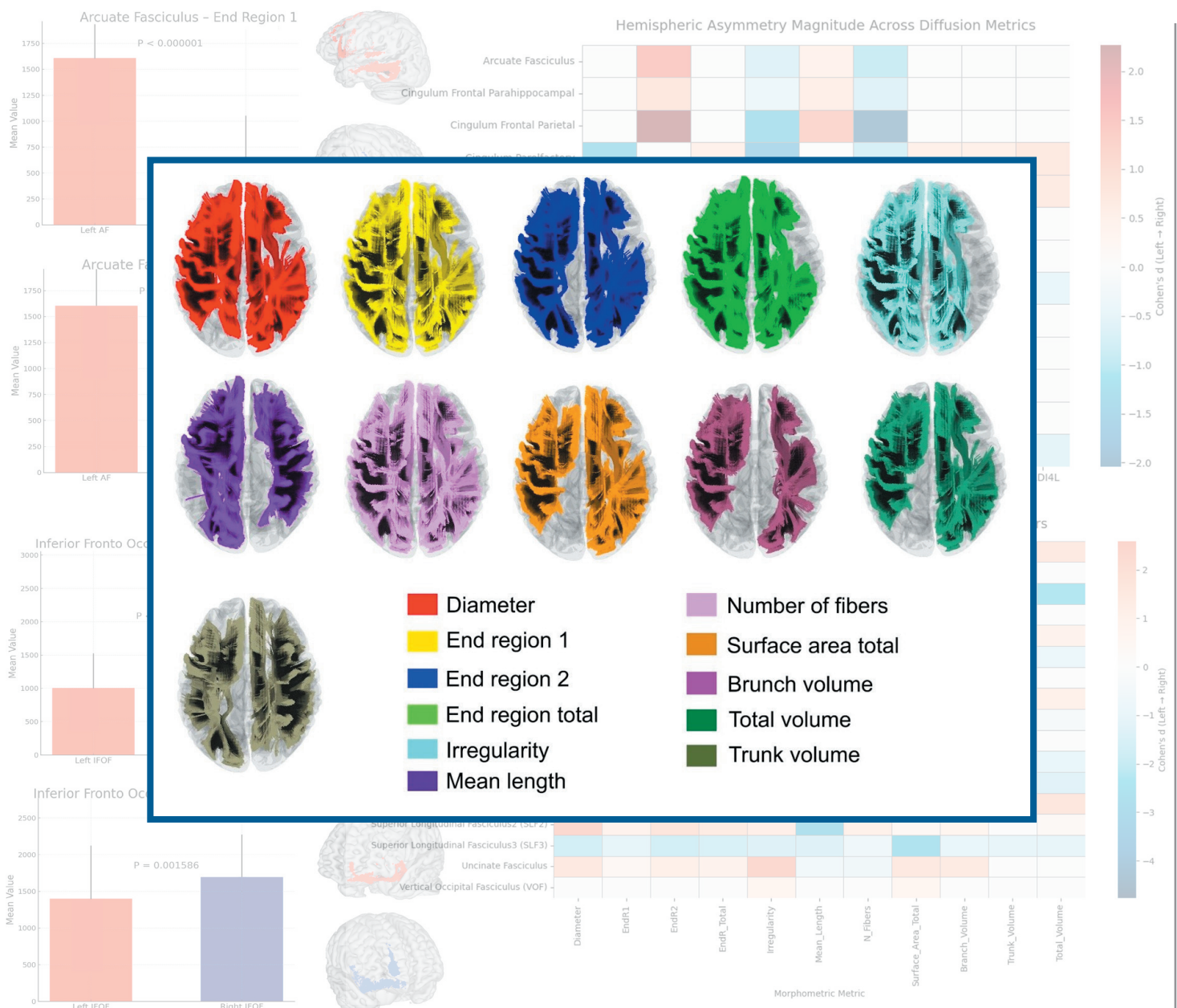




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Ramoni D, Sgura C, Liberale L, Montecucco F, Ioannidis JPA, Carbone F. Artificial intelligence in scientific medical writing: Legitimate and deceptive uses and ethical concerns. *European Journal of Internal Medicine*, Volume 127, 31 - 35

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Beyond Mean Arterial Pressure: Critical Nuances in Hemodynamic Targeting for Severe Traumatic Brain Injury

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Endoscopic-Assisted Chronic Subdural Hematoma Evacuation as an Adjunct to Middle Meningeal Artery Embolization: A Case Series and Systematic Review

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ABSTRACT

AIM: Chronic subdural hematoma (cSDH) is a common neurosurgical condition in elderly patients, frequently associated with trauma, anticoagulant use, and chronic comorbidities. While surgical evacuation and now middle meningeal artery embolization remain the predominant treatment options, endoscopic-assisted techniques have been increasingly used as a surgical adjunct. We evaluated the safety, clinical outcomes, and recent advancements in endoscopic-assisted evacuation of cSDH through both a retrospective case series and an updated review of the current literature.

MATERIAL and METHODS: A retrospective analysis of 39 patients undergoing 44 endoscopic-assisted evacuations of subdural hematomas between October 2021 and May 2025 was performed. Patient demographics, imaging, operative details, complications, and recurrence were analyzed. A systematic review of 15 studies published between 2022 and 2025 was added to a prior review performed by our group to assess outcomes associated with endoscopic approaches to cSDH.

RESULTS: Of the 39 patients (67% male, ages 20 to 73), four experienced recurrence, three prior to middle meningeal artery (MMA) embolization and one after. All patients received postoperative subdural drains, and no intraoperative complications related to the endoscope occurred. The literature review included an additional 16 recent studies (n=1060 patients) in addition to 13 studies from a previous systematic review, reporting recurrence rates of 0% to 16.7%. Endoscopic evacuation was associated with reduced recurrence, shorter hospital stays, and improved hematoma clearance compared to traditional techniques.

CONCLUSION: Endoscopic-assisted evacuation of cSDH appears to be a safe and effective adjunct to conventional surgical methods through improved visualization, potential coagulation of distal meningeal artery territories, and reduced recurrence. While results are promising, larger prospective studies are needed to confirm long-term benefits and refine patient selection.

KEYWORDS: Chronic subdural hematoma, Endoscope, Middle meningeal artery, Case series, Systematic review

ABBREVIATIONS: cSDH: Chronic subdural hematoma, MMA: Middle meningeal artery, EBHC: Endoscopic-assisted burr hole craniostomy, TBHC: Traditional two-burr hole craniostomy

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INTRODUCTION

Chronic subdural hematoma (cSDH), or non-acute subdural hematoma (NASH), is one of the most common neurosurgical conditions, particularly among the elderly (10,27). The exact pathophysiological mechanism of cSDH remains unclear and is attributed to an ischemic-hypoxic mechanism governed by inflammatory signaling cascade at the level of the dura-membrane interface (3,17,22). Multiple factors play a role, including advanced age, use of anticoagulant or antithrombotic agents, a history of falling or head trauma, and chronic comorbidities such as hypertension (3,17,22).

CSDH management is based on severity of clinical symptoms, hematoma size, and associated mass effect. Surgical intervention remains the standard treatment in symptomatic patients (14,16,21). Twist drill evacuation, burr hole aspiration, mini-craniotomy, and craniotomy are among the surgical methods used to remove cSDH (4,5,12,33). Recurrence of cSDH remains a clinical challenge, despite advancements in surgical techniques and perioperative care. Several recent studies have sought to identify and validate predictive risk factors for patient stratification and treatment optimization. Recent popularity of middle meningeal artery embolization has especially emerged in the west with completion of the EMBOLISE trial (7). In recent years, the endoscope-assisted approach, a minimally invasive technique, has held attention for providing a clear visualization, reducing invasiveness, and better hematoma evacuation (1,12,13,25,26,29,33). However, comprehensive data assessing the efficacy and safety of endoscope-assisted techniques in cSDH management remain limited.

In this study, we evaluated the feasibility, safety, efficacy, and clinical outcomes of surgical evacuation of cSDH using endoscope assistance through a single-center consecutive case series and systematic literature review.

MATERIAL and METHODS

Case Series

We conducted a retrospective, single-surgeon (MK), multi-institutional consecutive case series of patients undergoing endoscopic-assisted cSDH evacuation between October 2021 and May 2025. Institutional review board approval was obtained for all retrospective patients (University of Utah #001530; Global Neuroscience Institute #20200568; University of Michigan HUM00266268) with informed consent for all case presentations. A subset of patients in this series (n=9) were previously published (6).

Surgical Technique

Endoscopic-assisted surgery utilized a 30-degree endoscope and flexible 8F suction coblator via a widened burr hole or mini-craniotomy. The technique evolved to two burr holes, with the posterior enlarged for combined endoscope/coblator use (Figure 1). Removal of the inner table with saucerization of the outer table aided the angles required for endoscope use. Bridging vessels and membranes were coagulated when

feasible. Dura along the inner table within the location of the middle meningeal artery was coagulated. Two 10F JP drains tunneled anteriorly/posteriorly and placed on suction for 24-48 hours. A postoperative CT head was obtained at 24 hours.

Patient Selection for Combined Therapy

Patients selected for combined endoscopic evacuation and MMA embolization were those with recurrent or refractory cSDH after initial drainage, complex or septated hematoma morphology, extensive membranes, or at high risk of recurrence (ongoing anticoagulant use, advanced age, or significant comorbidities). This approach aimed to maximize hematoma clearance and minimize recurrence risk. The treatment algorithm outlining the decision-making process for managing cSDH, including traditional burr-hole surgery and endoscopic evacuation are noted in Figure 2.

Data Collection

Patients were excluded if presenting with an acute subdural hematoma requiring urgent evacuation. Patient demographics, pathology, surgical approach, complications, pre- and postoperative imaging, and recurrence were collected. Recurrence was defined as a postoperative increase in subdural fluid volume that required repeat operative intervention. The study was conducted in accordance with the PROCESS (Preferred Reporting of Case Series in Surgery) guidelines for surgical case series.

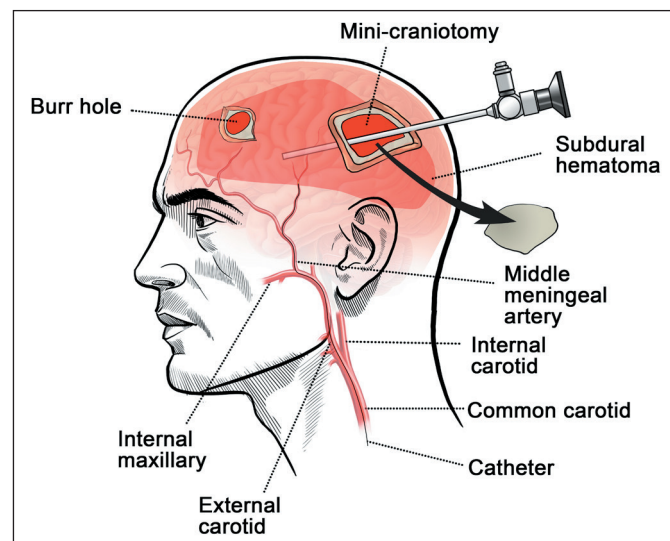


Figure 1: Schema of endoscopic-assisted chronic subdural hematoma (cSDH) evacuation in conjunction with middle meningeal artery (MMA) embolization. Inline burr holes with a posterior burr hole enlargement or minicraniectomy can aid in the use of a 30 degree endoscope for hematoma visualization and evacuation, hemostasis, coagulation of bridging veins, and coagulation of membranes along the path of the distal MMA. Endovascular MMA embolization remains a key method for proximal and distal coagulation as a method to interrupt the hypoxic-ischemic mechanism of cSDH formation.

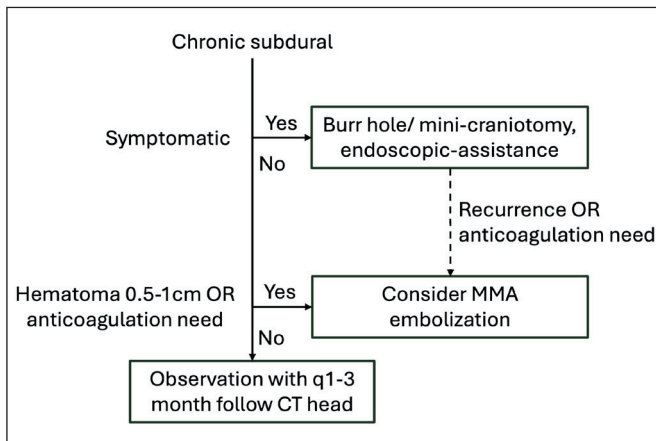


Figure 2: cSDH treatment algorithm. Schema illustrating cSDH patient decision making to proceed with traditional burr-hole surgery, direct endoscopic evacuation, or combined treatment.

Systematic Literature Review

To evaluate recent advancements in the management of cSDH, we conducted an updated systematic review that expands upon the previous systematic analysis by Cutler et al. (2022) of 13 total studies and used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (6).

A systematic literature review was conducted using PubMed, Web of Science, and Embase, identifying studies published between 2022 and 2025. Targeted keywords included “chronic subdural hematoma” or “cSDH”; “neuroendoscopy,” “endoscopic evacuation,” or “endoscope-assisted”; “middle meningeal artery embolization”; “membranectomy”; and “minimally invasive neurosurgery”. Studies were eligible for inclusion if they discussed endoscopic surgical approaches to non-acute subdural hematomas and were published in English. Articles were excluded if they were review papers, single-patient case reports, not written in English, or published before 2022.

After eliminating duplicate records, two independent reviewers screened the remaining studies for eligibility using titles, abstracts, and relevant keywords as the basis for selection. Eligible studies included those reporting on endoscopic evacuation and any other strategy for cSDH evacuation including surgical treatment or MMA embolization. Data on recurrence rates, antiplatelet/anticoagulation therapy use preoperatively, continuation of postoperative drain, and overall patient outcomes were extracted and qualitatively synthesized. This review was registered on PROSPERO.

RESULTS

Case Series

A total of 39 patients (age range: 20–73 years; 67% male) underwent 44 endoscopic-assisted procedures for the treatment of subdural hematoma (SDH): 10 on the left side, 22 on the right, and 12 bilateral. Recurrence occurred in 4 patients - 3 prior to middle meningeal artery embolization and 1 following

the procedure. Postoperative subdural drains were placed in all cases. No intraoperative or postoperative complications related to the use of endoscopic use or endoscopic assisted coagulation were observed.

The decision to combine MMA embolization with endoscopic evacuation was made in patients with one or more of the following: recurrent cSDH after burr-hole evacuation, evidence of thick or vascularized membranes on imaging or intraoperative inspection, high risk for recurrence (such as with anticoagulant use or bilateral hematomas), or when intraoperative findings suggested incomplete hemostasis of distal MMA branches (7,12).

Illustrative Case 1

A 73-year-old male presented with altered mental status and left-sided weakness (Figure 3). His medical history was notable for atrial fibrillation managed with warfarin (admission INR: 2.0) and multiple recent falls (Figure 3A, B). He underwent right-sided burr hole evacuation and craniotomy (Figure 3C, D), followed by endoscopic-assisted hematoma evacuation (Figure 3E), membrane coagulation (Figure 3F, G), and subdural drain placement (Figure 3H). His postoperative course was uneventful, and he was discharged on postoperative day 4.

Illustrative Case 2

Another 73-year-old male presented with altered mental status, lethargy, and asymmetric weakness (left greater than right) following a ground-level fall two weeks prior (Figure 4A). Initial bilateral burr hole drainage resulted in near-complete resolution of the right-sided hematoma and clinical improvement; however, the left-sided SDH persisted with new acute components (Figure 4B). Bilateral MMA embolization was performed 4 days later (Figure 4C, D). Despite this, follow-up imaging at 7 days demonstrated ongoing left-sided mass effect (Figure 4E). The patient underwent a left-sided reoperation with enlargement of the posterior burr hole via craniotomy, endoscopic-assisted hematoma evacuation, membrane coagulation, and drain placement. At 1-month follow-up, imaging revealed significant improvement of the hematoma (Figure 4F).

Systematic Review

A total of 15 studies met the inclusion criteria for this literature review, each examining the use of endoscopy in the management of subdural hematomas (Figure 5, Table I). Collectively, these studies encompassed 1060 patients with a mean age of 66.4 years. Reported recurrence rates following endoscopic treatment for cSDH ranged from 0% to 16.7% with an overall average of 12.44%. Middle meningeal artery embolization was addressed in only two studies, while preoperative alcohol use was reported in two papers, with prevalence ranging from 19.6% to 47.9%. The use of a novel brain retractor was discussed in two papers. Membranectomy was discussed in 8 of the 15 studies. Preoperative use of antiplatelet or anticoagulant medications varied widely, ranging from 3.2% to 83.3%. All but one study reported the use of a postoperative drain, with most utilizing subdural drains and two specifying subgaleal drain placement.

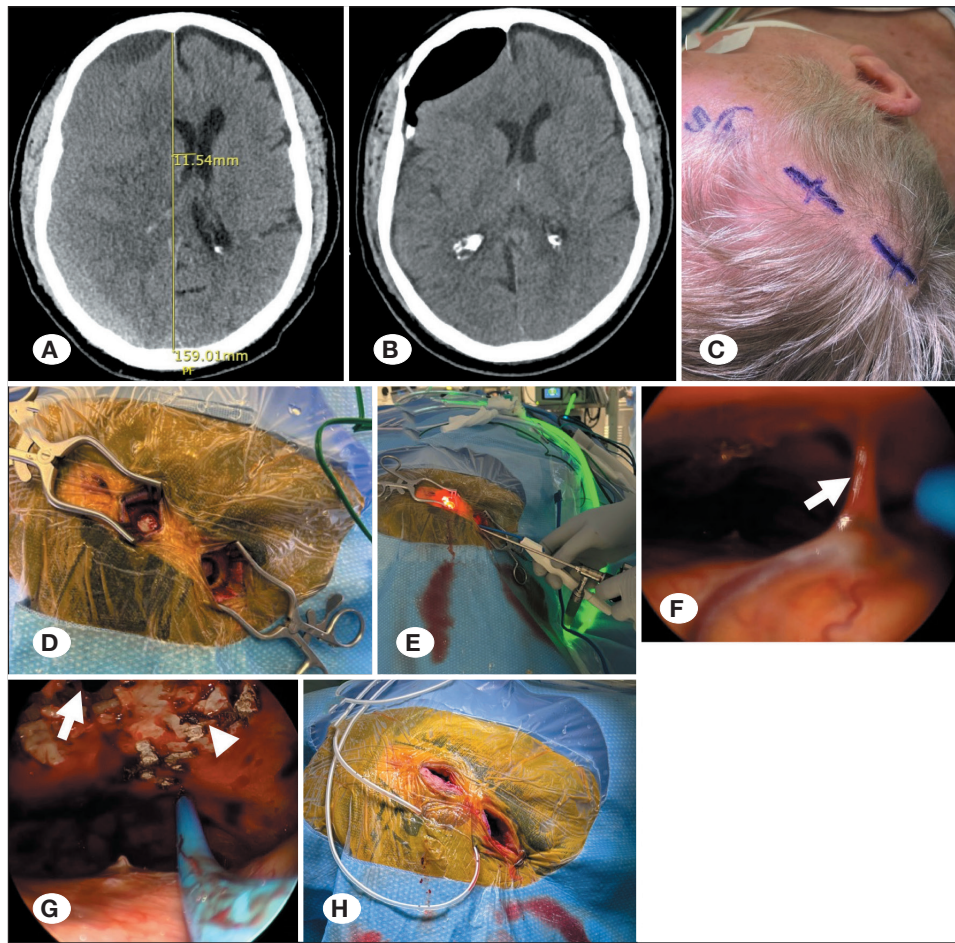


Figure 3: Illustrative Case 1.

A) A 73 year old male presenting with right sided cSDH underwent evacuation. **B)** Postoperative images are shown. **C)** Supine positioning with the head in a horseshoe headrest demonstrates placement of burr holes along the superior temporal line. **D)** Burr hole generation is shown with enlargement and saucerization of the posterior burr hole. **E)** A 30 degree endoscope with 8F suction coagulator is used for hematoma evacuation and coagulation. **F)** Coagulation of bridging veins (arrow) at risk for rehemorrhage can be coagulated. **G)** Coagulation of distal dural membranes (arrowhead) along the distribution of the middle meningeal artery can be used to disrupt the mechanism of cSDH formation. The anterior burr hole is seen (arrow). **H)** Anterior and posterior directed 10F JP drains can be used for evacuation of hematoma and air from the surgical cavity.

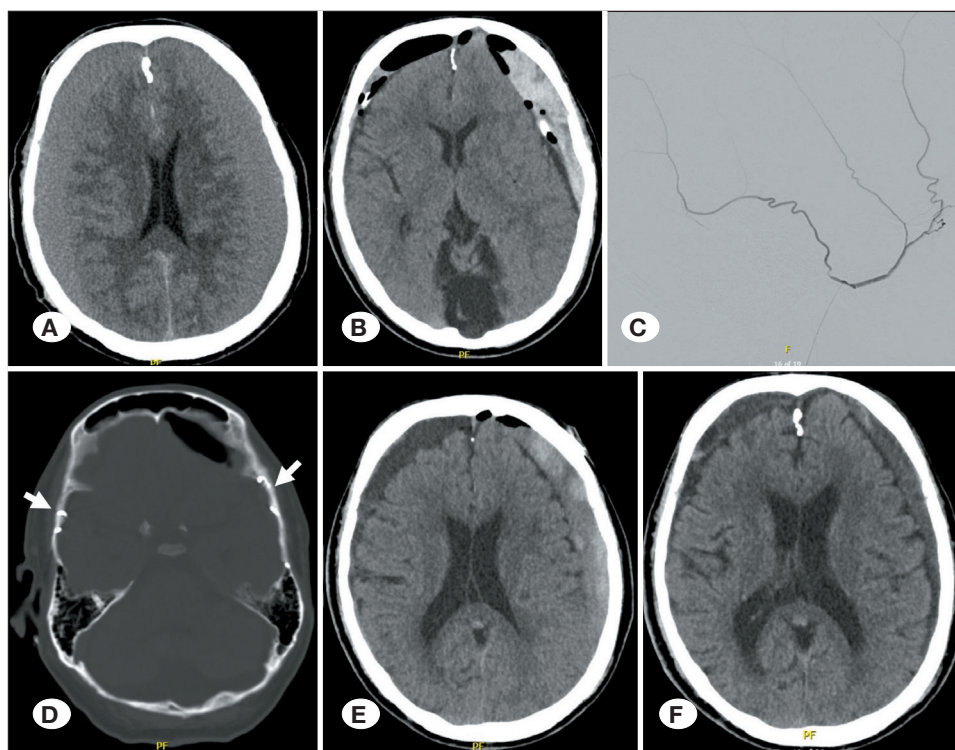


Figure 4: Illustrative Case 2.

A) A 73 year old male presenting with bilateral cSDH underwent burr hole evacuation. **B)** Postoperative images demonstrated adequate right side evacuation but early recurrence of acute SDH component. **C, D)** An MMA embolization was successfully performed bilaterally with embolizate identified postoperatively (arrows). **E)** Delayed recurrence and persistence of left side cSDH hematoma underwent a repeat drainage with endoscopic-assisted evacuation. **F)** 1 month followup scan demonstrated bilateral improvement of cSDH components.

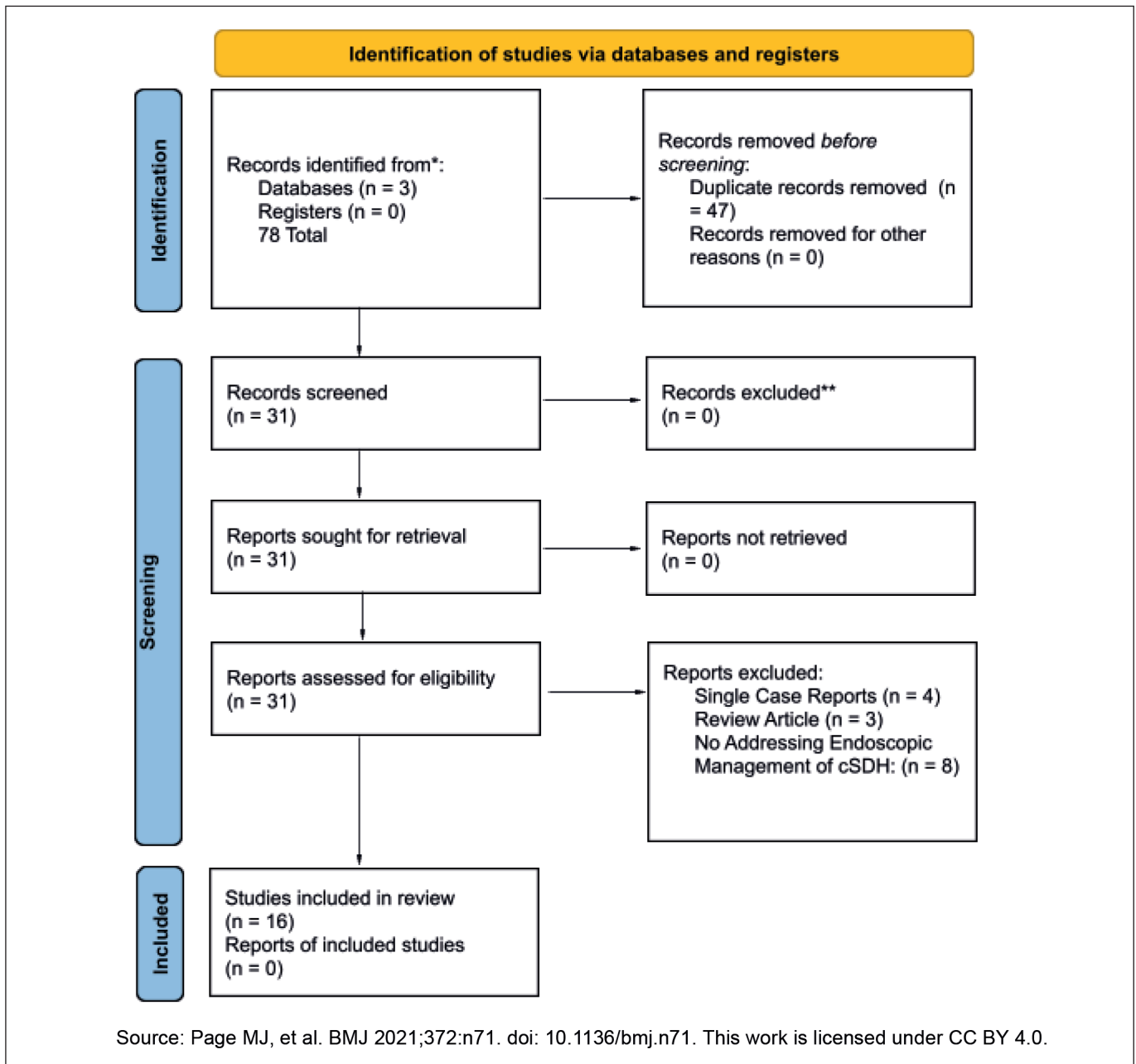


Figure 5: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram depicting study selection for a literature review on endoscopic treatment of nonacute subdural hematomas.

DISCUSSION

Our findings support the safety and feasibility of endoscope-assisted evacuation for patients with non-acute subdural hematoma. Among the 39 patients treated, 4 (10%) experienced recurrence including “1” patient despite MMA embolization. No complications related to endoscope use were seen. One case of ours underwent both combined MMA embolization and endoscopic-assisted evacuation with dural coagulation with post-treatment recurrence. Both surgical procedures were technically successful. Risk factors for this specific patient included recurrent falls and alcoholism. These

results suggest that recurrence despite aggressive treatment may still occur but in low numbers of patients as evident by our results and the literature. The systematic review demonstrated recurrence rates for cSDH ranging from 0-16.7% with an overall average of 12.44%. Modern series have increasingly discussed the use of endoscopic-assisted treatment with middle meningeal artery embolization (Table I).

Endoscopic-assisted treatment was effective in visualization of hematoma evacuation cavities, inspection of the brain, identification of active hemorrhage sites, and coagulation of membranes or distal MMA vessels. Endoscopic-assisted

Table 1: Comparative Summary of Included Studies on Endoscopic-Assisted and Combined Approaches to cSDH

Reference	No. of Patients	Mean Age (years)	Recurrence Rate (%)	MMA Embolization Rate (%)	Alcohol Use (%)	Operative Duration (min)	Complication Rate (%)	Surgical Technique	Membranectomy Performed	Antiplatelet/Anticoagulant Use Pre-op (%)	Drain Type	Notes / Key Outcomes
An et al., 2025 (2)	48	73.75	12.5	-	47.9	103.6 (EBHC) vs 50.8 (TBHC)	-	30° endoscope	Outer 25%	-	Subdural	EBHC: shorter drainage (18.7h), longer operation time
Egemen et al., 2024 (8)	21	65.63	NR	-	-	-	Minimal	0° rigid endoscope	-	23.8	Subdural	Safe/effective in septated hematomas
Fang et al., 2024 (9)	41	64.3	2.4	-	19.6	-	-	Rigid endoscope	-	Patients excluded	Subdural	Higher clearance, shorter stay vs BHC, lower recurrence
Guo et al., 2023 (11)	20	62.25	0	100	-	-	No adverse postop complications	Rigid short endoscope	-	35	Subdural	Combined MMA + endoscopy reduced recurrence
Hong et al., 2022 (15)	13	71.1	0	-	-	128.5 (Endo) vs 65.2 (Non)	No surgical complications in either group	0° & 30° (2.7mm) post-BHC	Yes	15.4	None	No recurrence in Endo group
Li et al., 2023 (18)	45	67.89	2.2	-	-	67 (NHE) vs 55 (BHC)	Recurrence: 2.2% (NHE) vs 18.8% (BHC)	0° endoscope	Outer	-	Subdural	Faster recovery, lower drainage, improved clearance vs BHC
Ma et al., 2022 (19)	48	64.12	2.0	-	-	104.9 (Endo) vs 65.2 (BHC)	0 (Endo) vs 12.5 (BHC)	Neuroendoscope	-	-	Subdural	Shorter stay: 8.46d (Endo) vs 10.22d (BHC)
Nomura et al., 2022 (20)	4	74.75	NR	75	-	-	-	Variable	-	-	Subdural	Embolization enhances the healing process
Park et al., 2023 (23)	6	71	16.67	-	-	-	No surgery related complications	0° or 30° endoscope	-	83.3	Subdural	Effective in cSDH + hygroma
Priyadharshan et al., 2023 (24)	19	60.4	0	-	-	43.3 for endoscopic membranectomy	No post op seizures, wound healing issues, or infections	Rigid 0° / 30° endoscope	Inner	15.8	Subdural	Lower recurrence and faster recovery
Sharma et al., 2024 (25)	248	69	2.0	-	-	56 for novel brain retractor	Lower complications with endoscopy vs TBH	0°/30° endoscope	Yes	3.2	Subgaleal	Improved visualization and hematoma removal with brain retractor
Singh et al., 2022 (26)	68	68.8	2.0	-	-	157.5 with endoscope	No infections with endoscope	0° rigid endoscope	Yes	39.7	Subdural	Reduced recurrence and complications
Wang et al., 2022 (30)	61	57.26	2.0	-	-	Longer for endoscopy	None reported for neuroendoscopy group	Rigid Storz	Yes	-	Subdural	Clear visualization, lower recurrence
Wang et al., 2023 (31)	42	55.3	NR	-	-	60	-	Rigid Storz (0°)	-	-	Subdural	CT-based positioning to optimize access
Yadav et al., 2023 (32)	341	67	0.06	-	-	60	None	0°/30° endoscope	-	3.2	Subgaleal	Retractor improved access, low recurrence

coagulation was especially useful in cases when MMA embolization could not be performed due to tortuous vessels or if patients recurred in spite of embolization. Challenges remain in the treatment of patients with narrow subdural spaces and limited use of rigid endoscopes or current suction coblators.

Literature Review

Along with our case series findings, recent studies also support the safety of endoscopic evacuation for cSDH (19,24,25,29). This technique has been associated with lower rates of hematoma reaccumulation, infection, or mortality compared to conventional surgical methods (8,24). This is especially beneficial for recurrent hematomas or in elderly or anticoagulated patients, for whom minimally invasive approaches reduce perioperative risk (10,27,28). These findings were supported by the literature reviewed. A previous systematic review from our group identified 13 studies evaluating the use of endoscope-assisted cSDH evacuation (6), and our current analysis adds another 15 studies between 2022 to 2025.

Priyadharshan et al. reported excellent clinical outcomes: 100% of patients were neurologically intact at follow-ups, and 89.5% showed no recurrence on 6-month CT scans (24). Singh et al. found similar benefits, with endoscopic evacuation offering superior visualization and clearance of cSDH, potentially reducing recurrence compared to common interventions (26). An et al. provided direct comparison between endoscopic-assisted burr hole craniostomy (EBHC) and traditional two-burr hole craniostomy (TBHC), highlighting that EBHC offers benefits such as shorter drainage times and hospitalization (2).

Our results support that endoscopic intervention, through improved intraoperative visualization, enables safer, more complete hematoma evacuation and drain placement similar to other studies (18,32). Furthermore, these studies highlight the minimally invasive nature of the endoscope-assisted techniques. Endoscopic approaches, whether performed via a burr-hole or mini-craniotomy, allow for smaller incisions and reduced brain manipulation. Minimization of surgical incisions via burr holes or mini-craniotomies may improve postoperative recovery but requires further study to support for cSDH treatment (9,18,32). Regardless of technique chosen, endoscopic visualization could be used as an adjunct for surgical treatment.

Combining MMA Embolization and the Endoscope

Additionally, combining endoscopic evacuation with MMA embolization may help further reduce recurrence in cSDH. Current multicenter level 1 evidence from the EMBOLISE trial suggests MMA embolization results in a recurrence rate of 4.1% vs. 11.3% (relative risk, 0.36; 95% confidence interval [CI], 0.11 to 0.80; $p=0.008$) (7). Embolization may interrupt vascular supply to the outer membrane, reducing inflammation and regrowth; endoscopy enables direct visualization to confirm embolization effectiveness and guide treatment (20). This approach may be beneficial in recurrent or refractory cases (11,30). Endoscopic treatment may offer additional disruption

to potential cSDH membranes or be used in cases where embolization cannot be safely performed due to vessel tortuosity or unsafe reflux into vessels supplying critical neurological structures (e.g., ophthalmic artery).

Future studies could benefit from a morphology-based stratification model to guide treatment selection. For example, patients with non-septated, homogenous hematomas might be adequately treated with burr-hole drainage with or without MMA embolization, whereas those with septated or multiloculated collections, thick vascular membranes, or recurrent hematomas could be prioritized for endoscopic-assisted evacuation with or without MMA embolization (9,15,18). Such models could be based on preoperative imaging (CT/MRI) scoring systems and refined by intraoperative findings.

Limitations of the Endoscope

While endoscope-assisted evacuation of cSDH has shown promising outcomes, several studies also note potential challenges with this technique. Wang et al. emphasized the requirement for general anesthesia and a relatively larger craniotomy compared to traditional burr hole procedures, which may limit its use in certain patient populations (30). An et al. reported that EBHC resulted in a significantly longer operative time compared to TBHC (103.6 vs. 50.8 minutes, $p<0.001$) (2). However, this was offset by benefits such as shorter drainage duration (18.7 vs. 55.9 hours, $p<0.001$) and reduced hospital stay (4.66 vs. 6.02 days, $p<0.001$) (2). Similarly, Hong et al. reported a longer average operative time in the endoscope group (128.5 vs. 65.2 minutes, $p<0.0001$), though they noted that the approach was particularly effective for patients with compartmentalized hematomas (15).

Priyadharshan et al. further highlights the technical demands of endoscopic methods, pointing to the need for precise optimal alignment between the patient and the endoscope (24). For example, the flexible endoscope offers mobility but lacks image clarity compared to rigid scopes. The endoscope technique learning curve is high, specifically for membranectomy or complex septations (24). To mitigate this learning curve, structured training in neuroendoscopy, including simulation-based practice, stepwise integration into simpler cSDH cases, and mentorship by experienced surgeons, should be emphasized. Early in the learning curve, cases with larger subdural spaces and less septation may be preferable, reserving complex hematomas for more experienced operators (2,15,24). Despite these challenges, the overall benefits of endoscopic evacuation, such as reduced recurrence rates and improved patient outcomes, make it an advantageous alternative to conventional approaches (23,26,31).

Recent research has explored the use of adjunctive tools such as soft brain retractors to address these technical challenges of endoscopy. Sharma et al. and Yadav et al. both demonstrated that retractors improve access to complex hematoma structures, facilitating removal (25,32). Their use was associated with low recurrence, no complications, and improved outcomes, making this an important avenue for future exploration (25,32).

Study Limitations

This study design may have several limitations. In regards to the case series, patient selection was limited to a single surgeon's practice with significant heterogeneity of patient presentations, comorbidities, and cSDH configurations, which may limit external validity and generalizability to other practices and centers. Our study and the overall advantages of endoscopic techniques limited our ability to incorporate a matched control group of patients receiving alternative treatment options. Further, we did not specifically analyze operative time as a marker of the learning curve over this multi-year, multi-institutional series which could be an area of future study. Additional markers could include some component of MMA territory coagulation on postoperative imaging or degree of hematoma evacuation. However these findings would be limited unless performed in a multi-surgeon, multi-institutional manner.

In regard to the literature review, technical details such as the type of endoscope used, surgeon experience, and adjunct instrumentation (e.g., retractors, embolization materials) were variably reported, reducing reproducibility and comparability across studies. These variations highlight the need for standardized operative protocols, discussion of standardized surgical steps, and reporting guidelines. Differences in endoscope type (rigid vs. flexible), visualization angle, coblation tools, and use of adjunctive devices such as retractors may influence operative time, evacuation completeness, and complications (2,24,25,32). Likewise, surgeon experience with neuroendoscopic techniques plays a critical role in patient outcomes. Multi-center studies with clearly defined instrumentation, procedural steps, and surgeon training levels are necessary to enhance reproducibility.

CONCLUSION

Endoscopic-assisted evacuation, especially in combination with MMA embolization, offers a safe, effective, and minimally invasive option for selected patients with cSDH. Integration of endoscopy into modern cSDH management, guided by patient stratification and standardized protocols, may improve outcomes and reduce recurrence. Although current evidence supports the benefits of endoscope-assisted evacuation in cSDH, the need for larger, prospective trials to validate these findings is imperative.

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AUTHORSHIP CONTRIBUTION

Study conception and design: MK

Data collection: MK

Analysis and interpretation of results: DB, HF, CP, ED, MZ, MK

Draft manuscript preparation: DB, HF, CP, ED, MZ

Critical revision of the article: DB, HF, CP, ED, MZ, MK

All authors (DB, HF, CP, ED, MZ, MK) reviewed the results and approved the final version of the manuscript.

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Development and External Validation of a Nomogram for Predicting the Survival Outcomes of Patients with Ki-67 Positive Grade 4 Diffuse Gliomas

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ABSTRACT

AIM: To establish a nomogram model of Ki-67-positive grade 4 diffuse gliomas that can predict the survival rate of patients and has certain guiding values that are useful in treatment.

MATERIAL and METHODS: Data from 146 patients with Ki-67-positive grade 4 diffuse gliomas was retrospectively obtained and analyzed using the R software. Statistically significant indicators were identified via Cox regression analysis and used to establish the nomogram. The nomogram was corrected using the C-index, area under the curve (AUC), calibration curve, and decision curve analyses (DCA). Finally, the model was externally validated using the Chinese Glioma Genome Atlas database.

RESULTS: Age, treatment, and IDH status were significant. The models had a C-index of 0.743, and the time-dependent receiver operating characteristic curve had an AUC of 0.832 at 3 months and 0.829 at 6 months, indicating good discriminatory ability. Finally, a nomogram was constructed and validated using the validation and DCA curves.

CONCLUSION: Age, treatment, and IDH were independent prognostic factors in patients with Ki-67-positive grade 4 diffuse gliomas. The constructed model can accurately assess the disease-specific survival rates of these patients and help inform treatment options.

KEYWORDS: Grade 4 diffuse gliomas, Ki-67 positive, Nomogram, Survival, The time-dependent receiver operating characteristic (ROC)

ABBREVIATIONS: GBM: Glioblastoma, **C-index:** Concordance index, **ROC:** Time-dependent receiver operating characteristic, **AUC:** Area under the curve, **DCA:** Decision curves analysis, **HR:** Hazard ratio, **CGGA:** Chinese Glioma Genome Atlas, **RCas:** Radiation and Chemotherapy after surgery, **Ras:** Radiation after surgery, **Cas:** Chemotherapy after surgery, **WHO:** World Health Organization

INTRODUCTION

Glioblastoma (GBM) is the most common primary malignant brain tumor, accounting for about 16% of all primary brain and central nervous system tumors

(19). The average age-adjusted incidence of GBM is 3.2 per 100,000 (13,14). Despite being almost exclusively found in the brain, GBM can also be found in the brainstem, cerebellum, and spinal cord. Approximately 61% of primary gliomas occur

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the frontal (25%), temporal (20%), parietal (13%), and occipital (3%) lobes of the brain (2). GBM was previously thought to originate only from glial cells, but emerging evidence suggests that it can develop from various cell types with neural stem cell-like properties. These cells are at multiple stages of differentiation, from stem cells to neurons to glia, and their phenotypes largely vary based on molecular alterations in signaling pathways rather than differences in cell type and origin (16). In 2021, the World Health Organization (WHO) pointed out that grade 4 diffuse gliomas included the former IDH wild-type GBM and grade 4 IDH mutant astrocytoma (9). Such patients often present with symptoms of increased intracranial pressure, including headache and focal or progressive neurological deficits. Seizures occur in up to 25% of patients and may appear later in the disease in up to 50% of patients (15).

A multidisciplinary approach is essential in the treatment of newly diagnosed grade 4 diffuse gliomas. The current standard of care includes maximal safe surgical resection followed by concurrent radiation therapy with temozolomide (TMZ) (Temo-dar®, Merck Sharp & Dohme Company, Kenworth, NJ, USA), an oral alkylating chemotherapeutic agent, then by adjuvant chemotherapy with TMZ (11). However, the complete surgical removal of GBMs is difficult due to their aggressive nature and often unfavorable locations, which typically include functional areas that control language, motor function, and sensation. Due to their highly invasive nature, radical resection of the primary tumor mass is also inefficient, because the infiltrating tumor cells always remain in the surrounding brain, eventually resulting in disease progression or recurrence (22).

Ki-67 is a nonhistone nuclear protein associated with ribosomal RNA (rRNA) transcription and is expressed when cells enter the mitotic cycle. Ki-67 expression is positively correlated with the histological grade of gliomas. Accordingly, Ki-67 levels have also been correlated with poor prognosis across various malignancies (1).

Mutations in genes encoding the cytoplasmic and mitochondrial forms of isocitrate dehydrogenase (IDH1 and IDH2; collectively known as IDH) are often detected in various sources of cancer, including but not limited to acute myeloid leukemia (20%), cholangiocarcinoma (20%), chondrosarcoma (80%), and glioma (80%). In all cases, the new form activity of the mutated enzymes causes the production of d-2-hydroxyglutamate, a tumor metabolite that exerts profound cellular and non-cellular autonomic effects. IDH mutations have a widespread impact across epigenetic, differentiation, and metabolic processes, as well as have a high prevalence in various cancer types, early presence in tumor development, and uniform expression in tumor cells. These features make mutated IDH an ideal therapeutic target (17).

Previous studies have investigated the outcomes of Ki-67-positive grade 4 diffuse gliomas, although none have established a nomogram model. Accordingly, this study aims to establish a nomogram model of Ki-67-positive grade 4 diffuse gliomas that can predict the survival rate of patients and has certain guiding values that are useful in treatment.

■ MATERIAL and METHODS

Data Sources

This study retrospectively retrieved data from 146 cases of grade 4 diffuse gliomas in the brain between 2020 and 2021 (Table I). All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was

Table I: Clinic-Pathological Characteristics of Patients

Variables	Number of patients
Age (years)	146
<66	95
≥66	51
Sex	146
Female	61
Male	85
Size (mm)	146
<37.5	44
≥37.5	102
Location	146
Frontal lobe	41
Other	105
Treatment	146
Chemotherapy after surgery	4
Radiotherapy after surgery	8
Surgery	62
Radiotherapy and Chemotherapy after surgery	72
S100	146
(-)	11
(+)	135
p53	146
(-)	16
(+)	130
ATRX	146
(-)	25
(+)	121
Syn	146
(-)	26
(+)	120
IDH	146
(-)	129
(+)	17

IDH: Isocitrate dehydrogenase

obtained from all subjects and/or their legal guardians for the purpose of this research. Independent prognostic factors were identified using the R software.

The prognostic outcomes of patients were predicted using the nomogram. The receiver operating characteristic (ROC) curve was used to verify the accuracy of the model. Finally, the model was calibrated using the calibration curve and decision curves analysis (DCA). The model was validating using 121 patients with grade 4 diffuse gliomas from the Chinese Glioma Genome Atlas (CGGA) database (<http://www.cgga.org.cn/>).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1) patients with Ki-67-positive grade 4 diffuse gliomas; 2) a positive histopathological diagnosis for grade 4 diffuse gliomas performed between 2020 and 2021; 3) complete treatment information available; 4) follow-up data available; 5) malignant behavior recode; and 6) underwent gross total resection. Patients who were lost to follow-up and with unknown tumor sizes were excluded (Figure 1).

Data Variables

The collected data included age, sex, tumor size, treatment (i.e., surgery and postoperative chemotherapy and/or radiotherapy), tumor location (i.e., frontal lobe or other locations), S100, P53, ATRX, Syn, and IDH status. All cases had well-defined return dates. Pathological assessment was performed using the WHO 2021 classification system.

Statistical Analysis

Univariate Cox regression analysis was used to identify the possible prognostic risk factors at a threshold of $p < 0.05$, which were then used to create a prediction model. The Akaike information criterion was used to select the best prediction model (6), which was visualized on a nomogram. Concordance index (C-index) and time-dependent ROC curves were used to assess the precision and discriminative abilities of the model (5,24). Comparisons between the actual probability and predicted outcomes of the model were visualized using calibration curves (4). The 100 resampling method was used to evaluate the calibration curves and discrimination.

The X-tile software was used to establish the best cutoff values. Statistical analyses were performed using R version 4.2.1 (<http://www.r-project.org/>).

RESULTS

Clinicopathological Characteristics of the Patients

This study enrolled 146 patients with Ki-67-positive grade 4 diffuse gliomas, among which 41.8% were female. The best cutoff values obtained using the X-tile software were an age of 66 years and tumor size of 37.5 mm. Based on these cutoffs, 34.9% of patients were above 66 years old, while 69.9% had tumors larger than 37.5 mm. Regarding tumor characteristics, 28.1% were located in the frontal lobe, while 88.4% were IDH-negative. All patients were diagnosed based on positive histology findings. Each patient was followed up via telephone every three months until death. The overall survival of patients was determined by asking their family members.

Univariate Analysis

Cox univariate analysis revealed that age, treatment, and IDH were significant risk factors (Figure 2). Other factors ($p < 0.2$) were included in the multivariate analysis.

Independent Prognostic Factors

Findings from the multivariate analysis are shown in Figure 3. Age, treatment, and IDH were found to be significant. Therefore, the multivariate analysis included treatment (chemotherapy after surgery, hazard ratio [HR] [95% CI] = 0.2341 [0.05517–0.9935], $p=0.049$; radiotherapy after surgery, HR [95% CI] = 0.5447 [0.22320–1.3294], $p=0.182$; radiation and chemotherapy after surgery; HR [95% CI] = 0.2862 [0.17888–0.4579], $p<0.01$), age (age ≥ 66 years, HR [95% CI] = 2.4115 [1.55357–3.7433], $p<0.01$) and IDH (IDH-positive status, HR [95% CI] = 0.3892 [0.16185–0.9361], $p=0.0351$). The effects of all dependent prognostic factors on patient survival were presented using a Kaplan–Meier curve (Figure 4).

Prognostic Nomogram for Overall Survival

The independent prognostic factors are shown in the nomogram (Figure 4D), wherein each variable was matched to a

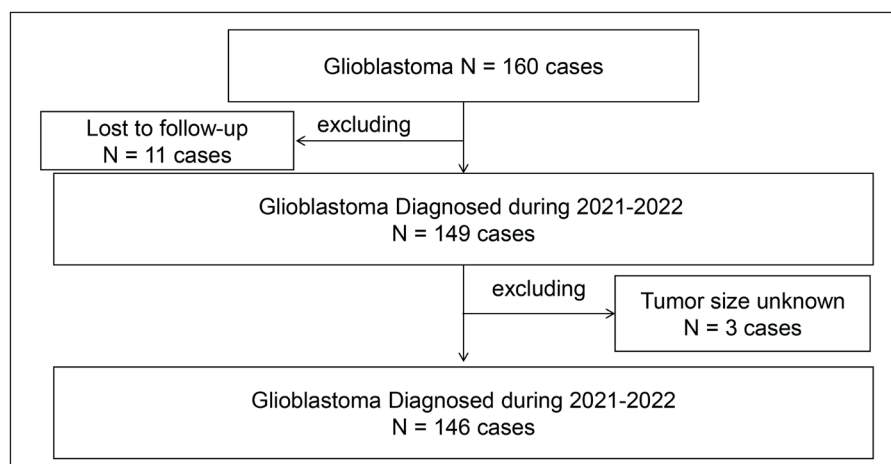


Figure 1: Flow chart of patient selection.

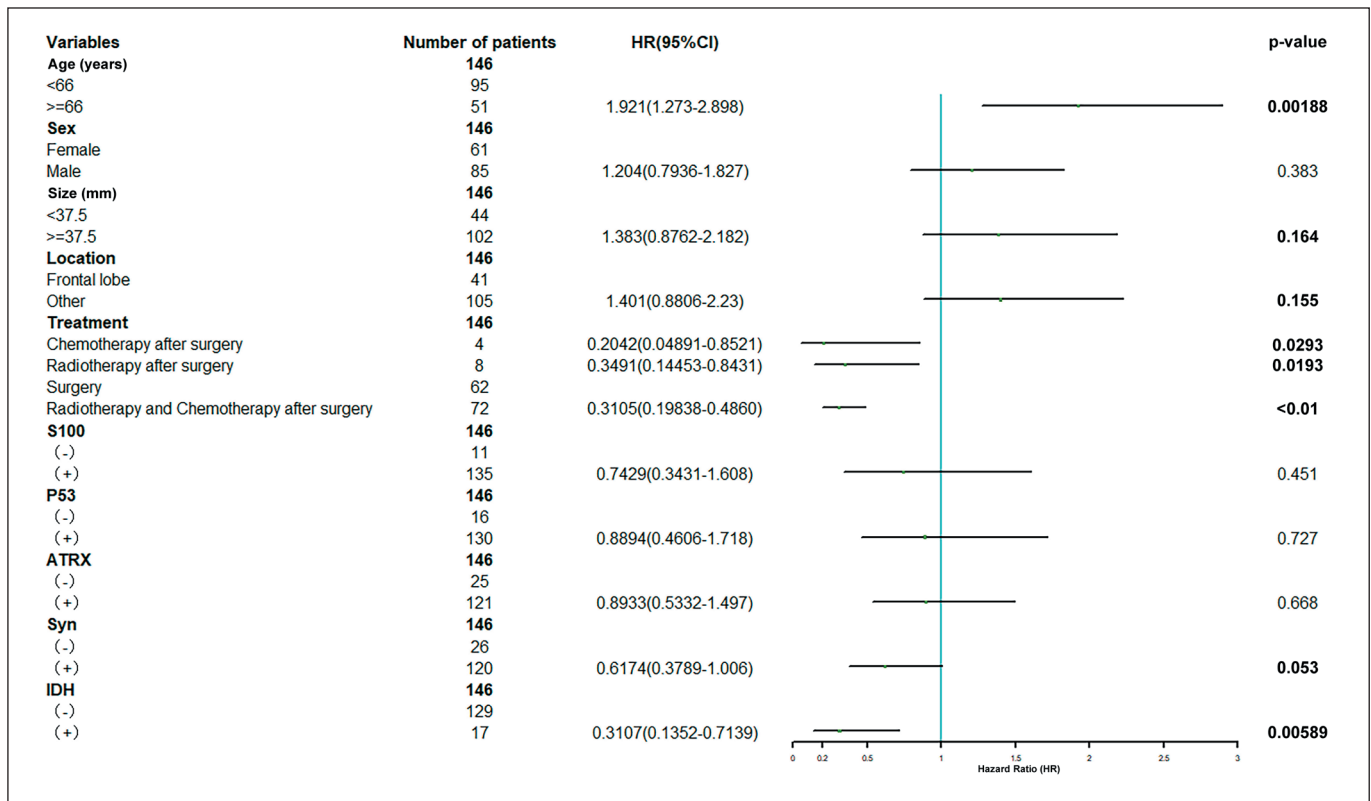


Figure 2: Clinicopathological features of the patients and results of the univariate Cox proportional hazards analysis (HR, 95%confidence interval).

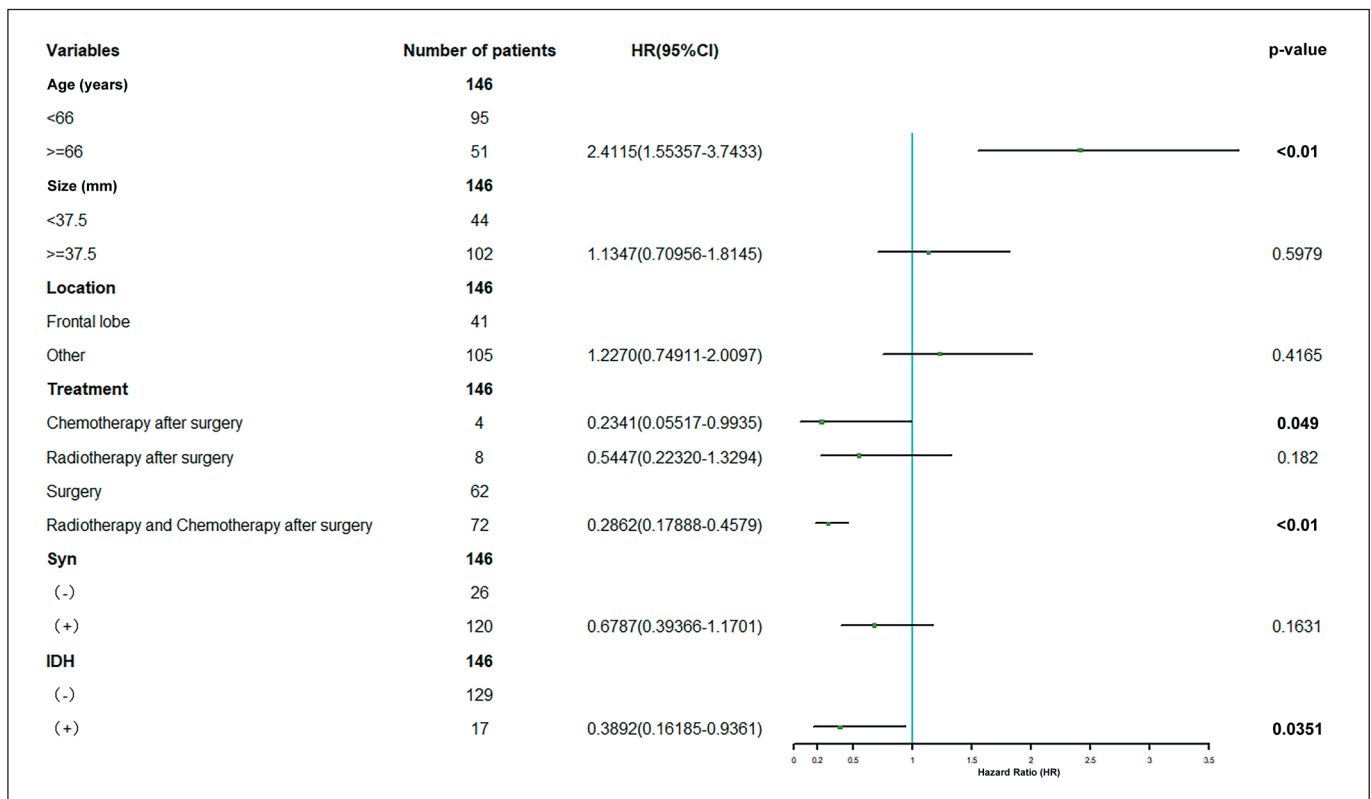


Figure 3: Results of the multivariate analysis of various factors (HR, 95% confidence interval).

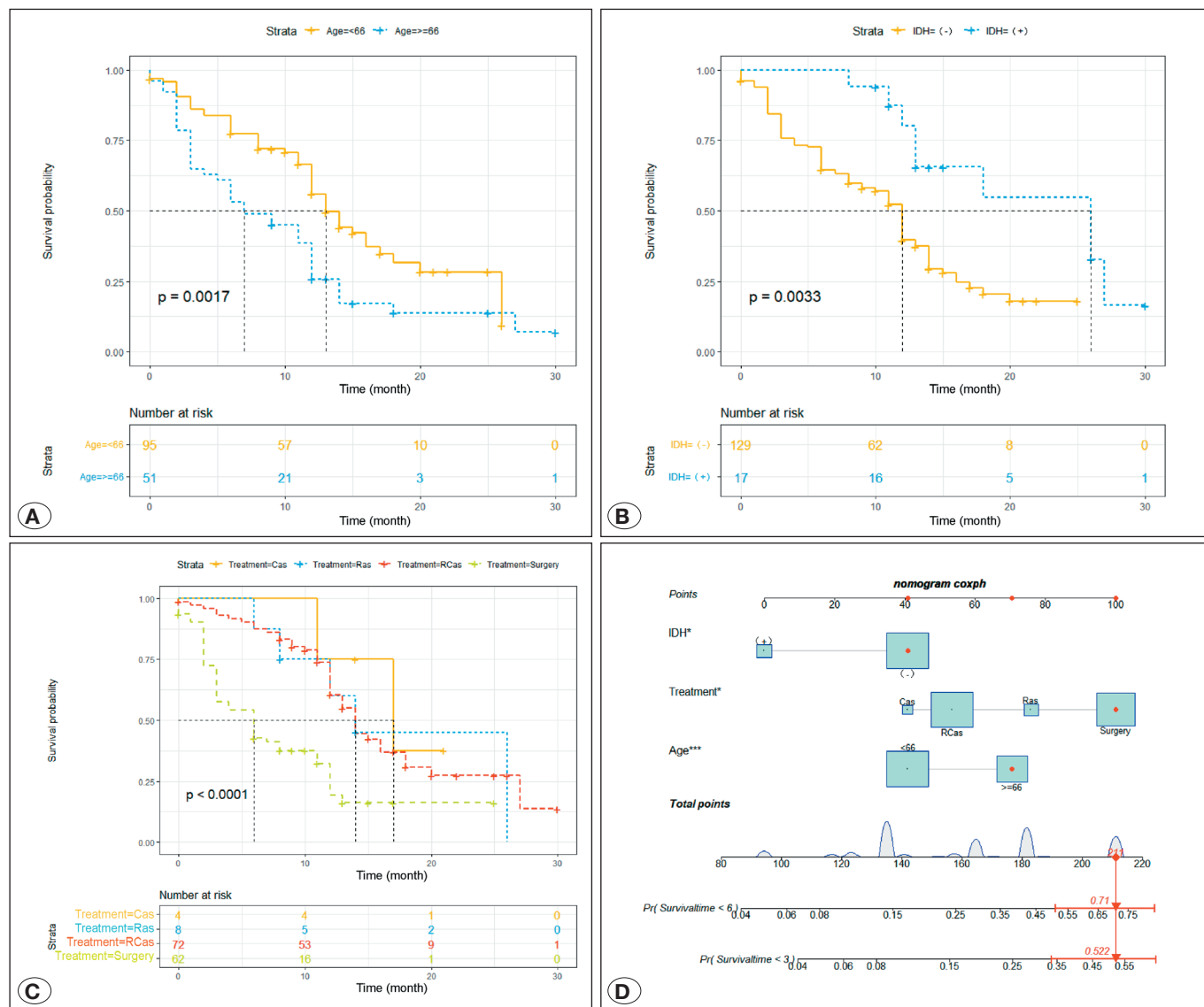


Figure 4: Kaplan-Meier curves for patients with Ki-67 positive grade 4 diffuse gliomas. Age (A), IDH (B), Treatment (C). Nomogram predicting cancerspecific survival at 3-month and 6-month in patients with Ki-67 positive grade 4 diffuse gliomas (D). Prognostic factors included Age, IDH, and Treatment. Each variable on the nomogram could match the scores on the scale and overall scores could be obtained by summing the scores for each variable. For example, a score of 211 represents a mortality rate of 71% at 6-month and 50% at 3-month. The lower the score, the lower the mortality rate of patients at 3-month and 6-month. **Cas:** Chemotherapy after surgery, **Ras:** Radiotherapy after surgery, **RCas:** Radiotherapy and Chemotherapy after surgery.

score on the scale, and the scores of individual variables were totaled. Finally, the survival rate was determined based on the corresponding score scale of the total score. The largest and smallest proportions were seen with treatment and age, respectively.

Internal Validation of the Nomogram

The C-index for the cohort was 0.743. The time-dependent ROC curve showed that the area under the curve (AUC) values were 0.832 at 3 months and 0.829 at 6 months, indicating good discriminatory ability (Figure 5A,B). Calibration curves were used to indicate the comparisons between the actual

probability and predicted outcomes (Figure 5C,D). Figure 5E and 5F shows the decision curve of the cohort to predict the survival probability at 3 and 6 months. The blue line represents the net benefit when no patient dies from cancer, while the green line represents the net benefit when all patients die from cancer with a certain threshold probability. When the curve of the model is between the blue and green lines, it indicates that the model has great clinical value. This prediction model demonstrated great net benefits for almost all threshold probabilities at 3 months (Figure 5E) and 6 months (Figure 5F).

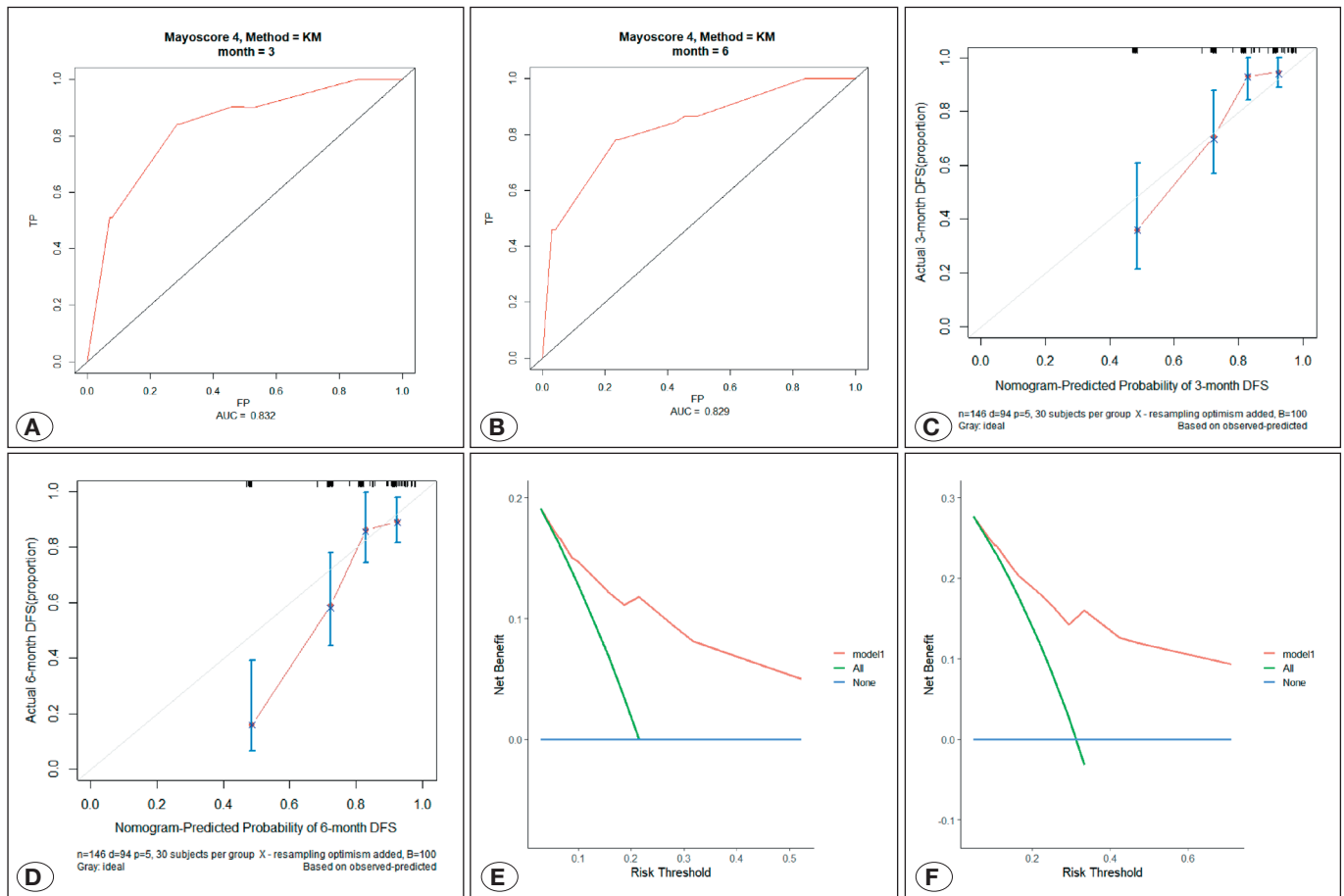


Figure 5: ROC at 3-month and 6-month (A, B). Calibration of nomogram (C, D). Nomogram decision curves to predict cancer-specific-death at 3-month (E) and 6-month (F). x-axis represents the threshold probability and y-axis represents the net benefit calculated by adding true minus false positive. The blue line parallel to the x-axis assumes that no patient will experience a cancer-specific death, while the solid green line assumes that all patients will die from a cancer-specific death with a specific threshold probability. The red line representing the net gain with the nomogram.

External Validation of the Nomogram

In the CGGA database, the time-dependent ROC curve (Figure 6A,B) showed AUCs of 0.739 for 3 months and 0.74 for 6 months. The effects of all dependent prognostic factors on patient survival were presented using the Kaplan-Meier curve (Figure 6C-E).

DISCUSSION

Grade 4 diffuse gliomas are highly malignant tumors, and Ki-67-positivity is known to influence its prognosis. Accordingly, there is a need to identify risk factors that affect prognosis in patients with Ki-67-positive grade 4 diffuse gliomas using high-quality clinical data, but a prospective study design would be challenging because the disease is initially difficult to diagnose. This retrospective study included 146 cases of Ki-67-positive grade 4 diffuse gliomas, revealing that IDH status, treatment, and age were significant risk factors on multivariate analysis.

The clinical features and prognostic models for Ki-67-positive grade 4 diffuse gliomas have not been conclusively established. Using a nomogram reportedly yields better predictive values than the traditional model (3,10). Therefore, we constructed a nomogram using data from 146 cases of Ki-67-positive grade 4 diffuse gliomas. The AUC, C-index, calibration curves, and DCA curves were used to assess the discriminatory ability and accuracy of the model. Lastly, the nomogram was externally validated using data from grade 4 diffuse gliomas (7,20,25) in the CGGA database.

Age, an important prognostic factor in cancer (18), is also considered an independent prognostic predictor in GBM (21). The multivariate Cox analysis in this study revealed age (≥ 66 years) as a significant prognostic factor (HR = 2.4115 compared to age < 66 years, $p < 0.01$), which is consistent with previous findings (18,21).

Tumor size was not a significant prognostic factor in the multivariate Cox analysis. Tumor size ≥ 37.5 mm had an HR of

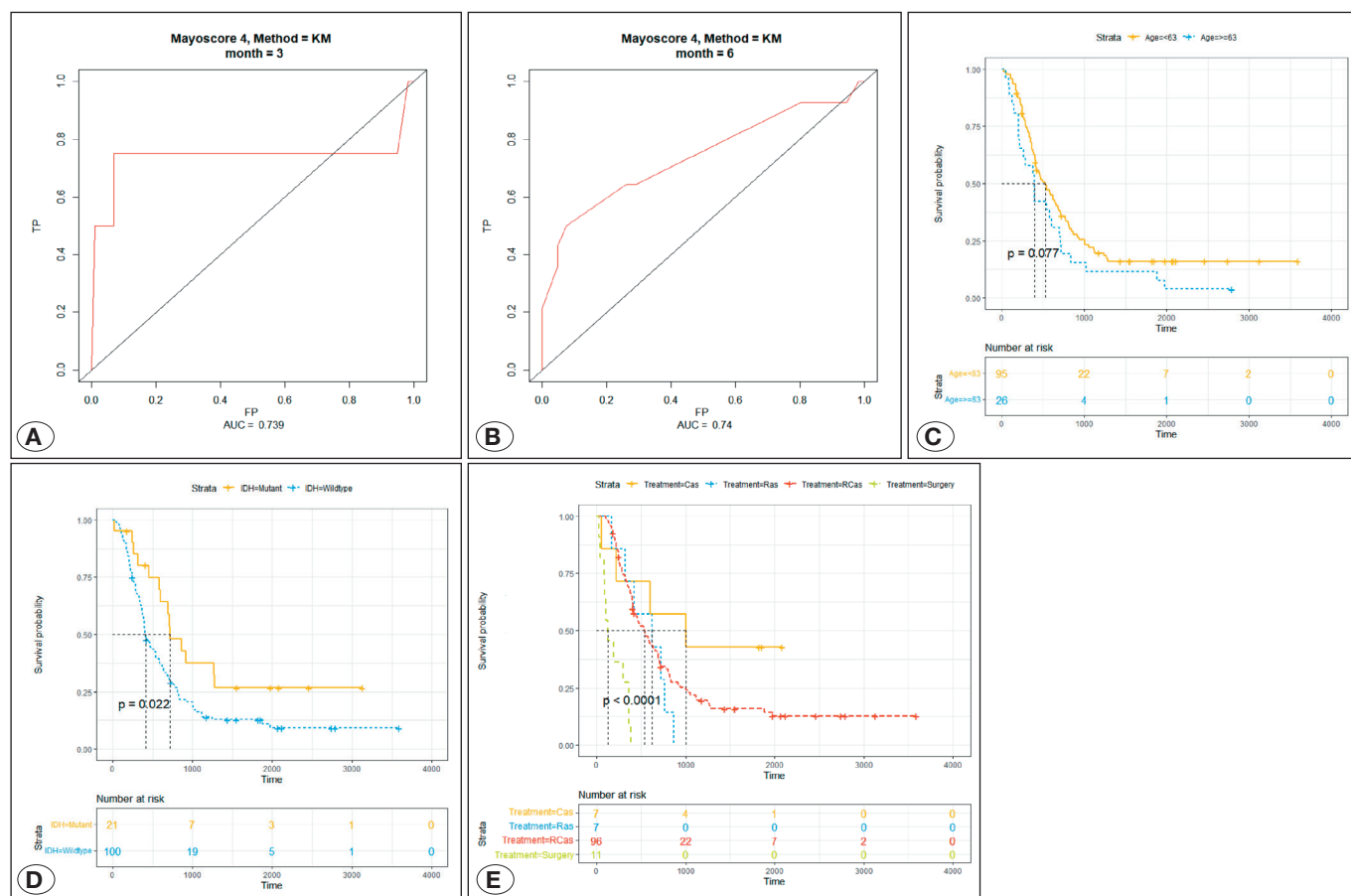


Figure 6: ROC at 3-month and 6-month in the CGGA database (A, B). Kaplan-Meier curves for patients with Ki-67 positive grade 4 diffuse gliomas in the CGGA database. Age (C), IDH (D), Treatment (E). **Cas:** Chemotherapy after surgery, **Ras:** Radiotherapy after surgery, **RCas:** Radiotherapy and Chemotherapy after surgery.

1.1347 compared to tumor size < 37.5 mm ($p=0.5979$). In contrast, other studies found that tumor size was an independent predictor of prognosis in GBM (8), although this discrepancy may be attributed to the small sample size of this study.

IDH status was a significant prognostic factor on multivariate Cox analysis. IDH-positive status had an HR of 0.3892 compared to IDH-negative status ($p=0.0351$). In line with this, previous studies have found that patients with IDH mutations (i.e., IDH-positive) have better prognostic outcomes (12), and specific point mutations in genes encoding IDH 1/2 are associated with favorable outcomes (23).

Regarding treatment, postoperative chemotherapy, radiotherapy, and chemoradiotherapy each had better prognosis than surgery alone on univariate analysis. Meanwhile, postoperative chemoradiotherapy and chemotherapy were both linked to better prognosis on the multivariate analysis. Thus, postoperative chemoradiotherapy remains crucial in the treatment of such cases.

Previous studies have similarly shown that age, treatment modalities, and IDH can influence prognosis (12,21). This study

expounds on this knowledge by using a nomogram to predict survival in patients with Ki-67-positive grade 4 diffuse gliomas. The total score of each prognostic factor can be obtained using the nomogram, enabling us to determine the final survival at 3 and 6 months. This can serve as a useful aid for both physicians and patients in deciding the best treatment to achieve optimal outcomes.

This study has certain limitations, such as the relatively short time period and retrospective study design, which could introduce selection bias. Nevertheless, this study provides a useful framework for predicting the survival patients with Ki-67-positive grade 4 glioma. This information can be used to guide clinical practice.

CONCLUSION

IDH status, treatment, and age are independent prognostic factors in patients with Ki-67-positive grade 4 diffuse gliomas. A nomogram was established using these prognostic factors, which can help clinicians predict the prognosis of patients and suggest optimal treatment plans.

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Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

Ethics approval and consent to participate: The experiment was approved by the Medical Ethics Committee of the Affiliated Hospital of Qingdao University. The case number was QYFY WZLL 28163. Patient consent were obtained from all patients.

AUTHORSHIP CONTRIBUTION

Study conception and design: HL

Data collection: PL

Analysis and interpretation of results: JZ

Draft manuscript preparation: HL, PL

Critical revision of the article: PS

Other (study supervision, fundings, materials, etc...): PS

All authors (HL, PL, JZ, PS) reviewed the results and approved the final version of the manuscript.

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Statistical Geometric Morphometric Shape Analysis of Ventricular Shape Changes in Giant Pituitary Adenomas Invading the Third Ventricle

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ABSTRACT

AIM: To investigate the preoperative, early and late postoperative differences in the anterior callosal angle, lateral and third ventricle shapes of patients with pituitary macroadenoma operated via the transsphenoidal approach.

MATERIAL and METHODS: Shape data of the third and lateral ventricles were collected from the two-dimensional digital images. The generalised Procrustes analysis was used to obtain mean shapes in the preoperative, early and late postoperative phases. The shape deformation of the ventricles from pre- to postoperative phases was evaluated using the thin plate spline method. Anterior callosal angle (ACA) was measured pre- to postoperative images and was analyzed statistically.

RESULTS: There was no significant lateral ventricle shape and ACA measurement difference in the pre and postoperative phases. The high-level deformations from the pre- to postoperative phase were seen in thin plate spline graphs. The highest deformation was observed at the third ventricle. Third ventricle deformation continued from the early to the late postoperative period, but this deformation is more limited than in preoperative comparisons.

CONCLUSION: We demonstrated that shape changes in the third ventricle of patients with pituitary macroadenoma persisted during the postoperative period through statistical geometric morphometric shape analysis. This phenomenon may result from dysfunction of the ventricular surface cilia due to chronic tumor compression and surgery-related neurotrauma. Additionally, we identified the diagnostic limitations of ACA in patients without radiological signs of hydrocephalus.

KEYWORDS: Anterior callosal angle, Statistical shape analysis, Pituitary adenoma, Third ventricle, Hydrocephalus

ABBREVIATIONS: EVDS: External ventricular drainage system, VP: Ventriculoperitoneal MRI: Magnetic resonance imaging, CSF: Cerebrospinal fluid, PCA: Principal component analysis, TPS: Thin plate spline, GT: Generalizability theory, ACA: Anterior callosal angle, INPH: Idiopathic normal pressure hydrocephalus



■ INTRODUCTION

Pituitary adenomas are one of the most common brain tumors, accounting for 14% of all intracranial central nervous system tumors (10). Etiologically, these neoplasms are classified into functional (46%–64%) and non-functional (36%–54%) tumors (2,33). Although pituitary adenomas are histologically benign, especially the functional ones, they can lead to significant morbidities due to excessive hormone secretion and compression of surrounding neurovascular structures (5,6). Hence, early diagnosis and effective treatment are key to reducing morbidity and minimizing mortality.

Based on size, pituitary adenomas are classified into macroadenomas (>10 mm) and microadenomas (<10 mm) (6); however, those measuring ≥ 40 mm are defined as giant pituitary adenomas (11). In macroadenomas, mass effect is the most common finding, including visual disturbances; occasionally, hydrocephalus may be observed due to obstruction of the ventricular system and cranial nerves (15,31,35). It is known that tumors with suprasellar extension that destroy the floor of the third ventricle may lead to obstructive hydrocephalus (16–18).

With recent developments in imaging technologies and statistical modeling, it is possible to objectively assess changes in the shape of anatomical structures using landmark-based morphometric data. Anatomically significant reference points called “landmarks” can be translated using coordinate systems, making detecting subtle morphological differences through multivariate analysis possible. This is done using statistical shape analysis, a subfield of geometric morphometrics; this technique is increasingly becoming popular in clinical disciplines owing to its capacity to describe and visualize structural adaptations in anatomical features related to growth, pathology, or treatment. It has been applied to various anatomical regions, such as the sacroiliac joint, prostate, brainstem, and spine, effectively identifying disease-related structural variations and treatment-associated morphological changes (24–28,32,36). Likewise, existing studies suggest that shape-based evaluation methods may enhance our understanding of both pathological alterations and physiological adaptations in the female pelvis, contributing to obstetric risk assessment and surgical planning.

Accordingly, this study employed the landmark-based geometric morphometric method to investigate the preoperative and postoperative changes in ventricular morphology and radiological features in patients with giant pituitary adenomas who did not originally meet the radiological or clinical criteria for hydrocephalus.

■ MATERIAL and METHODS

Study Patients and Selection Criteria

We included patients who underwent tumor removal surgery for pituitary macroadenomas with suprasellar extension (Hardy-Vezina grades C and D) at the Department of Neurosurgery, Faculty of Medicine, Bursa Uludag University between September 2016 and March 2020.

In particular, patients with giant pituitary adenomas showing radiological evidence of third-ventricle indentation or partial intraluminal protrusion, without radiological or clinical signs of hydrocephalus, were considered for this study. Among these, patients with (i) Evans index of <0.30 , (ii) absence of headache, papilledema, somnolence, or gait/cognitive disturbance, and (iii) no need for additional cerebrospinal fluid (CSF) diversion procedures, such as an external ventricular drain or a ventriculoperitoneal (VP) shunt, during follow-up, were included.

All included patients underwent contrast-enhanced pituitary magnetic resonance imaging (MRI) (Philips Achieva, Best, Netherlands; 3T scanner with 32-channel head coil) on three occasions: preoperatively, postoperative day 3, and six months postoperatively. Pre- and postoperative scans confirmed patent CSF pathways and third-ventricle indentation by the suprasellar tumor.

Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided informed consent before inclusion. Ethical approval for the study was obtained from the Bursa Uludag University local institutional review board (decision number: 2025/580-7/13, dated March 19, 2025).

Surgical Approach

All surgeries were performed by a single neurosurgeon using a binostril endoscopic endonasal transsphenoidal approach (EETA). Tumor removal was conducted without transventricular or intraventricular manipulation and without intentional ependymal violation. Standard multilayer skull-base reconstruction was used; no intra- or postoperative CSF diversion was required.

Collection of Two-Dimensional Ventricular Landmarks

Morphometric data were extracted from pre- and postoperative two-dimensional midsagittal MR images of all patients. We identified 14 anatomical landmarks that represent the shape of the lateral and third ventricles (Figure 1). Detailed definitions of these ventricular landmarks are provided in Table I. All landmarks were manually placed on each image using the TPSDIG 2.04 software.

Geometric Morphometric Analysis

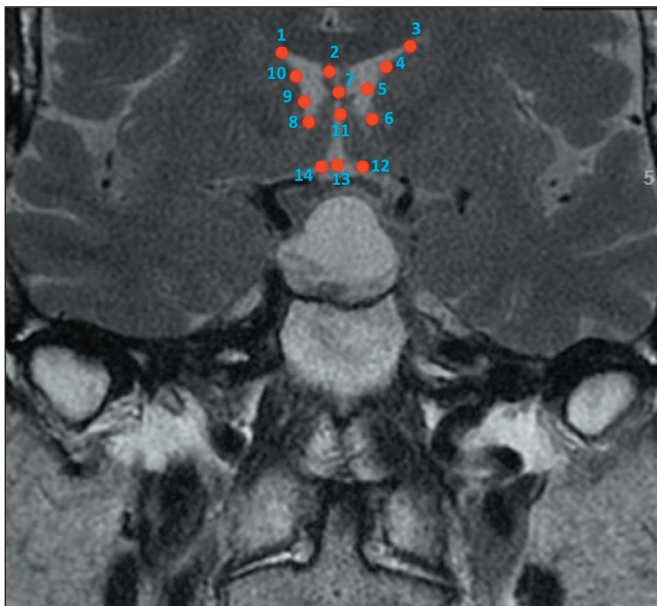
Statistical shape analysis

The analysis focused on evaluating morphological changes in the lateral and third ventricles, which are anatomically interconnected through the foramen of Monro. In this context, we applied the generalized Procrustes analysis, a method known for minimizing the sum of squared differences between homologous landmarks, to obtain the mean shape and corresponding tangent coordinates of the ventricular system across the three time points (8). The tangent coordinates so obtained were then subjected to principal component analysis, and the resulting principal component scores were used for shape comparisons.

Pairwise comparisons were conducted between preoperative versus early postoperative (day 3), preoperative versus late

Table I: Descriptions of the Landmarks Used in the Study

Landmark No.	Definition	Landmark No.	Definition
1	Right ventricle's frontal horn	8	Right Rostrum of Corpus Callosum
2	Genu of Corpus Callosum	9	Right Stria Terminalis
3	Left ventricle's frontal horn	10	Head of right caudat nucleus
4	Head of left caudat nucleus	11	Roof of Third Ventricle
5	Left Stria Terminalis	12	Left side of Third Ventricle's floor
6	Left Rostrum of Corpus Callosum	13	Median side of Third Ventricle's floor
7	Inferior of Septum Pellucidum	14	Right side of Third Ventricle's floor

**Figure 1:** Landmark markings used for geometric morphometric analysis, targeting the sagittal plane of the ventricular system, including the third and lateral ventricles and their connection via the foramen of Monro, as visualized on coronal magnetic resonance imaging scans.

postoperative (six months), and early postoperative versus late postoperative periods using the multivariate paired Hotelling's T^2 test. Statistical significance was assessed using a Bonferroni-adjusted threshold of $\alpha/3 = 0.05/3 \approx 0.0167$ to control for type I error due to multiple comparisons. Shape deformation across the time points was further evaluated using the thin plate spline (TPS) method; regions showing the most prominent expansion or contraction were identified as the primary deformation zones. All analyses were performed using R software (34) and PAST software (12).

General statistical analysis

The anterior callosal angle (ACA; in degrees) was measured on coronal slices using the method described by Mantovani et al. (21). The normality of the distribution of angle measurements was assessed using the Shapiro-Wilk test, according to which the measurements for all three time points were nor-

mally distributed ($p > 0.05$). Therefore, descriptive statistics for these variables were expressed using mean $\pm$ standard deviation. To evaluate differences in measurements across the time points, a repeated measures analysis of variance (ANOVA) was used. Throughout the analysis process, the type I error rate was set at 5%. This analysis was performed using SPSS (IBM SPSS Statistics for Windows, version 25.0; IBM Corp., Armonk, NY).

Landmark reliability

Based on generalizability theory, the reliability coefficient (G) was calculated for a two-facet crossed design. The same researcher marked all landmarks; after two weeks, 10 randomly selected patients were re-marked by the same researcher to compute the G coefficient. The resulting G value reflected a high level of repeatability ($G = 0.946$). Calculations related to landmark reliability were performed using the calculator available at: http://biostat.home.uludag.edu.tr/landmark_reliability/G_coefficient.html.

RESULTS

The study included 25 patients (14 females and 11 males) with a mean age of 50.1 ± 14 years (range: 17–76 years) whose MRI data were used for geometric morphometric analysis.

The mean shapes of the third and lateral ventricles generated using Procrustes analysis were compared across the preoperative, early postoperative, and late postoperative periods in patients with giant pituitary adenomas (Figure 2). Pairwise comparisons revealed p-values of 0.048, 0.245, and 0.982 for the preoperative versus early postoperative period, preoperative versus late postoperative period, and early versus late postoperative period, respectively. Considering the Bonferroni-adjusted significance threshold due to multiple comparisons, none of these differences reached statistical significance.

The TPS analysis was performed using the mean shapes obtained from Procrustes analysis. Figure 3 illustrates the morphological changes observed between the preoperative and early postoperative periods in the region connecting the lateral and third ventricles. Figure 4 demonstrates the shape differences between the preoperative and late postoperative periods, and Figure 5 highlights the morphological changes

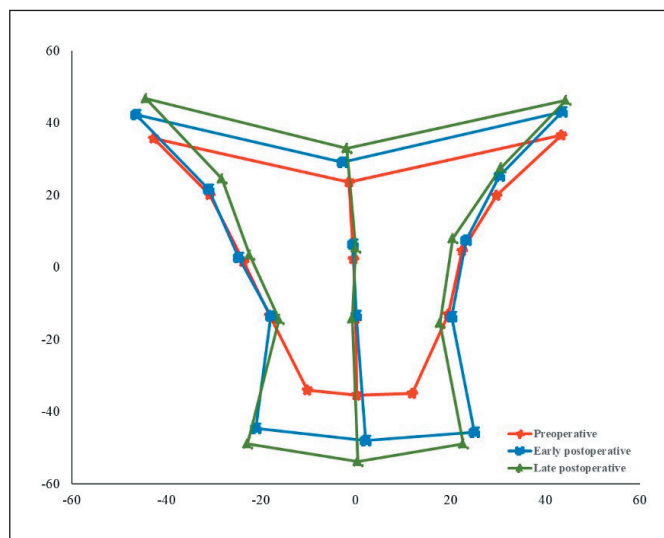


Figure 2: Procrustes mean shapes of the lateral and third ventricles, interconnected through the foramen of Monro, obtained from coronal magnetic resonance images in the preoperative, early postoperative, and late postoperative periods of patients with giant pituitary adenomas.

between the early and late postoperative periods. The TPS analysis visualizes shape deformations for each comparison, where the color gradient represents the degree of deformation; red and yellow regions indicate the highest degree of expansion, whereas blue regions indicate minimal change. In all analyses (Figures 3–5), the positions of the landmarks are indicated with black dots.

When the mean shapes and deformation maps were evaluated together, we observed marked morphological changes indicating expansion in the third ventricular region from the preoperative period to both early and late postoperative periods. Additionally, structural changes continued from the early to late postoperative period, although these changes were more limited compared to preoperative structures. A representative case demonstrating these temporal contour changes on coronal MRI is shown in Figure 6; it illustrates the progressive expansion-oriented deformation of the third ventricle, particularly around landmarks 11–14 identified in the morphometric model.

The mean ACA value was $140.98^\circ \pm 4.95^\circ$ in the preoperative period, $140.06^\circ \pm 5.10^\circ$ in the early postoperative period, and $139.46^\circ \pm 5.77^\circ$ in the late postoperative period. For the re-

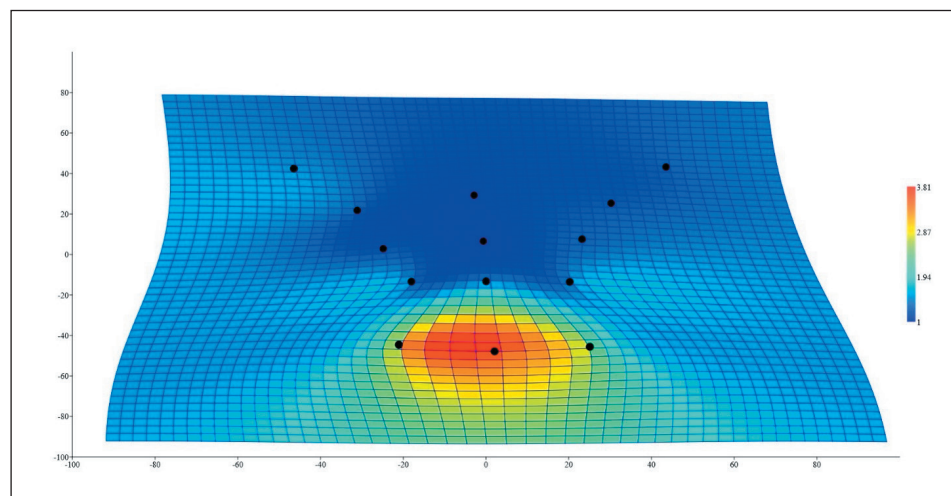


Figure 3: Thin plate spline analysis demonstrating the transformation of the mean shape of third ventricle region between the lateral and third ventricles from the preoperative to the early postoperative period.

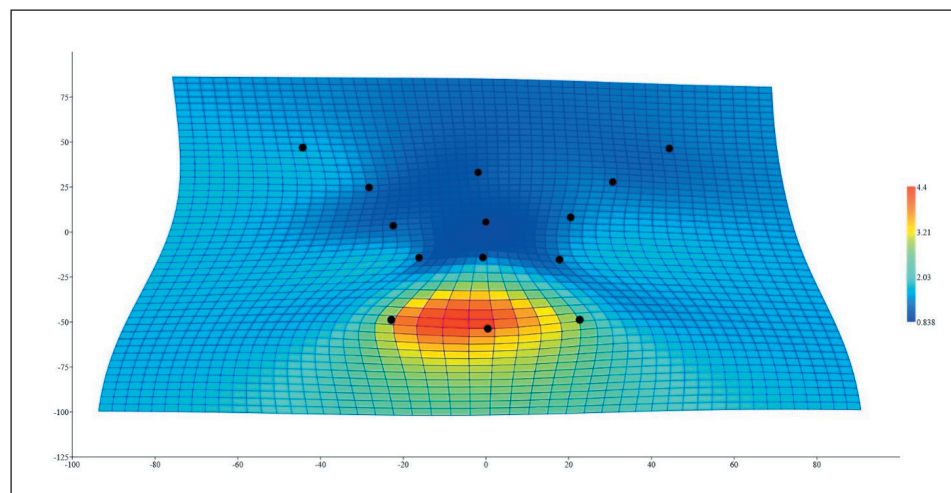


Figure 4: Thin plate spline analysis demonstrating the transformation of the mean shape of third ventricle region between the lateral and third ventricles from the preoperative to the late postoperative period.

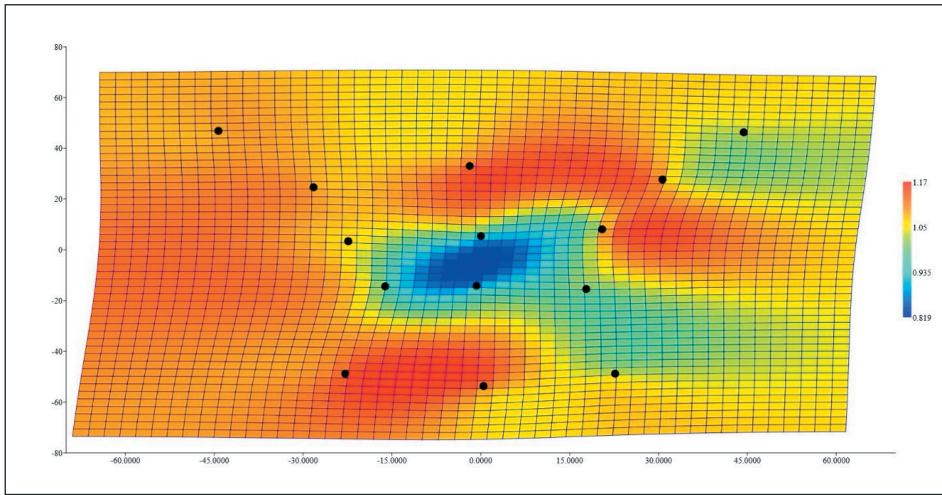


Figure 5: Thin plate spline analysis demonstrating the transformation of the mean shape of third ventricle region between the lateral and third ventricles from the early to the late postoperative period.

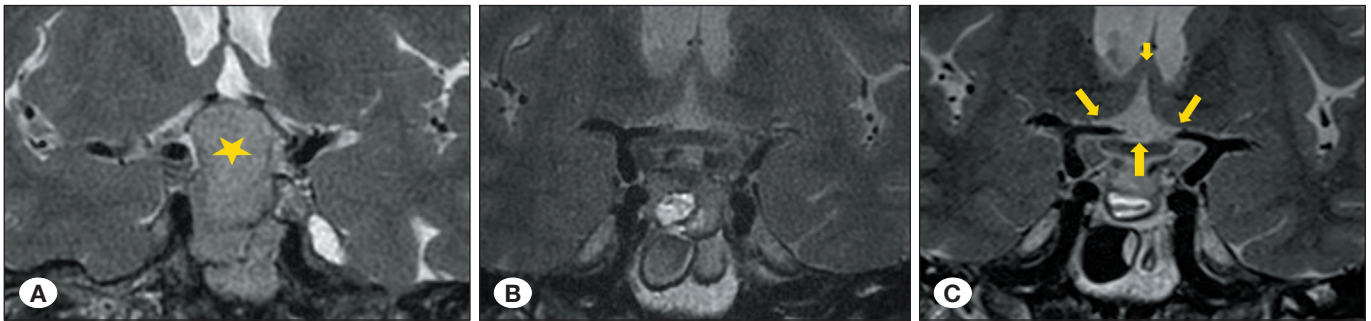


Figure 6: Representative case demonstrating the evolution of the third ventricle contour at three different time points on coronal magnetic resonance imaging (MRI) scans. **A)** Preoperative coronal T1-weighted image: A giant pituitary adenoma with suprasellar extension (asterisk) has invaded the third ventricle, nearly filling it. **B)** Early postoperative (day 3) coronal MRI: Following endoscopic endonasal decompression, the ventricle appears decompressed, the optic chiasm has returned to its normal position, and cerebrospinal fluid pathways are clearly re-established. **C)** Late postoperative (6-month) coronal MRI: The third ventricle exhibits a progressive, expansion-oriented contour deformation corresponding to landmarks 11, 12, 13, and 14 in the morphometric model (yellow arrows). Arrows indicate ventricular boundaries and areas of deformation.

peated measures ANOVA, the assumption of sphericity was considered acceptable (Huynh-Feldt epsilon value = 0.946). This test revealed no statistically significant main effect of time ($F = 1.47$, $p > 0.05$), indicating no significant change in the ACA across the three time points. Further trend analysis also revealed that neither the linear trend ($p = 0.154$) nor the quadratic trend ($p = 0.802$) was significant.

DISCUSSION

Hydrocephalus in pituitary macroadenomas can be observed both clinically and radiologically, and the condition can be monitored via radiological follow-up imaging (15,31,35). To the best of our knowledge, there is no prior study in the literature analyzing ventricular changes using geometric morphometric measurements in giant pituitary adenomas with third ventricular invasion. In our study, we wanted to address this issue and analyze the ventricular shape changes during the follow-up period. The patient cohort consisted of individuals without radiological signs of hydrocephalus (Evans index < 0.3) who did not require additional cerebrospinal fluid diversion

procedures (such as EVDS or VP shunting). Using statistical shape analysis, we evaluated morphological changes in the ventricular system during the preoperative, early postoperative, and late postoperative periods.

Tumors that completely occupy the third ventricle can obstruct the aqueduct of Sylvius, leading to hydrocephalus (17), whereas adenomas with a dumbbell-shaped growth pattern may obstruct the foramen of Monro, resulting in lateral ventricular enlargement (9). Our cases did not fully obstruct the foramen of Monro, showed no signs of increased intracranial pressure, and did not completely occupy the third ventricle. In our shape analysis, no significant deformation was observed at landmarks 1 through 10, which represent the lateral ventricles in coronal sections, across the preoperative, early postoperative, and late postoperative periods. Significant shape differences were particularly noted between the preoperative and early postoperative periods at landmarks 11, 12, 13, and 14, which define the boundaries of the third ventricle. Following the excision of the tumor that had invaded the third ventricle in the preoperative period, the ventricle was decom-

pressed and refilled with CSF, resulting in changes in its morphology. Moreover, deformation was observed to persist in the direction of expansion from the early to late postoperative period (Figure 5).

According to the current hypothesis of CSF dynamics, CSF exhibits a pulsatile flow regulated by cerebral circulation and respiration (4,14). This flow is also supported by a constant microcurrent generated by motile cilia on the ventricular wall surface (37). Several studies have reported that dysfunction of these cilia can lead to ventricular enlargement (3,7,20,29). In acquired conditions such as viral infections, loss of cilia and gliosis along the ventricular walls may result in secondary hydrocephalus (1). For instance, Omran et al., in an experimental animal study, examined ciliary activity in the brains of mice with chronic alcohol consumption and detected hydrocephalus (30). The relationship between ciliary function and hydrocephalus has become a prominent research topic, supported by studies in rodent models demonstrating suppression of gliosis to prevent hydrocephalus (23), and genetic analyses examining ciliary function (13,19).

In our study, the continued deformation and expansion of the third ventricle from the early to late postoperative period may be explained by loss or reduction of ciliary function in the third ventricular ependyma due to chronic tumor compression/invasion and neurosurgical trauma. This may disrupt CSF flow dynamics, contributing to third ventricular dilation. The absence of shape change in the lateral ventricles, which were unaffected by either the tumor or surgical intervention, further supports the notion of localized third ventricular impact. However, the deformation in the direction of expansion continued in the late postoperative period in the 3rd ventricle, which was the area affected by the surgery and the tumor (Figure 5). Our shape analysis using geometric morphometric measurements supports this notion and represents the first such analysis on this topic in the literature.

This study also evaluated whether the anterior callosal angle (ACA) might serve as an early morphometric marker of CSF flow disturbance, even in patients without radiological hydrocephalus. Mantovani et al. suggested that ACA could be used to differentiate idiopathic normal pressure hydrocephalus (iNPH) from Alzheimer's disease, reporting that a value of $\leq 119^\circ$ demonstrates high sensitivity and specificity for iNPH. The mean ACA value in healthy individuals was found to be $133.85^\circ \pm 5.86$, and this value was significantly lower in iNPH patients (21). A subsequent study noted that ACA can also serve as a radiological parameter for monitoring the response to shunt surgery in iNPH patients (22). In our study, the mean ACA value in the preoperative period was $140.98^\circ \pm 4.95$, with no significant change in the early ($140.06^\circ \pm 5.10$) and late postoperative periods ($139.46^\circ \pm 5.77$) ($F = 1.47$, $p > 0.05$). All values were well above the diagnostic threshold reported in the iNPH literature. All ACA values were consistent with those reported in healthy adults, and none of the patients met the criteria for hydrocephalus. We suggest that future large-scale, prospective studies investigate the utility of ACA not only in differentiating iNPH from Alzheimer's disease but also as a potential novel diagnostic parameter for hydrocephalus.

This study is the first to demonstrate the temporal shape changes of the ventricular system in by third ventricular invasion of giant pituitary adenomas using a landmark-based geometric morphometric method. Our findings suggest that ventricular deformation is not solely related to tumor excision, but may also be associated with postoperative alterations in CSF dynamics. Although no significant shape changes were observed in the lateral ventricles, the expansion-oriented deformation of the third ventricle persisted, which may be attributed to impaired cerebrospinal fluid dynamics secondary to ciliary dysfunction, as previously discussed.

Clinical Relevance of Non-hydrocephalic Shape Change

In the absence of radiological or clinical hydrocephalus, the observed third-ventricle deformation most likely reflects localized CSF–ependymal remodeling secondary to chronic suprasellar compression, rather than a global intracranial pressure elevation. Persistent expansion after decompression may further indicate ependymal ciliary dysfunction, as prolonged tumor indentation can alter cilia-mediated CSF propulsion and the mechanical compliance of the ventricular wall.

Given that all patients underwent endoscopic endonasal transphenoidal surgery without transventricular manipulation, any direct operative contribution is expected to be minimal. Altogether, these findings support a local, cilia-driven biomechanical remodeling process rather than a pressure-driven hydrocephalic mechanism.

Accordingly, the landmark-based shape descriptors presented here should be regarded as physiomorphic, subclinical markers, reflecting subtle CSF–ependymal interactions rather than symptomatic hydrocephalus. At present, these parameters are not proposed as diagnostic thresholds; instead, they may (i) provide quantitative monitoring of ventricular contour evolution after decompression and (ii) serve as hypothesis-generating variables for prospective studies correlating shape with neurocognitive outcomes, endocrine status, visual performance, and longitudinal CSF metrics. Elucidating these associations will be essential before any clinically actionable cut-points can be defined.

Limitations and Future Directions

This study has several limitations. It represents a single-center, retrospective series with a relatively small sample size, focusing exclusively on non-hydrocephalic giant pituitary adenomas with third-ventricle involvement. While this homogeneity minimizes confounders, it also limits the generalizability of our findings to other pathologies with more pronounced clinical sequelae, such as craniopharyngiomas, colloid cysts, or intraventricular metastases.

In addition, our analysis relied solely on two-dimensional pituitary MRI sections. Future prospective, multicenter studies involving larger cohorts and incorporating three-dimensional volumetric reconstructions and statistical geometric morphometric analyses may provide more comprehensive and reproducible insights.

Moreover, integrating such morphometric data with experimental animal models could contribute valuable mechanis-

tic information about ependymal ciliary function and its role in ventricular shape remodeling. Collectively, these extensions will be essential to translate current physiopathologic findings into clinically actionable and pathophysiologically grounded tools.

CONCLUSION

This study investigated ventricular shape alterations in patients with non-hydrocephalic pituitary macroadenomas treated via the transsphenoidal approach, utilizing a landmark-based geometric morphometric method across preoperative, early postoperative, and late postoperative time points. Additionally, it assessed the potential applicability of the anterior callosal angle (ACA)—a parameter traditionally used to differentiate idiopathic normal pressure hydrocephalus (iNPH) from Alzheimer's disease—in the diagnosis of non-hydrocephalic conditions. The observed persistent postoperative expansion-related deformation of the third ventricle may be attributed to ciliary dysfunction within the ventricular epithelium. We hope the findings of this study will inform and inspire future research in this field.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare that there are no conflicts of interest related to this study.

AUTHORSHIP CONTRIBUTION

Study conception and design: MOT, GO

Data collection: OA

Analysis and interpretation of results: GO

Draft manuscript preparation: OA, NB

Critical revision of the article: MOT, GO, SY

Other (study supervision, fundings, materials, etc.): SY

All authors (OA, NB, GO, MOT, SY) reviewed the results and approved the final version of the manuscript.

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Minimally Invasive Endoscopic Approach to Large Intraventricular Tumors

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ABSTRACT

AIM: To analyze the safety and effectiveness of the minimally invasive endoscopic approach in the treatment of large intraventricular tumors.

MATERIAL and METHODS: We retrospectively reviewed the demographic, radiological, and surgical data of 8 patients who were operated on using the endoscope-plus-port technique for large (>5 cm) intraventricular tumors at our clinic between 2015 and 2020. All procedures were performed using the minimally invasive endoscopic approach.

RESULTS: The cohort comprised 3 females and 5 males, with a mean age of 40.88 years. All tumors were located in the lateral ventricle; near-total resection was achieved in 3 patients and subtotal resection in 5 patients. External ventricular drainage was inserted in all patients postoperatively. The histological diagnosis was neurocytoma in 3 patients, glioblastoma in 2 patients, metastasis in 2 patients, and a grade II meningioma in 1 patient. No complications or mortality were reported in the 31-month follow-up period.

CONCLUSION: Safe and effective tumor resection of intraventricular tumors is possible using the endoscope-plus-port, even in tumors >5 cm. This technique permits dynamic mobilization and facilitates bimanual operation, increasing resection rates and improving outcomes for these tumors.

KEYWORDS: Intraventricular, Tumor, Endoscopy, Surgery, Minimally invasive

ABBREVIATIONS: MRI: Magnetic resonance imaging, CT: Computed tomography, TR: Total resection, NTR: Near total resection, STR: Subtotal resection

INTRODUCTION

Intraventricular tumors comprise 1%-10% of all intracranial mass lesions; they arise from periventricular structures, including the ventricular walls, septum pellucidum, and choroid plexus (21,22), and form a heterogeneous group in terms of histology and treatment, often similar in clinical history and radiological features. The majority of intraventricular tumors are benign and low-grade lesions, such as choroid plexus papilloma, meningioma, central neurocytoma, and ependymoma (2,7,14). Tumors arising from the adjacent brain tissue with significant growth in the ventricular cavity are defined as

secondary ventricular tumors with transependymal invasion; most of these are gliomas (15,22).

Although the classical treatment of intraventricular tumors involves microsurgical resection of the lesion by performing craniotomy under microscopic vision via transcortical-transcallosal-transventricular or interhemispheric-transcallosal route (22), the deep intracranial location of these tumors and their proximity to critical neurovascular structures often make microsurgical access to these lesions difficult. The choice of approach for surgical resection depends on the type, size, and location of the lesion, as well as the ventricular size and its

proximity to adjacent anatomical structures (22). Furthermore, resection usually requires retraction and dissection of important brain structures to protect the corridor created to reach the lesion and to proceed with bimanual microsurgical resection (10,13). This surgical insult may damage important brain structures, such as the thalamus, caudate nucleus, fornix, and others, leading to complications, such as seizures, neurological deficits, and sometimes cognitive impairment related to venous infarction in the postoperative period, and even mortality (7).

Although traditional microsurgical techniques are the gold standard for intraventricular tumor resection, their invasiveness and the resultant morbidity and mortality have increased interest in more minimally invasive treatments, such as neuroendoscopic resection (15). With advances in surgical skills and experience, the use of endoscopic surgery has expanded, particularly in the treatment of brain tumors and tumor-related hydrocephalus (1,6). Endoscope-assisted microsurgical excision of intraventricular tumors reportedly minimizes neural tissue retraction and provides a better and more comfortable surgical approach with less traumatic surgical sequelae (12). While it allows direct tumor visualization with minimal brain retraction, major limitations were noted when resecting large tumors (16). Initially, the use of endoscopy was limited to the biopsy stage when approaching intraventricular tumors, especially when accessing potentially hazardous areas with important neurovascular structures. Although microsurgery is the gold standard method for resection of intraventricular tumors, endoscopy is still the first-line modality for biopsy owing to its effectiveness and reliability in providing accurate pathological specimens (14,18,19). Additionally, the use of endoscopic methods allows access to the hydrocephalus condition (6,9); in selected cases, it also allows for partial or total resection. In this study, we present a retrospective analysis to demonstrate the effectiveness and safety of the minimally invasive endoscopic resection (endoscope-plus-port technique) for intraventricular tumors larger than 5 cm in their maximum dimension.

■ MATERIAL and METHODS

Patient Population

Between 2015 and 2020, eight patients with intraventricular tumors (>5 cm) were operated on using the endoscope-plus-port technique at our clinic. We retrospectively reviewed the medical records, radiological images, pathology reports, and surgical reports of these patients to collect data regarding demographic information, preoperative signs and symptoms, anatomical location and size of the lesion, presence of associated hydrocephalus, endoscopic maneuvers performed, resection rate, intraoperative or postoperative complications, histopathological diagnosis, follow-up period, and recurrence.

Ethical approval for this retrospective study was obtained from the Gülhane Training and Research Hospital Ethics Board (approval number: 22.04.2021/185). Written informed consent was obtained from all participants.

Preoperative Evaluation

Routine cranial magnetic resonance imaging (MRI), computed

tomography (CT), and CT-angiography were performed in all patients to evaluate the relationship of the tumor with the surrounding vascular structures. In addition, navigation MRI was performed preoperatively to facilitate follow-up of the transcortical trace and port placement in the appropriate location during surgery.

Based on MRI scans taken at three months postoperatively, tumor resection was classified as total resection (TR), near-total resection (NTR), and subtotal resection (STR). TR was defined as radiographic removal of the entire lesion; NTR was defined as the removal of $\geq 95\%$ of the lesion, while STR was used to indicate the removal of $< 95\%$ of the lesion. Table I presents a summary of the demographic, clinical, and operative outcomes of the study patients.

In preoperative images, tumor volume was calculated using the modified formula $[A \times B \times C] / 2$, where A, B, and C represent the maximum diameter of the tumor in the three dimensions. Colloid cysts and tumors < 5 cm in size were excluded from the study.

Surgical Strategy

All intraventricular tumors were accessed via the transcortical-transventricular and transcortical-transventricular-transforaminal routes. Patients were positioned according to lesion localization and surgical strategy; an intraoperative navigation system (Stealth Station®, Medtronic, MN, USA) was introduced for each patient.

Under general anesthesia, a 3-pin head holder was inserted in the patient's cranium. A lazy-S-shaped incision was made at the Kocher point or the posterior parietal region, passing through the skin and subcutaneous tissue. Next, a craniotomy was performed (approximately 3×3 cm²) and the dura was opened in an "X" shape. After a 1-cm corticotomy, the lateral ventricle was reached with navigation-guided parenchymal dissection, and a port was placed there. The endoscope was advanced to visualize the intraventricular choroid plexus, fornix, vascular structures, and the tumor. Continuous irrigation was performed using Ringer's lactate solution to provide clear images and maintain hemostasis during the procedure. The use of 3D endoscopy increased our functional depth perception and facilitated anatomical orientation. The tumor was excised under endoscopic vision.

After adequate resection and hemostasis maintenance, the endoscope, followed by the thoracopore, was carefully and gradually removed. After bleeding control was achieved in the port cavity, the ventricular system was filled with plenty of Ringer's lactate solution. In all patients, an external ventricular drainage (EVD) catheter was placed in the lateral ventricle using the trace. Finally, the dura was sutured, and the bone flap was placed back in the cranium.

■ RESULTS

Among the 8 patients, there were 5 males and 3 females; the mean age of the patients was 40.88 years (range: 21-71 years). The most common complaint was headache, followed by memory disturbance, seizures, and visual symptoms. The mean duration of surgery in the study cohort was 65.63 min-

Table I: Age, Gender, Tumor Location and Size, Clinical Presentation, Resection Rates, Operative Time, Blood Loss, Pathological Diagnosis, and Follow-Up Times of The Cases

Case	Age/ Sex	Location	Clinical Presentation	Tumor size (mm)	Approach	Resection	Operative time (min)	Blood Loss (mL)	Diagnosis	Follow-up (month)
1	30/M	LV	Headache, seizure	51x55x49	Kocher- TC-TV	STR	45	150	Glioblastoma	14
2	29/F	LV (Atrium)	Headache, vomiting	53x35x50	Posterior parietal-TC	NTR	40	100	Atypical meningioma	58
3	71/M	LV	Headache and memory disturbance	71x61x90	Kocher- TC-TV	STR	110	250	Central Neurocytoma	17
4	21/M	LV	Visual disturbance	75x45x55	Posterior parietal-TC	STR	90	200	Central Neurocytoma	36
5	51/M	LV	Seizure, visual disturbance	55x35x50	Posterior parietal-TC-TV	STR	50	100	Glioblastoma	9
6	64/M	LV	Headache	55x60x53	Kocher-TC	STR	60	50	Metastasis	47
7	27/F	LV	Headache	64x43x54	Posterior parietal-TC	NTR	70	70	Metastasis	12
8	34/F	LV	Memory disturbance	54x58x50	Posterior parietal-TC	NTR	60	120	Central Neurocytoma	56

M: Male, **F:** Female, **LV:** Lateral Ventricle, **TC:** Transcortical, **TV:** Transventricular, **NTR:** Near total resection, **STR:** Subtotal resection, **EVD:** External ventricular drainage

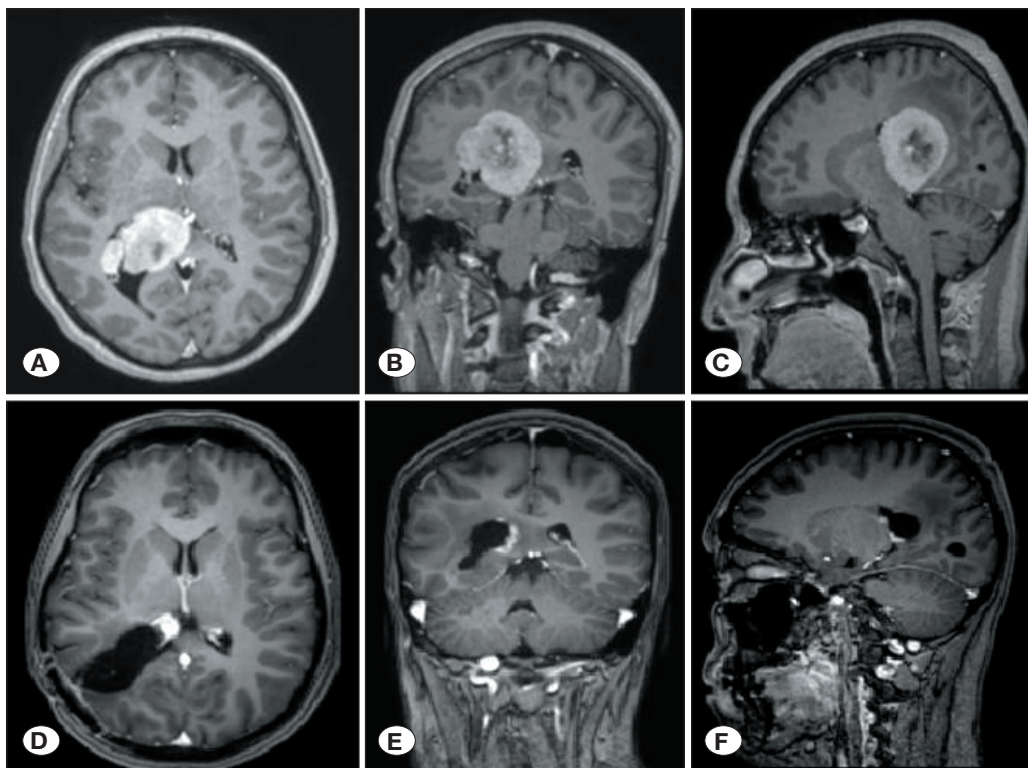


Figure 1: Illustrative case of near-total resection of an intraventricular tumor in a 29-year-old female patient. Preoperative **A)** axial, **B)** coronal, and **C)** sagittal T1-weighted magnetic resonance imaging (MRI) scans with contrast show a large intraventricular tumor located in the right atrium of the lateral ventricle. The tumor was removed using the minimally invasive endoscopic approach, and the histological diagnosis was confirmed as a grade II atypical meningioma. Postoperative **D)** axial, **E)** coronal, and **F)** sagittal T1-weighted MRI scans with contrast confirmed near-total resection of the tumor.

utes, and the mean blood loss was 130 ml; STR was achieved in five patients and NTR in three patients (Table I). Figures 1-3 present illustrative cases of NTR and STR achieved using the endoscope-plus-port technique.

No intraoperative or postoperative complications were reported in any patient. EVD catheters placed during the intraoperative period were monitored for an average of 3 days. The catheter was eventually removed as no patient developed hydrocephalus or required a ventriculoperitoneal shunt.

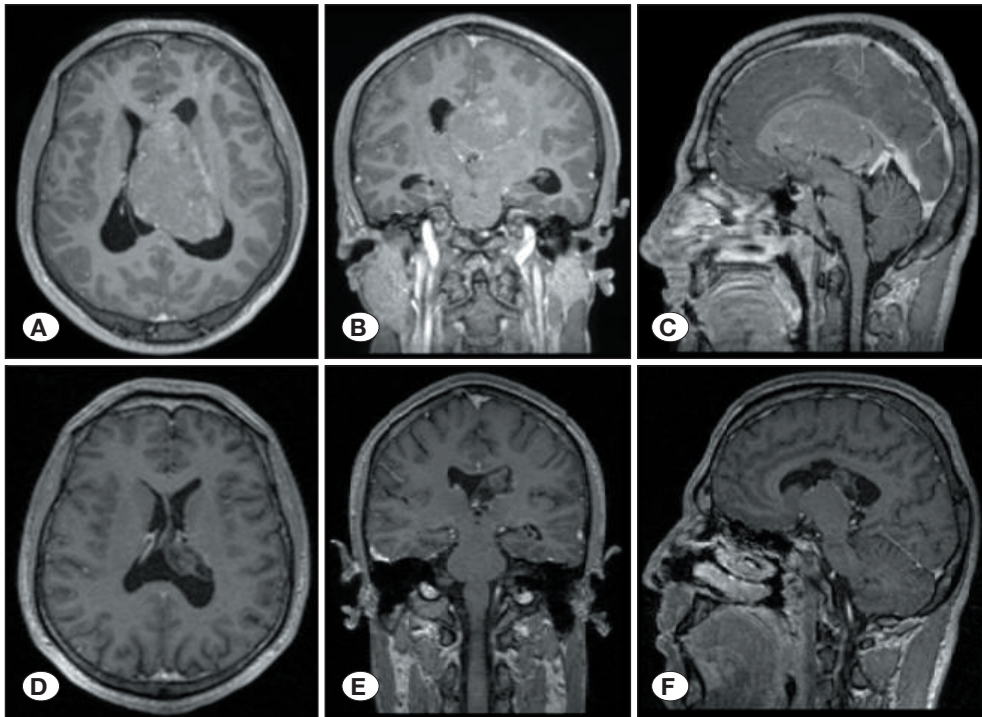


Figure 2: Illustrative case of subtotal resection of an intraventricular tumor in a 71-year-old male patient. Preoperative **A)** axial, **B)** coronal, and **C)** sagittal T1-weighted magnetic resonance imaging (MRI) scans with contrast show a large intraventricular tumor located in the lateral ventricle. The tumor was removed using the minimally invasive endoscopic approach. The diagnosis was confirmed as a central neurocytoma. Postoperative **D)** axial, **E)** coronal, and **F)** sagittal T1-weighted MRI scans with contrast confirmed subtotal resection of the tumor.

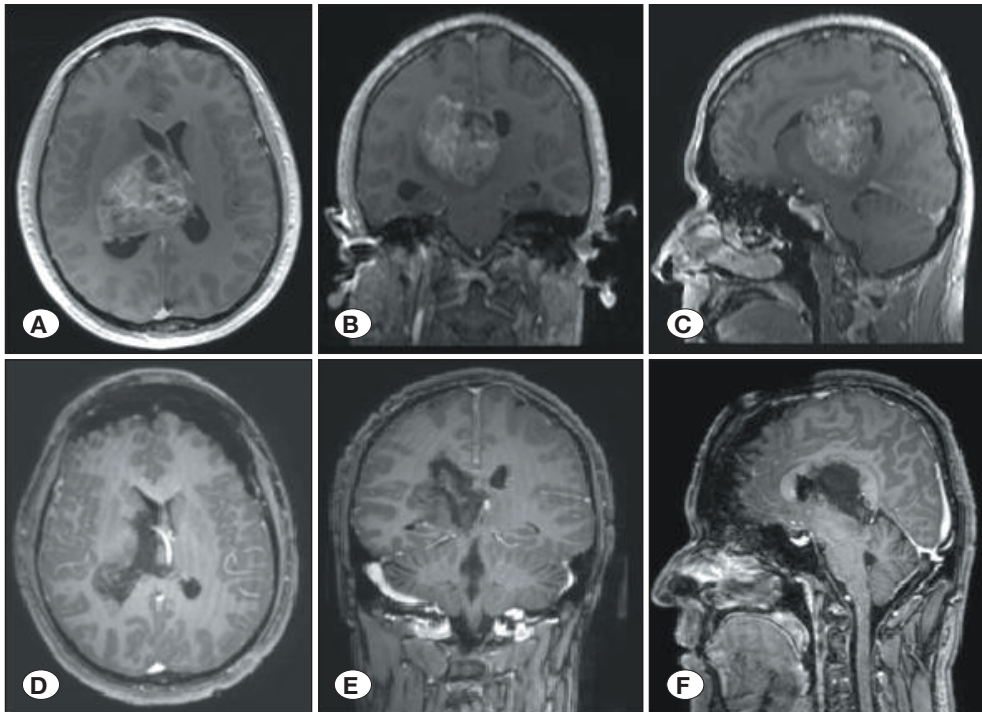


Figure 3: Illustrative case of subtotal resection of an intraventricular tumor in a 30-year-old male patient. Preoperative **A)** axial, **B)** coronal, and **C)** sagittal T1-weighted magnetic resonance imaging (MRI) scans with contrast show a large intraventricular tumor located in the lateral ventricle. The tumor was removed using the minimally invasive endoscopic approach. The diagnosis was confirmed as a glioblastoma. Postoperative **D)** axial, **E)** coronal, and **F)** sagittal T1-weighted MRI scans with contrast confirmed subtotal resection of the tumor.

Serial MRI scans were performed at patients were followed-up with MRI scans at 3, 6, and 12 months postoperatively with in the first year if there was no deterioration in neurological status. In addition, all cases were referred to the radiation oncology clinic after the histopathological diagnosis was confirmed. None of the patients required reoperation during the follow-up period.

DISCUSSION

Intraventricular and paraventricular brain tumors often present with similar clinical and radiological symptoms (15,17). Intraventricular tumors are usually deep-seated intracranial pathologies that pose a diagnostic and therapeutic challenge (20); these tumors are treated by microsurgical resection under

a microscope by performing a standard craniotomy (21,22). However, due to the proximity of intra- and paraventricular tumors to critical centers monitoring vascular and neural structures, patients may develop functional, cognitive, and even life-threatening complications in the postoperative period (7,11,15).

Sufficient retraction of the brain tissue is required to reach these deep-seated lesions (13,16). Traditional retraction methods disrupt the nutrition of the surrounding brain tissue, leading to seizures, focal neurological deficits, and cognitive impairments. To address this concern, neurosurgeons now use endoscopic ports to access these deep-seated tumors instead of traditional retractor systems using spatulas (10,11,13). The port technique leads to radial distribution of forces over a large number of points (17), minimizing the net force applied to a given surface area. The port also provides a means for stereotactic removal of deep-seated intracranial lesions and protects the surrounding tissues from iatrogenic injuries resulting from instrument entry and re-entry. Many studies using the microscope-plus-port technique have reported less damage to the surrounding neurovascular structures in the postoperative period, highlighting the potential of endoscopic methods to be an even less invasive technique.

The advent of modern endoscopic techniques, together with the recent development of endoscopic-specific instrumentation, has greatly increased microsurgical access to the ventricular system. In the context of intraventricular tumors, endoscopy is primarily used for correcting cerebrospinal fluid (CSF) obstruction, clarifying the histology of a specimen, and, if possible, complete tumor removal. Endoscopic methods offer a number of advantages, some of which include the capacity for panoramic vision, close-up images, clear detail, and ideal illumination of the operating field. In addition, the inherent benefits of minimally invasive techniques, such as minimal brain retraction, reduced surgical time, improved cosmetic results, shorter hospital stay, and lower costs, enhance the effectiveness of neurosurgical endoscopy for the treatment of intraventricular tumors (18,23).

In recent years, endoscopes and ports have been used together to obtain a wider corridor for more convenient maneuverability of surgical instruments during endoscopic surgery (15). In particular, the endoscopic-plus-port technique is widely used in the treatment of intraventricular tumors owing to its ability to facilitate dynamic mobilization and bimanual operation (10,11,13,15). Earlier, endoscopic resection of intraventricular tumors was only performed at the biopsy stage (9); many studies have described the benefits of neuroendoscopy in determining the pathological diagnosis of intra- and paraventricular tumors (15,17,23). However, emerging evidence suggests that complete endoscopic resection of intraventricular brain tumors is safe and feasible in selected cases, such as lesions that are generally < 2-3 cm, mild to moderately vascular, and have a soft consistency (15).

Despite its popularity, endoscopic intraventricular surgery is also associated with several intraoperative and postoperative complications, which can be categorized as vascular, neural, and technical failures (8). Bleeding is an important intraoper-

ative vascular complication of endoscopic surgery secondary to rupture of tumor feeders or thin subependymal vascular structures; it can be controlled using unipolar or bipolar cauterization (8). Postoperative infection is another serious complication that results in significant morbidity. Prolonged use of an EVD device is the primary cause of postoperative infection that may manifest as a wound infection or ventriculitis. Seizures constitute an important late postoperative complication of endoscopic surgery. Neurological deficit after endoscopic surgery can be avoided by selecting distant routes to the eloquent brain areas (1). Other technical complications of endoscopic ventricular surgery include visual field defects, cognitive deficits, recurrence, CSF leak, and hydrocephalus (8); among these, hydrocephalus is the most common complication, with studies suggesting that CSF leak and hydrocephalus are more frequent in endoscopic surgery than in microsurgical technique (1).

A study reporting the results of 33 cases of endoscopic removal described that TR was achieved in only three cases (9.3%) (two of subependymoma, and one oligodendroglioma) (19). In another review of 649 intraventricular tumors resected with the endoscopic technique, including colloid cysts and other intraventricular lesions, TR or NTR was achieved in only 36 patients (45.5%) with non-colloid cyst cases (2). Notably, this review study emphasized that the probability of TR or NTR is higher in tumors < 2 cm. Likewise, a study including 20 intra-paraventricular tumors operated on with the combined endoscope plus microscope technique using a port described that 70% of patients achieved GTR, 20% achieved NTR, and 10% were deemed as STR (15). Engh et al. used the endoscope-plus-port technique and described GTR/TYR in 80% of the cases (11). Thus, careful selection of patients, pre-operative evaluation and planning, and adequate experience with surgical technique, neuroendoscopic anatomy, surgical approaches, and equipment are very important to achieve adequate resection and surgical success (15,17,20,22). In our study, 5 out of 8 patients (62.5%) achieved STR, whereas the remaining 3 achieved NTR (Table I), demonstrating similar results as the existing literature. Although we could not achieve TR in any of the patients, our findings indicate that the endoscope-plus-port technique may help increase the effectiveness of adjuvant treatment in the postoperative period by reducing the tumor burden. TR is usually not possible in high-grade glial tumors due to their infiltrative nature and lack of a clear surgical plane. Accordingly, STR was achieved in patients with intraventricular glioblastoma. Moreover, achieving TR is also difficult in large intraventricular central neurocytoma and metastasis cases because of delicate intraventricular anatomical structures and poorly defined surgical borders between the tumor and ventricular walls (5,24). Thus, small intraventricular tumors are more suitable for TR using the endoscopic technique, while NTR and STR are pragmatic outcomes with large tumors (2). Improvements in endoscopic instruments may allow better resection rates in the future.

Russo et al. reported meningitis, seizures, intraventricular hemorrhage, subdural collection, and transient hemiparesis as chief complications in the postoperative period after undergoing intraventricular tumor removal using microscopic

techniques (19). In this study, nine patients developed hydrocephalus requiring a ventriculoperitoneal shunt, whereas one patient died due to ventriculitis (3%). Likewise, Chaves et al. reported a case where surgery was terminated due to intraoperative bleeding within a 12-year-old giant central neurocytoma operated on using the microscopic transcortical method; postoperatively, the patient developed diabetes insipidus, hemiparesis, and meningitis (5). Other studies on intraventricular tumors undergoing endoscopic biopsy described the infection rate as 0%-6.5%, the morbidity rate as 6%-18%, and the mortality rate as 0%-6.3% (7,14,18,24). A 2.33%-3.6% incidence was reported for bleeding during endoscopic biopsy (23). Another study described infarction due to thalamostriate vein thrombosis (3).

With endoscopic resection, the bleeding rates were reported to be between 0% and 9.7% (2,17,18,20). Memory loss due to fornix injury during endoscopic resection of intraventricular tumors is reported by multiple studies (6,23); other complications include epileptic seizure and hydrocephalus requiring ventriculoperitoneal shunt (23). In a study involving intraventricular tumors operated on with the endoscopic method, the authors described seven cases of Parinaud syndrome, one of oculomotor paralysis, two of meningitis, four of motor weakness, one with partial pituitary insufficiency, one with memory loss, and one with hydrocephalus in the postoperative period (4). In our series, none of the patients developed Parinaud Syndrome or other neurological deficits during the 31-month follow-up period; no other morbidity or mortality occurred during the intraoperative and postoperative periods. This complication-free outcome may be attributed to the use of the port with the endoscope during the surgery, as well as the utilization of Ringer's lactate solution for irrigation to control intraoperative bleeding. No re-operation was required in any of our cases during the follow-up period.

Despite the surgical success, the main limitation of our study is the small sample size, which should be considered when interpreting our results. The absence of a control group also precludes the applicability of our results because of the interference of potential confounding factors. However, we mainly focused on the safety and efficacy of the endoscopic approach in large intraventricular tumors.

CONCLUSION

The endoscope-plus-port technique allows for safe and effective resection of intraventricular tumors, even for those >5 cm. While TR is extremely difficult in some cases due to the nature and size of tumors, this technique facilitates the dynamic mobilization of neural structures and bimanual operation, increasing the overall resection rates in these tumors.

Declarations

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Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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AUTHORSHIP CONTRIBUTION

Study conception and design: MK

Data collection: AD

Analysis and interpretation of results: SK

Draft manuscript preparation: AD

Critical revision of the article: AD, MK

Other (study supervision, fundings, materials, etc...): AD, MK

All authors (AD, SK, MK) reviewed the results and approved the final version of the manuscript.

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Gamma Knife Radiosurgery for Brain Metastasis from Primary Thyroid Cancer

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ABSTRACT

AIM: To analyze the efficacy and safety of Gamma Knife radiosurgery (GKRS) in the management of thyroid cancer brain metastases (TCBM).

MATERIAL and METHODS: This retrospective study analyzed patients who underwent GKRS for TCBM at two centers between September 2005 and February 2025. Patients' clinical and radiological outcomes, including local tumor control and overall follow-up, were investigated.

RESULTS: Among the 3,834 patients who underwent GKRS for brain metastases at two centers, only 0.26% had primary thyroid cancer. A total of 10 patients with 40 TCBM were treated by GKRS, with a median of two metastases per patient. The most common metastasis site was the frontal lobe (47.5%), and 60% of patients had multiple metastases. Papillary carcinoma was the most frequent histological subtype (57.1%). The median latency from thyroid cancer diagnosis to the development of brain metastases was 22 months. The median GKRS dose was 23 Gy, and local failure occurred in 5% of treated metastases. Radiation-induced necrosis was observed in one case and resolved without clinical impact. Intracranial distant metastases developed in two patients. The median follow-up was 8 months, and 80% of patients died during follow-up, with one death attributed to brain metastasis.

CONCLUSION: The limited number of patients and the short follow-up period, partly reflecting the aggressive nature of TCBM, may have influenced the study results. Nevertheless, despite the short follow-up, GKRS provided favorable local control without significant adverse effects, suggesting that it may be an effective treatment option for TCBM.

KEYWORDS: Thyroid neoplasms, Brain neoplasms, Radiosurgery, Treatment outcome

ABBREVIATIONS: GKRS: Gamma knife radiosurgery, TCBM: Thyroid cancer brain metastasis, SRS: Stereotactic radiosurgery, WBRT: Whole brain radiotherapy, RT: Radiotherapy

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■ INTRODUCTION

The presence of brain metastases represents a significant neurological challenge for patients with cancer. While lung cancer accounts for the majority of brain metastases ($\geq 50\%$), the incidence of thyroid cancer is relatively rare, with a reported incidence ranging from 0.15% to 1.3% (2,11). Although brain metastases are uncommon in thyroid cancer, their presence is associated with a poor prognosis and reflects a more aggressive disease course (8,18).

Since TCBM is a rare condition, there is still no consensus on the optimal treatment approach. Several treatment approaches, including surgical resection, external beam radiotherapy, radioiodine therapy, stereotactic radiosurgery (SRS), tyrosine kinase inhibitors, and whole brain radiotherapy (WBRT), are available. Resection of one or more foci of brain metastases has been reported to significantly improve survival (9). The disease-specific median survival following the diagnosis of brain metastases is significantly longer in patients who undergo local resection of one or more metastatic lesions (16.7 months) than in those who do not receive surgical intervention (3.4 months) (7). In patients with brain metastases from thyroid cancer who are not candidates for surgical resection, or as a first-line treatment, SRS offers a safe and effective therapeutic option (5,21).

SRS delivers focused high-dose radiation to intracranial tumors in single or multiple sessions, offering a precise and minimally invasive therapeutic option. In most cases, it has become a standard treatment modality for brain metastases originating from various primary cancers, used either as a first-line therapy or as an adjunct to other treatments, such as surgical resection and/or WBRT (1,14,20,24). Notably, SRS has been shown to provide superior preservation of cognitive function compared with WBRT (4,6). Despite these treatment approaches, the management of TCBM remains challenging because of the limited clinical experience with this rare condition. In this study, we aimed to evaluate the efficacy of GKRS on brain metastases in the management of TCBM.

■ MATERIAL and METHODS

Eligibility and Demographic Data

The data of patients who underwent GKRS treatment for TCBM at two centers between September 2005 and February 2025 were analyzed.

The study inclusion criteria were as follows: (a) age ≥ 18 years, (b) histologically verified thyroid malignancy, (c) radiologically confirmed brain metastases, and (d) patients who received GKRS for brain metastases. Patients with inadequate follow-up information (< 2 months) were excluded. All data were retrieved from the patient charts and neuroimaging databases. Available histological findings and targeted systemic therapies were collected for each patient.

Radiosurgical Technique

Gamma Knife radiosurgery was performed using the Leksell Gamma Knife® Model 4C, Perfexion, and Icon (Elekta Instrument AB, Stockholm, Sweden). Target delineation was based

on T1-contrast weighted MRI, and the gross tumor volume was considered equivalent to the clinical and planning target volumes. Shots with 4, 8, and 16 mm collimators were placed within the target and adjusted to simultaneously achieve high target coverage, high selectivity, gradient index < 3 , and reasonable treatment times using the best-fit isodose method until a clinically acceptable plan was formulated by a team of neurosurgeons, medical physicists, and radiation oncologists. The organs at risk were contoured, and the treatment planning objective was to minimize radiation exposure to the normal brain as much as possible.

Follow-up and Outcome Parameters

After GKRS, patients underwent routine clinical neurological assessment and brain diagnostic imaging every 2–4 months, depending on imaging results and clinical features. All pre-treatment and posttreatment radiological examinations were evaluated by a team comprising a radiation oncologist, neurosurgeon, and neuroradiologist. Radiological response was evaluated according to the Response Assessment in Neuro-Oncology Brain Metastases criteria (13). Partial response was defined as $\geq 30\%$ reduction in the longest diameter of target lesions, and complete response as the disappearance of all target lesions. Both partial and complete responses were considered local controls. Progression was defined as a $\geq 20\%$ increase in the smallest recorded target lesion diameters on the study, with an absolute increase of ≥ 5 mm. Local failure was defined as progression within the previously treated lesion, whereas distant failure referred to new or progressive lesions outside the treated field. In equivocal cases, advanced imaging (e.g., perfusion MRI, MRS) or histopathology was used for clarification. LC was assessed throughout the study until local failure or death. All patients were classified using the recursive partitioning analysis and graded prognostic assessment classification systems of the Radiation Therapy Oncology Group (RTOG) (10,25).

Statistical Analysis

All analyses were conducted using SPSS 21.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize patient and tumor characteristics. Continuous variables were presented as median [minimum–maximum], whereas categorical variables were expressed as frequencies and percentages. The median was selected as the measure of central tendency because of the positively skewed distribution of the data. Local control and clinical outcomes were assessed on both a per patient and per-tumor basis. Radiological and clinical follow-up data were analyzed using descriptive methods.

■ RESULTS

Ten patients received GKRS treatment for a total of 40 metastases. Of these, six patients were male (60%), and the median age at the diagnosis of brain metastases was 67 years [range, 23–84]. Each patient had a median of 2 [range, 1–18] brain metastases, and 60% of patients had > 1 metastatic brain tumor. The most common location of metastases was the frontal lobe (47.5%). Histological data were unavailable for three patients. Among those with known thyroid cancer histol-

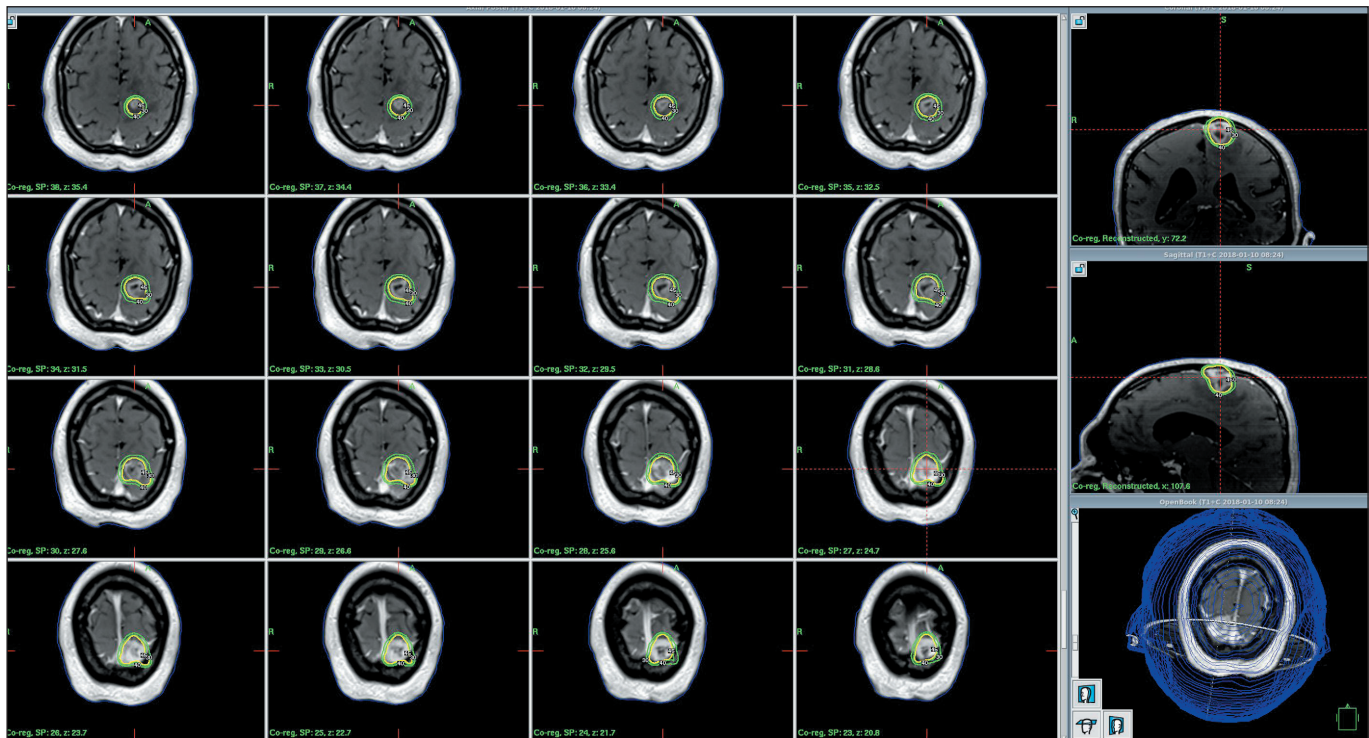


Figure 1: Gamma Knife treatment plan for a brain metastasis from thyroid carcinoma. Axial, coronal, and sagittal post-contrast T1-weighted MRIs show a single parenchymal brain metastasis originating from thyroid carcinoma. The lesion is delineated by the yellow contour line, representing the gross tumor volume. The green isodose lines indicate the radiosurgical dose distribution, which conforms tightly to the tumor borders. High conformality and a steep dose fall-off are achieved to minimize radiation exposure to the surrounding normal brain tissue.

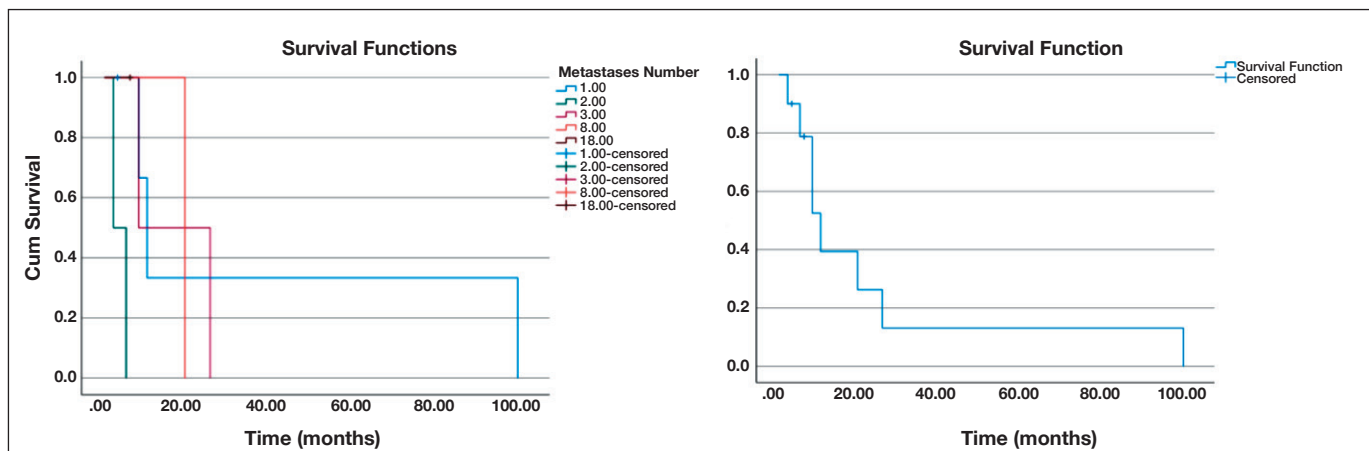


Figure 2: Kaplan–Meier survival curves showing (left) overall survival according to the number of brain metastases and (right) overall survival following Gamma Knife radiosurgery.

ogy, the most common type was papillary carcinoma (57.1%), followed by follicular carcinoma (28.5%) and anaplastic carcinoma (14.2%). 50% of patients had distant metastases (lung, bone, spine, and adrenal gland). One patient presented with brain metastasis at diagnosis; all other patients had undergone prior thyroidectomy (90%). Most patients had favorable clinical status at the time of GKRS, with a median KPS score of 90 [range 70–90]. Detailed patient characteristics are presented in Table I.

Histopathological examination of the previous thyroidectomy specimen showed a BRAF V600E mutation in one patient, a TERT mutation in one patient, and both mutations in one patient. Nuclear atypia was detected in 30% of patients, and all patients had multiple (≥ 2) brain metastases.

Before GKRS treatment, 40% of patients had undergone prior surgery for TCBM. The median duration from thyroid cancer diagnosis to the detection of brain metastasis was 22 months

Table I: Patient Characteristics

Patient No.	Age at diagnosis of BM / Gender	Pathology	Mutation-Atypia	KPS before GKRS	RPA/GPA	Distant organ metastasis	Metastasis Number / Location	Symptom	Interval from thyroid cancer to BM diagnosis / BM to GKRS (months)	Follow-up (months) / Status / Cause of death	Additional treatments
1	45 / Male	Anaplastic	TERT, Nuclear atypia	90	I / 4	-	3 / Frontal, temporal, cerebellum	Headache	5 / 0	8 / Dead / Progression of brain metastases	Pre-GKRS: thyroidectomy
2	72 / Male	Papillary	BRAF V600E, TERT, Nuclear atypia	90	II / 3	-	2 / Cerebellum, parietal	Headache	37 / 2	5 / Dead / Multisystem failure	Pre-GKRS: thyroidectomy, RAI
3	74 / Female	Papillary	-	90	II / 3	-	1 / Frontal	Dysphasia	0 / 0	10 / Dead / Sepsis	-
4	67 / Female	Follicular	Nuclear atypia	70	II / 1	Lung, bone	2 / Cerebellum, frontal	Headache	47 / 3	2 / Dead / Pneumonia	Pre-GKRS: thyroidectomy, craniotomy, WBRT, RAI
5	67 / Male	Papillary	-	90	II / 3	-	1 / Frontal	Amnesia	0 / 24	98 / Dead / Multisystem failure	Pre-GKRS: thyroidectomy, craniotomy, RAI
6	60 / Male	Papillary	BRAF V600E	70	II / 1	Lung	1 / Frontal	Hemiparesis	168 / 1	8 / Dead / Multisystem failure	Pre-GKRS: thyroidectomy, WBRT, RAI
7	84 / Male	Follicular	-	90	II / 1	Lung, bone, spine, adrenal gland	8 / Frontal (2), parietal (1), occipital (2), cerebellum (2), temporal (1)	Amnesia	53 / 0	19 / Dead / Multisystem failure	Pre-GKRS: thyroidectomy, craniotomy, RAI. After-GKRS: LINAC and CyberKnife treatment for distant metastases
8	69 / Female	N/A	Data not available	90	II / 2	Lung, bone, spine	1 / Temporal	Headache	7 / 0	2 / Unknown	Pre-GKRS: thyroidectomy, RAI, RT for spine metastasis
9	23 / Female	N/A	Data not available	80	II / 1	Lung, bone	18 / Frontal (10), parietal (4), occipital (3), cerebellum (1)	(Incidental)	2 / 0	6 / Unknown	Pre-GKRS: thyroidectomy, RAI, RT for lung metastasis
10	50 / Male	N/A	Data not available	90	I / 4	-	3 / Frontal (2), temporal (1)	Headache	48 / 3	25 / Dead / Progression of extracranial metastases	Pre-GKRS: thyroidectomy, RAI

BM: Brain metastasis, **GPA:** Graded prognostic assessment, **RPA:** Recursive partitioning analysis, **GKRS:** Gamma Knife radiosurgery, **RAI:** Radioactive iodine, **RT:** Radiotherapy

Table II: Gamma Knife radiosurgery treatment characteristics

	Median [range]	Mean – std. deviation
Treatment volume (cm ³)	0.108 [0.01-17.4]	1.476±1.57
Margin dose (Gy)	23 [15-24]	21.7±1.77
Maximal dose (Gy)	44 [20-50]	42.48±6.02

[range, 0–168 months]. The median latency period between the diagnosis of brain metastasis and SRS was 0.5 months [range, 0–27]. At the time of diagnosis, the most common symptom was headache (50%). Two patients had amnesia, one had dysphasia, one had hemiparesis, and one was diagnosed incidentally.

The median treatment volume was 0.108 cm³ [range, 0.01–17.4]. The median marginal dose was 23 Gy [range, 15–24 Gy] (Table II). Local failure was detected in 2 (5%) metastases treated with GKRS. One case of radiation-induced necrosis was identified on radiological follow-up; however, this radiological finding regressed on subsequent imaging and did not result in additional clinical symptoms. This patient had eight metastases, six of which developed radiation-induced necrosis after GKRS treatment. These six lesions received a dose of 24 Gy at a median isodose line of 67.5% [range: 50–85%], with a median lesion volume of 0.122 cm³ [range: 0.014–0.372 cm³]. Intracranial distant metastases were detected in two patients during radiological follow-up. One patient received additional radiological treatment for intracranial distant metastases. Before GKRS, two patients had received WBRT, and eight patients (80%) had received radioactive iodine treatment.

The median follow-up period was 8 months [range 2–98 months]. Long-term follow-up data were unavailable for two patients (3 and 6 months). Eighty percent of patients died during follow-up; one death was due to brain metastasis, whereas the others were attributed to oncological comorbidities.

DISCUSSION

Morbidity and mortality in patients with primary thyroid cancer are higher among those with distant metastases. Individual prognosis depends on factors, such as the histology of the primary tumor, its distribution, and the number of metastatic sites (19). According to the literature, the most common site of distant metastasis in thyroid cancer is the lungs, followed by the brain (12,27). Although numerous studies have evaluated treatment outcomes for brain metastases from lung or breast cancer, there is a dearth of research on treatment outcomes for TCBM because of its rarity; the incidence of brain metastasis from thyroid cancer is less than 1% (11). Although patients with primary thyroid cancer generally have better survival outcomes than those with other cancers, such as lung or gastrointestinal cancers, the prognosis for patients with TCBM is significantly poorer (16,29). In our study, long-term follow-up data were unavailable for two patients. Eight patients died during the follow-up period: one due to the progression of

brain metastases, one due to the progression of extracranial metastases, and six due to systemic complications, such as sepsis, pneumonia, and multisystem failure.

TCBMs are predominantly located in the supratentorial region (9). These metastases are often asymptomatic; however, a subset of patients may present with clinical symptoms, most commonly with headache and visual disturbances (28). In our series, the most frequent metastasis location was the frontal lobe (47.5%), and the most common presenting complaint was headache.

The BRAF V600E and TERT promoter mutations are frequently associated with thyroid carcinomas characterized by a more aggressive prognosis (22,28). Osborne et al. reported that these mutations can occur simultaneously, and their synergistic effect significantly reduces overall survival rates (19). In our series, although the mean survival time after GKRS was 21.87 months, one patient had BRAFV600E/TERT mutations and survived for only 5 months after GKRS.

Current guidelines recommend complete surgical resection of TCBM as the first-line treatment for patients whose performance status permits craniotomy (12). Several studies have demonstrated that total surgical resection is associated with improved survival outcomes, particularly in cases of single brain metastasis (7,15). According to the American Thyroid Association guidelines, stereotactic radiotherapy is considered equally effective as surgical intervention for patients with a limited number of brain metastases (<3) and can be re-administered if new intracranial lesions develop (12). WBRT or SRS is recommended as the primary treatment for patients with multiple (>3) metastatic lesions (9). The CNS guideline for metastatic brain tumors states that SRS alone can be considered equivalent to surgery plus WBRT based on level III evidence (17). Vlachos et al. conducted a meta-analysis comparing postoperative SRS with WBRT in 248 patients (128 WBRT, 120 SRS) who underwent resection of solitary brain metastases. Their findings demonstrated no statistically significant difference in local recurrence rates between the two treatment modalities (RR = 0.92, 95% CI 0.51–1.66, *p* = 0.78). Importantly, the study demonstrated that SRS was associated with equivalent or superior neurocognitive outcomes and quality of life measures compared to WBRT, while maintaining comparable efficacy in local tumor control (26).

Although WBRT provides effective control of both local and distant diseases, it does not improve overall survival. Moreover, it has significant negative impacts on patients' quality of life, causing symptoms, such as fatigue, headaches, cognitive decline, and behavioral changes (3). These adverse effects can significantly impair patients' daily functioning and overall well-being. RAI therapy is not commonly used for treating brain metastases, as limited data support its effectiveness (27).

SRS offers a more favorable toxicity profile compared to WBRT, with significantly reduced short- and long-term adverse effects, including fatigue, headaches, cognitive impairment, and behavioral changes. Notably, SRS has demonstrated effectiveness in patients with multiple brain metastases (30). SRS, alone or in combination with WBRT, has demon-

strated impressive local control rates for brain metastases (7). Furthermore, studies have shown that SRS provides outcomes comparable to surgical resection in terms of both local and distant control (23). In a series of 42 patients, Bunevicius et al. reported that during a mean imaging follow-up period of 25.2 months after SRS, local failure—defined as tumor progression and/or radiation necrosis—occurred in only 4% of the treated brain metastases. These failures were observed at a mean of 7.2 months following SRS (5). In this study, we observed a similarly favorable local control rate of 95% with no significant treatment-related complications.

The scarcity of robust clinical data necessitates a highly individualized treatment approach, taking into consideration factors, such as the number, size, and location of metastatic lesions, as well as the patient's overall clinical status and prognosis.

CONCLUSION

The small number of patients and the short follow-up period due to the aggressive course of TCBM limit the study's findings. Nevertheless, during this follow-up period, GKRS achieved favorable local control without any significant adverse effects.

Declarations

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Availability of data and materials: The datasets are available from the corresponding author upon reasonable request.

Disclosure: The authors declare that there are no conflicts of interest related to this study.

Ethics approval and consent to participate: This retrospective study, based on prospectively managed data, was approved by the Institutional Review Board of Koç University (2022.022.IRB1.017, date: 19.12.2025) and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

AUTHORSHIP CONTRIBUTION

Study conception and design: SP, AG

Data collection: MAT, EV, VK, MOA

Analysis and interpretation of results: MAT, SP, AG

Draft manuscript preparation: MAT, DCY,

Critical revision of the article: SP, AG

Other (study supervision, fundings, materials, etc.): SP, AG

All authors (MAT, DCY, AHD, MOA, EV, VK, AG, SP) reviewed the results and approved the final version of the manuscript.

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Posterior Atlantoaxial Fixation in a Single-Center Consecutive Series: Anatomy-Driven C2 Anchorage Selection

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ABSTRACT

AIM: To present a single-center experience with posterior C1–C2 fixation for atlantoaxial instability, emphasizing an anatomy-driven approach to C2 anchorage selection, construct strategy, complications, and clinical outcomes.

MATERIAL and METHODS: We retrospectively reviewed 45 patients who underwent posterior C1–C2 fixation between June 2020 and January 2026. Constructs were categorized as pedicle, hybrid, bilateral laminar, planned C2 omission (C1–C3 extension), or transarticular fixation. Demographics, etiology, operative variables, complications, reoperations, mechanical failure, and fusion were analyzed. Exploratory categorical comparisons were performed using Fisher's exact test. Fusion was evaluated using postoperative computed tomography (CT) obtained ≥ 6 months postoperatively and was defined as osseous bridging without implant loosening.

RESULTS: The mean patient age was 47.8 ± 20.1 years, and 25 patients (55.6%) were women. Etiologies included trauma (31.1%), basilar invagination (22.2%), Chiari malformation (15.6%), os odontoideum (8.9%), atlantoaxial subluxation (8.9%), tumor (8.9%), and other causes (4.4%). Construct types included pedicle fixation in 31 patients (68.9%), hybrid constructs in 5 (11.1%), bilateral laminar fixation in 5 (11.1%), planned C2 omission in 3 (6.7%), and transarticular fixation in 1 patient (2.2%). The median follow-up duration was 6.3 months (IQR, 1.2–22.3 months). CT-based fusion assessment was available for 26 patients at a median follow-up of 19.5 months, and fusion was observed in 20 patients (76.9%). Radiographic mechanical abnormalities were identified in 7 patients (15.6%), including 6 (13.3%) who underwent revision surgery. Construct strategy was not significantly associated with either mechanical abnormalities or CT-confirmed fusion. Mechanical abnormalities were significantly more frequent in patients with os odontoideum or nontraumatic atlantoaxial subluxation than in those with other etiologies ($p < 0.001$).

CONCLUSION: An anatomy-driven escalation strategy for C2 anchorage selection provided a practical framework for managing variable craniovertebral anatomy during freehand posterior atlantoaxial fixation. Hybrid constructs, bilateral laminar fixation, and planned C2 omission served as feasible alternatives when pedicle fixation was limited by anatomical constraints or pathology.

KEYWORDS: Atlantoaxial instability, C1–C2 fixation, C2 pedicle screw, C2 laminar screw, Craniovertebral junction

ABBREVIATIONS: **BI:** Basilar invagination, **CT:** Computed tomography, **CTA:** Computed tomography angiography, **HRVA:** High-riding vertebral artery, **IQR:** Interquartile range, **MRI:** Magnetic resonance imaging, **POD1:** Postoperative day 1, **STIR:** Short tau inversion recover, **VA:** Vertebral artery

INTRODUCTION

Atlantoaxial instability may result from trauma, congenital malformations, inflammatory disorders, neoplasms, as well as iatrogenic and degenerative conditions (3, 6). Because of the unique biomechanics of the craniovertebral junction, rigid stabilization is often required once stability is compromised (13).

Magerl and Seemann first described transarticular screw fixation as a reliable technique for posterior atlantoaxial stabilization (20). Subsequently, Harms and Melcher introduced C1 lateral mass–C2 pedicle screw fixation, which improved intraoperative flexibility and expanded the applicability of posterior fixation techniques (13). Goel and Laheri further demonstrated the biomechanical superiority of segmental screw constructs compared with traditional wiring techniques (10).

Wright later introduced C2 laminar screw fixation as a vertebral artery–sparing alternative for cases with unfavorable pedicle anatomy (26). Subsequent clinical studies have confirmed the safety and biomechanical reliability of laminar screw fixation when appropriately indicated, including in Turkish populations (14,22).

In the present study, we evaluate a consecutive series of posterior C1–C2 instrumentation procedures performed at a tertiary referral center for traumatic, congenital, deformity-related, neoplastic, iatrogenic, and degenerative pathologies. The primary objective was not to compare fixation techniques directly, but rather to describe a pragmatic, anatomy-driven framework for selecting C2 anchorage strategies in routine clinical practice. In addition, we aimed to evaluate operative indications, early clinical and radiographic outcomes, complication patterns, reoperation rates, and interim CT-based fusion outcomes in patients with adequate follow-up.

MATERIAL and METHODS

Study Design and Patient Population

This retrospective study included 45 consecutive patients who underwent posterior C1–C2 instrumentation at a tertiary neurosurgical center between June 2020 and January 2026. Demographic characteristics, indications, operative details, and postoperative outcomes were extracted from institutional records. Institutional ethics approval was granted by the Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (18.02.2026/107), and the requirement for informed consent was waived owing to the retrospective design and anonymized use of patient data.

Etiology Classification

Etiologies were categorized as trauma, basilar invagination, Chiari malformation, os odontoideum, nontraumatic atlantoaxial subluxation, tumor, and spondylosis.

Traumatic subtypes were classified using thin-slice cervical CT (1-mm sections) and magnetic resonance imaging (MRI), including short tau inversion recovery (STIR) sequences.

Imaging and Preoperative Planning

All patients underwent preoperative CT and CT angiography (CTA) to evaluate vascular anatomy relevant to screw placement planning. Imaging findings were reviewed to assess the feasibility of C2 pedicle screw placement, identify vertebral artery constraints, and guide the selection of pedicle or alternative C2 anchorage techniques.

Surgical Technique

All procedures were performed with the patient in the prone position using a posterior midline approach. Subperiosteal dissection was carried out to expose the C1 posterior arch and lateral masses, as well as the C2 lamina and pars/pedicle region. The integrity of the C2 spinous process and the muscles attached to its inferior aspect was preserved in all cases, except in procedures involving C3 fixation.

Bone grafting was performed at the surgeon's discretion. When an autograft was used, graft material was harvested from the occipital bone, C1 posterior arch, and/or iliac crest. Allograft material was also used depending on availability and surgeon preference. All screws were inserted freehand using anatomical landmarks and preoperative imaging guidance; intraoperative navigation was not used.

C1 lateral mass screws were placed according to standard trajectories. C2 pedicle screws were used when morphometric evaluation permitted a safe trajectory. In cases with unfavorable anatomy, alternative C2 anchoring techniques, including laminar or pars fixation, were selected according to the predefined construct strategy.

The C2 nerve root was preserved whenever feasible. When necessary to achieve adequate exposure or facilitate safe implant placement, limited mobilization of the C2 nerve root was performed; routine sacrifice of the root was not part of the standard surgical technique.

C1–C2 facet preparation, including cartilage removal and decortication, as well as graft placement, was performed at the surgeon's discretion according to intraoperative exposure and feasibility. A standardized facet preparation protocol was not applied uniformly across all patients.

Construct Strategy Classification

Construct strategies were classified a priori according to the type of C2 anchorage into the following categories:

1. Pedicle: bilateral C2 pedicle screws (primary option).
2. Hybrid: unilateral C2 pedicle screw + contralateral laminar or pars anchor.
3. Bilateral laminar: bilateral C2 laminar screws due to bilateral unfavorable anatomy (e.g., thin pedicles and/or high-riding vertebral artery).
4. Planned C2 omission (C1–C3): at least one side planned omission of C2 anchoring with intentional extension to C3 for secure distal fixation in select cases where C2 anchoring was not feasible or safe.

C1 lateral mass screws were used in all cases whenever feasible. A single transarticular fixation case was analyzed separately.

Decision framework for C2 anchor selection

Bilateral C2 pedicle screw fixation was preferred when preoperative CT/CTA demonstrated adequate pedicle morphometry and a safe vertebral artery corridor. Unfavorable pedicle anatomy was defined as the presence of a high-riding vertebral artery (HRVA), characterized by a C2 isthmus height ≤ 5 mm and/or C2 internal height ≤ 2 mm measured 3 mm lateral to the spinal canal, or a narrow C2 pedicle (< 4 mm). These anatomical features increase the risk of vertebral artery injury and limit safe pedicle screw placement (17,29).

When unilateral pedicle fixation remained feasible, a hybrid construct consisting of a unilateral pedicle screw and a contralateral laminar or pars anchor was used. Bilateral laminar fixation was selected in cases with bilateral anatomical constraints. Planned omission of C2 fixation with extension to C3 was reserved for cases in which secure C2 fixation was not feasible on at least one side. The proposed anatomy-driven construct selection algorithm is illustrated in Figure 1.

Fusion Assessment

Fusion was assessed using postoperative CT obtained at least 6 months after surgery and independently evaluated by two neurosurgeons (23,25). Fusion was defined as osseous bridging across the intended C1–C2 fusion site, including

one or more of the following: bridging between the C1 anterior arch and the odontoid process, across the C1–C2 lateral mass/facet complex, or through the interlaminar region, in the absence of radiographic evidence of implant loosening. Implant loosening was defined as halo formation or radiolucency surrounding the screws, rod or screw breakage, or implant pullout.

Disagreements between reviewers were resolved by consensus. Patients without postoperative CT follow-up beyond 6 months were excluded from fusion rate analysis. Consequently, the absence of adequate radiographic surveillance in some patients may have introduced selection bias into the CT-based fusion assessment.

Outcomes

Recorded outcomes included operative duration, construct type, screw strategy, vertebral artery injury, neurological complications, wound infection, C2 neuralgia, 30-day reoperation, overall reoperation, mechanical failure, and fusion.

Neurological complication was defined as newly developed postoperative motor weakness. C2 neuralgia was defined as neuropathic occipital pain, such as lightning-like or shock-like pain, documented in the clinical records.

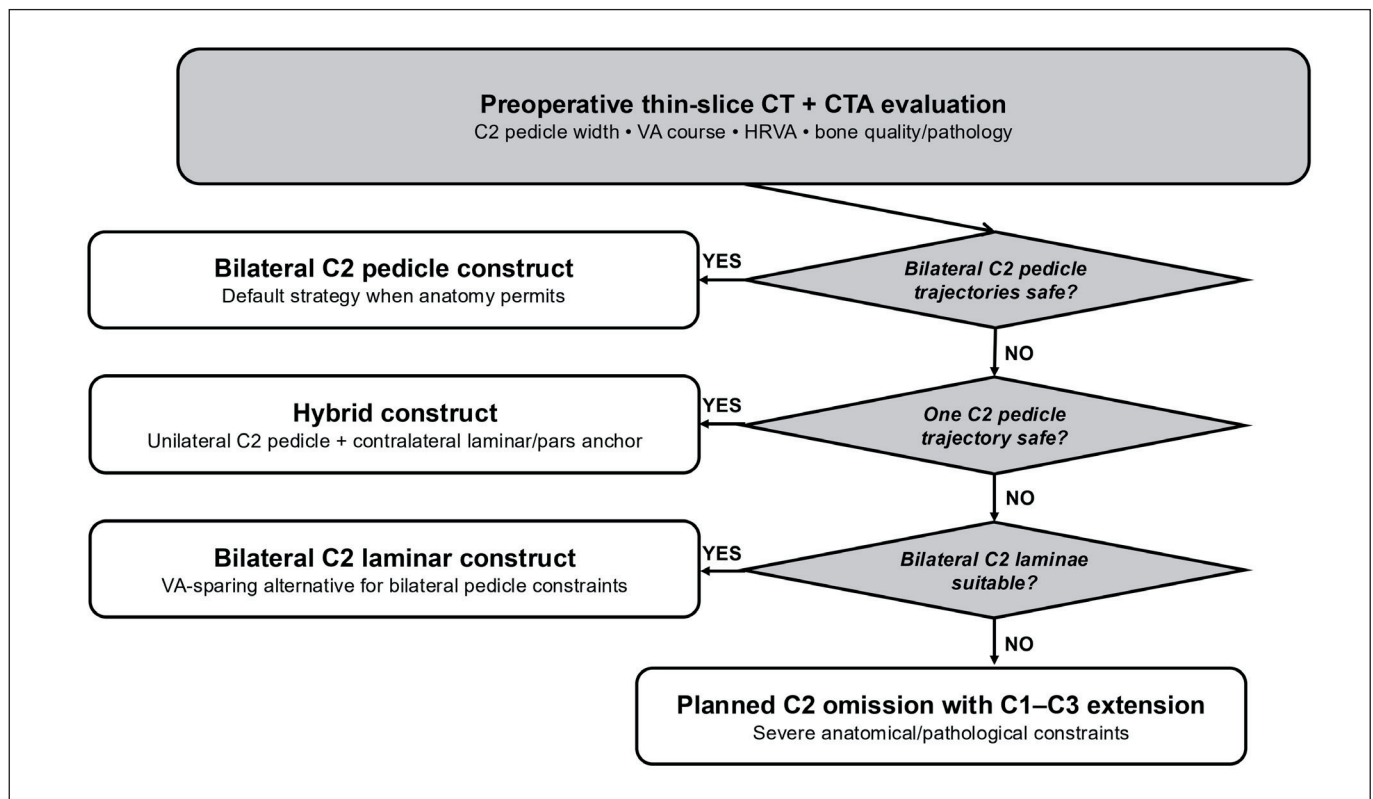


Figure 1: Anatomy-driven framework for C2 anchorage selection during posterior atlantoaxial fixation. Bilateral C2 pedicle fixation was preferred when pedicle morphology and vertebral artery anatomy permitted safe trajectories. Hybrid constructs were used for unilateral pedicle constraints, bilateral laminar fixation for bilateral unfavorable pedicle anatomy, and planned C2 omission with C1–C3 extension for severe anatomical or pathological constraints. HRVA: high-riding vertebral artery; VA: vertebral artery.

Mechanical failure was categorized as follows:

1. Radiographic mechanical findings: Asymptomatic construct-related abnormalities, including screw loosening, rod or screw breakage, pseudoarthrosis, or implant pull-out.
2. Clinically significant mechanical failure: Mechanical instability requiring revision surgery because of symptomatic instability, progressive deformity, or construct failure.

Because of the limited subgroup sizes and low number of events, exploratory categorical comparisons were performed using Fisher's exact test. These analyses included comparisons between construct strategy and radiographic mechanical findings, construct strategy and CT-confirmed fusion as well as selected etiology-based comparisons. Multivariable analysis was not performed because the number of events was insufficient to permit reliable statistical adjustment.

■ RESULTS

Baseline Characteristics

A total of 45 patients were included in the study. The mean age was 47.8 ± 20.1 years, and 20 patients (44.4%) were male. The mean operative duration was 261.9 ± 69.5 minutes, with a median duration of 265 minutes (IQR, 215–300 minutes). The median length of hospital stay was 3 days (IQR, 3–5 days). Median follow-up for the overall cohort was 6.3 months (IQR, 1.2–22.3 months). Baseline demographic and perioperative characteristics are summarized in Table I.

Etiologies

The distribution of surgical indications was as follows: trauma in 14 patients (31.1%), basilar invagination in 10 (22.2%), Chiari malformation in 7 (15.6%), os odontoideum in 4 (8.9%), nontraumatic atlantoaxial subluxation in 4 (8.9%), tumor in 4 (8.9%), and spondylosis in 2 patients (4.4%). The relationship between etiology and construct strategy is presented in Table II.

Table I: Baseline and Perioperative Characteristics

Variable	Value
Age, mean $\pm$ SD (years)	47.8 $\pm$ 20.1
Sex, n (%)	Female 25 (55.6); Male 20 (44.4)
Etiology, n (%)	Trauma 14 (31.1); Basilar invagination 10 (22.2); Chiari malformation 7 (15.6); Os odontoideum 4 (8.9); Atlantoaxial subluxation 4 (8.9); Tumor 4 (8.9); Spondylosis 2 (4.4)
Operative duration, mean $\pm$ SD (minutes)	261.9 $\pm$ 69.5; median 265 (IQR 215–300)
Length of stay (days)	median 3 (IQR 3–5)
Follow-up, full cohort (months)	median 6.3 (IQR 1.2–22.3)
Follow-up, fusion-assessed subgroup (n=26) (months)	median 19.5 (IQR 10.5–41.2)

Values are presented as mean $\pm$ SD, median (IQR), or n (%), as appropriate. Fusion was assessed on thin-slice (1 mm) CT scans obtained ≥ 6 months postoperatively when available and defined as osseous bridging across C1–C2 (anterior arch–dens, lateral mass/facet region, interlaminar space) without radiographic loosening.

Table II: Etiology by Construct Strategy

Etiology	n	Pedicle	Hybrid	Bilateral laminar	Planned C2 omission	Transarticular
Trauma	14	12	0	1	1	0
Basilar invagination	10	5	1	2	1	1
Chiari malformation	7	6	1	0	0	0
Os odontoideum	4	1	2	1	0	0
Atlantoaxial subluxation	4	2	1	1	0	0
Tumor	4	3	0	0	1	0
Spondylosis	2	2	0	0	0	0
Total	45	31	5	5	3	1

Pedicle = bilateral C2 pedicle screws (primary option). Hybrid = unilateral C2 pedicle screw with contralateral alternative anchor (laminar or pars). Bilateral laminar = bilateral C2 laminar screws due to bilaterally unfavorable anatomy (e.g., thin pedicles and/or high-riding vertebral artery). Planned C2 omission = at least one side planned omission of C2 fixation with intentional C1–C3 construct. Transarticular reported separately.

Within the trauma subgroup ($n = 14$), the most common injury pattern was odontoid fracture. Anderson–D’Alonzo type II odontoid fractures accounted for 7 patients (50.0%), whereas type III fractures accounted for 4 patients (28.6%) (2). The remaining traumatic indications included C1 ring fractures associated with transverse atlantal ligament injury in 2 patients (14.3%) and a dislocated Hangman fracture in 1 patient (7.1%).

Notably, five odontoid fracture cases represented delayed or complex presentations. These included four cases of type III odontoid fracture with nonunion or progressive displacement following an initial period of conservative management and one salvage case involving loosening of a previously placed anterior odontoid screw for a type II fracture, which ultimately required posterior C1–C2 stabilization.

Construct Strategy Distribution

Construct strategies included pedicle fixation in 31 patients (68.9%), hybrid constructs in 5 (11.1%), bilateral laminar fixa-

tion in 5 (11.1%), planned C2 omission with C1–C3 extension in 3 (6.7%), and transarticular fixation in 1 patient (2.2%). A representative standard pedicle construct using bilateral C2 pedicle screws (Harms technique) is shown in Figure 2.

Figure 3 illustrates a representative anatomy-driven hybrid construct strategy, including preoperative CTA demonstrating narrow pedicle morphology and postoperative axial CT confirming hybrid fixation. In two patients (4.4%), C1 lateral mass screws were not used, and either occiput–C2 fixation or transarticular C1–C2 fixation was preferred.

Outcomes Stratified by Construct Strategy

Reoperations included one wound revision procedure; all remaining reoperations were performed because of mechanical failure, including screw loosening or breakage, rod breakage, pseudoarthrosis, and implant pullout.

Safety events, complications, and reoperation outcomes stratified according to construct strategy are summarized in

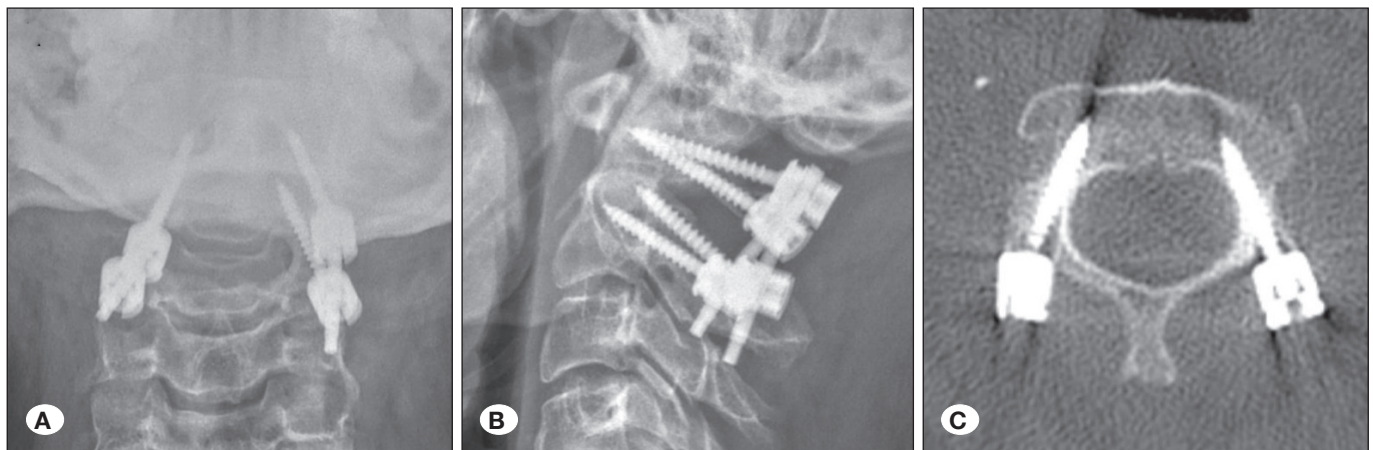


Figure 2: Posterior C1–C2 fixation in basilar invagination associated with Chiari malformation. A 31-year-old female underwent posterior fossa decompression with duraplasty and C1–C2 fixation. **A)** Postoperative anteroposterior radiograph. **B)** Lateral radiograph. **C)** Axial computed tomography confirming bilateral C2 pedicle screw positioning.

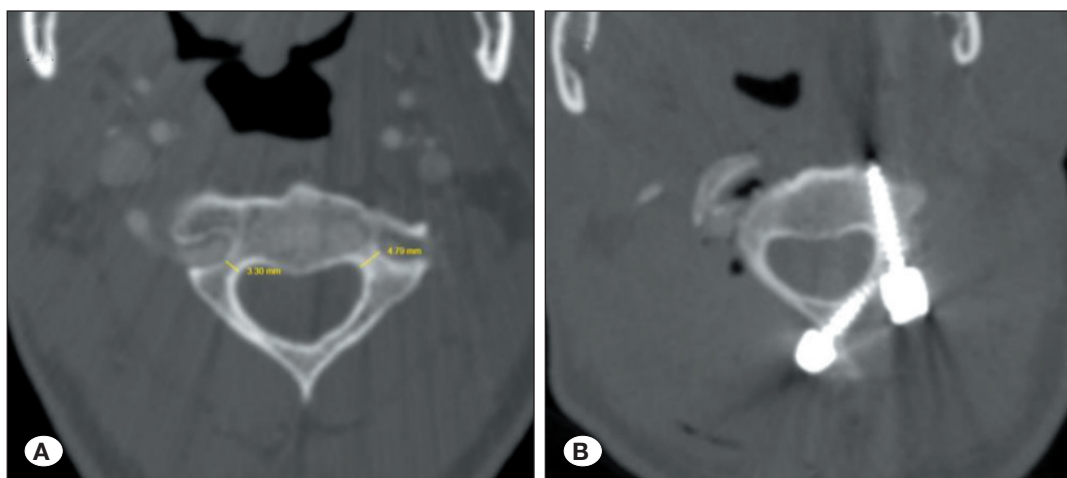


Figure 3: Hybrid C1–C2 construct in os odontoideum with narrow C2 pedicle. A 50-year-old male underwent C1–C2 fusion. **A)** Preoperative computed tomography angiography (CTA) demonstrating narrow right C2 pedicle (3.30 mm) compared with the left (4.79 mm). **B)** Postoperative axial CT showing hybrid construct with the right C2 laminar screw and left C2 pedicle screw.

Table III. Mechanical failure and CT-based fusion outcomes in the fusion-assessed subgroup are summarized in Table IV.

Because of the limited subgroup sizes and low event rates, exploratory categorical analyses were performed using Fisher's exact test. Construct strategy was not significantly associated with radiographic mechanical findings ($p = 0.287$) or CT-confirmed fusion among patients with evaluable postoperative CT follow-up ($p = 1.000$).

Radiographic mechanical findings were not observed in trauma cases (0/14) and occurred in 7 of 31 nontraumatic cases (22.6%); however, this difference did not reach statistical significance ($p = 0.081$). In contrast, radiographic mechanical findings were significantly more common among patients with os odontoideum or nontraumatic atlantoaxial subluxation than among patients with other etiologies (5/8 [62.5%] vs. 2/37 [5.4%], $p < 0.001$). These analyses were exploratory in nature and underpowered for definitive comparative conclusions.

Radiological progression in a representative trauma case, from preoperative displacement to postoperative day 1 reduction and one-year fusion, is illustrated in Figure 4.

Fusion Outcomes

CT-based fusion assessment was available for 26 of 45 patients (57.8%). Nineteen patients (42.2%) did not undergo postoperative CT evaluation beyond 6 months and were therefore excluded from the fusion analysis denominator. Fusion was observed in 20 of 26 patients (76.9%). Fusion outcomes according to the construct strategy are summarized in Table IV.

Complications

Overall, 17 of 45 patients (37.8%) experienced at least one complication. The most common complication was C2 neuralgia, which occurred in 8 patients (17.8%) and was characterized by neuropathic occipital pain with lightning-like or shock-like features.

Radiographic mechanical abnormalities occurred in 7 patients (15.6%) and included screw loosening, pseudoarthrosis, implant pullout, and construct-related hardware failure. Six patients (13.3%) developed clinically significant mechanical failure requiring revision surgery.

Table III: Complication and Reoperation Outcomes by Construct Strategy

Construct strategy	n	VA Injury	Neural Complication	Wound Infection	C2 Neuralgia	Reop 30d	Reop any
Pedicle	31	0 (0.0)	0 (0.0)	0 (0.0)	5 (16.1)	1 (3.2)	4 (12.9)
Hybrid	5	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (20.0)
Bilateral laminar	5	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	1 (20.0)
Planned C2 omission (C1–C3)	3	0 (0.0)	1 (33.3)	2 (66.7)	1 (33.3)	0 (0.0)	1* (33.3)
Transarticular	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Values are presented as n (% within construct strategy), unless otherwise indicated. "Reop 30d" denotes return to the operating room within 30 postoperative days; "Reop any" denotes return to the operating room at any time during available follow-up. The asterisk denotes reoperation for wound revision; remaining reoperations were performed for mechanical failure. C2 neuralgia/occipital neuralgia was defined as neuropathic-character occipital pain, such as lightning or shocking occipital pain, documented in routine clinical records; incidence and severity may be underestimated because standardized pain instruments were not used. "Neural Complication" denotes postoperative neurological deterioration; the single neurological complication occurred in a patient with an intramedullary tumor and was attributed to the intramedullary tumor procedure rather than the fixation construct. VA, vertebral artery.

Table IV: Mechanical and Fusion Outcomes by Construct Strategy

Construct strategy	n	Radiographic Mechanical Failure	Revision Requiring Mechanical Failure	Fusion Assessed (n)	Fused n (%)
Pedicle	31	4 (12.9)	4 (12.9)	15	13 (86.7)
Hybrid	5	2 (40.0)	1 (20.0)	5	3 (60.0)
Bilateral laminar	5	1 (20.0)	1 (20.0)	3	2 (66.7)
Planned C2 omission	3	0 (0.0)	0 (0.0)	3	2 (66.7)
Transarticular	1	0 (0.0)	0 (0.0)	0	—

Values are presented as n (% within construct strategy), unless otherwise indicated. Radiographic mechanical failure included screw loosening, pseudoarthrosis, implant pullout, or construct-related hardware failure. Revision-requiring mechanical failure was defined as clinically significant mechanical failure requiring revision surgery because of symptomatic instability, progressive deformity, or construct failure. Fusion assessment was restricted to patients with available postoperative CT obtained ≥ 6 months after surgery. "Fusion assessed" indicates the number of evaluable patients within each construct strategy; fused percentages were calculated only among patients with evaluable CT follow-up. Exploratory Fisher exact testing did not demonstrate statistically significant associations between construct strategy and radiographic mechanical failure ($p=0.287$) or CT-assessed fusion ($p=1.000$). These analyses were exploratory and underpowered for definitive comparative inference; no multivariable modeling was performed.

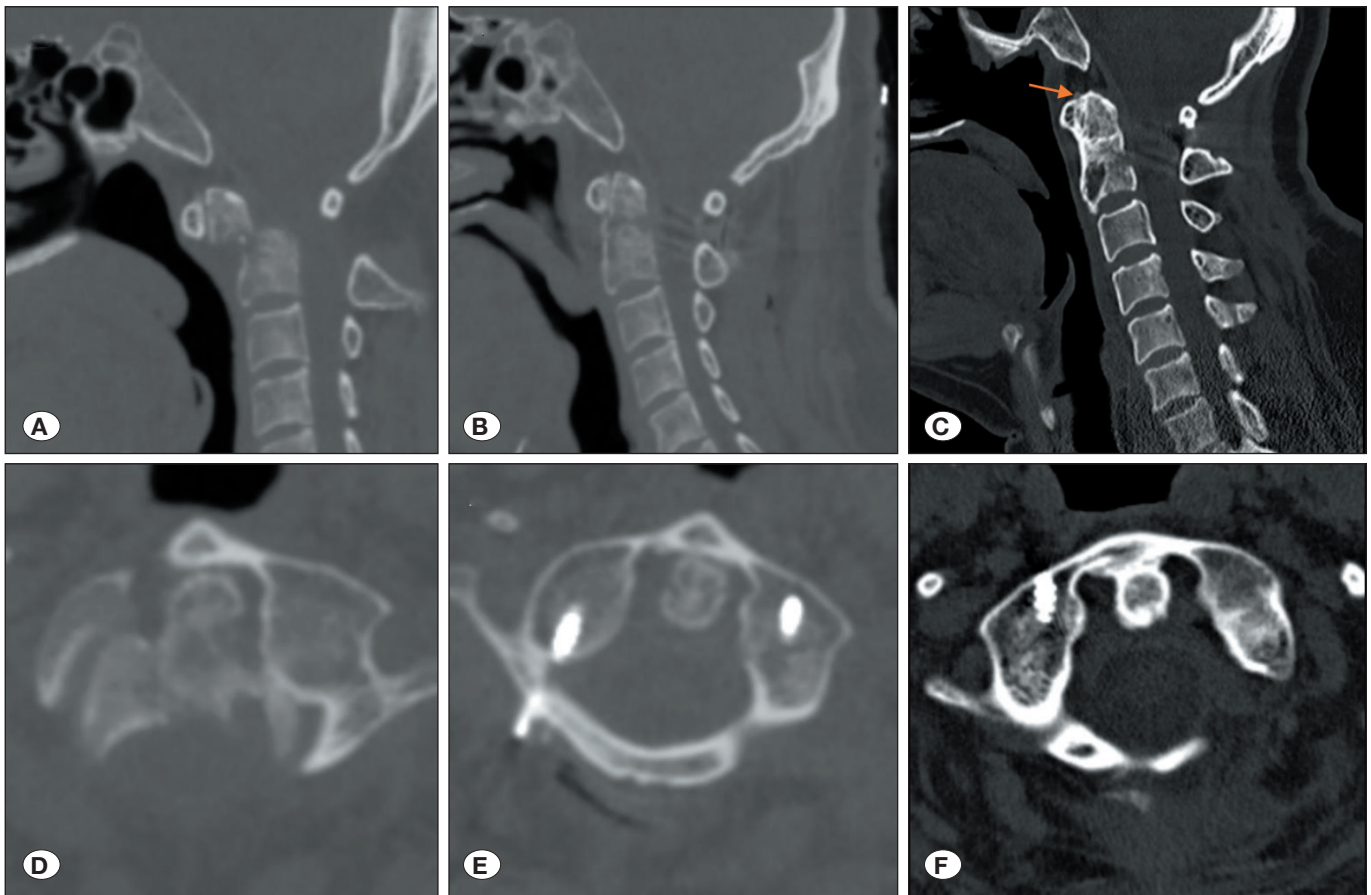


Figure 4: Radiologic evaluations following posterior C1–C2 fixation for Anderson–D’Alonzo type II odontoid fracture. A 55-year-old male underwent reduction and fixation. **A, D)** Preoperative sagittal and axial computed tomography (CT) scans. **B, E)** Postoperative day 1 CT demonstrating reduction and construct positioning. **C, F)** One-year follow-up CT demonstrating maintained alignment and solid fusion. Arrow indicates fusion between the C1 anterior arch and C2 dens.

Wound infection occurred in 2 patients (4.4%); one of these patients required surgical wound revision. One patient (2.2%) developed new postoperative motor weakness in the setting of surgery for a C1–C2 intramedullary tumor. This neurological deficit was attributed to the intramedullary tumor procedure rather than to the instrumentation itself.

No vertebral artery injury occurred in this series (0/45, 0%).

DISCUSSION

Posterior C1–C2 fixation has evolved from transarticular constructs to segmental screw–rod techniques that provide greater intraoperative flexibility and broader anatomical applicability (5,20). Magerl’s transarticular approach and the subsequent segmental construct described by Harms and Melcher established the foundation of modern screw-based atlantoaxial stabilization, supported by biomechanical and clinical evidence favoring rigid fixation over posterior wiring techniques (6,10,13,20). These advances allow fixation strategies to be tailored to patient-specific anatomy while maintaining the reduction capability and fusion potential required for atlantoaxial instability (7,10).

In this consecutive series, the predominance of bilateral C2 pedicle anchorage reflects current practice in anatomically favorable cases (7), whereas the use of hybrid, bilateral laminar, and planned C2 omission constructs reflects deliberate escalation when C2 morphology and/or vertebral artery anatomy limited safe pedicle trajectories. The etiologic heterogeneity of our cohort mirrors real-world management of atlantoaxial instability, with trauma representing the most common indication, followed by craniovertebral junction deformity and other causes. Trauma remains a common indication for atlantoaxial surgery, particularly Anderson–D’Alonzo type II odontoid fractures, in which posterior segmental fixation is frequently selected when instability is substantial, reduction is required, or anterior odontoid screw fixation is unsuitable (2,12). Conversely, basilar invagination and Chiari malformation represent craniovertebral junction deformity paradigms in which posterior stabilization is commonly used in selected patients to facilitate reduction and decompression (9,11). Across this spectrum, maintaining construct rigidity while adapting to patient-specific anatomy remains a central practical requirement (7,26).

Accordingly, our institutional approach may be summarized as a structured construct-selection framework focused on C2 anchorage. Bilateral C2 pedicle screw fixation served as the preferred option when morphometric assessment permitted safe trajectories (30). When unilateral anatomical constraints existed, such as a narrow pedicle, HRVA, or unfavorable vascular anatomy, a hybrid strategy preserved pedicle fixation on the feasible side while using a contralateral alternative anchor (laminar or pars) to maintain stability while reducing vascular risk (21,30). When bilateral constraints precluded safe pedicle placement, bilateral C2 laminar fixation provided a vertebral artery-sparing alternative supported by morphometric and clinical evidence (15). In selected cases in which secure C2 fixation was not feasible or safe on at least one side, planned omission of C2 fixation with intentional extension to C3 provided reliable distal fixation (24). In our series, this escalation strategy was used for destructive unilateral C2 pathology (neoplastic or traumatic) and complex congenital anatomy, including C2–C3 Klippel–Feil anomaly with bilaterally thin pedicles and high-riding vertebral arteries, in which fixation was achieved with bilateral C3 pedicle screws. The single transarticular case reflects that transarticular fixation remains an option in selected anatomical situations but is used less frequently in modern practice because of reduction requirements and vascular considerations (20,30). A separate radiographic analysis from this cohort evaluated arcuate foramen and congenital anomalies affecting C1 screw entry; however, those anatomy-focused findings are outside the scope of the present outcomes- and C2 anchorage-focused report.

All screws in this cohort were placed freehand. Although navigation systems and patient-specific guides have gained increasing interest, freehand atlantoaxial fixation is safe when meticulous preoperative imaging assessment and anatomical landmarks are used (16,27). Vertebral artery injury remains a recognized risk during C2 pedicle and transarticular screw placement; therefore, preoperative three-dimensional vascular assessment is critical for selecting the safest anchor strategy and supports escalation toward hybrid or laminar fixation when high-risk anatomy is identified (1,30). Importantly, no vertebral artery injuries occurred in this series, supporting the practical value of a predefined escalation framework rather than attempting pedicle placement in high-risk corridors.

Comparison with published series should consider differences in indication profiles, construct-selection philosophy, imaging modalities, and follow-up protocols. A large series by Isik et al. reported favorable outcomes after posterior atlantoaxial screw–rod fixation and emphasized the importance of preoperative radiologic planning and surgical experience. The authors also described C2 laminar screws as a successful alternative in anatomically constrained cases (14). Additional Turkish studies have reported alternative anchorage strategies in the setting of vertebral artery anomalies or complex C2 anatomy, highlighting that a single construct strategy may not apply to all patients (24). Our findings are consistent with these reports, emphasizing the importance of anatomy-driven anchor selection in safe posterior atlantoaxial fixation (14,24).

Fusion assessment warrants cautious interpretation. In this study, fusion was evaluated by two independent neurosurgeons using postoperative CT scans obtained at ≥ 6 months. CT is widely regarded as the most specific modality for assessing osseous bridging (23), and CT-based criteria have been evaluated against surgical exploration in cervical fusion and nonunion assessment (25). However, fusion rates may appear lower when strict CT-based bridging criteria are applied, particularly in studies with heterogeneous pathology and non-standardized follow-up. Published atlantoaxial fixation studies vary considerably with respect to pathology, follow-up duration, grafting strategy, fusion biology, and methods of fusion assessment, including dynamic radiographs, clinical stability, CT, or combined criteria (6,18,23). Meta-analyses have generally reported high fusion rates for screw–rod constructs. Elliott et al. reported a pooled fusion rate of 97.5% for screw–rod constructs, whereas Lvov et al. reported a nonunion rate of 4.2% for the Goel–Harms technique (6,18). Our CT-confirmed fusion rate of 76.9% was therefore lower than many published technique-specific estimates, but this finding should be interpreted in the context of strict CT-based criteria, heterogeneous pathology and follow-up, variable fusion biology, and incomplete CT availability for the full cohort. Standardized CT follow-up protocols would improve benchmarking in future studies (23).

In our cohort, the complication profile consisted primarily of C2 neuralgia (17.8%), radiographic mechanical findings (15.6%), wound infection (4.4%), and a single neurological complication, with no vertebral artery injuries observed. The absence of vertebral artery injury compares favorably with pooled estimates in the literature. Ghaith et al. reported vertebral artery injury rates of approximately 2% per operated patient and 1% per screw placed, whereas Lvov et al. reported a vertebral artery injury rate of 2.8% in a meta-analysis of the Goel–Harms technique (8,18). Our C2 neuralgia rate was higher than the 6.1% rate of clinically significant C2 nerve root irritation reported by Lvov et al.; however, comparisons remain difficult because studies differ in C2 root handling techniques, reporting definitions, and patient-reported outcome assessment (18,28). Yeom et al. demonstrated that postoperative occipital neuralgia may be clinically significant and technique-dependent, particularly with respect to C2 nerve root management (28). The wound infection rate of 4.4% and wound revision rate of 2.2% in our series were within the low single-digit range reported in contemporary posterior atlantoaxial datasets, although definitions and follow-up periods vary across studies (19). The single neurological complication occurred in a patient undergoing resection of a C1–C2 intramedullary tumor and was therefore attributed to the intramedullary procedure rather than the fixation construct itself.

Our relatively broad definition of radiographic mechanical findings likely contributed to rates that appear higher than those reported in some indication-specific series and technique-focused meta-analyses (4,18). This likely reflects both the inclusive radiographic definition and the heterogeneous nature of our cohort, which included acute trauma, chronic instability/

deformity, tumor-related instability, and degenerative pathology. Differences in bone quality, reducibility, chronic deformity, and fusion biology may increase implant stress and pseudarthrosis risk compared with more homogeneous cohorts. Exploratory Fisher's exact analyses did not demonstrate statistically significant associations between construct strategy and either radiographic mechanical findings or CT-confirmed fusion. Although radiographic abnormalities appeared descriptively more common in hybrid constructs, this should be interpreted cautiously because hybrid fixation was preferentially selected in anatomically constrained and often chronic instability cases, resulting in likely confounding by indication. Instead, mechanical findings clustered more prominently in chronic instability phenotypes, particularly os odontoideum and nontraumatic atlantoaxial subluxation. These observations suggest that underlying pathology, chronic deformity, reducibility, and fusion biology may influence mechanical outcomes more strongly than construct category alone; however, these findings remain exploratory because of the limited subgroup sizes. Nevertheless, the observed pattern is consistent with the concept that chronic deformity and altered biomechanics may impose greater demands on fixation constructs than acute traumatic instability (6).

C2 neuralgia remains a clinically relevant outcome after C1–C2 fixation (18). In this study, neuralgia was identified from routine clinical documentation rather than standardized patient-reported instruments; therefore, both incidence and severity may have been underestimated. We intentionally avoided formal risk-factor analysis and instead reported this outcome descriptively, reserving definitive evaluation for future studies incorporating standardized pain instruments and detailed operative variables, including C2 root management.

Stratified analyses suggested that mechanical failure and reoperation clustered in chronic instability phenotypes, particularly os odontoideum and nontraumatic atlantoaxial subluxation, whereas traumatic cases demonstrated no mechanical failures or reoperations in this cohort. These findings should be considered hypothesis-generating because of the small subgroup sizes and variable follow-up duration. In addition, shorter follow-up in recently operated patients may have limited the detection of delayed failure or late nonunion.

Overall, this consecutive series supports the practical feasibility of freehand posterior atlantoaxial fixation across heterogeneous indications using a structured, anatomy-driven construct-selection strategy focused on C2 anchorage (6,26). Prospective follow-up with standardized CT fusion assessment and patient-reported outcome measures would improve benchmarking and enable more robust risk-factor analyses across construct categories.

This study has several limitations. First, the retrospective single-center design introduces inherent selection and information biases, and the heterogeneous etiologic spectrum limits direct subgroup comparisons. Second, construct-strategy subgroups were small; therefore, analyses stratified by strategy or etiology should be considered descriptive and hypothesis-generating rather than confirmatory. Statistical analyses

were intentionally limited because subgroup sizes were insufficient for robust multivariable modeling. Third, radiologic fusion was assessed by CT in only 26 of 45 patients (57.8%), whereas 19 patients (42.2%) lacked postoperative CT at ≥ 6 months. This may have introduced selection bias and limited definitive benchmarking for the entire cohort. Imaging intervals were not standardized, and interobserver reliability for fusion assessment was not formally evaluated. Fourth, important patient-centered outcomes, particularly occipital pain and C2 neuralgia, were derived from routine clinical documentation rather than standardized patient-reported instruments, potentially underestimating symptom burden and severity. Finally, follow-up duration was variable, and shorter follow-up in recently operated patients may have limited the detection of delayed mechanical complications or late nonunion.

CONCLUSION

In this consecutive single-center series, an anatomy-driven construct-selection strategy demonstrated the practical feasibility of safe freehand posterior atlantoaxial fixation across a heterogeneous spectrum of C1–C2 instability. Bilateral pedicle fixation served as the preferred strategy when anatomically feasible, whereas hybrid constructs, bilateral laminar fixation, and planned C2 omission with C1–C3 extension provided practical preplanned alternatives in the setting of predictable anatomical or pathological constraints. CT-confirmed fusion was achieved in most evaluable patients, with acceptable complication and reoperation profiles. Prospective studies with standardized CT-based fusion assessment and patient-reported outcome measures are needed to improve benchmarking and better define strategy-specific risks and long-term outcomes.

Declarations

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Availability of data and materials: De-identified data may be made available by the corresponding author upon reasonable request.

Disclosure: The authors declare no conflicts of interest related to this work.

Declaration of Generative AI Use: The authors used a generative artificial intelligence tool (ChatGPT, OpenAI) to assist with English-language editing of the manuscript, including grammar, clarity, and style. No patient-level data were entered into the tool. All content was reviewed and edited by the authors, who take full responsibility for the accuracy and integrity of the final manuscript.

AUTHORSHIP CONTRIBUTION

Study conception and design: ATB

Data collection: ATB, BT

Analysis and interpretation of results: ATB, BT

Draft manuscript preparation: ATB

Critical revision of the article: ATB, BT

Other (study supervision, fundings, materials, etc...): n/a

All authors (ATB, BT) reviewed the results and approved the final version of the manuscript.

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Pro-Con Debate for Thenar Tissue Oxygenation in Prone Position during Lumbar Discectomy

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This study has been presented as an oral presentation at the 56th National Congress of the Turkish Society of Anesthesiology and Reanimation between 3 and 6 November, 2022 at Antalya, Türkiye

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ABSTRACT

AIM: To compare the regional tissue oxygen saturation under general, spinal, and epidural anesthetics during the posterior lumbar discectomy procedures performed in the prone position.

MATERIAL and METHODS: A total of 90 patients with an American Society of Anesthesiologists score I-III were evaluated. Using the research randomizer program, the patients were split into three groups: group of general anesthesia (GA, Group I), group of spinal anesthesia (SA, Group II), and group of epidural anesthesia (EA, Group III). Each patient received non-invasive peripheral arterial oxygen saturation (SpO₂), three-lead electrocardiography, non-invasive mean arterial blood pressure (MAP), and the in Spectra TM StO₂ Spot Check device with near-infrared spectroscopy (NIRS) technology. The group GA also received end-tidal CO₂ monitoring and tissue hemoglobin index (THI), and StO₂ monitoring.

RESULTS: The data of 90 patients showed that age, weight, height, American Society of Anesthesiologists score, amount of bleeding, duration of surgery, and anesthesia were not statistically significant. Tissue oxygen saturations were detected between groups at the 15th, 30th, 45th, and 60th minutes. The values of group EA at the 15th, 30th, and 45th minutes were higher than group SA (p=0.001; p<0.05).

CONCLUSION: This study shows that general anesthesia, as opposed to spinal and epidural anesthesia, offers superior thenar tissue oxygenation in a prone position during posterior lumbar discectomy surgery, despite the ongoing debate over the pros and cons of this position.

KEYWORDS: General anesthesia, Prone position, Spinal anesthesia, Tissue oxygen saturation

ABBREVIATIONS: EA: Epidural anesthesia, GA: General anesthesia, NA: Neuraxial anesthesia, NIRS: Near-infrared spectroscopy, SA: Spinal anesthesia

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■ INTRODUCTION

To meet the many obstacles presented in the perioperative treatment of patients for neurosurgical procedures, the field of neuroanesthesia has grown dramatically in recent years. The frequency of surgeries performed under regional anesthesia has significantly increased in recent years. Patients are generally placed in a prone posture during spinal procedures. Changes in this position can significantly affect the physiology of the patient. Maintaining oxygen homeostasis is a crucial objective of anesthesiologists when managing patients in the prone position. One of the most common causes for lower back pain is degenerative disc disease. Lumbar discectomy is a frequent spinal surgical procedure used for patients with lumbar disc herniation who do not improve with conventional therapy (2,3,6). During lumbar disc surgery, general anesthesia (GA) or neuraxial anesthesia (NA) can be used. In spinal anesthesia (SA) and epidural anesthesia (EA), the sympathetic nervous system is blocked, so the microcirculatory dynamics around the surgical field can be different from the circulatory dynamics. The field of anesthesia has grown significantly over the last few decades. The importance of fluids and vasopressors in maintaining tissue oxygenation through appropriate cardiac output and perfusion pressure has become increasingly evident. In order to maintain organ function, microcirculatory homeostasis must be maintained. Regional oxygen saturation (rSO_2) is measured in real time using a technique called near-infrared spectroscopy (NIRS), which decodes oxy- and deoxyhemoglobin signals. NIRS is a low-cost, simple, and non-invasive technique that has been shown to be safe and feasible for use during surgery. Compared to a single venous saturation measurement, it reveals hemodynamic changes earlier, but the effects of the prone position on tissue oxygenation have not been studied well. Annually, the number of spine surgeries performed globally is increasing at an astounding rate. Despite advances in technology (8), the effects of tissue oxygenation have not been studied well during lumbar discectomy in the prone position, under general or SA. The Pro-Con debate of the issue still continues. We investigated the effects of GA, SA and EA on tissue oxygenation in patients who would be operated on in a prone position during the lumbar discectomy procedure.

■ MATERIAL and METHODS

Ethical approval for this study was provided by the Ethical Committee of Recep Tayyip Erdogan University (2021/129; July 14th, 2021). Volunteer patients were determined with American Society of Anesthesiologists (ASA) classifications 1-3 between the ages of 18 and 65 who were operated on electively for lumbar disc herniation between July 2021 and December 2022. The patients were divided into three groups as Group GA (Group I), Group SA (Group II), and Group EA (Group III) through the research randomizer program. Demographic data such as age, gender, weight, height, duration of anesthesia and surgery, and operative data such as the amount of intraoperative bleeding were recorded. Each patient underwent non-invasive mean arterial blood pressure (MAP), three-lead electrocardiography, peripheral arterial oxygen saturation (SpO_2), and in Spectra TM StO_2 Spot Check

Model 300 (Hutchinson Technology Inc, Hutchinson, MN, USA) device with near-Infrared Spectroscopy (NIRS) technology over a probe placed in the left-hand thenar region, receiving StO_2 and tissue hemoglobin index (THI) monitoring and end-tidal CO_2 monitoring to the group GA.

All patients were premedicated with 0.02 mg/kg midazolam. In Group I patients, after preoxygenation and denitrogenation with 100% oxygen for 3 minutes (min) after premedication, endotracheal intubation was performed with 1 μ g/kg fentanyl, 2 mg/kg propofol, and 0.6 mg/kg rocuronium with an intravenous (iv) induction spiral tube. In volume-controlled mode after endotracheal intubation, a mixture of oxygen (40%) and air (60%) was applied for an ideal body weight of 6 ml/kg tidal volume, 5 cmH₂O positive end-expiratory pressure, and oxygenation. The respiratory frequency of EtCO₂ was adjusted to 35-40 mmHg. Anesthesia was maintained as an IV infusion with desflurane at a minimum alveolar concentration of 4-5 and remifentanyl at 0.1-0.3 μ g/kg/min.

In Groups II and III, O₂ was administered with a 5 L/min nasal cannula to patients undergoing neuraxial anesthesia. After premedication, the patient was given 15-17.5 mg hyperbaric bupivacaine in a seated position with a 25-G Quincke-tipped needle for SA after obtaining appropriate antisepsis from one or two levels above the level of disc herniation. For EA, an 18-G Tuohy needle was administered, the epidural interval was determined using the resistance loss method, and a test dose was performed with 3 cc of 2% lidocaine and 0.15 μ g of adrenaline. After that, 75 μ g of fentanyl and 0.05% bupivacaine were injected at the dose calculated according to the patient's height. After a neuraxial block, patients were followed up in a supine position for 10 min, and patients with sufficient block were taken to the prone position. A headrest foam pillow was used to position and keep the patient's head in a neutral position. The breathing circuit was reconnected, and a recruiting maneuver was carried out. The knees and hips of the legs were padded, and they were slightly flexed. The patient's abdomen was examined for any unusual pressure. Periodically, the airway, face, and eyes were also examined. Each patient underwent maintenance intravenous fluid therapy by the intraoperative 4-2-1 rule (4 mL for the first 10 kilos, 2 mL for the second 10 kilos, and 1 mL for every subsequent 10 kilos) by taking into account the fasting period.

Intraoperative heart rate (HR), MAP, EtCO₂, SpO_2 , StO_2 , THI data of the patients who were supine at 0 minutes (S0) and 10 minutes (S10) and prone at 15 minutes (P15), 30 minutes (P30), 45 minutes (P45), 60 minutes (P60), and postoperative (PPOSTOP) were recorded in the supine position after extubation.

At the end of the surgical procedures, patients who underwent GA underwent decurularization with 0.02 mg/kg IV atropine and 0.04 mg/kg IV neostigmine. Patients with spontaneous breathing, return of protective reflexes, and the ability to hold the head in the air for 5 seconds were extubated.

IV ephedrine was administered to patients with intraoperative MAP basal blood pressure decreases of more than 25%, and patients in need of vasopressors were excluded from the study. Intraoperative complications were recorded.

Statistical Analysis

The statistical analysis was performed using the Number Cruncher Statistical System (NCSS) (2007, Kaysville, Utah, USA) application. The Shapiro-Wilk test was used to assess the distribution of the study data as well as the descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum). When comparing three or more groups of quantitative data without a normal distribution, the Kruskal-Wallis test is used; when a normal distribution is present, ANOVA is used; and the Mann-Whitney U test is used for the comparison of the two groups that could not show a normal distribution and the Student's t-test is used for the normal distribution. To determine the relationship between the quantitative data, Pearson correlation analysis was used when it showed a normal distribution, and

Spearman correlation analysis was used when it did not show a normal distribution. Significance was accepted as $p < 0.01$ and $p < 0.05$.

A power analysis was performed. As for the percentage measurement values of the methods, the effect size was 0.4, and the power was 80%. The margin of error was 0.05, and the total sample size found using the G-POWER program was $n=66$.

RESULTS

A total of 115 patients were included in this study, and the data of 90 patients, 30 in each group, were evaluated. There was no significant difference between demographic data such as age, weight, height, and gender in all three groups (Table I) ($p > 0.05$). The flowchart is seen in Figure 1. When the effects

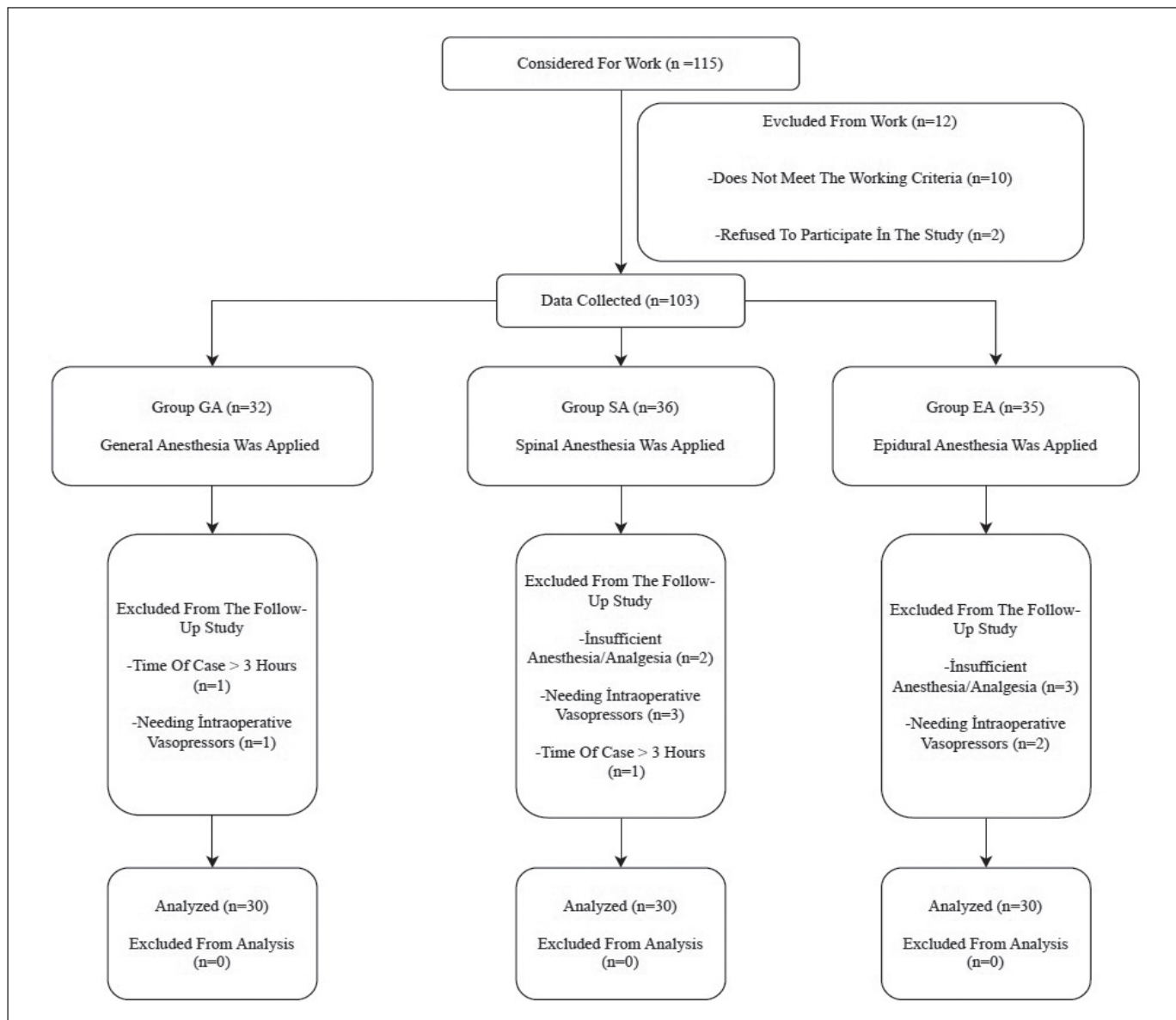


Figure 1: The flowchart of the study.

Table I: Demographic Data

	Group GA (n=30)	Group SA (n=30)	Group EA (n=30)	p-value
Age (years) (mean±SD)	47.1±11.3	50.43±10.49	44.83±11.05	0.107
Weight (kg) (mean±SD)	81.13±12.28	83.2±12.02	80.93±11.58	0.767
Height (m) (mean±SD)	1.69±0.09	1.68±0.09	1.73±0.08	0.094
Female/Male, n	13/17	15/15	8/22	0,164
ASA 1/2/3, n	5/23/2	5/19/6	1/26/3	

GA: General anesthesia, **SA:** Spinal anesthesia, **EA:** Epidural anesthesia, **ASA:** American Society of Anesthesiologists

Table II: Intraoperative StO₂ Values (mean ± standard deviation)

	Group GA (n=30)	Group SA (n=30)	Group EA (n=30)	p-value
0 min	83.17±6.1	82.2±6.78	84.03±6.84	0.556
10 min	86±6.04	83.97±5.74	89±5.29	0.005
15 min	89.17±4.62	76.57±9.22	83.93±7.75	0.001
30 min	88.07±5.73	76.57±8.29	82.3±8.63	0.001
45 min	88±5.94	74.57±9.93	81.2±9.45	0.001
60 min	87.23±6.94	75.23±7.2	78.93±8.65	0.001
Postoperative	80.57±8.6	77.13±6.17	79.13±7.71	0.236

min: Minutes, **StO₂:** Tissue oxygen saturation, **GA:** General anesthesia, **SA:** Spinal anesthesia, **EA:** Epidural anesthesia

of the anesthesia method on tissue oxygenation were evaluated by StO₂ from the thenar region, it was found that the StO₂ values of Group GA were higher than those of Group SA and Group EA at 15th, 30th, 45th, and 60th minutes in the prone position ($p=0.001$; $p<0.05$) (Table II, Figure 2). When neuraxial anesthesia methods were compared among themselves, StO₂ data of Group EA were significantly higher in the prone 15th, 30th, and 45th minutes than in Group SA ($p=0.001$; $p<0.05$). The results of the study are presented in the graphical abstract (Figure 3).

■ DISCUSSION

Main Results

To the best of our knowledge, this study represents the first research to determine the effects of GA, SA, and EA on tissue oxygenation in prone patients undergoing spinal surgery. This study indicates that GA provides better tissue oxygenation than SA and EA in a prone position during posterior lumbar discectomy surgery.

Interpretation

A sufficient oxygen supply is important to support proper cellular metabolism (7). The hypothesis of this study is that hemodynamics and respiratory complications for patients in prone or supine positions are not the same. Patients are more likely to have tracheal discomfort and cough when they are moved from the prone position to the supine position (5). Both physiological function and cellular signaling depend on oxi-

dative stress. Oxidative stress, which is linked to disruptions in reduction/oxidation (redox) regulation, cellular malfunction, organ failure, and illness, is caused by an imbalance between the generation of reactive oxygen species and antioxidant defense. Anesthesia, surgery, and the patient all play a part in the complicated reaction known as perioperative oxidative stress. Surgery is an acute event that causes systemic dysfunction in addition to localized tissue damage. Providing tissues and organs with an appropriate supply and delivery of oxygen is a major goal in perioperative settings.

In the supine posture, the dorsal alveoli are more likely to experience atelectasis, and the ventral alveoli are more likely to experience over-inflation because the dorsal transpulmonary pressure (airway opening pressure minus pleural pressure) is higher than the ventral transpulmonary pressure.

Pro: GA in the prone position

Pressure on the intra-abdominal organs in the prone position, especially during thoracic procedures, can impact the hemodynamics and lung mechanics because of surgical compression (1). The dynamic lung compliance decreases when a patient under GA is placed in the prone position because there are no unrestricted movements of the chest wall or abdomen (1). A higher airway pressure is necessary to provide proper breathing when lung compliance is decreased (1). These patients need methods aimed at enhancing oxygenation, such as the prone posture (4). Healthcare providers must take precautions against endotracheal tube dislodgement, hemodynamic compromise, line disconnection, eye and pressure injuries,

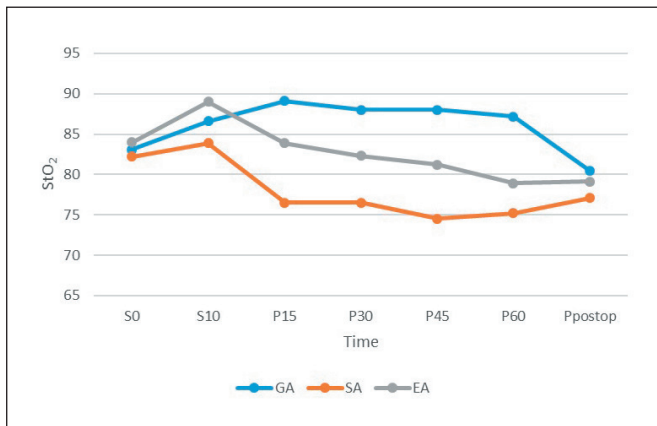


Figure 2: StO₂ graph of all patients over time.

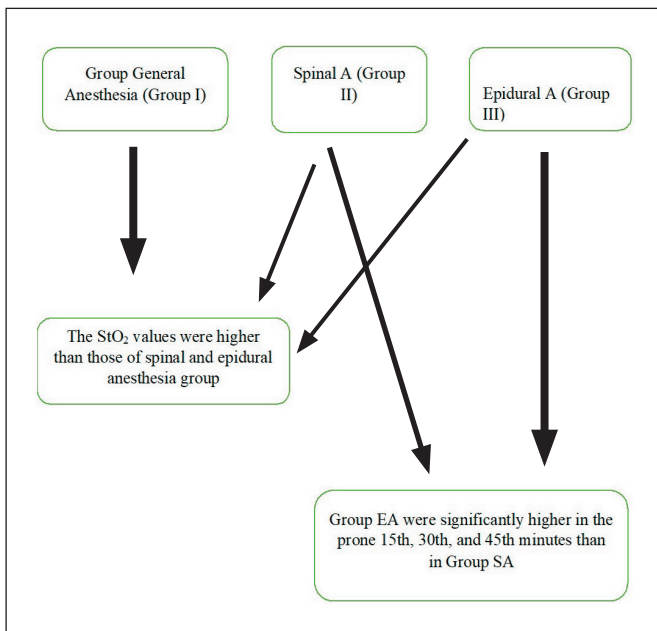


Figure 3: The study's findings are summarized in the graphical abstract.

and maintain access to the chest, central lines, arterial lines, and urinary catheters, even though the clinical advantages of proning greatly exceed any potential negative event (4).

Con: EA or SA under the prone position: Can it be a panacea?

Previous studies have shown that the prone posture improves oxygenation in a number of cases of acute lung damage, or ARDS (1). The prone position is frequently used to enhance oxygenation in patients with acute respiratory distress syndrome who are on mechanical ventilation and during specific surgical operations. Compared to the supine position, the prone posture produces more uniform ventilation, lung aeration, and strain distribution because the difference between the dorsal and ventral transpulmonary pressures is reduced.

Increased oxygenation is a result of opening the collapsed dorsal lung sections, boosting homogenous ventilation, improving ventilation/perfusion ratios, decreasing alveolar shunt volume, raising functional residual capacity, and enabling secretion clearance (1). By improving lung circulation, decreasing dorsal lung compression, and adjusting the ventral-dorsal transpulmonary pressure gradient, the prone posture enhances gaseous exchange. In the prone position, there was an increase in functional residual capacity (1). There is little information available regarding the effects of the prone position on healthy lungs under GA, SA, or EA, despite the anesthesiologists' familiarity with its effects on damaged lungs. We hypothesized that tissue microcirculation can be impaired in the prone position. Tissue hypoperfusion may lead to numerous complications. Because arterial hyperoxemia increases the production of free oxygen radicals, it may result in end-organ damage. Follow-up of tissue perfusion and early detection of insufficiency allow early diagnosis and management of organ damage. In this study, microperfusion alterations of tissue were assessed by NIRS. We evaluated the effect of the anesthesia method on tissue oxygenation and microcirculation of patients undergoing lumbar discectomy in a prone position, with the measurement of StO₂ from the thenar region to observe changes in microcirculation. A null hypothesis, which is commonly used in statistical testing, asserts that certain outcomes (9) (such as the same StO₂ values under SA or GA in the prone position of lumbar discectomy surgery) are affected by methods (such as general versus spinal epidural anesthesia in this study) in the same way; however, in the prone position, Group GA's StO₂ values were higher than those of Group SA and Group EA when the effects of the anesthetic technique on tissue oxygenation were assessed using StO₂ from the thenar region ($p=0.001$; $p<0.05$).

The tissue oxygenation differences between the groups in this investigation were statistically significant, and the values were reasonably close to one another. Since compromised tissue oxygenation during surgery is linked to higher rates of post-operative mortality and morbidity, we believe that those little variations have a therapeutic significance. It has been demonstrated that tissue oxygenation monitoring during surgery is crucial for minimizing and preventing somatic damage, post-operative mortality, and morbidity.

Limitations

The study is single-centered with a relatively small sample size ($n=30$ per group) and lacks blinding, which may introduce bias. Furthermore, the exclusion of patients requiring vasopressor support may limit the generalizability of the findings to real-world surgical populations. There is no doubt that there are many parameters that affect blood oxygen parameters, such as patients' internal diseases. It can be better to include it and perform another multivariate analysis. Furthermore, the preoperative values of the patients can be compared with each other, and the statistical significance of the change can be evaluated. Therefore, these parameters can be considered as insufficient. These points are other limitations of the present study.

CONCLUSION

Although both SA and GA have been utilized in lumbar disc herniation procedures, GA is today utilized nearly exclusively (10). In this study, we compared the anesthesia methods and found that tissue oxygenation was better in the group where GA was applied than in the group treated with SA or EA. When neuraxial anesthesia methods were compared among themselves, it was found that tissue oxygenation was higher in EA application. Although there is ongoing debate on the pros and cons of prone positioning during lumbar discectomy, this study suggests that GA, as opposed to SA and EA, offers superior oxygenation of the thenar tissue during posterior lumbar discectomy surgery. Given the recent increase in the use of SA and EA in spinal surgery, neurosurgeons may find this study to be of interest. The findings of the study might serve as a caution that spinal anesthetics should not be used while a patient is prone, particularly if they have tissue oxygenation issues. More comprehensive studies are required.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials: No new data were created or analysed during this study. Data sharing is not applicable to this article.

Disclosure: The authors declare that there are no conflicts of interest related to this study.

AUTHORSHIP CONTRIBUTION

Study conception and design: MNS

Data collection: MNS

Analysis and interpretation of results: LK

Draft manuscript preparation: SB

Critical revision of the article: AK

Other (study supervision, fundings, materials, etc...): OS

All authors (MNS, LK, SB, OS, AK) reviewed the results and approved the final version of the manuscript.

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Effects of Sodium Nitrite on Neural Tube Development in Early-Stage Chick Embryos

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ABSTRACT

AIM: To investigate the effects of sodium nitrite on spinal cord development in early-stage chick embryos.

MATERIAL and METHODS: Sixty specific-pathogen-free fertile Leghorn-type eggs at Day 0 of incubation were used. Group 1 (control) received saline, Group 2 (low-dose) was administered 0.0042 mg of sodium nitrite, and Group 3 (high-dose) received 0.0084 mg. Embryonic disks were microscopically examined after 72 hours of incubation.

RESULTS: In the control group, the surface ectoderm was intact, the neural tube was properly closed, and the neuroepithelium, basement membrane, somites, and notochord exhibited normal morphology. Neural tube defects were identified in seven embryos in the low-dose group and nine embryos in the high-dose group. Statistical analysis revealed that both sodium nitrite-exposed groups exhibited a significantly higher incidence of neural tube defects compared with the control group ($p < 0.05$). However, no statistically significant difference was observed between the low- and high-dose groups.

CONCLUSION: Exposure to low and high doses of sodium nitrite induced neural tube defects in chick embryos, suggesting potential embryotoxic effects.

KEYWORDS: Chick embryo, Embryotoxicity, Neural tube defects, Sodium nitrite

INTRODUCTION

Congenital malformations such as meningocele, myelomeningocele, encephalocele, tethered cord, and diastematomyelia are frequently encountered in neurosurgical practice. Neural tube defects (NTDs), occurring in approximately 1 in 1,000 live births, arise from multifactorial etiologies, including environmental factors, chromosomal abnormalities, maternal folic acid deficiency, and maternal diabetes or elevated glycemic index levels (16). Disruptions at any stage of primary or secondary neurulation can result in these malformations. Additionally, maternal exposure to medications, environmental agents, and dietary additives has been implicated in congenital anomalies.

The clinical spectrum of NTDs ranges from anencephaly to sacral agenesis and is often associated with high morbidity and mortality (8,16). Infants with NTDs have a markedly increased risk of mortality before reaching 5 yr of age.

Sodium nitrite, a common additive in processed meat products, is used primarily as a coloring and antimicrobial agent. Exceeding the recommended maximum daily intake of 0.07 mg/kg/day (4,5) has been linked to carcinogenicity, hypertension, and adverse reproductive outcomes (6,13). Experimental studies also suggest that sodium nitrite may impair brain development and negatively affect learning and memory (9). Although previous research has explored its effects on the nervous system, no study to date has specifically investigated its impact on spinal cord development.

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MATERIAL and METHODS

Experimental Design

A total of 60 specific pathogen-free (SPF), fertile, zero-day Leghorn-type chicken eggs (average weight: 65 ± 5 g) were obtained from the Bornova İzmir Veterinary Experimental Animals Department. The eggs were randomly divided into three groups ($n = 20$ per group): control, low-dose sodium nitrite, and high-dose sodium nitrite.

Eggs were incubated for 24 hours at $37.8 \pm 0.2^\circ\text{C}$ and $60 \pm 5\%$ relative humidity, positioned with the pointed end downward. A Cimuka CT60 S incubator (Ankara, Türkiye) was used to ensure uniform temperature, humidity, and automated rotation every 90 minutes to facilitate optimal embryonic development.

Sodium Nitrite Administration

Sodium nitrite was administered at Hamburger–Hamilton (HH) Stage 6, corresponding to approximately 24 hours of incubation. Doses were calculated according to the European Food Safety Authority's recommended human daily limit of 0.07 mg/kg (4,5), using a proportional adjustment for chick embryo mass. Thus, the low-dose group received 0.0042 mg sodium nitrite, whereas the high-dose group received 0.0084 mg (double the low dose).

Group 1 (control) received 0.1 mL of saline. Group 2 received 0.0042 mg/0.1-mL sodium nitrite, and Group 3 received 0.0084-mg/0.1 mL sodium nitrite. A 5-mm hole was aseptically drilled in the eggshell near the blastoderm, and injections were delivered beneath the embryonic disk. The holes were sealed with sterile tape, and the eggs were re-incubated until 72 hours.

At HH Stage 20 at 72 hours, embryonic disks were excised and transferred to distilled water maintained at 35°C .

Histological Analysis

Embryos were fixed in 10% neutral buffered formalin at room temperature. Standard tissue-processing procedures were performed, including graded ethanol dehydration, xylene clearing, and paraffin embedding. Sections $4 \mu\text{m}$ thick were

obtained using a rotary microtome (Leica RM2155, Germany) and mounted on glass slides.

Sections were stained with hematoxylin and eosin (H&E) to evaluate morphological alterations in the neural tube, notochord, and neuroepithelium. Images were captured using a light microscope (Olympus BX51, Tokyo, Japan) equipped with a charge-coupled device camera (Olympus DP 72, Tokyo, Japan).

Ethics Statement

In accordance with the European Directive 2010/63/EU, ethical approval was not required for experiments involving chick embryos.

Statistical Analysis

Data were analyzed using MATLAB R2022B (Statistics and Machine Learning Toolbox, Version 12.4). Fisher's exact test was applied to compare the incidence of NTDs among groups. A p value <0.05 was considered statistically significant.

RESULTS

Light microscopic analysis of transverse and sagittal sections from 20 chick embryos in the control group revealed clearly identifiable neural tube and notochord structures. The surface ectoderm was intact, the neural tube was appropriately closed for the developmental stage, and the neuroepithelium, basement membrane, somites, and notochord demonstrated normal morphology (Figure 1A).

In the low-dose sodium nitrite group (0.0042 mg), neural tube and notochord structures were visible in transverse, sagittal, and oblique planes. Three embryos exhibited NTDs characterized by distinct cervical openings (Figure 2A-D). Compared with the intact morphology of the 72-h control group, four embryos displayed various luminal irregularities (Figure 2E-H). In three embryos, the lumen was partially occluded due to neuroepithelial proliferation at the cervical level (Figure 2E-G), whereas one embryo showed abnormal lumen patency at the caudal level (Figure 2H). The remaining 13 embryos had intact neural tubes comparable to those in the control group (Figure 1B).

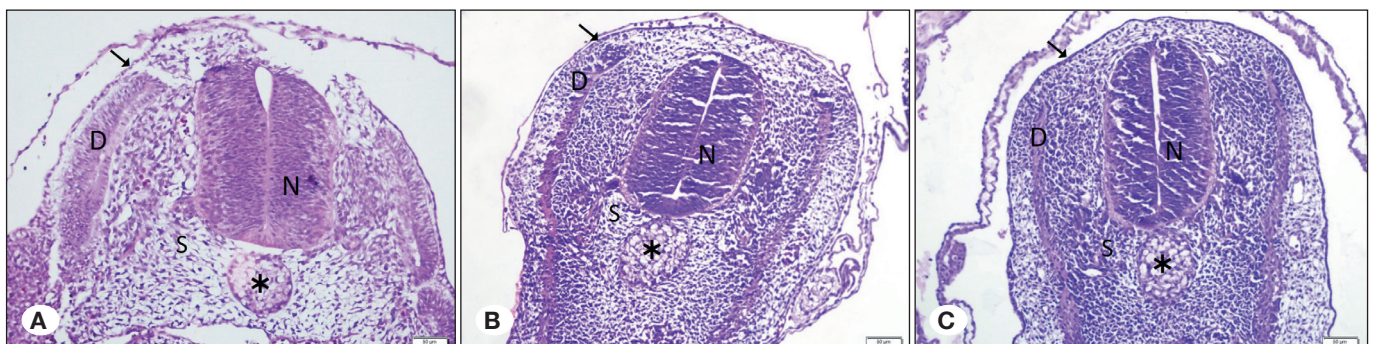


Figure 1: Hematoxylin and eosin–stained photomicrographs showing intact structures in the control (A), low-dose (0.0042 mg; B), and high-dose (0.0084 mg; C) groups. ↑: Surface ectoderm; N: Neural tube; Notochord; D: Dermomyotome; S: Sclerotome. Scale bars = $50 \mu\text{m}$.

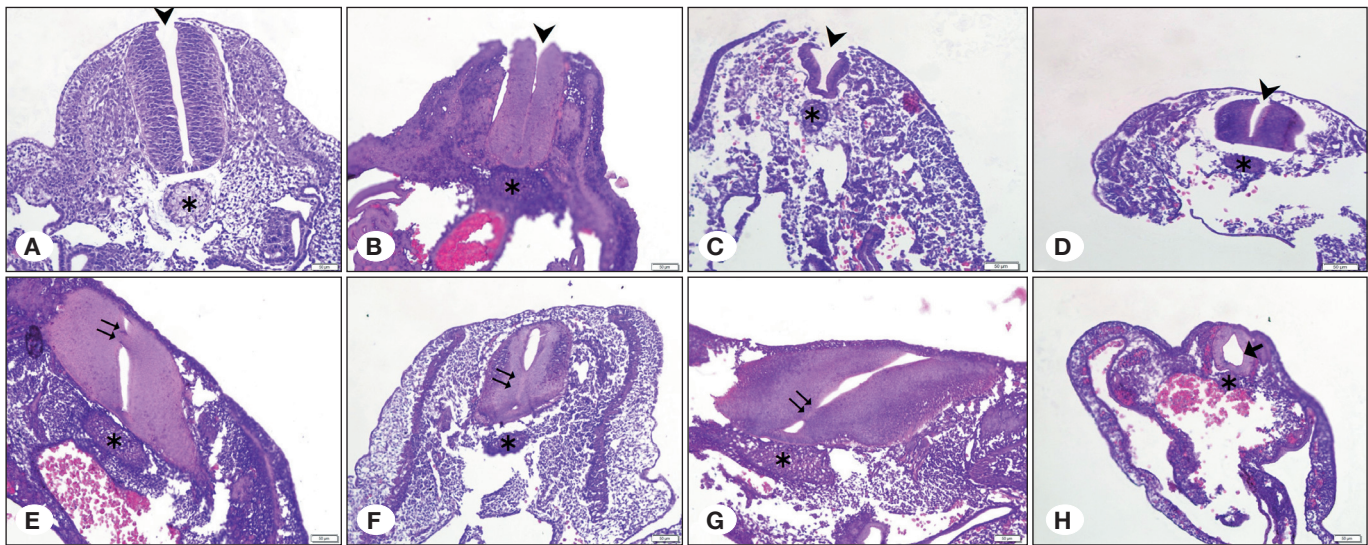


Figure 2: Representative photomicrographs of neural tube defects (A–D) and luminal anomalies (E–H) in the low-dose (0.0042 mg) group. One embryo with NTD exhibits cervical (B) and caudal (C) openings. **Arrowhead:** NTD; **Double arrow:** Neuroepithelial proliferation; **Arrow:** Abnormal luminal opening; **Asterisk:** Notochord. Hematoxylin and eosin staining. Scale bars = 50 µm.

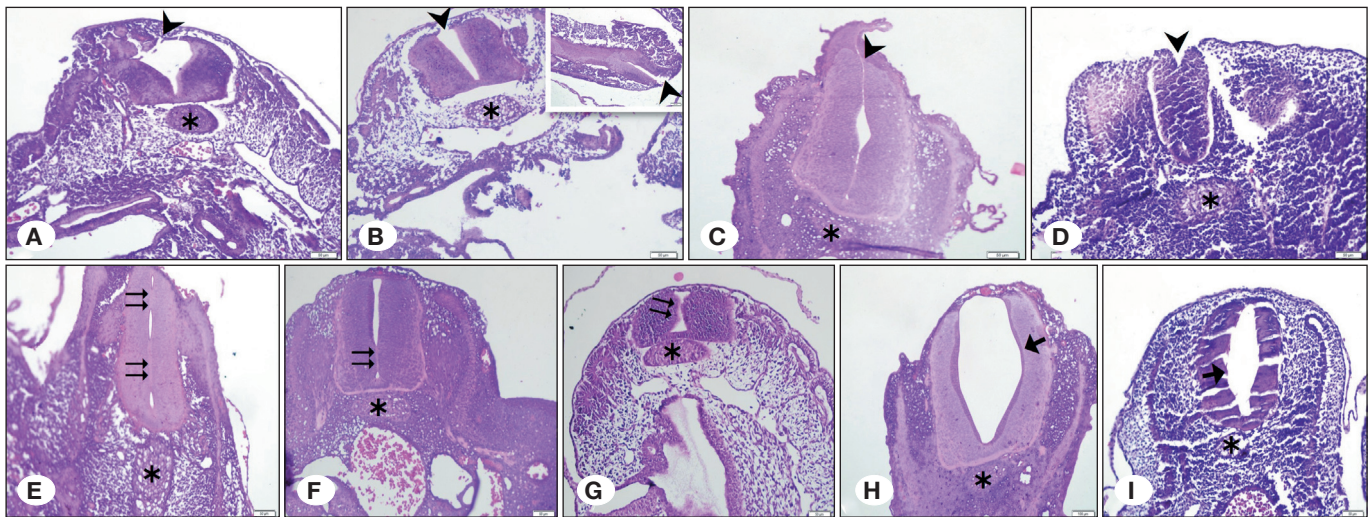


Figure 3: Representative photomicrographs of neural tube defects (A–D) and luminal anomalies (E–I) in the high-dose (0.0084 mg) group. **Arrowhead:** NTD; **Double arrow:** Neuroepithelial proliferation; **Arrow:** Abnormal luminal opening; **Asterisk:** Notochord. Hematoxylin and eosin staining. Scale bars = 50 µm.

In the high-dose group (0.0084 mg), four embryos exhibited NTDs (Figure 3A–D), and five embryos presented with luminal anomalies (Figure 3E–I). Neuroepithelial proliferation (Figure 3E–G) and abnormal lumen patency (Figure 3H,I) were evident among these cases. Eleven embryos maintained normal neural tube morphology similar to the control group (Figure 1C).

Statistical Results

A significance level of $p < 0.05$ was considered statistically meaningful. Compared with the control group, the incidence of NTDs was significantly higher in the low-dose sodium nitrite group ($p = 0.0083$) and in the high-dose group ($p = 0.0012$). However, no statistically significant difference was observed between the low- and high-dose groups ($p = 0.7475$) (Table I–III).

DISCUSSION

Neural tube defects represent a group of congenital malformations ranging from mild vertebral closure defects, such as spina bifida occulta, to severe abnormalities involving the spinal cord, including meningocele and myelomeningocele. These defects often result in vertebral anomalies, neural tissue damage, and are frequently accompanied by cardiac, skeletal, urogenital, or distal bowel abnormalities. Multiple environmental and maternal factors contribute to their development, including folate deficiency, maternal smoking, air pollution, exposure to specific medications such as anticonvulsants, and exposure to food additives (3,12,15). Substances such as colorants, preservatives, and contaminants in soil or wa-

Table I: Comparison Between the Control Group (daily dose) and the Low-Dose Sodium Nitrite Group

	Daily Dose	Control	p-value
Normal	13	20	0.0083
Defect	7	0	

Table II: Comparison Between the Control Group and the High-Dose Sodium Nitrite Group

	High Dose	Control	p-value
Normal	11	20	0.0012
Defect	9	0	

Table III: Comparison Between the Low-Dose Group and the High-Dose Sodium Nitrite Group

	Daily Dose	High Dose	p-value
Normal	13	11	0.7475
Defect	7	9	

ter may increase the risk of congenital spinal malformations during early gestation (15).

The chick embryo is a well-established model for investigating developmental anomalies, particularly of the spinal cord, due to its rapid embryonic growth, the similarity of its neurulation process to that of humans, and the feasibility of *in ovo* manipulation. Therefore, this model was selected to examine the potential teratogenic effects of sodium nitrite on neural tube closure.

Sodium nitrite and nitrate are water-soluble compounds widely used in processed meats—such as sausages, bacon, jerky, and deli products—as curing and preservative agents to enhance color, stabilize flavor, and extend shelf life (16,19). Sodium nitrite reacts with myoglobin to form nitrosomyoglobin, producing the characteristic reddish-pink color of cured meats (16,19). However, once ingested, nitrite can react with amines to form nitrosamines, compounds known to increase carcinogenic risk (6,18). The World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) have classified processed meats as “probably carcinogenic to humans,” largely due to these nitrosamine-mediated effects (11,14).

Nitrites also induce oxidative stress, contributing to genotoxicity, mutagenesis, and reproductive and embryotoxic effects (6,16,18,19). Additionally, dietary exposure to nitrites and nitrates has been linked to hypertension and adverse reproductive outcomes (3,4). The European Food Safety Authority (EFSA) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) have established acceptable daily intakes (ADIs) of 0.07 mg/kg and 0.06 mg/kg body weight, respectively (4,5). Sodium nitrite is naturally found in vegetables such as

lettuce and beets but is primarily ingested through processed meats, where consumption may exceed the recommended limits.

In this study, a dose equivalent to the EFSA-defined ADI (0.07 mg/kg) was designated as the low-dose group, whereas the high-dose group received twice that concentration. Notably, developmental abnormalities of the spinal cord were detected even at doses corresponding to the accepted daily limit. While spinal dysraphisms typically occur in the lumbosacral region, three cases in this study exhibited rare cervical localization.

Acute toxicity of sodium and potassium nitrite has been associated with smooth muscle relaxation, vasodilation, hypotension, and methemoglobinemia. Prior studies indicate that sodium nitrite exerts embryotoxic and teratogenic effects at high concentrations (1,10,15). Prolonged maternal exposure may impair fetal growth, disrupt neural and skeletal development, reduce maternal and fetal weight gain, and cause congenital anomalies (17). Chronic or high-dose exposure has also been linked to infertility, placental dysfunction, and fetal loss (7). Furthermore, impaired dendritic development associated with nitrite exposure may contribute to cognitive impairment (2).

Similarly, sodium nitrite exposure in zebrafish embryos has been shown to produce mild anxiogenic behaviors and altered brain metabolic profiles, including decreased levels of GABA, glutamine, and certain fatty acids, indicating disruption of neurochemical balance (6).

In our study, NTDs and spinal cord closure defects occurred even at exposure levels equivalent to the upper threshold of the acceptable daily intake. Although the frequency of NTDs was greater in the high-dose group, the difference between dose levels was not statistically significant. These findings underscore the potential developmental risks associated with sodium nitrite exposure, even within current safety margins.

This study is the first, to the best of our knowledge, to demonstrate the adverse effects of sodium nitrite on embryonic spinal cord development. As a preliminary investigation, our results emphasize the need to re-evaluate the safety thresholds of sodium nitrite exposure during pregnancy and encourage further research using larger sample sizes and additional vertebrate models.

■ CONCLUSION

The findings of this study indicate that sodium nitrite exerts a direct teratogenic effect on neural tube development in chick embryos. Statistically significant neural tube closure defects were observed in low- and high-dose groups. Notably, cervical spinal dysraphism—a rare presentation—was detected in three cases. These results suggest that sodium nitrite may induce embryotoxic effects even at low exposure levels. However, as the chick embryo model does not fully replicate human developmental conditions, these findings cannot be directly extrapolated to humans. Nevertheless, the results highlight the importance of regulating sodium nitrite intake and warrant further studies to elucidate its teratogenic potential.

Declarations

Funding: This study did not receive any funding or financial support.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Disclosure: We don't have any conflict of interest and any financial support.

Ethical approval: In accordance with the European Directive 2010/63/EU, ethical approval was not required for experiments involving chick embryos.

AUTHORSHIP CONTRIBUTION

Study conception and design: EA, ST

Data collection: EA, EBKO, DSA, DA, ST

Analysis and interpretation of results: EA, DSA, ST

Draft manuscript preparation: EA

Critical revision of the article: EA, ST

Other (study supervision, fundings, materials, etc...): EA

All authors (EA, EBKO, DSA, DA, ST) reviewed the results and approved the final version of the manuscript.

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Early and Effective Surgical Treatment of Ossified Cephalohematoma Using a Simple Technique

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ABSTRACT

AIM: To retrospectively analyze infants treated with early surgical management using the simple excision technique and discusses the outcomes in light of the existing literature.

MATERIAL and METHODS: Ten infants with OCH who underwent surgery were included in this study. The following parameters were recorded: age, sex, mode of delivery (normal vaginal delivery, cesarean section, vacuum extraction, or forceps delivery), presence of hematologic disorders or bleeding diathesis, comorbidities or anomalies, lesion localization, lesion size, duration of surgery and anesthesia, estimated blood loss, need for transfusion, postoperative complications, neurological findings, presence of additional pathologies, classification type, duration of hospital stay, and postoperative follow-up period.

RESULTS: The mean age of the 10 infants was 3.7 months, with a male-to-female ratio of 9:1. The OCH was located in the occipital region in one patient, the parietal region in eight patients, and bilaterally in the parietal region in one female infant. The lesion size ranged from 37 to 90 mm. The duration of surgery ranged from 40 to 80 min, while anesthesia lasted between 70 and 120 min. The mean intraoperative blood loss was 30 mL. All patients were discharged within an average of 2 days. According to Wang's classification, all cases were categorized as Type 1. The follow-up period ranged from 1 to 66 months.

CONCLUSION: Initial management of cephalohematoma should involve careful monitoring. However, when ossification occurs, early neurosurgical intervention is advisable. Early surgical treatment of OCH using the simple excision technique is a safe, effective, and minimally invasive approach associated with short operative time, minimal blood loss, and excellent cosmetic and functional outcomes. Therefore, early surgical management should be considered the preferred treatment option for OCH.

KEYWORDS: Cephalhematoma, Ossifying cephalhematoma, Birth trauma, Calvarial ossification

INTRODUCTION

Cephalohematoma is the collection of blood behind the scalp, specifically in the subperiosteal area (Figure 1) (9). It is caused by the buildup of blood between the bone and the periosteum as a result of several unfavorable occurrences or interventions during birth. Postnatal cephalohematoma affects 0.4%–2.5% of all live births. It is more common in first pregnancies, heavier newborns, those with

cephalopelvic disproportion, and following assisted births with forceps or vacuum extractors (2,3,6,13). It is more common in male babies than in females, but the explanation for this is uncertain (11). However, this could be explained by the fact that male infants are often larger.

Cephalohematomas may be single or numerous. The lesions are not hazardous and normally resolve spontaneously within a month. Subperiosteal blood is rarely resorbed, and osteo-

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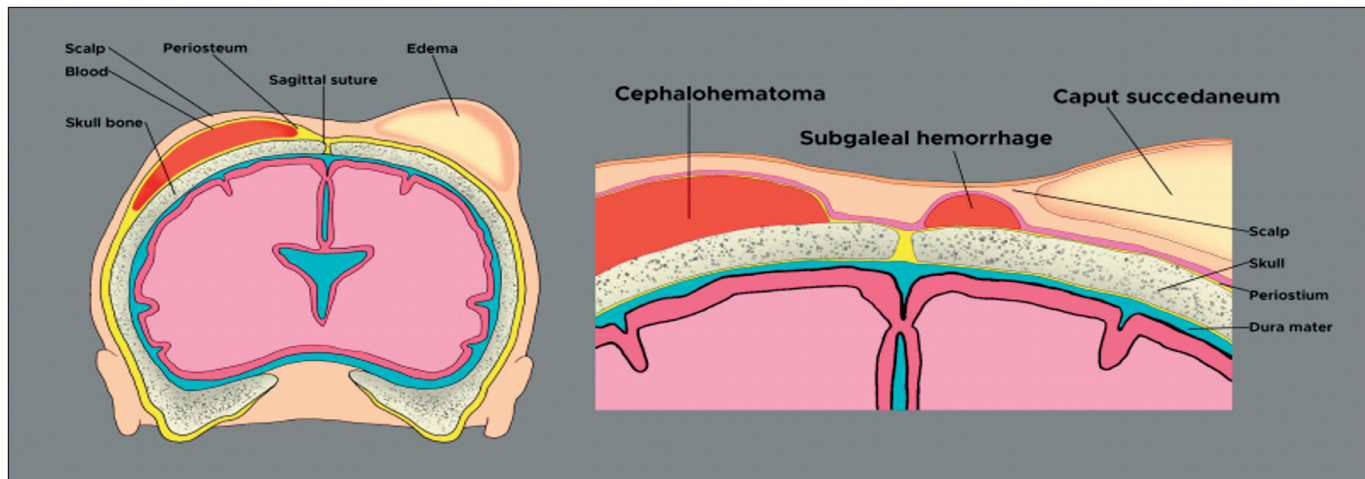


Figure 1: Cephalohematoma. Illustration depicting cephalohematoma, subgaleal hemorrhage, and caput succedaneum. The illustration (left) shows the scalp, skull, periosteum, dura mater, edema, sagittal suture, and edema. Contributed by C Rowe (Copyright © 2025, StatPearls Publishing LLC, used under the express permission statement stated in the publication) (9).

genesis at the hematoma's perimeter begins within the first month (3,8,14). The incidence of cephalic ossification is unclear; however, it is extremely uncommon (3).

Ossified cephalic hematoma (OCH) can result in significant calvarial asymmetry and cosmetic abnormalities. It can cause calvarial enlargement and compress the brain by pressing on the true bone with hematoma compression (2,13). In some cases, surgical intervention is required. The majority of procedures performed in the literature comprise complex and limited case reports in which cranioplasty repair techniques are used with excision of OCH and in place autograft (3,13).

This article presents a series of 10 cases that were successfully treated with early use of a simple and effective surgery using the technique of "simple excision and reattachment of periosteum by laying it on the bone." Despite the limited number of cases in our study, it is the third largest series in the literature with long-term results from the same surgeon who performed this surgical procedure.

■ MATERIAL and METHODS

The study comprised ten instances of OCH treated surgically by the same surgeon (NSB) in two different tertiary-referral institutions from 2019 and 2025. All of these had the simple OCH excision and reattachment of the periosteum by laying it on the bone technique as a surgical procedure, which is detailed below.

The patient's families provided a detailed anamnesis of their birth and postnatal periods as well as their publishing agreement. The size of the OCH was next calculated using 3D computed tomography (CT), followed by surgical planning (Figure 2). Cases having an OCH area of 3 cm or more in diameter and 1 cm or more in height were considered for surgery. Smaller OCH instances were omitted from surgery.

All patients received general anesthesia, and there were no perioperative difficulties; they were all monitored in the in-patient ward during the postoperative period. None of the patients needed blood transfusions. All patients were discharged after 1 to 3 days of hospitalization and follow-up, which included normal medical care. Patients were followed up in the first week, first month, and third month (Figure 3), except for six patients conducted during the previous year, 1 yr after discharge. In addition, post-3- to 5-yr follow-ups were acquired for four individuals who underwent early surgery. The anamnesis acquired from the patient's parents included information such as age, gender, birth type (typical vaginal delivery, vacuum or forceps use, or section), hematological disease, bleeding diathesis, the existence of comorbidities, and abnormalities. Furthermore, localization, size, operation time, duration of anesthesia, amount of blood loss, need for transfusion, presence of complications, neurological examination, presence of additional pathology, OCH classification type, hospital stay, and postoperative follow-up durations were documented (Table I).

Surgical Technique

The patient was positioned supine on the operating table, general anesthesia was delivered, and the side of the cranium was operated on because the OCH was on top, with the head turned to the opposite side. If the OCH was bilateral, the head was neutrally positioned in the midline, and the surgery was initiated by turning the head to the opposite side in sequence. A curvilinear incision is created around the whole OCH. The skin flap containing the epicranial aponeurosis is peeled away from the periosteum and elevated. The periosteum is meticulously separated as a single piece from the OCH within the width of the skin incision and reflected on the skin flap. A hole is bored from the apex of the OCH using a high-speed drill, revealing the ossified shell and the original calvarial bone underneath. The ossified shell is removed with a rongeur or Kerrison punch up to the edges, where it emerges from the

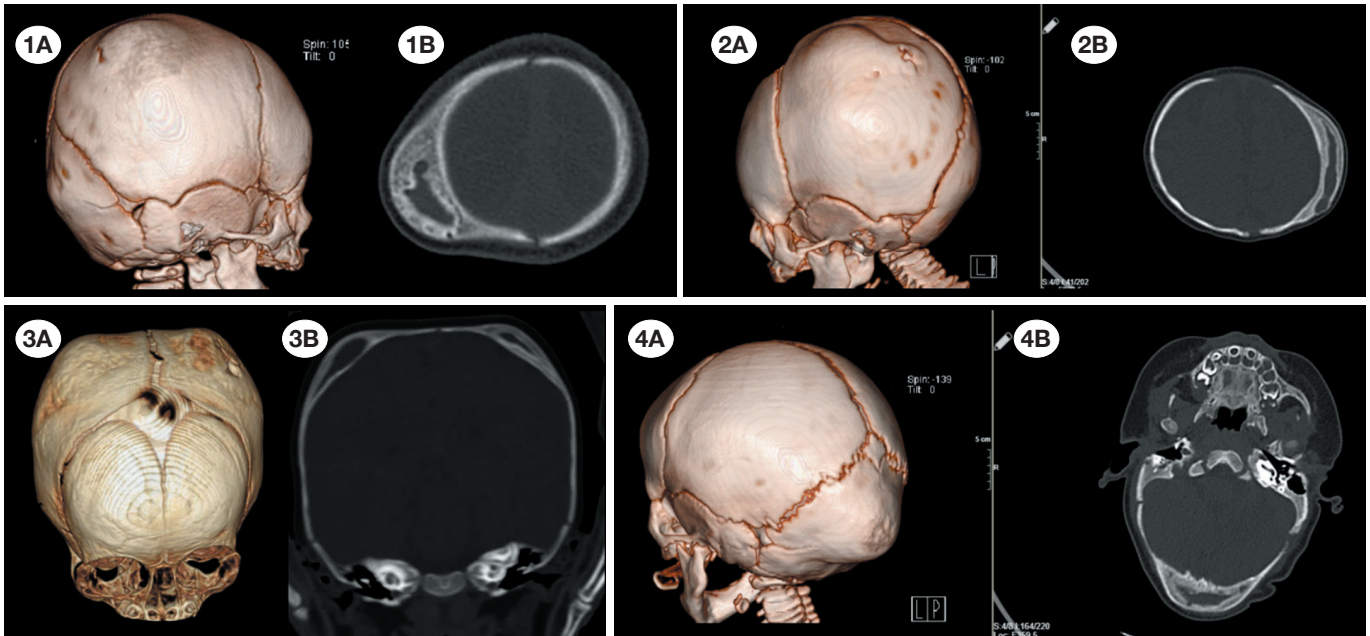


Figure 2: 3D and axial computed tomography images of the cases. 1A-B Right, 2A-B left, 3A-B bilateral and 4A-B occipital ossified cephalic hematoma.



Figure 3: Postoperative first month control of occipital OCH case (A), postoperative 3rd-month control of bilateral parietal OCH case (B).

calvarium. Curettage and aspiration are used to empty the old, compacted hematoma. Trimming with a high-speed drill flattens the protrusions and imperfections on the original calvarial bone, which is thin and uneven. As a result, a smooth contour is achieved without stepping outside the calvarium. Minimal bone hemorrhages are sealed with little particles of

bone wax. The periosteum, which has been carefully peeled off in one piece, is then applied to the smooth and nonbleeding calvarium, and primary closure is completed. After bleeding management is required, a drain is inserted, and the skin is closed. All patients are given prophylactic perioperative and early postoperative antibiotherapy (Figures 4 and 5).

Table I: Patient Assessment Chart

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age (month)	2	4	4	4	4	4	3	4	4	4
Gender	M	M	M	M	F	M	M	M	M	M
OCH localization	L P	R P	R P	R P	L / R P	R P	R P	O	L P	R P
OCH diameter (mm)	72	84	60	57	37 / 55	38	55	67	90	54
Operation time (minute)	40	60	60	65	80	50	60	50	75	50
Anesthesia time (minute)	70	90	120	100	120	90	90	100	110	90
Blood loss (ml)	20	30	25	35	40	30	25	30	30	20
Blood Transfusion(ml)	No	No	No	No	No	No	No	No	No	No
Complication	No	No	No	No	No	No	No	No	No	No
Length of stay (day)	2	3	1	2	1	2	2	2	1	2
Type of birth	NVD	NVD	NVD	NVD	NVD	NVD	NVD	NVD	NVD	NVD
Hematological disease	No	No	No	No	No	No	No	No	No	No
Neurological examination	N	N	N	N	N	N	N	N	N	N
OCH Type	Type 1	Type 1	Type 1	Type 1	Type 1	Type 1	Type 1	Type 1	Type 1	Type 1
Follow-up period (month)	66	55	44	38	12	10	6	5	4	1
Additional pathology	No	No	No	No	No	No	No	No	ES	No

M: Male, **F:** female, **P:** parietal, **O:** occipital, **NVD:** normal vaginal delivery, **ES:** esophageal stricture, **N:** normal, **R:** right, **L:** left.

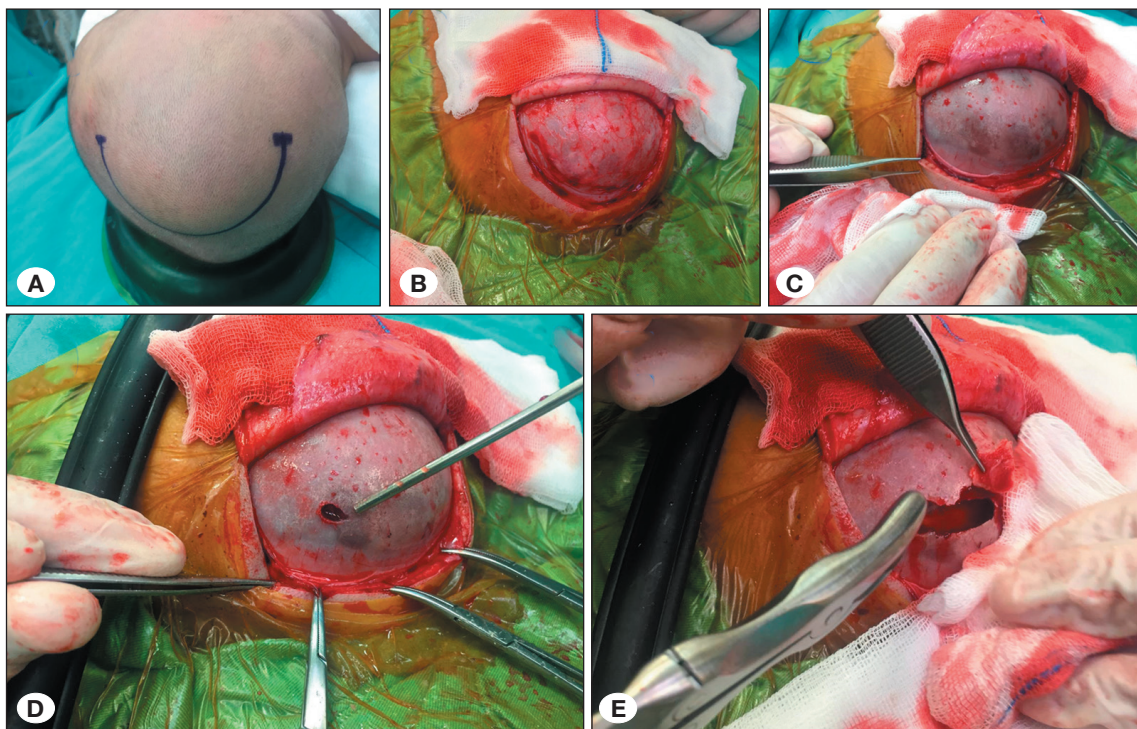


Figure 4: **A)** Marking the skin incision, **B)** incision of the skin and periosteum, **C)** view of the ossified cephalic hematoma (OCH) following periosteal elevation, **D)** drilling a burr hole on the OCH, **E)** excision of the OCH following enlargement of the burr hole using a rongeur.

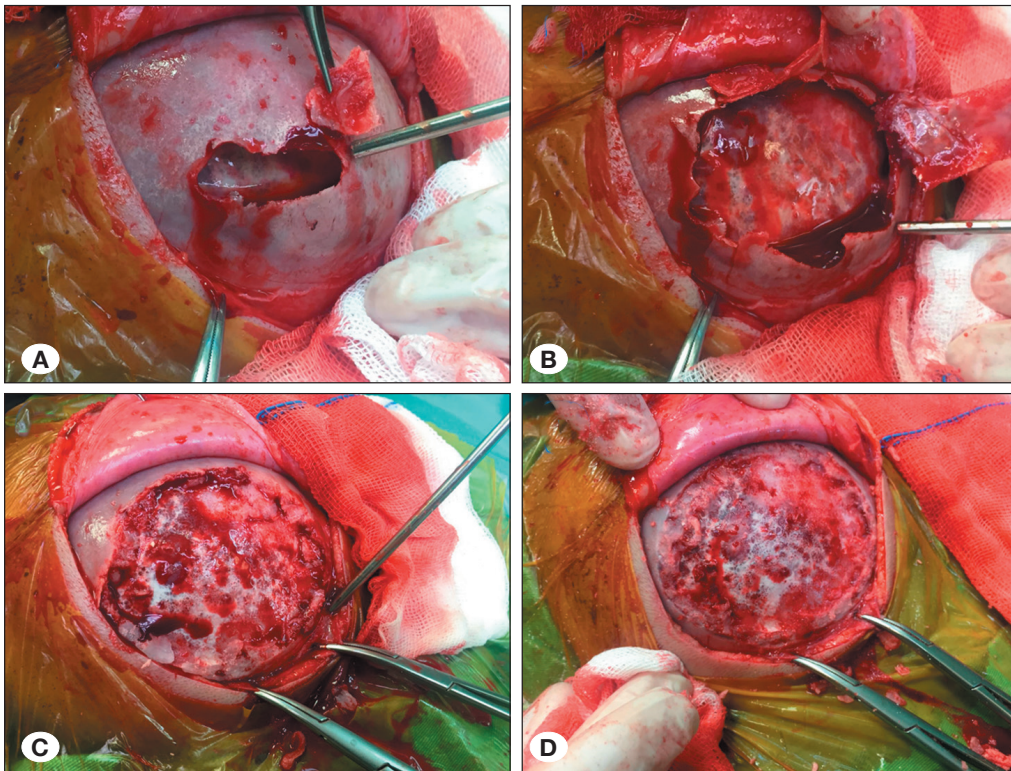


Figure 5: **A)** Blood products within the ossified cephalic hematoma (OCH), **B)** excision of the OCH and aspiration of blood components, **C)** excision of the OCH down to the true boundaries of the calvarial bone, showing thinning and irregularities on the underlying bone, **D)** the appearance of the stepped and irregular bone margins after removal.

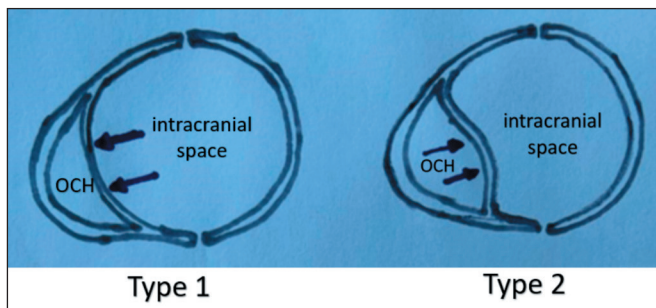


Figure 6: Wong classification; if the original calvarial bone under the ossified cephalic hematoma (OCH) retains its normal convex contour, it is classified as Type 1 (arrows); if it becomes depressed and concave, exerting pressure on the intracranial region, it is classified as Type 2 (arrows).

RESULTS

The average age of the 10 infants in our study was 3.7 months (range: 2–4 months), and the male-to-female ratio of 9:1. OCH was found in the parietal region in nine, with six having right-sided involvement, two having left-sided involvement, the only female having bilateral parietal involvement, and one having occipital involvement. The OCH diameters range from 37 to 90 mm, with an average of 61 mm. The longest operative time was 80 min in the bilateral case, whereas unilateral procedures ranged from 40 and 75 min (average: 60 min). An-

esthesia lasted from 70 to 120 min, with an average of around 100 min. Surgical blood loss varied between 20 and 40 mL, and no patient required a transfusion. There were no surgical or postoperative problems, and all patients were discharged from the hospital after an average of 2 days. It was found that all patients were born through normal vaginal delivery, with no birth trauma or the use of assisted delivery equipment such as vacuum or forceps. All patients had normal neurologic tests, and no hematologic illness was detected. Only one patient had an esophageal stricture diagnosed as an extra pathology. Laboratory testing, including a complete blood count and coagulation investigations, was within normal ranges. Cranial CT scans revealed that all patients were classified as Type 1 by Wong's (Figure 6). The infants' postoperative follow-up lengths ranged from 1 to 66 months (Figure 7), with an average follow-up period of 25 months (Table I).

DISCUSSION

Cephalohematomas are typically found in the parietal region and less frequently in the occipital region, but they can occur on any cranial bone. Unlike caput succedaneum and subgaleal hematomas, cephalohematomas are subperiosteal blood collections that are bordered by suture lines and do not cross the midline (5–9). In 5%–20% of cases, the cephalohematoma may be caused by a linear skull fracture. Intracranial damage is also rarely infrequent (6).

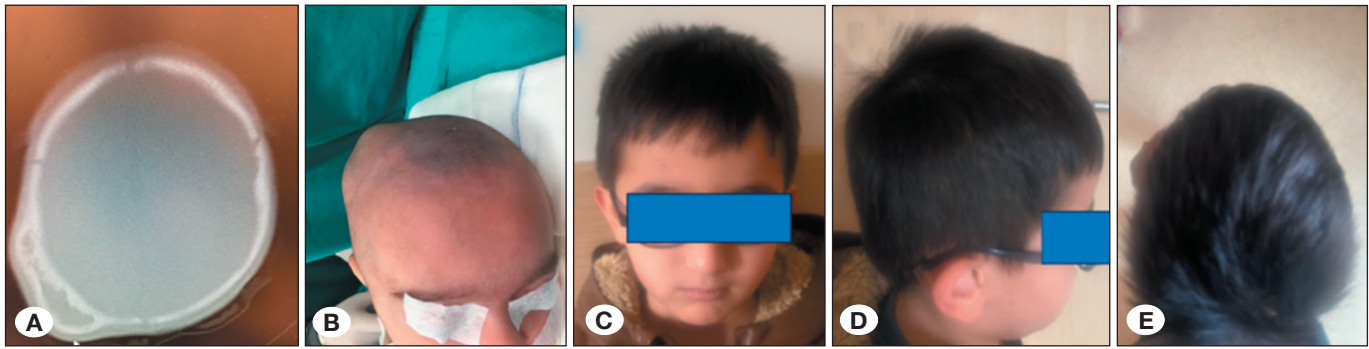


Figure 7: Right parietal ossified cephalic hematoma (OCH) belonging to the same patient; **A)** axial CT image, **B)** perioperative photograph, patient at 4-month-old, **C-E)** view from the front, right side, and vertex at the age 5 years.

The specific process of cephalic hematoma development after labor is unknown; however, it is assumed to be an injury induced by the strong and recurrent compression effect of the mother's pelvic bone on the bones of the baby's head, particularly the parietal bones. During birth, contractions and shearing cause bleeding of the diploic arteries into the subperiosteal layer (11). This mechanism also explains why cephalohematomas are more commonly found in the parietal bones. 90% of the patients in our series had a lesion in the parietal region, which is consistent with the literature. The literature reports a 10% rate of bilateral occurrence, and our series included only one female patient with bilateral OCH. One patient has been diagnosed with occipital OCH. This condition is compatible with occipital OCH, the second most common kind reported in the literature.

Cephalohematoma is treated and managed mostly by close monitoring and observation. Because clotted blood resorbs slowly, the enlargement of a cephalohematoma can last for weeks. A calcified cephalohematoma is characterized by a swelling over one or more bones that has been present since birth, initially soft and fluctuant, until firming up. It may be unilateral or bilateral. Cranial sutures establish the limits of cephalohematomas (5,9,13).

Resorption in cephalohematomas is often predicted to occur by the end of the first month or within 4–6 weeks at most (6). If resorption does not occur at this time, the cephalohematoma undergoes ossification, moving from the periphery to the center and producing a firmer calvarial bulge. A microscopic histopathological study of this surgically removed eggshell-like mass revealed dense, fibrous connective tissue with well-formed mature bone trabeculae. Hematopoietic tissue can be found in bone marrow voids surrounded by mature trabeculae. Cytokines and growth factors in the hematoma and osteogenic progenitor cells in the periosteum are hypothesized to contribute to the ossification process. These findings show that in cephalohematoma, rather than simple calcification, apparent ossification occurs beneath the periosteum and above the previous hematoma (6,8,14). Based on these findings, a more drastic surgical approach to ossified hematomas is advocated over a conservative approach (14). However, it should be highlighted that the osteogenesis in the subpericranium differs among patients (13).

A cranial CT scan (3D if possible) is recommended for patients whose cephalic hematoma does not resolve within 6 weeks. CT not only confirms the diagnosis but also eliminates other pathologies in the differential diagnosis (such as subgaleal hematoma, caput succedaneum, leptomeningeal cyst, or cranial meningocele). It also allows for the calculation of the lesions in all three dimensions, which helps to understand the status of the brain parenchyma and plan surgery (5,6,13). Cranial MRI was not required in any of our patients because the diagnosis was made using the 3D Cranial CT and standard anamnestic information.

Cranial CT reveals a double-contour bone picture in the OCH region, which contains soft tissue density. The OCH hardens, forming a clearly defined outer and inner layer of bone around the lesion (3,13). The infant's calvarium forms the inner layer of the OCH, whereas the outer layer is made up of ossified subpericranial bone from the elevated pericranium (6,13). The contour of the inner layer of the OCH might follow the convex curve of the skull or become concave, compressing the intracranial region. Wong categorizes OCHs into two kinds. According to Wong's classification, if the original calvarial bone beneath the OCH retains its normal contour, it is categorized as Type 1, and if it becomes depressed and concave, creating intracranial pressure, it is classified as Type 2 (Figure 6) (13). Every instance in our study was classified as Type 1. As a result, basic excision surgery and periosteum fixation by laying it over the afflicted calvarium were sufficient.

There has been a controversy about whether to treat cephalohematoma conservatively or with early surgical intervention. Some writers documented spontaneous resorption not just in the early phase, but even in instances of OCH followed up for 1 yr or more, and thus suggested cautious treatment. Daglioglu et al. described two cases of calcified cephalic hematoma, which resolved spontaneously after 10 and 16 months (4). They advocated conservative therapy and follow-up. In another case report, Yoon described spontaneous OCH resorption in a 9-month-old infant (15). Üçer et al. reported an ossification rate of approximately 10% in their series of 94 cases of cephalic hematoma >50 mm in size and suggested that these cases were completely or partially resorbed after 1 yr of follow-up, implying that early intervention in the routine treatment of these cases was unnecessary (11).

However, simply seeing OCH cases raises the mental, psychological, and financial load on families due to the stress produced by the unpredictable outcome of resorption and the necessity for recurrent hospital visits (6,14). Furthermore, many physicians believe that early intervention, such as puncture drainage or surgical procedures, may be required to correct cosmetic deformities, confirm the diagnosis, prevent restricted brain growth, lower the risk of elevated intracranial pressure, and avoid secondary craniosynostosis (2,6,8,13,14).

Although some publications recommend against puncturing cephalic hematomas due to the risk of infection and late-onset anemia (5,6,9), others report successful treatment without infection by performing single or multiple punctures for the hematoma in the early stages. In a research by Brichtová, 109 out of 123 cephalohematoma patients with nonossified lesions received repeated serial punctures (1–7 times), resulting in permanent remission without the need for additional surgical intervention, and no infections were reported. In the remaining 14 cases, he reported that the cephalohematomas had ossified and required neurosurgical surgery (2). Blanc et al. performed cephalic hematoma evacuation by puncture with local anesthetic under operating room setting in 68 newborns in the early postnatal period (between 15 and 30 days) and found the treatment safe (1). There were no complications noted during or after the procedure. Indeed, attitudes toward puncture treatment have shifted in recent years. Some authors believe that following aseptic principles and conducting early punctures in large infant cephalohematomas can help prevent infection (14). Additionally, cephalohematomas can be linked to hyperbilirubinemia and cerebral bleeding. It has been proposed that puncture drainage of a cephalohematoma may aid in relieving intracranial problems (14).

However, once ossification occurs in a cephalohematoma, puncture is no longer an option. In terms of open surgical interventions to be conducted in these circumstances, the literature contains few surgical series, most of which were undertaken in the late period and included large craniotomies and cranioplasty surgeries. There are reports that in surgeries conducted in the latter phases, when ossification has advanced over months or years, more sophisticated, prolonged, and relatively significant blood loss procedures, such as craniotomy, craniectomy, and cranioplasty, are needed (3,5,6,10,13).

Chung et al. performed a craniotomy and cranioplasty operation in two of their three instances with calvarial bone depression and reported effective repair (3). Wong et al. presented three examples of Type 2 OCH in their publication and explained the cranioplasty surgical procedure method (13). According to an article containing a large series in which Ulma et al. published their 25 yr of experience, surgery was performed in 30 cases with an average age of 8.6 months out of 72 cephalohematoma patients included in the study, and 70% of these patients required bone grafts, and 26.7% required blood transfusions (10).

Despite these late cranioplasty surgeries, Jang et al. described for the first time in 2007 the early “simple excision and periosteal reattachment” technique in a 3-month-old case (7), which we also used in our cases, and concluded that complex

cranioplasty surgeries may be unnecessary in OCH cases. In 14 of Brichtová’s 123 cases of OCH (2), he performed a surgery consisting of simple excision of the ossified layer with neurosurgical intervention at an early period of 1–3 months and closure of the periosteum and skin in three layers after calvarial correction with a high-speed drill, with excellent long-term outcomes. Among these articles, Jang et al.’s study is the most similar to our strategy (7), and the first to detail a 3-month case treated using our manner. Brichtová’s series is especially noteworthy because it is the second largest, with 14 cases treated using a similar procedure with outstanding results. In 2025, Xi et al. published the largest series in the recent decade, performing a single puncture and aspiration in 83% of 75 nonossifying cephalohematoma patients and treating 98 OCH cases with the same neurosurgical surgery without cranioplasty (14). Our series, albeit being limited to 10 patients, is the third largest after these investigations and employs the identical surgical method described in the literature. Our experience and findings support the previous three authors’ conclusions. Furthermore, the authors state that neonatal cephalohematoma puncture and aspiration is a safe and effective way to prevent ossification. They also urge early neurosurgical intervention for OCH as it is less technically demanding and reduces the risk of severe surgical trauma (14). Furthermore, postponing surgery may result in resorption, thinning, and irregularity of the original calvarial bone forming the inner layer, increasing compression on the brain parenchyma. This condition, which may demand more sophisticated and lengthy cranioplasty procedures, also raises the possibility of surgical consequences such as dural and parenchymal injury. Vigo et al. described the example of an 11-year-old female who had a chronic ossified OSH that resulted in skull malformation and delayed electroencephalography (EEG). The female underwent surgical removal of her OSH for aesthetic reasons. The EEG abnormalities were resolved following surgery, supporting the theory that there is a link with “brain compression” from the OSH. OSH-related skull malformation necessitates a delayed follow-up period (12).

For these reasons, early surgical intervention is encouraged as it prevents the need for cranioplasty and other difficult surgeries, improves cosmetic outcomes, and is simpler and safer. Our experience fits this perspective (2,14).

Dural injury might arise with the repair of patients’ thinning original calvarial bone surface. Infection and unexpected bleeding are two possible complications. There were no difficulties in our series. However, the small number of cases limits statistically significant findings. Increasing the number of cases may increase the risk of problems.

■ CONCLUSION

When a cephalohematoma is diagnosed, the patient should be closely monitored for the first month. However, if ossification occurs, early neurosurgical intervention should be considered. This method is easier in the early stages and provides good cosmetic outcomes without the need for complex surgical procedures such as craniotomy and cranioplasty. Early surgical treatment of OCH with the described method is a

straightforward, safe, and successful procedure with a short operating time and little blood loss. As a result, OCH patients should have a more drastic therapy strategy and early surgical interventions.

Declarations

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Availability of data and materials: The data that support the findings of this study are not publicly available due to [reason why data are not public; their containing information that could compromise the privacy of research participants] but are available from [the corresponding author upon reasonable request]

Disclosure: The authors declare that there are no conflicts of interest related to this study.

Ethics approval and consent to participate: This study was performed by the Declaration of Helsinki. This human study was approved by the ethics committee of the Kanuni Sultan Suleyman Training and Research Hospital (Document No: 2025.03.73, Date: 13 March 2025).

AUTHORSHIP CONTRIBUTION

Study conception and design: NSB, AO, AT

Data collection: NSB, AT, EC, ES, LA, SD, IB, SC

Analysis and interpretation of results: NSB, AO, AT

Draft manuscript preparation: NSB, IB

Critical revision of the article: NSB, AO, IB

Other (study supervision, fundings, materials, etc...): NSB, AT, EC, ES, LA, SD, SC

All authors (NSB, AO, AT, EC, ES, LA, SD, IB, SC) reviewed the results and approved the final version of the manuscript.

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Nomogram-Based Independent Risk Factor Analysis and Recurrence Prediction for Chronic Subdural Hematoma After Single Burr Hole Drainage

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ABSTRACT

AIM: To identify independent risk factors and propose a predictor scoring system in chronic subdural hematoma (CSDH).

MATERIAL and METHODS: Through retrospective analysis, we analyzed the data from 279 patients with CSDH from 2010 to 2020. Independent risk factors for recurrence were identified through univariate and logistic regression analyses. A risk-scoring model was developed using a nomogram, which was applied to all patients considering postoperative recurrence as a target. ROC curve analysis was done to assess the accuracy of the estimated scoring system.

RESULTS: The results revealed significant differences in Glasgow outcome scale (GOS), brain re-expansion after drainage, postoperative use of atorvastatin, side and density of hematoma, the history of trauma, hematoma separated, History of diabetes, and midline shift between patients with recurrent CSDH and non-recurrent. A scoring parameter was developed through a nomogram based on a combination of scored risk factors that were significantly higher in patients with recurrent CSDH (P-value <0.001). The sensitivity and specificity of the predictor score confirmed its efficacy in predicting the recurrence risk of CSDH (sensitivity: 70.5%, specificity: 45.9 %; cutoff: 0.74 and 95% confidence interval: 6.57-0.74).

CONCLUSION: A scoring system was finally obtained for the prediction of postoperative recurrence risk. The establishment of a predictor scoring system will help clinicians better monitor and adopt efficient management strategies for high-risk patients.

KEYWORDS: Chronic subdural hematoma, Burr hole drainage, Recurrence rate, Glasgow coma scale, Prognostic risk, Grading system.

ABBREVIATIONS: CSDH: Chronic subdural hematoma, GOS: Glasgow outcome scale, GCS: Glasgow coma scale, ROC: Receiver operating characteristic, AUC: Area under the curve, CT: Computed tomography, MRI: Magnetic resonance imaging, SDH: Subdural hematoma, PreHTh: Preoperative hematoma thickness, PostHTh: Postoperative hematoma thickness, mRS: Modified rankin scale, MGS: Markwalder grading scale, IQR: Interquartile range, CI: Confidence interval

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■ INTRODUCTION

Subdural hematoma (SDH) refers to an intracranial hemorrhage when bleeding occurs between the dura mater and arachnoid mater of the meninges (10). This condition, often due to traumatic brain injury or non-traumatic injuries caused by anticoagulant medication and spontaneous bleeding factors, can increase intracranial pressure and cause brain damage. CSDH develops over weeks or months after a brain injury and usually has a better prognosis (10).

Symptoms of a subdural hematoma are usually not specified. Patients complain of complicated manifestations such as headaches, visual and cognitive difficulties, lethargy, numbness in limbs, and sometimes nausea, vomiting, or confusion (37). The thickness of the hematoma, the degree of mass effect (such as midline shift or compression of the brain structure) on the brain, and the presence of edema are considered in imaging results (29). In subdural hematoma, the density of extra-axial fluid collection between the inner layer of the skull and the brain surface varies from hyper to hypodense in acute, subacute, and CSDH (26).

Recent studies have demonstrated that not all CSDH cases are associated with trauma, especially in older patients, with a relatively higher proportion of non-trauma-related patients. However, not all CSDH are transformed by acute subdural hematoma (5,27).

Considering global aging, it is necessary to explore the risk factors that increase the CSDH recurrence rate. Assessing the risk of postoperative recurrence of CSDH is clinically important (17,30,35,36). The recurrence rate of CSDH after burr hole drainage ranges from 4% to 38%, and the postoperative mortality rate of the cases ranges from 1.8% to 32% (8,40).

Several studies explore CSDH recurrence risk factors after hematoma drainage, including gender, age, trauma history, anticoagulant or antiplatelet use, preoperative Glasgow coma scale (GCS) which evaluates consciousness levels from 3 to 15, diabetes mellitus, hypertension, bilateral hematoma, hematoma volume, midline shift, and density (1,3,7,12,13,15,22,23,25,34,38,39). Age is one of these factors, so some studies have reported aging as a risk factor for CSDH recurrence, while other studies have reported that aging could be a protective factor against it. The scoring system will provide clinical grounding for the perioperative management strategy of CSDH, reduce the postoperative recurrence, mortality, and morbidity rate, and improve the postoperative quality of life for patients (7).

Currently, no scoring system predicts CSDH recurrence; studies focus on risk factors without a cohesive model for unilateral and bilateral cases. This gap hinders clinicians from stratifying patients by recurrence risk and optimizing care. This study aims to develop a grading model based on independent risk factors from a retrospective analysis of patients treated with single-burr hole drainage, providing a tool to improve management and reduce recurrence rates.

■ MATERIAL and METHODS

Study Design

We retrospectively analyzed clinical data of all patients with CSDH admitted to the Seventh Medical Center of the PLA General Hospital from 2010 to 2020. This study was approved by the Ethics Committee of the Seventh Medical Center of the PLA General Hospital (approval number: 2021-133, approval date: November 14, 2021). All procedures were performed in accordance with the relevant guidelines and regulations of the Ethics Committee. All patients provided informed consent for participation and the use of anonymized data. Inclusion criteria were patients aged 18–96 years who underwent burr hole drainage for CSDH, with complete medical records including preoperative, intraoperative, and postoperative data, documented follow-up for recurrence, and at least one postoperative imaging study to evaluate recurrence. Exclusion criteria included age <18 years, craniotomy within the past 6 months, acute subdural hematoma, incomplete medical records, lack of follow-up, or patients undergoing other neurosurgical procedures except burr hole drainage. Postoperative imaging findings were used to confirm recurrence, which was defined based on hematoma re-accumulation on imaging combined with clinical symptoms (34).

Imaging Analysis

In patients with clinical symptoms, the diagnosis of CSDH was confirmed using documented results of cranial CT or MRI. The important finding in these two techniques included the age of the hematoma that can be estimated through T1 and T2-weighted images. In this case, hypo-, iso-, or hyper-density is noted due to the presence of blood, with CSDH typically appearing T1-hypointense compared to gray matter and showing variable T2 signal characteristics. The degree of midline shift reflects the mass effect and raised intracranial pressure associated with subdural hematomas. Brain herniation signs, such as subfalcine or uncal herniation, are also relevant. Skull fractures are assessed, along with various hemorrhage types, including intraparenchymal and epidural. Other findings include contusions, calcifications, the origin and side of the hematoma, and the presence of residual blood products post-surgery. Changes in burr hole drainage are monitored after surgery (16).

Surgical Procedure

The surgical intervention followed standard protocol. Burr hole surgery with twist-drill drainage is indicated for symptomatic patients with CSDH. Indications for burr hole drainage include: a) Clinical symptoms of subdural hematoma; b) Hematoma thickness over 10 mm and/or midline shift exceeding 5 mm; c) Midline shift from mass effect of hematoma causing consciousness disturbance, hemiplegia, paresthesia, seizures, and other neurological dysfunction; d) Progressive hematoma volume increase after conservative treatment. In bilateral subdural hematoma cases, the choice of unilateral or bilateral drainage depends on the thickness of the hematoma and associated clinical symptoms. If one side has a hemato-

ma thickness over 10 mm and causes symptoms, unilateral drainage is performed; if both sides cause symptoms, bilateral drainage is indicated (23).

Anesthesia was selected based on the patient's condition and cooperation. The patient was positioned supine, and the thickest part of the hematoma was chosen for incision based on preoperative CT/MRI. A hole was drilled into the skull, and a cross-shaped incision exposed the dura mater. The hematoma envelope was cut open for slow release, followed by irrigation with warm saline until clear. A drainage tube was placed in the hematoma cavity and connected to a closed drainage device, with the catheter entering posteriorly to the anterior part and the tip placed in the frontal region to reduce hematoma recurrence (22,38,39). The drainage tube's direction and length were considered to place the front end in the hematoma cavity, protecting the brain parenchyma from drainage damage. Closed drainage was performed slowly and continuously post-operation, with daily monitoring of drainage volume and fluid characteristics. Postoperative management included atorvastatin to potentially reduce recurrence rates at a dosage of 20 mg daily. Patients already on statin treatment preoperatively continued in the postoperative statin group for consistency and to maintain potential therapeutic benefits during the perioperative period.

CT scans confirmed brain re-expansion, leading to drainage tube removal when daily volume fell below 30 ml. Monitoring pneumocephalus post-surgery is crucial for assessing outcomes, though our study lacked precise measurement, an aspect future research should address (14,18,20,23). The brain re-expansion rate assesses treatment effectiveness and recurrence risk in subdural hematoma. It calculates brain tissue volume changes before and after surgery. Factors affecting the re-expansion rate include cerebral atrophy, age, and injury duration.

Recurrence Follow-Up

All patients were followed up for at least 6 months after discharge. During follow-up, if the patient shows aggravation of the existing symptoms or new signs of neurological dysfunction, and the CT scan shows more hematoma on the surgical side and requires a second operation, then the patient is diagnosed with CSDH recurrence. In our study, hematoma recurrence was defined as the reaccumulation of subdural blood or fluid at the original hematoma site, requiring subsequent surgical intervention within six months post-initial surgery.

Data Collection

General data included were gender, age, trauma history, past medical history (history of hypertension, hyperlipidemia, diabetes), clinical symptoms (high intracranial pressure symptoms such as headache, nausea, and vomiting, focal neurological disorders such as a decline in the muscle strength or sense of numbness, advanced neurological disorders, bladder, and bowel dysfunction, mental disorders and seizures), history of anticoagulant or antiplatelet therapy, alcoholism, the interval between onset of symptoms to operation, GCS score at admission, postoperative use of atorvastatin tablets, injection of urokinase into the hematoma cavity, drainage time, Glasgow Outcome Scale (GOS) score at discharge.

GOS is a useful tool for evaluating the outcome of patients with brain injury; categorizing ranges from 1. full recovery, 2. partial recovery, 3. no change in condition, 4. death, and 5. progressive deterioration and aggravation. GOS helps physicians predict the long-term outcomes of patients with brain injuries. A lower GOS score indicates poorer neurological function and a higher likelihood of recurrence due to factors such as increased intracranial pressure and larger subdural space, which predispose patients to hematoma reaccumulation. The imaging data include preoperative hematoma thickness (PreHTh) and postoperative hematoma thickness (PostHTh) (thickness of the thickest plane of the axial image), midline shift (measured at the level of interventricular foramen on axial image), separated and delaminated hematoma, brain atrophy, hematoma density (including hypodense, isodense, hyperdense and mixed density), hematoma (unilateral or bilateral) and the extent of brain re-expansion after drainage. The extent of brain re-expansion after drainage, based on the CT scan before the drainage tube was removed, was calculated as follows: $(\text{PreHTh} - \text{PostHTh}) / \text{PreHTh} \times 100\%$ (32).

The clinical and imaging data of all patients were independently evaluated by two neurosurgeons and one neuroimaging specialist, all of whom were blinded to the study outcomes. For patients with bilateral hematomas, hematoma density was determined based on the operative side. In cases of bilateral drainage, density was assessed according to the hematoma on the recurrent side. If recurrence occurred on both sides, the side with the thicker hematoma was considered the reference, as greater thickness and higher or mixed density are more likely to indicate bleeding tendency and risk of recurrence.

Statistical Analysis

Statistical analyses were conducted with Statistical Package for Social Sciences (SPSS, IBM SPSS Statistics Inc., Chicago, IL, Windows version 21.00). All continuous variables were assessed for normality with the Kolmogorov-Smirnov normality test. Variables with normal distribution are presented as means $\pm$ standard deviation ($\bar{x} \pm s$), and variables with skewed distribution are presented as median (Interquartile range, IQR). The nominal variables and also ranked variables were expressed in terms of count (%), and the univariate analysis was performed with Fisher's Exact Chi-Square (χ^2) test. Continuous variables were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$), and their differences between patients with recurrence SDH and non-recurrence were compared using the Student's *t*-test. To estimate probable confounding factors on recurrence risk, multivariable logistic regression analysis considering the aforementioned test results was performed using variables with a *p*-value < 0.1 . A nomogram scoring system for predicting the recurrence rate was constructed using the Orange data mining toolbox (version 3.36.2) based on the ranked top important factors that were determined from the univariate analyses. Following the nomogram construction, a scoring predictor parameter was developed. Since the results of the Kolmogorov-Smirnov normality test indicated skewed distribution, the difference in predictor scores between patients with recurrence of SDH and lack of recurrence was compared

using the Student's t-test. Finally, a receiver operating characteristic (ROC) curve was created from the predictor score obtained from the nomogram. The area under the curve (AUC) and 95% confidence interval (CI) of the predictor scores were calculated. The data from the Second Affiliated Hospital of Anhui Medical University was used as external validation and not included in any analysis of nomogram development; the nomogram was finally tested on that dataset to compare the results. For all statistical analyses, the p-values less than 0.05 were considered significant.

RESULTS

General Characteristics

A total of 397 patients with CSDH were admitted to the Seventh Medical Center of the PLA General Hospital between 2010 and 2020. Ninety-six patients received medication, but no burr hole drainage was performed. Six patients died after surgery during hospitalization, and 16 patients were lost

during follow-up or incomplete data collection. Therefore, these cases were excluded from the research. Finally, 279 patients (males: 233 [83.5%]; females: 46 [16.5%]) who met the inclusion criteria and all of them who received burr hole external drainage surgery were screened out for the study. The average age of all patients was 68.7 ± 16.1 years (age range: 18-96). A total of 32 patients had CSDH recurrence after drainage, with a recurrence rate of 11.5%. There were 25 males and seven females among the recurrent patients. There were 171 cases (61.3%) of unilateral hematoma and 108 cases (38.7%) of bilateral hematoma, including 14 cases of unilateral hematoma recurrence and 18 cases of bilateral hematoma recurrence.

Univariable Analysis

The clinical and imaging data of all patients were analyzed by univariate analysis. The results of the univariate analysis of all data are shown in Table I. The patients with history of trauma and diabetes had a higher recurrence rate ($p=0.01$ and

Table I: Univariate Analysis of CSDH Recurrence After Drainage

Factors		Number of patients (%)		p-value
		Recurrence 32 (11.5)	No recurrence 247 (88.5)	
Gender	Male	25 (10.7)	208 (89.3)	0.655
	Female	7 (15.2)	39 (84.8)	
Age, mean $\pm$ SD (years)		69.97 $\pm$ 15.15	68.37 $\pm$ 16.62	0.747
History of trauma	Yes	27 (13.6)	171 (86.4)	0.010
	No	5 (6.2)	76 (93.8)	
Hypertension	Yes	17 (12.8)	116 (87.2)	0.745
	No	15 (10.3)	131 (89.7)	
Diabetes mellitus	Yes	10 (18.5)	44 (81.5)	0.039
	No	22 (9.8)	203 (90.2)	
Hyperlipemia	Yes	3 (13.6)	19 (86.4)	1.00
	No	29 (11.3)	228 (88.7)	
Alcoholism	Yes	8 (14.5)	47 (85.5)	0.220
	No	24 (10.7)	200 (89.3)	
Antiplatelet or anticoagulant therapy	Yes	9 (12.9)	61 (87.1)	0.848
	No	23 (11)	186 (89)	
Headache and vomiting	Yes	29 (12.1)	211 (87.9)	0.479
	No	3 (7.7)	36 (92.3)	
Advanced neurological disorder	Yes	10 (12.2)	72 (87.8)	0.637
	No	22 (11.2)	175 (88.8)	
Focal neurological disorders	Yes	23 (11.9)	171 (88.1)	1.00
	No	9 (10.6)	76 (89.4)	
Epileptic seizure	Yes	2 (18.2)	9 (81.8)	0.427
	No	30 (11.2)	238 (88.8)	

Table I: Cont.

Factors		Number of patients (%)		p-value
		Recurrence	No recurrence	
		32 (11.5)	247 (88.5)	
Bladder and bowel dysfunction	Yes	1 (6.7)	14 (93.3)	0.709
	No	31 (11.7)	233 (88.3)	
Mental disorders	Yes	2 (22.2)	7 (77.8)	0.303
	No	30 (11.1)	270 (88.9)	
GCS score	3-8	3 (30)	7 (70)	0.149
	9-12	2 (5.9)	32 (94.1)	
	13-15	27 (11.5)	208 (88.5)	
The interval between injury and onset of symptoms (month)	< 1	15 (12.2)	108 (87.8)	0.463
	1- 3	14 (12.7)	96 (87.3)	
	> 3	3 (6.5)	43 (93.5)	
Injection of urokinase into the hematoma cavity	Yes	2 (25)	6 (75)	0.119
	No	30 (11.1)	241 (88.9)	
Drainage time (days)		3.78±2.15	3.22±1.92	0.256
Postoperative use of atorvastatin	Yes	2 (2.4)	80 (97.6)	< 0.001
	No	30 (15.2)	167 (84.8)	
GOS score at discharge	5	5 (3.8)	125 (96.2)	<0.001
	4	19 (14.4)	113 (85.6)	
	3	4 (57.1)	3 (42.9)	
	1-2	4 (40)	6 (60)	
Hematoma thickness,mean±SD (cm)		2.31±0.67	2.16±0.73	0.212
Midline shift, mean±SD (cm)	0	3 (7.1)	39 (92.9)	0.058
	<0.5	11 (11.5)	85 (88.5)	
	0.5-1	13 (13.5)	83 (86.5)	
	1-2	4 (9.1)	40 (90.9)	
	>2	1 (100)	0 (0.0)	
Hematoma separated and delaminated	Yes	7 (30.4)	16 (69.6)	0.029
	No	25 (9.8)	231 (90.2)	
Brain atrophy	Yes	17 (14.3)	102 (85.7)	0.142
	No	15 (9.4)	145 (90.6)	
Hematoma density	Hypodense	0 (0.0)	26 (100)	0.049
	Isodense	10 (6.9)	135 (93.1)	
	Hyperdense	1 (10)	9 (90)	
	Mixed density	21 (21.4)	77 (78.6)	
Extent of brain re-expansion after drainage	>75%	4 (3.1)	123 (96.9)	<0.001
	50%-75%	20 (14.9)	114 (85.1)	
	25%-50%	6 (50)	6 (50)	
	<25%	2 (33.3)	4 (66.7)	
Side of hematoma	Unilateral	14 (8.2)	157 (91.8)	0.003
	Bilateral	18 (16.7)	90 (83.3)	

Note: Significant P-values are represented in bold type. **GCS**: Glasgow Coma Scale, **GOS**: Glasgow Outcome Scale.

Table II: Multivariate Regression Analysis of CSDH Recurrence After Drainage

Factors	Adjusted OR	95%CI	p-value
Trauma history	5.383	1.024-28.280	0.047
Diabetes mellitus	0.843	0.245-2.907	0.787
Postoperative use of atorvastatin	0.139	0.027-0.710	0.018
GOS score at discharge	0.854	0.045-1.389	0.013
Hematoma side	0.089	0.022-0.362	0.001
Midline shift	7.253	1.546-24.015	0.123
Hematoma density	0.869	0.281-2.692	0.683
Hematoma separated and delaminated	6.557	1.328-32.377	0.021
Extent of brain re-expansion after drainage	0.78	0.049-12.519	0.01

Significant *p* values are in bold type. **GOS:** Glasgow Outcome Scale, **CI:** Confidence interval, **OR:** Odds Ratio.

Table III: Point Assignment and Prognostic Score for Recurrence of Subdural Hematoma

Variables and prognostic scores	Score	Estimated recurrence risk (%)	Variables and prognostic scores	Score	Estimated recurrence risk (%)
GOS			Density of hematoma		
Fully recovered	-0.82	0	Hyperdense	0.18	14
Partial recovered	0.3	14	Isodense	-0.47	0
Death	-	-	Mixed density	0.43	31
Unchanged condition	1.79	55	Hypodense	0.46	31
Progression and aggravation	2.89	77	Diabetes mellitus		
Brain re-expansion after drainage			Yes	0.62	31
> 75 %	- 1.42	0	No	-0.18	0
50 – 75 %	0.09	14	Midline shift		
25 – 50 %	1.28	55	<0.5	-0.43	0
< 25 %	1.65	55	0.5-1.5	0.06	14
Post-surgery medication			1.5-2.5	0.32	14
Yes	-1.28	0	>2.5	-0.18	0
No	0.31	14	Total predictor score*		
Side of hematoma			-1.5-0		0
Left	-0.74	0	0.01-0.99		14
Right	-0.21	0	1-1.99		31
Bilateral	0.5	14	2-2.99		55
Whether to separate			3-3.99		77
Yes	1.03	31	4-4.99		90
No	-0.11	0	> 5		100
History of trauma					
Yes	0.24	14			
No	-0.83	0			

*For score-recurrence estimation please refer to nomogram (Figure 1)

$p=0.039$, respectively), The GOS score at discharge was significantly lower in the recurrence group than in the no recurrence group ($p<0.001$), midline shift was significantly higher in the recurrence group ($p=0.058$), hematoma separated and delaminated ($p=0.029$), low extent of brain re-expansion after drainage ($p<0.001$), bilateral hematoma ($p=0.003$) and no postoperative use of Atorvastatin ($p=0.001$) resulted in a higher recurrence rate. At last, patients with hyperdense and mixed-density hematoma had a higher recurrence rate than those with iso and hypodense hematoma ($p=0.049$).

Multivariate Regression Analysis

Logistic multivariate regression analysis was performed to analyze the nine recurrence risk factors, which were significantly different in the univariable analysis (Table II). The results showed that the history of trauma ($p=0.047$), no use of atorvastatin postoperatively ($p=0.018$), low GOS at discharge ($p=0.013$), bilateral hematoma ($p=0.001$), hematoma separated and delaminated ($p=0.021$), and low extent of brain re-expansion after drainage ($p=0.01$) are independent risk factors in predicting the CSDH recurrence after drainage.

Establishing a Risk Scoring System for CSDH Recurrence After Drainage

According to the outcomes of Fisher's Exact Chi-Square (χ^2) test, a nomogram for scoring a predictor model was con-

structed to predict the probability of the recurrence of SDH (Figure 1).

In this model, a statistical scoring parameter was adjusted to each variable that had already shown a significant effect on the recurrence of SDH. The scoring predictor model is presented in Table I. Using this scoring system, a total of 279 patients were scored. The resulting grading scores and the corresponding number of recurrent patients, along with the recurrence rate, are calculated (Table III).

The results showed that the probability of recurrence rate of SDH increases in line with the predictor score. In addition, a significant difference was observed where predictor scores were compared between patients with recurrence of SDH and non-recurrence individuals, with a $p<0.001$ (Figure 2). The results showed that the score was -0.5 ± 0.66 in the recurrent group and -0.91 ± 0.63 in the non-recurrent group with $p<0.001$ (Table IV).

ROC Curve Analysis

The predictor score for recurrence of SDH obtained from the nomogram was applied in the ROC curve for analysis. According to the results of ROC, the area under the curve (AUC), confidence interval (CI), cutoff value, sensitivity, and specificity were calculated (Figure 3). The data from Second Affiliated Hospital of Anhui Medical University, which consisted of 64

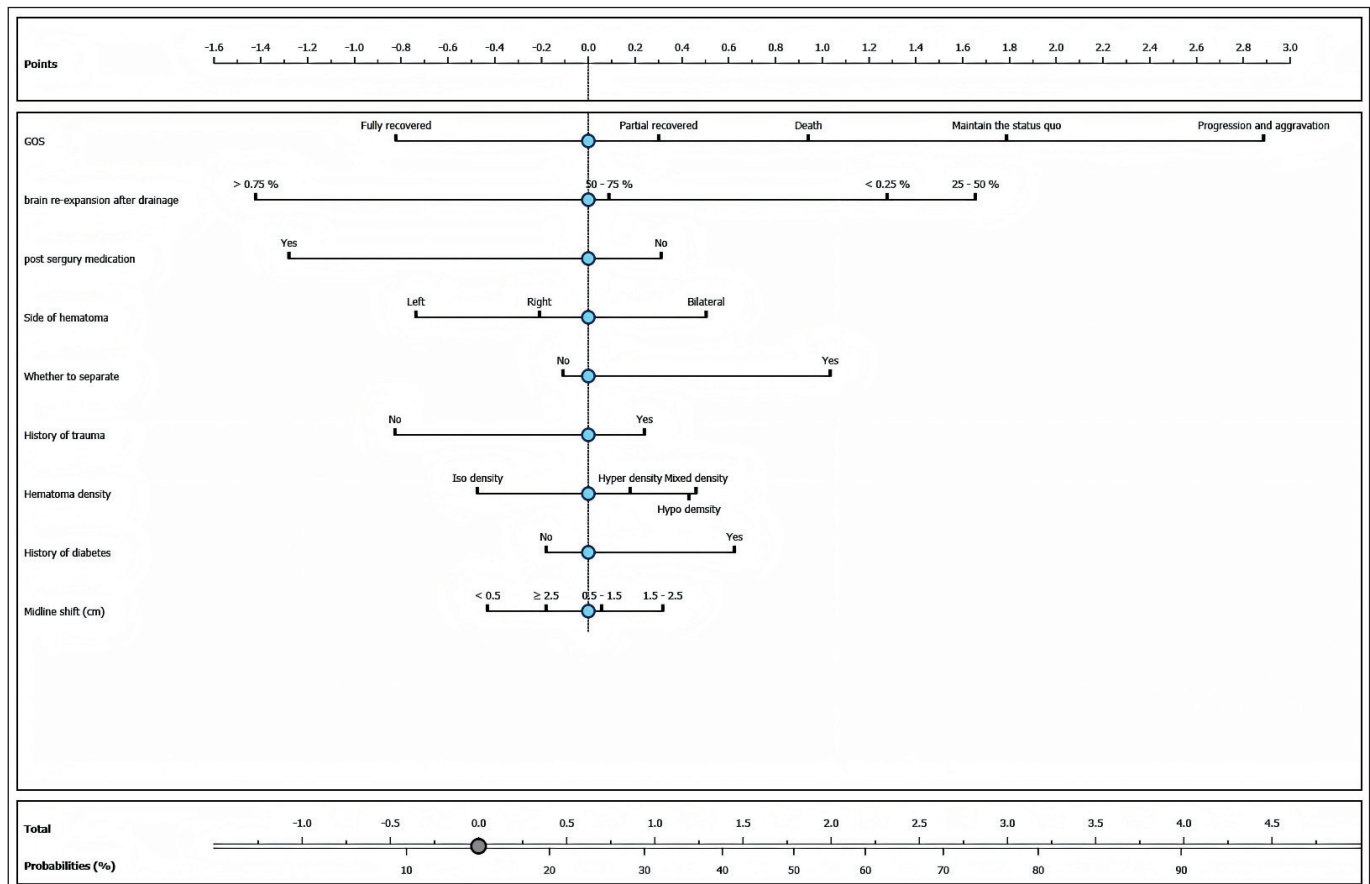


Figure 1: Nomogram for scoring the predictor mode.

Table IV: Comparisons of the Scores of Patients in Recurrent and Non-Recurrent Groups Using T-Test

Variable	Number	Average score	Standard deviation	p-value
Recurrent	32	-0.5	0.66	<0.001
Non-recurrent	247	- 0.91	0.63	

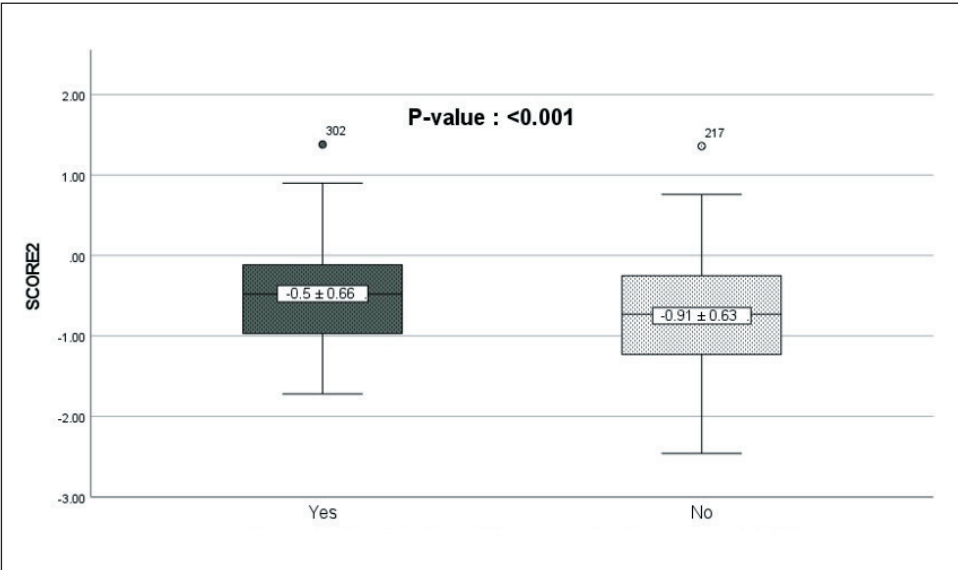


Figure 2: Boxplot of predictor scores by recurrence of SDH.

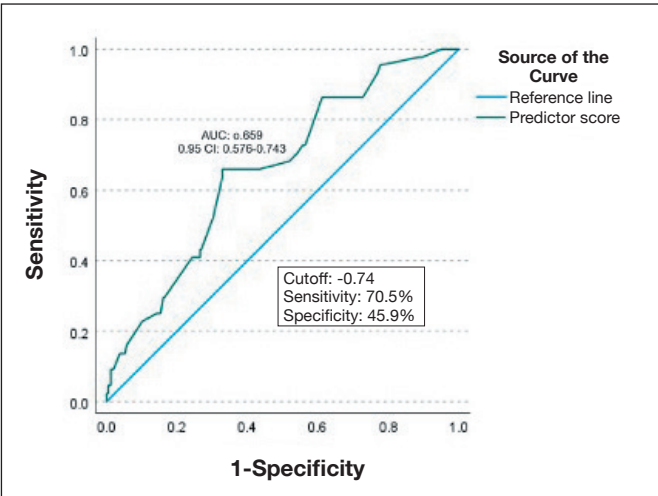


Figure 3: ROC curve analysis for the predictor score that was obtained from the nomogram.

patients, was used in this stage to assess the performance of the nomogram model. The resulting AUC was 0.618 (95% CI: 0.476 - 0.760). In the external validation set, sensitivity and specificity at the cutoff value were 0.696 and 0.561, respectively.

Image Analysis

The study identified that patients with preoperative midline shifts and hyperdense hematomas had higher recurrence

rates post-surgery. This highlighted the critical nature of pre-operative assessment. The study found that the absence of atorvastatin administration post-surgery significantly increased the risk of CSDH recurrence. This emphasized the need for comprehensive medical management, including the use of atorvastatin, to reduce postoperative recurrence risk.

The postoperative CT scan revealed successful drainage of the subdural hematoma. There was evident brain re-expansion, though some residual pneumocephalus was present. Effective brain re-expansion post-surgery was essential for reducing recurrence risk. The study underscored that residual pneumocephalus can impair brain re-expansion, increasing the likelihood of recurrence. Postoperatively, residual air within the cranial cavity was carefully monitored and managed to ensure optimal recovery and minimize recurrence risk. The follow-up CT scan demonstrated a significant reduction in hematoma size and improved midline shift. The brain re-expansion was satisfactory, with minimal residual subdural fluid. Follow-up imaging was crucial to assess the extent of brain re-expansion and the presence of any residual hematoma. This follow-up image showed a favorable outcome, suggesting a lower risk of recurrence due to adequate brain re-expansion and minimal residual fluid (Figure 4). Each image represents a different patient, selected to illustrate characteristic imaging features associated with recurrence risk. None of the patients depicted required repeat surgery, suggesting that meticulous follow-up can guide postoperative management without necessarily needing reoperation.

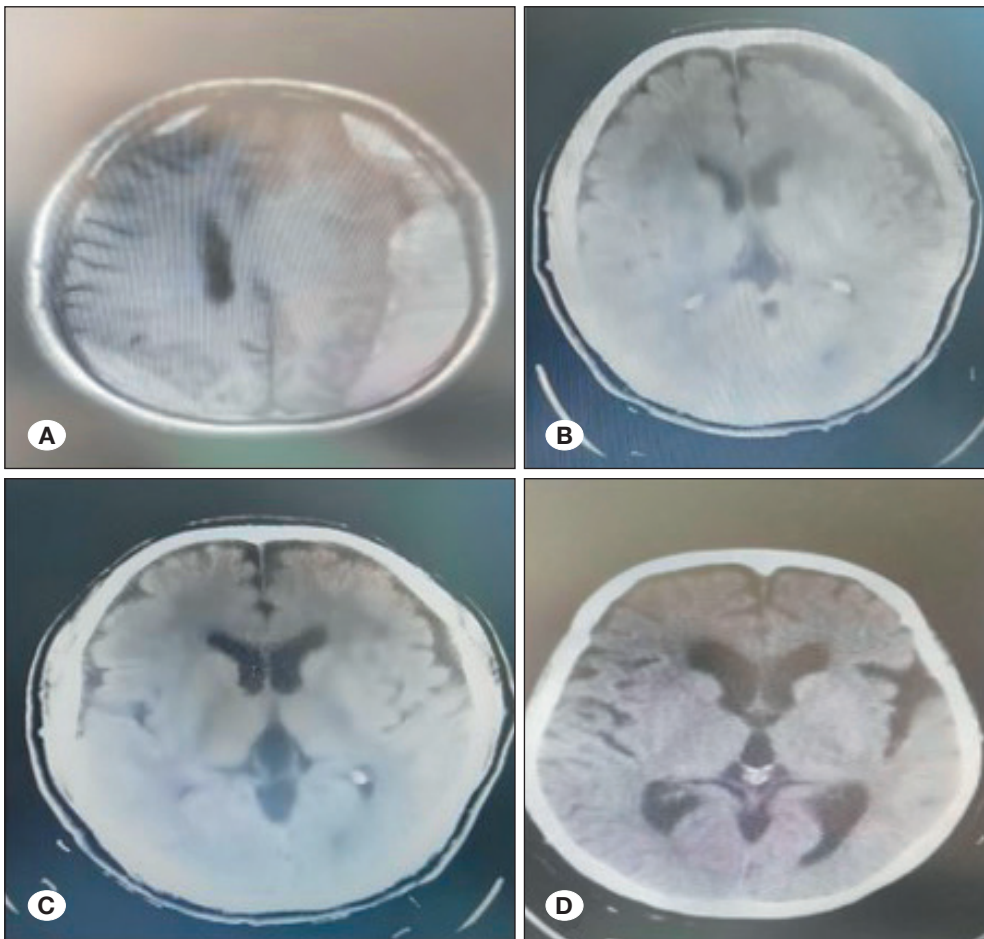


Figure 4: Follow-up CT scan image of patients. **A)** This preoperative CT scan image demonstrates chronic subdural hematoma (CSDH) with significant midline shift and mass effect. The hematoma appears hyperdense, indicating the presence of fresh blood within the subdural space. **B)** This image shows the subdural hematoma prior to the administration of atorvastatin and surgical drainage. The hematoma is still present with evident separation and layering within the subdural space. **C)** The postoperative CT scan indicates successful drainage of the subdural hematoma. The brain re-expansion is evident, though there may still be some residual pneumocephalus present. **D)** The follow-up CT scan demonstrates a significant reduction in the size of the hematoma and improved midline shift. The brain re-expansion appears satisfactory with minimal residual subdural fluid.

DISCUSSION

The present study evaluated independent risk factors for post-operative CSDH recurrence after single burr hole drainage and proposed a comprehensive predictor scoring system for post-operative recurrence risk. This proposed scoring system was constructed by applying a mixture panel of some general independent risk factors that were proposed previously. Based on our scoring system, patients with a recurrence of SDH had a higher score in comparison with those who were completely cured (i.e., no recurrence of SDH). Our proposed scoring system consists of GOS, brain re-expansion after drainage, post-operation medication, side of hematoma, history of trauma, density of hematoma, history of diabetes, and score of midline shift (stratified based on predictor importance). The findings of our study can provide a probable advancement in the prediction and management of the recurrence of SDH following single burr hole drainage (24). Although the history of diabetes, midline shift, and hematoma density were not independent predictors in multivariate analysis, they were significant in univariate tests and were therefore included in the nomogram to preserve clinically meaningful factors and improve predictive performance.

As stated before, the recurrence of SDH is one important challenge in patients who have undergone surgery. The patho-

physiology of CSDH recurrence is multifactorial and may involve persistent inflammation, angiogenesis, repeated microbleeding, and impaired brain re-expansion (9). The scoring system effectively correlates with recurrence rates, demonstrating a clear increase in recurrence probability when the score rises.

The majority of the previous studies on CSDH recurrence after drainage were focused on the general characteristics and clinical symptoms of patients; some studies analyzed the imaging features, and a few studies focused on both by combining clinical and imaging traits. According to these studies, a confusing mixture of heterogeneous risk factors, including old age, diabetes, anticoagulant or antiplatelet medication, aphasia, headache, neurological symptoms, the thickness of hematoma, the density of hematoma, hematoma stratification and separation, no postoperative drainage, a higher degree of midline shift, brain atrophy, and bilateral hematoma were all introduced as risk factors for recurrence of SDH. Age is one factor since some studies have reported that aging is a risk factor for SDH recurrence, whereas other studies have refuted its prognostic feature (4,13,24). We found only one published article that proposed some scoring systems based on imaging findings and not on the clinical data (6). It should be emphasized that these reported risk factors were not all statistically

significant in our multivariate analysis, and their inclusion here reflects previously published evidence rather than findings from the current study.

In this study, GOS at discharge was an independent risk factor for hematoma recurrence, which was consistent with the findings of some previous studies (13). GOS, as the most important index for patients' prognosis, shows the importance of monitoring the status of patients after surgery. A lower GOS score corresponds to poorer consciousness and neurological status and increases the likelihood of CSDH recurrence (6). GOS potentially reflects patients' consciousness and general improvement, which can better predict prognosis and recurrence than individual clinical symptoms. While GCS and GOS are widely recognized and utilized tools in the assessment of neurological status and outcomes in various conditions, we acknowledge that the modified Rankin Scale (mRS) and the Markwalder Grading Scale (MGS) are also established metrics specifically used in the context of CSDH (2,28).

Hematoma density and midline shift were also listed as risk factors for hematoma recurrence in previous studies (11). In this study, while significant differences were observed in univariate analysis, a small predictive importance was found in multivariate logistic regression analysis, and also in the nomogram result. Regarding hematoma density, the findings align with previous studies, indicating that hypodense and mixed-density hematomas are more prone to recurrence compared to hyperdense and isodense hematomas. Hypo- and mixed-density hematomas are unstable and often accompany hematoma separation, leading to incomplete liquefaction and difficulty in fully removing the hematoma and inflammatory factors through irrigation and drainage alone, potentially resulting in hematoma recurrence (31).

The complexity of the midline shift in CSDH presents differing conclusions across studies. Some studies suggest that postoperative midline shift may damage adhesion between the inner and outer membranes of the hematoma cavity, contributing to recurrence (13,15). We propose that preoperative midline shift also influences recurrence due to adhesion between newly formed membranes and impaired brain elasticity. Separated hematomas have been proposed as an additional risk factor. One probable justification is inadequate drainage, leaving residual blood and inflammatory factors that potentially result in recurrence (15).

Our study identified brain re-expansion as a key factor influencing the recurrence of SDH after drainage. Reduced brain re-expansion post-surgery correlates with a higher recurrence probability, likely due to prolonged hematoma compression that impairs brain recovery, especially in elderly patients with poor tissue elasticity. Even with effective drainage, residual compression may enlarge the subdural space, increasing recurrence risk. Postoperative pneumocephalus can hinder brain re-expansion and contribute to recurrence (21). Furthermore, postoperative pneumocephalus was present in some of our patients, but it was not measured or entered into the analysis. This should be considered for further studies.

Upon pre- and post-surgery analyses of CT or MRI images of all SDH patients, we observed a proportional relationship between the thickness of the hematoma cavity and the hematoma's long axis distance and the number of layers. This indicates that changes in hematoma layer thickness correspond to alterations in hematoma volume. Thus, hematoma thickness is a parameter used to calculate brain re-expansion.

The situation on the side of a hematoma is relatively complicated, especially for a bilateral subdural hematoma. In our study, the sides of the hematoma are considered to contribute to the scoring system for predicting hematoma recurrence. Therefore, bilateral drainage is not indicated for all patients; in addition, the side of surgery mainly depends on the maximum thickness of the hematoma, the midline shift, and the main symptoms of the hematoma. In our study, the recurrence rate of unilateral CSDH was lower than that of bilateral CSDH. This may be due to the poor brain re-expansion of bilateral CSDH compared with unilateral CSDH, which can lead to a brain shift and subsequent complications of hematoma after surgery and, therefore, a higher recurrence probability. One proposed theory is that patients with bilateral CSDH are prone to brain atrophy, which leads to poor re-expansion and a higher recurrence rate (19).

This study had some limitations. First, the study design is retrospective, which inherently carries limitations such as selection bias, incomplete data, and reliance on medical records that may not have captured all relevant variables. In addition, in the collection of imaging materials, the classification standard of hematoma density is not fine enough. Despite attempts to identify independent risk factors, there may be unaccounted confounding variables that influence CSDH recurrence, such as comorbidities, medication use, or surgical technique variations. Also, there is still a lack of quantitative indicators to determine the standard of brain atrophy in patients. The analysis is based on data from a single institution, which may limit the generalizability of the findings to other populations or healthcare settings. In the future, prospective clinical trials need to be designed in multicenter cases to verify the sensitivity and effectiveness of the risk-scoring system for CSDH recurrence after burr holes and drainage (33). Moreover, we did not perform active monitoring and measurement of post-operative pneumocephalus, which are important factors in predicting surgery outcome, brain re-expansion, and CSDH recurrence. This should be addressed in future studies. In addition to postoperative pneumocephalus the presence of which leads to residual intracranial air that can physically impede brain re-expansion, and quantitative measures from the literature have shown a direct relationship between air volume and recurrence risk and pre-existing cerebral atrophy, our study lacked the quantification of cerebral atrophy, which creates a pre-existing subdural space that can lead to poor brain re-expansion and subsequent re-accumulation of fluid.

Our study primarily focused on identifying independent risk factors for the recurrence of CSDH and developing a predictive scoring system. The data analyzed included a broad age range from 18 to 96 years, allowing for a comprehensive analysis across different age groups.

CONCLUSION

Our study identified key independent risk factors for SDH recurrence after single-burr hole drainage, including trauma history, lack of atorvastatin, low GOS score at discharge, bilateral hematoma, hematoma separation, and poor brain re-expansion. Other factors, like residual hematoma and pneumocephalus, also contribute to recurrence. Residual hematoma can act as a nidus for further bleeding, while pneumocephalus can impair brain re-expansion, leading to fluid persistence. Future studies should include these factors for a more comprehensive risk assessment. Our scoring system provides clinicians with a practical tool to predict recurrence and guide postoperative management of CSDH patients. While factors such as age, male gender, alcohol use, and anticoagulant therapy were not incorporated, future larger studies can further validate the system and refine its predictive accuracy.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, not-for-profit, or commercial sectors.

Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Disclosure: The authors declare that there are no conflicts of interest related to this study.

AUTHORSHIP CONTRIBUTION

Study conception and design: XZ, HZ

Data collection: XZ, FJ, YS, XX, PZ

Analysis and interpretation of results: XZ, FJ, YS, HZ

Draft manuscript preparation: XZ, FJ

Critical revision of the article: YS, XX, PZ, HZ

Other (study supervision, fundings, materials, etc.): HZ, XZ and FJ are co-first authors.

All authors (XZ, FJ, YS, XX, PZ, HZ) reviewed the results and approved the final version of the manuscript.

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Determination of Optic Nerve Sheath Diameter Cut-off after Cerebrospinal Fluid Drainage in Adults with Elevated Intracranial Pressure: A Prospective Study

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ABSTRACT

AIM: To evaluate the relationship between optic nerve sheath diameter (ONSD) and intracranial pressure (ICP) in patients with acute ICP elevation controlled through external ventricular drainage (EVD).

MATERIAL and METHODS: In this prospective observational study, simultaneous measurements of right and left ONSD, ICP, and cerebral perfusion pressure (CPP) were recorded in 46 adult patients undergoing EVD. Two patients were excluded due to ophthalmic pathology and missing data, resulting in a final cohort of N = 44 patients. After we obtained the baseline measurements, 5 mL of cerebrospinal fluid (CSF) were drained, and the measurements were repeated 2 minutes (min) later.

RESULTS: CSF drainage led to significant reductions in both ICP and bilateral ONSD ($p = .001$ for all), while CPP significantly increased ($p = .038$). We identified an ONSD cut-off of 5.35 mm for detecting ICP values ≥ 15 mmHg, and this cut-off had 53% sensitivity and 86% specificity (Youden index: 0.395). However, we could not determine a reliable cut-off for detecting ICP values ≥ 20 mmHg ($p = .076$).

CONCLUSION: When ICP is controlled through EVD, the linear relationship between ONSD and ICP observed during acute pressure elevations may be disrupted, particularly at higher ICP values (≥ 20 mmHg). Although we identified a cut-off ONSD value of 5.35 mm for detecting ICP values ≥ 15 mmHg, the low sensitivity of this cut-off significantly limits its clinical utility. Additionally, since no reliable cut-off could be established for ICP values ≥ 20 mmHg, ONSD may have limited value for monitoring pressure following CSF drainage.

KEYWORDS: Cerebral perfusion pressure, Intracranial pathology, Intracranial pressure, Elevated, Normal, Optic nerve sheath

INTRODUCTION

The rapid detection of elevated intracranial pressure (ICP) is essential when managing critically ill patients with brain pathology (3). The optic nerve sheath is essentially an extension of the dura mater, and as it can stretch, the optic nerve sheath diameter (ONSD) changes when ICP changes (12). Measuring the ONSD using ultrasound offers a practical approach, as it is non-invasive, cost-effective, and can be carried out at the bedside. A meta-analysis by Berhanu et al. involving 2,824 patients found that ONSD cut-off values

between 5.6–6.3 mm were effective for detecting ICP values around 20–22 mmHg. These ONSD cut-off values had good specificity and maintained reasonable sensitivity compared to lower thresholds in the 4.9–5.5 mm range (2).

However, most previous studies have focused on patients during the acute illness phase when ICP values were actively increasing. Moreover, there is limited information on how ONSD relates to ICP in patients whose ICP is being controlled using CSF drainage via the external ventricular drainage (EVD) method. Consequently, our main goal in this study was to

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identify the best ONSD cut-off values for detecting ICP values ≥ 15 mmHg and ≥ 20 mmHg in patients undergoing EVD. Additionally, we aimed to explore the correlation between ONSD measurements and actual ICP from intraventricular catheter monitoring.

MATERIAL and METHODS

Study Design and Ethical Approval

This prospective observational study was performed over a 13-month period at the Neurosurgical Intensive Care Unit, Cerrahpasa School of Medicine, Istanbul University-Cerrahpasa, following ethics committee approval. The Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine, Istanbul, Türkiye (Chairperson Prof Ozgur Kasapcopur) provided ethical approval on September 7, 2021 (Ethical Committee Approval No: 179951, ClinicalTrials.gov identifier: NCT06367868).

Participants

This study was performed with 46 adult patients who had intraventricular drainage catheters due to intracranial pathology. To participate in the study, written informed consent had to be given by the patients or their relatives. Patients with orbital tumors, Graves' disease, exophthalmos, sarcoidosis, optic neuropathy, meningitis, ocular trauma, and severe lung disease with ventilation requirements greater than 5 cm H₂O PEEP were excluded from the study (4). Two patients were excluded due to ophthalmic pathology and missing data, resulting in a final cohort of 44 patients.

Data Collection and Measurements

In the intensive care unit, with routine ASA monitoring, ICP and cerebral perfusion pressure (CPP) were continuously monitored using an intraventricular catheter, with transducers placed at the level of the tragus.

All patients underwent continuous ICP monitoring using an EVD catheter, with the transducer placed at the level of the tragus, and cerebral perfusion pressure (CPP) monitoring following the standard protocols of the American Society of Anesthesiologists (ASA). ONSD measurements were performed using an ARIETTA 65 ultrasound system (Hitachi, Japan) with an L64 high-frequency linear probe (5–18 MHz). A transbulbar approach was applied in the transverse plane, with the probe angled medially and superiorly, thus ensuring that no pressure was applied to the globe. This technique allowed for clear visualization of the globe, the hyperechoic retrobulbar fat, and the hypoechoic optic nerve. After obtaining the clearest image of the optic nerve at its thickest point, the ONSD was measured 3 mm posterior to the globe. To minimize inter-observer variability, all of the measurements were performed bilaterally by a single experienced sonographer.

The baseline measurements included the bilateral ONSD, ICP, and CPP, which were recorded simultaneously. Subsequently, 5 mL of CSF were drained through the EVD catheter over 30–60 seconds under sterile conditions. At 2 minutes (min) after drainage, repeated measurements of the bilateral ONSD, ICP, and CPP were made to assess acute changes in these

variables. The 2 min interval was chosen based on previous studies suggesting that the ONSD rapidly adapts to changes in the ICP (12). All of the measurements were performed under standard conditions with patients maintained in a neutral head position and with stable ventilation settings.

Power Analysis

The minimum sample size of (n=44) was based on the detection of a Cohen's d effect size of 0.5 with a type I error of 0.05 and power of 0.8.

Statistical Analysis

Descriptive statistics for the continuous variables were expressed as the mean $\pm$ standard deviation (SD) for normally distributed data and as the median, minimum, and maximum for non-normally distributed data. The categorical data were presented as frequency and percentage values. Normality was assessed using the Shapiro-Wilk test ($n < 50$) and skewness-kurtosis tests. Paired t-tests were used to compare the pre- and post-CSF drainage measurements for normally distributed variables, while the Wilcoxon signed-rank test was used for non-normal data. Between-group comparisons for non-normal data were carried out using the Mann-Whitney U test (two groups) or Kruskal-Wallis test (multiple groups), and post-hoc corrected p-values were used to identify significant differences. Categorical variables were compared using the Chi-square test, whereas Pearson or Spearman correlation tests were used to evaluate the relationships between the continuous variables (i.e., ONSD, ICP, and CPP). A receiver operating characteristic (ROC) analysis was used to determine the ONSD cut-off values for detecting ICP ≥ 15 mmHg and ≥ 20 mmHg, and the sensitivity, specificity, and Youden index were calculated. All of the statistical analyses were conducted using SPSS (version 26.0, IBM Corp.), and $p < 0.05$ was considered significant.

RESULTS

Of the 46 enrolled patients, 44 were included in the final analysis (Figure 1). The patient's demographic characteristics, diagnoses, and Glasgow coma scale (GCS) scores are presented in Table I. CSF drainage significantly reduced ICP values ($p = 0.001$), right ONSD ($p = 0.001$), and left ONSD ($p = 0.001$) and increased CPP ($p = 0.038$) (Table II, Figures 2–4). A significant correlation was observed between bilateral ONSD and ICP before and after CSF drainage (Table III).

The ROC analysis identified an ONSD cut-off of 5.35 mm for identifying ICP values ≥ 15 mmHg (sensitivity: 53%; specificity: 86%; Youden index: 0.395; Table IV,V, Figure 5). However, no significant ONSD cut-off was identified for ICP values ≥ 20 mmHg ($p = 0.076$; Table VI). No differences in ONSD measurements were observed based on patient diagnosis or GCS scores (Tables VII,VIII).

DISCUSSION

This study aimed to investigate the relationship between ONSD and ICP in patients with ICP controlled via EVD and revealed a significant reduction in both ICP and bilateral ONSD

following CSF drainage, alongside increased CPP. We also identified an ONSD cut-off value of 5.35 mm for detecting ICP values ≥ 15 mmHg, and this cut-off had 53% sensitivity and 86% specificity. However, no cut-off could be determined for ICP values ≥ 20 mmHg, which suggests that the linear ONSD-ICP relationship may be disrupted at higher ICP levels following CSF drainage.

The ONSD cut-off of 5.35 mm for ICP values ≥ 15 mmHg is relatively similar to the cut-off of 5.49 mm reported by Padayachy et al. in their pediatric work with children over 4 years

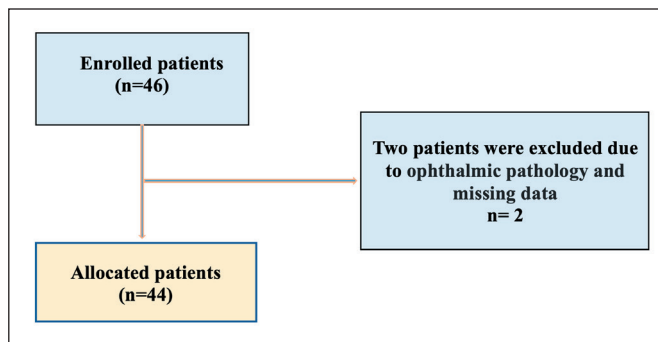


Figure 1: The flowchart.

Table I: Patient's demographic values, diagnosis and Glasgow Coma Scores

Variables	Values	
Age, mean $\pm$ SD (years)	51.55 $\pm$ 17.66	
Body mass index, mean $\pm$ SD (kg/m ²)	25.71 $\pm$ 4.99	
Gender	n	%
Female	15	34.1
Male	29	65.9
Diagnosis	n	%
Intracranial haemorrhage	19	43.2
Vascular	7	15.9
Tumor	18	40.9
GCS score	n	%
3-8	12	27.3
9-13	14	31.8
14-15	18	40.9

Data are presented as mean $\pm$ standard deviation (SD) for continuous variables and as number (n) and percentage (%) for categorical variables. **GCS:** Glasgow Coma Scale.

Table II: Intracranial Pressure, Right and Left Optic Nerve Sheath Diameters and Cerebral Perfusion Pressure Before and After Cerebrospinal Fluid Drainage

	ICP (mmHg)		R-ONSD (mm)		L-ONSD (mm)		CPP	
	mean $\pm$ SD	p-value	mean $\pm$ SD	p-value	mean $\pm$ SD	p-value	mean $\pm$ SD	p-value
Before CSF drainage	14.68 $\pm$ 9.31	0.001*	5.12 $\pm$ 0.55	0.001*	5.18 $\pm$ 0.53	0.001*	77.82 $\pm$ 19.05	0.038*
After CSF drainage	9.89 $\pm$ 7.86		4.52 $\pm$ 0.53		4.54 $\pm$ 0.53		80.32 $\pm$ 16.50	

Values expressed as mean $\pm$ SD (standard deviation). **ICP:** Intracranial Pressure, **CPP:** Cerebral perfusion pressure, **R-ONSD:** Right optic nerve sheath diameter, **L-ONSD:** Left optic nerve sheath diameter, **CSF:** Cerebrospinal fluid. * Paired t-test, statistically significant values ($p < 0.05$)

Table III: The Correlation between the Right and Left Optic Nerve Sheath Diameters as well as Intracranial Pressure Before and After Cerebrospinal Fluid Drainage

	R-ONSD (mm)		L-ONSD (mm)		Mean-ONSD (mm)	
	mean ± SD	p-value	mean ± SD	p-value	mean ± SD	p-value
Before CSF drainage	5.12±0.55	0.001*	5.18±0.53	0.001*	5.16±0.49	0.001*
After CSF drainage	4.52±0.53		4.54±0.53		4.53±0.48	
	R-ONSD-1		L-ONSD-1		Mean-ONSD-1	
	p-value	r	p-value	r	p-value	r
ICP-1	0.002*	0.463	0.028*	0.332	0.003*	0.442
	R-ONSD-2		L-ONSD-2		Mean-ONSD-2	
	p-value	r	p-value	r	p-value	r
ICP-2	0.029*	0.329	0.095	0.255	0.032*	0.325

Spearman's rank correlation and Paired t test, r: correlation coefficient. **ICP-1:** Intracranial pressure before cerebrospinal fluid (CSF) drainage, **ICP-2:** Intracranial pressure after CSF drainage, **ONSD-1:** Optic Nerve Sheath Diameter before CSF drainage, **ONSD-2:** Optic Nerve Sheath Diameter after CSF drainage

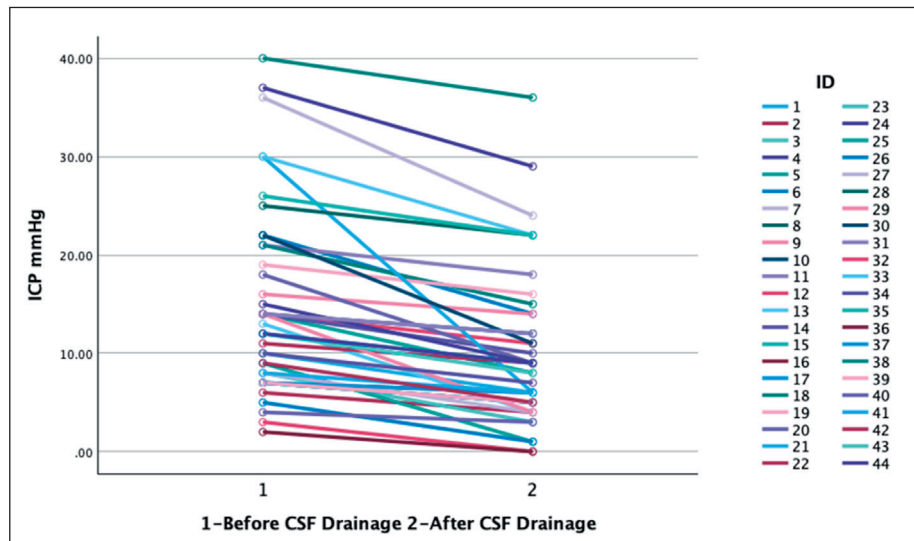


Figure 2: Changes in intracranial pressure after cerebrospinal fluid drainage.

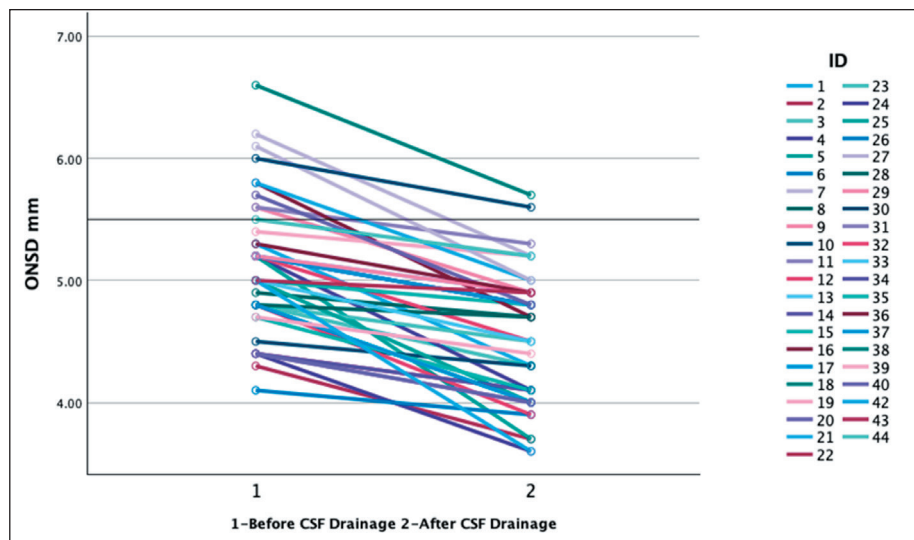


Figure 3: Changes in right optic nerve sheath diameters after cerebrospinal fluid drainage.

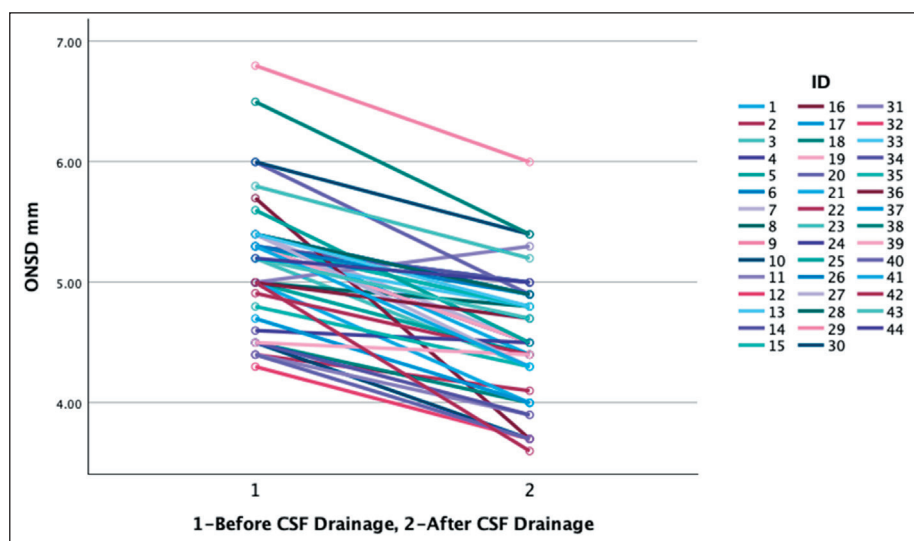


Figure 4: Changes in left optic nerve sheath diameters after cerebrospinal fluid drainage.

Table IV: The Number of patients with Intracranial Pressure ≥ 15 mmHg and < 15 mmHg Before Cerebrospinal Fluid Drainage

ICP-1	n (number)
≥ 15 mmHg	15
< 15 mmHg	29

ICP-1: Intracranial pressure before cerebrospinal fluid drainage

old. Notably though, the sensitivity of 53% in this study is considerably lower than the sensitivity values reported previously in acute ICP elevation scenarios (13). For example, Berhanu et al. (2) achieved sensitivities ranging from 70% to 90% using ONSD cut-offs between 5.6 and 6.3 mm (2).

This discrepancy between the present study and the previous literature warrants closer examination, and several factors may be involved.

Table V: ROC Analyses for Intracranial Pressure ≥ 15 mmHg before Cerebrospinal Fluid Drainage and Right Optic Nerve Sheath Diameter before Cerebrospinal Fluid Drainage

Variable	AUC	Std.Error	p-value	Cut-off	Specificity	Sensitivity	Youden Index	95% Confidence Interval	
								Upper limit	Lower limit
R-ONSD-1	0.701	0.087	0.030*	5.35	0.862	0.533	0.395	0.530	0.872

ROC (Receiver operating characteristic) Curve Analyses. **R- ONSD-1:** Right optic nerve sheath diameter before CSF drainage, **AUC:** Area Under Curve

Table VI: ROC Analyses for Intracranial Pressure ≥ 20 mmHg before Cerebrospinal Fluid Drainage and Right Optic Nerve Sheath Diameter before Cerebrospinal Fluid Drainage

Variable	AUC	Std.Error	p-value	95% Confidence Interval	
				Upper limit	Lower limit
R-ONSD-1	0.680	0.096	0.076	0.492	0.869

ROC (Receiver operating characteristic) Curve Analyses. **R- ONSD-1:** Right optic nerve sheath diameter before CSF drainage, **AUC:** Area Under Curve

Table VII: Relationship among Right and Left Optic Nerve Sheath Diameters Before and After Cerebrospinal Fluid Drainage with Patients Diagnosis

	Diagnosis	n	mean $\pm$ SD	p-value
R-ONSD-1	Intracranial Haemorrhage	19	5.02 $\pm$ 0.65	0.578
	Tumor	18	5.16 $\pm$ 0.45	
	Vascular	7	5.25 $\pm$ 0.49	
L-ONSD-1	Intracranial Haemorrhage	19	5.15 $\pm$ 0.55	0.854
	Tumor	18	5.23 $\pm$ 0.55	
	Vascular	7	5.11 $\pm$ 0.50	
R-ONSD-2	Intracranial Haemorrhage	19	4.49 $\pm$ 0.56	0.639
	Tumor	18	4.59 $\pm$ 0.52	
	Vascular	7	4.37 $\pm$ 0.50	
L-ONSD-2	Intracranial Haemorrhage	19	4.43 $\pm$ 0.52	0.261
	Tumor	18	4.70 $\pm$ 0.56	
	Vascular	7	4.41 $\pm$ 0.42	

Independent t-test. **ONSD-1:** Optic nerve sheath diameter before CSF drainage, **ONSD-2:** Optic nerve sheath diameter after CSF drainage, **R:** Right, **L:** Left, **n:** number, **SD:** Standard deviation

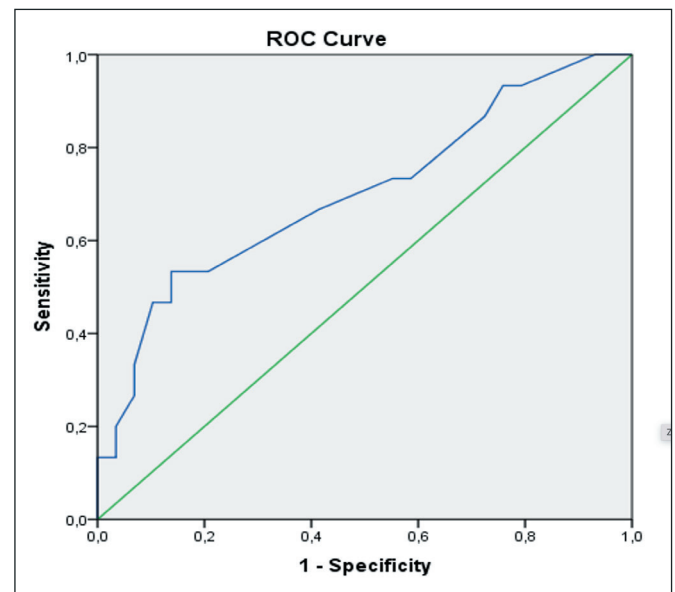
**Figure 5:** ROC Analyses for intracranial pressure ≥ 15 mmHg before cerebrospinal fluid drainage and right optic nerve sheath diameter before cerebrospinal fluid drainage.

Table VIII: Relationship among Intracranial Pressure, Right and Left Optic Nerve Sheath Diameters Before and After Cerebrospinal Fluid Drainage with Patients Glasgow Coma Score

	GCS	n	mean± SD	p-value
ICP-1	3-8	12	13.67±10.65	0.881
	9-13	14	14.57±9.56	
	14-15	18	15.44±8.65	
R-ONSD-1	3-8	12	4.97±0.71	0.168
	9-13	14	4.99±0.43	
	14-15	18	5.30±0.48	
L-ONSD-1	3-8	12	5.20±0.61	0.542
	9-13	14	5.05±0.46	
	14-15	18	5.26±0.54	
ICP-2	3-8	12	10.50±10.15	0.911
	9-13	14	10.14±7.78	
	14-15	18	9.28±6.54	
R-ONSD-2	3-8	12	4.58±0.57	0.414
	9-13	14	4.35±0.47	
	14-15	18	4.59±0.55	
L-ONSD-2	3-8	12	4.59±0.49	0.494
	9-13	14	4.40±0.50	
	14-15	18	4.61±0.58	

One-way analysis of variance (or one-way ANOVA)

GCS: Glasgow Coma Scale, **ICP-1:** Intracranial pressure before cerebrospinal fluid (CSF) drainage, **ICP-2:** Intracranial pressure after CSF drainage, **ONSD-1:** Optic nerve sheath diameter before CSF drainage, **ONSD-2:** Optic nerve sheath diameter after CSF drainage, **R:** Right, **L:** Left, **n:** number, **SD:** Standard deviation

Firstly, CSF drainage could be changing the mechanical properties of the optic nerve sheath itself, making it less responsive to fluctuations in ICP. Additionally, our measurement timing (2 min after drainage) may not have been optimal for capturing the full dynamic range of ONSD changes; for example, Moretti et al. used a shorter 1 min interval, which may have elicited different results (12). Biological variability between patients may also be involved; indeed, the elasticity of the optic nerve sheath varies among individuals and can be affected by factors such as age or how long they have experienced increased intracranial pressure (14). Taken together, these findings indicate that relying on a single ONSD measurement for clinical decisions may not be sufficient. Instead, patient-specific calibration of the ONSD-ICP relationship may be necessary to improve sensitivity and make this technique more clinically reliable.

The most significant finding in this study is that we could not establish a reliable ONSD cut-off for ICP values ≥ 20 mmHg. This issue is notable because previous studies on acute ICP

elevation have consistently reported that ONSD cut-offs between 5.6–6.3 mm are effective for detecting these higher ICP values (2). However, the patients differed from those in previous studies in an important way, as they all had functioning EVDs, meaning their ICP was being actively managed. As such, this controlled environment seems to change how ONSD relates to ICP, which needs more investigation.

Our findings are in line with observations from other groups who studied patients with managed ICP. For example, Kersch et al. found non-linear correlations between ONSD and ICP in children, which suggests the optic nerve sheath might hit biomechanical limits at very high ICP values (8). Lochner et al. also reported that ONSD values became less sensitive when the ICP values exceeded 20 mmHg in patients whose ICP had been stabilized (11). The authors suggested that this reduced sensitivity may occur due to sheath fibrosis or decreased compliance after repeated pressure fluctuations, which aligns with the fact that many of these brain conditions are chronic.

Further to the control of ICP in this work, the patients were in a post-drainage state, which likely complicated the situation. When CSF drains through an EVD, the ICP drops quickly, sometimes within minutes. In these cases, the ONSD might need longer to respond to these rapid changes. Individual variation in how elastic each person's optic nerve sheath is should also be considered. Indeed, factors such as age and how long someone has had elevated ICP may affect the compliance of the tissue (14).

Another consideration is hysteresis, which researchers have described in patients with long-standing intracranial hypertension (6,8). In hysteresis, the optic nerve head undergoes structural changes, as does the trabecular structure inside the sheath, and these changes may limit how well the tissue can respond to pressure shifts in real time. As such, hysteresis could explain why ONSD is not always a reliable indicator for monitoring ICP.

In terms of future research, future studies need to track ONSD measurements over longer periods after procedures such as EVD. We measured at 2 min post-drainage, but ONSD may continue adapting for hours afterward. Obtaining longitudinal data would support the current understanding of this timeline and help to identify the best time for taking measurements.

Even though there were issues with using ONSD measurements at higher ICP levels, we did confirm an important finding that others have reported before (1,7,8,9); specifically, ONSD measurements from both eyes correlated well with ICP. This outcome supports measuring just one side in clinical practice, which is both more practical and faster.

Finally, it should be noted that our results did not match with those of Komut et al., who reported higher ONSD in patients with GCS scores ≤ 13 in acute settings (10). Conversely, in this work, we did not identify any connection between GCS and ONSD. The difference in findings is likely due to patient condition, as the patients in the work of Komut et al. were acutely deteriorating (10), whereas ours had already undergone drainage and were hemodynamically stable. This comparison

highlights the significance of the clinical situation when using ONSD to assess ICP.

Limitations

Several limitations should be acknowledged in this study. All of the patients had controlled ICP through the use of functioning EVD, which limits the generalizability of these findings to patients with acute, unmanaged intracranial hypertension. Our cohort was also heterogeneous in terms of underlying pathology, as the patients presented with different diagnoses, and this variation may have influenced the relationship between ONSD and ICP in ways that we did not fully account for. We chose to measure ONSD at 2 min post-drainage, but this timepoint may not capture the complete adaptation process. As such, longer observation periods are needed to determine when the ONSD stabilizes after acute pressure changes. Finally, we used a single sonographer for all measurements to minimize inter-observer variability. While this improved consistency in our data, the outcomes may not reflect the measurement variability that occurs in routine clinical settings where multiple operators perform ultrasound examinations (5).

CONCLUSION

We found an ONSD cut-off of 5.35 mm for identifying ICP values ≥ 15 mmHg, but the sensitivity of this cut-off was only 53%, which limits its utility in clinical practice. There are several possible explanations for this low sensitivity. CSF drainage likely changes how compliant the optic nerve sheath is, potentially making it less responsive to pressure shifts. The timing of our measurements may also have been influential; we measured at 2 min after drainage, but the ONSD could be adjusting either faster or slower than that, and the timeline of these changes is unclear from the literature. There is also natural variation among patients in the elasticity of their optic nerve sheath, and the nerve sheaths of individuals with chronic brain problems may respond differently from others.

Another key finding is that we could not find a reliable cut-off value for ICP ≥ 20 mmHg, which suggests ONSD may plateau or simply become unreliable once pressures become high, at least after CSF drainage. A potential solution to this issue would be taking multiple ONSD measurements over time rather than relying on a single value. Indeed, having multiple measurements might also help to calibrate the measurement to each individual patient rather than using universal cut-offs.

Overall, more research is needed to understand the timing and biomechanical aspects of how ONSD responds to ICP when the pressure is being actively managed. Indeed, controlling the ICP environment appears to change the relationship in ways that are, as yet, not fully clear.

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AUTHORSHIP CONTRIBUTION

Study conception and design: GO, YT

Data collection: GO

Analysis and interpretation of results: GO

Draft manuscript preparation: OKD

Critical revision of the article: GO, EFA, YT

Other (study supervision, fundings, materials, etc.): n/a

All authors (GO, OKD, EFA, YT) reviewed the results and approved the final version of the manuscript.

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Results of a Long-Term Follow-Up on the Dry-Field Maneuver Application in Hemorrhage Control During Neuroendoscopic Procedures

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ABSTRACT

AIM: To present the long-term follow-up results of dry-field maneuver in neuroendoscopy.

MATERIAL and METHODS: The dry-field maneuver has been used in our clinic since 2012, leading to a retrospective review of patients undergoing neuroendoscopic procedures from 2012 to 2024.

RESULTS: The dry-field maneuver was successfully implemented in 13 patients in our clinic, achieving effective control of bleeding without any postoperative complications. No neurological or vascular issues or deaths associated with this method were reported in any patient throughout the long-term follow-up period.

CONCLUSION: The dry-field maneuver is a successful and reliable technique for controlling bleeding in neuroendoscopic procedures. It may also be used in certain cases during elective procedures.

KEYWORDS: Cerebral intraventricular hemorrhage, Dry field, Neuroendoscopy, Surgical hemostasis

ABBREVIATIONS: CSF: Cerebrospinal fluid, CP: choroid plexus, ETV: endoscopic third ventriculostomy, IR: infundibular recess, MB: mammillary bodies, SV: septal vein, TC: tuber cinereum, TSV: thalamostriate vein

INTRODUCTION

Neuroendoscopic surgery is increasingly applied in treating hydrocephalus, ventricular system disorders, and selected skull base lesions. Also, the complications related to these procedures are reported more frequently. Among these, hemorrhage is one of the most significant challenges for neurosurgeons (1,10). The narrow endoscopic working space and limited options for intraoperative hemostasis make bleeding control difficult. Even a minor hemorrhage can obscure the field of view, prolong the surgery, and increase postoperative risks. Therefore, careful intraoperative management of bleeding is essential for both patient safety and operative success. In cases where severe bleeding can-

not be controlled, morbidity and mortality may occur, underscoring the need for improved strategies for complication management.

The risk and severity of bleeding during neuroendoscopic procedures depend on several factors. These factors include the type of procedure performed, the patient's medical history or comorbidities influencing coagulation, the size and location of the lesion, the surgeon's level of experience, and the instruments employed.

Endoscopic third ventriculostomy (ETV) is generally associated with a low risk of bleeding, whereas procedures such as tumor biopsy or resection carry a higher risk. Though rare, massive hemorrhages can occur during ETVs. A meta-anal-



ysis of 2,984 ETVs performed on 2,884 patients detected an intraoperative bleeding rate of 3.7%, with massive bleeding occurring in 0.6% of cases (2). The mortality rate was 0.21% (6 patients), with four deaths attributed to bleeding-related complications. Thus, two-thirds of mortalities during ETV are due to bleeding. A more recent meta-analysis of 3,749 patients from 46 case series reported bleeding rates during ETVs performed with flexible and rigid endoscopes at 4% and 6%, respectively (1). In a case series of 60 patients undergoing endoscopic tumor biopsy, bleeding occurred in 21 (35%) patients, with severe hemorrhage in 2 cases (4). A systematic review evaluating the use of ultrasonic aspirators in endoscopic tumor resections reported a bleeding incidence of 7.5%, identifying hemorrhage as the most frequent complication (10). Overall, available studies indicate that bleeding occurs more often in biopsy and resection procedures than in ETV alone.

Conventional methods to address bleeding in neuroendoscopic procedures typically involve irrigation and electrocauterization. However, these techniques may be insufficient, especially in cases of massive bleeding where the source is unclear.

Dry-Field Maneuver

In neuroendoscopy, the dry-field maneuver is employed when conventional methods of controlling hemorrhage, such as irrigation and cauterization, fail to work within a 3-minute period. The effectiveness of this maneuver in controlling bleeding de-

pends on the principle of allowing dispersed platelets in the fluid to come together at the site of vascular injury because of gravity in a dry environment. Another important goal of this maneuver is to improve the clarity of the surgical field by eliminating the blurriness caused by bleeding in the fluid environment, thereby allowing the continuation of the surgical procedure.

The dry-field maneuver was first successfully used during an animal study in 2012 (14). This method was employed on seven patients in our clinic between 2012 and 2017, and the results were published in 2017 (13). Following our study, Oertel and colleagues published outcomes using the same technique in a series of six patients in 2018 (9). In 2022, Spennato and colleagues reported successfully using the dry-field maneuver to control bleeding in a case where irrigation and cauterization had failed (12).

The steps involved in this maneuver were detailed in a previously published study (13), and are shown in Figure 1. They are summarized as follows:

1. Irrigation is stopped if it fails to stop the bleeding after being performed effectively for 3 minutes. The cerebrospinal fluid (CSF) is slowly and carefully drained from the ventricle using a suction catheter.
2. During this process, the irrigation line is removed from the endoscope and left open to allow air to flow easily into the ventricular system in place of the withdrawn CSF. At least one

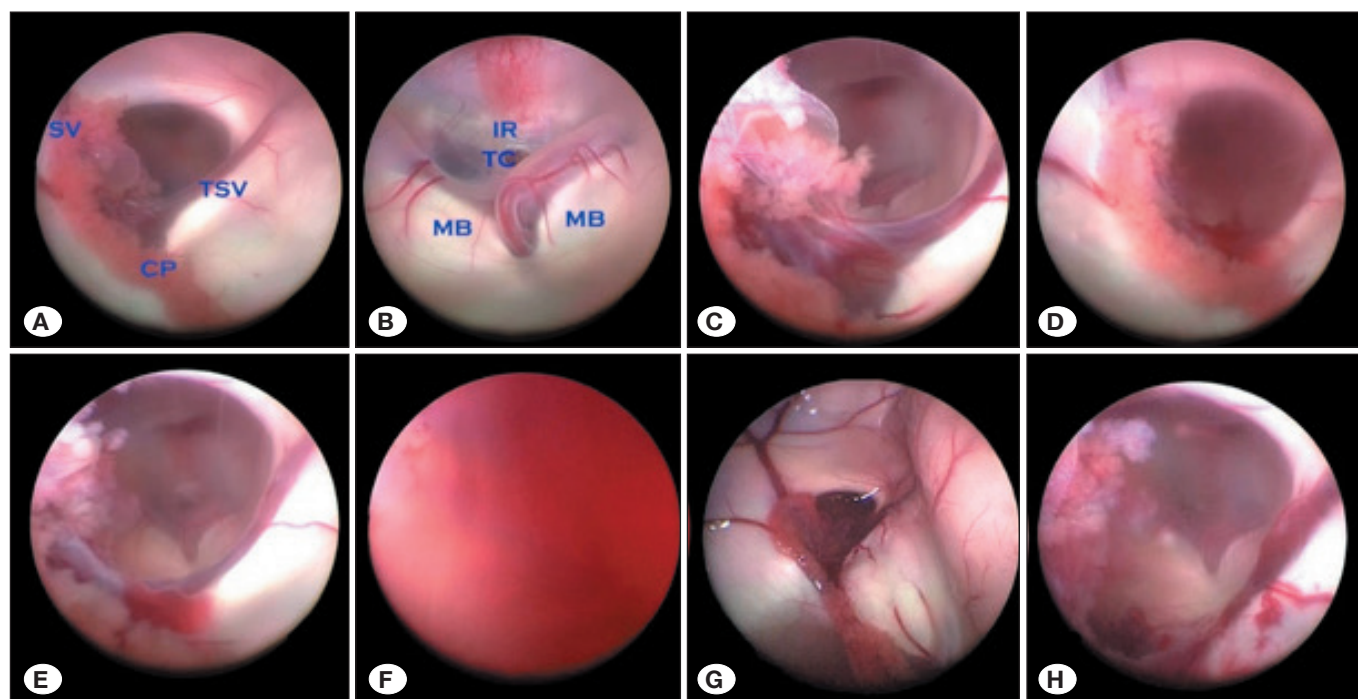


Figure 1: Dry-field maneuver demonstrated through a sample case. **A)** Choroid plexus (CP), septal vein (SV), and thalamostriate vein (TSV) were observed at the level of the foramen of Monro. **B)** Upon entering the third ventricle, the mammillary bodies (MB), tuber cinereum (TC), and infundibular recess (IR) were visualized. **C)** As the view became blurred while working within the third ventricle, the camera was withdrawn to investigate the etiology. **D)** A venous source of bleeding was identified. **E)** Progression of the bleeding was observed. **F)** Image clarity was lost due to bleeding, and irrigation could not control it. **G)** Entire cerebrospinal fluid in the ventricular system was drained. Active bleeding ceased, and clot formation was observed. **H)** Ventricular system was refilled with Ringer's lactate solution, and the bleeding was noted to have stopped.

channel of the telescope remains open to prevent ventricular collapse. If there is any suspicion of ventricular collapse, CSF drainage is stopped and air is introduced into the ventricle if necessary.

3. Once all the CSF has been drained, a waiting period of approximately 2–3 min is observed over the bleeding site to allow platelet aggregation and control the hemorrhage.

4. After the bleeding has stopped, the ventricles are slowly filled with Ringer's lactate solution while allowing air to escape through the previously opened channel.

This study examined the effectiveness and long-term outcomes of using the dry-field maneuver to manage hemorrhagic complications during neuroendoscopic surgeries.

MATERIAL and METHODS

The dry-field maneuver has been used in our clinic since 2012 (13,14). Therefore, the operating-room records of all patients treated using neuroendoscopy between 2012 and 2024, including patient files and video recordings from our clinic, were retrospectively reviewed. The study included patients identified from these records, in whom the dry-field maneuver was used. Storz–Lotta telescopes and a Xenon–Nova 175-W light source (Karl Storz GmbH & Co KG, Tuttlingen) were used in all surgeries.

RESULTS

The dry-field maneuver was used for hemorrhage control on 13 patients undergoing neuroendoscopic procedures. Before deciding on the dry-field maneuver, at least 3 min of Ringer's lactate irrigation was attempted. The maneuver was applied in cases where this was unsuccessful.

The age of the patients varied from 6 months to 51 years, with a mean age of 17 years. The group had a male predominance, with a male-to-female ratio of 9:4. In pediatric cases, the average age was 8 years.

Biopsies were taken in two patients diagnosed with craniopharyngioma, and an Ommaya reservoir was placed into the cyst. Two patients underwent colloid cyst excision. Biopsies were taken from patients with pineal ($n = 2$), tectal ($n = 1$), thalamic ($n = 1$), and ependymal ($n = 1$) masses. One patient underwent arachnoid cyst fenestration, and one patient had an intraventricular hematoma evacuated endoscopically. Hemorrhage occurred during ETV procedures in two patients diagnosed with aqueductal stenosis.

Bleeding was completely controlled with the dry-field maneuver in all patients. No neurological or vascular complications were observed in any patient during the early postoperative period. Although routine biochemical tests showed no significant changes, radiological examinations revealed varying levels of pneumocephalus and minor intraventricular hemorrhage, particularly in the atrial horns, as expected in all patients. These radiological changes resolved completely during follow-up, and no long-term complications related to them were observed.

Patients were followed up for an average duration of 5 years. No acute or chronic vascular or neurological complications associated with the dry-field maneuver were reported in these patients. Two patients required the placement of a ventriculoperitoneal shunt in the acute period. Morbidities related to the natural progression of the tumor were recorded in two cases. Also, no procedure-related mortality was noted. The results are shown in Table I.

Table I: Information on Patients Undergoing the Dry Field Maneuver

	Location	Procedure	Bleeding origin	Age (years)	Gender	Follow-up (years)
Craniopharangioma	Suprasellar	TR	Arterial	8	Male	10
Cyst	Colloid	TR	Venous	13	Male	5
Cyst	Colloid	TR	Venous	31	Male	1
Aqueduct stenosis	Aqueduct	E3V	Venous	36	Male	1
SEGA	Ependymal	TR	Venous	13	Female	10
Aqueduct stenosis	Aqueduct	E3V	Venous	9	Female	10
Hemorrhage	Intraventricular	Hematoma evacuation	Arterial	9	Male	4
Tumor	Thalamic	TR + E3V	Venous	11	Female	6
Tumor	Pineal gland	TR	Venous	51	Male	9
Arachnoid cyst	Temporal	Cystostomy	Arterial	2	Male	1
Craniopharangioma	Suprasellar	Cystostomy	Venous	11	Male	1
Glioma	Tectal	TR + E3V	Venous	26	Female	2
Tumor	Pineal gland	E3V + TB	Venous	0.5	Male	1
				Mean: 17		Mean: 5

E3V: Endoscopic third ventriculostomy; **SEGA:** Subependymal giant cell astrocytoma; **TB:** Tumor biopsy; **TR:** Tumor resection.

■ DISCUSSION

Bleeding in neuroendoscopic procedures is one of the most serious complications. Controlling bleeding is challenging due to the narrow surgical field and the fact that the surgery is performed in a fluid environment. Therefore, measures to prevent bleeding have been the initial focus of investigation.

As an example of a preventive strategy for avoiding vascular injury during ETV, Yadav et al. introduced the “water jet dissection” technique in patients with a thick and opaque third ventricular floor (15). This method is not intended to control bleeding once it occurs; however, it represents an important effort to prevent hemorrhagic complications during endoscopic procedures. The “water jet dissection” technique was used during the ETV procedure, when the ventricular floor appeared thick and opaque enough to obscure the basilar artery, to prevent potential basilar artery injury while creating the stoma. In the first step of this technique, a starting point was created on the floor of the third ventricle, located just behind the dorsum sellae, using bipolar forceps. A water jet was then created by injecting Ringer’s lactate solution through a 2-mm catheter. During this process, aspiration was performed to clear soft tissues and prevent an increase in potential pressure. The water jet dissection to create the stoma typically took 2–5 min. When water jet techniques were insufficient for stoma creation, bipolar forceps were used to expand the opening. This method was applied to 36 patients and was sufficient to create the stoma in 31 of them; however, it was inadequate in 5 patients. No vascular injury or bleeding was reported in the patients who underwent the procedure.

Nishihara et al. noted that using a transparent endoscopic sheath during the endoscopic evacuation of intracerebral hematomas allowed for a clearer visualization of the boundary between the hematoma and the surrounding brain tissue, thus enabling easier and quicker identification of bleeding points (8).

The primary methods used for surgical hemostasis are irrigation and, where the source of bleeding can be identified, electrocauterization. The most significant limitation of neuroendoscopic procedures is the difficulty in controlling bleeding, which has led to the search for various techniques and equipment to assist surgeons in surgical hemostasis. The “small-chamber irrigation technique,” described by Manwarig et al. (6), is one approach used to control bleeding during endoscopic procedures. The method aims to reduce visual obstruction caused by blood, which can rapidly cloud the irrigation fluid and obscure the surgical field. In this technique, a small chamber is created between the endoscope sheath and the camera, allowing the surgeon to better visualize the bleeding source. Once identified, bleeding can be managed with irrigation and cauterization. However, the limitations of this technique include situations where the source of bleeding remains outside the camera’s field of view or when bleeding stems from free-floating vessels.

Cappabianca et al. developed a method to stop bleeding that could not be controlled with irrigation (3). In this method, direct pressure is applied to the bleed using a cotton pad placed inside the endoscope cannula. The endoscope is first

removed from the cannula, followed by placing the pad into the cannula and then positioning the pad in a way that stops the bleeding using the imaging tip of the endoscope. Applying short-term pressure effectively controls the bleeding. However, this technique seems limited to situations where the source of bleeding is visible.

Nagasaka et al. introduced the “balanced irrigation-suction technique” (7). This method uses a multifunctional aspiration cannula that enables simultaneous and balanced irrigation and suction to maintain a clear view for controlling bleeding during intracerebral hematoma evacuation surgeries. This technique aims to preserve the surgeon’s field of vision during the procedure, thereby creating more favorable conditions for addressing the bleeding area.

In a case report, a 5-year-old child experienced bleeding during an endoscopic cyst fenestration. Despite a 2-min attempt at effective irrigation, the bleeding could not be controlled, leading to the endoscopic application of Floseal. After applying Floseal and waiting for 2 minutes, irrigation was performed, and a clear fluid flow was observed, indicating that the bleeding had been successfully stopped (11).

Endoscopic irrigation techniques have also been described for removing intraventricular blood. Etus et al. reported in a multicenter study that early endoscopic ventricular irrigation could be applied safely and was associated with reduced complication rates (5). These findings highlight the diversity of endoscopic strategies aimed at managing intraventricular bleeding and hematoma.

The dry-field maneuver is a technique used to control severe bleeding that can occur during intraventricular neuroendoscopic procedures. This maneuver aids in hemostasis by creating a dry surgical field, which allows platelets to aggregate at the site of the injured vessel. Additionally, it provides a better surgical view during bleeding events. The dry-field maneuver has been used in our clinic for more than a decade, and the cases have been followed up to the present day. No serious neurological complications have been observed during an average follow-up period of 5 years.

Since its introduction, the maneuver has been implemented in 13 patients in our clinic and 7 patients in other clinics, with published results (9,12). In these outcomes, no vascular or neurological complications associated with the technique have been reported, consistent with our clinic’s experience.

Theoretically, significant expected complications of the dry-field maneuver include ventricular collapse and the development of a subdural hematoma during the procedure. However, neither our clinical practice nor previous related studies reported these expected complications. Postoperative radiological imaging in patients often revealed pneumocephalus and intraventricular hematomas, but these spontaneously regressed during follow-up.

Reviewing the literature on hemorrhagic control in neuroendoscopic procedures reveals that all studies focus on developing techniques to create a clearer surgical field during bleeding. In terms of achieving hemostasis, no other effective method exists besides the dry-field maneuver. Although Floseal can be

used in all surgical procedures, it is not specific to neuroendoscopic procedures. Considering the mechanism of action of FloSeal, its combined use with the dry-field maneuver may also be more effective.

The dry-field maneuver has been effectively used for intraventricular hemorrhages. Previous findings support the hemostatic efficacy and safety of the dry-field maneuver. Given these characteristics, it raises the question of whether the dry-field maneuver can be used in elective surgeries when necessary. The use of the dry-field maneuver as a prophylactic measure can be considered, particularly in surgeries with an anticipated high likelihood of bleeding. This can offer a new perspective in developing surgery-specific hemostatic strategies, thereby enhancing the safety and efficacy of surgeries. Existing studies demonstrate the successful application of this method in major bleeding cases, but data regarding its use in elective surgeries are lacking.

CONCLUSION

The dry-field maneuver has been effective in managing intraventricular hemorrhages, with studies demonstrating its hemostatic efficacy and safety. Future studies should focus on conducting more clinical experimentation related to the dry-field maneuver and consider its broader integration into surgical practice.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

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Ethics approval and consent to participate: This study was approved by the Ege University Medical Research Ethics Committee (Decision No: 2024-208024-1.1T/15). Written informed consent was obtained from all patients or their legal guardians.

AUTHORSHIP CONTRIBUTION

Study conception and design: EB, TT

Data collection: EB, EEC

Analysis and interpretation of results: EEC

Draft manuscript preparation: EB, EEC, TT

Critical revision of the article: TT

Other (study supervision, fundings, materials, etc.): TT

All authors (EB, EEC, TT) reviewed the results and approved the final version of the manuscript.

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Diffusion Tensor Imaging Metrics Reveal Pronounced Hemispheric Asymmetry in Major White Matter Tracts

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ABSTRACT

AIM: To determine hemispheric asymmetries in major white matter tracts using diffusion tensor imaging (DTI) metrics and morphometric measurements, as comprehensive multitract analyses remain limited.

MATERIAL and METHODS: Diffusion MRI data from 102 healthy adults enrolled in the Human Connectome Project (HCP) were analyzed using DSI Studio to reconstruct 17 major white-matter tracts bilaterally. For each tract, diffusion metrics (fractional anisotropy [FA], mean diffusivity [MD], radial diffusivity [RD], axial diffusivity [AD], quantitative anisotropy [QA], isotropic value [ISO], restricted diffusion imaging [RDI], and normalized RDI [nrDI]) and morphometric parameters (fiber count, mean length, trunk volume, branch volume, total volume, and termination region areas) were quantified. Paired t-tests compared left-right hemispheric differences. Multiple comparison corrections were performed with the Benjamini–Krieger–Yekutieli procedure, and effect sizes were reported as Cohen's d.

RESULTS: Significant hemispheric asymmetries were observed in most tracts. FA was significantly higher in the left hemisphere ($p < 0.001$) for the arcuate fasciculus (AF), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), and uncinate fasciculus (UF). Mean diffusivity (MD) demonstrated left dominance in the UF and SLF2-3 ($p = 0.009$). QA was predominantly left-lateralized across multiple tracts, including AF, IFOF, ILF, and frontal aslant tract (FAT) ($p < 0.01$, Cohen's d: 0.42 to 1.17), except for the vertical occipital fasciculus (VOF), where rightward dominance was noted (Cohen's d: -0.55). Tract-trunk-branch volumes were predominantly left-lateralized in frontal lobe pathways such as AF, SLF1, SLF2, FAT, and UF ($p < 0.01$). Rightward dominance was observed in SLF3, parietal aslant tract (PAT), IFOF, ILF, and middle longitudinal fasciculus (MLF) ($p < 0.05$). Similar asymmetries were observed in termination region areas, fiber counts, and fiber lengths ($p < 0.001$).

CONCLUSION: Widespread hemispheric asymmetries were observed across multiple pathways. Such asymmetry may reflect distinct hemispheric functional specialization and the neurological basis of lateralized functions.

KEYWORDS: DTI, Metrics, Morphometric measurements, Functional topography

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■ INTRODUCTION

Diffusion tensor imaging (DTI) and tractography have emerged as indispensable tools in neuroscience and clinical neuroimaging, enabling the non-invasive, in vivo characterization of white matter tracts in the human brain (2,32,33,69). These techniques provide quantitative measures of the geometric, morphometric, and microstructural properties of fiber tracts, enhancing our understanding of the brain's structural connectivity in both healthy individuals and those with neurological disorders, including neurosurgical diseases such as brain tumors, while complementing emerging diagnostic neuroimaging techniques (6,36,39,41,46,50,70).

Previous studies have demonstrated hemispheric asymmetries in specific white matter tracts. Notably, structural lateralization of the arcuate fasciculus (AF), which is implicated in language processing, and the inferior longitudinal fasciculus (ILF), which contributes to visual integration, has been well documented (10,51). Similarly, lateralization has also been observed in subdivisions of the superior longitudinal fasciculus (SLF), which connects the frontal and parietal cortices (16,45). However, most previous studies have examined only a limited number of tracts or relied on a narrow set of DTI metrics. To date, few studies have comprehensively examined tract asymmetries across a wide array of measurements, including fiber count, fiber length, trunk and branch volumes, termination region areas, and diffusion metrics, including fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), quantitative anisotropy (QA), isotropic value (ISO), restricted diffusion imaging (RDI), and normalized RDI (nRDI).

Beyond its theoretical importance, hemispheric asymmetry also has significant clinical relevance. In neurosurgical practice, knowledge of lateralized white matter anatomy can inform resection strategies and facilitate the preservation of neurological function (17,18,31,34). Identifying hemisphere-specific structural differences in white matter tracts can help predict potential postoperative deficits in functions such as language, motor control, and vision. However, such predictions require a systematic and multidimensional evaluation of white matter anatomy.

To address this need, we analyzed 17 major white matter pathways using DTI-based tractography. By examining bilateral microstructural diffusion metrics and macrostructural morphometric measures, we aimed to elucidate the extent and patterns of hemispheric asymmetry in the healthy human brain. The findings may serve as a reference for neuroscience research and clinical applications in neurosurgery, neurology, and neurorehabilitation.

■ MATERIAL and METHODS

Participants and Data Source

This study analyzed diffusion MRI and handedness data from 102 healthy adults in the Human Connectome Project S2000 database (22). Participants were randomly selected from the publicly available dataset to ensure population-level representativeness. Handedness was assessed using the Edinburgh Handedness Inventory (EHI) (48). As specified in the HCP

dataset, hand dominance was determined using a Laterality Quotient (LQ) threshold of $\pm 40\%$, with positive values indicating right-handedness and negative values denoting left-handedness. Individuals with LQ values equal to ± 40 or falling between -40 and $+40$ were categorized as ambidextrous.

Diffusion MRI Acquisition and Tractography

Diffusion MRI data were acquired at a 3T Siemens Connectom Skyra scanner using the standard HCP multishell diffusion protocol, with b-values of 990, 1985, and 2980 s/mm² and 90 sampling directions per shell. The preprocessed HCP diffusion data, aligned to the MNI space, were resampled to 1-mm isotropic resolution.

Seventeen major white matter pathways were bilaterally reconstructed in each participant's brain using DSI Studio (<https://dsi-studio.labsolver.org/>), a dedicated diffusion imaging analysis platform. The reconstructed tracts included the AF; frontal, frontoparietal, parietal, parolfactory, and parahippocampal segments of the cingulum; capsula extrema; frontal aslant tract (FAT); inferior fronto-occipital fasciculus (IFOF); ILF; middle longitudinal fasciculus (MLF); parietal aslant tract (PAT); SLF 1, 2, and 3; uncinate fasciculus (UF); and vertical occipital fasciculus (VOF). Anatomical termination regions and functional roles of each tract are summarized in Table I.

Diffusion Reconstruction and Tracking Parameters

Diffusion data were reconstructed using generalized q-sampling imaging with a diffusion sampling length ratio of 1.7 (67). RDI was additionally computed within the DSI Studio processing pipeline. The b-table orientation was confirmed through DSI Studio's automated quality control procedure.

Tract generation for individual bundles was conducted using tract templates provided by DSI Studio. Deterministic fiber tracking was subsequently performed using 1,000,000 seed points. To reduce false-positive streamlines, a topology-informed pruning algorithm was applied iteratively for 16 cycles. Tracking was conducted with an anisotropy threshold of 0.063922, while the angular threshold was randomly varied between 15° and 90°. Step size was randomly selected between 0.5 and 1.5 voxels, and streamline length was constrained to a range of 30–300 mm. For atlas-based tract mapping, a distance tolerance of 16 mm was applied. Regions of avoidance were defined at coordinates 75, 96, 62 with a total volume of 1.6×10^6 mm³.

Measurement Parameters

For each white matter tract, bilateral morphometric and microstructural measurements were obtained. Morphometric parameters included fiber count, mean fiber length, trunk volume, branch volume, total tract volume, and areas of termination regions. Furthermore, multiple DTI-derived microstructural metrics were evaluated, including FA, MD, RD, AD, QA, ISO, RDI, and nrdi. The clinical implications and interpretations of these DTI metrics are presented in Table II.

Statistical Analysis

Statistical analyses were performed using graphpad Prism version 8.4.2. The Shapiro–Wilk and Kolmogorov–Smirnov tests

Table I: Cortical Endpoints and Functional Roles of Study-Included White Matter Tracts

Tract	Origin	Termination	Functional Role
Arcuate Fasciculus (AF)	Posterior superior temporal gyrus	Inferior frontal gyrus	Dorsal language pathway; phonological processing (10)
Cingulum – Frontal	Medial prefrontal cortex	Anterior cingulate cortex	Executive functions, emotional regulation (7,40,62)
Cingulum – Frontoparietal	ACC/dorsal cingulate	Posterior cingulate/precuneus	Default mode network connectivity (7,40,62)
Cingulum – Parietal	Posterior cingulate	Angular gyrus	Episodic memory and visuospatial integration (7,40,62)
Cingulum – Parolfactory	Medial orbitofrontal cortex	Paraterminal gyrus	Limbic–prefrontal communication (7,40,62)
Cingulum – Parahippocampal	Posterior cingulate	Parahippocampal gyrus	Memory encoding and retrieval (7,40,62)
Capsula Extrema	Superior temporal gyrus	Inferior frontal gyrus	Ventral semantic language pathway (45)
Frontal Aslant Tract (FAT)	SMA / pre-SMA	Inferior frontal gyrus	Speech initiation, volitional control (44)
Inferior Front-Occipital Fasciculus (IFOF)	Occipital cortex	Inferior frontal gyrus/OFC	Semantic processing, visual–language integration (14)
Inferior Longitudinal Fasciculus (ILF)	Occipital pole	Anterior temporal lobe	Object recognition, face processing (35)
Middle Longitudinal Fasciculus (MLF)	Superior temporal gyrus	Inferior parietal lobule	Auditory–parietal semantic pathway (19)
Parietal Aslant Tract (PAT)	Inferior parietal lobule	angular gyrus/posterior temporal lobe	Pragmatic language, working memory integration (49)
SLF-I	Superior parietal lobule	Medial premotor cortex/SMA	Motor planning and spatial attention (59)
SLF-II	Supramarginal/Angular gyrus	Dorsolateral prefrontal cortex	Working memory, attentional control (38,59)
SLF-III	Supramarginal gyrus	Inferior frontal gyrus	Phonological processing and articulation (39)
Uncinate Fasciculus (UF)	Temporal pole/Amygdala	Orbitofrontal cortex	Semantic memory, social–emotional evaluation (60)
Vertical Occipital Fasciculus (VOF)	Lateral occipital cortex	Fusiform/ITG	Reading, dorsal–ventral visual integration (48)

were used to assess data normality. Paired two-tailed t-tests were performed for evaluating left-right hemispheric differences across all metrics. A p value of <0.05 was considered statistically significant. Statistical correction for multiple comparisons was applied using the false discovery rate two-stage step-up procedure of Benjamini, Krieger, and Yekutieli, with a q value of <0.01 considered statistically significant. Effect sizes were quantified using Cohen's d for each tract and parameter.

■ RESULTS

Results were analyzed in two separate categories: DTI metrics and morphometric results. Among the 102 participants included in the study, 87 were right-handed (85.3%), 2 were left-handed (2.0%), and 13 were ambidextrous (12.7%). Since

most participants were right-handed, additional statistical analyses of both DTI metrics and morphometric measurements were conducted within the right-handed subgroup to mitigate the potential confounding effect of handedness on hemispheric asymmetry.

Diffusion Tensor Imaging Metrics

Analysis of diffusion metrics revealed significant hemispheric asymmetries across multiple tracts. FA was significantly higher in the left hemisphere in the arcuate fasciculus (AF) ($p<0.0001$, $d=1.43$), inferior fronto-occipital fasciculus ($p<0.0001$, $d=0.71$), inferior longitudinal fasciculus ($p<0.0001$, $d=0.72$), and frontal aslant tract ($p<0.0001$, $d=0.82$). Conversely, rightward FA asymmetry was observed in SLF2 ($p<0.01$, $d=-0.50$) and SLF3 ($p<0.0001$, $d=-0.75$).

Table II: DTI Metrics and Clinical Implications of Study-Included White Matter Tracts

Metric	Clinical implication	Interpretation
Fractional anisotropy (FA)	FA is nonspecifically associated with axonal integrity	decreases: demyelination, inflammation, edema, axonal loss (13)
Axial diffusivity (AD)	AD is interpreted as a marker of axonal integrity	decreases: axonal loss (8,54)
Radial diffusivity (RD)	RD is nonspecifically associated with myelination	increases: demyelination (8,55,56)
Mean diffusivity (MD)	MD is associated with edema and cell infiltration	increases: vesogenic edema, decreases: cytotoxic edema (55,56)
Quantitative diffusivity (QA)	QA is associated with axonal density	decreases: axonal loss (53,68)
Isotropic value (ISO)	ISO is associated with edema	increases: edema (68)
Restrictive diffusion imaging (RDI)	RDI is associated with cellular infiltration related to inflammation or tumor presence.	increases: cell infiltrations (inflammation or tumor infiltration) (16,65)
Normalized RDI	NRDI is associated with edema	increases: edema due to inflammation (66)

MD demonstrated rightward dominance in the AF ($p<0.0001$, $d=-0.61$), frontoparietal cingulum ($p<0.0001$, $d=-1.25$), frontal-parahippocampal cingulum ($p<0.01$, $d=-0.37$), and parolfactory cingulum ($p<0.0001$, $d=-1.53$), whereas leftward MD dominance was observed in SLF2 ($p<0.001$, $d=0.50$), SLF3 ($p<0.001$, $d=0.51$), IFOF ($p<0.01$, $d=0.43$), and uncinate fasciculus ($p<0.0001$, $d=0.69$).

RD exhibited rightward dominance in the AF ($p<0.0001$, $d=-0.90$), frontoparietal cingulum ($p<0.0001$, $d=-2.04$), frontal-parahippocampal cingulum ($p<0.0001$, $d=-0.60$), parolfactory cingulum ($p<0.0001$, $d=-0.73$), and IFOF ($p<0.001$, $d=-0.49$). In contrast, SLF2 ($p<0.0001$, $d=0.60$) and SLF3 ($p<0.001$, $d=0.54$) exhibited leftward RD asymmetry.

QA was predominantly left lateralized, with significant asymmetry in the AF ($p<0.01$, $d=0.44$), FAT ($p<0.0001$, $d=0.83$), IFOF ($p<0.001$, $d=0.54$), ILF ($p<0.01$, $d=0.42$), frontal-parahippocampal cingulum ($p<0.0001$, $d=0.56$), and frontoparietal cingulum ($p<0.0001$, $d=1.17$). The vertical occipital fasciculus showed rightward QA asymmetry ($p<0.001$, $d=-0.55$).

AD showed leftward asymmetry in the FAT ($p<0.0001$, $d=0.60$), ILF ($p<0.0001$, $d=0.86$), and SLF1 ($p<0.0001$, $d=0.57$). Rightward AD asymmetry was noted in the PAT ($p<0.0001$, $d=-1.10$), parolfactory cingulum ($p<0.0001$, $d=-1.26$), and VOF ($p<0.0001$, $d=-0.84$).

ISO was significantly greater in the left hemisphere in the FAT ($p<0.0001$, $d=0.57$) and parolfactory cingulum ($p<0.001$, $d=0.49$), whereas the VOF exhibited rightward ISO dominance ($p<0.001$, $d=-0.47$).

RDI and normalized RDI2L (nrDI2L) values demonstrated leftward asymmetry in the parolfactory cingulum (RDI: $p<0.001$, $d=0.52$; nrDI2L: $p<0.01$, $d=0.52$) and FAT (RDI: $p<0.0001$, $d=0.62$; nrDI2L: $p<0.0001$, $d=0.59$), whereas rightward dominance was observed in the VOF (RDI: $p<0.001$, $d=-0.50$; nrDI2L: $p<0.001$, $d=-0.50$). Notably, increasing the normalized RDI level (nrDI-L) from 02 to 04 revealed additional rightward asymmetry in the PAT ($p<0.01$, $d=-0.45$), indicating that greater q-space sensitivity may detect additional hemispheric lateralization patterns.

All statistically significant DTI metric results are detailed in Table III and summarized in Table IV. Additionally, the significant tract data are illustrated in Figure 1 using color-coded visualizations. Mean AD, FA, MD, and RD values for six tracts (FAT, IFOF, AF, UF, SLF2, and ILF) in both hemispheres, along with their hemispheric asymmetry graphs and statistical significance levels, are displayed in Figure 2.

Morphometric Results

Morphometric analysis revealed consistent hemispheric asymmetries across major white matter tracts. Leftward dominance was observed in the AF, FAT, ILF, SLF1, SLF2, and UF for most morphometric measures.

The FAT exhibited leftward asymmetry in all parameters except for fiber count, where no significant difference was observed. Significant leftward asymmetry in the AF was also noted across all morphometric parameters except for mean length, which exhibited rightward dominance ($p<0.0001$, $d=-1.05$).

SLF1 and SLF2 demonstrated left-sided dominance, whereas SLF3 displayed rightward asymmetry in all morphometric parameters. The IFOF exhibited rightward asymmetry across most morphometric features. Exceptions included mean length ($p<0.0001$, $d=1.49$), which was greater in the left hemisphere, and trunk volume, which did not differ significantly between hemispheres.

The parahippocampal and parolfactory segments of the cingulum were predominantly left lateralized, whereas the frontoparietal and parietal-parahippocampal segments were right-dominant. The extreme capsule exhibited significant rightward asymmetry in the second end-region area ($p<0.0001$, $d=-0.70$), total end-region area ($p<0.01$, $d=-0.39$), and mean length ($p<0.01$, $d=-0.43$).

The PAT demonstrated rightward asymmetry across most parameters with no significant laterality in irregularity, mean length, and branch volume. The VOF exhibited leftward asymmetry only in irregularity ($p<0.0001$, $d=0.63$) and total surface

Table III: Results of Diffusion Tensor and Advanced Diffusion Metrics Across Major White Matter Tracts. This table presents mean diffusion parameters for the left and right hemispheres, including axial diffusivity (AD), fractional anisotropy (FA), isotropic value (ISO), mean diffusivity (MD), radial diffusivity (RD), quantitative anisotropy (QA), restricted diffusion imaging (RDI), and normalized RDI (nRDI2L, nRDI4L). Differences (L–R), standard errors, dominant hemispheres, and corresponding Cohen's d values are shown for each tract.

Tract	p-value	Left	Right	Difference (L–R)	SE of difference	Dominant side	Cohen's d value
Axial diffusivity (AD)							
Cingulum Parolfactory	< 0.0001	0.7603	0.8046	–0.0443	0.004934	Right	–1.26
Frontal Aslant Tract	< 0.0001	0.7871	0.7704	+0.0167	0.003864	Left	0.60
Inferior Longitudinal Fasciculus	< 0.0001	0.8447	0.8172	+0.0275	0.004494	Left	0.86
Parietal Aslant Tract	< 0.0001	0.8289	0.8632	–0.0343	0.004367	Right	–1.10
Superior Longitudinal Fasciculus1	< 0.0001	0.7775	0.7648	+0.0127	0.003132	Left	0.57
VOF (Vertical Occipital Fasciculus)	< 0.0001	0.7958	0.8201	–0.0243	0.004027	Right	–0.84
Fractional anisotropy (FA)							
Arcuate Fasciculus	< 0.0001	0.4185	0.3874	+0.03116	0.003052	Left	1.43
Cingulum Frontal Parahippocampal	< 0.0001	0.3958	0.3749	+0.02086	0.003969	Left	0.74
Cingulum Frontal Parietal	< 0.0001	0.4088	0.3532	+0.05561	0.003428	Left	2.27
Frontal Aslant Tract	< 0.0001	0.3616	0.3453	+0.01631	0.002782	Left	0.82
IFOF (Inferior Fronto Occipital)	< 0.0001	0.4154	0.4006	+0.01479	0.002911	Left	0.71
ILF (Inferior Long. Fasc.)	< 0.0001	0.3941	0.3787	+0.01542	0.003005	Left	0.72
Middle Longitudinal Fasc.	< 0.001	0.3465	0.3584	–0.01186	0.003322	Right	–0.50
Parietal Aslant Tract	< 0.0001	0.3965	0.3820	+0.01448	0.002947	Left	0.69
SLF2	< 0.001	0.3878	0.3987	–0.01089	0.003034	Right	–0.50
SLF3	< 0.0001	0.3750	0.3928	–0.01772	0.003326	Right	–0.75
Isotropic value (ISO)							
Cingulum Parolfactory	< 0.001	0.3170	0.2972	+0.01985	0.005663	Left	0.49
Frontal Aslant Tract	< 0.0001	0.3667	0.3375	+0.02916	0.007142	Left	0.57
VOF (Vertical Occipal Fasciculus)	< 0.001	0.4583	0.4914	–0.03312	0.009801	Right	–0.47
Mean diffusivity (MD)							
Arcuate Fasciculus	< 0.0001	0.5305	0.5399	–0.009385	0.002140	Right	–0.61
Cingulum Frontal Parahippocampal	< 0.01	0.5341	0.5415	–0.007448	0.002796	Right	–0.37
Cingulum Frontal Parietal	< 0.0001	0.5311	0.5545	–0.02342	0.002615	Right	–1.25
Cingulum Parolfactory	< 0.0001	0.5376	0.5717	–0.03413	0.003116	Right	–1.53
IFOF	< 0.01	0.5510	0.5429	+0.008101	0.002623	Left	0.43
ILF	< 0.001	0.5555	0.5652	–0.009634	0.002687	Right	–0.50
MLF (Middle Long. Fasc.)	< 0.01	0.5760	0.5689	+0.007146	0.002519	Left	0.40
Parietal Aslant Tract	< 0.0001	0.5596	0.5698	–0.01021	0.002543	Right	–0.56
SLF2	< 0.001	0.5499	0.5418	+0.008116	0.002295	Left	0.50
SLF3	< 0.001	0.5625	0.5526	+0.009950	0.002721	Left	0.51
Uncinate Fasciculus	< 0.0001	0.5713	0.5567	+0.01465	0.002977	Left	0.69
VOF (Vertical Occipital Fasciculus)	< 0.001	0.5483	0.5576	–0.009281	0.002514	Right	–0.52

Table III: Cont.

Tract	p-value	Left	Right	Difference (L-R)	SE of difference	Dominant side	Cohen's d value
Normalized restricted diffusion imaging 02L (nRDI2L)							
Cingulum Parolfactory	< 0.01	0.2674	0.2512	+0.01614	0.004373	Left	0.52
Frontal Aslant Tract	< 0.0001	0.3089	0.2842	+0.02475	0.005850	Left	0.59
VOF (Vertical Occipital Fasciculus)	< 0.001	0.3933	0.4247	-0.03148	0.008806	Right	-0.50
Normalized restricted diffusion imaging 04L (nRDI4L)							
Cingulum Parolfactory	< 0.00001	0.03870	0.03512	+0.003583	0.0007244	Left	0.69
Frontal Aslant Tract	< 0.00001	0.04272	0.03884	+0.003881	0.0008179	Left	0.66
Parietal Aslant Tract	< 0.01	0.04360	0.04657	-0.002965	0.0009239	Right	-0.45
VOF (Vertical Occipital Fasciculus)	< 0.001	0.05599	0.06068	-0.004687	0.001257	Right	-0.52
Quantitative anisotropy (QA)							
Arcuate Fasciculus	< 0.01	0.2322	0.2178	+0.01441	0.004543	Left	0.44
Cingulum Frontal Parahippocampal	< 0.0001	0.2053	0.1887	+0.01661	0.004164	Left	0.56
Cingulum Frontal Parietal	< 0.0001	0.2136	0.1793	+0.03434	0.004121	Left	1.17
Frontal Aslant Tract	< 0.0001	0.2153	0.1893	+0.02600	0.004387	Left	0.83
IFOF	< 0.001	0.2480	0.2295	+0.01851	0.004774	Left	0.54
ILF	< 0.01	0.2376	0.2228	+0.01481	0.004889	Left	0.42
VOF (Vertical Occipital Fasciculus)	< 0.001	0.2591	0.2836	-0.02448	0.006255	Right	-0.55
Radial diffusivity (RD)							
Arcuate Fasciculus	< 0.0001	0.4060	0.4230	-0.01698	0.002632	Right	-0.90
Cingulum Frontal Parahippocampal	< 0.0001	0.4124	0.4264	-0.01401	0.003243	Right	-0.60
Cingulum Frontal Parietal	< 0.0001	0.4092	0.4555	-0.04636	0.003189	Right	-2.04
Cingulum Parolfactory	< 0.0001	0.4536	0.4717	-0.01810	0.003463	Right	-0.73
IFOF (Inferior Fronto Occipital Fasc.)	< 0.001	0.4264	0.4372	-0.01074	0.003093	Right	-0.49
Parietal Aslant Tract	< 0.0001	0.4386	0.4676	-0.02904	0.002881	Right	-1.41
SLF2	< 0.0001	0.4308	0.4199	+0.01090	0.002547	Left	0.60
SLF3	< 0.001	0.4495	0.4369	+0.01254	0.003230	Left	0.54
VOF	< 0.0001	0.4411	0.4557	-0.01465	0.002993	Right	-0.69
Restricted Diffusion Imaging (RDI)							
Cingulum Parolfactory	< 0.001	0.4059	0.3773	+0.02857	0.007671	Left	0.52
Frontal Aslant Tract	< 0.0001	0.4699	0.4323	+0.03766	0.008467	Left	0.62
VOF (Vertical Occipital Fasciculus)	< 0.001	0.5811	0.6281	-0.04697	0.01320	Right	-0.50

area ($p < 0.0001$, $d = 0.60$), with no significant differences in other morphometric parameters.

All statistically significant morphometric parameter results are presented in Table V and summarized in Table VI. Additionally, the significant tract data are illustrated in Figure 3 employing color-coded visualizations. Figure 4 presents a schemat-

ic illustration of the morphometric workflow, including their graphical representation and 3D brain projection for the AF and IFOF, encompassing the number of tracts, end regions, and branch volume. Figure 5 schematically depicts Cohen's d effect sizes derived from the measurements of all DTI metrics and morphometric parameters included in the study.

Table IV: Summary of Hemispheric Dominance for Diffusion Metrics Across Major White Matter Tracts. This table summarizes the lateralization patterns (Left [L], Right [R], or non-significant [-]) observed for each diffusion metric, including axial diffusivity (AD), fractional anisotropy (FA), isotropic value (ISO), mean diffusivity (MD), quantitative anisotropy (QA), radial diffusivity (RD), restricted diffusion imaging (RDI), and normalized RDI values (nRDI2L and nRDI4L).

Tract	AD	FA	ISO	MD	QA	RD	RDI	nRDI2L	nRDI4L
Arcuate Fasciculus	-	L	-	R	L	R	-	-	-
Cingulum Frontal Parahippocampal	-	L	-	R	L	R	-	-	-
Cingulum Frontal Parietal	-	L	-	R	L	R	-	-	-
Cingulum Parahippocampal	-	-	-	-	-	-	-	-	-
Cingulum Parahippocampal Parietal	-	-	-	-	-	-	-	-	-
Cingulum Parolfactory	R	-	L	R	-	R	L	L	L
Extreme Capsule	-	-	-	-	-	-	-	-	-
Frontal Aslant Tract	L	L	L	-	L	-	L	L	L
Inferior Fronto Occipital Fasciculus (IFOF)	-	L	-	L	L	R	-	-	-
Inferior Longitudinal Fasciculus (ILF)	L	L	-	R	L	-	-	-	-
Middle Longitudinal Fasciculus (MLF)	-	R	-	L	-	-	-	-	-
Parietal Aslant Tract	R	L	-	R	-	R	-	-	R
Superior Longitudinal Fasciculus1 (SLF1)	L	-	-	-	-	-	-	-	-
Superior Longitudinal Fasciculus2 (SLF2)	-	R	-	L	-	L	-	-	-
Superior Longitudinal Fasciculus3 (SLF3)	-	R	-	L	-	L	-	-	-
Uncinate Fasciculus (UF)	-	-	-	L	-	-	-	-	-
Vertical Occipital Tract (VOF)	R	-	R	R	R	R	R	R	R

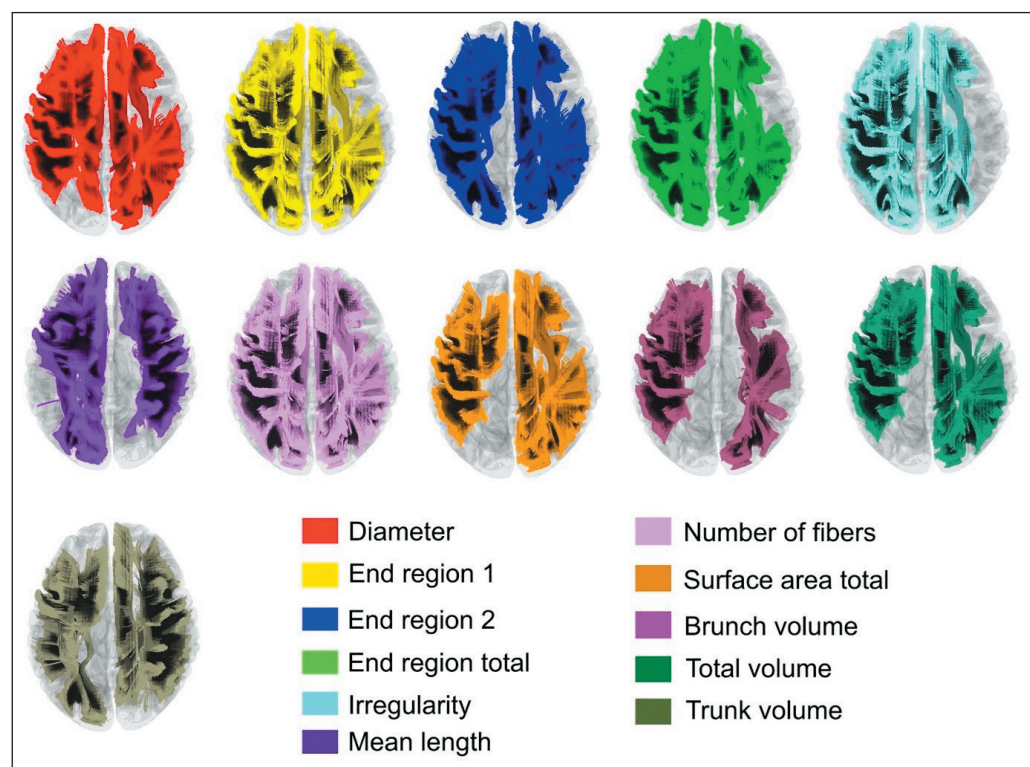


Figure 1: Color-coded representation of white matter tracts depicting statistically significant hemispheric asymmetry based on diffusion tensor imaging metrics. Each tract is displayed on the hemisphere, demonstrating dominant expression of the corresponding DTI parameter.

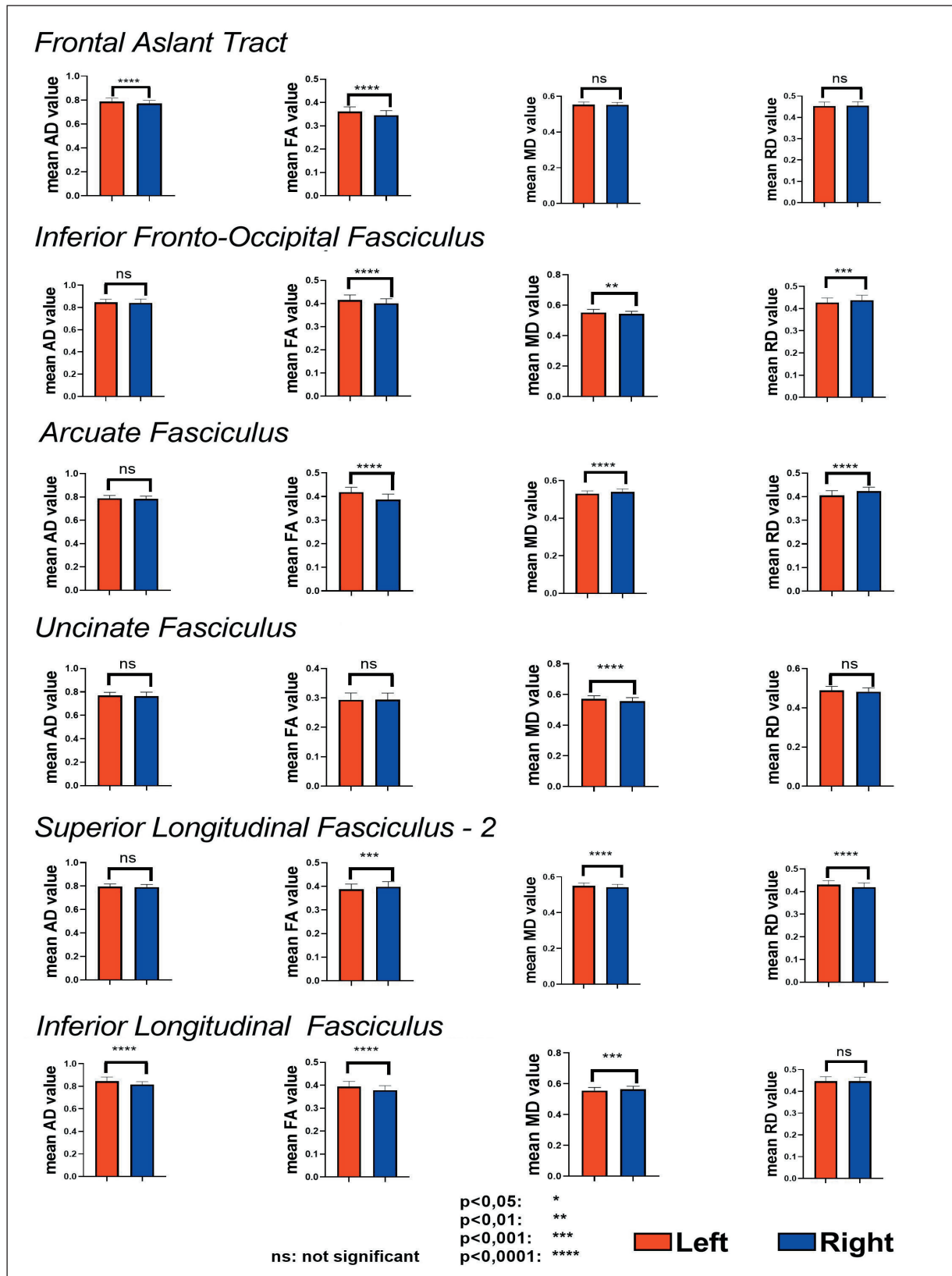


Figure 2: Graphical representation of the mean AD, FA, MD, and RD values for six white- matter tracts (frontal aslant tract, inferior fronto-occipital fasciculus, arcuate fasciculus, uncinate fasciculus, superior longitudinal fasciculus II, and inferior longitudinal fasciculus), along with the statistical significance levels of their hemispheric asymmetries.

Table V: Quantitative Morphometric Measurements of Major White Matter Tracts. This table presents the mean morphometric parameters (diameter, end region areas, irregularity, length, fiber count, surface area, and volume measures) for the left and right hemispheres. Differences (L–R), standard errors, and Cohen's d values are provided for each tract, with the dominant hemisphere indicated.

Tract	p-value	Left	Right	Difference (L–R)	SE of difference	Dominant side	Cohen's d value
Diameter (mm)							
Arcuate Fasciculus	< 0.0001	12.72	7.284	+5.432	0.2948	Left	2.58
Cingulum Parahippocampal	< 0.0001	12.12	10.68	+1.447	0.1991	Left	1.02
Cingulum Parolfactory	< 0.0001	9.377	7.323	+2.055	0.1361	Left	2.11
Frontal Aslant Tract	< 0.0001	16.14	13.61	+2.521	0.2775	Left	1.27
Superior Longitudinal Fasciculus1 (SLF1)	< 0.0001	11.11	7.905	+3.207	0.1887	Left	2.38
Superior Longitudinal Fasciculus2 (SLF2)	< 0.0001	17.34	12.51	+4.834	0.2855	Left	2.37
Uncinate Fasciculus	< 0.0001	12.69	10.77	+1.912	0.1774	Left	1.51
Cingulum Frontal Parietal	< 0.0001	9.509	13.55	–4.043	0.1466	Right	–3.86
Cingulum Parahippocampal Parietal	< 0.0001	6.940	8.717	–1.777	0.1800	Right	–1.38
Inferior Fronto Occipital Fasciculus (IFOF)	< 0.0001	10.10	11.71	–1.611	0.2282	Right	–0.99
Middle Longitudinal Fasciculus (MLF)	< 0.0001	5.836	8.583	–2.746	0.2744	Right	–1.40
Parietal Aslant Tract	< 0.0001	16.08	19.76	–3.678	0.2680	Right	–1.92
Superior Longitudinal Fasciculus3 (SLF3)	< 0.0001	13.84	16.18	–2.342	0.1918	Right	–1.71
Area of end region - 1st (mm³)							
Arcuate Fasciculus	< 0.0001	1609	569.5	+1040	75.33	Left	1.93
Cingulum Frontal Parahippocampal	< 0.0001	365.2	282.6	+82.6	17.97	Left	0.64
Cingulum Parahippocampal	< 0.0001	1580	1068	+512.2	54.74	Left	1.31
Cingulum Parolfactory	< 0.0001	1414	885.7	+528.5	52.63	Left	1.41
Frontal Aslant Tract	< 0.0001	2041	1523	+518.3	92.35	Left	0.79
Inferior Longitudinal Fasciculus (ILF)	< 0.0001	2260	1608	+651.8	112.5	Left	0.81
Superior Longitudinal Fasciculus1 (SLF1)	< 0.0001	1152	436.5	+715.8	40.37	Left	2.48
Superior Longitudinal Fasciculus2 (SLF2)	< 0.0001	1980	1363	+616.8	92.78	Left	0.93
Uncinate Fasciculus	< 0.01	1605	1392	+212.7	63.80	Left	0.47
Cingulum Frontal Parietal	< 0.0001	995.2	1934	–938.9	58.79	Right	–2.24
Cingulum Parahippocampal Parietal	< 0.0001	482.8	964.3	–481.5	47.06	Right	–1.43
Inferior Fronto Occipital Fasciculus (IFOF)	< 0.0001	1008	1905	–896.8	78.23	Right	–1.61
Middle Longitudinal Fasciculus (MLF)	< 0.0001	231.3	492.9	–261.6	34.79	Right	–1.05
Parietal Aslant Tract	< 0.0001	2708	4120	–1412	144.0	Right	–1.37
Superior Longitudinal Fasciculus3 (SLF3)	< 0.0001	1427	1940	–512.7	68.01	Right	–1.06
Area of end region – 2nd (mm³)							
Arcuate Fasciculus	< 0.0001	1605	553.8	+1051	73.81	Left	1.99
Cingulum Parolfactory	< 0.0001	998.1	656.5	+341.6	31.10	Left	1.54
Frontal Aslant Tract	< 0.0001	2266	1556	+710.1	93.37	Left	1.06
Inferior Longitudinal Fasciculus (ILF)	< 0.0001	1841	1198	+643.6	84.13	Left	1.07
Superior Longitudinal Fasciculus1 (SLF1)	< 0.0001	1014	389.2	+625.1	37.59	Left	2.33
Superior Longitudinal Fasciculus2 (SLF2)	< 0.0001	2399	1258	+1141	94.78	Left	1.69

Table V: Cont.

Tract	p-value	Left	Right	Difference (L-R)	SE of difference	Dominant side	Cohen's d value
Uncinate Fasciculus	< 0.0001	1371	878.1	+492.8	63.40	Left	1.09
Cingulum Frontal Parietal	< 0.0001	1097	2664	-1567	63.39	Right	-3.46
Cingulum Parahippocampal Parietal	< 0.0001	271.4	416.7	-145.4	23.35	Right	-0.87
Extreme Capsule	< 0.0001	329.6	551.4	-221.9	44.34	Right	-0.70
Inferior Fronto Occipital Fasciculus (IFOF)	< 0.01	1398	1692	-294.8	92.08	Right	-0.45
Middle Longitudinal Fasciculus (MLF)	< 0.0001	347.7	906.7	-559.0	59.88	Right	-1.31
Parietal Aslant Tract	< 0.0001	2067	3080	-1013	103.9	Right	-1.36
Superior Longitudinal Fasciculus3 (SLF3)	< 0.0001	1477	2329	-852.3	70.76	Right	-1.69
Area of end region – total (mm³)							
Arcuate Fasciculus	< 0.0001	3214	1123	+2090	143.3	Left	2.04
Cingulum Frontal Parietal	< 0.0001	2092	4598	-2505	111.6	Right	-3.14
Cingulum Parahippocampal	< 0.0001	2405	1859	+546.4	88.76	Left	0.86
Cingulum Parahippocampal Parietal	< 0.0001	754.2	1381	-626.9	64.06	Right	-1.37
Cingulum Parolfactory	< 0.0001	2412	1542	+870.1	72.61	Left	1.68
Extreme Capsule	< 0.01	761.1	1015	-254.3	92.29	Right	-0.39
Frontal Aslant Tract	< 0.0001	4307	3078	+1228	174.8	Left	0.98
Inferior Fronto Occipital Fasciculus (IFOF)	< 0.0001	2405	3597	-1192	159.8	Right	-1.04
Inferior Longitudinal Fasciculus (ILF)	< 0.0001	4101	2806	+1295	187.2	Left	0.97
Middle Longitudinal Fasciculus (MLF)	< 0.0001	579.0	1400	-820.6	91.16	Right	-1.26
Parietal Aslant Tract	< 0.0001	4775	7200	-2424	233.8	Right	-1.45
Superior Longitudinal Fasciculus1 (SLF1)	< 0.0001	2167	825.6	+1341	72.63	Left	2.59
Superior Longitudinal Fasciculus2 (SLF2)	< 0.0001	4379	2621	+1758	180.6	Left	1.36
Superior Longitudinal Fasciculus3 (SLF3)	< 0.0001	2904	4269	-1365	129.4	Right	-1.48
Uncinate Fasciculus	< 0.0001	2976	2270	+705.4	111.1	Left	0.89
Irregularity							
Arcuate Fasciculus	< 0.0001	9.435	7.124	+2.312	0.1660	Left	1.95
Cingulum Frontal Parietal	< 0.0001	7.831	9.548	-1.717	0.08410	Right	-2.86
Cingulum Parahippocampal	< 0.0001	8.921	8.152	+0.7686	0.09134	Left	1.18
Cingulum Parahippocampal Parietal	< 0.0001	6.463	7.317	-0.8538	0.09538	Right	-1.25
Cingulum Parolfactory	< 0.0001	7.362	6.222	+1.140	0.09303	Left	1.72
Frontal Aslant Tract	< 0.0001	9.789	9.307	+0.4823	0.09076	Left	0.74
Inferior Fronto Occipital Fasciculus (IFOF)	< 0.0001	8.427	9.123	-0.6960	0.1075	Right	-0.91
Inferior Longitudinal Fasciculus (ILF)	< 0.001	10.92	11.34	-0.4250	0.1170	Right	-0.51
Superior Longitudinal Fasciculus1 (SLF1)	< 0.001	8.904	8.144	+0.7594	0.2217	Left	0.48
Superior Longitudinal Fasciculus2 (SLF2)	< 0.0001	12.44	10.54	+1.904	0.2323	Left	1.15
Superior Longitudinal Fasciculus3 (SLF3)	< 0.0001	9.929	10.99	-1.059	0.1116	Right	-1.33
Uncinate Fasciculus	< 0.0001	8.968	7.184	+1.784	0.1038	Left	2.41
Vertical Occipital Fasciculus (VOF)	< 0.0001	9.414	8.820	+0.5943	0.1318	Left	0.63

Table V: Cont.

Tract	p-value	Left	Right	Difference (L-R)	SE of difference	Dominant side	Cohen's d value
Mean lenght (mm)							
Arcuate Fasciculus	< 0.0001	120.9	130.4	-9.508	1.272	Right	-1.05
Cingulum Parolfactory	< 0.0001	75.97	118.0	-41.98	1.233	Right	-4.77
Extreme Capsule	< 0.01	93.06	96.32	-3.263	1.051	Right	-0.43
Superior Longitudinal Fasciculus2	< 0.0001	68.12	96.61	-28.49	1.444	Right	-2.76
Superior Longitudinal Fasciculus3	< 0.0001	61.32	70.95	-9.633	1.034	Right	-1.30
Uncinate Fasciculus	< 0.0001	70.52	74.67	-4.149	1.044	Right	-0.56
Cingulum Frontal Parahippocampal	< 0.01	115.3	110.6	+4.711	1.570	Left	0.42
Cingulum Frontal Parietal	< 0.0001	108.6	99.10	+9.530	1.384	Left	0.96
Cingulum Parahippocampal	< 0.0001	47.16	44.47	+2.690	0.4263	Left	0.88
Cingulum Parahippocampal Parietal	< 0.0001	96.51	90.39	+6.119	1.109	Left	0.77
Frontal Aslant Tract	< 0.0001	79.42	76.48	+2.946	0.5391	Left	0.77
Inferior Fronto Occipital Fasciculus (IFOF)	< 0.0001	174.0	162.2	+11.78	1.105	Left	1.49
Inferior Longitudinal Fasciculus (ILF)	< 0.01	114.2	111.5	+2.718	0.9309	Left	0.41
Middle Longitudinal Fasciculus (MLF)	< 0.0001	108.6	91.29	+17.31	1.546	Left	1.57
Number of fibers							
Arcuate Fasciculus	< 0.0001	36649	15581	+21068	2290	Left	1.29
Cingulum Frontal Parahippocampal	< 0.001	17287	12604	+4682	1289	Left	0.51
Cingulum Parolfactory	< 0.0001	94122	41694	+52428	3119	Left	2.35
Inferior Longitudinal Fasciculus (ILF)	< 0.0001	48886	26110	+22776	2626	Left	1.21
Superior Longitudinal Fasciculus1 (SLF1)	< 0.0001	26135	6794	+19341	1116	Left	2.43
Superior Longitudinal Fasciculus2 (SLF2)	< 0.0001	38310	22479	+15832	2093	Left	1.06
Cingulum Frontal Parietal	< 0.0001	31100	59366	-28266	2184	Right	-1.81
Cingulum Parahippocampal Parietal	< 0.0001	16550	24995	-8446	1958	Right	-0.60
Inferior Fronto Occipital Fasciculus (IFOF)	< 0.0001	25763	40216	-14454	2313	Right	-0.87
Middle Longitudinal Fasciculus (MLF)	< 0.0001	7836	27625	-19790	2314	Right	-1.20
Parietal Aslant Tract	< 0.0001	71595	101522	-29926	4856	Right	-0.86
Superior Longitudinal Fasciculus3 (SLF3)	< 0.0001	42916	54937	-12021	2634	Right	-0.64
Uncinate Fasciculus	< 0.0001	67505	84464	-16959	3854	Right	-0.62
Total surface area (mm³)							
Arcuate Fasciculus	< 0.0001	45999	21685	+24314	1343	Left	2.53
Cingulum Frontal Parietal	< 0.0001	25608	40283	-14674	731.5	Right	-2.81
Cingulum Parahippocampal	< 0.0001	16132	12244	+3888	388.6	Left	1.40
Cingulum Parahippocampal Parietal	< 0.0001	13706	18215	-4509	500.8	Right	-1.26
Frontal Aslant Tract	< 0.0001	39517	30523	+8994	846.8	Left	1.49
Inferior Fronto Occipital Fasciculus (IFOF)	< 0.0001	47033	54678	-7645	1455	Right	-0.74
Middle Longitudinal Fasciculus (MLF)	< 0.0001	14783	18966	-4183	887.4	Right	-0.66
Parietal Aslant Tract	< 0.0001	36625	45280	-8655	844.8	Right	-1.43
Superior Longitudinal Fasciculus1 (SLF1)	< 0.0001	23347	15685	+7662	666.8	Left	1.61

Table V: Cont.

Tract	p-value	Left	Right	Difference (L-R)	SE of difference	Dominant side	Cohen's d value
Superior Longitudinal Fasciculus2 (SLF2)	< 0.001	46166	40856	+5310	1586	Left	0.47
Superior Longitudinal Fasciculus3 (SLF3)	< 0.0001	26434	39629	-13195	715.4	Right	-2.58
Uncinate Fasciculus	< 0.0001	25346	18401	+6944	655.5	Left	1.48
Vertical Occipital Fasciculus (VOF)	< 0.0001	22211	20025	+2185	506.3	Left	0.60
Branch volume (mm³)							
Arcuate Fasciculus	< 0.0001	7769	2806	+4964	333.4	Left	2.08
Cingulum Parahippocampal Parietal	< 0.0001	1627	2136	-509	124.9	Right	-0.57
Frontal Aslant Tract	< 0.001	2258	1526	+732.2	208.9	Left	0.49
Inferior Fronto Occipital Fasciculus (IFOF)	< 0.0001	7974	9941	-1967	454.7	Right	-0.61
Inferior Longitudinal Fasciculus (ILF)	< 0.001	10472	12360	-1889	521.4	Right	-0.51
Middle Longitudinal Fasciculus (MLF)	< 0.01	1423	1888	-465.2	142.7	Right	-0.46
Superior Longitudinal Fasciculus1 (SLF1)	< 0.001	2514	1924	+589.9	167.8	Left	0.49
Superior Longitudinal Fasciculus2 (SLF2)	< 0.0001	10262	7597	+2665	501.1	Left	0.74
Superior Longitudinal Fasciculus3 (SLF3)	< 0.0001	3744	5859	-2115	307.1	Right	-0.96
Uncinate Fasciculus	< 0.0001	4809	2755	+2054	204.2	Left	1.41
Trunk volume (mm³)							
Arcuate Fasciculus	< 0.0001	7858	3112	+4746	464.8	Left	1.43
Cingulum Frontal Parietal	< 0.0001	3012	9046	-6034	371.2	Right	-2.28
Cingulum Parahippocampal	< 0.0001	4335	3062	+1273	204.5	Left	0.87
Cingulum Parahippocampal Parietal	< 0.0001	2167	3372	-1204	202.2	Right	-0.83
Frontal Aslant Tract	< 0.0001	14252	9796	+4456	601.6	Left	1.04
Inferior Longitudinal Fasciculus (ILF)	< 0.0001	6443	3593	+2850	439.8	Left	0.91
Middle Longitudinal Fasciculus (MLF)	< 0.0001	1839	3769	-1931	285.2	Right	-0.95
Parietal Aslant Tract	< 0.0001	10425	16751	-6326	700.6	Right	-1.26
Superior Longitudinal Fasciculus1 (SLF1)	< 0.0001	4841	1959	+2882	249.8	Left	1.62
Superior Longitudinal Fasciculus3 (SLF3)	< 0.0001	5601	8822	-3222	438.9	Right	-1.03
Total volume (mm³)							
Arcuate Fasciculus	< 0.0001	15628	5918	+9710	543.1	Left	1.43
Cingulum Frontal Parietal	< 0.0001	7854	14352	-6498	304.2	Right	-2.28
Cingulum Parahippocampal	< 0.0001	5555	4047	+1507	179.8	Left	0.87
Cingulum Parahippocampal Parietal	< 0.0001	3794	5507	-1713	203.8	Right	-0.83
Frontal Aslant Tract	< 0.0001	16511	11322	+5188	508.3	Left	1.04
Inferior Fronto Occipital Fasciculus (IFOF)	< 0.0001	14432	17673	-3241	625.6	Right	-0.33
Middle Longitudinal Fasciculus (MLF)	< 0.0001	3262	5658	-2396	315.0	Right	-0.95
Parietal Aslant Tract	< 0.0001	13712	20168	-6456	489.1	Right	-1.26
Superior Longitudinal Fasciculus1 (SLF1)	< 0.0001	7356	3884	+3472	216.5	Left	1.62
Superior Longitudinal Fasciculus2 (SLF2)	< 0.0001	16212	12466	+3746	629.8	Left	0.33
Superior Longitudinal Fasciculus3 (SLF3)	< 0.0001	9345	14682	-5337	349.7	Right	-1.03
Uncinate Fasciculus	< 0.0001	9028	6935	+2094	279.9	Left	0.02

Table VI: Summary of Morphometric Lateralization Patterns Across Major White Matter Tracts. This table summarizes the dominant hemisphere (Left [L] or Right [R]) for each morphometric parameter, as detailed in Table IV.

Tract	Diam.	EndR1	EndR2	EndR Total	Irreg.	Mean Length	N. of Fibers	Surf. Area Total	Vol. Branch	Vol. Total	Vol. Trunk
AF	L	L	L	L	L	R	L	L	L	L	L
CFPH	-	L	-	-	-	L	L	-	-	-	-
CFP	R	R	R	R	R	L	R	R	-	R	R
CPH	L	L	-	L	L	L	-	L	-	L	L
CPHP	R	R	R	R	R	L	R	R	R	R	R
CP	L	-	L	L	L	R	L	-	-	-	-
EC	-	-	R	R	-	R	-	-	-	-	-
FAT	L	L	L	L	L	L	-	L	L	L	L
IFOF	R	R	R	R	R	L	R	R	R	R	-
ILF	-	L	L	L	R	L	L	-	R	-	L
MLF	R	R	R	-	-	L	R	R	R	R	R
PAT	R	R	R	R	-	-	R	R	-	R	R
SLF1	L	L	L	L	L	-	L	L	L	L	L
SLF2	L	L	L	L	L	R	L	L	L	L	-
SLF3	R	R	R	R	R	R	R	R	R	R	R
UF	L	L	L	L	L	R	R	L	L	L	-
VOF	-	-	-	-	L	-	-	L	-	-	-

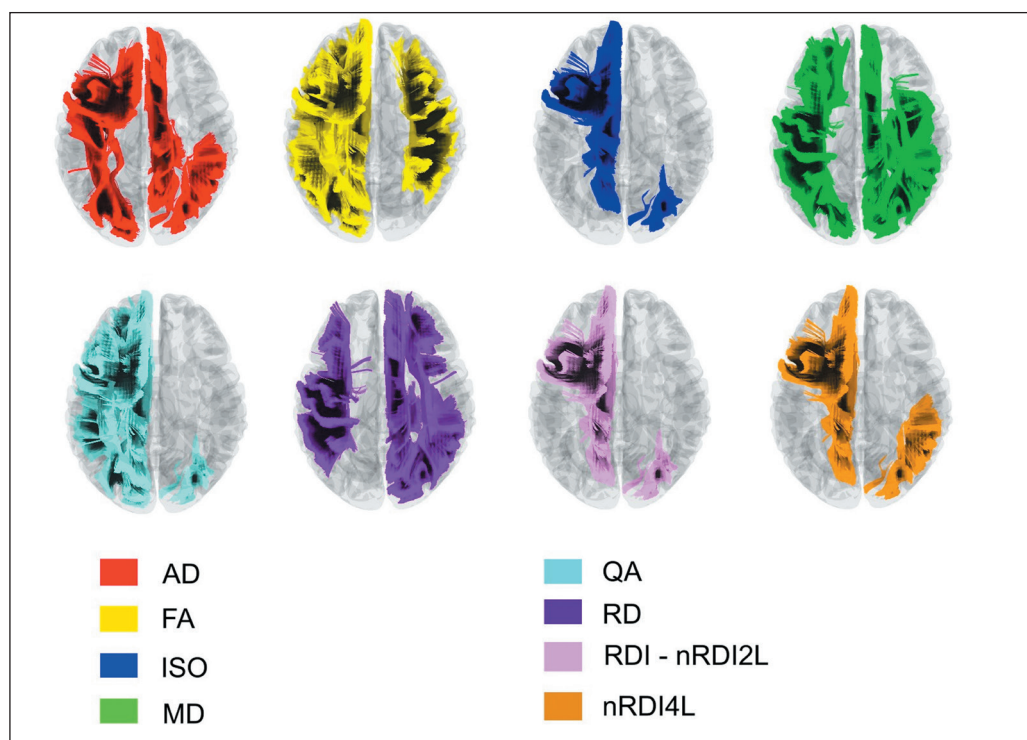


Figure 3: Color-coded representation of white matter tracts demonstrating statistically significant hemispheric asymmetry based on morphometric measurements. Each tract is displayed on the hemisphere where the corresponding morphometric parameter is dominant.

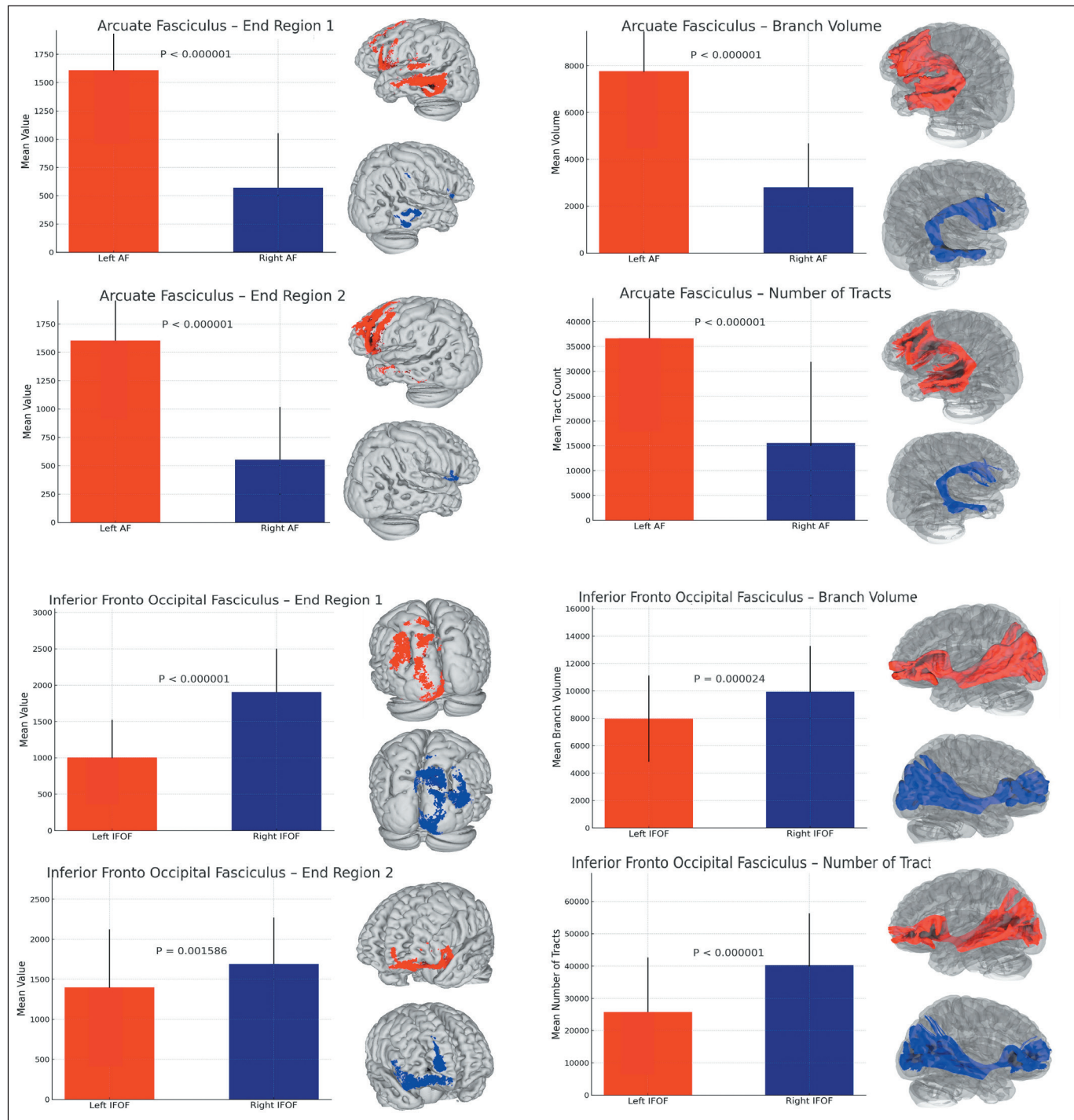


Figure 4: Graphical representation of the mean number of tracts, end-region distributions, and branch volumes of the arcuate fasciculus and inferior fronto-occipital fasciculus, together with their corresponding representations projected onto a three-dimensional brain model.

Right-Handed Subgroup Analysis

All statistical analyses were repeated in the right-handed subgroup to assess robustness and to control for potential confounding by handedness. The results were consistent with

those of the full cohort. Subgroup analysis revealed no statistically significant deviations or newly emerging effects. The direction and magnitude of hemispheric asymmetries in both DTI metrics and morphometric measures remained consistent.

In the AF, leftward asymmetry was noted for FA, number of tracts, and total volume, whereas MD, RD, and mean length demonstrated rightward asymmetry (each $p < 0.0001$). Within SLF2, FA was right lateralized, whereas MD and RD demonstrated leftward asymmetry. Mean length exhibited rightward asymmetry, whereas the number of tracts and total volume demonstrated leftward asymmetry (mean length, number of tracts, and volume: $p < 0.0001$; FA, MD, and RD: $p < 0.01$). No significant asymmetry was detected in SLF1 for FA or MD; however, tract volume, number of tracts, and AD were left-lateralized (each $p < 0.0001$). In SLF3, FA exhibited rightward asymmetry ($p < 0.0001$), while MD and RD showed leftward asymmetry ($p < 0.01$); additionally, mean length, number of tracts, and total volume demonstrated rightward dominance (all $p < 0.0001$).

Within the cingulum, FA demonstrated leftward asymmetry in the frontal-parahippocampal segment ($p < 0.0001$), while the frontal-parietal segment exhibited rightward asymmetry ($p < 0.0001$). RD was right-lateralized in both the frontal-parietal and frontal-parahippocampal segments (each $p < 0.0001$). Mean length demonstrated leftward asymmetry across all cingulum segments except the parolfactory subdivision (each $p < 0.01$). Regarding the number of tracts, leftward dominance was recorded in the parolfactory and frontal-parahippocampal segments, whereas rightward dominance was detected in the frontal-parietal and parietal-parahippocampal segments (each $p < 0.001$).

■ DISCUSSION

This study systematically examined hemispheric asymmetries in major white matter tracts by combining DTI metrics with morphometric measurements (Figure 5). Our results indicate that lateralization varies across tracts or modalities, showing highly tract-specific and metric-specific patterns rather than a uniform organization. Language-related tracts, including the AF, FAT, ILF, and UF, demonstrated pronounced leftward asymmetry across multiple microstructural indices (FA, MD, and QA) and morphometric parameters (tract volume and termination area). However, the rightward asymmetry observed in the MD of the AF represents an exception to this overall pattern. These findings are consistent with established left-hemisphere dominance for language processing and provide further insight into the structural basis for this functional lateralization (10,21). In contrast, tracts such as SLF2, SLF3, PAT, and VOF demonstrated rightward asymmetry, particularly in FA, RD, and morphometric measures, consistent with their roles in attentional, motor, and visuospatial processing. The IFOF showed rightward asymmetry in morphometric indices but not consistently in diffusion metrics, suggesting that lateralization may be primarily macrostructural without corresponding microstructural differences.

Our findings align with previous studies reporting leftward asymmetry in language-related tracts and rightward asymmetry in attentional and visuospatial pathways (49,56). Nevertheless, structural lateralization of the AF, particularly in monolingual individuals, has been linked to language abilities, including vocabulary and semantic fluency (1,62). In one

study, AF fiber counts demonstrated leftward asymmetry in both right- and left-handed individuals, while FA remained symmetrical (1). No association between right-handedness and AF lateralization was identified. The authors further reported that the streamline lateralization of the AF correlated with language performance, whereas FA lateralization did not; however, these findings did not remain significant after correction for multiple comparisons (1). Unlike our findings, a previous study reported lower MD values in the right AF compared with the left AF irrespective of handedness, with no significant differences in total volume or mean fiber length (64). In our study, however, MD values were lower on the left, mean fiber length was greater on the right, and both total volume and trunk volume were left-lateralized. Notably, this study included trilingual participants, and the authors reported a correlation between fMRI-determined language lateralization and DTI findings in monolingual individuals. The observed discrepancy between the two studies may therefore be related to the random selection of participants in our cohort, independent of the number of languages spoken.

Furthermore, some studies report increased fiber density in the AF independent of handedness or functional language lateralization, suggesting that structural AF asymmetry may not directly determine hemispheric language dominance (60). However, the authors reported that right-handedness was associated with fMRI language lateralization ($p = 0.001$). This discrepancy may reflect differences in the functional connectivity patterns captured by DTI and fMRI methodologies. In this context, one study reported AF-related bilateral language lateralization in 52% of participants using DTI, compared with only 4% in the same cohort using fMRI (64). Overall, these findings indicate a more complex relationship between AF tractographic lateralization and functional connectivity lateralization than previously assumed, with the present study providing a useful reference framework.

The SLF, a key pathway for visuospatial attention, is generally considered symmetric when evaluated as a whole (16). Nevertheless, the right SLF is often reported to have greater volume than the left (38,47). In our study, SLF1 and SLF2 exhibited leftward dominance in total volume, whereas SLF3 was right-dominant. For trunk volume, SLF1 was left-dominant and SLF3 right-dominant, while SLF2 demonstrated no significant asymmetry. Previous studies frequently attribute the apparent overall symmetry of the SLF to the inclusion of SLF1 within the total structure (16,38). Conversely, some studies have reported leftward lateralization of SLF2, which connects frontoparietal and frontotemporal regions (5,57,59,61) and has been linked to language lateralization. Overall, the literature remains inconclusive regarding the lateralization of the SLF and its subcomponents. These inconsistencies underscore the need for further randomized controlled studies with robust datasets to better elucidate structural and functional lateralization and the relationship between them.

In a study of the cingulum, a fiber-based approach rather than an ROI-based analysis revealed significantly higher left hemispheric FA values across all segments except the posterior portion, with no significant association between lateralization

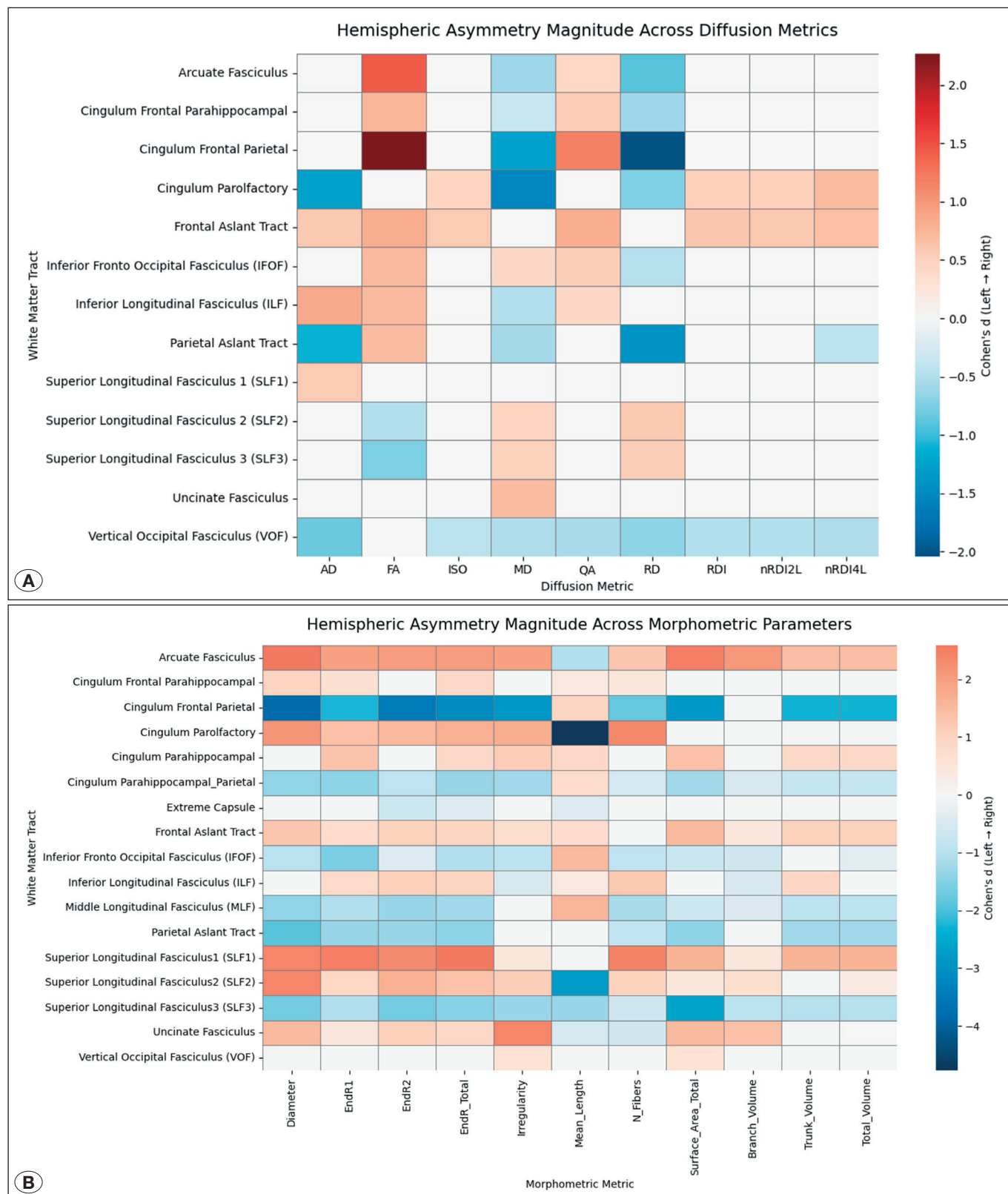


Figure 5: Hemispheric asymmetry heatmaps for diffusion and morphometric metrics. **A)** Heatmap depicting tract-specific hemispheric asymmetries across diffusion measures (FA, MD, AD, RD, QA, ISO, RDI, nrdi2l, and nrdi4l). Positive Cohen's d values (blue tones) denote leftward dominance, whereas negative values (red tones) indicate rightward dominance. **B)** Corresponding heatmap illustrating asymmetry profiles across morphometric parameters (diameter, fiber count, mean length, end-region area, surface area, and tract volumes). Color intensity reflects the magnitude of Cohen's d, representing the strength of lateralization for each tract and metric.

and handedness (23). In that study, bilateral FA elevation was observed only in right-handed individuals, a finding consistent with the results of our study. Similarly, in our cohort, significant leftward FA dominance was observed in the frontoparietal and frontal-parahippocampal segments, with no significant lateralization in the posterior segments. The absence of significant differences between the DTI results of the entire cohort and those of the right-handed subgroup further supports previous evidence that handedness is not consistently associated with the lateralization of DTI findings.

The observed divergences between metrics, such as leftward asymmetry in QA alongside rightward asymmetry in RD within the same tract, indicate that white matter asymmetry is multidimensional and cannot be captured by a single metric. These patterns, evident across both diffusion- and geometry-based analyses, underscore the complexity of hemispheric specialization and emphasize the need for a multimodal approach to evaluate white matter asymmetry. By incorporating additional measures of microstructural and diffusional heterogeneity, such as QA, ISO, and RDI, this study offers a more nuanced perspective on lateralization. The use of RDI and nrDI , in particular, has enabled the detection of fiber density variations that are not readily captured by conventional tensor models. Increased q -space sensitivity in nrDI further revealed rightward asymmetry in the PAT, highlighting the sensitivity of higher-order diffusion models (9). These results may help explain cross-modal discrepancies in lateralization and emphasize the importance of high-resolution, multishell acquisition schemes, such as those in the HCP dataset. Moreover, incorporating techniques such as neurite orientation dispersion and density imaging and multi-compartment modeling may better delineate the microstructural asymmetries and their linkage to cortical functions (15,71).

Another key strength of this study lies in its methodological rigor. By using a consistent ROI-based segmentation approach across 17 bilaterally tracked fiber bundles and analyzing diverse metrics under the same pipeline, we minimized variability and maximized comparability across participants and tracts. Moreover, effect sizes were systematically reported alongside significance values to reflect both statistical and practical relevance. The combined assessment of macrostructural and microstructural asymmetries offers a robust basis for future research exploring sex differences, developmental trajectories, or neuropathological alterations in white matter lateralization. In this context, group-wise tractometry pipelines, such as tractseg and bundlewarp, provide scalable tools for delineating variability and asymmetry in large neuroimaging cohorts (52).

Importantly, these asymmetry profiles have substantial clinical relevance, particularly for neurosurgical planning. Tracts such as the AF and FAT, which consistently demonstrated leftward dominance, are frequently located near eloquent cortical regions supporting language production and executive function. Recognizing normative asymmetry in these structures is essential for differentiating physiological lateralization from pathological changes, such as tumor-induced displacement or edema. The use of lateralized morphometric and micro-

structural profiles may enhance preoperative risk stratification and help inform resection boundaries to minimize postoperative functional deficits. Moreover, the observed dissociation between morphometric and diffusion-based asymmetries in certain tracts (e.g., IFOF and VOF) suggests that reliance on a single modality may yield incomplete or potentially misleading interpretations. Therefore, multimodal tractography protocols incorporating both geometric and diffusion metrics may enhance intraoperative decision-making, especially in patients with lesions in close proximity to high-risk fiber bundles. These normative asymmetry maps may serve as a valuable reference for individualized, function-preserving neurosurgical approaches (3,18,33,49,62). Recent studies emphasize that integrating tractography into neuronavigation systems and 3D models improves the localization of eloquent pathways and surgical safety margins during resection (4,24-28).

Nevertheless, some limitations should be acknowledged. While the study used a relatively large and well-curated dataset, its cross-sectional design limits inference on developmental or age-related changes. Additionally, DTI-based metrics, while informative, are indirect proxies of histological properties and require cautious interpretation, especially when making clinical extrapolations (50,65). Furthermore, hemispheric asymmetries may be influenced by individual differences in handedness, cognitive strategies, or structural anomalies not explicitly controlled for in this dataset. Previous studies have demonstrated that metrics derived from both the whole brain and major white matter tracts may be affected by extrinsic factors. Although studies in children link handedness to the lateralization of functional connectivity, mean DTI metrics also vary by sex and age (53,58). Similar variability has been observed in monozygotic twins, where male twins, concordant twin pairs, and right-handed twins tend to exhibit a leftward predisposition in AF lateralization (30), suggesting nongenetic influences on cerebral network asymmetry. Accordingly, it is increasingly recognized that accounting for individual variability in white matter structure is critical for accurately characterizing lateralization patterns, particularly in clinical populations (20). However, due to the random selection of participants in this study, the number of left-handed and ambidextrous individuals was inadequate for sufficiently powered subgroup analyses. Future studies with larger samples of left-handed and ambidextrous participants are therefore warranted to more definitively clarify the relationship between handedness and white matter lateralization.

Future studies may benefit from integrating large-scale datasets and leveraging machine learning techniques to predict functional lateralization patterns from structural features. Additionally, incorporating three-dimensional tract models into augmented and virtual reality-based intraoperative navigation systems could further improve surgical planning and outcomes. Integrating diffusion metrics with AI-assisted diagnostic tools, large clinical datasets, and 3D segmentations may enable the development of personalized asymmetry maps, thereby improving diagnostic accuracy, treatment, and rehabilitation strategies in both research and clinical neurosurgical settings (11,12,29,37,42,43,63).

CONCLUSION

This study comprehensively evaluated hemispheric asymmetry in major white matter tracts using morphometric and advanced diffusion metrics. The findings confirm distinct lateralization patterns, particularly leftward dominance in language-related tracts and rightward dominance in attentional and visuospatial pathways. These normative asymmetry profiles may inform neurosurgical planning, enhance tract-specific risk assessment, and enable personalized neurorehabilitation. Future work integrating AI, large-scale datasets, and 3D visualization tools may further refine clinical applications of tractography-based asymmetry analysis.

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Ethics approval and consent to participate: The present study used de-identified, publicly available data from the Human Connectome Project (HCP). No new participant recruitment or data collection was performed. Therefore, additional institutional review board approval was not required for this secondary analysis.

AUTHORSHIP CONTRIBUTION

Study conception and design: TK, EC, MYA, SH

Data collection: TK, EC, SNK, BK, MP, SH

Analysis and interpretation of results: TK, EC, MYA, EG, SNK, BK, MP, SH

Draft manuscript preparation: TK, EC, MYA, SH

Critical revision of the article: TK, EC, MYA, EG, SH

Other (study supervision, fundings, materials, etc.): TK, EC, MYA, EG, SNK, BK, MP, SH

All authors (TK, EC, MYA, EG, SNK, BK, MP, SH) reviewed the results and approved the final version of the manuscript.

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Case Report

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Recurrent and De Novo Internal Carotid Artery Aneurysms with Severe Stenosis Following Radiation Therapy for Nasopharyngeal Carcinoma: A Rare Case Report

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ABSTRACT

Rapid formation and recurrence of aneurysms accompanied by severe arterial stenosis following radiation therapy (RT) for nasopharyngeal carcinoma (NPC) is an uncommon clinical phenomenon. We present the case of a 51-year-old man who developed subarachnoid hemorrhage years after undergoing RT for NPC. Digital subtraction angiography revealed a ruptured, irregular, wide-neck aneurysm at the posterior communicating segment of the right internal carotid artery (ICA), along with significant stenosis (approximately 80%) at the cervical segment of the same artery. The cervical ICA stenosis was initially treated with stenting, followed by LVIS stent-assisted coil embolization of the aneurysm. Over the next four years, the patient developed three entirely new ICA aneurysms—one of which arose from within the middle portion of the previously placed LVIS stent (a finding not previously reported)—as well as one recurrent aneurysm. This rare case highlights the dynamic nature of RT-induced ICA aneurysm formation and recurrence. Lifelong monitoring and individualized endovascular management are crucial. Considering the fragility of irradiated tissues, extensive arterial involvement, and increased surgical risk from repeat procedures, endovascular treatment was favored over open surgery.

KEYWORDS: Radiation therapy, Endovascular treatment (EVT), Nasopharyngeal carcinoma (NPC), Intracranial aneurysm, Recurrence

ABBREVIATIONS: RT: Radiation therapy, NPC: Nasopharyngeal carcinoma, ICA: Internal carotid artery, CT: Computed tomography, SAH: Subarachnoid hemorrhage, DSA: Digital subtraction angiography, aSAH: Aneurysmal subarachnoid hemorrhage, CTA: Computed tomography angiography, EVT: Endovascular treatment, GCS: Glasgow Coma Scale

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is predominantly a squamous cell carcinoma arising from the columnar epithelium of the nasopharynx, with a marked geographic prevalence in Southeast and East Asia (4). Radiation therapy (RT) remains the cornerstone of NPC treatment and has significantly improved patient survival (7). However, its potential adverse effects on cerebral vasculature are increasingly recognized. Although RT-induced aneurysms are rare, they

can lead to aneurysmal subarachnoid hemorrhage (aSAH)—a severe and often fatal complication associated with high morbidity and mortality rates (3). Considering these risks, greater clinical attention should be directed toward the detection and management of RT-related aneurysms.

Intracranial aneurysms following RT for NPC occur at an estimated incidence of 47.8 per 100,000 person-years (15). However, the sequential development and rupture of multiple new and recurrent internal carotid artery (ICA) aneurysms



within a relatively short time frame—particularly in the setting of severe post-RT ICA stenosis—remains exceedingly rare in clinical reports. We present the case of a 51-year-old man with a history of RT for NPC who developed three entirely new ICA aneurysms and one recurrent aneurysm over a 4-year period. Notably, this case represents the first reported instance of an aneurysm arising from the mid-segment of an LVIS stent coverage zone—a previously undocumented phenomenon with important implications for endovascular treatment in irradiated vessels. Through detailed angiographic follow-up and hemodynamic analysis, this case offers rare insights into the progressive nature of radiation-induced vasculopathy. Our findings highlight the urgent need for evidence-based surveillance strategies and tailored therapeutic approaches for managing these complex and evolving vascular complications.

CASE REPORT

A 51-year-old man was diagnosed with NPC in 2008, confirmed pathologically as undifferentiated carcinoma (Figure 1). He underwent chemotherapy and RT, receiving 2 Gy per session

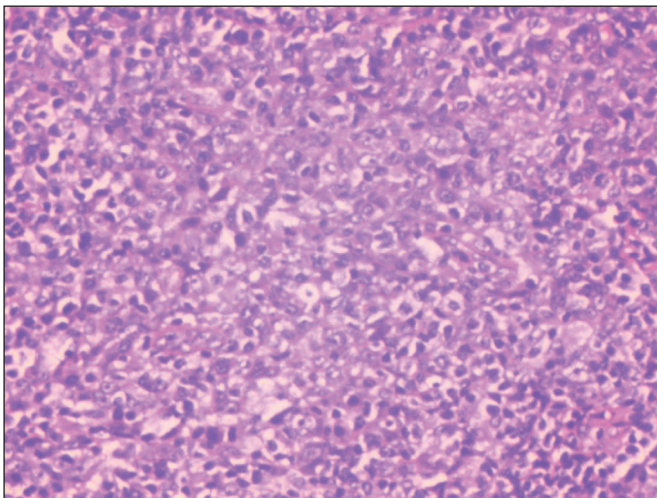


Figure 1: Histopathological examination confirmed undifferentiated nasopharyngeal carcinoma, visualized using Hematoxylin and Eosin stain, $\times 40$ magnification.

over 30 sessions, for a total dose of 60 Gy. Following several years of radiological, clinical, and oncological surveillance, he achieved complete remission. His medical history included hypertension, intermittent headaches, and a 10-year history of smoking.

First Admission (August 2017): The patient was admitted to our hospital with a 3-day history of headache. Neurological examination showed nuchal rigidity, with no other abnormal findings. Emergency computed tomography (CT) at admission revealed SAH (Figure 2A), and CT angiography (CTA) revealed approximately 80% eccentric stenosis accompanied by a dissecting aneurysm at the cervical segment of the right ICA (Figure 2B). Digital subtraction angiography (DSA) further identified a ruptured, wide-neck, irregular aneurysm at the posterior communicating segment of the right ICA (Figure 2C), with no abnormalities in other cerebral vessels. Given the significant cervical ICA stenosis that could hinder endovascular treatment (EVT), a self-expanding Xact stent (Abbott Vascular, Abbott Park, IL, USA) was first deployed in the affected segment. Subsequently, the ruptured aneurysm was successfully embolized using coils with assistance from an LVIS stent (MicroVention, Tustin, CA, USA). Post-procedural angiography confirmed complete occlusion of the aneurysm with no residual neck (Figure 2D, E). The patient recovered well and was discharged without any neurological deficits.

Second Admission (February 2019): Eighteen months later, the patient was readmitted to our hospital due to impaired consciousness. Immediate brain CT revealed SAH (Figure 3A). DSA detected a newly formed, wide-neck, irregular ruptured aneurysm located at the choroidal segment of the left ICA (Figure 3B, C). This aneurysm had not been present on the initial DSA, and the previously treated aneurysm remained stable, with no signs of recurrence or neck remnant. No additional aneurysms were identified. Considering the successful outcome of the prior EVT, the patient's family opted for the same therapeutic approach. Under general anesthesia, the newly ruptured aneurysm was embolized using coils with the assistance of an LVIS stent. Post-procedure DSA showed a small residual neck (Figure 3D, E). The patient made a full recovery and was discharged without neurological deficits or complications.

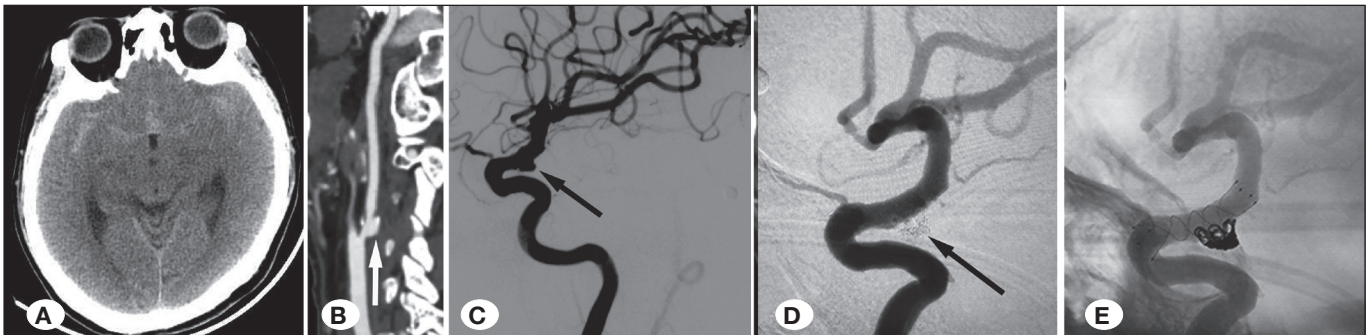


Figure 2: Images of the first procedure (August 2017). **A)** Brain CT revealed subarachnoid hemorrhage. **B)** CTA revealed approximately 80% eccentric stenosis with a dissecting aneurysm at the cervical segment of the right internal carotid artery. **C)** DSA revealed a ruptured, wide-neck, irregular aneurysm at the posterior communicating segment of the right ICA. **D, E)** Immediate post-procedural angiography confirmed complete occlusion with no residual neck.

Third Admission (March 2019): Only 1 month after the second procedure, the patient experienced a third episode of aSAH, presenting with a Hunt–Hess grade of 3 and a Glasgow Coma Scale score of 9 upon admission. Emergency brain CT revealed SAH accompanied by hydrocephalus (Figure 4A). Subsequent DSA showed that the previously treated aneurysm at the choroidal segment of the left ICA remained stable, with no signs of recurrence (Figure 4B). However, a newly developed pseudoaneurysm was identified at the choroidal segment of the right ICA, which had not been present in prior imaging (Figure 4C). No additional aneurysms were detected. Following multidisciplinary consultation and consensus on treatment strategy, the new aneurysm was embolized using LVIS stent-assisted coils, and external ventricular drainage of the right lateral ventricle was performed. Immediate and 20-day follow-up DSA confirmed complete occlusion of the aneurysm with no residual neck (Figure 4D, E). Although recovery was slow, the patient was eventually discharged with limited functional independence but able to manage basic self-care.

Fourth Admission (January 2021): Over time, the patient's neurological deficits related to hydrocephalus gradually improved. However, he was readmitted to our institution with complaints of intermittent headaches lasting 4 days. Emergency brain CT showed no evidence of SAH but revealed mild hydrocephalus (Figure 5A). Considering his complex medical history, a routine DSA was performed. The angiography confirmed no recurrence of the previously treated aneurysms at the poste-

rior communicating and choroidal segments of the right ICA (Figure 5B). Remarkably, however, the coils from the second treated aneurysm had shifted from their original position at the choroidal segment of the left ICA (Figure 5C). Furthermore, a third new aneurysm had developed at the posterior communicating segment of the left ICA (Figure 5D, E). Due to the wide-necked and irregular morphology of the new aneurysm, along with fragility of the parent vessel, the patient was pretreated with daily aspirin (100 mg) and clopidogrel (75 mg) for approximately 1 week before the procedure. Subsequently, both aneurysms were successfully treated with LVIS stent-assisted coil embolization (Figure 5F, G). No new neurological deficits were observed during the perioperative period, and the patient was discharged uneventfully. Ongoing neuroimaging and clinical monitoring have been maintained diligently.

Fifth Admission (November 2021): During the most recent follow-up in November 2021, DSA revealed a recurrence of the aneurysm at the choroidal segment of the left ICA (Figure 6A), likely associated with a small neck remnant from the previously treated lesion. To address this, an additional LVIS stent was deployed within the existing stent to reinforce coverage of the aneurysm neck, without performing coil embolization (Figure 6B). Immediate post-procedural DSA demonstrated intra-aneurysmal contrast stagnation (Figure 6C). The patient was discharged without any new neurological deficits. A summary of the patient's clinical course is provided in Table I.



Figure 3: Images of the second procedure (February 2019). **A)** Brain CT revealed subarachnoid hemorrhage. **B, C)** DSA and three-dimensional DSA identified a wide-neck, ruptured, irregular aneurysm at the choroidal segment of the left ICA. **D, E)** Post-procedure angiography performed immediately revealed a small neck remnant.

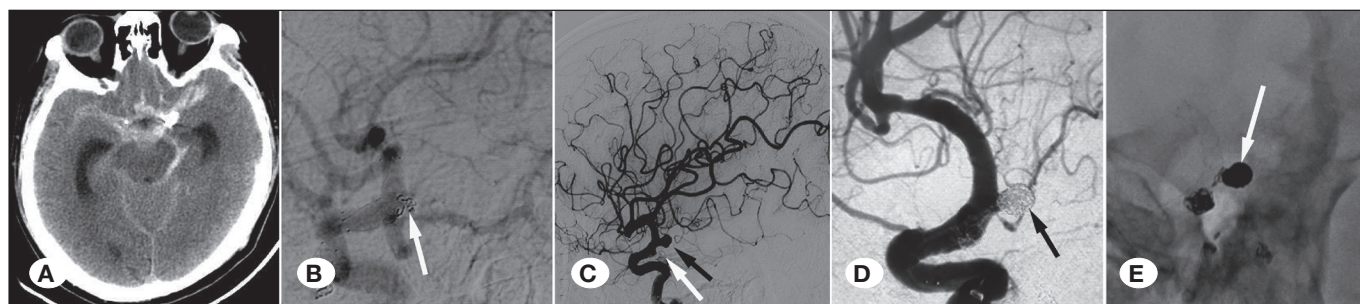


Figure 4: Images of the third procedure (March 2019). **A)** Brain CT indicated subarachnoid hemorrhage coupled with hydrocephalus. **B)** DSA revealed that the coils of the second treated aneurysm at the choroidal segment of the left ICA were in position. **C)** DSA revealed that the first treated aneurysm at the posterior communicating segment of the right ICA was stable (white arrow) and identified a newly developed pseudoaneurysm at the choroidal segment of the right ICA (black arrow). **D, E)** The postoperative DSA revealed complete occlusion of the aneurysm at the choroidal segment of the right ICA.

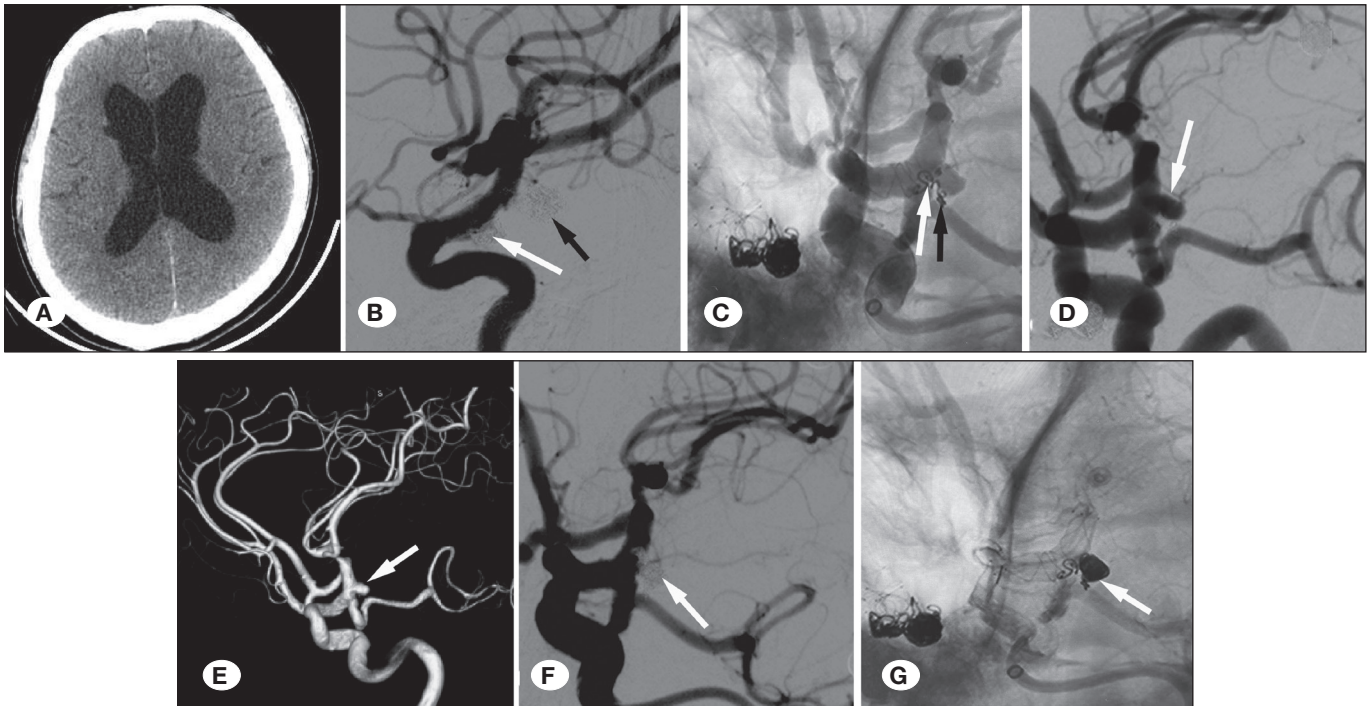


Figure 5: Images of the fourth procedure (January 2021). **A)** Brain CT revealed no sign of subarachnoid hemorrhage, but mild hydrocephalus. **B)** DSA revealed that the first (white arrow) and third (black arrow) treated aneurysms, respectively, at the posterior communicating and choroidal segments of the right ICA, were stable. **C)** DSA demonstrated that the coils of the second treated aneurysm at the choroidal segment of the left ICA were shifted from the previous position (shifting from the black arrow to the white arrow). **D, E)** DSA and 3D-DSA revealed a newly developed aneurysm at the posterior communicating segment of the left ICA. **F, G)** Postoperative DSA revealed complete occlusion of the aneurysms at the posterior communicating and choroidal segments of the left ICA.

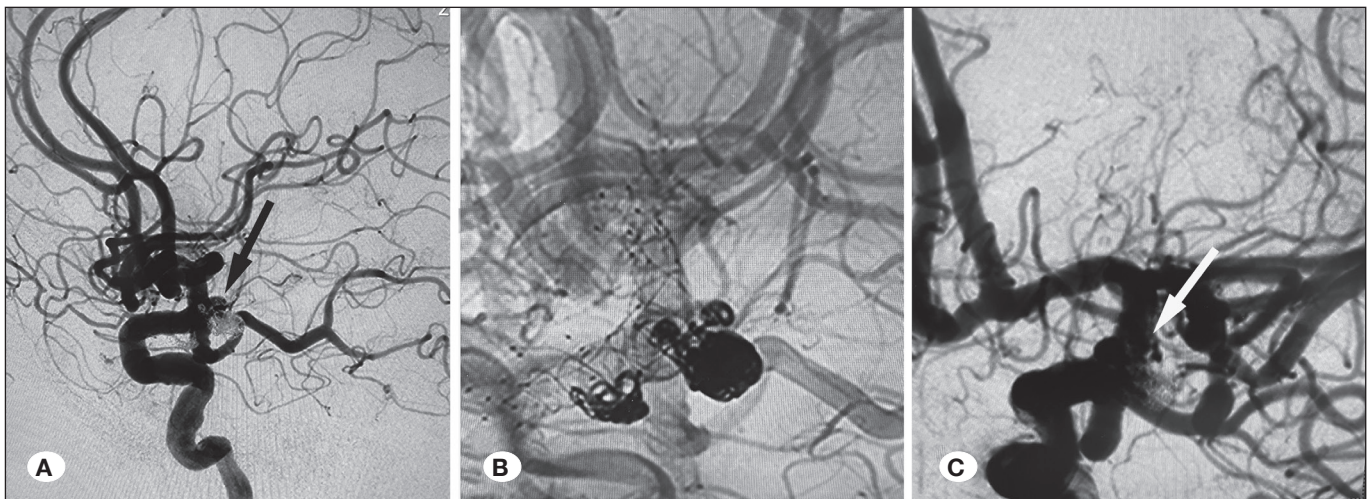


Figure 6: Images of the fifth procedure (November 2021). **A)** DSA indicated the recurrence of the aneurysm (black arrow) at the choroidal segment of the left ICA (the second treated aneurysm). **B)** DSA revealed that the LVIS stent was deployed to cover the aneurysm neck without coil embolization. **C)** The immediate postoperative DSA showed intra-aneurysmal contrast stasis (white arrow).

DISCUSSION

RT induces complex vascular injury through multiple inter-related mechanisms. These include endothelial dysfunction and chronic inflammation, which promote atherosclerosis and compromise vessel wall integrity (14); activation of molecu-

lar pathways, where ionizing radiation stimulates NF- κ B and matrix metalloproteinases (MMPs), facilitating aneurysm development and rupture (6,8,10,13); impaired adventitial repair due to RT-induced fibroblast dysfunction (11); and hemodynamic stress, wherein altered shear forces exacerbate structural vessel fragility (9). The average latency between cancer

Table 1: Timeline of Disease Progression of after Patient

Admission time	Symptom	Physical Examination	Hunt and Hess Scale (Grade)	GCS	CT scan	Lesion location	Procedure	Follow up time/ results	Measures
August 2017	Headache	Nuchal rigidity	1	15	SAH	Posterior communicating segment of the right ICA; 80% eccentric stenosis with dissecting aneurysm at the cervical segment of the right ICA	LVIS stent with coils, Xact stent	February 2019 (no recurrence) March 2019 (no recurrence) January 2021 (no recurrence) November 2021 (no recurrence)	DSA surveillance
February 2019	Impaired consciousness	Noncooperation	3	10	SAH	Choroidal segment of the left ICA (the first newly developed aneurysm)	LVIS stent with coils (a small neck remnant)	March 2019 (a small neck remnant, no recurrence) January 2021 (coils shifting) November 2021 (recurrence)	Surveillance LVIS stent with coils LVIS stent alone
March 2019	Headache	Nuchal rigidity	3	9	SAH with hydrocephalus	Pseudoaneurysm choroidal segment of the right ICA (the second newly developed aneurysm)	LVIS stent-assisted coils	January 2021 (no recurrence) November 2021 (no recurrence)	Surveillance Surveillance
January 2021	Intermittent headache	Slow response	0	15	No SAH but mild hydrocephalus	Posterior communicating segment of the left ICA (the third newly developed aneurysm)	LVIS stent with coils	November 2021 (no recurrence)	Surveillance

GCS: Glasgow coma scale, **CT:** computed tomography, **SAH:** subarachnoid hemorrhage, **LVIS:** low-profile visualized intraluminal support, **ICA:** internal carotid artery

diagnosis and intracranial aneurysm formation has been reported as 4.3 ± 3.1 years (15). However, this case is exceptionally rare—demonstrating the sequential formation of three entirely new aneurysms and one recurrence within just 4 years. In this patient, the compounding effects of hypertension and smoking-related atherosclerosis likely intensified RT-induced vascular damage. Although the primary NPC was localized in the nasopharynx, standard radiation fields often encompass the skull base and proximal intracranial arteries due to potential tumor spread along neural pathways. The dose-dependent relationship between RT and intracranial aneurysms is well documented: 1) the carotid siphon receives substantial scatter radiation during NPC treatment (typically 60–70 Gy to the primary tumor site) (15); 2) histological analyses have revealed similar features of radiation vasculopathy—such as vasa vasorum obliteration and medial necrosis—in both cervical and intracranial carotid segments (2); and 3) hemodynamic compensation for proximal stenosis, as seen in this patient's 80% cervical ICA narrowing, increases stress on distal arterial walls, thereby accelerating aneurysm formation in irradiated but non-stenotic intracranial regions (5).

Typically, LVIS stent-assisted coil embolization for small aneurysms carries a low recurrence rate, reported at 7.4% (12), and there have been no prior reports of new aneurysm formation within the stent-covered segments. Remarkably, this case represents the first documented instance of a de novo aneurysm arising from the mid-portion of an LVIS stent's coverage area (Figure 5D, E)—a novel and clinically significant event with important implications for endovascular device selection in radiation-compromised vasculature. In the context of post-RT vasculopathy, even unruptured aneurysms may warrant a lower threshold for intervention, though the choice between EVT and surgery must be individualized. Moreover, DSA revealed coil displacement in the previously treated aneurysm, likely due to inflammation-induced endothelial instability. Taking into account the patient's medical history, family preferences, and financial considerations, LVIS stent-assisted coil embolization was successfully performed for both aneurysms. However, during the most recent procedure (November 2021), the recurrent aneurysm was treated with an LVIS stent alone—without coils—to cover the aneurysm neck (Figure 6B), considering the risks of coil migration and potential compromise of the choroidal artery. Postoperative DSA showed contrast stagnation within the aneurysm sac (Figure 6C), suggesting effective flow diversion. In such complex cases, flow diverters may also serve as a viable alternative.

In summary, while LVIS stent-assisted coiling provided immediate aneurysm occlusion in RT-induced cases, its long-term durability was limited (Figure 6A, Figure 3D-E, and Figure 5G), and coil migration was observed at irradiated sites, likely due to ongoing inflammation and vascular remodeling (Figure 5C). Therefore, an adaptive treatment strategy was employed: for the recurrent aneurysm (Figure 6A-C), standalone LVIS stent placement—without coiling—was used to prioritize parent vessel reconstruction over direct aneurysm filling, achieving

effective contrast stasis through flow diversion. This case yields several clinical insights: patients with NPC who have a history of smoking, hypertension, and received radiation doses exceeding 60 Gy should undergo lifelong vascular surveillance. We recommend follow-up DSA at 6, 12, and 24 months post-EVT. Regarding treatment approach, stent-assisted coiling remains a valid first-line option for primary aneurysms, whereas flow diverters may offer a superior alternative for recurrent lesions, particularly to prevent coil migration.

The consistent use of endovascular treatment in this case was guided by three primary factors: First, irradiated tissues are prone to poor wound healing and carry an increased risk of surgical complications, such as carotid blowout (1,2). Second, the stepwise development of aneurysms across multiple segments of the ICA—from cervical to intracranial—would necessitate overly extensive and invasive surgical exposure. Third, repeated open surgeries would impose significant cumulative morbidity, especially given the patient's radiation-induced tissue fibrosis (2). These considerations support the current clinical consensus, which favors endovascular intervention over open surgery for radiation-induced vasculopathy when anatomically feasible.

CONCLUSION

This case underscores the dynamic and recurrent nature of RT-induced internal carotid artery aneurysms. Despite achieving “complete” initial treatment, rigorous and ongoing angiographic monitoring is essential for early detection of de novo or recurrent lesions. In irradiated vasculature, endovascular strategies should shift from solely focusing on aneurysm occlusion to prioritizing vessel preservation and long-term vascular integrity.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

Ethics approval and consent to participate: This study was approved by the Ethics Committee of Taizhou Municipal Hospital (NO. LW011). Written informed consent was obtained from the patient.

AUTHORSHIP CONTRIBUTION

Study conception and design: XX, YT, LQ

Data collection: LQ

Analysis and interpretation of results: XX, YT, LQ

Draft manuscript preparation: LQ

Critical revision of the article: XX, LQ

Other (study supervision, fundings, materials, etc...): XX, YT, LQ

All authors (XX, YT, LQ) reviewed the results and approved the final version of the manuscript.

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Case Report

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Advanced Detection of a Small Intracranial Aneurysm Using Photon-Counting Computed Tomography Angiography

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ABSTRACT

Using intravenous contrast, photon-counting computed tomography angiography (PCCT-A) provides detailed images of intracranial vessels. We report a case in which PCCT-A revealed a 1.5 mm aneurysm at the bifurcation of the middle cerebral artery that was not seen on magnetic resonance angiography. This case highlights the clinical value of PCCT-A in noninvasively detecting small intracranial aneurysms.

KEYWORDS: Photon-counting computed tomography angiography, Small intracranial aneurysm, Neurovascular imaging, Noninvasive angiography, Middle cerebral artery bifurcation

INTRODUCTION

Intracranial aneurysms are serious cerebrovascular conditions that can have life-threatening consequences if they remain undiagnosed or untreated (19). Widely used imaging tools such as computed tomography angiography (CT-A) and magnetic resonance angiography (MR-A) often lack sufficient spatial resolution, which limits their ability to reveal very small aneurysms (20). Although highly informative, even 2D digital subtraction angiography (DSA) can be hindered by overlapping vascular structures or unfavorable viewing angles in complex regions, such as arterial bifurcations. Therefore, 3D rotational angiography remains the most reliable approach for detecting small aneurysms (25).

In recent years, photon-counting computed tomography (PCCT) has been introduced as a noninvasive technique that markedly improves vascular imaging and may enhance the detection of aneurysms (18). In our institution, after adopting PCCT angiography (PCCT-A) as the routine vascular imaging method in patients with suspected stroke, we observed an

increase in the number of aneurysms detected (24). PCCT provides higher spatial resolution, improved contrast between tissues, and fewer artifacts compared to conventional computed tomography (CT) systems (14). These technical advances allow recognition of vascular changes that might otherwise remain undetected with standard imaging modalities (18).

Here, we present a case in which a 1.5 mm aneurysm at the bifurcation of the middle cerebral artery (MCA) was detected incidentally by PCCT-A, and we discuss the potential implications of this observation for clinical practice.

CASE REPORT

A 60-year-old man presented to the emergency department with ongoing hypotension and dizziness. His past medical history was unremarkable, with no neurological deficits or chronic illnesses. A non-contrast cranial CT obtained on a 128-slice SOMATOM AS+ scanner (Siemens, Erlangen, Germany) showed no signs of intracranial hemorrhage or ischemia. How-

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ever, a hyperdense appearance of the proximal basilar artery raised suspicion of possible thrombosis or imaging artifact (8). To investigate this suspicion further, a contrast-enhanced PCCT-A was performed with 70 mL of iodinated contrast material. This examination confirmed patency of the basilar artery with no evidence of thrombus, thereby resolving the concern raised by the initial non-contrast CT. This outcome highlights the advantage of PCCT-A in evaluating vascular patency. Incidentally, a 1.5 mm saccular aneurysm was detected at the bifurcation of the left MCA (Figure 1). The aneurysm was not detectable on MR-A. Given its small size and low aspect ratio, a conservative management approach was adopted with regular follow-ups.

Technical Notes

PCCT is a cutting-edge imaging modality that offers improved spatial resolution, enhanced tissue contrast, and reduced artifacts compared to conventional CT. These features allow the identification of small vascular anomalies that conventional imaging methods may miss.

In this case, the PCCT-A was performed using a NAEOTOM Alpha Photon-Counting CT scanner (Siemens, Erlangen, Germany). The scan protocol used the following parameters: slice thickness of 0.6 mm, X-ray tube voltage of 140 kV, DW of 21.6 cm, 70 mL of Imeron 300 M contrast medium (Bracco, Milan, Italy), and intravenous injection of 300 mg of iodine/mL with a flow rate of 5 mL/s.

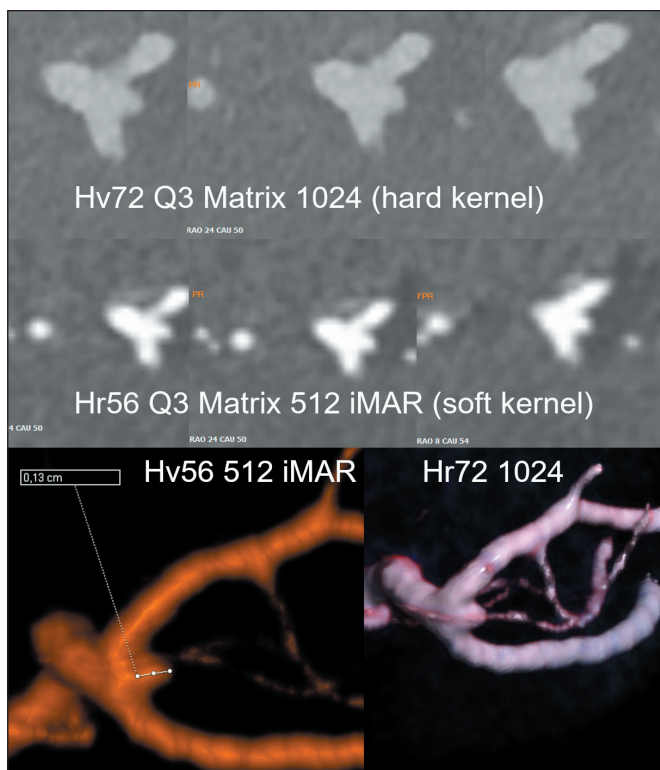


Figure 1: PCCT-A of an aneurysm at the bifurcation of the MCA. Hard and soft kernel (para-coronary) with resulting 3D reconstructions.

The dose length product for this case was 653 mGy*cm (132 effective mAs, CTDIvol*mGy 15.4 L, SSDE 26.00 mGy), which is comparable to or slightly lower than conventional CT-A protocols. These parameters optimized the detection of small vascular structures while minimizing patient radiation exposure. Today, the (theoretically) maximal resolution of PCCT can reach 0.11 mm in-plane (3,23).

DISCUSSION

Identifying small aneurysms remains clinically challenging, as their progression and risk of rupture are not yet fully clarified in the current literature (22). In this setting, PCCT enhances diagnostic confidence by offering superior spatial resolution and clearer delineation of vascular abnormalities compared to conventional CT-A and MR-A (23).

In this case, the detection of the aneurysm was facilitated by the improved spatial resolution and noise reduction capabilities of PCCT-A. Studies have suggested that aneurysms with a size ratio greater than 3 mm and an aspect ratio (the ratio of aneurysm height to neck width) greater than 1.6 are more prone to rupture (28). However, given the small size and favorable aspect ratio of the aneurysm in this case, conservative management was adopted, aligning with current guidelines (10).

Invasive vs. Noninvasive Imaging for Aneurysm Detection

Three-dimensional rotational DSA remains the gold standard for detecting and evaluating intracranial aneurysms due to its unmatched spatial resolution and ability to visualize dynamic vascular processes, such as flow patterns and associated arteriovenous fistulas or malformations. However, its invasiveness carries inherent procedural risks, including arterial injury, hemorrhage, infection, and allergic reactions to the contrast agent. In patients with subarachnoid hemorrhage, a thorough assessment may involve as many as four separate 3D DSA scans, since both carotid and vertebral arteries on each side must be examined individually. This approach inevitably adds to the patient's total radiation exposure (1,27).

In the past, conventional imaging often failed to detect small aneurysms (<3 mm). Indeed, a systematic review revealed a sensitivity of only 61% for CT-A and 38% for MR-A (28). In contrast, PCCT-A offers a noninvasive alternative with moderate radiation exposure that can visualize such small aneurysms and eliminate the procedural risks associated with DSA (16). The photon-counting detector technology enables significantly improved spatial resolution and reduced radiation exposure, offering a safer option for patients who require multiple imaging studies.

He et al. demonstrated that ultra-high-resolution PCCT-A substantially improves diagnostic accuracy and morphological characterization of unruptured aneurysms (9). This enhanced spatial resolution enables a more precise assessment of the shape and size of the aneurysm, both of which are critical for evaluating rupture risk and treatment planning.

The diagnostic performance of PCCT-A has been shown to closely align with that of DSA, the current gold standard. De

Beukelaer et al. demonstrated that PCCT-A provides comparable accuracy in assessing stents, flow diverters, and aneurysms after coiling or clipping, while offering the significant advantage of being noninvasive (5,6).

Another notable feature of PCCT-A is its ability to generate virtual non-contrast reconstructions from contrast-enhanced datasets. Decker et al. validated a novel calcium-preserving reconstruction algorithm, which reliably simulates non-contrast images, potentially eliminating the need for separate non-contrast scans in patients with vascular implants (7).

Regarding follow-up imaging after flow diversion, PCCT-A offers high-quality visualization of the aneurysm lumen and associated thrombus formation. Wei et al. and Marque et al. highlighted the potential of PCCT-A for accurate monitoring of treatment response and long-term outcomes (15,26). Furthermore, Higaki et al. emphasized its value in both pre- and post-operative settings for cranial and spinal vascular pathologies (12).

However, PCCT-A has limitations in assessing associated dynamic vascular processes, such as arteriovenous fistulas and arteriovenous malformations, where DSA remains the superior modality.

Technical Comparisons: PCCT-A vs. 3D DSA

PCCT-A outperforms conventional CT-A in terms of sharpness and signal-to-noise ratio, enabling the detection of small vascular anomalies with greater clarity (23). Compared to 3D rotational DSA, PCCT-A offers competitive spatial resolution and eliminates artifacts caused by overlapping vascular structures. The ability to distinguish blood from iodine enhances the applicability of PCCT-A (2). Additionally, the reduced radiation dose and lower contrast agent requirements of PCCT-A make it a more patient-friendly option for routine screening and follow-up evaluations (13).

However, when combined with cone beam CT, 3D rotational DSA remains the preferred method for assessing dynamic vascular abnormalities and real-time blood flow, which are crucial for evaluating arteriovenous shunts and other flow-related pathologies (28). Despite these advantages, DSA is limited by its inability to detect fully thrombosed aneurysms or aneurysms in border zones, such as small anterior communicating artery aneurysms, which can be more easily detected using PCCT-A (17,24).

Future Implications for PCCT-A in Clinical Practice

Although 3D DSA is still regarded as the gold standard for detecting aneurysms, advances in PCCT-A may gradually shift this perspective. PCCT-A combines noninvasiveness with high spatial resolution and lower radiation exposure, making it an attractive option for routine imaging, particularly in follow-up examinations (4). Its potential role in detecting incidental aneurysms also warrants further study, and the possibility of screening patients at increased risk without exposing them to invasive procedures could be a significant benefit (18).

Nevertheless, PCCT-A has limitations that prevent it from entirely replacing DSA at present. For instance, dynamic processes such as arteriovenous fistulas or flow characteristics are not well visualized with this method. Due to its high temporal resolution, dual-source CT may complement PCCT-A by offering improved visualization of these phenomena (21). Progress in both technologies could help close these gaps and strengthen their contribution to cerebrovascular imaging. Additionally, it remains uncertain whether PCCT-A is sufficiently sensitive to reveal small dissecting or blister-type aneurysms.

Further innovations are also underway. For example, Hernandez-Fajardo et al. reported on color K-edge angiography with gadolinium-based contrast, demonstrating that enhanced spectral resolution may improve tissue differentiation and vascular assessment (11).

CONCLUSION

This case demonstrates that PCCT-A is capable of detecting very small incidental aneurysms that conventional imaging may miss. The improved spatial resolution and reduced noise of PCCT-A enable more accurate assessment, which in turn supports earlier diagnosis, better-informed treatment decisions, and—when appropriate—timely intervention that may help to prevent rupture-related complications. However, the high level of detail inevitably increases the interpretive workload for neuroradiologists, who must carefully evaluate additional subtle findings. While the results of this case are encouraging, further clinical experience and systematic research are required to establish how PCCT-A should be incorporated into everyday workflows. Its role in initial detection, risk assessment, and long-term follow-up of aneurysms remains to be clarified in future studies.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

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AUTHORSHIP CONTRIBUTION

Study conception and design: HK, SJM

Data collection: HK

Analysis and interpretation of results: HK

Draft manuscript preparation: HK, SJM

Critical revision of the article: EK, ED, DB, MP

Other (study supervision, fundings, materials, etc...): DB

All authors (HK, EK, ED, DB, MP, SJM) reviewed the results and approved the final version of the manuscript.

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Case Report

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Gamma Knife Radiosurgery-Induced Acute Facial Palsy in Vestibular Schwannoma: A Case Report

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Stereotactic radiosurgery (SRS) is an established treatment for vestibular schwannoma, offering high tumor control rates and a favorable safety profile. SRS-induced facial palsy is typically a late-onset complication, with acute-onset cases being exceedingly rare. We report the case of a 42-year-old man with a left-sided Koos grade I vestibular schwannoma who underwent single-fraction Gamma Knife radiosurgery with a prescription dose of 11 Gy to the 50% isodose line. Baseline facial nerve function was intact. Seventy-two hours post-treatment, the patient developed House-Brackmann (HB) grade V peripheral facial palsy, accompanied by severe vestibular symptoms. Magnetic resonance imaging obtained on post-treatment day 6 demonstrated reduced contrast enhancement, partial capsular breakdown, and central hypointensity within the tumor, suggestive of acute necrotic change. Vestibular symptoms improved rapidly following corticosteroid therapy; however, facial palsy recovery was gradual, improving to HB grade II at 12 months, with persistence at final follow-up (20 months). The tumor remained radiologically stable. Acute-onset facial palsy following SRS for vestibular schwannoma is extremely rare, with only four previous cases reported in the literature. This is the first reported case to occur following a relatively low margin dose—11 Gy—in contrast to the 13-14 Gy doses prescribed in earlier reports.

KEYWORDS: Schwannoma, Gamma Knife radiosurgery, facial palsy**ABBREVIATIONS:** SRS: Stereotactic radiosurgery, GKRS: Gamma Knife radiosurgery, HB: House-Brackmann**INTRODUCTION**

Stereotactic radiosurgery (SRS) is a well-established and effective treatment modality for vestibular schwannomas, offering excellent long-term tumor control rates and a favorable safety profile (6,7,10). According to the European Association of Neuro-Oncology guidelines (5), SRS may be preferred over microsurgery for smaller vestibular schwannoma cases where preservation of facial nerve and hearing function is the primary therapeutic goal. However, despite its overall favorable safety profile, SRS can cause complications in a subset of patients, including hearing deterioration, ves-

tibular symptoms, facial numbness, and facial nerve-related adverse effects, such as facial spasm and palsy (7,15).

Previous studies have reported facial nerve preservation rates ranging from 92.9% to 96.2% following Gamma Knife radiosurgery (GKRS) for vestibular schwannomas (8,15). Typically, SRS-induced facial palsy is a late-onset complication that may be either transient or permanent (7). In contrast, acute-onset facial palsy is extremely rare following SRS, with only a few cases reported in the literature (2,9,11,14). Herein, we present a patient with vestibular schwannoma who developed acute facial palsy shortly after receiving GKRS.

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■ CASE REPORT

A 42-year-old man presented with left-sided tinnitus, persisting for more than two years, and progressive hearing loss on the same side that had developed over the preceding months. He had no complaints suggestive of vestibular dysfunction. The patient had a medical history of hypertension and anxiety disorder, both of which were well controlled with regular medication. He was also an active smoker.

On physical examination, there was no response to conversational speech on the left side. Audiometric evaluation revealed severe sensorineural hearing loss on the left, with a pure tone average of 75 dB. Facial nerve function was intact bilaterally. In addition, there were no clinical signs of vestibular nerve dysfunction, such as gait instability, spontaneous nystagmus, or a positive Romberg sign.

Magnetic resonance imaging (MRI) revealed a Koos grade I vestibular schwannoma measuring 11 × 8 mm, located within the left internal auditory canal. Single-fraction, frame-based GKRS was delivered with a prescription dose of 11 Gy to the 50% isodose line (Figure 1). Radiosurgery parameters are summarized in Table I. The maximum dose to the left cochlea was 10.8 Gy, with a mean dose of 5.3 Gy. The facial nerve received a maximum dose of 10.4 Gy, measured along its visible cisternal segment, as the intracanalicular portion was obscured by tumor-related compression.

Approximately 72 hours after radiosurgery, the patient presented with left-sided facial weakness and severe vestibular symptoms—including nausea, vomiting, dizziness, imbalance, and vertigo—and required hospitalization. Physical examination revealed grade V peripheral left facial palsy, according to the House-Brackmann (HB) scale.

MRI obtained on post-treatment day 6 demonstrated a centrally hypointense area within the lesion. The peripheral enhancing rim appeared irregular, with multiple discontinuities suggestive of partial capsular breakdown. Quantitative assessment was performed using region of interest analysis on contrast-enhanced T1-weighted MRI. This revealed a decrease in the tumor-to-brainstem signal intensity ratio from 1.7 pre-GKRS to 1.1 at day 6, reduced to 0.8 in the central portion of the lesion, consistent with early necrotic change (Figure 2).

Vestibular symptoms markedly improved within days following corticosteroid therapy. However, the recovery from facial palsy was gradual, requiring several months. Three months after radiosurgery, vestibular symptoms had completely resolved, and facial palsy had improved to HB grade III. At 12 months, facial function had further improved to HB grade II, and the tumor remained radiologically stable. At the final follow-up, conducted 20 months after treatment, facial palsy persisted at HB grade II.

■ DISCUSSION

Several risk factors for facial palsy have been investigated extensively in patients undergoing SRS for vestibular schwannoma (8,15). A recent review comprising 15 studies and 3,155 patients treated with single-fraction GKRS reported a long-

term facial nerve preservation rate of 92.9%, with a median follow-up of 59.4 months (8). Among all patients, those who received a margin dose of ≤13 Gy had a facial nerve preservation rate of 96.5%. Factors such as prior surgery, age over 60, and larger tumor volume have been associated with poorer facial nerve outcomes (8,15).

The facial palsies reported in these studies typically represent late-onset toxicity following SRS (8,15). Indeed, cranial nerve palsies are also well-recognized late-onset and progressive complications of conventional radiotherapy (3). In contrast, the patient described in this case report developed an acute and unexpected facial palsy shortly after treatment. Furthermore, although central tumor necrosis is a well-recognized long-term effect of SRS in vestibular schwannomas—typically appearing several months post-treatment as an asymptomatic radiological finding (1,12)—it was observed on MRI within days of GKRS in this instance.

The coexistence of facial palsy and MRI findings suggestive of acute tumor necrosis raises the possibility of a mechanistic association; however, the lack of histopathological or

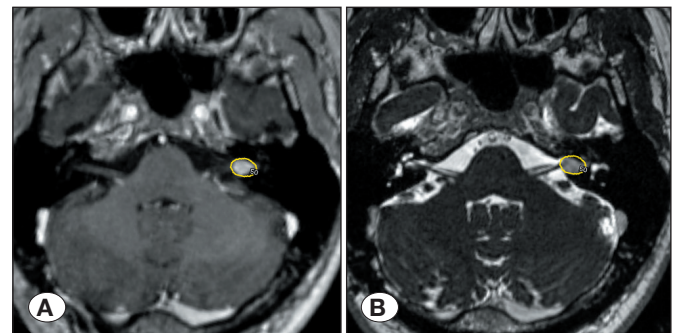


Figure 1: Axial post-contrast T1-weighted magnetic resonance imaging (A) and high-resolution T2-weighted constructive interference in steady state (CISS) image (B) obtained as part of the Gamma Knife radiosurgery planning protocol. The tumor is clearly visualized on both sequences, while the seventh and eighth cranial nerves are distinctly delineated on the CISS image. A margin dose of 11 Gy was prescribed to the 50% isodose line (yellow contours).

Table I: Radiosurgery Parameters

Parameter	Value
Margin Dose	11 Gy
Maximum Tumor Dose	22 Gy
Mean Tumor Dose	16.3 Gy
Isodose Line	50%
Coverage	100%
Gradient Index	3.04
Selectivity	0.83
Number of Shots	8

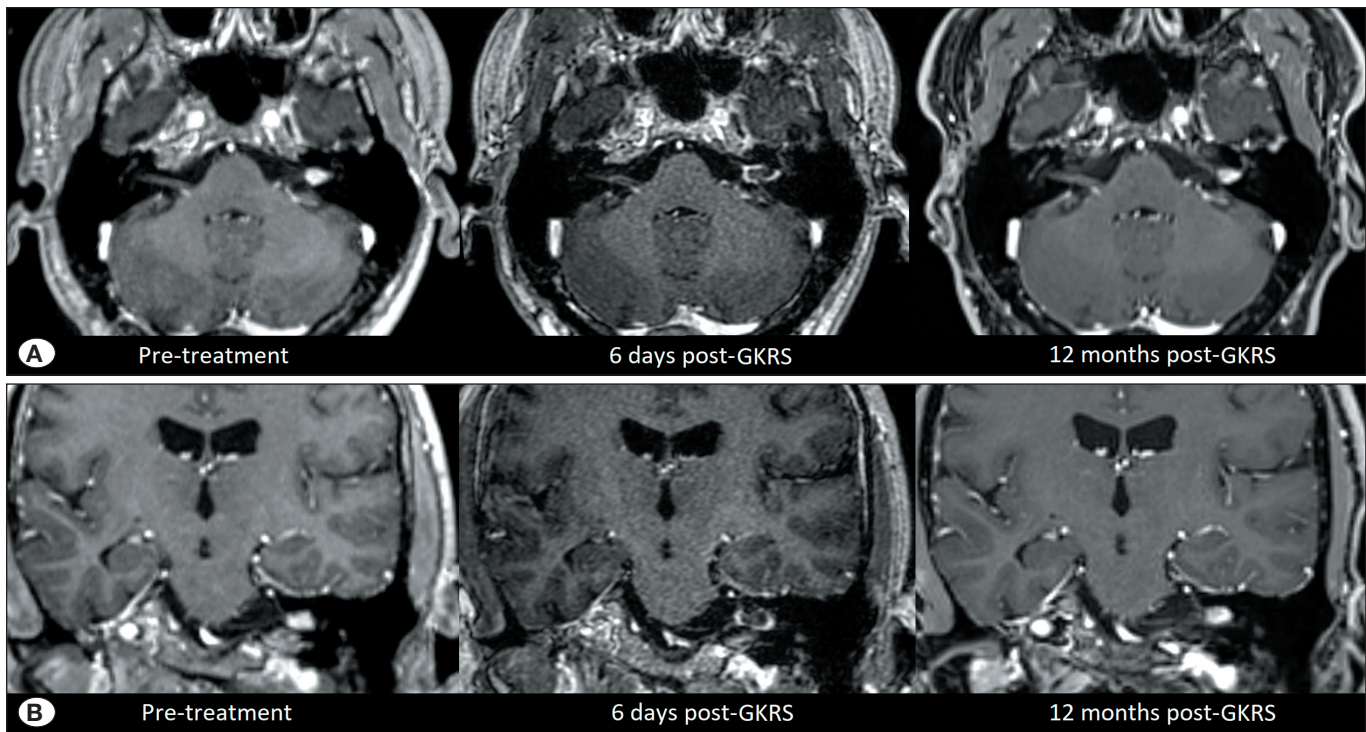


Figure 2: Axial (A) and coronal (B) post-contrast T1-weighted magnetic resonance images obtained pre-treatment, and at 6 days and 12 months post-Gamma Knife radiosurgery.

advanced imaging confirmation limits definitive conclusions. The incomplete recovery of facial function (HB grade II at 20 months) may be related to partial and irreversible facial nerve injury secondary to acute necrotic or inflammatory changes, or to acute or delayed radiosurgery-induced nerve damage.

A small number of similar cases have previously been described in the literature (2,9,11,14). To our knowledge, the first detailed case was reported by Tago et al. in 2000, and only four cases have been documented over the past quarter-century (14). In contrast to our case, in which a margin dose of 11 Gy was prescribed, previous reports involved higher margin doses, ranging from 13 to 14 Gy. Although our routine practice for single-fraction GKRS is a margin dose of 12 Gy to the 50% isodose line for vestibular schwannomas (5), a reduced margin dose of 11 Gy is prescribed for a subset of patients based on recent studies (4,13). This was applied in the present case to minimize the cochlear dose, as the tumor was located in close proximity to the cochlea.

In all previously reported cases (2,9,11,14), and the present instance, symptoms developed within 36 hours to 4 days after radiosurgery. None of the patients had a prior history of facial palsy, and the newly developed deficits ranged from HB grade III to V. A common feature among all cases was the presence of additional cranial nerve-related symptoms—such as hearing loss or vestibular dysfunction—in addition to facial palsy, as also observed in our patient. Moreover, all cases—including ours—demonstrated reduced contrast enhancement on early post-radiosurgery MRI, possibly reflecting acute tumor response.

CONCLUSION

The mechanism underlying SRS-induced acute facial palsy remains unclear, and only four cases have been previously reported in the literature. To the best of our knowledge, this is the fifth well-documented case of acute facial palsy following SRS. Notably, it is the first reported case occurring after a relatively low margin dose of 11 Gy, compared to higher doses in all previously reported cases.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

Ethics approval and consent to participate: This case report did not require formal Institutional Review Board approval; written informed consent was obtained from the patient.

AUTHORSHIP CONTRIBUTION

Study conception and design: OBC, MR

Data collection: OBC

Analysis and interpretation of results: OBC, MR

Draft manuscript preparation: OBC

Critical revision of the article: OBC, MR

Other (study supervision, fundings, materials, etc...): OBC, MR

All authors (OBC, MR) reviewed the results and approved the final version of the manuscript.

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Case Report

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An Unusual Complication After Posterior Thoracolumbar Stabilization Surgery, Renal Hernia: A Case Report

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ABSTRACT

Grynfeltt-Lesshaft hernia is a rare type of posterolateral abdominal wall hernia that may be either congenital or acquired. Only a few cases have been reported following surgical procedures. The risk of herniation increases after surgeries involving this region due to the weakening of the musculofascial structures, particularly in operations involving the thoracolumbar junction. Proper dissection and reconstruction of the paravertebral and deep back muscles are therefore crucial in minimizing the risk of herniation. In this paper, we discuss the mechanisms underlying the development of Grynfeltt-Lesshaft hernia following posterior thoracolumbar stabilization surgery—a procedure that is increasingly performed in neurosurgical practice. We also address the predisposing factors and emphasize the importance of meticulous reconstruction of the musculofascial structures within the superior lumbar triangle to prevent this rare complication.

KEYWORDS: Grynfeltt - Lesshaft hernia, renal hernia, posterolateral abdominal wall, thoracolumbar instrumentation

■ INTRODUCTION

Grynfeltt and Lesshaft described a hernia developing in the superior lumbar triangle in 1886 and 1870, respectively. The superior lumbar (Grynfeltt-Lesshaft) triangle is bordered medially by the quadratus lumborum and erector spinae muscles, laterally by the posterior margin of the internal abdominal oblique muscle, and superiorly by the 12th rib (3). The floor of this triangle is formed by the aponeurosis of the transversalis muscle, while its roof consists of the latissimus dorsi and external oblique muscles (Figures 1,2). Grynfeltt-Lesshaft hernias account for approximately 1% of all abdominal wall hernias (1).

In this paper, we discuss the mechanisms underlying the development of Grynfeltt-Lesshaft hernia following posterior thoracolumbar stabilization surgery—a procedure increasingly utilized in neurosurgical practice. We also highlight the predisposing factors and the importance of meticulous recon-

struction of the musculofascial structures in the superior lumbar triangle to prevent this rare complication.

■ CASE REPORT

A 46-year-old female presented to the outpatient clinic with low back pain and anterior bilateral thigh pain persisting for four months. On neurological examination, there was tenderness over the thoracolumbar region on palpation, but no motor or sensory deficits were noted. Lumbar magnetic resonance imaging (MRI) and computed tomography (CT) scans revealed a cystic lesion in the L1 vertebral body (Figure 3A). With a preliminary diagnosis of aneurysmal bone cyst, the patient underwent tumor resection, T11-L3 posterior thoracolumbar instrumentation, and T12-L1 laminectomy.

Her symptoms resolved in the postoperative period, and she was fitted with a steel underwire lumbar corset for six weeks. Histopathological examination confirmed the diagnosis of

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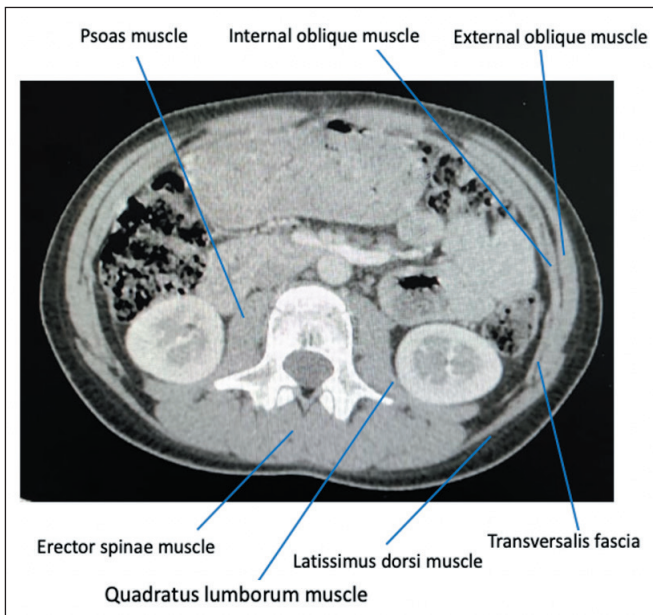


Figure 1: Axial abdominal CT image demonstrating anatomical structures adjacent to the superior lumbar (Grynfeltt-Lesshaft) triangle, including the quadratus lumborum, erector spinae, internal oblique, external oblique, latissimus dorsi muscles and transversalis fascia.

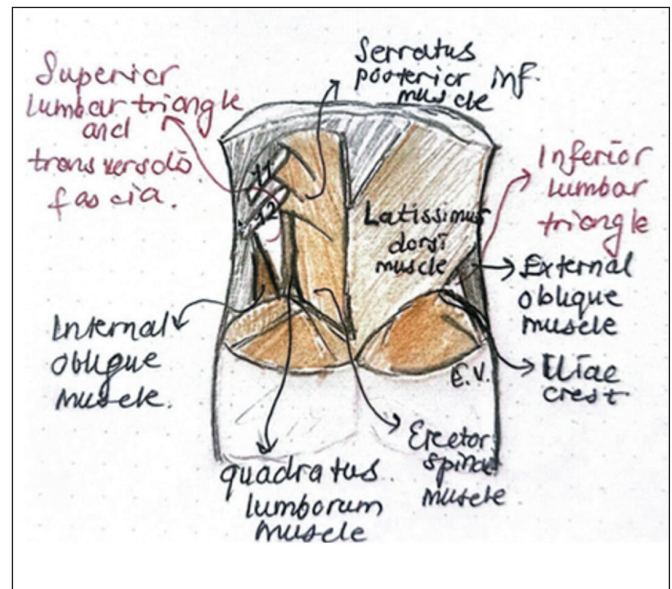


Figure 2: Schematic illustration of the superior lumbar (Grynfeltt-Lesshaft) triangle. The triangle is bordered medially by the quadratus lumborum and erector spinae muscles, laterally by the posterior border of the internal abdominal oblique muscle, and superiorly by the 12th rib. The floor is formed by the transversalis fascia, and the roof is formed by the latissimus dorsi and external oblique muscles.

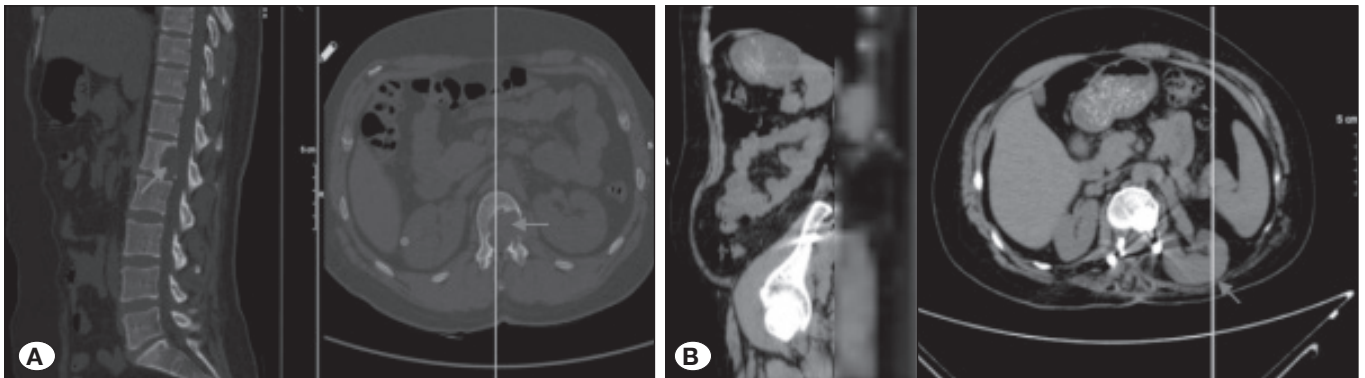


Figure 3: Preoperative CT (A) midsagittal and midaxial reconstruction shows a cystic lesion located in the L1 vertebra corpus (arrows), postoperative CT (B) sagittal and axial reconstruction shows left renal hernias (arrows).

aneurysmal bone cyst. Three years postoperatively, the patient presented again with recurrent low back pain lasting two months. Imaging revealed a rod fracture, and revision surgery (T10-S1 instrumentation) was performed. The patient's complaints resolved completely after the revision.

At the 10th postoperative month, a palpable, painless swelling was detected in the left flank region. Ultrasonography performed with the Valsalva maneuver revealed no apparent fascial defect, but the left kidney was seen adjacent to the lateral abdominal wall. Subsequent CT and MRI imaging demonstrated a left-sided renal herniation secondary to atrophy and weakening of the paravertebral muscles and fascia (Figures 3B, Figure 4). Laboratory tests, including renal function tests, were within normal limits. The patient was evaluated by a mul-

tidisciplinary team, and conservative management with periodic physical examinations and renal function monitoring was recommended. No significant changes were observed during follow-up.

DISCUSSION

Lumbar hernias account for approximately 2% of all abdominal wall hernias. They may be congenital or acquired; about 20% are congenital, typically occurring in infants as a result of weakness of the lateral abdominal wall. Acquired lumbar hernias constitute roughly 80% of cases and can be classified as spontaneous (primary) or secondary. The two types occur with similar frequency (5).

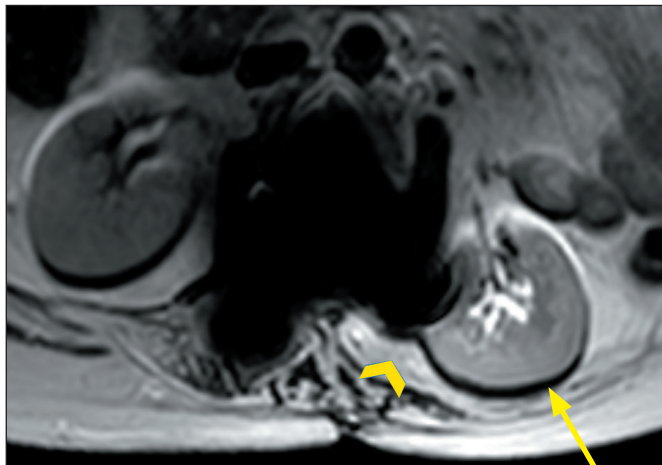


Figure 4: T2-weighted axial MRI image showing atrophy of the left paravertebral muscles (arrowhead) and weakening of the fascia compared to the right side, resulting in left-sided renal herniation (arrow).

The first reported case of Grynfeltt-Lesshaft hernia was published by Presti et al., describing a 42-year-old female who presented with low back pain and hematuria and was found to have Grynfeltt-Lesshaft hernia involving the kidney and ureteropelvic junction (5). Surgical repair was performed successfully. Another case was reported in a patient who had undergone laparoscopic adrenalectomy for Cushing's syndrome (4).

Primary lumbar hernias are associated with risk factors such as obesity, tall stature, chronic bronchitis, and muscular atrophy, whereas secondary lumbar hernias may result from trauma, benign or malignant lesions of the lumbar bones or muscles, retroperitoneal hematoma, or previous surgery (2,4). Review of the literature indicates that postoperative lumbar hernias have been described following laparoscopic adrenalectomy, pyeloplasty, and colectomy, with a higher prevalence among female patients around 60 years of age (6).

Clinical presentation may vary from asymptomatic swelling to severe pain, hematuria, or renal impairment. On physical examination, a flank bulge that increases with the Valsalva maneuver may be observed, sometimes accompanied by tenderness. Incarcerated hernias may lead to elevated urea and creatinine levels. Imaging modalities such as ultrasonography, CT, MRI, and intravenous pyelography are valuable diagnostic tools (1,6).

To the best of our knowledge, this is the first reported case of Grynfeltt-Lesshaft hernia developing after posterior thoracolumbar stabilization surgery. Factors contributing to herniation may include the use of cautery to detach paravertebral muscle groups from posterior vertebral elements, postoperative muscle atrophy, inadequate or excessively wide muscle dissection, and insufficient reconstruction of musculofascial structures at the end of the procedure, all of which reduce regional strength.

The risk of hernia formation increases in patients with comorbidities such as diabetes, hypertension, and hypothyroidism,

in older female patients, in surgeries involving the thoracolumbar junction due to its proximity to the Grynfeltt-Lesshaft triangle, and in revision surgeries (5,6).

CONCLUSION

For surgical procedures at the thoracolumbar junction, careful dissection of paravertebral muscles, minimal use of cautery, anatomically accurate reconstruction of the musculofascial structures, and limiting the extent of dissection are critical for preserving the integrity of the posterior abdominal wall and minimizing the risk of Grynfeltt-Lesshaft hernia.

Declarations

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Availability of data and materials: The data supporting the findings of this study are available from the corresponding author on reasonable request.

Disclosure: The authors declare that they have no conflicts of interest regarding the publication of this case report.

Ethics approval and consent to participate: This case report did not require formal Institutional Review Board approval; written informed consent was obtained from the patient.

AUTHORSHIP CONTRIBUTION

Study conception and design: EV, MOU

Data collection: EV, IK, AMD

Analysis and interpretation of results: EV, IK

Draft manuscript preparation: EV, IK

Critical revision of the article: EFA, MOU

Other (study supervision, fundings, materials, etc...): MOU

All authors (EV, IK, AMD, EFA, MOU) reviewed the results and approved the final version of the manuscript.

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Beyond Mean Arterial Pressure: Critical Nuances in Hemodynamic Targeting for Severe Traumatic Brain Injury

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Dear Editor,

The multi-center study by Jiang et al. provides a provocative challenge to the traditional systolic blood pressure (SBP) <90 mmHg hypotension threshold in severe traumatic brain injury (sTBI) (3). However, several methodological gaps warrant discussion before these findings can influence clinical guidelines.

First, the authors conclude that mean arterial pressure (MAP) is the strongest predictor of one-week mortality. Yet, in neurosurgical practice, MAP is primarily a surrogate for cerebral perfusion pressure (CPP=MAP-ICP). Without concurrent data on intracranial pressure (ICP), a high MAP may simply be a compensatory response to intracranial hypertension rather than an independent driver of survival. This distinction is vital; targeting a specific MAP range without acknowledging the underlying intracranial physiology risks mismanaging the very perfusion the authors aim to optimize.

Furthermore, the optimal SBP range (120–129 mmHg) must be viewed through the lens of potential confounding by indication. Admission blood pressure and lactate are heavily influenced by pre-hospital fluid resuscitation and vasopressor use—variables not explicitly controlled for in this analysis (1,2). This raises questions about whether the authors' preference for MAP over SBP is a statistical artifact of their specific cohort rather than a universal physiological truth.

Finally, while the utility of lactate is emphasized for resource-limited settings, its lack of specificity for neuro-metabolic crises—as opposed to systemic polytrauma—remains a limitation. Did the authors adjust for extracranial injury severity to isolate lactate's neuro-specific prognostic value?

Even though Jiang et al. correctly highlighted the inadequacy of binary hypotension definitions, clinicians should exercise caution in adopting these narrow numerical targets until the

interplay between systemic hemodynamics and intracranial physiology is clarified (3).

Declarations

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Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Disclosure: The author declares that there are no conflicts of interest related to this study.

AUTHORSHIP CONTRIBUTION

The author (OOA) confirm responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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