# GLIOMA-RELATED EPILEPSY - CHARACTERISTICS AND IMPLICATIONS ON TREATMENT AND PROGNOSIS IN THE CONTEXT OF MOST RECENT BRAIN TUMOR MANAGEMENT GUIDELINES

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GLIOMA-RELATED EPILEPSY-CHARACTERISTICS AND IMPLICATIONS ON TREATMENT AND PROGNOSIS IN THE CONTEXT OF MOST RECENT BRAIN TUMOR MANAGEMENT GUIDELINES (Abstract): Diffuse low-grade gliomas, neoplasms originating from glial tissue, exhibit a propensity to evolve into tumors of a higher grade over time. The management of low-grade glioma presents a multifaceted challenge in clinical decision-making, given its complex diagnostic profile. Numerous factors have been identified as critical in determining the outcomes of various treatment modalities and in serving as prognostic indicators with predictive significance. Among these, glioma-associated epilepsy stands out as a principal clinical indicator, playing a pivotal role in both the management strategies and prognostication post-treatment. **Materials and methods:** A retrospective analysis was conducted on a cohort of 38 patients diagnosed with low-grade glioma (LGG), World Health Organization (WHO) grade 2 or 3, who were treated within our neurosurgical department from 2013 to 2023. This study primarily focused on the occurrence of glioma-related epileptic seizures. Additionally, an extensive review of the pertinent literature was undertaken to enrich the analysis. The evaluation encompassed the assessment of Engel outcomes six months following surgical resection, along with the examination of the anti-seizure medication (ASM) regimens implemented. Furthermore, a comprehensive review and synthesis of the current National Institute for Health and Care Excellence (NICE) guidelines pertaining to the management of low-grade gliomas were conducted, highlighting the latest recommendations and therapeutic strategies. **Results:** Within the cohort of 38 patients diagnosed with glioma, 30 were definitively identified as having diffuse astrocytoma (grade 2 and 3), while the remaining 8 were diagnosed with oligodendroglioma. Among those experiencing glioma-related epilepsy (n=25), a management approach involving biopsy only was applied to 8% (n=2) of the cases, gross total resection (GTR) was performed on 40% (n=10), subtotal resection (StR) was administered to 32% (n=8), and partial resection (PaR) was executed on 20% (n=5) of the patients. The investigation did not uncover a significant correlation between the occurrence of seizures and variables such as tumor volume, rate of growth, or histological findings. However, a notable positive effect of the extent of surgical resection on patient outcomes was observed, as measured by the Engel classification system, six months subsequent to oncological intervention. **Discussion:** Several researchers have illustrated that the presence of seizures during the initial stages serves as a favorable prognostic indicator for both malignant progression-free survival and overall survival

in patients diagnosed with glioma. Furthermore, the manifestation of epilepsy as a presenting symptom significantly impacts the quality of life of individuals afflicted with glioma. **Conclusions:** Exploration into a more intricate approach to epilepsy surgery specifically targeting glioma-related seizures could yield considerable advantages, with the potential to enhance the quality of life for patients post-treatment. **Keywords**: GLIOMA-RELATED EPILEPSY, LOW-GRADE GLIOMA, EPILEPSY SURGERY, ENGEL CLASSIFICATION, NICE BRAIN TUMOR GUIDELINES.

## INTRODUCTION

Diffuse low-grade gliomas, classified as tumors originating from glial tissue, possess the inherent capability to evolve into higher-grade malignancies over time (1, 2). Consistent with established guidelines for glioma management, the patient's treatment trajectory post-diagnosis is recommended to adhere to a predefined algorithm. This commences with diagnostic procedures, prioritizing imaging techniques for the presumptive identification of glioma. Initial imaging should include a comprehensive structural MRI protocol, incorporating T2-weighted, Diffusion-Weighted Imaging (DWI), Fluid-Attenuated Inversion Recovery (FLAIR), and T1-weighted sequences both pre- and post-contrast administration. A consensus on the management strategy should be sought through discussion within a multidisciplinary team upon the initial imaging diagnosis. Furthermore, the deployment of advanced MRI methodologies, such as MR perfusion and MR spectroscopy, is advocated where feasible, to facilitate the identification of potential high-grade transformations within gliomas that may initially present as low-grade on standard structural MRI scans (3) (fig. 1).

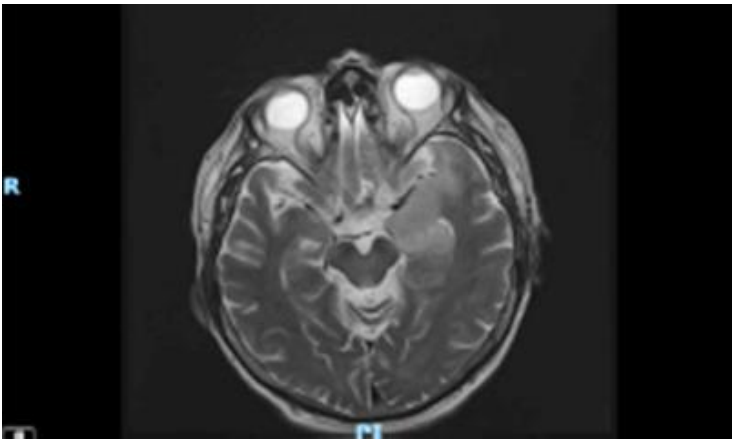


**Fig. 1.** Axial T2W images of 69M with WHO grade 2 diffuse astrocytoma (Left Temporal Lobe)

The management of glioma should incorporate surgical resection ideally within a six-month period following the imaging diagnosis. The primary objectives of the initial surgical intervention are to secure a histological diagnosis and to excise as

much of the glioma as is feasibly safe, subsequent to a thorough and thoughtful deliberation with the patient and their kin. In instances where surgical resection is deemed infeasible, pursuing a biopsy for histological determination is advised. Additionally, the option of active surveillance without histological confirmation may be considered, albeit exclusively for tumors exhibiting characteristic imaging signatures of low-grade tumors, such as Dysembryoplastic Neuroepithelial Tumors (DNET) or optic pathway glioma. Facilities specialized in neurosurgery for glioma treatment should be equipped with at least some advanced operational capabilities, including but not limited to, the ability to conduct awake craniotomies with language and functional monitoring, intra-operative neurophysiological monitoring, and intra-operative imaging guidance (3).

The surgical approach to glioma management necessitates the incorporation of various contemporary guideline recommendations to enhance treatment efficacy and patient safety. The use of 5-aminolevulinic acid (5-ALA)-guided surgery is recommended as a significant adjunctive measure to enhance the extent of resection during the initial surgery of gliomas that are radiologically suspected to be high-grade. Furthermore, the employment of intraoperative magnetic resonance imaging (MRI) is advocated to facilitate the precise removal of tumor tissue while concurrently preserving neurological function. The integration of intraoperative ultrasound and diffusion tensor imaging (DTI), alongside traditional neuro-navigation methods, is crucial for minimizing damage to critical neuronal pathways. Additionally, the execution of awake craniotomy stands out as a paramount technique for the maximal preservation of neurological functions, necessitating the involvement of neuropsychologists and speech and language therapists to ensure optimal outcomes. This comprehensive and nuanced surgical strategy underscores the importance of employing advanced technological interventions and multidisciplinary collaboration in the management of glioma, aiming to achieve the best possible patient-centric outcomes.

Within the realm of contemporary advancements in the treatment of brain tumors, laser interstitial thermal therapy (LITT) emerges as a noteworthy mention, having been progressively recognized as a minimally invasive therapeutic modality (4). Research conducted by Hawasli *et al.*, in 2013 (5), has validated LITT as a secure and efficacious ablative approach for addressing intracranial lesions, while also acknowledging the potential morbidities associated with its use, such as aphasia, hemiparesis, hyponatremia, meningitis, and deep vein thrombosis (DVT).

Moreover, the employment of molecular markers has become instrumental in the prognostication and therapeutic stratification of glioma. Notable markers include IDH1 and IDH2 mutations, ATRX mutations (pertinent to IDH mutant astrocytomas and glioblastomas), 1p/19q codeletion (indicative of oligodendrogliomas), histone H3.3 K27M mutations (associated with midline gliomas), and BRAF fusion and mutations (relevant to pilocytic astrocytoma) (3).

In the intricate landscape of glioma pathology, significant effort has been devoted to identifying and delineating factors that profoundly impact the quality of life of individuals diagnosed with this condition. Through a retrospective examination of cases handled within our neurosurgical

department, it has been observed that patients who presented with or developed epileptic seizures postoperatively experienced a notable deterioration in their quality of life. This adverse impact extends beyond physical health, exerting a considerable psychological burden on the affected individuals over both short and long-term periods.

Per the National Institute for Health and Care Excellence (NICE) guidelines, the management of epilepsy or seizure control is identified as one of the three paramount outcomes following glioma surgery, alongside progression - free survival and neurological function (assessed via the Neurological Function Scale or NIH Stroke Scale). These outcomes have been recognized as pivotal in assessing the risks associated with the decision to proceed with or forego tumor resection. Among these, progression-free survival is deemed to hold greater importance over overall survival, as it more accurately reflects the tumor-specific outcomes influenced by the decision to ablate the tumor (3).

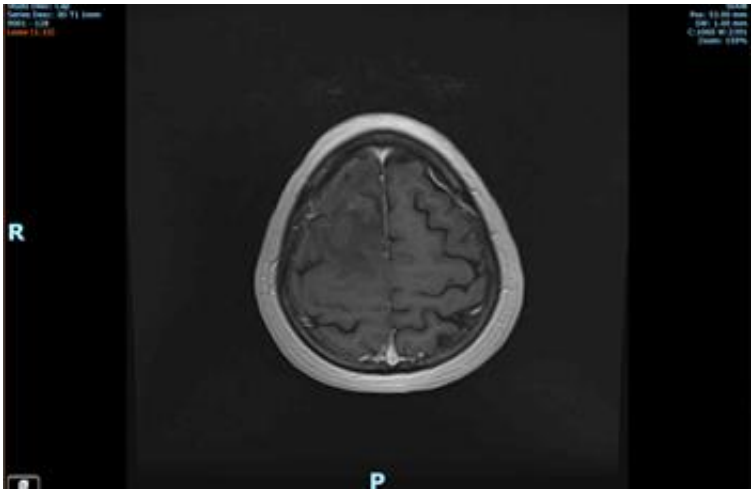


**Fig. 2.** Axial T2W images of 61F with WHO grade 3 astrocytoma (Frontal area)

Epileptic seizures presenting as initial symptoms significantly affect the quality of life for individuals diagnosed with glioma. Various studies have sought to identify factors influencing the incidence of epileptic seizures during the neurosurgical perioperative period, as well as potential interventions to enhance epilepsy-related outcomes in patients undergoing glioma surgical resection (6). Seizures typically manifest first in patients who are later diagnosed with glioma, particularly those with low-grade gliomas located in the frontotemporal regions, which are associated with an elevated risk of postoperative seizures. The presence of drug-resistant epilepsy (DRE) and notable peritumoral edema are linked to a higher occurrence of peri-operative seizures, whereas gross total resection has been shown to diminish the incidence of postoperative seizures (6) (fig. 2).

The Engel system is employed for classifying epilepsy outcomes following surgery, originally developed for assessing results in patients after epilepsy surgery (7).

TABLE I

**Engel classification of postoperative outcome (Engel 1993)** (7)

| Class | Characteristics |
|---|---|
| Class I | Free of disabling seizures |
| | A: Completely seizure-free since surgery<br>B: None disabling; simple partial seizures only since surgery<br>C: Some disabling seizures after surgery, but free of disabling seizures for at least 2 years<br>D: Generalized convulsions with AED discontinuation only |
| Class II | Rare disabling seizures (“almost seizure free”) |
| | A: Initially free of disabling seizures but rare seizures now<br>B: Rare disabling seizures since surgery<br>C: More than rare disabling seizures since surgery, but rare seizures for the last 2 years<br>D: Nocturnal seizures only |
| Class III | Worthwhile improvement |
| | A: Worthwhile seizure reduction<br>B: Prolonged seizure-free intervals mounting to greater than half the followed up.,<br>But not<2 years |
| Class IV | No worthwhile improvement |

## MATERIALS AND METHODS

A retrospective analysis was conducted on a cohort of 38 patients diagnosed with low-grade gliomas (LGG), WHO grades 2-3, who were treated in our neurosurgical department over the decade spanning 2013 to 2023. This analysis placed a particular emphasis on the incidence of glioma-related epileptic seizures, supplemented by a thorough review of pertinent literature on the subject. The study evaluated the Engel outcome six months post-resection, in addition to reviewing the anti-seizure medication (ASM) protocols employed.

Our neurosurgical department, situated within the Emergency University Hospital (SUUB) in Bucharest, serves an approximate population of one million individuals. Glioma cases are typically referred to our department either through the General Practitioner service or by direct admission via the Accident and Emergency Department. Upon a clinical and radiological presumptive diagnosis of a central nervous system (CNS) tumor, patients are integrated into a clinical pathway that includes Neurosurgery, Neuroradiology, and Oncology. This multidisciplinary team approach is facilitated by weekly meetings, known as the “Tumor Board,” at the Emergency University Hospital Bucharest.

The scope of our investigation encompassed a comprehensive review of clinical and imaging data, diagnostic approaches, and treatment modalities from 2013 to 2023. This review included an analysis of surgical procedure records, patient clinical notes, histology findings, and outpatient follow-up clinical data for all patients diagnosed with diffuse low-grade glioma. Parameters such as patient age, gender, initial presenting symptoms, lesion locali-

zation, eloquence, the occurrence of epileptic seizures, adjuvant treatments, as well as pre-operative seizure characteristics (type, duration, and frequency) and post-operative Engel classification outcomes were meticulously examined (fig. 3).

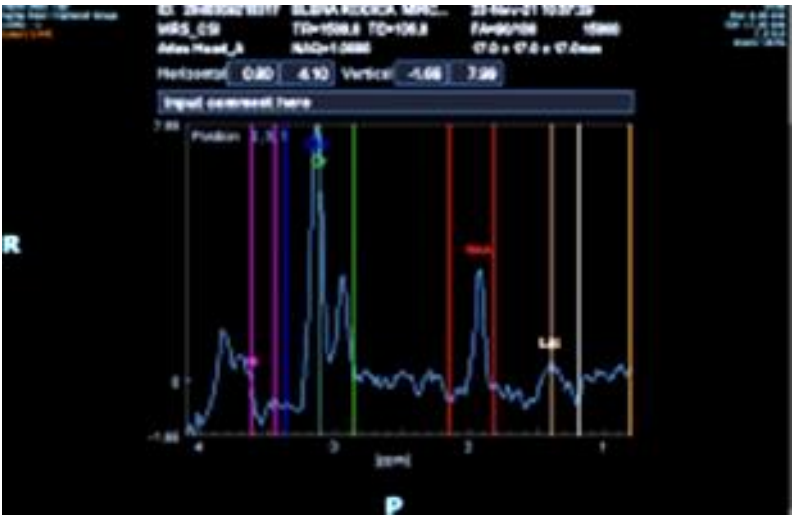

**Fig. 3.** MR Spectroscopy of 37F with WHO grade 3 oligodendroglioma

The analysis of preoperative and post-operative imaging focused on various dimensions, including the glioma's location, lateralization (dominant vs. non-dominant hemisphere), eloquence, and distinctive features observed in MR spectroscopy sequences, particularly the choline/N-acetyl aspartate (Cho/NAA) high ratio. Additionally, the study examined the correlation between the variability of peritumoral edema, as evidenced on imaging, and the incidence of epileptic seizures.

MRI examinations discussed in this research were conducted within the Radiology Department of the Emergency University Hospital Bucharest, serving both as an integral component of the preoperative diagnostic process and as part of the post-operative follow-up regimen.

## RESULTS

Among the 38 patients diagnosed with glioma, 30 were conclusively identified with diffuse astrocytoma (grades 2 and 3), while 8 were diagnosed with oligodendroglioma. The median age of the cohort was 50 years old, with females comprising 60% of the patient population. Tumor localization was diverse: frontal lobe (n=24), temporal lobe (n=6), parietal lobe (n=6), and insular region (n=2). The majority of gliomas (n=28) were situated in the dominant hemisphere, with the remainder (n=10) in the non-dominant hemisphere. Presenting symptoms varied widely, including asymptomatic cases (n=3), motor deficits (n=16), visual deficits (n=2), seizures (n=25), aphasia (n=9), and intracranial hypertension (n=6).

Surgical interventions were categorized as follows: biopsy only (n=6), gross total resection (GTR) (n=14), subtotal resection (StR) (n=10), and partial resection (PaR) (n=8).

Regarding glioma-related epilepsy (n=25), management strategies included biopsy only (8%, n=2), GTR (40%, n=10), StR (32%, n=8), and PaR (20%, n=5). Seizure presentation varied from simple partial (focal) seizures to complex generalized tonic-clonic seizures, with seizure frequency ranging from daily to monthly prior to diagnosis. Beyond surgical resection, seizure management involved anti-seizure medication (ASM) from the initial presentation, adhering to standard guidelines. In complex epilepsy cases, specialized adjustments to ASM types and doses were necessary. The most responsive treatments involved Carbamazepine, Levetiracetam, Valproic acid, Topiramate, Phenytoin, or Lamotrigine, with combinations used for more complicated cases.

The study found no significant correlation between seizure presence and tumor volume, growth rate, or histological findings. However, the extent of surgical resection significantly influenced outcomes, as determined by the Engel classification system, six months post-treatment. Notably, 76% of patients undergoing maximal resection were seizure-free (Engel class IA) at the 6-month mark, whereas 20% of those with StR achieved Engel class IA, and 46% reached Engel Class IIB during the same follow-up period.

## DISCUSSION

In examining the scholarly work pertaining to epilepsy associated with glioma, it is critical to acknowledge the nuanced impact of epilepsy on patients with glioma. Despite the adverse effects on quality of life, several pieces of research have underscored the prognostic significance of epilepsy in individuals with glioma (1). These studies underscore the necessity of further research into the prognostic implications of epilepsy in patients diagnosed with diffuse low-grade glioma, calling for extensive cohort analyses over extended follow-up periods. A notable study, utilizing a large patient cohort (1,509) from a multi-centric French national database, incorporated a variety of variables to explore both spontaneous and post-treatment seizure risk predictors, as well as the prognostic relevance of epileptic seizures. This research aimed to comprehensively assess the impact of epileptic seizures on the diagnosis and progression of diffuse low-grade glioma, in addition to evaluating the influence of such gliomas on the incidence of epilepsy, whether as a preoperative or postoperative condition (1).

Concurrent efforts are directed towards attaining a more profound and intricate comprehension of seizure mechanisms within the glioma context and the innovation of next-generation anti-seizure medications (ASM). Tripathi *et al.*, 2024 (8), delve into the proinflammatory immune dimension of epilepsy, contrasting it with the immunosuppressive milieu observed in patients experiencing glioma-related epilepsy. According to their findings, the epileptic condition characterized by excessive neuronal activity is proposed to encourage immunosuppression, thereby exacerbating glioma progression. The study highlights the IDH1 mutation’s role in metabolic modulation, offering a dual approach to counteracting immune suppression and diminishing seizure occurrences. This insight into the interplay between neuronal activity and immune responses presents a promising avenue for the development of advanced anticonvulsant therapies (8).

Pallud *et al*., 2014 (1) elucidated that risk factors for seizures in the initial stages of glioma are predominantly associated with the tumor's topographic location and its eloquence. Additionally, the presence of other symptoms, such as neurological deficits and increased intracranial pressure, does not favor the control of epileptic seizures, which, paradoxically, may not improve but rather deteriorate over the natural progression of diffuse low-grade glioma. The control of seizures post-treatment is likely influenced by the glioma's topographic characteristics and the extent of surgical resection. Notably, the initial presence of seizures is identified as a positive prognostic indicator for malignant progression-free survival and overall survival.

Avila *et al*., 2017 (9) posited that employing an epilepsy surgery strategy, including preoperative invasive recording in patients with brain tumor-related epilepsy (BTRE), could significantly aid in delineating the epileptogenic zone, potentially leading to enhanced Engel outcomes. Furthermore, for tumors located in the temporal lobe, such as dysembryoplastic neuroepithelial tumor (DNET) or ganglioglioma, a temporal lobectomy coupled with hippocamp-ectomy is suggested to yield a more favorable seizure prognosis than merely excising the lesion.

The approach to surgical management in glioma encompasses a paradigm distinctly different from that applied in focal non-tumor related epilepsy surgery, which often incorporates direct cortical recording or extra-operative invasive techniques. These methods are generally not utilized in glioma surgery, indicating a potential area for further research to ascertain their utility in enhancing seizure outcomes for glioma patients (9).

The exploration of a possible link between molecular markers and epilepsy in glioma remains a critical and imperative field of study. Some research suggests that seizures associated with glioma may not necessarily be triggered by specific tumor characteristics (10). It has been demonstrated that seizures typically originate from the peritumoral neocortex, where infiltrated glioma cells pervade (11).

Recent advancements in the identification of non-invasive pre-operative tumor markers have markedly progressed, poised to revolutionize the rapidly evolving cancer treatment paradigm. Innovations in imaging techniques, such as the apparent diffusion coefficient (ADC), cerebral blood volume (CBV), and the identification of T2FLAIR mismatch, are set to enhance the diagnostic capabilities in the pre-operative phase (12, 13) (fig. 4).

A pivotal concern in the management of gliomas pertains to the progression observed following radiotherapy treatment. This area of discussion is particularly relevant for cases that demonstrate radiological signs of tumor progression at varying intervals after undergoing radiotherapy, with or without surgical excision (14, 15). At this juncture, a critical question arises, one that is essential for determining the subsequent approach to patient care. This question stems from the challenge of distinguishing between radiation necrosis and actual tumor growth or progression, a task that often presents a complex diagnostic dilemma. The body of literature addressing this topic is extensive, highlighting the significance of this dichotomy. Indeed, the issue of differenti-

ating between radiation-induced changes and tumor progression is so critical that it warrants being the focal point of an entire research endeavor (16).

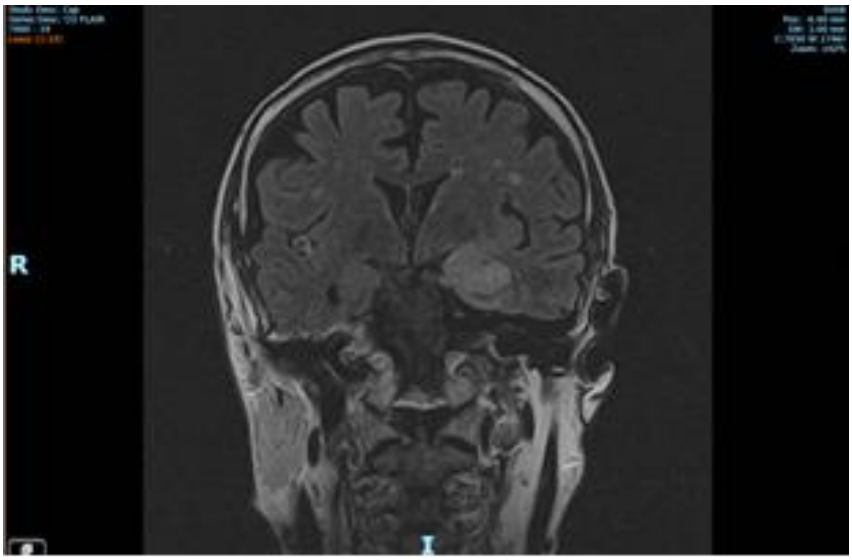


**Fig. 4.** Coronal FLAIR images of 69M with WHO grade 2 diffuse astrocytoma (Left Temporal Lobe)

## CONCLUSIONS

Our examination of existing literature, coupled with a small-scale retrospective study, has provided us with clearer insights into the optimal strategies for addressing the challenging decision of whether and when to surgically intervene in cases of slow-growing low-grade glioma, particularly among relatively young patients exhibiting minimal or no neurological symptoms.

Maximal surgical resection offers not just substantial oncological advantages but also plays a significant role in influencing the epilepsy outcomes for patients diagnosed with diffuse low-grade glioma. A crucial benefit of early and maximally aggressive resection of low-grade tumors lies in the potential for controlling the glioma prior to its progression to a more advanced stage. This approach not only aims to enhance life expectancy but also to improve the quality of life for patients. Furthermore, surgical intervention stands as the sole method for obtaining tumor samples for molecular and histological sub typing, such as determining IDH status. This capability is immensely valuable for more accurately discussing prognoses or tailoring treatment strategies based on the tumor's specific characteristics.

Epilepsy has emerged as a pivotal factor in the intricate and often challenging diagnosis of glioma, serving variously as an early indicator and a quantifiable outcome following surgical resection.

## CONFLICT OF INTEREST AND FUNDING

The authors have declared that there are no conflicts of interest in relation to this research, and no funding was secured for the study.

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