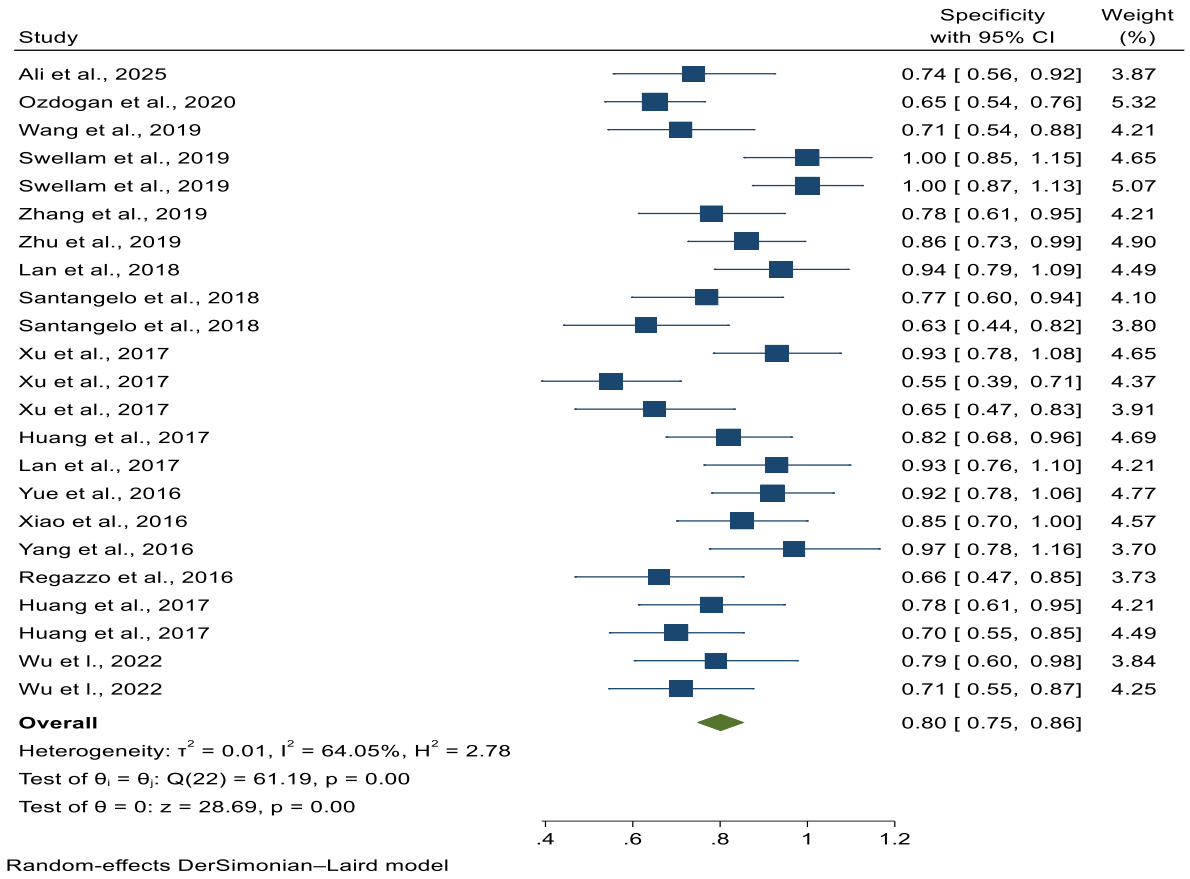

Figure 4. forest plot showed specificity of circulating microRNAs for diagnosing patients with brain tumors.

To examine the effect of sample type (Exo-Serum, Plasma, Serum) and cancer type (GBM and Non-GBM), a subgroup analysis with a fixed-effects, inverse-variance model was performed.

The results of the subgroup meta-analysis showed that the diagnostic performance of circulating miRNAs in brain tumors was affected by sample type, but cancer type (GBM vs. non-GBM) did not play a decisive role in changing the effect. In the analysis based on sample type (Exo-Serum, Plasma, and Serum), the highest diagnostic accuracy was related to the serum sample group; as the AUC of this group was reported to be 0.871 (95% CI: 0.833-0.910) (Figure 5). This value was significantly higher than the other two groups, and the test of difference between subgroups showed that the difference between them was statistically significant (Q_b (2) =6.23, p=0.04) (Figure 5).

Analysis by cancer type showed that miRNAs performed relatively similarly in both GBM (AUC= 0.859) and non-GBM (AUC = 0.835) (Figure 5), and the difference between these two subgroups was not statistically significant (Q_b (2) = 0.22, p=0.64) (Figure 5).

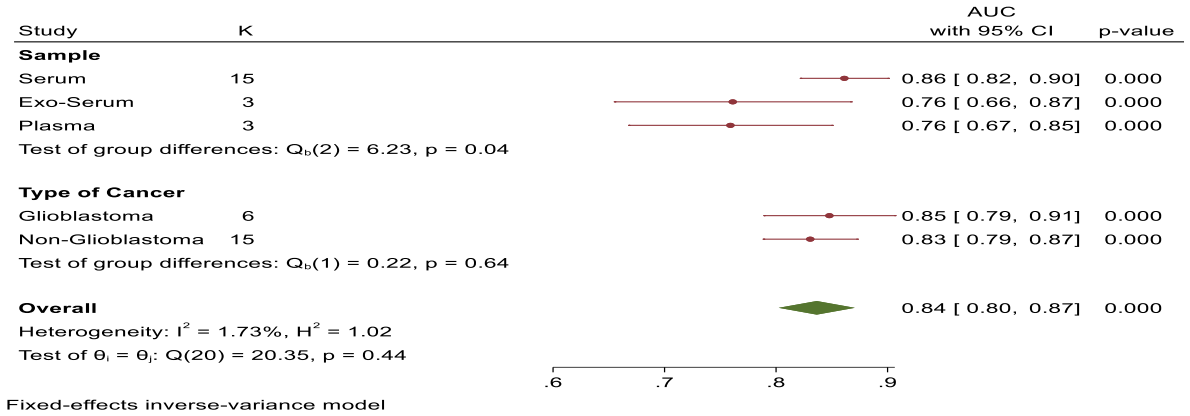

Figure 5. forest plot showed subgroup meta-analysis AUC for miRNAs in brain tumor diagnosis

Discussion

The present meta-analysis showed that circulating miRNAs in the blood, whether in the form of serum, plasma, or exosomes, have a significant ability to detect brain tumors, and a high AUC indicates the favorable accuracy of these biomarkers for differentiating patients with brain tumors from healthy individuals. The findings of the present study are in line with the growing evidence that has highlighted the role of miRNAs as non-invasive biomarkers in brain cancers over the past decade. The present findings are consistent with the results of a meta-analysis by Wang et al., 2019, which showed that serum miRNAs act more stable than plasma and their diagnostic performance is superior due to greater molecular stability. The study by Smolarz et al., 2021 also showed that serum exhibits higher concentrations of tumor-associated miRNAs due to the release of miRNAs from tumor cells and exosomes in more advanced stages of the disease, thus achieving greater sensitivity. Aalami, et al., 2022 review of 26 diagnostic studies in brain cancers concluded that serum samples had less heterogeneity and higher sensitivity than plasma. Another systematic review by Hong et al., 2023 of seven diagnostic studies showed that the performance of miRNAs in exosomes is generally better than free miRNAs in plasma (35), due to their structural protection, but the limited number of exosome studies prevented definitive results. The present findings, despite the small number of exosome studies (two studies), showed that the accuracy of this group remains at an average level (AUC=0.761) and requires more extensive studies.

The present meta-analysis showed no significant difference between the diagnostic accuracy of miRNAs in glioblastoma and non-glioblastoma tumors. This result is consistent with the studies of Amorim et al., 2021 and Abeysinghe et al.,2021 who reported that the miRNA response is more a reflection of general tumorigenic processes in the CNS and is not necessarily specific to glioblastoma or less aggressive tumors. In a meta-analysis by Li et al., 2017 that examined the diagnostic performance of circulating miRNAs in brain tumors, a combined sensitivity of 0.82 and specificity of 0.82 were reported(34), the findings are consistent. A more comprehensive meta-analysis showed that the overall sensitivity of miRNAs was 0.82 and the specificity was 0.78.

Several limitations should be addressed in the present study, 1. Small sample size in studies; 2. Inter-study heterogeneity in plasma subgroup; 3. Differences in extraction methods (TRIzol, column kits, and exosome-based methods), measurement platforms (qRT-PCR, NGS); 4. Use of different reference genes. Many studies lacked assessor blinding and a single standard for cut-off thresholds, a factor that suggests an increased risk of diagnostic bias in the QUADAS-2 assessment. Another limitation was the lack of sufficient data for some miRNAs. In most articles, insufficient information was provided about hemolysis status, sample storage time, freeze-thaw conditions, and preanalytical processes, while these factors can directly affect miRNA stability and test accuracy.

Conclusion

The present meta-analysis showed that the sample source played a significant role in the diagnostic accuracy of miRNAs, and serum sample provided the best AUC, while cancer type did not significantly affect the diagnostic performance of miRNAs. Accordingly, the use of serum samples is recommended for the development and standardization of non-invasive miRNA-based tests in brain tumors. Circulating microRNAs had a high performance in distinguishing healthy individuals from brain tumor patients. Circulating microRNAs have a high diagnostic ability and can be considered as potential diagnostic and prognostic biomarkers in adult brain tumors. These findings demonstrate the importance of using circulating miRNAs in non-invasive diagnosis and prognostic assessment of patients with brain tumors and can guide the design of future studies and the development of miRNA-based diagnostic tools.

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No potential conflict of interest reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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