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Serotonin, Dopamine, GABA, and VEGF in IDH-wildtype- Glioblastoma and Meningioma: A Comparative Study of Tissue and Serum Concentrations and Prognostic Impact

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Abstract

Background: IDH-wildtype Glioblastoma is the most aggressive primary brain tumor with a poor prognosis and its microenvironment influences the nervous system heavily. We investigated the levels and functional relevance of the neurotransmitters Serotonin, Dopamine, and GABA, along with Vascular Endothelial Growth Factor (VEGF), in IDH-wildtype Glioblastoma compared to the relatively benign meningioma, aiming to determine their potential as diagnostic and prognostic biomarkers.

Methods: Tissue and peripheral blood samples were collected from IDH-wildtype Glioblastoma patients and meningioma controls. Concentrations of all four molecules were measured using ELISA. Statistical significance was assessed using Student's t-test ($p < 0.05$). The relationship between molecules was determined using Pearson's correlation, while prognostic and diagnostic potentials were evaluated via Kaplan-Meier survival analysis and Receiver Operating Characteristic (ROC) analysis, respectively.

Results: Our study, statistically significant positive correlation was observed between VEGF and all three neurotransmitters (Serotonin, Dopamine, and GABA) exclusively within the tumor tissue of both IDH-wildtype Glioblastoma and meningioma patients, but this correlation was absent in peripheral blood. Kaplan-Meier analysis revealed that elevated levels of all four molecules in both tissue and blood were strongly associated with significantly shorter overall survival in IDH-wildtype Glioblastoma patients. In contrast, no significant prognostic effect was observed in meningioma patients. ROC analysis conducted to differentiate IDH-wildtype Glioblastoma from meningioma showed inferior diagnostic potential for all four molecules, both in blood and tissue.

Conclusion: Our results show that neurotransmitters and VEGF are critical components of the malignant IDH-wildtype Glioblastoma microenvironment, characterized by a potent, localized neuro-angiogenic drive and poor survival outcomes. Crucially, despite their strong prognostic power in predicting survival in IDH-wildtype Glioblastoma, the peripheral and tissue concentrations of these molecules lack the necessary discriminative capacity to serve as effective standalone diagnostic biomarkers for distinguishing IDH-wildtype Glioblastoma from meningioma. We think; all of them (Dopamine, GABA, Serotonin, VEGF), the initiation and progress of IDH-wildtype Glioblastoma has led to these developments.

Introduction

IDH-wildtype Glioblastoma, classified as the most aggressive and prognostically challenging subtype (WHO Grade IV) of central nervous system tumors, continues to pose a formidable therapeutic challenge. Despite standard aggressive treatments involving surgery, radiation, and temozolomide (TMZ), the median survival for patients remains critically low, typically ranging from 12 to 14 months (Ruiz et al., 2021; Gupta et al., 2024). This poor prognosis stems from the tumor's intrinsic biological properties, including its highly invasive nature, pronounced cellular heterogeneity, and rapid resistance to current therapeutic modalities. Consequently, there is an urgent need to identify and target novel signaling pathways that underpin IDH-wildtype Glioblastoma pathogenesis and survival (Gupta et al., 2024).

Neurotransmitters, traditionally recognized as prominent signaling molecules governing neurogenesis and homeostasis in the central nervous system (CNS) (Jiang et al., 2020; Teleanu et al., 2022) are broadly

classified into families such as biogenic amines (e.g., dopamine, serotonin), amino acids (e.g., GABA, glutamate), and neuropeptides (Chen et al., 2025). Although governing vital functions like emotion and sensation, recent investigations have revealed that tumors exploit these pathways to establish a supportive microenvironment, thereby making an overall impact on IDH-wildtype Glioblastoma behaviors (Caragher et al., 2018). Emerging evidence suggests that these molecules, released from both neuronal and non-neuronal sources (including tumor cells) (Jiang et al., 2020), Regulates IDH-wildtype Glioblastoma processes like proliferation, migration, and angiogenesis by activating various receptors and associated intracellular pathways (Caragher et al., 2025; Li et al., 2025). This neuro-signaling is pivotal because neurotransmitters assume a dual role in cancer progression, where the ultimate effect depends on specific transmitter types, receptor expression, and microenvironmental factors (Jiang, et al., 2020; Zhang et al., 2025; Huang et al., 2022; Chen et al., 2025)). Recent results have identified ten neurotransmitters as key players in IDH-wildtype Glioblastoma behaviors (Joghataei et al., 2023; Huang et al., 2022). Considering the complexity and duality of these signaling pathways, our study specifically focuses on Dopamine (DA), Serotonin (5-HT), and Gamma-aminobutyric acid (GABA) due to their intricate and often conflicting roles in IDH-wildtype Glioblastoma pathogenesis. DA is primarily noted for its anti-angiogenic and pro-autophagic effects, inhibiting IDH-wildtype Glioblastoma invasiveness by suppressing the vascular endothelial growth factor (VEGF) pathway and inducing autophagy (Wang et al., 2015; Mendoza-Torreblanca et al., 2023). However, the precise anti-angiogenic mechanism remains under investigation (Huang et al., 2022). 5-HT is a multifaceted regulator; while implicated in promoting progression, targeting its receptors can induce apoptosis and potentially serve as reinforcement to chemotherapy (Lu et al., 2020; Kast RE, 2010; Bi et al., 2021) Finally, GABA, the major inhibitory neurotransmitter, has been shown to inhibit IDH-wildtype Glioblastoma growth (Smits et al., 2012; Badalotti et al., 2024; D'Ursa et al., 2012).

VEGF signaling pathway has become a prime therapeutic target in IDH-wildtype Glioblastoma treatment over the past decade (Nowacka et al., 2025). Therefore, the presented study investigates the levels of these three different neurotransmitters simultaneously with the angiogenic factor VEGF in tissue and blood samples of IDH-wildtype Glioblastoma patients, and evaluates their potential as clinically prognostic and therapeutic biomarkers.

Materials and Methods

Patients and specimens

Due to ethical and practical constraints, obtaining brain tissue from healthy individuals is not feasible in clinical research. Therefore, in the present study, meningioma tissue samples obtained during routine surgical resection were used as the comparison group for patients with IDH-wildtype Glioblastoma. Meningiomas are primary central nervous system tumors that are generally benign and exhibit lower proliferative and invasive potential compared to malignant gliomas. Consequently, meningioma samples provide a clinically accessible and ethically acceptable reference group for investigating IDH-wildtype Glioblastoma associated molecular and biochemical alterations.

Fresh tissue samples were collected from a total of 80 patients who underwent surgery at the Department of Neurosurgery, Erciyes University Medical Faculty Hospital. The study population consisted of two main

groups: IDH-wildtype Glioblastoma patients (n = 42), histopathologically confirmed as WHO Grade IV, and Intracranial meningioma patients (n = 38), confirmed as WHO Grade I–III, who were used as the control group. Ethics and Consent All participants provided written informed consent before their inclusion in the study. The study protocol and investigation were approved by the Clinical Research Ethics Committee of Erciyes University (Decision No: 2023/128). The characteristics and clinicopathological features of all patients were summarized in Table 1. Other details on all of the patients were listed in supplementary information (Table S1).

Table 1.

Patients	**Ages (years) (Mean ± SD)**	**Survival (day) (Mean ± SD)**	**Ki 67 (%) (Mean ± SD)**
GBM (n = 42)	58.50 ± 12.42	357.1 ± 197.5	36.76 ± 16.55
Meningioma (n = 38)	53.11 ± 12.92	535.2 ± 29.85****	10.38 ± 11.76****

Table 1

Patient Demographic and Clinical Characteristics. There is no age difference between GBM patients and meningioma patients. GBM patients had significantly shorter overall survival compared to Meningioma and significantly higher Ki-67 index (****$p < 0.0001$). **Supplementary Table 1.**

Patients	Gender	Age/ years	Histologic grade	Ki67	Region	Tumor volume cm^3	Alive/Died	Survival/ day
GBM 1	M	68	IV	20	Right Parietal	7.3	Alive	540
GBM 2	M	54	IV	50	Left Frontal	43	Died	509
GBM 3	F	74	IV	25	Right Parietal	44	Died	246
GBM 4	F	66	IV	50	Right Parietal	16.5	Died	540
GBM 5	M	51	IV	15	Left Parietal	21.2	Alive	540
GBM 6	F	59	IV	50	Left Parietal	58.5	Died	152
GBM 7	F	55	IV	50	Left Frontal	21.4	Died	517
GBM 8	F	64	IV	30	Left Frontal	23.9	Died	492
GBM 9	M	51	IV	20	Right Frontal	99.1	Died	188
GBM 10	M	51	IV	20	Right Parietal	46.2	Alive	540
GBM 11	M	80	IV	20	Left Frontal	23.2	Died	540
GBM 12	F	36	IV		Right Parietal	23.2	Alive	540
GBM 13	M	60	IV	50	Right Parietal	74,5	Died	162
GBM 14	F	45	IV	20	Right Temporal	17.5	Died	184
GBM 15	F	68	IV	30	Left Parietal	5.9	Died	48
GBM 16	M	64	IV	70	Left Frontal	93.7	Died	371
GBM 17	F	70	IV	40	Right Temporal	37.3	Died	58
GBM 18	F	64	IV	50	Left Temporal	44.3	Died	81
GBM 19	M	59	IV	40	Right Temporal	24.2	Died	357
GBM 20	M	75	IV	10	Right Occipital	57.1	Alive	540
GBM 21	F	34	IV	60	Left Frontal	95.4	Died	255
GBM 22	M	50	IV	50	Left Parietal	13.9	Died	540
GBM 23	M	42	IV	60	Right Frontal	33.5	Died	40
GBM 24	F	67	IV	30	Right Parietal	34.1	Died	71
GBM 25	F	62	IV		Right Occipital	3.3	Alive	540
GBM 26	F	58	IV	20	Left Frontal	67.8	Alive	540

Patients	Gender	Age/ years	Histologic grade	Ki67	Region	Tumor volume cm^3	Alive/Died	Survival/ day
GBM 27	F	73	IV	70	Right Temporal	23.3	Alive	540
GBM 28	M	31	IV		Right Frontal	30.4	Alive	540
GBM 29	M	44	IV	40	Right Parietal	30.8	Died	214
GBM 30	F	56	IV	30	Left Temporal	77.4	Died	167
GBM 31	F	60	IV	25	Left Parietal	10.3	Alive	540
GBM 32	M	43	IV		Left Frontal	37.1	Alive	540
GBM 33	F	76	IV	40	Left Temporal	30.4	Died	138
GBM 34	F	46	IV		Left Parietal	50.2	Died	246
GBM 35	M	47	IV	50	Left Temporal	9.2	Alive	540
GBM 36	F	54	IV	50	Left Frontal	58.6	Died	468
GBM 37	F	79	IV	15	Left Parietal	51.2	Died	117
GBM 38	F	56	IV		Left Frontal	17.6	Died	145
GBM 39	M	62	IV		Left Frontal	9.8	Alive	540
GBM 40	M	55	IV	30	Right Temporal	41.5	Alive	540
GBM 41	M	74	IV		Left Parietal	4	Died	52
GBM 42	M	74	IV	20	Left Frontal	15.6	Died	540
Men 1	F	63	I	2	Cerebellar	37	Alive	540
Men 2	M	64	II	20	Olactor Grout	75.6	Alive	540
Men 3	F	51	I	1	Frontal	80.5	Alive	540
Men 4	F	50	I	2	Frontal	53.2	Alive	540
Men 5	M	56	II	20	Frontoparietal	36.4	Alive	540
Men 6	F	37	II	5	Olactor Grout	10.2	Alive	540
Men 7	F	56	I	1	Parietal	20.2	Alive	540
Men 8	F	40	II	20	Parietoccipital	33.6	Alive	540
Men 9	F	46	II	40	Spheonid Wing	43.2	Alive	540
Men 10	F	72	I		Sphenoid Wing	13.6	Alive	540
Men 11	M	63	I	5	Temporal	72.6	Alive	540
Men 12	F	52	I	2	Parietal	31.3	Alive	540

Patients	Gender	Age/ years	Histologic grade	Ki67	Region	Tumor volume cm^3	Alive/Died	Survival/ day
Men 13	M	22	I	5	Temporal	6.1	Alive	540
Men 14	F	52	I	5	Tuberculum Sella	7.1	Alive	540
Men 15	M	29	I		Occipital	25.8	Alive	540
Men 16	F	65	I		Frontoparietal	65.9	Alive	540
Men 17	M	57	III	25	Retroorbital	24.8	Alive	540
Men 18	F	54	I	4	Cerebellar	4.8	Alive	540
Men 19	F	70	I	5	Paraphalx Frontal	78.1	Alive	540
Men 20	M	72	I	7,5	Paraphalx	13.2	Alive	540
Men 21	F	63	II	25	Parietal	84.7	Alive	540
Men 22	F	44	I	2,5	Occipital	26.6	Alive	540
Men 23	M	46	I	3	Frontal	22.1	Alive	540
Men 24	F	39	I	3	Frontal	15	Alive	540
Men 25	M	77	II	15	Frontal	37.6	Alive	540
Men 26	M	73	I	10	Parietotemporal	61.2	Died	356
Men 27	F	41	II	20	Frontal	3.1	Alive	540
Men 28	M	37	I	7,5	Frontal	83.7	Alive	540
Men 29	F	63	I	5	Temporal	2.9	Alive	540
Men 30	F	60	II	3	Parietal	9.8	Alive	540
Men 31	F	31	I		İnterventricular	23.8	Alive	540
Men 32	M	70	III	50	Parietal	31.5	Alive	540
Men 33	F	45	I	10	Pontocerebellar Corner	8.8	Alive	540
Men 34	F	51	I	5	Frontal	30.9	Alive	540
Men 35	F	34	I	2	Birontal	22.1	Alive	540
Men 36	F	54	II		Parietal	66.5	Alive	540
Men 37	M	26	I	1,5	Olactor Grout	4.7	Alive	540
Men 38	F	46	II	20	Temporal	6.9	Alive	540

Supplementary Table 1. Demographic and clinicopathologic characteristics of non-treatment primary GBM and Meningioma patients. Men: Meningioma, F: Female, M: Male

Fresh tumor tissue samples were removed from the patients during surgery. Immediately after excision, the tissue specimens were snap-frozen and stored in liquid nitrogen at -196°C (MVE, USA) until subsequent analysis. Additionally, 15mL of venous blood was collected from each patient into vacuum tubes during the operation. The blood samples were then centrifuged at 1000xg for 10 minutes (Beckman Coulter Allegra 25R, USA), and the resulting serum was collected. Serum samples were divided into aliquots and stored at -80°C (Panasonic, Japan, deep freezer) until subsequent analysis.

Measurement of GABA, Dopamine, Serotonin, and VEGF levels in serum and tissue samples of IDH-wildtype Glioblastoma and Meningioma patients

The concentrations of **GABA** (Manufacturer, Cat. No: Sunred 201-12-1527 for serum and tumor), **Serotonin** (Manufacturer, Cat. No: ELK8524 for serum- Sunred 201-12-1316 for tumor), **Dopamine** (Manufacturer, Cat. No: ELK9845 for serum- Sunred 201-12-1302 for tumor), and **VEGF** (Manufacturer, Cat. No: ELK1129 for serum-Sunred 201-12-0051 for tumor) were determined in tissue and serum samples using specific **human ELISA kits** (Enzyme-Linked Immunosorbent Assay) according to the manufacturer's instructions. Optical density was measured using an **ELISA Reader** (Promega GloMax Multi, USA).

Tissue and Serum Sample Preparation

Prior to analysis, all tissue and serum samples were brought to room temperature.

Tissue Homogenization: Fresh tissue samples were first minced into small pieces and rinsed in ice-cold Phosphate-Buffered Saline (PBS) (0.01M, pH = 7.4). The tissues were then homogenized in PBS at a ratio of Tissue Weight (g): PBS Volume (mL) = 1:9 using a homogenizer (Scilogex Homogenizer, USA). The homogenates were centrifuged at 5000xg for 10 minutes at + 4°C to obtain supernatant. This supernatant was then used immediately for the ELISA procedure according to the kit protocol.

Serum Preparation

Serum samples were prepared directly following the instructions provided in the respective ELISA kit protocols.

Statistical analysis

We used the Student's t-test to determine statistical significance, with a p-value of less than 0.05 considered significant. Pearson's correlation analysis and Linear Regression were employed to evaluate the association between GABA, Dopamine, Serotonin, and VEGF. The discriminatory power of GABA, Dopamine, Serotonin, and VEGF was further evaluated through Receiver Operating Characteristic (ROC) analysis and Kaplan-Meier survival analysis to determine their potential as diagnostic or prognostic biomarkers. Statistical analyses were performed using GraphPad Prism (version 10.4.1; GraphPad Software, USA). Results were summarized as the mean ± standard deviation (mean ± SD).

Results

Patient Demographics and Survival Analysis

The study included two similar-aged cohorts: 42 IDH-wildtype Glioblastoma patients and 38 meningioma patients (serving as the control group). The survival analysis revealed that meningioma patients exhibited significantly higher survival rates compared to IDH-wildtype Glioblastoma patients (Table 1). All patients were followed for a period of 1.5 years (540 days) following surgery. Within this follow-up period, 29 of the 42 Glioblastoma patients succumbed to the disease (18 female, 11 male), resulting in an overall 1.5-year survival rate of 31% (18% for females and 45% for males). Conversely, only 1 male patient from the 38 meningioma cohort died. The average survival time for deceased female Glioblastoma patients was 231 days (median: 167 days), while deceased male Glioblastoma patients survived for an average of 319 days (median: 357 days) (Table 2). Ki67 percentage was determined to be substantially higher in Glioblastoma patients than in meningioma patients, consistent with the observed difference in survival (Table 1).

Table 2.

Table 2

Post-Operative Survival Rate by Gender. Post-operative survival status (Died/Alive) and rates for GBM and Meningioma patients, stratified by gender. A total of 42 patients were included, with an overall mortality rate of 69% (29 patients). The mortality rate was 82% (18 out of 22) for females and 55% (11 out of 20) for males. Meningioma: A total of 38 patients were included, with an overall mortality rate of 3% (1 patient).

Gender	GBM			MENINGIOMA		
	n	Died	Alive	n	Died	Alive
Female	22	(%82) 18	(%18) 4	25	(%0) 0	(%100) 25
Male	20	(%55) 11	(%45) 9	13	(%8) 1	(%92) 12
n	42	(%69) 29	(%31) 13	38	(%3) 1	(%97) 37

Neurotransmitter and Vascular Endothelial Growth Factor (VEGF) Levels in IDH-wildtype Glioblastoma and Meningioma

Recent results suggest that altered levels of neurotransmitters play a significant role in IDH-wildtype Glioblastoma behaviors. Therefore, we investigated the levels of the neurotransmitters GABA, dopamine, and serotonin in blood and tissue samples from Glioblastoma patients and meningioma controls. Our findings indicated no significant difference in dopamine and GABA levels between the Glioblastoma and meningioma groups, either in blood or tissue samples. However, tissue samples from Glioblastoma patients showed a significantly higher level of serotonin compared to the meningioma control group (Table 3, Fig. 1a-b).

Table 3.

Table 3

Neurotransmitter and VEGF Concentrations in Blood and Tissue The mean ± standard deviation (Mean ± SD) concentrations of Serotonin, Dopamine, GABA, and VEGF measured in the blood and tumor tissue samplesfor both the GBM and Meningioma patients. Serotonin concentration was significantly higher in GBM tissue. Dopamine, GABA, and VEGF concentrations were similar between the two tumor tissues, with no significant differences reported (* $p < 0.05$).

Patients (Blood samples)	Serotonin (ng/ml) (Mean ± SD)	Dopamine (ng/ml) (Mean ± SD)	GABA (ug/dl) (Mean ± SD)	VEGF (ng/ml) (Mean ± SD)
Sample	**Blood**			
GBM (n = 42)	171.5 ± 288.8	194.9 ± 305.7	76.74 ± 79.56	69.83 ± 60.73
Meningioma (n = 38)	123.0 ± 192.8	127.2 ± 146.2	73.27 ± 74.57	66.50 ± 50.29
Sample	**Tissue**			
GBM (n = 42)	421,5 ± 554,2	259,4 ± 341,1	163,7 ± 193,0	104,3 ± 118,9
Meningioma (n = 38)	227,3 ± 79,60*	150,0 ± 48,91	101,4 ± 30,75	71,92 ± 22,75

Considering the reported links between neurotransmitter activity and VEGF, we analyzed VEGF levels in tissue and blood samples from both Glioblastoma and meningioma patients, and both tissue and blood samples found no significant difference in VEGF levels between the Glioblastoma and meningioma groups (Table 3, Fig. 1a-b).

The levels of the neurotransmitters serotonin, dopamine, GABA, and VEGF were compared between the tissue and blood samples of Glioblastoma patients. Our analysis revealed a significantly higher concentration of Serotonin in Glioblastoma tissue samples compared to blood samples ($p = 0.0113$). Similarly, the concentration of GABA was also found to be significantly elevated in Glioblastoma tissue samples relative to blood samples ($p = 0.0084$). Conversely, there was no significant difference found when comparing dopamine levels between tissue and blood. Furthermore, the analysis of VEGF concentration showed no significant difference between the tissue and blood compartments in Glioblastoma patients (Fig. 1c).

We analysed to compare the levels of serotonin, dopamine, GABA, and VEGF between the tissue and blood samples of the control meningioma group. Similar to Glioblastoma patients, the meningioma tissue samples found a significantly higher concentration of Serotonin compared to the blood samples ($p = 0.0029$). Additionally, the GABA concentration was also significantly elevated in the meningioma tissue compared to the blood $p = 0.0354$) (Fig. 1d). However, Dopamine and VEGF exhibited no significant difference between the tissue and blood samples in the meningioma control group (Fig. 1d).

Our results demonstrated that the tissue concentrations of dopamine, GABA, and VEGF showed no significant difference when Glioblastoma tissue was directly compared with meningioma tissue. In contrast,

tissue serotonin levels were significantly higher in Glioblastoma tissue samples compared to those from the meningioma control group ($P < 0.05$). This suggests a potential role for Serotonin specifically in the pathology of high-grade gliomas. The tissue concentrations of Dopamine, GABA, and VEGF showed no significant difference when Glioblastoma tissue was directly compared with meningioma tissue (Fig. 1b).

Furthermore, a simple linear regression analysis was performed to investigate the relationship between the angiogenic factor, Vascular Endothelial Growth Factor (VEGF), and the measured neurotransmitter concentrations (Serotonin, Dopamine, and GABA) across all patient tissue samples. The analysis revealed statistically significant positive linear correlations between VEGF and all three neurotransmitters (VEGF and Serotonin: $R = 0,7236$, $p < 0.001$; VEGF and Dopamin: R 0,7894, $p < 0.001$; VEGF and GABA: $R = 0.7846$, $p < 0.001$) (Fig. 2a). Similar, positive correlations were observed in meningioma tissue (VEGF and Serotonin: $R =$ 0,9011, $p < 0.001$; VEGF and Dopamine: R 0,9147, $p < 0.001$; VEGF and GABA: R 0,8968, $p < 0.001$) (Fig. 2c). Analysis of the tumor microenvironment revealed significant positive correlations between VEGF levels and the concentrations of Serotonin, Dopamine, and GABA within the tissue samples of both Glioblastoma and meningioma patients (Fig. 2a-c).

Parallel to the tissue analysis, a linear regression was performed to assess the correlation between systemic VEGF levels and circulating all neurotransmitter concentrations in the blood samples of Glioblastoma and menongioma patients. In contrast to tissue samples, peripheral blood samples from both patient groups showed no correlation between VEGF and the three neurotransmitters ($p > 0.05$ for all comparisons) (Fig. 2b-d), suggesting the neurotransmitters are a localized event within the tumor microenvironment.

Diagnostic and Prognostic Potential of Neurotransmitters

Kaplan-Meier survival analysis highlighted the prognostic significance of these neurotransmitters, revealing a pronounced differential impact between the two tumor types (Fig. 3a-b). In Glioblastoma patients, elevated levels of Serotonin, Dopamine, GABA, and VEGF in both the tissue and blood samples were strongly associated with significantly shorter overall survival, indicating these molecules serve as poor prognostic markers in Glioblastoma (Fig. 3a). Conversely, the survival analysis for meningioma patients demonstrated that neither the tissue nor the blood levels of Serotonin, Dopamine, GABA, or VEGF had a significant predictive effect on overall survival (Fig. 3b). Survival probability remained consistently high across all groups in meningioma, underscoring that the negative prognostic implications of elevated neurotransmitters and VEGF levels are specific to Glioblastoma.

Subsequently, Receiver Operating Characteristic (ROC) analysis was performed to evaluate the potential of these molecules to differentiate Glioblastoma from the control group, meningioma. Interestingly, our results indicated very poor diagnostic. Blood levels for Serotonin (AUC = 0.5060, $p = 0.9292$), Dopamine (AUC = 0.5000, $p > 0.9999$), GABA (AUC = 0.6137, $p = 0.0803$), and VEGF (AUC = 0.5341, $p = 0.5995$) all showed an Area Under the Curve close to 0.5 (Fig. 4). Similarly, tissue levels of Serotonin (AUC = 0.5981, $p = 0.1316$), Dopamine (AUC = 0.5758, $p = 0.2437$), GABA (AUC = 0.5952, $p = 0.1431$), and VEGF (AUC = 0.5930, $p =$ 0.1525) all failed to reach statistical significance (Fig. 4). This complex finding suggests that while the tumor microenvironment exhibits distinct, prognostically relevant alterations (as seen in the survival curves), these

neurotransmitters cannot be effective diagnostic threshold markers to distinguish between the Glioblastoma and control group.

Discussion

Neurotransmitters act on a wide variety of cells within the IDH-wildtype Glioblastoma microenvironment, including neurons, tumor cells, glial cells, and vascular endothelial cells, mediating a broad regulatory effect on Glioblastoma survival, progression, recurrence, and chemo-/radio-resistance (Chen et al., 2025). Due to the diversity of receptor subtypes and environmental factors, the influence of neurotransmitters on Glioblastoma is highly complex; consequently, understanding these interactions is a matter of great significance for clinical research (Chen et al., 2025)

Therefore, the investigation of neurotransmitters in Glioblastoma is fundamental to understanding their role in tumor biology, specifically regarding how Glioblastoma cells hijack signaling pathways to promote growth, stimulate angiogenesis, and evade therapeutic interventions. Therefore, this study aimed to quantify the levels of neurotransmitters in both the blood and tumor tissue of Glioblastoma patients to better understand their function in tumor biology; determining these concentrations is important to unraveling the mechanisms by which neural signals drive tumor progression and therapeutic resistance.

Recent results identified ten neurotransmitters as key players in Glioblastoma behaviors (Huang et al., 2022; Caragher SP et al., 2018). Our study specifically focused on three distinct neurotransmitter classes: Dopamine, Serotonin, and GABA. Our specific selection of these three neurotransmitters was based on their complex, dual roles in Glioblastoma pathogenesis. Dopamine was chosen for its reported inhibitory and anti-angiogenic effects. It inhibits Glioblastoma invasiveness and migration (Huang et al., 2022). It is shown that it inhibited tumor angiogenesis through the VEGF pathway (Wang et al., 2015; Caragher et al., 2018). 5-HT was selected by its role in promoting cancer progression and its potential ability to influence blood flow and angiogenesis, which are critical factors affecting tumor growth in Glioblastoma (Caragher et al., 2018). It also activates multiple subtypes of receptors and induces Glioblastoma heterogeneity (Sturzu et al., 2012). GABA was chosen due to its inhibitory properties. It is a positive regulator of Glioblastoma proliferation and inhibits Glioblastoma Growth (Hujber, et al., 2018; Huang et al., 2022). Our results revealed a significantly higher serotonin (5-HT) concentration in Glioblastoma tissue compared to meningioma. This finding is consistent with recent studies linking serotonin-related signaling to survival and progression in Glioblastoma patients (Caragher et al., 2018). Serotonin acts as a mitogenic signal for cancer cells and contributes to cell proliferation in various cancers (Olfati et al.,2020; Balakrishna et al., 2021). Our previous work demonstrated that aggressive breast cancer cells exhibited an increase in cell viability in a dose-dependent manner after being treated with 5-HT, and predominantly promoted cell proliferation of aggressive breast cancer cells (Cınar et al., 2022). Recent studies showed linking serotonin-related signaling to survival and progression in Glioblastoma (Caragher et al., 2018) and mediating glioma growth and migration (Merzak et al., 1996; Sarrouilhe et al., 2019). Silvia Snider et al 2024 showed significantly lower serum 5-HT levels in Glioblastoma patients compared to healthy individuals (Snider et al., 2025) Interestingly, no significant differences were observed between Glioblastoma and meningioma in the tissue or blood levels of Dopamine, GABA.

Furthermore, the presented study demonstrated that both Serotonin and GABA were significantly elevated in the tissue relative to the blood in both cohorts. These results suggest a distinct partition between systemic depletion and local tissue enrichment, suggesting these neurochemical signals function as localized mediators within the tumor microenvironment. Moreover, this localized accumulation positions serotonin as a may be an attractive target for both precision imaging and therapeutic intervention (Sturzu et al., 2012).

Glioblastomas are the most vascularized solid tumors (Hicks et al., 2015; Zeng et al., 2015) because of their ability to initiate angiogenesis via the release of regulatory factors that promote endothelial cell migration. Vascular endothelial growth factor (VEGF), which is a key regulator of vascular development, also modulates neuronal developmental processes. (Zhang et al., 2015) This molecule stimulates angiogenesis by binding to VEGF receptor 2 (VEGFR2) (Senger et al., 1983). When dopaminergic neurons were ablated in a murine model of glioma, tumor vascularization increased (Basu et al., 2004). In another study, exogenous administration of dopamine reduced angiogenesis and tumor growth in both breast-cancer- and colon-cancer-bearing mice (Sarkar et al., 2008). Dopamine can inhibit the functions of adult endothelial cells by suppressing phosphorylation of vascular endothelial growth factor receptor 2 (VEGFR2) (Sarkar et al., 2008). Serotonin has a potent ability to influence blood flow and angiogenesis. As discussed above, tumor vascularization is a critical problem in the treatment of Glioblastoma. Low-dose treatment with serotonin has been shown to inhibit tumor growth by reducing blood supply (Sarrouilhe et al., 2015). Guérit S et al. reported that VEGF enhances the gamma-aminobutyric acid (GABA) (Guérit S et al., 2014).

Therefore, we investigated links between neurotransmitter activity and key tumor growth factors VEGF (Beylerli et al., 2025). Interestingly, no significant differences were observed between Glioblastoma and meningioma in the tissue or blood VEGF concentration. Interestingly, no significant differences were observed between Glioblastoma and meningioma in the tissue or blood levels of VEGF.

A pivotal finding of our study was the statistically significant positive linear correlations between VEGF and all three neurotransmitters (Serotonin, Dopamine, and GABA) within the tumor tissue of both Glioblastoma and meningioma patients. This correlation was absent in peripheral blood samples. This striking dissociation strongly supports that the interaction between the neuro-modulatory system and angiogenesis is a highly localized event confined to the tumor microenvironment (Jiang et al., 2020; Teleanu et al., 2022)

Interestingly, our other finding demonstrated that elevated levels of Serotonin, Dopamine, GABA, and VEGF in both tissue and blood samples were associated with significantly shorter overall survival in Glioblastoma patients. Conversely, we found that these molecules had no significant predictive effect on survival in meningioma. This differential prognostic impact underscores the finding that neurotransmitter correlates with the unfavorable prognosis of Glioblastoma, suggesting these neurotransmitters are involved in aggressive Glioblastoma pathology by regulating tumor microenvironment. Despite this strong prognostic power, our findings showed that the neurotransmitters and VEGF exhibited very poor diagnostic ability between the Glioblastoma and control groups. This complex result suggests that while these neurochemical alterations are highly relevant indicators of biological aggressiveness, they do not establish an effective diagnostic distinction between Glioblastoma and the control group.

As a result, this suggests that while these neurochemical changes are highly relevant to tumor aggressiveness, they do not establish effective diagnostic thresholds. Ultimately, our results suggested that targeting neurotransmitters could be a promising novel approach for Glioblastoma treatment.

Declarations

Acknowledgments

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Disclosure

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Conflict of Interest

The authors declare no conflict of interest. Also, the authors declared that they have no relevant financial or non-financial interests to disclose. that could have appeared to influence the work reported in this paper and approved the final version of the manuscript being submitted. The results presented in this paper have not been published previously in whole or part.

Ethics Statement

Approval of the research protocol by an Institutional Reviewer Board: This study was approved by Clinical Research Ethics Committee of Erciyes University (ethical approval Protocol No. 2023/128) and implemented in accordance with the Helsinki Declaration of Principles.

Informed Consent: IDH-wildtype Glioblastoma cancer samples were obtained from Erciyes University Medical Faculty Hospital, Neurology Department. All patients provided their signatures on the written informed consent document

Registry and the Registration No. of the study/trial: N/A

Animal Studies: N/A.

Author contributions

All authors analyzed the results and approved the final version of the manuscript. **Zuhal Hamurcu**: conceptualized, coordinated, administered the study, performed experiments, and wrote the paper. **Selda Taşdemir**: helped performing the experiments. **Halil Ulutabanca and Aykut Ilikhan**: coordinated obtaining and use of patient samples.

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Figures

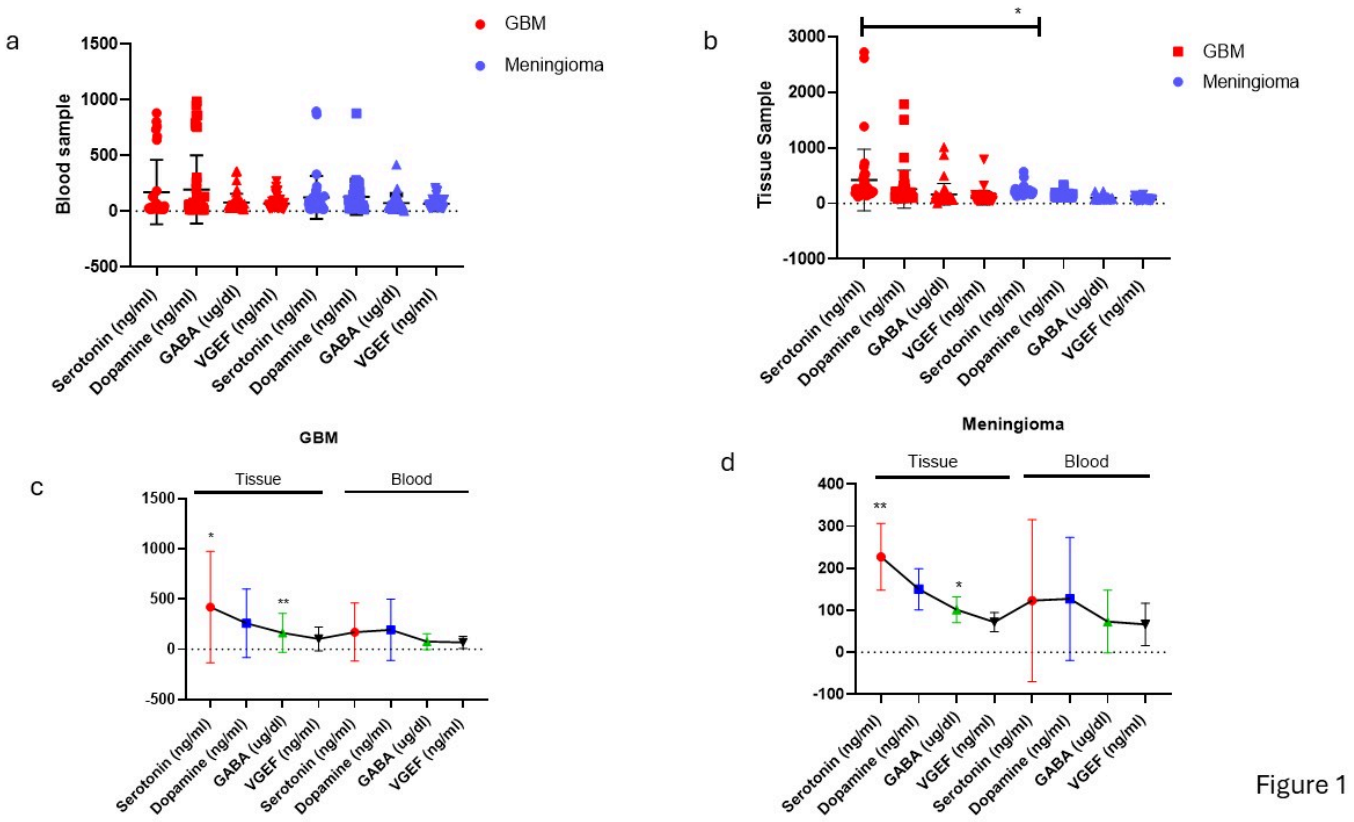


Figure 1

Comparison of Neurotransmitter and VEGF Concentrations in Blood and Tissue Samples of GBM and Meningioma Patients. Measured concentrations of Serotonin, Dopamine, GABA, and VEGF in GBM and Meningioma, comparing levels across blood (a) and tissue samples (b). In the tissue found significantly higher Serotonin levels in GBM compared to Meningioma ($P < 0.05$). Compared mean concentrations in Tissue vs. Blood within the GBM cohort (c) and the Meningioma cohort (d). Serotonin and GABA are significantly higher in tissue than in blood for both patients types. Scatter plot showing the concentration data and Mean ± SD for Serotonin (ng/ml), Dopamine (ng/ml), GABA ug/dl) and VEGF (ng/ml) (*$p < 0.05$; **$p < 0.01$).

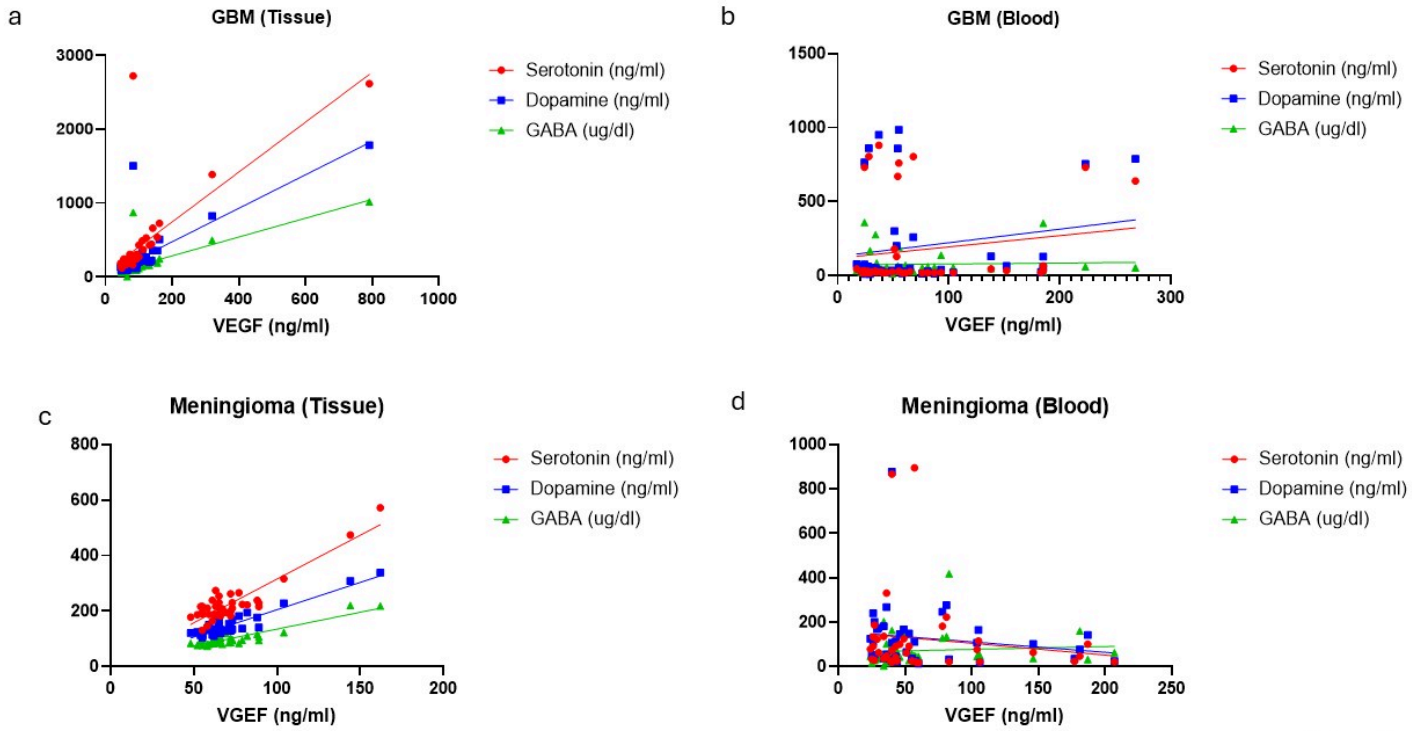


Figure 2

Figure 2

Correlation Analysis Between VEGF and Neurotransmitter Concentrations in Tissue and Blood Samples of GBM and Meningioma Patients. Positive linear correlations are observed between VEGF and Serotonin,Dopamine, GABA in the GBM (a, VEGF and Serotonin: R = 0,7236, $p < 0.001$; VEGF and Dopamin: R= 0,7894, $p < 0.001$; VEGF and GABA: R=0,7846, $p < 0.001$) and Meningioma (c,VEGF and Serotonin: R = 0,9011, $p < 0.001$; VEGF and Dopamin: R= 0,9147, $p < 0.001$; VEGF and GABA: R= 0,8968, $p < 0.001$). tissue samples. No significant correlations are found between VEGF and Serotonin, Dopamine, GABA in the systemic blood circulation (b, d, $p > 0.05$).

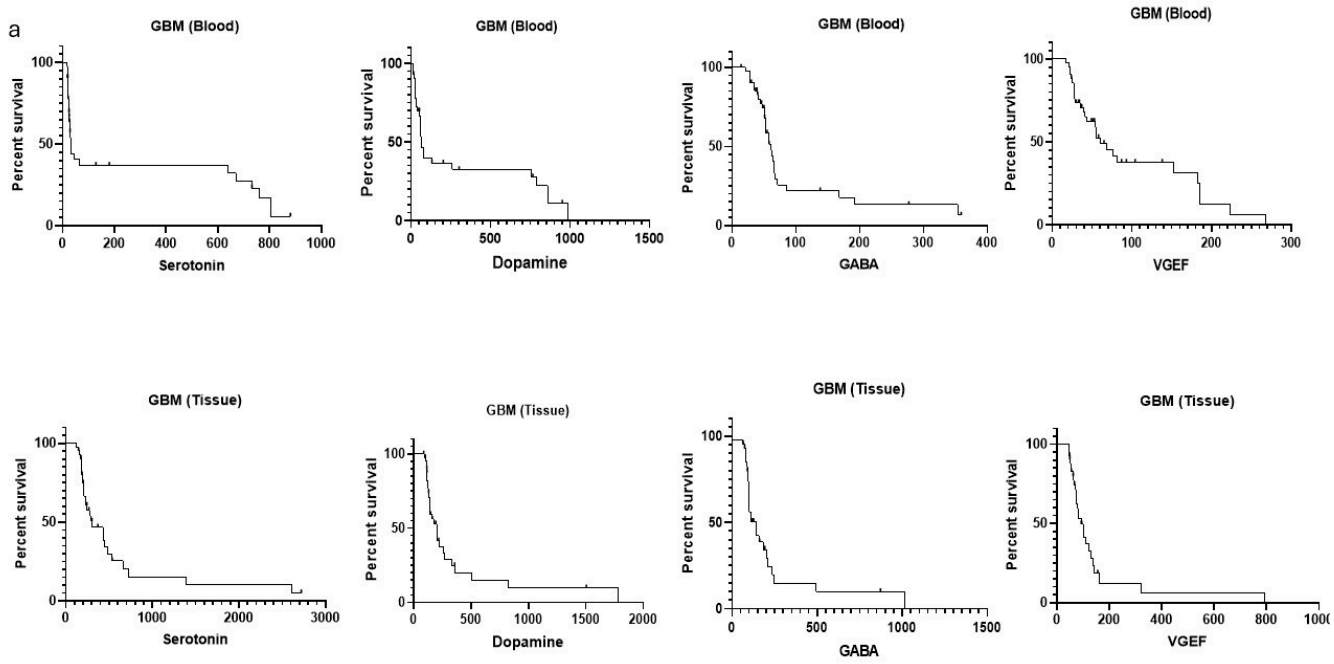


Figure 3a

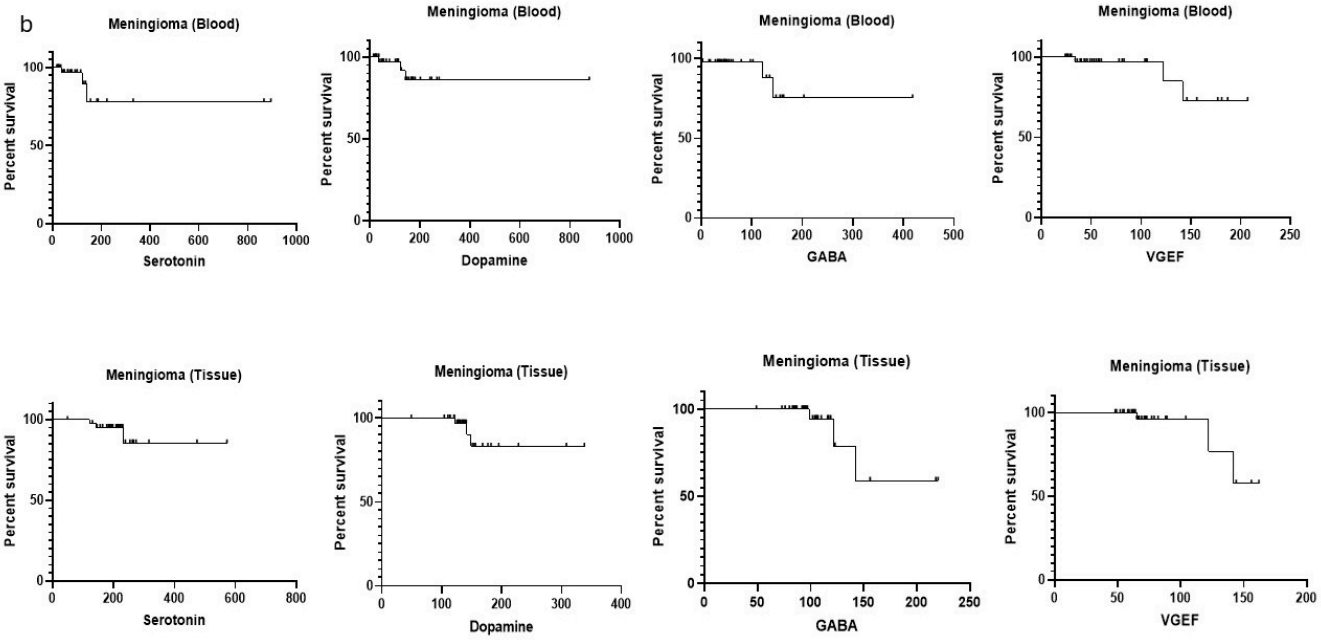


Figure 3b

Figure 3

Correlation Analysis Between VEGF and Neurotransmitter Concentrations in Tissue and Blood Samples of GBM and Meningioma Patients. Positive linear correlations are observed between VEGF and Serotonin,Dopamine, GABA in the GBM (a, VEGF and Serotonin: R = 0,7236, p < 0.001; VEGF and Dopamin: R= 0,7894, p < 0.001; VEGF and GABA: R=0,7846, p < 0.001) and Meningioma (c,VEGF and Serotonin: R = 0,9011, p < 0.001; VEGF and Dopamin: R= 0,9147, p < 0.001; VEGF and GABA: R= 0,8968, p < 0.001). tissue samples.

No significant correlations are found between VEGF and Serotonin, Dopamine, GABA in the systemic blood circulation (b, d, p > 0.05).

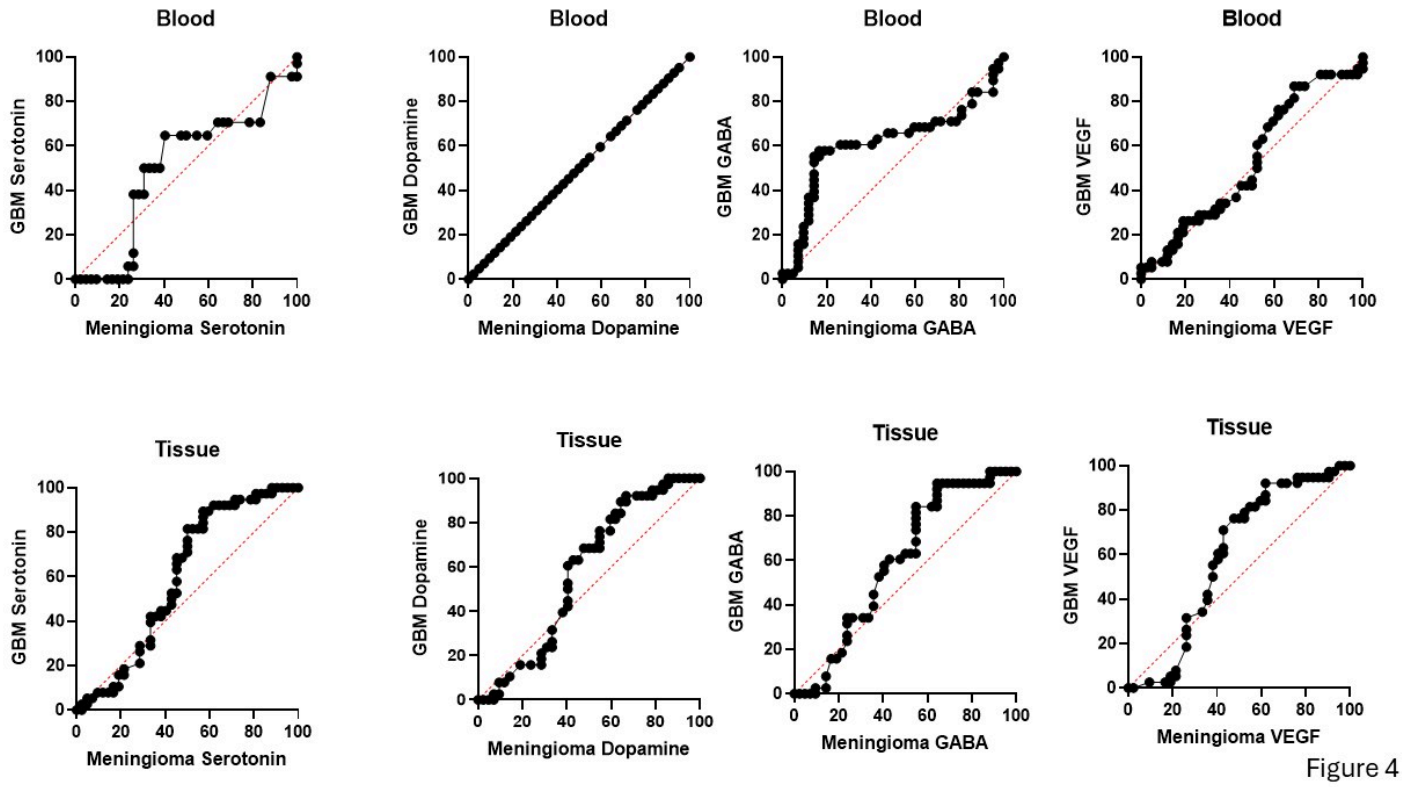


Figure 4

ROC Curve Analysis for Differentiating Glioblastoma (GBM) from Meningioma. ROC curve analysis performed to evaluate the diagnostic potential of Serotonin, Dopamine, GABA, and VEGF concentrations in distinguishing Glioblastoma (GBM) patients from Meningioma patients.The analysis shows that the AUC values are generally low (approximately 0.5), indicating poor diagnostic capability for these four molecules in distinguishing between the two tumor types. A curve closest to the upper left corner indicates the highest diagnostic accuracy (AUC close to 1.0), while a curve along the diagonal line (AUC close to 0.5) indicates no diagnostic utility.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable27.01.2026.docx