ORIGINAL ARTICLE

DOI: 10.37047/jos.galenos.2026.2026-2-2
J Oncol Sci 2026;12(2):186-194

Prognostic Significance of Postoperative Edema in Surgically Treated Non-glioblastoma Diffuse Glioma

Erkam KOCAASLAN[1], Gülşah ÖZDEN[2], Melek Hazal FİLİZCAN[3], Ayşe Pelin AÇMA[3], Fırat AKAGÜNDÜZ[1], Ahmet DEMİREL[1], Mustafa Alperen TUNÇ[1], Burak PAÇACI[1], Yeşim AĞYOL[1], Pınar EREL[1], Ali Kaan GÜREN[1], Osman KÖSTEK[1], İbrahim Vedat BAYOĞLU[1]

[1]Marmara University Pendik Training and Research Hospital, Department of Medical Oncology, İstanbul, Türkiye
[2]Marmara University Pendik Training and Research Hospital, Department of Radiation Oncology, İstanbul, Türkiye
[3]Marmara University Pendik Training and Research Hospital, Department of Internal Medicine, İstanbul, Türkiye

ABSTRACT

Objective: Tumor-associated edema has been implicated as a marker of aggressive tumor biology in gliomas, yet most existing evidence is derived from preoperative imaging and glioblastoma-focused cohorts. The prognostic significance of postoperative edema in non-glioblastoma diffuse gliomas remains insufficiently characterized.

Material and Methods: This retrospective cohort study included patients with histologically confirmed non-glioblastoma diffuse gliomas who underwent surgical intervention at a single tertiary center between October 2010 and January 2024. Postoperative edema was assessed using routine magnetic resonance imaging and classified as present or absent. Overall survival (OS) was defined as the time from diagnosis to death from any cause or to last follow-up. Survival analyses were performed using Kaplan-Meier methods and Cox proportional hazards regression models. Multivariable models were constructed using clinically relevant covariates selected a priori, with sensitivity analyses incorporating performance status and comorbidity burden.

Results: A total of 79 patients were included. Postoperative edema was present in 34 patients (54.8%). Median OS was significantly shorter in patients with postoperative edema compared with those without edema (69 vs. 108 months; log-rank p=0.007). In multivariable Cox regression analysis, postoperative edema was independently associated with worse OS (hazard ratio: 2.86; 95% confidence interval: 1.41-5.88; p=0.004), after adjustment for tumor grade, tumor location, surgical procedure, and adjuvant treatment. Tumor grade and non-supratentorial location were also independently associated with poorer survival. The association between postoperative edema and OS remained significant in sensitivity analyses that included Eastern Cooperative Oncology Group performance status and the Charlson Comorbidity Index.

Conclusion: Postoperative edema is a independently associated with OS in patients with non-glioblastoma diffuse glioma. These findings suggest that routine assessment of postoperative edema may provide clinically meaningful prognostic information beyond established clinicopathological factors and may support its potential role in postoperative risk stratification.

Keywords: Glioma; postoperative edema; overall survival; magnetic resonance imaging; prognosis; Cox regression

INTRODUCTION

Gliomas represent the most common primary malignant tumors of the central nervous system and encompass a biologically heterogeneous group of neoplasms with highly variable clinical outcomes. Despite advances in molecular classification and multimodal treatment strategies, high-grade gliomas remain associated with poor survival, underscoring the need for improved prognostic stratification beyond traditional clinicopathological factors.[1,2]

Current prognostic assessment in glioma relies on a combination of patient-related factors, tumor grade, molecular characteristics, and treatment-related variables.[3] However, increasing evidence suggests that imaging-derived features may capture additional aspects of tumor biology

Correspondence: Erkam KOCAASLAN MD; Osman KÖSTEK MD;
Marmara University Pendik Training and Research Hospital, Department of Medical Oncology, İstanbul, Türkiye
E-mails: erkamkocaaslan@gmail.com; osmankostek@yahoo.com
ORCID IDs: orcid.org/0000-0002-8994-2904; orcid.org/0000-0002-1901-5603

Received: 05.02.2026 **Accepted:** 13.06.2026 **Epub:** 13.07.2026 **Publication Date:** 31.08.2026

Cite this article as: Kocaaslan E, Özden G, Filizcan MH, et al. Prognostic significance of postoperative edema in surgically treated non-glioblastoma diffuse glioma. J Oncol Sci. 2026;12(2):186-194

Available at journalofoncology.org

©Copyright 2026 The Author(s). Published by Galenos Publishing House on behalf of Turkish Society of Medical Oncology.
Licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

that are not fully reflected by histopathology alone.[4] Tumor-associated cerebral edema has gained attention as a potential marker of aggressive behavior and adverse outcome in malignant gliomas.

Peritumoral edema in glioma is predominantly vasogenic, arising from blood–brain barrier disruption driven by abnormal tumor angiogenesis and inflammatory signaling.[5] Importantly, the edematous region may contain infiltrative tumor cells beyond contrast-enhancing margins, contributing to local recurrence and treatment resistance.[6] Several studies have demonstrated that the extent of preoperative peritumoral edema is associated with reduced survival in glioblastoma, supporting its prognostic relevance.[7]

Although much of the existing evidence linking tumor-associated edema to prognosis originates from glioblastoma-focused studies, it remains unclear whether these observations extend to the broader spectrum of gliomas with varying histological grades and biological behavior. Glioblastoma represents the end of the glioma continuum and is characterized by pronounced vascular permeability and edema formation; findings derived from this subgroup may not be directly generalized to lower- and intermediate-grade gliomas. Moreover, the prognostic relevance of edema assessed in the postoperative setting—where imaging findings reflect a composite of residual infiltrative disease, surgical effects, and early postoperative tissue responses—has not been systematically evaluated across heterogeneous glioma populations.

Clarifying the prognostic significance of postoperative edema across the glioma spectrum may, therefore, provide clinically meaningful insights into disease biology and postoperative risk stratification, thereby addressing an important gap in the existing literature. This study aimed to examine the association between postoperative cerebral edema and overall survival (OS) in patients with surgically treated non-glioblastoma diffuse gliomas, and to determine whether postoperative edema provides independent prognostic value beyond established clinicopathological factors.

MATERIAL AND METHODS

Study Design, Setting, and Participants

This retrospective cohort study was conducted at Marmara University Hospital, a tertiary referral center. Patients treated between October 2010 and January 2024 were identified using the institutional oncology archive database and the electronic medical records. The initial screened population comprised 291 patients with a diagnosis of diffuse glioma.

To focus the analysis on non-glioblastoma diffuse gliomas and ensure consistency with the 2021 World Health Organization (WHO) classification of central nervous system tumors, patients with glioblastoma (WHO grade 4) were excluded (n=180). Among the remaining 111 patients with non-glioblastoma diffuse glioma, 32 were additionally excluded because postoperative imaging was unavailable or not assessable for postoperative edema evaluation, or because survival follow-up data (vital status and/or date of last follow-up) could not be reliably retrieved. The final study cohort therefore consisted of 79 patients who were included in the survival analyses (Figure 1).

This study was approved by the Marmara University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (approval number: 09.2024.1472, date: 21.12.2024).

Imaging Assessment and Definition of Postoperative Edema

Postoperative edema, the primary exposure of interest, was assessed using routine postoperative magnetic resonance imaging (MRI) performed as part of standard clinical care. Edema assessment was based primarily on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences, in which vasogenic edema typically appears as a hyperintense signal in the surrounding brain parenchyma. Because non-

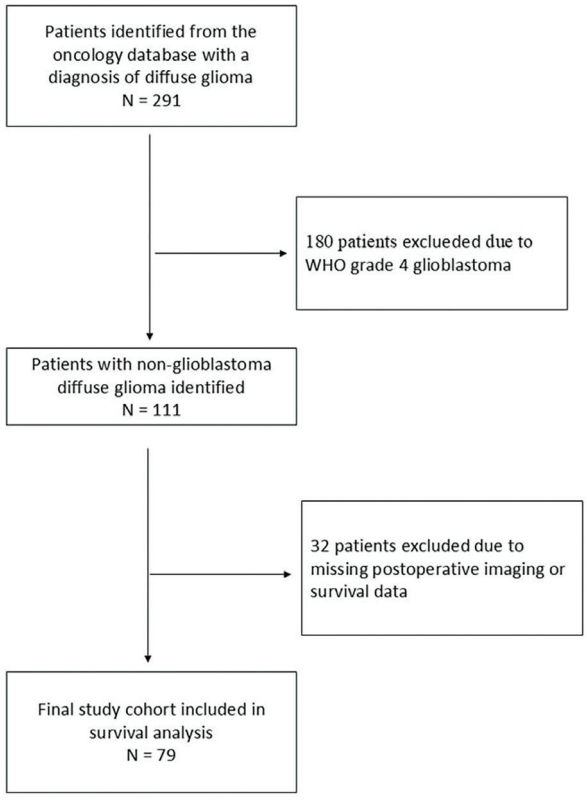

FIGURE 1: Flow diagram of patient selection for the study cohort.

enhancing tumors and edema can overlap on T2/FLAIR and postoperative reactive changes may confound interpretation, edema status was determined using a structured approach aligned with widely accepted neuro-oncology imaging principles. Postoperative edema was recorded as present when a perilesional T2/FLAIR hyperintense region, consistent with vasogenic edema, was visible adjacent to the operative bed and/or residual lesion, and as absent when no such edematous signal abnormality was identified. Postoperative edema was assessed using the first MRI, which was routinely performed within 72 hours after surgery as part of standard clinical care. It was coded as a binary variable (present vs. absent).

To reduce misclassification related to early postoperative effects, T2/FLAIR findings were interpreted in conjunction with other routinely available sequences, particularly diffusion-weighted imaging (DWI) when available, because evidence suggests that resection-related ischemia and postoperative tissue injury may increase non-enhancing FLAIR/T2 signal, which can be better contextualized by DWI. This is consistent with published observations that early postoperative MRI can overestimate non-enhancing abnormalities on FLAIR due to operative effects and ischemia, and that DWI can improve the distinction between postoperative change and residual disease. In addition, interpretation of non-enhancing T2/FLAIR signal changes is a recognized challenge in glioma imaging assessment frameworks, which emphasize qualitative evaluation of non-enhancing disease components.[8] Edema status was assessed by two readers experienced in neuro-oncologic MRI interpretation who were blinded to survival outcomes. Discrepancies were resolved by consensus. Although no formal quantitative or volumetric framework was applied, the assessment approach was aligned with widely accepted neuro-oncology imaging principles used in routine clinical practice.

Outcome and Variables

The primary outcome was OS, defined as the time from initial diagnosis to death from any cause. Patients alive at the last clinical contact were censored at the date of the last follow-up. Demographic, clinical, tumor-related, imaging, and treatment-related variables were retrospectively abstracted from electronic medical records, operative reports, pathology reports, and oncology treatment records using prespecified definitions. Tumor grade was recorded based on histopathological assessment and categorized as grades 1-3, consistent with the non-glioblastoma composition of the study cohort. Tumor location was dichotomized into supratentorial and non-supratentorial (including deep, midline, and brainstem) to avoid sparse subgroups and to preserve model stability.

The type of surgical procedure was classified as biopsy or debulking, and adjuvant treatment was categorized as radiotherapy alone or radiotherapy combined with temozolomide. Eastern Cooperative Oncology Group (ECOG) performance status and the Charlson Comorbidity Index (CCI) were assessed at the postoperative referral time point, concurrently with the evaluation of postoperative edema. Given the potential temporal overlap between these variables and the primary exposure of interest, ECOG performance status and comorbidity burden were not included in the primary multivariable model, but were instead evaluated in prespecified sensitivity analyses to assess the robustness of the main findings.

Statistical Analysis

OS was summarized using the Kaplan-Meier method and compared between postoperative edema groups using the log-rank test. Univariable Cox proportional hazards regression analyses were performed to examine associations between individual covariates and OS, with results reported as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). A multivariable Cox proportional hazards model was prespecified to include age, postoperative edema status, tumor grade, tumor location, surgical procedure, and adjuvant therapy. All variables were entered simultaneously using the enter method. The proportional hazards assumption was assessed using log-minus-log plots, and no major violations were observed. Primary multivariable analyses were conducted using complete-case data for the prespecified model. Exposure to bevacizumab was evaluated only in univariable analyses and was not included in multivariable survival models because of its post-baseline, time-dependent nature and the associated risk of immortal time bias. To assess the stability of the multivariable model and mitigate concerns regarding overfitting, internal validation was performed using bootstrap resampling with 1,000 iterations, focusing on the robustness of HR estimates. Prespecified sensitivity analyses were conducted by additionally including ECOG performance status and the CCI in the multivariable Cox model to assess the robustness of the association between postoperative edema and OS. In addition to the primary survival analyses, exploratory analyses were performed to examine the association between the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACE/ARB) and postoperative edema. Differences in the frequency of postoperative edema between ACE/ARB users and non-users were initially assessed using Fisher's exact test. A multivariable logistic regression model was subsequently constructed to evaluate the independent association between ACE/ARB use and the presence of postoperative edema, adjusting for age, tumor grade, tumor location, surgical procedure,

and adjuvant therapy. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient Characteristics

A total of 79 patients with non-glioblastoma diffuse glioma were included in the analysis. The median age at diagnosis was 35 years (interquartile range, 29-50), and 31 patients (39.2%) were male. With respect to tumor grade, 7 patients (10.1%) had grade 1 tumors, 36 (52.2%) had grade 2 tumors, and 26 (37.7%) had grade 3 tumors.

The majority (85.7%) of tumors were located in the supratentorial compartment, 9.1% in deep or midline structures, and 5.2% in the pons. Postoperative edema was present in 34 patients (54.8%). Most patients (91.0%) underwent debulking surgery rather than a biopsy.

Regarding adjuvant treatment, 46.8% of patients received radiotherapy alone and 53.2% received radiotherapy combined with temozolomide. ACE/ARB use was documented in 17.7% of patients, and 70.9% of patients had received bevacizumab at any point during their disease course. At the postoperative assessment, 67.1% of patients had a CCI of 0, and 50.8% had an ECOG performance status of 0 (Table 1).

Survival Outcomes and Prognostic Analyses

Median OS was 72.0 months (95% CI: 51.9-92.1) in the overall cohort. The median follow-up duration, estimated using the reverse Kaplan-Meier method, was 213.0 months (95% CI: 122.1-303.9). During follow-up, 59 deaths were observed, and 20 patients were censored at the last follow-up. Median OS differed significantly according to postoperative edema status. Kaplan-Meier analysis demonstrated that patients with postoperative edema had significantly shorter OS than those without edema: median OS was 69.0 months (95% CI: 51.4-86.6) for patients with postoperative edema and 108.0 months (95% CI: 56.8-159.2) for those without edema (log-rank p=0.007) (Figure 2).

In univariable Cox regression analyses, postoperative edema, tumor grade, tumor location, and ACE/ARB use were significantly associated with OS. Postoperative edema was associated with an increased risk of death (HR: 2.36; 95% CI: 1.24-4.49; p=0.009). In univariable analyses, tumor grade and tumor location demonstrated significant associations with OS, whereas age, sex, ECOG performance status, CCI, surgical procedure, adjuvant treatment modality, and bevacizumab exposure were not significantly associated with OS (Table 2).

In multivariable Cox regression analysis, the presence of postoperative edema was independently associated with an increased risk of death (HR: 2.86; 95% CI: 1.41-5.88; p=0.004) (Table 3, Figure 3). Tumor grade remained a strong independent prognostic factor, with patients in the highest-grade group exhibiting a substantially higher risk of death compared with those with lower-grade tumors. Non-supratentorial tumor location was also independently associated with worse OS (HR: 5.26; 95% CI: 1.16-25.00; p=0.031). Age, type of surgical procedure, and adjuvant treatment modality were not independently associated OS in the multivariable model. ECOG performance status and CCI were not included in the primary multivariable model because their assessment was contemporaneous with postoperative edema, creating a potential risk of overadjustment; their impact was therefore evaluated in prespecified sensitivity analyses. The overall model was statistically significant

TABLE 1: Baseline demographic, clinical, and tumor characteristics of the study cohort (n=79).

Variable	Value
Age at diagnosis, years	35 (29-50)
Sex, male	31 (39.2%)
Tumor grade	
Grade 1	7 (10.1%)
Grade 2	36 (52.2%)
Grade 3	26 (37.7%)
Primary tumor location	
Supratentorial	66 (85.7%)
Deep/midline	7 (9.1%)
Pons	4 (5.2%)
Postoperative edema, present	34 (54.8%)
Surgical procedure, debulking	71 (91.0%)
Adjuvant treatment	
Radiotherapy alone	37 (46.8%)
Radiotherapy + temozolomide	42 (53.2%)
ACE/ARB use	14 (17.7%)
Bevacizumab exposure, ever	56 (70.9%)
Charlson Comorbidity Index, 0	
0	53 (67.1%)
≥1	26 (32.9%)
ECOG performance status	
0	31 (50.8%)
≥1	30 (49.2%)

Age is presented as median (interquartile range). RT: Radiotherapy; TMZ: Temozolomide; ACE/ARB: Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ECOG: Eastern Cooperative Oncology Group.

(Omnibus χ^2=31.82; p<0.001), indicating good explanatory power. Bootstrap internal validation demonstrated consistent HR estimates across resampled datasets. In particular, postoperative edema remained independently associated with OS after bootstrap resampling (bootstrap p=0.042; BCa 95% CI: -2.01 to -0.69), supporting the robustness of the primary multivariable findings. In sensitivity analyses that additionally adjusted for ECOG performance status and CCI, postoperative edema remained independently associated with OS (HR: 3.34; 95% CI: 1.17-9.55; p=0.024), consistent with the primary multivariable analysis (Supplementary Table S1). Neither ECOG performance status nor comorbidity burden was independently associated with survival.

Exploratory Analysis: ACE/ARB Use and Postoperative Edema

In exploratory analyses, the association between use of ACE/ARB and postoperative edema was evaluated. In unadjusted analyses, postoperative edema was numerically less frequent among patients receiving ACE/ARB therapy compared with non-users; however, this difference did not reach statistical significance (Fisher's exact p=0.220).

In multivariable logistic regression analysis, adjusting for age, tumor grade, tumor location, surgical procedure, and adjuvant therapy, ACE/ARB use was not independently associated with

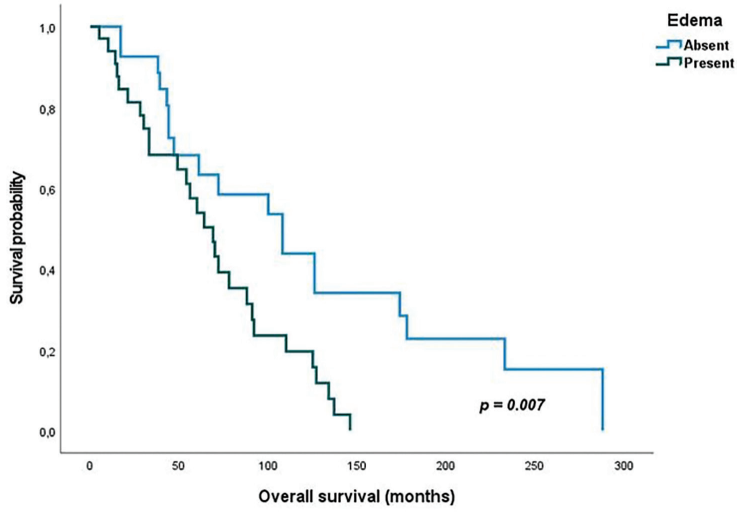

FIGURE 2: Kaplan-Meier curves for overall survival stratified by postoperative edema status. Patients with postoperative edema had significantly shorter overall survival compared with those without edema.

TABLE 2: Univariable Cox proportional hazards analysis for overall survival.

Variable	Hazard ratio (95% CI)	p-value
Age (per year increase)	1.01 (0.99-1.04)	0.375
Sex (male vs. female)	0.90 (0.53-1.53)	0.688
ECOG (≥1 vs. 0)	1.00 (0.55-1.84)	0.997
CCI (≥1 vs. 0)	2.90 (0.78-10.84)	0.113
Tumor grade (overall)	—	0.006
Grade 1 vs. grade 3	1.93 (0.77-4.87)	0.162
Grade 2 vs. grade 3	0.50 (0.27-0.91)	0.022
Tumor location (non-supratentorial vs. supratentorial)	2.22 (1.10-4.46)	0.026
Postoperative edema (present vs absent)	2.36 (1.24-4.49)	0.009
Surgical procedure (biopsy vs. debulking)	1.83 (0.77-4.30)	0.169
Adjuvant therapy (RT alone vs. RT+TMZ)	1.36 (0.81-2.29)	0.241
ACE/ARB use (yes vs. no)	2.66 (1.19-5.94)	0.017
Bevacizumab exposure (ever vs. never)	1.36 (0.73-2.54)	0.328

Reference categories for categorical variables were as follows: female for sex, ECOG 0 for performance status, Charlson Comorbidity Index 0, supratentorial location for tumor site, absence of postoperative edema, debulking for surgical procedure, radiotherapy plus temozolomide for adjuvant treatment, no use for ACE/ARB, and no exposure for bevacizumab. ACE/ARB: Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ECOG: Eastern Cooperative Oncology Group; RT: Radiotherapy; TMZ: Temozolomide; CI: Confidence interval.

postoperative edema (odds ratio: 2.21; 95% CI: 0.49-10.06; p=0.304) (Supplementary Table S1). Model calibration was acceptable based on the Hosmer-Lemeshow goodness-of-fit test (p=0.437).

DISCUSSION

In this retrospective cohort study of patients with histologically confirmed non-glioblastoma diffuse glioma, postoperative edema emerged as an independent factor associated with OS. Patients without postoperative edema experienced significantly longer survival compared with those with edema, and this association remained robust after adjustment for tumor grade, anatomical location, and treatment-related factors. Notably, the adverse prognostic impact of postoperative edema persisted after additional adjustment for functional status and comorbidity burden, indicating that edema conveys prognostic information beyond general health status or baseline performance alone.

The prognostic relevance of tumor-associated edema has been investigated predominantly in the preoperative setting, with most available evidence derived from studies of glioblastoma and other high-grade gliomas. Several investigations have demonstrated that the presence and extent of peritumoral edema on baseline MRI are associated with shorter OS, independent of age, tumor grade, and extent of resection. Schoenegger et al.[9] showed that preoperative peritumoral edema was an independent adverse prognostic factor in glioblastoma, while Wu et al.[7] similarly reported poorer outcomes in glioma patients with more extensive edema on routine MRI. Collectively, these findings support the concept that edema reflects aggressive tumor biology rather than being a purely reactive imaging phenomenon.

TABLE 3: Multivariable Cox proportional hazards analysis of overall survival.

Variable	HR	95% CI	p-value
Age (per 1-year increase)	1.02	0.99-1.06	0.207
Postoperative edema (present vs. absent)	2.86	1.41-5.88	0.004
Grade (overall)	—	—	<0.001
Grade (highest vs. lower)	16.7	3.7-50.0	<0.001
Grade (highest vs. intermediate)	7.7	1.7-33.3	0.008
Adjuvant therapy (RT alone vs. RT + TMZ)	1.06	0.51-2.22	0.858
Surgical procedure (biopsy vs. debulking)	1.47	0.35-6.25	0.598
Tumor location (non-supratentorial vs. supratentorial)	5.26	1.16-25.00	0.031

RT: Radiotherapy; TMZ: Temozolomide; HR: Hazard ratio; CI: Confidence interval.

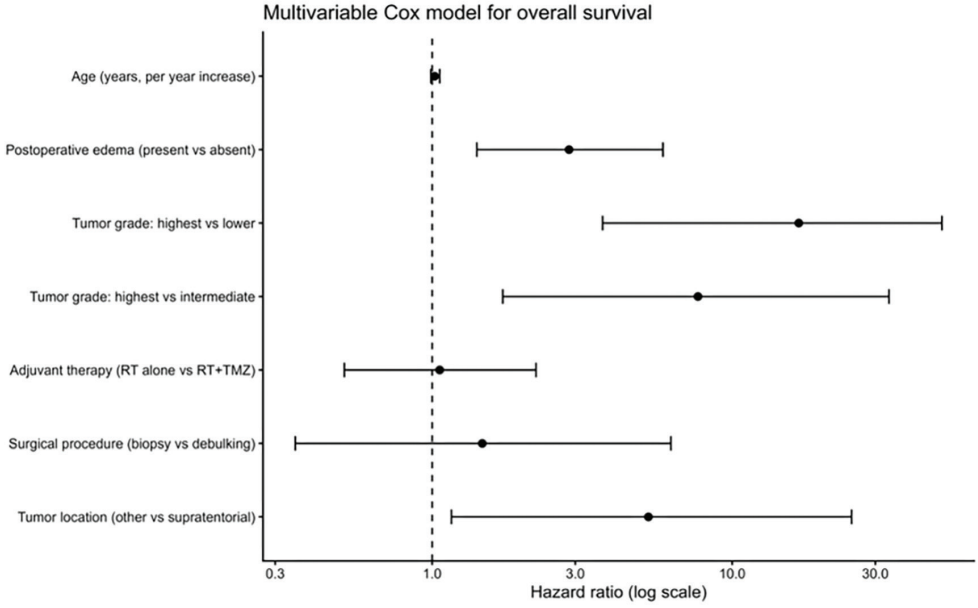

FIGURE 3: Forest plot showing hazard ratios from the multivariable Cox proportional hazards model for overall survival. Hazard ratios greater than 1 indicate increased risk of death relative to the reference category.

RT: Radiotherapy; TMZ: Temozolomide

Data addressing the prognostic role of edema in non-glioblastoma diffuse gliomas are limited, and most mechanistic and prognostic insights are extrapolated from high-grade disease. Nevertheless, the biological processes underlying edema formation—including blood-brain barrier disruption, abnormal tumor vasculature, and inflammatory signaling—are not unique to glioblastoma and are observed across the broader glioma spectrum.[4,10,11] In this context, our findings extend observations in high-grade gliomas by demonstrating that postoperative edema retains independent prognostic significance in non-glioblastoma diffuse gliomas, supporting the generalizability of edema-associated adverse biology beyond WHO grade 4 disease.

The postoperative setting deserves consideration. Early postoperative MRI is routinely performed to assess residual tumor and surgical complications, and edema detected at this time may reflect persistent microvascular dysfunction, residual infiltrative tumor burden, or an early postoperative inflammatory milieu. Prior imaging studies have highlighted the complexity of interpreting non-enhancing T2/FLAIR abnormalities and edema in glioma patients, emphasizing their association with survival and treatment resistance.[4,11] Our results suggest that postoperative edema, even when assessed qualitatively using routine clinical imaging, provides clinically meaningful prognostic information that may be readily incorporated into postoperative risk stratification frameworks.

Tumor grade remained one of the strongest independent predictors of survival in our cohort, consistent with extensive clinical evidence demonstrating progressively worse outcomes with increasing histological grade in diffuse gliomas.[2] Patients with lower- and intermediate-grade tumors exhibited substantially improved survival compared with those harboring higher-grade disease, in line with large cohort studies showing a strong and independent association between WHO grade and OS.[12] In addition, supratentorial tumor location was independently associated with better outcomes than non-supratentorial locations, a finding that has been previously attributed to differences in surgical accessibility, extent of resection, and the intrinsic biological behavior of deep and midline gliomas.[13] The lack of a significant association between surgical procedure and survival in our cohort should be interpreted cautiously, because the simplified classification of surgical extent (biopsy vs. debulking) and the limited number of biopsy cases may have reduced the statistical power to detect a true effect.

Although use of ACE/ARB was associated with worse OS in univariable analyses, this relationship was attenuated after multivariable adjustment, suggesting confounding by baseline clinical and treatment-related factors.[14-17] In our cohort, ACE/ARB exposure was not independently associated with postoperative edema, and the observed survival signal did not persist after adjustment. Therefore, this exploratory finding should be considered hypothesis-generating rather than evidence of a direct causal effect.

The persistence of the postoperative edema-survival association after adjustment for the ECOG performance status and the CCI is noteworthy. Performance status and comorbidity burden are well-established prognostic factors in glioma and other solid tumors, with poorer ECOG scores and higher comorbidity indices consistently associated with inferior survival outcomes.[18,19] The continued significance of postoperative edema after accounting for these variables suggests that edema captures disease-specific biological information rather than merely reflecting patient frailty or functional impairment. This observation is consistent with prior studies demonstrating that imaging-based biomarkers in glioma may provide incremental prognostic value beyond traditional clinical measures, reflecting underlying tumor biology and disease burden rather than patient frailty per se.[4,20] To minimize the risk of model overfitting in this modest-sized cohort, a parsimonious multivariable strategy was deliberately employed, with clinically relevant covariates selected a priori and contemporaneous variables evaluated separately in sensitivity analyses, consistent with established methodological recommendations.[21,22]

Study Limitations

Several limitations should be acknowledged. The retrospective, single-center design introduces potential selection bias and residual confounding despite multivariable adjustment. The relatively modest sample size limits statistical power for subgroup and exploratory analyses, and increases susceptibility to model instability. Postoperative edema was assessed on routine clinical MRI and evaluated qualitatively as a binary variable; this qualitative evaluation may be influenced by postoperative changes and does not capture volumetric or morphological heterogeneity. In addition, heterogeneity in adjuvant treatment strategies over the extended study period and the lack of uniformly available molecular tumor data may have limited comprehensive risk stratification and adjustment. Importantly, comprehensive molecular classification data, including IDH mutation status and 1p/19q co-deletion, were not uniformly available due to the retrospective design and long inclusion period. Given the central role of molecular markers in the current WHO classification of diffuse gliomas, this limitation may have introduced residual confounding. Prospective studies incorporating standardized volumetric edema assessment, serial postoperative imaging, and integrated molecular profiling may help address these limitations and further

clarify the biological underpinnings of edema-associated risk.

Despite these limitations, several strengths of this study deserve emphasis. First, the analysis focused on postoperative edema assessed using routinely acquired clinical MRI, which represents a clinically relevant and underexplored time point in glioma prognostication. Second, the study cohort predominantly comprised non-glioblastoma diffuse gliomas, thereby addressing an important gap in the literature, which has largely focused on glioblastoma and other high-grade tumors. Third, a rigorous and parsimonious multivariable modeling strategy was employed, with covariates selected a priori and sensitivity analyses performed to assess the robustness of the findings thereby minimizing the risk of overfitting. Edema assessment relied on standard imaging sequences without specialized software or advanced post-processing, enhancing applicability of the findings in routine clinical settings. Prospective studies incorporating standardized volumetric assessment of edema and integrated molecular profiling are warranted to validate these findings.

CONCLUSION

Postoperative edema is independently associated with OS in patients with non-glioblastoma diffuse glioma, retaining prognostic significance after comprehensive multivariable adjustment. Routine assessment of postoperative edema may therefore aid postoperative risk stratification, inform the intensity of follow-up and the planning of adjuvant treatment, and serve as a stratification factor in future clinical trials. Further studies are warranted to elucidate the biological mechanisms linking edema to adverse outcomes and to explore whether targeted interventions aimed at edema modulation can translate into improved survival.

Ethics

Ethics Committee Approval: This study was approved by the Marmara University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (approval number: 09.2024.1472, date: 21.12.2024).

Informed Consent: Retrospective study.

Acknowledgements

The authors would like to thank the Department of Neurosurgery, Department of Radiology, and Department of Radiation Oncology at Marmara University Pendik Training and Research Hospital for their contribution to patient care and data acquisition. We also acknowledge the efforts of all healthcare professionals involved in the multidisciplinary management of the patients included in this study.

Footnotes

Authorship Contributions

Concept: E.K., Design: E.K., O.K., İ.V.B., Data Collection or Processing: E.K., G.Ö., M.H.F., A.P.A., Analysis or Interpretation: E.K., F.A., A.D., M.A.T., B.P., Y.A., P.E., A.K.G., O.K., İ.V.B., Literature Search: E.K., F.A., A.D., M.A.T., B.P., Y.A., P.E., A.K.G., O.K., İ.V.B., Writing: E.K., M.A.T., Y.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

AI Disclosure Statement: During the preparation of this work, the author(s) utilized OpenAI's ChatGPT to assist in language editing and improving the clarity of the manuscript. The outputs generated by the AI tool were carefully reviewed, verified, and edited by the authors to ensure scientific accuracy and consistency with the original data. After these evaluations, full responsibility for the content of the publication is taken by the author(s). The use of this AI tool primarily affected the language and stylistic quality of the manuscript and did not influence the study design, data analysis, or interpretation of results.

Supplementary Table 1: https://d2v96fxpocvxx.cloudfront.net/65bdf192-201e-4bb0-813a-d69339a28cf1/content-images/c93e7fb0-646b-4aa3-aca8-dcb35bad0683.pdf

REFERENCES

1. Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014-2018. Neuro Oncol. 2021;23(12 Suppl 2):iii1-iii105. [Crossref] [PubMed] [PMC]
2. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol. 2021;23(8):1231-1251. [Crossref] [PubMed] [PMC]
3. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol. 2021;18(3):170-186. Erratum in: Nat Rev Clin Oncol. 2022;19(5):357-358. [Crossref] [PubMed] [PMC]
4. Pope WB, Sayre J, Perlina A, Villablanca JP, Mischel PS, Cloughesy TF. MR imaging correlates of survival in patients with high-grade gliomas. AJNR Am J Neuroradiol. 2005;26(10):2466-2474. [Crossref] [PubMed] [PMC]
5. Sarkaria JN, Hu LS, Parney IF, et al. Is the blood-brain barrier really disrupted in all glioblastomas? A critical assessment of existing clinical data. Neuro Oncol. 2018;20(2):184-191. [Crossref] [PubMed] [PMC].
6. Jain RK, di Tomaso E, Duda DG, Loeffler JS, Sorensen AG, Batchelor TT. Angiogenesis in brain tumours. Nat Rev Neurosci. 2007;8(8):610-622. [Crossref] [PubMed]
7. Wu CX, Lin GS, Lin ZX, Zhang JD, Liu SY, Zhou CF. Peritumoral edema shown by MRI predicts poor clinical outcome in glioblastoma. World J Surg Oncol. 2015;13:97. [Crossref] [PubMed] [PMC]
8. Wen PY, van den Bent M, Youssef G, 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(33):5187-5199. [Crossref] [PubMed] [PMC]
9. Schoenegger K, Oberndorfer S, Wuschitz B, et al. Peritumoral edema on MRI at initial diagnosis: an independent prognostic factor for glioblastoma? Eur J Neurol. 2009;16(7):874-878. [Crossref] [PubMed]
10. Ohmura K, Tomita H, Hara A. Peritumoral edema in gliomas: a review of mechanisms and management. Biomedicines. 2023;11(10):2731. [Crossref] [PubMed] [PMC]
11. Zhang M, Ye F, Su M, et al. The prognostic role of peritumoral edema in patients with newly diagnosed glioblastoma: a retrospective analysis. J Clin Neurosci. 2021;89:249-257. [Crossref] [PubMed]

12. Claus EB, Walsh KM, Wiencke JK, et al. Survival and low-grade glioma: the emergence of genetic information. Neurosurg Focus. 2015;38(1):E6. [Crossref] [PubMed] [PMC]
13. Sawaya R, Hammoud M, Schoppa D, et al. Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. Neurosurgery. 1998;42(5):1044-1055; discussion 1055-1056. [Crossref] [PubMed]
14. Levin VA, Chan J, Datta M, Yee JL, Jain RK. Effect of angiotensin system inhibitors on survival in newly diagnosed glioma patients and recurrent glioblastoma patients receiving chemotherapy and/or bevacizumab. J Neurooncol. 2017;134(2):325-330. [Crossref] [PubMed]
15. Januel E, Ursu R, Alkhafaji A, et al. Impact of renin-angiotensin system blockade on clinical outcome in glioblastoma. Eur J Neurol. 2015;22(9):1304-1309. [Crossref] [PubMed]
16. Carpentier AF, Ferrari D, Bailon O, et al. Steroid-sparing effects of angiotensin-II inhibitors in glioblastoma patients. Eur J Neurol. 2012;19(10):1337-1342. [Crossref] [PubMed]
17. Kourilsky A, Bertrand G, Ursu R, et al. Impact of angiotensin-II receptor blockers on vasogenic edema in glioblastoma patients. J Neurol. 2016;263(3):524-530. [Crossref] [PubMed]
18. Curran WJ Jr, Scott CB, Horton J, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst. 1993;85(9):704-710. [Crossref] [PubMed]
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-383. [Crossref] [PubMed]
20. Ellingson BM, Wen PY, Cloughesy TF. Modified criteria for radiographic response assessment in glioblastoma clinical trials. Neurotherapeutics. 2017;14(2):307-320. [Crossref] [PubMed] [PMC]
21. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-1379. [Crossref] [PubMed]
22. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol. 2007;165(6):710-718. [Crossref] [PubMed]