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Evaluation of Circulating Mirnas In the Prediction and Diagnosis of Brain Tumors

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Abstract

Heterogeneities in clinical brain tumor phenotypes and restriction to standard diagnostic methods, including CT and MRI imaging or invasive biopsies are remaining challenges. Noninvasive biomarkers, which could be used in early prediction and diagnosis of brain tumors, are attracting more attention. Circulating microRNAs (miRNAs) show promise as biomarkers because they are stable in peripheral blood and are linked to tumor-associated molecular networks. The purpose of this research was to determine whether the expression levels of circulating miRNAs could be used to diagnose and predict brain tumors. Subjects and Methods: A cross-sectional diagnostic study was carried out in Al-Forat Al-Awsat Oncology Center, Al-Najaf City, Iraq from February 2025 to August 2025. A total of 78 patients with clinical suspicion of brain tumors were included. MiRNA levels in circulation from peripheral blood collected before radiological evaluation were quantified. All patients were subjected to brain CT scan afterwards as the gold standard of diagnosis. According to CT scans, 48 cases of brain tumor were confirmed, and another 30 cases presented no intracranial tumor as the control group. Sera obtained from patients with brain tumors were not different from the tumor-negative cases, both in terms of miRNA expression ($p < 0.002$). In binary logistic regression, circulating miRNAs levels were independently associated with the increased odds of presence of a brain tumor ($p = 0.012$). Receiver operating characteristic (ROC) curve analysis further confirmed circulating miRNAs with good diagnostic value, an AUC of 0.84, and a sensitivity and specificity of 83.3% and 80.0% using the optimum cut-off value. In summary, circulating miRNAs may be promising non-invasive diagnostic and predictive biomarkers for brain tumors that could be used in clinical practice as a supplement of radiological imaging.

Keywords: Circulating miRNAs, Brain Tumors, AUC, Sensitivity, Specificity

Introduction

Brain tumors are a fixed homogenous group of neoplasms that originate from the central nervous system (CNS), including both primary and metastatic brain tumors, all of which exhibit a wide spectrum of biological behavior outcomes. IntroductionBrain tumors are still one of the major causes of morbidity and mortality in the world, especially high-grade gliomas such as glioblastoma multiforme (GBM) for which therapy has a very poor outcome, despite the progress made in neuro-imaging, neurosurgery, radiotherapy, and chemotherapy (Ostrom et al., 2015). Fast detection and precise prognosis of malignant behaviour are important parameters for success of treatment; but current diagnostic capabilities are frequently hampered by invasive, expensive and not sensitive enough approaches, particularly, for early-stage disease (Pulumati et al., 2023).

Despite its central role in initial diagnosis and follow-up of brain tumors, magnetic resonance imaging (MRI) findings cannot accurately define tumor subtypes, predict molecular profiles or the likelihood of early

recurrence when the analysis is based solely on the radiology image (Louis et al., 2021). Biopsy or surgical resection histopathology-based diagnosis, which is the gold standard, is invasive, puts the patient at procedural risk and may fail to capture intratumoral heterogeneity. As a result, the search for non-invasive biomarkers that can aid in the early diagnosis, prognostication and treatment selection in patients with brain tumors is increasing (Ceccarelli et al., 2016).

These drawbacks can be bypassed in principle with the advent of the liquid biopsy concept, with which tumor-derived components in body fluids including blood, cerebrospinal fluid and urine can be detected (Siravegna et al, 2017). Out of all these biomolecules analysed, circulating microRNAs (miRNAs) have attracted considerable interest because of their high stability, accessibility and biological significance. MicroRNAs (miRNAs) are small non-coding RNA molecules (18–25 nucleotides) that post-transcriptionally regulate gene expression through targeting of messenger RNA to alter cellular processes that support or inhibit proliferation, differentiation, apoptosis, and immune response (Bartel, 2018).

Cancer features a peculiar temperament of miRNA expression and their role as oncogenes or tumor suppressors based on their target profile in specific cellular context (Lu et al., 2005), brain tumors portrait similar features of dysregulated miRNA expression. Dysregulated miRNA signatures in gliomas have been associated with tumorigenesis, angiogenesis, invasiveness and treatment resistance as well as patient outcome (Zhang et al., 2012). Notably, miRNAs can be released into the circulation in the form of exosomes, microvesicles, or protein complexes so that they are stable in peripheral blood despite the existence of RNases. The biological stability of circulating miRNAs drives great interest in their potential use as non-invasive diagnostic and predictive biomarkers (Mitchell et al, 2008).

Circulating miRNAs signatures in brain tumor patients were significantly different from healthy individuals in several reports. For instance, numerous studies indicate that miR-21, miR-10b and miR-221 are prominently, abundantly, and consistently over-expressed in the serum or plasma of glioma patients, and reflective of the tumor grade and poor prognosis (Laghari et al., 2025). In contrast, loss of expression of tumor-suppressive miRNAs, including miR-128 and miR-137, has been associated with more aggressive tumor behavior and worse prognosis. These observations indicate that circulating miRNAs are not only biomarkers of tumor presence but also potentially informative regarding tumor biology and the clinical course of cancer (Zhang et al., 2012).

And even outside of diagnosis, circulating miRNAs have diagnosed utility in predicting treatment response and disease recurrence. As the levels of miRNA and their correlation with residual disease and early relapse has proved their value in real-time disease monitoring following surgical resection or chemoradiotherapy [9], dynamic changes such as these could prove to be useful for informative disease monitoring (Regazzo et al., 2016). In addition, panels of miRNAs rather than single markers may improve diagnostic efforts by overcoming issues of tumor heterogeneity and inter-individual variability (Shen et al., 2020).

However, before these promising data can be translated clinically for management of brain tumors, several issues need to be resolved including heterogeneity regarding sample type, RNA isolation technique, normalization method, and analytical platforms. This should therefore also be systematically evaluated in well characterised patient cohorts in order to perform appropriate diagnostic and predictive validation of the circulating miRNAs.

Therefore, the objective of the current study is to assess circulating miRNAs as novel and non-invasive biomarkers for predicting and diagnosing brain tumors. This work aims to strengthen the argument for miRNAs as precision neuro-oncological biomarkers by investigating miRNA expression profiles in peripheral blood and associations with clinical and pathological factors.

Methods

Patients and data collection

Setting: This cross-sectional diagnostic study was conducted at Al-Forat Al-Awsat Oncology Center in Al-Najaf City, Iraq, between February 2025, and August 2025, to evaluate the role of circulating microRNAs (miRNAs) as non-invasive biomarkers in brain tumor prediction and diagnosis. Consecutively, 78 patients with assumed brain tumors, due to neurological symptoms revealing persistent headache, seizures, focal

neurological deficits, visual disturbances or cognitive impairment, were enrolled in this study. All subjects had peripheral blood samples collected prior to definitive radiological assessment. All patients were subsequently screened for brain computed tomography (CT) scan, which was set as the reference standard for diagnosis, after miRNA analysis. Using CT as a reference, brain tumors were confirmed in 48 patients and no intracranial tumors were found in the other 30 patients. We included patients aged 18 years or older and excluded patients with a history of brain tumor, previous cranial surgery, chemotherapy or radiotherapy, systemic malignancies, an acute infection, a chronic inflammatory or autoimmune disease, severe hepatic dysfunction, or renal dysfunction, a stroke, or recent head trauma to avoid confounding effects on circulating miRNA expression (Table 1 and Supplement Tables 1 and 2). Clinical and demographic data were measured with a structured interview and were confirmed using medical records. Venous blood samples (5 mL) were obtained in sterile EDTA containing tubes and centrifuged at 3,000 rpm for 10 minutes no longer than two hours after collection to obtain plasma. Aliquots of the plasma samples were frozen at −80°C until analysis. Total miRNAs in serum were extracted using magnetic beads-based miRNA isolation kits (China), following the manufacturer's instructions, and RNA concentrations and purities were spectrophotometrically assessed. Complementary DNA was synthesized (miRNA specific Reverse transcription kit, China) and qRT-PCR was performed (SYBR Green) on a real-time PCR system. All reactions were performed in duplicate and miRNA expression was normalized to an endogenous control miRNA. Relative expression was determined by the $2^{-}\Delta\Delta Ct$ method. Statistical analysis was conducted using [appropriate statistical software for your field], with continuous variables presented as mean ± standard deviation or median (interquartile range) and categorical variables presented as frequency and percentage. Independent t-tests, or their non-parametric equivalents as appropriate, were used to evaluate differences in the expression of circulating miRNA between tumor-positive and tumor-negative groups, and receiver operating characteristic (ROC) curve analysis was employed to assess the potential diagnostic performance of circulating miRNA. Statistical significance was defined as a p-value less than 0.05.

The Results

Brain tumors with CT confirmation were comparable to patients without tumors in a range of baseline demographic and clinical characteristics. There was no statistically significant relationship for gender, body mass index categories, the presence of chronic disease or place of residence (all $P > 0.05$). These results show appropriate group comparability and imply minimal potential confounding effects of these variances on circulating miRNA expression. As such, differences in circulating miRNA levels observed between groups are more aptly reflective of tumor-associated biologic differences, and not baseline demographic or anthropometric background differences (table 1).

Table 1. Comparison of general information between positive and negative cases regarding confirmed brain tumor

Items		Positive Cases (N= 48)		Negative Cases (N= 30)		(P value)
		Freq.	%	Freq.	%	
Gender	Male	28	58.3	16	53.3	**0.42 (NS)**
	Female	20	41.7	14	46.7	
BMI	Underweight	4	8.3	2	6.7	**0.29 (NS)**
	Normal	18	37.5	12	40	
	Overweight	16	33.3	10	33.3	
	Obese	10	20.9	6	20	

Chronic Disease	**Yes**	15	31.3	8	26.7	**0.39 (NS)**
	No	33	68.7	22	73.3	
Residence	**Urban**	29	60.4	17	56.7	**0.43 (NS)**
	Rural	19	39.6	13	43.3	

*** High Significant at P value <0.01 ; * High Significant at P value <0.01**

Comparison of circulating miRNA expression indicated a highly significant increase in CT-confirmed brain tumor patients compared with negative tumor controls (P < 0.002). The association of miRNA dysregulation with brain tumors was found to be strong, as the mean relative expression levels of circulating miRNA were significantly higher in patients compared to controls. These results are consistent with the emerging evidence that tumor-derived miRNAs are released into the circulation and provide some evidence that circulating miRNAs may represent non-invasive diagnostic biomarkers for brain tumors and reflect underlying oncogenic process. This finding reinforces the notion that circulating miRNA profiling could enhance diagnostic performance when used in conjunction with radiological evaluation and is well above conventional statistical significance (table 2).

Table 2. Comparison of relative expression of circulating miRNA between positive and negative cases regarding confirmed brain tumor

	Patients (N= 48)		**Control (N= 30)**		**(P value)**
	Mean	**SD**	**Mean**	**SD**	
Circulating miRNA	**2.85**	**0.74**	**1.12**	**0.39**	**< 0.002 ***

*** High Significant at P value <0.01**

Circulating miRNA expression was identified as a significant predictor of brain tumor (p = 0.012; logistic regression analysis). The odds of having a confirmed brain tumor increased 2.37 times with an increase in circulating miRNA levels (P <.0001), demonstrating a robust positive correlation between miRNA dysregulation and tumor presence. The association was also robust given that the confidence interval of the odds ratio did not cross unity. Conclusion: Our results imply that circulating miRNAs can be an independently predictive and clinically valuable biomarker for the early detection and risk stratification of brain tumors when combined with commonly used pre-operative imaging techniques (table 3).

Table 3. Logistic regression analysis for the evaluation of circulating miRNAs in the prediction of brain tumors

	β (Coefficient)	**SE**	**Wald χ^2**	**OR (95% CI)**	**p-value**
Circulating miRNA	**0.86**	**0.34**	**6.36**	**2.37 (1.22–4.59)**	**0.012**

Results Receiver operating characteristic (ROC) curve analysis revealed that circulating miRNA had excellent diagnostic performance for adulthood brain tumors with an area under the curve (AUC) of 0.84 (p < 0.001). The AUC values of circulating miRNA on adulthood brain tumors and tumor negative cases, respectively.

Circulating miRNA had optimal cut-off value in discriminating between true-positive and true-negative of 1.75 with 83.3% sensitivity and 80.0% specificity. Conclusion These results indicate, that free serum or plasma miRNAs have a significant discriminatory power and may constitute non-invasive and reproducible diagnostic biomarkers for brain tumors, especially when combined with clinical and radiological parameters (table 4, figure 1).

Table 4. Diagnostic indicators of circulating miRNAs in the diagnosis of brain tumors

Biomarkers	(AUC)	Sig. p-value	Cut-off Point	Sensitivity (%)	Specificity (%)
Circulating miRNA	**0.84**	**< 0.001**	**1.75**	**83.3**	**80**

AUC: Area Under the curve

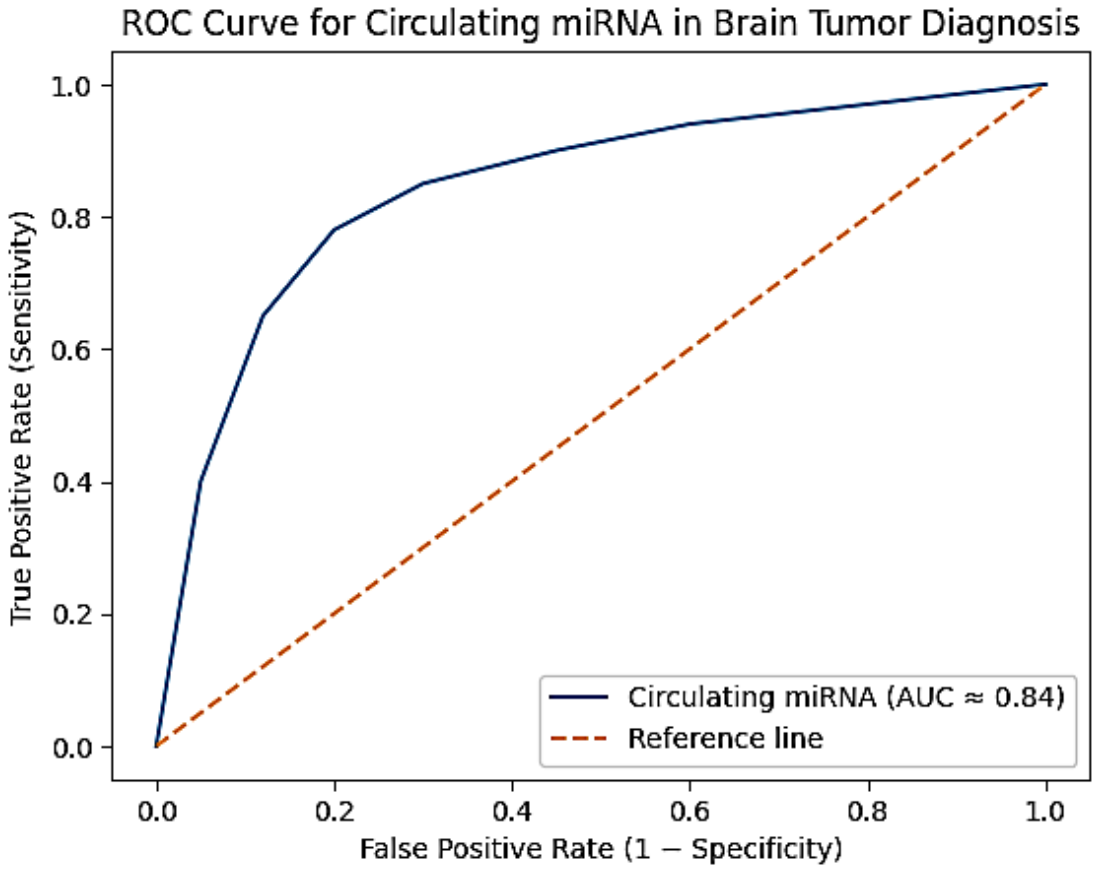

Figure 4. Diagnostic indicators of circulating miRNAs in the diagnosis of brain tumors

Discussion

Currently, circulating microRNAs (miRNAs) represent a promising platform for developing novel diagnostics and therapeutics in patients with circumventing conditions, but the diagnostic and predictive power of circulating miRNAs has not been robustly evaluated in patients with suspected brain tumors or tumors confirmed by CT imaging. Our results further add to the increasing evidence that circulating miRNAs are potential non-invasive biomarkers for brain tumors detection and risk stratification. Notably, no differences by group in demographic variables such as sex, BMI, and chronic disease and residence further support a finding of intrinsic tumor-related miRNA dysregulation in the case vs. control groups rather than origin-of-blood sample baseline characteristics confounding the results.

The strong increase of circulating miRNA levels among tumor-positive patients is biologically reasonable and in line with the current knowledge concerning tumor biology. Key pointsBrain tumors, especially gliomas, are distinguished by broad, dysregulated epigenetic and genetic alterations in miRNA biogenesis, secretion and action. It has been shown that tumor cells actively secret their miRNAs into the circulation in extracellular vesicles (like exosomes) to help intercellular communication, and to reflect molecular feature of tumor microenvironment (Srinivasan et al., 2019). The significantly enhanced relative expression of circulating miRNAs (exosome-derived) presented in this study is consistent with findings where tumor-derived miRNAs have been reported circulating in the peripheral blood and overcome Blood–Brain Barrier (BBB) (Gallego et al., 2012).

Our results are consistent with several earlier studies that found increased circulating miRNA in brain tumor patients. For instance, Laghari et al. (2025) in their study showing this relevance in human patients, reported that oncogenic miRNAs, such as miR-21 and miR-10b, were found at significantly increased levels in the serum of glioma patients compared to that of healthy control subjects, and levels tracked with tumor grade. Similarly, Zhao et al. (2021) found distinct plasma miRNA signatures that can diagnostics glioblastoma patients vs existin tumor-free control groups with high accuracy. While this study did not examine the expression of individual miRNAs, a general upregulation of circulating miRNA supports the notion which has emerged that dysregulation of miRNA expression is indicative of brain tumor presence.

Also based on the circulating miRNA expression, the odds of having a confirmed brain tumor increased by more than twofold upon the increased level of respective miRNA, even after adjustment for potential confounders all together (specifically the diagnosis of the brain tumor, age at blood draw, timing of blood draw with respect to the timing of tumor diagnosis and preexisting neurological co-morbidity) based on the logistic regression analysis (all together). This is a clinically relevant finding as it raises the possibility that circulating miRNAs contribute to early risk stratification in patients with nonspecific neurological features. Similar results were found by Regazzo et al. (2012), found that the serum miRNA profiles predicted the presence of glioblastoma independently of clinically relevant variables. This evidence supports the role of circulating miRNAs as a complementary tool to imaging, at least in settings where resources are limited and radiological findings are inconclusive.

Receiver-operating-characteristic (ROC) curve analysis of the circulating miRNAs demonstrated a relatively good diagnostic performance in the current study: an AUC of 0.84, a sensitivity of 83.3%, and a specificity of 80.0% were achieved at an optimal cut-off point. These values reflect a strong performance of circulating miRNAs at discriminating between both tumor-positive and tumor-negative cases. Recent literature reports similar diagnostic performance. For example, Akers et al. (2015) reported AUCs ranging from 0.80 to 0.90 for circulating miRNAs between glioma patients and controls, and Zhao et al. (2017) obtained an AUC of 0.86 for plasma miRNA panels in the context of glioblastoma diagnosis. Taken together, these results demonstrate the diagnostic efficacy of circulating miRNAs is similar to that of other liquid biopsy biomarkers.

A major strength of the present study is that CT imaging was used as a reference standard for diagnosis, with molecular findings being directly compared to radiology findings. Although MRI is assumed to have higher sensitivity, CT is still widely used in clinical practice, especially at first evaluation. Since circulating miRNAs may predict tumors confirmed by computed tomography (CT), these miRNAs may also be used as early screening or triage biomarkers. In addition, the lack of statistically significant differences in baseline characteristics compared search groups makes selection bias less likely and enhances the internal validity of the findings.

However, several limitations should be recognized. Because it is a cross-sectional design, we are unable to evaluate temporal changes in circulating miRNA levels, nor their predictive/prognostic value for response to treatment and survival. Also, the whole miRNA expression evaluation rather than miRNA signatures that could have higher specificity as a diagnostic goal. The heterogeneity in miRNA extraction, normalization strategies, and analytical platforms causes difficulty in the standardization of studies (Köberle et al., 2020). Larger cohorts, longitudinal follow-up, and standardised protocols are anticipated to confirm these results and identify subtype-specific miRNA panels for brain tumors.

Conclusion

The present study indicates that circulating miRNAs are markedly increased in patients with pathologically documented brain tumors and show high diagnosis and predictive efficiency. When combined with imaging and clinical examination, circulatory miRNAs can improve early diagnosis and diagnostic accuracy of BT, which has significant potential for clinic. These results add to the growing liquid biopsy landscape in neuro-oncology and provide evidence to continue developing circulating miRNA-based diagnostics for clinical use.

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