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Expression Dynamics and Diagnostic Potential of miR-124-3p, miR-485-5p, MAPKAPK5-AS1, and PKMYT1AR in Glioblastoma

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Abstract

Introduction: Glioblastoma (GBM) Glioblastoma, the most common primary malignant brain tumor in adults, exhibits aggressive behavior and resistance to conventional therapies, resulting in poor prognosis with median survival of approximately 15 months. Early diagnosis and identification of novel therapeutic targets are critical for improving patient outcomes. This study investigates the expression profiles of miR-124-3p, miR-485-5p, lncRNA MAPKAPK5-AS1, and lncRNA PKMYT1AR, and their interrelationships in GBM tissues.

Method: We conducted a case-control study involving 29 GBM patients and 16 adjacent normal brain tissue samples. Quantitative real-time PCR was employed to analyze the expression levels of the target genes. Statistical analyses included Mann-Whitney U tests for group comparisons and Spearman's correlation for association assessments.

Results:

miR-124-3p and miR-485-5p were significantly downregulated in GBM tissues compared to normal controls ($p = 0.045$ and $p = 0.018$, respectively), while lncRNAs MAPKAPK5-AS1 and PKMYT1AR showed no significant differential expression. Notably, positive correlations were observed between the lncRNAs and each miRNA, as well as between the two miRNAs themselves. A four-marker panel comprising all investigated transcripts demonstrated moderate diagnostic potential (AUC = 0.76) for GBM detection.

Conclusion: The downregulation of tumor-suppressive miR-124-3p and miR-485-5p, coupled with their positive correlations with oncogenic lncRNAs, suggests a reorganized non-coding RNA regulatory network in GBM. These findings highlight potential biomarkers for early diagnosis and therapeutic intervention in this aggressive malignancy.

Introduction

Glioblastoma (GBM), categorized as grade IV astrocytoma, is the most primary malignant brain tumor in adults, and its aggressive and lethal. The incidence of GBM is higher in men than in females, coupled with a worse outcome(1). clinical features of glioblastoma are headache, weakness, seizure, vertigo, visual changes, memory loss and confusion(2, 3). It is known as an aggressive tumor that is resistant to therapy. GBM has a poor prognosis despite aggressive treatment and has a low overall survival of about 15 months(4). therefore, the early diagnosis of glioblastoma can be helpful. Glioblastoma is characterized by the presence of invasive malignant cells that disseminate throughout neural tissue, complicating the possibility of complete surgical resection and contributing to postoperative recurrences, which represent the primary cause of mortality associated with this condition(5).

Recent advances in molecular oncology have revealed the critical role of non-coding RNAs (ncRNAs) in cancer development and progression. Long non-coding RNAs (lncRNAs), exceeding 200 nucleotides in length, and microRNAs (miRNAs), small non-coding RNAs of approximately 22 nucleotides, regulate

gene expression through diverse mechanisms including transcriptional modulation, mRNA degradation, and translational inhibition (6). Emerging evidence suggests that dysregulation of specific miRNA-lncRNA networks contributes to gliomagenesis and tumor progression(7). Among the miRNAs implicated in GBM pathogenesis, miR-124-3p and miR-485-5p have garnered particular attention. miR-124-3p functions as a tumor suppressor by targeting oncogenic pathways including NRP1, P62, and SDCBP (8, 9), while miR-485-5p inhibits tumor proliferation and angiogenesis through modulation of Wnt7B and PI3K/AKT/mTOR signaling. Conversely, lncRNAs such as MAPKAPK5-AS1 and PKMYT1AR have been reported to promote oncogenic activities in various cancers, though their roles in GBM remain incompletely understood(10–12).

The present study was designed to investigate the expression patterns of miR-124-3p, miR-485-5p, MAPKAPK5-AS1, and PKMYT1AR in GBM tissues and adjacent normal brain, and to elucidate the regulatory relationships among these molecules. By characterizing this molecular profile, we aim to identify potential diagnostic biomarkers and therapeutic targets that could improve GBM management and patient outcomes.

Materials and methods

Study Design and Ethical Considerations

This case-control study was conducted in accordance with the Declaration of Helsinki and The study protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences under the ethics approval code: IR.TUMS.MEDICINE.REC.1402.249. Written informed consent was obtained from all participants prior to enrollment in the study.

Formalin-fixed, paraffin-embedded (FFPE) tissue samples were obtained from 29 patients with histologically confirmed GBM who underwent surgical resection at Shohada-Tajrish between 2022–2024. Adjacent normal brain tissue samples were collected from the same patients as controls. Inclusion criteria included: age ≥ 18 years, histopathological confirmed GBM, and availability of complete clinical data. Exclusion criteria comprised: prior chemotherapy or radiotherapy, incomplete clinical records, and poor RNA quality.

RNA extraction and cDNA synthesis

Total RNA was extracted from 50 mg tissue samples using the RNA extraction kit (Anacell - Iran) according to the manufacturer's protocol. RNA concentration and purity were assessed using a Nanodrop spectrophotometer (Thermo Fisher Scientific), with 260/280 nm ratios between 1.8–2.1 considered acceptable. RNA integrity was evaluated by agarose gel electrophoresis.

Complementary DNA (cDNA) was synthesized utilizing a cDNA synthesis kit provided by Anacell in Iran. This process was based on the reverse transcription of RNA using a modified MMLV enzyme. Oligo dT

and random hexamer primers were employed to synthesize cDNA from gene lncRNA, and stem-loop RT-specific primers were used to synthesize cDNA from gene miRNA. The cDNAs were stored at -20°C.

Real-time quantitative PCR

The levels of expression for the target genes were evaluated utilizing real-time PCR, employing relative quantification methods. Quantitative real-time PCR was performed using 2x Master Mix Green (Ampliqon). Melting curve analysis was performed to verify product specificity. miR-124-3p and miR-485-5p were normalized to U6 small nuclear RNA, while MAPKAPK5-AS1 and PKMYT1AR were normalized to 18S rRNA. All reactions were performed in triplicate, and relative expression was calculated using the 2^-ΔΔCt method.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR), whereas categorical variables are summarized as counts and percentages. Because expression values were not normally distributed, differences in non-coding RNA expression between glioblastoma tissues and adjacent normal brain samples were assessed using the Mann–Whitney U test. When applicable, paired Wilcoxon signed-rank tests could be used in matched tumor–normal pairs as a sensitivity analysis.

Associations between non-coding RNA expression and clinicopathological features in glioblastoma patients (age, sex, tumor location and side, maximal tumor diameter, KPS, and extent of resection) were evaluated using Spearman rank correlation for continuous variables and the Mann–Whitney U or Kruskal–Wallis tests for two- and multi-category factors, respectively. A Spearman's rho analysis of pairwise correlation was performed on PKMYT1AR, MAPKAPK5-AS1, miR-124-3p, and miR-485-5p in both tumor and normal tissue samples. The purpose of this analysis was to investigate the possible interaction patterns between lncRNAs and miRNAs.

To investigate the combined diagnostic performance of the four non-coding RNAs, multivariable logistic regression models with tissue type (glioblastoma versus normal brain) as the dependent variable and the four transcripts as predictors were fitted. The evaluation of model discrimination was performed by utilizing receiver operating characteristic (ROC) curves and calculating the area under the ROC curve (AUC). All statistical analyses were carried out using GraphPad Prism and R software (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p-value of less than 0.05 was deemed statistically significant. Due to the exploratory nature of the study and the limited sample size, p-values were interpreted descriptively and were not adjusted for multiple testing.

Results

Patient and sample characteristics

The final study comprised 29 glioblastoma tissues and 16 adjacent normal brain samples with complete expression data for PKMYT1AR, MAPKAPK5-AS1, miR-124-3p, and miR-485-5p. Clinical characteristics of the GBM patients, including age distribution, sex ratio, tumor location and side, maximal tumor diameter, KPS, and extent of resection, are summarized in Table 1. As expected for GBM, most tumors were located in the supratentorial compartment, with a slight predominance of right-sided lesions and male patients.

Table1. *Clinical and demographic characteristics of glioblastoma patients included in the expression analysis.Clinical characteristics of the 29 glioblastoma patients enrolled in the study, including age, sex distribution, Karnofsky Performance Status (KPS), tumor side, and extent of resection (gross total resection, GTR, versus subtotal resection, STR).*

Characteristic	Glioblastoma (n = 29)
Age, years – mean ± SD	51.7 ± 12.4
Age, years – median (IQR)	53 (42–60)
Sex, male/female – n (%)	17 (58.6%) / 12 (41.4%)
KPS – median (IQR)	100 (90–100)
Tumor side, right/left – n (%)	19 (65.5%) / 10 (34.5%)
Extent of resection, GTR/STR – n (%)	23 (79.3%) / 6 (20.7%)

Differential expression of PKMYT1AR, MAPKAPK5-AS1, miR-124-3p and miR-485-5p

Relative expression levels of the two lncRNAs (PKMYT1AR and MAPKAPK5-AS1) and the two miRNAs (miR-124-3p and miR-485-5p) were quantified in GBM and adjacent normal brain tissues. Non-parametric analyses revealed no significant differences in the expression levels of PKMYT1AR or MAPKAPK5-AS1 between tumor and normal tissues (Table 2, Fig. 1). In glioblastoma, PKMYT1AR showed a median fold change of roughly 1.1, compared to 0.6 in normal brain tissue, while MAPKAPK5-AS1 displayed similar median expression levels in both tumor and normal samples.

In contrast, both investigated miRNAs were significantly down-regulated in GBM. The median fold change of miR-124-3p was significantly reduced in tumor tissues in comparison to neighboring normal brain tissue, and miR-485-5p showed a similar pattern, with significantly reduced expression in GBM (Table 2). Violin and boxplots of log2-transformed fold changes illustrate the apparent down-regulation

of miR-124-3p and miR-485-5p in GBM, alongside the broader and overlapping distributions observed for the two lncRNAs (Fig. 1).

Table 2. Comparison of PKMYT1AR, MAPKAPK5-AS1, miR-124-3p and miR-485-5p expression between glioblastoma and adjacent normal brain.

Gene	Normal_median_IQR	GBM_median_IQR	p_value
PKMYT1AR	0.58 (0.46-1.26)	1.14 (0.26-7.75)	0.803
MAPKAPK5-AS1	0.75 (0.39 -1.61)	0.68 (0.37-2.94)	0.878
miR-124-3p	3.38 (0.15-8.83)	0.36 (0.12-0.67)	0.045
miR-485-5p	0.87 (0.59-2.08)	0.44 (0.18-0.96)	0.018

Median (interquartile range) expression values and p-values from Mann–Whitney U tests are shown for glioblastoma tissues and adjacent normal brain samples. Statistically significant p-values ($p < 0.05$) indicate down-regulation of miR-124-3p and miR-485-5p in glioblastoma.

Correlation patterns among lncRNAs and miRNAs

We find the pairwise correlations between the four non-coding RNAs. In tissues affected by glioblastoma, a notable positive correlation was found between PKMYT1AR and MAPKAPK5-AS1, with Spearman's rho exceeding 0.9 and a significance level of $p < 0.001$ (Table S2 and Fig. 2). Both lncRNAs also showed moderate positive correlations with miR-124-3p and miR-485-5p, and miR-124-3p and miR-485-5p were positively correlated with each other, indicating that lower expression of one miRNA tends to co-occur with lower expression of the other in GBM.

In the adjacent normal brain, PKMYT1AR and MAPKAPK5-AS1 remained very strongly correlated, suggesting shared regulation of these lncRNAs in non-neoplastic tissue. However, their relationships with miR-124-3p tended to be negative, although these trends did not reach conventional statistical significance. No reliable correlation pattern was detected between the lncRNA and miR-485-5p in healthy tissues. Altogether, these findings indicate that the interaction landscape between lncRNAs and miRNAs varies between normal brain tissue and glioblastoma, highlighting a tendency for coordinated positive co-expression of all four transcripts in tumor tissue.

Associations between non-coding RNA expression and clinicopathological features

Clinicopathological correlations were evaluated in the 29 glioblastoma patients (Supplementary Table S3, Fig. 3). Spearman rank analyses revealed no significant associations between the expression of any of the four non-coding RNAs and patient age, maximal tumor diameter, or KPS. Similarly, tumor location and extent of resection were not significantly related to the expression levels of PKMYT1AR, MAPKAPK5-AS1, miR-124-3p, or miR-485-5p.

In sex-stratified analyses, PKMYT1AR and miR-124-3p expression were higher in males, and miR-485-5p expression was moderately higher in right-sided tumors compared with left-sided tumors. Given the limited sample size and the number of comparisons performed, these associations should be interpreted cautiously and considered exploratory.

Exploratory diagnostic performance of the four-marker panel

The potential diagnostic utility of the four non-coding RNAs was explored using ROC analysis. In univariable analyses, PKMYT1AR and MAPKAPK5-AS1 alone displayed limited discrimination between glioblastoma and normal brain, whereas lower expression of miR-124-3p and miR-485-5p was associated with the presence of GBM, with AUC values in the modest range.A logistic regression model incorporating all four transcripts as predictors reached an AUC of around 0.76 in this group, demonstrating moderate discrimination (Fig. 4). Given that these estimates come from a relatively small sample size without external validation, the diagnostic capabilities of this four-marker panel should be considered preliminary and a basis for further hypothesis generation.

Discussion

GBM is the most aggressive and deadly tumor in the CNS, and despite extensive studies on the causes of the disease, the leading cause of the disease has not been identified. Given the progress of this disease worldwide and the decrease in patient survival after diagnosis, extensive studies have been conducted on the causes of the disease, diagnosis, and treatment(13). In recent years, the study of non-coding RNAs has led to new insights into the molecular mechanisms involved in GBM. Oncogenic lncRNAs can promote glioblastoma growth and progression by inhibiting some tumor suppressor miRNAs(14). This study aimed to investigate the expression levels of miR-124-3p, miR-485-5p, the lncRNA MAPKAPK5-AS1, and the lncRNA PKMYT1AR and the relationship between these genes. The present study showed a significant decrease in the expression of miR-124-3P and miR-485-5p in patients with GBM compared to normal tissue. Our findings regarding the downregulation of miR-124-3p and miR-485-5p in glioblastoma align with several previous studies. miR-124-3p has been consistently reported as a tumor suppressor in GBM, with multiple studies demonstrating its role in inhibiting tumor proliferation, invasion, and migration through targeting of NRP1, P62, SDCBP, and Fra-2 pathways ((8, 9, 15–18). Studies show that miR-124-3p is a tumor suppressor in GBM and inhibits tumor proliferation, invasion, migration, and progression by inhibiting NRP1, P62, SDCBP, and Fra-2. Consequently, decreased expression of miR-124-3p will lead to tumor progression(16–19).

Similarly, miR-485-5p has been implicated as a tumor suppressor that inhibits cell proliferation, invasion, metastasis, and angiogenesis by modulating Wnt7B, TPD52L2, PAX3, E2F1, and PI3K/AKT/mTOR signaling (20–23). miR-485-5p has also been implicated as a tumor suppressor in GBM. It inhibits cell proliferation, invasion, metastasis, and angiogenesis by inhibiting Wnt7B, TPD52L2, PAX3, E2F1, and PI3K/AKT/mTOR signaling. As a result, reduced expression of miR-485 5p contributes to tumor progression(20–24).

However, our observation that lncRNAs PKMYT1AR and MAPKAPK5-AS1 did not show significant differential expression between tumor and normal tissues contrasts with some previous reports suggesting upregulation of these lncRNAs in various cancers. This discrepancy may reflect tissue-specific expression patterns or differences in sample characteristics between studies. Notably, while previous research has documented negative correlations between these lncRNAs and miRNAs in other cancer types our study revealed positive correlations in GBM tissues, suggesting a reorganized non-coding RNA network in this aggressive brain tumor, these lncRNAs are known as oncogenes in multiple cancers, but their role in GBM has not been investigated (10, 25–27).

The positive correlations observed between the oncogenic lncRNAs (PKMYT1AR and MAPKAPK5-AS1) and tumor-suppressive miRNAs (miR-124-3p and miR-485-5p) in GBM tissues suggest a complex regulatory network that deviates from the conventional competing endogenous RNA (ceRNA) mechanism. In typical ceRNA networks, tumor-suppressive miRNAs are downregulated while oncogenic lncRNAs are upregulated, with expected negative correlations between them. However, our findings indicate that in GBM, these molecules may be co-regulated or participate in alternative regulatory pathways. One possible explanation is that both miRNA and lncRNA expression could be influenced by common upstream regulators or transcription factors that are altered in glioblastoma. Alternatively, the tumor microenvironment in GBM may impose selective pressures that coordinate the expression of these non-coding RNAs. The strong positive correlation between PKMYT1AR and MAPKAPK5-AS1 suggests potential co-regulation or shared regulatory elements, which warrants further investigation into their genomic organization and transcriptional control mechanisms.

The diagnostic potential of the identified molecular profile holds significant clinical implications. The four-marker panel demonstrated moderate discriminatory ability (AUC = 0.76) for distinguishing GBM from normal brain tissue, suggesting potential utility as a minimally invasive diagnostic tool. However, the limited sample size and lack of external validation necessitate caution in interpreting these findings. The observed sex-specific expression patterns, particularly the higher expression of PKMYT1AR and miR-124-3p in males, and lateralization of miR-485-5p expression, warrant investigation in larger cohorts to determine their potential as prognostic biomarkers. The positive correlations between these molecular markers and clinical features, though exploratory, suggest that they may reflect biological differences in tumor behavior across patient subgroups. Future studies should evaluate whether these molecular profiles correlate with treatment response, progression-free survival, or overall survival, which would strengthen their clinical utility. Additionally, the identification of these markers opens avenues for

therapeutic intervention, as miRNA mimics or lncRNA inhibitors could potentially restore normal regulatory networks disrupted in GBM.

Conclusion

Our findings demonstrate a significant downregulation of miR-124-3p and miR-485-5p in GBM, consistent with their established roles in suppressing proliferation, invasion, and angiogenesis. In contrast, MAPKAPK5-AS1 and PKMYT1AR did not show significant differential expression, suggesting that their oncogenic functions may be context-dependent or regulated through mechanisms not reflected solely by expression levels.

Importantly, the strong positive correlations observed among all four transcripts in GBM—indicate a reorganization of the non-coding RNA regulatory landscape in tumor tissue. This coordinated expression pattern deviates from classical ceRNA expectations and suggests shared upstream regulation or tumor-specific transcriptional programs that warrant further mechanistic investigation.

The exploratory diagnostic analysis revealed that a combined four-marker panel provides moderate discriminatory power (AUC = 0.76), highlighting the potential of integrating miRNA and lncRNA signatures into early diagnostic frameworks for GBM. Although preliminary, these results underscore the promise of non-coding RNA profiling as a complementary tool for improving diagnostic accuracy.

Overall, this study contributes to the growing understanding of ncRNA dysregulation in glioblastoma and identifies a novel miRNA–lncRNA expression profile with potential diagnostic relevance. Future studies with larger cohorts, functional validation, and mechanistic exploration are needed to clarify the biological interactions among these transcripts and to assess their utility as biomarkers or therapeutic targets in GBM.

Declarations

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Author Contribution

A.B led the clinical conceptualization of the study from a neurosurgical perspective, coordinated patient recruitment and tissue sampling, designed the overall research workflow, performed the primary qRT-PCR experiments, and drafted the initial manuscript.S.H. contributed to RNA extraction, sample processing, and optimization of laboratory procedures and assisted in maintaining experimental consistency across all runs.S. A. H. J. supported molecular data validation, coordinated patient recruitment, and assisted in preparing figures and visual summaries and analysis.D.R.F. played a role in statistical analysis, including correlation assessments and construction. He also contributed

substantially to refining the analytical strategy and interpreting the diagnostic performance of the biomarkers.A. K contributed extensively to laboratory experiments, including qPCR optimization, technical troubleshooting, and quality control of expression data. He also assisted in methodological refinement and manuscript editing.A. Z and Gh. P provided overarching supervision, guided the scientific and clinical direction of the project, contributed substantially to the study design and interpretation of findings, and critically revised the manuscript for important intellectual content. Their strategic leadership and continuous oversight were essential to the successful completion of the research.All authors reviewed and approved the final version of the manuscript.

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Figures

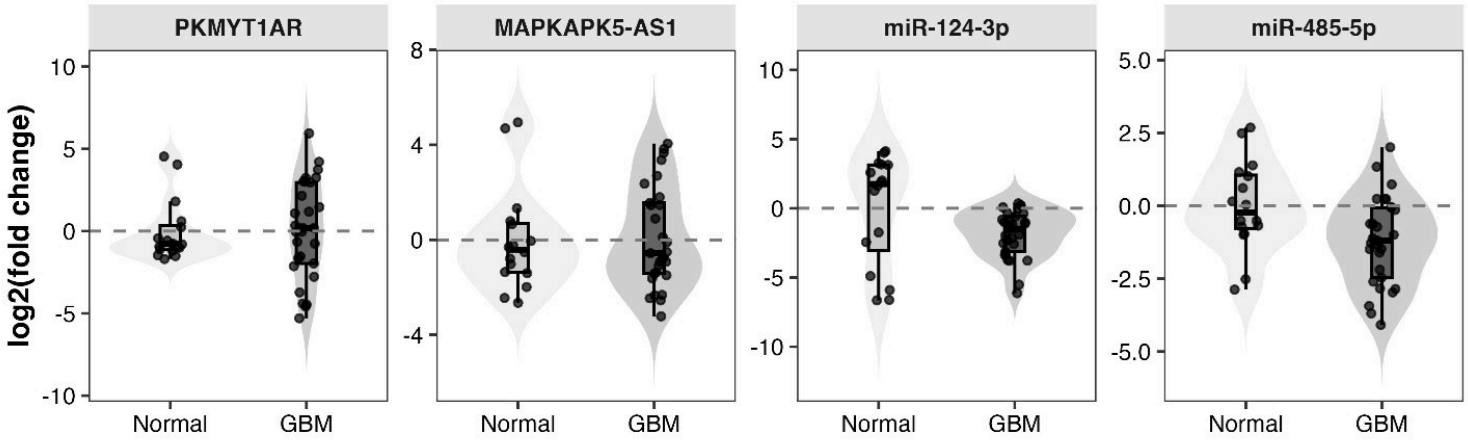


Figure 1

Relative expression of PKMYT1AR, MAPKAPK5-AS1, miR-124-3p, and miR-485-5p in glioblastoma and normal brain.Violin plots with overlaid boxplots and individual data points show log2-transformed relative expression values of PKMYT1AR, MAPKAPK5-AS1, miR-124-3p, and miR-485-5p in glioblastoma tissues (GBM, n = 29) and adjacent normal brain samples (Normal, n = 16). Central lines represent medians, and boxes indicate interquartile ranges. P-values were calculated using the Mann–Whitney U test. miR-124-3p and miR-485-5p are significantly down-regulated in GBM compared with normal brain, whereas PKMYT1AR and MAPKAPK5-AS1 show no statistically significant difference between groups.

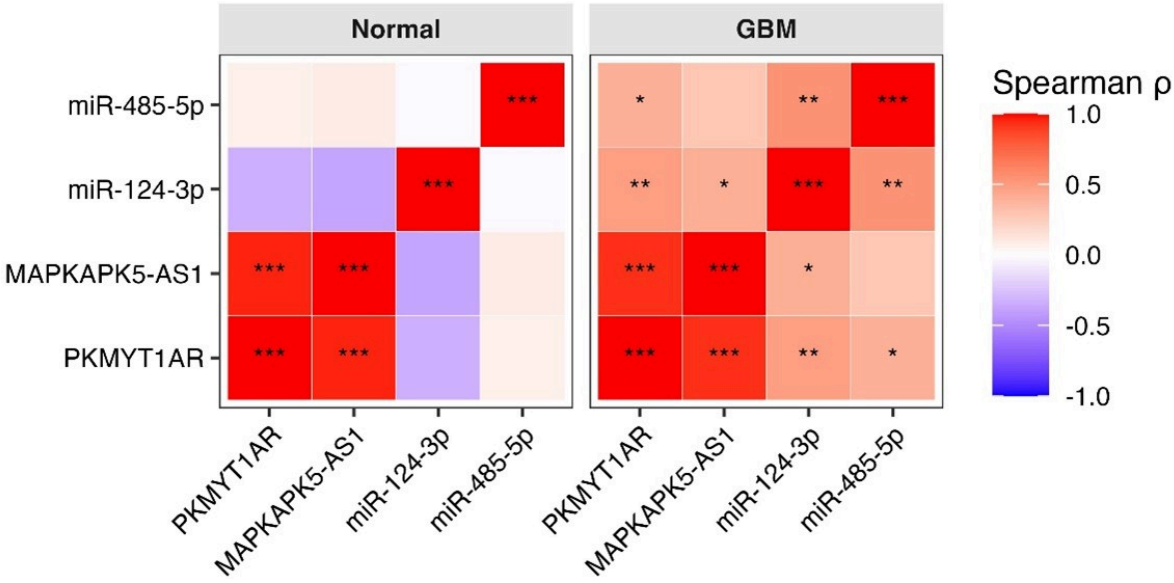


Figure 2

Correlation patterns among non-coding RNAs in glioblastoma and normal brain.

*(A) Spearman correlation heatmap for PKMYT1AR, MAPKAPK5-AS1, miR-124-3p and miR-485-5p in glioblastoma tissues (n = 29). (B) Corresponding heatmap in adjacent normal brain samples (n = 16). Colors represent Spearman's correlation coefficient (rho), ranging from negative (blue) to positive (red). Asterisks indicate statistically significant correlations (*p < 0.05, **p < 0.01, ***p < 0.001). In both tissue types, PKMYT1AR and MAPKAPK5-AS1 are strongly positively correlated, whereas the relationships between lncRNAs and miR-124-3p differ between normal brain (trend towards inverse correlations) and glioblastoma (positive correlations), suggesting reorganization of the non-coding RNA network in tumor tissue.*

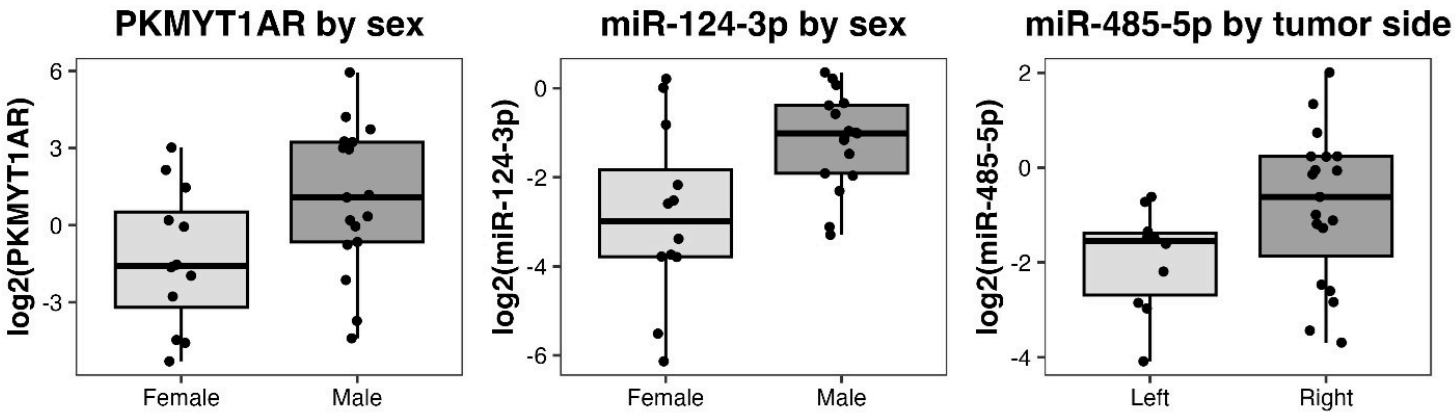


Figure 3

Exploratory associations between non-coding RNA expression and clinicopathological features in glioblastoma.

(A) Boxplots comparing PKMYT1AR expression between male and female glioblastoma patients. (B) Boxplots comparing miR-124-3p expression between male and female patients. (C) Boxplots showing miR-485-5p expression in right-sided versus left-sided tumors. Boxes represent interquartile ranges, whiskers indicate ranges, and central lines denote medians. P-values were calculated using the Mann–Whitney U test. PKMYT1AR and miR-124-3p expression were higher in males than in females, while miR-485-5p expression was moderately higher in right-sided tumors. These associations are exploratory and require confirmation in larger cohorts.

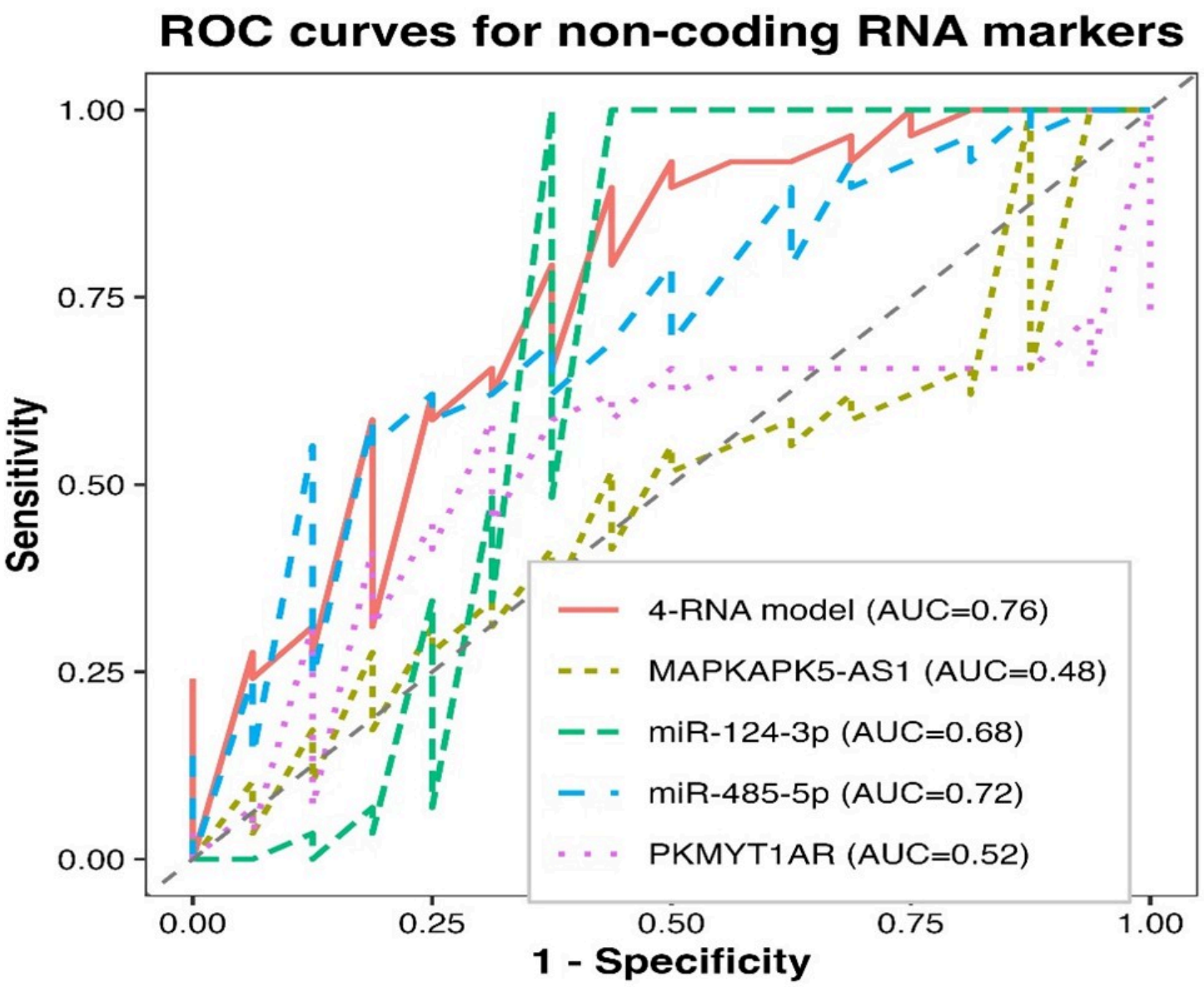


Figure 4

Diagnostic performance of individual non-coding RNAs and a four-marker panel for distinguishing glioblastoma from normal brain.Receiver operating characteristic (ROC) curves illustrating the ability of individual non-coding RNAs and a combined four-marker panel to discriminate glioblastoma tissues (n = 29) from adjacent normal brain samples (n = 16). For miR-124-3p and miR-485-5p, lower expression was coded as indicative of glioblastoma. In univariable analyses, PKMYT1AR and MAPKAPK5-AS1 showed limited discriminative ability, whereas miR-124-3p and miR-485-5p achieved modest AUC values. A multivariable logistic regression model including all four transcripts yielded an AUC of about 0.76. These results suggest that combining lncRNAs and miRNAs into a composite signature may enhance diagnostic performance, although external validation is required.