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ORIGINAL ARTICLE

B7-H3 expression reflects magnetic resonance imaging (MRI)-derived tumour burden and peritumoral brain oedema in adult gliomas: a radiopathological correlation study

Fatima Juković-Bihorac[1,2*], Emir Begagić[3], Slaviša Đuričić[2,4], Alma Efendić[5], Semir Vranić[6]

[1]Department of Pathology, Cantonal Hospital Zenica, Zenica, Bosnia and Herzegovina; [2]Department of Pathology, Faculty of Medicine, University of Zenica, Zenica, Bosnia and Herzegovina; [3]Department of Neurosurgery, Cantonal Hospital Zenica, Zenica, Bosnia and Herzegovina; [4]Department of Pathology, Faculty of Medicine, University of Banja Luka, Banja Luka, Bosnia and Herzegovina; [5]Department of Radiology, Faculty of Medicine, University of Zenica, Zenica, Bosnia and Herzegovina; [6]Department of Pathology, College of Medicine, QU Health, Qatar University, Doha, Qatar

ABSTRACT

Aim To determine whether immunohistochemical B7-H3 expression is associated with magnetic resonance imaging (MRI)-derived tumour volume, peritumoral brain oedema volume, and oedema index in adult gliomas.
Methods This retrospective radiopathological correlation study included 99 consecutive patients with histopathologically confirmed intracranial gliomas surgically treated between 2013 and 2021. B7-H3 expression (clone RBT-B7H3, Bio SB, USA) was evaluated using staining intensity, percentage of positive tumour cells, and a composite immunoreactive score (IRS). Tumour volume (TV), peritumoral brain oedema volume (PTBE), and oedema index (EI) were calculated from orthogonal MRI measurements. Spearman correlation and crude and adjusted linear regression were used. Adjusted models included age, sex, tumour grade, and Ki-67.
Results Median TV was 29.31 cm3 (IQR 12.17-49.12), median PTBE was 84.51 cm3 (IQR 47.59-178.18), and median EI was 4.56 (IQR 3.83-5.00). B7-H3 IRS correlated strongly with TV ($r = 0.921$, $p < 0.001$) and PTBE ($r = 0.920$, $p < 0.001$), but not with EI ($r = -0.105$, $p = 0.299$). After adjustment, B7-H3 IRS remained associated with ln(TV) (beta = 0.228, 95% CI 0.190-0.265, $p < 0.001$) and ln(PTBE) (beta = 0.178, 95% CI 0.152-0.204, $p < 0.001$), but not with EI (beta = 0.001, 95% CI -0.083 to 0.084, $p = 0.990$).
Conclusion B7-H3 expression is independently associated with MRI-derived tumour volume and peritumoral brain oedema volume in adult gliomas, but not with oedema index, supporting its relationship with absolute MRI-visible lesion burden.

Keywords: B7-H3, oedema, glioma, immunohistochemistry, magnetic resonance imaging

INTRODUCTION

Gliomas are heterogeneous tumours of the central nervous system whose behaviour is influenced by histopathological grade, molecular alterations, proliferative activity, and radiological phenotype (1). The World Health Organization (WHO) classification formally incorporated molecular parameters into the diagnosis of central nervous system tumours, making integrated diagnosis part of routine glioma classification rather than an optional add-on (2). Adult diffuse gliomas are therefore interpreted through both morphological and molecular information, because tumour biology may not be fully captured by histology alone (2). Molecularly targeted therapeutic strategies in glioblastoma have also been systematically reviewed, with emphasis on growth-factor receptors, angiogenesis, intracellular signalling pathways, and immune-related targets as major areas of investigation (3). MRI remains the central method for preoperative evaluation, surgical planning, and longitudinal assessment of glioma patients (4). Apart from localization and contrast enhancement, quantitative MRI-derived features, including tumour volume and peritumoral brain oedema, may provide clinically useful information on lesion burden, mass effect, vascular permeability, and the interaction between tumour tissue and the surrounding brain microenvironment (5).

*Corresponding author:
Fatima Juković-Bihorac
Department of Pathology, Cantonal Hospital Zenica, Zenica, Bosnia and Herzegovina
E-mail: fatima.bihorac@live.com
ORCID ID: 0000-0002-4151-2235

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B7-H3 (also known as CD276), a member of the B7 family of immune checkpoint proteins, is highly expressed in cancer cells and activated tumour-infiltrating immune cells. B7-H3 gained attention as a marker of aggressive tumour biology and as a potential therapeutic target (6). The broader B7-H3 literature describes both immune-related and non-immune functions, including effects on tumour-cell behaviour, invasion, angiogenesis, and treatment resistance (6). In brain malignancies, B7-H3 has been linked to immune escape and immunotherapeutic development (7). In glioblastoma specifically, B7-H3 has been discussed as a biologically relevant target with therapeutic implications (8). A previous publication from the same cohort confirmed the diagnostic and prognostic value of B7-H3 for differentiating high-grade from low-grade gliomas and for predicting progression and survival (9).

The relationship between B7-H3 expression and MRI-derived radiomorphometric characteristics has not been sufficiently addressed. This question is relevant because a tissue marker that correlates with MRI-visible tumour and oedema burden could help connect adverse histopathological parameters with the radiological phenotype. It may also support future radiopathological and radiogenomic models aimed at non-invasive prediction of biologically relevant therapeutic targets.

This study aimed to evaluate whether immunohistochemical B7-H3 expression is associated with MRI-derived tumour volume, peritumoral brain oedema volume, and oedema index in patients with gliomas.

MATERIAL AND METHODS

Study design and patients

A retrospective study was conducted using archival clinical, radiological, and histopathological data from patients with intracranial gliomas who underwent surgical treatment and follow-up at the Department of Neurosurgery, Cantonal Hospital Zenica, Bosnia and Herzegovina, between 1 January 2013 and 31 December 2021.

Inclusion criteria were a histopathologically confirmed intracranial glioma, surgical treatment and follow-up at Cantonal Hospital Zenica, available preoperative and postoperative neuroradiological documentation, available representative tumour tissue, and no neoadjuvant oncological treatment. Exclusion criteria were multiple primary intracranial tumours, haemorrhagic or incidental intracranial tumours, a history of other malignancies, incomplete follow-up data, and unavailable or non-representative tissue material.

Methods

Tumour samples were collected and processed according to a standard protocol. B7-H3 (clone RBT-B7H3, Bio SB, USA) expression was assessed using staining intensity, the percentage of immunoreactive tumour cells, and a composite immunoreactive score (IRS). Staining intensity was scored as 0 for negative staining, 1 for weak staining, 2 for moderate staining, and 3 for strong staining. The percentage of immunoreactive cells was scored as 0 for no staining, 1 for fewer than 10% positive tumour cells, 2 for 10-50% positive tumour cells, and 3 for more than 50% positive tumour cells. The composite B7-H3 IRS was calculated by multiplying the intensity score by the percentage score. Predefined intensity and extent categories are commonly used in semi-quantitative tissue-stain assessment because they support reproducible reporting and reduce ambiguity in observer-based scoring (10).

Radiomorphometric analysis was performed using the IMPAX system (version 6.5.1.144, AGFA HealthCare, Mortsel, Belgium). Tumour volume (TV) and peritumoral brain oedema (PTBE) volume were determined using the spheroid volume formula, as each tumour was approximately spherical in shape: $V = 4/3\pi \times a/2 \times b/2 \times c/2$ (11). Coronal, axial, and sagittal diameters were measured to calculate the cumulative volume of TV and PTBE. PTBE volume was then obtained by subtracting TV from the cumulative value. The relationship between TV and PTBE was assessed using the oedema index (EI): EI = (TV + PTBE)/TV (12). Tumour size was analysed on contrast-enhanced T1 sequences, while oedema size was analysed on T2 sequences (Figure 1). Measurements were expressed in cm^3.

The primary outcome variables were TV and PTBE, and the secondary outcome variable was EI.

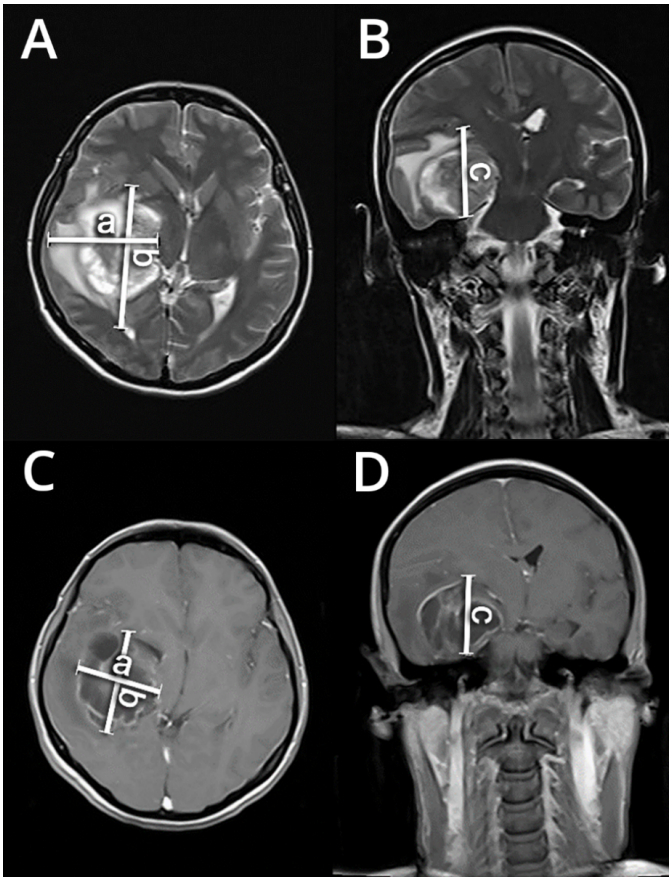

Figure 1. MRI-based radiomorphometric assessment of glioblastoma and peritumoral brain oedema: A) Axial measurement of two orthogonal diameters of the combined tumour-plus-oedema region, B) Sagittal measurement of the combined tumour-plus-oedema region, C) Axial measurement of two orthogonal tumour diameters, D) Sagittal measurement of tumour diameter

Statistical analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as n (%), and continuous variables were presented as median (IQR) because distributions were skewed. Spearman correlation was used to evaluate associations between B7-H3 expression pa-

Table 1. Clinicopathological and radiomorphometric characteristics of the cohort

Variable	Total cohort (N=99)
Demographic characteristics	
Age (years), median (IQR)	56 (46–63)
Male sex, *n* (%)	57 (57.6)
WHO grade, *n* (%)	
G1	12 (12.1)
G2	30 (30.3)
G3	21 (21.2)
G4	36 (36.4)
Immunohistochemistry analysis, median (IQR)	
Ki-67 (%)	20.0 (8.0–35.0)
B7-H3 staining intensity score (A)	2.0 (1.0–3.0)
B7-H3 immunoreactive cell percentage score (B)	3.0 (2.0–4.0)
B7-H3 IRS (A × B)	6.0 (3.0–8.5)
Radiographic analysis, median (IQR)	
Tumour volume (cm^3)	29.31 (12.17–49.12)
Peritumoral brain oedema volume (cm^3)	84.51 (47.59–178.18)
Oedema index	4.56 (3.83–5.00)

IRS, immunoreactive score; IQR, interquartile range; WHO, World Health Organization.

rameters and MRI-derived radiomorphometric variables. Linear regression was used to estimate crude and adjusted associations between B7-H3 IRS and each MRI-derived outcome. TV and PTBE were natural-log transformed because of right-skewed distribution. Adjusted models included age, sex, WHO grade, and Ki-67. Patients with missing Ki-67 were excluded from adjusted models, and patients with PTBE = 0 were excluded from models using ln(PTBE). WHO grade was recorded for cohort description and was used as an adjustment variable in multivariable models, while B7-H3 expression was analysed primarily as a semiquantitative immunohistochemical variable in relation to continuous MRI-derived measurements. Statistical significance was set at $p < 0.05$.

RESULTS

The study included 99 consecutive patients with intracranial gliomas. The median age was 56 years (IQR 46-63), with male predominance (57.6%). The cohort included WHO grade I, II, III, and IV tumours. Median Ki-67 was 20.0% (IQR 8.0-35.0). Median B7-H3 staining intensity score (A) was 2.0 (IQR 1.0-3.0), median percentage score of immunoreactive tumour cells (B) was 3.0 (IQR 2.0-4.0), and median composite B7-H3 IRS was 6.0 (IQR 3.0-8.5). Median TV was 29.31 cm^3 (IQR 12.17-49.12), median PTBE was 84.51 cm^3 (IQR 47.59-178.18), and median EI was 4.56 (IQR 3.83-5.00) (Table 1).

B7-H3 IRS showed strong positive correlations with TV ($r = 0.921$, $p < 0.001$) and PTBE ($r = 0.920$, $p < 0.001$). B7-H3 staining intensity (A) and the percentage score of immunoreactive tumour cells (B) also correlated positively with TV and PTBE. In contrast, EI did not correlate significantly with B7-H3 IRS ($r = -0.105$, $p = 0.299$). The correlation matrix is presented as Figure 2 to summarize the full pattern of associations; B7-H3 A and B are included in the matrix because their descriptive values are reported in Table 1, and their scoring method is defined in the Methods section.

Crude and adjusted regression results for all model variables are shown in Table 2. In crude models, B7-H3 IRS was associated with ln(TV) (beta = 0.239, 95% CI 0.213 to 0.266, $p < 0.001$) and ln(PTBE) (beta = 0.181, 95% CI 0.162 to 0.201, $p < 0.001$),

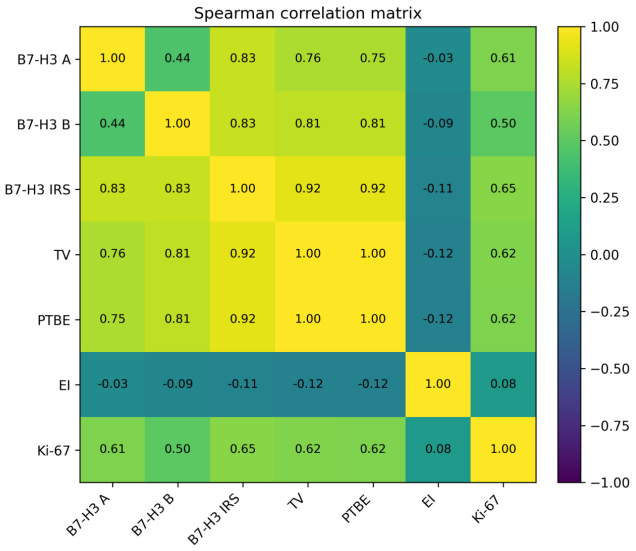

Figure 2. Spearman correlation matrix
B7-H3 A, staining intensity; B7-H3 B, percentage score of immunoreactive tumour cells; B7-H3 IRS, the composite immunoreactive score; EI, oedema index; PTBE, peritumoral brain oedema volume; TV, tumour volume

but not with EI (beta = 0.034, 95% CI -0.032 to 0.100, $p = 0.311$). After adjustment for age, sex, WHO grade, and Ki-67, B7-H3 IRS remained associated with ln(TV) (beta = 0.228, 95% CI 0.190 to 0.265, $p < 0.001$) and ln(PTBE) (beta = 0.178, 95% CI 0.152 to 0.204, $p < 0.001$), but not with EI (beta = 0.001, 95% CI -0.083 to 0.084, $p = 0.990$). In the adjusted EI model, WHO grade was positively associated with EI (beta = 0.867, 95% CI 0.481 to 1.253, $p < 0.001$), while Ki-67 had a negative association with EI (beta = -3.140, 95% CI -5.755 to -0.525, $p = 0.019$).

DISCUSSION

This study found that B7-H3 expression was strongly associated with adverse radiological features of gliomas, such as MRI-derived tumour volume and peritumoral brain oedema volume.

Table 2. Crude and adjusted associations of B7-H3 IRS, demographic variables, WHO grade, and Ki-67 with MRI-derived radiomorphometric outcomes

		Univariate analysis		Multivariate analysis	
Outcome	**Predictor**	**Crude β (95% CI)**	p	**Adjusted β (95% CI)**	p
ln(TV)	B7-H3 IRS	0.239 (0.213–0.266)	<0.001	0.228 (0.190–0.265)	<0.001
	Age	−0.001 (−0.015–0.012)	0.847	0.001 (−0.006–0.009)	0.732
	Female sex	−0.040 (−0.459–0.380)	0.851	0.031 (−0.200–0.262)	0.791
	WHO grade	0.535 (0.371–0.699)	<0.001	0.103 (−0.069–0.274)	0.237
	Ki-67	3.796 (2.729–4.862)	<0.001	−0.063 (−1.224–1.098)	0.915
ln(PTBE)	B7-H3 IRS	0.181 (0.162–0.201)	<0.001	0.178 (0.152–0.204)	<0.001
	Age	−0.002 (−0.012–0.008)	0.676	−0.001 (−0.006–0.004)	0.726
	Female sex	−0.018 (−0.327–0.292)	0.909	−0.017 (−0.181–0.147)	0.838
	WHO grade	0.293 (0.147–0.439)	<0.001	−0.094 (−0.226–0.037)	0.158
	Ki-67	2.469 (1.623–3.315)	<0.001	0.590 (−0.235–1.414)	0.158
EI	B7-H3 IRS	0.034 (−0.032–0.100)	0.311	0.001 (−0.083–0.084)	0.990
	Age	0.005 (−0.012–0.021)	0.577	0.011 (−0.005–0.028)	0.173
	Female sex	0.122 (−0.383–0.627)	0.633	0.323 (−0.197–0.843)	0.220
	WHO grade	0.405 (0.183–0.627)	<0.001	0.867 (0.481–1.253)	<0.001
	Ki-67	1.092 (−0.501–2.685)	0.177	−3.140 (−5.755–−0.525)	0.019

CI, confidence interval; EI, oedema index; IRS, immunoreactive score; PTBE, peritumoral brain oedema volume; TV, tumour volume; WHO, World Health Organization.

The association remained present after the adjustment for age, sex, WHO grade, and Ki-67. In contrast, B7-H3 expression was not associated with EI, suggesting that B7-H3 reflects absolute tumour and oedema burden rather than the proportional oedema-to-tumour relationship. This distinction is relevant because RANO 2.0 continues to place MRI-based assessment at the centre of glioma evaluation, while acknowledging that imaging interpretation must be standardized across both high-grade and lower-grade tumours (4).

The association between B7-H3 and tumour volume is biologically plausible. B7-H3 has been linked to tumour cell proliferation, metastasis, and therapeutic resistance. Furthermore, its marked difference in protein expression levels between healthy and tumour tissues suggests that targeting B7-H3 with drugs may lead to cancer-specific toxicity, minimizing harm to healthy cells (6).

Experimental glioma data showed that B7-H3 overexpression facilitated sustained glioma growth and promoted glioma cell invasion through a JAK2/STAT3/Slug-dependent signalling pathway (13). In that context, larger MRI-derived tumour volume among tumours with higher B7-H3 expression may represent a radiological manifestation of a more aggressive tissue phenotype. The relevance of imaging-based tumour characterization is supported by a recent MRI radiomics meta-analysis, which reported the diagnostic value of MRI-derived radiomic features for differentiating high-grade from low-grade gliomas (5). Although the present work did not use a radiomics pipeline, it follows the same general premise that measurable MRI features can reflect biologically meaningful tumour variation.

The correlation between B7-H3 expression and PTBE is also clinically relevant. Peritumoral oedema is a major contributor to mass effect and neurological impairment in brain tumours, and it is usually interpreted as a consequence of vascular permeability, blood-brain barrier disruption, and tumour-microenvironment interactions. B7-H3-related pathways may contribute to an invasive and pro-tumorigenic microenvironment (7). This interpretation is supported by glioblastoma-focused literature on B7-H3 therapeutic relevance (8) and by experimental evidence linking B7-H3 with glioma invasion (13). Pan-cancer data also support the broader therapeutic relevance of B7-H3 as an actionable target across human malignancies (14), while antibody-based B7-H3 immunotherapy has been reviewed as a developing anticancer strategy (11).

In a previous study from this cohort (3), the composite B7-H3 IRS discriminated high-grade from low-grade gliomas with an AUC of 0.816, and high B7-H3 expression independently predicted disease progression (OR = 4.9, 95% CI 2.4-10.1) (9). Patients with high B7-H3 expression also had shorter overall survival, with median values of six months versus 42 months, and shorter progression-free survival, with median values of three months versus 25 months (9).

The lack of association with EI is important. EI is a ratio and does not measure the same phenomenon as absolute oedema volume (12). A tumour with high B7-H3 expression may have large tumour and oedema volumes, but the amount of oedema may not be disproportionate to tumour size. This distinction explains why B7-H3 was associated with TV and PTBE but not with EI. From a practical perspective, TV and PTBE may be closer to overall lesion burden, whereas EI may depend on additional factors such as tumour location, vascular architecture, corticosteroid exposure, timing of imaging, and individual differences in blood-brain barrier permeability.

Several limitations should be acknowledged. The retrospective single-centre design may introduce selection bias and limit generalizability. Volumetric assessment was based on orthogonal diameter measurements and spheroid approximation rather than fully segmented three-dimensional volumetry. Molecular variables beyond *IDH* status, including 1p/19q codeletion, *MGMT* promoter methylation, *TERT* promoter mutation, and *EGFR* amplification, were not incorporated into the present multivariable models. Future studies should validate these findings in larger cohorts using standardized MRI acquisition protocols, segmentation-based volumetry, and integrated molecular profiling.

CONCLUSION

B7-H3 expression is independently associated with MRI-derived tumour volume and peritumoral brain oedema volume in gliomas, but not with oedema index. These findings suggest that B7-H3 reflects absolute MRI-visible lesion burden and support further radiopathological studies evaluating B7-H3 as a tissue marker linked to glioma imaging phenotype.

FUNDING

No specific funding was received for this study.

CONFLICTS OF INTEREST

None to declare.

ETHICS STATEMENT

The study was approved by the Ethics Committee of Cantonal Hospital Zenica (approval number 00-03-35-464-11/23, 29 April 2024) and by the Faculty of Medicine, University of Banja Luka.

DATA AVAILABILITY STATEMENT

The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request, subject to institutional and ethical approval requirements.

AUTHOR CONTRIBUTIONS (CRediT)

Conceptualization: F.J.-B., E.B., S.V.; **Data curation:** F.J.-B., E.B.; **Formal analysis:** E.B.; **Investigation:** F.J.-B., S.Đ.; **Methodology:** F.J.-B., E.B., S.Đ.; **Project administration:** F.J.-B., E.B.; **Supervision:** S.Đ., S.V.; **Writing – original draft:** F.J.-B., E.B.; **Writing – review & editing:** F.J.-B., E.B., S.Đ., A.E., S.V. All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011-2015. Neuro Oncol 2018;20:iv1-86. doi:10.1093/neuonc/noy131
2. WHO Classification of Tumours Editorial Board. Central nervous system tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2021.
3. Begagić E, Pugonja R, Bečulić H, Čeliković A, Tandir Lihić L, Kadić Vukas S, et al. Molecular Targeted Therapies in Glioblastoma Multiforme: A Systematic Overview of Global Trends and Findings. Brain Sci 2023;13:1602. doi:10.3390/brainsci13111602
4. Wen PY, van den Bent M, Youssef G, Cloughesy TF, Ellingson BM, Weller M, et al. RANO 2.0: Update to the Response Assessment in Neuro-Oncology Criteria for High- and Low-Grade Gliomas in Adults. J Clin Oncol 2023;41:5187-5199. doi:10.1200/JCO.23.01059
5. Wang J, Chen Z, Chen J. Diagnostic value of MRI radiomics in differentiating high-grade glioma from low-grade glioma: A meta-analysis. Oncol Lett 2023;26:436. doi:10.3892/ol.2023.14023
6. Getu AA, Tigabu A, Zhou M, Lu J, Fodstad Ø, Tan M. New frontiers in immune checkpoint B7-H3 (CD276) research and drug development. Mol Cancer 2023;22:43. doi:10.1186/s12943-023-01751-9
7. Guo X, Chang M, Wang Y, Xing B, Ma W. B7-H3 in Brain Malignancies: Immunology and Immunotherapy. Int J Biol Sci 2023;19:3762-3780. doi:10.7150/ijbs.85813
8. Babič D, Jovčevska I, Zottel A. B7-H3 in glioblastoma and beyond: Significance and therapeutic strategies. Front Immunol 2024;15:1495283. doi:10.3389/fimmu.2024.1495283
9. Juković-Bihorac F, Đuričić S, Begagić E, Bečulić H, Efendić A, Vranić S, et al. B7-H3 as a Reliable Diagnostic Biomarker for the Differentiation of High-Grade Gliomas (HGGs) and Low-Grade Gliomas (LGGs). Brain Sci 2025;15:872. doi:10.3390/brainsci15080872
10. Meyerholz DK, Beck AP. Principles and approaches for reproducible scoring of tissue stains in research. Lab Invest 2018;98:844-855. doi:10.1038/s41374-018-0057-0
11. Kontos F, Michelakos T, Kurokawa T, Sadagopan A, Schwab JH, Ferrone CR, et al. B7-H3: An Attractive Target for Antibody-based Immunotherapy. Clin Cancer Res 2021;27:1227-1235. doi:10.1158/1078-0432.CCR-20-2584
12. Pugonja R, Bečulić H, Begagić E, Skomorac R, Selimović E, Moranjkić M. Morphometric and Ki-67 proliferative index-related characteristics of meningiomas and their correlation with demographic, clinical, histopathological, and postoperative features. Med Glas (Zenica) 2024;21:132-139. doi:10.17392/1650-23
13. Zhong C, Tao B, Chen Y, Guo Z, Yang X, Peng L, Xia X, Chen L. B7-H3 Regulates Glioma Growth and Cell Invasion Through a JAK2/STAT3/Slug-Dependent Signaling Pathway. OncoTargets Ther 2020;13:2215-2224. doi:10.2147/OTT.S237841
14. Miller CD, Lozada JR, Zorko NA, Elliott A, Makovec A, Radovich M, Heath EI, et al. Pan-Cancer Interrogation of B7-H3 (CD276) as an Actionable Therapeutic Target Across Human Malignancies. Cancer Res Commun 2024;4:1369-1379. doi:10.1158/2767-9764.CRC-23-0546