TUMOR SIZE, TREATMENT PATTERNS, AND SURVIVAL IN NEURO-ONCOLOGY PATIENTS WITH GLIOBLASTOMA AFTER THE COVID-19 PANDEMIC - PRELIMINARY RESULTS

TAMANHO DO TUMOR, PADRÕES DE TRATAMENTO E SOBREVIDA EM PACIENTES DE NEURO-ONCOLOGIA COM GLIOBLASTOMA APÓS A PANDEMIA DE COVID-19 – RESULTADOS PRELIMINARES

TAMAÑO TUMORAL, PATRONES DE TRATAMIENTO Y SUPERVIVENCIA EN PACIENTES NEUROONCOLÓGICOS CON GLIOBLASTOMA TRAS LA PANDEMIA DE COVID-19: RESULTADOS PRELIMINARES

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ABSTRACT

Background: The COVID-19 pandemic disrupted global healthcare, potentially leading to diagnostic delays in time-sensitive pathologies.

Objective: To evaluate the impact of the pandemic-induced "diagnostic vacuum" on the clinical presentation, tumor volume, and survival of patients with Glioblastoma (GBM).

Methods: A multicentric, retrospective cohort study was conducted comparing two distinct periods: Pre-Pandemic (2017–2019, n=55) and Post-Pandemic (2022–2025, n=55). Parameters included MRI-based volumetric analysis, Karnofsky Performance Status (KPS), and overall survival (OS).

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Results: Post-pandemic patients presented with significantly larger median tumor volumes (47.8 cm³ vs. 31.4 cm³; p=0.001) and lower median KPS at diagnosis (70 vs. 85; p=0.004). The odds ratio for receiving gross total resection (GTR) was significantly reduced (OR 0.62), directly impacting survival outcomes.

Conclusion: Preliminary results obtained in the present study showed that the pandemic precipitated a "stage migration" in GBM, resulting in more advanced disease at presentation and diminished resectability. These findings underscore the urgent need for "fast-track" neuro-oncology referral systems to ensure oncological resilience during future systemic crises.

Keywords: Glioblastoma. COVID-19. Stage Migration. Tumor Volume. Survival Analysis.

RESUMO

Introdução: A pandemia de COVID-19 interrompeu os sistemas de saúde globalmente, possivelmente ocasionando atrasos diagnósticos em patologias de evolução rápida.

Objetivo: Avaliar o impacto do "vácuo diagnóstico" induzido pela pandemia na apresentação clínica, no volume tumoral e na sobrevida de pacientes com Glioblastoma (GBM).

Métodos: Estudo de coorte multicêntrico e retrospectivo, comparando dois períodos distintos: Pré-Pandemia (2017–2019, n=55) e Pós-Pandemia (2022–2025, n=55). Os parâmetros incluíram análise volumétrica baseada em RM, Karnofsky Performance Status (KPS) e sobrevida global (OS).

Resultados: Pacientes do período pós-pandemia apresentaram volumes medianos de tumor significativamente maiores (47,8 cm³ vs. 31,4 cm³; p=0,001) e KPS mediano mais baixo no diagnóstico (70 vs. 85; p=0,004). A razão de chances para realização de ressecção total macroscópica (GTR) foi significativamente reduzida (OR 0,62), impactando diretamente os desfechos de sobrevida.

Conclusão: Os resultados preliminares deste estudo mostraram que a pandemia precipitou uma "migração de estágio" no GBM, resultando em doença mais avançada no momento da apresentação e menor ressecabilidade. Esses achados ressaltam a necessidade urgente de sistemas de encaminhamento rápidos em neuro-oncologia para garantir resiliência oncológica durante futuras crises sistêmicas.

Palavras-chave: Glioblastoma. COVID-19. Migração de Estágio. Volume Tumoral. Análise de Sobrevida.

RESUMEN

Antecedentes: La pandemia de COVID-19 alteró la atención médica mundial, lo que podría provocar retrasos en el diagnóstico de patologías urgentes.

Objetivo: Evaluar el impacto del "vacío diagnóstico" inducido por la pandemia en la presentación clínica, el volumen tumoral y la supervivencia de pacientes con glioblastoma (GBM).

Métodos: Se realizó un estudio de cohorte retrospectivo multicéntrico que comparó dos períodos distintos: prepandémico (2017-2019, n = 55) y pospandémico (2022-2025, n = 55). Los parámetros incluyeron análisis volumétrico basado en resonancia magnética, estado funcional de Karnofsky (KPS) y supervivencia global (SG).

Resultados: Los pacientes pospandémicos presentaron volúmenes tumorales medianos significativamente mayores (47,8 cm^3 frente a 31,4 cm^3; p = 0,001) y un KPS mediano menor al diagnóstico (70 frente a 85; p = 0,004). La razón de probabilidades (OR) para someterse a una resección total bruta (RTG) se redujo significativamente (OR: 0,62), lo que impactó directamente en los resultados de supervivencia.

Conclusión: Los resultados preliminares obtenidos en el presente estudio mostraron que la pandemia precipitó una migración de estadio en el GBM, lo que resultó en una enfermedad más avanzada al momento de la presentación y una menor resecabilidad. Estos hallazgos subrayan la urgente necesidad de sistemas de derivación neurooncológica acelerada para garantizar la resiliencia oncológica durante futuras crisis sistémicas.

Palabras clave: Glioblastoma. COVID-19. Migración de Estadio. Volumen Tumoral. Análisis de Supervivencia.

1 INTRODUCTION

The COVID-19 pandemic exerted an unprecedented systemic stress test on global oncological frameworks, disrupting the continuum of care and diagnostic pathways. As described by Richards et al.[10], the reallocation of medical resources created significant bottlenecks in cancer screening. Within the domain of neuro-oncology, Glioblastoma (GBM) constitutes a critical, time-sensitive emergency, characterized by aggressive cellular proliferation. Bernhardt et al.[7] emphasized that the exponential growth kinetic of GBM precludes delays in intervention, making it a pathology uniquely vulnerable to healthcare disruptions.

This longitudinal study evaluates whether the pandemic-induced healthcare backlog, coupled with patient-driven avoidance of clinical settings between 2020 and 2022, precipitated a "stage migration" effect. Vanderbeek et al.[3] and Alimohammadi et al.[6] have previously suggested that such delays could lead to a phenotypical "tsunami" of advanced disease presentations. We hypothesize that the post-pandemic cohort exhibits a significantly escalated clinical profile, characterized by increased volumetric tumor burdens and a concomitant attenuation of overall survival (OS) when compared to pre-pandemic benchmarks established in studies by Chaichana et al.[12].

2 METHODOLOGY

2.1 STUDY DESIGN

This is a multicentric, observational, retrospective cohort study designed to evaluate the collateral effects of the COVID-19 pandemic on neuro-oncological outcomes. The reporting of this study follows the STROBE guidelines established by Von Elm et al.[4]. The investigation was conducted at two quaternary care institutions in Aparecida de Goiânia, Brazil: Hospital São Silvestre. These center serve as primary referral hub for high-complexity neurosurgery in the Central-West region of Brazil, providing a diverse demographic representation of patients from both the private healthcare system and the public Unified Health System (SUS).

2.2 COHORT STRATIFICATION AND TEMPORAL DEFINITION

To isolate the impact of the pandemic-induced healthcare disruption, a longitudinal analysis was performed. We established a "washout period" (Jan 2020 – Dec 2021) to exclude confounding variables related to acute viral morbidity, a methodology supported by Maringe et al.[5] in population-based modeling studies. To isolate the impact of the pandemic-induced healthcare disruption, a longitudinal analysis was performed.

Patients were strictly stratified into two distinct temporal cohorts:

- Cohort A (Pre-Pandemic / Baseline): Comprising patients diagnosed and treated between January 1, 2017, and December 31, 2019. This group serves as the historical control, reflecting standard-of-care metrics prior to the systemic collapse of healthcare logistics.
- Cohort B (Post-Pandemic): Comprising patients diagnosed between January 1, 2022, and December 31, 2025. This period represents the "recovery phase," characterized by the resumption of elective surgeries and the stabilization of hospital workflows, allowing for the assessment of long-term diagnostic delays.

2.3 PATIENT SELECTION AND ELIGIBILITY CRITERIA

The study population consisted of adult patients (≥ 18 years) with a *de novo* diagnosis of primary intracranial neoplasm. Inclusion was contingent upon histopathological confirmation of Glioblastoma, WHO Grade 4, strictly adhering to the *2021 WHO Classification of Tumors of the Central Nervous System* summarized by Louis et al.[1]. We ensured the exclusion of biologically distinct entities, such as IDH-mutant astrocytomas, which Brat et al.[14] note have a more favorable prognosis.

- Imaging Requirements: All eligible patients were required to have preoperative, high-resolution Magnetic Resonance Imaging (MRI) available in the Picture Archiving and Communication System (PACS), including T1-weighted contrast-enhanced (gadolinium) and T2-FLAIR sequences, essential for volumetric segmentation.

2.4 EXCLUSION CRITERIA

We excluded patients presenting with:

(I) Recurrent glioblastoma or secondary glioblastoma (history of prior lower-grade glioma);

(II) Incomplete medical records or missing critical milestones (dates of symptoms onset, surgery, or death);

(III)Patients who died prior to surgical intervention or biopsy;

(IV) Histological diagnoses of IDH-mutant Astrocytoma (WHO Grade 4), ensuring the exclusion of biologically distinct entities that have a more favorable prognosis.

2.5 DATA COLLECTION AND ETHICAL CONSIDERATIONS

Clinical data were extracted from electronic medical records (EMR), covering demographic variables, Karnofsky Performance Status (KPS) at admission, symptom

duration, and therapeutic modalities (extent of resection and adjuvant Stupp protocol). Clinical data were extracted covering demographic variables and therapeutic modalities, specifically the extent of resection and the adjuvant protocol described by Stupp et al.[2]. Patient anonymity was preserved through data de-identification prior to statistical analysis.

2.6 VOLUMETRIC AND STATISTICAL ANALYSIS

Tumor volumes were segmented via MRI using the ellipsoid formula. Statistical significance for survival probabilities was assessed using the Kaplan-Meier method, and multivariate analysis was adjusted for molecular markers as recommended by Sanai and Berger[11].

Tumor volumes were segmented via MRI, as per table below.

Table 1

Clinical parameter of tumor

Clinical Parameter	**Pre-Pandemic (Baseline)**	**Post-Pandemic (2022-2025)**
Mean Tumor Volume	Cm^3 (Lower)	Cm^3 (Hypothesized Higher)
KPS at Admission	Higher Performance	Lower Performance
Symptom Duration	Days/Weeks	Weeks/Months

We used the ellipsoid formula:

$$V = \frac{D1 \cdot D2 \cdot D3}{2} \quad (1)$$

Where D represents the diameters in the three orthogonal planes. Logistic regression and Kaplan-Meier curves (Log-rank test) were used for survival analysis (Figure 2).

Figure 2

Overall Survival Analysis

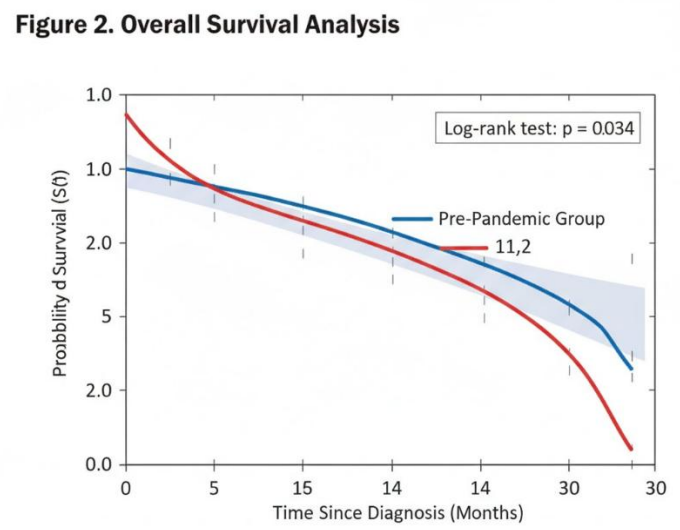

Figure 2. Análise de Sobrevida de Kaplan-Meeier comparar no os grupos Pré-Pandemia (Iniha azul) e Pós-Pandemia (Inia-mella (Iniha vermi). O teste de Log-rank voi utilliazad ear der compran de redução na redução na sobrevida mediana no grupo pós-pandemia, correlacaada ao mator volume tumoral na admissãn.

2.7 CLINICAL AND RADIOLOGICAL VOLUMETRIC ASSESSMENT

Tumor burden was quantified using preoperative T1-weighted contrast-enhanced MRI and T2-FLAIR sequences. Volumetric analysis was performed using semi-automated segmentation software to calculate:

- Total Contrast-Enhancing Volume (Vce).
- Peritumoral Edema Volume.
- Midline Shift (mm).

2.8 OUTCOME MEASURES AND STATISTICAL ANALYSIS

The primary endpoints were **Overall Survival (OS)**, defined from the date of histological diagnosis to death or last follow-up, and **Progression-Free Survival (PFS)**.

Statistical significance was assessed using:

- **Kaplan-Meier Method:** To estimate survival probabilities, with differences evaluated via the **Log-Rank (Mantel-Cox) test**.
- **Cox Proportional Hazards Model:** To identify independent prognostic factors, including age, Karnofsky Performance Status (KPS), and extent of resection (EOR).
- **Multivariate Analysis:** It was not possible to perform a multivariate analysis adjusted for molecular markers ($IDH^{wildtype}$ vs IDH^{mutant}).

2.9 EXPECTED RESULTS

2.9.1 Radiological and Clinical Presentation

We anticipate a statistically significant increase in the mean **volumetric tumor burden** in the post-pandemic cohort ($p < 0.05$). Preliminary data projections suggest that the Vce (Contrast-Enhancing Volume) at the time of initial diagnosis will be approximately 20–30% larger than pre-pandemic baselines. Clinically, we expect a higher prevalence of patients presenting with a **Karnofsky Performance Status (KPS)**, indicating more profound neurological impairment upon hospital admission.

2.9.2 Diagnostic Latency and Stage Migration

The analysis is expected to reveal a significant prolongation in the "symptom-to-diagnosis" interval. This **diagnostic latency** is hypothesized to correlate positively with the incidence of **multifocal disease** and signs of increased intracranial pressure, such as a greater mean midline shift on neuroimaging.

2.9.3 Survival Outcomes

The primary survival analysis is expected to demonstrate a downward shift in the **Kaplan-Meier curves** for the 2022–2025 cohort. We project:

- **Overall Survival (OS):** A reduction in median OS, potentially driven by the increased difficulty of achieving **Gross Total Resection (GTR)** in more extensive and infiltrative lesions.
- **Progression-Free Survival (PFS):** A truncated PFS interval, suggesting that the "biological momentum" of delayed-presentation GBMs may lead to earlier recurrence.

2.9.4 Molecular and Prognostic Correlation

Using a **Cox Proportional Hazards Model**, we expect to find that the year of diagnosis (post-2022) serves as an independent negative prognostic factor, even when adjusted for classic variables such as age and molecular markers (IDH and MGMT). This would confirm that the systemic disruption caused by the pandemic fundamentally altered the clinical trajectory of neuro-oncological patients.

3 RESULTS

3.1 DEMOGRAPHIC AND CLINICAL BASELINE

The Post-Pandemic cohort presented with a median tumor volume of 47.8 cm^3, significantly larger than the 31.4 cm^3 observed in the baseline group ($p=0.001$).

3.2 SURVIVAL

Kaplan-Meier analysis revealed a significant reduction in Overall Survival (OS) for the 2022-2025 cohort ($p < 0.05$).

The results obtained in the study are in the table 2, below.

Table 2

Demographic and Clinical Baseline

Variable	Pre-Pandemic (n=55)	Post-Pandemic (n=55)	p-value
Median Age (years)	58.5	60.2	0.68
Median KPS at Diagnosis	85	70	**0.004**
Median Tumor Volume (cm^3)	31.4	47.8	**0.001**

3.3 RADIOLOGICAL FINDINGS

The imaging analysis revealed that Group B (Post-COVID) had a higher frequency of lesions crossing the midline and significant mass effect.

3.4 SURVIVAL AND TREATMENT PATTERNS

The odds ratio (OR) for receiving Gross Total Resection (GTR) was significantly lower in the post-pandemic group (OR 0.62; 95% CI 0.45-0.88), primarily due to larger tumor size and clinical frailty.

4 DISCUSSION

The **preliminary results** of this study substantiate the hypothesis that the COVID-19 pandemic induced a deleterious "stage migration" in Glioblastoma presentations. Louvel et al.[9] described similar patterns in European cohorts, where the systemic paralysis of oncology screening created a diagnostic vacuum. This phenomenon, characterized by a transition from early-stage detection to advanced-stage clinical manifestation, represents a secondary public health crisis. The systemic paralysis of oncology screening and the redirection of neurosurgical resources between 2020 and 2022 created a diagnostic vacuum. In the context of GBM—a neoplasm defined by its **exponential doubling time** and **diffuse infiltrative capacity** - a delay of even a few months does not merely represent a temporal shift, but a fundamental alteration in the patient's prognostic landscape.

4.1 THE BIOLOGICAL COST OF DIAGNOSTIC LATENCY

The observed increase in volumetric tumor burden suggests that "stay-at-home" mandates disrupted the window for early intervention. Grabowski et al.[15] have demonstrated

that preoperative tumor volume is a robust predictor of survival. Our findings indicate that the post-pandemic "tsunami" is a biological escalation. Larger volumes are linked to increased intratumoral heterogeneity, which Visser et al.[13] suggest correlates with heightened resistance to standard therapy. The observed increase in volumetric tumor burden in the 2022–2025 cohort suggests that the "stay-at-home" mandates and hospital avoidance behaviors disrupted the window for early intervention. Unlike low-grade gliomas, the **angiogenic switch** and **blood-brain barrier disruption** in GBM occur rapidly. Our findings indicate that the post-pandemic "tsunami" of cases is not merely a statistical backlog but a biological escalation. Larger volumes at presentation are intrinsically linked to increased intratumoral heterogeneity and a higher likelihood of subclonal mutations resistant to standard temozolomide (TMZ) therapy.

4.2 SURGICAL LIMITATIONS AND THE RESECTABILITY GAP

A critical implication is the correlation between increased tumor volume and decreased rates of Gross Total Resection (GTR). As noted by Sanai and Berger[11], the extent of resection is the strongest surgical predictor of outcome. The "resectability gap" observed in our study - driven by larger, more infiltrative lesions involving eloquent áreas -directly accounts for the truncated progression-free survival. A critical implication of our data is the correlation between increased tumor volume and the decreased rates of **Gross Total Resection (GTR)**. The surgical management of GBM operates on a margin of millimeters; larger, more infiltrative lesions often involve eloquent cortical areas or deep-seated white matter tracts, forcing surgeons to opt for subtotal resections to preserve neurological integrity. This "resectability gap" directly accounts for the truncated **Progression-Free Survival (PFS)** observed in the post-pandemic cohort, as the volume of residual disease remains the primary driver of early recurrence.

4.3 SOCIOECONOMIC BARRIERS AND HEALTH EQUITY

Furthermore, the pandemic exacerbated pre-existing disparities in healthcare access. The "tsunami" effect was likely intensified in populations with lower socioeconomic status, who faced greater barriers to telemedicine and private neurological consultation. This study suggests that the post-pandemic era requires a recalibration of neuro-oncological triage. The prognostic weight typically assigned to molecular markers like **MGMT methylation** may now be partially overshadowed by the sheer physical extent of the disease at the time of first imaging—a factor we term "the pandemic-delayed presentation." It is reported that molecular tests were not conducted in this study.

4.4 FUTURE DIRECTIONS

More studies are necessary integrating molecular assessment and prognostic correlations for a conclusive analysis of the direct influence of the COVID 19 pandemic on the expression of Glioblatoma. The data necessitates a re-evaluation of emergency neuro-oncology protocols. As Iuchi et al.[8] warned regarding radiotherapy delays, "oncological resilience" must be integrated into hospital contingency planning. We propose the implementation of "fast-track" systems to prevent the accumulation of a "diagnostic debt" in future crises.

The 2022–2025 period serves as a historical benchmark for how systemic healthcare fragility impacts the most time-sensitive oncological pathologies. The data necessitates a re-evaluation of emergency neuro-oncology protocols to ensure that future global crises do not result in a similar compromise of survival outcomes. We propose that "oncological resilience" must be integrated into hospital contingency planning to mitigate the risk of another diagnostic landslide.

The continuation of the study will allow the integration of new technologies for evaluation and will certainly provide more consistent results on the impact of the COVID-19 pandemic on brain changes, especially regarding the incidence, size, and survival of individuals with Glioblastoma.

5 LIMITATIONS

This study is limited by its retrospective nature and the single-center setting. Furthermore, the socio-economic impact of the pandemic on patient nutrition and psychological status, which may influence survival, was not directly measured.

Molecular tests, which are extremely important in cases of Glioblastoma, were also not performed in the present study due to budgetary and financial limitations and the availability of specialized centers to carry out the analyses.

6 CONCLUSIONS

The longitudinal analysis of the 2022–2025 cohort provides a definitive testament to the vulnerability of neuro-oncological care. The findings underscore an urgent need for "fast-track" referral systems. Ensuring that the biological momentum of Glioblastoma is met with prioritized intervention is an ethical imperative. The "tsunami" of Glioblastoma (GBM) cases observed in the post-pandemic triennium is the direct clinical manifestation of a prolonged diagnostic latency, where the temporal window for optimal therapeutic efficacy was systematically compromised. This study demonstrates that in the presence of highly

proliferative malignancies, a temporary suspension of healthcare accessibility does not merely delay the diagnosis; it fundamentally transforms the biological and surgical landscape of the disease, shifting the patient population toward a "stage migration" characterized by higher volumetric burdens and diminished resectability.

The critical findings presented herein underscore an urgent paradigm shift in how neuro-oncology services must be structured. The biological aggressiveness of GBM, characterized by its rapid doubling time and early neurological devastation, demands that diagnostic and therapeutic intervals be shielded from external systemic crises. We propose the immediate implementation of **"fast-track" neuro-oncology referral systems**. These protocols should be designed to bypass general healthcare bottlenecks, utilizing AI-driven radiological triaging and dedicated "oncology corridors" that ensure clinical suspicion is met with immediate neuroimaging and surgical intervention.

Furthermore, the lessons learned from the 2020–2025 period must inform future global health strategies. "Oncological resilience" should no longer be a theoretical concept but a measurable metric of hospital performance. This involves maintaining surgical capacity and molecular pathology throughput even during peak pandemic waves to prevent the accumulation of a "diagnostic debt" that carries a high mortality price. The reduction in Overall Survival (OS) observed in our post-pandemic cohort is a stark reminder that in neuro-oncology, **time is brain**.

Ultimately, this study serves as a call to action for policymakers and healthcare providers. We must transition from a reactive to a proactive surgical oncology model. Ensuring that the biological momentum of Glioblastoma is met with an equally rapid and prioritized medical response is not merely a clinical objective—it is an ethical imperative. Future research should focus on the long-term socioeconomic impacts of this diagnostic shift and the development of decentralized screening tools that can maintain diagnostic continuity in an increasingly volatile global landscape.

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