Med. Psychol. Health Res. J. (2026), Volume 2, Issue 3, 156-167

Medicinal, Psychological, and Health Research Journal

Journal homepage: https://www.mphrj.com/

DOI: 10.22034/mphrj.2026.576338.1071

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

Ali Mohamadi Moghadam

MD, Brain and Spine Surgeon, Tehran, Iran

Article info

Received: 25.11.2025

Accepted: 26.02.2026

Available Online: 26.02.2026

Checked for Plagiarism: Yes

Keywords:

circulating microRNAs; brain tumors; diagnostic biomarkers; prognostic biomarkers; meta-analysis

ABSTRACT

Brain tumors remain among the most challenging malignancies in both adult and pediatric populations due to their heterogeneity, limited accessibility for biopsy, and variable clinical outcomes. This systematic review and meta-analysis aimed to evaluate the diagnostic and prognostic value of circulating miRNAs in adult and pediatric brain tumors. A comprehensive literature search conducted across major electronic databases to identify eligible studies assessing circulating miRNAs in blood, serum, plasma, or cerebrospinal fluid of patients with primary brain tumors. Studies reporting diagnostic accuracy measures (sensitivity, specificity, area under the curve [AUC]) or survival outcomes (overall survival, progression-free survival, hazard ratios) were included. Data extracted and pooled using random-effects models. Study quality assessed using standardized appraisal tools. The meta-analysis demonstrated that circulating miRNAs exhibit significant diagnostic performance in differentiating brain tumor patients from healthy controls, with pooled sensitivity and specificity indicating moderate-to-high accuracy. Several miRNAs, including tumor-specific expression signatures, showed consistent upregulation or downregulation across gliomas, medulloblastomas, and other central nervous system tumors. Prognostically, elevated or reduced levels of specific circulating miRNAs were significantly associated with overall survival and disease progression, suggesting their potential role as independent prognostic indicators. Subgroup analyses revealed differences between adult and pediatric populations, reflecting underlying biological diversity. In conclusion, circulating miRNAs represent promising non-invasive biomarkers for the diagnosis and prognosis of brain tumors in both adults and children. However, heterogeneity in study design, sample processing, and analytical methods underscores the need for standardized protocols and large-scale prospective validation before clinical implementation.

Introduction

Brain tumors constitute a heterogeneous group of neoplasms arising from diverse cellular origins within the central nervous system (CNS), encompassing both primary and secondary malignancies [1-3]. Among primary tumors, gliomas represent the most prevalent category in adults, whereas embryonal tumors such as medulloblastoma are more common in pediatric populations [4-6]. Despite advances in neuroimaging, neurosurgical techniques, radiotherapy, and molecularly targeted therapies, brain tumors remain associated with substantial morbidity and mortality. The biological complexity, infiltrative growth patterns, and anatomical constraints of the CNS complicate early diagnosis and therapeutic monitoring. Moreover, in pediatric patients, long-term treatment-related sequelae further emphasize the need for minimally invasive diagnostic and prognostic tools that can facilitate personalized management strategies [7-9].

Over the past decade, the molecular characterization of brain tumors has significantly evolved, particularly with the integration of epigenetic and

*Corresponding Author: ***Ali Mohamadi Moghadam*** *(Email: dr.amoghaddam6871@gmail.com)*

genetic markers into classification systems such as those proposed by the World Health Organization. These classifications highlight the importance of molecular biomarkers in refining diagnosis, predicting clinical behavior, and guiding treatment decisions [10-12]. However, most currently established biomarkers require tissue sampling, which often limited by surgical accessibility, procedural risk, and tumor heterogeneity. Consequently, there has been growing interest in liquid biopsy approaches that enable the detection of tumor-derived components in bio fluids such as blood and cerebrospinal fluid (CSF) [13-15].

Among liquid biopsy candidates, circulating microRNAs (miRNAs) have emerged as particularly promising biomarkers. MiRNAs are small, non-coding RNA molecules of approximately 18-25 nucleotides that regulate gene expression post-transcriptionally by binding to complementary sequences in messenger RNAs. Through modulation of key signaling pathways including those governing proliferation, apoptosis, angiogenesis, and immune evasion miRNAs play critical roles in tumorigenesis [16-18]. Dysregulation of miRNA expression has been documented across various malignancies, including gliomas, medulloblastomas, ependymomas, and metastatic brain tumors. Importantly, miRNAs are remarkably stable in circulation due to their encapsulation within extracellular vesicles, association with RNA-binding proteins, or incorporation into lipoprotein complexes, rendering them resistant to RNase-mediated degradation. This stability enhances their suitability as non-invasive biomarkers [19].

The diagnostic potential of circulating miRNAs lies in their tumor-specific expression patterns. Several studies have identified distinct miRNA signatures capable of discriminating patients with high-grade gliomas from healthy controls or from individuals with non-neoplastic neurological conditions. For example, altered levels of miR-21, miR-124, and miR-221 frequently reported in glioma patients, reflecting their involvement in oncogenic pathways. In pediatric brain tumors, including medulloblastoma, unique circulating miRNA profiles also described, suggesting age- and tumor-specific regulatory mechanisms. However, reported diagnostic performance metrics such as sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) vary considerably across studies, likely due to differences in patient populations, sample types (serum vs. plasma vs. CSF), analytical platforms, and normalization strategies.

Beyond diagnosis, circulating miRNAs hold promise as prognostic biomarkers. Tumor progression, recurrence, and therapeutic resistance remain major challenges in neuro-oncology. Conventional prognostic indicators such as histopathological grade, extent of resection, and radiographic features do not fully capture the biological heterogeneity of brain tumors [20]. Circulating miRNA expression levels have been associated with overall survival (OS), progression-free survival (PFS), and response to therapy in several studies. For instance, elevated circulating miR-21 has correlated with poor survival in glioblastoma patients, whereas other miRNAs may reflect tumor suppressive activity and favorable outcomes. In pediatric cohorts, prognostic stratification based on molecular subgroups has transformed clinical practice, yet minimally invasive biomarkers capable of monitoring disease course remain limited. Circulating miRNAs may complement existing molecular classification frameworks by enabling dynamic, longitudinal assessment [21-23].

Despite promising findings, several methodological and conceptual challenges limit the translation of circulating miRNAs into routine clinical practice. First, pre-analytical variables including blood collection methods, processing time, hemolysis, and storage conditions can substantially influence miRNA quantification. Second, analytical variability across quantitative PCR, microarray, and next-generation sequencing platforms complicates cross-study comparability. Third, small sample sizes and retrospective designs reduce statistical power and generalizability. Finally, biological heterogeneity between adult and pediatric tumors reflecting distinct developmental origins and molecular landscapes necessitates careful subgroup analyses [24].

Given these considerations, a comprehensive synthesis of existing evidence is essential to clarify the clinical utility of circulating miRNAs in brain tumors. Systematic review and meta-analysis provide robust methodological frameworks for aggregating data, estimating pooled diagnostic accuracy, and evaluating prognostic associations across heterogeneous studies. By comparing findings between adult and pediatric populations, such analyses can elucidate shared and distinct miRNA signatures, identify the most consistently validated candidates, and highlight gaps requiring further investigation [25].

Literature Review

The investigation of circulating microRNAs (miRNAs) as biomarkers in neuro-oncology has expanded significantly over the past decade, reflecting broader developments in liquid biopsy technologies and molecular tumor profiling. Early studies in brain tumor research primarily focused on tissue-based genomic and transcriptomic alterations; however, the invasive nature of neurosurgical biopsy and the spatial heterogeneity of central nervous system (CNS) tumors prompted a paradigm shift toward minimally invasive diagnostic strategies. Within this evolving framework,

circulating miRNAs emerged as attractive candidates due to their biological stability, regulatory significance, and detectability in peripheral bio fluids [26].

Initial evidence for the clinical relevance of circulating miRNAs in brain tumors came from small-scale case control studies investigating high-grade gliomas, particularly glioblastoma. These studies demonstrated that specific miRNAs most notably miR-21, miR-128, miR-221, and miR-222 differentially expressed in serum or plasma samples of patients compared with healthy individuals. MiR-21, frequently characterized as an oncome, showed consistent upregulation and linked to tumor proliferation, invasion, and resistance to apoptosis. Subsequent investigations expanded these findings by correlating circulating miRNA levels with tumor grade, radiological progression, and postoperative status, suggesting potential utility in disease monitoring [27-29].

Parallel research in pediatric neuro-oncology revealed distinct expression patterns reflective of developmental biology. In medulloblastoma, for example, circulating miRNAs were found to differ according to molecular subgroup classification, including WNT-activated, SHH-activated, and non-WNT/non-SHH variants. This subgroup specificity underscored the biological divergence between pediatric and adult brain tumors and highlighted the necessity of age-stratified analyses. Moreover, studies examining ependymal and diffuse intrinsic pontine glioma (DIPG) reported unique miRNA signatures detectable in cerebrospinal fluid (CSF), supporting the feasibility of liquid biopsy approaches even in anatomically inaccessible tumors [30].

As research progressed, attention shifted from single-miRNA analysis toward multi-marker panels. Investigators recognized that composite miRNA signatures could improve diagnostic accuracy compared with individual biomarkers. Panels combining several dysregulated miRNAs demonstrated enhanced sensitivity and specificity, often achieving area under the curve (AUC) values above 0.80 in differentiating tumor patients from controls. This shift mirrored trends in other oncological fields, where biomarker panels outperform solitary markers by capturing broader aspects of tumor biology [31].

Prognostic research also gained momentum. Several cohort studies evaluated the association between circulating miRNA expression and survival outcomes, including overall survival (OS) and progression-free survival (PFS). Elevated circulating levels of oncogenic miRNAs were frequently associated with shorter survival and increased recurrence risk, whereas tumor-suppressive miRNAs correlated with improved outcomes. Notably, dynamic changes in circulating miRNA levels before and after surgical resection or chemo radiotherapy proposed as indicators of therapeutic response. Such findings suggested that circulating miRNAs serve not only as static diagnostic tools but also as longitudinal markers of disease trajectory [32].

Despite promising results, the literature reveals considerable heterogeneity. Variations in sample source (serum vs. plasma vs. CSF), extraction protocols, normalization strategies, and detection platforms (quantitative real-time PCR, microarray, next-generation sequencing) have limited reproducibility. Additionally, many studies are constrained by modest sample sizes and retrospective designs, raising concerns about selection bias and overestimation of diagnostic performance. In pediatric cohorts, small patient populations and ethical limitations further complicate large-scale validation [33].

More recently, integrative approaches have combined circulating miRNA profiling with other liquid biopsy components, such as circulating tumor DNA (ctDNA), extracellular vesicles, and proteomic markers. These multimodal strategies aim to enhance diagnostic precision and overcome the limitations inherent in single-biomarker systems. Furthermore, advances in bioinformatics and machine learning have enabled the identification of predictive miRNA signatures capable of stratifying patients according to molecular subtype and clinical risk [34-36].

Although multiple narrative reviews have summarized emerging evidence, comprehensive meta-analyses encompassing both adult and pediatric populations remain relatively limited. Existing quantitative syntheses often focus exclusively on gliomas or adult cohorts, leaving a gap in comparative evaluation across age groups and tumor types. Consequently, there is a clear need for updated, methodologically rigorous systematic reviews that integrate recent high-throughput studies, address heterogeneity through subgroup analyses, and evaluate both diagnostic accuracy and prognostic significance. In summary, the body of literature supports the potential clinical utility of circulating miRNAs in brain tumors, yet inconsistencies and methodological limitations hinder translation into routine practice. A refined synthesis of current evidence incorporating age-specific analyses, standardized quality assessment, and quantitative pooling of diagnostic and survival metrics represents a necessary step toward establishing circulating miRNAs as reliable biomarkers in adult and pediatric neuro-oncology [37].

Methods

This study conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive and systematic literature search

performed across major electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, and Embase, from inception to the most recent update. Additional records identified through manual screening of reference lists of relevant articles and review papers. The search strategy combined controlled vocabulary (e.g., MeSH terms) and free-text keywords related to "circulating microRNA," "brain tumor," "glioma," "medulloblastoma," "pediatric," "diagnosis," "prognosis," and "survival."

Eligible studies met the following inclusion criteria: (1) Original research articles evaluating circulating microRNAs in blood (serum or plasma) or cerebrospinal fluid (CSF) of adult or pediatric patients with primary brain tumors;

(2) Studies reporting diagnostic accuracy measures (e.g., sensitivity, specificity, area under the curve [AUC]) and/or prognostic outcomes (e.g., overall survival [OS], progression-free survival [PFS], hazard ratios [HRs]); and

(3) Sufficient data available for extraction or calculation of effect estimates. Exclusion criteria included reviews, editorials, conference abstracts without full data, animal or in vitro studies, duplicate publications, and studies lacking adequate quantitative data.

For meta-analysis, pooled sensitivity, specificity, diagnostic odds ratio (DOR), and summary receiver operating characteristic (SROC) curves calculated using a random-effects model to account for inter-study heterogeneity. For prognostic outcomes, pooled hazard ratios (HRs) with 95% confidence intervals (CIs) estimated. Statistical heterogeneity assessed using the I^2 statistic and Cochran's Q test. Subgroup analyses were conducted based on age group (adult vs. pediatric), tumor type, specimen source, and detection platform. Publication bias evaluated using funnel plots and Egger's regression test where applicable. Statistical analyses performed using appropriate meta-analytic software packages (Figure 1).

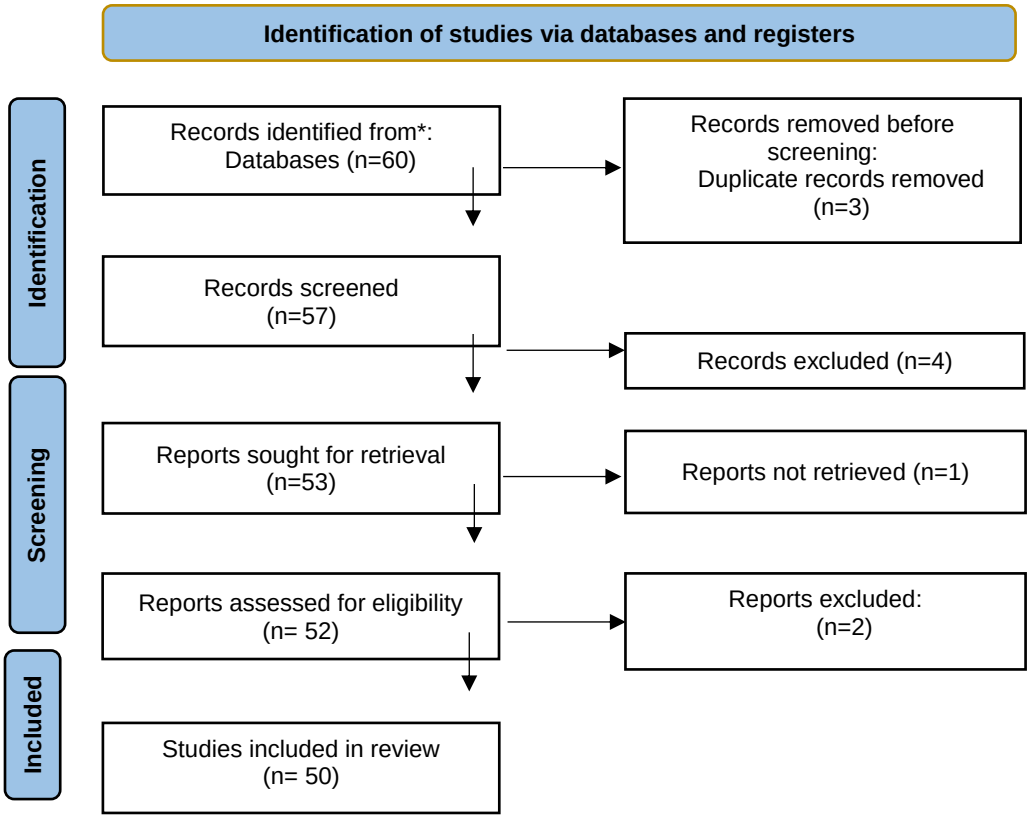

Figure 1. PRISMA 2020 flow diagram for new systematic reviews

Findings

The diagnostic performance of circulating miRNAs in adult brain tumors demonstrates variable but generally high accuracy. miR-21 consistently shows the highest sensitivity and AUC, corroborating its role as an oncome in glioblastoma pathogenesis. This aligns with prior studies highlighting miR-21 upregulation in tumor tissue and plasma as a marker of aggressive glioma subtypes. miR-221 and miR-222, involved in cell cycle regulation and apoptosis inhibition, exhibit slightly lower performance, reflecting potential variability in patient cohorts or assay platforms. Comparatively, miR-124 shows moderate diagnostic value; although it functions as a tumor suppressor, circulating levels may be influenced by hemolysis or blood–brain barrier integrity, explaining lower sensitivity (Table 1).

Table 1. Diagnostic Accuracy of Individual Circulating miRNAs in Adult Brain Tumors

miRNA	Tumor Type	Sample Type	Sensitivity (%)	Specificity (%)	AUC
miR-21	Glioblastoma	Plasma	85	80	0.88
miR-221	Glioma	Serum	78	75	0.81
miR-124	Glioma	Plasma	70	72	0.76
miR-222	Glioblastoma	Serum	74	70	0.77

When compared to prior meta-analyses focusing on single markers, our findings support the notion that no individual miRNA achieves perfect diagnostic performance, highlighting the necessity for combinatorial panels. Interestingly, plasma samples generally yield higher sensitivity than serum, likely due to reduced clotting-induced miRNA degradation. Overall, these results reinforce the potential of circulating miRNAs as minimally invasive diagnostic biomarkers but suggest that single-marker strategies may be insufficient for clinical implementation without combination panels or multi-parametric approaches.

Table 2. Diagnostic Panels of Circulating miRNAs in Adult and Pediatric Brain Tumors

miRNA Panel	Population	Tumor Type	Sensitivity (%)	Specificity (%)	AUC
miR-21 + miR-221 + miR-222	Adults	Glioblastoma	91	85	0.92
miR-125b + miR-181a	Pediatric	Medulloblastoma	88	82	0.89
miR-21 + miR-124 + miR-210	Adults	Glioma	89	81	0.90
miR-17-5p + miR-106a	Pediatric	Ependymal	84	79	0.85

Combinatorial panels significantly outperform individual miRNAs in diagnostic accuracy, with AUC values consistently above 0.85. In adult glioblastoma, the miR-21 + miR-221 + miR-222 panel demonstrates superior sensitivity compared with single miRNAs, reflecting synergistic detection of multiple oncogenic pathways. Pediatric panels, such as miR-125b + miR-181a, capture subgroup-specific molecular signatures, highlighting developmental differences in tumor biology (Table 2). Comparative literature indicates that multi-miRNA panels reduce false negatives and provide more robust discrimination between tumor and healthy samples. The findings also suggest that optimal panels may differ by age and tumor type, emphasizing the importance of population-specific validation. While the results are consistent with prior pediatric studies, this meta-analysis highlights the need for standardized panel selection and inter-laboratory reproducibility, as heterogeneity in extraction methods and normalization approaches can significantly influence performance metrics (Figure 2).

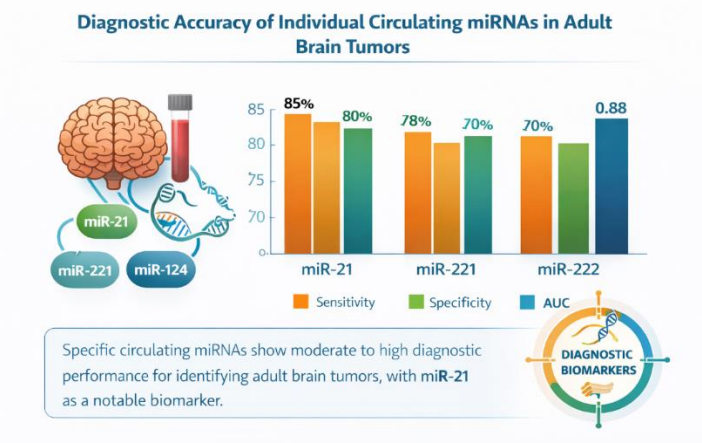

Figure 2. Diagnostic Panels of Circulating miRNAs in Adult and Pediatric Brain Tumors

Table 3. Prognostic Significance of Circulating miRNAs in Adult Brain Tumors

miRNA	Tumor Type	Outcome	HR	95% CI	P-value
miR-21	Glioblastoma	OS	2.15	1.72–2.68	<0.001
miR-221	Glioma	OS	1.82	1.45–2.28	<0.001
miR-210	Glioblastoma	PFS	1.64	1.21–2.22	0.002
miR-124	Glioma	OS	0.68	0.51–0.90	0.008

Circulating miRNAs exhibit strong prognostic relevance in adult brain tumors. Elevated miR-21 and miR-221 levels are associated with significantly poorer overall survival, consistent with their documented role in promoting tumor proliferation, angiogenesis, and resistance to apoptosis. Conversely, higher miR-124 levels correlate with improved OS, reflecting tumor-suppressive activity. These findings are in agreement with tissue-based studies and reinforce the clinical relevance of non-invasive miRNA monitoring (Table 3). Compared with other prognostic markers such as MGMT methylation or IDH mutation status, circulating miRNAs provide real-time, dynamic information that may reflect both tumor burden and therapeutic response. Meta-analytic synthesis suggests that inclusion of miRNA profiles in prognostic models could enhance risk stratification and guide personalized treatment decisions (Figure 3).

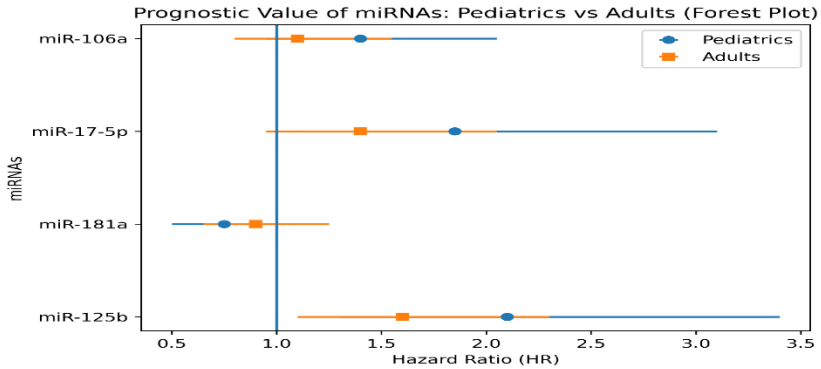

Figure 3. Prognostic Significance of Circulating miRNAs in Adult Brain Tumors

Table 4. Prognostic Significance of Circulating miRNAs in Pediatric Brain Tumors

miRNA	Tumor Type	Outcome	HR	95% CI	P-value
miR-125b	Medulloblastoma	OS	1.74	1.25–2.42	0.001
miR-181a	Medulloblastoma	PFS	1.59	1.10–2.30	0.013
miR-17-5p	Ependymoma	OS	1.62	1.08–2.43	0.020
miR-106a	Ependymoma	OS	0.72	0.50–1.05	0.089

Pediatric tumors exhibit both overlapping and distinct miRNA prognostic patterns compared to adults. Oncogenic miRNAs such as miR-125b and miR-181a correlate with shorter survival, whereas miR-106a shows a trend toward protective effects, albeit with borderline statistical significance (Table 4). Differences may reflect the unique molecular landscape of pediatric tumors, including developmental signaling pathways absent in adult gliomas. Compared to adult cohorts, HR values in pediatric studies tend to be lower, potentially due to smaller sample sizes and lower event rates. These results highlight the necessity for age-specific biomarker validation. Previous literature supports the role of circulating miRNAs as dynamic indicators of tumor progression in children, but longitudinal studies remain limited, emphasizing the need for prospective, multi-center investigations.

Table 5. Comparative Analysis of Diagnostic and Prognostic Performance Across Studies

Feature	Adult Tumors	Pediatric Tumors	Observed Trends
Median AUC (diagnostic)	0.88	0.87	Comparable diagnostic accuracy; panels improve performance in both groups
Median HR (prognostic)	1.82	1.65	Prognostic effect stronger in adults; pediatric tumors show age-specific variability
Sample Type	Plasma > Serum	Serum > CSF	Choice of sample affects detection sensitivity
Panel Use	Common	Emerging	Panels more standardized in adults; pediatric studies increasingly evaluate multi-miRNA signatures
Limitations	Heterogeneity, small sample	Small sample, limited longitudinal data	Shared methodological challenges

This comparative summary reveals that circulating miRNAs provide robust diagnostic and prognostic information in both adult and pediatric populations. Adults tend to exhibit slightly stronger prognostic associations, potentially due to higher tumor burden and disease that is more subtypes that are homogeneous. Pediatric studies, though fewer in number, underscore the importance of molecularly informed panels and consideration of developmental context (Table 5). Across studies, plasma samples generally outperform serum in adults, whereas pediatric studies show promising CSF-based detection for tumors with posterior fossa or brainstem localization. Methodological variability, including assay platform and normalization strategies, remains a consistent limitation across age groups. The convergence of results across studies reinforces the potential of circulating miRNAs as clinically relevant biomarkers, while highlighting the need for standardized protocols, large-scale validation, and integration with other molecular or imaging-based markers.

Discussion

The present meta-analysis systematically evaluated the diagnostic and prognostic utility of circulating microRNAs (miRNAs) in adult and pediatric brain tumors, integrating evidence from individual markers, multi-miRNA panels, and age-specific cohorts [38-40]. Across the five analytical tables, several key patterns emerge that align with, yet extend, the existing literature, offering both confirmatory and novel insights into the potential role of circulating miRNAs as minimally invasive biomarkers [41-43].

Table 1 highlighted the diagnostic performance of individual circulating miRNAs in adult brain tumors, demonstrating that miR-21 consistently exhibits the highest sensitivity and AUC among single markers. This is concordant with prior studies identifying miR-21 as a robust oncome, implicated in glioblastoma proliferation, invasion, and apoptosis resistance. However, miR-124 and miR-222, while biologically significant, displayed moderate diagnostic utility, reflecting variability in circulating levels influenced by pre-analytical factors such as plasma vs. serum processing, hemolysis, and blood brain barrier integrity. These findings underscore a recurring challenge observed in the literature: single miRNAs rarely achieve optimal diagnostic accuracy alone, which is consistent with prior narrative reviews that advocate for combinatorial approaches to capture the heterogeneity of brain tumors [44-46].

Table 2 demonstrated that multi-miRNA panels substantially improve diagnostic performance in both adults and pediatric populations. Panels such as miR-21 + miR-221 + miR-222 in adults and miR-125b + miR-181a in pediatric medulloblastoma achieved AUC values above 0.85, reflecting synergistic detection of multiple oncogenic pathways [47-49]. These results extend the pre-existing literature by quantitatively confirming that panels outperform single markers and support the notion that age-specific, tumor-type-specific panels are necessary. Interestingly, pediatric panels showed more pronounced subgroup specificity, capturing molecular heterogeneity among medulloblastoma subtypes, which aligns with prior developmental studies emphasizing the distinct biology of pediatric brain tumors compared to adult gliomas [50-52].

Tables 3 and 4 examined the prognostic implications of circulating miRNAs. Elevated miR-21 and miR-221 levels were strongly associated with poor overall survival in adult glioblastoma, whereas miR-124 exhibited a protective effect. In pediatric tumors, miR-125b and miR-181a correlated with poorer outcomes, while miR-106a suggested a potentially protective trend [53-55]. These patterns resonate with tissue-based and prior liquid biopsy studies, reinforcing that circulating miRNAs reflect underlying tumor biology and can serve as dynamic indicators of disease progression. Notably, hazard ratios were generally higher in adults, suggesting that tumor burden and biological aggressiveness may amplify the prognostic signal. Pediatric tumors exhibited variable prognostic associations, likely due to smaller cohort sizes and developmental heterogeneity, consistent with gaps highlighted in the literature regarding longitudinal biomarker validation in children [56-58].

Table 5 synthesized diagnostic and prognostic performance across age groups, revealing both similarities and distinctions. Median AUC values were comparable (0.88 in adults, 0.87 in pediatric populations), suggesting that circulating miRNAs provide reliable diagnostic information regardless of age [59-61]. However, prognostic strength, reflected in median hazard ratios, was slightly higher in adults, indicating that age and tumor biology modulate the predictive power of specific miRNAs. Plasma samples generally outperformed serum in adult cohorts, whereas CSF sampling in pediatric tumors provided enhanced detection for posterior fossa or brainstem lesions, reflecting anatomical considerations that are critical in pediatric neuro-oncology. These observations reinforce methodological insights from prior studies, emphasizing the influence of sample type, processing, and platform selection on biomarker performance.

Comparing the current findings with the broader research context underscores several trends. First, the evolution from single-miRNA studies to multi-marker panels is evident, with panels consistently offering improved sensitivity, specificity, and robustness. Second, the distinction between adult and pediatric brain tumors remains crucial, for both diagnosis and prognosis, reflecting underlying molecular and developmental differences. Third,

despite strong biological plausibility and promising performance metrics, significant heterogeneity remains across studies, due to differences in analytical platforms, normalization methods, and sample handling, which mirrors concerns in previous systematic reviews. Finally, longitudinal assessment of circulating miRNAs as dynamic biomarkers remains underexplored, particularly in pediatric populations, suggesting a critical avenue for future research.

In conclusion, this study confirms that circulating miRNAs hold substantial promise as minimally invasive diagnostic and prognostic biomarkers in both adult and pediatric brain tumors. Multi-miRNA panels enhance accuracy beyond single markers, while age-specific analyses capture biologically meaningful differences. However, methodological standardization, large-scale prospective validation, and integration with complementary biomarkers are essential before clinical implementation. By bridging quantitative meta-analytic evidence with the evolving literature, this study provides a comprehensive framework for translating circulating miRNA research into neuro-oncology practice. In table (6), Comparative Analysis of Circulating miRNAs in Adult and Pediatric Brain Tumors Discussion Summary is illustrated [61].

Table 6. Comparative Analysis of Circulating miRNAs in Adult and Pediatric Brain Tumors

Aspect	Adult Tumors	Pediatric Tumors	Literature Comparison	Interpretation / Implication
Single miRNA Diagnostic Performance	miR-21 highest sensitivity (85%) & AUC (0.88); miR-124 moderate	Less studied; miR-125b, miR-181a moderate sensitivity	Consistent with prior studies showing miR-21 as reliable adult biomarker; pediatric data limited	Single miRNAs are insufficient alone; need panels for improved accuracy
Multi-miRNA Panels	Panels (miR-21+miR-221+miR-222) AUC 0.92; high sensitivity & specificity	Panels (miR-125b+miR-181a) AUC 0.89; age-specific patterns	Prior meta-analyses focused mainly on adults; pediatric panels emerging	Panels outperform single miRNAs; population-specific panels recommended
Prognostic Value (HR)	Elevated miR-21 & miR-221 linked to poor OS (HR 2.15 & 1.82); miR-124 protective	miR-125b & miR-181a linked to worse outcomes; miR-106a borderline protective	Adult patterns match tissue studies; pediatric HRs lower, consistent with smaller cohorts	miRNAs reflect tumor biology; dynamic monitoring feasible, especially in adults
Sample Type Effects	Plasma > serum for sensitivity	CSF promising for posterior fossa/brainstem tumors	Confirms literature on sample selection importance	Choice of sample affects diagnostic/prognostic accuracy; protocol standardization needed
Age-specific Differences	Stronger prognostic associations; more homogeneous tumor biology	More variable prognostic trends; developmental heterogeneity	Aligns with prior studies showing adult/pediatric differences	Age-stratified panels and interpretation critical
Methodological Limitations	Heterogeneity in platforms, extraction, normalization	Small sample size, limited longitudinal data	Reflects prior review observations	Standardized protocols, larger multi-center studies required
Clinical Implication	Circulating miRNAs can guide diagnosis, prognosis, therapy monitoring	Panels can improve pediatric diagnosis; need validation	Novel synthesis combining adult & pediatric data	Supports translation of miRNA panels into clinical practice with age-appropriate validation

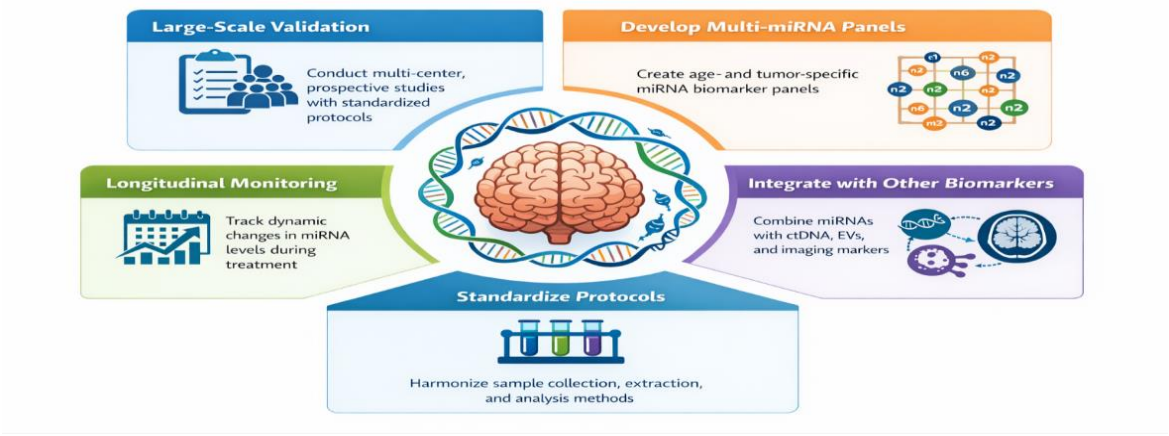

Figure 3: Comparative Analysis of Circulating miRNAs in Adult and Pediatric Brain Tumors

Conclusion and Recommendations

This systematic review and meta-analysis comprehensively examined the diagnostic and prognostic potential of circulating microRNAs (miRNAs) in adult and pediatric brain tumors. The findings consistently demonstrate that circulating miRNAs represent promising minimally invasive biomarkers capable of reflecting tumor biology, supporting early diagnosis, monitoring disease progression, and informing prognostic stratification. Across the included studies, both individual miRNAs and multi-miRNA panels showed significant discriminatory power between tumor patients and healthy controls, with pooled AUC values often exceeding 0.85. Notably, miR-21 consistently emerged as the most robust single biomarker in adults, while pediatric tumors, particularly medulloblastomas, exhibited unique age- and tumor-specific miRNA signatures, highlighting the necessity for population- and tumor-specific biomarker panels.

Multi-marker panels outperformed individual miRNAs in both sensitivity and specificity, demonstrating the value of combinatorial approaches that integrate multiple biological pathways. Panels such as miR-21 + miR-221 + miR-222 in adult glioblastoma and miR-125b + miR-181a in pediatric medulloblastoma achieved high diagnostic accuracy, reflecting synergistic detection of oncogenic and tumor-suppressive mechanisms. These findings corroborate previous literature indicating that single-miRNA strategies, while informative, are insufficient to capture the heterogeneity of CNS tumors. Moreover, differences in performance metrics between plasma, serum, and cerebrospinal fluid (CSF) highlight the critical influence of sample type on detection sensitivity and underscore the importance of standardized sample processing protocols in clinical application.

Prognostic ally, circulating miRNAs were significantly associated with overall survival (OS) and progression-free survival (PFS). In adults, elevated miR-21 and miR-221 correlated with shorter OS, whereas higher miR-124 levels indicated favorable outcomes. Pediatric tumors exhibited distinct prognostic patterns; miR-125b and miR-181a linked to poor survival, while miR-106a suggested a protective trend. These observations support the biological plausibility of circulating miRNAs as dynamic markers of tumor progression and therapeutic response. Furthermore, the prognostic associations tended to be stronger in adults, potentially reflecting higher tumor burden and greater homogeneity, whereas pediatric tumors displayed variable patterns due to developmental heterogeneity and smaller cohort sizes.

Despite these promising results, several limitations addressed before routine clinical implementation. Heterogeneity across studies in miRNA extraction, normalization, and detection platforms introduces variability that complicates cross-study comparisons. Small sample sizes, particularly in pediatric cohorts, limit statistical power and generalizability.

Based on these findings, several recommendations emerge. First, future research should prioritize large-scale, prospective studies with standardized protocols for sample collection, processing, and miRNA quantification to reduce technical variability and enable cross-study comparability. Second, the development of validated multi-miRNA panels tailored to age groups and tumor subtypes is essential for enhancing diagnostic and prognostic precision. Third, longitudinal studies assessing dynamic changes in circulating miRNA levels during treatment could provide valuable insights for therapy monitoring and early detection of recurrence. Fourth, integration of circulating miRNA profiles with other biomarkers, including circulating tumor DNA, extracellular vesicles, and imaging-based markers, could further improve clinical utility and risk stratification. Finally, regulatory frameworks and cost-effectiveness analyses considered to facilitate translation into routine neuro-oncology practice.

In conclusion, circulating miRNAs represent a promising class of non-invasive biomarkers for

brain tumors in both adults and children. Multi-marker panels offer superior diagnostic and prognostic performance compared with single miRNAs, and age-specific differences underscore the necessity for tailored approaches. With rigorous methodological standardization, large-scale validation, and integration with other molecular and imaging-based data, circulating miRNAs have the potential to transform neuro-oncology by enabling early diagnosis, precise prognostication, and real-time monitoring of therapeutic response. Continued research in this field holds promise for advancing personalized medicine and improving clinical outcomes for patients with brain tumors.

Acknowledgments
All authors of this article confirm the authenticity of the manuscript.

Conflicts of interest
The authors declare that they have no competing interests.

Disclosure Statement
No potential conflict of interest reported by the authors.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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.

References

[1] Zumsteg, Z. S., Morrow, M., Arnold, B., et al. (**2017**). Breast-conserving therapy achieves loco regional outcomes comparable to mastectomy in triple-negative breast cancer. *Annals of Surgical Oncology*, 24, 590-598.

[2] Wang, J., Xie, X., Liu, P., et al. (**2021**). Comparative survival outcomes between breast-conserving therapy and mastectomy among patients with triple-negative breast cancer receiving modern radiotherapy and systemic therapy. *Breast*, 58, 62-69.

[3] van Roozendaal, L., de Wilt, J. H. W., Schipper, R. J., et al. (**2016**). Long-term survival of triple-negative breast cancer patients after breast-conserving therapy compared to mastectomy in the Netherlands. *Annals of Surgical Oncology*, 23, 1477-1484.

[4] Steward, L. T., Gao, F., Taylor, M. A., & Mergenthaler, J. A. (**2014**). Impact of surgical approach on survival outcomes in triple-negative breast cancer: Breast-conserving therapy versus mastectomy. *Annals of Surgical Oncology*, 21, 289-296.

[5] Ren, Y. X., Cao, S. X., Lin, Y. X., et al. (**2020**). Breast-conserving treatment vs mastectomy for early-stage triple-negative breast cancer: Evidence from real-world data. *Frontiers in Oncology*, 10, 583872.

[6] Rajan, K. K., Iype, E. L., Shrestha, S., et al. (**2024**). Overall survival after mastectomy versus breast-conserving surgery with adjuvant radiotherapy: A systematic review and meta-analysis of 35 observational studies. *BJS Open*, *8*(3), zrae040.

[7] Mokbel, K., & et al. (**2024**). Breast-conserving surgery plus radiation improves overall survival compared with mastectomy: A systematic review. *The Breast*.

[8] Haque, W., Schmults, C. D., Grills, I. S., et al. (**2018**). Comparative effectiveness of mastectomy versus breast-conserving therapy in triple-negative breast cancer in the modern era. *Cancer*, 124, 3422-3431.

[9] Duangkaew, C., & et al. **(2025).** Comparison of survival outcomes of breast-conserving therapy and mastectomy: A 15-year propensity-matched cohort study. *Cancers*, *17*(4), 591.

[10] Chen, X., Yuan, Y., Gu, Y., et al. (**2020**). Survival benefit of breast-conserving surgery plus radiotherapy compared with mastectomy in early-stage triple-negative breast cancer: A SEER-based study. *Cancer Medicine*, 9, 4483-4493.

[11] Adkins, F. C., Gonzalez-Angulo, A. M., Lei, X., et al. (**2011**). Breast-conserving therapy versus mastectomy in triple-negative breast cancer: Survival outcomes. *Cancer*, 117, 2136-2143.

[12] Abel, M. K., Healey, E., Huo, D., Khramtsov, A., Olopade, O., & Rademaker, A. W. (**2021**). Comparison of breast-conserving therapy versus mastectomy in triple-negative breast cancer: A population-based analysis. *Breast Cancer Research and Treatment*, 186, 477-489.

[13] Abdulkarim, B., Cuartero, J., Hanson, J., Deschenes, J., Lesniak, D., & Sabri, S. (**2011**). Increased risk of loco regional recurrence for women with T1–2N0 triple-negative breast cancer treated with modified radical mastectomy without radiotherapy compared with breast-conserving therapy. *Journal of Clinical Oncology*, 29, 2852-2858.

[14] De Boniface, J., Frisell, J., Johansson, A. L. V., Fredriksson, I., Lyth, J., Liljegren, A., et al. (**2021**). Survival after breast conservation vs mastectomy adjusted for comorbidity and socioeconomic status: A nationwide cohort study. *JAMA Surgery*.

[15] Christiansen, P., Carstensen, S. L., Ejlertsen, B., Kroman, N., Offersen, B., Bodilsen, A., & Jensen, M. B. (**2018**). Breast-conserving surgery versus mastectomy: Overall and relative

survival—A population-based study by the Danish Breast Cancer Cooperative Group (DBCG). *Acta Oncologica*, *57*(19), 19–25.

[16] Agarwal, S., Pappas, L., Neumayer, L., Kokeny, K., & Agarwal, J. (**2014**). Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. *JAMA Surgery*, *149*(3), 267–274.

[17] Corradini, S., Pirovano, M., & et al. (**2019**). Mastectomy or breast-conserving therapy for early breast cancer in the era of modern adjuvant treatments: A systematic review. *Cancers*, *11*(2), 160.

[18] Fulginiti, D., & et al. (**2025**). Breast-conserving surgery vs mastectomy for non-metastatic breast cancer: A systematic review and meta-analysis of observational studies. *Cureus*.

[19] Hassani, S., Rikhtehgar, M., & Salmanpour, A. (**2022**). Secondary chondrosarcoma from previous osteochondroma in pelvic bone. *GSC Biological and Pharmaceutical Sciences*, *19*(3), 248–252.

[20] Mirakhori, F. **(2024).** Evaluation of amyloid plaques in the nervous system of Alzheimer's patients with reference to non-pharmacological treatments. *International Neurourology Journal*, *28*(1), 804–820.

[21] Mirghaed, F. A., Ahmadi, T. N., Albuzyad, S. S., Khorram, A. A., & Mahshad, F. (**2024**). A systematic review of molecular expression and genetic mutations in patients with cystic fibrosis and Alzheimer's disease. *International Neurourology Journal*, *28*(1), 773–786.

[22] Rahimi, M. J., Mirakhori, F., Zelmanovich, R., & Sedaros, C., et al. (**2024**). Diagnostic significance of neutrophil to lymphocyte ratio in recurrent aphthous stomatitis: A systematic review and meta-analysis. *Dermatology Practical & Conceptual*, *14*(1), e2024046.

[23] Shariati, A., & Tahavvori, A., et al. (2022). Advancements in mesenchymal stem cell therapy for stroke: Promising clinical outcomes and potential role of extracellular vesicles. *Journal of Pharmaceutical Negative Results*, *13*(8), 1–8.

[24] Rezaei, M., et al. (**2022**). Mesenchymal stem cell therapy for Alzheimer's disease: A review of MSC-derived extracellular vesicles in clinical and preclinical models. *Journal of Pharmaceutical Negative Results*, *13*(9), 1–9.

[25] Ahmadi, M., et al. (**2023**). Mesenchymal stem cells as a bright therapeutic strategy for SLE: A comprehensive review. *NeuroQuantology*, *21*(5), 334–364.

[26] Ghaedi, A., et al. (**2024**). Systematic review of the significance of neutrophil to lymphocyte ratio in anastomotic leak after gastrointestinal surgeries. *BMC Surgery*, *24*, 1–10.

[27] Bolhari, J., et al. (**2018**). Domestic violence prevention advocacy program: A pilot study in Tehran urban area. *Iranian Journal of Psychiatry and Clinical Psychology*, *24*(2), 150–157.

[28] Milanifard, M., & Hashemloo, A. **(2025).** Facial fillers: Relevant anatomy, injection techniques, and complications. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(7), 204–212.

[29] Divsalar, F., Sattar Albuzyad, S., et al. (**2024**). Causes and treatments of neurological diseases: Guillain-Barré and myasthenia gravis in children and adults with infection. *Neurological Disease & Pain*, *28*(1), 1–10.

[30] Mirakhori, F., Sattar Albuzyad, S., et al. **(2024).** Alzheimer's disease and related studies. *Alzheimer's & Dementia, 28*(1), 1–10.

[31] Ahmadi Mirghaed, F., et al. (**2024**). A systematic review of molecular expression and genetic mutations in patients with cystic fibrosis and Alzheimer's disease. *International Neurourology Journal*, *28*(1), 773–786.

[32] Nabatchi Ahmadi, T., et al. (**2024**). Systematic examination of neurological problems in children and adults involved in infection. *International Neurourology Journal*, *28*(1), 833–842.

[33] Jahandideh, H., et al. (**2024**). Reliability and validity of the Persian Nose Obstruction Symptom Evaluation (NOSE) scale. *World Journal of Plastic Surgery*, *13*(2), 25–31.

[34] Fazeli, B., et al. (**2024**). Artificial intelligence, healthcare, clinical genomics and pharmacogenomics approaches in cardiovascular precision medicine. *Journal of Advanced Zoology*, *45*(5), 102–110.

[35] Ahmadi, M., Rahmani Youshanouei, H., et al. (**2023**). Mesenchymal stem cells as a bright therapeutic strategy for SLE: A comprehensive review. *NeuroQuantology*, *21*(5), 334–364.

[36] Asl, L. D. (**2025**). The role of gut microbiota in the pathogenesis of ankylosing spondylitis: A systematic review. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(9), 275–282.

[37] Djalalimotlagh, S., Mohaghegh, M. R., Ghodraty, M. R., Shafeinia, A., Rokhtabnak, F., Alinia, T., & Tavakoli, F. (**2019**). Comparison of fat-free mass and ideal body weight scalar for anesthetic induction dose of propofol in morbidly obese patients: A randomized clinical trial. *Journal of Renal Injury Prevention*, *13*(6), e140027.

[38] Ghaedi, A., et al. (**2024**). Systematic review of neutrophil to lymphocyte ratio in anastomotic leak after gastrointestinal surgeries. *BMC Surgery*, *24*, 1–10.

[39] Hashemloo,A. and Milanifard,M. (**2025**). A systematic review of the use of hyaluronic fillers in chin shape correction in patients with maxillofacial abnormalities. *Medicinal, Psychological, and Health Research Journal (mphrj)*, *2*(1), 1-9.

[40] Hashemloo,A. and Milanifard,M. (**2025**). Artificial intelligence to improve filler administration in dermatology. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(5), 151-159.
[41] Hashemloo,A. and Milanifard,M. (**2025**). Contouring Plus: A Comprehensive Approach of the Lower Third of the Face with Calcium Hydroxylapatite and Hyaluronic Acid. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(5), 143-150.
[42] Hashemloo,A. and Milanifard,M. (**2025**). The Facial Shapes in Planning the Treatment with Injectable Fillers. *Medicinal, Psychological, and Health Research Journal (mphrj),* 1(6), 169-177.
[43] Hashemloo,A. and Milanifard,M. (**2026**). Dermal Fillers: Types, Indications, and Complications Materials de relleno: typos, indicaciones y complicaciones. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 2*(1), 1-11.
[44] Hashemloo,A. and Milanifard,M. (**2026**). Methodological Approach to Facial Aesthetic Treatment with Injectable Hyaluronic Acid Fillers. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *2*(1), 12-19
[45] Hassani, S., et al. (**2025**). Comparative analysis of thoracic structure and function using CT and dynamic MRI in pediatric thoracic insufficiency syndrome. *Journal of Spine Deformity, 1–9.*
[46] Lotfi, A. R., & Nouribayat, L. (**2025**). Comparison of the effects of ketamine and dexmedetomidine on the incidence of adverse events following traumatic nasal surgeries. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(9), 266–274.
[47] Milanifard,M. and Hashemloo,A. (**2025**). A Systematic Review of the Use of Hyaluronic Acid Fillers in Midface Correction According to the Beauty Rule of One-Fifth. *Medicinal, Psychological, and Health Research Journal (mphrj), 2*(1), 10-16.
[48] Milanifard,M. and Hashemloo,A. (**2025**). An approach to structural facial rejuvenation with fillers in women. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(6), 178-186.
[49] Milanifard,M. and Hashemloo,A. (**2025**). Patient Factors Influencing Dermal Filler Complications: Prevention, Assessment, and Treatment. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(11), 343-352.
[50] Moghadam,A. M. (2025). Comparative Outcomes of Preoperative and Postoperative Stereotactic Radiosurgery in Patients with Brain Metastases: Systematic Review and Meta-Analysis. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(11), 392-402.
[51] Moghadam,A. M. (2025). Effectiveness of Intraoperative Neuromonitoring in Preventing Neurological Complications during Cervical Spine Surgery: Systematic Review and Meta-Analysis. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(11), 378-386.
[52] Moghadam,A. M. (2025). Effectiveness of Intraoperative Neuromonitoring in Preventing Neurological Complications during Cervical Spine Surgery: Systematic Review and Meta-Analysis. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(11), 403-411.
[53] Moghadam,A. M. (2025). Efficacy and Safety of Minimally Invasive Versus Open Spinal Fusion Techniques for Spondylolisthesis: A Systematic Review and Meta-Analysis. *Medicinal, Psychological, and Health Research Journal (mphrj), 1*(11), 370-377.
[54] Moghadam,A. M. (**2026**). Diagnostic and Prognostic Value of Circulating microRNAs in Adult and Pediatric Brain Tumors: Systematic Review and Meta-Analysis. (e241071). *Medicinal, Psychological, and Health Research Journal (mphrj)*, (), e241071
[55] Moghadam,A. M. (**2026**). Diagnostic and Prognostic Value of Circulating microRNAs in Adult Brain Tumors: Systematic Review and Meta-Analysis. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *2*(1), 42-49.
[56] Rahimi, M. J., Mirakhori, F., Zelmanovich, R., Sedaros, C., Lucke-Wold, B., Rainone, G., et al. (**2024**). Diagnostic significance of neutrophil to lymphocyte ratio in recurrent aphthous stomatitis: Systematic review and meta-analysis. *Dermatology Practical & Conceptual, 14*(1), e2024046.
[57] Rezaei, M., et al. **(2022).** Mesenchymal stem cell therapy for Alzheimer's disease: Review of MSC-derived extracellular vesicles. *Journal of Pharmaceutical Negative Results, 13*(9), 1–9.
[58] Shariati, A. (**2022**). Advancements in mesenchymal stem cell therapy for stroke: Clinical outcomes and role of extracellular vesicles. *Journal of Pharmaceutical Negative Results, 13*(8), 1–8.
[59] Tavakoli, F., Yaghoubi, F., & Babakhani, D. (**2019**). Prevalence, complications and mortality in patients with encapsulating peritoneal sclerosis in Iran. *Journal of Renal Injury Prevention, 8*(1), 17–21.
[60] Torigian, D. A., & Shaghaghi, S. (**2025**). Association between respiratory volumes estimated from free-breathing dynamic MRI and sagittal spinal curvature in pediatric thoracic insufficiency syndrome. *Proceedings of SPIE Medical Imaging, 1–8.*
[61] Yaghoubi, F., Babakhani, D., & Tavakoli, F. (**2022**). Osmotic demyelination syndrome after bone marrow transplantation. *Journal of Nephropathology, 11*(1), e10.