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Original Article

Association between serum response factor, microvascular density, and postoperative recurrence in glioma patients

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Abstract: Objectives: To investigate the expression of serum response factor (SRF) in glioma patients and its association with microvessel density (MVD) and postoperative recurrence. Methods: This retrospective study included 100 glioma patients who underwent surgery at the Second Affiliated Hospital of Air Force Medical University between January 2021 and March 2024. Glioma specimens were collected to assess MVD. Meanwhile, preoperative serum samples were analyzed to measure SRF levels. The associations between SRF, MVD, and postoperative recurrence were analyzed. The diagnostic value of SRF and MVD for glioma progression and their predictive potential for postoperative recurrence were evaluated using receiver operating characteristic (ROC) curves. Univariate and multivariate analyses were conducted to identify independent risk factors for postoperative recurrence in glioma patients. Results: Serum levels of SRF and MVD were significantly higher in high-grade glioma patients than those in low-grade glioma patients. The area under the curve (AUC) for SRF in diagnosing glioma progression was 0.716, while that for MVD was 0.693; however, the combined use of SRF and MVD improved the AUC to 0.760. In glioma, SRF and MVD levels were not correlated with gender, tumor size, or age ($P > 0.05$), but were significantly correlated with lymph node metastasis ($P < 0.05$). There was a positive correlation between SRF and MVD levels in glioma patients ($P < 0.05$). Patients with recurrent gliomas exhibited significantly higher SRF and MVD levels than those without recurrence ($P < 0.05$). Logistic regression analysis identified lymph node metastasis, SRF, and MVD as independent risk factors for glioma recurrence ($P < 0.05$). The AUC for predicting postoperative recurrence was 0.676 for SRF and 0.730 for MVD. When combined, the AUC increased to 0.782. Conclusion: SRF is highly expressed in high-grade glioma and is positively correlated with MVD. It is closely associated with postoperative recurrence and may serve as a potential biomarker for glioma progression and recurrence prediction.

Keywords: Glioma, surgery, serum response factor, microvessel density, recurrence

Introduction

Glioma is a type of craniocerebral tumor arising from the malignant transformation of glial cells in the brain and spinal cord. It is relatively common in clinical practice [1]. Reports show that the annual incidence of glioma ranges from 3 to 8 per 100,000 people [2], with a high mortality rate. Currently, surgical resection remains the primary treatment modality, aiming to remove most of the tumor mass and alleviate clinical symptoms. However, not all patients achieve significant therapeutic benefits [3, 4]. Furthermore, the inherent heterogeneity and highly invasive nature of gliomas often present major therapeutic challenges, and there is no definitive curative treatment for high-grade gliomas [5, 6]. Notably, even with optimal treatment outcomes, tumor recurrence rate remains high [7]. Given these challenges, there is a pressing need to identify and validate serum biomarkers capable of predicting postoperative recurrence. Such biomarkers could enhance glioma management by enabling timely and personalized clinical interventions, ultimately improving patient outcomes.

Studies have pointed out that serum response factor (SRF) is closely associated with tumor initiation and progression, with elevated expression observed in various malignancies [8, 9]. However, research on SRF expression dynamics

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before and after glioma surgery remains limited, and its association with neovascularization and postoperative recurrence has not been well explored. Microvessel density (MVD) serves as a key indicator of angiogenesis [10]. This study investigates SRF expression in glioma patients and its relationship with MVD and postoperative recurrence, aiming to provide a foundation for improved clinical treatment strategies.

Materials and methods

Case selection

This retrospective study involved 100 glioma patients admitted to the Second Affiliated Hospital of Air Force Medical University between January 2021 and March 2024. According to the WHO classification and grading criteria for central nervous system tumors and pathological examination findings, the distribution of glioma grades was as follows: grade I (n = 5), grade II (n = 48), grade III (n = 28), and grade IV (n = 19). Patients with grade I and II gliomas (n = 53) were classified as the low-grade glioma group, while those with grade III and IV gliomas (n = 47) were assigned to the high-grade glioma group.

Inclusion criteria: Diagnosed with glioma based on established clinical and pathological criteria; No prior history of glioma treatment; Normal mental, cognitive, and communication functions; Capable of complying with required examinations; Aged 18 years or older; Available clinical data and follow-up.

Exclusion criteria: Presence of other primary brain tumors or malignancies; Concurrent infectious or hematologic disorders; Systemic conditions such as diabetes, hyperthyroidism, or rheumatoid arthritis; History of anti-inflammatory or glucocorticoid therapy within the preceding three months; Concurrent cerebral hemorrhage or ischemic events. This study was approved by the Ethics Committee of The Second Affiliated Hospital of Air Force Medical University.

Data collection

(1) SRF level. Venous blood (5 mL) was drawn from all patients after a 12-hour fasting period prior to the surgical procedure. Serum samples were separated, and the levels of SRF was analyzed using an automated enzyme-linked immunosorbent assay (ELISA) analyzer (Shanghai Zhennuo Biotechnology Co., Ltd., A51119600C) following the protocols provided by the kit's supplier (Wuhan Amyjet Technology Co., Ltd., G-Biosciences).

(2) MVD value. Brain tissue samples from all patients were harvested following the surgery and then cryopreserved at -80°C. Tissue processing involved methanol fixation (10% concentration), paraffin embedding, and sectioning. Histological examination was conducted using an optical microscope (Contour Elite, Beijing Yicheng Hengda Technology Co., Ltd.). Microvessel identification and quantification were performed using CD105 as an endothelial cell marker. MVD values were calculated as the mean microvessel count across five randomly selected high-power fields (HPF) per specimen.

(3) Postoperative recurrence. Recurrence status was monitored through a standardized 6-month follow-up protocol. Recurrence was objectively defined as the radiographic identification of new lesions through neuroimaging studies.

Statistical methods

Data analysis was performed using SPSS 19.0. Categorical data were represented as n (%) and compared using χ^2 test. Continuous variables were presented as mean ± standard deviation ($\bar{x}$ ± sd) and analyzed using the Student's t-test. Correlation analysis was performed using logistic regression and Spearman's correlation analysis. The diagnostic value of SRF, MVD, and their combination in predicting glioma progression, as well as their predictive utility for postoperative recurrence, were evaluated using the receiver operating characteristic curve (ROC) analysis. Univariate analysis (Chi-square test or Student's t-test) and multivariate analysis (binary logistic regression) were conducted to identify factors associated with postoperative recurrence in glioma patients. A *P*-value < 0.05 was considered statistically significant.

Results

Comparison of general characteristics between the high- and low-grade glioma patients

No significant differences were observed in general characteristics between the low-grade and high-grade glioma groups in terms of gen-

Table 1. Comparison of general characteristics between high- and low-grade glioma patients

General data	n	Low-grade glioma group (n = 53)	High-grade gliomagroup (n = 47)	χ^2	*P*
Gender				1.237	0.266
Male	58	28 (52.83)	30 (63.83)		
Female	42	25 (47.17)	17 (36.17)		
Age (years)				0.403	0.526
< 50	33	16 (30.19)	17 (36.17)		
≥ 50	67	37 (69.81)	30 (63.83)		
Tumor size (cm)				0.284	0.594
< 5	56	31 (58.49)	25 (53.19)		
≥ 5	44	22 (41.51)	22 (46.81)		
Lymph node metastasis				0.020	0.889
Without	73	39 (73.58)	34 (72.34)		
With	27	14 (26.42)	13 (27.66)		
Family medical history				1.755	0.185
Without	82	46 (86.79)	36 (76.60)		
With	18	7 (13.21)	11 (23.40)		

Table 2. Comparison of SRF levels and MVD between high- and low-grade glioma patients

Groups	n	SRF (pg/mL)	MVD (pcs/view)
Low-grade glioma group	53	147.00±19.02	42.04±6.71
High-grade glioma group	47	161.64±18.20	46.96±7.72
t		3.920	3.410
P		< 0.0001	< 0.0001

Note: SRF, serum response factor; MVD, microvessel density.

der distribution, age, tumor size, lymph node status, and family medical history (all $P > 0.05$). Details are presented in **Table 1**.

Comparison of SRF levels and MVD between high- and low-grade glioma patients

Remarkably higher SRF levels and greater MVD were observed in the high-grade glioma group compared with the low-grade glioma group (both $P < 0.001$; **Table 2**).

Diagnostic value of SRF and MVD for glioma progression

The ROC curve analysis demonstrated that the area under the curve (AUC) for SRF in diagnosing glioma progression was 0.716, with specificity, sensitivity, and optimal cutoff of 56.60%, 78.72%, and 146.5 pg/mL, respectively. For MVD, its AUC for diagnosing glioma progression was 0.693, with the specificity, sensitivity, and optimal cutoff of 43.40%, 93.62%, and 39.5 pcs/view, respectively. When SRF and MVD were combined, the AUC increased to 0.760, with a specificity of 54.72%, a sensitivity of 87.23%, and an optimal cutoff value of 0.34. The details are shown in **Figure 1** and **Table 3**.

Relationship between SRF, MVD, and clinicopathological features of glioma

Expressions of SRF and MVD were not significantly associated with tumor size, gender, or age in glioma patients (all $P > 0.05$), but were related to lymph node metastasis ($P < 0.05$). More details are shown in **Table 4**.

Correlation analysis between SRF and MVD

A positive correlation was observed between serum SRF and MVD in glioma patients through Pearson correlation coefficient analysis ($r = 0.307$, $P < 0.05$; **Figure 2**).

Univariate and multivariate analyses of postoperative recurrence in glioma patients

Among the total cohort, 22 patients experienced postoperative recurrence. In the recurrence group, the SRF level was 163.68±19.25 pg/mL, and MVD was 48.64±5.21 pcs/view. In the non-recurrence group, the SRF level was 151.12±19.37 pg/mL and the MVD was 43.14±7.72 pcs/view. Notably, both the SRF level and MVD in the recurrence group were

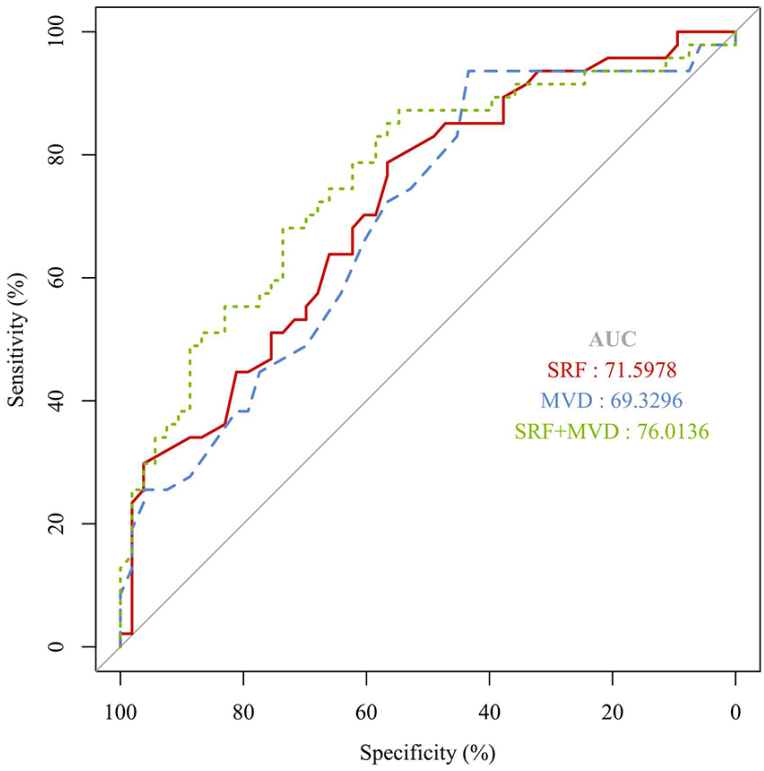

Figure 1. ROC curve analysis for SRF and MVD in predicting glioma progression. Note: ROC, receiver operating characteristic; SRF, serum response factor; MVD, microvessel density.

Table 3. Diagnostic performance of SRF and MVD for glioma progression

Indicators	AUC	SE	*P* value	Specificity	Sensitivity	Optimal cutoff
SRF	0.716	0.051	< 0.001	56.60%	78.72%	146.5 pg/mL
MVD	0.693	0.053	< 0.001	43.40%	93.62%	39.5 pcs/view
SRF+MVD	0.760	0.049	< 0.001	54.72%	87.23%	0.34

Note: SRF, serum response factor; MVD, microvessel density; AUC, area under the curve.

considerably higher than those in the non-recurrence group (both $P < 0.05$). Logistic regression analysis identified lymph node metastasis ($P = 0.008$), SRF ($P = 0.003$), and MVD ($P = 0.004$) as independent risk factors associated with postoperative recurrence in glioma patients (all $P < 0.05$). Refer to **Tables 5-7** for details.

Predictive implications of SRF and MVD for postoperative recurrence in glioma patients

ROC curve analysis demonstrated that the AUC of SRF in predicting postoperative recurrence of glioma patients was 0.676, with specificity, sensitivity, and optimal cut-off value of 72.73%, 69.23%, and 160.5 pg/mL, respectively. Regarding MVD, the AUC for predicting the postoperative recurrence of glioma patients was 0.730, and its specificity, sensitivity, and optimal cut-off were 72.73%, 70.51%, and 46.5 pcs/view, respectively. When SRF and MVD were jointly employed to predict the postoperative recurrence of glioma patients, the AUC reached 0.782, with specificity, sensitivity, and optimal cut-off of 90.91%, 62.82%, and 0.83, respectively. See **Figure 3** and **Table 8** for details.

Discussions

Gliomas are primary intracranial tumors, accounting for about 40% to 50% of all primary brain tumors [11]. Surgical resection remains the primary treatment approach. Despite advancements in modern medicine, including the widespread adoption of microsurgical techniques, many patients still experience unsatisfactory prognoses [12]. The challenges in glioma treatment are largely attributed to its highly invasive nature, rapid proliferation, and resistance to apoptosis. Additionally, gliomas exhibit a high recurrence rate, and with each recurrence, tumor genetic mutations may lead to the development of more malignant variants, further complicating eradication [13]. Recent study has increasingly focused on elucidating glioma pathogenesis. Although the exact mechanisms remain unclear, studies have identified key genes and cytokines involved in glioma initiation and malignant transformation. These molecular factors hold potential clinical significance, and serum response factor (SRF) has emerged as one such candidate [14].

SRF is a member of the MADS-BOX transcription factor superfamily, which is highly con-

Table 4. Correlation of SRF and MVD with clinicopathological features of glioma patients

Clinicopathological features	n	SRF (pg/mL)	*t/P*	MVD (pcs/view)	*t/P*
Gender			0.567/0.572		1.829/0.070
Male	58	152.91±20.51		43.68±7.18	
Female	42	155.21±19.30		46.35±7.24	
Age (years)			0.243/0.809		1.640/0.104
< 50	33	153.39±23.43		46.49±7.82	
≥ 50	67	154.43±18.33		43.97±6.92	
Tumor size (cm)			1.444/0.152		1.438/0.154
< 5	56	151.34±20.97		43.88±7.28	
≥ 5	44	157.11±18.28		45.98±7.21	
Lymph node metastasis			2.531/0.013		7.764/< 0.0001
Without	73	150.89±19.10		42.08±5.85	
With	27	161.96±20.26		52.16±5.52	

Note: SRF, serum response factor; MVD, microvessel density.

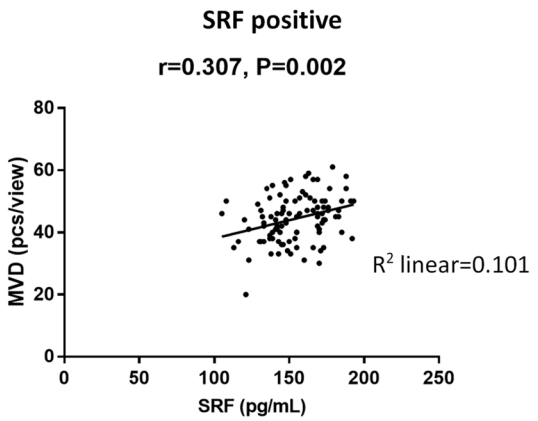

Figure 2. Correlation analysis between SRF and MVD. Note: SRF, serum response factor; MVD, microvessel density.

served in eukaryotes and widely expressed across various tissues and organs. SRF plays a crucial role in cell differentiation, proliferation, apoptosis, and cell cycle regulation [15, 16]. As an important multifunctional transcription factor, SRF plays a significant role in tumor cell development and metastasis. Studies have demonstrated that SRF is highly expressed in gastric cancer, prostate cancer, and other malignancies, actively contributing to tumor initiation and progression [2, 17]. This study analyzed SRF expression in glioma and found that SRF levels were significantly elevated in the high-grade glioma group. Angiogenesis is a critical factor in the malignant biological behavior of tumors, facilitating tumor cell metastasis to other tissues and organs [18]. Microvessel density (MVD) serves as a key indicator of angiogenesis and has prognostic value in assessing tumor progression [19]. In this study, MVD levels were significantly higher in the high-grade glioma group than those in the low-grade glioma group, suggesting that glioma progression is associated with increased MVD and enhanced angiogenesis. Furthermore, ROC curve analysis demonstrated that the AUC of SRF in diagnosing glioma progression was 0.716, while that of MVD was 0.693. Notably, the combination of SRF and MVD improved the AUC to 0.760, indicating that SRF may serve as an auxiliary diagnostic biomarker for glioma progression, with its diagnostic efficacy further enhanced when combined with MVD.

Migration and invasion are key biological characteristics of malignant tumors, significantly influencing treatment outcomes and prognosis [20]. By analyzing the correlation between SRF, MVD and the clinicopathological characteristics of glioma, it was found that SRF and MVD were not significantly associated with age, gender, or tumor size, but with pathological grade and lymph node metastasis, suggesting that elevated SRF and MVD levels contribute to tumor migration and invasion. MVD is a critical biomarker of tumor angiogenesis. As glioma progresses to higher pathological grades, tumor cell growth and proliferation intensify, increasing the demand for microcirculation. This results in localized hypoxia, which stimulates neovascularization [21]. Additionally, high SRF expression may promote vascular endothelial growth factor (VEGF) expression, thereby enhancing angiogenesis and glioma progression

Table 5. Univariate analysis of postoperative recurrence in glioma patients

Clinicopathological features	n	Recurrence group (n = 22)	Non-recurrence group (n = 78)	χ^2/t	*P*
Gender				0.138	0.710
Male	58	12 (54.55)	46 (58.97)		
Female	42	10 (45.45)	32 (41.03)		
Age (years)				0.144	0.704
< 50	33	8 (36.36)	25 (32.05)		
≥ 50	67	14 (63.64)	53 (67.95)		
Tumor size (cm)				0.412	0.521
< 5	56	11 (50.00)	45 (57.69)		
≥ 5	44	11 (50.00)	33 (42.31)		
Pathological grading				5.080	0.024
I+II	53	7 (31.82)	46 (58.97)		
III+IV	47	15 (68.18)	32 (41.03)		
Lymph node metastasis				7.570	0.006
Without	73	11 (50.00)	62 (79.49)		
With	27	11 (50.00)	16 (20.51)		
SRF (pg/mL)	100	163.68±19.25	151.12±19.37	2.690	0.008
MVD (pcs/view)	100	48.64±5.21	43.14±7.72	3.140	0.002

Note: SRF, serum response factor; MVD, microvessel density.

Table 6. Assignment table

Clinicopathological features	Variable	Assignment
Pathological grading	X1	I+II = 0, III+IV = 1
Lymph node metastasis	X2	Without = 0, with = 1
SRF (pg/mL)	X3	Continuous variable
MVD (pcs/view)	X4	Continuous variable
Postoperative recurrence	Y	Without = 0, with = 1

Note: SRF, serum response factor; MVD, microvessel density.

[22]. In this study, correlation analysis demonstrated a positive correlation between SRF and MVD in glioma patients, suggesting that higher SRF expression is linked to increased tumor neovascularization and more aggressive malignant behaviors. Furthermore, SRF and MVD were closely associated with postoperative glioma recurrence. Evidence suggests that glioma recurrence is closely related to epithelial-mesenchymal transition (EMT), a process in which SRF plays a regulatory role. SRF promotes tumor progression by disrupting cell-cell adhesion, facilitating tumor cell migration, and enhancing malignant tumor development. Moreover, the upregulation of matrix metalloproteinase-9 (MMP-9) promotes tumor cell infiltration and invasion [23]. Further in-depth analysis confirmed that the AUCs of SRF and MVD for predicting postoperative recurrence were 0.676 and 0.730, respectively, with their combined predictive model increasing the AUC to 0.782. These findings suggest that SRF and MVD, particularly in combination, hold significant potential for prognosticating postoperative recurrence in glioma patients.

This study has several limitations. First, the relatively small sample size may affect the precision and reliability of the findings. Second, the lack of fundamental research, particularly in vitro and in vivo experiments, limits our understanding of the specific mechanisms by which SRF mediates glioma recurrence. Incorporating such studies would significantly enhance our mechanistic insights. Finally, the relatively short postoperative follow-up period restricts our ability to evaluate the long-term prognostic relationship between SRF and glioma outcomes. Extending the follow-up duration would provide more comprehensive data for prognostic analysis. Future research will focus on addressing these limitations to further improve the quality and depth of glioma-related investigations.

Conclusion

SRF is highly expressed in high-grade glioma tissues and is positively correlated with MVD,

Table 7. Multivariate analysis of postoperative recurrence in glioma patients

Factors	β	SE	Wald	*P*	OR	95% CI
Pathological grading	1.154	0.627	3.386	0.066	3.170	0.928-10.838
Lymph node metastasis	1.763	0.661	7.118	0.008	5.832	1.597-21.302
SRF	0.054	0.018	8.779	0.003	1.055	1.018-1.093
MVD	0.130	0.045	8.423	0.004	1.138	1.043-1.243

Note: SRF, serum response factor; MVD, microvessel density.

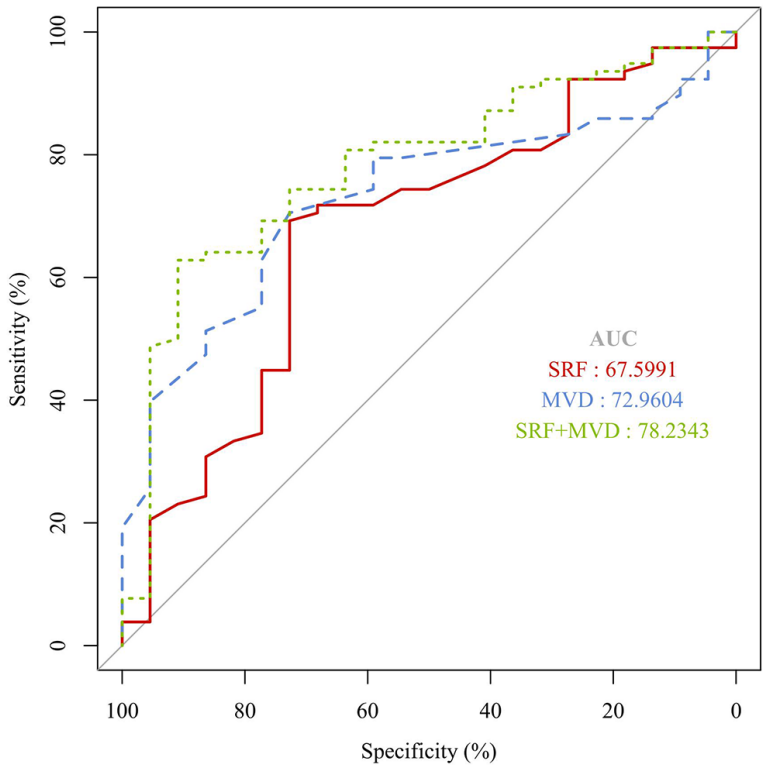

Figure 3. Predictive value of SRF and MVD for postoperative recurrence in glioma patients. Note: SRF, serum response factor; MVD, microvessel density; AUC, area under the curve.

Table 8. Predictive performance of SRF and MVD for postoperative recurrence in glioma patients

Parameters	AUC	SE	*P* value	Specificity	Sensitivity	Optimal cut-off
SRF	0.676	0.066	0.012	72.73%	69.23%	160.5 pg/mL
MVD	0.730	0.054	0.001	72.73%	70.51%	46.5 pcs/view
SRF+MVD	0.782	0.053	< 0.001	90.91%	62.82%	0.83

Note: SRF, serum response factor; MVD, microvessel density; AUC, area under the curve.

demonstrating a strong association with postoperative recurrence. SRF expression levels can serve as a valuable indicator for assessing disease progression and postoperative recurrence in glioma patients.

Disclosure of conflict of interest

None.

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