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Expression of Epithelial-Mesenchymal Transition-Related Genes in Primary Brain Tumors

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ABSTRACT

Background: Gliomas are the most common malignant primary brain tumors in adults. Meningiomas, on the other hand, are benign primary brain tumors treated by surgical resection. Epithelial-to-mesenchymal transition (EMT), stemness, and leader behavior are among the most important complex processes contributing to tumor progression and aggressiveness. Thus, the evaluation of molecular targets involved in the EMT processes in primary brain tumors can help elucidate the molecular mechanisms underlying glioma aggressiveness, ultimately identifying potential areas for further research.

Methods: We conducted expression analysis of zinc finger E-box homeobox 1 (*ZEB1*), Sry-related HMG box (*SOX2*), and *p21* in 31 glioma (15 glioblastoma [GBM] and 16 non-GBM) and 44 meningioma samples using quantitative real-time PCR. We also compared expression levels between glioma and meningioma, as well as between GBM and non-GBM tumor samples.

Results: The expression levels of *SOX2* and *ZEB1* showed a significant increase in gliomas compared to meningiomas (p = 0.016 and 0.017, respectively). However, *p21* did not reveal any significant difference in expression between the two groups. Notably, p21 was the only gene that exhibited a significant increase in expression in GBM samples compared to non-GBM samples, with a p value of 0.027.

Conclusion: Our results suggest that *SOX2* and *ZEB1* expression levels have a significant role in glioma progression. Interestingly, based on the elevated *p21* expression level in the GBM, we also suggest that aggressive tumor features arise from distinct molecular mechanisms depending on tumor subtype, not a single universal pathway. ***DOI: 10.22034/IBJ.30.1.59***

Keywords: Glioma, Meningioma, SOX2, ZEB1

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1. INTRODUCTION

Primary brain tumors are heterogeneous neoplasms derived from various cell types of the central nervous system (CNS). Among these tumors, glioma and meningioma are the two most common primary brain tumors in adults, each exhibiting distinct malignant potential.

Glioma primarily originates from glial cells and is mostly found in the CNS. Generally, these tumors are more prevalent in men than in women. Gliomas can be classified into several cell types: astrocytic (astrocytoma), oligodendrocytic (oligodendroglioma), ependymal (ependymoma), or mixed. The World Health Organization classified gliomas into grades I to IV

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based on differentiation, anaplasia, aggressiveness, and histopathological features[1]. Glioblastoma (GBM), the most lethal subtype, has a five-year survival rate ranging from 0.05% to 4.7% after diagnosis and occurs in 0.59 to 3.69 per 100,000 individuals[2-4]. GBM comprises approximately 82% of all glioma cases, with an age-adjusted incidence rate ranging from 4.67 to 5.73 per 100,000 people[5,6]. Although GBM tumors are highly invasive and tend to infiltrate the surrounding parenchyma, they are restricted to the CNS and rarely metastasize to regional lymph nodes, lungs, and pleura, and occasionally to the bone and liver.

Meningioma, the most common non-malignant brain tumor, arises from the arachnoid cap cells located at various sites in the CNS, including the spinal cord. More than 80% of these tumors remain benign with silent progression, which limits the availability of comprehensive epidemiological data on their characteristics. The overall five-year survival rate for meningioma patients is 70%, though it decreases with age. Meningioma can often be treated with surgical resection due to its benign nature; however, 15-20% of these tumors may display aggressive behavior, necessitating further adjuvant therapies[2].

A wide range of mechanisms has been studied and proven to be implicated in glioma aggressiveness. It has been confirmed that glioma stem-like cells have features that allow for self-renewal and production of progenitors that facilitate tumor progression[7]. Furthermore, mutations in isocitrate dehydrogenase 1 and changes in methylation patterns of O-6-methylguanine-DNA methyl transferase gene are also among the contributing factors in tumor malignancy[8,9]. A key mechanism contributing to tumor aggressiveness is the ability of glioma cells to invade and migrate into the surrounding normal brain tissue in the brain, leading to incomplete removal and resistance to radiotherapy[10].

Epithelial-to-mesenchymal transition (EMT) is a complex process through which tumor cells lose their epithelial characteristics, such as E-cadherin expression, and attain mesenchymal features, resulting in decreased adhesion to adjacent cells. EMT leads to increased motility and migration, giving tumor cells more malignant properties. Beyond EMT itself, accompanying epigenetic changes in these cells can drive the formation of cancer stem cells, a feature associated with increased tumor aggressiveness and unfavorable prognosis[11,12]. These reversible changes are significantly influenced by the tumor microenvironment. A plethora of signaling pathways, including Wnt, play important roles in the EMT process, in which tumor cells acquire metastatic abilities[11].

Zinc finger E-box homeobox 1 (*ZEB1)* is a key transcription factor involved in EMT and cancer progression[13-16]. There is increasing evidence for its role in drug resistance to temozolomide[17], and its expression is a contributing factor to shorter survival of patients.

p21 is a cell cycle regulator involved in the induction of senescence in response to DNA damage and p53 activation. It has also been proven to play a significant role in the self-renewal of neural stem cells by repressing Sry-related HMG box (*SOX2)* expression, a transcription factor that is also important in cancer stem cell biology. Recently, studies have suggested that p53, p21, and cyclin-dependent kinase (CDK) inhibition, the genes that are developmentally controlled or induced by injury, may significantly influence collective leader-driven cell migration[18]. p53 is a well-documented key factor in leader-driven cell migration by modulating downstream p21 and CDK activity[18].

Given the role of *SOX2*, *ZEB1,* and *p21* in stemness, EMT, leader cell behavior, and migration processes, these factors were selected for further analysis in this study. Since glioma is a malignant brain tumor with high potential for metastasis, invasion, and relapse, and knowing that meningioma is a known benign brain tumor, we hypothesized that these types of brain tumors might be appropriate in vivo models for comparison. Thus, this study analyzed the expression levels of *SOX2, ZEB1,* and *p21* in primary brain tumors to assess the significance of these molecules in brain tumorigenesis. The same comparison was conducted between GBM, as the most malignant glioma grade, and lower-grade gliomas treated as non-GBM cases. This approach aligns with recent literature that recognizes the distinct malignant features of GBM. Our study was in line with previous studies[19-24], demonstrating the upregulation of stemness and EMT markers, specifically *SOX2* and *ZEB1* ($p = 0.016$ and $p = 0.017$), in glioma tumors compared to meningioma tumors. This is most likely due to cancer-specific mechanisms modulating the expression of these molecules. Furthermore, our findings support the data previously acquired by other investigators[19-24].

2. MATERIALS AND METHODS

2.1. Patient samples

Seventy-five fresh brain tumor samples, 31 glioma (15 GBM and 16 non-GBM) and 44 meningioma samples, were collected from Shariati Hospital affiliated to Tehran University of Medical Sciences, Tehran, Iran, from 2014 to 2016. All pathology results and definitive diagnoses of tumor types and grades were confirmed by an expert neuropathologist.

2.2. RNA extraction, DNase treatment, and complementary DNA (cDNA) synthesis

All procedures related to RNA extraction, DNase I treatment, and cDNA synthesis have been described

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previously and followed the MIQE guidelines[19]. The steps of total RNA extraction were based on a modified Tripure Isolation Reagent protocol. Briefly, tissue samples were subjected to cycles of freeze and thaw, followed by homogenization with the lysis buffer for the simultaneous isolation of RNA, DNA, and protein in a single-step liquid-phase separation. Following centrifugation of the top aqueous phase containing RNA, RNA was precipitated using isopropanol and then purified using ethanol 70% for the removal of the residual salts. After air-drying, the RNA pellet was resuspended in RNase-free water. The yield and purity of the extracted RNA were ultimately assessed using a NanoDrop spectrophotometer (A260/A280 and A260/A230 ratios). To remove any residual genomic DNA contamination and obtain RNA with higher purity for downstream analyses, we treated the samples with RNase-free DNase I according to the manufacturer's instructions. For the synthesis of the first-strand cDNA, PrimeScript RT Reagent kit (Takara Bio Inc., Shiga, Japan) was applied to the RNA templates, and reverse transcription of the templates was carried out accordingly, utilizing random hexamers and oligo dT primers.

2.3. Quantitative real-time PCR (qRT-PCR)

Specific primers of mRNA expression were designed by primer-design (NCBI) and Gene Runner or adopted (Table 1). The primer efficiency and R^2 values for each of *GAPDH*, *p21*, *SOX2*, and *ZEB1* genes were assessed using a standard curve. qRT-PCR was performed by utilizing SYBR Premix Ex Tag™ (Takara Bio Inc.) and Light Cycler® 96 System (Roche Life Science, Germany). The steps of real-time PCR cycles were as follows: initiation for 30 s at 95°C, followed by 40 cycles including 6 s at 95°C and 20 s at 60°C. Melting curves were analyzed at the end of each real-time PCR reaction to check the presence of any primer dimers and the specificity of the amplicon peaks. To ensure the removal of any genomic DNA from each RNA sample, we performed qRT-PCR reactions using *SOX2* primers. Absence of an amplification peak was a confirmation of the perfect function of DNase I treatment. Expression data for each tissue sample was normalized to *GAPDH* gene expression as the housekeeping gene. All experiments were performed in duplicates.

2.4. Statistical analysis

Statistical analysis was performed with SPSS (IBM Corp., Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp., USA). Data were presented with mean, standard deviation, and range. The Q-Q plot and the Kolmogorov-Smirnov test were used to evaluate normal distribution. The analysis of variance (ANOVA) and the Mann-Whitney test were conducted to compare groups. The Bonferroni method was used for multiple comparisons. The ROC curve and the area under the curve (AUC) were used to evaluate the sensitivity and specificity of each mRNA. The Pearson correlation coefficient was assessed between the rankings of two variables. A p value less than 0.05 was deemed statistically significant for a confidence interval of 95%.

3. RESULTS

3.1. Patients' demographic and histopathologic data

The summarized demographic data of the patients are presented in Table 2.

3.2. Gene expression analysis results

Each primer pair was validated using standard curves. All the primers demonstrated high linearity with R^2 values ranging from 0.95 to 0.99. The calculated amplification efficiencies derived from the slopes fell between 93% and 118%, rendering the primers reliable for use in downstream tests. The expression levels of *ZEB1*, *SOX2*, and *p21* were evaluated by qRT-PCR in glioma and meningioma samples, and *GAPDH* was used as the housekeeping gene. *GAPDH*[25] was selected as a control gene based on the existing literature, including the one by Said et al, suggesting the use of GAPDH since its expression is not affected by various conditions and remains stable. According to Mathur et al.[26], *GAPDH* is among the panel of genes that are frequently used as endogenous controls in 80% of gene expression in glioma tumors. In this study, we used a different

Table 1. Primer sequences for the analysis of *SOX2*, *ZEB1*, and *p21* mRNA expression using RT-PCR

Gene name	Primer	Sequence	Tm	Product length (bp)
p21	Forward	GACTCTCAGGGTCGAAAACG	58	93
	Reverse	GGATTAGGGCTTCCTCTTGG	57	
ZEB1	Forward	CATTTTTCCTGAGGCACCTG	56	91
	Reverse	TGAAAATGCATCTGGTGTTCC	57	
SOX2	Forward	CAGCTCGCAGACCTACATGA	59	152
	Reverse	TGGAGTGGGAGGAAGAGGTA	58	

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Table 2. Patients' demographic data in glioma vs. meningioma and GBM vs. non-GBM subgroups

Age	Glioma vs. meningioma	GBM vs. non-GBM
Mean	43.1 vs. 58.4	45.3 vs. 40.9
Minimum	10 vs. 31	10 vs. 23
Maximum	77 vs. 80	64 vs. 77
Male/female ratio	61%/39% vs. 30%/70%	53%/47% vs. 69%/31%

approach to find significant differential expression in a spectrum of primary brain tumors, concerning aggressiveness, including glioma versus meningioma and GBM versus non-GBM. At first, we focused on the aggressive features of primary brain tumors and studied the expression levels of *ZEB1*, *SOX2*, and *p21* in glioma samples, as malignant primary brain tumors, versus meningioma samples, as benign primary brain tumors. We found that *ZEB1* and *SOX2* as EMT and stemness factors, were upregulated in glioma samples compared to meningioma samples, with $p = 0.017$ and $p = 0.016$ and fold change of 2.8 and 16.9, respectively. On the contrary, *p21* displayed an elevated expression level with $p = 0.027$ in the most aggressive glioma grade, GBM. GBM is now considered a distinct entity with an utterly different biological landscape compared to the lower-grade non-GBM tumor samples, which therefore justifies the comparison carried out between the two subgroups. The relevant fold change was found to be approximately 2.5. The results of gene expression analyses are presented in Figure 1 and Table 3. In order to differentiate glioma from meningioma, we measured the specificity and sensitivity of our studied genes using the ROC curve and AUC (Fig. 2 and Table 4).

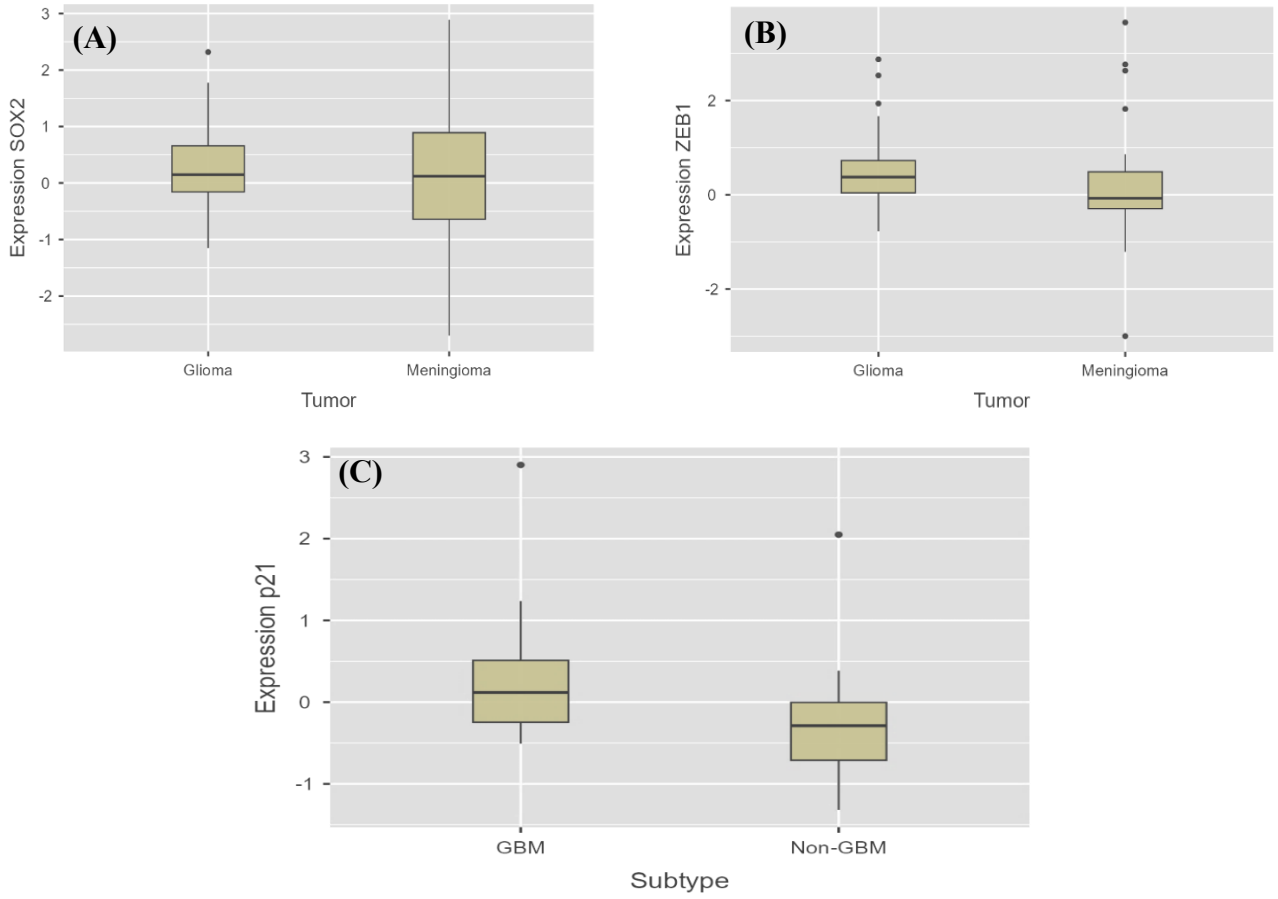

Fig. 1. The log-transformed $2^{-\Delta\Delta CT}$ values for the differentially expressed genes. (A) *SOX2* and (B) *ZEB1* in glioma vs. meningioma; (C) p21 in GBM vs. non-GBM subgroups.

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Table 3. Relevant *p* values and effect sizes of *SOX2*, *ZEB1*, and *p21* expression in glioma vs. meningioma and GBM vs. non-GBM

Comparison	Gene	Test	Statistic (U)	*p* value	Effective size (Rank-biserial correlation)
Glioma vs. meningioma	*P21*	Mann-Whitney U	603	0.492	0.0953
	ZEB1	Mann-Whitney U	460	0.017	-0.3255
	SOX2	Mann-Whitney U	425	0.016	-0.3320
GBM vs. non-GBM	*P21*	Mann-Whitney U	64	0.027	-0.467
	ZEB1	Mann-Whitney U	93	0.299	0.225
	SOX2	Mann-Whitney U	106	0.593	-0.117

4. DISCUSSION

The two most common types of primary brain tumors are glioma and meningioma, and most importantly, the deadliest tumor is glioma grade IV, known as GBM. Glioma is the most common malignant primary brain tumor in adults, with most cases showing malignant features[27]. In contrast, 80% of meningiomas are benign, making them suitable candidates for a comparison of biological characteristics.

There are several mechanisms contributing to glioma pathogenesis, including EMT. Multiple genes, such as *ZEB1*, *SOX2*, and *p21*, are known to play roles in EMT. These genes were selected for this study because they had previously been studied by our research group in skin cancer[28]. Thus, these three molecular targets were chosen for further investigation in glioma and compared to benign meningioma tumors to elucidate possible underlying factors contributing to their differing behaviors from an EMT perspective.

Herein, we reported a significant upregulation of *ZEB1* and *SOX2* in glioma samples compared to meningioma samples, which is in agreement with previous studies[19-24]. Additionally, we observed elevated expression of *p21* in GBM in comparison to non-GBM glioma samples.

Regarding the null findings of *p21*, it is important to note that this gene plays a dual role in cancer, acting both as a tumor suppressor and as a factor that promotes tumor survival under stress conditions. The lack of significant difference in *p21* expression between gliomas and meningiomas suggests that this gene is not a reliable marker for distinguishing tumor types. This observation is in agreement with the reports indicating that *p21* expression varies widely across brain tumors and may be influenced more by microenvironmental stressors or therapeutic exposure than by the inherent biology of the baseline tumor. However, the notable increase in *p21* levels in GBM compared to non-GBM reflects the heightened DNA damage, hypoxia, and cellular stress typically associated with GBM.

SOX2, a key transcription factor and a stemness molecule belonging to the SOX protein family and containing the SOX2 DNA-binding domain, has been reported to be involved in tumor invasion and migration in malignant gliomas. Downregulation of *SOX2* using small interfering RNAs has been shown to reduce invasive capabilities[29]. This gene has also been studied in medulloblastomas, which is implicated in resistance to chemotherapy in these tumors[30]. Our findings demonstrated that *SOX2* expression was significantly upregulated in glioma compared to meningioma. Likewise, expression of SOX2 protein was verified in

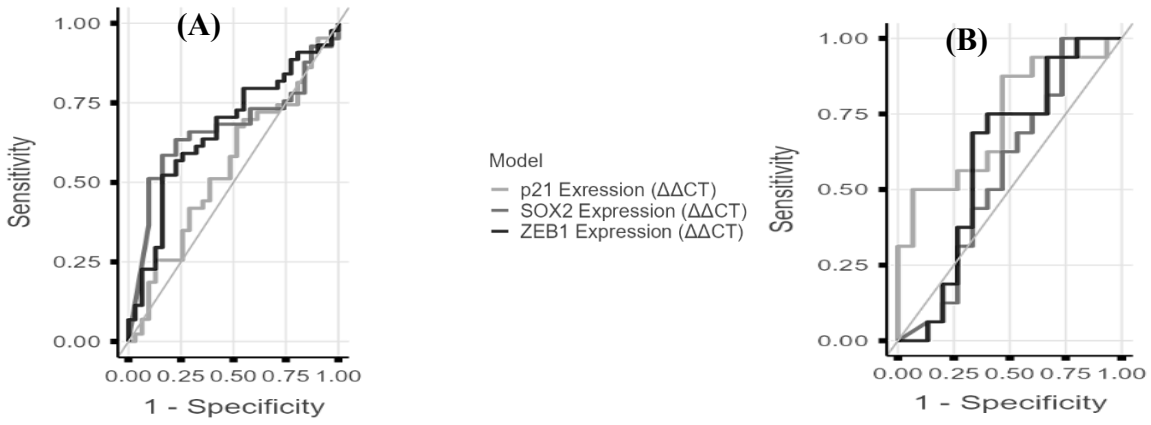

Fig. 2. The ROC curves for *p21*, *SOX2,* and *ZEB1* genes in (A) glioma vs. meningioma and (B) GBM vs. non-GBM.

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Table 4. ROC curve summary for gene expression (ΔΔCT) in glioma vs. meningioma and GBM vs. Non-GBM

Comparison	Gene	AUC	Std. error	95% CI	*p* value
Glioma vs. meningioma	*P21*	0.548	0.0688	0.413-0.682	0.488
	ZEB1	0.663	0.0642	0.537-0.789	0.011
	SOX2	0.666	0.0657	0.537-0.795	0.012
GBM vs. non-GBM	*P21*	0.733	0.0923	0.552-0.914	0.011
	ZEB1	0.612	0.1103	0.396-0.829	0.308
	SOX2	0.558	0.1101	0.343-0.774	0.596

The table corresponds to the ROC curves presented in Figure 2.

GBM biopsies using immunohistochemistry and Western blotting[31]. One study reported low or negative expression of SOX2 protein in meningioma, while another study reported its positive expression in 11 samples of grade I meningioma[22,32]. Therefore, more studies are needed to confirm and clarify the importance of expression levels of SOX2 at the mRNA and protein levels across different brain tumors, particularly concerning its role in tumorigenesis.

ZEB1 is a transcription factor involved in tumor invasion and metastasis by inducing the EMT process in epithelial tumors. Additionally, it is believed to suppress the expression of E-cadherin, an epithelial biomarker, and promote mesenchymal traits by suppressing its targets, including *Crumb3*, *HUGL2*, and *PATJ*, all leading to tumor metastasis. *ZEB1* overexpression has been reported in various cancers, including bladder, colon, and breast[33-39]. In a genomic study, Edwards and colleagues observed *ZEB1* deletion in 15% of glioma patients and suggested it as a poor prognostic marker[40]. Similarly, another genomic study demonstrated *ZEB1* deletion in 15% of grades II and III gliomas and also in 50% of GBM samples[39]. Our finding of increased *ZEB1* expression does not contradict previous studies, as *ZEB1* expression can be regulated independently of its copy number status. The elevated expression levels of *ZEB1* observed in our cohort support the notion that gliomas rely on stemness and EMT pathways to sustain their malignant phenotype, distinguishing them from the less aggressive meningioma tumors. Moreover, the absence of a significant difference in *ZEB1* and *SOX2* expression between GBM and non-GBM samples highlights that these genes may be more useful for distinguishing tumor type (glioma vs. meningioma), rather than explaining grade progression within gliomas. Overall, these findings, similar to previous studies on other organ systems[28], highlight the importance of adopting a comprehensive approach when investigating brain tumors with opposing features, based on their aggressive characteristics. This approach could help identify key regulatory molecules involved in their distinct behaviors, emphasizing the need for further studies on the mechanistic roles of *ZEB1* and *SOX2* genes at the protein level.

5. CONCLUSION

Our results suggest that the molecular pathways modulating *SOX2 and ZEB1* markers are cancer-specific and likely distinct across tumor types. Future studies should include tumor grades, increase sample size, and examine classic EMT markers (E-cadherin and N-cadherin) as well as stemness and leader-cell behavior to better elucidate the molecular network driving aggressiveness and invasion in CNS tumors.

DECLARATION

Acknowledgments

Not applicable.

Generative AI and AI-assisted technologies

The authors declare that no AI-assisted technologies were used during the preparation of this manuscript.

Ethical approval

All experimental procedures in this study were in accordance with the Helsinki Declaration of 1975, as revised in 1983 and approved by the ethical standards of Tehran University of Medical Sciences, Tehran, Iran (ethical code: IR.TUMS.MEDICINE.REC.1395.1689).

Consent to participate

All participants signed the written informed consent.

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

SB: contributed to the study design, experimental procedures, and drafted the manuscript; NM: and FVR: contributed to the experimental procedures;

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AM: contributed to the analysis of the findings; MT: contributed to the study design, supervision of the work, interpretation of the results, and revision of the manuscript; AK: contributed to the samples' surgical resection and diagnosis of the tumor types.

Data availability

All relevant data can be found within the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Supplementary information

The online version does not contain supplementary material.

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