Intraventricular Glioblastomas: A Systematic Review of Multimodal Treatment Strategies

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AIM: Intraventricular glioblastomas (IVGBMs) are rare tumors within the central nervous system characterized by unique challenges in diagnosis and management due to their location within the ventricular system. Despite their rarity, these tumors necessitate comprehensive study to refine diagnostic approaches and optimize therapeutic strategies.

METHODS: A systematic review was conducted using PubMed, Scopus, Web of Science, and Google Scholar databases to identify relevant literature published up to January 2024. Inclusion criteria encompassed studies in English focusing on clinical characteristics, radiological features, pathology, and treatment of IVGBM. Data synthesis and analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

RESULTS: Twenty-four articles met the inclusion criteria, comprising 47 patients with IVGBM. The median age was 47 years, with a male predominance (32 males, 15 females). Common symptoms included increased intracranial pressure and seizures. Tumors predominantly affected the lateral ventricles (body and trigone). Surgical resection (subtotal or gross total) was the primary treatment approach, with adjuvant therapies (radiotherapy, chemotherapy) administered postoperatively.

CONCLUSIONS: IVGBM present distinct diagnostic and therapeutic challenges due to their ventricular location. Current treatments primarily involve surgical resection followed by adjuvant therapies, though outcomes remain guarded. Further research is needed to enhance understanding and management of this rare glioblastoma subset.

Keywords: glioblastoma; intraventricular; treatment strategies; systematic review; multimodal treatment

Introduction

Glioblastoma, previously known as glioblastoma multiforme (GBM), stands as the primary tumor of the central nervous system, constituting a significant proportion, with 45% of all cases and 15% of intracranial neoplasms falling within its purview [1]. Discernible radiological characteristics and consistent location often facilitate its identification, typically appearing as an irregularly shaped cystic lesion with ring enhancement observed in T1-weighted sequences upon scrutiny via magnetic resonance imaging (MRI). This pathology predominantly occupies the subcortical white matter and deep gray matter nuclei within the cerebral hemispheres, with a preference for the frontotemporal region, followed by involvement in the parietal lobes [2].

However, within the spectrum of glioblastomas, a subset poses a unique challenge due to their intraventricular location. These intraventricular glioblastomas (IVGBMs), characterized by their unusual siting within the ventricular system, have garnered relatively limited attention in the scientific literature. They are classified as secondary ventricular tumors, presumed to originate primarily from cerebral tissue with subsequent extension into the ventricles through trans ependymal dissemination. This distinct presentation complicates their differentiation from more commonly encountered lesions within the ventricular system, presenting diagnostic challenges and therapeutic complexities.

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Table 1. Clinical characteristics and outcomes of patients with intraventricular glioblastomas (1950–2024).

Authors, year	Number of patients	Age	Sex	Presenting symptoms	Tumor location	Surgical approach	Extent of resection	Isocitrate dehydrogenase (IDH) mutation	Adjuvant therapy	Outcome	PFS/OS
Shapiro, 1950 [3]	1	69	F	Signs of increasing intracranial pressure, behaviour disorders	Occipital horn of the lateral ventricle	Not mentioned	STR	Not mentioned	Not mentioned	Respiratory failure	Died on Postoperative day (POD)-30
Wilson and Gardner, 1964 [4]	1	5	M	Signs of increasing intracranial pressure, partial seizures	Trigone of the lateral ventricle	Not mentioned	Biopsy	Not mentioned	Not mentioned	Respiratory failure	Died on POD-30
Lee and Manzano, 1997 [5]	1	59	M	Signs of increasing intracranial pressure, behaviour disorders	Anterior third ventricle	Not mentioned	STR	Not mentioned	RT + CT	Not mentioned	OS 7 months
Park *et al*., 2005 [6]	1	32	F	Signs of increasing intracranial pressure, memory loss	Trigone of the lateral ventricle	Not mentioned	STR	Not mentioned	RT + CT	Not mentioned	PFS 24 months
Prieto *et al*., 2006 [7]	1	29	F	Neurologic deterioration	Anterior third ventricle	Not mentioned	STR	Not mentioned	Not mentioned	Not mentioned	PFS 2 months
Klein and Marchal, 2007 [8]	1	9	M	Signs of increasing intracranial pressure	Body of the lateral ventricle	Not mentioned	STR	Not mentioned	RT + CT	Not mentioned	OS 12 months
Kim *et al*., 2008 [9]	1	64	M	Signs of increasing intracranial pressure, motor deficits	Occipital horn of the lateral ventricle	Not mentioned	STR	Not mentioned	RT only	Not mentioned	Not mentioned
Secer *et al*., 2008 [10]	9	19	M	Not mentioned	Body of the lateral ventricle	Not mentioned	STR	Not mentioned	RT only	Not mentioned	OS 12 months
		21	M	Not mentioned	Body of the lateral ventricle	Not mentioned	STR	Not mentioned	RT + CT	Not mentioned	PFS 21 months
		28	F	Not mentioned	Lateral ventricles	Not mentioned	STR	Not mentioned	RT only	Not mentioned	OS 19 months
		43	M	Not mentioned	Body of the lateral ventricle	Not mentioned	STR	Not mentioned	RT + CT	Not mentioned	PFS 27 months
		45	M	Not mentioned	Body of the lateral ventricle	Not mentioned	STR	Not mentioned	RT only	Not mentioned	OS 14 months
		45	F	Not mentioned	Body of the lateral ventricle	Not mentioned	STR	Not mentioned	RT only	Not mentioned	OS 21 months
		54	M	Not mentioned	Lateral ventricles	Not mentioned	GTR	Not mentioned	Not mentioned	hepatic encephalopathy and intraventricular hemorrahage	Died on POD-30
		63	M	Not mentioned	Body of the lateral ventricle	Not mentioned	STR	Not mentioned	RT + CT	Not mentioned	PFS 33 months
		67	M	Not mentioned	Body of the lateral ventricle	Not mentioned	STR	Not mentioned	RT only	Not mentioned	OS 28 months

Table 1. Continued.

Authors, year	Number of patients	Age	Sex	Presenting symptoms	Tumor location	Surgical approach	Extent of resection	Isocitrate dehydrogenase (IDH) mutation	Adjuvant therapy	Outcome	PFS/OS
Hambly *et al*., 2009 [11]	1	57	M	Complex partial seizures	Trigone of the lateral ventricle	Not mentioned	Biopsy	Not mentioned	RT only	Not mentioned	Not mentioned
Sarsilmaz *et al*., 2010 [12]	1	16	M	Signs of increasing intracranial pressure, behaviour disorders	Body of the lateral ventricle/Occipital horn	Not mentioned	STR		RT + CT	Not mentioned	OS 24 months
Mandour and El Mostarchid, 2014 [13]	1	40	F	Signs of increased intracranial pressure	Trigone of the lateral ventricle	Not mentioned	Biopsy	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Asha *et al*., 2014 [14]	1	66	M	Complex partial seizures	Occipital and temporal horns of the lateral ventricle	Not mentioned	STR	Not mentioned	RT + CT	Not mentioned	PFS 14 months
Sarikafa *et al*., 2015 [15]	1	65	F	Signs of increased intracranial pressure	Body of the lateral ventricle	Not mentioned	Biopsy	Not mentioned	RT + CT	Not mentioned	OS 3 months
Ben Nsir *et al*., 2016 [16]	8	10	M	Signs of increasing intracranial pressure, hemiparesis (BMRC 2/5)	Trigone of the lateral ventricle	Posterior parietal transcortical	STR	Wildtype	RT only	Mild hemiparesis (BMRC 4/5)	OS 12 months
		74	M	Brachial paresis (BMRC 2/5), behaviour disorders	Occipital horn of the lateral ventricle	Posterior parietal transcortical	Biopsy	Wildtype	RT only	Mild brachial paresis (BMRC 4/5)	OS 8 months
		6	F	Signs of increased intracranial pressure	Anterior third ventricle	Right frontal transcortical	STR	Mutant	RT + CT	Uneventful	PFS 108 months
		14	M	Signs of increased intracranial pressure	Anterior third ventricle	Interhemispheric trans-lamina terminalis	GTR	Mutant	Not performed	Uneventful	PFS 72 months
		19	F	Signs of increased intracranial pressure, seizures	Body of the right lateral ventricle	Right frontal transcortical	GTR	Mutant	Not performed	Uneventful	PFS 36 months
		28	M	Signs of increased intracranial pressure	Lateral ventricles	Right frontal transcortical	STR	Wildtype	Not performed	Pulmonary embolism	Died at POD-4
		59	M	Signs of increased intracranial pressure	Body of the right lateral ventricle	Right frontal transcortical	STR	Wildtype	RT + CT	Uneventful	OS 9 months
		27	F	Signs of increased intracranial pressure	Lateral ventricles	Right frontal transcortical	GTR	Wildtype	RT + CT	Uneventful	OS 12 months

Table 1. Continued.

Authors, year	Number of patients	Age	Sex	Presenting symptoms	Tumor location	Surgical approach	Extent of resection	Isocitrate dehydrogenase (IDH) mutation	Adjuvant therapy	Outcome	PFS/OS
Patnaik *et al*., 2017 [17]	1	27	M	Headache, vomiting, progressive decline in visual acuity, blindness	Frontal horn and body of right lateral ventricle	Right frontal transcortical approach	GTR	Not mentioned	Not mentioned	Uneventful	Not mentioned
Tan and Mankad, 2018 [18]	1	16	M	Headache, vomiting	Left lateral ventricle, extending into the left foramina of Monro	Not mentioned	GTR	Wildtype	RT + CT	Uneventful	PFS 24 months
Nitta *et al*., 2018 [19]	1	47	F	Headache, nausea, dysphagia, hoarseness, shallow breathing, bilateral oculomotor palsy, left facial palsy	Right lateral ventricle	Right superior parietal transcortical	STR	Wildtype	Not mentioned	Respiratory failure	Died on POD-33
Garcia *et al*., 2019 [20]	1	83	M	Seizures	Left lateral ventricle extending into the right lateral ventricle	Left frontal transcortical	Biopsy	Wildtype	RT + CT	Not mentioned	Not mentioned
Takigawa *et al*., 2021 [21]	1	73	F	Headache	Anterior horn of lateral ventricle	Not mentioned	GTR	Wildtype	RT + CT	Uneventful	PFS 6 months
Liu *et al*., 2022 [22]	1	20	M	Altered consciousness, nausea, headaches, vomiting	Lateral ventricles	Endoscopic	Biopsy	Wildtype	Not performed	Seizures	OS 24 months
Zanuttini *et al*., 2023 [23]	1	56	F	Drug-resistant headache, short-term memory loss	All ventricular system	Stereotactic needle biopsy	Biopsy	Wildtype	Not performed	Rapid clinical deterioration, worsened dysphasia, loss of movement autonomy, daytime sleepiness	Died on POD-7

Table 1. Continued.

Authors, year	Number of patients	Age	Sex	Presenting symptoms	Tumor location	Surgical approach	Extent of resection	Isocitrate dehydrogenase (IDH) mutation	Adjuvant therapy	Outcome	PFS/OS
Parker *et al*., 2023 [24]	9	57	M	Seizures, headaches	Temporal horn of right lateral ventricle	Right temporal transcortical	STR	Not mentioned	Not mentioned	Lost to follow-up	Not mentioned
		65	M	Confusion, memory deficit	Lateral ventricles	Right anterior transcallosal	GTR	Not mentioned	Not performed	36 days	36 days
		37	M	Headache, ophthalmoplegia, facial droop, ataxia	Fourth ventricle	Suboccipital transvermian	STR	Not mentioned	RT only	Lost to follow-up	Not mentioned
		71	M	Confusion, memory deficit	Lateral ventricles	Right frontal transcortical	STR	Not mentioned	RT + CT	5 months	5 months
		77	M	Confusion, memory deficit	Lateral ventricles	Right frontal transcortical	STR	Not mentioned	Not performed	19 days	19 days
		61	F	Headache, confusion, memory deficit, sleepiness	Lateral ventricles	Stereotactic needle biopsy	Biopsy	Wildtype	RT +CT	4 months	4 months
		68	F	Transient ischemic attack	Atrium of right lateral ventricle	Right parietal transcortical	STR	Wildtype	RT + CT	5 months	5 months
		56	M	Confusion	Atrium of right lateral ventricle	Right temporal transcortical	GTR	Wildtype	RT + CT	16 months	16 months
		69	M	Headaches, nausea/vomiting, confusion, memory deficit	Atrium of right lateral ventricle	Right anterior transcallosal	STR	Wildtype	Not performed	18 days	18 days
Prieto *et al*., 2024 [25]	1	40	M	Cervical and occipital pain, sleep disorders	Atrium of the left lateral ventricle	Left parietal paramedian transcortical	GTR	Wildtype	RT + CT	Uneventful	PFS 6 months
Liu *et al*., 2024 [26]	1	20	M	Modified state of consciousness, nausea, headache, vomiting	Lateral ventricles	Endoscopic	Biopsy	Wildtype	Not performed	Died about a month later due to status epilepticus	OS 1 month

Table 1: Table of clinical characteristics and outcomes of patients with intraventricular glioblastomas (IVGBMs) treated between 1950 and 2024. The table includes details on age, sex, presenting symptoms, tumor location, surgical approach, extent of resection, isocitrate dehydrogenase (IDH) mutation status, adjuvant therapy, outcomes, and Progression-Free Survival (PFS) or Overall Survival (OS). RT, radiotherapy; CT, chemotherapy; GTR, gross total resection; STR, subtotal resection; F, female; M, male.

Despite their rarity, IVGBMs represent a critical area of investigation, necessitating a thorough understanding to refine diagnostic approaches and optimize therapeutic strategies. In this review, we aim to explore the intricacies of IVGBMs, elucidating their clinical characteristics, radiological features, pathological findings, and therapeutic considerations. Additionally, we will present an emblematic case example to complement our systematic review, providing a practical illustration of the challenges and management strategies associated with this distinctive glioblastoma location.

Materials and Methods

To comprehensively identify relevant literature on IVGBMs, we developed a robust search strategy utilizing both Medical Subject Headings (MeSH) terms and keywords. The strategy encompassed databases such as PubMed, Scopus, Web of Science, and Google Scholar, ensuring a thorough exploration of available literature. Our search strategy included Mesh terms and keywords related to glioblastomas, intraventricular tumors, and treatment modalities, such as "Glioblastoma", "Brain Neoplasms", "Intracranial Neoplasms", "Intraventricular Neoplasms", "Treatment Outcome", and "Therapeutics". This strategy was tailored for each database, aiming to capture all relevant articles published up to January 2024, without restrictions on publication date.

We applied rigorous inclusion criteria to ensure the selection of pertinent studies. Included studies needed to be written in English and exclusively focus on purely IVGBMs (defined as tumors growing solely within the ventricular system) and covering clinical characteristics, radiological features, pathological aspects, and treatment modalities.

We considered various study designs, including retrospective and prospective studies, case series, case reports, and clinical trials, provided they offered relevant data on the topics of interest. Exclusion criteria were applied to studies not specifically addressing IVGBMs or lacking relevant data on clinical characteristics, radiological features, pathological findings, or treatment modalities.

Following the search, duplicates were removed, and titles and abstracts were screened independently by two reviewers for relevance. Full-text articles meeting the inclusion criteria were retrieved for further assessment. Any discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

Systematic data extraction was conducted from the selected articles, covering study characteristics, patient demographics, clinical presentations, radiological findings, pathological features, treatment modalities, and outcomes. Data were extracted independently by two reviewers and cross-checked for accuracy (Table 1) (Ref. [3–26]).

Data synthesis and analysis were performed to identify common themes, trends, and gaps in the existing literature regarding IVGBMs. Subgroup analyses were conducted where appropriate to explore variations in treatment responses, and survival.

Throughout the study selection process, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and reproducibility [27]. A PRISMA flow diagram was constructed to illustrate the study selection process, including the number of records identified, screened, assessed for eligibility, and included in the final analysis (Fig. 1). This systematic review was conducted in accordance with the PRISMA checklist (**Supplementary Material**) to ensure transparency, completeness, and accuracy in the reporting of the review process and findings.

The included articles provided valuable insights into the clinical management and outcomes associated with IVGBMs, forming the basis of this systematic review.

Results

In total, 24 articles met the inclusion criteria and were included in the final analysis, comprising a total of 47 patients spanning a wide age range, from 5 to 83 years old, with an average age of 44.95 years (Table 2). This indicates a diverse patient population with representation across different age groups. The median age of 47 suggests a relatively balanced distribution of ages. However, the standard deviation of 22.92 years signifies considerable variability around the mean age, highlighting the heterogeneity of the cohort. Among the 47 patients included, there are 32 males and 15 females.

The most common presenting symptoms reported by patients are related of increased intracranial pressure, observed in 13 cases. These signs may include headaches, nausea, vomiting, and altered mental status, indicating potential intracranial pathology such as tumor-related hydrocephalus. Following closely, complex partial seizures are documented in 5 patients, indicating a subset of patients presenting with seizure activity. Other presenting symptoms, such as memory loss, motor deficits, and behavioral disorders, are also noted but with varying rates, mirroring the diverse clinical manifestations associated with intracranial tumors.

Tumor location plays a crucial role in determining clinical presentation, treatment options, and prognosis. Our analysis reveals diverse tumor locations within the ventricular system, with the temporal horn of the lateral ventricle and others identified as the most common site, documented in 27.66% of cases, body of the lateral ventricle in 19.15% of cases. Following closely, the trigone of the lateral ventricle was observed in 14.89% of cass. The anterior third ventricle is also noted in 10.64% of patients, highlighting the variability in tumor distribution within the ventricular system. Other less frequent locations, including the occipital horn, frontal horn, atrium of the lateral ventricle, fourth ventricle, are also documented (Fig. 2).

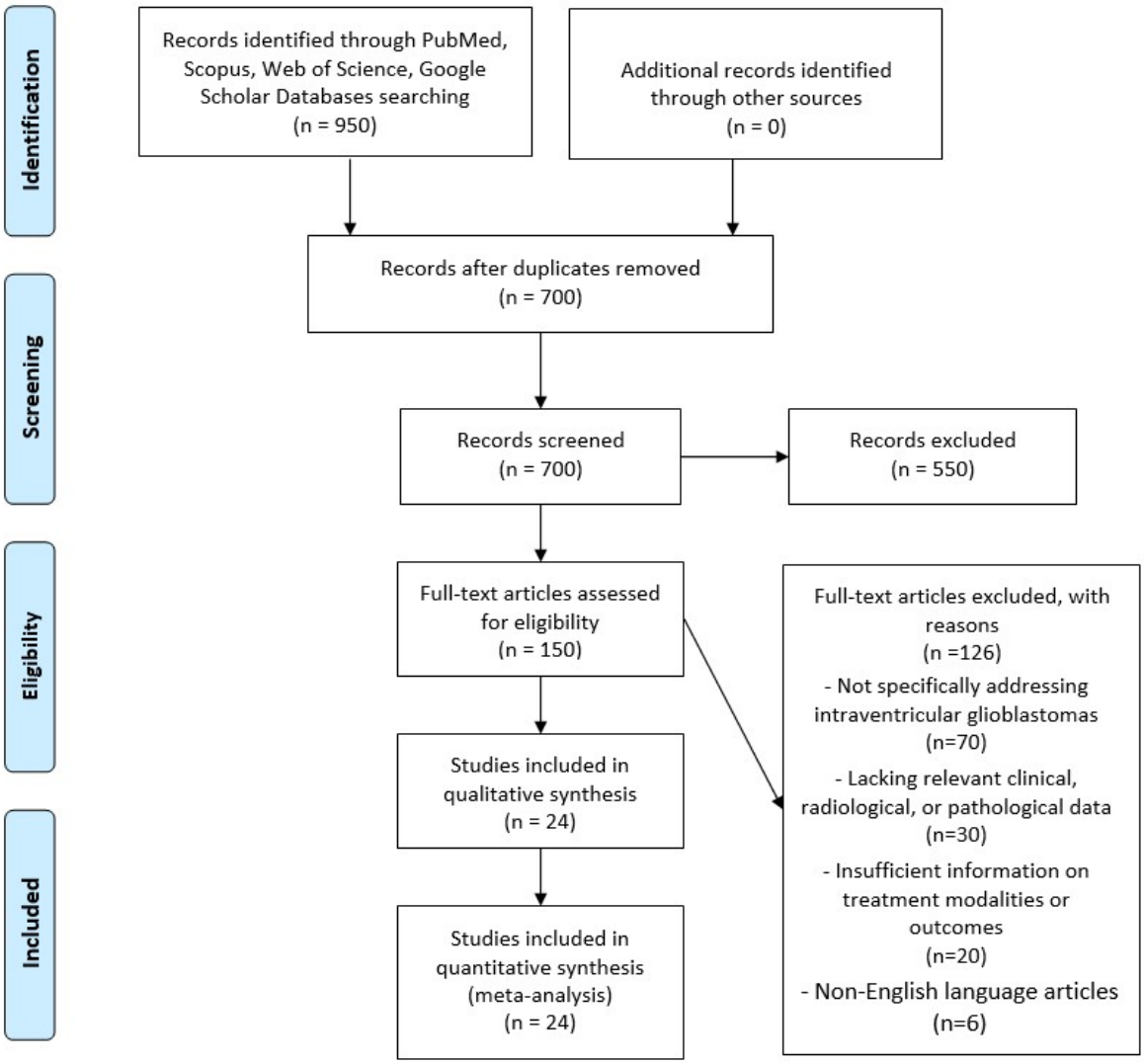

Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrates the study selection process for the systematic review on intraventricular glioblastomas (IVGBMs). Out of the 950 articles initially identified through PubMed, Scopus, Web of Science, and Google Scholar, 250 were removed as duplicates. A total of 700 articles were screened by titles and abstracts, of which 550 were excluded for not being relevant. Subsequently, 150 full-text articles were assessed for eligibility, with 126 excluded for various reasons, such as not specifically addressing IVGBMs or lacking relevant data. Finally, 24 studies were included in the qualitative synthesis and final analysis, providing valuable insights into the clinical management and outcomes associated with IVGBMs.

The choice of surgical approach is influenced by various factors, including tumor location, size, and proximity to critical neurovascular structures. Additionally, the decision depends on the extent of resection (gross total resection (GTR) or subtotal resection (STR)), patient functional status, comorbidities, cerebral edema, patient and family preferences, as well as available surgical techniques and innovations such as intraoperative navigation and fluorescence-guided surgery. Preoperative imaging results and advancements in functional imaging technologies further impact surgical planning to optimize outcomes and minimize risks for the patient.

In the dataset, subtotal resection (STR) emerges as the primary surgical approach, performed in 29 patients. This approach aims to remove most of the tumor while preserving neurological function. Gross total resection (GTR) is conducted in 5 patients, indicating complete removal of visible tumor tissue, which may be feasible in selected cases. Stereotactic biopsy procedures, conducted in 4 cases, provide histopathological diagnosis without extensive tissue manipulation, allowing for targeted treatment planning.

Among the patients with available data, 11 have a mutant isocitrate dehydrogenase (IDH) status, while 17 exhibit a wildtype IDH status. The presence or absence of the IDH

Table 2. Descriptive statistical analysis of 47 patients with intraventricular glioblastomas.

Parameter	Details
Total patients	47
Age range (years)	5–83
Average age (years)	44.95
Median age (years)	47
Standard deviation (years)	22.92
Gender distribution	32 males, 15 females
Presenting symptoms	
- Increased intracranial pressure	13
- Complex partial seizures	5
- Other (memory loss, motor deficits, behavioral disorders)	29
Tumor location	
- Body of lateral ventricle	9
- Trigone of lateral ventricle	7
- Anterior third ventricle	5
- Occipital horn, frontal horn, atrium of the lateral ventricle, fourth ventricle, other locations	26
Surgical approach	
- Subtotal resection (STR)	29
- Gross total resection (GTR)	5
- Stereotactic biopsy	4
- Unspecified	9
IDH mutation status	
- Mutant	11
- Wildtype	17
- Unspecified	19
Adjuvant therapy	
- Radiotherapy (RT) + chemotherapy (CT)	20
- RT alone	10
- CT alone	0
- Unspecified	17
Patient outcomes	
- Surviving	27
- Mortality	20
Median Progression-Free Survival (PFS)	27 months
Median Overall Survival (OS)	12 months

Table 2: This table summarizes descriptive statistical analysis compared to Table 1 for 47 patients with ventricular tumors, detailing age distribution, gender, presenting symptoms, tumor locations, surgical approaches, IDH mutation status, adjuvant therapies, patient outcomes, median PFS, and median OS.

mutation may have prognostic implications. Additionally, 19 cases have an unspecified IDH mutation status.

Adjuvant therapy, including radiotherapy (RT), chemotherapy (CT), or a combination of both (RT + CT), is administered to patients following surgical resection to target residual tumor cells and improve treatment outcomes. Among the patients, 20 individuals receive a combination of RT + CT, 10 patients undergo RT alone, and none of patients receive CT alone.

The outcomes of patients following treatment are diverse, with 27 individuals surviving and 20 patients dying. The following treatment-related complications were observed: respiratory failure occurred in 6.38% of cases, while hepatic encephalopathy and intraventricular hemorrhage, pulmonary embolism, seizures, rapid clinical deterioration with worsened dysphasia, occurred in 2.13% of cases. 4 out of 47 patients (8.51%) died due to disease progression.

Progression-Free Survival (PFS), defined as the time from intervention, if any, to progression, and Overall Survival (OS), defined as the time from diagnosis to death, are critical endpoints used to assess treatment efficacy and long-term prognosis. The median OS is 12 months, and the median PFS is 27 months. However, incomplete follow-up data or loss of patients during follow-up may lead to an overestimation of PFS, especially due to the historical unavailability of diagnostic exams, such as magnetic resonance imaging and contrast-enhanced computed tomography, able to perform timely detection of any early progres-

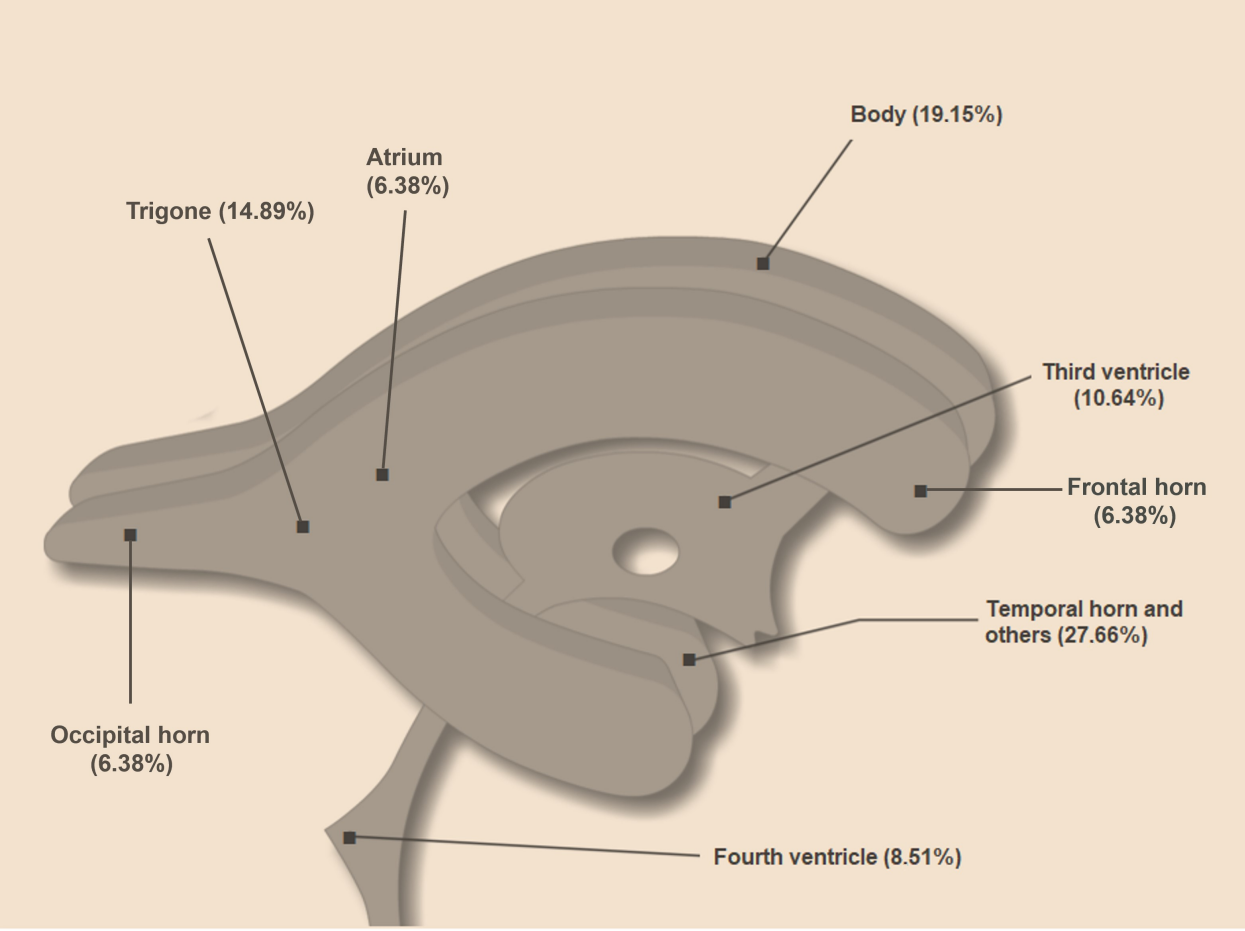

Fig. 2. IVGBMs location image. This image was created using GIMP (version 2.10.x, open-source community of the GNOME Project, Boston, MA, USA).

sion among the older cases collected here. Additionally, it is important to note that the seemingly counterintuitive divergence between OS and PFS is due to the lack of granular data specifying both parameters, as the studies retrieved report these outcomes differently. Specifically, PFS, by definition, is available only for patients who were followed up by imaging. Patients for whom only OS data was available were excluded from PFS calculation, as they could have died from causes unrelated to cancer progression (e.g., surgical complications, non-cancer-specific deaths).

The Kaplan-Meier curves indicate that Group A (RT + CT) and Group B (RT only) show similar cumulative survival for the first 12–15 months. However, over the longer term, a trend emerges showing a survival advantage for the CT + RT group compared to the RT alone group, although this difference is not statistically significant. Additionally, the number of events appears to be notably higher in Group B, which also has only three censored case compared to multiple censored cases in Group A (Fig. 3A).

However, a log-rank test did not reach statistical significance, indicating that the observed numerical disparity in event rates between the groups is not statistically meaningful.

Regarding the three groups (GTR, STR, Biopsy), distinct survival patterns were observed. Group A (GTR) exhibited only a modest early decline in survival (approximately 10%), suggesting low variability over time. Group B (STR) initially demonstrated high survival rates with a gradual decline, diverging significantly from Group A. Group C (Biopsy) exhibited poor initial survival rates; within a few weeks after the biopsy, 40% of the patients had already died, resulting in a surviving fraction of only 60% (Fig. 3B). The observed differences in survival rates between the three groups are statistically significant, with a *p*-value of less than 0.05, indicating that these differences are not due to random chance but reflect true variations in the survival outcomes of the groups.

In summary, the Kaplan-Meier curves show that both treatment groups (RT + CT and RT only) have similar survival rates initially, but over time, the RT + CT group shows a trend towards better survival, though this difference isn't statistically significant. The RT only group has more events and fewer censored cases compared to the RT + CT group, but the log-rank test indicates that this difference is not statistically meaningful. For the different treatment approaches (GTR, STR, Biopsy), distinct survival patterns are

evident. The GTR group shows a survival curve with a flat slope, the STR group starts with high survival rates that gradually decline, and the Biopsy group has poor initial survival with a rapid decline shortly after procedure.

Furthermore, the survival distributions between the IDH wildtype group (Group A) and the IDH mutant group (Group B) were analyzed using Kaplan-Meier curves and compared using the log-rank test. The analysis demonstrated a pronounced divergence in survival outcomes between the two cohorts (Fig. 3C). Specifically, the IDH wildtype group exhibited a significantly higher number of observed events, corresponding to a lower median survival time compared to the IDH mutant group. Quantitative assessment indicated that patients in the IDH mutant group experienced a survival advantage, with survival times extending beyond those of their IDH wild-type counterparts. The log-rank test confirmed that this difference was statistically significant ($p < 0.05$), highlighting the prognostic implications of IDH mutation status in this patient population. The survival curves vividly depict this distinction, with the IDH mutant group showing no decline in survival probability over time, whereas the IDH wildtype group experienced a rapid decrease in survival rates. These findings align with existing literature, suggesting that IDH mutations confer a protective effect, likely due to altered metabolic pathways and reduced tumor aggressiveness. This evidence underscores the importance of molecular characterization in prognosticating patient outcomes.

Case Example

A 77-year-old right-handed male patient presented to our Institution with a history of intense headache, vomiting, and gait disturbances persisting for the past three days. The headache was described as severe and continuous, not relieved by over-the-counter pain medications. The patient reported several episodes of vomiting, which were not preceded by nausea or associated with food intake. Additionally, he noted difficulties with walking independently, experiencing unsteadiness and imbalance, which progressively worsened over the preceding days.

Upon admission, a thorough neurological examination was conducted. The patient was alert and oriented to person, place, and time, but appeared visibly distressed due to the severity of his headache. Cranial nerve examination revealed intact visual fields, extraocular movements, and facial sensation. However, there was mild bilateral papilledema noted on fundoscopic examination. Motor examination demonstrated normal strength in all extremities, but gait assessment revealed ataxia and difficulty with tandem walking. Sensory examination was unremarkable, with intact sensation to light touch, pinprick, and proprioception in all extremities.

Given the clinical presentation suggestive of an intracranial pathology, further diagnostic workup was initiated. An urgent non-contrast CT scan of the brain was performed, revealing a large, hyperdense lesion located in the right nucleo-capsular and mesial temporal regions. The lesion exhibited significant surrounding vasogenic edema, causing compression of adjacent structures and midline shift towards the contralateral hemisphere. Specifically, there was evidence of incarceration with dilation of the temporal horn of the right lateral ventricle and initial tentorial herniation of the uncus, resulting in compression of the contralateral cerebral peduncle.

In order to obtain a more detailed characterization of the lesion, an MRI of the brain with contrast enhancement was subsequently performed. The MRI revealed a voluminous intra-axial lesion centered within the deep right temporal lobe. The lesion displayed heterogeneous signal intensity on T1-weighted and T2-weighted sequences, with surrounding hyperintense signal indicative of vasogenic edema. After the administration of gadolinium-based contrast agent, a significant enhancement of the lesion was observed, particularly in the medial aspect. However, there was also a lateral component of the lesion demonstrating hypointense signal on post-contrast sequences, suggestive of reduced contrast enhancement. Additionally, there was a fluid-cystic component noted anteriorly and superiorly within the lesion, with thin peripheral enhancement on post-contrast imaging (Fig. 4).

Given the concerning radiological findings, surgical intervention was deemed necessary for both diagnostic and therapeutic purposes. The patient underwent a right temporoparietal craniotomy for microsurgical resection of the intraventricular temporal mass. Intraoperative electrophysiological monitoring, including transcranial motor evoked potentials (MEP), somatosensory evoked potentials (PESS), and continuous electromyography (EMG), was utilized to minimize the risk of neurological injury during the procedure. Additionally, neuronavigation was employed intraoperatively to ensure accurate localization and delineation of the lesion boundaries.

Postoperatively, the patient was transferred to the Intensive Care Unit (ICU) for close monitoring and management. He was initially sedated and mechanically ventilated to facilitate neurological recovery and prevent intracranial hypertension. Gradual weaning from sedation was initiated once hemodynamic stability was ensured, with close monitoring of neurological status and vital signs. Serial neurological examinations were conducted to assess for any new-onset deficits or signs of neurological deterioration.

In the immediate postoperative period, the patient demonstrated gradual improvement in neurological status, with resolution of his headache and vomiting. Gait disturbances also showed improvement, with the patient demonstrating increased stability and coordination with assistance. Repeat imaging studies, including CT and MRI scans of the brain with contrast enhancement, were performed to assess for postoperative complications and evaluate the extent of resection. These studies demonstrated satisfactory surgical

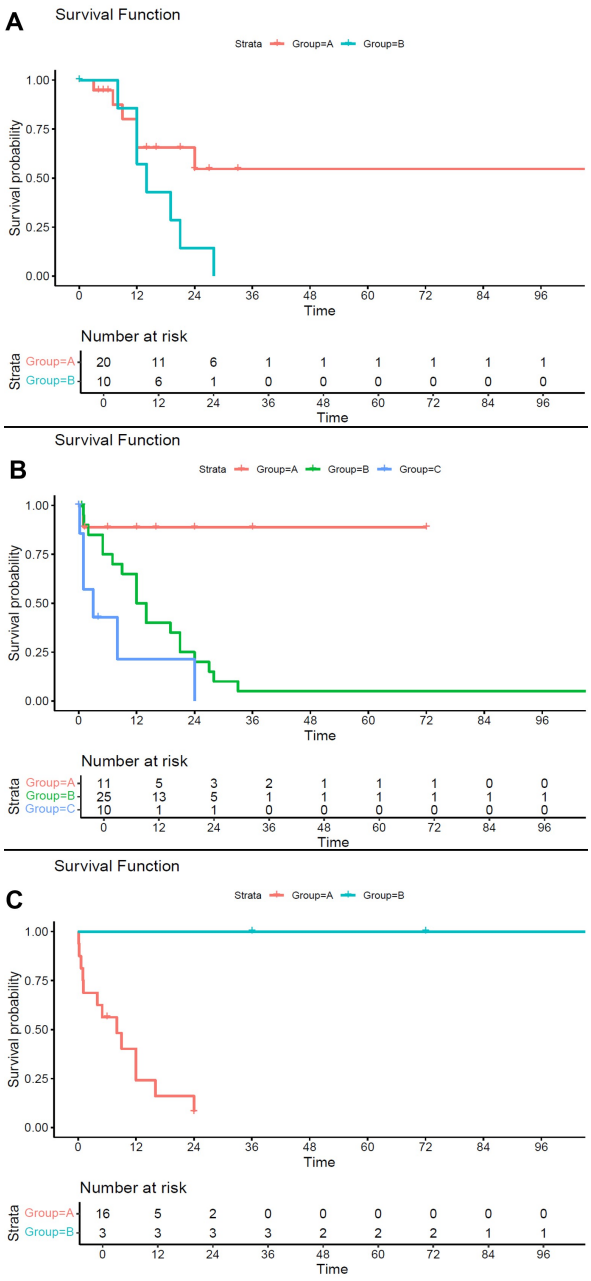

Fig. 3. Kaplan-Meier survival analysis stratified by treatment approach and IDH mutation status. (A) Kaplan-Meier curves comparing cumulative survival between Group A (RT + CT) (red) and Group B (RT only) (light blue) over time. Initial survival rates are similar, but a trend towards improved long-term survival is observed in Group A. Group B shows a higher number of events and fewer censored cases. The numbers below the x-axis indicate the number of patients at risk at corresponding time points. The differences in survival trends between the groups are not statistically significant ($p = 0.179$). (B) Kaplan-Meier survival curves illustrating distinct survival patterns among patients categorized by treatment approach: GTR (Group A) (red), STR (Group B) (green), and Biopsy (Group C) (blue). Group A shows a modest early decline in survival. Group B exhibits high initial survival rates with a gradual decline over time. Group C demonstrates poor initial survival, with a significant proportion of patients deceased shortly after biopsy, resulting in a low surviving fraction. The numbers below the x-axis indicate the number of patients at risk at corresponding time points. The differences in survival patterns among the groups are statistically significant ($p < 0.05$). (C) Kaplan-Meier survival curves comparing survival outcomes between patients with IDH wildtype (Group A) (red) and IDH mutant (Group B) (light blue) IVGBMs. The curves illustrate a significant divergence in survival probabilities, with the IDH mutant group showing prolonged median survival compared to the IDH wildtype group. The patient-at-risk numbers are indicated below the x-axis, providing a visual representation of the number of patients remaining in each group at various time points. Statistical analysis using the log-rank test confirmed this difference as statistically significant ($p < 0.05$), underscoring the prognostic relevance of IDH mutation status in this patient cohort.

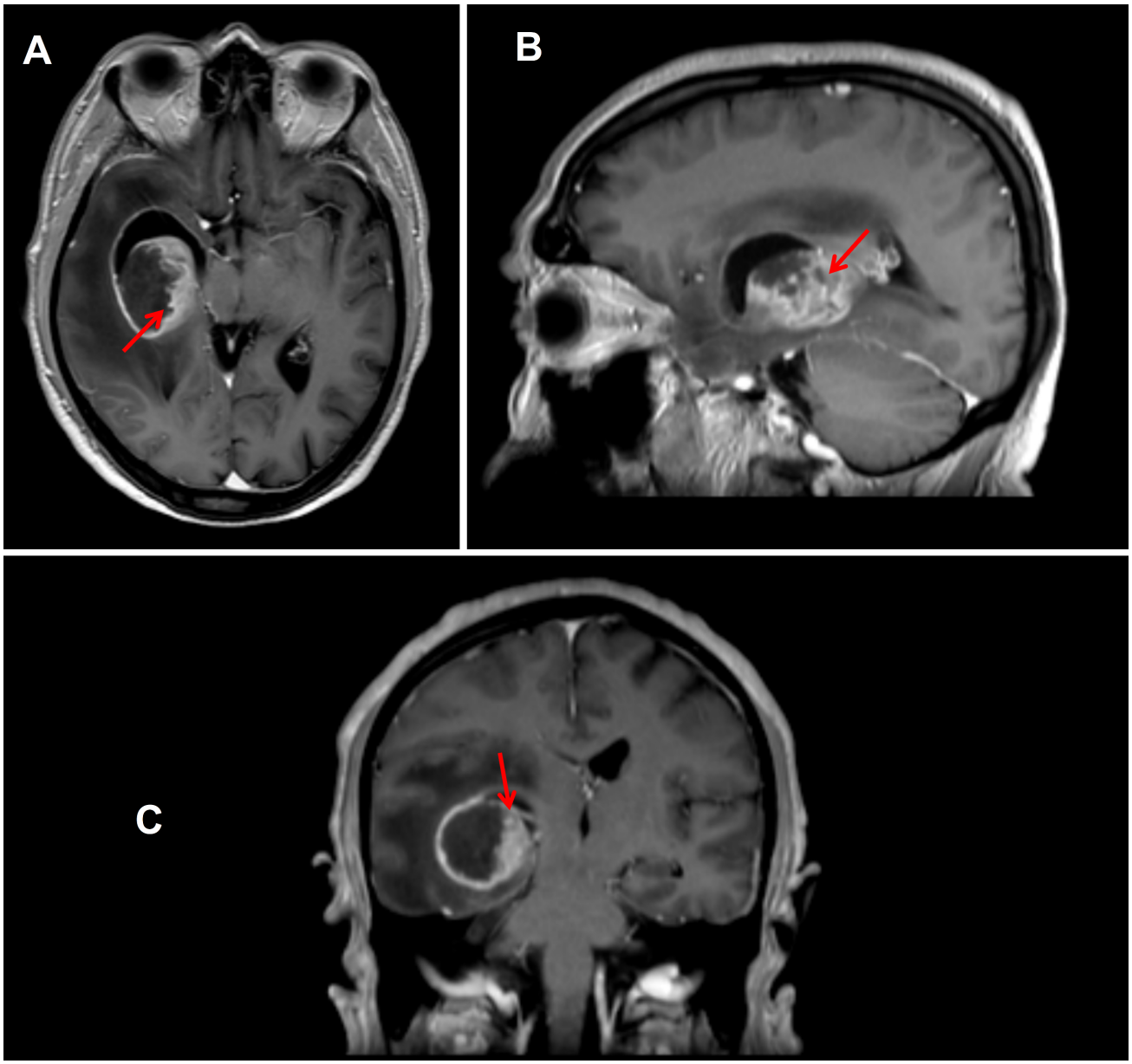

Fig. 4. Magnetic resonance imaging (MRI) brain images with gadolinium contrast demonstrate a voluminous intra-axial lesion centered within the deep right temporal lobe. The lesion exhibits heterogeneous signal intensity on T1-weighted (A) axial, (B) sagittal, and (C) coronal sequences. Surrounding the lesion is a hyperintense signal indicative of vasogenic edema. Post-contrast administration reveals significant enhancement of the lesion, particularly in the medial aspect (red arrows), with a lateral component showing hypointense signal suggestive of reduced contrast enhancement. Anteriorly and superiorly within the lesion, a fluid-cystic component is noted, displaying thin peripheral enhancement on post-contrast imaging. This image is from Garibaldi Hospital, Catania, Italy, and informed consent was obtained from the patient for this study.

outcomes, with gross total resection of the temporal mass and resolution of midline shift and ventricular dilation (Fig. 5).

Histopathological analysis of the surgical specimen revealed a diagnosis of glioblastoma, World Health organization (WHO) grade 4, with characteristic histological features including cellular pleomorphism, microvascular proliferation, and necrosis. Immunohistochemical staining showed positivity for glial fibrillary acidic protein (GFAP), consistent with glial differentiation. Additionally, the tumor was negative for IDH-1 mutation (R132H), confirming an IDH-wild type status. Expression of alpha-thalassemia/mental retardation syndrome X-linked (ATRX) protein was preserved, while p53 protein showed heterogeneous positivity. The proliferation index, as assessed by Ki-67 staining, was approximately 10%, indicative of high proliferative activity (Fig. 6).

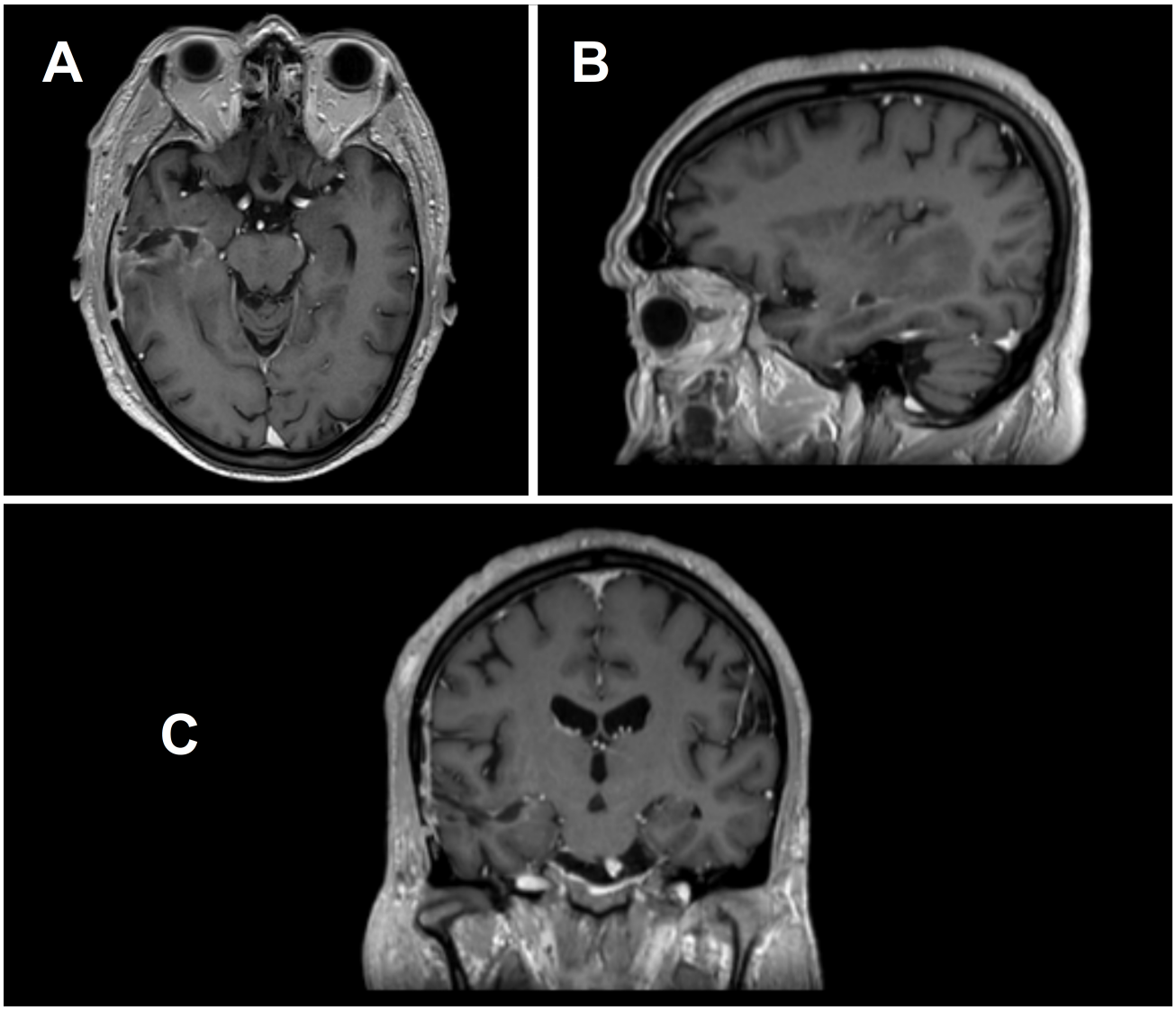

Fig. 5. Postoperative MRI scans of the brain with gadolinium contrast were performed to assess for complications and evaluate the extent of resection. These images (A) axial, (B) sagittal, and (C) coronal sequences demonstrate satisfactory surgical outcomes, showing gross total resection of the temporal mass. There is resolution of the midline shift and ventricular dilation, indicating successful intervention and no significant postoperative complications. This image is from Garibaldi Hospital, Catania, Italy, and informed consent was obtained from the patient for this study.

Given the diagnosis of glioblastoma, adjuvant treatment options including radiotherapy and chemotherapy were discussed with the patient and his family. However, due to the advanced age and comorbidities of the patient, a personalized treatment plan was formulated in consultation with the multidisciplinary team, considering the patient's overall performance status and treatment preferences.

During the hospitalization, the patient was also evaluated by the infectious diseases team due to isolation of Methicillin-sensitive Staphylococcus aureus (MSSA) from nasal swab culture. Antibiotic therapy was initiated as per infectious diseases recommendations, and the patient showed clinical improvement with resolution of nasal colonization.

After a period of stabilization and rehabilitation, the patient was discharged home on the 7th postoperative day with instructions for close follow-up with the neurosurgical and oncology teams. A comprehensive discharge plan was implemented, including arrangements for home health care services, physical therapy, and supportive care measures. The patient and his family were provided with education regarding the nature of the diagnosis, the expected course of the disease, and available supportive resources. The first clinical follow-up was scheduled for 3 months after the surgery.

In conclusion, this case highlights the clinical presentation, diagnostic evaluation, surgical management, and histopathological characteristics of IVGBM in an elderly

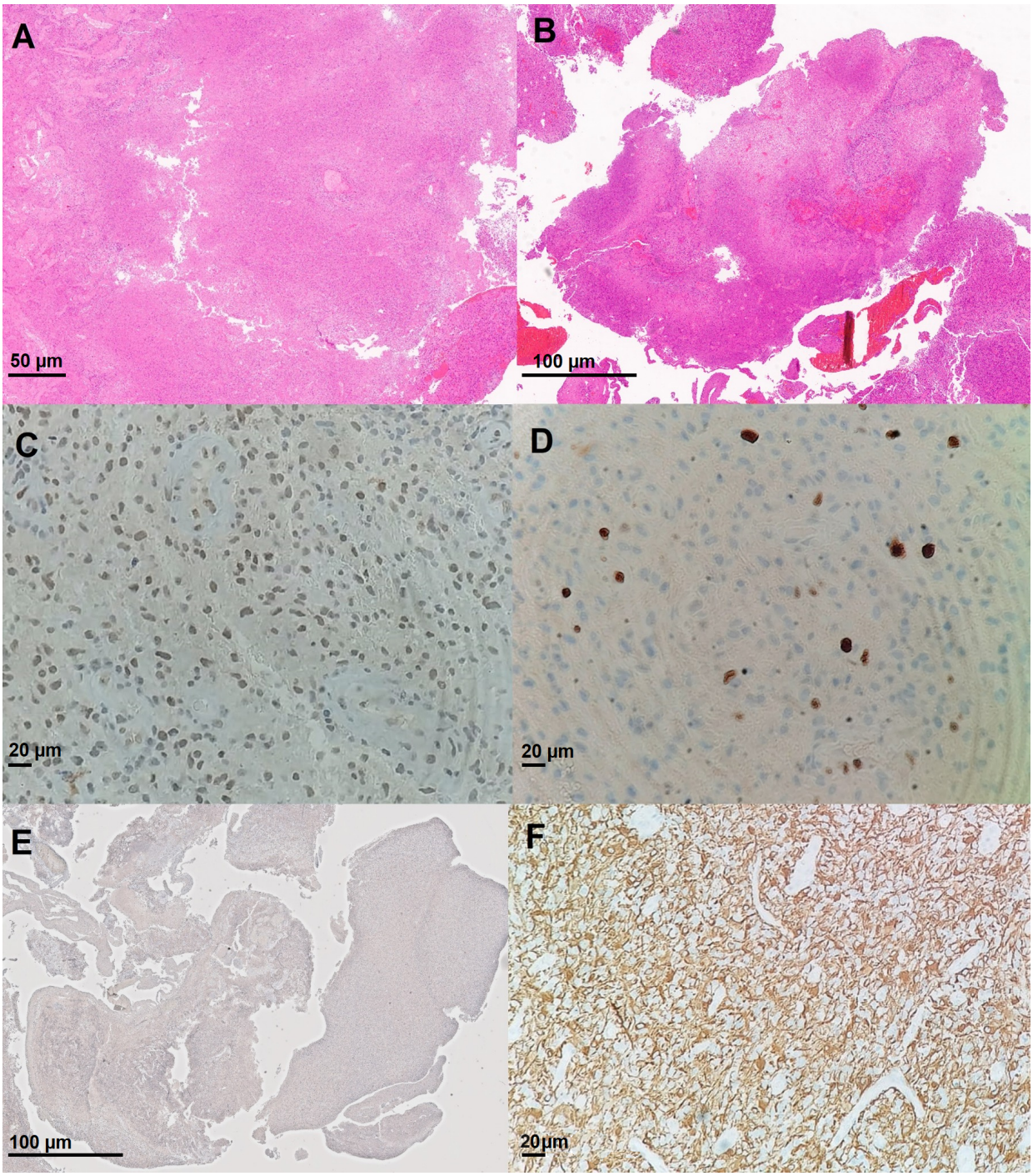

Fig. 6. Histopathological images of IVGBMs. (A) Markedly hypercellular neoplasm was observed under Hematoxylin and Eosin (H&E) staining at 400× magnification. (B) Hypercellular lesion with cellular atypia and palisading tumor cells surrounding central necrosis, shown under H&E staining at 200× magnification. (C) Alpha-thalassemia/mental retardation syndrome X-linked (ATRX) immunohistochemistry reveals retained ATRX expression in tumor cells, observed at 1000× magnification. (D) Increased proliferative activity indicated by Ki-67 immunostaining, seen at 1000× magnification. (E) Negative immunostaining for IDH1 (R132H mutant protein) at 200× magnification. (F) The neoplastic cells are positive for glial fibrillary acidic protein (GFAP) immunostaining at 1000× magnification. This image is from Garibaldi Hospital, Catania, Italy, and informed consent was obtained from the patient for this study.

patient. Despite the aggressive nature of the disease, early recognition, prompt intervention, and multidisciplinary care are essential for optimizing outcomes.

Discussion

GBM is the most prevalent and aggressive primary malignant brain tumor in adults and can originate anywhere within the central nervous system (CNS), but they pre-

dominantly arise in the cerebral cortex, particularly in the frontal and temporal lobes. IVGBM are exceptionally rare, representing a unique clinical and pathological subset of glioblastomas. Their rarity is reflected in the limited number of reported cases in the medical literature, making them an area of particular interest for further study and understanding [1, 24, 26].

Epidemiology and Anatomical Considerations

IVGBM typically arise from the neuroglial cells of the septum pellucidum or the fornix. The proximity of these structures to the ventricular system facilitates tumor growth into the ventricle through transependymal invasion. This close relationship suggests that the initial site of tumorigenesis might be within or adjacent to the ventricular system. The subependymal zone, known for its population of pluripotent stem cells, is also considered a potential origin site for these tumors. This theory is supported by observations of IVGBM predominantly in the lateral ventricle, particularly in the frontal horn or body, and rarely in the fourth ventricle [2, 19]. The rarity of these tumors can be attributed to several factors. Firstly, the ventricular system is a relatively protected environment, with a unique microenvironment and limited exposure to external carcinogenic factors compared to the cortical or subcortical brain regions. Additionally, the neuroglial cells within the ventricular system might have different susceptibilities to oncogenic mutations, resulting in fewer instances of malignant transformation compared to other brain regions. Understanding these factors is crucial for developing targeted therapies and diagnostic tools for this unique subset of GBMs [22, 28].

Clinical Presentation and Diagnosis

The clinical presentation of intraventricular glioblastomas (IVGBMs) often involves symptoms related to increased intracranial pressure, such as headaches, visual deficits, and signs of obstructive hydrocephalus. Headaches are typically the first symptom, resulting from increased pressure within the skull due to the tumor's obstruction of cerebrospinal fluid (CSF) flow. Visual deficits can arise from direct compression of the optic pathways or increased intracranial pressure affecting the visual cortex. Symptoms like ataxia, focal motor deficits, and psychiatric disturbances are less common but can occur depending on the tumor's location and its impact on adjacent brain structures [23, 29]. Imaging modalities, particularly MRI, play a crucial role in diagnosing IVGBMs. These tumors typically appear as irregularly shaped hypodense lesions with contrast enhancement on CT scans. MRI offers superior delineation of tumor location, margins, and extent. The characteristic imaging features of IVGBMs include heterogeneous or ring-like contrast enhancement, surrounding edema on T2-weighted images, and central necrosis. Positron emission tomography (PET) scans and magnetic resonance (MR) spectroscopy can assist in differential diagnosis, particularly in distinguishing GBMs from other intraventricular tumors such as ependymomas, central neurocytomas, and lymphomas [24, 30]. Accurate diagnosis is essential for planning the appropriate treatment strategy. IVGBMs can be challenging to differentiate from other ventricular tumors based on imaging alone, necessitating histopathological confirmation through biopsy or surgical resection. Histopathological examination reveals the characteristic features of GBMs, including marked cellular atypia, high mitotic activity, microvascular proliferation, and necrosis. Molecular and genetic analyses further aid in confirming the diagnosis and stratifying prognosis [22, 23, 31]. When comparing IVGBMs with ependymomas, central neurocytomas, and choroid plexus papillomas, notable differences emerge. Ependymomas often present with similar symptoms and appear as well-demarcated, heterogeneous masses with calcifications on imaging, and are characterized histopathologically by perivascular pseudorosettes and true rosettes. Central neurocytomas, typically presenting in younger adults, appear as well-circumscribed, often calcified intraventricular masses with a "bubbly" appearance due to multiple small cystic areas and show uniform round cells with neuronal differentiation on histopathology. Choroid plexus papillomas, more common in children, appear as well-circumscribed, lobulated masses with intense homogeneous contrast enhancement and are characterized histopathologically by papillary structures lined by epithelial cells. Accurate differentiation through imaging and histopathology is crucial for appropriate treatment planning and prognosis stratification.

Surgical Management

Surgical resection remains the cornerstone of treatment for IVGBMs. The primary goal of surgery is to achieve maximal safe resection of the tumor while preserving neurological function. Various surgical approaches, including transcallosal and transcortical routes, are employed based on tumor size, location, ventricular size, and vascular considerations. The transcallosal approach involves accessing the tumor through the corpus callosum, minimizing cortical disruption, and preserving neurological function. The transcortical approach, on the other hand, provides a more direct route to the tumor but carries a higher risk of cortical damage [32]. The choice of surgical approach aims to minimize damage to healthy CNS structures while achieving maximal tumor resection. Gross total resection (GTR) is preferred over subtotal resection (STR) or biopsy, as it correlates with improved survival outcomes. However, the impact of the extent of resection on OS in IVGBMs remains contentious due to the limited number of cases as show in our Kaplan-Meyer curve analysis (Fig. 3). Postoperative complications, such as hydrocephalus, infection, and neurological deficits, are significant concerns and require careful perioperative management [33]. Advancements in surgical techniques and intraoperative technologies, such

as neuronavigation, intraoperative MRI, and fluorescence-guided surgery, have improved the accuracy and safety of tumor resection. These tools assist in precisely locating the tumor, defining its margins, and ensuring maximal resection while preserving critical brain structures. Despite these advancements, complete resection of IVGBMs is often challenging due to the tumor's infiltrative nature and proximity to vital brain regions [34].

Prognosis and Survival Outcomes

The prognosis for patients with IVGBMs is generally poor, with reported median survival times ranging from 25 to 35 weeks postoperation in various studies, based on limited case reports available in the literature. However, some reports suggest a median survival of 18.8 months, indicating survival outcomes that are similar to those observed in patients with parenchymal glioblastomas (approximately 15 months). Several factors influence the prognosis of IVGBMs, including patient age, tumor size and location, extent of resection, and molecular characteristics. Younger patients and those able to undergo GTR or enroll in clinical trials may experience improved outcomes. For instance, Sarsilmaz *et al*. [12] reported a 16-year-old boy with a lateral ventricle GBM which showed a 24-month PFS after GTR. Conversely, older patients and those with extensive tumor involvement or significant comorbidities tend to have poorer outcomes [20, 21, 24, 35, 36]. The aggressive nature of these tumors often results in rapid disease progression and recurrence, necessitating close postoperative monitoring and timely intervention. Adjuvant therapies, such as radiotherapy and chemotherapy, play a crucial role in managing residual disease and prolonging survival [37]. Despite these efforts, the overall prognosis remains guarded, highlighting the need for novel therapeutic approaches and improved understanding of IVGBM biology [38].

Molecular and Genetic Characteristics

The molecular landscape of IVGBMs mirrors that of their parenchymal counterparts, with common alterations in genes such as Tumor Protein p53 (TP53), Epidermal Growth Factor Receptor (EGFR), Phosphatase and Tensin Homolog (PTEN), Nuclear Factor of Kappa Light Polypeptide Gene Enhancer in B-Cells Inhibitor, Alpha (NFKBIA). The presence of these mutations influences tumor behavior and patient prognosis. For example, TP53 mutations are associated with increased genomic instability and tumor progression, while EGFR amplification and overexpression contribute to enhanced tumor cell proliferation and survival. PTEN mutations result in activation of the Phosphoinositide 3-Kinase (PI3K)/Protein Kinase B (AKT) pathway, promoting cell growth and resistance to apoptosis [39]. Recent advancements in next-generation sequencing (NGS) have provided insights into the genetic alterations in IVGBMs. Notable findings include EGFR amplification, PTEN and neurofibromatosis type 1 (NF1) mutations, and alterations in genes such as breast Cancer Type 2 Susceptibility Protein (BRCA2) and Retinoblastoma Protein (RB1). For instance, targeted therapies aimed at inhibiting the EGFR pathway or restoring PTEN function are being explored in clinical trials [40]. The identification of IDH mutation status significantly influences prognostication. Gliomas with IDH-wildtype typically demonstrate more aggressive behavior and poorer prognosis compared to those with IDH-mutant status [41].

Therapeutic Strategies and Future Directions

The management of IVGBMs involves a multimodal approach, including surgery, chemoradiotherapy, and optimal supportive care. Radiation therapy targeting the subventricular zone (SVZ) has shown promise in improving survival outcomes, as the SVZ houses neural stem cells implicated in GBM pathogenesis. Clinical trials exploring SVZ radiation and intrathecal chemotherapy highlight the need for novel therapeutic strategies tailored to this rare tumor subset [42, 43]. Chemoradiotherapy, typically involving the alkylating agent temozolomide (TMZ), remains the standard adjuvant treatment for GBMs. TMZ is administered concurrently with radiotherapy and followed by maintenance cycles. Despite its widespread use, resistance to TMZ remains a significant challenge, necessitating the exploration of alternative agents and combination therapies. Novel approaches, such as immune checkpoint inhibitors, oncolytic viruses, and personalized vaccines, are being investigated to enhance therapeutic efficacy and overcome resistance [44]. Given the rarity and clinical complexity of IVGBMs, further research is essential to understand their pathophysiology and optimize treatment protocols. Collaborative efforts in collecting and analyzing patient data, along with advancements in molecular profiling, will contribute to developing personalized therapeutic approaches and improving patient outcomes. Additionally, integrating advanced imaging techniques and minimally invasive surgical methods will enhance the precision and safety of tumor resection [45].

Limitations

Despite the comprehensive nature of this review, several limitations should be acknowledged. Firstly, the rarity of IVGBMs results in a limited number of case studies and clinical reports, and there is a significant chronological bias spanning from studies as early as 1950 (Shapiro [3]) to the present day. This wide timeframe encompasses substantial changes in surgical and radiotherapeutic approaches, which undoubtedly impact outcomes. Notably, the introduction of temozolomide (TMZ) in 2009, as per the Stupp protocol, has revolutionized the treatment landscape for MGMT-methylated tumors, potentially altering the disease history [28]. It's crucial to recognize that this chronological bias influences the heterogeneity of outcomes observed in the literature. Additionally, the risk of publication bias must

be considered. Given the rarity of IVGBMs, there is a tendency for selective reporting, where studies with positive or significant findings are more likely to be published than those with negative or inconclusive results. This selective reporting can skew the understanding of treatment efficacy and survival outcomes for IVGBMs. The small sample sizes typical of IVGBMs studies also pose a risk, as they may not provide a comprehensive view of the disease and are more prone to variability. Moreover, language and geographic bias may contribute to publication bias, with studies published in non-English languages or from regions with less research infrastructure being underrepresented in the literature. The case report focus prevalent in IVGBM literature highlights unusual or particularly interesting cases, which may not accurately reflect the typical presentation and progression of the disease.

Future research should aim for standardized data collection and reporting, alongside larger, multicenter studies to increase sample sizes and provide a more comprehensive understanding of IVGBMs. Longitudinal studies with long-term follow-up are also essential to assess the impact of newer treatments over time. Encouraging the publication of all research findings, including negative or inconclusive results, is crucial to provide a balanced view of the evidence.

Conclusions

IVGBMs are rare, aggressive brain tumors that present significant diagnostic and treatment challenges. Advanced imaging and histopathological confirmation are crucial for accurate diagnosis. Surgical resection is the primary treatment, but achieving complete removal is difficult due to the tumor's location. Prognosis remains poor, with survival rates like those of parenchymal GBMs. Key factors influencing outcomes include patient age, extent of resection, and molecular characteristics such as IDH mutation status. Standard treatments involve radiotherapy and chemotherapy, though resistance is common. Future research should focus on better understanding these tumors, optimizing treatments, and developing new therapeutic strategies. Collaboration and advancements in molecular profiling and surgical techniques are essential for progress in managing these conditions.

Availability of Data and Materials

Data to support the findings of this study are available on reasonable request from the corresponding author.

Author Contributions

GS, FG, GF, GEU, GFN, and SM conceived, designed, and performed the systematic review, and wrote the initial draft. GS, GF, EG, MGG, OA, MFa, and MFu analyzed and interpreted the data and provided statistical analysis. All authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors and contributor declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.3529.

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