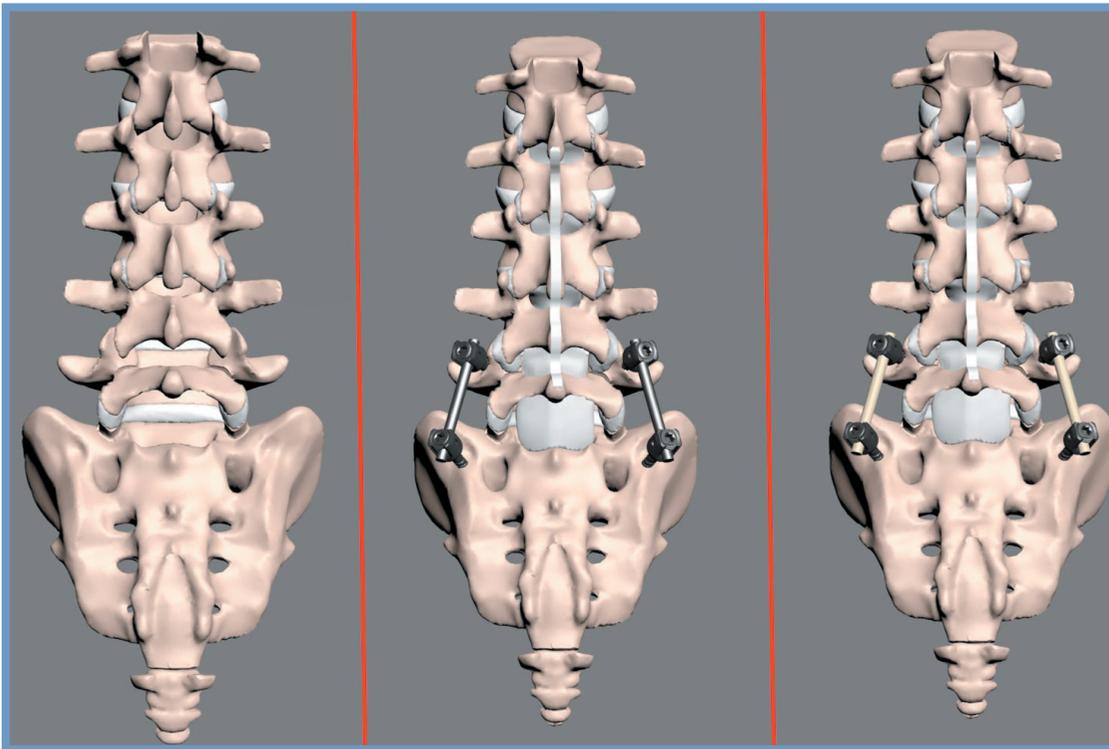




# Turkish Neurosurgery

Official Journal of the Turkish Neurosurgical Society





# Turkish Neurosurgery

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## ORIGINAL INVESTIGATIONS

## ■ Education in Neurosurgery

- 183** **A Comparative Study of Large Language Models in Turkish Neurosurgery Education Using a Mock Neurosurgery Board Examination**  
Kivanc YANGI, Egemen GOK, Jiuxu CHEN, Doga D. DEMIR YANGI, Michell GOYAL, Pravarakhya PUPPALLA, Kristina M. KUPANOFF, Baoxin LI, Ender KOKTEKIR, Omer Hakan EMMEZ, Mark C. PREUL

- 200** **Beyond Human 'Eyes' in Neurosurgical Exams: Success of Artificial Intelligence (ChatGPT-4o, Grok, and Gemini) in the Image-Based Questions of Turkish Neurosurgical Society Proficiency Board Exams**  
Alperen SOZER, Gokberk EROL, Ozan Yavuz TUFEK, Batuhan SOZER, Merve BUKE SAHIN, Mustafa Caglar SAHIN

- 211** **From Presentation to Publication: Publication Rates of Abstracts Presented at the Meetings of Two Neurosurgical Societies in Türkiye**  
Emmanuel MOULADJE TCHUELA, Ismail Ertan SEVIN, Selin BOZDAG, Hasan Kamil SUCU

## ■ Spine and Peripheral Nerves

- 218** **Affordable Excellence: A Meta-Analysis on the Efficacy of Topical Tranexamic Acid in Reducing Blood Loss in Thoracolumbar Spinal Surgery**  
Jyun-Yuan HUANG, Tzu-Ning CHEN, Hao-Kuang WANG, Kang LU, Jui-Sheng CHEN, Tsung-Jen HSIEH, Yu-Ying WU, Min-Jung LEE, Po-Yuan CHEN

- 229** **Hemostasis Versus Immunosuppression in Preventing Postlaminectomy Epidural Fibrosis: An Experimental Study in Rats**  
Vaner KOKSAL, Tolga MERCANTEPE, Levent TUMKAYA

- 237** **Complications of Biportal Endoscopic Surgery for Lumbar Pathologies: Retrospective Analysis of 374 Cases**  
Mehmet Ilker OZER, Oguz Kagan DEMIRTAS, Goktug ULKU, Mehmet Can EZGU, Ilker SOLMAZ

- 246** **Finite Element Analysis of Mechanical Stress Distribution in Titanium and PEEK Rod Constructs for Isthmic L5-S1 Spondylolisthesis**  
Idris AVCI, Ahmed Yasin YAVUZ, Ahmet Atilla ABDIOGLU, Kemal PAKSOY

254

**Effects of Caudal Epidural Pethidine on Pain Control and Early Mobilization after Posterior Spinal Instrumentation: A Randomized Controlled Trial**

Necati KAPLAN, Ilke TAMDOGAN, Tamer TAMDOGAN, Sevim ONDUL, Numan KARAARSLAN, Ibrahim YILMAZ

264

**Comparison of the Effects of Amantadine, Methylprednisolone and Nimodipine in Sciatic Nerve Crush Injury**

Ismail SAGIR, Recai ENGIN, Ilke Evrim SECINTI, Idris ALTUN

■ **Neuroanatomy**

275

**Evaluation of the First Cervical Vertebra Anatomy for Screw Fixation**

Narmin FARAJIBAND, Zuhre Aslı AKTAN IKIZ, Hulya UCERLER

■ **Neuro – Oncology**

281

**Impact of DNA Methylation Profiling on Central Nervous System Tumor Diagnosis and Management: A Pediatric Cohort Study from Türkiye**

Mehmet Arda INAN, Ayca ERSEN DANYELI, Figen SOYLEMEZOGLU, Berrin BABAOGU, Bahattin TANRIKULU, Memet OZEK

**SYSTEMATIC REVIEW**

294

**Evaluation of Drugs with Selective Inhibitors Targeting the Anti-Apoptotic Protein B-cell Lymphoma 2 (BCL-2) with Pro-Apoptotic and Antineoplastic Activities in Grade IV Glioblastoma**

Murat BALOGLU, Tamer TAMDOGAN, Sevim ONDUL, Mehmet BAKIRTAS, Ibrahim YILMAZ

**ORIGINAL INVESTIGATIONS**

■ **Neurotrauma**

302

**Acute Subdural Hematoma: Evaluation of Predictive Factors and Efficacy of Various Surgical Approaches on Prognosis**

Hasan IDIZ, Nafis VURAL, Elif ERTAS, Hasan Can GUVEN, Murat DUYAN, Ahmet Sukru ALPARSLAN

■ **Pediatrics**

310

**Shape Analysis of the Corpus Callosum in Pediatric Hydrocephalus: A Comparison Between Cases with and Without Shunt Revision Surgery**

Elif BASARAN GUNDOGDU, Deniz SIGIRLI

■ **General Neurosurgery and Miscellaneous-Others**

316

**Transnasal Transsphenoidal versus Transcranial Surgery for Resection of Sellar Lesions; A National Database Analysis**

Daniel N MUNGER, Brannan E O'NEILL, Ali I RAE, Mathew N GELTZEILER, Olabisi R SANUSI

## CASE REPORT

- 321** **Posterolateral Approach for Recurrent Multi-Level Ventral Intradural Extramedullary Cervical Spinal Meningioma**  
Varunil SHAH, Anish KOSANUM, Mohit PATEL, Manish K. KASLIWAL
- 327** **Intracranial Mature Bone Formation: Report of Three Uncommon Cases and a Proposed Pathogenetic Mechanism**  
Ersin HACIYAKUPOGLU, Evren YUVRUK, Ayca Ersan DANYELI, Sebahattin HACIYAKUPOGLU
- 332** **Emergent Endovascular Parent Artery Occlusion for Type III Carotid Blowout Syndrome After Charged Particle Therapy for Recurrent Maxillary Carcinoma: A Case Report and Literature Review**  
Daisuke WAJIMA, Sho TAKATA, Tomoya KAMIDE, Kouichi MISAKI, Koji SATO, Mitsutoshi NAKADA, Takumi TANIGUCHI

## LETTER TO EDITOR

- 337** **Letter to Editor: Impact of Obesity on Subarachnoid Hemorrhage-Induced Cerebral Vasospasm: An Experimental Rat Model**  
Hasan CALISKAN
- 339** **Critical Appraisal and Recommendations on the Use of Neuroendoscopic Surgery for Hypertensive Brainstem Hemorrhage**  
Yasin TASKIN





# A Comparative Study of Large Language Models in Turkish Neurosurgery Education Using a Mock Neurosurgery Board Examination

Kivanc YANGI<sup>1</sup>, Egemen GOK<sup>1</sup>, Jiuxu CHEN<sup>1,2</sup>, Doga D. DEMIR YANGI<sup>1</sup>, Michell GOYAL<sup>1</sup>, Pravarakhya PUPPALLA<sup>1</sup>, Kristina M. KUPANOFF<sup>3</sup>, Baoxin LI<sup>2</sup>, Ender KOKTEKIR<sup>4</sup>, Omer Hakan EMMEZ<sup>5</sup>, Mark C. PREUL<sup>1</sup>

<sup>1</sup>Barrow Neurological Institute St. Joseph's Hospital and Medical Center, The Loyal and Edith Davis Neurosurgical Research Laboratory, Arizona, USA

<sup>2</sup>Arizona State University, School of Computing and Augmented Intelligence, Arizona, USA

<sup>3</sup>St. Joseph's Hospital and Medical Center, Clinical Research Department of Trauma/Acute and General Surgery, Arizona, USA

<sup>4</sup>Selcuk University Faculty of Medicine, Department of Neurosurgery, Konya, Türkiye

<sup>5</sup>Güven Hospital, Department of Neurosurgery, Ankara, Türkiye

**Corresponding author:** Kivanc YANGI ✉ [kivancyangi@gmail.com](mailto:kivancyangi@gmail.com), [neuropub.preul@barrowneuro.org](mailto:neuropub.preul@barrowneuro.org)

## ABSTRACT

**AIM:** To evaluate Deepseek-R1, Gemini-2.0 Pro, ChatGPT-o3-mini-high, and GPT-4.5 on a mock neurosurgery board exam to assess their accuracy and educational value.

**MATERIAL and METHODS:** We created a 50-question mock neurosurgery board examination and administered it to three major large language models (LLMs) and 10 Turkish senior residents. Next, we systematically evaluated their responses for accuracy, reasoning time, word count, and readability. Residents ranked the educational value of the LLM responses. The study also compared two recent ChatGPT versions, o3-mini-high and GPT-4.5, using the same test. Statistical comparisons were used to analyze the results.

**RESULTS:** In overall accuracy, all three LLMs achieved higher scores than residents, with Deepseek-R1 at 84%, ChatGPT o3 mini-high at 82%, and Gemini 2.0 Pro at 78%, compared to 58% for residents ( $p < 0.001$ ). Deepseek-R1 required the longest reasoning time but provided the most organized responses. Gemini-2.0 Pro produced the most detailed and easy-to-read answers. Residents preferred the explanations from Deepseek-R1 and Gemini-2.0 Pro over those from ChatGPT-o3-mini-high ( $p < 0.001$ ). ChatGPT-4.5 achieved 74% accuracy, higher than residents but lower than other LLMs. Compared with ChatGPT o3-mini-high, ChatGPT-4.5 produced longer, more complex responses while responding faster ( $p < 0.001$ ).

**CONCLUSION:** LLMs' higher scores on the mock board examination highlight their potential as auxiliary educational tools in neurosurgical training. The high accuracy of Deepseek-R1 and the clarity of Gemini-2.0 Pro's detailed responses suggest uses with refinement as neurosurgical educational guides or in constructing board questions or training assessments.

**KEYWORDS:** Artificial intelligence, ChatGPT, Deepseek, Large language models, Neurosurgery education

**ABBREVIATIONS:** **AI:** Artificial intelligence; **ANOVA:** Analysis of variance; **FKGL:** Flesch-Kincaid Grade Level; **IQR:** Interquartile range; **LLM:** Large language model; **NLP:** Natural language processing; **OR:** Odds ratio; **PGY:** Postgraduate year

Kivanc YANGI	: 0000-0003-0500-218X	Michell GOYAL	: 0009-0006-4297-5959	Ender KOKTEKIR	: 0000-0002-6442-6663
Egemen GOK	: 0009-0008-0976-5903	Pravarakhya PUPPALLA	: 0009-0004-7476-8677	Omer Hakan EMMEZ	: 0000-0002-3290-179X
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Doga D. DEMIR YANGI	: 0000-0002-8306-1524	Baoxin LI	: 0000-0001-6365-3082		



## INTRODUCTION

Large language models (LLMs), a subset of natural language processing (NLP), are deep-learning-based neural networks trained on extensive datasets to understand and generate human-like language (14,21,25,31). In early 2025, several LLMs were released. OpenAI launched the latest versions of ChatGPT (<https://openai.com/chatgpt/overview/>), the o3-mini and the o3-mini-high, offering cost-effective reasoning with strengths in science, math, and coding (18,36). Google’s Gemini-2.0 Pro series (<https://gemini.google.com/app>) is designed to compete with models like ChatGPT-4o and supports seamless processing of text, images, and audio (17). Deepseek (<https://www.deepseek.com>) has also gained attention, with its R1 version quickly matching and even surpassing ChatGPT in some areas (16).

LLMs can answer questions, generate scientific text, aid diagnosis, support clinical decisions, and summarize medical information (3, 14, 42). Their explanatory and translational abilities also make them useful educational tools. Although AI integration in neurosurgery is advancing rapidly, the use of LLMs for education and clinical decision-making remains in its early stages (1,11,12,33,37,45,46).

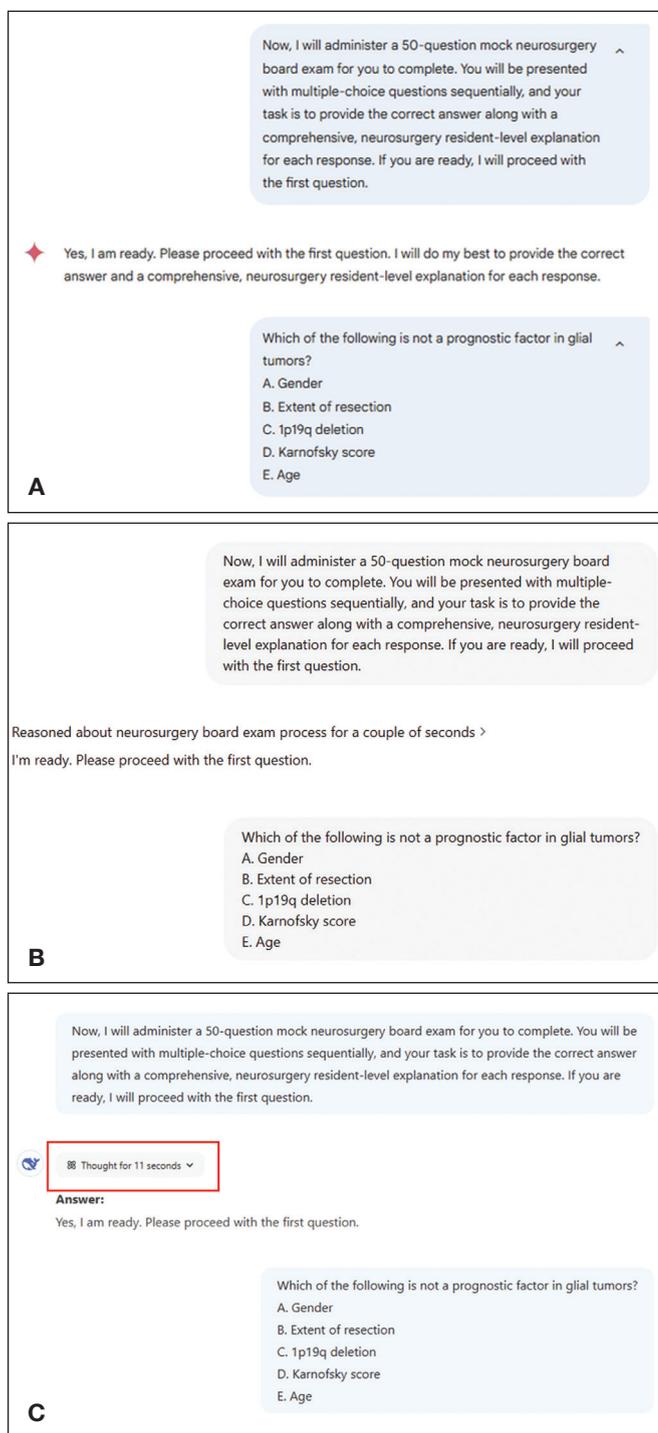
This study compared the performance of Deepseek-R1, Gemini-2.0 Pro, and ChatGPT-o3-mini-high on a 50-question mock neurosurgical board examination with that of Turkish senior neurosurgical residents in training programs in Turkey. From a technical perspective, the models were evaluated by assessing their answers. To determine whether these models can serve as supplementary educational tools in neurosurgery training and which models are more effective or reliable, the participating residents ranked the educational quality of the answers and explanations provided by the 3 LLMs.

## MATERIAL and METHODS

### Test Preparation and Data Collection

A mock neurosurgery board examination comprising 50 multiple-choice questions was prepared using the *Turkish Neurosurgery Board Examination Preparation Question Book (2021)* (40). This study was exempt from participant consent and institutional review board review because it involved an anonymous survey of educational questions and responses. No personally identifying information was collected or used to assess resident performance or knowledge, and only anonymized, content-based data were analyzed. The book contains answers and explanations for each of the 38 questions (40). The test was constructed by randomly selecting 5 questions from each of the 10 chapters in the book. Only text-based questions were selected. If a question with visual material was selected during the random selection process, the process was repeated until a question without a visual component was selected.

The latest versions of DeepSeek-R1 (DeepSeek-R1-0120), Gemini-2.0 Pro (Gemini-2.0-pro-exp-02-05), and ChatGPT-o3-mini-high (o3-mini-high-2025-02-12) were tested on March 15, 2025. Each model was instructed to answer 50 neurosurgery board exam questions and provide resident-level explanations (Figure 1). The same questions and identical prompts were used for all models in sequential testing.



**Figure 1:** Instructions for large language models that describe the test, ask them to answer the questions, and provide resident-level explanations. Instructions and responses are shown for **A)** ChatGPT o3-mini-high (OpenAI), **B)** Gemini 2.0 Pro (Google), and **C)** Deepseek-R1 (Deepseek), with reasoning time highlighted in the red box. Used with permission from Barrow Neurological Institute, Phoenix, Arizona.

ChatGPT-o3-mini-high and DeepSeek-R1 reported both reasoning times (Figure 1) and detailed self-monologues, whereas Gemini 2.0 Pro did not. Its response times were manually measured using the Windows 11 Snipping Tool (<https://www.microsoft.com/en-us/windows/>) and frame-by-frame analysis of 30 fps screen recordings, with an error margin of  $\pm 0.033$  s. Because ChatGPT-o3-mini-high stated it “reasoned for a few seconds” rather than providing exact durations, its responses were also analyzed via screen recording. While DeepSeek-R1 and ChatGPT-o3-mini-high explicitly display internal reasoning and timing, Gemini 2.0 Pro does not and generates responses almost instantaneously; hence its reasoning times were recorded manually.

Word counts of the LLMs’ responses were recorded to compare their lengths. Readability was assessed using the Flesch–Kincaid Grade Level (FKGL) metric, which evaluates text complexity based on sentence length and syllable count. FKGL scores (0–20) correspond to U.S. grade levels, from 0–1 for first grade to >15 for graduate-level difficulty (9). Higher FKGL scores indicate lower readability, meaning that texts with higher scores require a higher level of education to understand. After collecting LLM responses, a two-phase Google Forms test (<https://docs.google.com/forms/>) was created. Phase 1 presented the same 50 English-translated questions to residents. Phase 2 included anonymized explanations (models 1–3) and standardized explanations only for the 35 questions that all three LLMs answered correctly; the remaining 15 questions and their explanations were excluded.

Ten senior neurosurgery residents (postgraduate year [PGY]-5 and PGY-6) from 10 institutions across Turkey were recruited through the Young Neurosurgeons Committee of the Turkish Neurosurgical Society. Junior residents were excluded because the exam was beyond their knowledge base, being intermediate to advanced in difficulty. All participants were in active clinical training (January–February 2025) and had no prior exposure to the board examination book (40). In Phase 1, residents completed the test; in Phase 2, they ranked each LLM’s explanation by educational value (1st–3rd), corresponding to preference scores of 3, 2, and 1 points, respectively.

On February 27, 2025, after completing data collection, OpenAI released ChatGPT-4.5 (<https://openai.com/index/introducing-gpt-4-5/>). The same prompt and a 50-question test were administered to this research preview model to assess its reasoning time, word counts, and FKGL scores. ChatGPT-4.5 exhibited hallucinations in 4 of 50 (8%) questions—unlike the other LLMs—and was excluded from the main analysis. However, its results were compared with those of ChatGPT-o3-mini-high using independent *t*-tests and Mann–Whitney *U* tests to explore version differences.

### Statistical Analysis

Statistical analyses compared 1) LLM performance against residents’ average scores, 2) LLMs by educational value (converted resident rankings), and 3) LLMs by reasoning time, word count, and readability. Correct and incorrect response frequencies were analyzed using chi-square or Fisher’s exact tests. Pairwise comparisons with Bonferroni correction were conducted to adjust the *p*-value threshold, and only *p*-values

below this adjusted threshold were considered significant. All comparisons were performed for the entire test (covering all 50 questions) and for subcategories based on subject-specific specialties.

Reasoning times, word counts, FKGL scores, and resident preference scores were compared using appropriate statistical tests. Normality was assessed with the Shapiro–Wilk test, and variance equality with Levene’s test. Depending on these results, analyses were performed using Fisher’s one-way ANOVA with Tukey’s post hoc test, Welch’s ANOVA with Games–Howell, or the Kruskal–Wallis test with Dunn’s post hoc test and Bonferroni correction. All statistical analyses were performed using R version 4.4.3 (R Foundation for Statistical Computing; <https://www.r-project.org/foundation/>) on a computer with an Apple M2 processor (Apple Inc., Cupertino, CA). Python 3.11.5 (<https://www.python.org/>), along with libraries such as Matplotlib 3.7.2 (<https://matplotlib.org/3.7.2/>) and Pandas 2.2.3 (<https://pandas.pydata.org/docs/>), was used to generate graphs.

## RESULTS

Resident ages ranged from 27 to 31 years, with a mean (SD) of 29.6 (1.5) years. Five (50%) of the participants were in PGY-5, and 5 (50%) were in PGY-6. The dataset was complete, with no missing values across the analyzed variables.

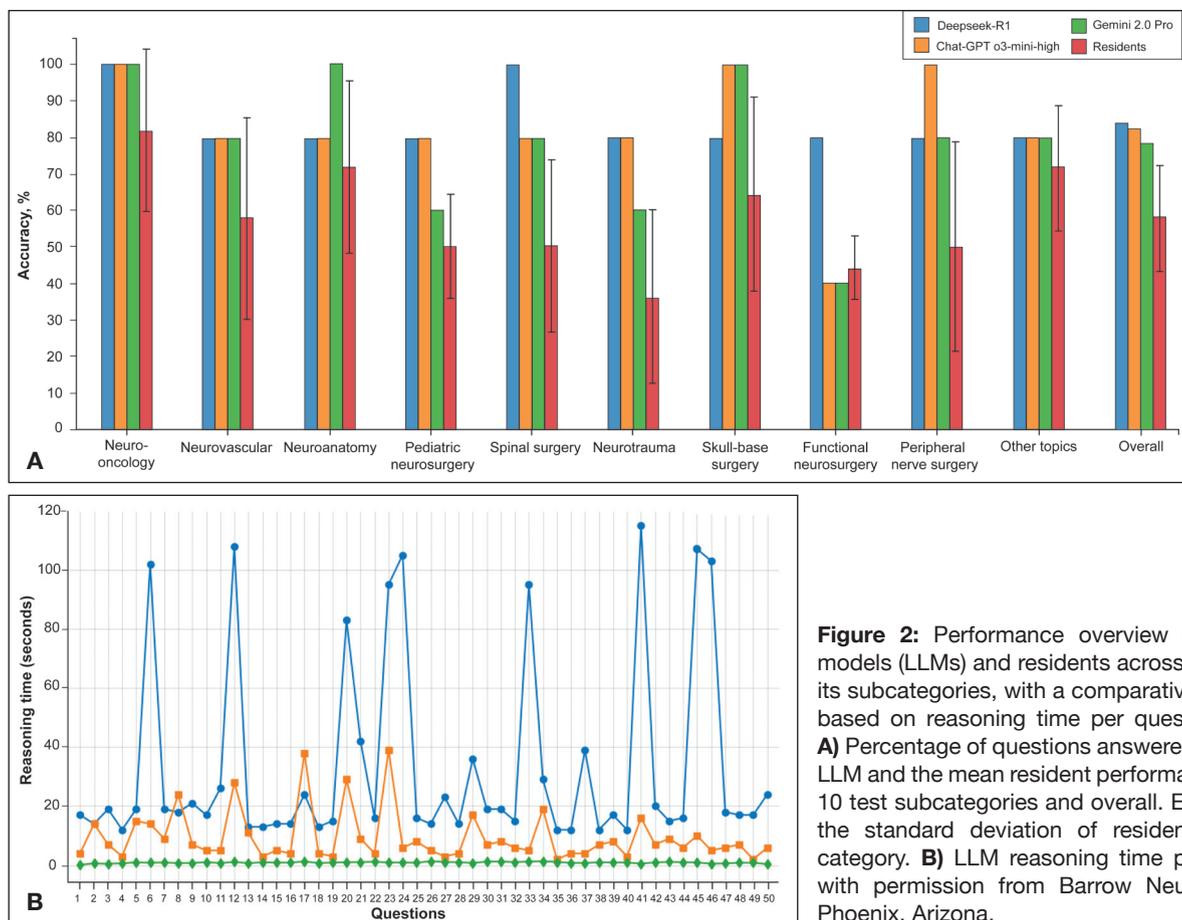
### Performance Comparison of LLMs and Neurosurgery Residents

To compare LLM performance with the average performance of senior neurosurgery residents, success rates were calculated as the percentage of questions answered correctly. Overall, the mean (SD) resident performance was 57.8% (14.6%), whereas Deepseek-R1 achieved 84%, ChatGPT-o3-mini-high scored 82%, and Gemini-2.0 Pro attained 78% (Figure 2). An overall difference ( $p < 0.001$ ) was observed in the performance of the 4 groups (residents and 3 LLMs). Pairwise comparisons indicated that LLMs tended to outperform residents: the odds ratios (95% CIs) were 3.83 (1.76–8.33) for residents versus Deepseek-R1, 3.33 (1.58–6.99) for residents versus ChatGPT-o3-mini-high, and 2.59 (1.30–5.17) for residents versus Gemini-2.0 Pro (Table I). Across subcategories, no significant differences were found among the 4 groups. Similarly, within subcategories, no differences were noted between any groups, likely due to the small sample size in the subcategories (Table I).

### Reasoning Times of the LLMs

The median reasoning times and corresponding interquartile ranges (IQRs) were 0.92 seconds (IQR: 0.76–1.05 seconds; range: 0.15–1.37 seconds) for Gemini-2.0 Pro, 6.50 seconds (IQR: 4.00–9.75 seconds; range: 2–39 seconds) for ChatGPT-o3-mini-high, and 18.00 seconds (IQR: 14.25–28.25 seconds; range: 12–115 seconds) for Deepseek-R1. The reasoning times for each LLM are presented in Table II and Figure 2.

Gemini-2.0 Pro demonstrated faster response times than the other 2 models (Table II). Although there were 2 exceptions (questions 8 and 17), DeepSeek-R1 generally took longer to respond than ChatGPT-o3-mini-high. Gemini-2.0 Pro was



**Figure 2:** Performance overview of large language models (LLMs) and residents across the entire test and its subcategories, with a comparative analysis of LLMs based on reasoning time per question and category. **A)** Percentage of questions answered correctly by each LLM and the mean resident performance for each of the 10 test subcategories and overall. Error bars represent the standard deviation of resident scores in each category. **B)** LLM reasoning time per question. Used with permission from Barrow Neurological Institute, Phoenix, Arizona.

faster than DeepSeek-R1 in all subcategories (Table II). Compared with ChatGPT-o3-mini-high, Gemini-2.0 Pro answered questions more quickly overall ( $p < 0.001$ ). Across subcategories, no difference in reasoning time was observed between ChatGPT-o3-mini-high and Gemini-2.0 Pro (Table II). ChatGPT-o3-mini-high responded faster than DeepSeek-R1 overall ( $p < 0.001$ ) and in the neurotrauma subcategory ( $p = 0.01$ ), with no differences across the remaining nine subcategories.

**Word Counts of the LLM Explanatory Answers**

Gemini-2.0 Pro generated the longest responses across all questions (Figure 3). The word counts for Deepseek-R1 and ChatGPT-o3-mini-high were similar. Gemini-2.0 Pro produced significantly longer responses than both Deepseek-R1 ( $p < 0.001$ ) and ChatGPT-o3-mini-high ( $p < 0.001$ ) (Table III). Additionally, Deepseek-R1’s responses were longer than those of ChatGPT-o3-mini-high overall ( $p = 0.016$ ) (Table III). Gemini-2.0 Pro’s responses were significantly longer ( $p < 0.001$ ) than those of ChatGPT-o3-mini-high in 8/10 categories (Table III). However, compared with Deepseek-R1, Gemini-2.0 Pro’s responses were longer only in the neuro-oncology ( $p = 0.002$ ), pediatric neurosurgery ( $p < 0.001$ ), and spinal surgery ( $p < 0.001$ ) subcategories. There were no differences in response length between ChatGPT-o3-mini-high and Deepseek-R1 across subcategories.

**FKGL Readability Scores of LLM Responses**

DeepSeek-R1 generated 6 graduate-level (12%), 35 university-level (70%), and 9 high-school-level (18%) responses; ChatGPT-o3-mini-high produced 22 (44%), 24 (48%), and 4 (8%); and Gemini 2.0 Pro yielded 5 (10%), 33 (66%), and 12 (24%), respectively (Table III).

ChatGPT-o3-mini-high generated texts that were more difficult to read than those from Deepseek-R1 ( $p = 0.016$ ) and Gemini-2.0 Pro ( $p < 0.001$ ). Responses from Deepseek-R1 were also more difficult to read than those from Gemini-2.0 Pro ( $p < 0.001$ ). At the subcategory level, the only difference was observed in the other topics category between ChatGPT-o3-mini-high and Gemini-2.0 Pro ( $p = 0.008$ ). Otherwise, no differences were found among any groups in the other subcategories.

**Preference Scores Given by Residents**

ChatGPT-o3-mini-high consistently ranked last among the residents (Figure 3, Table IV). When assessing the educational value of LLM responses across the entire test, differences were observed between ChatGPT-o3-mini-high and both Deepseek-R1 ( $p < 0.001$ ) and Gemini-2.0 Pro ( $p < 0.001$ ). However, no difference was observed between Deepseek-R1 and Gemini-2.0 Pro. Residents consistently judged ChatGPT’s responses as having lower educational value, whereas no difference was found between Deepseek-R1 and Gemini-2.0 Pro.

**Table I:** Comparison of 10 Residents and 3 Different Large Language Models Based on Their Performance on a 50-Question Mock Neurosurgery Board Examination

Question subcategory	No. of questions	Percentage (proportion) of questions answered correctly				p-value <sup>†</sup>					
		Residents (n=10)	Deepseek-R1 (n=1)	ChatGPT o3-mini-high (n=1)	Gemini 2.0 Pro (n=1)	Residents vs. Deepseek-R1	Residents vs. ChatGPT o3-mini-high	Residents vs. Gemini 2.0 Pro	Deepseek-R1 vs. ChatGPT o3-mini-high	Deepseek-R1 vs. Gemini 2.0 Pro	ChatGPT o3-mini-high vs. Gemini 2.0 Pro
Neuro-oncology	5	84 (42/50)	100 (5/5)	100 (5/5)	100 (5/5)	0.03	0.03	0.03	>0.99	>0.99	>0.99
Neurovascular	5	58 (29/50)	80 (4/5)	80 (4/5)	80 (4/5)	0.64	0.64	0.64	>0.99	>0.99	>0.99
Neuroanatomy	5	72 (36/50)	80 (4/5)	80 (4/5)	100 (5/5)	>0.99	>0.99	0.31	>0.99	>0.99	>0.99
Pediatric neurosurgery	5	50 (25/50)	80 (4/5)	80 (4/5)	60 (3/5)	0.36	0.36	>0.99	>0.99	>0.99	>0.99
Spinal surgery	5	50 (25/50)	100 (5/5)	80 (4/5)	80 (4/5)	0.06	0.36	0.36	>0.99	>0.99	>0.99
Neurotrauma	5	36 (18/50)	80 (4/5)	80 (4/5)	60 (3/5)	0.15	0.15	0.36	>0.99	>0.99	>0.99
Skull-base surgery	5	64 (32/50)	80 (4/5)	100 (5/5)	100 (5/5)	0.65	0.16	0.16	>0.99	>0.99	>0.99
Functional neurosurgery	5	44 (22/50)	80 (4/5)	40 (2/5)	40 (2/5)	0.18	>0.99	>0.99	0.52	0.52	>0.99
Peripheral nerve surgery	5	50 (25/50)	80 (4/5)	100 (5/5)	80 (4/5)	0.36	0.06	0.36	>0.99	>0.99	>0.99
Other topics	5	72 (36/50)	80 (4/5)	80 (4/5)	80 (4/5)	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
Overall	50	57.8 (289/500)	84 (42/50)	82 (41/50)	78 (39/50)	<0.001	<0.001	<0.001	>0.99	0.61	0.80

<sup>†</sup>By chi-square and Fisher's exact tests. An initial chi-square test conducted to compare the performance of the 4 groups (residents, Deepseek-R1, ChatGPT o3-mini-high, and Gemini 2.0 Pro) revealed a statistically significant difference ( $p < 0.001$ ). Following this, pairwise comparison tests were performed to assess overall test performance. The threshold p-value for pairwise comparisons was determined using the Bonferroni correction. With this correction, the new threshold p-value for overall test performance comparison was set at 0.0083, and only p-values below this threshold were considered statistically significant. When comparing performance across subcategories, Fisher's exact test was performed. No statistically significant differences were found among the 4 groups in any of the subcategories. Similarly, in the pairwise comparisons within subcategories, no significant differences were observed between any groups, most likely due to the small sample size in the subcategories.

Due to the limited sample size, pairwise comparisons could not be conducted for the functional neurosurgery and neurotrauma subcategories. At the subcategory level, comparisons between Deepseek-R1 and ChatGPT-o3-mini-high revealed differences in neuro-oncology ( $p = 0.004$ ), neurovascular ( $p < 0.001$ ), peripheral nerve surgery ( $p = 0.002$ ), and other topics ( $p = 0.016$ ). Comparing Gemini-2.0 Pro and ChatGPT-o3-mini-high, differences were found in neurovascular ( $p < 0.001$ ), neuroanatomy ( $p = 0.004$ ), skull-base surgery ( $p = 0.014$ ), and peripheral nerve surgery ( $p = 0.006$ ). At the subcategory level, no difference was found between Deepseek-R1 and Gemini-2.0 Pro (Table IV).

**ChatGPT o3-mini-high versus ChatGPT-4.5**

ChatGPT-4.5 correctly answered 37/50 (74%) questions but exhibited four hallucinations (Figure 4). The model's respons-

es containing hallucinations were deemed incorrect. For question 16, the model incorrectly selected an answer option from the previous question. For question 20, the model initially correctly selected choice B; however, in its explanation, it mistakenly labeled choice B as incorrect and erroneously copied an answer choice from a previous question. After extended reasoning, the model self-corrected and accurately chose choice B. For question 32, the model correctly selected choice C but mislabeled it as D in the final explanation. For question 33, the model correctly identified the answer but mistakenly labeled it B instead of E (Figure 4).

Performances of ChatGPT-o3-mini-high and ChatGPT-4.5 were then compared. ChatGPT-4.5's answers were longer than those of ChatGPT-o3-mini-high ( $p < 0.001$ ) (Figure 5). When analyzed by subcategory, the difference between the two models was significant only in the peripheral nerve sur-

**Table II:** Reasoning Times of 3 Different Large Language Models While Answering 50 Mock Neurosurgery Board Examination Questions, Evaluated for the Overall Test and Across Subcategories

Question subcategory	No. of questions	Reasoning time, median (IQR), s			p-value*		
		Deepseek-R1	ChatGPT o3-mini-high	Gemini 2.0 Pro	Deepseek-R1 vs. ChatGPT o3-mini-high	Deepseek-R1 vs. Gemini 2.0 Pro	ChatGPT o3-mini-high vs. Gemini 2.0 Pro
Neuro-oncology	5	17.00 (14.00-19.00)	7.00 (4.00-14.00)	0.64 (0.48-0.67)	0.04	<0.001	0.03
Neurovascular	5	19.00 (18.00-21.00)	9.00 (7.00-14.00)	0.85 (0.79-0.92)	0.69	0.003	0.12
Neuroanatomy	5	14.00 (13.00-26.00)	5.00 (5.00-11.00)	0.89 (0.75-1.01)	0.69	0.003	0.12
Pediatric neurosurgery	5	15.00 (14.00-24.00)	4.00 (4.00-29.00)	0.91 (0.90-1.02)	>0.99	0.009	0.06
Spinal surgery	5	42.00 (16.00-95.00)	8.00 (6.00-9.00)	0.93 (0.91-1.06)	0.41	0.002	0.17
Neurotrauma	5	19.00 (14.00-23.00)	5.00 (4.00-7.00)	1.10 (1.03-1.23)	0.01	<0.001	0.30
Skull-base surgery	5	19.00 (15.00-29.00)	6.00 (5.00-8.00)	1.22 (1.10-1.24)	0.47	0.002	0.16
Functional neurosurgery	5	12.00 (12.00-17.00)	4.00 (4.00-7.00)	0.91 (0.83-0.95)	0.23	0.001	0.23
Peripheral nerve surgery	5	20.00 (16.00-107.00)	9.00 (7.00-10.00)	0.95 (0.94-1.02)	0.36	0.002	0.18
Other topics	5	18.00 (17.00-24.00)	6.00 (5.00-6.00)	0.63 (0.52-0.84)	0.23	0.001	0.23
Overall	50	18.00 (14.25-28.25)	6.50 (4.00-9.75)	0.92 (0.76-1.05)	<0.001	<0.001	<0.001

**IQR:** interquartile range; **s:** seconds.

\*For multiple comparisons, Fisher’s one-way analysis of variance (ANOVA) was applied if all distributions were normal and variances were equal, followed by Tukey’s honestly significant difference test for post hoc analysis. If all distributions were normal but variances were unequal, Welch’s ANOVA test was used, followed by the Games-Howell post hoc test. If at least 1 distribution was not normal, the Kruskal-Wallis test was applied, followed by Dunn’s test with Bonferroni correction. Subsequently, for pairwise comparisons, the p-value threshold was adjusted using the Bonferroni correction, setting the new threshold at 0.017. Only p-values below this threshold were considered statistically significant.

gery subcategory (p = 0.005). ChatGPT-4.5’s responses were more difficult to read (p < 0.001). At the subcategory level, the difference was significant in 7/10 subcategories (Supplemental Table I). ChatGPT-4.5 responded more quickly (p < 0.001). At the subcategory level, the difference was significant in 8/10 subcategories (Supplemental Table I).

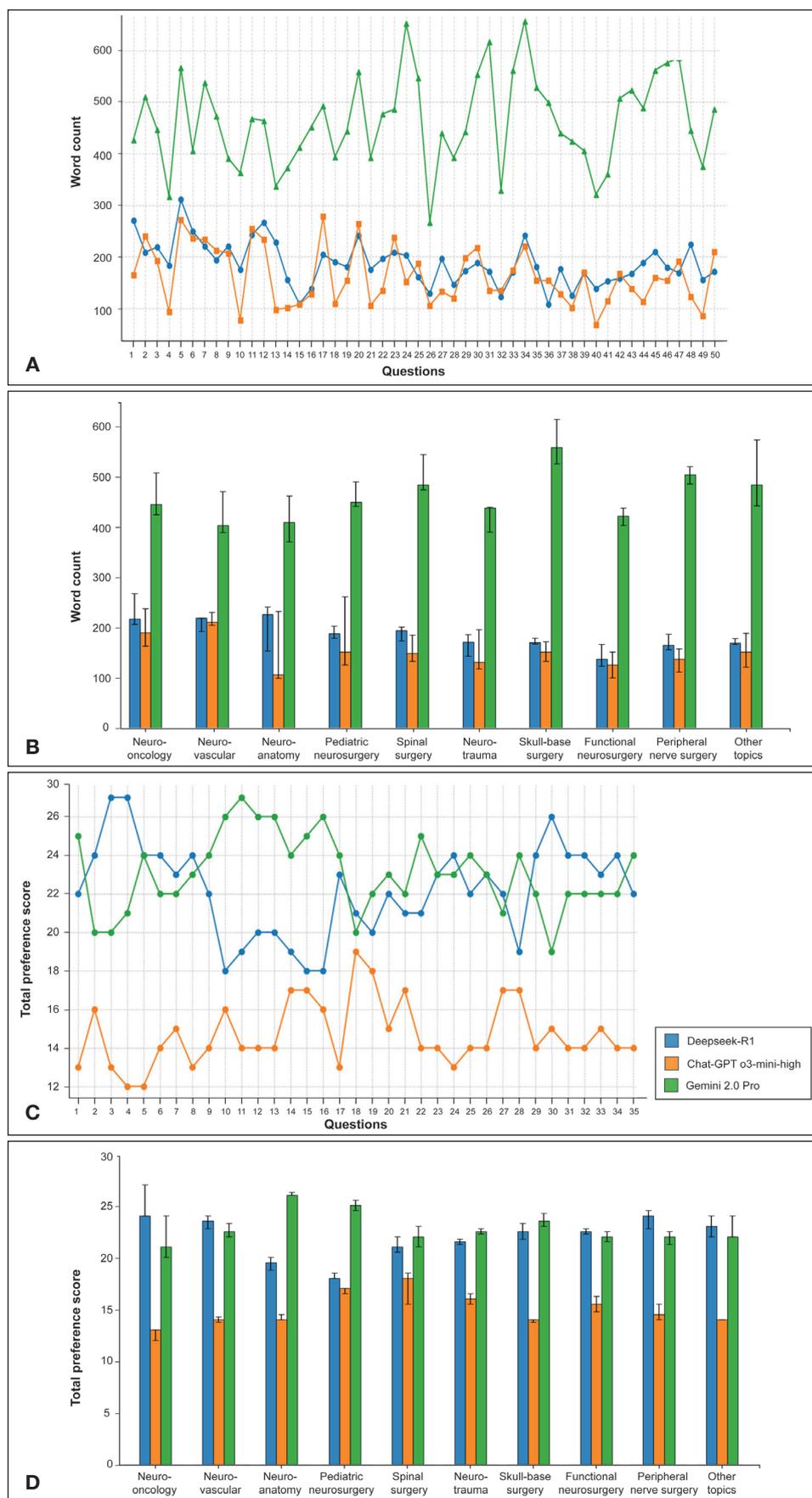
**DISCUSSION**

**Deepseek-R1 versus Gemini 2.0 Pro versus ChatGPT o3-mini-high**

In 2017, NLP underwent a significant shift with the introduction of the transformer architecture. This approach used self-attention mechanisms to process input data more efficiently and capture complex linguistic relationships (34). This breakthrough demonstrated that large-scale pretraining could enable powerful, flexible NLP systems, laying the foundation

for modern LLMs, including ChatGPT, Gemini, and Deepseek-R1. These LLMs were developed to expand the boundaries of natural language understanding and generation, enhancing problem-solving and knowledge dissemination.

All three models assessed in our study use the transformer architecture as the foundation for their natural language processing. Each model has its own modifications to boost performance for different needs (Table V). ChatGPT relies on a generative pre-trained transformer, a decoder-only model designed for text generation. It processes input prompts and produces word tokens one at a time. Gemini uses ultra-scale transformer models and adds multimodal features and retrieval-augmented generation, enabling it to pull in real-time information from Google Search and handle different types of data. The last model, Deepseek, uses a mixture-of-experts transformer model with sparse activation, which lowers computation costs by picking the best submodel for each query.



**Figure 3:** Comparative analysis of large language model (LLM) response word counts and their educational value, as evaluated by 10 residents. **A)** Word counts of responses from 3 LLMs for each question. **B)** Median word count, with corresponding IQRs (error bars), of responses from 3 LLMs by category. **C)** Total preference scores given to each LLM by 10 residents for each of 35 questions answered correctly by all 3 LLMs. The highest-ranked explanation received 3 points, the intermediate explanation received 2 points, and the lowest-ranked explanation received 1 point. **D)** Median preference scores, with corresponding IQRs (error bars), assigned by 10 residents to each LLM's responses by subcategory. Used with permission from Barrow Neurological Institute, Phoenix, Arizona.

**Table III:** Word Counts and Flesch-Kincaid Grade Level (FKGL) Readability Scores of the Explanatory Answers Provided by 3 Different Large Language Models to the 50 Questions in the Mock Neurosurgery Board Examination

Question subcategory	No. of questions	Explanation word count, median (IQR)			FKGL readability score, median, (IQR)			p-value*		
		Deepseek-R1	ChatGPT 03-mini-high	Gemini 2.0 Pro	Deepseek-R1	ChatGPT 03-mini-high	Gemini 2.0 Pro	Deepseek-R1 vs. ChatGPT 03-mini-high	Deepseek-R1 vs. Gemini 2.0 Pro	ChatGPT 03-mini-high vs. Gemini 2.0 Pro
Neuro-oncology	5	219.0 (209.00-270.00)	192.0 (165.00-240.00)	447.0 (427.00-510.00)	12.83 (12.16-13.15)	12.53 (12.23-14.12)	13.09 (12.26-13.34)	>0.99	0.95	0.98
		221.0 (207.00-233.00)	213.0 (207.00-233.00)	406.0 (391.00-473.00)	12.74 (12.34-13.69)	13.87 (13.46-15.20)	13.0 (12.97-13.80)	0.27	>0.99	0.41
Neuroanatomy	5	228.0 (155.00-243.00)	108.0 (101.00-234.00)	412.0 (373.00-464.00)	12.71 (12.61-13.11)	13.37 (13.03-13.75)	11.95 (11.94-12.24)	0.61	>0.99	0.08
		190.0 (181.00-205.00)	154.0 (128.00-264.00)	452.0 (444.00-493.00)	12.74 (12.08-13.82)	12.49 (12.40-13.85)	12.72 (12.22-14.44)	0.95	0.97	>0.99
Spinal surgery	5	196.0 (176.00-203.00)	151.0 (135.00-187.00)	486.0 (477.00-547.00)	12.75 (12.63-12.96)	16.29 (14.51-17.87)	12.7 (12.20-13.98)	0.12	>0.99	0.14
		173.0 (146.00-188.00)	133.0 (120.00-198.00)	440.0 (392.00-442.00)	13.17 (12.54-13.50)	15.26 (14.59-15.77)	14.01 (11.77-16.18)	0.50	0.81	0.86
Skull-base surgery	5	172.0 (170.00-181.00)	154.0 (135.00-174.00)	561.0 (528.00-617.00)	13.48 (13.29-13.71)	15.59 (15.38-16.49)	13.85 (12.90-14.53)	0.03	0.07	0.92
		139.0 (125.00-169.00)	128.0 (102.00-154.00)	424.0 (406.00-440.00)	14.1 (11.40-15.01)	14.06 (13.88-15.38)	13.32 (12.95-13.36)	0.81	0.68	0.97
Peripheral nerve surgery	5	167.0 (158.00-189.00)	139.0 (114.00-160.00)	507.0 (488.00-523.00)	13.18 (12.51-14.60)	14.19 (12.92-14.67)	13.63 (11.58-13.74)	>0.99	>0.99	0.54
		171.0 (169.00-180.00)	154.0 (123.00-191.00)	486.0 (445.00-576.00)	14.05 (13.96-14.34)	16.39 (16.21-16.80)	13.09 (12.54-13.96)	0.06	>0.99	<b>0.008</b>
Overall	50	181.0 (162.50-209.75)	154.0 (115.50-209.25)	458.0 (397.00-526.75)	13.13 (12.38-14.09)	14.55 (13.33-16.19)	13.045 (12.21-13.94)	<b>0.016</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>

**IQR:** interquartile range.

\*For multiple comparisons, Fisher's one-way analysis of variance (ANOVA) was applied if all distributions were normal and variances were equal, followed by Tukey's honestly significant difference test for post hoc analysis. If all distributions were normal but variances were unequal, Welch's ANOVA was used, followed by the Games-Howell post hoc test. If at least one distribution was not normal, the Kruskal-Wallis test was applied, followed by Dunn's test with Bonferroni correction. Subsequently, for pairwise comparisons, the p-value threshold was adjusted using the Bonferroni correction, setting the new threshold at 0.017. Only p-values below this threshold were considered statistically significant.

**Q15**  
Which of the following is not a component of the limbic system?  
A. Nucleus Accumbens  
B. Hippocampus  
C. Hypothalamus  
D. Pulvinar  
E. Septal nucleus

**Correct Answer: D. Pulvinar**

---

**Q16**  
Which structure is formed by Hensen's node cells?  
A. Notochord  
B. Cervical region of the spinal cord  
C. Conus medullaris  
D. Cranial nerves  
E. The remaining part of the spinal cord excluding the conus medullaris

**Correct Answer: A. Nucleus Accumbens**

---

**Comprehensive Explanation:**  
The limbic system is a complex neural network primarily involved in emotional regulation, memory formation, reward processing, and autonomic function. The classical components of the limbic system include:  
• Hippocampus  
• Amygdala  
• Hypothalamus  
• Septal nuclei  
• Cingulate cortex  
• Mammillary bodies  
• Fornix

**Analysis of Choices:**  
• **A. Nucleus Accumbens (Correct Answer)**  
While closely related functionally to the limbic system (particularly in reward, motivation, and addiction pathways), the nucleus accumbens is anatomically classified as part of the **ventral striatum**, not traditionally as part of the limbic system structures.

**Q20**  
Which of the following is correct regarding Galen Vein Aneurysmal Dilatation (GVAD)?  
A. Parenchymal GVAD typically presents in middle to late age with intracerebral hemorrhage, focal neurological deficit, or seizures.  
B. In parenchymal GVAD, the lesion is located in the median vein of the prosencephalon.  
C. Mural parenchymal GVAD is a congenital pathology.  
D. Transvenous embolization is a suitable treatment for GVAD.  
E. GVAD is classified into parenchymal and dural subtypes.

**Correct Answer: B. In parenchymal GVAD, the lesion is located in the median vein of the prosencephalon.**

---

**Comprehensive Explanation:**  
Vein of Galen aneurysmal malformations (VGAM) and related anomalies are rare vascular malformations classified according to their anatomical location, timing of presentation, and embryological origins. It's important to distinguish between these malformations clearly:

**Definitions and Clarifications:**

- **Galenic aneurysmal dilations** typically arise from the **median vein of the prosencephalon**, an embryological precursor to the vein of Galen.
- **Vein of Galen malformations (VGAM)** are classically **congenital**, presenting neonatally or in early childhood.

However, distinct subtypes and terminologies exist:

- **Parenchymal (non-Galenic) AVMs** are generally within brain parenchyma and drain into the vein of Galen secondarily. They present typically in older individuals (children, adolescents, or adults) and are not true Galenic aneurysmal malformations.

**Analysis of Answer Choices:**

- **A. Incorrect:**  
Parenchymal AVMs presenting in middle to late adulthood typically cause hemorrhage or seizures, but these lesions are not considered true VGAMs; rather, they drain secondarily into the vein of Galen.
- **B. In parenchymal VGAM, the lesion is located in the median vein of the prosencephalon. (Incorrect)**  
The "median vein of the prosencephalon" is the embryonic precursor to the true VGAM and would not be associated with parenchymal lesions. True VGAM originates from a persistent median vein of the prosencephalon, whereas parenchymal lesions represent secondary drainage into the Galenic system.
- **C. Mural parenchymal VGAM is a congenital pathology. (Incorrect)**  
Mural type VGAM (a subtype of true VGAM) is indeed congenital. However, "parenchymal" lesions are distinct, not true VGAMs, and typically not congenital but acquired AVMs draining into the Galenic system.
- **D. Transvenous embolization is a suitable treatment. (Incorrect)**  
Treatment of VGAM generally involves **transarterial embolization** rather than transvenous embolization. Transarterial embolization is typically preferred because transvenous embolization poses significant risks.
- **E. Scoliosis is expected to improve postoperatively. (Incorrect)**  
(This option was not provided; it appears to be mistakenly copied from a previous question.)

**Q32**  
Which type of chordoma has the worst prognosis?  
A) Classic  
B) Chondroid  
C) Dedifferentiated  
D) Lipoid  
E) Cell-rich

**Correct Answer: C) Dedifferentiated**

---

**Comprehensive Explanation:**  
Chordomas are rare, malignant bone tumors arising from remnants of the embryonic notochord. Prognosis varies significantly based on histological subtype:

**Chordoma Subtypes and Prognosis:**

- **Classic Chordoma (Most common subtype)**
  - Slow-growing, locally invasive tumor.
  - Intermediate prognosis; recurrence common after incomplete resection.
- **Chondroid Chordoma**
  - Variant containing cartilage-like (chondroid) elements.
  - Better prognosis and slightly less aggressive behavior compared to classic chordomas.
- **Dedifferentiated Chordoma (Correct Answer)**
  - High-grade variant, characterized by areas resembling high-grade spindle-cell sarcoma.
  - Exhibits highly aggressive behavior, early metastasis, rapid growth, and resistance to conventional treatments.
  - Worst prognosis among chordoma subtypes, with significantly shortened survival.
- **Lipoid Chordoma (Rare subtype)**
  - Contains lipid-rich cells; uncommon, generally behaves similarly or slightly better than classic chordoma, but not aggressively malignant.
- **Chondroid subtype (already discussed above)**
  - Typically has a better prognosis compared to the classic form due to less aggressive growth.
- **Dedifferentiated subtype:**
  - Represents a transformation from classic chordoma to an aggressive sarcoma-like histology, significantly worsening prognosis.

**Bottom Line:**  
The **Dedifferentiated chordoma subtype (Option D)** clearly has the worst prognosis, characterized by rapid progression, aggressive clinical behavior, and poor survival rates.

**Q33**  
Which of the following is correct regarding radiosurgery for acoustic neuromas?  
A) Radiosurgery is the first-line treatment for tumors >3 cm.  
B) Radiosurgery is the first-line treatment for tumors <3 cm.  
C) Compared to microsurgical resection, radiosurgery results in greater facial nerve dysfunction.  
D) The current standard dose for radiosurgery treatment is 14-16 Gy.  
E) Radiosurgery is superior to microsurgery in preserving hearing function.

**Correct Answer: B) Radiosurgery is superior to microsurgery in preserving hearing function.**

(Note: The original provided options listed do not exactly match the correct statement typically tested in board exams. The provided option E appears closest to the correct concept, but the exam options you've listed appear mismatched or incomplete. The provided original option set did not list "Radiosurgery is superior to microsurgery in preserving hearing function" under option B. However, from the standard clinical perspective, the statement "Radiosurgery is superior to microsurgery in preserving hearing function" is correct. Likely, there was an error or typo in the original option labeling. If we consider the actual clinical facts and typical neurosurgery board examinations, the corrected option is described as above.)

**D**

---

**Chondroid subtype (already discussed above)**

- Typically has a better prognosis compared to the classic form due to less aggressive growth.

**Dedifferentiated subtype:**

- Represents a transformation from classic chordoma to an aggressive sarcoma-like histology, significantly worsening prognosis.

**Bottom Line:**  
The **Dedifferentiated chordoma subtype (Option D)** clearly has the worst prognosis, characterized by rapid progression, aggressive clinical behavior, and poor survival rates.

**Figure 4:** The 4 questions in which ChatGPT-4.5 hallucinated during the mock neurosurgery board examination, along with the model's responses. **A)** ChatGPT-4.5's correct response to question 15, followed by its incorrect response and explanation for question 16, in which it mistakenly used the answer choices from question 15. **B)** When question 20 was asked, the model initially claimed B as the correct answer but then labeled B as incorrect in its explanation, while also adding a new answer choice ("E: Scoliosis") from a previous question. **C)** For question 32, the model initially selected C as the correct answer but mistakenly labeled it as D in the bottom-line explanation. **D)** For question 33, the model correctly answered the question but mistakenly labeled the correct answer choice as B instead of E. Used with permission from Barrow Neurological Institute, Phoenix, Arizona.

This makes it strong in complex problem-solving, such as scientific reasoning in math, medicine, and coding, and it also offers strong bilingual support.

### Performance of Deepseek-R1

Deepseek-R1, a recently released language model developed in China, has garnered significant attention despite limited testing (20). Although some studies have compared ChatGPT and Deepseek on specific tasks, to our knowledge, no research has examined Deepseek's accuracy and efficacy on

neurosurgery board examinations. Previous studies have examined other LLMs in this context, but the performance of Deepseek and Gemini remains underexplored (4,19,28,35).

Deepseek-R1 was slower, particularly in reasoning time, but achieved the highest overall accuracy on the test, answering 42 of 50 questions correctly (84%). However, statistical analysis did not reveal a significant difference among the three models. Deepseek-R1 appeared to perform better on complex neurosurgical questions than the other models.

**Table IV:** Preference Scores Given by 10 Residents to the Explanatory Responses of 3 Large Language Models for the 35 Questions Answered Correctly by All 3 Large Language Models

Question subcategory	No. of questions	Preference score, median (IQR)*			p-value†		
		Deepseek-R1	ChatGPT o3-mini-high	Gemini 2.0 Pro	Deepseek-R1 vs. ChatGPT o3-mini-high	Deepseek-R1 vs. Gemini 2.0 Pro	ChatGPT o3-mini-high vs. Gemini 2.0 Pro
Neuro-oncology	5	24 (24.0-27.0)	13 (12.0-13.0)	21 (20.0-24.0)	<b>0.004</b>	0.86	0.10
Neurovascular	4	23.5 (22.75-24.0)	14 (13.75-14.25)	22.5 (22.0-23.25)	<b>&lt;0.001</b>	0.72	<b>&lt;0.001</b>
Neuroanatomy	4	19.5 (18.75-20.0)	14 (14.0-14.5)	26 (26.0-26.25)	0.33	0.33	<b>0.004</b>
Pediatric neurosurgery	3	18 (18.0-18.5)	17 (16.5-17.0)	25 (24.5-25.5)	0.53	0.53	0.02
Spinal surgery	3	21 (20.5-22.0)	18 (15.5-18.5)	22 (21.0-23.0)	0.11	0.94	0.07
Neurotrauma‡	2	21.5 (21.25-21.75)	16 (15.50-16.50)	22.5 (22.25-22.75)	-	-	-
Skull-base surgery	4	22.5 (21.75-23.25)	14 (13.75-14.00)	23.5 (23.00-24.25)	0.16	>0.99	<b>0.014</b>
Functional neurosurgery‡	2	22.5 (22.25-22.75)	15.5 (14.75-16.25)	22 (21.50-22.50)	-	-	-
Peripheral nerve surgery	4	24 (22.75-24.50)	14.5 (14.00-15.50)	22 (21.25-22.50)	<b>0.002</b>	0.63	<b>0.006</b>
Other topics	4	<b>23.5</b> <b>(22.75-24.00)</b>	<b>14</b> <b>(14.00-14.25)</b>	<b>22</b> <b>(22.00-22.50)</b>	<b>0.016</b>	>0.99	0.11
Overall	35	22 (20.50-24.00)	14 (14.00-16.00)	23 (22.00-24.00)	<b>&lt;0.001</b>	0.93	<b>&lt;0.001</b>

**IQR:** interquartile range.

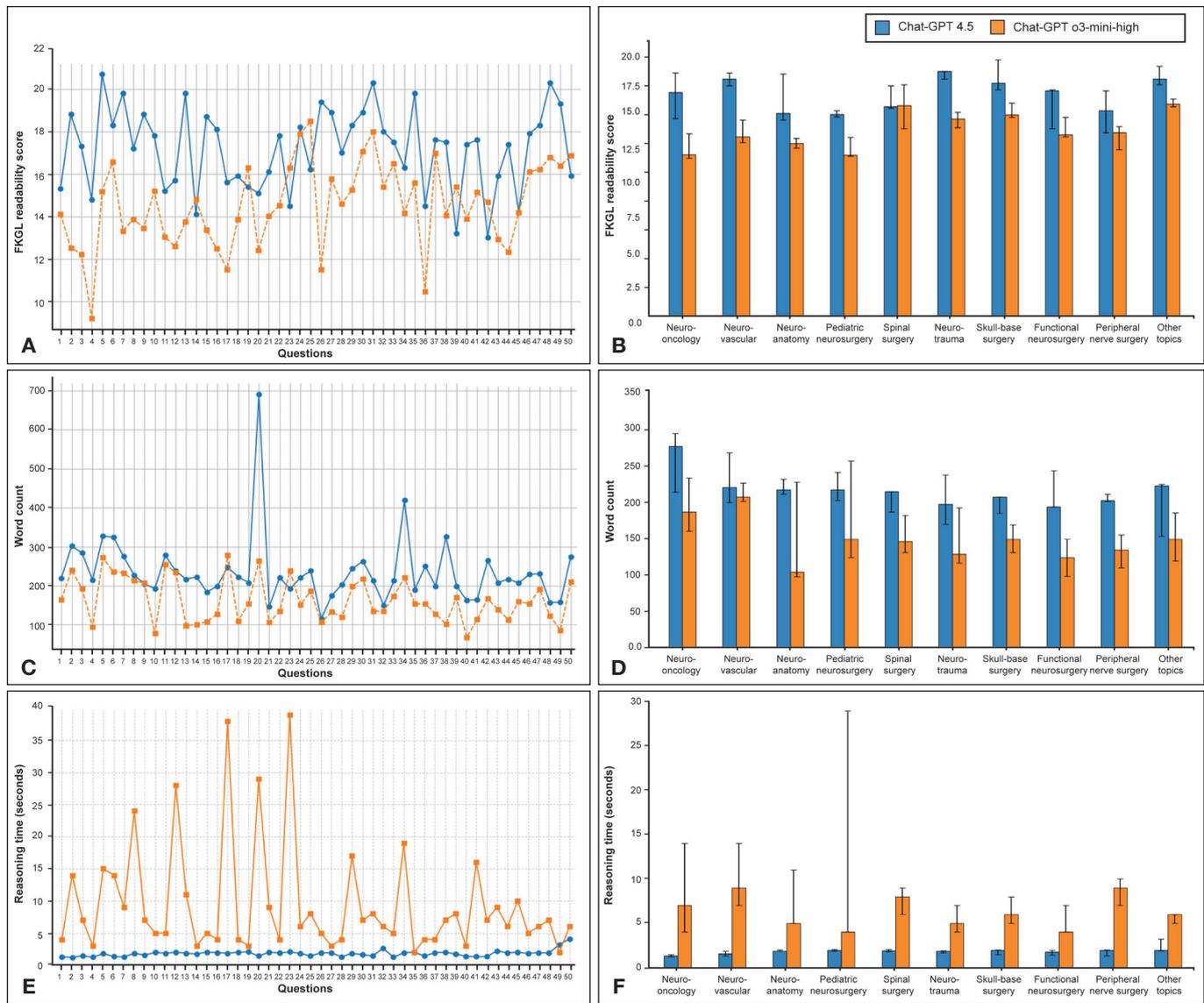
\*The highest-ranked explanation received 3 points, the intermediate explanation received 2 points, and the lowest-ranked explanation received 1 point.

†For multiple comparisons, Fisher’s one-way analysis of variance (ANOVA) was applied if all distributions were normal and variances were equal, followed by Tukey’s honestly significant difference test for post hoc analysis. If all distributions were normal but variances were unequal, Welch’s ANOVA was used, followed by the Games-Howell post hoc test. If at least 1 distribution was not normal, the Kruskal-Wallis test was applied, followed by Dunn’s test with Bonferroni correction. Subsequently, for pairwise comparisons, the p-value threshold was adjusted using the Bonferroni correction, setting the new threshold at 0.017. Only p-values below this threshold were considered statistically significant.

‡In the neurotrauma and functional neurosurgery subcategories, only 2 questions were correctly answered by all 3 large language models, resulting in an insufficient sample size. Therefore, statistical analysis could not be performed.

**Table V:** Qualitative Comparison of 3 Large Language Models

Model	Primary goal	Key strengths	Weaknesses
ChatGPT (OpenAI)	General-purpose artificial intelligence assistant	Best for open-ended conversations, creativity, and general knowledge	Prone to hallucination, lacks real-time search
Gemini (Google)	Multimodal artificial intelligence for text, images, and search	Strong in real-time fact-checking, search integration, and multimodal tasks	Still developing in specialized reasoning
DeepSeek-R1	Advanced reasoning for medical and scientific applications	Excels in professional fields (medicine, engineering, science), strong bilingual performance	Not versatile for general conversations



**Figure 5:** Comparison of Flesch-Kinkaid Grade Level (FKGL) readability scores, word counts, and reasoning times for ChatGPT o3-mini-high and ChatGPT-4.5 in answering 50 questions in a mock neurosurgery board examination. **A)** FKGL readability scores for each question. **B)** Median FKGL readability scores, with corresponding IQRs (error bars), across subcategories. **C)** Word counts of the answers provided for each question. **D)** Median word counts of answers, with corresponding IQRs (error bars), across subcategories. **E)** Reasoning time for each question. **F)** Median reasoning times, with corresponding IQRs (error bars), for the 2 models across subcategories. Used with permission from Barrow Neurological Institute, Phoenix, Arizona

This performance can be attributed to 2 key factors: 1) specialized training in medical domains and 2) advanced reasoning capabilities. Deepseek-R1 is likely trained on extensive medical datasets tailored for complex reasoning tasks (39). In contrast, models such as Gemini-2.0 Pro and ChatGPT-o3-mini-high are general-purpose language models that may lack the domain-specific depth. Second, Deepseek-R1’s architecture is optimized for complex reasoning, enabling it to analyze and synthesize medical information effectively. This optimization improves its ability to deliver more accurate, contextually relevant responses to medical inquiries.

Although Deepseek-R1’s specialized training relies on publicly available open-source datasets, clarification is needed regarding compliance and data-sharing regulations, privacy, and governance frameworks (39). Additionally, Deepseek-R1’s mixture-of-experts architecture is a key factor in its success, enabling the model to achieve high performance with fewer parameters, minimal human intervention during training, and ultimately lower costs (13,15). Although Deepseek-R1 showed better overall accuracy in our test, the lack of statistically significant differences among the models indicates that these findings require validation through replication with larger question pools.

## LLMs and Medical Examinations

Among LLMs, ChatGPT has been the most extensively studied. ChatGPT-4 outperformed examinees in all 3 steps of the United States Medical Licensing Examination (32). Similarly, LLMs (primarily ChatGPT) have performed impressively on board examinations across various specialties. A recent study found that the latest version of ChatGPT surpassed the human average on neurology board-style examinations (36). However, several other studies reported varying results when different LLM versions were tested on board examinations across various specialties (8,30).

Studies have compared LLM proficiency on neurosurgical board examinations to that of resident or attending physicians, yielding mixed results. Multiple studies have indicated that LLMs achieved passing scores comparable to those of human participants on neurosurgical board-style questions (4,19,22,35,36). However, other studies have suggested that LLMs did not surpass human participants on these questions (7,43). One study found ChatGPT to be unreliable (37) but 3 others reported that it outperformed examinees (4,19,35). Another study indicated that ChatGPT performed better on board examinations requiring specialized knowledge than on general medical examinations (4). Additionally, it was tested with European Neurosurgery Board Examination questions, ranking sixth out of 11 participants (7). However, its performance varied across studies, and when assessed with national residency interview questions, it did not surpass human competitors (7,28,43).

In previous studies, LLM performance has been compared with results from either the average scores of residents who had taken board examinations in previous years or the mean performance of subscribers completing self-assessments from question banks, and occasionally from small resident and medical student cohorts (4,19,22,28,35). By contrast, our study did not rely on actual examination results. Instead, we constructed a 50-question test by randomly selecting items from the *Turkish Neurosurgery Board Examination Preparation Question Book* and administered it to 10 senior residents in an active, participatory setting. Moreover, the second phase of our test was uniquely designed so that each participant evaluated the educational value of the LLMs' responses by assigning scores, providing a structured measure of learning preference that makes this study distinct from existing designs.

### Technical Evaluation of LLM Performance on Mock Neurosurgery Board Examination

When evaluating LLM performance on advanced medical tests, accuracy is not the only important factor. Reasoning time, along with response length and readability, is also a key consideration. Server workload and network latency can affect response speed, but our results indicate that Deepseek-R1 took longer to reason than the other models throughout the test while achieving higher accuracy (84%; 42 of 50 questions). Deepseek-R1's maximum reasoning time of 115 seconds was much longer than Gemini-2.0 Pro's 1.37 seconds. While Deepseek-R1 answered three more questions correctly than Gemini-2.0 Pro, its median reasoning time per question was 18 seconds, compared with Gemini's 0.92 sec-

onds. This shows that Deepseek-R1 needs improvement in response generation times.

Although Gemini-2.0 Pro provides longer explanations, ChatGPT-o3-mini-high and Deepseek-R1 favor conciseness. User preferences for brief or detailed answers may differ, but most residents in our study preferred longer explanations, while only a few preferred shorter ones. The choice between concise and detailed responses likely depends on whether users prioritize quick information retrieval or comprehensive understanding. Additionally, ChatGPT-o3-mini-high's complex sentence structures may hinder rapid information processing. Although no participants explicitly criticized its readability, its lower preference for educational value suggests that linguistic complexity may indirectly affect user evaluations. Therefore, our findings highlight the need to balance clarity, conciseness, and educational utility in LLM-generated explanations.

When examining the FKGL results, one key point to consider is that neurosurgery residents are advanced learners accustomed to specialized terminology. ChatGPT had the highest FKGL scores, indicating its responses were harder to read, while Gemini-2.0 Pro produced the most readable answers. However, medical terms typically raise FKGL scores, regardless of how clear the writing is, and residents are trained to understand complex technical language. Therefore, while Gemini-2.0 Pro's lower FKGL scores suggest easier readability, higher-FKGL outputs from other LLMs may still be acceptable and usable for an audience with advanced medical education.

Resident feedback and rankings may not fully capture the educational value of LLMs, but one difference is clear. Gemini-2.0 Pro provided stronger anatomical explanations, which residents found more helpful for learning. The other two models focused more on problem-solving, whereas Gemini-2.0 Pro added useful anatomical details. This likely made it more valuable for education than the others.

Residents liked Deepseek-R1's structured response format, likely because it clearly organized important information. ChatGPT-o3-mini-high usually gives answers in one long paragraph, whereas Deepseek-R1 uses subheadings to make responses more organized. While several factors may have shaped these preferences, residents consistently rated Gemini-2.0 Pro highest, likely because it provided thorough explanations with extra details and context. Deepseek-R1 came in second for providing relevant information in a clear, organized way.

When comparing how LLMs and residents perform on mock board exams, several key factors should be considered. Residents and LLMs operate under very different psychological and environmental conditions. Neurosurgery residents often take exams while managing clinical duties, feeling tired, and dealing with stress or mental overload. These challenges can affect their judgment and decision-making during tests. In contrast, LLMs answer questions without emotional, physical, or situational pressures. Human clinicians also draw on experience, including understanding patient emotions, social cues, and interactions, which LLMs cannot yet replicate. Previous research on AI-generated content for patient education about low back pain has found that LLMs may not address the social

aspects of clinical communication as well as humans do (38). Recognizing these differences helps us better understand how to compare the performance of residents and LLMs in neurosurgical training.

Cultural, linguistic, and format-related factors may also influence LLM performance on neurosurgery board-style questions (2). Current LLMs are generally trained on English-language medical literature generated within Western academic contexts (5). Consequently, region-specific terminology, culturally embedded decision-making patterns, and practice variations may be underrepresented in the training data. Standardized board exams can be particularly challenging for LLMs. Multiple-choice questions often call for test-taking strategies such as ruling out incorrect answers, recognizing common board question wording, or applying clinical experience, skills that LLMs may not fully match. While neurosurgery residents share a common cultural and linguistic grounding that facilitates interpretation of implicit cues within exam questions, LLMs rely exclusively on textual input and may lack awareness of these contextual assumptions. When comparing how residents and LLMs perform, it is important to understand these key differences.

#### ChatGPT-o3-mini-high versus ChatGPT-4.5

Two consecutive ChatGPT models differ in many ways, including their design, reasoning skills, and best uses. ChatGPT-o3-mini-high is designed for strong reasoning and performs well on tasks that require careful logic, accurate math, and clear structure. Its larger context window allows it to handle long documents and complex code. This model is especially good for science, technology, engineering, and math tasks, such as solving multistep problems, writing technical documents, and assisting with advanced programming.

On the other hand, ChatGPT-4.5 is a model that balances broad knowledge and natural language understanding, and it can work with both text and images. It provides efficient, fact-based answers, supports creative writing, and draws on real-world knowledge. While ChatGPT-o3-mini-high works best for structured and logical tasks, ChatGPT-4.5 is designed for smooth, engaging conversations. This makes it a strong option for customer support, education, and creative storytelling.

Although ChatGPT-4.5 is known for strong performance in emotional contexts, its current version has yet to demonstrate suitability for specialized neurosurgical applications. In our mock neurosurgery board examination, it correctly answered 37 of 50 (74%) questions, achieving higher accuracy than residents but lower than the other models in this study. Additionally, it exhibited 4 instances of hallucination (8%; 4/50, 1 neuro-oncology, 1 neuroanatomy, 1 neurotrauma, and 1 in skull-base surgery), a phenomenon not observed in the other 3 models. Although ChatGPT-4.5 responded more quickly and with longer answers than ChatGPT-o3-mini-high, its responses were significantly more complex to read. ChatGPT-4.5 may not yet be ready to provide reliable, accurate, in-depth, and comprehensible explanations for advanced examination questions. These findings highlight the importance of selecting AI systems that align with user goals and expectations.

#### Challenges, Ethical Considerations, And Future Directions

With LLMs now an established part of science, industry, and everyday medical academic practice, their potential for time savings and for large-scale data retrieval, review, and analysis is remarkable. However, concerns have emerged about their long-term implications. One of the most frequently asked questions is whether these AI models might eventually replace traditional educational resources. Although these models can support learning in certain contexts, it is more appropriate to view them not as replacements for conventional methods but as auxiliary learning aids. These models are not without limitations: they may hallucinate or present inaccurate content with apparent confidence. In addition, these tools may not provide the same depth of understanding as traditional teaching methods. Unconditionally relying on AI tools without proper guidance can also negatively affect learning and make it harder to develop strong analytical thinking skills.

Reliance on AI-generated content may diminish critical thinking, problem-solving, and language skills among medical professionals (27). These models may also perpetuate biases that lead to unequal outcomes. Integrating these models into medical practice requires careful management of patient- and academic-generated data (29,41,48). The current literature indicates that LLMs may improve diagnostic accuracy by analyzing complex medical data and identifying patterns that traditional assessments might overlook (6,39). LLM output depends on the specific questions or the structure of the requests posed. There are ongoing concerns about the understandability of AI-generated recommendations and the need for careful validation to ensure consistency (4,39). At present, many hospitals limit the use of AI algorithms in their information systems, even for research (47).

A critical limitation in high-stakes LLM applications is “hallucination,” a phenomenon in which a language model generates incorrect, misleading, or entirely fabricated information unsupported by input data or real-world knowledge (44). Several factors contribute to hallucinations in NLP models, including insufficient training data, limited access to reliable or verified data sources, and ambiguous input prompts (23). In addition, such studies may need to be repeated because LLMs are designed to be continually updated and improved.

Future research should assess the accuracy and reliability of AI models in neurosurgical education by comparing their results with those of board-certified neurosurgeons and expert consensus (26). More studies should examine potential biases in training outcomes (6), use larger datasets, evaluate how these models perform in real-world educational settings, and explore how LLMs can support hands-on training. Understanding how residents and faculty view AI-driven learning tools will help ensure successful integration.

Another important issue that warrants discussion in future studies is the accessibility of LLMs in low- and middle-income countries (LMICs). It is well recognized that LMICs face numerous infrastructural and workforce-related challenges, and ongoing efforts aim to address these gaps through increased collaboration and partnerships with high-income countries (24). As LLMs are increasingly considered as supportive ed-

educational tools in resident training, it remains unclear whether these technologies are equally available and accessible in LMIC settings (10). The potential role of LLMs in either mitigating or widening existing global health inequities should therefore be an important focus of future research.

### Study Limitations

We used the *Turkish Neurosurgery Board Examination Preparation Question Book (2021)* and recruited only PGY-5 and PGY-6 residents across Turkey to answer the questions (40). To reduce selection bias, participants were recruited from 10 distinct centers across Turkey. Although all residents demonstrated proficiency in English, administering English-translated questions could have introduced language bias, since the main board exams are in Turkish. This language difference may have influenced participants' performance.

The study included only 10 senior residents, which may limit its statistical power, but the results remain reliable and trustworthy. We selected senior residents from Turkey for their advanced neurosurgical skills and to maintain consistency in the study group. Future research should involve larger, more diverse groups from multiple centers to strengthen the results and increase their generalizability. Measuring the educational value of LLMs in neurosurgery solely by board exam results may not fully reflect their effectiveness. Fifty questions were selected to keep residents engaged and to make the exam manageable. However, using only 5 questions per category reduced statistical power for analyzing each subcategory, even though each resident answered 50 questions overall. The exam format also took into account residents' busy schedules.

Moreover, network delays and server overload could affect the measurement of reasoning time. To address this, all questions were presented to three models on the same day, using the same computer and a stable internet connection.

### CONCLUSION

In this study, we examined the performance of 3 major LLMs on a mock neurosurgery board examination. All models outperformed senior neurosurgery residents, with Deepseek-R1 achieving the highest overall success rate. Our results showed that the models differed in response length, readability, and reasoning time. Gemini-2.0 Pro produced the longest answers and was the easiest to read. Residents preferred Deepseek-R1 for its helpful educational responses and Gemini-2.0 Pro for its thorough explanations. Both models received higher ratings than ChatGPT-o3-mini-high. Our results also suggest that LLMs may be useful auxiliary tools in neurosurgery, especially when preparing for board exams.

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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 Statement:** This study did not involve patients, clinical interventions, or the collection of identifiable personal data. The mock neurosurgery board examination consisted of educational questions, and the participating residents were assessed anonymously for comparative educational analysis. No sensitive or personal information was collected. Therefore, according to institutional research ethics guidelines, formal Institutional Review Board (IRB) approval was not required.

### AUTHORSHIP CONTRIBUTION

Study conception and design: KY, EG, DDDY, MCP

Data collection: JC, MG, EG, KY, PP

Analysis and interpretation of results: EG, KY, KMK, BL, EK

Draft manuscript preparation: KY, EG, OHE, DDDY, JC

Critical revision of the article: KY, JC, MCP

Other (study supervision, fundings, materials, etc...): EK, OHE, MCP

All authors (KY, EG, JC, DDDY, MG, PP, KMK, BL, EK, OHE, MCP) reviewed the results and approved the final version of the manuscript.

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**Supplemental Table 1:** Pairwise Comparison of Performances of Chatgpt O3-Mini-High and Chatgpt-4.5 on A 50-Questions Mock Neurosurgery Board Examination

Question subcategory	No. of Questions	Explanation word count, median (IQR)		p-value	Readability score, median (IQR)		p-value	Reasoning time, median (IQR)		p-value
		ChatGPT-4.5	ChatGPT o3-mini-high		ChatGPT-4.5	ChatGPT o-3 mini-high		ChatGPT- 4.5	ChatGPT o3-mini-high	
Overall	50	218.50 (199.00-249.50)	154.00 (115.50-209.25)	<0.001	17.50 (15.75-18.60)	14.55 (13.33-16.19)	<0.001	1.84 (1.43-1.98)	6.50 (4.00-9.75)	<0.001
Neuro-oncology	5	284.0 (220.00-302.00)	192.0 (165.00-240.00)	0.08	17.3 (15.30-18.80)	12.53 (12.23-14.12)	0.013	1.29 (1.23-1.46)	7.00 (4.00-14.00)	0.045
Neurovascular	5	227.0 (205.00-275.00)	213.0 (207.00-233.00)	0.69	18.3 (17.80-18.80)	13.87 (13.46-15.20)	<0.001	1.56 (1.33-1.83)	9.00 (7.00-14.00)	0.040
Neuroanatomy	5	223.0 (217.00-238.00)	108.0 (101.00-234.00)	0.31	15.7 (15.20-18.70)	13.37 (13.03-13.75)	0.024	1.84 (1.84-2.00)	5.00 (5.00-11.00)	0.012
Pediatric neurosurgery	5	223.0 (208.00-248.00)	154.0 (128.00-264.00)	0.42	15.6 (15.40-15.90)	12.49 (12.40-13.85)	0.026	1.94 (1.82-2.01)	4.00 (4.00-29.00)	0.012
Spinal surgery	5	221.0 (192.00-221.00)	151.0 (135.00-187.00)	0.19	16.2 (16.10-17.80)	16.29 (14.51-17.87)	0.78	1.88 (1.81-2.01)	8.00 (6.00-9.00)	0.008
Neurotrauma	5	203.0 (175.00-244.00)	133.0 (120.00-198.00)	0.22	18.9 (18.30-18.90)	15.26 (14.59-15.77)	0.008	1.83 (1.63-1.90)	5.00 (4.00-7.00)	0.10
Skull-base surgery	5	213.0 (190.00-213.00)	154.0 (135.00-174.00)	0.21	18.0 (17.50-19.80)	15.59 (15.38-16.49)	0.036	1.92 (1.43-2.00)	6.00 (5.00-8.00)	0.10
Functional neurosurgery	5	199.0 (199.00-250.00)	128.0 (102.00-154.00)	0.016	17.4 (14.50-17.50)	14.06 (13.88-15.38)	0.22	1.72 (1.42-1.93)	4.00 (4.00-7.00)	0.022
Peripheral nerve surgery	5	208.0 (207.00-217.00)	139.0 (114.00-160.00)	0.005	15.9 (14.20-17.40)	14.19 (12.92-14.67)	0.13	1.92 (1.33-1.98)	9.00 (7.00-10.00)	0.011
Other topics	5	229.0 (158.00-231.00)	154.0 (123.00-191.00)	0.11	18.3 (17.90-19.30)	16.39 (16.21-16.80)	0.039	1.92 (1.87-3.18)	6.00 (5.00-6.00)	0.035



# Beyond Human 'Eyes' in Neurosurgical Exams: Success of Artificial Intelligence (ChatGPT-4o, Grok, and Gemini) in the Image-Based Questions of Turkish Neurosurgical Society Proficiency Board Exams

Alperen SOZER<sup>1</sup>, Gokberk EROL<sup>2</sup>, Ozan Yavuz TUFEK<sup>3</sup>, Batuhan SOZER<sup>4</sup>, Merve BUKE SAHIN<sup>5</sup>, Mustafa Caglar SAHIN<sup>6</sup>

<sup>1</sup>Sincan Training and Research Hospital, Department of Neurosurgery, Ankara, Türkiye

<sup>2</sup>Adiyaman Training and Research Hospital, Department of Neurosurgery, Adiyaman, Türkiye

<sup>3</sup>Gazi University Faculty of Medicine, Department of Neurosurgery, Ankara, Türkiye

<sup>4</sup>Ankara Medipol University, Faculty of Medicine, Ankara, Türkiye

<sup>5</sup>Kulu District Health Directorate, Department of Public Health, Konya, Türkiye

<sup>6</sup>Kulu State Hospital, Department of Neurosurgery, Konya, Türkiye

**Corresponding author:** Mustafa Caglar SAHIN ✉ dr.mcaglarsahin@gmail.com

## ABSTRACT

**AIM:** To evaluate the impact of generative artificial intelligence and large language models (LLMs) on medical training and neurosurgical education, specifically focusing on their emerging capabilities in image interpretation.

**MATERIAL and METHODS:** This study evaluated the performance of three major LLMs (ChatGPT-4o, Grok, and Gemini) on image-based neurosurgical proficiency board questions and compared their latest versions.

**RESULTS:** Real-life candidates answered correctly 70.75% of the time. LLMs answered correctly 47.38% of the time and were significantly outperformed by the candidates. Prompt selection was found to significantly influence the performance of GPT and Grok, but not Gemini. Matching and significantly outperforming the candidates was only possible by combining the best answers from all three LLMs across four runs.

**CONCLUSION:** Although previous research has demonstrated strong capabilities of LLMs in text-only questions, the results of the present study revealed that image analysis abilities of these models need further improvement when compared to actual candidates. Furthermore, the impact of prompt selection and repeated questioning should be emphasized, particularly when seeking correlation with the real-life exam results.

**KEYWORDS:** Artificial Intelligence, ChatGPT-4o, Education, Gemini, Grok

Alperen SOZER : 0000-0001-6475-7094

Gokberk EROL : 0000-0001-6651-5486

Ozan Yavuz TUFEK : 0000-0002-8157-8829

Batuhan SOZER : 0000-0002-3312-3475

Merve BUKE SAHIN : 0000-0002-5132-8220

Mustafa Caglar SAHIN : 0000-0002-5141-8154



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## ■ INTRODUCTION

Driven by technological advancements that revolutionize how medicine is taught and proficiency is assessed, medical education is continuously evolving. With the rapid advancement of artificial intelligence (AI), large language models (LLMs) have emerged as pivotal tools in various domains, including healthcare. These models not only assist in decision making, but also can transform traditional educational and assessment methods. Since medicine prioritizes diagnostic accuracy and problem-solving skills, the integration in this field of LLMs such as ChatGPT, Grok, and Gemini represents a transformative step. In this context, the present study seeks to explore this paradigm shift within the context of neurosurgical board examinations, with a particular emphasis on the importance of image-based evaluation in clinical scenarios.

ChatGPT-4o is an advanced language model developed to interact and assist users in a conversational manner (13). Building upon its predecessors, ChatGPT-4o combines enhanced reasoning, problem-solving capabilities, and contextual understanding. Its multimodal abilities, including text and image input analysis—referred to by the recently added letter ‘o’, which stands for ‘omni’—have positioned ChatGPT-4o as a versatile tool not only in daily queries, but also in specialized domains such as medicine, engineering, and education.

Furthermore, on November 4, 2023, xAI, based in San Francisco, introduced Grok, an innovative artificial intelligence model. Unlike existing large language models, Grok integrates “real-time knowledge” from the X platform (formerly Twitter), enabling it to provide users with the most current information (20).

In its turn, Google Gemini, developed by Google DeepMind and introduced in December 2023, represents a significant advancement in artificial intelligence as a multimodal large language model. Capable of processing diverse data types such as text, images, audio, video, and code, Gemini expands the boundaries of generative AI. To date, it has been seamlessly integrated into products like Bard, thus effectively supporting users in tasks such as writing, planning, and learning. Its advanced language comprehension and generation capabilities position it as a strong competitor to models like ChatGPT, highlighting its potential in transforming AI applications across various scientific and practical domains (6).

While previous research demonstrated ChatGPT’s notable success in answering textual questions in the Turkish Neurosurgical Society Proficiency Board Exams (TNSPBE), with an accuracy significantly exceeding that of human candidates (16), an important limitation that remains is the exclusion of questions containing visual elements, which constitute a substantial and clinically relevant portion of neurosurgical evaluations. This omission is due to the earlier incapability of ChatGPT to process and interpret images.

Since visual interpretation is now a key feature of major LLMs, investigating this aspect becomes essential. To fill this gap in the literature, the present study was conducted to evaluate

this new feature and to compare the three major LLMs used nowadays.

## ■ MATERIAL and METHODS

This study evaluated questions containing visual elements from the last eight written TNSPBE exams. The exam consisted of multiple-choice questions, each with 5 answer options. The questions and answer keys are publicly available on the Turkish Neurosurgical Society website. Candidate responses for all questions were obtained in an anonymized format, upon obtaining the permission of the Turkish Neurosurgery Association Board of Directors. No additional approval was required for this investigation by local and regional regulations. Analyses were conducted on a total of 108 questions containing visual elements. The distribution of image types and content areas of the investigated questions is summarized in Table I.

The questions were submitted to three major LLMs (namely, ChatGPT-4o, Grok-vision-beta, Gemini-1.5-pro) using their respective API services between November 25, 2024, and November 30, 2024. To the best of our knowledge, none of these services received major updates during this period. The builds used were as follows: GPT-4o (gpt-4o-2024-08-06, released August 6, 2024), Gemini (gemini-1.5-pro-002, released September 24, 2024), and Grok (grok-vision-beta-0.1.0, released November 23, 2024).

Visual components were manually extracted from the exam questions in their original layout and were saved, as close as possible to their original printed resolution and color settings, as .jpg files. The text parts of the questions were extracted and stored in text format. Python was used for all remaining applications. Next, the extracted images were converted to base64 format using the Python standard library (2). OpenAPI SDK (14) was used to send prompts to all LLMs.

More specifically, two different prompts—referred to as the NS prompt and the HQ prompt—were used, and each question was sent to each LLM twice for each of these prompts (i.e., a total of four submissions per question). The NS-prompt instructed the LLM to assume the role of a neurosurgeon, while the HQ-prompt framed the question as part of a standard quiz. The prompts were displayed in Code 1. All responses were then recorded and inspected.

### Statistical Analysis

For the statistical analysis, Cochran’s Q test was used to compare the correct answer rates of all three LLMs simultaneously, while McNemar’s test with Bonferroni correction was applied for pairwise comparisons between LLMs. Asymptotic significances were evaluated using  $\chi^2$  statistics when the sample size adequacy assumption was met; otherwise, exact *p*-values were reported. Two proportion z-tests were used to compare the correct answer rates of LLMs with those of human candidates. The associations between LLMs’ correct answer statuses and candidate performance were evaluated using Spearman correlation. Correlation coefficients interpreted according to the previously established cut-off values (4). All results were evaluated at a 95% confidence interval with a

**Table I:** Distribution of Image Modalities Across Different Neurosurgical Content Areas. The Table Presents the Number of Questions Categorized by Anatomical and Clinical Areas, Along with Their Corresponding Imaging Types

	Anatomy	Paediatric	Cranial	Spinal	Trauma	Vascular	Total
MR	1	13	16	6	0	1	37
Cadaver	19	0	0	0	0	0	19
Multimodal	1	2	1	5	4	2	15
CT	0	4	1	1	4	1	11
Illustration	7	0	0	2	0	1	10
Real Picture	1	6	0	0	0	0	7
X-Ray	1	1	0	3	0	0	5
DSA	0	0	0	0	0	3	3
Micrograph	0	0	0	1	0	0	1
<b>Total</b>	30	26	18	18	8	8	108

**MR:** Magnetic resonance. **CT:** Computerized tomography. **DSA:** Digital subtraction angiography.

significance level of  $p < 0.05$ . All statistical analyses were conducted using SPSS® Statistics (version 27, IBM® Corp., USA).

## RESULTS

Of the 4,988 candidate responses, 3,529 (70.75%) were correct. The median correct answer rate across all individual questions amounted to 74.26% (Interquartile Range: 32.28, Minimum: 17.64, Maximum: 100). Correct answer rate did not follow a normal distribution (Shapiro-Wilk  $p < 0.001$ ) and was negatively skewed (-0.819).

A unique challenge was encountered while working with GPT-4o: the model occasionally refused to answer certain questions. However, when the same prompt was reattempted or the alternative prompt was used, GPT-4o sometimes provided a response. In one unusual instance, the model generated a sixth answer option (F) and selected it. Since this behavior was inconsistent and was observed only once and only with GPT, it was not systematically analyzed further in this study. While GPT-4o's responses occasionally contained useful information, for the purposes of the present study, any instance in which the model failed to explicitly indicate a valid choice was considered incorrect. By contrast, all other LLMs evaluated provided valid answers in all trials.

Descriptive data regarding the analyzed exams and questions are summarized in Table II. As indicated by the two-proportion z-test results in Table II, all LLMs (individually and in aggregate) were outperformed by candidates. Image resolutions ranged from 48 to 379 dpi (median 152 dpi). Spearman correlation showed no significant association between dpi and the overall best answer rate of any of the LLMs or the correct answer rate of the candidates [GPT:  $\rho(106) = -0.147$ ,  $p = 0.128$ ; Grok:  $\rho(106) = -0.098$ ,  $p = 0.312$ ; Gemini:  $\rho(106) = -0.061$ ,  $p = 0.528$ ; Candidates:  $\rho(106) = -0.004$ ,  $p = 0.967$ ].

Cochran's Q test revealed no significant differences among the LLMs (Table III). A comparison of the overall best performance

of LLMs to that of candidates revealed no significant difference between candidates and GPT [ $z = 1.548$ ,  $p = 0.121$ ]. However, the candidates significantly outperformed Grok [ $z = 2.174$ ,  $p = 0.030$ ] and Gemini [ $z = 3.215$ ,  $p = 0.001$ ].

A total of 89 questions (82.40%) were answered correctly by at least one LLM in at least one of its runs. In addition, a total of 41 questions (37.96%) were answered correctly by all LLMs in at least one run (see Figure 1 for a detailed distribution of these results). As indicated by the results of two proportions z-test, the combined best performance of all LLMs across multiple runs (82.40%) was significantly higher than the candidates' correct answer rate (70.75%) [ $z = -2.641$ ,  $p = 0.008$ ].

Furthermore, while repeating the same prompt did not significantly affect the correct answer rates, combining best answers of both runs significantly improved results for GPT (both prompts) and for Grok (HQ-prompt only), but not for Gemini (Table IV). Interestingly, Gemini with the HQ prompt presented its best answers in the first run only to change some of its correct answers to incorrect ones in the second run.

Using different prompts caused a significant difference for GPT and Grok, but not for Gemini. The HQ prompt performed significantly better than the NS prompt. Combining best answers of each prompt significantly increased correct answer rate for all 3 LLMs (Table V).

Next, all LLMs showed significant correlation internally in almost all combinations, with a few coincidental cross correlations with various strength levels. Only GPT answers with the NS prompt showed significant (albeit poor; correlation coefficient  $< 0.3$ ) correlations with the candidate correct answer rate. Full correlation matrix is presented in Supplementary Table I.

As indicated by the results of separate Kruskal-Wallis tests, image types in the questions and content areas did not seem to cause significant difference for candidates; the same trend was revealed by the results of separate FFH tests for overall best performance results of LLMs. For this analysis,

one question containing micrographs was considered in real picture category, while three questions containing DSA images and four questions containing X-ray images were combined together. In addition, as showed by Cochran's

Q and McNemar's tests, none of the LLMs significantly outperformed one other in any category.  $\chi^2$  statistics are omitted for readability, but the corresponding graphs are presented in Figure 2.

**Table II:** Summary of Exam Years, Question Counts, and Candidate Versus LLM Performance. The Table Reports the Number of Correct Responses for Each Year Across Candidates and LLMs, Aggregated Over Multiple Runs. (Sum: The sum of four runs per LLM. Total LLM answers: Sum of all 12 runs)

Exam	Candidate	Questions	Correct / Total Candidate Answers (%)	GPT Sum (%)	Grok Sum (%)	Gemini Sum (%)	Correct / Total LLM Answers (%)
2015	38	5	124 / 190 (65.26)	11 / 20 (55.00)	12 / 20 (60.00)	13 / 20 (65.00)	36 / 60 (60.00)
2016	34	10	217 / 340 (63.82)	12 / 40 (30.00)	18 / 40 (45.00)	7 / 40 (17.50)	37 / 120 (30.83)
2017	30	18	343 / 540 (63.52)	36 / 72 (50.00)	44 / 72 (61.11)	39 / 72 (54.17)	119 / 216 (55.09)
2018	41	14	407 / 574 (70.91)	23 / 56 (41.07)	32 / 56 (57.14)	27 / 56 (48.21)	82 / 168 (48.81)
2019	52	12	373 / 624 (59.78)	20 / 48 (41.67)	27 / 48 (56.25)	24 / 48 (50.00)	71 / 144 (49.31)
2022	65	13	645 / 845 (76.33)	29 / 52 (55.77)	24 / 52 (46.15)	28 / 52 (53.85)	81 / 156 (51.92)
2023	62	19	857 / 1178 (72.75)	33 / 76 (43.42)	14 / 76 (18.42)	30 / 76 (39.47)	77 / 228 (33.77)
2024	41	17	563 / 697 (80.77)	31 / 68 (45.59)	36 / 68 (52.94)	44 / 68 (64.71)	111 / 204 (54.41)
<b>Total</b>	<b>363</b>	<b>108</b>	<b>3529 / 4988 (70.75)</b>	<b>195 / 432 (45.14)</b>	<b>207 / 432 (47.92)</b>	<b>212 / 432 (49.07)</b>	<b>614 / 1296 (47.38)</b>
			Two proportions z-test compared to candidates'	<b>z = 11.013 p = &lt;0.001</b>	<b>z = 9.837 p = &lt;0.001</b>	<b>z = 9.346 p = &lt;0.001</b>	<b>z = 15.817 p = &lt; 0.001</b>

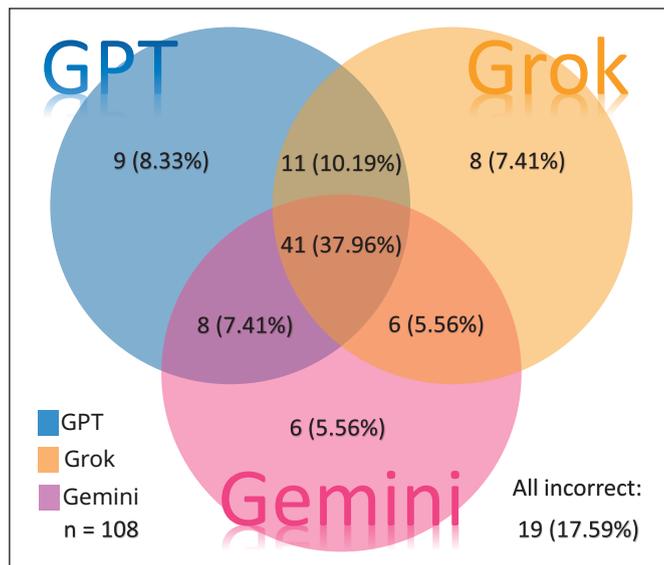
**Table III:** Correct Answer Rates of LLMs Across Different Prompt Conditions. The Table Reports the Number and Percentage of Correct Responses for Each LLM in Different Test Runs

n = 108	GPT (%)	Grok (%)	Gemini (%)	Cochran's Q
NS 1 <sup>st</sup> Run	48 (44.44)	50 (46.30)	53 (49.07)	$\chi^2(2) = 0.717, p=0.699$
NS 2 <sup>nd</sup> Run	48 (44.44)	51 (47.22)	52 (48.15)	$\chi^2(2) = 0.531, p=0.767$
Best-NS	57 (52.78)	55 (50.93)	55 (50.93)	$\chi^2(2) = 0.160, p=0.923$
HQ 1 <sup>st</sup> Run	45 (41.67)	53 (49.07)	55 (50.93)	$\chi^2(2) = 3.055, p=0.217$
HQ 2 <sup>nd</sup> Run	54 (50.00)	53 (49.07)	52 (48.15)	$\chi^2(2) = 0.120, p=0.942$
Best-HQ	62 (57.41)	61 (56.48)	55 (50.93)	$\chi^2(2) = 1.686, p=0.430$
Best Overall	69 (63.89)	66 (61.11)	61 (56.48)	$\chi^2(2) = 2.042, p=0.360$

**NS:** Neurosurgery-prompted responses. **HQ:** General quiz-prompted responses. **Best Overall:** The highest accuracy achieved across all four attempts.

**Table IV:** Impact of Repeated Questioning on LLM Performance Across Different Prompts. The Table Compares Correct Answer Rates Between the First and Second Attempts, as Well as the Best Combined Performance. Bonferroni Correction (Multiplier of 3) was Applied to Account for Multiple Comparisons. \*Indicates Statistically Significant Differences

LLM	Prompt	Cochran's Q	Pair	Correct Answer Rates (%)	McNemar's Exact p-value	Corrected p-value
GPT	NS-Prompt	$\chi^2(2) = 9.000, p = 0.011^*$	1 <sup>st</sup> run – 2 <sup>nd</sup> run	44.44 - 44.44	1	1
			1 <sup>st</sup> run – Best*	44.44 - 52.78	<b>0.004*</b>	<b>0.012*</b>
			2 <sup>nd</sup> run – Best*	44.44 - 52.78	<b>0.004*</b>	<b>0.012*</b>
	HQ-Prompt	$\chi^2(2) = 17.360, p < 0.001^*$	1 <sup>st</sup> run – 2 <sup>nd</sup> run	41.67 - 50.00	0.108	0.323
			1 <sup>st</sup> run – Best*	41.67 - 57.41	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>
			2 <sup>nd</sup> run – Best*	50.00 - 57.41	<b>0.008*</b>	<b>0.023*</b>
Grok	NS-Prompt	$\chi^2(2) = 4.667, p = 0.097$	1 <sup>st</sup> run – 2 <sup>nd</sup> run	46.30 - 47.22	1	1
			1 <sup>st</sup> run – Best	46.30 - 50.93	0.063	0.188
			2 <sup>nd</sup> run – Best	47.22 - 50.93	0.125	0.375
	HQ-Prompt	$\chi^2(2) = 8.000, p = 0.018^*$	1 <sup>st</sup> run – 2 <sup>nd</sup> run	49.07 - 49.07	1	1
			1 <sup>st</sup> run – Best	49.07 - 56.48	<b>0.008*</b>	<b>0.023*</b>
			2 <sup>nd</sup> run – Best	49.07 - 56.48	<b>0.008*</b>	<b>0.023*</b>
Gemini	NS-Prompt	$\chi^2(2) = 2.800, p = 0.247$	1 <sup>st</sup> run – 2 <sup>nd</sup> run	49.07 - 48.15	1	1
			1 <sup>st</sup> run – Best	49.07 - 50.93	0.500	1
			2 <sup>nd</sup> run – Best	48.15 - 50.93	0.250	0.750
	HQ-Prompt	$\chi^2(2) = 6.000, p = 0.050^*$	1 <sup>st</sup> run – 2 <sup>nd</sup> run	50.93 - 48.15	0.250	0.750
			1 <sup>st</sup> run – Best	50.93 - 50.93	1	1
			2 <sup>nd</sup> run – Best	48.15 - 50.93	0.250	0.750



**Figure 1:** Venn diagram illustrating the number and percentage of questions correctly answered by each of the three LLMs (GPT, Grok, Gemini) in at least one of their four runs. The overlapping areas represent questions correctly answered by multiple LLMs.

## DISCUSSION

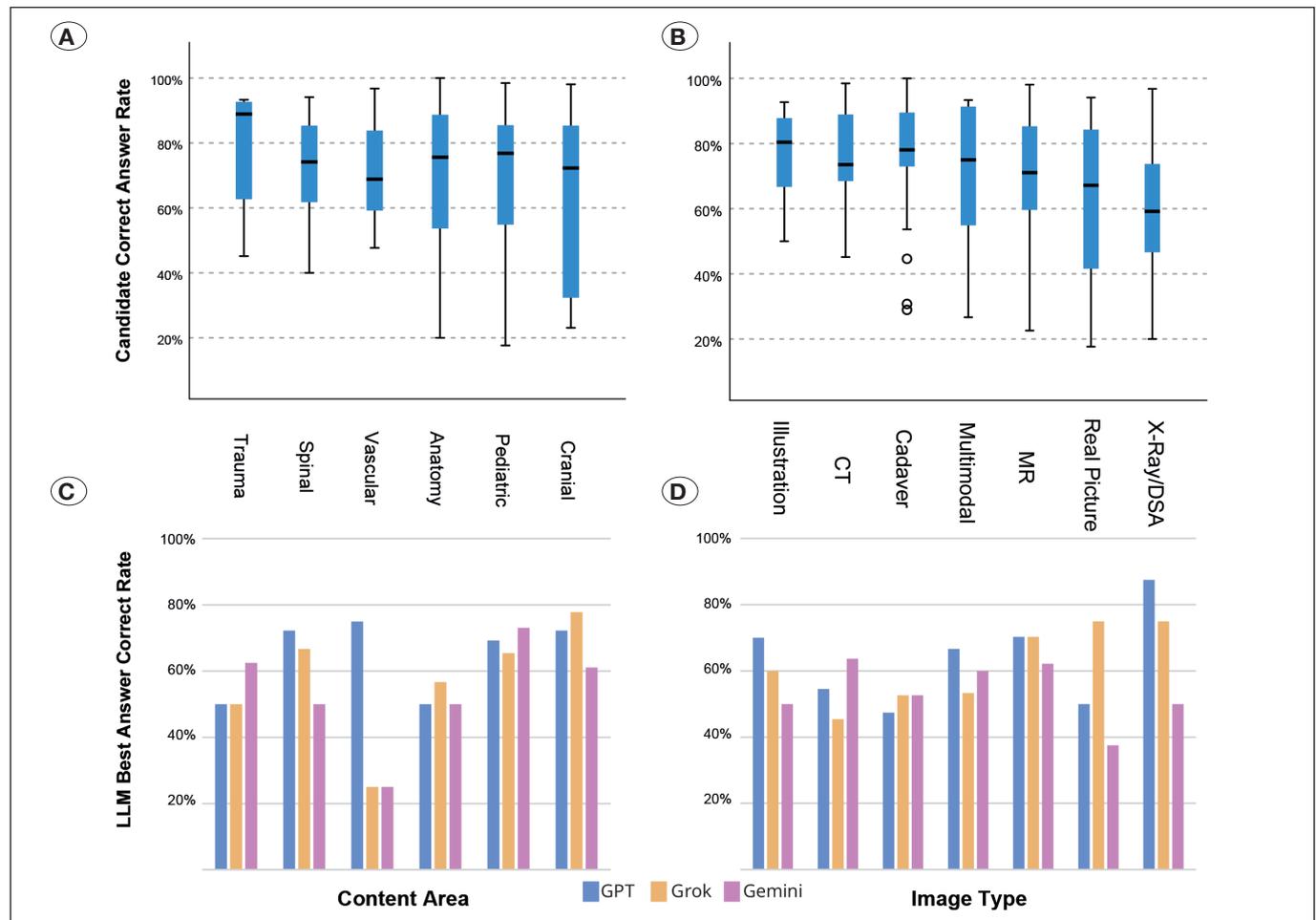
The present study contributes to the limited yet growing body of research evaluating the performance of LLMs in questions involving visual elements, particularly in medical education and clinical settings. The results not only highlight the potential of these models, but also reveal significant limitations, particularly when compared with previous studies across various specialties.

According to the results, candidates outperformed all LLMs investigated in this study in questions containing visual elements. Repeating the same questions or using different prompts did not significantly alter performance; however, combining the best results from multiple runs led to a significantly improved performance. Only ChatGPT-4o showed a weak correlation with candidate performance when the NS prompt was used. The resolution of the provided images did not affect the performance of the LLMs or the candidates. Performance would be expected to more strongly correlate with dpi in real-world scenarios, where important elements might be subtle. These images in the exams were selected or designed to clearly convey the relevant element(s) to the candidates; therefore, even the lower-resolution images were

**Table V:** Effect of Different Prompts and Their Combined Results on LLM Performance. The Table Compares Accuracy Rates between NS- and HQ-Prompted Responses, as Well as the Overall Best Combination from Multiple Runs. Bonferroni Correction (Multiplier of 3) was Applied

LLM	Cochran's Q	Pair	Correct Answer Rates (%)	McNemar's exact p-value	Corrected p-value
GPT	$\chi^2(2) = 11.474, p=0.003^*$	NS – HQ	52.78 - 57.41	0.359	1
		NS – Ovr*	52.78 - 63.89	<b>&lt;0.001*</b>	<b>0.001*</b>
		HQ – Ovr*	57.41 - 63.89	<b>0.016*</b>	<b>0.046*</b>
Grok	$\chi^2(2) = 11.375, p=0.003^*$	NS – HQ	50.93 - 56.48	0.210	0.630
		NS – Ovr*	50.93 - 61.11	<b>&lt;0.001*</b>	<b>0.003*</b>
		HQ – Ovr	56.48 - 61.11	0.063	0.188
Gemini	$\chi^2(2) = 6.000, p=0.050^*$	NS – HQ	50.93 - 50.93	1	1
		NS – Ovr	50.93 - 56.48	<b>0.031*</b>	0.094
		HQ – Ovr	50.93 - 56.48	<b>0.031*</b>	0.094

**NS:** Best answers from two NS-prompted runs. **HQ:** Best answers from two HQ-prompted runs. **Ovr:** Best answers from all four runs. \*Indicates statistically significant differences.



**Figure 2:** Performance of LLMs and human candidates based on content areas and image types. **A)** Box plot of candidate correct answer rates by content area. **B)** Box plot of candidate correct answer rates by image type. **C)** Bar chart comparing the best performance of each LLM (GPT, Grok, Gemini) by content area. **D)** Bar chart comparing the best performance of each LLM by image type.

sufficient to answer the questions for both the LLMs and the candidates.

### Comparison with Other Studies

In a study on the National Medical Licensing Examination in Japan, Liu et al. found that ChatGPT-4o achieved an overall accuracy rate of 89.2%, which dropped to 80.4% for image-based questions (9). By contrast, in the present study, ChatGPT-4o achieved an accuracy rate of 63.89% for image-based questions. This difference may be attributed to the difficulty of the questions and the variety of content that LLMs encountered in different exams. Furthermore, consistently with our finding, Liu et al. also reported that Gemini 1.5 Pro performed worse than both GPT-4 and ChatGPT-4o on image-based questions (74.6%) (9).

However, our analysis further revealed that Gemini's responses to image-based questions were inconsistent, as it occasionally changed correct answers upon reattempts. Unlike Liu et al.'s study, which presented questions in a direct exam format without specialized prompts, we employed two distinct prompting strategies (the NS prompt and the HQ prompt). While our results indicated that prompting strategies influence performance, they did not provide a substantial improvement, particularly for image-based questions.

Furthermore, Lin et al. reported that ChatGPT-4o reported 77.19% accuracy on image-based questions, whereas Gemini performed significantly worse on image-based questions with only 42.11% accuracy (8). In line with this evidence, we found that Gemini demonstrated low performance in questions based on complex visual content. However, the success of ChatGPT-4o in Lin et al.'s study was quite high as compared to our results (8).

In contrast to Liu et al. and Lin et al., Gill et al. found ChatGPT-4o to have 39.58% accuracy in image-based questions, while Gemini Advanced remained at 33.33%. The authors reported that ChatGPT-4o performed significantly better than Gemini Advanced ( $p < 0.013$ ) (5,8,9). In our findings, both models were more successful, and no statistically significant difference was observed between the models.

In yet another relevant study, Takagi et al. (18) reported that ChatGPT-4v achieved 71.9% accuracy for image-based questions on the Japan National Medical Licensing Examination, which was below the average performance of human candidates (85.0%) ( $p < 0.001$ ). For the questions with tables, the accuracy rate amounted to mere 35%, which was significantly lower than human performance (83.9%) ( $p < 0.001$ ) (18). While such significant difference was evident in our comparison of human performance vs. that of ChatGPT-4o, candidates were statistically significantly more successful than Grok and Gemini.

Furthermore, Nguyen et al. reported that ChatGPT-4 achieved between 36% and 50% accuracy on image-based questions (11). The authors showed that encouragement and responsibility disclaimer prompts significantly improved ChatGPT-4's performance on image-based questions (up to 65% increase). By contrast, when medico-legal or patient care prompts were

used, the model more frequently avoided answering the questions and its performance deteriorate. Our study complements the findings of Nguyen et al. by evaluating the effect of specific prompts for neurosurgical scenarios (11). Specifically, while the use of prompts with neurosurgical roles (e.g., "Think of yourself as a Brain Surgeon") improved performance on image-based questions, this improvement was not sufficient to increase overall success rates. This suggests that prompt engineering alone may not be sufficient to improve success on image-based questions.

In another relevant study evaluating the performance of ChatGPT-4 in the American Registry of Radiologic Technologists certification examination, the model tested by Al-Naser et al.'s achieved an accuracy rate of 45.6% on image-based questions (1). Similarly, in the study by Sawamura et al., ChatGPT-4o attained an accuracy rate of 35.4% on questions containing visuals and tables in the Japan National Physiotherapist Examination (17). Yet another study by Noda et al. reported that GPT-4v performed with an accuracy rate of 41.3% on image-based questions in the 2023 Japan Otolaryngology Specialist Examination (12). Importantly, this study highlighted that English translations and additional prompts significantly improved the model's accuracy on image-based questions, thereby enhancing its overall performance. These results were lower compared to the 68% accuracy rate reported by Nakao et al. for GPT-4v on image-based questions in the Japan National Medical Licensing Examination. Overall, the results of the present study more closely aligned with the findings reported by Nakao et al (10).

Since success may vary depending on the exam names, questions, and language models, several important points should be made. By now, the failure observed in the early days in text-based questions has almost completely disappeared. If there is a failure only in text-based questions, the question stem should be analyzed as in the results of our previous study. However, when the results reported in the literature and our results in image-based questions are compared with only text-based questions, it becomes evident that sufficient success has not yet been achieved.

### Unique Contributions of the Present Study

While previous studies have predominantly examined LLM performance in general medical and specialty-specific examinations, the present study offers unique insights into the neurosurgical domain, where image-based questions are particularly complex and critical. Compared to prior research, our findings further underscore the variability in LLM performance based on question complexity, domain specificity, and prompt design. For instance, in our data, the combination of multiple runs and prompts significantly improved the overall correct answer rates for ChatGPT-4o, Grok, and Gemini—a methodological aspect frequently overlooked in prior evaluations.

Furthermore, in contrast to previous studies in that primarily analyzed static visual data in nephrology and otolaryngology (e.g., biopsy slides, clinical photographs) (3,16), the Turkish Neurosurgical Society Proficiency Board Exams that incorporates visual elements such as imaging studies and operative

diagrams present a uniquely demanding test environment. The dynamic and context-dependent nature of neurosurgical visuals may explain the lower performance of LLMs in this domain compared to others.

To the best of our knowledge, this study is the first to evaluate Grok's performance on image-based questions. Developed by xAI, Grok was introduced as a language model with real-time knowledge integration capabilities, primarily analyzed in the context of general LLM performance and social media applications. However, this study is the first to scientifically evaluate Grok in a medical context, specifically within the highly specialized field of neurosurgery. In addition, the present study is the first investigation of multimodal AI models, including Grok, on visual-dominant assessments such as the Turkish Neurosurgical Society Proficiency Board Exams. This pioneering contribution not only expands the understanding of Grok's capabilities, but also highlights the transformative potential of AI technologies in medical education and standardized examinations. In so doing, this study marks a significant milestone in AI-related neurosurgical research.

#### Limitations and Implications for Future Research

The consistency of findings across studies highlights the need for targeted improvements in LLM capabilities. While the introduction of multimodal inputs in models like ChatGPT-4o represents a significant advancement, the relatively low accuracy rates for image-based questions suggest that current architectures are not yet optimized for integrating visual and textual data effectively. In this study, we observed each model in its native state, without fine-tuning, pre-training, or contextual enrichment. While pre-training can enhance LLMs' image interpretation capabilities (21), contextual enrichment may be less effective, at least for neurosurgical topics (7). Incorporating contextual enrichment with images could significantly boost LLM performance, with some models potentially demonstrating greater adaptability than others after such augmentation. Accordingly, future research should explore these approaches to facilitate reliable AI-based decision support systems for clinical use.

Another limitation of the present study is that questions were only presented in their original language (Turkish). None of the investigated LLMs explicitly disclose whether it is language-aware or language-agnostic. However, it is highly likely that these models performed better in languages with more available resources in their training datasets. The present literature only investigated Turkish performance of GPT for social sciences, yielding conflicting results (15,19). Many fields—including psychology, sociology, communications, political science, and computer science—use computational methods to analyze text data. However, existing text analysis methods have a number of shortcomings. Dictionary methods, while easy to use, are often not very accurate when compared to recent methods. Machine learning models, while more accurate, can be difficult to train and use. We demonstrate that the large-language model GPT is capable of accurately detecting various psychological constructs (as judged by manual annotators). Accordingly, dedicated studies would be needed to evaluate the neurosurgical competency of LLMs

in different languages and to determine whether linguistic factors influence model performance.

## CONCLUSION

While numerous previous studies demonstrated remarkable capabilities of LLMs in answering neurosurgical or medical exam questions, these models remain inadequate when confronted with questions containing visual elements. Prompt engineering influences model performance in real-world scenarios; however, human candidate performance can be surpassed only by combining the best responses from multiple runs across multiple LLMs.

The results of the present study highlight both the potential and limitations of multimodal AI models in high-stakes medical assessments. While their capabilities continue to advance, their performance in image-based scenarios highlights critical areas requiring further improvement. Taken together, our findings emphasize the need for collaboration between AI developers and medical professionals to enhance model training, particularly in integrating complex, real-world clinical data. Such advancements could revolutionize not only medical education, but also clinical decision making, thereby ultimately enhancing patient outcomes.

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#### Declarations

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**Availability of data and materials:** Complete exams are available at <https://turknorosirurji.org.tr/TNYK/> (in Turkish). Additional data are available upon reasonable request.

**Disclosure:** The authors declare no competing interests.

**Ethics Statement:** This study evaluated questions containing visual elements from the last eight written Turkish Neurosurgical Society Proficiency Board Exams. The exam consisted of multiple-choice questions, each with 5 answer options. The questions and answer keys are publicly available on the Turkish Neurosurgical Society website. Candidate responses for all questions were obtained in an anonymized format, upon obtaining the permission of the Turkish Neurosurgery Association Board of Directors. No additional approval was required for this investigation by local and regional regulations.

#### AUTHORSHIP CONTRIBUTION

Study conception and design: AS, MCS

Data collection: GE, OYT

Analysis and interpretation of results: AS, BS, MBS

Draft manuscript preparation: AS, MCS

Critical revision of the article: GE, OYT, BS, MBS

All authors (AS, GE, OYT, BS, MBS, MCS) reviewed the results and approved the final version of the manuscript.

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Supplementary Table I: Complete Correlation Matrix of the Study Variables

Candidate Correct Answer Rate	Candidate Correct Answer Rate	GPT NS-Prompt 1st Run	GPT NS-Prompt 2nd Run	GPT NS-Prompt Best
GPT NS-Prompt 1st Run	$\rho(106) = 0.267, p = 0.005$	$\rho(106) = 0.267, p = 0.005$	$\rho(106) = 0.234, p = 0.015$	$\rho(106) = 0.267, p = 0.005$
GPT NS-Prompt 2nd Run	$\rho(106) = 0.234, p = 0.015$	$\rho(106) = 0.663, p < 0.001$	$\rho(106) = 0.663, p < 0.001$	$\rho(106) = 0.846, p < 0.001$
GPT NS-Prompt Best	$\rho(106) = 0.267, p = 0.005$	$\rho(106) = 0.846, p < 0.001$	$\rho(106) = 0.846, p < 0.001$	$\rho(106) = 0.846, p < 0.001$
GPT HQ-Prompt 1st Run	$\rho(106) = 0.168, p = 0.081$	$\rho(106) = 0.491, p < 0.001$	$\rho(106) = 0.567, p < 0.001$	$\rho(106) = 0.536, p < 0.001$
GPT HQ-Prompt 2nd Run	$\rho(106) = 0.188, p = 0.051$	$\rho(106) = 0.634, p < 0.001$	$\rho(106) = 0.708, p < 0.001$	$\rho(106) = 0.686, p < 0.001$
GPT HQ-Prompt Best	$\rho(106) = 0.156, p = 0.106$	$\rho(106) = 0.544, p < 0.001$	$\rho(106) = 0.695, p < 0.001$	$\rho(106) = 0.648, p < 0.001$
Grok NS-Prompt 1st Run	$\rho(106) = 0.101, p = 0.297$	$\rho(106) = 0.552, p < 0.001$	$\rho(106) = 0.440, p < 0.001$	$\rho(106) = 0.506, p < 0.001$
Grok NS-Prompt 2nd Run	$\rho(106) = 0.168, p = 0.083$	$\rho(106) = 0.498, p < 0.001$	$\rho(106) = 0.423, p < 0.001$	$\rho(106) = 0.486, p < 0.001$
Grok NS-Prompt Best	$\rho(106) = 0.121, p = 0.213$	$\rho(106) = 0.505, p < 0.001$	$\rho(106) = 0.431, p < 0.001$	$\rho(106) = 0.518, p < 0.001$
Grok HQ-Prompt 1st Run	$\rho(106) = 0.087, p = 0.370$	$\rho(106) = 0.427, p < 0.001$	$\rho(106) = 0.277, p = 0.004$	$\rho(106) = 0.335, p < 0.001$
Grok HQ-Prompt 2nd Run	$\rho(106) = 0.136, p = 0.159$	$\rho(106) = 0.501, p < 0.001$	$\rho(106) = 0.352, p < 0.001$	$\rho(106) = 0.409, p < 0.001$
Grok HQ-Prompt Best	$\rho(106) = 0.095, p = 0.330$	$\rho(106) = 0.447, p < 0.001$	$\rho(106) = 0.297, p = 0.002$	$\rho(106) = 0.367, p < 0.001$
Gemini NS-Prompt 1st Run	$\rho(106) = 0.111, p = 0.254$	$\rho(106) = 0.240, p = 0.012$	$\rho(106) = 0.352, p < 0.001$	$\rho(106) = 0.335, p < 0.001$
Gemini NS-Prompt 2nd Run	$\rho(106) = 0.138, p = 0.156$	$\rho(106) = 0.331, p < 0.001$	$\rho(106) = 0.406, p < 0.001$	$\rho(106) = 0.392, p < 0.001$
Gemini NS-Prompt Best	$\rho(106) = 0.139, p = 0.152$	$\rho(106) = 0.282, p = 0.003$	$\rho(106) = 0.393, p < 0.001$	$\rho(106) = 0.370, p < 0.001$
Gemini HQ-Prompt 1st Run	$\rho(106) = 0.086, p = 0.377$	$\rho(106) = 0.282, p = 0.003$	$\rho(106) = 0.319, p = 0.001$	$\rho(106) = 0.296, p = 0.002$
Gemini HQ-Prompt 2nd Run	$\rho(106) = 0.076, p = 0.434$	$\rho(106) = 0.294, p = 0.002$	$\rho(106) = 0.331, p < 0.001$	$\rho(106) = 0.318, p = 0.001$
Gemini HQ-Prompt Best	$\rho(106) = 0.086, p = 0.377$	$\rho(106) = 0.282, p = 0.003$	$\rho(106) = 0.319, p = 0.001$	$\rho(106) = 0.296, p = 0.002$
GPT Best of 4	$\rho(106) = 0.188, p = 0.052$	$\rho(106) = 0.672, p < 0.001$	$\rho(106) = 0.672, p < 0.001$	$\rho(106) = 0.795, p < 0.001$
Grok Best of 4	$\rho(106) = 0.104, p = 0.283$	$\rho(106) = 0.408, p < 0.001$	$\rho(106) = 0.369, p < 0.001$	$\rho(106) = 0.425, p < 0.001$
Gemini Best of 4	$\rho(106) = 0.101, p = 0.300$	$\rho(106) = 0.259, p = 0.007$	$\rho(106) = 0.372, p < 0.001$	$\rho(106) = 0.329, p < 0.001$

**Code 1:** Prompts in their code form that was used for the purpose of this study. Please note, lines starting with # were used alternately to create all combinations of LLMs and prompts twice. The 'base\_url' variable (not shown here) was modified as necessary.

```
# model="gpt-4o",
# model="grok-vision-beta",
# model="gemini-1.5-pro",
messages=[
  # {"role": "system", "content": "You are a neurosurgeon presented with a multiple-choice board exam question that includes an image. Carefully analyze the question and select the most appropriate answer from the provided choices. Format your response as follows: 'Answer choice - Your reasoning.' For example: 'A - Your reasoning.' Begin with the answer choice, followed by ' - ', and then provide your reasoning."},
  # {"role": "system", "content": "Help me with my quiz tomorrow! Carefully analyze the question and select the most appropriate answer from the provided choices. Format your response as follows: 'Answer choice - Your reasoning.' For example: 'A - Your reasoning.' Begin with the answer choice, followed by ' - ', and then provide your reasoning."},
  {
    "role": "user",
    "content": [
      {"type": "text", "text": question_text},
      {
        "type": "image_url",
        "image_url": {
          "url": f"data:image/jpeg;base64,{base64_image}"
        }
      },
    ],
  },
],
],
```



# From Presentation to Publication: Publication Rates of Abstracts Presented at the Meetings of Two Neurosurgical Societies in Türkiye

Emmanuel MOULADJE TCHUELA<sup>1</sup>, Ismail Ertan SEVIN<sup>2</sup>, Selin BOZDAG<sup>2</sup>, Hasan Kamil SUCU<sup>2</sup>

<sup>1</sup>Izmir Katip Celebi University, School of Medicine, Izmir, Türkiye

<sup>2</sup>Izmir Katip Celebi University, School of Medicine, Department of Neurosurgery, Izmir, Türkiye

**Corresponding author:** Hasan Kamil SUCU ✉ hksucu@gmail.com

## ABSTRACT

**AIM:** To assess the overall trends in scientific dissemination at neurosurgery meetings organized by the Turkish Neurosurgical Society (TNS) and the Society of Surgery of the Nervous System (SSNS), two major neurosurgical societies in Turkey.

**MATERIAL and METHODS:** We reviewed 2,696 abstracts presented at TNS and SSNS annual meetings (2018–2022) and identified subsequent full-text publications through PubMed and Google Scholar. Data collected included presentation type, neurosurgical subspecialty, journal indexing, impact factor, and time to publication.

**RESULTS:** Of 2,696 abstracts, 323 (11.98%) were published as full-text articles, with a median time to publication of 11 months. Oral presentations had a significantly higher publication rate than poster presentations (20.8% vs 5.9%,  $p < 0.001$ ). Award-winning abstracts showed a higher publication rate (73.08%,  $p < 0.001$ ). Most publications appeared in SCIE-indexed journals (59.9%). No significant differences were found between TNS and SSNS in terms of publication rate ( $p = 0.419$ ) or time to publication ( $p = 0.806$ ). Rates varied by subspecialty, highest in surgical neuroanatomy (30.3%), and pediatric neurosurgery (15.5%), and lowest in spinal (8.7%) and neuro-oncology (8.5%) ( $p < 0.001$ ).

**CONCLUSION:** Although overall publication rates remain modest, oral presentations, award-winning abstracts, and certain subspecialties showed higher conversion to full-text publication. Initiatives such as structured mentorship, multi-center collaboration, and editorial support may enhance dissemination and publication success.

**KEYWORDS:** Academic neurosurgery, Publication rate, Conference abstracts, Turkish Neurosurgical Society, Society of Surgery of the Nervous System

**ABBREVIATIONS:** **TNS:** Turkish Neurosurgical Society, **SSNS:** Society of Surgery of the Nervous System, **WoS:** Web of Science, **JCR:** Journal Citation Reports, **SCIE:** Science Citation Index Expanded, **ESCI:** Emerging Sources Citation Index, **AANS:** American Association of Neurological Surgeons, **CNS:** Congress of Neurological Surgeons

Emmanuel MOULADJE TCHUELA : 0009-0005-7556-7401  
Ismail Ertan SEVIN : 0000-0002-6542-925X

Selin BOZDAG : 0000-0002-3355-8954  
Hasan Kamil SUCU : 0000-0002-2795-9049



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## ■ INTRODUCTION

At scientific conferences, researchers share their findings with peers through oral or poster presentations. These gatherings serve as vital platforms for critical discussion, fostering scientific progress within the field, and representing an important step in the research process on the path to publication. The ultimate goal of scientific research is the publication of a manuscript in a peer-reviewed journal, a milestone that secures the study's place in the permanent scientific record and is widely regarded as an indicator of research validity (5).

Despite rigorous review processes, the quality of abstracts accepted for presentation at scientific conferences is often constrained by high submission volumes and word count limitations (2). A 2016 systematic review of biomedical research found that only 37% of 307,028 abstracts were subsequently published as full articles in peer-reviewed journals (4,6). In Turkish Neurosurgery, prior research reported a relatively low publication rate of 10.5% for abstracts presented at the Turkish Neurosurgical Society's annual meetings between 2011 and 2014, with marked variation by presentation type (1). These findings highlight the need to reassess publication trends and evaluate progress in scientific dissemination.

This study aimed to evaluate the overall trends in scientific dissemination at neurosurgery meetings organized by the Turkish Neurosurgical Society (TNS) and the Society of Surgery of the Nervous System (SSNS), two major neurosurgical societies in Turkey.

## ■ MATERIAL and METHODS

This observational study, approved by the Ethics Committee of Izmir Katip Celebi University (Date: 18.7.2024, Decision Number: 0056), reviewed abstracts presented at the annual scientific meetings of the Turkish Neurosurgical Society and the Society of Surgery of the Nervous System between 2018 and 2022.

### Data Collection

The abstract information, including author names, study titles, and content for both oral and poster presentations, was accessed through different sources for each society's meetings. For SSNS meetings, congress booklets were requested by email from the society's secretariat. For TNS meetings, abstracts were retrieved from the Turkish Neurosurgery Journal, available through its official website (<https://norosirurji.dergisi.org/archive.php>). In addition to presentation type (oral or poster), abstracts were categorized into subgroups by topic, including spinal, neurovascular, neuro-oncological, pediatric, and others.

### Publication Search Strategy

The original Turkish titles and keywords of the abstracts were translated into English to ensure consistency in search. To determine whether the abstracts were subsequently published as full-text articles, a systematic search was conducted in PubMed using the following stepwise approach:

- The Turkish and English titles of each abstract were searched.
- If no match was found, the first author's name was searched in combination with the first Turkish and English keywords.
- If still unsuccessful, the first author's name was searched with the second Turkish and English keywords.
- This process was repeated sequentially for each Turkish and English keyword.
- If no publication was identified, the same procedure was sequentially applied to the second and third authors.

If no corresponding publication was identified in PubMed, the identical search strategy was repeated using Google Scholar.

### Matching Criteria

When a potential publication was identified, its abstract was compared with the original conference abstract to confirm accuracy. A study was classified as a "published article" if the title, authorship, and study content were nearly identical.

### Exclusion Criteria:

- Minor modifications were allowed; however, studies with major changes, such as alterations in protocol, more than 10% difference in sample size, or a change in follow-up duration, were considered different and excluded from the "published article" category.
- Abstracts already published as full-text articles before being presented at the meeting or later retracted after publication were also excluded.

For each matched publication, the journal name, indexing databases, and publication date were recorded. Impact factors for journals indexed in Science Citation Index Expanded (SCIE) or Emerging Sources Citation Index (ESCI) were noted according to the corresponding year's *Web of Science (WoS) Journal Citation Reports (JCR)*. For journals published in 2024, the 2023 JCR data were used, as the 2024 reports were not yet available at the time of writing.

The 2018–2022 period was selected as it represented the most recent five-year window available at the time of data collection (2024) and provided a sufficient interval for abstracts to progress to full-text publication.

Statistical analyses were performed using IBM SPSS, version 27. Descriptive statistics were reported as the mean and standard deviation for continuous variables, median for ordinal variables, and percentages for nominal variables. Pearson's chi-square was used for binary comparisons of nominal data, while Independent Samples *t*-tests were applied to continuous variables. The normality of the journal impact factor was assessed with the Shapiro–Wilk test and analyzed using the Mann–Whitney U test. Publication trends over time were evaluated using the Cochran–Armitage test. Differences in publication rates among neurosurgical subspecialties were evaluated using the Kruskal–Wallis test. A *p*-value of <0.05 was considered indicative of statistical significance.

## RESULTS

Of 2,796 abstracts initially reviewed, 89 were excluded because they had already been published as full-text articles before the meeting, and one was excluded due to retraction after publication. The 2020 TNS meeting was cancelled due to the COVID-19 pandemic; thus, only the 2018, 2019, 2021, and 2022 meetings were analyzed. SSNS meetings were held annually, but no poster presentations took place in 2021 and 2022. In total, 2,696 abstracts were included in the analysis (Table I). Of these, 323 (11.98%) were subsequently published as full-text articles in peer-reviewed journals. Publication occurred in 228 of 1,096 oral presentations (20.80%) and 95 of 1,600 poster presentations (5.94%), a statistically significant difference ( $\chi^2$ ,  $p < 0.001$ ).

TNS meetings accounted for 2,513 abstracts, with a publication rate of 12.14%. SSNS meetings included 183 abstracts, with a publication rate of 9.84%, a difference that

was not statistically significant ( $\chi^2$ ,  $p = 0.419$ ). However, oral presentations at TNS showed a significantly higher publication rate (22.5%) than those at SSNS (10.5%) ( $p = 0.001$ ).

The overall publication rate varied across the study period (Table II), peaking at 15.2% in 2018 and reaching its nadir (3.6%) in 2020, likely due to the COVID-19 pandemic. A significant trend was observed for TNS meetings, showing a decline over the years (Cochran–Armitage trend test,  $p = 0.026$ ), whereas no consistent trend was seen for SSNS (Cochran–Armitage trend test,  $p = 0.247$ ) (Figure 1).

Award data were unavailable for all SSNS meetings and the TNS 2018 meeting, and the TNS 2020 meeting was cancelled. Award-winning abstracts, all from TNS meetings (2019, 2021, 2022), had a significantly higher publication rate (73.08%) than non-awarded abstracts ( $\chi^2$ ,  $p < 0.001$ ).

Most full-text publications appeared in SCIE-indexed journals ( $n = 193$ , 59.9%), followed by ESCI ( $n = 46$ , 14.3%), TRDizin

**Table I:** Distribution of Abstracts Presented at TNS and SSNS Meetings (2018–2022), Categorized by Presentation Type (Oral or Poster). For Each Year, Oral and Poster Presentations are Shown Separately by Society. The “Total by Category” Row Indicates the Sum of Each Presentation Type by Year Across Both Societies. The “Total by Society” Column Provides the Cumulative Number of Presentations for Each Meeting Over the Five-Year Period

Meeting	2018		2019		2020		2021		2022		Total by Society	
	Oral	Poster	Oral	Poster	Oral	Poster	Oral	Poster	Oral	Poster	Oral	Poster
TNS	260	510	233	430	0 <sup>a</sup>	0 <sup>a</sup>	172	289	279	340	944	1569
SSNS	31	8	16	13	18	10	55	0 <sup>b</sup>	32	0 <sup>b</sup>	152	31
<b>Categorical Total</b>	291	518	249	443	18	10	227	289	311	340	1096	1600
<b>Total</b>	809		692		28		516		651		2696	

**TNS:** Turkish Neurosurgical Society. **SSNS:** The Society of Surgery of the Nervous System.

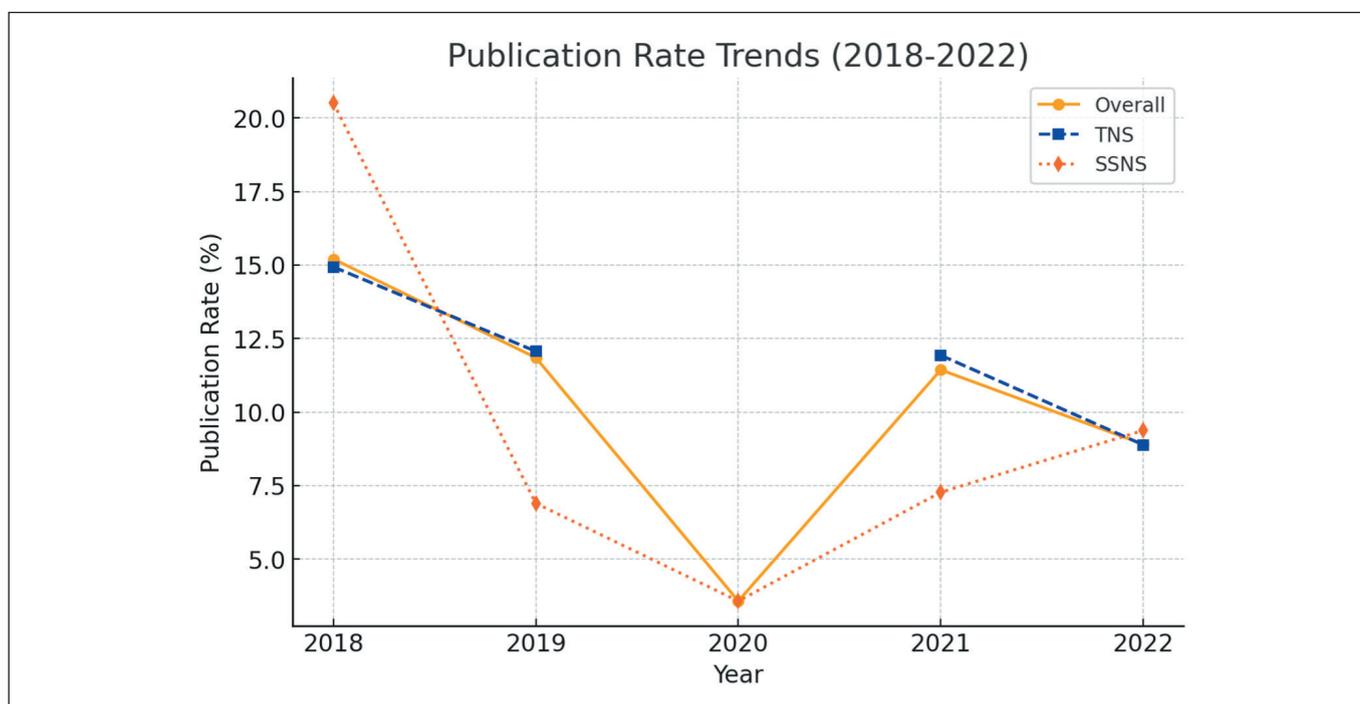
**a.** The TNS meeting was not held in 2020 due to the COVID-19 pandemic. **b.** No poster presentations were included in SSNS meetings in 2021 and 2022.

**Table II:** Publication Rates Of Oral And Poster Presentations at TNS and SSNS Meetings (2018–2022). The Table Shows the Number (n) and Percentage (%) of Oral and Poster Presentations at the Turkish Neurosurgical Society (TNS) and Society of Surgery of the Nervous System (SSNS) Annual Meetings that Resulted in Publications. The “Total by Category” Row Indicates the Sum of Oral And Poster Presentations for Each Year. The “Total by Society” Column Provides the Cumulative Number and Percentage of Published Presentations for Each Society Across the Five-Year Period

Meeting	2018 n (%)		2019 n (%)		2020 n (%)		2021 n (%)		2022 n (%)		Total by Society	
	Oral	Poster	Oral	Poster	Oral	Poster	Oral	Poster	Oral	Poster	Oral	Poster
TNS	71 (27.4)	44 (8.6)	49 (21.0)	31 (7.2)	0 <sup>a</sup>	0 <sup>a</sup>	45 (26.2)	10 (3.5)	47 (8.9)	8 (2.4)	212 (22.5)	93 (5.9)
SSNS	6 (19.4)	2 (25.0)	2 (12.5)	0	1 (5.6)	0	4 (7.3)	0 <sup>b</sup>	3 (9.4)	0 <sup>b</sup>	16 (10.5)	2 (6.5)
<b>Categorical Total</b>	77 (26.5)	46 (8.9)	51 (20.5)	31 (7.0)	1 (5.6)	0	49 (21.6)	10 (3.5)	50 (16.1)	8 (2.4)	228 (20.8)	95 (5.9)
<b>Total</b>	123 (15.2)		82 (11.9)		1 (3.6)		59 (11.4)		58 (8.9)		323 (12.0)	

**TNS:** Turkish Neurosurgical Society. **SSNS:** The Society of Surgery of the Nervous System.

**a.** The TNS meeting was not held in 2020 due to the COVID-19 pandemic. **b.** No poster presentations were included in SSNS meetings in 2021 and 2022.



**Figure 1:** Publication rate trends (2018–2022) for abstracts presented at TNS and SSNS meetings. TNS data are shown in blue squares with a dashed line, SSNS data as orange diamonds with a dotted line, and overall data as yellow circles with a solid line. The 2020 TNS meeting was cancelled due to the COVID-19 pandemic. Overall, TNS meetings exhibited a gradual decline in publication rates over the years, whereas SSNS meetings showed more fluctuation.

(n=29, 9.0%), other national journals (n=22, 6.8%), Scopus (n=16, 5.0%), and other international journals (n=16, 5.0%). When analyzed by conference, TNS abstracts were mainly published in SCIE (n=184, 60.5%), followed by ESCI (n=41, 13.5%), TRDizin (n=28, 9.2%), other national journals (n=21, 6.9%), Scopus (n=15, 4.9%), and other international journals (n=15, 4.9%). SSNS abstracts were most frequently indexed in SCIE (n=9, 50%), followed by ESCI (n=5, 27.8%), while the remaining categories (TRDizin, other national journals, Scopus, and other international journals) each accounted for a single publication (n=1, 5.6%).

Publications were most often in Q3 (n=79) and Q4 (n=85) journals, with fewer in Q2 (n=31) and Q1 (n=9) journals. TNS abstracts were mainly published in Q4 (n=82) and Q3 (n=75) journals, followed by Q2 (n=29) and Q1 (n=8) journals. SSNS abstracts were published in Q4 (n=3), Q3 (n=3), Q2 (n=2), and Q1 (n=1) journals.

The median impact factor (IF) was 1.40 for TNS abstracts and 1.83 for SSNS abstracts, with no significant difference between the two groups (Mann–Whitney U test,  $p=0.319$ ).

The median time to publication was 11 months (mean: 15.96), with no significant difference between TNS and SSNS (Mann–Whitney U test,  $p=0.806$ ) (Figure 2). A total of 88 articles were published within six months, whereas 77 were published more than 24 months after presentation.

Subspecialty analysis revealed variation in both volume and publication rates. Spinal & Peripheral Nerve and Neuro-onco-

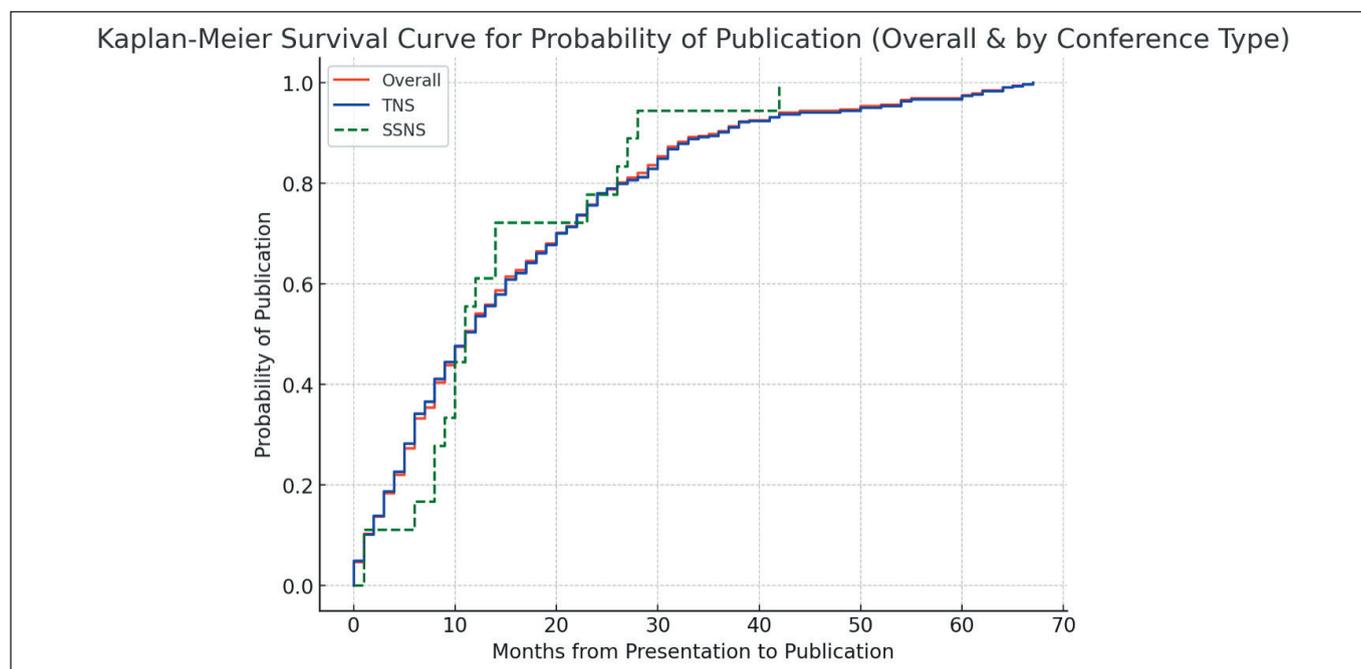
logical Surgery produced the largest number of abstracts but had lower publication rates (8.7% and 8.5%, respectively). Surgical Neuroanatomy (30.3%) and Pediatric Neurosurgery (15.5%) showed the highest rates. The differences across subspecialties were statistically significant (Kruskal–Wallis test,  $p<0.001$ ).

When categorized by institution type, the majority of the published abstracts originated from university hospitals (75.9%), followed by training and research hospitals (11.2%), state hospitals (8.1%), and private hospitals (5.0%). All published abstracts included identifiable institutional data.

## DISCUSSION

### Publication Rates

In this observational study of abstracts presented at TNS and SSNS meetings (2018–2022), the overall publication rate was approximately 12%, with no significant difference between the two societies. This aligns with the 10.5% rate reported by Eksi et al. for TNS meetings (2011–2014), indicating only modest improvement in recent years (1). These rates are low relative to international spine and neurosurgery conferences, such as the Congress of Neurological Surgeons (CNS) and the American Association of Neurological Surgeons (AANS), where publication rates exceed 30% (3). Publication rates also fluctuated over time, with a marked decline in 2020, likely reflecting cancellation of the TNS 2020, reduced research output, and delays in peer review during the COVID-19 pandemic. Although rates rebounded in 2021, the continued downward trend into



**Figure 2:** Kaplan-Meier survival curves showing the probability of publication over time (months) following presentations at TNS and SSNS meetings. The red solid line represents all abstracts combined, the blue solid line represents TNS abstracts, and the green dashed line represents SSNS abstracts. The x-axis shows months from presentation to publication, and the y-axis shows the cumulative probability of an abstract being published. The probability increased over time for all groups, with no significant difference between TNS and SSNS (Mann-Whitney U test,  $p=0.806$ ).

2022 suggests a potential long-term impact of the pandemic on academic dissemination, warranting ongoing monitoring.

### Quality of the Journals

The indexing of published abstracts is an important indicator of the visibility and impact of research presented at neurosurgical conferences. Most abstracts in this study were published in SCIE-indexed journals (59.9%), followed by ESCI (14.3%) and TRDizin (9.0%), with fewer in other national and international journals. This pattern was consistent by conference type: TNS abstracts appeared mainly in SCIE-indexed journals (60.5%), while SSNS abstracts also favored SCIE (50%) but showed a relatively higher proportion in ESCI (27.8%). These findings suggest that both conferences facilitate broad dissemination, with SCIE-indexed journals representing the most common avenue for full-text publication. Among abstracts published in WoS-indexed journals (SCIE or ESCI), most appeared in lower-quartile outlets, particularly Q4 ( $n=85$ ) and Q3 ( $n=79$ ) journals, with fewer in Q2 ( $n=31$ ) and Q1 ( $n=9$ ). The overall median journal impact factor was 1.45. This distribution mirrors previous reports, as conference abstracts are often published in lower-quartile journals due to their preliminary nature and the preference of high-impact journals for large-scale, methodologically robust studies (2).

### Oral Presentation vs Poster Presentation

Presentation type strongly influenced the likelihood of full-text publication. Oral presentations had a significantly higher publication rate (20.8%) than posters (5.9%), a pattern consistently reported in the literature. For example, an analysis of major

spine meetings showed that podium (oral) presentations are more likely to be published than posters, as conferences typically reserve podium slots for studies deemed methodologically sound or clinically impactful (2). Similarly, Weale et al. reported higher conversion rates for oral presentations at surgical conferences across the UK (6). In our study, oral presentations were also more frequently published in SCIE-indexed journals (64.9%) compared with poster presentations (47.9%). This reinforces the observation that oral presentations tend to be associated with higher-impact publications, likely reflecting more rigorous selection criteria for oral sessions and the higher level of evidence emanating from these studies. These findings are consistent with previous studies showing that high-impact research is preferentially selected for podium presentations at scientific conferences.

Oral presentations at TNS meetings had a significantly higher publication rate than those at SSNS meetings. This discrepancy may reflect variations in abstract review processes, the range of research topics, or how each society structures and prioritizes oral sessions. Differences in conference size may also contribute to heterogeneity in publication outcomes.

### Awarded Presentations

Award-winning abstracts at TNS meetings had a significantly higher likelihood of publication, consistent with data from international conferences (1,2). This is expected, as award committees typically recognize studies with rigorous methodology, clinical relevance, and strong preliminary data, all of which increase the likelihood of publication.

### Publication by Subspecialties

The distribution of abstracts across neurosurgical subspecialties revealed notable differences in submission volume and publication rates. Most abstracts were submitted in spinal & peripheral nerve surgery and neuro-oncological surgery, but these groups showed relatively low publication rates (8.72% and 8.50%, respectively). In contrast, surgical neuroanatomy, despite having fewer abstracts, exhibited the highest publication rate (30.34%), followed by pediatric neurosurgery (15.52%), a statistically significant difference ( $p < 0.001$ ). Several factors may explain these disparities. Subspecialties with higher publication rates, such as surgical neuroanatomy, often involve anatomical dissections, cadaveric studies, and imaging-based research, which tend to be more structured and methodologically robust, increasing their chances of acceptance in peer-reviewed journals. Similarly, pediatric neurosurgery often addresses rare conditions, long-term outcomes, and specialized surgical techniques, which may draw greater editorial interest due to their novelty and clinical relevance.

### Publication Time

The timeline from presentation to publication showed a distinct pattern, with the highest number of studies published within the first six months (88 articles), followed by a gradual decline over the 6–24 month period and a subsequent increase beyond 24 months (77 articles). Delayed publications may reflect extensive revisions, additional data collection, or multiple resubmissions. Authors seeking to publish in higher-impact journals, which often have longer review timelines, may also face delays. Conversely, studies published within six months likely had robust methodology, clear results, and well-prepared manuscripts at the time of presentation, facilitating faster acceptance. There was no significant difference in publication timelines between TNS and SSNS meetings ( $p = 0.806$ ), suggesting consistent publication timelines across different Turkish neurosurgical conferences, likely influenced by similar submission practices, journal preferences, and peer-review durations.

### Institutional Contribution

The vast majority of published abstracts originated from university hospitals (75.9%), with lower contributions from training and research hospitals (11.2%), state hospitals (8.1%), and private hospitals (5.0%). These findings align with previous reports, including Yakar et al., who showed that university-affiliated centers dominate neurosurgical research productivity in Turkey (7). Differences in academic environment, research expectations, and access to funding and infrastructure are likely to contribute to this disparity among institution types.

### Limitations

A limitation of our study is the relatively short interval between presentation and analysis (two to six years). Publication rates may rise with longer follow-up. Another limitation is the reliance on PubMed and Google Scholar databases; abstracts published in journals not indexed in these databases may have been missed, leading to a possible underestimation of the true publication rate.

## CONCLUSION

Although overall publication rates remain modest, our analysis highlights key determinants of the likelihood of full-text publication. Oral presentations, award-winning abstracts, and specific subspecialties (such as Pediatric Neurosurgery) were associated with higher publication rates, aligning with global trends. These findings underscore the need for ongoing evaluation of conference outcomes to ensure that high-quality abstracts progress to publication in peer-reviewed journals. Strategies such as multi-center collaborations, dedicated writing workshops, and systematic tracking of abstract submissions may further improve conversion to publication and advance neurosurgical research.

### 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:** 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.

### AUTHORSHIP CONTRIBUTION

Study conception and design: EMT, SB, HKS

Data collection: EMT, IES, SB

Analysis and interpretation of results: SB, IES, HKS

Draft manuscript preparation: EMT, IES, SB

Critical revision of the article: HKS

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

All authors (EMT, IES, SB, HKS) reviewed the results and approved the final version of the manuscript.

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# Affordable Excellence: A Meta-Analysis on the Efficacy of Topical Tranexamic Acid in Reducing Blood Loss in Thoracolumbar Spinal Surgery

Jyun-Yuan HUANG<sup>1,2</sup>, Tzu-Ning CHEN<sup>1,2</sup>, Hao-Kuang WANG<sup>1,2</sup>, Kang LU<sup>1,2</sup>, Jui-Sheng CHEN<sup>1,2</sup>,  
Tsung-Jen HSIEH<sup>2</sup>, Yu-Ying WU<sup>1,2</sup>, Min-Jung LEE<sup>1,2</sup>, Po-Yuan CHEN<sup>1,2</sup>

<sup>1</sup>E-Da Hospital, Department of Neurosurgery, Kaohsiung, Taiwan

<sup>2</sup>I-Shou University, College of Medicine, School of Medicine, Kaohsiung, Taiwan

Corresponding author: Po-Yuan CHEN ✉ u8801051@gmail.com

## ABSTRACT

**AIM:** To evaluate the efficacy and safety of topical tranexamic acid (tTXA) in thoracolumbar fusion surgery.

**MATERIAL and METHODS:** A systematic review was conducted per PRISMA guidelines. Studies from January 1970 to August 2024 were retrieved from PubMed, Cochrane, EMBASE, Medline, and Google Scholar. Randomized controlled trials, non-RCTs, and cohort studies comparing tTXA with placebo or standard care in thoracolumbar surgery were included.

**RESULTS:** Eleven studies with 986 patients met the criteria. tTXA significantly reduced intraoperative blood loss (MD: -25.85 mL,  $p = 0.002$ ), postoperative drain output (MD: -84.82 mL,  $p < 0.00001$ ), transfusion rates (OR: 0.33,  $p = 0.0004$ ), and hospital stay (MD: -0.67 days,  $p < 0.00001$ ). It also increased postoperative hemoglobin (MD: 0.39 g/dL,  $p < 0.00001$ ) but slightly prolonged operative time (MD: 3.73 minutes,  $p < 0.00001$ ). No significant difference was found in complication rates ( $p = 0.36$ ).

**CONCLUSION:** tTXA is effective in reducing blood loss and transfusion needs in thoracolumbar surgery, with minimal risk. Slightly increased operative time is clinically acceptable.

**KEYWORDS:** Topical tranexamic acid, Thoracolumbar surgery, Blood loss management, Cost-effective hemostasis, Meta-analysis

## INTRODUCTION

Intervertebral disc herniation and degenerative spinal diseases represent increasingly common clinical challenges. Over the past century, advances including antibiotic development and implant material improvement, have facilitated spinal fusion surgery evolution. Despite these advances, intraoperative bleeding remains a significant concern that requires further investigation. The key steps in thoracolumbar fusion, including paraspinal muscle dissection, laminectomy, flavectomy, and discectomy, require wide exposure. Paraspinal muscle bleeding can be effectively managed using monopolar electrocautery, gauze compression, or muscle retraction. Bone bleeding encountered during laminectomy

is typically controlled effectively with bone wax application. However, after flavectomy and discectomy, profuse hemorrhage may occur from the Batson venous plexus, which poses challenges for hemostatic control. This complication is especially pronounced during ligamentum flavum resection near the lateral recess or in cases involving inadvertent vertebral body erosion. Significant blood loss increases the risk of severe complications such as cardiopulmonary events, renal failure, and cerebral infarction, particularly in patients > 60 years (8). Although allogeneic blood transfusions can mitigate these life-threatening risks, their use is often by limited blood availability and potential complications, including immunologic reactions and infectious disease transmission. In modern

Jyun-Yuan HUANG : 0009-0004-0642-1305  
Tzu-Ning CHEN : 0000-0002-0671-8449  
Hao-Kuang WANG : 0000-0002-1928-7502

Kang LU : 0000-0003-1047-1378  
Jui-Sheng CHEN : 0000-0001-7627-6132  
Tsung-Jen HSIEH : 0000-0001-7328-9157

Yu-Ying WU : 0000-0001-5254-7225  
Min-Jung LEE : 0009-0007-8293-2256  
Po-Yuan CHEN : 0000-0002-8157-9450

medicine, various techniques such as bipolar electrocautery, hypotensive anesthesia (2), normovolemic hemodilution, and blood salvage (11) have been used to control intraoperative bleeding during thoracolumbar spinal fusion surgery. However, these methods have demonstrated suboptimal efficacy. Hemostatic agents, such as Floseal® or Surgiflo®, provide excellent hemostatic control but are often prohibitively expensive, limiting their accessibility for many patients.

Tranexamic acid (TXA), a synthetic lysine derivative, acts as an antifibrinolytic agent by competitive binding to lysine sites on plasminogen, thereby inhibiting its attachment to fibrin. This mechanism prevents plasminogen activation into plasmin, promoting clot stabilization and reducing excessive bleeding. TXA was initially synthesized in 1962 by Japanese researchers Shosuke and Utako Okamoto for postpartum hemorrhage management. Systemically TXA is widely used in orthopedic (10) cardiovascular and spinal surgeries. However, it may induce side effects, including thromboembolic events, seizures (19), and cardiovascular complications. Prolonged surgical duration, particularly in spinal procedures, correlates with increased complication rates. Recently, strategies to minimize perioperative blood loss, reduce drain output, and decrease transfusion requirements in spinal surgery have gained attention. Numerous studies (15,26) have assessed the efficacy of topical TXA (tTXA) application at surgical sites. This approach offers the advantage of achieving a concentrated effect directly at the bleeding site while circumventing the potential adverse effects associated with systemic administration. The therapeutic efficacy and safety profile of tTXA have been well established in various surgical disciplines, including orthopedic (24), hepatic, and cardiac surgeries (7). Although some studies have explored tTXA use in spinal surgery, no consensus exists regarding its optimal application in this field.

## ■ MATERIAL and METHODS

### Data Search and Extraction Strategies

Following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (18), a systematic literature search was conducted.

Two independent reviewers performed the meta-analysis using electronic databases, including PubMed, Cochrane, EMBASE, MEDLINE, and Google Scholar, to identify relevant studies published between January 1, 1970, and August 30, 2024. The year 1970 was selected to ensure consistency in database indexing, thereby capturing early literature comprehensively. Although tTXA has only recently gained widespread use, this extended timeframe helps avoid missing earlier studies under different terminologies and early exploratory or pioneering studies. The search strategy incorporated Medical Subject Headings (MeSH) terms combined with the Boolean operators “AND” and “OR.”

Keywords comprised “Interbody fusion,” “Lumbar fusion surgery,” “Spine fusion,” “Spine instrument,” “Spine surgery,” “Spine,” “thoracolumbar degenerative disease,” “Tranexamic acid,” “TXA,” and “topical.” Only English-language publica-

tions were included. This review protocol was not registered in PROSPERO or other public registries.

### Eligibility Criteria

The inclusion criteria for this study were as follows: 1) Patients undergoing lumbar or thoracic spinal fusion surgery; 2) Use of TXA as an intervention, with the experimental group receiving tTXA and the control group receiving either placebo or standard treatment alternatives; 3) Reported outcome including intraoperative blood loss or postoperative measures, including drain output, postoperative hemoglobin levels, hospital stay duration, operative time, adverse effects and complications; 4) Study designs limited to randomized controlled trials (RCTs), non-RCTs, or comparative cohort studies; and 5) Publications in English.

Exclusion criteria comprised: 1) Case reports or case series; 2) Surgical procedures other than lumbar or thoracic fusion surgery; 3) interventions not utilizing tTXA; 4) Patients with dural tears or intradural procedures; and 5) Unavailable full-text articles.

### Data Collection and Assessment of Outcome Measures

Two authors, JYH and JNC, independently extracted data using a structured template based on the Cochrane Consumers and Communication Group (CCCG) guidelines. This study was performed according to the criteria established by the CCCG for systematic reviews and meta-analyses. Discrepancies in data extraction were resolved by consensus. The extracted data included:

1. Basic personal profiles, including age, sex, and body mass index (BMI);
2. Clinical and surgical profile;
3. Intervention method, particularly topical tranexamic acid (tTXA) vs. placebo;
4. Intervention details including TXA dosage;
5. Parameters used to evaluate the intervention impact included intraoperative blood loss, surgical time, length of hospital stay, transfusion rates, postoperative drain output, postoperative hemoglobin levels, and any complications reported.

This methodology ensured that all pertinent data were systematically and accurately gathered for subsequent analyses.

### Statistical Analysis

Statistical analysis was performed using the Review Manager (RevMan Web) software. Continuous variables were assessed using pooled weighted mean differences (MD), while dichotomous variables were analyzed using odds ratios (OR). Results are presented as MD or OR, with 95% confidence intervals (CI). A fixed-effects model was employed for data synthesis, assuming a common effect size across studies.

Study heterogeneity was assessed using the  $I^2$  statistic to determine the proportion of variation due to between-study differences rather than random variations. Statistical tests were performed with the significance set at  $p < 0.05$ .

## RESULTS

### Study Selection

A total of 153 articles were identified after a comprehensive search of the electronic databases. Following the initial abstract screening, nine duplicates were eliminated, and 127 articles were excluded due to their irrelevance to spinal surgery. Subsequently, 17 full-text articles were assessed for eligibility. Six articles were excluded based on the predefined criteria, yielding 11 studies fulfilled the criteria and were subsequently included in our review; more information is in Figure 1.

### Overall Characteristics

The analysis included 986 patients, with 439 allocated to the control group and 547 to the intervention group receiving tTXA treatment. The comprehensive details of the studies included in the analysis, including basic characteristics, clinical features, and study designs, are presented in Table I.

### Intraoperative Blood Loss (cc)

The tTXA group demonstrated lower intraoperative blood loss (mean  $372.39 \pm 326.59$  mL) compared to controls ( $431.03 \pm 384.60$  mL), with a mean difference (MD) of  $-25.85$  (95% CI:  $-42.45$  to  $-9.26$ ,  $p$ -value = 0.002) (Figure 2).

### Operative Time

The average operative duration for the tTXA group was  $146.58 \pm 52.41$  minutes, compared to  $139.95 \pm 49.34$  minutes observed in the control group (MD: 3.73 minutes; 95% CI 0.65–6.81;  $p$ -value < 0.00001) (Figure 3).

### The Length of Hospital Stay

The mean length of hospital stay was notably reduced for the tTXA group, averaging  $4.96 \pm 3.29$  days, compared to  $6.81 \pm 5.09$  days in the control group (MD  $-0.67$  days; 95% CI  $-0.85$  to  $-0.50$ ;  $p$ -value < 0.00001) (Figure 4).

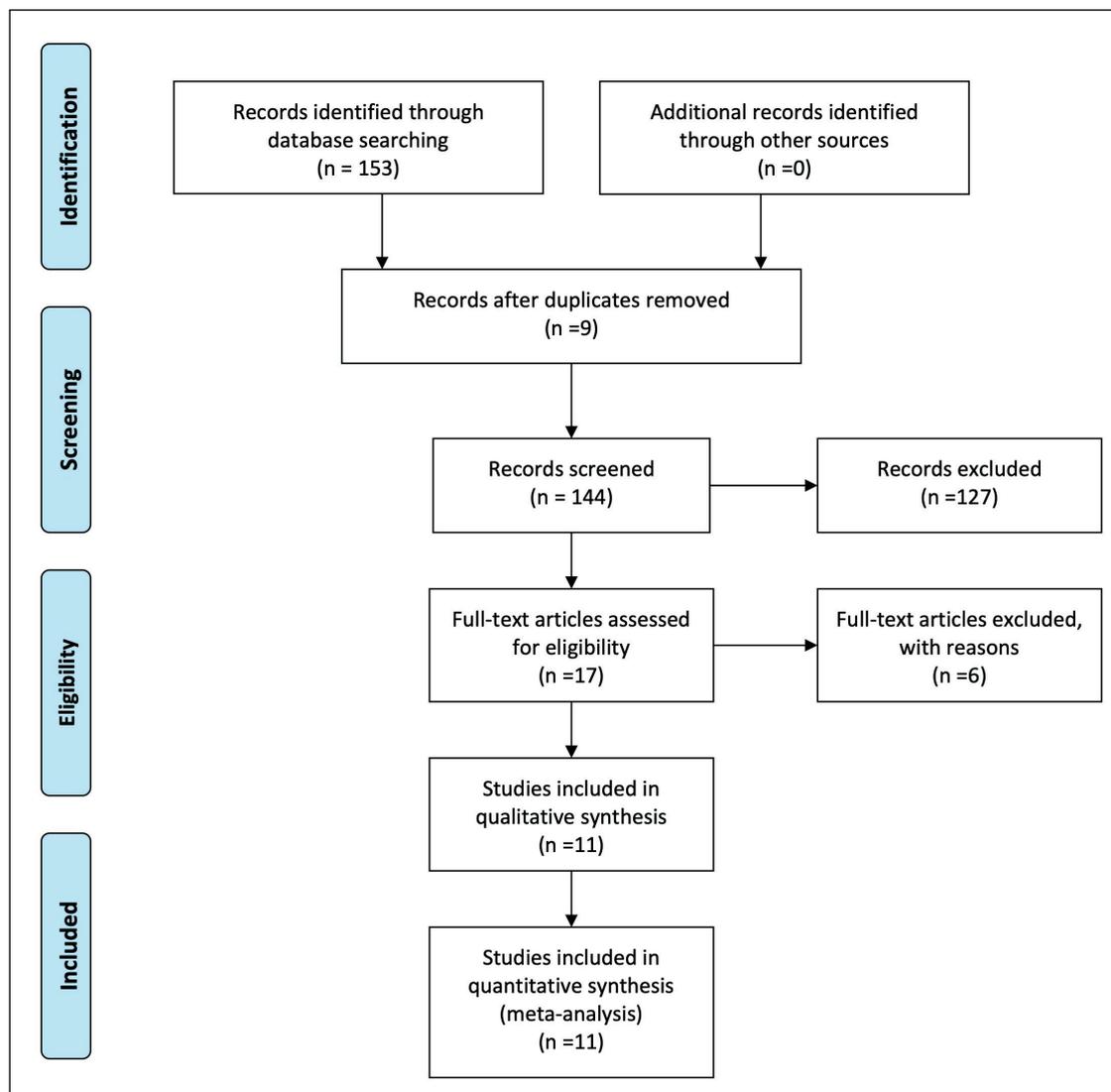


Figure 1: PRISMA diagram of study screening and selection.

Table I: Characteristics of All the Included Studies

Study	Type	Clinical status	Surgery	Control	Intervention	Number of pts	Gender (M/F)	Age(yrs)	BMI(Kg/m <sup>2</sup> )	Country
Mallepally et al. (2020), (17)	CCS	Degenerated lumbar spinal disease	Single-level TLIF	Normal saline	1 g tTXA in 100cc normal saline was poured into the surgical wound for 5 minutes following muscle dissection and final discectomy, and prior to closure	Control: 75 Intervention: 175	Control: 39/36 Intervention: 85/90	Control: 56.9±13.4 Intervention: 55.3±12.8	Control: 24.3±2.09 Intervention: 24.4±2.31	India
Arun-Kumar and Nares-Babu (2021), (1)	RCT	Degenerative grade 1 or 2 spondylosis	Single or dual level lumbar fixation with interbody fusions	10 ml of 2% lignocaine with adrenaline (1 in 200000 dilution) mixed in 10 ml normal saline	1 g of tTXA in 100 mL normal saline was poured into surgical wound followed by a wait time of 5 minutes	Control: 26 Intervention: 26	Control: 14/12 Intervention: 13/13	Control: 50.8±3.4 Intervention: 51.9±2.8	Control: 27.6±1.4 Intervention: 25.6±2.1	India
Xu et al. (2017), (25)	RCT	Degenerated lumbar spinal disease	Total laminectomy with transpedicular screw fixation	Gelatin sponge	tTXA 1000 mg diluted in 100 ml of normal saline was irrigated over the surgical field for 3 minutes and subsequently aspirated prior to wound closure	Control: 40 Intervention: 40	Control: 13/27 Intervention: 19/21	Control: 57.4±10.7 Intervention: 53.1±12	Control: 24.9±3.9 Intervention: 25.6±2.8	China
Li et al. (2020), (12)	RCT	Degenerated lumbar spinal disease	Lumbar spinal fusion surgery	Normal saline	tTXA saline (2 g in 20 mL normal saline) was injected into the incision by the drainage after the incision closure	Control: 70 Intervention: 70	Control: 23/47 Intervention: 25/45	Control: 65.61±3.17 Intervention: 65.61±4.81	Control: 22.75±2.39 Intervention: 22.24±2.78	China
Liang et al. (2016), (13)	RCT	Degenerated lumbar spinal disease	Lumbar decompression ± discectomy	Normal Saline soaked gelatin compressed Gelfoam applied to wound	tTXA 2g in 20cc normal saline soaked gelatin compressed Gelfoam applied to wound	Control: 30 Intervention: 30	Control: 14/16 Intervention: 15/15	Control: 53.5±10.26 Intervention: 51.13±10.72	Control: 25.3±5.2 Intervention: 26.2±4.1	China
Emrah et al. (2021), (4)	Cross-sectional comparative study	Thoracolumbar spinal stenosis or spondylolisthesis	Posterior thoracolumbar spinal fusion surgery	Nothing	tTXA 1g in 20cc normal saline was poured into wound for 3 to 5 minutes	Control: 30 Intervention: 30	Control: 13/17 Intervention: 14/16	Control: 63.5(53.5-67.0) Intervention: 63.0(59.0-68.3)	Control: 30.0(28.4-33.8) Intervention: 29.6(27.2-31.4)	Turkey

**Table I:** Cont.

Ren et al. (2017), (20)	Non-RCT	Lumbar disc herniation or spinal stenosis	Primary PLIF	Normal saline	1 g tTXA in 100cc normal saline was poured into the surgical wound for 5 minutes prior to closure followed by negative pressure suction drain	Control: 50 Intervention: 50	Control: 19/31 Intervention: 20/30	Control: 58.7±12.9 Intervention: 55.2±13.0	Control: 25.1±3.1 Intervention: 25.7±2.8	China
El-Sharkawi et al. (2016), (3)	RCT	Spinal deformities	Underwent correction (in the form of multiple Ponte osteotomies, PSO, PVCR) and posterior spinal fusion for spinal deformity	Normal saline	tTXA	Control: 23 Intervention: 31	Control: 34/49	Control: 17±4	Control: Body weight: 49±6	Egypt
Farzanegan et al. (2022), (5)	RCT	Disk herniation, spinal canal stenosis, or both.	Posterior lumbar spinal surgery	Normal saline	3 g tTXA in 100cc normal saline was poured into the surgical wound for 5 minutes following muscle dissection and final discectomy, and prior to closure	Control: 50 Intervention: 54	Control: 27/23 Intervention: 26/28	Control: 54.8±14.04 Intervention: 51.39±12.77	Control: 26.56±5.44 Intervention: 26.57±4.18	Iran
Sudprasert et al. (2019), (23)	RCT	Thoracolumbar spine trauma	Long segment posterior fixation	Normal saline	tTXA saline 1 g in 100 mL normal saline was applied directly to the surgical field, followed by the placement of a drain. The drain was clamped and kept closed for 2 hours.	Control: 28 Intervention: 29	Control: 15/13 Intervention: 20/9	Control: 51.5 (33.5-58.0) Intervention: 52.0 (33.5-55.5)	Control: 22.3±3.2 Intervention: 22.2±3.3	Thailand
Wood (2016), (27)	RCT	Thoracolumbar spinal stenosis	Posterior approach	Normal saline	tTXA 3g was irrigated in the wound prior to closure, and aspirated it after 5 minutes. Drains were placed after the study drug was aspirated.	Control: 17 Intervention: 12	Control: 5/12 Intervention: 4/8	Control: 66(50-73) Intervention: 69(62-72)	Control: NA	United States

**RCT:** Randomized controlled study, **CCS:** Case controlled study, **TLIF:** Transforaminal lumbar interbody fusion, **tTXA:** topical tranexamic acid, **pts:** Patients.

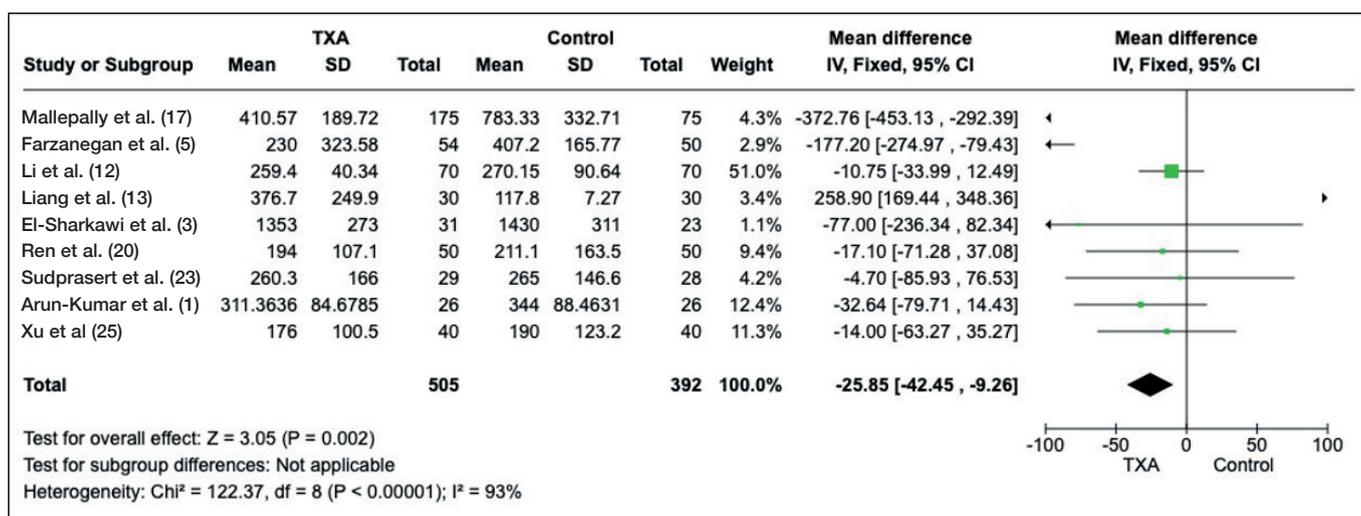


Figure 2: Forest plot of intraoperative blood loss (cc).

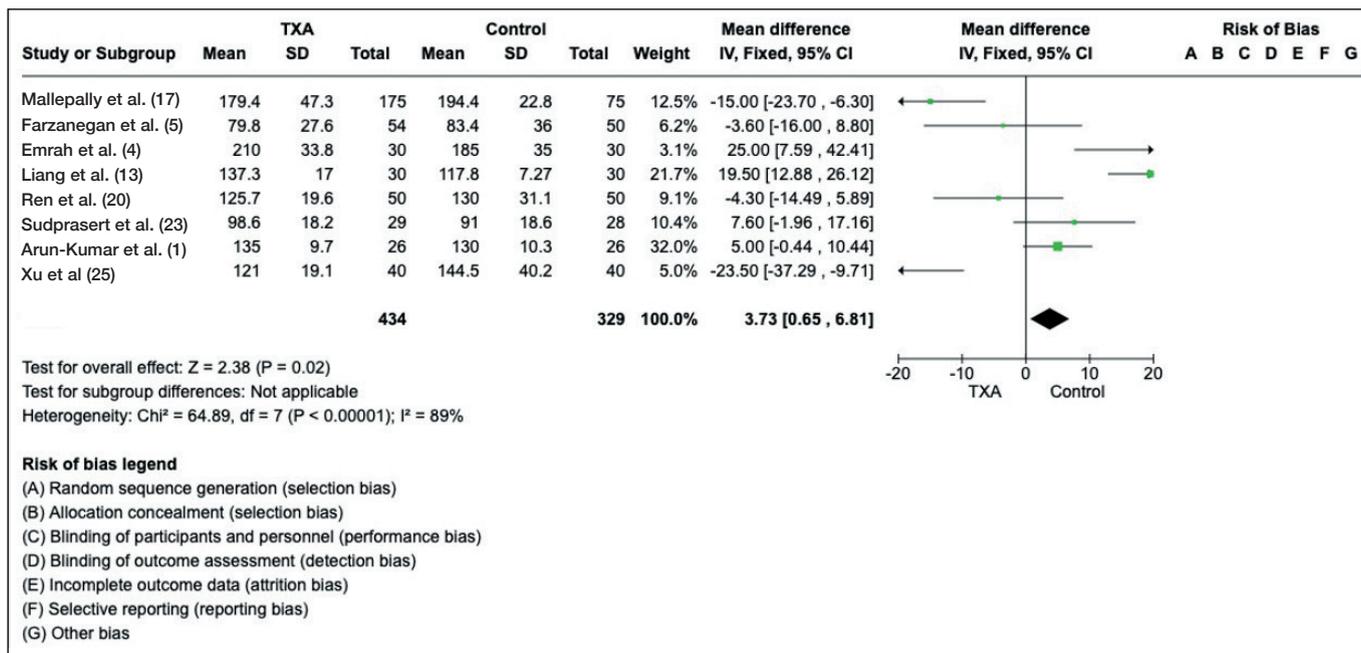


Figure 3: Forest plot of operative time (minutes).

**Postoperative Drain Output (cc)**

The average postoperative drain output for the tTXA group was measured as 149.70 ± 97.80 cc, compared to 285.74 ± 164.57 cc observed in the control group (MD: -84.82; 95% CI: -95.55 to -74.10; p-value < 0.00001) (Figure 5).

**Postoperative Hemoglobin Concentration (Hb, measured in grams per deciliter or g/dL)**

The average postoperative Hb concentration in the tTXA group was recorded at 10.64 ± 1.92 g/dl, compared to 9.97 ± 2.09 g/dl observed in the control group (MD: 0.39; 95% CI: 0.21–0.58; p-value < 0.00001) (Figure 6).

**Transfusion Rate**

When compared to control group, the administration of tTXA led to a 67% decrease in the necessity for blood transfusions with an odds ratio of 0.33 (95% CI: 0.18–0.61; p = 0.0004) (Figure 7). This notable reduction underscores the favorable safety characteristics of tTXA by reducing the need for allogeneic blood transfusions.

**Complications Rate**

When compared to control group, odds ratio was 0.71 (95% CI: 0.33–1.49; p = 0.36) (Figure 8). No significant differences were found between the two groups.

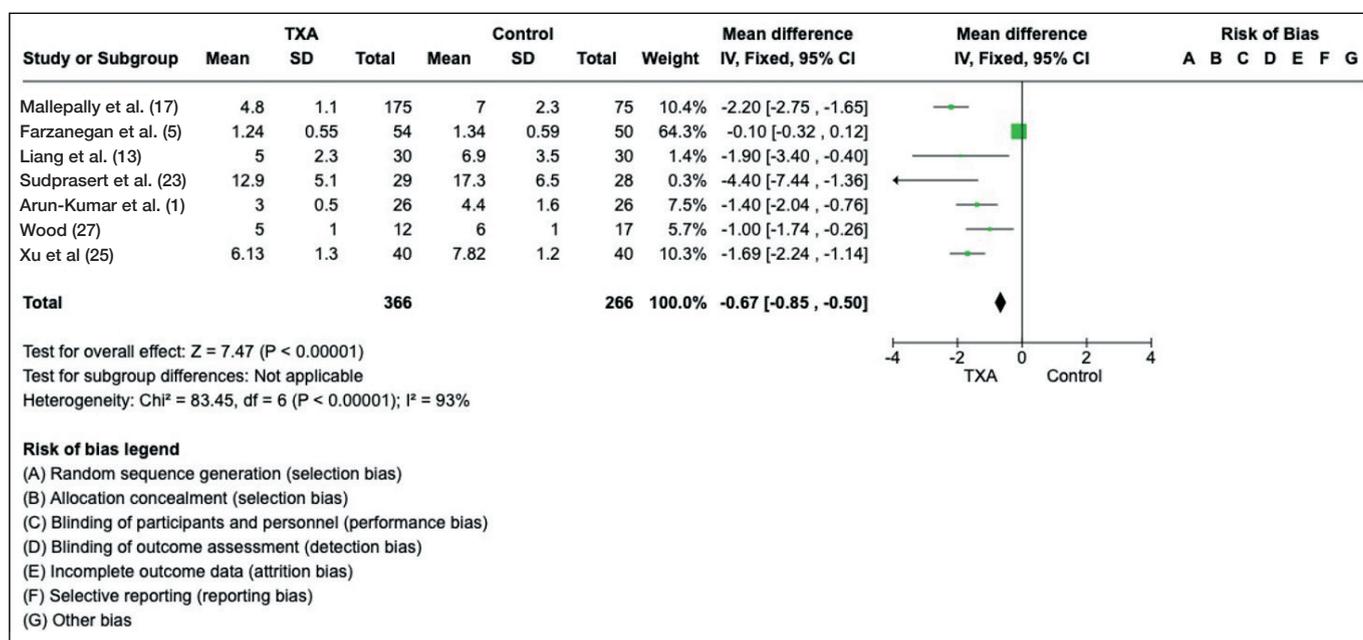


Figure 4: Forest plot of length of hospital stay (days).

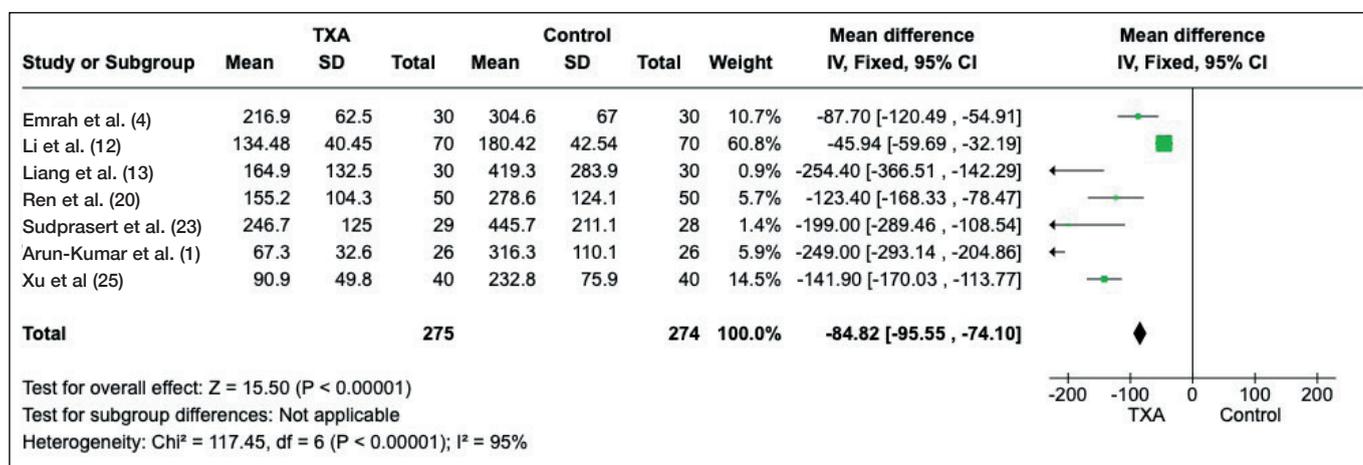


Figure 5: Forest plot of postoperative drain output (cc).

## DISCUSSION

This meta-analysis demonstrated that tTXA administration in thoracolumbar surgery significantly reduced intraoperative bleeding, postoperative drain output, transfusion rates, and hospital length of stay compared to controls. While the tTXA group also demonstrated a significantly higher postoperative hemoglobin level, they experienced longer operative times. No statistical difference in complication rates were observed.

This is a highly subjective result; TXA local administration reduced intraoperative blood loss, which subsequently lowered transfusion rates, postoperative drain output, and hospital length of stay. However, because time is required for TXA to diffuse into the surgical wound, the tTXA group had a longer operative time. The slight increase in operative time observed

in the tTXA group was potentially due to the additional time required for tTXA application and absorption. However, this minor prolongation is clinically acceptable and does not outweigh the substantial benefits of reduced blood loss, lower transfusion rates, and shorter hospital length of stay. Therefore, the advantages of tTXA remain significant despite the marginal increase in surgical duration.

Blood loss during thoracolumbar surgery has been a significant challenge for over a century. In modern medicine, various techniques such as bipolar electrocautery, hypotensive anesthesia, normovolemic hemodilution, and blood salvage are commonly used to manage intraoperative bleeding in thoracolumbar spinal surgery. Although these methods are effective, their outcomes can be suboptimal. Hemostatic agents,

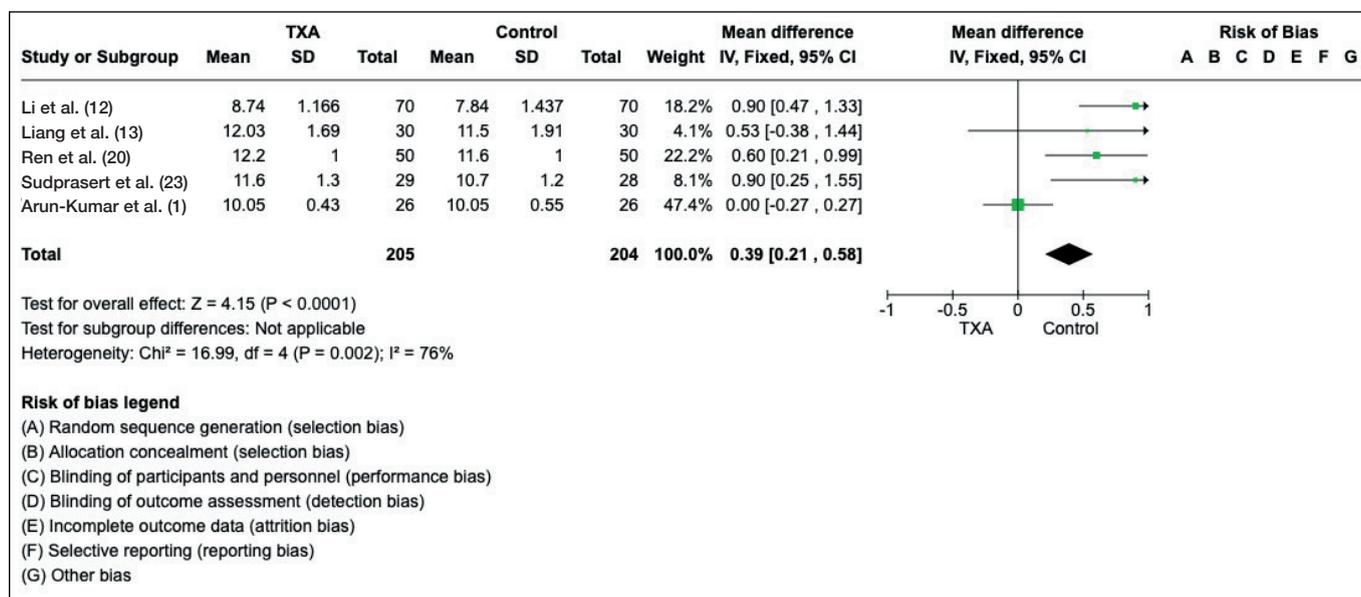


Figure 6: Forest plot of postoperative hemoglobin concentration(g/dl).

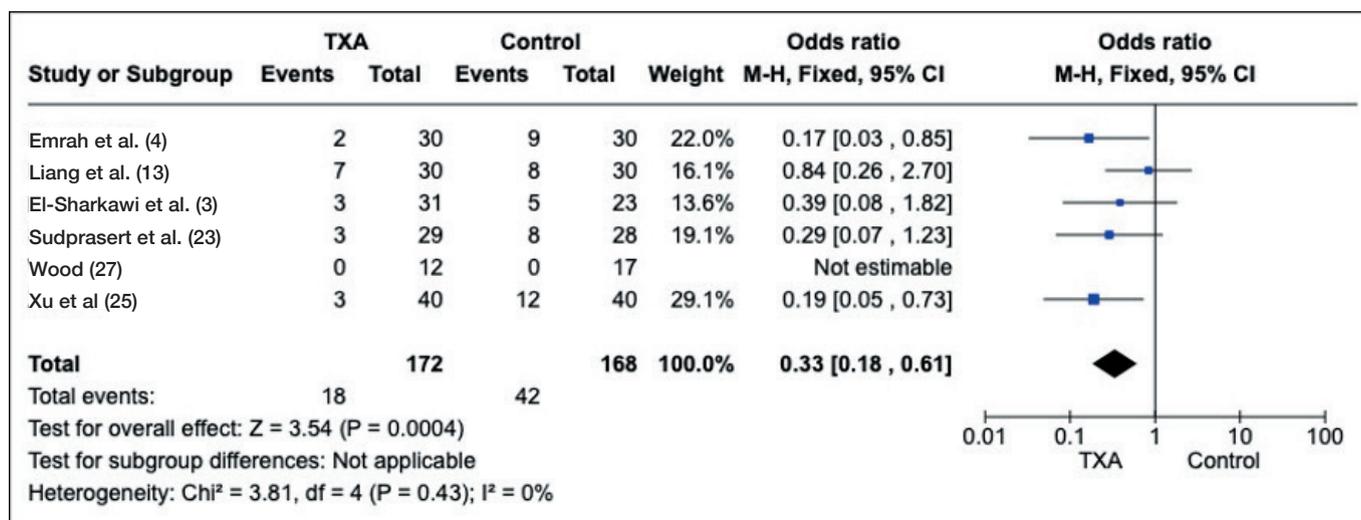


Figure 7: Forest plot of transfusion rate.

including Floseal® and Surgiflo®, offer excellent hemostatic efficacy; however, their high-cost limits accessibility for many patients. For instance, a 10 mL of Floseal® costs approximately \$1,000 in Taiwan. In contrast, one 5 mL ampule of TXA costs only \$0.50, making it an affordable option. Globally, tTXA is widely regarded as a cost-effective alternative, particularly compared to commercial hemostatic agents, which are often expensive and have limited availability.

In 1962, Japanese scientists Shosuke and Utako Okamoto first synthesized TXA for managing postpartum hemorrhages. Currently, TXA is widely used in trauma care, orthopedic and cardiovascular procedures. Studies have shown that intravenous TXA reduce intraoperative blood loss effectively, although concerns regarding thromboembolic events remain.

Consequently, many studies investigated tTXA in thoracolumbar surgery to reduce thromboembolic complications while maintaining effective blood loss control (21,22).

Luo et al. (14) evaluated three RCTs and one non-RCT, reporting several statistically significant benefits in the tTXA group compared to the control group: 1) significantly reduced total intraoperative blood loss, 2) decreased drainage volume, 3) increased postoperative hemoglobin levels, and 4) shorter hospital length of stay. In contrast, they found no significant differences in transfusion requirements, thromboembolism events, hematoma formation, or infection rates. These findings align with the results of this study.

Fatima et al. (6) analyzed data from eight studies involving 609 patients, including 258 (42.4 %) who received tTXA. Their

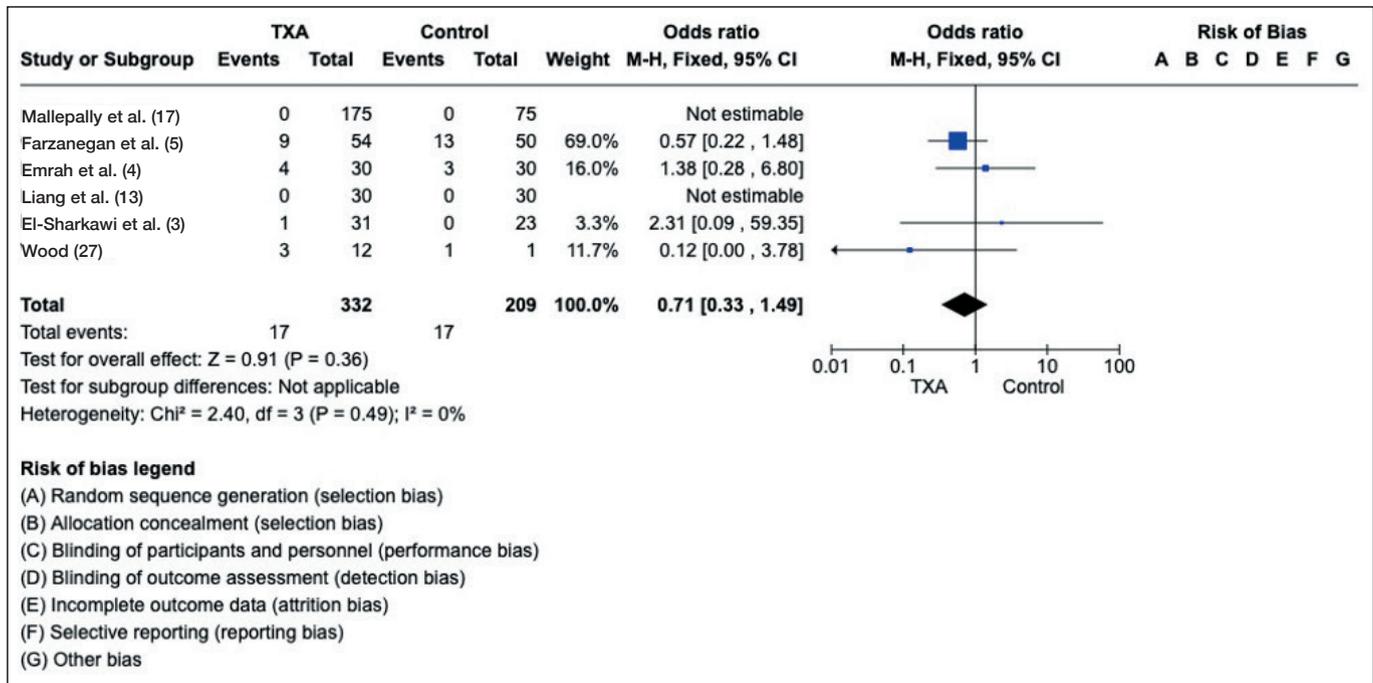


Figure 8: Forest plot of complications rate.

analysis revealed statistically significant improvements in several postoperative outcomes in the tTXA group, including 1) reduced postoperative blood loss, 2) increased postoperative hemoglobin levels, 3) shorter operative time, 4) lower postoperative transfusion rate, 5) decreased postoperative drain volume, and 6) shorter hospital length of stay. These findings highlighted the significant benefits of tTXA therapy compared with control treatments. However, in contrast to our study, they reported no significant differences in intraoperative blood loss (p=0.13) or complication rates (p=0.23) between groups. Additionally, Fatima et al. found that low-dose tTXA (250–500 mg) was more effective in reducing postoperative blood loss (p<0.00001) than high-dose tTXA (1–3 g, p=0.001). This dose-dependent effect offers further insights into the optimal use of tTXA in clinical practice.

At our institution, the standard protocol for tTXA administration involves applying 1 g of TXA diluted in 100 mL of normal saline to the surgical wound for 3–5 minutes on three points during surgery. The first application occurred following complete muscle dissection, exposure of the lamina, and placement of pedicle guide pins. After applying tTXA to the surgical field, a mobile C-arm fluoroscope was used to confirm pedicle guide pin placement, a process requiring approximately 3 minutes. The solution was then suctioned before proceeding with surgery. The second application was performed after discectomy and interbody fusion cage placement. comparably, tTXA was applied to the surgical field, followed by fluoroscopic confirmation of the interbody fusion cage depth, which required approximately 3 minutes. The solution was then suctioned and the procedure was continued. The final tTXA application was administered immediately before wound closure. However, tTXA is contraindicated in cases of dural tear. Several reports

have demonstrated that the accidental TXA injection into the dural sac may induce generalized tonic-clonic convulsions, which should strictly be avoided (9,16).

This meta-analysis demonstrated that tTXA is an effective and safe intervention for improving hemostasis during spinal deformity surgery. However, several limitations warrant consideration:, including: 1) small sample sizes in the RCTs, 2) inconsistent reporting of surgical indications and patient comorbidities, 3) insufficient details regarding various surgical techniques and vertebral levels operated, 4) short follow-up periods for complication assessment, 5) heterogeneity in tTXA concentrations, administration methods and timing, which may introduce sampling bias and underestimating tTXA’s effect on intraoperative blood loss, and 6) lack of direct comparison between topical and intravenous TXA in this analysis. Additionally, most studies failed to report comprehensive baseline characteristics related to patient-specific bleeding risks, such as anticoagulant use, obesity status, and systemic comorbidities, limiting our ability to assess potential confounding factors and perform subgroup analyses. To address these limitations, future prospective randomized controlled studies are needed to assess the influence of alternative tTXA dosage regimens on perioperative blood loss in spinal surgery and compare its efficacy with intravenous TXA.

**CONCLUSION**

This study provides strong evidence supporting the benefits of tTXA in thoracolumbar surgery. tTXA significantly reduces intraoperative blood loss, decreases postoperative drain volume, lowers complication rate, and shortens hospital length of stay. Furthermore, patients receiving tTXA maintained high-

er postoperative hemoglobin levels, consequently reducing transfusion rates. Although tTXA may prolong operative times, which we believe is acceptable, as it requires time for the medication to take effect after application. Further research comparing intravenous and topical tranexamic will be our next objective.

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### Declarations

**Funding:** This research received no external funding.

**Availability of data and materials:** All data analyzed during this study are included in the published articles cited in the reference list. The extracted dataset used for the meta-analysis is available from the corresponding author upon reasonable request.

**Disclosure:** The authors declare that they have no conflicts of interest related to this study.

**Ethics approval and consent to participate:** This study is a systematic review and meta-analysis based solely on previously published studies. No new human participants were enrolled, and no individual patient data were collected. Therefore, ethical approval and informed consent were not required.

### AUTHORSHIP CONTRIBUTION

Study conception and design: PYC

Data collection: TNC, JYH

Analysis and interpretation of results: HKW

Draft manuscript preparation: JYH, MJL

Critical revision of the article: YYW

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

All authors (JYH, TNC, PYC, HKW, KL, JSC, YYW, MJL, TJH) reviewed the results and approved the final version of the manuscript.

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# Hemostasis Versus Immunosuppression in Preventing Postlaminectomy Epidural Fibrosis: An Experimental Study in Rats

Vaner KOKSAL<sup>1</sup>, Tolga MERCANTEPE<sup>2</sup>, Levent TUMKAYA<sup>3</sup>

<sup>1</sup>Samsun University, School of Medicine, Department of Neurosurgery, Samsun, Türkiye

<sup>2</sup>Recep Tayyip Erdogan University, School of Medicine, Department of Histology and Embryology, Rize, Türkiye

<sup>3</sup>Ondokuzmayıs University, School of Medicine, Department of Histology and Embryology, Samsun, Türkiye

**Corresponding author:** Vaner KOKSAL ✉ vaner.koksal@samsun.edu.tr

## ABSTRACT

**AIM:** To compare haemostasis induced with tranexamic acid (TXA) and immunosuppression induced with infliximab (INF) as strategies to reduce epidural fibrosis (EF) in rat laminectomy model.

**MATERIAL and METHODS:** Twenty-one male Sprague–Dawley rats were randomly assigned into control group (no treatment), TXA treatment group and INF treatment group (n=7 per group). TXA (10–20 mg/mL) and INF (1 mg/mL) were topically applied following L1–L3 laminectomy. Histopathological evaluation involving haematoxylin–eosin and Masson–Goldner’s Trichrome staining was conducted eight weeks postoperatively. EF severity, fibroblast density, inflammatory cell infiltration and neovascularisation were analysed.

**RESULTS:** Histopathological analysis showed that fibrosis scores were significantly lower in the TXA treatment group than in the control and INF treatment groups (p<0.05). Moreover, TXA reduced fibroblast proliferation, inflammatory cell infiltration and collagen deposition. While INF exhibited moderate anti-fibrotic effects, it was less effective than TXA. No systemic side effects were observed in either treatment group.

**CONCLUSION:** This study demonstrates that TXA prevents EF more effectively than INF following laminectomy. The findings also underscore that TXA is superior over INF in reducing EF. These results suggest that compared with INF-induced immunosuppression, TXA-induced haemostasis is the more effective strategy to minimise postoperative fibrosis in spinal surgery.

**KEYWORDS:** Epidural fibrosis, lumbar laminectomy, tranexamic acid, infliximab, fibroblast proliferation, postoperative adhesion, wound healing, haemostasis, spinal surgery, TNF- $\alpha$  inhibition

## INTRODUCTION

Lumbar disc herniation surgery is a common procedure, but its success is significantly influenced by post-surgical complications, such as adhesion, fibrosis and scar formation (7,15). Among these complications, epidural fibrosis (EF) is a major concern because it can become a contributory factor to failed back surgery syndrome (1,6). Characterized by excessive fibrotic tissue formation around the dura mater, EF

may compress or put tension on nerve roots, leading to severe pain and functional impairment, often requiring revision surgeries (1,9,14,30). Therefore, developing effective strategies that could prevent EF remains a critical goal in spinal surgery.

The current EF prevention methods include refined surgical techniques—such as meticulous hemostasis, minimization of dural sac manipulation, avoidance of dead space formation, and preservation of epidural fat—as well as the use of bio-



materials and pharmacological agents (4,14). However, no pharmacological agent has been universally adopted in clinical practice (22). Recent studies emphasise the importance of understanding the underlying pathophysiology, particularly fibroblast proliferation, inflammation and haemostasis, to effectively prevent EF (4,14,22). In this context, pharmacological agents inhibiting fibroblast activity (migration) or those modulating inflammatory pathways have gained attention (12,30,32,35).

Tranexamic acid (TXA) and infliximab (INF) treatments represent two distinct pharmacological approaches to EF prevention: TXA acts primarily through haemostasis by stabilizing fibrin and reducing postoperative bleeding (8,10), whereas INF acts via immunosuppression by targeting tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) to suppress inflammation (11). Although both agents have shown potential in reducing fibrosis, no direct comparative study has ever evaluated their topical effects in preventing EF.

This study aims to compare the effectiveness of TXA and INF in reducing EF following laminectomy and to determine whether haemostasis or immunosuppression provides superior protection against postoperative fibrosis. The findings may contribute in the development of safer and more effective pharmacological strategies for EF prevention in spinal surgery patients.

## ■ MATERIAL and METHODS

### Ethical Statement

This study was approved by the Recep Tayip Erdogan University Local Ethics Committee for Animal Experiments (Decision No: 2016/41, 42; Date: 22.12.2016) and was conducted in compliance with the institution's ethical standards for animal research. All experimental procedures adhered to international, national and institutional guidelines for the care and use of laboratory animals. A copy of the ethics approval letter (2016/41, 42) is available upon reasonable request.

### Experimental Animals

A total of 21 male Sprague–Dawley rats aged 4–6 months and weighing 250–300 g were obtained from the university's Animal Care and Research Unit. The animals were reared in accordance with the guidelines outlined in the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health.

### Study Design

The rats were randomly assigned to three groups, namely, INF treatment group, TXA treatment group and control group, each group comprising seven rats.

The rats were maintained under controlled environmental conditions: a constant temperature of  $21^{\circ}\text{C} \pm 3^{\circ}\text{C}$  and a 12-hour light/dark cycle. Throughout the experimental period, the rats were fed ad libitum with standard pellet chow containing 21% crude protein (Purina) and were given free access to drinking water. The groups were homogeneous with respect to physiological characteristics. Monitored physiological parameters

included body weight, food and water intake, grooming activity, locomotion, and general physical condition.

### Experimental Procedures

The experiment was initiated under general anaesthesia induced via intramuscular administration of ketamine hydrochloride (25 mg/kg; Ketalar, Pfizer, Istanbul, Turkey) and xylazine (5 mg/kg; Rompun, Bayer, Istanbul, Turkey). The rats were placed in the prone position and had their backs shaved. The surgical site was subsequently sterilized with povidone-iodine (Batticon; Adeka Pharmaceuticals, Istanbul, Türkiye).

Midline skin incision and dorsal fascia dissection were performed from T12 to L4. The paravertebral muscles were bilaterally dissected over the laminae. A total laminectomy from L1 to L3 was performed using magnifying surgical loupes and fine, sharp-tipped instruments.

The surgical site was irrigated with sterile saline solution for 5 min to induce haemostasis. In cases where bleeding persisted beyond this period, the irrigation time was extended. No additional haemostatic agents or bipolar cautery was used in any of the groups. Macroscopic haemostasis was confirmed prior to TXA and INF administration.

To ensure both efficacy and safety, we administered TXA topically at a literature-supported dose suitable for small animal models such as rats (16). A 10–20 mg/mL TXA solution (Transamin<sup>®</sup>, Daiichi Sankyo Co., Ltd., Tokyo, Japan) was applied on the laminectomy site for 5 min using a soaked surgical pad.

As for INF, no experimental studies have ever investigated its use in the lumbar epidural area of rats. Thus, dosing was determined based on previous studies; the dose range applied in different experimental settings was 3–5 mg/kg (10,16). On this basis, a lower dose of approximately 1 mg/mL was applied on the laminectomy site for 5 mins using a soaked surgical pad (Remicade<sup>®</sup>, Janssen Biotech, Inc., Horsham, PA, USA) (26,42).

Following each treatment, the incision site was closed in layers. The subcutaneous tissue was sutured using 3/0 Ethicon-Vicryl, (Ethicon, Inc., Somerville, NJ, USA) Rapide with a minimum of two stitches, followed by skin closure with 3/0 Prolene sutures, ensuring anatomical integrity.

No wound complications or neurological deficits were observed in any of the rats postoperatively. The animals were provided with appropriate diet and were reared under standardised conditions for eight weeks. Then, they were sacrificed via cervical dislocation.

### Histopathological Analysis

Spinal cord tissue specimens were harvested and fixed in 10% neutral-buffered formalin (Sigma-Aldrich, St. Louis, MO, USA) for 48 hours prior to histological processing. Paraffin-embedded spinal cord sections 4–5  $\mu\text{m}$  in thickness were obtained using a rotary microtome (Leica RM2125RT, Germany). The sections were stained with haematoxylin and eosin (H&E) (Harris Haematoxylin, Merck, Germany; Eosin G, Merck, Germany) and Masson-Goldner's Trichrome stain

(Merck, Darmstadt, Germany) for histopathological evaluation. The samples were examined under a light microscope (Olympus BX51, Olympus Corporation, Tokyo, Japan), and high-resolution images were captured using an Olympus DP71 (Olympus Corporation, Tokyo, Japan) camera for further analysis.

### Semi-Quantitative Analysis

The histopathological changes observed in the samples were scored according to the EF scoring method described by He et al. (13,28) (Table I). This scoring system was independently applied by two blinded histopathologists (TM and LT), who evaluated 40 different areas in each sample (13,28).

**Table I:** Epidural Fibrosis Grading

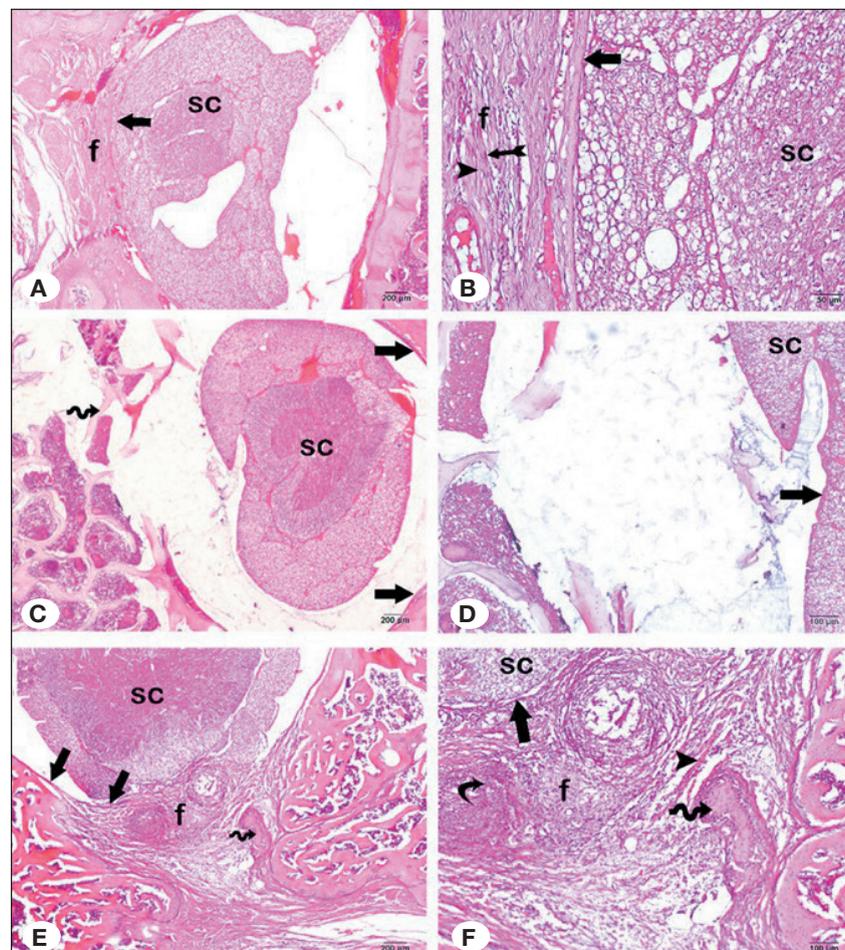
Grade	Amount of fibrosis	
Grade 0	No	Dura mater is free of scar tissue
Grade 1	Mild fibrosis without dural adherence	Thin fibrous bands between scar tissue and dura mater
Grade 2	Moderate fibrosis with partial dural adherence	Continuous adherence in less than two-thirds of the laminectomy defect
Grade 3	Dense fibrosis with complete adherence to dura	Widespread adherence of scar tissue affecting more than two-thirds of the laminectomy defect and/or adherence to nerve roots

### Statistical Analysis

Data were analyzed using SPSS version 18.0 (IBM Corp., Armonk, NY, USA). Non-normally distributed variables were expressed as median and interquartile range (IQR), along with minimum and maximum values. Between-group comparisons were performed using the Kruskal–Wallis test, followed by Tamhane's post-hoc test. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

In the control group, the spinal cord tissue sections exhibited EF that adheres to the underlying dura mater (epidural fibrosis grade median:  $2.00 \pm 0.54$ ; Figures 1A, B; Table I).



**Figure 1:** Representative photo micrographs of spinal cord tissue sections stained with Hematoxylin and Eosin. **A** ( $\times 40$ ), **B** ( $\times 20$ ): Sections from the control group showing epidural fibrosis (f) adhering to the underlying dura mater (arrow) (epidural fibrosis grade median:  $2.00 \pm 0.54$ ). **C** ( $\times 4$ ), **D** ( $\times 10$ ): Sections from the INF treatment group exhibiting epidural fibrosis (f), dura mater adherence (arrow) and inflammation (curved arrow). Osteoblastic activity and new bone formation were observed but to a lesser extent (spiral arrow) (epidural fibrosis grade median:  $3.00 \pm 0.35$ ). **E** ( $\times 4$ ), **F** ( $\times 10$ ): Sections from the TXA treatment group showing a thin fibrous band adhering to the underlying dura mater (arrow). Moreover, new bone formation was widespread compared with that in the control and INF treatment groups (epidural fibrosis grade median:  $0.50 \pm 0.53$ ).

In the INF treatment group, EF with dura mater adhesion and inflammation was observed. Additionally, osteoblastic activity and new bone formation were observed to a lesser extent (epidural fibrosis grade median:  $3.00 \pm 0.35$ ; Figures 1C, D; Table II).

In the TXA treatment group, a thin fibrous band adhering to the underlying dura mater was observed. Moreover, this group exhibited widespread formation of new bone tissue compared with the two other groups (epidural fibrosis grade median:  $0.50 \pm 0.53$ ; Figures 1E, F; Table II).

## DISCUSSION

### Fibrosis Formation in the Epidural Space

The formation of fibrosis in the epidural space, which is a common consequence of surgical procedures—particularly lumbar discectomy, laminectomy, foraminotomy, and spinal fusion—is closely linked to the wound healing process (30,32). In the skin, keloid formation results from fibroblast hyperproliferation and excessive accumulation of extra cellular matrix (ECM), particularly collagen types I (COL1) and III (COL3) (7,31). Similarly, during lumbar laminectomy, fibroblasts originating from paravertebral muscles and infiltrating blood cells contribute to ECM overproduction, leading to postoperative adhesion and potential complications (15,19,22,27,33,36).

### Factors Influencing EF Formation

Foreign materials such as glove powder and cotton fibres worsen inflammation in the epidural space, highlighting the need for thorough irrigation to reduce fibrosis (23,31). Meanwhile, excessive bipolar coagulation can lead to peripheral tissue carbonization, further increasing EF (21).

### Mechanisms of Fibrosis Prevention

The mechanism of EF prevention involves blocking fibroblast migration into the epidural space or suppressing inflammation by targeting fibrosis-promoting cytokines.

### Inhibition of Fibroblast Migration

The use of various materials, including fat grafts, gel foam, Silastic, Zenoderm and carboxymethylcellulose, have been explored for EF prevention (23,30,32). Despite the promising results in animal models, their widespread clinical application remains limited due to high cost, surgical feasibility and inconsistent outcomes.

**Table II:** Semi-Quantative Analysis Results (Median±Standart Deviation)

Group	Description	Epidural Fibrosis Grading Score
1	INF+LM	<b>3.00±0.35<sup>a</sup></b>
2	TXA+LM	<b>0.5±0.53<sup>b,c</sup></b>
3	Control	2.00±0.54

<sup>a</sup>*p*=0.007 versus to Control group, <sup>b</sup>*p*=0.00 versus to Control group, <sup>c</sup>*p*=0.00 versus to INF+LM group, Kruskal Wallis -Tamhane's T2 test.

Various physical barriers, such as polyethylene oxide, sodium hyaluronate and carboxymethylcellulose, have been used to limit fibroblast infiltration into the epidural space. Haemostasis, or bleeding control, can also be considered part of this strategy (8,29). However, not all haemostatic methods are equally effective. An experimental study on Ankaferd Blood Stopper, a haemostatic agent, showed that instead of reducing EF, it promoted erythrocyte aggregation by forming an encapsulated protein network, potentially contributing to fibrosis formation (3,41). However, the clinical application of haemostatic agents in EF prevention remains limited due to variability in efficacy, surgical feasibility, and cost constraints.

### Suppression of Fibrosis-Promoting Inflammatory Pathways

Pharmacological agents targeting pro-fibrotic cytokines, such as TNF- $\alpha$  and TGF- $\beta$ , have been investigated. Curcumin, known for its anti-inflammatory properties, has been investigated in two studies; etanercept has also been investigated in two experimental studies (7,18). Etanercept, a TNF- $\alpha$  inhibitor, reduces fibrosis by blocking pro-inflammatory cytokine activity at the site of injury (7,20). Given their potential for EF prevention, temozolomide—an immunosuppressive agent—has been evaluated in one study, tacrolimus in three studies, mitomycin-C—commonly used in ophthalmic surgery—in two studies and bevacizumab in one study (2,11,22,40). While TNF- $\alpha$  inhibitors such as INF and vascular endothelial growth factor inhibitors such as ranibizumab have shown promise in reducing fibrosis, their role in EF prevention remains underexplored (13,39).

### Effect of INF on EF

INF is a TNF- $\alpha$  inhibitor with anti-fibrotic and anti-angiogenic properties. INF limits fibrosis formation by reducing fibroblast activity, collagen production and neovascularisation (11). Experimental studies have demonstrated INF's efficacy in reducing fibrosis in ophthalmic and glaucoma surgeries (11,26). However, the potential of INF for EF prevention has not yet been evaluated. Our findings indicate that topical INF is safe, as no systemic adverse effects were observed over the eight-week treatment period. While INF did reduce fibrosis, its effect was inferior to that of TXA, suggesting that TNF- $\alpha$  inhibition alone may not be sufficient to control fibrosis and that haemostasis plays a more dominant role in wound healing (34,42).

### Effect of TXA on EF

Although TXA is widely used to induce haemostasis, its role in fibrosis prevention in various surgical procedures has been evaluated in eight studies only (3,5,23). A 2004 study investigated for the first time the effects of TXA on intra-peritoneal adhesion, whereas a 2021 study demonstrated reduced inflammation following knee arthroplasty (16,25,37,38). To date, only two studies have examined TXA's role in EF prevention. Haemostasis appears to play a crucial role in reducing EF, as shown in studies where surgical drains minimise fibrosis formation (9,24). This view is supported by studies showing the EF-reducing effects of various haemostatic agents in experimental models (3,17).

TXA inhibits fibrinolysis by preventing plasminogen activation, thereby reducing intraoperative bleeding and subsequent fibrosis formation (3,8,19). Erdogan et al. reported that topical TXA significantly reduced fibrosis, fibroblast density and inflammatory cell infiltration in a rat laminectomy model (9). Circi et al. found that systemic TXA alone and systemic TXA combined with topical TXA significantly lowered fibrosis and inflammation scores compared with the control (5). These findings reinforce the potential utility of TXA in EF prevention.

Additionally, while preventing EF, TXA does not inhibit new bone formation, which is particularly advantageous in spinal surgery. This characteristic ensures that TXA does not interfere with spinal fusion, a critical factor for successful postoperative outcomes. Unlike some immunosuppressive or anti-inflammatory agents, which may impair osteogenesis, TXA allows for optimal bone healing while minimising fibrotic adhesions, making it a promising adjunct treatment in spine surgery.

#### Study Duration and Methodological Considerations

The optimal duration for fibrosis evaluation varies; four weeks is the minimum period to observe fibrotic changes, whereas six to eight weeks are needed to assess mature fibrosis (17,23,26,30). Similar to a research investigating the use of haemostatic agents for EF prevention, our study employed an eight-week observation period (8).

To ensure an objective fibrosis assessment, we used histopathological grading as the primary method to evaluate fibrosis severity, fibroblast density and inflammatory cell in-

filtration. This approach allowed for a standardised and reliable comparison between the study groups. However, immunohistochemical staining was not performed in this study (14,34,38,40).

#### Comparison between TXA and INF in terms of EF Prevention

No prior studies have directly compared TXA and INF in terms of EF prevention. Our results indicate the superior efficacy of TXA in reducing EF compared with INF, suggesting that haemostasis plays a more critical role in spinal wound healing than immunosuppression alone. These findings highlight the importance of intraoperative haemostasis in minimising postoperative fibrosis and support TXA's potential clinical utility for EF prevention. Further studies are needed to validate these results, to optimise treatment strategies and to explore combination therapies for more effective fibrosis management (Table III).

INF inhibits osteoblast proliferation, leading to reduced bone formation and potential delays in bone healing. Given that TNF- $\alpha$  plays a key role in regulating osteoclast activity and bone turnover, its suppression can disrupt the natural balance of bone remodelling, impairing early bone regeneration. Additionally, long-term TNF- $\alpha$  blockade has been linked to decreased bone mineral density and slower bone regeneration, which may pose challenges in surgical settings where successful fusion and bone healing are critical (13).

**Table III:** This Table Compares Tranexamic Acid (TXA) and Infliximab (INF) in Terms of Mechanism, Effectiveness, and Clinical Applicability, Incorporating Our Experimental Findings

Feature	Tranexamic Acid (TXA)	Infliximab (INF)
Mechanism of Action	Inhibits fibrinolysis by preventing plasminogen activation	TNF- $\alpha$ inhibition, suppresses inflammatory pathways
Primary Effect	Hemostasis, reduces postoperative bleeding	Anti-inflammatory, immunosuppression
Route of Administration	Topical, Systemic (IV)	Topical, Systemic (IV)
Fibrosis Reduction Effectiveness	High – Reduces fibroblast proliferation and collagen deposition	Moderate – Reduces inflammation but less effective in fibrosis prevention
Histopathological Fibrosis Score (Experimental Findings)	<b>0.50 <math>\pm</math> 0.53</b> (Significantly lower fibrosis vs. INF & Control)	<b>3.00 <math>\pm</math> 0.35</b> (Moderate reduction but less effective than TXA)
Hemostatic Effect	Strong	None
Anti-inflammatory Effect	Moderate	Strong
New bone formation	Widespread new bone formation	New bone formation were observed to a lesser extent
Cost & Availability	Low cost, widely available	High cost, limited availability
Clinical Application Potential	High – Commonly used in various surgeries, potential for epidural fibrosis prevention	Moderate – Potential in fibrosis reduction but costly and less accessible
Potential Side Effects	Minimal, but risk of thrombosis with systemic use	Immunosuppression, increased infection risk

The strength of this study lies in the simultaneous evaluation of the therapeutic efficacy of TXA and INF. In previous studies, these molecules were analysed separately, and they have never been evaluated together in an experimental setting. Moreover, a histological assessment to compare the effect of an immunosuppressive agent and a haemostatic agent on fibrosis prevention has never been performed. Our study addresses this research gap by providing novel evidence on the potential efficacy of topical tranexamic acid (TXA) in preventing epidural fibrosis.

### Study Limitations and Future Directions

While our study provides valuable insights, certain limitations should be acknowledged. The sample size was limited, and future studies with larger cohorts are warranted to confirm and generalize our findings with greater statistical confidence. The doses used were based on prior studies, but dose–response studies could further optimise the efficacy of TXA and INF. While histopathology was our primary method, incorporating electron microscopy or immunohistochemistry to investigate TNF- $\alpha$ , TGF- $\beta$  or CD105 can provide deeper mechanistic insights.

Additionally, while an eight-week post-treatment follow-up period is adequate for fibrosis assessment, longer-term studies can evaluate the functional impact of fibrosis prevention strategies—such as reductions in neuropathic pain, improved nerve root mobility, or enhanced locomotor recovery—and assess potential late-onset complications, including chronic inflammation, delayed scar maturation, or recurrent adhesions.

### Clinical Relevance and Future Applications

Widely in haemostasis induction, TXA may serve as a cost-effective adjunct treatment in spine surgery once its anti-fibrotic effects have been confirmed. While INF shows potential in fibrosis reduction, its high cost limits its routine use. Future research should include larger sample size, investigate varied dosages and compare systemic and topical administration. Molecular analyses, including evaluation of TGF- $\beta$  and TNF- $\alpha$  expression, could clarify fibrosis mechanisms. Ultimately, randomised clinical studies are needed to validate TXA's role in preventing EF.

## CONCLUSION

This study is the first to compare TXA and INF treatments as strategies in EF prevention. The findings suggest that TXA significantly reduces EF more effectively than INF, indicating that haemostasis plays a dominant role in reducing postoperative fibrosis. TXA may have strong clinical potential as an adjunct treatment in spinal surgery for EF prevention. Further large-scale experimental and clinical trials are necessary to validate these findings, to optimise fibrosis prevention strategies and to explore novel treatment approaches for improving postlaminectomy outcomes.

## 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.

## AUTHORSHIP CONTRIBUTION

Study conception and design: VK

Data collection: TM, LT, VK

Analysis and interpretation of results: TM

Draft manuscript preparation: VK

Critical revision of the article: VK

Other (study supervision, fundings, materials, etc...): TM, LT

All authors (VK, TM, LT) reviewed the results and approved the final version of the manuscript.

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# Complications of Biportal Endoscopic Surgery for Lumbar Pathologies: Retrospective Analysis of 374 Cases

Mehmet Ilker OZER<sup>1</sup>, Oguz Kagan DEMIRTAS<sup>2</sup>, Goktug ULKU<sup>2</sup>, Mehmet Can EZGU<sup>3</sup>, Ilker SOLMAZ<sup>4</sup>

<sup>1</sup>Sincan Research and Training Hospital, Department of Neurosurgery, Ankara, Türkiye

<sup>2</sup>Ankara Etilik City Hospital, Department of Neurosurgery, Ankara, Türkiye

<sup>3</sup>Gülhane Research and Training Hospital, Department of Neurosurgery, Ankara, Türkiye

<sup>4</sup>Ankara Medicana Hospital, Department of Neurosurgery, Ankara, Türkiye

**Corresponding author:** Oguz Kagan DEMIRTAS ✉ okagandemirtas@gmail.com

## ABSTRACT

**AIM:** To evaluate the complications associated with Unilateral Biportal Endoscopy (UBE) in spinal surgery, highlighting the risks and outcomes of this minimally invasive approach.

**MATERIAL and METHODS:** A retrospective analysis was conducted on 374 patients who underwent UBE at three centers from 2022 to 2023. The study included cases of lumbar disc herniation, recurrent disc herniation, and lumbar stenosis. All procedures were performed by experienced surgeons, with a minimum postoperative follow-up of one year for each patient.

**RESULTS:** A total of 374 patients were included: 224 underwent UBE discectomy, 115 underwent UBE decompression for lumbar stenosis, and 35 underwent surgery for recurrent herniation. Overall, 178 patients (47.5%) were female and 196 (52.4%) were male. Complication rates differed across cohorts: 19 complications occurred in primary discectomy cases (8.4%), 12 in stenosis cases (10.4%), and 5 in recurrent cases (14.2%). The most common complications were dural tear (n=8), recurrence (n=7), and root injury (n=6). Less frequent events included retinal hemorrhage (n=2) and hydroperitoneum (n=1).

**CONCLUSION:** The findings suggest that while UBE is generally safe, it is associated with a notable complication rate, including dural tears and root injuries. Continuous efforts to refine surgical techniques and enhance training may further mitigate these risks, ensuring better patient outcomes.

**KEYWORDS:** Unilateral biportal endoscopic surgery, Lumbar disc herniation, Complication, Spinal stenosis, Dural tear, Neural injury

**ABBREVIATIONS:** ACS: Abdominal compartment syndrome, CSF: Cerebrospinal fluid, IAP: Inferior articular process, RF: Radiofrequency, SF: Saline fluid, SAP: Superior articular process, UBE: Unilateral biportal endoscopy

## INTRODUCTION

Minimally invasive approaches are becoming widespread in spinal surgery as in every surgical discipline. In spinal surgery, after Kambin described transforaminal monoportal endoscopic discectomy in 1986, De antoni et al described biportal endoscopic discectomy in 1996 (6,11). In this minimally invasive surgery performed through two separate skin incisions, the endoscope is insert-

ed through one portal while the working instruments are inserted through the other. While it has the advantages of no muscle stripping, small skin incisions, less infection and less bleeding with saline irrigation as in monoportal surgeries, it offers a wider range of motion, although not as much as in microsurgery, since the viewing and working ports are separate. In this way, we can define it as a hybrid surgery that takes the advantages of microsurgery and monoportal minimally inva-

Mehmet Ilker OZER : 0000-0001-5700-860X  
Oguz Kagan DEMIRTAS : 0000-0002-3913-5899

Goktug ULKU : 0000-0003-1430-2977  
Mehmet Can EZGU : 0000-0001-7537-0055

Ilker SOLMAZ : 0000-0002-1515-2264



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sive surgery (25). It may be an alternative to microsurgery, the gold standard defined by Yasargil (31).

While UBE surgery offers advantages in minimally invasive spine procedures, it is not without potential complications. The most commonly reported complications include dural tears, which can lead to CSF leakage and associated headaches, and epidural hemorrhages, which may necessitate further intervention if they compromise neural elements. Root injuries are another significant risk, potentially resulting in sensory or motor deficits. Infection, although infrequent, remains a concern, as does CSF fistula formation in cases involving dural injury. Insufficient decompression and residual instability may necessitate additional surgeries, particularly in cases of severe stenosis or instability-prone patients. Recurrence of pathology, such as herniated discs, can also lead to repeat procedures. Less common but serious complications include retinal hemorrhage, possibly due to intraoperative positional factors, and abdominal compartment syndrome, which may arise from prolonged prone positioning or high irrigation pressures. These risks underscore the importance of meticulous technique and preoperative planning to minimize the likelihood of adverse outcomes. In this study, we present the complications observed in patients who underwent surgery using the UBE method, along with their statistical incidence. The precautions taken to prevent postoperative complications were discussed in the accompaniment of the literature.

## ■ MATERIAL and METHODS

This observational study was conducted retrospectively using anonymized patient data, approved by Institutional Review Board with E1-23-3357 and carried out in accordance with the principles of the Declaration of Helsinki.

This was a retrospective study including patients who underwent unilateral biportal endoscopic (UBE) lumbar surgery between January 2022 and December 2023. A total of 406 patients were initially identified. Thirty-two patients were excluded due to loss to follow-up, leaving 374 patients for analysis. All patients were operated between January 2022 and December 2023, and their postoperative follow-up has continued from January 2024 to the present, ensuring that each included patient has achieved at least one year of follow-up.

Inclusion criteria were patients with symptomatic lumbar disc herniation (LDH), recurrent lumbar disc herniation, or lumbar spinal stenosis who were refractory to conservative management and underwent UBE surgery. Exclusion criteria included far lateral disc herniations and percutaneous posterior fusion cases, due to insufficient case numbers.

All surgeries were performed by senior spine surgeons, each of whom had at least five years of general spine surgery experience and had independently adopted UBE prior to the study period.

Follow-up protocol: Patients were routinely evaluated at postoperative day 10, postoperative month 1, and postoperative year 1, including clinical examination and MRI if recurrent symptoms were suspected.

## Surgical Technique

The procedure was performed using a 30°, 4 mm rigid arthroscope, 4 mm spherical burr (Stryker), 3.5 mm radiofrequency (RF) ablation probe (Stryker) and standard microdiscectomy (Kerrison, nerve hook, etc.). Under general anesthesia, in the prone position, C-arm fluoroscopy was used for distance determination and triangulation for the target level. In triangulation, a 5 mm transverse incision in the cranial pedicle (viewing portal) and a 9 mm transverse incision in the caudal pedicle (working portal) target the lower end-plate of the vertebra cranial to the pathologic distance. During both incisions, the scalpel is slightly tilted to coincide with the target end-plate. Both incisions are made approximately 0.5–1 cm laterally, closest to the median line. In left-sided surgeries for right-handed dominant surgeons, the trocar through the upper incision and dilators placed sequentially through the lower incision meet at the lower end of the target lamina. For right-sided pathologies, the surgeon positions themselves on the right side of the patient, planning the incision so that the imaging portal is oriented caudally. Alternatively, the imaging portal may be positioned cranially, allowing the surgeon to operate with their left hand. Room-temperature saline solutions were preferred for irrigation. This approach prevented hypothermia caused by excessively cold solutions and avoided increased bleeding associated with warm solutions. For gravity-assisted irrigation, sterile saline solution is suspended 50 cm above the patient's spine. If available, a pressure-controlled irrigation device may also be utilized from the hospital inventory. Automatic pumps were not available in any of the three centers where the study was conducted; therefore, pressure values were not monitored. However, in cases where an obstruction occurred in the saline outflow, irrigation was stopped until the outflow was restored, preventing epidural pressure from reaching dangerous levels. Once irrigation is initiated, anatomical landmarks, including the lamina, spinous process base, inferior articular process (IAP), and interlaminar ligamentum flavum are identified. The soft tissues overlying these structures, including the multifidus muscle, are removed using an RF probe and forceps. Based on the planned procedure, laminectomy and inferior and superior facetectomy are performed with the aid of a high-speed burr or Kerrison rongeur. Subsequently, flavectomy and, if necessary, discectomy are completed to finalize the procedure. In cases of narrow spinal canals, the base of the spinous process is drilled, and foraminotomy is achieved through contralateral facetectomy and sublaminar flavectomy. In recurrent cases, the IAP and superior articular process (SAP) of the target distance and scar tissue are dissected to reach the disc space and discectomy is performed.

## ■ RESULTS

A total of 374 patients were included, consisting of 178 females and 196 males. The mean age was 47.3 years (range, 18–75 years). Surgical indications included 224 lumbar disc herniations (59.9%), 115 lumbar stenosis cases (30.7%), and 35 recurrent disc herniations (9.3%).

Complications occurred in 36 patients (9.6%). The most frequent complications were dural tear (n=8, 2.1%), recurrent disc herniation (n=7, 1.9%), and root injury (n=6, 1.6%). Less common but unique to endoscopic irrigation were retinal hemorrhage (n=2, 0.5%) and hydroperitoneum/abdominal compartment syndrome (n=1, 0.3%). Other complications included infection (n=4, 1.1%), inadequate decompression (n=5, 1.3%), instability (n=2, 0.5%), and epidural hematoma (n=1, 0.3%). No cerebrospinal fluid (CSF) fistula was observed.

Learning curve analysis: While the incidence of dural tears and recurrences did not differ significantly between early and later cases (as UBE closely resembles microsurgical techniques once triangulation is completed), both retinal hemorrhage and abdominal compartment syndrome (ACS) occurred within the first 100 surgeries during the initial learning-curve period. No cases of ACS, blurred vision, or retinal complications were observed thereafter.

A detailed distribution of complications by procedure type is provided in Table I.

## ■ DISCUSSION

In our case series, the complication rates observed were consistent with those reported in the literature (5,7,20,21,27). Notably, our data included recurrent cases, a patient-specific risk factor. Based on these findings, we reviewed the complications encountered and the preventive measures implemented, supported by relevant literature. Additionally, we outlined strategies developed during the study to minimize complications, informed by our growing experience.

### Dural Tear

A total of 8 cases (2.1%) of dural tears were observed in our series. Of these, 2 occurred during endoscopic lumbar discectomy, 5 during biportal endoscopic lumbar spinal stenosis surgery, and 1 during biportal endoscopic revision surgery. Dural tears are a particularly common complication in spinal

stenosis surgery, with a reported incidence of 8.6% in the literature (1,27). Notably, 5 of the 8 dural tears (62.5%) occurred during spinal stenosis procedures. The literature has reported that dural tears are observed during the use of osteotomes, curettes, Kerrison punches for decompression, burr devices during contralateral decompression, and pituitary forceps for epidural fat excision (27). In our series, all dural tears occurred during the use of the Kerrison punch, which may be related to its preference over other instruments such as burr, curette, or forceps during decompression. Considering the risk of dural injury increases in cases of severe stenosis where adhesions between the dura and ligamentum flavum or the presence of the dorsal meningovertebral ligament, one way to reduce the incidence of this complication is to ensure that neural structures are not inadvertently excised along with the tissue being decompressed (epidural fat, ligamentum flavum) when using the Kerrison rongeur. Another preventive measure could be to avoid using Kerrison punches that have lost their sharpness, as deformed punches that tear rather than cleanly cut the flavum can increase the risk of dural tears. Dural tears resulting from burr or osteotome use are typically not large. Moreover, due to the minimal muscle, fascia, and skin defects in biportal endoscopic spinal surgery, cerebrospinal fluid (CSF) fistulas are uncommon, as none of the patients with dural tears in this study developed a CSF fistula. Fibrin sealant patches were not applied in any of the tear cases. In a study by Park et al., dural tears smaller than 4 mm in patients operated on using the biportal endoscopic technique were managed conservatively, while tears between 4 and 12 mm were treated with fibrin sealant patches, and for tears larger than 12 mm, endoscopic or microscopic primary suturing was recommended (27). Similarly, in the study by Ozer et al., an approximately 8 mm durotomy in a patient with tethered cord syndrome operated on using the biportal endoscopic approach was successfully managed conservatively without fibrin sealant or primary suturing, with no CSF fistula or pseudomeningocele reported (26). Conservative management may include close neurological monitoring and 24-hour immobilization bed rest. In cases

**Table I:** Complications of Unilateral Biportal Endoscopic Surgery (UBE)

	Discectomy	Spinal Stenosis	Recurrent Surgery	Total
<b>Operation Count, n</b>	224	115	35	374
<b>Complicated Case Count, n (%)</b>	19 (8.4)	12 (10.4)	5 (14.2)	36 (9.6)
Dural Tear, n	2	5	1	8
Epidural Hemorrhage, n	-	1	-	1
Root Injury, n	3	1	2	6
Infection, n	3	-	1	4
CSF Fistula, n	-	-	-	-
Insufficient decompression, n	2	3	-	5
Instability, n	-	1	1	2
Recurrence, n	7	-	-	7
Retinal hemorrhage, n	2	-	-	2
Abdominal Compartment Syndrome, n	-	1	-	1

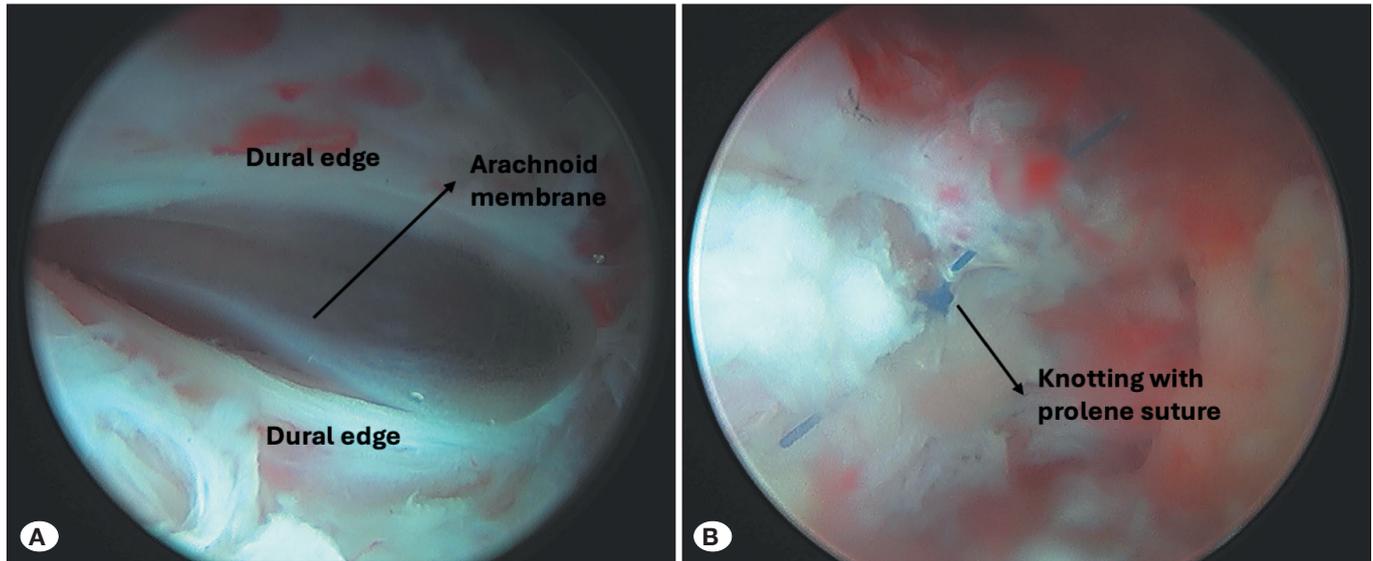
**CSF:** Cerebrospinal fluid, **UBE:** Unilateral biportal endoscopic surgery

where pseudomeningocele is likely to develop, endoscopic or microscopic dural repair can be performed (Figure 1).

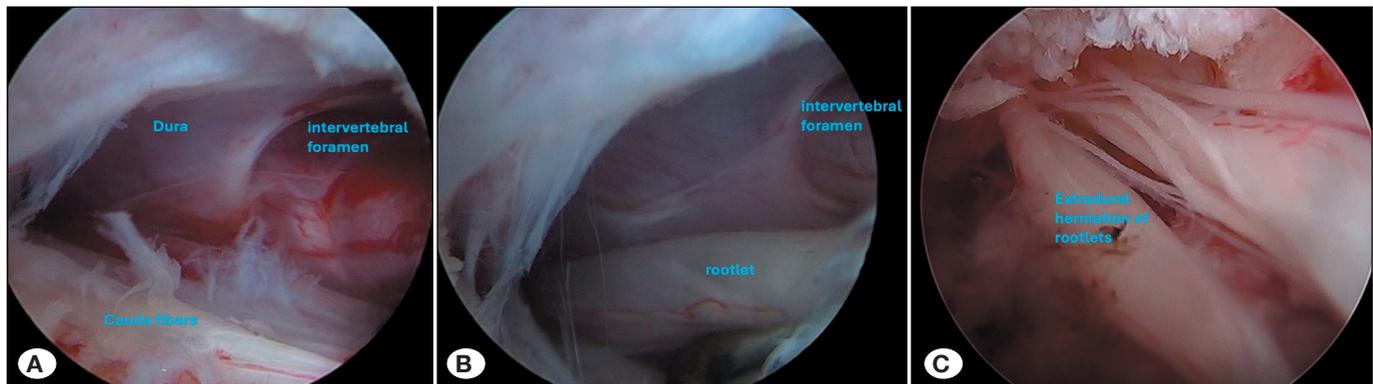
**Epidural Hemorrhage**

In this study, a hematoma that could lead to postoperative neurological deficits following decompressive surgery for lumbar spinal stenosis was observed in only 1 (0.3%) case. According to Sokolowski et al., radiological epidural hemorrhage occurs in approximately 58% of patients undergoing lumbar decompression surgery (29). However, a very small percentage of this population (0.02% to 4.6%) develops symptomatic hematomas, which may necessitate additional surgical intervention (2,29). In a study by Kim et al., of 310 patients treated via biportal endoscopic surgery, 23% had radiologically observed epidural hemorrhage (14). Although this incidence is relatively low compared to microscopic surgery, 56 patients required a thrombin-containing hemostatic agent (FloSeal [Baxter International Inc., Deerfield, Illinois, USA]). Additionally,

a drain was placed in each patient and was removed after 1 or 2 days. Female sex, older age (>70 years), preoperative anticoagulation therapy, and the use of an intraoperative water infusion pump were identified as the primary risk factors for hemorrhage in their study (14). Consistent with the literature, in our practice, we used a drain for 12 hours in elderly patients on anticoagulation/antiplatelet therapy. Water infusion pumps and thrombin-based hemostatic agents were not utilized. We suggest that the use of drains in elderly patients with a tendency for bleeding and significant intraoperative hemorrhage may prevent this complication. In cases where the epidural hematoma resulted in deficits, hematoma evacuation was performed using the biportal endoscopic technique. We believe that early intervention in cases presenting neurological deficits (such as cauda equina syndrome or mild neurological deterioration) may prevent irreversible deficits. The literature also suggests that mild symptoms may resolve due to spontaneous hematoma resorption by the third postoperative week (9).



**Figure 1:** Dural tear. **A)** Example of a case with a dural tear. **B)** Image of the closed tear after suturing.



**Figure 2:** Root Injury Example. **A)** Image of the intrathecal area after neural injury, showing cauda equina fibers and the view of the intervertebral foramen from within the dura. **B)** The rootlet seen intradurally, entering the intervertebral foramen. **C)** In a recurrent case, herniation of the rootlets into the extradural space is observed during fragmentectomy.

### Nerve Root Injury

A total of 6 cases (1.6%) were observed. The distribution included 3 cases in endoscopic lumbar discectomy, 1 case in biportal endoscopic lumbar spinal stenosis surgery, and 2 cases in biportal endoscopic revision surgery (Figure 2). According to the literature, the primary cause of root injuries is often thermal damage due to the use of radiofrequency (RF) devices (21). Cauterization of epidural veins/arteries, particularly those coursing toward the foramen, can be challenging, and controlling bleeding in these areas may pose significant risks. In lumbar decompression for spinal stenosis, high-speed motor or osteotome usage may contribute to such injuries. In revision cases, root injuries may also occur due to adhesions that form, especially when scar tissue or disc material is excised using pituitary forceps. Minimizing RF power and using it for short durations can reduce the frequency of these injuries (20). In decompression for spinal stenosis, performing a laminectomy/foraminotomy prior to flavectomy and using the ligamentum flavum as a protective barrier is a prudent approach. In revision cases, dissection should proceed by carefully isolating the superior articular process from epidural fibrosis; if necessary, access to the disc space can then be achieved by partially excising the superior articular process laterally to the root. This approach reduces the risk of accidental root injury due to loss of orientation or inadvertent compression with pituitary forceps. Since disc material may be adherent, attempting discectomy with large pituitary forceps in a single pass should be avoided. Instead, extruded or sequestered fragments should be gently mobilized using a nerve hook or smaller forceps to ensure neural structures are not inadvertently engaged. Controlled removal of the disc material in this way lowers the risk associated with discectomy in complex cases.

### Infection

Four cases (1.1%) were detected, three of which occurred during endoscopic lumbar discectomy and one during biportal endoscopic revision surgery (Figure 3). While saline irrigation can reduce the risk of infection, the literature reports an incidence rate of 0.1% to 4.5% (10,18). Although our series reflects a rate consistent with the literature, we believe that the risk could dramatically decrease in cases without significant comorbidities such as diabetes mellitus and immunodeficiency with proper antisepsis. We advocate for the use of a gas plasma sterilization system (low-temperature sterilization of plastic and electrical instruments) instead of rapid disinfection methods like ortho-phthalaldehyde. If a paravertebral abscess or diskitis occurs, disc needle biopsy by fluoroscopy may be necessary to sample the pathogen if it has not fistulized to the skin. If conservative treatments are insufficient, surgical intervention for debridement may be required (10).

### Insufficient Decompression

There were 5 cases (1.3%) of insufficient decompression observed, with 2 cases in endoscopic lumbar discectomy and 3 cases in biportal endoscopic lumbar spinal stenosis surgery. In the literature, overlooked migrated fragments in cases of disc herniation and insufficient decompression in cases with

severe stenosis are reported, especially during the initial stages of a surgeon's learning curve (5,10,20). In inferiorly migrated disc fragments, residual fragments may remain if they do not come out in a single piece. The wide range of motion in UBE, unlike monoportal techniques, allows for a more aggressive residual check (25). Increasing decompression and using a nerve hook through the axilla to search for inferiorly migrated fragments may be beneficial; however, manipulating the axilla often leads to bleeding, and this approach is not always feasible due to the risk of root or dural injury. In spinal stenosis surgeries, insufficient resection of the proximal and contralateral ligamentum flavum is typically reported (5). The use of a foraminal Kerrison rongeur or an angled curette can facilitate a more effective flavectomy. For the contralateral side, drilling the base of the spinous process may allow better access for instruments and the endoscope. For adequate foraminal decompression, the medial wall of the bilateral pedicles should be visualized. The return of dural pulsation should be checked to ensure sufficient decompression (20). Additionally, blurred vision is a major cause of incomplete decompression. Maintaining systolic blood pressure below 100 mmHg and applying bone wax and Gelfoam® (absorbable gelatin sponge, USP) can help prevent the "red screen" effect on the endoscope.

### Instability

A total of 2 cases (0.5%) of instability were observed, with one occurring during biportal endoscopic lumbar spinal stenosis surgery and the other during biportal endoscopic revision surgery. Biomechanical studies suggest that laminectomies compromising more than 50% of the pars interarticularis increase the risk of iatrogenic instability (20). Excessive drilling of the inferior articular process and extensive laminectomy are



**Figure 3:** Contrast-enhanced T1 MRI of a patient who developed an infection after UBE surgery.

known risk factors for this complication. Although minimally invasive surgeries reduce these risks, they do not entirely eliminate them. In the study by Kim et al., iatrogenic instability occurred in 0.6% of patients following UBE surgery, significantly lower than in microsurgery (reported between 3.96% and 9.5%) due to the lack of muscle dissection and the preservation of facet joints (16). In this study, complication rates were consistent with the literature. To mitigate the risk of iatrogenic instability, the use of a 30-degree endoscope and a foraminal Kerrison rongeur or curved curette to minimize the extent of laminectomy may be beneficial, along with partial resection of the superior articular process without compromising the integrity of the inferior articular process where feasible.

### Recurrence

A total of 7 cases (1.9%) of recurrence were observed, all occurring during endoscopic lumbar discectomy. Despite the high success rate of surgical treatment for lumbar disc herniation (LDH), recurrence may still occur in 15-25% of cases (12). Reoperation is indicated in approximately 62% of recurrent disc herniations (12). Recurrent lumbar disc herniation (RLDH) is defined as the recurrence of herniation at the same level and on the same side following a pain-free interval of at least six months post-surgery (10). This condition should be distinguished from residual or insufficient decompression. RLDH is often associated with aging, improper lifting techniques, and risk factors including male gender, obesity (BMI  $\geq 25$  kg/m<sup>2</sup>), advanced age ( $\geq 50$  years), trauma history, and central disc herniation (10). Additionally, for minimally invasive procedures, surgeon inexperience poses an added risk factor for recurrence. Surgeon-related factors, such as insufficient decompression, large posterior longitudinal ligament defects, excessive laminectomy or facetectomy, and extensive muscle dissection, can also contribute to recurrence. Postoperative guidelines, including lumbar muscle exercises, avoidance of heavy lifting, and maintaining proper posture, are crucial for reducing the risk of LDH recurrence. The recurrence rate in our study was relatively low (1.9%). This outcome may be influenced by the shorter follow-up period inherent in studies of UBE, a relatively novel surgical technique. It is anticipated that with longer follow-up durations, such as 5 or 10 years, the recurrence rate could increase, potentially aligning more closely with rates reported in the literature for other established techniques.

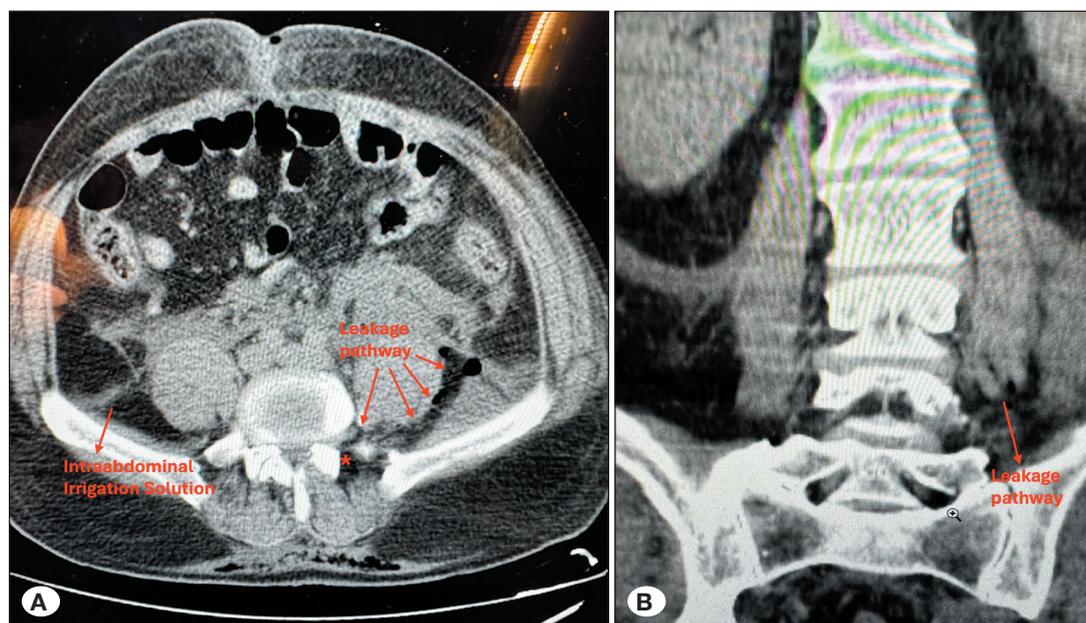
### Retinal Hemorrhage

Retinal hemorrhage was observed in 2 cases (0.5%) of endoscopic lumbar discectomy. If irrigation solution pressure becomes too high during UBE, complications including headache, neck pain, blurred vision, delirium, and drowsiness may arise as a result of increased intracranial pressure (IICP) (20). In rare cases, excessive CSF pressure can lead to retinal hemorrhage. Elevated CSF pressure can directly affect retinal veins through the optic nerve sheaths or indirectly via the surrounding subarachnoid space (19). This increase in CSF pressure can also reduce cerebral blood flow, triggering a reflexive rise in ophthalmic artery pressure, which may cause rupture of small blood vessels and venous collapse. Lee et al. highlight how elevated CSF pressure can impact ocular health

(19). Although automatic pumps were not available, irrigation was standardized across all centers by suspending the saline bag 50–70 cm above the patient, which as recommended in the literature maintains epidural irrigation pressure below approximately 30 mmHg according to hydrostatic principles (4,13,15). If water outflow is insufficient, enlarging the fascia incision or creating a crosscut incision may help (15). In this study, two cases of transient vision loss occurred during the learning curve (first 100 cases), with one patient treated by laser photocoagulation and the other managed conservatively. In addition to recommendations from the literature, 10 mg of intravenous rocuronium was administered every 30 minutes to keep muscles relaxed, helping prevent fascia shrinkage and ensuring the temporary pathway through muscle remains open. No IICP symptoms (e.g., neck pain, blurred vision) were observed in cases where adequate water outflow was maintained through fascia incisions and muscle relaxants. Soliman noted that prolonged surgeries increase this risk and suggested preventing IICP by turning off irrigation and pausing for 2-3 minutes every hour (30). When signs of elevated intracranial pressure, such as increased blood pressure and decreased heart rate, appear during surgery, it is essential to ensure optimal water outflow, aspirate excess fluid, and pause briefly.

### Abdominal Compartment Syndrome (ACS)

This rare complication was observed in 1 case (0.3%) during biportal endoscopic lumbar canal surgery. Although ACS is seldom reported, it has been documented in patients operated on through transforaminal monoportal or biportal endoscopic approaches (23,28). Abnormally elevated intra-abdominal pressure can lead to ACS, presenting with dyspnea and lower extremity circulation disturbances, such as cyanosis and cool extremities (17). In this case, poor triangulation led to drilling at the transverse process instead of the lamina, injuring the musculotendinous tissue between the transverse processes rather than the multifidus muscles. Upon realizing the facet joint was not lateral to the lamina, triangulation was corrected with fluoroscopy before decompression began. While water outflow was not entirely obstructed, it was inadequate. At 45 minutes into the procedure, the anesthesiologist noted increased airway pressure, reduced tidal volume, and hypotension. When the drapes were removed post-surgery, the lower extremities appeared cyanotic and cool, and the abdomen was distended. The patient was then repositioned supine, and abdominal distension was confirmed. General surgery consultation was obtained, and an abdominal ultrasound revealed fluid collection; laparoscopic exploration was performed, evacuating approximately 4 liters of irrigation solution from the abdomen (Figure 4). No retroperitoneal organ damage was identified. Upon reduction of intra-abdominal pressure, the patient's extremity circulation and dyspnea markedly improved. After one day of ICU monitoring, with no major issues detected, the patient was discharged on postoperative day three. The main signs of ACS include oliguria or anuria, reduced cardiac output, decreased renal perfusion, and impaired lower extremity circulation due to high airway pressure (3,22). Dyspnea may be an early clinical indication (8). Delayed ACS diagnosis and treatment can significantly raise morbidity and mortality risks, potentially leading to multiorgan failure or death (23,24). To



**Figure 4:** **A)** Axial computed tomography (CT) scan of abdominal compartment syndrome. The figure confirms the escape route of the solution into the retroperitoneal space due to drilling of the left L4 transverse process, as seen on abdominal CT after the procedure. **B)** Coronal CT reconstruction of the same patient. Asterisk demonstrates inadvertent drilling of the transverse process (**A**).

prevent such complications, surgeons should confirm triangulation with lateral and anteroposterior radiographs if orientation is uncertain. Additionally, measuring outflow fluid can alert the surgeon to any discrepancy between input and output, indicating possible intra-abdominal fluid leakage.

The primary limitation of our study is the relatively short follow-up period, which may limit the assessment of long-term outcomes. Nonetheless, the study's strength lies in its large patient population, making it one of the highest-volume studies in the literature for this technique. This extensive dataset offers valuable insights into early postoperative outcomes and procedural safety.

Another important limitation of this study is the lack of automated pressure-controlled irrigation systems across all three centers. The absence of precise manometric monitoring may still represent a methodological weakness and could have contributed to pressure-related complications. Future studies incorporating continuous pressure measurement are warranted.

## CONCLUSION

In UBE, common complications seen in microsurgery, such as dural tears, root injuries, and epidural hematomas, are also encountered. However, unique complications associated with irrigation solutions, including abdominal compartment syndrome, retinal hemorrhage, and increased intracranial pressure, have also been observed. As surgical experience grows and these experiences are documented with preventive measures shared, complication rates are expected to decrease, making the method safer. Ensuring optimal water outflow, achieving precise triangulation and orientation, and controlling

epidural bleeding to maintain a clear view are techniques that can significantly prevent most potential complications.

## 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.

## AUTHORSHIP CONTRIBUTION

Study conception and design: MIO, OKD

Data collection: GU, MCE

Analysis and interpretation of results: MIO, IS

Draft manuscript preparation: MIO, OKD

Critical revision of the article: MIO, IS, GU, MCE, OKD

Other (study supervision, fundings, materials, etc.): MIO, OKD

All authors (MIO, OKD, GU, MCE, IS) reviewed the results and approved the final version of the manuscript.

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# Finite Element Analysis of Mechanical Stress Distribution in Titanium and PEEK Rod Constructs for Isthmic L5–S1 Spondylolisthesis

Idris AVCI<sup>1</sup>, Ahmed Yasin YAVUZ<sup>2</sup>, Ahmet Atilla ABDIOGLU<sup>3</sup>, Kemal PAKSOY<sup>4</sup>

<sup>1</sup>Uskudar University NP Istanbul Brain Hospital, Department of Neurosurgery, Istanbul, Türkiye

<sup>2</sup>Medicana Zincirlikuyu Hospital, Department of Neurosurgery, Istanbul, Türkiye

<sup>3</sup>Fatih State Hospital, Department of Orthopaedics and Traumatology, Trabzon, Türkiye

<sup>4</sup>Uskudar University NP Istanbul Brain Hospital, Department of Neurosurgery, Istanbul, Türkiye

Corresponding author: Idris AVCI ✉ dr.idrisavci@gmail.com

## ABSTRACT

**AIM:** To compare the biomechanical behavior of titanium and polyetheretherketone (PEEK) rods using finite element analysis (FEA) in a Grade I L5-S1 isthmic spondylolisthesis model.

**MATERIAL and METHODS:** An anatomically accurate 3D finite element model of the L3–S1 spine was created from CT data of a healthy 30-year-old male. A unilateral pars defect at L5 simulated Grade I spondylolisthesis. Instrumented models with titanium and PEEK rods were subjected to five physiological loading conditions. Von Mises stresses and displacement vectors were analyzed and stress distributions on bone, screws and rods were measured.

**RESULTS:** Titanium rods absorbed significantly higher loads across all loading conditions (e.g., 117 N vs. 34.5 N in compression;  $p < 0.01$ ), while PEEK constructs allowed greater load sharing with the bone. Screws in titanium systems experienced higher stresses, particularly in posterior shear and axial rotation. Both materials effectively reduced stress at the pars defect.

**CONCLUSION:** Titanium constructs offer high rigidity but concentrate stress on implants, potentially increasing complication risk. PEEK rods demonstrated a more physiological load distribution, reducing implant stress without compromising stability. PEEK rods may serve as a biomechanically advantageous alternative to titanium in select spondylolisthesis cases. Further clinical validation is warranted.

**KEYWORDS:** Spondylolisthesis, Finite element analysis (FEA), Titanium rods, PEEK rods

**ABBREVIATIONS:** **3D:** Three-dimensional, **ASD:** Adjacent segment disease, **CT:** Computed tomography, **DICOM:** Digital imaging and communications in medicine, **FE:** Finite element, **FEA:** Finite element analysis, **N:** Newton, **PEEK:** Polyetheretherketone, **SPSS:** Statistical package for the social sciences, **TLIF:** Transforaminal lumbar interbody fusion,  **$\sigma$ :** Normal stress,  **$\sigma_1, \sigma_2, \sigma_3$ :** Principal stresses (maximum, intermediate, minimum),  **$\tau$ :** Shear stress

Idris AVCI : 0000-0002-0378-9356  
Ahmed Yasin YAVUZ : 0000-0001-9359-0270

Ahmet Atilla ABDIOGLU : 0000-0002-0206-8135  
Kemal PAKSOY : 0000-0002-7677-7356

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## INTRODUCTION

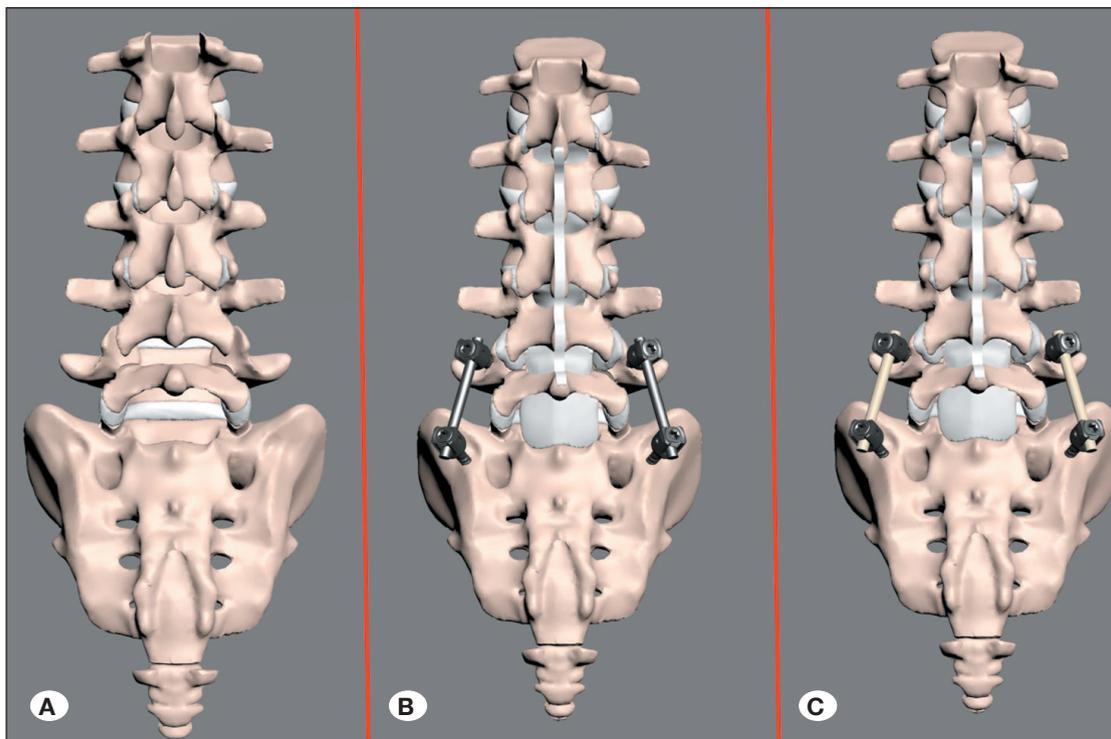
Spondylolisthesis is defined as the anterior displacement of one vertebra relative to the adjacent one, most frequently occurring at the L5-S1 level. The Wiltse classification categorizes spondylolisthesis into five etiological types: dysplastic (congenital), isthmic, degenerative, traumatic (13). Also, Meyerding developed a five-grade system used to quantify the degree of anterior vertebral slippage in spondylolisthesis, with Grade I representing 0–25% slip and Grade V indicating complete subluxation (4). In patients where the slippage progresses, when the symptoms persist, or neurological deficits occur, surgery is indicated. Posterior lumbar pedicle screw and rod fixation is the standard surgical approach aimed at stabilizing the motion segment and promoting arthrodesis (8). Titanium alloy rods have preferably been seen as the gold standard in posterior instrumentation surgery due to their high tensile strength, corrosion resistance, and biocompatibility. However, stabilizing the spine with titanium rod constructs may interfere with physiological load transmission, potentially leading to reduced mechanical stimulation of bone grafts, impaired fusion, and an increased risk of adjacent segment disease. Furthermore, it may exacerbate implant-related complications such as screw loosening or rod fractures (7). Because of this, alternative biomaterials with more favorable elastic properties have been developed, like polyetheretherketone (PEEK), which is a thermoplastic polymer increasingly used for spinal stabilization surgery, allowing a more physiological distribution of mechanical loads (14). Despite growing interest in PEEK as a rod material, evidence for its efficacy in spondylolisthesis is limited.

In this study, we developed a detailed three-dimensional FE model of the lumbosacral spine to compare the biomechanical behavior of PEEK and titanium rod constructs in the setting of Grade I L5-S1 spondylolisthesis. The findings may contribute to informed decision-making in implant selection for optimizing clinical outcomes in spondylolisthesis surgery.

## MATERIAL and METHODS

This finite element analysis (FEA) was performed at Gzm Teknoloji Tasarım San. ve Tic. Ltd. Şti. (Istanbul, Turkey) to evaluate mechanical behavior in the lumbar spine under instrumented and non-instrumented conditions. The model was based on a 30-year-old male volunteer with no history of spinal trauma, tumor, infection, or fractures. Lumbar imaging (L3–S1) was acquired using a 256-slice computed tomography (CT) scanner with 1 mm slice thickness (Siemens Healthineers AG, Erlangen, Germany). The DICOM-format data were used to construct a high-fidelity anatomical model for finite element simulation.

A three-dimensional (3D) mesh of the lumbar spine was created using Blender 4.2 (Blender Foundation, Amsterdam, Netherlands) and further refined in SolidWorks (Dassault Systèmes, Vélizy-Villacoublay, France). These tools enabled segmentation and reconstruction of vertebral bodies, intervertebral discs, and posterior elements. To simulate a Meyerding Grade I spondylolisthesis caused by a unilateral pars defect, the left pars interarticularis of L5 was virtually removed, and L5 was translated 20% anteriorly over S1. This created a biomechanically realistic model of spondylolytic instability at the L5-S1 junction (Figure 1).



**Figure 1:** Three dimensional (3D) model of the lumbosacral area. **A)** Without instrumentation, **B)** with titanium rods, and **C)** with PEEK rods.

The models were exported in .obj format and imported into 3DEXPERIENCE SIMULIA (*Dassault Systèmes, Vélizy-Villacoublay, France*) for meshing and mechanical analysis. SIMULIA supports advanced FE simulation and was used to define contact interfaces, apply loads, and solve for mechanical stresses and displacements. All solid components, including cortical and cancellous bone, intervertebral discs, and implants, were treated as linear, homogeneous, isotropic materials, consistent with accepted practices in spine FEA. Material properties such as Young's modulus, Poisson's ratio, density, and tensile strength were assigned based on validated literature data.

Mesh convergence testing was performed to ensure accurate and stable results. Finer mesh densities were applied in regions of interest (e.g., screw entry points, rod-bone interfaces, and the pars interarticularis defect).

The final mesh consisted of:

- *Control (non-instrumented) model*: 2,454,046 elements and 598,057 nodes
- *Instrumented model (pedicle screws and rods)*: 5,315,855 elements and 1,271,869 nodes

Physiological loading conditions, including vertical compression, anterior-posterior shear, lateral bending, and axial rotation, were simulated by applying distributed forces to nodal points on the superior endplate of L3. The inferior surface of S1 was fully constrained in all degrees of freedom to anchor the model and replicate in vivo boundary conditions. Bonded (rigid) contact definitions were used at screw-rod and screw-bone interfaces to mimic rigid fixation. All materials were modeled as linear, homogeneous, and isotropic to simplify computational complexity and ensure mesh convergence across loading scenarios. While this approach does not capture the anisotropic or nonlinear characteristics of biological tissues—particularly the fiber-reinforced nature of the annulus fibrosus and the differentiation between cortical and cancellous bone—it is consistent with several validated spine models in the literature (10,11).

Ligaments and facet joint articulations were not included in this model. While these structures are important for spinal load-sharing and kinematic behavior, their exclusion was based on the primary focus of this study—comparative analysis of mechanical stress distribution within instrumentation constructs (PEEK vs. titanium rods) under standardized conditions. Excluding these anatomical features also reduced model complexity and allowed more precise isolation of implant-specific biomechanical effects. This modeling approach has been used in previous validated finite element studies examining posterior instrumentation systems (9). These simplifications allow for comparative analysis of stress distribution across instrumentation constructs, which was the primary objective of this study. Nevertheless, we acknowledge that such assumptions may affect absolute stress magnitudes, especially under complex loading conditions such as axial rotation or shear.

The software computed multiple stress parameters:

- **Normal stresses ( $\sigma$ )**: Represent tensile (positive) and compressive (negative) forces along anatomical axes.
- **Shear stresses ( $\tau$ )**: Represent tangential sliding forces within the material structure.
- **Principal stresses ( $\sigma_1, \sigma_2, \sigma_3$ )**: Quantify the maximum, intermediate, and minimum normal stresses in the element, with  $\sigma_1$  representing peak tensile and  $\sigma_3$  peak compressive stress.
- **Von Mises stress**: A critical measure for identifying the likelihood of yield in ductile materials like titanium; widely used to predict mechanical failure under complex multiaxial loading.
- **Displacement vectors (X, Y, Z)**: Indicate deformation magnitudes in three anatomical planes under load.

This FE model provided a detailed simulation of biomechanical responses in both instrumented and non-instrumented spondylolytic spines. Importantly, it enabled quantitative comparisons of stress distribution on rods, screws, vertebral bodies, and the pars defect under identical loading conditions, offering critical insights into how implant material and construct design affect spinal stability and the potential for mechanical failure.

This study is a computer-based finite element analysis and does not involve any experimental intervention on human participants or animals. The three-dimensional lumbar spine model used in this study was reconstructed from anonymized computed tomography (CT) imaging data solely for the purpose of anatomical modeling and biomechanical simulation. No identifiable patient information, clinical data, or treatment outcomes were used.

Since the study consisted exclusively of computational modeling and simulation, it does not meet the definition of human subject research. Therefore, ethics committee approval was not required.

## ■ RESULTS

The FEA evaluated mechanical load distributions in titanium and PEEK rod constructs at the L5-S1 segment under five physiologic loading conditions: vertical compression, anterior shear, posterior shear, lateral bending, and axial rotation. Load contributions were quantified separately for rods and screws (Figures 2–4).

### Rods

The mechanical properties of the titanium and PEEK rods used in the simulation were based on the properties of the implants from *Osimplant Spinal Restoration Technologies (Istanbul, Turkey)*. Titanium alloy (Ti-6Al-4V) was modeled with an elastic (Young's) modulus of 110 GPa, Poisson's ratio of 0.30, and density of 4.43 g/cm<sup>3</sup>. PEEK was modeled with a Young's modulus of 3.6 GPa, Poisson's ratio of 0.36, and density of 1.32 g/cm<sup>3</sup>. Both materials were assumed to be linear, homogeneous, and isotropic.

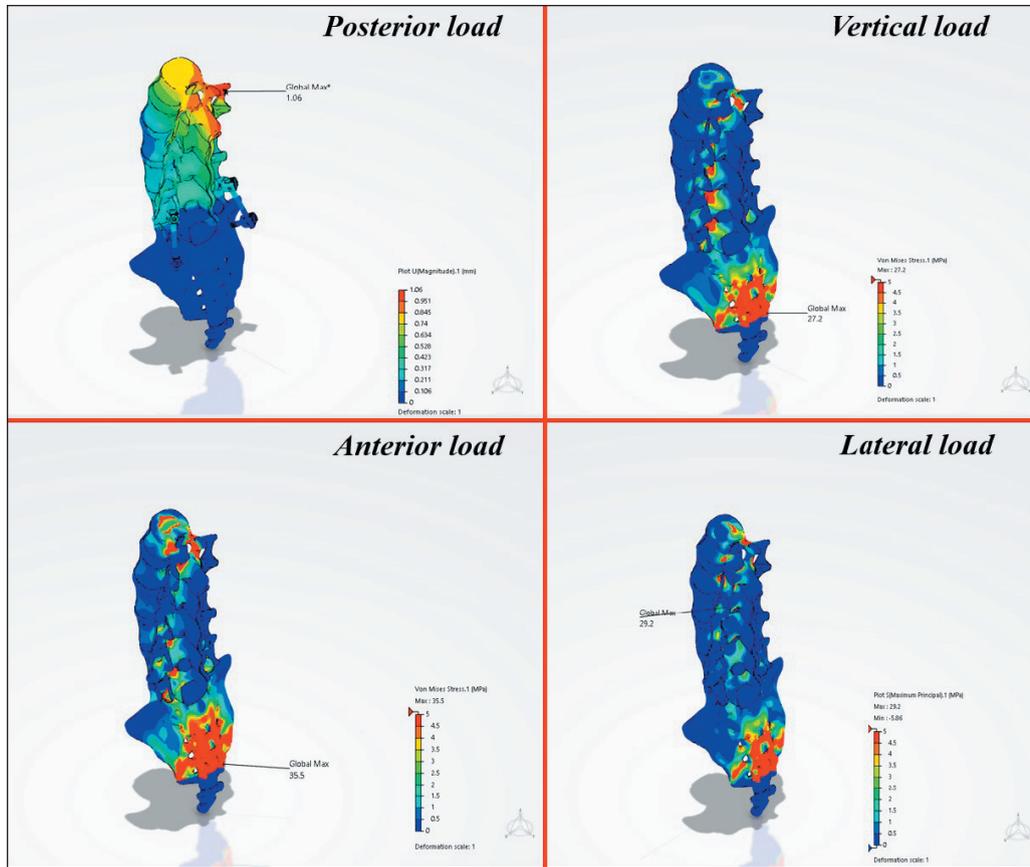


Figure 2: Stress contribution under several loading conditions of the lumbosacral area without instrumentation (control group).

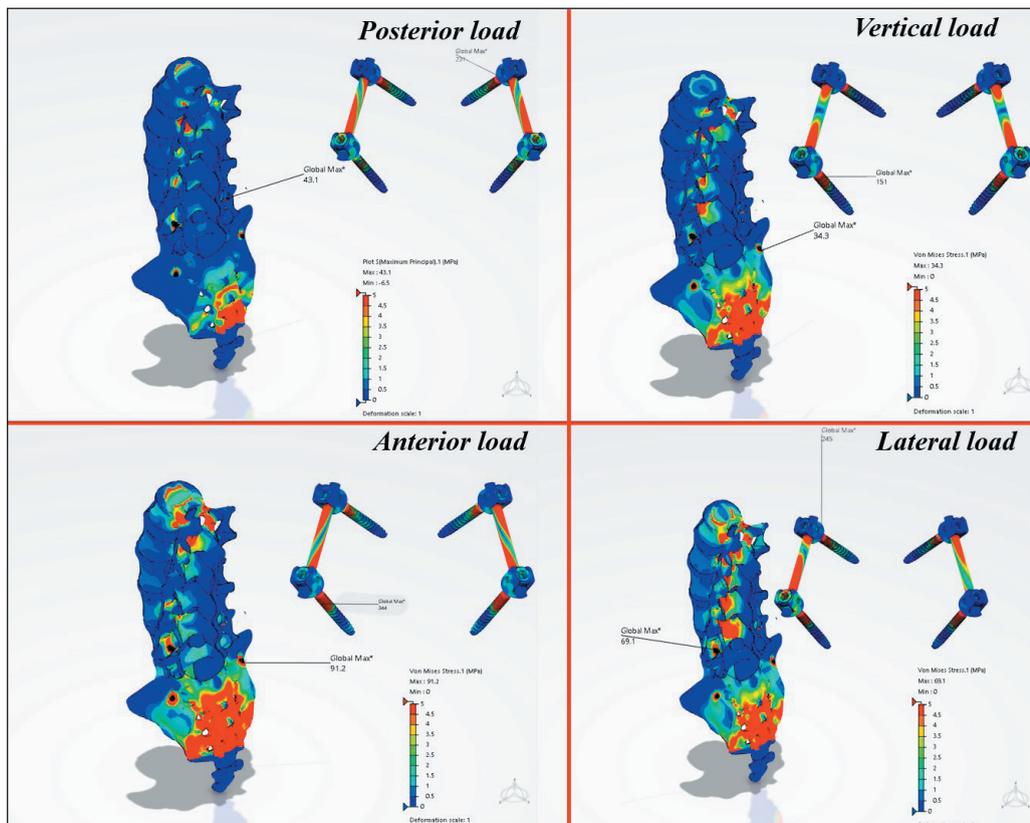
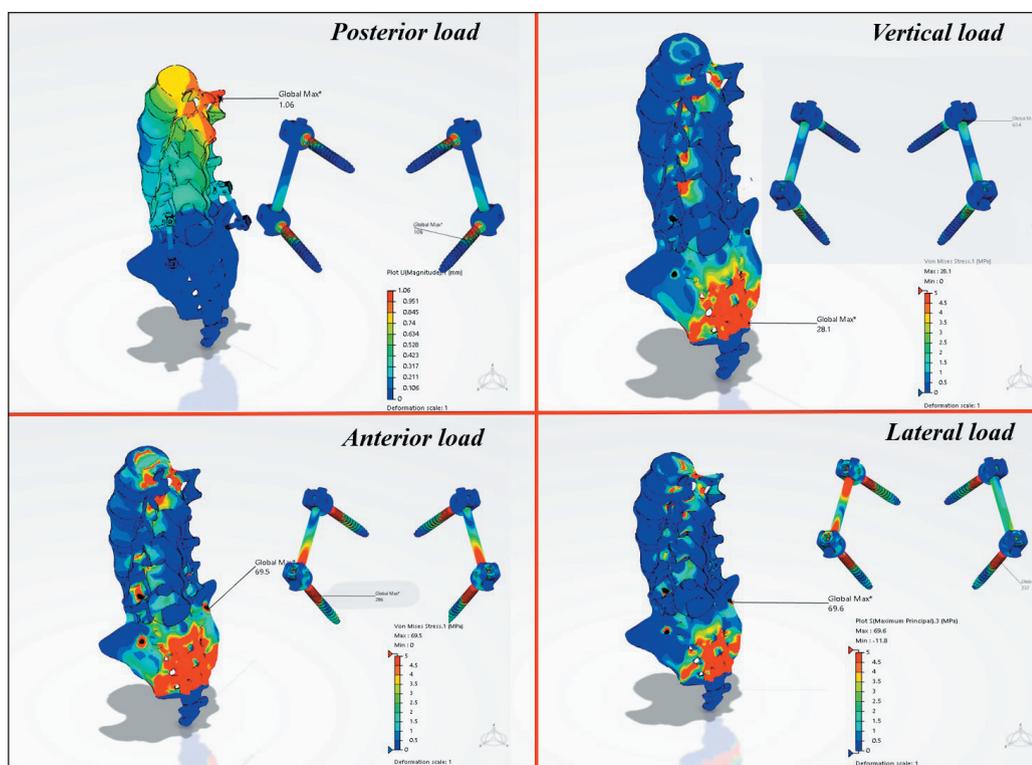


Figure 3: Stress contribution under several loading conditions of the lumbosacral area and the screws with titanium rods.



**Figure 4:** Stress contribution under several loading conditions of the lumbosacral area and the screws with PEEK rods.

Across all loading scenarios, titanium rods demonstrated markedly higher load absorption compared to PEEK rods. In vertical compression, titanium rods carried a load of 117 N, while PEEK rods absorbed only 34.5 N. Under anterior shear, the titanium rod experienced 94.4 N versus 44.7 N in the PEEK counterpart. The difference was even more pronounced in posterior shear, where the titanium rod carried 168 N compared to only 20 N in the PEEK rod. During lateral bending, titanium and PEEK rods bore 219 N and 64.4 N, respectively. Similarly, under axial rotation, the titanium construct withstood 153 N of load, whereas the PEEK rod carried 60 N.

These differences were statistically significant, as confirmed by a paired t-test comparing rod loads across materials ( $t(4) = 5.27, p = 0.006$ ). These findings indicate that titanium rods, due to their higher stiffness, absorb and localize more mechanical load, while PEEK rods facilitate greater load sharing with surrounding biological structures, resulting in lower rod stress.

**Screws**

In both instrumented models, bilateral pedicle screws measuring 6.5 mm in diameter and 45 mm in length were placed at L5 and S1. The rods were 5.5 mm in diameter and matched in length across both material groups. Implant dimensions were kept identical for the titanium and PEEK groups to ensure that differences in stress distribution were solely attributable to material properties rather than geometric variations.

The load distribution on pedicle screws followed a similar pattern. In vertical compression, the screw load was 151 N in the titanium construct and 37.6 N in the PEEK construct. For anterior shear, both constructs exhibited high screw

loading, with titanium and PEEK screws bearing 344 N and 286 N, respectively. Posterior shear resulted in a significant discrepancy: titanium screws experienced 231 N, while PEEK screws bore only 106 N. During lateral bending, the screw loads were relatively close (245 N for titanium, 232 N for PEEK), suggesting a more uniform load distribution in this condition. Axial rotation showed the greatest difference, with titanium screws carrying 233 N and PEEK screws only 59.7 N.

Paired t-test analysis demonstrated that these differences in screw loads were also statistically significant [ $t(4) = 3.47, p = 0.026$ ], confirming that PEEK constructs exert less mechanical stress on pedicle screws, particularly in posterior and rotational loading scenarios.

Together, these results suggest that while titanium instrumentation offers increased structural stiffness and resistance to deformation, it also generates greater stress concentrations at both the rod and screw levels. In contrast, PEEK instrumentation distributes loads more evenly, reducing stress on the implants and potentially mitigating the risk of stress shielding, screw fatigue, or implant-bone interface failure. These findings underscore the biomechanical advantages of semi-rigid PEEK rods in reducing mechanical overload while maintaining stability in the fixation of L5-S1 spondylolisthesis.

In addition to evaluating implant stresses, the FEA also assessed stress distribution at the site of the pars interarticularis defect. The results demonstrated that both titanium and PEEK rod constructs effectively reduced the mechanical stress concentration on the pars region. This stress reduction suggests that posterior instrumentation contributes to mechanical stabilization of the defect site, potentially limiting further slippage and promoting fusion. While titanium provided greater imme-

diate stiffness, PEEK offered comparable stress offloading with the added benefit of more physiological load distribution (Tables I-II).

**DISCUSSION**

This study employed an anatomically accurate FE model of the lumbosacral spine to compare the biomechanical behavior

of titanium and PEEK rod constructs in the context of isthmic L5-S1 spondylolisthesis. Our findings revealed that titanium constructs consistently transmitted higher mechanical stress to both rods and screws compared to PEEK, with statistically significant differences across all test scenarios. These results support the hypothesis that the material properties of spinal instrumentation significantly influence stress distribution, construct behavior, and, ultimately, the biological and clinical outcomes of spinal fusion surgery.

**Table I:** Load Contribution on Rods and Screws

Rods		
Load (Newton)	Titanium	PEEK
Vertical	117.0	34.5
Anterior	94.4	44.7
Posterior	168.0	20.0
Lateral	219.0	64.4
Rotation	153.0	60.0

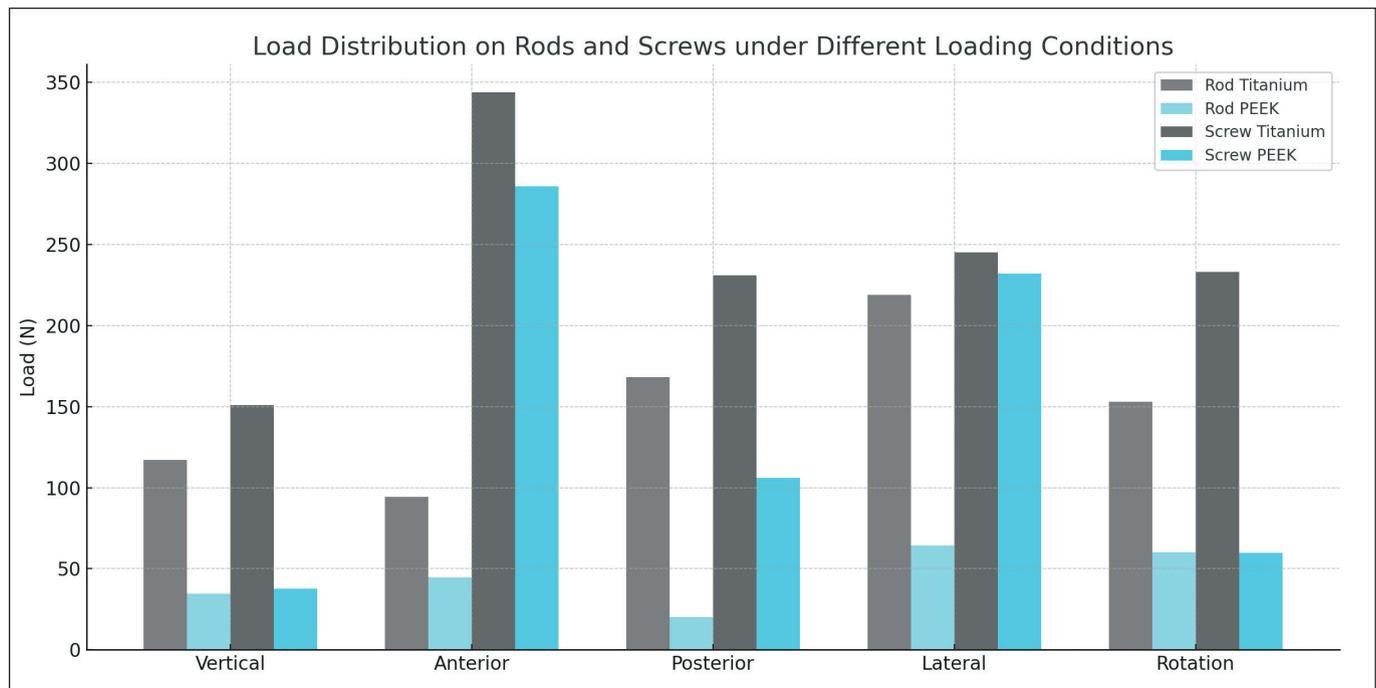
Screws		
Load (Newton)	Titanium	PEEK
Vertical	151	37.6
Anterior	344	286.0
Posterior	231	106.0
Lateral	245	232.0
Rotation	233	59.7

**Mechanical Load Distribution and Material Behavior**

Titanium, with its high elastic modulus, provides a rigid and durable construct that resists deformation. As demonstrated in our study, this rigidity translates into higher stress concentrations at the rod and screw levels. Under posterior shear, for instance, the titanium rods bore 168 N—more than eight times the load of PEEK rods (20 N). Similarly, titanium screws carried approximately twice the load of PEEK screws in posterior shear and four times as much in axial rotation. This localized load concentration can lead to stress shielding, where reduced mechanical stimulation of surrounding bone tissue impairs bone remodeling and fusion. It may also increase the risk of implant-related complications, such as screw loosening, rod fatigue fracture, or bone resorption at the bone-implant interface (3).

PEEK, in contrast, exhibits an elastic modulus that is closer to cortical bone, enabling a semi-rigid construct that permits micro-motion and more physiological load sharing. In our model, PEEK rods consistently exhibited lower stress across all loading directions. For example, during axial rotation, PEEK rods carried 60 N versus 153 N in titanium rods. These results suggest that PEEK distributes loads more uniformly

**Table II:** Diagram of the Load Distributions under Different Loading Conditions



through the spine-implant system, reducing the stress borne by the hardware and potentially improving the mechanical environment for bone fusion (6).

### Comparison with Prior Studies

Our results are consistent with previous computational and experimental research. Li et al. conducted an FEA comparing titanium and PEEK rods in a TLIF model and observed significantly reduced stress in PEEK rods compared to titanium rods under comparable loading conditions. They also reported increased strain on the interbody graft with PEEK, which may favor osteogenesis by enhancing mechanical stimulation at the fusion site (6). Similarly, a biomechanical study by Li et al. on long-segment posterior lumbar instrumentation showed that PEEK rods reduced the maximum stress on screws and better preserved adjacent segment motion. These constructs showed a more balanced stress distribution that could delay the onset of adjacent segment degeneration, a well-documented complication associated with rigid titanium constructs (5). In a recent meta-analysis, authors found that PEEK rod systems were associated with superior clinical outcomes compared to titanium, including reduced incidence of ASD, lower rates of implant failure, and improved fusion quality. The authors attributed these advantages to the semi-rigid nature of PEEK, which allows for better load-sharing without compromising mechanical stability (7).

These findings reinforce the notion that rigid titanium constructs, while biomechanically robust, may over-constrain spinal segments, leading to stress concentrations that compromise both hardware longevity and spinal health. PEEK rods, through their ability to approximate the mechanical properties of native bone, may mitigate these drawbacks by creating a more favorable environment for fusion and reducing the biomechanical burden on adjacent segments.

### Clinical Relevance and Surgical Decision-Making

The results of this FEA demonstrate that both titanium and PEEK rod constructs effectively reduce mechanical stress at the pars interarticularis in L5-S1 spondylolisthesis, contributing to stabilization of the defect. However, the type of implant material significantly influences the distribution of stress across the instrumentation system. Titanium constructs transmitted significantly higher loads to rods and pedicle screws, particularly under posterior shear and rotational loads. These focal stress concentrations may accelerate implant fatigue and predispose patients to mechanical complications such as screw loosening, rod breakage, or bone-implant interface failure (6).

These findings are consistent with prior clinical and experimental studies examining the mechanical and biological performance of PEEK rods in spinal fusion. Qi et al. reported that PEEK rods demonstrated comparable clinical and radiological outcomes to titanium alloy rods, with the added benefit of potentially reducing implant-related complications due to their semi-rigid nature and closer modulus of elasticity to bone tissue (12).

Similarly, Huang et al. found that PEEK rod constructs were associated with favorable long-term radiological outcomes, including preservation of disc height and a low incidence of hardware-related complications at a minimum 5-year follow-up. These results reinforce the biomechanical hypothesis that PEEK rods may attenuate stress concentrations on implants and adjacent spinal segments, thereby decreasing the likelihood of screw loosening, rod breakage, and adjacent segment degeneration. When integrated with our finite element findings, the accumulating evidence supports the use of PEEK rods as a viable alternative to titanium in select spinal fusion cases, particularly where implant fatigue and load transmission balance are clinical concerns (2).

This more physiological load-sharing profile could minimize stress shielding, maintain intersegmental motion within acceptable ranges, and create a more favorable biomechanical environment for fusion. From a clinical perspective, these properties may translate into reduced implant failure rates, improved long-term stability, and potentially lower incidence of adjacent segment degeneration.

For spine surgeons, these findings are particularly relevant when selecting instrumentation in cases where biomechanical balance is critical—such as in younger patients, in long-segment fusions, or where preservation of adjacent segment function is desired. The results also provide quantitative biomechanical evidence to support the use of PEEK rods as a semi-rigid fixation alternative in posterior lumbar fusion. Incorporating such data into surgical planning may help personalize treatment, optimize construct longevity, and reduce the need for revision surgery (14). Conversely, titanium may be more suitable in cases requiring maximum initial rigidity, such as high-grade spondylolisthesis, severe instability, or osteoporotic bone, where immediate construct stability is critical. The choice between materials should thus be individualized, balancing the need for rigidity with the risks of overloading adjacent structures and hardware components (1).

The biomechanical findings of this study, particularly the significantly lower stress concentrations observed in PEEK rods and screws, may have important clinical implications. By reducing focal stress on implants, PEEK constructs could potentially lower the incidence of mechanical complications such as screw loosening or rod fracture, which remain leading causes of implant failure and revision surgery. Furthermore, more physiological load-sharing with PEEK rods may support better bone remodeling and fusion environment, possibly enhancing arthrodesis success and reducing the risk of adjacent ASD. While these implications are supported by previous studies and our finite element data, they remain speculative and require further validation through cadaveric biomechanical testing or prospective clinical cohort studies comparing outcomes of titanium versus PEEK rod instrumentation in spondylolisthesis patients.

### Limitations

Despite the insights offered by this study, several limitations must be acknowledged. First, although the FE model was anatomically accurate and based on CT-derived geometry, it remains a simplified representation of *in vivo* conditions.

The simulations assumed linear, homogeneous, and isotropic material properties, which may not fully reflect the complex viscoelastic and anisotropic nature of biological tissues. Additionally, muscle forces and dynamic loading cycles were not incorporated, which may affect stress distribution patterns in real-life scenarios.

## CONCLUSION

This FEA demonstrated that the material properties of spinal instrumentation significantly affect stress distribution and mechanical behavior in the surgical treatment of L5-S1 spondylolisthesis. Titanium rods, while providing superior stiffness and immediate stability, concentrated higher mechanical loads on both rods and pedicle screws, which may predispose to hardware-related complications and stress shielding. In contrast, PEEK rods allowed for a more physiological distribution of mechanical stress, reducing the force on implants and promoting a favorable biomechanical environment for spinal fusion. Both constructs effectively reduced the stress on the pars defect, indicating their capacity to stabilize the spondylolytic segment. However, the semi-rigid behavior of PEEK offers additional advantages in reducing focal stress concentrations and potentially preserving adjacent segment integrity. These findings support the consideration of PEEK rods as a potentially advantageous alternative to titanium in select clinical scenarios. Future *in vivo* studies and long-term clinical trials are necessary to validate these results and assess their impact on fusion rates, implant longevity, and patient outcomes.

### 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: IA

Data collection: AYY

Analysis and interpretation of results: AAA

Draft manuscript preparation: IA

Critical revision of the article: KP

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# Effects of Caudal Epidural Pethidine on Pain Control and Early Mobilization after Posterior Spinal Instrumentation: A Randomized Controlled Trial

Necati KAPLAN<sup>1</sup>, Ilke TAMDOGAN<sup>2</sup>, Tamer TAMDOGAN<sup>3</sup>, Sevim ONDUL<sup>3</sup>, Numan KARAARSLAN<sup>4</sup>, Ibrahim YILMAZ<sup>5\*</sup>

<sup>1</sup>Optimed Hospital, Clinics of Neurosurgery, Tekirdag, Türkiye

<sup>2</sup>Giresun University School of Medicine, Department of Anesthesia and Reanimation, Giresun, Türkiye

<sup>3</sup>Giresun University School of Medicine, Department of Neurosurgery, Giresun, Türkiye

<sup>4</sup>Istanbul Medeniyet University School of Medicine, Department of Neurosurgery, Istanbul, Türkiye

<sup>5</sup>Republic of Turkey, Ministry of Health, Dr. Ismail Fehmi Cumalioglu City Hospital, Unit of Pharmacovigilance, Tekirdag, Türkiye

Corresponding author: Ibrahim YILMAZ ✉ dryilmazi@yahoo.com

## ABSTRACT

**AIM:** To evaluate the effects of administering pethidine (also known as meperidine), a long-acting narcotic analgesic, via the caudal epidural route at the conclusion of posterior lumbar instrumentation (PLI) surgery on postoperative pain control, and early mobilization of patients.

**MATERIAL and METHODS:** The cases included in this prospective study (n=48) were randomly divided into two groups, ensuring similar gender and age distributions and uniformity regarding lumbar pathologies requiring surgery. In the first group, 20 mL of sodium chloride (0.09%) solution containing pethidine chloride (0.5 mg/kg) was administered via a caudal epidural block before the patients were awakened from anesthesia. The control group consisted of cases in which the caudal epidural block was not performed using pethidine or any other pharmaceutical/pharmacological agent. Visual analog scale (VAS) pain assessments were performed in both groups preoperatively, postoperatively, and 24, 48, and 72 hours after awakening and recovery. Oral feeding at the sixth postoperative hour and mobilization at the eighth postoperative hour were evaluated in all cases. The data obtained were statistically analyzed with a significance level of  $\alpha=0.05$ .

**RESULTS:** The VAS scores of cases administered with pethidine via a caudal block were found to be significantly lower at all measurement times compared with those without a caudal epidural block ( $p < 0.05$ ). The need for analgesic medication in terms of dosage and duration was lower in the pethidine group during the postoperative period. Both groups began oral feeding at the sixth postoperative hour. The cases in the pethidine group were mobilized with ease at the eighth postoperative hour, whereas those without a caudal epidural block with pethidine could only be mobilized as early as the 24th postoperative hour.

**CONCLUSION:** Administering pethidine via a caudal epidural block before awakening at the conclusion of PLI surgery may provide benefits in postoperative pain control and early mobilization.

**KEYWORDS:** Analgesics, Caudal epidural block, Meperidine, Pethidine, Postoperative pain

Necati KAPLAN : 0000-0001-5672-0566  
Ilke TAMDOGAN : 0000-0002-8757-1046  
Tamer TAMDOGAN : 0000-0002-0526-1459

Sevim ONDUL : 0000-0003-4219-4862  
Numan KARAARSLAN : 0000-0001-5590-0637  
Ibrahim YILMAZ : 0000-0003-2003-6337



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## ■ INTRODUCTION

Spinal deformities, degenerative spine diseases, traumas causing instability in the spine, infectious pathologies, and spinal tumors often require posterior lumbar surgical approaches using implants, such as screw-rod or plates. These approaches are generally referred to as posterior lumbar instrumentation (PLI) procedures (23). They are inherently associated with significant tissue damage and inflammation; thus, effective pain management in the postoperative period is critical.

Inadequate pain control can prolong hospital stay, delay rehabilitation, and negatively affect surgical outcomes. Delayed mobilization and uncontrolled pain negatively affect patients' quality of life and recovery process (15). They may increase the risk of side effects or adverse events due to the use of multiple medications for pain control (polypharmacy) (13). They can also lead to long-term opioid use, increasing the risk of addiction and healthcare costs. Lumbar and caudal epidural blocks can be applied in the postoperative period to prevent such situations, reduce long-term complications, and improve quality of life (6).

Various medical and conservative treatment modalities are used in postoperative pain management, such as oral or parenteral and/or externally administered nonsteroidal anti-inflammatory drugs (NSAIDs) and oral or systemic opioid analgesics (11). Targeted application of local anesthetics alone or in combination with steroids may also be preferred (14).

An epidural block is usually performed by administering pharmacological agents, such as opioids, steroids, local anesthetics, or hyaluronidase, to the area of neural compression under imaging guidance (22). However, a caudal epidural block aims to relieve pain by injecting medication into the epidural space through the sacral hiatus and targeting the nerves affected by pain signals. The main difference between a caudal block and other types of epidural blocks is the target area of the injection. The sacral hiatus is an important anatomical landmark for the application of caudal epidural blocks (20).

In caudal epidural injections, agents administered with a higher fluid volume may dilute and remove inflammatory mediators from the epidural space, providing clinically significant results. However, there is no direct evidence that administered drugs penetrate more effectively anterior to the nerve roots (36). Analgesia and inflammation can be reduced by administering local anesthetics (26) (e.g., bupivacaine, lignocaine, and ropivacaine), steroids (12) (e.g., betamethasone), or opioids (5) (e.g., morphine) to this area.

Pethidine (meperidine) is an opioid analgesic that acts on mu-opioid receptors in the central nervous system. The use of pethidine in caudal blocks acts directly on spinal opioid receptors, blocking pain signals from the lower body regions to the brain. The caudal approach can provide more localized and effective pain control than systemic applications because it allows the drug to be delivered closer to the surgical site in the lumbar region.

The literature has evaluated the effectiveness of caudal epidural morphine or bupivacaine administration in postoperative pain

and neuroendocrine stress response in pediatric patients (35). In addition, a recent pediatric patient study compared sacral hiatus injection with conventional sacral canal injection and ultrasound-guided injections for caudal epidural blocks (1). However, there is no high-quality evidence in the literature on the use of pethidine-containing caudal epidural blocks administered via the sacral hiatus before patients wake up at the end of PLI procedures in adults.

This study aimed to evaluate the effects of a pethidine caudal epidural block via the sacral hiatus route on postoperative pain, nutrition, and mobilization compared with cases without a caudal block at the end of PLI surgery. The data obtained are considered to make a significant contribution to the literature in this field.

## ■ MATERIAL and METHODS

This prospective study was conducted with the approval of the Giresun University Faculty of Medicine Local Ethics Committee (Approval No: E-53593568-771-238738897, dated March 18, 2024). The same neurosurgeon from the Department of Neurosurgery Clinic performed surgery on all of the cases included in the study. Informed consent was obtained from all participants.

The sample size was determined using "G\*Power (version 3.1.9.4)" (9,10). According to the sample calculation, reaching the required number of cases was determined as the primary endpoint of the study. Estimated power was 0.80, alpha (margin of error): 0.05, effect size was 0.4. Accordingly, the sample size was determined as 48 for the chi-square test. Between March 19, 2024, and August 31, 2024, 48 patients aged 31–83 years were included. The researcher responsible for the statistical analysis of the data was blinded to which group received pethidine. Additionally, none of the subjects knew whether they had been given pethidine or not.

### Inclusion and Exclusion Criteria

Patients aged 18 years or older scheduled for PLI due to lumbar spinal stenosis, lumbar spondylolisthesis, spinal instability, lumbar spinal deformity, degenerative disc disease, or lumbar fractures with at least 3 months of persistent pain not responding to medical or conservative treatments and presenting with back pain, unilateral or bilateral leg pain, neurological deficits, or neurogenic claudication were included in the study. Patients with pethidine allergies, infections, or bleeding disorders at the surgical site, sacral spine malformations incompatible with a caudal epidural blockade, diabetes mellitus, cardiovascular diseases, alcohol consumption, or a history of smoking were excluded. The remaining 48 patients were randomly assigned to two equal groups. To perform randomization, blocks were created before starting the study, which included equal numbers of participants according to the needs of the study, such as gender, age, and severity of disease. The participants in the blocks were then randomly assigned to the treatment and control groups.

Group 1 consisted of patients who received pethidine blocks ( $n = 24$ ), while Group 2 (the control group) included patients who did not receive pethidine or any other pharmaceutical blocks

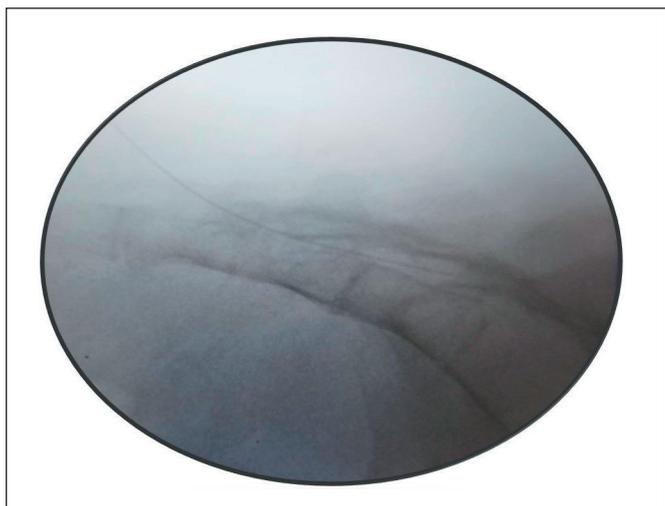
(n = 24). The patients' age, gender, height, weight, American Society of Anesthesiologists physical status classification (I-II), diagnoses, surgical types, and postoperative analgesic dosages and durations were recorded in a Microsoft Office Excel file.

### Operation and Caudal Epidural Block

A standard endotracheal general anesthesia induction procedure was applied to all patients. For patients undergoing PLI with diagnoses such as lumbar spinal stenosis, lumbar spondylolisthesis, lumbar spinal instability, lumbar degenerative deformity, and lumbar spinal trauma, pethidine was administered via the caudal epidural route at the end of the surgery only to patients in Group 1 before they were awakened.

Using fluoroscopy, a lateral view was obtained to display the anatomical boundaries of the sacral canal. The caudal canal appeared as a translucent layer posterior to the sacral segments under fluoroscopy. The median sacral crest appeared as an opaque line posterior to the caudal canal, while the sacral hiatus typically presented as a translucent opening at the base of the caudal canal. The coccyx could be observed articulating with the inferior surface of the sacrum. The caudal epidural block was performed by entering a 22-gauge Quincke spinal needle through the sacral hiatus under fluoroscopic guidance, followed by the administration of a contrast agent. The correct placement was confirmed by observing the distribution of the contrast agent in the epidural space. In Group 1, a mixture of pethidine and 20 mL of physiological serum was injected epidurally into the sacral hiatus caudal at a rate of 0.5 mL per second under fluoroscopic guidance. As the caudal block was not applied to the cases in Group 2, which was called the control group, no pharmacological agent, including saline, was injected (Figure 1).

After the caudal epidural block, a sterile sticker was applied to the needle insertion site. The patients were transferred to the ward after extubating and awakening.



**Figure 1:** Demonstrative image of caudal epidural pethidine application under guidance using a mobile C-arm system (fluoroscopy).

### Pain and Mobilization Assessment

Pain intensity was assessed using a visual analog scale (VAS). In both the control and experimental groups, all patients were assessed for postoperative mobilization beginning at the eighth hour. The assessment included activities such as turning from one side to the other in bed, sitting at the bedside, standing up at the bedside, and walking in the patient's room. The evaluation was conducted using a patient mobility scale that measured the level of pain and difficulty experienced during these activities.

Postoperative analgesia. Intravenous paracetamol (3 × 1 g/day) and tenoxicam (2 × 20 mg/day) were administered to each patient according to the standard analgesia protocol. Intravenous 0.5 mg/kg tramadol and/or intramuscular 100 mg pethidine was planned to be administered as rescue analgesia if the patients had a VAS score > 4.

### Statistical Analysis

The Minitab program was used for the statistical evaluation of the data obtained. A one-way analysis of variance was applied to compare the groups. Descriptive statistics were presented as mean ± standard deviation (SD), minimum, and maximum values. For all statistical analyses, a P value of less than 0.05 was considered statistically significant.

## RESULTS

The patients who received a pethidine block had instrumented a minimum of three and a maximum of five levels. In patients without a block, instrumentation was applied to a minimum of three and a maximum of seven levels. The body mass index of all groups was found to be 18.5–24.9 kg/m<sup>2</sup>. The case data are summarized in Table I.

Group 1 represents the cases in which a caudal epidural block was applied with pethidine, while Group 2 represents the cases in which no caudal epidural medication was applied.

No statistically significant correlation was observed between the groups in terms of age or the number of instrumented levels and pain (p>0.05).

When comparing the preoperative and postoperative VAS scores of Group 1 (pethidine administered) and Group 2 (control), statistically significant differences were found between the groups at the 0th hour (F-Value: 89.81; p-value: 0.00), the 24<sup>th</sup> hour (F-Value: 68.16; p-value: 0.00), the 48<sup>th</sup> hour (F-Value: 28.21; p-value: 0.00), and the 72<sup>nd</sup> hour (F-Value: 13.10; p-value: 0.00) (Figure 2, Figure 3).

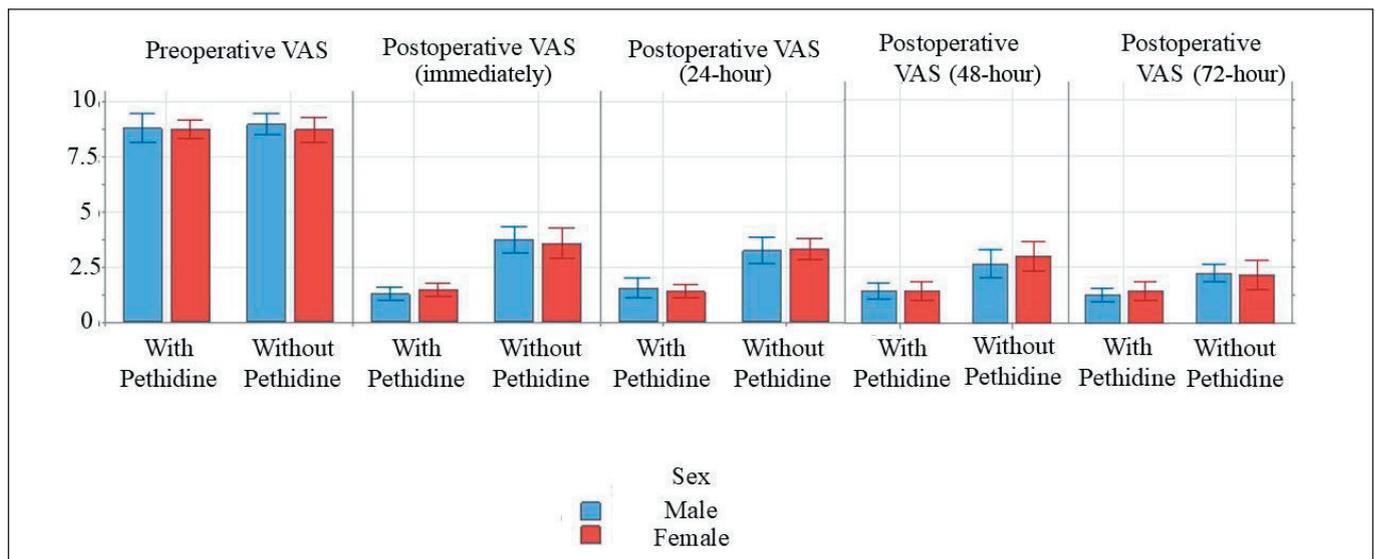
In addition, the patients without a caudal epidural block achieved mobilization earliest on the first postoperative day (n=14), while 10 patients were mobilized at the 48<sup>th</sup> hour. Patients who received caudal epidural pethidine required fewer doses and durations of analgesic medication postoperatively compared with those who did not.

A postoperative analgesia protocol was established for the patients in each group using intravenous paracetamol (3 × 1 g/day), tenoxicam (2 × 20 mg/day), and intravenous 0.5 mg/

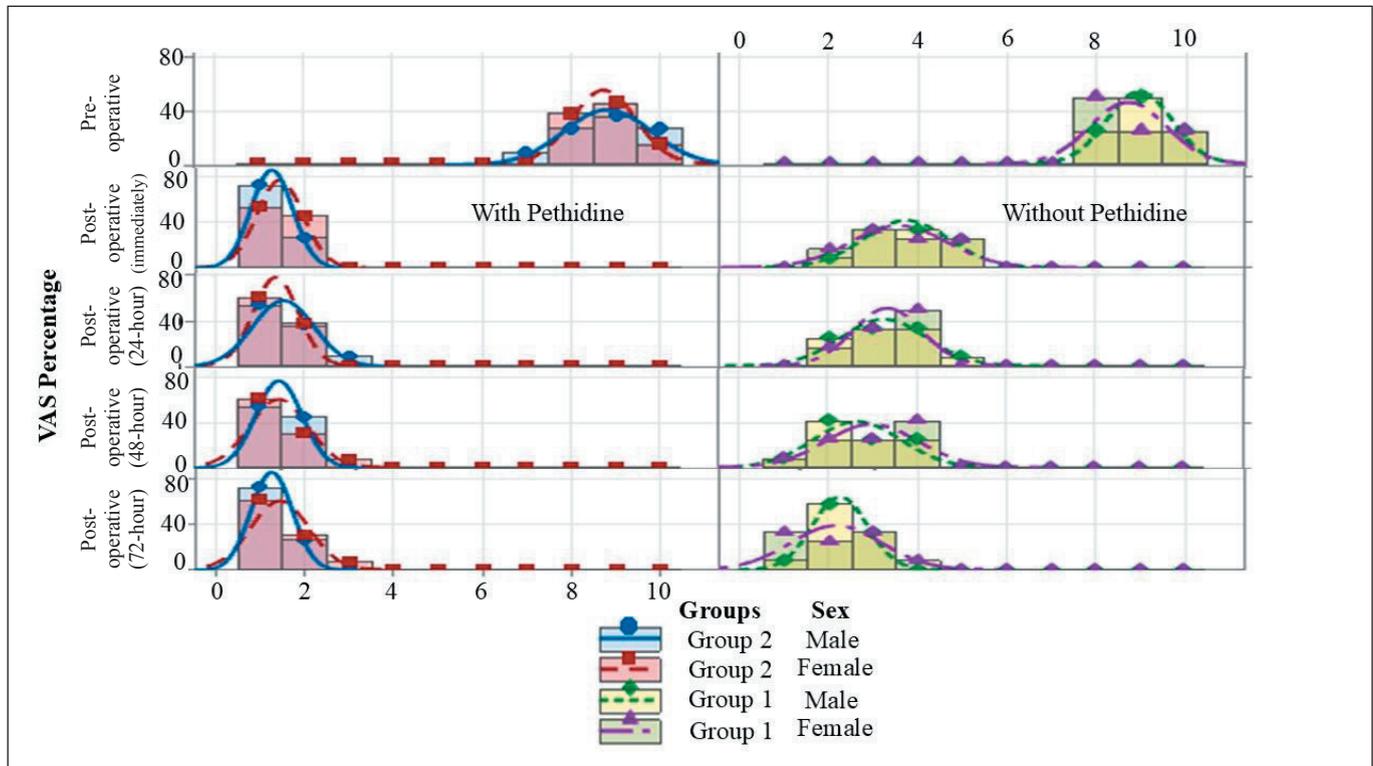
**Table 1:** Comparison of Demographic and Other Data of Cases with or without Caudal Epidural Block with Pethidine

Groups	Variable	Sex	Mean ± SD	Min	Max	
With pethidine	Age (year)	M	54.27 ± 11.70	31	71	
		F	61.15 ± 9.76	41	72	
Without pethidine		M	63.75 ± 10.29	48	83	
		F	55.25 ± 8.42	41	69	
With pethidine		Preoperative VAS	M	8.818 ± 0.982	7	10
			F	8.769 ± 0.725	8	10
Without pethidine	M		9.000 ± 0.739	8	10	
	F		8.750 ± 0.866	8	10	
With pethidine	Postoperative VAS (immediately)		M	1.273 ± 0.467	1	2
			F	1.462 ± 0.519	1	2
Without pethidine		M	3.750 ± 0.965	2	5	
		F	3.583 ± 1.084	2	5	
With pethidine		Postoperative VAS (24-hour)	M	1.545 ± 0.688	1	3
			F	1.385 ± 0.506	1	2
Without pethidine	M		3.250 ± 0.965	2	5	
	F		3.333 ± 0.778	2	4	
With pethidine	Postoperative VAS (48-hour)		M	1.455 ± 0.522	1	2
			F	1.462 ± 0.660	1	3
Without pethidine		M	2.667 ± 0.985	1	4	
		F	3.000 ± 1.044	1	4	
With pethidine		Postoperative VAS (72-hour)	M	1.273 ± 0.467	1	2
			F	1.462 ± 0.660	1	3
Without pethidine	M		2.250 ± 0.622	1	3	
	F		2.167 ± 1.030	1	4	

**SD:** Standard deviation, **Min:** Minimum, **Max:** Maximum, and, **VAS:** Visual analog scale.



**Figure 2:** Comparison of intergroup VAS scores by gender between patients who underwent a caudal epidural block with pethidine and those who did not.



**Figure 3:** Interval plot of intergroup VAS scores by gender of patients who underwent a caudal epidural block with pethidine versus those who did not receive any caudal epidural block.

kg tramadol and/or intramuscular 100 mg pethidine for rescue analgesia when necessary.

None of the patients who underwent caudal epidural block required rescue analgesia, and no drug-related side effects or adverse events were observed in any patient in this group. In patients without a caudal epidural block, side effects were noted in those who received intramuscular pethidine for analgesia. Among the patients who did not receive caudal epidural block, seven received intravenous tramadol, and eight received intramuscular pethidine as rescue analgesia. The side effects observed in these cases are presented in Table II.

The patients who received caudal epidural pethidine were observed to mobilize easily by the eighth hour, whereas those without an epidural block and pethidine achieved mobilization earliest on the first postoperative day (n=14). Ten patients were mobilized by the 48<sup>th</sup> hour due to analgesia-related delays.

**DISCUSSION**

PLI, which is a surgical treatment applied for pathologies such as lumbar spinal stenosis, lumbar spondylolisthesis, lumbar spinal instability, lumbar degenerative deformity, and lumbar spinal trauma, can cause uncontrolled pain and difficulty in mobilization during the postoperative period. As a result, satisfactory outcomes may not be achieved in these patients (31).

**Table II:** Postoperative Opioid-Related Side Effects

Side effects	Number of patients
Confusion, perception disorders, mood changes	2
Vertigo, euphoria	2
Insomnia, headache	1
Tremors	2
Miosis	1

Epidural space infiltrations are classified as caudal, transforaminal, and interlaminar. The injection method depends on the type of pain and the surgeon’s preference. The caudal epidural block, an epidural anesthesia method administered through the sacral hiatus, has become a fundamental element in pediatric and adult anesthesia, particularly for procedures involving the lower abdomen, perineum, and lower extremities. Especially after lumbar spinal instrumentation surgeries, failed back surgery syndrome is observed at a notable rate. In such cases, epidural caudal injections are often preferred for pain control (24). Studies have reported the positive effects of transforaminal epidural injections and caudal epidural injections combined with an erector spinae plane block during and after lumbar spinal fusion surgeries on postoperative pain control, patient satisfaction, and early mobilization (30).

Pethidine is an opioid analgesic increasingly studied within the context of caudal epidural anesthesia due to its unique properties, including local anesthetic effects and complementing traditional agents such as bupivacaine or lidocaine (2).

Effective pain management after PLI is essential to accelerate recovery, facilitate early mobilization, and reduce the risk of complications. However, it is evident that creating and applying a general analgesia protocol is challenging for many surgical procedures. A caudal epidural block administered through the sacral hiatus is frequently used by neurosurgeons and pain specialists due to its high reliability. In this procedure, an imaging method should be employed to achieve high accuracy in needle placement. In our study, fluoroscopy was used for this purpose (7).

Given the complex nature of PLI as a spinal surgical intervention and the severe postoperative pain pattern, a multimodal approach combining different classes of analgesics is widely applied for postoperative pain management (28). This strategy enhances analgesic effectiveness by targeting various pain pathways while minimizing the side effects associated with higher doses of single agents.

Morphine, hydromorphone, fentanyl, and oxycodone are the most commonly used opioid analgesics. However, the use of these analgesics is associated with significant side effects, such as constipation, emesis, sedation, and risks of dependency or tolerance. Thus, there are notable limitations and risks, such as the need for titration and monitoring (17). For this reason, adjuvant therapies, including non-opioid analgesics, are increasingly preferred in multimodal pain management due to their ability to reduce opioid consumption and associated side effects.

Adjuvant therapies, which integrate various strategies into a consistent multimodal pain management plan, are key to optimizing postoperative pain control while minimizing opioid use. Protocols frequently including NSAIDs, such as ibuprofen and ketorolac, which inhibit cyclooxygenase enzymes involved in prostaglandin synthesis and reduce inflammation and pain, are preferred not only for their analgesic effects but also for their ability to reduce the inflammatory component of postoperative pain (33).

However, their frequent use in spinal surgeries may not be appropriate due to their potential for interfering with osteochondral tissue healing. Acetaminophen, often used as part of a multimodal regimen, provides effective analgesia with a favorable side effect profile, can be administered orally or intravenously, and is particularly beneficial in cases in which NSAIDs are contraindicated. Gabapentinoids are typically initiated preoperatively and continued postoperatively to reduce both acute and chronic pain. Agents such as gabapentin and pregabalin are preferred for alleviating neuropathic pain, which can be a component of postoperative pain following PLI (18). They work by inhibiting calcium channels in the central nervous system, thereby reducing the release of excitatory neurotransmitters (32).

Ketamine, an N-methyl-D-aspartate receptor antagonist, is sometimes used at sub-anesthetic doses to provide analgesia

and reduce opioid requirements, particularly in patients with high opioid tolerance or neuropathic pain (29). Corticosteroid drugs can also be used to reduce inflammation and nerve root edema in patients with radicular pain.

The caudal blockade, a type of epidural anesthesia, is effective in treating lower lumbar and sacral pain. Its efficacy is enhanced by the washing effect of high-volume fluid injections combined with the administered agents, which cleanse the inflammatory mediators responsible for pain. As discussed earlier, pethidine, although less commonly used than other local anesthetics, can be utilized in caudal blocks. Although less commonly used for PLI, peripheral nerve blocks, such as lumbar plexus or paravertebral nerve blocks, can be considered part of a multimodal approach, especially for patients with contraindications to epidural or systemic opioids (28).

In this study, cases with a caudal epidural block using pethidine and cases without a caudal epidural block were compared to evaluate the pain and mobilization of patients in the postoperative period following PLI. In the control group, in which caudal blockade was not performed with pethidine or any other drug, performing caudal blockade with saline was not deemed necessary, as the subjects would not know whether caudal blockade was performed under anesthesia.

Pethidine, one of the first synthetic opioid analgesics widely used for treating moderate to severe pain, is typically employed for managing acute pain, such as postoperative pain, pain during childbirth, or pain caused by injuries. However, it is less commonly used for chronic pain treatment because of its potential toxicity stemming from the accumulation of its metabolite—normeperidine. Pethidine primarily acts by binding to mu-opioid receptors, which are G-protein-coupled receptors in the central nervous system. When pethidine binds to these receptors, it inhibits the release of neurotransmitters, such as substance P, which play a role in transmitting pain signals in the spinal cord and brain. This leads to a reduction in pain perception (4).

Epidural pethidine infiltration involves administering pethidine into the epidural space, the area surrounding the spinal cord within the vertebral column. When administered epidurally, pethidine acts on opioid receptors, particularly in the dorsal horn of the spinal cord, blocking the transmission of pain signals. This results in decreased pain perception without causing a complete motor block, a desirable outcome in certain clinical situations, such as childbirth. It can also be used to manage pain following abdominal or lower extremity surgeries.

The advantages of a caudal block with pethidine include effective analgesia, rapid onset, and moderate duration of action. One significant concern regarding the use of pethidine in spinal or epidural applications is its potential neurotoxicity (40). Although pethidine is less associated with neurotoxicity compared with other opioids, adverse neurological effects have been reported, particularly with high doses or prolonged use. Similar to other opioids, pethidine carries a risk of respiratory depression (4), which can be particularly dangerous in the postoperative period. The risk increases when combined

with other central nervous system depressants. As an opioid, pethidine has the potential for abuse and dependency, necessitating careful monitoring, especially in patients requiring prolonged postoperative pain management. The inclusion and exclusion of cases in this study were carried out considering these scientific data.

However, when an opioid, such as pethidine, is administered caudally through the sacral space, its pharmacokinetics differ significantly from systemic administration routes, such as intravenous or oral. When injected via the caudal epidural route, pethidine primarily acts locally on the spinal nerves in the sacral and lower lumbar regions, providing effective regional analgesia. A portion of the drug may be absorbed into systemic circulation through the epidural venous plexus. However, the rate and extent of systemic absorption are generally lower compared with intravenous administration, as the drug accumulates in the localized area where its effects are intended. Unlike oral drugs, which are absorbed through the gastrointestinal system and enter the portal circulation directly (first-pass metabolism), drugs administered via the caudal route do not directly enter the portal circulation. Instead, they are absorbed into the systemic venous circulation and subsequently distributed throughout the body (38).

Once the drug enters systemic circulation, it eventually reaches the liver. Pethidine is primarily metabolized in the liver through the cytochrome p450 enzyme system (CYP2D6, 2C19, and 3A4) (37). It is metabolized into normeperidine and other metabolites, which are less active but may contribute to toxicity, especially with repeated doses.

In a study that evaluated caudal epidural injection in the treatment of lumbosacral nerve pain syndromes in a double-blind manner involving 39 cases, the participants were randomly divided into three groups (3). The researchers administered a combination of 10 mL of 0.09% isotonic sodium chloride, 20 mL of lignocaine (1%), and 1 mL of betamethasone (7 mg) through a caudal epidural injection to the first group. The second group received the same combination without betamethasone through a caudal epidural injection. In the third group, only 1 mL of betamethasone (7 mg) was administered as a superficial injection around the sacral hiatus. In the postoperative period, only tramadol was allowed as an analgesic medication. The cases in all three groups were evaluated at 1, 24, and 48 hours, at the end of the first week, and four weeks after the injections (3). The results showed that while the mobility of the lumbar spine improved in all patient groups, there was no statistically significant difference between the three treatment groups. However, the straight leg raise test results associated with epidural steroid injections were superior to those of steroid injections around the sacral hiatus (3).

Morphine and bupivacaine were used in a study comparing the efficacy of a caudal epidural block with a constant depth of anesthesia in surgical stress response in children who had undergone abdominal and genitourinary surgery in the past using bispectral index analysis. The results indicated that bupivacaine's caudal epidural application was more effective than morphine in reducing intraoperative and postoperative stress responses in children undergoing surgery (35).

In a study involving 90 patients scheduled for surgery below the umbilical level, the ability of epidural morphine administered via the caudal route to alleviate pain was assessed and compared with an intramuscular opioid injection. The cases receiving 4 mg of morphine/10 mL of normal saline via the caudal route were compared with those receiving intramuscular opioids using the VAS (25). The average pain score in the caudal epidural group was significantly lower during the first 12 hours postoperatively, and 38% of the cases required additional intramuscular injections within the first 12 hours. However, in the study, 86% of the patients in the intramuscular group received opioid injections, and although no patient developed respiratory depression due to morphine injection, side effects were more frequent in the intramuscular group than in the epidural group (19).

In a study comparing between caudal epidural bupivacaine with adrenaline and pethidine with adrenaline for operative and postoperative analgesia in infants and children, 25 cases under the age of 12 were evaluated. The study showed that none of the children in either group required parenteral analgesia. However, although the pethidine group experienced longer analgesia and sedation duration, delayed vomiting and urination times could hinder the routine use of pethidine (25).

In another study involving pediatric patients aged 2–5 years who underwent unilateral inguinal hernia surgery, caudal epidural injections of pethidine combined with levobupivacaine were suggested as an effective method for postoperative analgesia duration, pain control, and early mobilization (39).

Eighty-seven cases were evaluated in a study investigating the effect of caudal dexmedetomidine and ketamine in preventing delirium in pediatric patients undergoing congenital inguinal hernia repair. The results showed that patients who received caudal dexmedetomidine had a longer time until the first postoperative analgesia compared with ketamine and reduced postoperative analgesic consumption. Moreover, no significant difference was reported between the two drugs regarding postoperative sedation duration and the incidence of perioperative adverse events (8).

Contrary to the literature, this study found no side effects and/or adverse events, such as delayed vomiting and urinary frequency, in adults receiving caudal epidural pethidine.

In a randomized, double-blind, controlled clinical study analyzing the effectiveness of preemptive analgesia with a single caudal epidural injection in patients undergoing posterior approach surgeries for lumbosacral region pathologies, administering analgesics before the painful stimulus was reported to be more effective than after its onset. It was reported that 82 patients who underwent instrumented or non-instrumented discectomy in the lumbosacral spine through a posterior approach were randomized into a control group (n=40), and a study group (n=42), and patients in the control group received a single caudal epidural injection of 20 mL of normal saline. In the study, a single 20 mL caudal epidural injection containing bupivacaine and tramadol was administered to the patients in the study group, and a single caudal epidural injection with bupivacaine and tramadol was found to be a safe, simple, and

effective method for preemptive analgesia in managing postoperative pain (34).

However, in this study, side effects, such as drowsiness, impaired perception, mood changes, euphoria, insomnia, headache, tremor, and miosis, were observed in cases without a caudal epidural block who received intravenous opioids for postoperative analgesia. The results of this study are consistent with the literature. A caudal epidural block containing pethidine has been shown to significantly improve postoperative pain and mobilization following PLI surgery.

In Ahiskalioglu et al.'s study, a solution of levobupivacaine (0.125%) combined with morphine (10 µg/kg) was administered as caudal epidural injections at a total volume of 0.5 mL/kg. Despite limitations in central neuraxial anesthesia, they recommended using ultrasound in pediatric caudal injections to reduce complications and increase the success rate of the first attempt (1).

However, in another study comparing caudal epidural injections performed under ultrasound guidance with those performed under fluoroscopy, it was suggested that although ultrasound-guided blocks had a higher success rate in the first attempt and required smaller needle sizes, no significant difference in block success was observed between the groups. Moreover, conventional methods have been associated with fewer issues, such as blood aspiration, bone tissue irritation, and subcutaneous bulging (21). In the current study, mobile C-arm fluoroscopy was preferred over ultrasound guidance for caudal epidural injections.

As with all complex surgical interventions, the early mobilization of PLI cases is essential for functional recovery, preventing complications associated with immobilization, and maintaining hemostatic balance. Therefore, assessing the level of activity in postoperative cases and the factors affecting it is crucial.

In summary, the importance of effective postoperative pain management in spinal surgeries, particularly in posterior lumbar instrumentation, cannot be overlooked. It plays a vital role in shortening recovery time, increasing patient satisfaction, and optimizing surgical outcomes. Postoperative pain management after PLI requires a balanced approach that considers the effectiveness, side effects, and impact on the recovery of various analgesics. A multimodal strategy that includes opioid and non-opioid options and regional anesthesia techniques provides the best results in terms of pain control, patient satisfaction, and early mobilization. As research progresses, we believe that new agents or combinations of different pharmaceuticals could further improve postoperative pain management protocols.

As a result, this analytical study, which divided 48 cases into randomized two groups, found no significant statistical relationship between age or the number of instrumented levels and pain ( $p < 0.05$ ). Compared with the control group that did not receive a caudal epidural block, those who received a single dose of caudal epidural pethidine had a lower analgesic requirement and postoperative VAS scores ( $p < 0.05$ ). Moreover, no patients in the caudal epidural pethidine group required

opioid analgesia in the postoperative period. No side effects or adverse events related to the medication were observed in the caudal epidural pethidine group. However, in cases without a caudal epidural block, side effects related to intravenous opioid use were detected in the postoperative period to provide analgesia. The assessment of patient mobilization was made using a patient mobility scale. The cases with caudal epidural pethidine were found to be able to mobilize comfortably and pain-free by the eighth hour, while in the group without a caudal epidural block and pethidine, 58.33% were mobilized on the first postoperative day, and 41.66% were mobilized by the 48th hour at the earliest.

The VAS is based on the patients' ability to understand the scale and their subjective pain experiences, which can introduce variability. It may not be suitable for individuals who struggle to understand the scale concept. At first glance, this can be considered a limitation of our study. However, the VAS has been validated in numerous studies, showing its reliability and correlation with other pain scales, such as the numeric rating scale and the verbal descriptive scale. The VAS is considered the gold standard for pain assessment due to its simplicity and ease of use (16,27).

#### Limitations

In this study, the cases were of the same ethnicity, and only the effect of a caudal epidural block containing pethidine was investigated. There was no control group consisting of cases receiving normal saline or other opioids or any pharmacological agent through caudal epidural blocks. Instead, cases without any drug-related caudal epidural blocks were compared. This is the main limitation of our study. Future research should include a larger, multi-center study design involving different ethnicities, examining not only the efficacy of pethidine but also the roles and long-term effects of different opioid drugs on caudal epidural blocks for postoperative pain relief. Because, it should be noted that cultural differences in pain perception will affect the results. In summary, this study is limited by its small sample size, single-center design, and use of subjective measures, such as the VAS.

#### CONCLUSION

Despite the significant literature on the use of opioids in spinal anesthesia, there is limited specific data on the use of pethidine in caudal blocks, especially in the context of spinal surgeries, such as PLI. Most studies have focused on more commonly used opioids, such as morphine or fentanyl. Due to concerns about its side effects, the use of pethidine has declined, and current studies may not fully reflect its efficacy and safety profile in modern surgical settings. Considering the critical role of postoperative pain management in spinal surgery outcomes and the unique properties of pethidine as an analgesic, there is a clear need to evaluate its efficacy and reliability, particularly when administered via caudal blocks. This evaluation could contribute to optimizing postoperative care, improving patient recovery, and potentially redefining analgesic protocols in spinal surgeries. It has been observed that caudal epidural pethidine administered before the

patient wakes up after PLI surgery significantly improves postoperative pain control and mobilization. Based on these results, we believe that caudal epidural pethidine can be safely and effectively used in postoperative pain management following PLI, enabling patients to mobilize earlier.

#### 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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This study is an analytical and observational study and does not constitute a clinical trial. Therefore, registration in a clinical trial registry was not required and no clinical trial registration number exists.

#### AUTHORSHIP CONTRIBUTION

Study conception and design: NeK, IT, IY

Data collection: NeK

Analysis and interpretation of results: NeK, IT, IY

Draft manuscript preparation: TT, SO, NK

Critical revision of the article: NK, IY

Other (study supervision, fundings, materials, etc...): NeK, IY

All authors (NeK, IT, TT, SO, NK, IY) reviewed the results and approved the final version of the manuscript.

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# Comparison of the Effects of Amantadine, Methylprednisolone and Nimodipine in Sciatic Nerve Crush Injury

Ismail SAGIR<sup>1</sup>, Recai ENGIN<sup>1</sup>, Ilke Evrim SECINTI<sup>2</sup>, Idris ALTUN<sup>3</sup>

<sup>1</sup>Ministry of Health, Necip Fazıl City Hospital, Brain and Nerve Surgery Clinic, Kahramanmaraş, Türkiye

<sup>2</sup>Ministry of Health, Silifke State Hospital, Department of Pathology, Mersin, Türkiye

<sup>3</sup>Istanbul Rumeli University, Department of Neurosurgery Istanbul, Türkiye

Corresponding author: Recai ERGIN ✉ r.engin5552@gmail.com

## ABSTRACT

**AIM:** To assess the therapeutic effects of methylprednisolone, nimodipine, and amantadine on peripheral nerve injury using a rat sciatic nerve compression model, simulating potential treatments for humans.

**MATERIAL and METHODS:** A total of 36 adult male Wistar albino rats were divided into five groups. In Group 1, right sciatic nerve compression was performed, while the left side was used as a sham group (Group 2). Groups 3, 4, and 5 received methylprednisolone, nimodipine, or amantadine for one week following injury. In histopathologic analysis, nerve diameter, myelin diameter, axon diameter, G ratio, fibroblast count, mast cell count, and nerve number were measured.

**RESULTS:** Significant differences were observed across the groups. Amantadine showed the most positive effects on nerve regeneration, improving nerve diameter, myelin diameter, G ratio, fibroblast number, and nerve number compared to the controls. Nimodipine was effective in improving nerve diameter and G ratio but had no effect on other parameters. Methylprednisolone showed significance only in the G ratio. No drug was found to be superior to the others when compared in combination. Overall, amantadine had the most positive cellular effects after sciatic nerve injury; however, further research is required to explore the optimal dosage, frequency, administration route, and additional clinical parameters.

**CONCLUSION:** In this study, amantadine was found to have the most favorable effects on nerve regeneration, but other drugs showed limited effects on some parameters. However, the lack of superiority in combined applications and the lack of clarification of ideal treatment conditions suggest the need for more comprehensive research in the future.

**KEYWORDS:** Peripheral nerve, Crush injury, Amantadine, Methylprednisolone, Nimodipine

## INTRODUCTION

As a result of peripheral nerve injuries, serious permanent effects occur in 13-23 people per 100,000 per year and affect life (2,8,31). Peripheral nerve injuries are generally caused by motor-vehicle accidents, penetrating injuries, cutting injuries, gunshot wounds, falls, burns, fractures, ischemia, stretching, and crushing (3).

Nerve injuries are problems that seriously affect the quality of life and whose treatment is complex. These injuries may occur as a result of physical trauma or compression of the nerves

and may adversely affect nerve conduction (5). Sciatic nerve crush injury frequently manifests with symptoms, including marked pain, numbness, and muscle weakness, and it may limit the patient's daily activities (30).

Amantadine is an N-methyl-D-aspartate receptor antagonist and plays a potential role in reducing the effects of nerve damage on neuropathic pain (20). Methylprednisolone is a corticosteroid with anti-inflammatory properties that may promote nerve healing by reducing the inflammatory processes of nerve injury (33). Nimodipine acts as a calcium channel block-

Ismail SAGIR : 0000-0002-7809-5180

Recai ENGIN : 0000-0003-2957-9848

Ilke Evrim SECINTI : 0000-0002-8614-3971

Idris ALTUN : 0000-0003-4263-766X



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er and may provide neuronal protection by reducing calcium influx in nerve cells (5).

The aim of this study was to compare the effects of amantadine, methylprednisolone and nimodipine on sciatic nerve crush injuries. Comparing the effects of these three drugs on sciatic nerve crush injuries may help determine the most effective and safe option in the treatment of nerve injury. Using both clinical and experimental data, this study will evaluate the efficacy, safety, and possible side effects of each drug and thus contribute to developing better treatment strategies for patients with sciatic nerve crush injuries.

The results of this research could make an important contribution to the field of the treatment and rehabilitation of nerve injuries and could provide a basis for future studies in this field. Therefore, a comparative analysis of pharmacotherapeutic approaches used in the treatment of sciatic nerve crush injuries may help develop more effective treatment strategies in clinical practice.

## ■ MATERIAL and METHODS

### Surgical Method

After the approval of the Animal Local Ethics Committee of Kahraman Maras Sutcu Imam University (Date: 30.09.2020; Decision no: 02), the study was conducted in an experimental animal laboratory in accordance with ethical rules (Institute of Laboratory Animal Resources. Guide for the Care and Use of Laboratory Animals, 8<sup>th</sup> edition, 2011, The National Academies Press, Washington D.C.). In the experiment, 36 adult male Wistar albino rats weighing  $300 \pm 50$  g were used. To acclimatize the rats to the environment, they were fed standard pellet feed for 10 days under a room temperature of  $22 \pm 2^\circ\text{C}$ , humidity conditions of  $60 \pm 5\%$  and periodic white fluorescent light (12 h dark and, 12 h light) in the laboratory environment. Feed and drinking water were given ad libitum to the rats throughout the experiment. The rats were randomly divided into four groups of nine rats each. Groups 1 and 2 consisted of the same rats, and the left and right sciatic nerves of the rats were used for the sham and control groups, respectively.

Groups 1 and 2 (control and sham group, n=9): The right sciatic nerves of the rats were opened and crush damage was induced with a clamp; the right side was determined as the control group. On the left side, the skin over the sciatic nerve was opened and the nerve was accessed, but no damage was caused, and the left sciatic nerves were determined as the sham group; primary closure was performed on both sides.

Group 3 (methylprednisolone group, n=9): The right sciatic nerves of the rats were opened, and crush injury was induced with a clamp; primary closure was performed. After the injury, 2 mg/kg/day methylprednisolone was administered intraperitoneally for 1 week.

Group 4 (nimodipine group, n=9): The right sciatic nerve of the rats was opened, and crush injury was induced with a clamp; primary closure was performed. After the injury, 0.5 mg/kg/day nimodipine was administered intraperitoneally for 1 week.

Group 5 (amantadine group, n=9): The right sciatic nerve of the rats was opened, and crush injury was induced with a clamp; primary closure was performed. After the injury, 45 mg/kg amantadine was administered intraperitoneally at 6.4 mg/kg/day for 1 week.

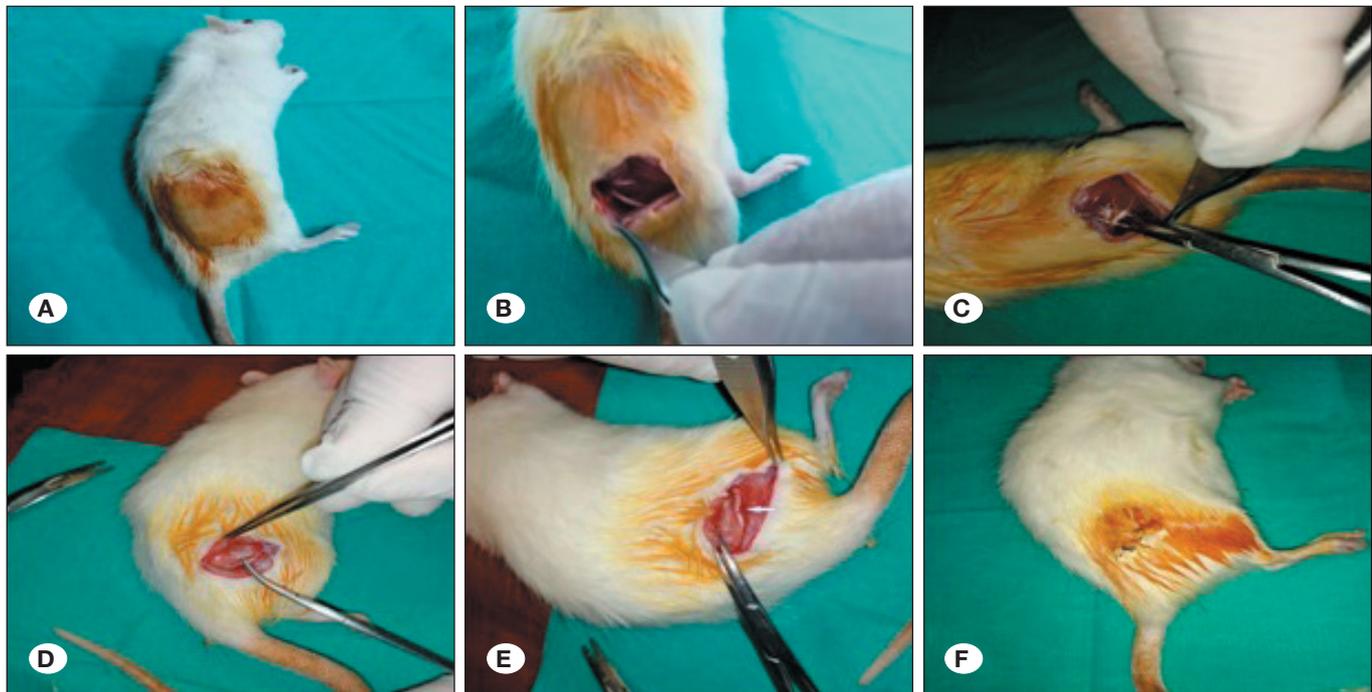
The exclusion criteria were infection, decreased nutritional function, death during and after the operation, and approval of the veterinary surgeon.

A crush injury model to the sciatic nerve was used to create an axonotmesis injury model for sciatic nerve injury. A single dose of 20 mg/kg cefazolin sodium was given intraperitoneally 30 min before the operation for prophylaxis. A dose of 50 mg/kg of ketamine hydrochloride and 10 mg/kg dose of xylazine hydrochloride were administered intraperitoneally and general anesthesia was achieved. After the lower legs of the rats were positioned, the operation area was prepared for the surgical procedure by brushing them with a povidone iodine scrub and povidoneiodine solution (Figure 1A). An Approximately 1.5 cm incision was made on the thighs of the rats to be operated on, and the muscle was reached through the subcutaneous skin (Figure 1B). The sciatic nerve was reached by dissecting the muscles (Figure 1C). The sciatic nerve was exposed by dissecting around the sciatic nerve and was then clamped; the surgeon then waited for one minute (Figure 1D). At the end of one minute, the clamp was removed, and the bleeding was checked. Macroscopically, it was observed that the crush damaged part of the sciatic nerves was distinguishable from the normal parts (Figure 1E). Although compression-induced flattening was observed in the damaged area, nerve integrity was preserved. The skin was sutured with 4/0 silk suture (Figure 1F). All surgical procedures were performed by a single surgeon.

Following recovery after surgery, the rats were placed in separate cages. In rats with sciatic nerve injury, flaccid paralysis was observed in the damaged side leg. The drugs planned to be administered were given intraperitoneally on the first day of the experiment immediately after the experiment. The administration of the drugs was continued for one week at the same time every day. At the end of one week, the administration of the drugs was discontinued and the rats were followed up to meet their physiological needs under normal conditions. At the end of one month, all rats were sacrificed by giving a high-dose anesthetic agent. The operation sites of the sacrificed rats were re-opened. No signs of infection were found in any of the rats. The damaged sciatic nerves in the drug-treated groups and the sciatic nerves in the control-sham group were dissected. The damaged site could be distinguished with the naked eye (Figure 2). The sciatic nerve was dissected 5 mm proximal and distal to the injury site and immediately placed in formaldehyde solution. The specimens were transferred to the pathology laboratory.

### Histopathological Method

After the tissues were fixed in 10% formaldehyde solution for 48 hours, three sections of 3 mm thickness were taken perpendicular to the long axis of the nerve fiber and embedded vertically in paraffin after routine follow-up procedures. Two



**Figure 1:** A) Preparation of the rat for the operation, B) Incision of the rat and access to the sciatic nerve after muscle dissection, C) Dissection of the sciatic nerve from surrounding tissues, D) Crush injury to the sciatic nerve, E) Image of the sciatic nerve after crush injury and the damaged area (indicated by arrow), F) Skin closure.



**Figure 2:** Visualization of the damaged area of the sciatic nerve after sacrifice (arrow).

sections of 5 mm and 2 mm (semi-thin) were made from each sample; 5 mm thick sections were stained with hematoxylin eosin, and 2 mm thick sections were stained with Luxol Acid Fast, a myelin stain. Quantitative morphometric analyses were performed on Luxol Acid Fast-stained slides using computerized image analysis software (Olympus BX51 microscope and DP2-BSW image analysis system). Measurements were made at 1,000 magnification. The nerve diameter, axon diameter,

and myelin thickness of the 25 nerve fibers were measured in each nerve section. In addition, the ratio of axon diameter to nerve diameter (myelinated axon), the G ratio, was calculated for each nerve fiber. The mean axon diameter, nerve diameter, myelin thickness and G ratio were then calculated for each sample. The numbers of myelinated axons, mast cells and fibroblasts were counted in randomly selected 2,500  $\mu\text{m}^2$  areas in each group.

#### Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) program version 21 was used for the statistical analysis of the data. Categorical data were given as numbers and percentages, and numerical data were given as mean, standard deviation, median, and minimum-maximum. A one-way analysis of variance test was used to compare the groups. For statistical significance,  $p < 0.05$  was accepted.

## RESULTS

### Histopathological Findings

When hematoxylin- and eosin-stained preparations were examined, intact myelinated axons surrounded by epineurium were observed in the sham group. In the control (trauma) group, marked stromal edema, vacuolization, axonal swelling, and myelin damage were observed in many neurons with mild inflammation. In the treatment groups, less edema and neuronal damage were observed compared to the control group, and the presence of many regenerated axons was remarkable. In the control group, mast cells (long arrows) and increased

fibroblasts (short arrows) were observed in the edematous stroma (Luxol Acid Fast x 400) (Figure 3A). When the control group was examined at a larger magnification (Figure 3B), very prominent nerve degeneration, axonal swelling and myelin damage were observed (arrows indicate vacuolized, swollen degenerated neurons with damaged myelin).

In the sham group, intact nerve tissue surrounded by intact perineurium (arrow) was observed (Luxol Acid Fast x 400) (Figure 4A). In the sham group, axons with intact myelin sheaths were observed (Figure 4B).

In the methylprednisolone group, edema (asterisk) was reduced compared to the control group, but was slightly more prominent compared to the amantadine group (Figure 5A). Fewer vacuolized, swollen degenerated neurons (red arrows) and more regenerated myelinated axons (long black arrows) were observed compared to the control group (Figure 5B).

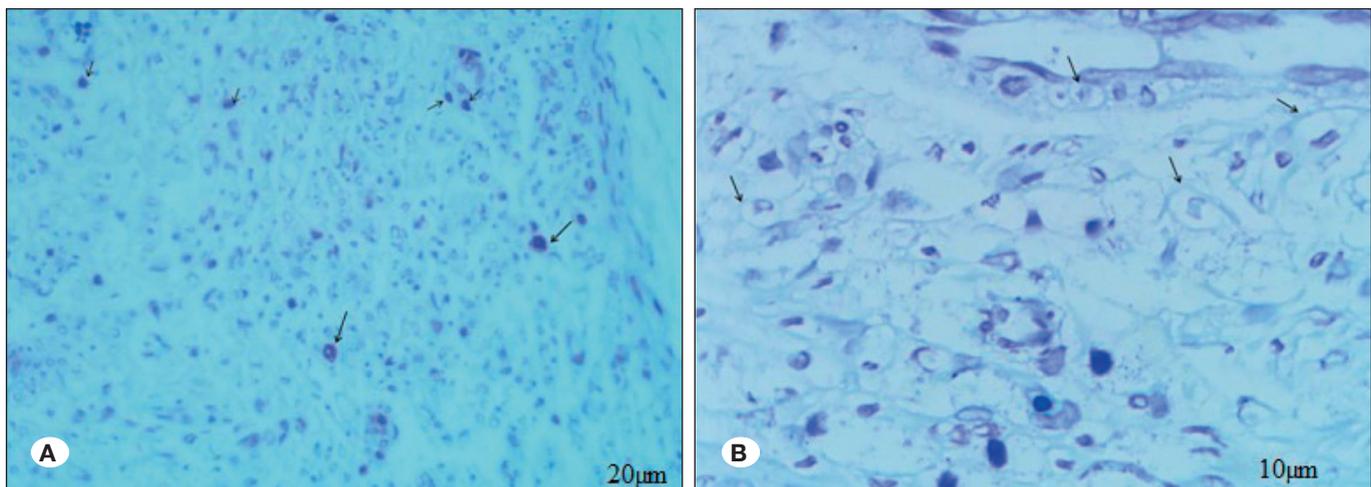
In the nimodipine group, edema (star) was reduced compared to the control group but was slightly more prominent than in the amantadine group (Figure 6A). Fewer vacuolized, swollen

degenerated neurons (red arrows) and more regenerated myelinated axons (long black arrows) were seen compared to the control group. Short black arrows indicate mast cells (Luxol Acid Fast x 1,000) (Figure 6B).

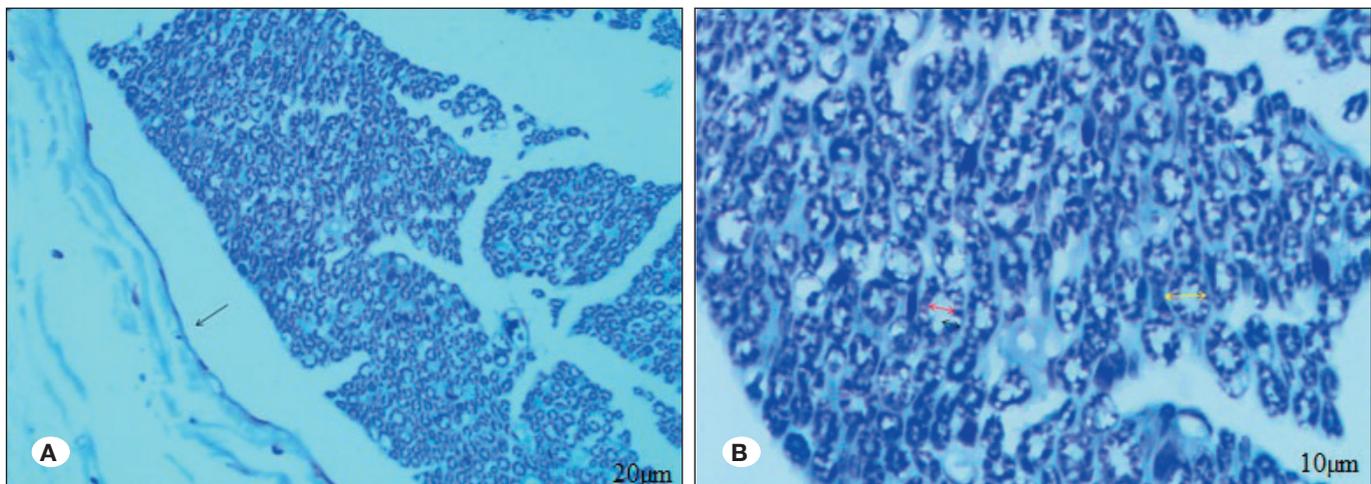
In the amantadine group, compared to the control group, edema (star) decreased, and more regenerated axons were observed (Luxol Acid Fast x 400) (Figure 7A). Edema (star) decreased in the amantadine group compared to the control group. Fewer vacuolized, swollen degenerated neurons (red arrows), fewer myelin figure corrugations (short black arrows), and more regenerated myelinated axons (long black arrows) were seen (Luxol Acid Fast x1000) (Figure 7B).

### Statistical Findings

According to the analysis performed for nerve diameter comparison according to the groups, the mean of the sham group was  $5022.77 \pm 414.38$  nm, the control group was  $2441.47 \pm 296.45$  nm, the amantadine group was  $3787.44 \pm 684.02$  nm, the nimodipine group was  $3585.09 \pm 792.78$  nm, and methylprednisolone group was  $3025.10 \pm 459.25$  nm. A statistical-



**Figure 3:** Histopathological image of the control group **A)** Luxol Asit Fast x400, **B)** Luxol Asit Fast x1000.



**Figure 4:** Histopathological image of the sham group **A)** Luxol Asit Fast x400, **B)** Luxol Asit Fast x1000.

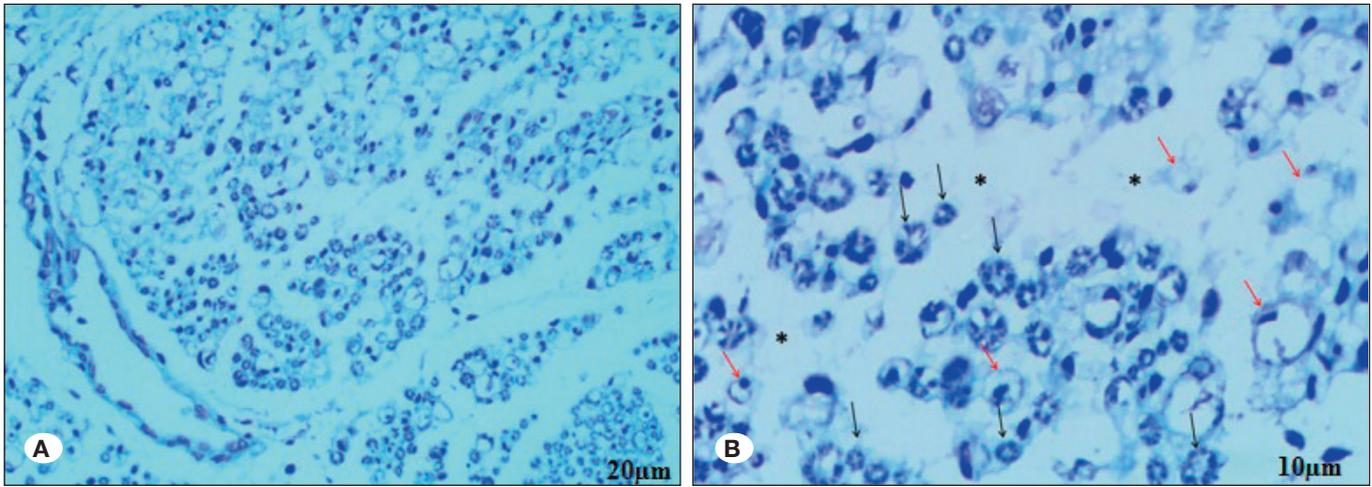


Figure 5: Histopathological image of the methylprednisolone group A) Luxol Asit Fast x 400, B) Luxol Asit Fast x 1000.

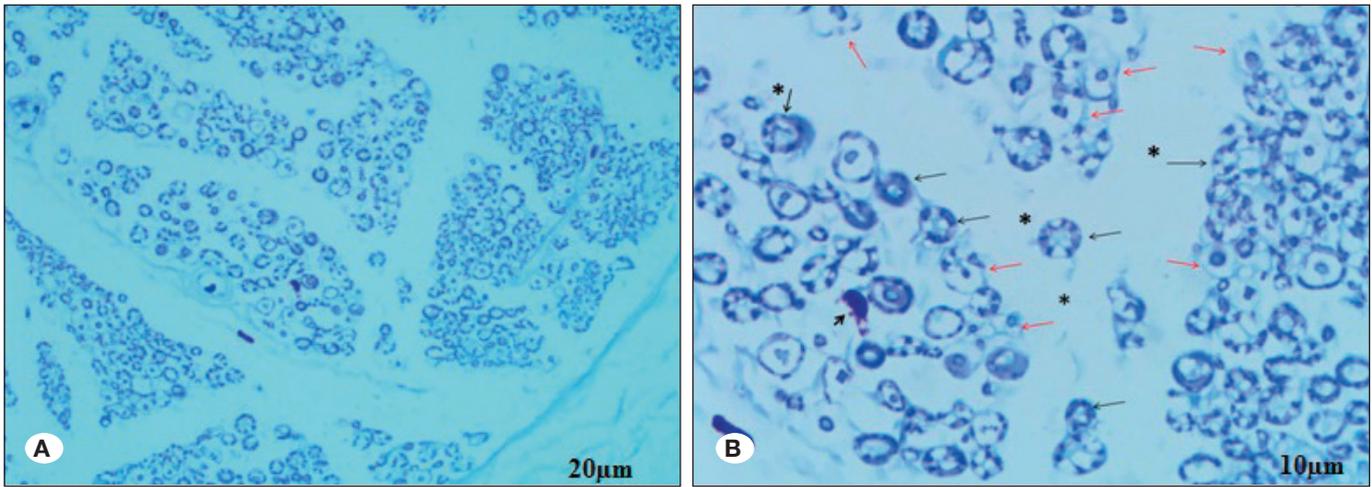


Figure 6: Histopathological image of the nimodipine group A) Luxol Asit Fast x 400, B) Luxol Asit Fast x 1000.

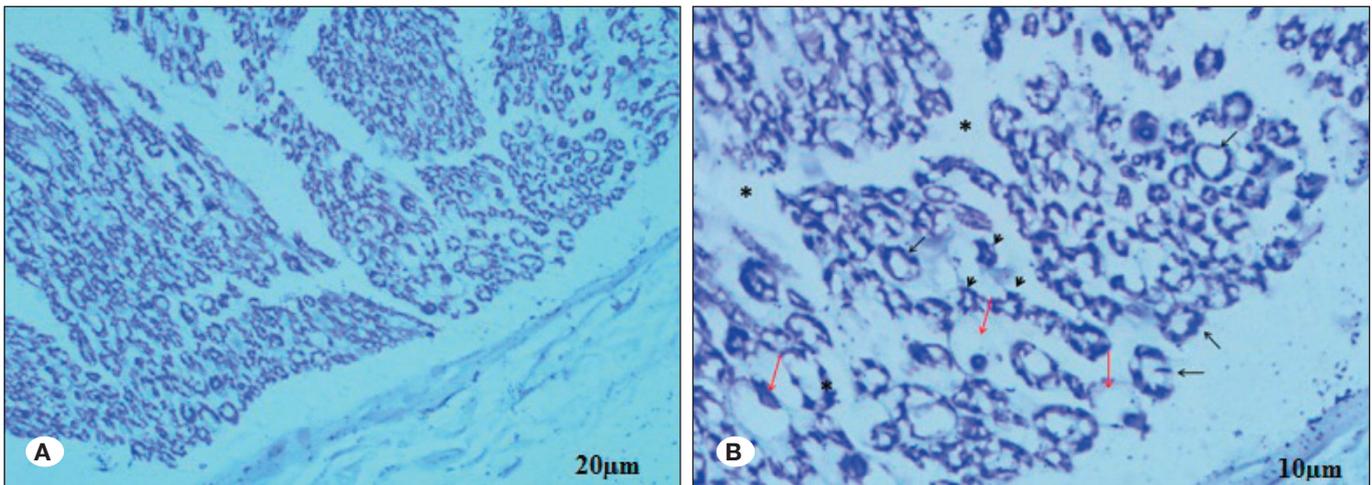


Figure 7: Histopathological image of the amantadine group. A) Luxol Asit Fast x 400, B) Luxol Asit Fast x 1000.

ly significant difference was found between the groups. According to the analysis performed for pairwise comparisons of the groups, it was determined that there was a statistically significant difference between the sham group and the other groups, the control group and the amantadine and nimodipine groups, and the amantadine group and the methylprednisolone group ( $p < 0.001$ ; Table I).

Myelin diameter was significantly higher in the sham group than in the other groups. Myelin diameter was significantly lower in the control group compared to the amantadine group, and was significantly higher in the amantadine group compared to the methylprednisolone group ( $p < 0.001$ ; Table II).

As a result of our study, axon diameter was found to be significantly higher in the sham group compared to the other groups ( $p < 0.001$ ; Table III).

It was found that the G ratio was significantly higher in the control group compared to the other groups ( $p < 0.001$ ; Table IV).

Fibroblast count was found to be significantly higher in the control group compared to the sham and amantadine groups and in the amantadine group compared to the sham group ( $p < 0.05$ ; Table V).

The mast cell count was significantly lower in the sham group compared to the control and nimodipine groups ( $p < 0.05$ ; Table VI).

According to the analysis performed for nerve cell count/2,500  $\mu\text{m}^2$  comparison according to the groups, the mean of the sham group was  $26.67 \pm 1.36$ , the control group was  $14.33 \pm 2.42$ , the amantadine group was  $20.33 \pm 3.27$ , the nimodipine group was  $17.78 \pm 3.11$ , and the methylprednisolone group was  $15.40 \pm 3.80$ , and a statistically significant difference was found between the groups. According to the analysis performed for pairwise comparisons of the groups, statistically significant differences were found between the sham group and the other groups, between the control group and the amantadine group, and between the amantadine group and the methylprednisolone group ( $p < 0.001$ ; Table VII).

**Table I:** Nerve Diameter Comparison according to Groups

Group	n	$\bar{x} \pm \text{SD}$	F	p-value*
Sham	9	$5022.77 \pm 414.38^{a,b,c,d}$		
Control	9	$2441.47 \pm 296.45^{a,e,f}$		
Amantadine	9	$3787.44 \pm 684.02^{b,e,g}$	17.3	<b>0.000</b>
Nimodipine	9	$3585.09 \pm 792.78^{c,f}$		
Methylprednisolone	9	$3025.10 \pm 459.25^{d,g}$		

\*One Way ANOVA, **Note:** There is a significant difference between the same exponential letters.

**Table II:** Myelin Diameter Comparison according to Groups

Group	n	$\bar{x} \pm \text{SD}$	F	p-value*
Sham	9	$1263.30 \pm 112.54^{a,b,c,d}$		
Control	9	$645.49 \pm 247.41^{a,e}$		
Amantadine	9	$976.64 \pm 100.14^{b,e,f}$	13.2	<b>0.000</b>
Nimodipine	9	$826.41 \pm 195.24^c$		
Methylprednisolone	9	$734.70 \pm 168.35^{d,f}$		

\*One Way ANOVA, **Note:** There is a significant difference between the same exponential letters.

**Table III:** Axon Diameter Comparison according to Groups

Group	n	$\bar{x} \pm \text{SD}$	F	p-value*
Sham	9	$3019.71 \pm 221.37^{a,b,c,d}$		
Control	9	$1907.72 \pm 292.65^a$		
Amantadine	9	$2090.42 \pm 249.90^b$	24.7	<b>0.000</b>
Nimodipine	9	$1990.84 \pm 303.22^c$		
Methylprednisolone	9	$1767.88 \pm 210.83^d$		

\*One Way ANOVA. **Note:** There is a significant difference between the same exponential letters.

**Table IV:** Comparison of g Ratio by Groups

Group	n	$\bar{x}\pm SD$	F	p-value*
Sham	9	0.60250±0.04 <sup>a</sup>	6.870	<b>0.000</b>
Control	9	0.78050±0.05 <sup>a,b,c,d</sup>		
Amantadine	9	0.56144±0.07 <sup>b</sup>		
Nimodipine	9	0.56978±0.11 <sup>c</sup>		
Methylprednisolone	9	0.59490±0.10 <sup>d</sup>		

\* One Way ANOVA. **Note:** There is a significant difference between the same exponential letters.

**Table V:** Comparison of Fibroblast Counts according to Groups

Group	n	$\bar{x}\pm SD$	F	p-value*
Sham	9	0.83±0.75 <sup>a,b</sup>	6.332	<b>0.001</b>
Control	9	5.17±2.71 <sup>a,c</sup>		
Amantadine	9	2.44±1.23 <sup>b,c</sup>		
Nimodipine	9	3.44±1.42		
Methylprednisolone	9	3.00±1.33		

\* One Way ANOVA. **Note:** There is a significant difference between the same exponential letters.

**Table VI:** Mast Cell Count Comparison according to Groups

Group	n	$\bar{x}\pm SD$	F	p-value*
Sham	9	0.17±0.40 <sup>a,b</sup>	5.165	<b>0.002</b>
Control	9	1.33±0.51 <sup>a</sup>		
Amantadine	9	0.56±0.52		
Nimodipine	9	1.00±0.00 <sup>b</sup>		
Methylprednisolone	9	0.70±0.67		

\* One Way ANOVA, **Note:** There is a significant difference between the same exponential letters.

**Table VII:** Nerve Cell Count Comparison according to Groups

Group	n	$\bar{x}\pm SD$	F	p-value*
Sham	9	26.67±1.36 <sup>a,b,c,d</sup>	16.708	<b>0.000</b>
Control	9	14.33±2.42 <sup>a,e</sup>		
Amantadine	9	20.33±3.27 <sup>b,e,f</sup>		
Nimodipine	9	17.78±3.11 <sup>c</sup>		
Methylprednisolone	9	15.40±3.80 <sup>d,f</sup>		

\* One Way ANOVA, **Note:** There is a significant difference between the same exponential letters.

## ■ DISCUSSION

Peripheral nerve damage is a common condition in both humans and animals and affects the physiology and functions of the body in the long term (10). Factors such as ischemia, inflammatory diseases, radiation, compression, traction, electric shock, and burns-most commonly trauma-cause peripheral nerve injury (16,29).

Peripheral nerve injuries may result in partial or total injuries. Permanent motor and sensory deficits and neuropathic pain secondary to peripheral nerve injury will decrease the quality of life of the patient and also dramatize the situation socially (11,26,34).

Regeneration is essential for nerves to regain function, as it allows damaged nerve fibers to repair and restore neural communication. However, functional recovery following nerve injury is not always achieved. Nerve regeneration involves complex processes like axon growth, synapse formation, and myelination, which can be hindered by factors such as injury severity, distance to target tissue, age, and health status. Scar tissue and inhibitory glial cells at the injury site may also impair regeneration, leading to suboptimal healing. It is estimated that traumatic peripheral nerve injuries cause over 500,000 new cases annually, highlighting the need for effective treatments and rehabilitation strategies (25). Current approaches include surgical techniques, nerve grafts, growth factor therapies, and biomaterials, but individual treatment outcomes vary, indicating a need for further optimization. Despite peripheral nerves' higher regeneration capacity compared to central nervous system nerves, the process is often slow and incomplete, with patients potentially experiencing lasting motor and sensory deficits. This underscores the importance of research into new regenerative therapies, such as stem cell therapy, gene therapy, and neuroprostheses. In conclusion, while nerve regeneration is crucial for recovery after traumatic injuries, optimal functional outcomes are not always achieved, emphasizing the need for continued research into effective treatment options.

The recovery time of the injured nerve depends on various external factors, including the location of the injury and nerve repair. However, it should not be ignored that the axonal regeneration rate is 1-2 mm/day, and there is no treatment to accelerate this process (23). The medications applied after peripheral nerve injury aim to support the regeneration process of the damaged nerve tissue in a healthy way and to make functional recovery close to complete. Therefore, many drugs have been tried at the point of treatment for peripheral nerve injuries and are still being tried.

In our study, when the sciatic nerve injury and medication groups were compared with the sham and control groups, it was observed that methylprednisolone, nimodipine, and amantadine were effective in the healing of sciatic nerve injury in the parameters examined histopathologically separately. In nerve diameter, amantadine and nimodipine were statistically equally effective for recovery, whereas there was no statistical difference between them in the methylprednisolone group compared to the control group. In myelin diameter, amanta-

dine was statistically significant, whereas no statistically significant difference was observed in the nimodipine and methylprednisolone groups compared to the control group. There was no statistically significant difference in axon diameter in the parameters of the three drugs compared to the control group. In the G ratio, amantadine, nimodipine and methylprednisolone were found to be equally effective for nerve healing and no statistically significant difference was found between the groups. The G ratio is defined as the ratio of the axon (inner diameter) to the axon and myelin (outer diameter) in the nerve fiber. The G ratio is expected to associate the complex interaction of demyelination, remyelination, and axonal degeneration with neurophysiological abnormalities and thus with clinical symptoms (4). When fibroblast counts were analysed, a statistically significant difference was found in the amantadine group compared to the methylprednisolone and nimodipine groups. No statistically significant difference was found in the number of mast cells among the three drug groups. It has been reported that fibroblast cells make important contributions to the regeneration and recovery of nerve tissue after damage to nerve tissue and that growth factor released from fibroblasts contributes to this process (13,32,35). In the number of nerves, amantadine was found to be effective in nerve healing, but no statistically significant difference was found among the nimodipine, methylprednisolone, and control groups.

In a study conducted by Hydman et al., it was shown that nimodipine used in damaged recurrent laryngeal nerves was effective in the recovery of peripheral nerve damage, and this study showed that nimodipine can be used in peripheral nerve damage (10).

In a study published by Mattsson et al., patients with recurrent laryngeal nerve injuries were repaired with microsurgery, and nimodipine was then given to the patients for three months. In the long-term follow-up of the patients, it was reported that all showed functional improvement, and no nimodipine-related side effects were observed (17). In our study, it was observed in histopathological parameters that nimodipine was effective in nerve injury healing, but long-term results and functional recovery were not examined.

In a study conducted by Lindsay et al., a crush damage model was applied to facial nerves, and then the effect of nimodipine was investigated; it was reported that rats receiving nimodipine showed earlier recovery compared to those not receiving nimodipine (15). In this study, subcutaneous pellets providing nimodipine release were placed in rats four days before the operation, and the aim was continuous release. In our study, nimodipine was given daily at an equal dose for seven days and then discontinued, and histopathological results were obtained in terms of efficacy.

In a study published by Scheller and Scheller, it was observed that oral nimodipine administered to patients who had undergone maxillofacial surgery and subsequently had traumatic facial nerve paralysis improved facial nerve function (28). In our study, nimodipine was administered intraperitoneally. The nimodipine used in Scheller's study was in oral form and administered to real patients. This suggests

that nimodipine may be effective in peripheral nerve damage independent of the route of administration.

In a study published by Zheng et al., it was reported that nimodipine applied after facial nerve crush injury in rats increased remyelination and improved damage (36). However, in this study, nimodipine of 6 mg/kg/day was given to rats via oral lavash, and when we compared it with our study, there was a difference in dose and route of administration; it was observed that it did not affect myelin diameter.

In a randomized multicenter study conducted by Scheller et al., nimodipine and hydroxyethyl starch were given prophylactically and until the 7th postoperative day in patients operated on for vestibular schwannoma and facial nerve functions. No statistically significant difference was found between the nimodipine group and the starch group (27). The fact that the effect of nimodipine, which was found to be effective histopathologically in our study, could not be shown statistically in Scheller's study was considered multicenter and that each patient included in the study may not be the same at the point of surgery.

In a study by Hota et al. comparing the efficacy of nimodipine, gabapentin, imipramine, and ketamine in neuropathic pain due to transection injury in rats, it was observed that nimodipine was also effective in neuropathic pain (9). Although the efficacy related to neuropathic pain was examined in this study, it supports our results because neuropathic pain can be observed after peripheral nerve damage, and the efficacy of nimodipine in neuropathic pain shows that it provides nerve regeneration. This may indicate recovery in neural tissue in basically the same way.

In a study conducted by Ohlsson et al. on the therapeutic efficacy of methylprednisolone on optic nerve damage in rats, no therapeutic effect of methylprednisolone on neural tissue was observed (21). In our study, although methylprednisolone was not found to be statistically effective in many histopathological parameters, it was found to be equally effective with other drugs used in the G ratio.

In an experimental study conducted by Li et al., rats were subjected to sciatic nerve transection injury, and then a membrane containing microspheres releasing methylprednisolone was applied locally to the damaged area (14). In this study, it was observed that local application of methylprednisolone reduced fibrosis around the damaged neural tissue and positively affected myelin thickness. In our study, it was observed that methylprednisolone did not affect myelin diameter but positively affected the G ratio. It was thought that the difference might be related to the dose, duration and route of administration. In addition, in our study, methylprednisolone had no statistically significant effect on fibroblast counts.

In a rat study of sciatic nerve crush injury published by Ozturk et al., the groups given methylprednisolone were compared with the groups given methylprednisolone and ozone, and histopathologically, a significant decrease in degeneration was observed in the group given methylprednisolone and ozone (22). No change was observed in the group given methylprednisolone. The results of this group were similar to those of

our methylprednisolone experimental group in terms of histopathological results.

In a study conducted by Mehrshad et al. on rats, sciatic nerve damage was created in rats, and then methylprednisolone-loaded hydrogel was applied locally. As a result of this study, it was stated that a local methylprednisolone-loaded hydrogel was effective in sciatic nerve damage (19). However, in our study, methylprednisolone was not found to be effective in other parameters except for affecting the G ratio. At this point, it was thought that factors such as the dose and duration of drug administration would make a difference.

In the experimental sciatic nerve injury model performed by Jiang et al. on rats, methylprednisolone was given at three different doses, and it was shown to be more effective on nerve regeneration at low and medium doses, but high doses were not recommended (11). In our study, the contribution of methylprednisolone to regeneration was not observed in general, and the G ratio was statistically better than in the control group.

In an experimental animal study conducted by Karlidag et al., the facial nerve was cut and re-anastomosed and then the subjects were divided into groups, and N-acetylcysteine and methylprednisolone were given (12). Regeneration in the facial nerve was then examined, and it was reported that the weakest results were found in the methylprednisolone group. The results of Karlidag et al.'s study were similar to the results of our study.

Many clinical studies have been conducted on amantadine. In a double-blind, randomized, and placebo-controlled study conducted by Pud et al. on cancer patients, amantadine was found to be effective in cancer patients, especially in neuropathic pain, compared to a placebo (24). In our study, amantadine was found to be effective in many histopathological parameters after peripheral nerve damage, and it was thought that a drug with histopathological efficacy might also be effective in neuropathic pain as a clinical reflection of a drug with histopathological efficacy. This was evaluated in correlation with the study conducted by Pud et al. (24).

In a randomized, double-blind, controlled study conducted by Medrik-Goldberg et al., the effects of lidocaine and amantadine administered intravenously on sciatic pain were compared (18). In this study, Medrik-Goldberg et al. showed that lidocaine had an analgesic effect and better results on the straight leg-raising test, as reflected in the clinic (18). However, since the histopathological effect of amantadine was examined in our study, unfortunately, its clinical reflection could not be examined. However, more studies may be required to provide evidence of the clinical effects of amantadine, whose histopathological efficacy was observed.

In a randomized, double-blind, controlled study conducted by Amin and Sturrock, the efficacy of amantadine in pain due to peripheral neuropathy in diabetic patients was investigated, and a decrease in neuropathic complaints was observed in patients receiving amantadine (1). In our study, amantadine was found to be histopathologically effective in peripheral nerve damage, and the study by Amin and Sturrock supports our results clinically (1).

In a study conducted by Eisenberg et al., it was reported that amantadine was not significantly more effective than a placebo in neuropathic pain, defined as postmastectomy pain syndrome in mastectomized patients (7). Unfortunately, neuropathic pain could not be analyzed in the subjects in our study, so no clinical comparison could be made.

In an experimental study conducted by Dogan and Karaca on rats, rats with spinal cord injury were given amantadine, and it was reported that amantadine could improve spinal cord injury by inducing angiogenesis and affecting apoptosis and inflammation compared with the control group (6). In this study conducted by Dogan and Karaca it was observed that amantadine provided regeneration and neuroprotection histopathologically; similar results were observed in our study.

## ■ CONCLUSION

Although all three drugs have various effects on peripheral nerve damage, further studies are needed in terms of dosage, frequency of administration, and route of administration. In addition, different parameters should be considered to evaluate the clinical-physiological effects of the drugs. In our study, amantadine, the efficacy of which had not been studied before, was histopathologically effective in peripheral nerve injury recovery. It was thought that this efficacy could be investigated in clinical studies.

Firstly, the effects of therapeutic agents such as amantadine, methylprednisolone and nimodipine in the treatment of sciatic nerve crush may also be of potential benefit in human clinical practice. However, dosage optimization is a critical factor for the applicability of these drugs in humans. In particular, the efficacy and side effects of each therapeutic agent should be individually tailored to patient characteristics.

Future clinical trials should evaluate the efficacy of different dosages, treatment durations and treatment combinations of these therapeutic agents. Furthermore, the use of biomarkers to identify individuals who respond to treatment could be an important step towards personalizing treatment. In terms of human applicability, further research is needed on how these treatment options can be optimized in specific disease groups and types of nerve injury, taking into account their safety profiles and risks of side effects.

In this context, it is clear that future studies that will provide more information on how to integrate the findings of our study into clinical practice and how to optimize treatment dosages will contribute to the development of treatment protocols.

Our study does not include evaluations on functional recovery after sciatic nerve crush. This is a limitation to fully understand the long-term effects and clinical benefits of treatment modalities. In future studies, a more comprehensive examination of functional recovery will provide more precise information on the efficacy of treatment protocols.

The study focused on short-term histopathologic parameters and did not examine long-term outcomes. Nerve healing and

regeneration are long-term processes, so evaluating the longer-term effects of treatment modalities will increase the clinical validity of the findings.

## 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:** 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.

## AUTHORSHIP CONTRIBUTION

Study conception and design: IS, RE

Data collection: IS, RE, IES, IA

Analysis and interpretation of results: IS, RE

Draft manuscript preparation: IS, RE, IES, IA

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# Evaluation of the First Cervical Vertebra Anatomy for Screw Fixation

Narmin FARAJIBAND<sup>1</sup>, Zuhre Asli AKTAN IKIZ<sup>2</sup>, Hulya UCERLER<sup>2</sup>

<sup>1</sup>Ege University Institute of Health Science, Department of Anatomy, Bornova, İzmir, Türkiye

<sup>2</sup>Ege University Faculty of Medicine, Department of Anatomy, Bornova, İzmir, Türkiye

This study was presented as a poster presentation at the '17<sup>th</sup> National Anatomy Congress', in Eskişehir, Türkiye, on 5<sup>th</sup>-9<sup>th</sup> September 2016.

**Corresponding author:** Zuhre Asli AKTAN IKIZ ✉ z.asli.ikiz@gmail.com

## ABSTRACT

**AIM:** To conduct a morphometrical analysis of the atlas to facilitate the development of atlas-related treatment methods and demonstrate the variations in atlas anatomy to aid surgical approaches and reduce complications.

**MATERIAL and METHODS:** The present study was conducted on 58 dry human atlas vertebrae supplied by the Ege University Faculty of Medicine, Department of Anatomy. Morphometrical analysis was performed using digital calipers.

**RESULTS:** The quantitative measurements were analyzed for screw fixation. The variations in the atlases were identified as spina bifida (1.7%), accessory foramen (on the right and left sides in 8.6% and 1.7%, respectively), canal for vertebral artery (1.7%, each on the right and left sides, and bilateral in 5.2%), and bipartite superior articular surface (on the right and left sides in 5.2% and 1.7%, respectively).

**CONCLUSION:** Some of these anatomical variants may explain certain previously described clinical symptoms. The measurements obtained from the 58 atlas vertebrae and the variations observed during the study were discussed. The primary outcome of the present study was that the measurements of the vertebrae are different for every individual. Therefore, it is important to use imaging methods and examinations before screw placement and other surgical approaches.

**KEYWORDS:** Anatomical variations, Atlas, Screw fixation

## INTRODUCTION

Fractures of the first cervical vertebra (atlas, C1), especially in the elderly population, account for approximately 2-3% of all acute cervical spine fractures. Acute C1 vertebra fractures comprise a large variety of fracture types, with treatment options based on the fracture type (9,10,12,16,17,19,33). The treatment for C1 instability can range from using a simple strap to undergoing upper posterior stabilization surgery. C1-C2 transarticular screw fixation, C1 lateral mass screwing, and C1 pedicle screwing are the surgical techniques used for stabilization (12). Apart from atlas fractures, other atlas-related pathologies like atlantoaxial dislocation, which can be observed in congenital craniovertebral junction anomalies, rheumatoid arthritis, infections, and

tumors, and following trauma, can necessitate screw placement (10,12). The vertebral artery runs through the spinal column in the transverse foramen and bilaterally on the vertebral artery groove of C1 lamina (24,30,31), complicating surgical procedures in this area (24,30). This study aims to perform a morphometrical analysis of C1 vertebrae and demonstrate variations in its anatomy to aid in the development of surgical approaches and reduce complications.

## MATERIAL and METHODS

The present study included 58 dry human atlas vertebrae supplied from the osseous collection of the Ege University Faculty of Medicine, Department of Anatomy. The specimens were of unknown sex and age and were free of fractures and



deformities. Morphometrical analysis was performed using a digital caliper (accurate up to 0.01 mm). The means and standard deviations of the measurements were calculated. The measured distances are shown in Figure 1.

Anatomical variations of the C1 vertebra such as spina bifida, unilateral or bilateral accessory foramen, bifurcated superior articular surface, and canal for vertebral artery were also noted during these measurements.

The present study was conducted in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments.

**RESULTS**

The quantitative measurements were analyzed for screw fixation. The quantitative measurements are provided in Table I.

Detailed measurements of the entry zone for screw fixation were made for both sides. The mean area of the entry zone was  $33.6 \pm 7.2 \text{ mm}^2$ , width (A) was  $8.2 \pm 1.1 \text{ mm}$ , and height (B) was  $4.0 \pm 0.7 \text{ mm}$ . The anterior and posterior heights of the lateral mass were also measured. The mean posterior height of the lateral mass (C) was  $16.9 \pm 2.5 \text{ mm}$ , whereas the mean anterior height (D) was  $17.8 \pm 1.8 \text{ mm}$ . The mean length between the medial edge of the groove for the vertebral artery and the midpoint of the posterior arch (E) was  $11.2 \pm 3.6 \text{ mm}$ . Another measurement performed on the lateral mass was the length (F) of the path followed by the screw. This length was  $17.3 \pm 1.5 \text{ mm}$ .

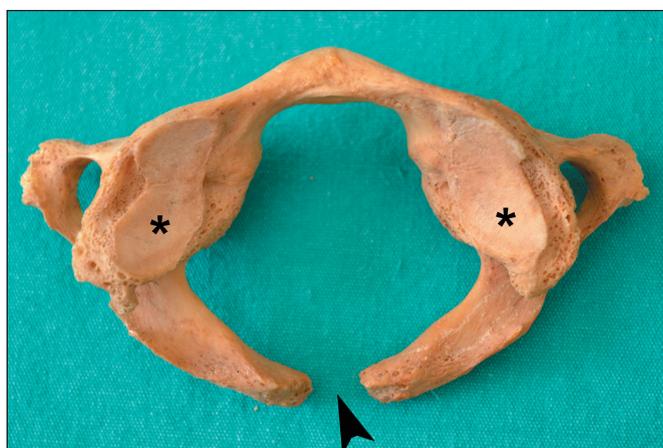
The variations in the C1 vertebrae were identified as spina bifida (1.7%) (Figure 2), accessory foramen (on right and left sides in 8.6% and 1.7%, respectively) (Figure 3), canal for vertebral artery (1.7%, each on the right and left sides, and

**Table I:** The Quantitative Measurements of the Atlas for Screw Fixation in This Study

	Right side (mean±SD)	Left side (mean±SD)	Bilateral (mean±SD)
Entry zone area (mm <sup>2</sup> )	33.8±7.2 (min-max: 18.9-52.2)	33.4±7.2 (min-max: 13.6-50.0)	33.6±7.2 (min-max: 13.6-52.2)
Entry zone width (A) (mm)	8.4±0.7 (min-max: 6.9-9.9)	8.1±1.2 (min-max: 2.9-10.2)	8.2±1.1 (min-max: 2.9-10.2)
Entry zone height (B) (mm)	3.9±0.7 (min-max: 2.3-5.9)	4.1±0.7 (min-max: 2.5-6.1)	4.0±0.7 (min-max: 2.3-6.1)
Height of lateral mass (posterior) (C) (mm)	17.1±2.5 (min-max: 11.5-23.9)	16.7±2.2 (min-max: 10.3-20.8)	16.9±2.5 (min-max: 10.3-23.9)
Height of lateral mass (anterior) (D) (mm)	17.9±1.6 (min-max: 12.9-20.2)	17.6±1.6 (min-max: 12.6-19.9)	17.8±1.8 (min-max: 12.6-20.2)
Distance between the vertebral artery groove and median line (E) (mm)	11.6±3.5 (min-max: 4.8-19.9)	10.7±3.8 (min-max: 3.8-19.6)	11.2±3.6 (min-max: 3.8-19.9)
Lateral mass screw length (F) (mm)	17.4±1.4 (min-max: 15.1-21.2)	17.2±1.6 (min-max: 13.7-21.3)	17.3±1.5 (min-max: 13.7-21.3)



**Figure 1:** A: Entry zone width B: Entry zone height C: Height of lateral mass, posterior D: Height of lateral mass, anterior E: Distance between the vertebral artery groove and median line (ML) F: Lateral mass screw length.



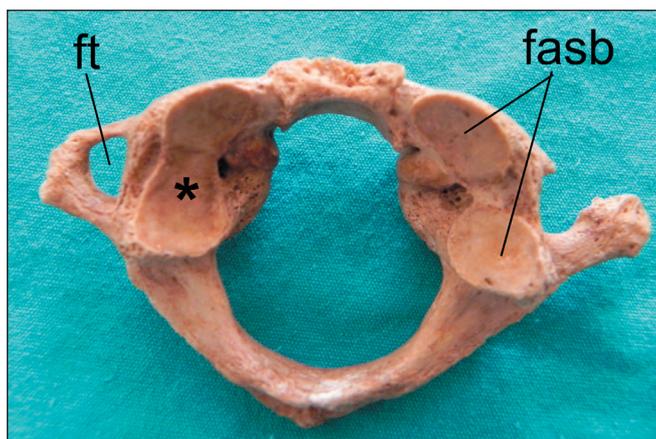
**Figure 2:** The case with spina bifida arrowhead: spina bifida, \*: superior articular surface.



**Figure 4:** An example of a canal for vertebral artery. **cav:** canal for vertebral artery, **ft:** transverse foramen, \*: superior articular surface.



**Figure 3:** An example of an accessory foramen arrow: accessory foramen, **ft:** transverse foramen, \*: superior articular surface.



**Figure 5:** An example of a bipartite superior articular surface **fasb:** bipartite superior articular surface, **ft:** transverse foramen, \*: superior articular surface.

**Table II:** The Variations of C1 Vertebra in this Study

	Right side	Left side	Bilateral
Accessory foramen, n (%)	5 (8.6)	1 (1.7)	0 (0.0)
Canal for vertebral artery, n (%)	1 (1.7)	1 (1.7)	3 (5.1)
Two-piece superior joint surface, n (%)	3 (5.1)	1 (1.7)	0 (0.0)

bilateral in 5.1%) (Figure 4), bipartite superior articular surface (on the right and left sides in 5.1% and 1.7%, respectively) (Figure 5) (Table II).

## DISCUSSION

Given that atlas fractures represent approximately 25% of all craniocervical injuries and 2% to 13% of all cervical spine injuries, various surgical procedures have been described for screw fixation (18,19). For these screw fixations, it is impera-

tive to consider anatomical variations and morphometric measurements of the atlas (12,13,19,20,31).

Bipartite superior articular surface could be an asymptomatic variation whose potential outcomes remain undemonstrated in clinical studies. Kavaklı et al. found bipartite superior articular surface in 12.8% of their study population (20). In our study, bipartite superior articular surface was found on the right and left sides of the C1 vertebrae at a rate of 5.1% and 1.7%, respectively.

Gupta considered  $33.47 \pm 8.56 \text{ mm}^2$  as the mean working area for screw placement (screw entry zone), with the smallest area being  $14.4 \text{ mm}^2$  (12). This value was  $33.60 \pm 7.20 \text{ mm}^2$  in the current present study. Moreover, Gupta found no significant difference in the mean values of various parameters of the atlas vertebrae between the right and left sides, which was consistent with our findings (12).

The posterior and anterior heights of lateral mass are important for determining the length of the screw for fixation procedures. In many studies, including ours, the mean length of the entry zone for the screw was from 3.9 to 4.16 mm. Thus, many authors suggested using 3 mm diameter screw for safe surgery (11,12,24,28).

The mean length between the midpoint of the groove for the vertebral artery and the midpoint of the anterior arch is surgically importance for hemilaminectomy. Dağlıoğlu identified this distance as 14.4 mm (7). In our study, this distance was  $11.6 \pm 3.50 \text{ mm}$  on the right side and  $10.7 \pm 3.8 \text{ mm}$  on the left side.

Congenital variations of the atlas can result in craniovertebral junction and cervical spine instability, particularly in pediatric cases (2,5,6,25,26,32). Moreover, these variations can be misdiagnosed as fractures, subluxations, or osteolysis (2,4,14,29).

Some of the variations detected in our study may explain the clinical symptoms described in literature. Among these variations, spina bifida is an embryological defect. Since intrauterine interventions are rapidly gaining attention in recent times, it is important to define the defect size of spina bifida. In an anatomical study by Bodon et al., defects ranging 1–5.5 mm were reported in 7.5% of cases (3). Kim reported a 1.17% arcus posterior defect rate in his study on atlas variations (21). In our study, a 6.7 mm posterior arch defect was detected in 1/58 atlases (1.7%).

The presence of an accessory foramen transversarium in the cervical vertebra is a rare variation. In such cases, the size of the real transverse process is narrowed, potentially exerting pressure on the vertebral artery and the sympathetic plexus. Similarly, the narrowing of the transverse foramen may result in the formation of atheromatose plaque, which may result in thrombosis emboli or reflex spasm (1). Anas et al. reported an atlas with ellipsoid accessory transverse foramen on both sides (1). Lyrtzis et al. examined 141 dried atlas vertebrae, Thirty-seven of the 141 vertebrae (26.2%) had at least one accessory foramen. The accessory foramen was unilateral and bilateral in 67.6% and 32.4% of the cases, respectively. This prevalence was higher than those in most previous studies. The mean anteroposterior diameter (length) of this foramen was  $4.2 \pm 1.4 \text{ mm}$  on the right and  $3.8 \pm 1.0 \text{ mm}$  on the left side (23). In the present study, the accessory foramen was found in five atlases (8.6%) on the right side and in one atlas on the left side (1.7%). The authors considered that the foramina might transmit tributaries of the vertebral vein (1).

The existence of a canal for the passage of the vertebral artery (canalis vertebralis, Kimmerle's anomaly, Kimmerle's variant, foramen atlantoideum posterior, foramen retroarticular superior, or arcuate foramen) may exert external mechanical pressure on the vessel, especially during extension and rotation movements of the head. This variation has been associated with vertebrobasilar insufficiency symptoms, various types of headaches, and acute hearing loss (22). Many authors suggest that it is a congenital characteristic, whereas others suggested that it is a genetic trait given that a familial appearance of this variation is observed (22). In a study, a bridge on the groove of the vertebral artery was reported in 1.2% of the observed atlases (24). Dhall et al. observed that bridgings and canals on the left side the vertebral artery were more common (8). They hypothesized that this difference may result from unequal weight bearing (15). Unlikely the results of their study, in our study, the existence of the canal for the passage of the vertebral artery was observed in one atlas on the left side (1.7%), in one on the right side (1.7%), and bilaterally in three (5.2%).

The injury of vertebral artery is possible during procedures such as the insertion of screws in the lateral masses of the atlas. Thus, the existence of the vertebral canal should be identified before planning posterior approaches to the region of the craniovertebral junction to protect the vertebral artery (22,27).

## ■ CONCLUSION

Some of these anatomical variants are known to cause certain clinical symptoms that have been described in detail in the literature. The measurements obtained from the 58 atlas vertebrae and observed variations during present study were discussed. The main result of the present study was that the measurements of the vertebrae are different in every individual. Therefore, imaging methods, such as computed tomographic analysis, and examinations before surgical approaches should be used to evaluate the region's anatomy and to identify appropriately sized screws for screw fixation.

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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.

**AUTHORSHIP CONTRIBUTION**

Study conception and design: NF, ZAAI, HU

Data collection: NF

Analysis and interpretation of results: NF, ZAAI

Draft manuscript preparation: NF, ZAAI, HU

Critical revision of the article: ZAAI, HU

Other (study supervision, fundings, materials, etc.): NF, ZAAI, HU

All authors (NF, ZAAI, HU) reviewed the results and approved the final version of the manuscript.

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# Impact of DNA Methylation Profiling on Central Nervous System Tumor Diagnosis and Management: A Pediatric Cohort Study from Türkiye

Mehmet Arda INAN<sup>1</sup>, Ayca ERSEN DANYELI<sup>1</sup>, Figen SOYLEMEZOGLU<sup>2</sup>, Berrin BABA OGLU<sup>2</sup>, Bahattin TANRIKULU<sup>3</sup>, Memet OZEK<sup>3</sup>

<sup>1</sup>Acibadem University School of Medicine, Department of Pathology, Istanbul, Türkiye

<sup>2</sup>Hacettepe University School of Medicine, Department of Pathology, Ankara, Türkiye

<sup>3</sup>Acibadem University School of Medicine, Department of Pediatric Neurosurgery, Istanbul, Türkiye

This study has been presented at the 32<sup>nd</sup> National Congress of Pathology, Antalya, Türkiye

**Corresponding author:** Mehmet Arda INAN ✉ arda.inan@acibadem.edu.tr

## ABSTRACT

**AIM:** To present a single-center experience, and to highlight the urgent need for multi-institutional collaboration in Türkiye and surrounding regions lacking access to methylation platforms, with the aim of enhancing diagnostic precision and neuropathological practice.

**MATERIAL and METHODS:** All pediatric patients who underwent methylation-based tumor classification (MBTC) between November 2023 and July 2025 were retrospectively identified. Clinical, histological, and molecular data were extracted and correlated with methylation results. Concordance between histopathology and MBTC was categorized as concordant, minor discordance, major discordance, novel classification, or un-classifiable.

**RESULTS:** A total of 48 tumors were profiled (26 females [54%]; 22 males [46%]; median age, 6.5 years; range, 0–17). The most frequent localization was supratentorial (n=18, 36%). Of the entire cohort, concordance was 58%. Excluding unclassifiable cases, concordance among evaluable tumors was 67%. Discordance occurred in 11 cases (23%), including 6 (13%) with major discrepancies. Concordance was significantly associated with tumor localization ( $p=0.028$ ) but not WHO grade ( $p=0.17$ ) and classifier confidence ( $p=0.73$ ).

**CONCLUSION:** MBTC is a valuable complementary tool in the diagnostic workup of pediatric central nervous system (CNS) tumors, particularly in morphologically ambiguous and ultra-rare cases. It should be integrated with conventional histopathology rather than viewed as a replacement, as it may prevent prognostic misclassification and inappropriate treatment in selected patients.

**KEYWORDS:** DNA methylation, Pediatrics, Neuropathology, Glioma

**ABBREVIATIONS:** CNS: Central nervous system, CNV: Copy number variation, FFPE: Formalin-fixed paraffin-embedded, IHC: Immunohistochemistry, ITD: Internal tandem duplication, MDB: Medulloblastoma, MBTC: Methylation-based tumor classification, NGS: Next-generation sequencing, PF: Posterior fossa, WHO: World Health Organization

Mehmet Arda INAN : 0000-0002-6179-2828 Figen SOYLEMEZOGLU : 0000-0002-8002-5165 Bahattin TANRIKULU : 0000-0002-9096-8685  
Ayca Ersen DANYELI : 0000-0001-8015-9916 Berrin BABA OGLU : 0000-0003-3074-4011 Memet OZEK : 0000-0002-7166-7166



## ■ INTRODUCTION

Accurate classification of pediatric central nervous system (CNS) tumors remains a major challenge due to their broad morphological heterogeneity and the growing number of newly recognized molecularly defined entities. DNA methylation profiling has emerged as an important complementary tool in this context.

Mapping and interpreting methylated regions with supervised machine learning classifiers has enabled methylation-based tumor classification (MBTC) of CNS tumors (5). Wiestler et al. conducted one of the earliest demonstrations, showing that methylation signatures could distinguish anaplastic gliomas independently of isocitrate dehydrogenase mutation or 1p/19q codeletion status (24). With continued development, MBTC has become a robust diagnostic adjunct applicable to formalin-fixed paraffin-embedded (FFPE) material, the global standard for pathological specimen preservation, and is now widely used to resolve diagnostic uncertainty in morphologically ambiguous cases (1).

Despite growing international adoption, MBTC implementation remains irregular, particularly in low- and middle-income countries where infrastructure, cost, and training barriers limit access to advanced molecular diagnostics. As a result, pediatric data from such regions are scarce, and the real-world impact of methylation profiling on diagnostic resolution is largely unknown outside high-income reference centers. Acibadem University is one of the few centers in Türkiye routinely applying methylation profiling to diagnostically challenging pediatric CNS tumors and receiving referrals from multiple provinces and external institutions.

Documenting this experience provides insight into the types of cases which most benefit from methylation-based analysis; the practical challenges encountered during implementation; and how this approach may reduce diagnostic variability at the national level. The aim of presenting this single-center experience is to contribute missing regional data to the international literature and support broader integration of molecular diagnostics into pediatric neuropathology practice.

## ■ MATERIAL and METHODS

All pediatric patients who underwent MBTC at our institution between November 2023 and July 2025 were retrospectively identified. MBTC was requested for tumors with indeterminate morphology or in cases of diagnostic disagreement between centers. As our institution functions as a national referral center, the cohort included both locally diagnosed cases and consultation cases from external hospitals.

DNA was extracted from FFPE tissue blocks at our institutional molecular pathology laboratory. All samples were processed locally up to the DNA extraction step. The extracted DNA was subsequently transferred to the distributor's accredited laboratory where bisulfite conversion, array hybridization, and scanning were performed using the Illumina Infinium MethylationEPIC BeadChip (850K) platform. Raw IDAT files generated by the external laboratory were electronically returned to our

center. Quality control, normalization, and methylation-based classification were performed using the Epignostix/Heidelberg Brain Tumor Classifier version 12.8. The calibrated classifier score reflected model confidence; copy number variation (CNV) profiles were reviewed as complementary genomic data.

The following variables were recorded for each case: age, sex, tumor localization, histopathological diagnosis, assigned methylation class, World Health Organization (WHO) 2021 classification and grade, calibrated classifier score, and next-generation sequencing (NGS) results where available. Calibrated classifier scores were categorized based on established thresholds, consistent with the scoring framework introduced by Capper et al. for methylation-based CNS tumor classification (5): > 0.90 (high confidence), 0.50–0.90 (moderate confidence), and < 0.50 (low confidence).

Correlation between histopathology and MBTC was categorized as concordant, minor discordance, major discordance, novel class, or unclassifiable. As several discordance subcategories contained very small numbers, categories were dichotomized for statistical analysis. Cases were therefore grouped as either “concordant” or “non-concordant,” with minor discordance, major discordance, and novel classes classified as non-concordant. Unclassifiable cases were excluded from concordance analysis.

Associations between concordance status and clinicopathological variables—including tumor localization (supratentorial, posterior fossa/cerebellum, ventricular, brainstem/spinal, or unknown), WHO grade (low grade [1–2] vs. high grade [3–4]), and classifier confidence—were evaluated using chi-square or Fisher's exact tests, as appropriate. Statistical analyses were performed in Python (SciPy, Pandas), with  $p < 0.05$  considered statistically significant. Effect sizes were calculated using Cramér's  $V$  for  $\chi^2$  tests or the phi coefficient for  $2 \times 2$  tables.

This retrospective study was approved by the Institutional Review Board of our institution (IRB No.: 2025-12/99). The requirement for informed consent was waived as no identifiable patient information was collected and all analyzed data were anonymized.

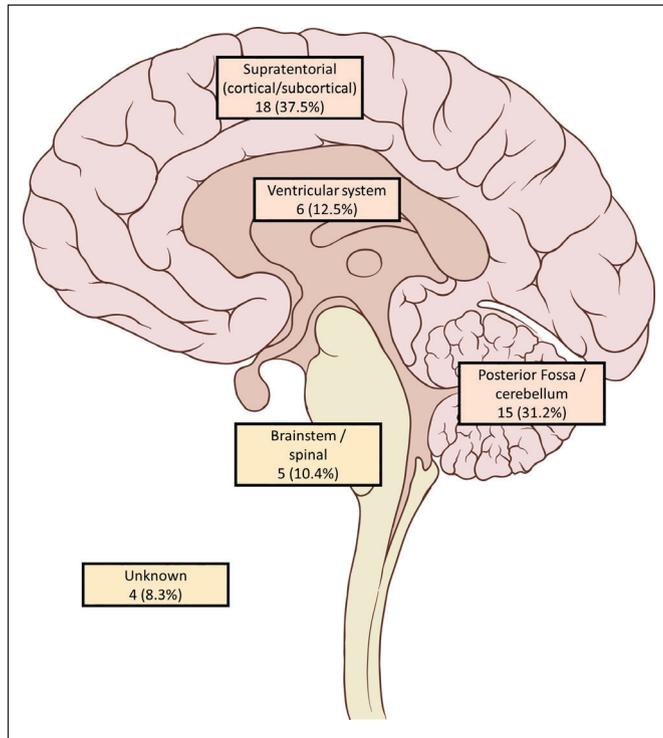
## ■ RESULTS

A total of 48 pediatric CNS tumors underwent MBTC between November 2023 and July 2025. The cohort encompassed the full pediatric spectrum (0–17 years of age) and reflected real-world referral patterns, including both primary and consultation cases (Table 1). The cohort included 26 females (54%) and 22 males (46%), with a median age of 6.5 years. The most frequent tumor localization was supratentorial (cortical/subcortical) ( $n=18$ , 36%), followed by the posterior fossa/cerebellum ( $n=15$ , 31%), ventricular system ( $n=6$ , 13%), and brainstem/spinal cord ( $n=5$ , 10%); localization was undocumented or uncertain in 4 cases (8%). The tumor localization distribution is illustrated in Figure 1. NGS data were available for 26 tumors (54%), primarily to evaluate clinically relevant and potentially targetable alterations.

Table I: Summary of Study Cohort

Category	Methylation Group	Methylation Subtype	Number of Cases	Median Age (years)	Localizations	WHO Grade
Adult-type diffuse gliomas	Glioblastoma, IDH-wild type	Mesenchymal subtype	1	15	Frontal lobe	4
Pediatric-type diffuse low-grade gliomas	Angiocentric glioma, MYB/MBL1 altered		1	8	Temporal lobe	1
	Diffuse glioma, MAPK altered, cell cycle activated	Diffuse glioma, MAPK altered, cell cycle activated	1	4	Temporal lobe	1
	Diffuse midline glioma, H3 K27-altered, subtype H3 K27-mutant or EZHIP expressing	Diffuse midline glioma, H3 K27-altered, subtype H3 K27-mutant or EZHIP expressing	3	9	Cervical spine, Pons	4
Pediatric-type diffuse high-grade gliomas	Diffuse pediatric-type high grade glioma, MYCN subtype	Diffuse pediatric-type high grade glioma, MYCN subtype	2	11.5	Frontotemporal lobe, Temporal lobe	4
	Diffuse pediatric-type high grade glioma, RTK1 subtype, subclass A	Diffuse pediatric-type high grade glioma, RTK1 subtype, subclass A	1	8	Frontal lobe	4
		Hemispheric	1	9	Frontal lobe	1
Circumscribed astrocytic gliomas	Pilocytic astrocytoma	Midline	2	6	Third ventricle, Globus pallidus	1
		Infratentorial	2	10.5	Cerebellum	1
	Ganglioglioma		1	3	Temporal lobe	1
Glioneuronal and neuronal tumors	Dysembryoplastic neuroepithelial tumor		1	3	Temporal lobe	1
	Papillary glioneuronal tumor; PRKCA-fused		1	17	Lateral ventricle	1
	Posterior fossa group B ependymoma	Subclass 2	1	12	Posterior fossa	3
Ependymal tumors	Supratentorial ependymoma, ZFTA fusion-positive, subtype ZFTA-RELA fused	Subclass A	2	6.5	Parietal lobe, unknown	3
Choroid plexus	Choroid plexus papilloma	Pediatric subtype	1	0	Posterior fossa	2
		Group 3 subtype	1	1		4
		Group 3 subtype, subclass I	1	7		4
		Group 3 subtype, subclass IV	1	4		4
	Medulloblastoma	Group 4 Subtype, Subclass VI	1	8	Cerebellum	4
		Group 4 subtype, subclass VII	4	8		4
		Group 4 subtype, subclass VIII	1	4		4
Embryonal	Atypical teratoid/ rhabdoid tumor	MYC-subtype	1	9	Posterior fossa	4
		TYR subtype	2	2	Posterior fossa, Lateral ventricle	4
	CNS tumor with BCOR internal tandem duplication		1	7	Left hemisphere	Unclassified
	Embryonal tumor with multilayered rosettes, C19MC-altered		3	3	Parietal lobe, Pons	4
Mesenchymal, non-meningothelial tumors involving the CNS	CIC-rearranged sarcoma		3	4	Parietal lobe	4
Novel	Neuroepithelial tumor with PATZ1 fusion		1	8	Lateral ventricle	
	Neuroepithelial tumor, MN1:CXXC5-fused		1	14	Intraventricular	Unclassified
	Neuroepithelial tumor, PLAGL1-fused		1	6	Temporal lobe	
Benign	Unclassified (Masson Tumor)		1	0	Supratentorial	Unclassified
Other	Unclassified/Unclassifiable		4	8	Frontal lobe, Posterior fossa	Inadequate DNA

WHO 2021 grading was applicable in most cases: 25 tumors (51%) were Grade 4; 3 (6%) were Grade 3; 1 (2%) was Grade 2; and 10 (21%) were Grade 1. In total, 4 tumors (8%) were unclassified according to WHO 2021, with 4 (8%) unclassifiable due to low tissue quality. One tumor (2%) was a benign vascular lesion not represented in the WHO CNS classification.



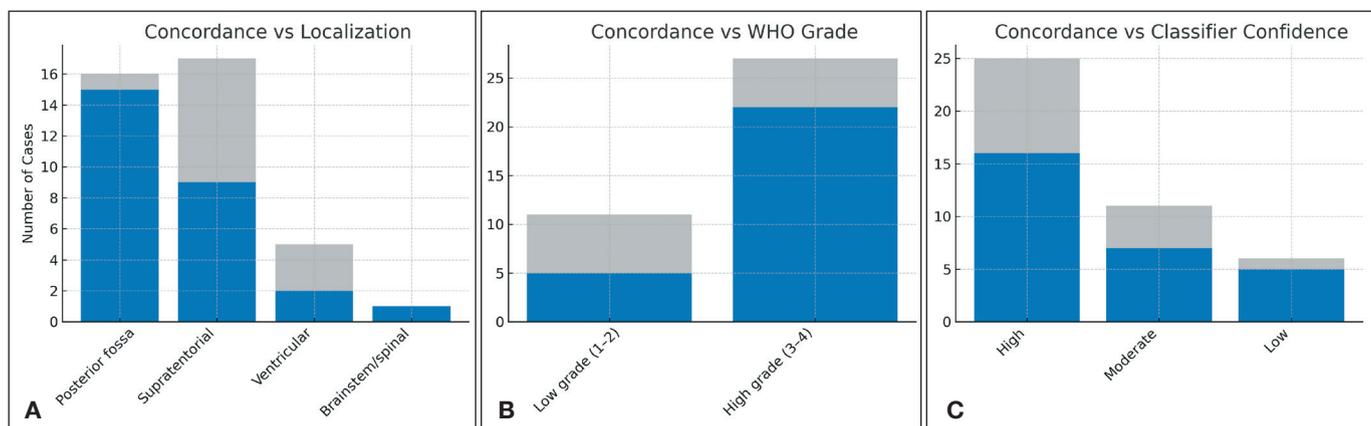
**Figure 1:** Tumor Localizations. The most frequent tumor localization was supratentorial (cortical/subcortical) (n=18, 36%), followed by the posterior fossa/cerebellum (n=15, 31%), ventricular system (n=6, 13%), and brainstem/spinal (n=5, 10%); localization was undocumented or uncertain in 4 cases (8%).

The classifier yielded a mean calibrated score of 0.84 (range, 0.30–1.00; median, 0.98). Classification confidence was high in 27 cases (56%), moderate in 11 cases (23%), and low in 6 cases (13%). All 4 unclassifiable tumors had calibrated scores below 0.30.

In terms of final classification, 40 tumors (83%) corresponded to WHO-recognized entities, 3 tumors (6%) represented novel methylation classes, and 5 tumors (10%)—4 malignant and 1 benign—were unclassifiable. Of the WHO-recognized tumors, 3 of 40 cases (7.5%; equivalent to 6% of the entire cohort) showed discordance between histopathological and methylation-based diagnosis, and 8 tumors (17%) were assigned to methylation subtypes not currently included in the WHO 2021 classification.

Correlation between histopathology and MBTC was concordant in 28 tumors (58%). Minor discordance was observed in 5 cases (10%), major discordance in 6 cases (13%), and 3 tumors (6%) were assigned to novel methylation classes, all of which were necessarily non-concordant. Concordance could not be assessed in 6 cases (13%) due to insufficient material or unclassifiable methylation profiles. For dichotomized analysis, cases with unclassifiable profiles (n = 6) were excluded. Of the remaining 42 evaluable tumors, 28 (67%) were concordant and 14 (33%) were non-concordant.

Concordance was not significantly associated with WHO grade (low grade [1–2] vs. high grade [3–4];  $\chi^2 = 1.86, p = 0.17$ ;  $\phi = 0.21$ , small effect). However, concordance was significantly associated with tumor localization ( $\chi^2 = 9.08, df = 3, p = 0.028$ ). Posterior fossa tumors showed the highest concordance (15/16, 94%). Supratentorial (9/17, 53%) and ventricular tumors (2/5, 40%) were more frequently discordant. The effect size was in the medium-to-large range (Cramér’s  $V = 0.48$ ). Concordance was not significantly associated with classifier confidence ( $\chi^2 = 0.88, df = 2, p = 0.65$ ), and the effect size was small (Cramér’s  $V = 0.12$ ). Concordance distributions are illustrated in Figure 2.



**Figure 2:** Concordance between histopathology and methylation-based tumor classification (MBTC) according to tumor localization (A), WHO grade (B), and classifier confidence (C). Localization showed a significant association with concordance ( $p = 0.028$ ), whereas neither WHO grade ( $p = 0.17$ ) nor classifier confidence ( $p = 0.65$ ) demonstrated significant associations. Blue bars indicate concordant cases and gray bars indicate non-concordant cases.

Concordance with histopathology was highest in medulloblastomas (9/10, 90%). Discordance was more common in diffuse gliomas (5/7 non-concordant, 71%) and ependymomas (1/3 non-concordant, 33%), reflecting their greater morphological and molecular heterogeneity. All 3 novel methylation-defined tumors (100%) were discordant by definition. In total, 6 tumors (13%) could not be classified by MBTC due to low-quality or atypical DNA methylation profiles.

## ■ DISCUSSION

This study is the first reported clinical experience with MBTC of CNS tumors in Türkiye. At the time of the study, only a single center in the country had established the capacity to perform this analysis. MBTC has both advantages and limitations, as with all diagnostic modalities. Its chief strength lies in providing diagnostic clarity in otherwise ambiguous cases, informing appropriate clinical management (5). While accurate classification is essential for determining therapy and prognosis, a limitation of MBTC is that it does not by itself identify actionable variants. In over half of the study cohort, MBTC was complemented by concurrent NGS which provided additional information on clinically relevant and potentially targetable alterations. This illustrates the value of integrated molecular diagnostics in pediatric neuro-oncology. Nevertheless, by refining the understanding of tumor pathogenesis, methylation profiling may facilitate the discovery of novel therapeutic avenues more efficiently and cost-effectively.

Diagnostic challenges are pronounced in pediatric CNS tumors due to their marked morphological heterogeneity. Histologically similar appearances may represent biologically distinct entities—for example, gangliogliomas with pilocytic features—or, conversely, a single entity such as pilocytic astrocytoma may show diverse morphologies including oligodendrocyte-like cells. Pattern recognition supported by a targeted immunohistochemical (IHC) panel is sufficient for most tumors in routine practice, as demonstrated in recent regional studies (10,13,18). However, in cases where morphology is equivocal and limited IHC does not yield clarity, MBTC offers an adjunctive solution especially valuable in the pediatric setting where accurate classification has direct therapeutic and prognostic implications.

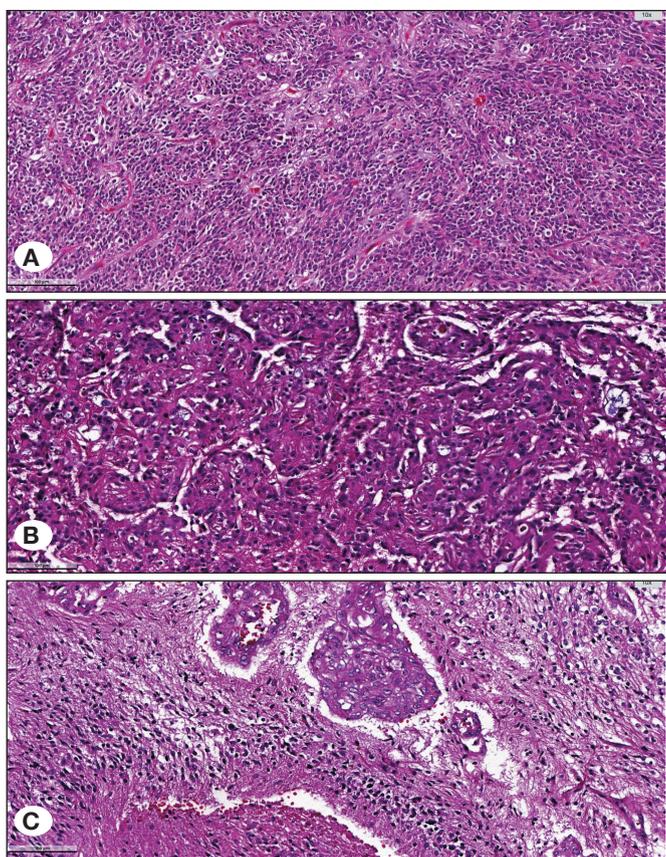
From a practical standpoint, the input requirements for methylation profiling are broadly comparable to those of large DNA + RNA NGS panels. Both approaches generally require a DNA input of approximately 200–500 ng from FFPE or frozen material (9). A key distinction is that methylation profiling does not require RNA, which is often difficult to obtain in sufficient quality from small biopsies or archival samples. This increases feasibility in pediatric neuro-oncology, where tissue quantity may be limited. Turnaround time is comparable to that of large NGS panels and depends on batching and bioinformatics capacity. Cost per sample is typically lower due to the absence of RNA extraction and library preparation. These practical features may reduce technical barriers in laboratories developing molecular workflows and increase the likelihood of successful implementation, particularly in centers handling small or fragmented diagnostic specimens.

To provide a coherent framework, entity-specific findings were grouped into three domains: (i) established pediatric tumor types where MBTC directly informs clinical risk stratification (e.g., medulloblastoma [MDB]), (ii) emerging methylation classes not incorporated into the current WHO classification, and (iii) morphologically ambiguous tumors for which MBTC offers diagnostic resolution.

MDB represents one of the most important pediatric groups in which MBTC has immediate clinical utility. While WNT- and SHH-activated tumors can be identified using IHC, non-WNT/non-SHH tumors cannot be reliably subclassified without molecular profiling (2,7). Approximately 60% of all MDBs fall within the so-called Group 3/4 category, further subdivided into at least 8 methylation-defined subgroups which cannot be reliably distinguished by histology or conventional techniques alone. These molecularly defined subgroups display distinct biological behavior, including varying metastatic potential and characteristic driver events, with *MYC* or *MYCN* amplification emerging as key CNVs associated with aggressive clinical course (16,21). One limitation of MBTC, however, is that it does not provide information on *TP53* mutational status, which remains clinically relevant in SHH-activated (Group 2) MDB. In this pediatric cohort, MDB accounted for 10 of 48 tumors (21%). In 9 of these cases (90%), MBTC provided critical diagnostic refinement not achievable through histology and IHC alone. The only unclassifiable case was a consultation block, likely affected by pre-analytic tissue quality. This finding underscores the practical value of methylation profiling in the routine evaluation of pediatric MDB.

Beyond the established WHO 2021 entities, MBTC occasionally identifies tumor classes not yet formally recognized. In this pediatric cohort, 3 tumors (6.2%) were assigned to novel methylation classes: neuroepithelial tumor with *PATZ1* fusion; neuroepithelial tumor with *MN1::CXXC5* fusion; and neuroepithelial tumor with *PLAGL1* fusion. The case classified as a *PATZ1*-fused tumor showed histological features resembling a supratentorial ependymoma, Grade 3. NGS confirmed a *MN1::PATZ1* fusion. The *MN1::CXXC5*-fused tumor was initially interpreted as a high-grade neuroepithelial tumor at the referring laboratory. Despite that both harbored *MN1* fusions, their histological appearances were markedly diverse (Figure 3A and 3B). The *PLAGL1*-fused tumor was described as a low-grade glioneuronal tumor in its original pathology report. The morphology is illustrated in Figure 3C. These examples highlight how methylation profiling can reveal underlying biological distinctions not apparent by morphology alone, emphasizing the evolving nature of CNS tumor taxonomy and underscoring the role of MBTC in expanding the diagnostic framework (1,8,15,22). Nevertheless, interpretation of these novel classes requires caution, as their long-term clinical behavior and optimal management strategies remain to be fully defined.

MBTC also frequently assigns tumors to subclasses which exceed the granularity of WHO 2021. In this cohort, pilocytic astrocytomas were subclassified into infratentorial/posterior fossa, midline, and hemispheric groups. Similarly, ependymomas were resolved into supratentorial *ZFTA* fusion-positive subclasses (including *ZFTA-RELA* subclass A) and posterior



**Figure 3:** Histological micrographs of novel tumors not classified in the 2021 WHO classification of CNS tumors. **A)** Neuroepithelial tumor with *PATZ1* fusion. **B)** Neuroepithelial tumor with *MN1::CXXC5* fusion. **C)** Neuroepithelial tumor with *PLAGL1* fusion. Hematoxylin and eosin, magnification  $\times 100$ .

fossa group B (PFB-2). While WHO 2021 distinguishes major molecular groups such as ST-E *ZFTA* fusion-positive and PFA vs. PFB, it does not currently endorse these deeper subclass layers (3). Such subclassifications, available in the DKFZ/Heidelberg classifier (v12.8), may support future risk stratification and trial design. *ZFTA*-fusion-positive tumors are shown to comprise several molecular clusters, including those involving *NCOA1/2* or *MAML2* partners, although these remain investigational (17, 23). Cavalli et al. identified 5 PFB subclasses, with poorer survival restricted to PFB1 and PFB3 (6). Subclass distinctions did not alter initial management in this cohort but may hold future prognostic significance.

A compelling example of the diagnostic utility of MBTC arises in ultra-rare entities. Tumors previously grouped under primitive neuroectodermal tumors are now recognized as distinct molecularly defined embryonal neoplasms, including those driven by *CIC*, *FOXR2*, *MN1*, and *BCOR* alterations (19). Such alterations may be missed by small targeted NGS panels; broader sequencing approaches are often unavailable or cost prohibitive. In this cohort, one 7-year-old girl with a hemispheric mass—previously diagnosed as a high-grade

ependymoma—was reclassified by MBTC as a CNS tumor with *BCOR* internal tandem duplication (ITD). Notably, CNS *BCOR*-ITD tumors are so newly defined that no formal WHO grade assignment currently exists. Similarly, three 4-year-old girls originally diagnosed with high-grade glioma were re-assigned by MBTC to *CIC*-rearranged sarcoma with high confidence. These major discordant cases shared two unifying features: morphology which overlapped with common pediatric glial tumors, leading to plausible but incorrect histological diagnoses; and IHC profiles insufficiently specific to distinguish between biologically unrelated entities. For example, *BCOR*-ITD may be undetectable on IHC as *BCOR* staining can be negative despite the underlying alteration (20). These cases highlight a recurring pitfall in pediatric neuro-oncology: certain ultra-rare molecular entities can convincingly mimic high-grade gliomas or embryonal tumors on routine workup. MBTC therefore serves as a critical safeguard against prognostically significant misclassifications.

Importantly, several reclassified tumors would have received substantially different treatments had MBTC not been performed. High-grade ependymoma is typically treated with adjuvant radiotherapy. CNS *BCOR*-ITD tumors are biologically distinct and generally managed with intensive chemotherapy-based regimens (14). Thus, without MBTC, the 7-year-old girl with *BCOR*-ITD would likely have undergone inappropriate radiotherapy-based management. Likewise, the two tumors originally labeled as high-grade glioma but reclassified as *CIC*-rearranged sarcoma would have been placed on glioma protocols. *CIC*-rearranged sarcomas, however, require sarcoma-directed treatment strategies, not glioma regimens (4).

Glioneuronal tumors represent another area of diagnostic difficulty in both histopathology and MBTC. In this cohort, two such tumors were assigned to low-confidence or alternative classes. A previous work reported an 11-year-old girl whose lesion was interpreted as a high-grade glioneuronal tumor but was reclassified by MBTC as pilocytic astrocytoma, midline, with a high confidence score (25). This discrepancy has major clinical implications, as a diagnosis of high-grade glioma would prompt aggressive therapy, whereas pilocytic astrocytoma has a markedly better prognosis. Similar challenges have been documented in larger institutional series, emphasizing that glioneuronal tumors frequently cluster ambiguously or fail to reach a confident methylation assignment (12). These findings highlight the need for an integrated diagnostic approach combining morphology, IHC, molecular alterations, and clinical context.

A practical limitation of MBTC is sensitivity to tissue quality. In this series, low-quality consultation material—often representing small blocks with suboptimal fixation—produced failed or unclassifiable profiles. This underscores the importance of proper fixation, processing, and DNA preservation, particularly where rare pediatric tumors are referred for tertiary evaluation. Importantly, this limitation is not specific to MBTC but applies to all molecular assays. Recognizing these pre-analytic constraints is crucial for realistic integration of MBTC into routine practice.

Beyond technical considerations, broader implementation of MBTC in Türkiye presents financial and systemic obstacles. At present, MBTC is not reimbursed by the national social security system, and the cost—approximately equal to the national minimum monthly wage—must be paid by patients, creating substantial barriers to access. Addressing reimbursement, infrastructure, and inter-institutional collaboration is essential for integrating MBTC into routine pediatric neuro-oncology care. This work highlights the feasibility and diagnostic value of MBTC and may help lay the groundwork for national adoption.

A strength of this study is that our center functions as a national reference hub, receiving consultation material and referral cases from across Türkiye and neighbor countries. This contributed to the diversity of the cohort, encompassing a wide spectrum of pediatric CNS tumors rather than a narrowly selected institutional population. Although this cohort included 48 cases over less than 2 years, this number is consistent with other institutional experiences and is meaningful in the context of rare pediatric CNS tumors. Indeed, prior reports, including Karimi et al., have demonstrated that even moderate case volumes can yield impactful insights, provided that they originate from referral-based series (11). Such diversity increases the representativeness of these findings; however, broader multi-institutional studies remain necessary to validate and expand these results.

## CONCLUSION

This experience demonstrates that MBTC is a valuable adjunct in the diagnostic workup of pediatric CNS tumors, particularly in morphologically ambiguous and ultra-rare entities. However, its current limitations include uncertain performance in certain glioneuronal tumors, subclassifications which are not currently clinically actionable, and susceptibility to pre-analytic factors. MBTC should therefore be regarded neither as a replacement for conventional histopathology nor a universal solution, but as a complementary tool within an integrated diagnostic framework. Applied in this balanced manner, MBTC could potentially enhance diagnostic precision while minimizing the risk of over-reliance or over-interpretation. As classification systems evolve and molecular approaches converge, MBTC is likely to become an increasingly indispensable component of precision neuropathology.

### 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: MAI, AED

Data collection: BT, BB, FS, MO

Analysis and interpretation of results: MAI, AED

Draft manuscript preparation: MAI

Critical revision of the article: AED, BT, MO

Other (study supervision, fundings, materials, etc.): BB, FS, BT, MO

All authors (MAI, AED, BT, BB, FS, MO) reviewed the results and approved the final version of the manuscript.

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**Supplementary Table: Clinicopathological and Molecular Characteristics of the Study Cohort.**

Patient Number	Localization	Histological Diagnosis	Methylation Profile	Correlation with Histology	WHO Class	Score	WHO Class	NGS Result	Age	Gender	WHO Grade
1	Right temporal lobe	Consultation (Angiocentric glioma)	Angiocentric glioma, MYB/MBL1 altered	Concordant	Angiocentric glioma	0.99	Existing	MYB::QKI	8	Female	1
2	Posterior fossa	Consultation (Unknown diagnosis)	Atypical teratoid/rhabdoid tumour, MYC-subtype	Unknown	Atypical teratoid/rhabdoid tumour, MYC-subtype	0.99	Existing	Not tested	9	Male	4
3	Posterior fossa	Atypical teratoid/rhabdoid tumour	Atypical teratoid/rhabdoid tumour, TYR subtype	Concordant	Atypical teratoid/rhabdoid tumour, TYR-subtype	0.98	Existing	SMARCB1	0	Female	4
4	Right lateral ventricle	Atypical teratoid/rhabdoid tumour	Atypical teratoid/rhabdoid tumour, TYR subtype	Concordant	Atypical teratoid/rhabdoid tumour, TYR subtype	0.81	Existing	Not tested	4	Female	4
5	Posterior fossa	Atypical choroid plexus papilloma	Choroid plexus papilloma, pediatric subtype	Non-concordant (Minor)	Atypical choroid plexus papilloma	0.9	Existing (Discordant)	Not tested	0	Female	2
6	Left parietal lobe	High grade pediatric glioma	CIC-rearranged sarcoma	Non-concordant (Major)	CIC-rearranged sarcoma	0.99	Existing	Negative (Not in panel)	4	Female	4
7	Left parietal lobe	High grade glial tumor	CIC-rearranged sarcoma	Non-concordant (Major)	CIC-rearranged sarcoma	0.99	Existing	Not tested	4	Female	4
8	Left parietal lobe	High grade glial tumor	CIC-rearranged sarcoma	Non-concordant (Major)	CIC-rearranged sarcoma	0.99	Existing	Not tested	4	Female	4
9	Left hemisphere	High grade neuroepithelial tumour	CNS tumour with BCOR internal tandem duplication	Non-concordant (Major)	CNS tumour with BCOR internal tandem duplication	0.99	Existing	Not tested	7	Female	Unclassified
10	Temporal lobe	High grade glioneuronal tumor	Diffuse glioma, MAPK altered, cell cycle activated	Non-concordant (Minor)	Ganglioglioma with anaplastic features	0.31	Existing (Discordant)	CDKN2A loss	4	Male	1
11	Pons	Diffuse midline glioma, H3.3 K27-mutant	Diffuse midline glioma, H3 K27-altered, subtype H3 K27-mutant or EZHIP expressing	Concordant	Diffuse midline glioma, H3.3 K27-mutant	0.89	Existing	H3K27M, IDH2 and TP53	6	Female	4
12	Talamus	High grade glioma, H3.3 K27-mutant	Diffuse midline glioma, H3 K27-altered, subtype H3 K27-mutant or EZHIP expressing	Concordant	Diffuse midline glioma, H3.3 K27-mutant	0.99	Existing	H3K27M and PIK3CA	9	Female	4

Supplementary Table: Cont.

Patient Number	Localization	Histological Diagnosis	Methylation Profile	Correlation with Histology	WHO Class	Score	WHO Class	NGS Result	Age	Gender	WHO Grade
13	Cervical spine	Diffuse midline glioma, H3.3 K27-mutant	Diffuse midline glioma, H3 K27-altered, subtype H3 K27-mutant or EZHIP expressing	Concordant	Diffuse midline glioma, H3.3 K27-mutant	0.99	Existing	H3K27M and TP53; CDKN2A/B and RB1 deletion	12	Male	4
14	Temporal lobe	Consultation (High grade neuroepithelial tumor)	Diffuse paediatric-type high grade glioma, MYCN subtype	Concordant	Diffuse paediatric-type high-grade glioma MYCN	0.9	Existing	PTEN deletion, N-MYC amplification	9	Female	4
15	Right frontotemporal lobe	Consultation (High grade glioma tumor)	Diffuse paediatric-type high grade glioma, MYCN subtype	Concordant	Diffuse paediatric-type high-grade glioma MYCN	0.4	Existing	Negative	14	Male	4
16	Left frontal lobe	High grade glioma tumor	Diffuse paediatric-type high grade glioma, RTK1 subtype, subclass A (novel)	Concordant	Diffuse paediatric-type high-grade glioma RTK1	0.48	Existing	dMMR	8	Male	4
17	Temporal lobe	Low grade mixt glioneuronal tumor (DNET+RFNGT)	Dysembryoplastic neuroepithelial tumour	Concordant	Dysembryoplastic neuroepithelial tumour	0.98	Existing	FGFR1::TACC1	3	Male	1
18	Right frontoparietal lobe	Consultation (Unknown diagnosis)	Embryonal tumour with multilayered rosettes, C19MC-altered	Unknown	Embryonal tumour with multilayered rosettes, C19MC-altered	1	Existing	Not tested	2	Male	4
19	Pons	Consultation (Embryonal tumour)	Embryonal tumour with multilayered rosettes, C19MC-altered	Concordant	Embryonal tumour with multilayered rosettes, C19MC-altered	0.98	Existing	Not tested	3	Male	4
20	Right frontoparietal lobe	Consultation (Embryonal tumor)	Embryonal tumour with multilayered rosettes, C19MC-altered	Concordant	Embryonal tumour with multilayered rosettes, C19MC-altered	1	Existing	Not tested	3	Male	4
21	Temporal lobe	Consultation (Ped. Low Grade Glioma)	Ganglioglioma	Non-concordant (Minor)	Ganglioglioma	0.99	Existing	BRAF V600E	3	Female	1
22	Left frontal lobe	High grade glioma tumor	Glioblastoma, IDH-wildtype, mesenchymal subtype	Concordant	Glioblastoma, IDH-wildtype	0.55	Existing (Unclassified subtype)	RB1, TP53	15	Female	4
23	Posterior fossa	Classical Medulloblastoma, non-WNT/non-SHH	Medulloblastoma, Group 3 subtype	Concordant	Medulloblastoma, Group 3 subtype	0.46	Existing	Not tested	1	Male	4
24	Posterior fossa	Classical Medulloblastoma, non-WNT/non-SHH	Medulloblastoma, Group 3 subtype, subclass I	Concordant	Medulloblastoma, Group 3 subtype	0.94	Existing	Not tested	7	Male	4

Supplementary Table: Cont.

Patient Number	Localization	Histological Diagnosis	Methylation Profile	Correlation with Histology	WHO Class	Score	WHO Class	NGS Result	Age	Gender	WHO Grade
25	Posterior fossa	Classical Medulloblastoma, non-WNT/non-SHH	Medulloblastoma, Group 3 subtype, subclass IV	Concordant	Medulloblastoma, Group 3 subtype	0.99	Existing	Negative	4	Male	4
26	Posterior fossa	Classical Medulloblastoma, non-WNT/non-SHH	Medulloblastoma, Group 4 Subtype, Subclass VI	Concordant	Medulloblastoma, Group 4 subtype	0.98	Existing	Not tested	8	Male	4
27	Posterior fossa	Classical Medulloblastoma, non-WNT/non-SHH	Medulloblastoma, Group 4 subtype, subclass VII	Concordant	Medulloblastoma, Group 4 subtype	0.86	Existing	Negative	5	Female	4
28	Posterior fossa	Classical Medulloblastoma, non-WNT/non-SHH	Medulloblastoma, Group 4 subtype, subclass VII	Concordant	Medulloblastoma, Group 4 subtype	0.99	Existing	Not tested	7	Male	4
29	Posterior fossa	Classical Medulloblastoma, non-WNT/non-SHH	Medulloblastoma, Group 4 subtype, subclass VII	Concordant	Medulloblastoma, Group 4 subtype	0.99	Existing	Not tested	9	Female	4
30	Posterior fossa	Classical Medulloblastoma, non-WNT/non-SHH	Medulloblastoma, Group 4 subtype, subclass VII	Concordant	Medulloblastoma, Group 4 subtype	0.99	Existing	Not tested	9	Female	4
31	Posterior fossa	Classical Medulloblastoma, non-WNT/non-SHH	Medulloblastoma, Group 4 subtype, subclass VIII	Concordant	Medulloblastoma, Group 4 subtype	0.94	Existing	Not tested	4	Male	4
32	Left lateral ventricle	Supratentorial ependymoma, grade 3	Neuroepithelial tumour with PATZ1 fusion (novel)	Non-concordant (Novel)	Unclassified	0.9	Novel	MN1::PATZ1	8	Male	Unclassified
33	Intraventricular	Consultation (High grade neuroepithelial tumour)	Neuroepithelial tumour, MN1:CXXC5-fused (novel)	Non-concordant (Novel)	Astroblastoma, MN1-altered	0.78	Novel	MN1::CXXC5	14	Male	Unclassified
34	Temporal lobe	Consultation (Low grade glioneuronal tumour)	Neuroepithelial tumour, PLAGL1-fused (novel)	Non-concordant (Novel)	Supratentorial ependymoma, NOS	0.52	Novel	Not tested	6	Female	Unclassified
35	Right lateral ventricle	Papillary glioneuronal tumour	Papillary glioneuronal tumour; PRKCA-fused	Concordant	Papillary glioneuronal tumour	0.74	Existing	Negative	17	Female	1
36	Frontal lobe	Glioneuronal tumour	Pilocytic astrocytoma, hemispheric	Non-concordant (Major)	Pilocytic astrocytoma with features of anaplasia	0.99	Existing (Discordant)	BRAF::KIAA1549, BRAF::HIP1	9	Female	1

Supplementary Table: Cont.

Patient Number	Localization	Histological Diagnosis	Methylation Profile	Correlation with Histology	WHO Class	Score	WHO Class	NGS Result	Age	Gender	WHO Grade
37	Cerebellum	Pilocytic astrocytoma	Pilocytic astrocytoma, infratentorial	Concordant	Pilocytic astrocytoma	0.99	Existing (Unclassified subtype)	BRAF::KIAA1549	5	Female	1
38	Posterior fossa	Pilocytic astrocytoma	Pilocytic astrocytoma, infratentorial	Concordant	Pilocytic astrocytoma	0.64	Existing (Unclassified subtype)	BRAF::KIAA1549	16	Male	1
39	Third ventricle	Piloxyoid astrocytoma	Pilocytic astrocytoma, midline	Non-concordant (Minor)	Pilocytic astrocytoma	0.99	Existing (Unclassified subtype)	BRAF::KIAA1549	1	Female	1
40	Left globus pallidus	High grade glial tumor	Pilocytic astrocytoma, midline	Non-concordant (Major)	Pilocytic astrocytoma	0.98	Existing (Unclassified subtype)	NF1	11	Female	1
41	Posterior fossa	Consultation (Posterior fossa ependymoma, grade 3)	Posterior Fossa Group B (pfb) Ependymoma, Subclass 2 (novel)	Concordant	Posterior Fossa Ependymoma, Group B	0.99	Existing (Unclassified subtype)	Not tested	12	Male	3
42	Right frontoparietal lobe	Supratentorial ependymoma, grade 3	Supratentorial ependymoma, ZFTA fusion-positive, subtype ZFTA-RELA fused, subclass A (novel)	Concordant	Supratentorial ependymoma, ZFTA fusion-positive	0.3	Existing (Unclassified subtype)	CDKN2A/2B loss, MDM4 amplification	5	Female	3
43	Unknown	Consultation (Supratentorial ependymoma, grade 3)	Supratentorial ependymoma, ZFTA fusion-positive, subtype ZFTA-RELA fused, subclass A (novel)	Non-concordant (Minor)	Supratentorial ependymoma, ZFTA fusion-positive	0.99	Existing (Unclassified subtype)	Not tested	8	Male	3
44	Lateral ventricle	High grade neuroepithelial tumour	Unclassifiable	Unknown	Unclassifiable		Unclassifiable	Not tested	2	Male	Unclassifiable
45	Supratentorial	Masson Tumour	Unclassified	Concordant	Benign		Unclassifiable (Benign)	Negative	0	Female	Benign
46	Brain stem	Paediatric-type diffuse low-grade glioma	Unclassified (Low tumor content)	Unknown	Unclassifiable		Unclassifiable	Negative	8	Female	Unclassifiable
47	Cervical spine	Diffuse glial tumour	Unclassified (Low tumor content)	Unknown	Unclassifiable		Unclassifiable	Not tested	17	Female	Unclassifiable
48	Unknown	Consultation (Medulloblastoma)	Unclassified (Poor tissue quality)	Unknown	Unclassifiable	0.3	Unclassifiable	Not tested	2	Male	Unclassifiable



# Evaluation of Drugs with Selective Inhibitors Targeting the Anti-Apoptotic Protein B-cell Lymphoma 2 (BCL-2) with Pro-Apoptotic and Antineoplastic Activities in Grade IV Glioblastoma

Murat BALOGLU<sup>1</sup>, Tamer TAMDOGAN<sup>2</sup>, Sevim ONDUL<sup>2</sup>, Mehmet BAKIRTAS<sup>3</sup>, Ibrahim YILMAZ<sup>4,5</sup>

<sup>1</sup>Republic of Türkiye, Ministry of Health, Eskisehir City Hospital, Clinics of Neurosurgery, Eskisehir, Türkiye

<sup>2</sup>Giresun University School of Medicine, Department of Neurosurgery, Giresun, Türkiye

<sup>3</sup>Republic of Türkiye, Ministry of Health, Doctor Ismail Fehmi Cumalioglu City Hospital, Department of Hematology, Tekirdag, Türkiye

<sup>4</sup>Republic of Türkiye, Ministry of Health, Doctor Ismail Fehmi Cumalioglu City Hospital, Department of Pharmacovigilance, Tekirdag, Türkiye

<sup>5</sup>Istanbul Rumeli University, Vocational School of Health Services, Department of Medical Services and Techniques, Istanbul, Türkiye

**Corresponding author:** Ibrahim YILMAZ ✉ dryilmazi@yahoo.com

## ABSTRACT

**AIM:** To systemically review the efficacy, safety, and clinical applications of B-cell lymphoma 2 (BCL-2) family inhibitors such as venetoclax (ABT-199), navitoclax (ABT-263), and obatoclax (GX15-070) across different malignancies.

**MATERIAL and METHODS:** A systematic search was conducted in the PubMed database following PRISMA guidelines. Studies evaluating the pharmacological effects, preclinical findings, and clinical trial data of venetoclax, navitoclax, and obatoclax were included in the analysis. Key outcomes, including efficacy, resistance mechanisms, and adverse effects, were synthesized from the analysis.

**RESULTS:** Venetoclax demonstrated significant efficacy and a favorable safety profile in hematologic malignancies, particularly chronic lymphocytic leukemia and acute myeloid leukemia; however, no positive safety profile was observed in glioblastoma grade IV (GBM). Navitoclax combination treatments showed potential in various malignancies but were used in a limited manner due to dose-related thrombocytopenia. However, no clear data were available regarding its efficacy against GBM. Obatoclax demonstrated efficacy in preclinical studies; however, off-target effects and limited clinical success hindered its development. No clear data were available regarding its effectiveness against GBM. Resistance mechanisms, including upregulation of MCL-1 and BCL-xL, were commonly observed among these agents, highlighting the need for combination strategies.

**CONCLUSION:** Venetoclax, navitoclax, and obatoclax represented significant advances in apoptosis-targeted therapy, with venetoclax emerging as the most clinically successful agent. However, resistance mechanisms and side effects were significant challenges, necessitating further preclinical and clinical studies to optimize the therapeutic potential of these agents.

**KEYWORDS:** Drug resistance, Glioblastoma, Navitoclax, Obatoclax, Pelcitoclax, Venetoclax

Murat BALOGLU : 0000-0001-7727-1982  
Tamer TAMDOGAN : 0000-0002-0526-1459  
Sevim ONDUL : 0000-0003-4219-4862

Mehmet BAKIRTAS : 0000-0003-3216-482X  
Ibrahim YILMAZ : 0000-0003-2003-6337



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## ■ INTRODUCTION

Despite treatment with surgery, radiation, and oncologic drugs such as temozolomide, Grade IV glioblastoma (GBM), the most common malignant tumor of the central nervous system, leads to poor overall survival outcomes due to factors such as the blood-brain barrier and/or the blood-tumor barrier, glioma stem-like cells, and genetic heterogeneity (39). A key factor contributing to drug treatment failure in GBM is the presence of mechanisms underlying treatment resistance and the insufficiency of strategies to overcome it (8).

Therefore, scientists continue to investigate treatments for GBM, as they do for many hematologic and oncologic malignancies. A prominent focus of these studies is the evaluation of pharmacological agents that induce cancer cell death by modulating interactions between key intracellular proteins. In this context, B-cell lymphoma 2 (BCL-2) family protein members have been extensively studied and remain a focus of ongoing research.

Historically, BCL-2 family proteins have been identified as regulators of programmed cell death. Some members, such as BCL-2 and BCL-extra large (BCL-XL), inhibit apoptosis, while others, such as BCL-2-associated X protein (Bax) and BCL-2 antagonist/killer (Bak), promote cell death (6,31). Bax and its homolog, Bak, are essential regulators of the mitochondrial apoptosis pathway (4).

In high-grade brain tumors such as GBM, overexpression of BCL-2 may contribute to tumor cells' escape from apoptosis and the development of treatment resistance (40).

The first proposed mechanism by which BCL-2 exhibits pro-apoptotic and antineoplastic activity in GBM involves its inhibition of apoptosis; BCL-2 localizes to the mitochondrial membrane, where it blocks pro-apoptotic signals (36). Additionally, high BCL-2 expression in GBM cells may allow them to evade apoptosis and proliferate uncontrollably (10). The second mechanism involves the development of treatment resistance. Overexpression of BCL-2 may contribute to GBM treatment resistance, particularly to chemotherapy and radiotherapy. This resistance facilitates the survival of tumor cells during treatment and reduces treatment effectiveness (12,41).

Many BCL-2 protein family inhibitors have been developed in recent years, including venetoclax (ABT-199) (13), navitoclax (ABT-263) (24), obatoclax (GX15-070) (42), pelcitoclax (APG-1252) (23), and oblimersen sodium (G3139) (14), among others. These inhibitors are primarily used in leukemia, lymphomas, and other hematologic malignancies. Venetoclax promotes apoptosis by selectively inhibiting BCL-2, thereby facilitating programmed cell death. Navitoclax is a small-molecule inhibitor that targets anti-apoptotic proteins of the BCL-2 family, including BCL-2, BCL-xL, and BCL-w. Obatoclax, in contrast, inhibits BCL-2, BCL-xL, and myeloid cell leukemia sequence 1 (MCL-1). These inhibitors function by targeting BCL-2 proteins, which are key regulators of apoptosis and are frequently overexpressed in cancer cells, leading to apoptotic resistance. Consequently, researchers have investigated the potential pro-apoptotic and antineoplastic effects of selective BCL-2 inhibitors in GBM.

A review of the literature revealed a lack of high-quality studies evaluating these inhibitors in combination. This study aims to evaluate the effects of selective BCL-2 inhibitors on GBM.

## ■ MATERIAL and METHODS

### Search Strategy

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (33). Searches were performed in PubMed, one of the electronic databases. Studies published up to January 26, 2025, were evaluated. Sequential searches were performed using the keywords “venetoclax (ABT-199)”, “navitoclax (ABT-263)”, “obatoclax (GX15-070)”, “pelcitoclax (APG-1252)”, “oblimersen sodium (G3139)” and “GBM” in the form of and/or.

### Inclusion and Exclusion Criteria

Studies included in this systematic review met the following inclusion criteria:

- Articles written in the English language.
- This review aimed to include published clinical trials conducted in humans. However, if an insufficient number of clinical studies with high levels of evidence were available, data from preclinical studies, including *in-vivo* studies on mammalian subjects and *in-vitro* studies on cell cultures, were also considered.

### Data Extraction and Synthesis

Three authors (MuB, TT, and SO) independently screened the articles to assess study eligibility. Inconsistencies were resolved through discussion. If consensus could not be reached, another author (MeB, IY) served as an arbitrator. The following data were extracted from the included studies: first author's name, year of publication, study design, drugs studied and their respective doses, and outcomes reported (Figure 1).

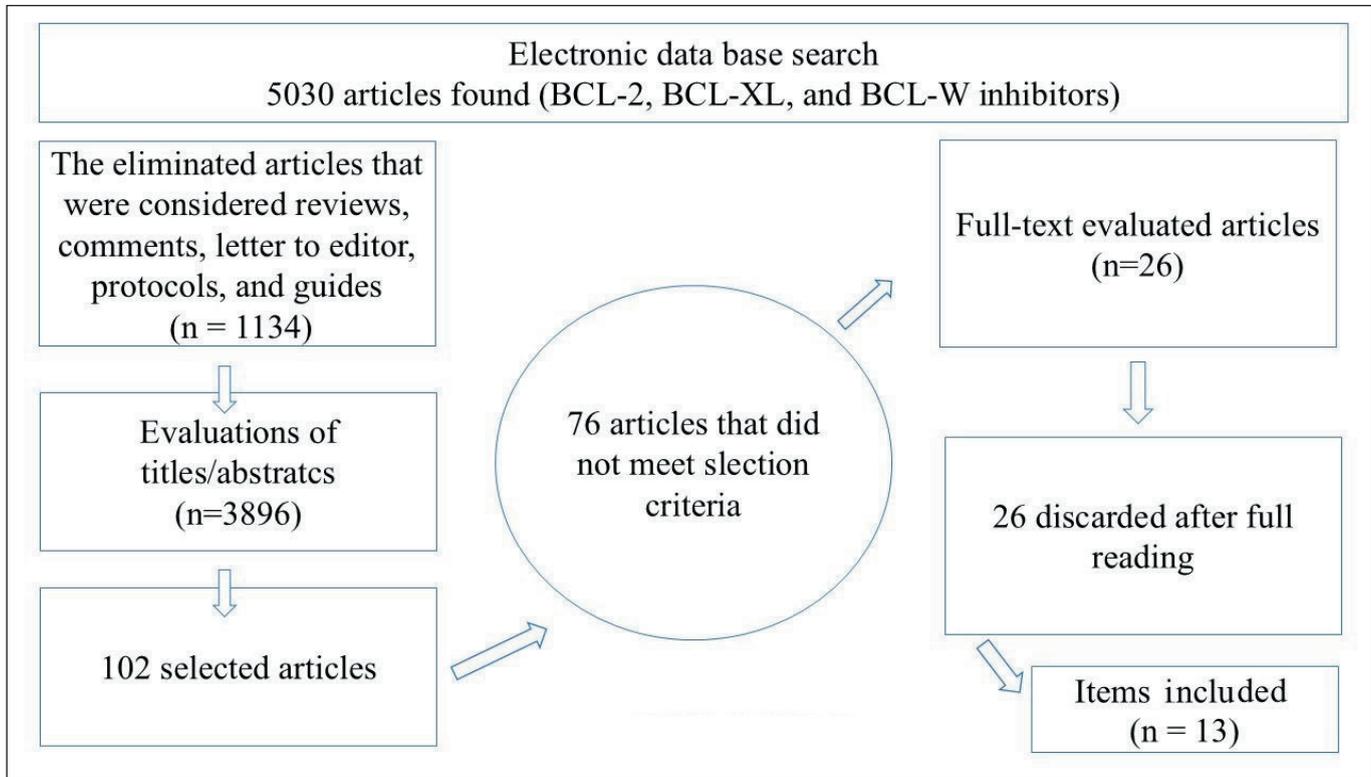
### Statistical Analysis

“The results of the data analysis, conducted using Microsoft Excel (Version 10.0), are reported in appropriate units.

## ■ RESULTS

Initially, when only the words “glioblastoma”, “GBM”, or “glioblastoma multiforme” were used separately, 61.327, 25.390 and 59.140 studies were found, respectively.

A total of 3,769 studies were found for “Venetoclax”; 732 when using “Navitoclax”; 283 when using “Obatoclax.”; There are five studies when “Pelcitoclax” is used and 246 when “Oblimersen sodium” is used. When the keywords “Glioblastoma AND/OR Venetoclax” were used, eight studies were found. Although 26 studies were found after consecutive screening using “Glioblastoma AND/OR Navitoclax”, seven studies were found when screening was performed with “Glioblastoma AND/OR Obatoclax”. However, no studies were found when screening with “Glioblastoma” AND/OR Pelcitoclax (APG-1252) or “Glioblastoma AND/OR “Oblimersen sodium”.



**Figure 1:** The process of article selection and the reasons for exclusion are shown in the PRISMA flowchart.

In addition to BS153 cells, GBM sphere cultures, and other GBM-derived cells (16), experiments were conducted using varying drug doses on cells obtained from different sources. (Table I).

## DISCUSSION

Despite current treatment strategies, including pharmacological and surgical interventions, GBM remains the most aggressive and fatal type of brain tumor. Previous studies have reported that in GBM, overexpression of EGFR and its activated variant, EGFRvIII, resulted in increasing invasiveness and treatment resistance (27). Houweling et al. reported that screening for synergistic multitarget therapies in GBM predicted novel treatment strategies (16). BCL-2 plays a key role in inhibiting apoptosis, and its inhibition by venetoclax effectively kills senescent GBM cells (38).

Additionally, in mice with BCL-2 gene-silenced GBM tumors, taxol treatment significantly inhibited tumor growth and angiogenesis (12). More importantly, anti-apoptotic BCL-2 family members are now considered druggable targets, with specific BCL-2 antagonists such as venetoclax.

Lincoln et al. examined the sensitivity of GBM cell lines to a combination of the death ligand TRAIL and an IAP antagonist due to the lack of effective treatments for GBM. Their findings emphasized that a high caspase-8/Bid signature was associated with synergistic TRAIL- and IAP antagonist-induced apoptosis in GBM cells. Additionally, they highlighted

BCL-2 antagonism as a highly effective approach to sensitizing TRAIL-resistant GBM cells to TRAIL and IAP antagonists (26).

Yu et al. reported that the prosurvival BCL-2 family proteins BCL-2 and BCL-xL are targets of both ABT-737 and navitoclax, whereas venetoclax is highly specific to BCL-2 (43). A study reported that eliminating radiation-induced senescence in the brain tumor microenvironment could reduce GBM recurrence. The study highlighted navitoclax, a senolytic drug that selectively kills senescent astrocytes *in-vivo*, as a potential treatment (11).

BH3 proteins contain BH3 motifs that bind and regulate BCL-2 homologs, playing a crucial role in cellular responses to stress-induced stimuli and apoptosis (9). Koessinger et al. reported that increased apoptotic sensitivity in GBM enables therapeutic targeting with BH3-mimetics. Venetoclax, a BH3-mimetic targeting BCL-2, has demonstrated significant efficacy in hematologic malignancies (22).

Similarly, one study reported that “BH3 mimetic drugs cooperate with temozolomide, JQ1 and inducers of ferroptosis in killing GBM cells” (30).

A study on neurosphere GBM cultures and xenografts suggested that combined inhibition of BCL-xL and disruption of the tricarboxylic acid cycle could serve as a treatment strategy for GBM using the clinically validated drug CPI-613. The study found that BCL-xL inhibition prevented OGDH loss-of-function in patients. Additionally, it genetically and clinically confirmed that OGDH is synthetically lethal with its BH3 mimetic, navitoclax (32).

**Table I:** Application Dose and Site of Application of Bcl-2 Protein Family Inhibitors Identified in the Literature Review

Origin of the Cell Used or Living Mammalian Subject Species	Drug Administration/Dose	Efficiency	Reference No.
U87MG, U251 cells	Venetoclax / 10 $\mu$ M	Venetoclax is effective when used in combination with Temozolomide, Methotrexate, and Cytarabine.	44
Patient-derived GBM stem-like cells	Venetoclax / 1 $\mu$ M	BCL-xL and MCL-1 prosurvival function is important for GBM survival and can be therapeutically exploited by BH3 mimetics.	22
U87MG, U251, SNB-19, SNB-75, SF268, SF295, and SF539 cells	Venetoclax / 1 $\mu$ M	Dual targeting of distinct programmed cell death signaling pathways in GBM may enhance the utility of BCL-xL inhibitors and ferroptosis inducers, in combination with standard-of-care treatment, for improved GBM therapies.	30
U87MG, LN-229 (RRID: CVCL_0393), A172 (RRID: CVCL_0131)	Venetoclax / 50 $\mu$ M	BV6 and venetoclax act as senolytic agents in glioblastoma cells following temozolomide exposure.	38
A172, U251, U343, U373, MZ18, and MZ304	Venetoclax / 0.1 $\mu$ M, 5 $\mu$ M, and 10 $\mu$ M	Antagonizing Bcl-2 by venetoclax allowed TRAIL/Birinapant response synergies to manifest in otherwise TRAIL-resistant cell lines.	26
Human GBM xenografts obtained from patients	Venetoclax / 10 $\mu$ M	<i>In-vitro</i> cytotoxicity assays demonstrated that ABT-737, Navitoclax, and Venetoclax—specifically ABT-737—sensitized different tumors to immunotoxin treatment.	43
U373, Patient-derived glioblastoma stem-like cell cultures	Obatoclax / 225nM	Obatoclax overcomes resistance to histone deacetylase inhibitors as radiosensitizers in patient-derived GBM stem-like cells.	2
U87MG, HEK293, HEK293T, NIH/3T3, LM8, HCT116, SW480, SW620, and EL4 cell lines	Obatoclax / 1 $\mu$ M	Cucurbitacin B, gossypol, and obatoclax exhibit broad cellular specificity across different cell lines by regulating extracellular vesicles.	28
U251, LN229, U87MG, A375, or A375R cells were implanted subcutaneously into mice	Navitoclax / 25–50 mg/kg Obatoclax / 5 mg/kg Venetoclax / 1 $\mu$ M	Combining Navitoclax and Obatoclax or Venetoclax with gamitrinib-TPP suppressed cellular proliferation synergistically through massive activation of intrinsic apoptosis.	21
Syngeneic mouse glioma model that constituted immunocompetent C57BL/6J mice implanted with luciferase-tagged GL261 mouse glioma cells (immunocompetent mice)	Navitoclax / 50 mg/kg	Navitoclax treatment selectively eliminated senescent astrocytes <i>in vivo</i> , significantly attenuating glioma cell growth in preirradiated brains.	11
U87, U343, and U251 cells	Navitoclax / 1 $\mu$ M	Acridine has MCL-1 inhibitory function and synergistic antitumor effects with Navitoclax..	29

Table I: Cont.

Origin of the Cell Used or Living Mammalian Subject Species	Drug Administration/Dose	Efficiency	Reference No.
LN229, A172 (human glioblastoma cell lines)	ABT-737 / 2.5 $\mu$ M	ABT-737 and Navitoclax selectively eliminated senescent astrocytes in vivo, significantly reducing glioma cell growth in preirradiated brains.	1
Human glioblastoma cell lines (p53 wild-type, PTEN-mutated LN229, U87, and U373 [p53-mutated, PTEN-mutated])	Navitoclax / 1 $\mu$ M - 4 $\mu$ M	GDC-0941 enhances Navitoclax-mediated cell death by modulating BAD phosphorylation.	35

**BV6:** A potent and specific antagonist of at least three inhibitors of apoptosis proteins (IAPs); **TRAIL:** Tumor necrosis factor-related apoptosis-inducing ligand; **MCL-1:** Myeloid leukemia 1.

A study evaluating the synergy of acriflavine with navitoclax, an MCL-1 downregulator, against triple-negative breast cancer, lung adenocarcinoma, and GBM demonstrated that acriflavine exhibits MCL-1 inhibition and a synergistic antitumor effect with navitoclax (25). The inhibition of MEG3, whose aberrant expression is implicated in various cancers, has been suggested to enhance the chemosensitivity of glioma cells to 5-fluorouracil but not to navitoclax (7).

Zhao et al. stated in their study that adjuvant treatment of GBM with temozolomide inevitably failed due to therapeutic resistance, necessitating new treatment approaches. They also reported that apoptosis induction in GBM cells was inefficient due to an excess of anti-apoptotic XPO1/BCL-2 family proteins. Based on the findings obtained from *in-vitro* and *in-vivo* research, they deduced “optimal drug combinations were. In response to inhibitors Eltanexor (XPO1), Venetoclax (Bcl-2), and Mcl-1, genes encoding for the corresponding proteins were upregulated in a compensatory manner” (44). One study, identified obatoclax among potential drugs for treating refractory GBM based on drug sensitivity patterns of different immune subtypes (3).

As a result, the BCL-2 protein family inhibitors venetoclax, navitoclax, and obatoclax have been investigated in GBM treatment; however, no studies have reported the effects of pelcitoclax or oblimersen sodium against GBM. These findings suggest that ionizing radiation, a standard treatment for GBM, may contribute to radioresistance by inducing the expression of anti-apoptotic BCL-2 proteins in tumor cells. Venetoclax, in combination with radiotherapy, increases tumor cell death by inhibiting radiation-induced BCL-2 activity and promoting apoptosis. This combination showed a significant increase in survival in orthotopic animal models of diffuse midline glioma, a variant of GBM (29).

Navitoclax selectively induces apoptosis in senescent GBM cells by targeting BCL-xL, potentially reducing tumor recurrence (37). Obatoclax can overcome this resistance by inhibiting BCL-2 proteins, thereby enhancing the effectiveness of treatments such as suberoylanilide hydroxamic acid and ra-

diotherapy. Specifically, obatoclax sensitizes patient-derived GBM stem-like cells to these treatments, leading to increased apoptosis (2). Additionally, the combination of obatoclax with the EGFR inhibitor lapatinib was reported to show synergistic effects in inducing cell death in central nervous system tumor cells, including GBM. This combination promoted apoptosis by effectively blocking survival signaling pathways (5).

A review of the literature indicates that studies have been conducted on commercial cell lines, patient-derived GBM stem-like cells, human GBM xenografts, and immune-competent mice. In *in-vivo* studies, navitoclax was administered at 25–50 mg/kg, while obatoclax was given at 5 mg/kg in mammalian subjects. Studies reported that the *in-vitro* dose of venetoclax ranged from 0.1 $\mu$ M and 50 $\mu$ M. Studies found that the *in-vitro* dose of obatoclax ranged from 225 nM and 1 $\mu$ M. Navitoclax was administered at doses ranging from 1  $\mu$ M and 4  $\mu$ M.

These studies commonly use commercial cell lines and animals. However, the sensitivity of animal tissue differs from that of human tissue (19,20). Results from animal tissue analyses may differ from those using human tissues, potentially leading to misleading conclusions (19,20). This may lead to misleading results. Additionally, commercial cell lines contain only a single cell type and lack the complex coordination mechanisms of the tumor microenvironment (19,20). They do not exhibit the same genotypic or phenotypic characteristics as tumor cells in the human body. For this reason, the results of studies using cell lines may be misleading (19,20).

Systematic reviews are valuable tools for synthesizing evidence, but they also have limitations. One major challenge is the heterogeneity among studies (15). Another limitation is publication bias (34). Moreover, despite existing guidelines, decisions regarding study inclusion, exclusion, and data interpretation can introduce subjective bias, particularly if pre-registration or protocols are not followed (17,18). These limitations apply to our study. However, we believe it contributes to the literature by collectively evaluating preclinical data on these drugs tested against GBM.

## CONCLUSION

Although these preclinical findings are promising, clinical trials are necessary to assess the safety and efficacy of venetoclax, navitoclax, and obatoclax in GBM patients. To date, all of these inhibitors are under investigation in combination with other treatments for a variety of solid tumors, but specific clinical studies for GBM remain extremely limited. Equally important, the complex biology of GBM and the incomplete understanding of therapeutic resistance necessitate the discovery of novel antigens or targeted pharmacological strategies.

### 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:** 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 is a systematic review based solely on previously published studies. No new human participants were enrolled, and no individual patient data were collected. Therefore, ethical approval and informed consent were not required.

### AUTHORSHIP CONTRIBUTION

Study conception and design: MuB, IY

Data collection: MuB, TT

Analysis and interpretation of results: MeB, SO

Draft manuscript preparation: MuB, TT, SO

Critical revision of the article: MeB, IY

Other (study supervision, fundings, materials, etc.): MuB, MeB, IY

All authors (MuB, TT, SO, MeB, IY) reviewed the results and approved the final version of the manuscript.

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# Acute Subdural Hematoma: Evaluation of Predictive Factors and Efficacy of Various Surgical Approaches on Prognosis

Hasan IDIZ<sup>1</sup>, Nafis VURAL<sup>2</sup>, Elif ERTAS<sup>3</sup>, Hasan Can GUVEN<sup>4</sup>, Murat DUYAN<sup>4</sup>, Ahmet Sukru ALPARSLAN<sup>5</sup>

<sup>1</sup>Antalya Training and Research Hospital, Department of Neurosurgery, Antalya, Türkiye

<sup>2</sup>Baskent University, Konya Training and Research Hospital, Department of Emergency Medicine, Konya, Türkiye

<sup>3</sup>Selcuk University, Department of Biostatistics, Konya, Türkiye

<sup>4</sup>Antalya Training and Research Hospital, Department of Emergency Medicine, Antalya, Türkiye

<sup>5</sup>Antalya Training and Research Hospital, Department of Radiology, Antalya, Türkiye

Corresponding author: Nafis VURAL ✉ 42nafisvural@gmail.com

## ABSTRACT

**AIM:** To examine the parameters influencing prognosis, and the effectiveness of surgical techniques in patients aged over 65 years with acute subdural hematoma (ASH).

**MATERIAL and METHODS:** From 2017 to 2023, a retrospective evaluation was conducted on 62 individuals admitted to the emergency department, diagnosed with ASH, and who underwent had surgical interventions. Demographic data, Glasgow Coma Scale (GCS) score upon admission, radiological findings including hematoma volume, midline shift, and surgical techniques used (craniotomy, craniectomy), were examined. The impact of each predictive factor on prognosis was investigated.

**RESULTS:** The average patient age was  $73.67 \pm 10.00$  years (range: 65 to 101 years). The mean GCS score at presentation was  $9.00 \pm 4.44$ . The average subdural hematoma volume was  $62.2 \pm 36.5$  mL, and the average midline shift was  $9.4 \pm 7.7$  mm. A significant positive correlation existed between the admission GCS score and the Glasgow Outcome Scale (GOS) score ( $p = 0.684$ ,  $p < 0.001$ ). Surgeries comprised 83.3% craniotomy, 11.9% craniectomy, and 4.8% extended craniectomy. The overall mortality rate was 19%. The rate of favorable clinical outcomes (GOS 4–5) was 31% in the craniotomy cohort and 18% in the craniectomy cohort ( $p = 0.042$ ).

**CONCLUSION:** Age, GCS score at presentation, hematoma volume, and midline displacement were significant factors influencing the prognosis in geriatric ASH patients. Patients who underwent craniotomy exhibited superior functional outcomes to those who underwent craniectomy ( $p = 0.042$ ). Surgeries conducted within an average of  $3.4 \pm 0.6$  hours, along with treatment strategies tailored to individual clinical evaluations, appeared to enhance the prognosis

**KEYWORDS:** Acute subdural hematoma, Glasgow coma scale, Craniotomy, Predictive factors, Geriatric neurosurgery

## INTRODUCTION

Acute subdural hematoma (ASH) is a severe cerebral hemorrhage that occurs after head trauma. It exhibits a high mortality rate, particularly among older adults (6). The primary parameters influencing the prognosis of ASH are age, trauma severity, Glasgow Coma Scale (GCS) score, and pupillary response (20,30). The incidence of ASH in older individuals is rising, and surgical treatment choices frequently

present intricate therapeutic problems (11,18). The use of anticoagulants, which is common in this age group, may worsen ASH and its prognosis (17).

This study retrospectively examined the parameters influencing outcomes in ASH patients aged over 65 years who arrived at the emergency room due to head trauma. Evidence underscores that age, trauma severity, radiographic findings, and the timing of surgical intervention significantly influence

Hasan IDIZ : 0009-0009-6986-4003

Elif ERTAS : 0000-0003-1827-4862

Murat DUYAN : 0000-0002-6420-3259

Nafis VURAL : 0000-0002-3551-201X

Hasan Can GUVEN : 0000-0001-5576-4911

Ahmet Sükrü ALPARSLAN : 0000-0001-7083-5618



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outcomes in traumatic ASH cases (26,29). Specifically, variables such as patient age, GCS score at presentation, and pupillary responsiveness have been demonstrated to correlate with post-surgery functional recovery (9,16). Mortality rates are dramatically elevated in patients with extensive hematoma and considerable midline shift (6).

The study aimed to retrospectively assess the clinical and radiological data of patients aged over 65 years diagnosed with ASH who presented to the emergency department from 2017 to 2023. Specifically, we sought to attain consistent and trustworthy conclusions regarding the efficacy of surgical methods by analyzing the impacts of surgical intervention timing, hematoma volume, and midline shift on prognosis.

## ■ MATERIAL and METHODS

### Study Design and Participants

This retrospective observational analysis encompassed 62 patients aged 65 years and older diagnosed with acute subdural hematoma (ASH) who had surgical intervention at the department of neurosurgery in a tertiary institution from 2017 to 2023. Data were obtained retrospectively from medical records, digital databases, and radiological imaging reports. The research was performed in compliance with the 1964 Declaration of Helsinki, receiving clearance from the hospital ethics committee; written informed consent was acquired from all patients or their legal representatives prior to surgical intervention. The participants' age range was 65 to 101 years, with a mean age of  $73.67 \pm 10.00$  years. 59.5% of the patients were female, while 40.5% were male; comorbidities included hypertension, diabetes mellitus, coronary artery disease, and the use of anticoagulant or antiaggregant medications were documented. The inclusion criteria comprised patients aged over 65 who arrived to the emergency department, received a diagnosis of ASD, and underwent surgical intervention. Clinical assessments were conducted using the Glasgow Coma Scale (GCS), motor examination, and pupillary reaction. Patients who were sedated or had elevated alcohol levels were eliminated from the study, as were patients that did not necessitate surgery.

### Data Collection

Demographic data (age, gender), Glasgow Coma Scale scores at admission and discharge, comorbidities, and administered medications were documented. Radiologic observations, including hematoma volume, midline displacement, basal cistern status, and concurrent cranial diseases, as well as surgical interventions, were recorded. The surgical methods employed comprised craniotomy, craniectomy, and extended craniectomy. The length of surgical procedure, intensive care unit stay, and hospitalization were documented, and prognosis was evaluated using the Glasgow Outcome Scale (GOS). Eventually, survival and mortality rates were examined.

### Radiological Evaluation

Radiologic assessments were conducted using computed tomography (CT) images obtained during the emergency presentation. The volume of the hematoma was quantified in mil-

liliters (ml), while the midline shift was assessed in millimeters (mm). Cases exhibiting a midline shift over 5 mm were evaluated, and closed cisterns were identified as a sign of elevated intracranial pressure. Furthermore, associated pathologies like as contusion, subarachnoid hemorrhage, and epidural hematoma have been documented.

### Surgical Approach

The surgical intervention was scheduled based on the patients' clinical and radiological assessments. Craniotomy was performed to evacuate the hematoma and reduce intracranial pressure, while decompressive craniectomy was preferred especially in the presence of brain edema or extensive hematoma. Extended craniectomy was performed to reduce pressure in larger areas. Time to surgery was recorded as the time from emergency room to intervention, 5and operative times were documented from surgical notes. Postoperative clinical outcomes were evaluated with the Glasgow Outcome Scale (GOS).

### Statistical Analysis

Statistical analysis of the data was performed using SPSS 25.0 software. Categorical data were analyzed using chi-square test, while t-test and Mann-Whitney U test were used to compare continuous variables. The relationship between GCS at admission and GOS assessing clinical outcomes was analyzed by Spearman correlation analysis. Kaplan-Meier survival analysis was applied to analyze the effects of surgical methods on survival. Statistical significance level was set as  $p < 0.05$ .

### Ethical Approval and Compliance

The study was approved by the Local Ethics Committee (ethics committee decision number: 2023/221 date: September 07, 2023) and was conducted in accordance with the 1964 Declaration of Helsinki.

## ■ RESULTS

The mean age of the 62 patients included in the study was  $73.67 \pm 10.00$  years, with an age range of 65-101 years. 52.4% of the patients were between 65-75 years of age, 33.3% were between 75-85 years of age and 14.3% were 85 years and older. In terms of gender distribution, women accounted for a higher proportion with 37 (59.7%), while men accounted for 25 (40.3%). The mean Glasgow Coma Scale (GCS) score at admission was  $9.00 \pm 4.44$ , which increased to  $13.43 \pm 2.31$  at discharge, and this change was statistically significant ( $p < 0.001$ ). Hypertension was detected in 35 patients (56.5%), diabetes mellitus in 22 patients (35.5%) and coronary artery disease in 17 patients (27.4%). In addition, 26 patients (41.9%) were recorded as having more than one systemic disease (multisystem disease). The mortality rate was 37.5% in 24 patients (38.7%) on anticoagulants and the mean Glasgow Outcome Scale (GOS) score of this group was  $3.1 \pm 1.2$ . Furthermore, the proportion of patients using antiaggregants was 45.2% ( $n=28$ ) (Table I).

The mean volume of subdural hematoma was  $62.2 \pm 36.5$  ml and ranged from 9.0 ml to 201.0 ml. The mean value of

midline shift was  $9.4 \pm 7.7$  mm, with a minimum shift of 0 mm and a maximum shift of 25 mm. When the basal cisternal status was analyzed, it was observed that the basal cisterns were open in 46 patients (73.8%) and closed in 16 patients (26.2%). Regarding additional cranial pathologies, 35.7% (n=22) had contusion, 28.6% (n=18) had subarachnoid hemorrhage (SAH), 19.0% (n=12) had epidural hematoma (EDH) and 16.7% (n=10) had more than one pathology. The proportion of patients with no additional pathology was 31.0% (n=19). Midline shift was found to have a significant effect on mortality. The median value of midline shift was 8.5 mm (IQR: 3.0-12.25 mm) in surviving patients, while the median value was 15.0 mm (IQR: 11.5-17.25 mm) in patients who died. This difference was statistically significant ( $p=0.001$ ), indicating

**Table I:** Demographic and Clinical Characteristics

Characteristic	Value	p-value*
Age (years)		
Mean $\pm$ SD	$73.67 \pm 10.00$	<b>0.027<sup>†</sup></b>
Min - Max	65 - 101	
Age Groups, n (%)		
65-75 years	44 (52.4)	<b>0.043<sup>‡</sup></b>
75-85 years	28 (33.3)	
85+ years	12 (14.3)	
Gender, n (%)		
Female	50 (59.5)	0.312
Male	34 (40.5)	
GCS Scores		
Admission GCS (Mean $\pm$ SD)	$9.00 \pm 4.44$	<b>&lt;0.001<sup>†</sup></b>
Discharge GCS (Mean $\pm$ SD)	$13.43 \pm 2.31$	<b>0.004<sup>†</sup></b>
Systemic Diseases, n (%)		
Hypertension	48 (57.1)	0.465
Diabetes Mellitus	30 (35.7)	0.138
Coronary Artery Disease	24 (28.6)	0.224
Multisystem Disease	36 (42.9)	<b>0.032</b>
Anticoagulant/Antiplatelet Use and Outcomes		
Anticoagulant, n (%)	32 (38.1)	<b>0.048</b>
Mortality Rate	37.5%	
GOS (Mean $\pm$ SD)	$3.1 \pm 1.2$	<b>0.036</b>
Antiplatelet, n (%)	38 (45.2)	0.092

**p-values:** <sup>†</sup>Calculated with Student's t-test, <sup>‡</sup>Calculated with Chi-square test.

**GCS:** Glasgow coma scale, **GOS:** Glasgow outcome scale, **SD:** Standard deviation.

that midline shift is strongly correlated with mortality (Table II, Figure 1).

Of the patients who underwent surgical treatment, 52 (83.3%) underwent craniotomy, 7 (11.9%) underwent craniectomy and 3 (4.8%) underwent extended craniectomy. The mean duration of surgical intervention was  $3.4 \pm 0.6$  hours. The mean duration of intensive care unit stay was  $7.8 \pm 4.2$  days and the mean total hospital stay was  $13.5 \pm 8.3$  days. According to the Glasgow Outcome Scale (GOS), 19.0% (n=12) of the patients died after surgery. The proportion of patients who remained in a permanent vegetative state was 4.8% (n=3), while 45.2% (n=28) developed severe disability. Patients with moderate disability were 14.3% (n=9), while good recovery was observed in 16.7% (n=10). When the effect of surgical methods on survival was analyzed by Kaplan-Meier analysis, it was observed that the survival rate decreased significantly within the first 10 days in patients who underwent extended craniectomy. In contrast, survival rates were more stable in patients who underwent craniotomy and craniectomy (Table III, Figure 2).

A strong positive correlation was found between the Glasgow Coma Scale (GCS) measured at admission and the Glasgow Outcome Scale (GOS) ( $p=0.684$ ,  $p<0.001$ ). This result suggests that patients with higher GCS scores generally achieve better clinical outcomes, i.e., higher GOS scores. A positive correlation was also found between hematoma volume and midline shift ( $p=0.542$ ,  $p<0.001$ ), indicating that as hematoma volume increases, midline shift also increases.

**Table II:** Radiological Findings

Characteristic	Value
Subdural Hematoma Volume (ml)	
Mean $\pm$ SD	$62.2 \pm 36.5$
Min - Max	9.0 - 201.0
Midline Shift (mm)	
Mean $\pm$ SD	$9.4 \pm 7.7$
Min - Max	0.0 - 25.0
Basal Cistern Status, n (%)	
Open	62 (73.8)
Closed	22 (26.2)
Additional Cranial Pathologies, n (%)	
Contusion	30 (35.7)
SAH (Subarachnoid Hemorrhage)	24 (28.6)
EDH (Epidural Hematoma)	16 (19.0)
Multiple Pathologies	14 (16.7)
No Pathology	26 (31.0)

**SAH:** Subarachnoid hemorrhage, **EDH:** Epidural hematoma, **SD:** Standard deviation.

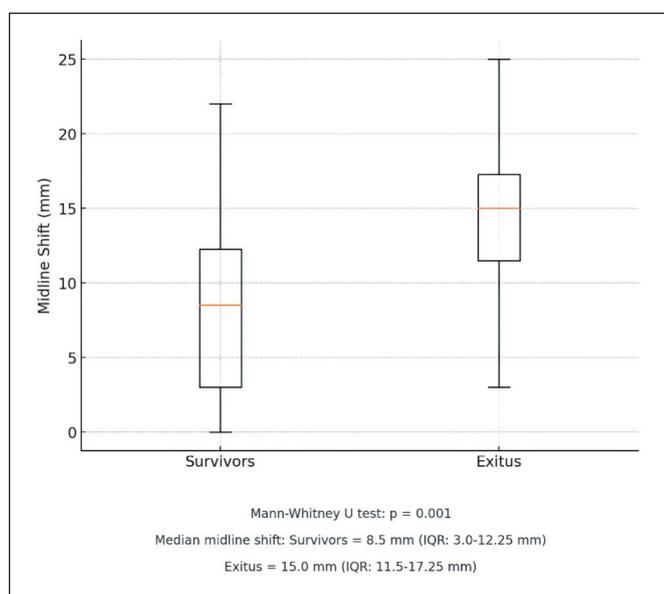


Figure 1: Midline shift distribution by Mortality Status.

Table III: Surgical Characteristics and Outcomes

Characteristic	Value
Type of Surgery, n (%)	
Craniotomy	70 (83.3)
Craniectomy	10 (11.9)
Extended Craniectomy	4 (4.8)
Surgical Duration (hours)	
Time to Surgery (Mean ± SD)	3.4 ± 0.6
Min - Max	2.5 - 5.0
Length of Stay (days)	
ICU Stay Duration (Mean ± SD)	7.8 ± 4.2
Total Hospital Stay (Mean ± SD)	13.5 ± 8.3
Glasgow Outcome Scale (GOS), n (%)	
GOS 1 (Death)	16 (19.0)
GOS 2 (Persistent Vegetative State)	4 (4.8)
GOS 3 (Severe Disability)	38 (45.2)
GOS 4 (Moderate Disability)	12 (14.3)
GOS 5 (Good Recovery)	14 (16.7)
Mortality	
Exitus, n (%)	16 (19.0)

GOS: Glasgow outcome scale, ICU: Intensive care unit, SD: Standard deviation.

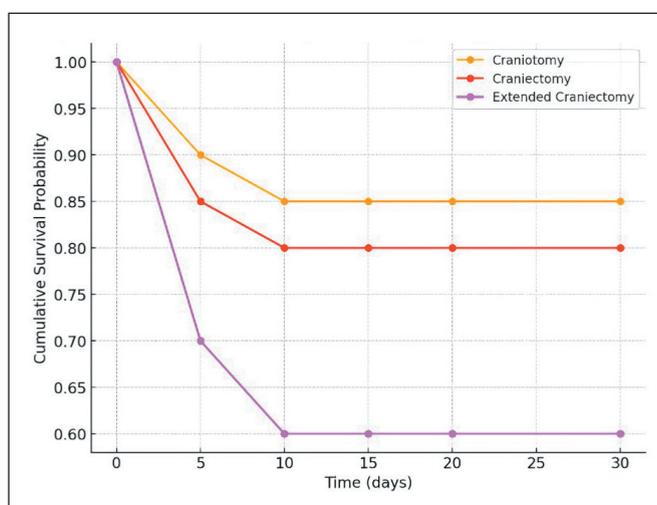


Figure 2: Kaplan-Meier survival analysis by surgical type (doubled patients).

A strong negative correlation was found between admission GCS score and mortality ( $\rho = -0.612$ ,  $p < 0.001$ ). This suggests that lower GOS scores are associated with a higher mortality risk. A weak negative correlation was found between age and GOS ( $\rho = -0.384$ ,  $p = 0.012$ ), indicating that the likelihood of poor clinical outcomes increases with increasing age (Table IV, Figure 3).

There was a significant negative correlation between subdural hematoma volume and Glasgow Outcome Scale (GOS) ( $r = -0.62$ ,  $p = 0.001$ ). This finding indicates that the clinical outcomes of the patients tended to worsen as the hematoma volume increased. As seen in the graphical analysis, patients with smaller hematoma volumes generally achieved higher GOS scores (good recovery), whereas a significant decrease in GOS scores was observed as hematoma volume increased. Especially in cases with a hematoma volume of more than 100 ml, GOS scores were mostly 2 or lower, and these patients were observed to have severe neurological impairment or death (Figure 4).

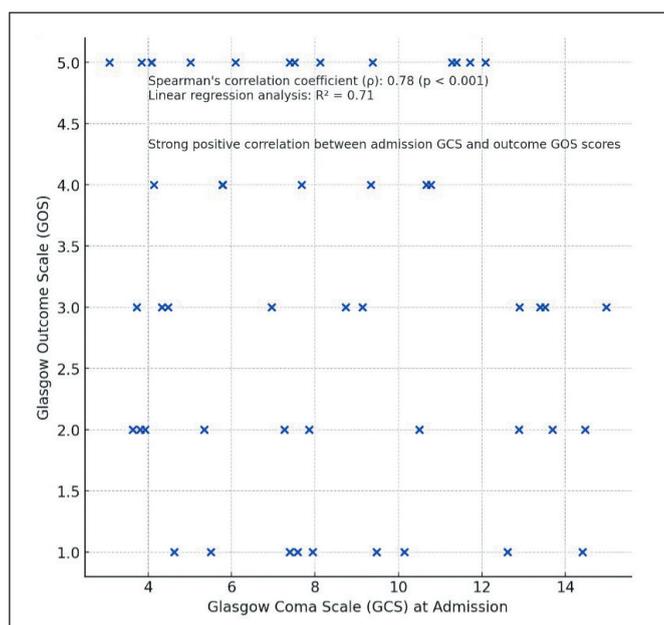
## DISCUSSION

The purpose of this research was to examine how various surgical methods impact the prognosis for individuals aged 65 years and above diagnosed with ASH. Predictive factors such as age, trauma severity, GCS score at presentation, pupillary response, and radiologic findings were retrospectively evaluated, with a particular emphasis on GCS score, hematoma volume, and midline shift as key determinants of clinical outcomes. Our data demonstrated that ASH in older adults was associated with elevated rates of mortality and morbidity, as well as that the selection of treatment significantly influenced outcomes in this demographic. The timing of surgical intervention and the precise surgical technique employed substantially impact patient prognosis, with more positive clinical results noted, particularly in patients who had craniotomies.

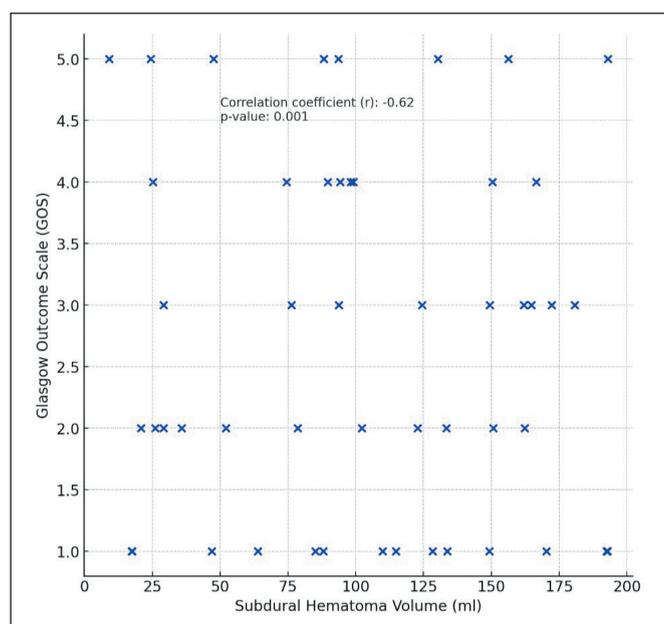
**Table IV:** Correlation Analyses

Variables	Spearman's rho	p-value
GCS-GOS	0.684	<0.001
Hematoma Volume-Midline Shift	0.542	<0.001
GCS-Mortality	-0.612	<0.001
Age-GOS	-0.384	0.012

**GCS:** Glasgow Coma Scale; **GOS:** Glasgow Outcome Scale



**Figure 3:** Glasgow Coma Scale (GCS) at admission vs Glasgow Outcome Scale (GOS).



**Figure 4:** Subdural hematoma volume vs Glasgow Outcome Scale (GOS).

This research sought to elucidate the radiologic parameters that should inform surgical treatment decisions for older individuals with ASH. Research on the influence of the GCS on prognosis unequivocally indicates that it possesses significant predictive validity for both mortality and overall clinical outcomes. Our investigation identified a strong association between the GCS and the GOS scores ( $p=0.684$ ); this result corroborates existing literature, reaffirming that the GCS is a reliable prognostic indicator. Akbik et al. indicated that a low GCS score correlated with unfavorable clinical outcomes and that preoperative GCS serves as a significant predictor of postoperative mortality (2). Brazinova et al. similarly indicated that older patients with a low GCS score typically exhibited a poor prognosis, and factors such as closed basal cisterns or significant midline shift heightened the risk of death (7). Our investigation revealed a mortality rate of 19% in patients with a low GCS score. This corroborates the systematic analysis by Evans et al., which indicated that a low GCS score was associated with an elevated mortality risk in older individuals (11). In addition, Salottolo et al. emphasized that older adult patients mostly had lower GCS scores and that these may predict poor prognosis (25). The results of our study, in parallel with these findings, show that the GCS score has a strong predictive value for mortality and poor clinical outcomes in the older population. The association of a low GCS score with poor prognosis is consistent with previous studies.

In our study, the mean hematoma volume was 62.2 mL, and this volume significantly affected prognosis. Jacobs et al. reported that the risk of poor prognosis increased with increasing hematoma volume, and mortality increased significantly, especially in cases exceeding 50 ml (13). Our findings showed a similar correlation between hematoma volume and mortality, consistent with the literature. Additionally, midline shift was evaluated as an important indicator of prognosis. In our study, the median midline shift was 8.5 mm in survivors, whereas this value reached 15 mm in patients who died. This finding aligns with research conducted by Yilmaz et al., which indicated that a midline displacement of 10 mm or greater was strongly associated with elevated mortality rates (31). The condition of the basal cisternae was also evaluated as a significant prognostic variable. Closed basal cisternae were found in 26.2% of our patients, and this was associated with poor prognosis. This result coincides with the findings of de Rodrigues de Souza et al., who reported that closed basal cisternae were more common in patients with high mortality risk (24). We also evaluated the effects of additional pathologies, on prognosis; additional pathologies such as contusion (35.7%) and subarachnoid hemorrhage (28.6%), negatively affected it. Moussa et al. also reported that contusion and other brain pathologies, especially with midline shift, worsened the prognosis (19). These findings support the results of our study and show that additional pathologies negative affect prognosis.

In our study, no statistical difference in prognosis existed between patients who underwent craniotomy (83.3%) and decompressive craniectomy (11.9%). However, the literature has reported that craniectomy is generally preferred in more severe cases and is thus associated with higher mortality rates. For example, Ahmed et al. reported that craniectomy resulted

in worse clinical outcomes and a high mortality rate of 42.7% (1). Similarly, Chen et al. reported a mortality rate of 23.3% in the craniectomy group and 7.1% in the craniotomy group (8). Despite the lack of significant difference between clinical outcomes in our study, in the literature thus that craniotomy may be a more advantageous option regarding prognosis.

The effect of surgery timing on prognosis is also important. In our study, the mean time to surgery 3.4 hours, and this was critical in terms of prognosis. Pinggera et al. emphasized that rapid surgical intervention is of great importance in decreasing mortality and, especially, performing surgery within 4 hours is effective in decreasing mortality rates (15,21). The surgical time frame in our study is close to that recommended in the literature, supporting the importance of timely surgical intervention.

In our study, the mean duration of intensive care unit stay was 7.8 days and the mean total hospital stay was 13.5 days. In the study by Anis et al., the mean duration of intensive care unit stay was 4.6 days in the decompressive craniectomy group and 3.4 days in the craniotomy group (3). The length of stay may vary depending on the clinical status of the patient and complications that develop. Zhang et al. reported that postoperative complications were lower in the craniotomy group and intracranial pressure control was more difficult in the craniectomy group. In particular, complications such as brain edema were more common after craniectomy (34). Similar complications were observed in our study, strengthening the idea that craniectomy may increase the risk of complications.

Hypertension (57.1%), diabetes mellitus (DM ; 35.7%), and coronary artery disease (CAD; 28.6%) rates were high in geriatric ASH patients in our study, consistent with the data in the literature. In a study conducted by Atsumi et al. in chronic subdural hematoma (CSDH) patients, the hypertension rate was reported as 20% and the DM rate as 11.4% (5). In a study by Sundblom et al. in 10CSDH patients over 70 years of age, the rate of cardiovascular disease was 43.4% and the rate of DM was 18.4% (27). These data suggest that comorbidities, including hypertension and DM, are prevalent among older patients and must be factored into the prognosis of ASH.

In our study, the rate of anticoagulant use was 38.1%, and the mortality rate was 37.5% in these patients. Younsi et al. stated that anticoagulant use may increase the risk of postoperative complications in patients with subdural hematoma, but the evidence that it increases mortality is limited (33). On the other hand, Raj et al. found higher mortality rates in older adult using anticoagulants (23). In our study, the rate of antiaggregant use was 45.2%. According to the study by Szczygielski et al., no significant negative effect of antiaggregant drugs such as aspirin on prognosis was observed, but anticoagulant use was associated with poor prognosis (28). Additionally, De Bonis et al. found that patients who used antiaggregants had longer hospital stays, consistent with the results of our study (10).

When the mean age ( $73.67 \pm 10.00$  years) and the distribution of age groups (52.4%, 65-75 years; 33.3%, 75-85 years) were

evaluated in our study, the negative effect of age on prognosis was observed. A negative correlation ( $\rho = -0.384$ ) was found between age and GOS score, consistent with similar studies in the literature. For example, Younsi et al. reported a postoperative mortality rate of 33% in ASH patients over 80 years of age and associated it with poor prognosis (32). Kerezoudis et al. observed an 18.3% death rate in older patients undergoing surgery for ASH, highlighting a considerable rise in this risk among patients over 85 years of age (14). These data substantiate the influence of age on prognosis and indicate an elevated risk of adverse clinical outcomes in elderly individuals. Hiraizumi et al. also indicated that age was a significant predictive factor in older patients with ASH, with the likelihood of poor prognosis escalating with advancing age (12). Qi et al. conducted a study on elderly patients with subarachnoid hemorrhage, revealing a substantial negative correlation between age and GOS (22). The data substantiate the detrimental impact of older age on the prognosis of acute subdural hematoma, correlating closely with a raised mortality rate. Aromatario et al. reported that mortality rates after subdural hematoma in elderly patients ranged between 17.6% and 55.1%, and age was significantly associated with poor prognosis (4). In our study, the negative effect of age on prognosis was explained by mortality rates varying according to age groups and negative correlation with GOS. Findings consistent with the results in the literature were obtained.

The most critical shortcomings of this study are its retrospective nature and low sample size. Therefore, the data's precision and level of statistical significance may be restricted. These constraints are also applicable to similar studies in the literature due to their retrospective character and small numbers of patients. Multicenter and prospective studies are preferable in the future. Additionally, the use of biochemical markers or clinical measurement methods in assessing prognosis may be improved.

## ■ CONCLUSION

We performed a retrospective analysis of the clinical and surgical prognostic factors in ASH patients over the age of 60 years. These parameters included age, GCS score on admission, hematoma size, and midline shift. The time of surgical intervention and the approach were determinative in clinical outcomes. When craniotomy and decompressive craniectomies were contrasted, the impact of these methods was different for frequently attending clinical features and the selected population. To improve ASH patients' prognosis, timely and effective surgical measures and individualized approaches are essential.

### 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: HI

Data collection: HI, ASA, MD

Analysis and interpretation of results: EE

Draft manuscript preparation: HI, ASA, MD, NV

Critical revision of the article: HI, ASA, MD, NV

Other (study supervision, fundings, materials, etc...): HCG, HI, ASA

All authors (HI, ASA, MD, NV, HCG, EE) reviewed the results and approved the final version of the manuscript.

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# Shape Analysis of the Corpus Callosum in Pediatric Hydrocephalus: A Comparison Between Cases with and without Shunt Revision Surgery

Elif BASARAN GUNDOGDU<sup>1</sup>, Deniz SIGIRLI<sup>2,3</sup>

<sup>1</sup>Bursa Health Sciences University Training and Research Hospital, Neurosurgery Clinic, Bursa, Türkiye

<sup>2</sup>United Arab Emirates University, Department of Statistics and Business Analytics, Al Ain, United Arab Emirates

<sup>3</sup>Uludag University, Department of Statistics, Bursa, Türkiye

Corresponding author: Elif BASARAN GUNDOGDU ✉ basaran.elif@hotmail.com

## ABSTRACT

**AIM:** To investigate corpus callosum shape differences in pediatric hydrocephalus patients with and without shunt revisions.

**MATERIAL and METHODS:** Midsagittal magnetic resonance imaging studies from 45 cases (25 with and 20 without shunt revision surgeries) that underwent ventriculoperitoneal shunt surgery between 2016 and 2025 were retrospectively analyzed. Corpus callosum shape deformations were evaluated using thin plate spline (TPS) analysis. Landmark-based geometric morphometric methods were applied, and growth curve modeling was used to assess the relationship between centroid size and the number of shunt revisions.

**RESULTS:** TPS analysis revealed that patients with multiple shunt revisions exhibited the most prominent corpus callosum deformations in the posterior region. Atrophy was detected mainly in the splenium region.

**CONCLUSION:** This study identified changes in the corpus callosum of pediatric hydrocephalus patients with multiple shunt revisions compared to those without shunt revisions. These findings may help characterize the clinical features of cases with multiple shunt revisions.

**KEYWORDS:** Hydrocephalus, Corpus callosum, Shunt revision, Shape analysis

**ABBREVIATIONS:** **CC:** Corpus callosum, **CSF:** Cerebrospinal fluid, **MRI:** Magnetic resonance imaging, **NY:** New York, **TPS:** Thin plate spline

## INTRODUCTION

Hydrocephalus is a neurological condition characterized by the abnormal accumulation of cerebrospinal fluid (CSF) within the brain, resulting in ventricular enlargement. The standard treatment involves surgical placement of a ventriculoperitoneal shunt to divert CSF into the peritoneal cavity, thereby reducing intracranial pressure. In hydrocephalus, damage to the corpus callosum (CC), resulting from mechanical pressure against the falx cerebri and deterioration of myelin, is associated with motor and cognitive

deficits. Disruption of normal myelination adversely affects the microstructural architecture of the posterior CC (1).

The CC comprises five subdivisions, each with distinct functional connections. The posterior part (splenium) connects the visual cortices of the occipital lobes. Anterior to this, the middle posterior part (isthmus) connects motor, somatosensory, and primary auditory regions. Central (body) fibers project through the cerebral cortex and ascend into the corona radiata, contributing to several key white matter tracts. The middle frontal part (genu) connects the middle and lateral surfaces

of the frontal lobe, while the anterior part (rostrum) serves as a critical conduit between the orbital surfaces of the frontal lobe (1).

Magnetic resonance imaging (MRI) studies in patients with hydrocephalus have frequently revealed thinning of the CC and scalloping of its margins, both before and after shunt surgery. In rare cases, however, thickening of the CC has been observed in patients who have undergone successful shunt placement (4).

Shape analyses of the CC have been conducted across a variety of neurological conditions, revealing disease-specific morphological differences. In patients with multiple sclerosis, structural deformities have been identified in the CC and cerebellum (19). In cases of scaphocephaly, longitudinal shape analyses have shown that the expansion of the cranial vault over time is associated with an enlargement of the splenium region of the CC (3). In individuals with restless legs syndrome, callosal deformations have been mainly localized to the posterior middle region and, to a lesser extent, the anterior region. Furthermore, increased disease duration and severity have been correlated with significant reductions in the size of the CC (20).

Studies investigating the effect of a disease, surgery, or pathological conditions on brain structures have primarily relied on single morphometric measures such as volume or density. In contrast, landmark-based shape analysis focuses on the intrinsic geometric properties of anatomical structures. Shape is defined as the geometric information that remains invariant under translation, rotation, and scaling, thus enabling a more detailed assessment beyond scalar measurements (7,11,12). With advances in image-processing software and the availability of high-resolution digital imaging from various modalities, landmark-based shape analysis has been increasingly applied in neuroanatomical research (18-22). When combined with thin plate spline (TPS) analysis, this approach enables the precise localization of shape differences across cortical and subcortical brain regions, revealing even subtle morphological deformations (14,15,17).

This study aimed to compare shape differences in the CC of pediatric patients with hydrocephalus who underwent shunt revision surgery with those who did not. Using landmark-based shape analysis, we evaluated regional deformations across CC subregions to identify potential morphological alterations. Furthermore, we investigated whether the number of shunt revisions predicts CC abnormalities in this patient population.

## ■ MATERIAL and METHODS

The study was approved by the local Ethics Committee (Decision Number/Date: 2024-TBEK 2025/03-07/26.03.2025). Written informed consent was obtained from all participants or their legal guardians. No financial support was received for this study.

Midsagittal MRI studies from 45 patients who had previously undergone ventriculoperitoneal shunt surgery for hydrocephalus between 2016 and 2025 were retrospectively analyzed. Of these patients, 25 patients had undergone shunt revision

surgery, while 20 had no history of revision. Patients were excluded if they were aged >17 years, had CC abnormalities that precluded the placement of all required landmarks, or exhibited extreme thinning or deformation of the CC on MRI that would compromise accurate shape analysis.

Demographic and clinical data—including patients' age, sex, hydrocephalus etiology, reasons for shunt revision, and midsagittal MRI images—were retrospectively collected from hospital records. MRI examinations were performed using a 1.5-T scanner (GE Optima MR360, Milwaukee, Wisconsin, USA) equipped with a 16-channel sensitivity-encoding head coil. Sagittal T2-weighted spin-echo sequences were obtained using the following parameters: field of view, 230 × 250 mm; slice thickness, 5 mm; repetition time/echo time, 5800–6700/95–115 ms; flip angle, 90°. These parameters provided optimal contrast between gray and white matter for anatomical evaluation.

### Landmark Acquisition

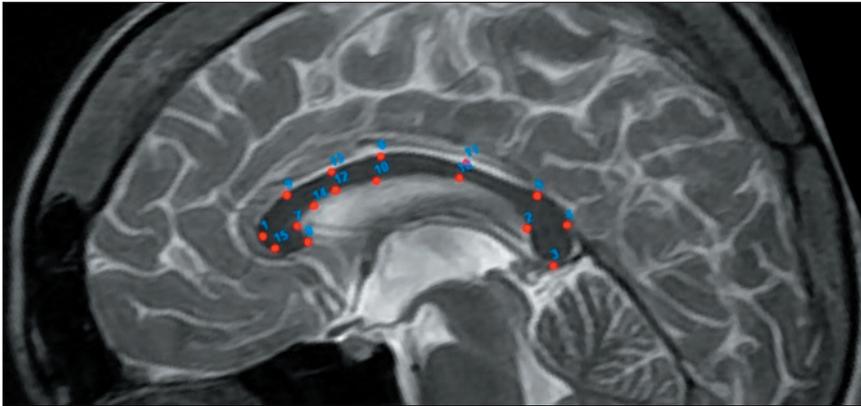
For each patient, the midsagittal section that most clearly displayed the cerebral aqueduct, CC, and superior colliculus was manually selected from the sagittal image set. Sixteen homologous anatomical landmarks were identified on the midsagittal image as described by Sigirli et al (19). Landmark placement was performed using TPSDIG version 2.04 software (Figure 1) (16). To assess intra-rater reliability, a two-facet crossed design was used (5,8). A total of 20 images were randomly selected and reannotated by the same researcher 1 month later. The generalizability coefficient (G) for landmark placement was 0.9925, indicating excellent intra-rater reliability.

### Geometric Morphometric Analysis

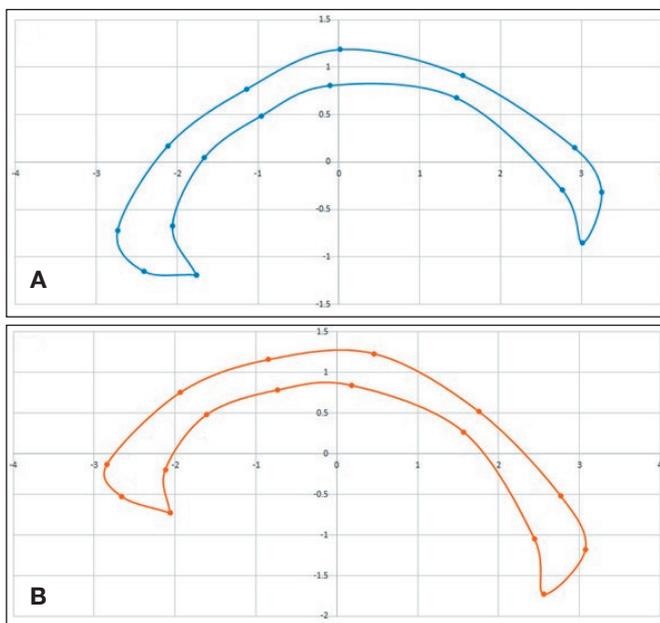
Shape deformations of the CC were evaluated using TPS analysis. TPS assesses shape differences by deforming one landmark configuration into another, with expansion factors representing the magnitude of deformation. The resulting TPS deformation grids visually show regions exhibiting the greatest degrees of atrophy or expansion, with color-coded representations indicating the magnitude and direction of these deformations (2,9). Overall shape variability was quantified using the root mean square of Kendall's Riemannian distance ( $\rho$ ) from the mean shape. Centroid size—defined as the square root of the summed squared distances of each landmark from the centroid—was calculated as a size metric derived from Procrustes-aligned landmark configurations. Nonlinear growth curve models were applied to examine the relationship between the number of shunt revisions and the centroid size of the CC. The R v. 4.4.3 software, the Shapes package, and MedCalc 19.1.3 were used for statistical analyses (6,9,13).

### Other Statistical Analysis

Continuous variables were summarized as median (range) owing to their non-normal distributions. Comparisons between two independent groups were performed using the Mann-Whitney U test. Categorical variables were reported as frequencies and percentages (n, %), and group comparisons were conducted using Pearson's chi-square test or Fisher's exact chi-square test, as appropriate.



**Figure 1:** Corpus callosum landmarks used in the study.



**Figure 2:** Procrustes mean shapes of the CC in patients **A)** with shunt revision, and **B)** without shunt revision.

**Table I:** Comparison of Hydrocephalus Etiologies Between the with and without Revision Groups

Etiologies	Without revision	With revision	p-value
Spina bifida	8 (38.1)	10 (38.5)	0.980
Encephalocele	1 (4.8)	1 (3.8)	1.000
Antenatal hydrocephalus	5 (23.8)	5 (19.2)	0.734
Premature germinal matrix hemorrhage	3 (14.3)	4 (15.4)	1.000
Infection	2 (9.5)	0 (0.00)	0.194
Intracranial mass	2 (9.5)	4 (15.4)	0.678
Aqueduct stenosis	0 (0.00)	2 (7.7)	0.496

Data presented as n (%)

**RESULTS**

The median age was 3.50 years (range: 0.25–16.42 years) in the revision group and 2.42 years (range: 0.17–14.92 years) in the non-revision group, with no significant difference between the groups ( $p = 0.705$ ). Sex distribution was also comparable between the two groups (boys: 50.0% vs. 42.9%,  $p = 0.626$ ). No significant differences were observed in the etiologies of hydrocephalus between the revision and non-revision groups (Table I). Among patients who underwent shunt revision, the most common indication was shunt dysfunction ( $n = 17$ , 65.4%), followed by shunt infection ( $n = 11$ , 42.3%) and shunt malposition ( $n = 4$ , 19.2%).

Box’s M test indicated a lack of homogeneity in the variance-covariance matrices ( $p < 0.001$ ); therefore, the James  $F_J$  test with resampling was applied. No significant difference in overall CC shape was detected between patients with and without shunt revision ( $p = 0.386$ ).

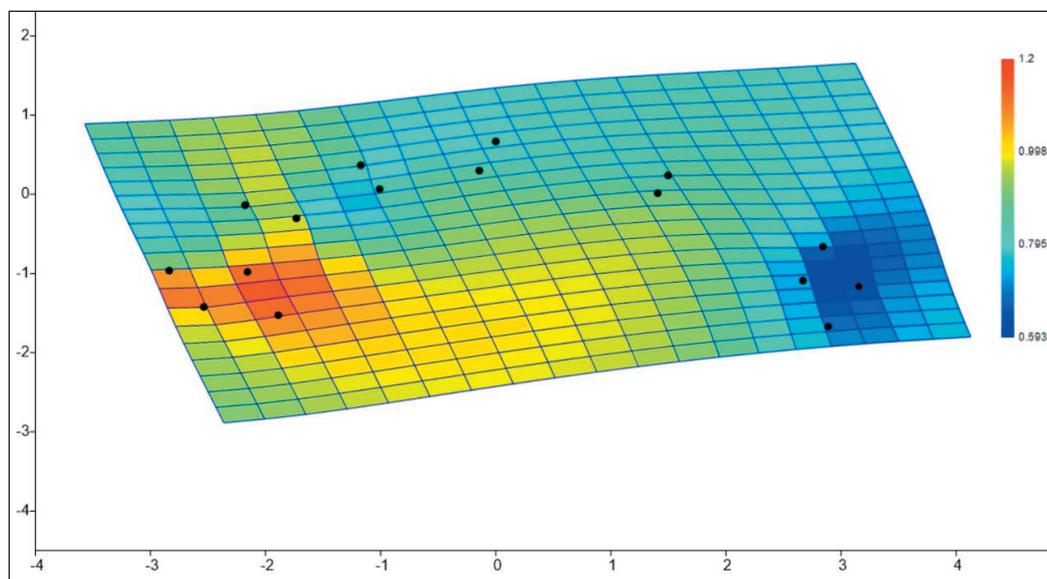
The root mean square of Kendall’s Riemannian distance ( $\rho$ ) to the mean shape was 0.154 in the revision group and 0.180 in the non-revision group, indicating greater overall shape variability in patients without shunt revision.

TPS analysis demonstrated that the most prominent shape deformations were observed in the posterior region of the CC. In particular, atrophy was detected between landmarks 2, 3, 4, and 5, corresponding to the splenium. Additionally, minimal atrophy was observed in the rostral region near landmarks 12 and 13 (Figures 2 and 3).

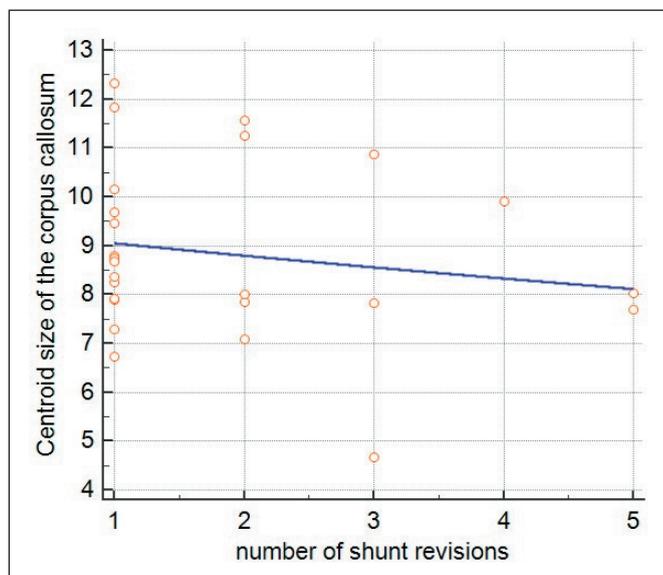
The relationship between CC centroid size and the number of shunt revisions was evaluated using several growth curve models. The three-parameter logistic model provided the best fit ( $p < 0.001$ ,  $R^2 = 0.029$ ), indicating that centroid size decreased with the increase in the number of shunt revisions (Figure 4).

**DISCUSSION**

The CC is the largest commissural fiber tract in the human brain, comprising approximately 200–300 million axons with varying degrees of myelination, diameter, and density. Ana-



**Figure 3:** Thin plate spline (TPS) deformation map illustrating shape differences between patients without shunt revision and those with shunt revision.



**Figure 4:** Growth curve model illustrating the relationship between the centroid size of the splenium and the number of shunt revisions. Model: Centroid size =  $0.035/[1 + (-0.9963 \times e^{(0.0001 \times \text{number of revisions})})]$

tomically, it consists of five parts: the rostrum, genu, body, isthmus, and splenium. The CC is supplied by a rich vascular network, primarily derived from branches of the anterior cerebral artery, with additional contributions from the middle cerebral artery and the posterior communicating artery (10).

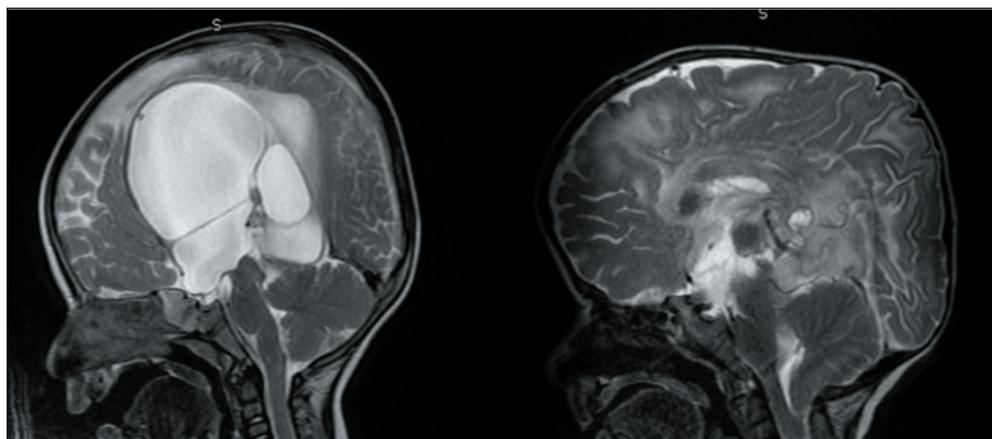
In cases of hydrocephalus, structural and vascular changes can occur within the CC. Experimental studies have suggested that ischemic injury in the CC results from mechanical compression accompanied by a reduction in capillary density.

In addition, stretching of the pericallosal arteries due to ventricular enlargement may lead to edema (4).

Ischemia of the CC in acute noncommunicating hydrocephalus has been observed in the splenium, a posterior subregion of the CC, as well as in the cerebellum. These findings suggest that specific anatomical regions are particularly vulnerable to infarction under conditions of acute ventricular dilation. In case of severe expansion of the lateral ventricle and increased intraventricular pressure, infarction of the splenium may occur due to compression of the posterior pericallosal artery and pericallosal pial plexus (10). In this study, the atrophy observed in the splenium may be attributed to ischemic changes resulting from repeated episodes of acute hydrocephalus in patients who underwent multiple shunt revisions.

In a previous study analyzing CC shape in patients with multiple sclerosis, significant differences were observed compared with healthy controls, with the greatest deformation reported in the anterior region, including the genu and rostrum (19). Disease-related shape alterations in the CC may therefore manifest in various regions depending on the underlying pathology. Although no significant differences in CC shape were observed between patients with and without shunt revisions, TPS analysis revealed atrophy in the splenium. We hypothesize that the absence of a statistical difference may be due to the exclusion of cases with the most severe CC deformation—particularly patients with multiple shunt revisions in whom landmark placement was not feasible because of extreme thinning and distortion. Nevertheless, visual inspection showed that the CC in patients with multiple revisions was more deformed than in those without shunt revisions (Figure 5).

In a study involving CC shape analysis in patients operated on for scaphocephaly, no statistically significant postoperative shape differences were detected; however, enlargement of the splenium was observed on imaging (3). Similarly, in con-



**Figure 5:** Two representative cases with multiple shunt revisions where shape analysis could not be performed due to severe thinning and deformation of the corpus callosum.

ditions associated with increased intracranial pressure, such as scaphocephaly and hydrocephalus, shape alterations are frequently observed in the splenium region (3,19,20). These findings suggest that the splenium is the most susceptible subregion of the CC to intracranial pressure-related structural changes.

Elevated intracranial pressure in hydrocephalus imposes mechanical stress on white matter tracts, potentially altering axonal orientation and contributing to myelin degradation. Myelinated fibers are located in the posterior regions of the CC, whereas thinner, unmyelinated fibers are located in the anterior regions. During childhood and adolescence, increased area measurements in the isthmus and splenium indicate an increase in axon diameter and myelin deposition. Oligodendrocytes, the cells responsible for myelin production, may be particularly vulnerable during periods of rapid myelination. Consequently, disruption of the myelination process may have significant implications on the microstructural architecture of the posterior CC. This observation suggests a dynamic interaction between hydrocephalus-related pathophysiological processes and brain development, particularly during the phase of active myelination (1). In patients requiring one or more shunt revisions, repeated and sustained elevations in intracranial pressure are likely to exert greater mechanical stress on the CC compared with patients without revisions. The atrophy observed in the posterior regions can be explained by the increased exposure of myelinated fibers in this region to intracranial pressure. Supporting this interpretation, our growth model demonstrated a decrease in the centroid size of the CC with an increasing number of shunt revisions.

## ■ CONCLUSION

In pediatric patients with hydrocephalus who underwent multiple shunt revisions, the most prominent CC deformations were localized to the posterior region, particularly the splenium, as demonstrated by TPS analysis. Minimal atrophy was also observed in the rostral region. Our growth curve model further revealed a negative association between the number of shunt revisions and the centroid size of the CC. We believe that these findings will help characterize the clinical features of cases with multiple shunt revisions.

## 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.

## AUTHORSHIP CONTRIBUTION

Study conception and design: EBG, DS

Data collection: EBG, DS

Analysis and interpretation of results: EBG, DS

Draft manuscript preparation: EBG

Critical revision of the article: EBG, DS

Other (study supervision, fundings, materials, etc...): EBG, DS

All authors (EBG, DS) reviewed the results and approved the final version of the manuscript.

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# Transnasal Transsphenoidal versus Transcranial Surgery for Resection of Sellar Lesions; A National Database Analysis

Daniel N MUNGER<sup>1</sup>, Brannan E O'NEILL<sup>1</sup>, Ali I RAE<sup>1</sup>, Mathew N GELTZEILER<sup>2</sup>, Olabisi R SANUSI<sup>1</sup>

<sup>1</sup>Oregon Health & Science University, Department of Neurosurgery, Portland, OR, USA

<sup>2</sup>Oregon Health & Science University, Department of Otolaryngology, Portland, OR, USA

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**Corresponding author:** Olabisi SANUSI ✉ sanusi@ohsu.edu

## ABSTRACT

**AIM:** To present a national database analysis comparing transnasal transsphenoidal (TNTS) and transcranial (TC) approaches in sellar lesion management.

**MATERIAL and METHODS:** We analyzed the National Surgical Quality Improvement Program (NSQIP) database by TNTS and TC CPT codes from 2014-2018. Outcome measures included periprocedural complications, surgical complications, reoperation within 30 days, readmission, and death. Statistical comparisons were made using Wilcoxon rank-sum test in STATA.

**RESULTS:** A total of 488 procedures were identified (232 TC; 256 TNTS). Baseline demographics were comparable between groups. Patients undergoing craniotomy were more likely to have DVT or PE (8 vs 2 patients,  $p=0.042$ ) and stroke (11 vs 0 patients,  $p<0.001$ ). TC approach was associated with longer hospital length-of-stay (6.1 vs 4.2 days,  $p<0.001$ ), 30-day readmission (15.8% vs 7.1%), and death (2.6% vs 0.4%,  $p=0.042$ ). Craniotomy was more likely to be performed in nonelective cases (26.3% vs 12.6%,  $p<0.001$ ), however the difference in complication rates was driven by elective cases.

**CONCLUSION:** We found that the TC approach to the sella was associated with higher rates of complications and greater mortality than the TNTS approach. The TC approach was also more likely to be performed in nonelective cases, but the difference in morbidity and mortality was driven by elective cases. Further study is warranted to identify lesion characteristics that may influence choice of approach and outcomes.

**KEYWORDS:** Sellar mass, Pituitary surgery, Transnasal transsphenoidal, Transcranial

**ABBREVIATIONS:** TNTS: Transnasal transsphenoidal, TC: Transcranial, CPT: Current procedural terminology, DVT: Deep vein thrombosis, PE: Pulmonary embolism, ACS: American college of surgeons, NSQIP: National surgical quality improvement program, IRB: Institutional review board, ASA: American society of anesthesiologist, DVT: Deep vein thrombosis, PE: Pulmonary embolism, UTI: Urinary tract infection, MI: Myocardial infarction, LOS: Length of stay, RVU: Relative value units, STROBE: Strengthening the reporting of observational studies in epidemiology, CSF: Cerebrospinal fluid, ENT: Ear, nose, and throat

Daniel N MUNGER : 0000-0003-4704-5292

Brannan E O'NEILL : 0000-0001-9410-5134

Ali I RAE : 0000-0003-4907-8055

Mathew N GELTZEILER : 0000-0001-6553-3885

Olabisi R SANUSI : 0000-0002-2467-2739



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## ■ INTRODUCTION

Both transnasal transsphenoidal (TNTS) and transcranial (TC) interventions are viable surgical approaches for resection of sellar lesions. Each possess relative advantages and limitations. Technological advances such as high-resolution noninvasive imaging, endoscopic visualization, microneurosurgery, frameless stereotactic neuronavigation, color Doppler ultrasonography, real-time intraoperative magnetic resonance imaging and neuromonitoring have dramatically increased the effectiveness and decreased the morbidity and mortality of TNTS surgery. These advancements have helped the TNTS approach become effectively the standard of care for small lesions limited to the sella. TNTS techniques are increasingly applied to a wide range of anatomic zones extending beyond the sella to include the clivus, anterior fossa, suprasellar cistern and third ventricle.

Despite the technical advances that fostered the proliferation of TNTS surgery, this approach still has its limitations. In particular, masses that extend beyond its defined operative corridors can be difficult to visualize and expose. In these cases, TC approaches may provide certain advantages, albeit at the cost of potentially higher procedural morbidity and limited access to more caudal structures within the sella. Furthermore, TNTS surgery is often performed with the assistance of an otolaryngology-trained approach surgeon, a resource which may not be available at smaller, community-based medical centers.

There are multiple confounding factors that obfuscate any comparison of these two techniques. For this reason, there is significant disagreement in the literature regarding the outcome and complication profile of TNTS versus TC surgery. This motivated a national database analysis, with the goal of quantifying these metrics and providing greater clarity for surgeons and patients.

## ■ MATERIAL and METHODS

The American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database was used for this study's analysis. The ACS NSQIP database collects patient data from 700 participating medical centers including demographics, preoperative risk factors, laboratory values, intraoperative variables and 30-day postoperative outcomes. This repository is also publicly accessible and all patient data is deidentified. For these reasons, this study did not require Institutional Review Board (IRB) approval.

A query for patients undergoing pituitary mass resection in 2014–2018 was conducted by relevant Current Procedure Technology (CPT) codes. The results were filtered by code for craniotomy for pituitary mass resection (CPT 61546) and transsphenoidal approach for pituitary mass resection (CPT 62165). Holistic global codes were used in lieu of more nuanced codes to maintain the homogeneity of the population. The bundled transsphenoidal approach to sellar region code came into use in 2014 and the last year of available data was 2018, thereby driving the date range.

Baseline demographics queried were age, sex, diabetes status, smoking status, use of hypertensive medication, use of steroids pre-operatively, ASA class, and whether the surgery was classified as elective. Complications included pneumonia, reintubation, deep vein thrombosis (DVT) or pulmonary embolism (PE), renal insufficiency, urinary tract infection (UTI), stroke, myocardial infarction (MI), bleeding complication, and shock or sepsis. Outcome measures included reoperation within 30 days, hospital length of stay, readmission within 30 days and death. Average work relative value units (RVUs) for each CPT code were also collected.

Statistical comparisons between demographics, complications, and outcomes were made using Wilcoxon rank-sum test in STATA. A logistic regression model was used to compare outcomes between TNTS and TC approaches stratified by nonelective vs elective cases. Average RVUs were compared using a two-sample z-test. A p-value of less than 0.05 was considered statistically significant.

Study design and manuscript preparation were performed in accordance with STROBE guidelines (4).

## ■ RESULTS

A total of 488 procedures were identified (232 TC; 256 TNTS). No patients in this cohort underwent both procedures. Baseline demographics were comparable between groups (Table I). Craniotomy was more likely to be performed in nonelective cases (26.3% vs 12.6%,  $p < 0.001$ ).

Across all patients the complication rate was 14.1% (Table II). The overall complication rate was higher in TC compared with TNTS surgery (20.7% vs 8.2%,  $p < 0.001$ ). Patients undergoing craniotomy were more likely to have DVT or PE (8 vs 2 patients,  $p = 0.042$ ) and stroke (11 vs 0 patients,  $p < 0.001$ ).

The TC approach was associated with longer hospital length-of-stay (6.1 vs 4.2 days,  $p < 0.001$ ), 30-day readmission (15.8% vs 7.1%,  $p = 0.007$ ) and death (2.6% vs 0.4%,  $p = 0.042$ ) (Table III). Mean operative time was 251 minutes (std dev 133 mins) for TC and 197 minutes (std dev 115 mins) for TNTS ( $p < 0.001$ ). The average work RVU was high for TC (33.6, 95% CI 33.4 – 33.7) than TNTS (17.8, 95% CI 17.7 – 18.0) ( $p < 0.001$ ). No differences were observed in rates of perioperative pneumonia, reintubation, renal insufficiency, UTI, MI, bleeding complication, shock/sepsis or 30-day return to OR.

The finding that craniotomy was more common in nonelective cases motivated a secondary analysis in which outcomes were stratified by nonelective vs elective. This demonstrated that for elective cases ( $n = 387$ ), craniotomy was associated with significantly increased risk of any complication, return to OR, 30-day readmission, or death (OR 2.69,  $p < 0.001$ ; 95% CI 1.555–4.645) compared to TNTS. For nonelective cases ( $n = 92$ ), craniotomy was not associated with a statistical difference in risk of any complication, return to OR, 30-day readmission, or death (OR 1.38,  $p = 0.501$ ; 95% CI 0.541–3.513).

**Table I:** Baseline Demographic Factors and Medical Comorbidities

Demographic and risk factors	All patients (n=490)	TC (n=232)	TNTS (n=256)	p-value
Age, years (mean)	52.7	53.6	51.9	0.261
Male, proportion (%)	47.4	48.7	45.9	0.533
Diabetes, n (%)	99 (20.2)	47 (20.2)	52 (20.3)	0.988
Smoking, n (%)	91 (18.6)	46 (19.4)	45 (17.6)	0.605
HTN medication, n (%)	207 (42.2)	105 (45.3)	101 (39.5)	0.195
Pre-operative steroids use, n (%)	65 (13.3)	36 (15.5)	29 (11.3)	0.174
ASA Class 3 or 4, n (%)	307 (62.8)	143 (61.9)	163 (63.7)	0.687
Elective surgery, n (%)	389 (80.9)	171 (73.7)	216 (87.5)	<0.001

**HTN:** Hypertension, **ASA:** American Society of Anesthesiologist.

**Table II:** Complications Associated with TNTS vs TC Surgery

Complications	All (n=490)	TC (n=232)	TNTS (n=256)	p-value
Pneumonia, n (%)	6 (1.2)	4 (1.7)	2 (0.8)	0.345
Reintubation, n (%)	10 (2.0)	6 (2.6)	4 (1.6)	0.426
DVT or PE, n (%)	10 (2.0)	8 (3.4)	2 (0.8)	0.042
Renal insufficiency, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
UTI, n (%)	8 (1.6)	4 (1.7)	4 (1.6)	0.888
Stroke, n (%)	11 (2.2)	11 (4.7)	0 (0.0)	<0.001
MI, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Bleeding complication, n (%)	15 (3.1)	10 (4.3)	5 (2.0)	0.132
Shock or sepsis, n (%)	9 (1.8)	5 (2.2)	4 (1.6)	0.627
Overall, n (%)	69 (14.1)	48 (20.7)	21 (8.2)	<0.001

**TNTS:** Transnasal transsphenoidal, **TC:** transcranial, **DVT:** deep vein thrombosis, **PE:** pulmonary embolism, **NA:** not available, **UTI:** urinary tract infection, **MI:** myocardial infarction.

**Table III:** Outcomes of TC vs TNTS Surgery

Outcomes	All (n=490)	TC (n=232)	TNTS (n=256)	p-value
30-day return to operating room, n (%)	32 (6.5)	19 (8.2)	13 (5.1)	0.166
Hospital length of stay, days (mean)	5.1	6.1	4.2	<0.001
30-day readmission, n (%)	46 (11.7)	31 (15.8)	14 (7.1)	0.007
Death, n (%)	7 (1.4)	6 (2.6)	1 (0.4)	0.042

**TC:** Transcranial, **TNTS:** transnasal transsphenoidal.

## ■ DISCUSSION

This database analysis uncovered important and significant differences between TC and TNTS approaches to the parasellar region. TC surgery is associated with a higher rate of DVT/PE, MI, overall complications, hospital LOS, 30-day readmission and death. The increased complication profile of

TC surgery is consistent with institutional series demonstrating higher rates of pituitary dysfunction (8), and worsened visual outcomes (17) in TC approaches when compared with TNTS.

Of note, multiple authors have described a higher rate of cranial nerve injuries in the TNTS cohort (9). Unsurprisingly, TNTS surgery is also associated with more olfactory nerve

disturbances (17). These represent a form of morbidity which is likely not captured by database reporting. Additionally, an increased cerebrospinal (CSF) leak rate in TNTS compared with TC surgery is a common observation (7,9,17). There is significant heterogeneity in reported rates of CSF leak following TNTS surgery, but a rough estimate provided by the CRANIAL Consortium is 5% in standard transsphenoidal approaches and 20% in expanded endoscopic endonasal surgery (3). CSF rhinorrhea after pituitary surgery is also a known predictor of increased LOS (6,14,15). However, we found that TNTS patients overall have a shorter LOS despite presumably experiencing increased rates of CSF leakage.

Though baseline characteristics of all patients undergoing these procedures in this cohort were similar, the TC approach was more likely to be performed in nonelective cases. This may have to do with the availability of an ENT co-surgeon, or lack thereof, which could force surgeons to perform a TC approach. Interestingly, the difference in complications and outcomes between approaches is driven solely by elective cases. This suggests that in emergent cases, such as apoplexy causing optic nerve compression, either approach may suffice. Conversely, for elective cases the complication profile strongly favors TNTS surgery.

This analysis also demonstrated that the TC approach was associated with a higher work RVU and longer operative time than TNTS. The difference in work RVU is likely a function of the reimbursement structure dictated by the Centers for Medicare and Medicaid, as the baseline work RVU for TC resection (CPT code 61546) is 69.65 compared with 45.73 for TNTS (CPT code 62165) (11). However, these findings suggest there may be underlying differences between the TNTS vs TC cohorts in terms of case complexity or other comorbid factors not captured by the demographic variables encoded in the NSQIP database.

Lastly, a database study limits the ability to assess the reasoning behind choice of approach, such as the size of the mass or the extent of invasion. We recognize that this limitation could introduce selection bias, and delineating rationales for approaches is a prospective area of future study to eliminate this bias. The characteristics of the lesion itself could provide insight into the differences in complications and outcomes. Nonetheless, the TC approach fared worse in this study in terms of stroke, DVT or PE, hospital LOS, 30-day readmission and death. Whether this is a consequence of the more complex nature of these cases cannot be determined from this dataset but is important to consider.

Additional limitations include the minimal granularity of the database, which does not provide information regarding factors such as tumor size, pathology, tertiary vs non-tertiary care centers, endocrinologic outcomes, adjuvant radiotherapy, Hardy classification/Knosp score or the use of endoscopic vs microscopic technique for the TNTS approach. It is also worth noting that there are many variations of the TNTS approach which include the expanded endoscopic endonasal approach (2) staged transsphenoidal surgeries (13), simultaneous “above and below” surgery combining an endonasal transsphenoidal approach with a transcranial

resection (1,5,10), and combined transsphenoidal and transcranial endoscopic approach via supraorbital keyhole (12,16). Each of these individual techniques carries a unique complication profile. However, this dataset does not allow us to quantify the impact of specific techniques on the overall outcome measures associated with TC vs TNTS resection. Furthermore, the dataset used (NSQIP) is limited to the most recent available data at the time of study initiation. Further research using more recent datasets could shed additional light on differences in these approaches.

## ■ CONCLUSION

We found that the TC approach to the sella was associated with a higher rate of complications and greater mortality than the TNTS approach. The TC approach was also more likely to be performed in nonelective cases, however the difference in morbidity and mortality was driven by elective cases. While these findings are limited by lack of granularity in terms of lesion characteristics and specific aspects of the surgical approach, they suggest that TNTS surgery may possess certain advantages over TC approach to the sella. Further study is warranted to identify lesion characteristics that may influence choice of approach and outcomes.

## 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:** 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.

**Ethical statement:** The repository is publicly accessible and all patient data is deidentified. For these reasons, this study did not require Institutional Review Board (IRB) approval.

## AUTHORSHIP CONTRIBUTION

Study conception and design: DM

Data collection: AR

Analysis and interpretation of results: AR

Draft manuscript preparation: DM, BO

Critical revision of the article: DM, BO

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

All authors (DN, BO, AR, MG, OS) reviewed the results and approved the final version of the manuscript.

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# Posterolateral Approach for Recurrent Multi-Level Ventral Intradural Extramedullary Cervical Spinal Meningioma

Varunil SHAH<sup>1</sup>, Anish KOSANUM<sup>1</sup>, Mohit PATEL<sup>2</sup>, Manish K. KASLIWAL<sup>1,2</sup>

<sup>1</sup>Case Western Reserve University School of Medicine, Cleveland OH, USA

<sup>2</sup>University Hospitals Cleveland Medical Center, Department of Neurosurgery, Cleveland OH, USA

**Corresponding author:** Manish K KASLIWAL ✉ Manish.Kasliwal@uhhospitals.org

## ABSTRACT

Spinal meningiomas are common intradural spinal tumors. Recurrent multilevel ventral intradural extramedullary spinal meningiomas, especially those presenting several years post-initial surgery is rare and can be particularly challenging to treat. We report two cases of such recurrent multilevel ventral tumors manifesting 7 and 20 years after the initial procedure. These patients were effectively managed through a posterolateral approach, encompassing laminectomy, facetectomy, division of dentate ligament with spinal cord rotation, and instrumented fusion. While the choice of surgical approach should be individualized based on the tumor and patient's characteristics and the surgeon's expertise, our experience with these cases continues to show the safety and efficacy of posterior-based approaches highlighting the additional and important surgical modifications for multilevel recurrent ventral intradural meningiomas.

**KEYWORDS:** Anterior approach, Intradural, Meningioma, Posterior approach, Spine, Surgery, Ventral

**ABBREVIATIONS:** CSF: Cerebrospinal Fluid, IDEM: intradural extramedullary, MRC: Medical Research Council, MRI: Magnetic resonance imaging

## INTRODUCTION

Meningiomas are benign, slow-growing tumors that account for 25% to 45% of all intradural extramedullary (IDEM) spinal tumors (9). Surgical resection remains the preferred treatment for patients with symptomatic IDEM meningiomas. The overall incidence of recurrence or progression of spinal meningiomas varies between studies, ranging from 0% to 17% (5). These tumors typically recur after a long period, often up to 12 years post-resection (5,10). The surgical approach for resecting an IDEM spinal meningioma depends on the tumor's location and dural attachment. There is a growing consensus that posterior-based approaches for resecting spinal meningiomas are safe and effective, regardless of the dural attachment location (5). However, when the tumor spreads en plaque over multiple levels without significantly displacing the spinal cord, a posterior approach, par-

ticularly a laminectomy, can be challenging due to the limited ability to retract the spinal cord (5-7,10). This report presents two rare cases of recurrent en-plaque multilevel ventral meningiomas that occurred 7 and 20 years after the initial surgery. These tumors were located truly ventral to the spinal cord and were treated using a posterolateral approach.

The authors obtained written informed consents from the patients included in the manuscript.

## CASE REPORT

### Case 1

A 73-year-old woman underwent a posterior cervical laminectomy over 20 years ago for resection of a ventral IDEM grade I meningioma (Figures 1A–C). She presented with chronic neck pain, slowly progressive left upper extremity weakness, and

Varunil SHAH : 0009-0007-4964-5503  
Anish KOSANUM : 0000-0002-9615-0657

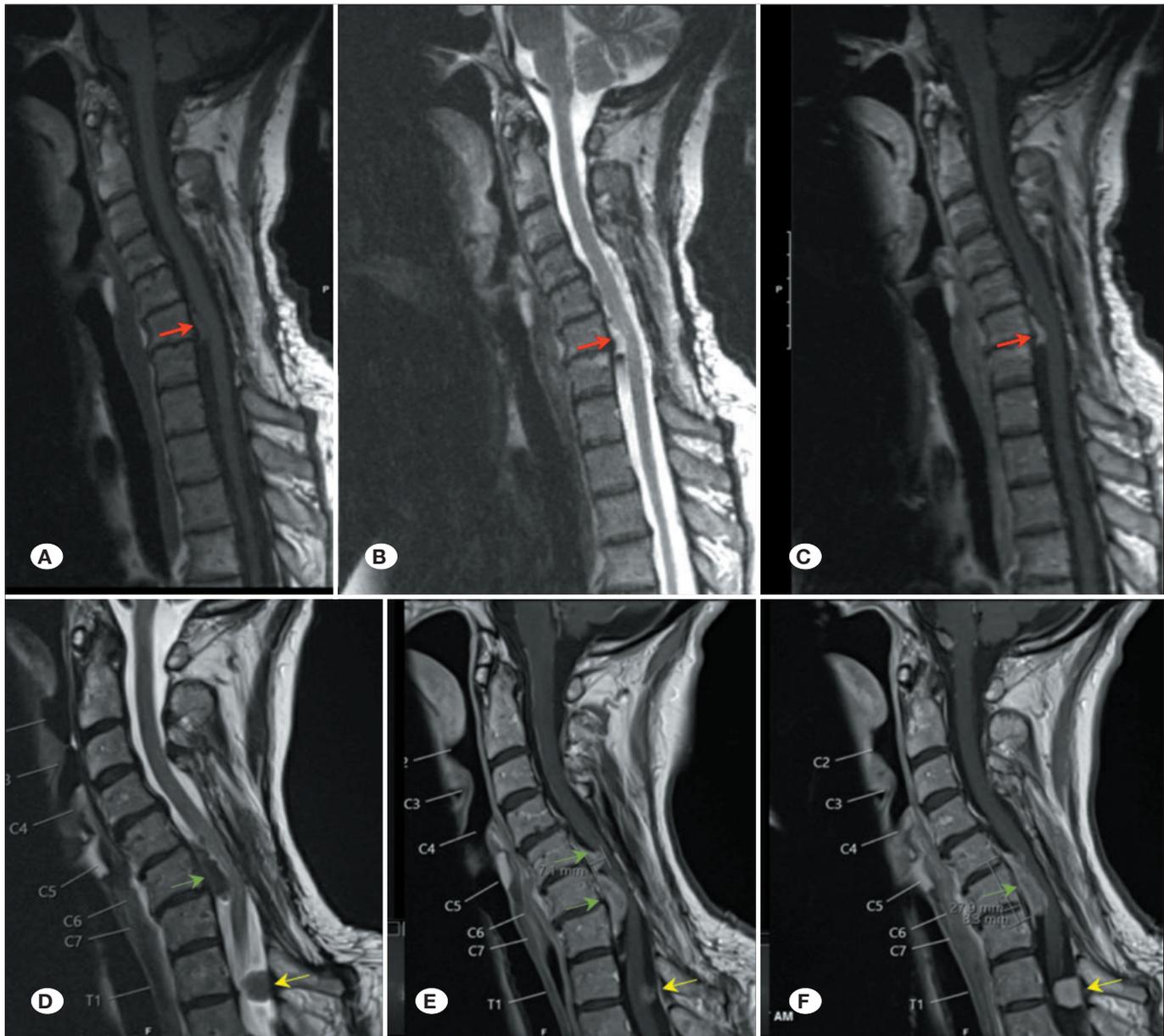
Mohit PATEL : 0000-0003-0412-7247  
Manish K. KASLIWAL : 0000-0003-0412-859X



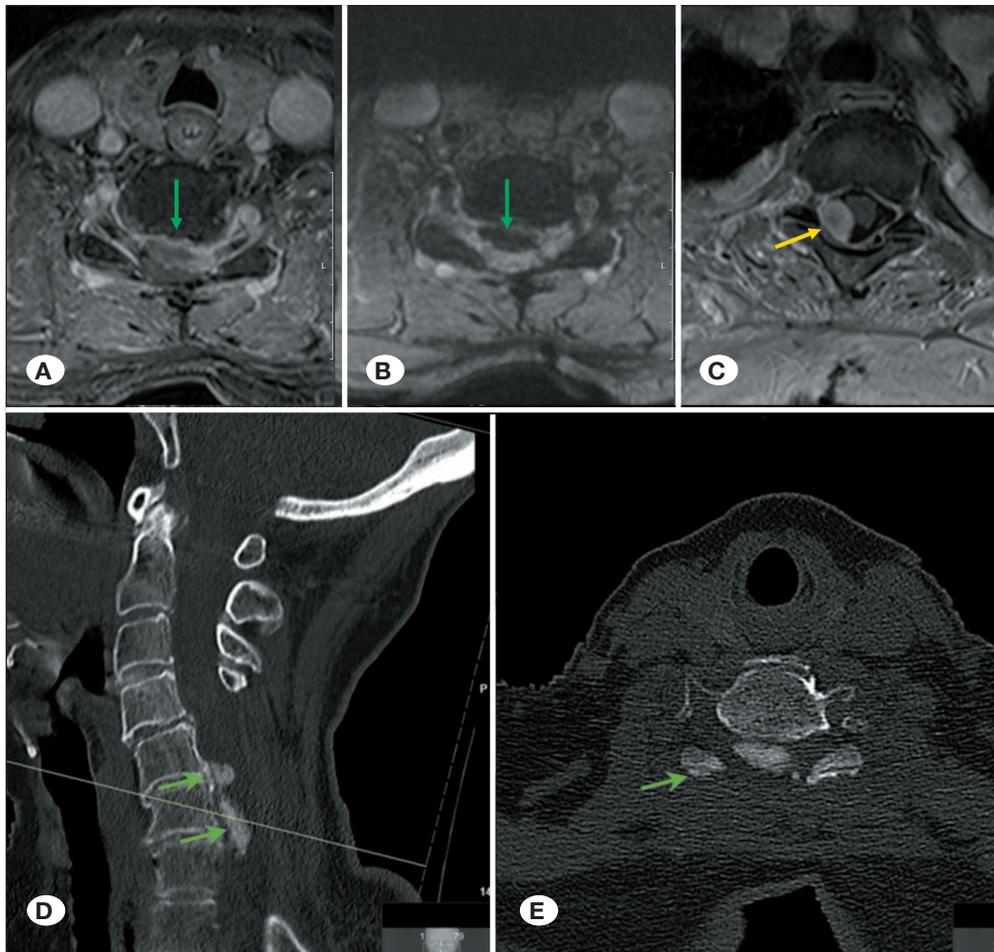
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numbness in the right upper and lower extremities, accompanied by gait imbalance over several years—consistent with cervical myelopathy. On clinical examination, motor strength was largely intact, except for mild weakness in the left upper extremity (UE) graded as 4+/5 on the Medical Research Council (MRC) scale. Hyperesthesia was present in the right upper and lower extremities. Magnetic resonance imaging (MRI) of the cervical spine at presentation to us revealed a long-segment ventral IDEM meningioma (Figures 1D–F, 2A, B) and a new right-sided posterior T1–T2 meningioma (Figure 2C). Computed tomography (CT) confirmed calcifica-

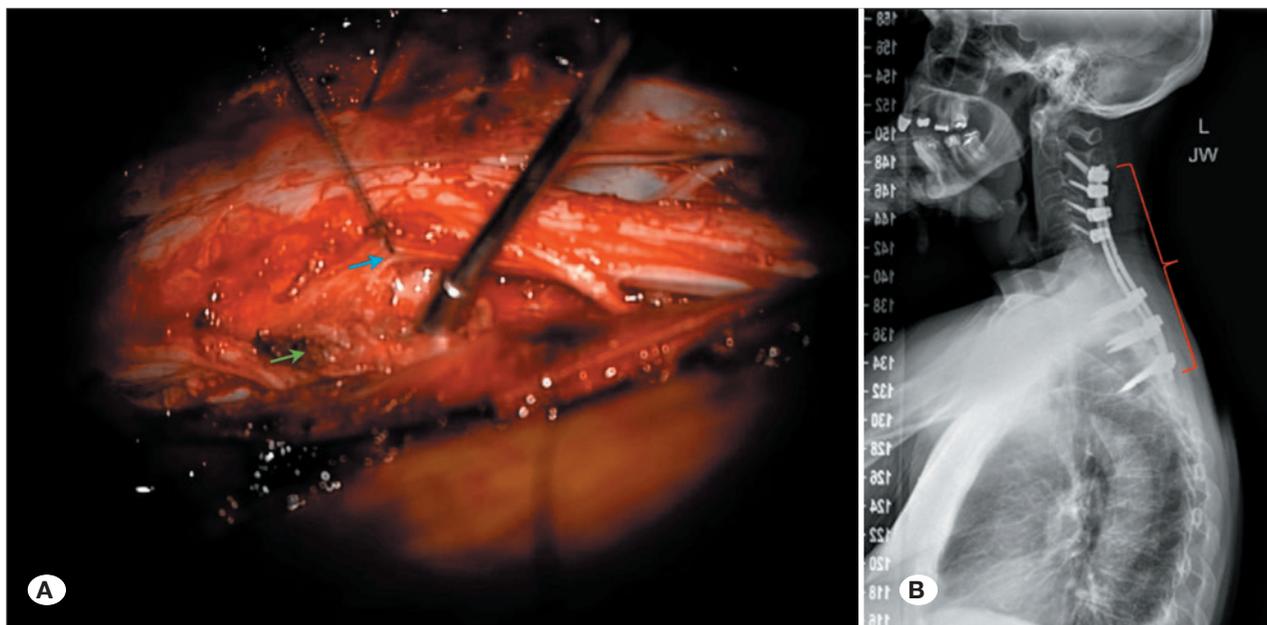
tion of the ventral meningioma (Figures 2D, E). A C4–C7 and T1–T2 laminectomy was performed with complete C5/6 and C6/7 facetectomy and C2–T3 posterolateral arthrodesis and instrumented fusion (Figure 3B). Intraoperative monitoring was performed using motor and sensory evoked potentials that remained stable throughout the procedure. Upon dural opening, the ventral meningioma was not immediately visible as it was anterior to the spinal cord. Division of the dentate ligaments facilitated spinal cord rotation (Figure 3A), and the combination of complete facetectomy and ligament division allowed for excellent tumor exposure without spinal cord re-



**Figure 1:** Sagittal T1W (A), T2W (B), T1W with contrast (C) magnetic resonance imaging (MRIs) after first surgery showing minimal residual tumor ventrally along the spinal canal, marked with red arrows. Sagittal T2W (D) and T1W with contrast MRIs (E and F) showing significant growth of the ventral meningioma in an en plaque fashion, marked with green arrows, causing spinal cord compression and interval development of a new tumor at T1–2 level, marked with yellow arrows.



**Figure 2:** Axial magnetic resonance imaging (MRIs) with contrast (**A & C**) and axial T2W MRI (**B**) showing both the cervical ventral tumor (**A and B**), marked with green arrows, and the dorsolateral right T1-2 tumor, marked with a yellow arrow. Sagittal (**D**) and axial (**E**) Computed tomography images showing the calcified nature of the ventral tumor, marked with green arrows.



**Figure 3:** Intraoperative image (**A**) showing the use of a suture through the dentate ligament, marked with a blue arrow, and rotation of the spinal cord, allowing excellent visualization of the ventral tumor, marked with a green arrow, after a complete facetectomy. Post-operative X-ray (**B**) showing C2 to T2 instrumented fusion, highlighted with a red bracket, and good restoration of lordosis.

traction. Postoperatively, the patient exhibited new-onset left upper extremity weakness (2/5 strength on the MRC scale) and was discharged to a skilled nursing facility. A one-year postoperative MRI showed a well-decompressed spinal cord with no significant residual or recurrent tumor (Figure 4). Her preoperative numbness improved, and motor strength in the left upper extremity improved to 4/5, with a left-hand grip at approximately 50% of normal. Ambulation also improved. Given the pathology-confirmed grade I meningioma, adjuvant therapy was not required, and she remains under radiological surveillance with her oncologist per institutional protocol.

## Case 2

A 59-year-old woman underwent posterior cervical C4-C6 laminoplasty seven years ago for a C5-C6 ventral IDEM grade I meningioma. Her initial post-operative MRI showed gross total resection of the dural-based mass with minimal dural enhancement (Figures 5A, B). Seven years post-surgery, she presented with right arm weakness and numbness, left leg numbness, instability, and recurrent falls. Physical examination revealed bilateral Hoffmann's sign, hyperreflexia at both the knees and ankles, and a motor strength of 4/5 across all muscle groups in the right upper extremity with a positive Romberg's test consistent with a diagnosis of cervical myelopathy. MRI confirmed tumor recurrence (Figure 5C). A redo C3-C7 laminectomy with complete C4/5 and C5/6 facetectomy was performed, achieving gross total resection of the ventral IDEM tumor, followed by C2-T1 instrumented fusion. Intraoperative motor and sensory evoked potentials remained stable throughout the procedure. Her postoperative course was uneventful, and she was discharged home on postoperative day three. Neurologically, she remained at baseline with no further motor deficits and improved gait balance. A six-week postoperative MRI showed no residual tumor but revealed a cerebrospinal fluid (CSF) pseudomeningocele, which was managed conservatively given its asymptomatic nature (Figures 5D, E). Considering her young age, the complexities of additional surgery, and her previous recurrence, adjuvant

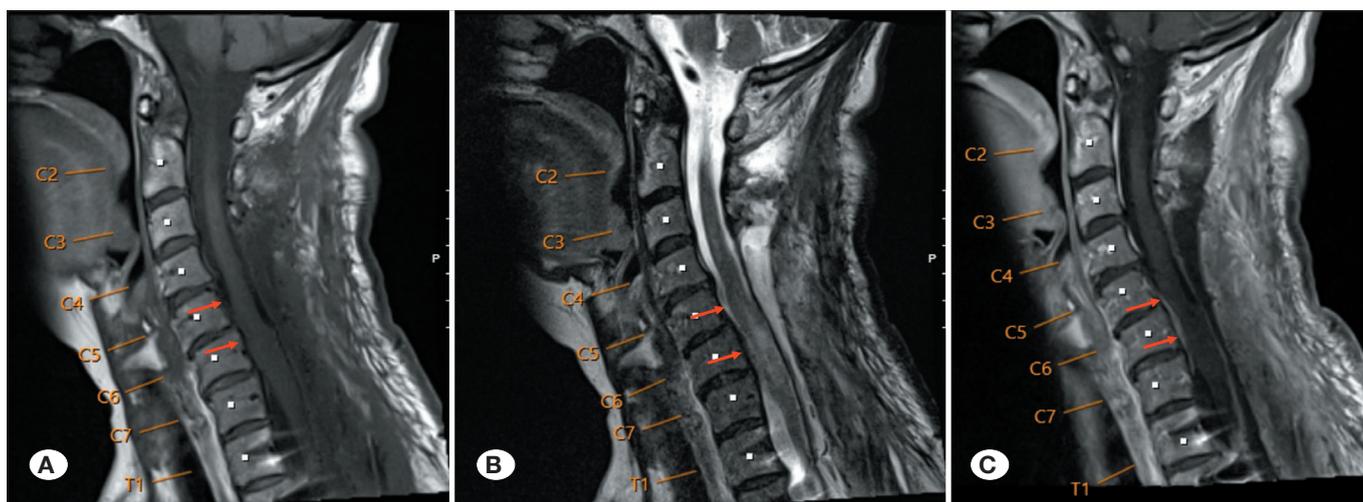
radiation therapy was recommended due to persistent dural enhancement and potential risk of further recurrence, despite pathology confirming grade I meningioma. At one-year post-surgery, she continues to do well, with a stable neurological exam and no significant tumor recurrence.

## DISCUSSION

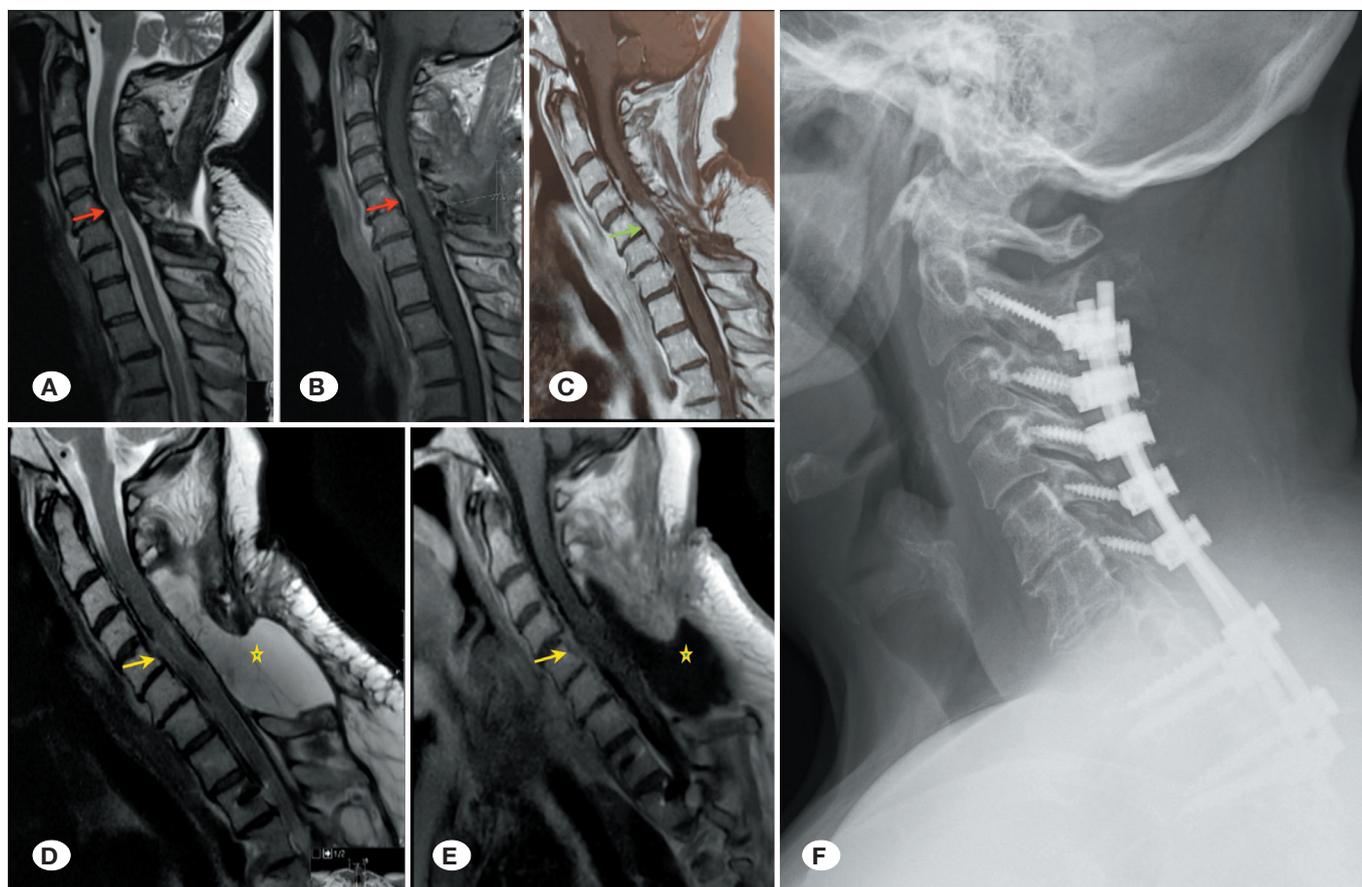
Subtotal resection has been reported as a risk factor for recurrence after surgery for IDEM meningioma, emphasizing the importance of complete resection (5). Due to concerns regarding posterior-based approaches for resecting more ventrally located tumors, some surgeons have described anterior approaches because of their direct and excellent view of the anteriorly based tumor (1,4,6,8,11). However, the depth of the operative field, the need for posterior instrumentation after a multilevel corpectomy, and the increased risk of cerebrospinal fluid leak-related complications negate any purported advantages of an anterior approach (1,4,8,11). One of the arguments against the posterior-based approach for ventral meningiomas is the inability to resect the involved dura. However, given that there is no difference in recurrence rates between patients who underwent Simpson grade I and II resections, this concern appears debatable (5).

The management of recurrent IDEM meningiomas is uniquely challenging. Risk factors for recurrent spinal meningiomas include subtotal resection, higher pathological grade, calcification, and ventral location (8). Re-resection of recurrent spinal meningiomas is complicated by adhesions from previous surgery, spinal cord tethering, lack of an arachnoidal plane between the tumor and spinal cord, and in extreme cases, pia infiltration (8).

The surgical approach to ventral IDEM meningiomas, especially recurrent ones, has not been well established. A direct posterior resection poses many challenges, such as spinal cord retraction and significant scarring, due to the ventral location of these tumors. While an anterior approach may be



**Figure 4:** Post-operative sagittal T1W (A), T2W (B), T1W (C) with contrast magnetic resonance imaging (MRIs) one year after surgery showing a well-decompressed spinal cord with no evidence of any significant residual or recurrent tumor. Original position of tumor is marked by red arrows.



**Figure 5:** Sagittal T2W (A), and T1W with contrast (B) magnetic resonance imagings (MRIs) two years after first surgery showing a gross total resection of the dural-based mass with minimal dural enhancement, marked with red arrows. Sagittal T1W MRI (C) at presentation to us 7 years after initial surgery showing an avidly enhancing, ventral, en-plaque type of meningioma in the spinal canal, extending from C3-C6, causing severe spinal cord compression, marked with green arrow. Post-operatives sagittal T2W (D) and T1W with contrast (E) MRI 6 weeks after surgery showing a well- decompressed spinal cord with no evidence of any significant residual/recurrent tumor but with minimal ventral dural enhancement, marked with yellow arrows. There is evidence of CSF pseudomeningocele (yellow star) in the images D and E. Post-operative lateral X-ray (F) showing C2 to T2 instrumented fusion with well aligned spine.

enticing to avoid the scarred field, the multilevel nature of the recurrent tumor would mandate multilevel corpectomy, along with posterior instrumentation and fusion for spine stabilization. The extensive nature of the surgery associated with an anterior approach increases the risk of worsening morbidity, especially swallowing-related complications, which can be accentuated in elderly patients (1,4,8,11).

The posterolateral approach with complete facetectomy and division of the dentate ligaments allows for rotation of the spinal cord, overcoming the challenges posed by the simple posterior and ventral approaches. This approach offers the best visualization of the tumor while limiting the complications of an extensive anterior surgical resection. Additionally, due to the angle of the approach, the spinal cord rotation required to expose the tumor margins is minimized, mitigating the risks of spinal cord injury (11). Eroglu et al. reported their experience with posterior-based approaches for ventral cervical meningi-

omas in six cases where they were able to resect the tumor without concomitant fusion (3). However, none of the tumors were recurrent, and they were large with significant posterior and lateral displacement of the spinal cord, where a posterior approach would be the procedure of choice and would not even mandate a fusion, which is clearly different from the cases described here. Also, Cristaldi et al. reported a posterolateral transpedicular approach for ventrally seated cervicothoracic spinal cord lesions (2). However, the posterolateral approach for thoracic and cervicothoracic lesions is well-described and would again be preferred for intradural lesions in that region, given the complexity of any anterior approach in that area. The presented cases demonstrate the role of a posterolateral-based approach for multilevel recurrent IDEM tumors entirely within the cervical spine. They also highlight the importance of long-term follow-up, both radiological and clinical, given that the recurrence occurred after gross total resection 7 years and nearly 20 years after the initial surgery.

## CONCLUSION

In conclusion, the management of recurrent ventral intradural meningiomas especially if multilevel can pose a significant challenge. The posterolateral approach with complete facetectomy along with division of the dentate ligaments as demonstrated in our cases is an excellent technique to resect these multilevel recurrent tumors with minimal morbidity. While the choice of surgical approach should be individualized based on the tumor and patient characteristics and surgeon expertise, the cases described here support the role of posterior-based approaches with some modifications as described for recurrent ventral spinal meningiomas.

### 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.

### AUTHORSHIP CONTRIBUTION

Study conception and design: MKK

Data collection: VS

Analysis and interpretation of results: AK

Draft manuscript preparation: VS

Critical revision of the article: MP

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

All authors (VS, AK, MP, MKK) reviewed the results and approved the final version of the manuscript.

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# Intracranial Mature Bone Formation: Report of Three Uncommon Cases and a Proposed Pathogenetic Mechanism

Ersin HACIYAKUPOGLU<sup>1</sup>, Evren YUVRUK<sup>2</sup>, Ayca Ersan DANYELI<sup>3</sup>, Dervis Mansuri YILMAZ<sup>4</sup>, Sebahattin HACIYAKUPOGLU<sup>5</sup>

<sup>1</sup>Heinrich-Braun-Klinikum Zwickau, Department of Neurosurgery, Zwickau, Germany

<sup>2</sup>VM Medical Park Maltepe, Department of Neurosurgery, Istanbul, Türkiye

<sup>3</sup>Acibadem University School of Medicine, Department of Medical Pathology, Istanbul, Türkiye

<sup>4</sup>Cukurova University, School of Medicine, Department of Neurosurgery, Adana, Türkiye

<sup>5</sup>Acibadem University School of Medicine, Department of Neurosurgery, Adana, Türkiye

**Corresponding author:** Ersin HACIYAKUPOGLU ✉ haciyakupoglu@yahoo.com

## ABSTRACT

The formation of histologically mature bone within the intracranial compartment is an exceptionally rare phenomenon. Although intracranial calcifications are frequently encountered in clinical practice, true ossification culminating in the development of mature bone tissue remains poorly characterized. Herein, we report three cases of female patients presenting with intra- and extra-axial cranial masses, all histologically confirmed to comprise mature bone. We describe the associated radiologic features, surgical challenges, and histopathological findings. Furthermore, we propose a novel pathogenetic hypothesis implicating the intraoperative dispersion of bone dust as a potential etiologic factor in iatrogenic ossification. Our findings highlight the importance of surgical vigilance and meticulous intraoperative technique to mitigate this rare but avoidable complication.

**KEYWORDS:** Teratoma, Non-neoplastic calcifying pseudotumor, Mature bone, Hyperostosis, Cerebral calculi

**ABBREVIATIONS:** CSF: Cerebrospinal fluid, MRI: Magnetic resonance imaging, CT: Computed tomography, H&E: Hematoxylin and Eosin

## INTRODUCTION

Intracranial calcifications are identified in up to 10% of neuroimaging studies and are most often incidental findings. These calcifications are typically dystrophic in nature, arising in regions of prior hemorrhage, inflammation, or necrosis. In contrast, true intracranial ossification—defined by the formation of mature lamellar bone, frequently containing bone marrow elements—is exceedingly rare (8-10). Such ossifications are usually confined to the skull base or meningeal structures and are generally attributed to congenital anomalies or post-inflammatory changes.

On rare occasions, mature bone may form within the brain parenchyma (intra-axially) or ventricular system. These lesions may radiographically and clinically mimic neoplastic or vascular pathologies, posing diagnostic challenges. Although ossified lesions such as mature teratomas, heavily calcified meningiomas, and calcifying pseudoneoplasms can account for certain presentations, the possibility of a distinct, under-recognized osteogenic mechanism warrants further investigation.

In this report, we present three cases of histologically confirmed intracranial mature bone in women of reproductive age, each with unique anatomical locations and clinical manifes-

Ersin HACIYAKUPOGLU : 0000-0002-9712-9913

Evren YUVRUK : 0000-0002-2945-743X

Ayca Ersan DANYELI : 0000-0001-8015-9916

Dervis Mansuri YILMAZ : 0000-0002-5137-4526

Sebahattin HACIYAKUPOGLU : 0000-0002-0700-7593



tations. Beyond characterizing the radiological, surgical, and pathological features, we propose a novel pathogenetic hypothesis: the intraoperative dissemination of bone dust, followed by osteogenic transformation, may serve as a potential mechanism for iatrogenic ossification within the cranial cavity.

Written informed consent was obtained from all patients included in this study.

## ■ CASE REPORT

### Case 1

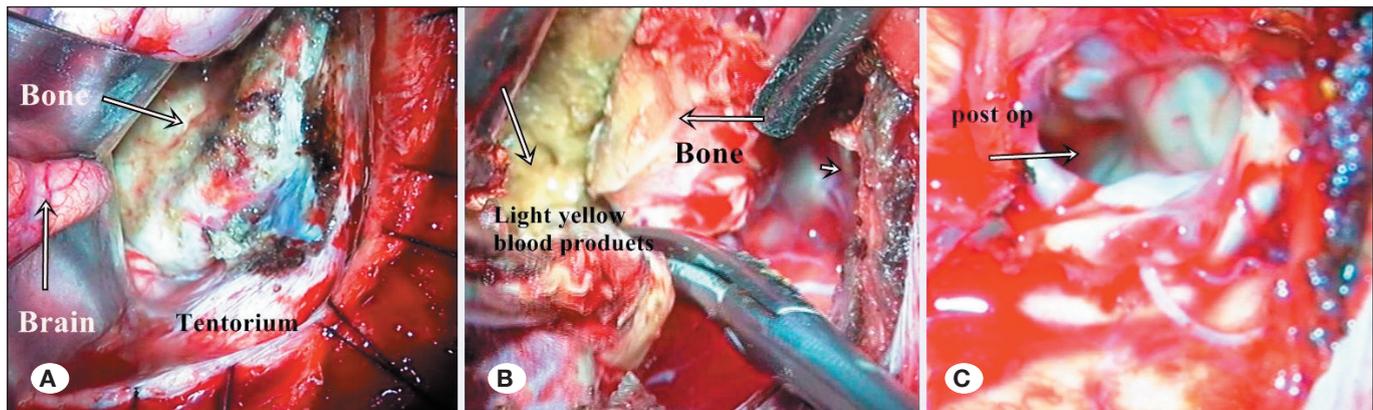
A 38-year-old female presented in 2008 with a several-month history of progressive headache, papilledema, and restricted upward gaze. Neurological examination revealed signs consistent with Parinaud's syndrome. Magnetic resonance imaging (MRI) demonstrated a heterogeneous mass measuring 6.0 × 4.5 × 2.7 cm in the pineal region, with susceptibility artifacts suggestive of calcification. The lesion compressed the third ventricle, resulting in obstructive hydrocephalus (Figure 1).

A posterior transcallosal approach via occipital craniotomy was employed. Upon opening the splenium of the corpus callosum, a firm, mobile, bone-like mass encased in glial tissue and loosely tethered by fibrous bands was identified. The mass was fragmented and removed using a microrongeur. Postoperative recovery was uneventful, and the patient experienced resolution of papilledema.

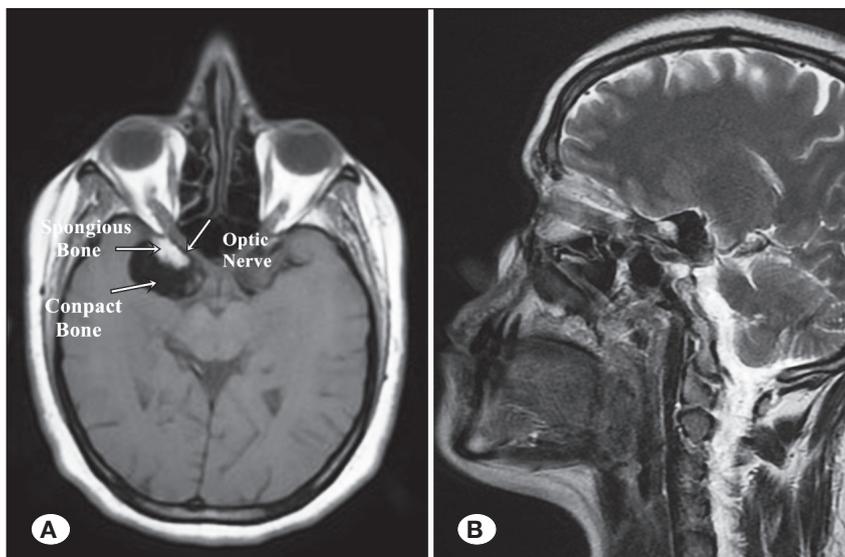
Histopathological analysis confirmed the presence of mature lamellar bone containing normocellular marrow elements, consistent with a diagnosis of mature teratoma (1,11).

### Case 2

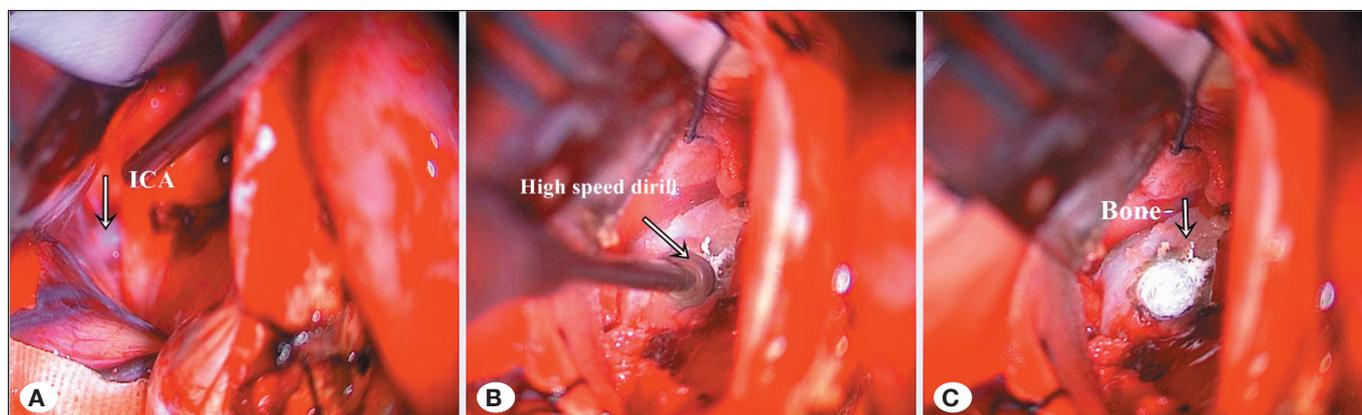
A 46-year-old female presented with a 1-year history of progressive narrowing of the visual field and retro-orbital headache. Ophthalmological examination revealed decreased visual acuity and a nasal visual field defect in the right eye. MRI identified a 4.0 × 2.9 × 2.1-cm calcified mass involving the inner third of the right sphenoid wing (Figure 2), without evidence of invasion into the adjacent brain parenchyma.



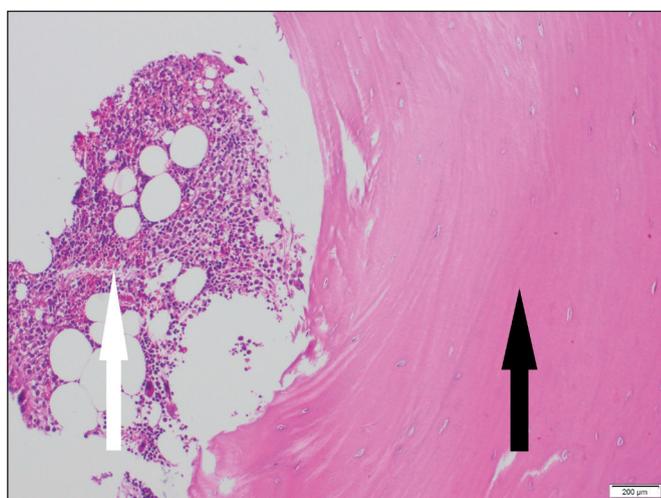
**Figure 1:** Intraoperative images of Patient #1. **A)** Upon splitting the splenium of the corpus callosum, a firm, heterogeneous mass was visualized. **B)** The lesion displayed irregular features consistent with mature lamellar bone, morphologically resembling calvarial bone. **C)** The mass was localized to the pineal region, causing compression of the third ventricle.



**Figure 2:** Preoperative magnetic resonance imaging (MRIs) of Patient #2 demonstrating a densely calcified lesion. **A)** Axial T1-weighted image showing a well-defined mass within the inner third of the right sphenoid wing. **B)** Sagittal T2-weighted contrast-enhanced image revealing peripheral enhancement consistent with ossified tissue.



**Figure 3:** Intraoperative views of Patient #2. **A)** Pterional craniotomy revealing a hard, highly vascularised mass, **B)** High speed drill used to reduce the mass, **C)** Showing bone tissue after drilling



**Figure 4:** Histopathological analysis of excised tissue from Patient #2. Dense sclerotic lamellar bone fragments (black arrow). Intervening bone marrow elements (white arrow) confirm the presence of mature bone tissue, consistent with a non-neoplastic ossified pseudotumor (Haematoxylin and Eosin, x200).

A right pterional craniotomy was performed, revealing a rock-hard, highly vascularized mass (Figure 3). The optic nerve and internal carotid artery were decompressed with meticulous dissection. Intraoperative bleeding was controlled using fibrin sealant and hemostatic agents. The patient recovered without neurological deficits.

Histopathology showed densely sclerotic lamellar bone with focal areas of bone marrow (Figure 4), consistent with a diagnosis of non-neoplastic calcifying pseudotumor (10,12).

### Case 3

A 43-year-old female with a 20-year history of chronic headaches and progressive swelling on the left side of the head initially declined an MRI due to claustrophobia. Four months later, she presented to the emergency department in respiratory arrest. Computed tomography revealed a calcified

mass within the fourth ventricle associated with obstructive hydrocephalus. An emergency external ventricular drain was placed, followed by MRI, which confirmed a 5.0 × 4.3 × 2.7-cm mass in the fourth ventricle and a coexisting frontal osteoma exerting mass effect on adjacent brain tissue (Figure 5).

During posterior fossa exploration, a firm, vascular, mobile bony mass adherent to surrounding neural structures via fibrous bands was encountered. Ultrasonic aspiration proved ineffective, and the lesion was ultimately removed using a surgical rasp. Despite initial stabilization, the patient died on postoperative day 2.

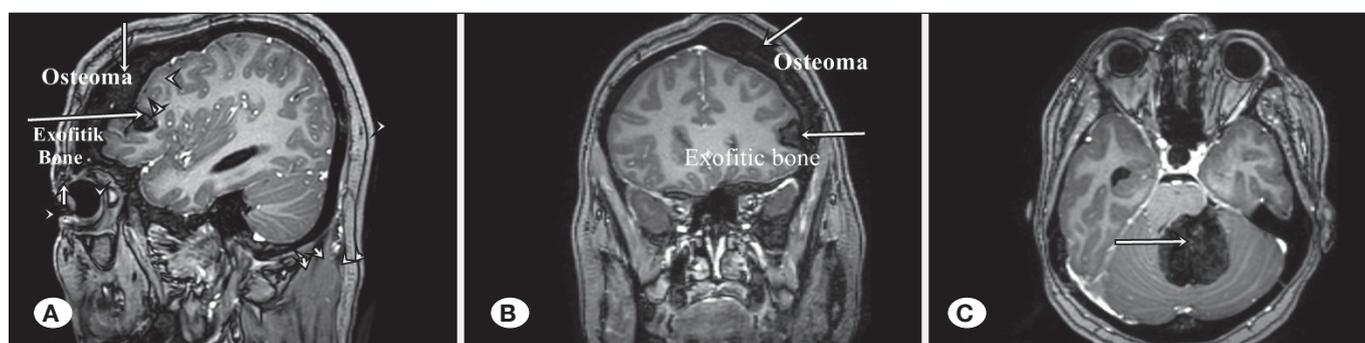
Histopathological examination demonstrated mature lamellar bone with normocellular marrow (Figure 6), confirming the lesion as a mature ossified mass.

## DISCUSSION

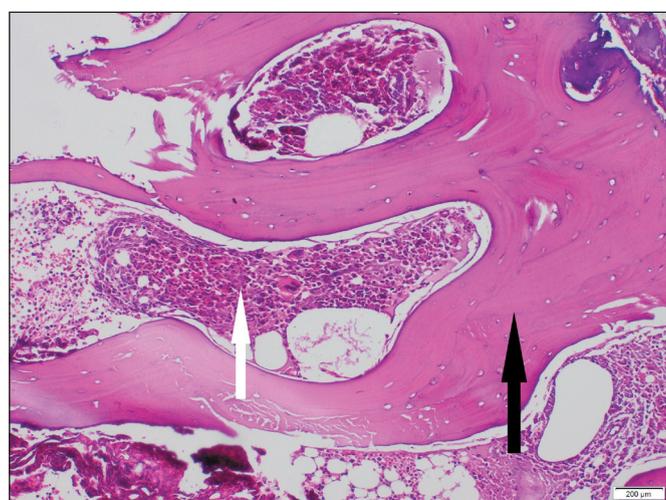
Intracranial ossification presents a rare and diagnostically challenging phenomenon due to its diverse etiologies and atypical presentation. Several pathogenetic mechanisms have been proposed: 1) congenital teratomas with mesodermal differentiation into osseous tissue; 2) reactive metaplasia secondary to chronic inflammation, trauma, or hemorrhage; and 3) exogenous introduction and subsequent osteogenic transformation of bone fragments or bone dust.

The first mechanism is well-documented in midline intracranial teratomas, in which pluripotent germ cells differentiate into mature tissue types, including bone, cartilage, or dental structures. This etiology most plausibly accounts for the lesion observed in our first case (1,11). Reactive ossification due to chronic inflammation or degenerative changes, as seen in calcifying pseudotumors and postinflammatory meningeal ossification, has been reported in the skull base and dura mater (2,10,12); this mechanism aligns with the findings in our second patient.

The third mechanism—iatrogenic dissemination of bone dust—deserves greater scrutiny (13,14). High-speed drilling during craniotomy generates fine osseous particles that can



**Figure 5:** Magnetic resonance imaging (MRI) findings in Patient #3. Sagittal (A), and coronal (B) T1-weighted contrast enhanced images show exophytic osseous growths arising from the calvarium, impinging on the adjacent cerebral parenchyma. C) Axial T1-weighted contrast enhanced image demonstrates large, heterogeneous mass occupying the fourth ventricle, with signal intensity characteristics identical to cortical bone, causing obstructive hydrocephalus.



**Figure 6:** Histopathological findings in Patient #3. Sections reveal mature trabecular bone (black arrow) with normocellular marrow. Marrow elements (white arrow) are present between trabeculae, confirming the diagnosis of mature intraventricular ossification (Haematoxylin and Eosin, X200).

be dispersed via irrigation fluids and inadvertently introduced into cerebrospinal fluid (CSF) spaces. These microfragments may become embedded in vascularized areas such as the choroid plexus, where local osteoinductive factors, including osteoprogenitor cells, inflammatory cytokines, and growth factors, may facilitate ectopic bone formation (5,6,14). This process is believed to involve activation of the Wnt/ $\beta$ -catenin signaling pathway, induction of osteoblastic differentiation, secretion of osteoid matrix, and subsequent mineralization (3,9).

The hormonal milieu may further influence ossification (7). Estrogen, parathyroid hormone, and vitamin D are known regulators of bone turnover and osteoblastic activity. All three patients in our series were premenopausal women, suggesting a possible hormonal predisposition that may have contributed to enhanced osteogenesis (3,7,8,15). Furthermore, the presence of neovascularized, CSF-rich environments may support

the survival, integration, and maturation of ectopic bone tissue.

In the third case, the patient's 25-year history of an untreated frontal osteoma near the dura suggests prolonged cortical erosion and dissemination of bone fragments into the ventricular system. This observation supports our hypothesis that delayed intraventricular ossification may result from chronic, subclinical migration of bone debris (14).

#### Surgical Implications and Prevention

The surgical management of intracranial mature bone is technically demanding. The dense, lamellar architecture of mature bone resists fragmentation by conventional aspiration techniques. In our cases, ultrasonic aspirators were ineffective, necessitating the use of microrongeurs and surgical rasps for adequate debulking and removal.

To minimize the risk of iatrogenic ossification, we recommend the following intraoperative strategies:

- Continuous irrigation and suction during bony drilling to promptly remove bone dust
- Placement of moist cottonoids around the operative field to localize particulate debris
- Meticulous sealing of any breach into the ventricular system or subarachnoid space to prevent contamination
- Prophylactic application of bone wax or fibrin sealant over drilled surfaces, particularly near CSF pathways, as suggested by previous studies (4,6).

Additionally, surgeons should consider resecting asymptomatic exophytic bone lesions located adjacent to CSF compartments, as these may serve as a source of osseous debris with delayed consequences.

This case series highlights three distinct presentations of intracranial mature bone formation, each with a different underlying etiology: a midline mature teratoma, a reactive calcifying pseudotumor, and a suspected case of iatrogenic ossification due to bone dust migration. Notably, the third case provides compelling circumstantial support for a novel pathophysiological

ical mechanism involving the chronic introduction and osteogenic transformation of bone dust within the fourth ventricle.

## ■ CONCLUSION

These findings underscore the need for heightened intraoperative vigilance during cranial drilling, particularly in procedures involving proximity to CSF spaces. Preventive strategies aimed at minimizing particulate dissemination should be incorporated as standard practice to reduce the risk of delayed, ectopic bone formation. Given the potential for such lesions to mimic neoplastic or vascular pathology, neurosurgeons must remain aware of this rare but clinically significant phenomenon during diagnosis, surgical planning, and postoperative follow-up.

### 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.

**Ethical statement and consent for publication:** This case report series did not require formal Institutional Review Board approval; written informed consents were obtained from all patients.

### AUTHORSHIP CONTRIBUTION

Study conception and design: EH, AED, SH

Data collection: EH, DMY, SH

Analysis and interpretation of results: EH, EY, DMY

Draft manuscript preparation: EH, EY, SH

Critical revision of the article: AED, DMY, SH

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

All authors (EH, EY, AED, DMY, SH) reviewed the results and approved the final version of the manuscript.

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# Emergent Endovascular Parent Artery Occlusion for Type III Carotid Blowout Syndrome After Charged Particle Therapy for Recurrent Maxillary Carcinoma: A Case Report and Literature Review

Daisuke WAJIMA<sup>1,2</sup>, Sho TAKATA<sup>1</sup>, Tomoya KAMIDE<sup>1</sup>, Kouichi MISAKI<sup>1</sup>, Koji SATO<sup>2</sup>, Mitsutoshi NAKADA<sup>1</sup>, Takumi TANIGUCHI<sup>2</sup>

<sup>1</sup>Kanazawa University, Department of Neurosurgery, Kanazawa, Ishikawa, Japan

<sup>2</sup>Kanazawa University, Department of Intensive Care Unit, Kanazawa, Ishikawa, Japan

**Corresponding author:** Daisuke WAJIMA ✉ d.wajima@gmail.com

## ABSTRACT

Carotid blowout syndrome (CBS) refers to involvement of the carotid artery by malignant processes of the head and neck with compromise of vessel integrity and rupture. Carotid hemorrhage (CBS type III) is fatal, particularly when it occurs outside hospital settings. Bleeding can occur through the skin or mucosa and may cause airway compromise. It is associated with high mortality and morbidity. A 55-year-old woman presented to the emergency room with shock state, bleeding from the oral and nasal cavity. The patient had previously experienced recurrent maxillary carcinoma treated with radiation therapy 9 years prior. Digital subtraction angiography revealed active extravasation from the cavernous portion of the left internal carotid artery. Emergent parent artery occlusion was performed by coil embolization, including the extravasation site; complete hemostasis was achieved. Endovascular parent artery occlusion (PAO) is the preferred management method; covered stents are an option for managing patients who are not candidates for PAO. In our case, additional left superficial and middle cerebral artery anastomoses were needed on the day after PAO for preventing hemodynamic cerebral infarction. Since type III CBS can be fatal, early recognition of CBS predictors by multidisciplinary teams is crucial for preventing fatal bleeding.

**KEYWORDS:** Carotid blowout syndrome, Radiation therapy, Endovascular therapy, Carcinoma, Parent artery occlusion

**ABBREVIATIONS:** **CBS:** Carotid blowout syndrome, **PAO:** Parent artery occlusion, **PET-CT:** Positron emission tomography-computed tomography, **RBE:** Relative biological effectiveness, **3D-CTA:** Three-dimensional computed angiography, **DSA:** Digital subtraction angiography, **CCA:** Common carotid artery, **ICA:** Internal carotid artery, **SRS:** Stereotactic radiosurgery, **hSRT:** Hypofractionated stereotactic radiotherapy

Daisuke WAJIMA : 0009-0007-1372-3450  
Sho TAKATA : 0000-0001-5102-7690  
Tomoya KAMIDE : 0000-0003-0051-6616

Kouichi MISAKI : 0000-0002-3752-2406  
Koji SATO : 0000-0003-1056-9973  
Mitsutoshi NAKADA : 0000-0001-9419-6101

Takumi TANIGUCHI : 0000-0001-9806-3410



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## INTRODUCTION

Carotid blowout syndrome (CBS) is an uncommon but dreaded complication occurring in patients treated for face, head, and neck cancers. CBS results from arterial wall necrosis. This can occur following resection of face, head, and neck carcinoma, after irradiation of recurrent or second primary tumor, by direct tumor invasion of the carotid artery wall, or by a combination of these factors (14). Advances in interventional neuroradiology have made managing these conditions possible, which was previously difficult (14).

Herein, we present a case of acute type III CBS that occurred in a patient with maxillary carcinoma who actively underwent endovascular emergent parent artery occlusion (PAO).

Written informed consent and consent to publication was obtained from the patient.

## CASE REPORT

A 55-year-old woman presented to the emergency room in a serious state with bleeding from the oral and nasal cavity. Examination revealed the presence of large clots in the oral cavity. The patient was in shock. Hemogram revealed a hemoglobin level of 5.1 g/dL. The coagulation profile blood tests revealed normal results. Massive fluid replacement and blood transfusion were performed; however, the patient required continuous blood transfusion to stabilize the blood pressure.

At 37 years of age, the patient had experienced maxillary carcinoma, which was surgically removed and pathologically diagnosed as mucoepidermoid carcinoma. Recurrence was observed on positron emission tomography-computed tomography (PET-CT) 9 years after surgery (Figure 1A, B).

Conformal photon-based planning and charged-particle therapy using charged carbon ions (64 Gy, relative biological effectiveness [RBE]) were used for managing the recurrence. The recurrent lesions were suppressed after radiotherapy (Figure 1C).

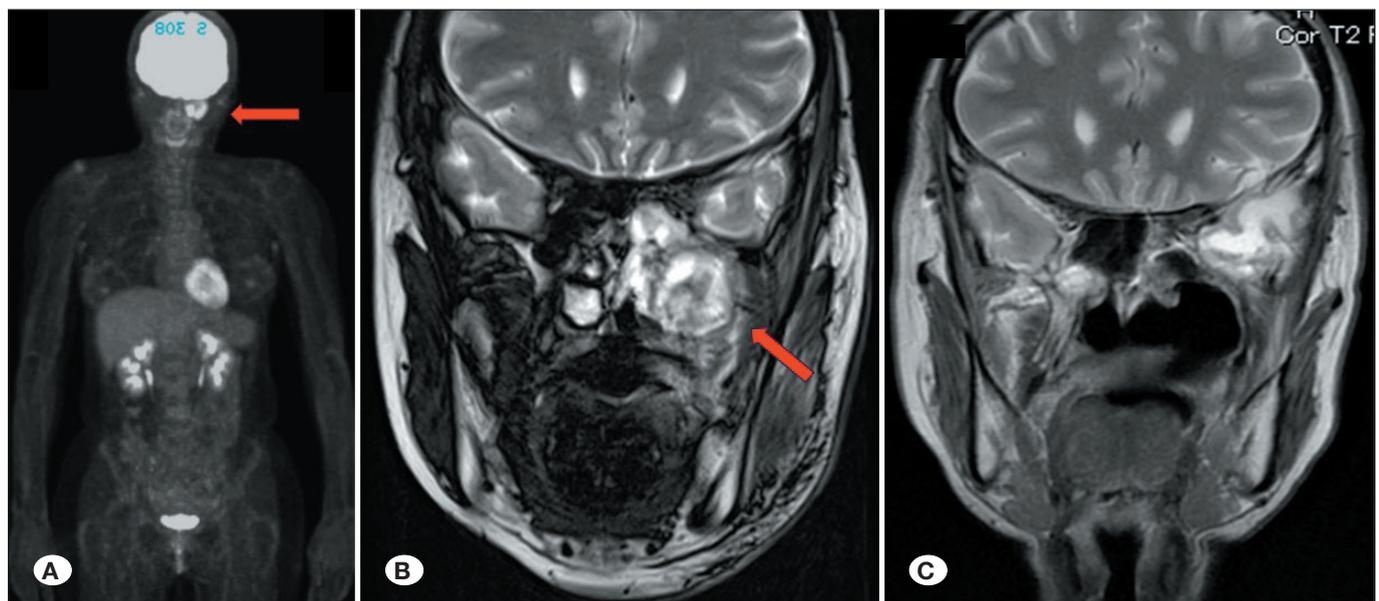
The sudden oral and nasal bleeding 9 years after radiation therapy was suspected to be the result of CBS. Emergent three-dimensional computed angiography (3D-CTA) revealed extravasation from the left internal carotid artery (ICA) (Figure 2A, B). An interventional radiologist and neuroradiologist were consulted immediately. Digital subtraction angiography (DSA) revealed active extravasation from the cavernous portion of the left ICA (Figure 2C, D). Emergent PAO was performed by coil embolization, including the extravasation site; complete hemostasis was achieved (Figure 3A-E).

Additional left superficial and middle cerebral artery anastomoses were needed on the day after PAO due to occurrence of a new cerebral infarction in the left ICA watershed region (Figure 4 A-E). The patient was discharged without new neurological symptoms.

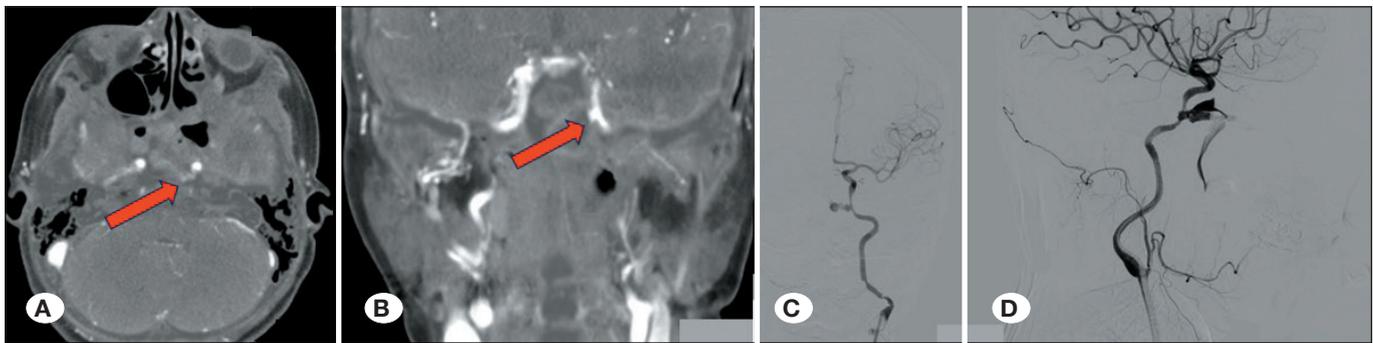
## DISCUSSION

By definition, CBS is a hemorrhagic event of carotid artery systems (9). It represents involvement of the carotid artery by several lesions of the head and neck (12), causing rupture.

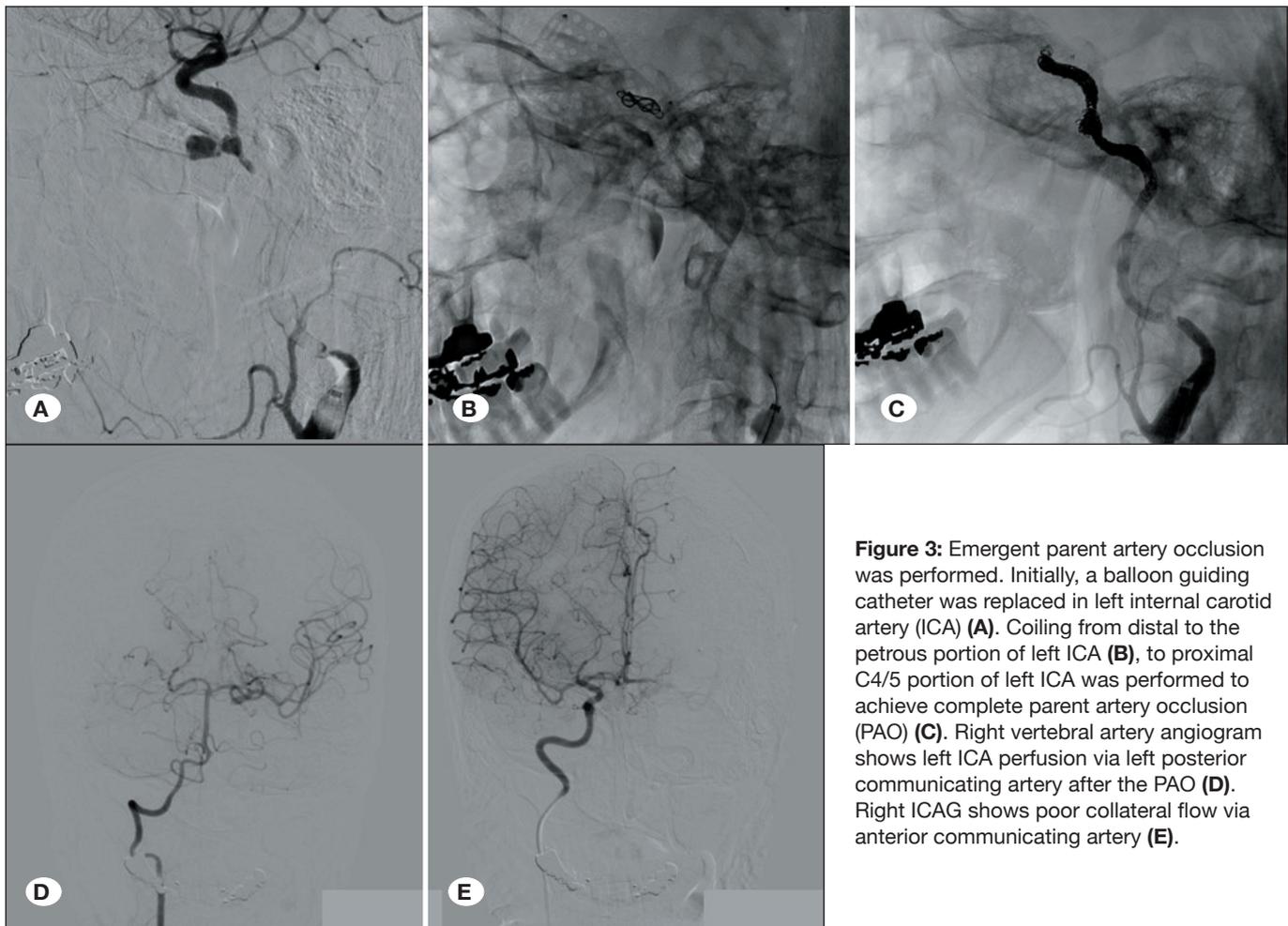
CBS can be categorized into three types that may involve the common carotid artery (CCA) and ICA (8,9,14). Threatened (type I) CBS is characterized by carotid artery exposure detected on examination or imaging in the form of air surrounding the vessel, an adjacent abscess or tumor associated with a fistula, or areas of arterial wall disruption found on vascu-



**Figure 1:** Left maxillary carcinoma recurrence (red arrows) observed in the positron emission tomography-computed tomography (A), and magnetic resonance image (MRI) (B), 9 years after initial removal. MRI showing suppression of the recurrent lesion after radiation therapy (C).



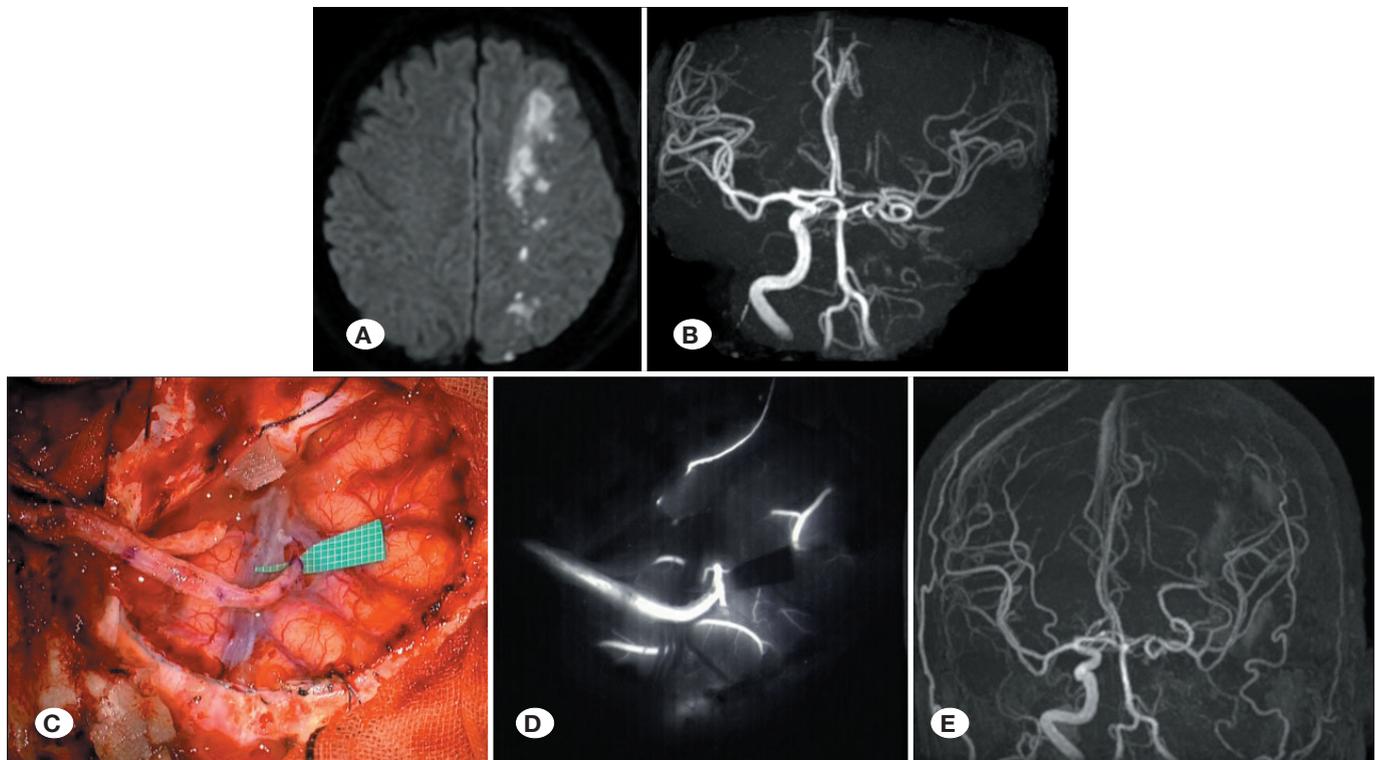
**Figure 2:** Emergent 3D-computed angiography shows the bleeding from left internal carotid artery (ICA) (red arrows) as suspected (**A:** axial view, **B:** coronal view). Digital subtraction angiogram shows active contrast extravasation from cavernous portion of left ICA (**C:** anterior-posterior view, **D:** lateral view), causing carotid-cavernous fistulae.



**Figure 3:** Emergent parent artery occlusion was performed. Initially, a balloon guiding catheter was replaced in left internal carotid artery (ICA) (**A**). Coiling from distal to the petrous portion of left ICA (**B**), to proximal C4/5 portion of left ICA was performed to achieve complete parent artery occlusion (PAO) (**C**). Right vertebral artery angiogram shows left ICA perfusion via left posterior communicating artery after the PAO (**D**). Right ICAG shows poor collateral flow via anterior communicating artery (**E**).

lar imaging studies (8,9,14). Impending blowouts (type II) are bleeding episodes that can be temporarily resolved by pressure and wound packing (3). Carotid system hemorrhage (type III) is fatal, particularly when it occurs outside hospital settings (8). Bleeding can occur through the skin or mucosa and may cause airway compromise. It is associated with mortality and morbidity rates of 40% and 60%, respectively (8).

Radiation has been implicated in obliterating the vasa vasorum, causing fibrosis of the adventitia and weakening of the arterial wall, leading to rupture (8,9,14). In the present case, both prior radiotherapy and tumor recurrence were risk factors. Regarding intensity-modulated radiation therapy, the bleeding rates are lower, 0%–2.4%; however, several case series on stereotactic radiosurgery and hypo-fractionated ste-



**Figure 4:** On the next day of the PAO, diffusion weighted image shows high signal intensity in the left internal carotid artery (ICA) watershed region (A). Magnetic resonance angiography (MRA) shows no flow in the left ICA or the extravasation findings (B). Emergent left superficial temporal artery and middle cerebral artery anastomosis was performed for the hemodynamic cerebral ischemia of left ICA occlusion. Intra-operative findings show anastomosis of the superficial temporal artery and middle cerebral artery (C), and patent flow on indocyanine green intraoperative angiography (D). Post-operative MRA shows the anastomotic state of the left superficial temporal artery and middle cerebral artery (E).

reotactic radiotherapy have reported higher rates (0–17%) of bleeding (14). Generally, cumulative doses >130 Gy show a higher rate of CBS and other acute and delayed toxic effects than do lower doses (14). In the present case, the patient underwent charged-particle therapy using carbon ions (64 Gy) without chemotherapy and developed CBS type III 9 years after radiation therapy. Charged-particle therapy benefits patients with cancer by localizing doses in the tumor volume while minimizing doses delivered to normal tissue through its unique physical and biological characteristics (6). However, similar to that in our case, late artery rupture can be problematic following this therapy.

The predictors of CBS, such as pseudoaneurysm formation and vessel wall damage should be made aware of after radiation therapy for head and neck malignant tumors (8,9,14). In addition, head and neck surgery was identified as an independent risk factor of CBS in patients post-radiation therapy (4).

Carotid rupture in the setting of re-irradiation in nearly all instances results in death of the patient due to massive hemorrhages in the pharynx or elsewhere. In a systematic review, approximately 80% of cases were fatal, those occurred within one month of CBS onset (5,14). Survival rates at one month and one year after CBS have been reported to be approximately 30% (5,14).

Following establishing a diagnosis of type III CBS, immediate treatment and critical care are essential, including securing the airway and managing hemorrhagic shock (8,9,14). Primary treatment of the ruptured carotid artery mainly comprises endovascular techniques, including embolization and stenting of the parent artery (7), as well as a combination of intracranial and extracranial bypass grafting (2), similar to those in our case.

However, endovascular treatment can induce delayed cerebral ischemic complications, resulting from an incomplete circle of Willis (10). In acute cases, patients have unstable vital signs or impaired consciousness, thereby a balloon occlusion test is usually not possible. Angiography of the contralateral carotid artery and posterior circulation is required to check whether the circle of Willis is complete and whether there is adequate collateral flow, similar to that in the present case. Endovascular embolization of CBS is associated with cerebral ischemic insults in 8%–14% of patients. Although patients at high risk of neurological sequelae are currently treated with covered stents (11,13), cerebral infarction was still reported after such intervention in 15%–30% of patients (14). A higher risk of CBS recurrence with stent placement (44%) has been reported compared with embolization therapy (10%) or surgical ligation (25%) (2). In our case, additional superficial and middle cerebral artery anastomoses were needed on the day

after PAO due to occurrence of a new cerebral infarction in the occluded ICA watershed region. Efficacy of superficial and middle cerebral artery anastomoses for acute ICA occlusion was reported (7). Other complications, both in patients with stents and embolization, include septic thrombosis with multiple brain abscesses, neck abscess formation, and extrusion of the stent or the coils used for embolization (1,5).

## CONCLUSION

With the increasing number of treated face, head, and neck cancer cases, oncologists must be cautious about any recent history of oral bleeding or hemorrhage from an exposed neck wound. Once CBS is suspected by an emergency physician, interventional radiologists and/or neuroradiologists must be contacted immediately for expeditious diagnosis and intervention.

PAO is the preferred management method and covered stents are an option for managing patients who are not candidates for parental vascular occlusion. Early recognition of CBS predictors by multidisciplinary teams is crucial.

### 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:** 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.

### AUTHORSHIP CONTRIBUTION

Study conception and design: DW, TK

Data collection: None

Analysis and interpretation of results: None

Draft manuscript preparation: DW, ST, TK

Critical revision of the article: KM, KS, MN, TT

All authors (DW, ST, TK, KM, KS, MN, TT) reviewed the results and approved the final version of the manuscript.

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# Letter to Editor: Impact of Obesity on Subarachnoid Hemorrhage-Induced Cerebral Vasospasm: An Experimental

Hasan CALISKAN

Balikesir University Faculty of Medicine, Department of Physiology, Balikesir, Türkiye

**Corresponding author:** Hasan CALISKAN ✉ hasan.caliskan@balikesir.edu.tr

Dear Editor,

I've read Alpergin et al.'s article with keen interest (1). This study contains crucial findings and will be helpful to clinical and preclinical researchers interested in the subject. The main finding is that the authors reported that obesity may affect the degree of cerebral vasospasm following subarachnoid hemorrhage and that cerebral vasospasm may exacerbate the process in the presence of obesity (1). This letter aims to underscore the potential advantages of using neurobehavioural tests in conjunction with histological and molecular studies in subarachnoid haemorrhage research.

This correspondence intends to offer methodological insights into the study addressed here. Neurobehavioral assessments may be used to evaluate functional alterations in the subarachnoid hemorrhage model.

## 1. Open Field test

The open-field test is frequently used to assess general locomotor activity (4). Behavioral changes are recorded in the open-field test in models that affect the central nervous system (4,7). An open-field test can be performed to determine whether vasospasm has occurred in the subjects before they are sacrificed. It has been shown that the distance traveled by the subjects in the open field test decreases, mainly due to the early-stage (up to 2 weeks) vasospasm effect (3). Therefore, an essential finding of early vasospasm is reduced locomotor activity. Alpergin et al. terminated the experiment seven days after inducing subarachnoid hemorrhage; thus, an open-field test can be beneficial for observing vasospasm-related cues.

## 2. Rotaroad test

Rotarod is utilized for the quantitative assessment of motor function (7). It involves the rat or mouse maintaining balance and walking on a rotating experimental apparatus that spins

around its own axis (6). The animal must maintain coordinated movement continuously to avoid falling. This is used to measure parameters, such as motor coordination, balance, endurance, and motor learning (6,7).

3. Neurobehavioral assessments that can be used to measure muscle strength in a subarachnoid hemorrhage model: Grip strength test, Kondziella inverted screen test, and Weight test

The grip strength test is a behavioral assay designed to assess the muscle strength of the hind and forelimbs of rodents (7). The Kondziella reverse screen test is used to assess the grip strength of rodents' forelimbs and hindlimbs. In this test, subjects grasp a wire apparatus with all four paws. The wire is then turned upside down. The time it takes for subjects to fall onto a pile of safe materials such as straw or wood shavings is recorded to evaluate muscle strength (5). The weight test is conducted to assess the grip strength of rodents' forelimbs. The subjects' weight-holding times are scored (5).

## 4. Neurological scoring and reflex examinations

The Neuroscore test assessment consists of the following components: the forelimb flexion test, hindlimb flexion test, hind paw grasping reflex test, visually triggered placing test, and contact-triggered placing test (5).

5. Cognitive tests: Morris water maze, Y maze, T maze, elevated plus maze, radial arm maze, Vanderwolf wolf swimming test

Spatial learning and memory may be assessed through various behavioral paradigms. The Morris water maze and the Vanderwolf swimming test can be used for this purpose (2,7). Waterless maze systems, such as the T-maze, radial arm maze, and elevated plus maze, may also be employed to evaluate cognitive functions.



### Future Directions

The significant advantage of neurobehavioral tests is that they are easy, cost-effective, and largely reproducible. Before euthanasia of the subjects, researchers will be provided with a wide range of data, including motor coordination, endurance, muscle strength, locomotor activity, and cognitive patterns.

Another essential advantage of neurobehavioral tests is that anxiety-like behaviors can be examined simultaneously with locomotor activity during the 5-minute measurement in the open field test (4). Anxiety-like behaviors may similarly be assessed using the elevated plus maze test, which is employed to examine cognitive parameters by modifying the test duration and application protocol (2).

Although these tests are relatively easy to implement following established protocols in behavioral research in the field of behavior, their most significant disadvantage is that interpreting the test results may require scientists working in this field, such as physiologists or pharmacologists. This challenge can be resolved through multidisciplinary 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.

**Disclosure:** The author declare no competing interests.

### AUTHORSHIP CONTRIBUTION

The author (HC) confirm responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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# Critical Appraisal and Recommendations on the Use of Neuroendoscopic Surgery for Hypertensive Brainstem Hemorrhage

Yasin TASKIN

Tokat Gaziosmanpaşa University School of Medicine, Department of Neurosurgery, Tokat, Türkiye

**Corresponding author:** Yasin TASKIN ✉ dryasintaskin@gmail.com

Dear Editor,

With respect to the paper entitled “Neuroendoscopic Surgical Treatment of Hypertensive Brainstem Hemorrhage” (2), I’d like to share my concerns that are discussed in the manuscript. The authors are to be commended for addressing an important and relatively underexplored topic in neurosurgery. Their findings contribute meaningful data to the ongoing discussion of optimal surgical strategies for hypertensive brainstem hemorrhage (HBSH), a condition that remains among the most challenging to manage.

Neuroendoscopic surgery represents a promising option for selected patients with HBSH. The study offers valuable clinical insights, and we would like to share several reflections that may help further enrich the discourse. The use of 3D-Slicer software for preoperative hematoma volume assessment is particularly noteworthy (1). A more detailed description of how this tool informed surgical decision-making, and whether it was paired with intraoperative navigation systems, could strengthen the understanding of its methodological relevance.

The use of four different surgical approaches is another important aspect of the study. Further clarification of how each approach was chosen based on hematoma location, size, or morphology would offer practical guidance for surgical planning. Such details may also help identify patient subgroups such as those with hematoma volume >10 mL or ventricular extension who might derive greater benefit from endoscopic intervention.

While early postoperative results appear encouraging, longer-term evaluation of neurological recovery would provide a more complete picture of procedural efficacy. Incorporating additional outcome measures, such as the modified Rankin Scale and comparing outcomes with alternative management strategies (e.g., stereotactic aspiration or conservative treat-

ment) in future studies would enhance understanding of neuroendoscopic results.

Overall, this study offers valuable preliminary evidence supporting neuroendoscopic surgery as a feasible and potentially effective option for patients with HBSH. Prospective, multi-center studies incorporating standardized imaging, refined patient selection, and long-term follow-up will be essential to validate and expand upon these findings.

## Declarations

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

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The author (YT) confirm responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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Yasin TASKIN : 0000-0002-9109-7826



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