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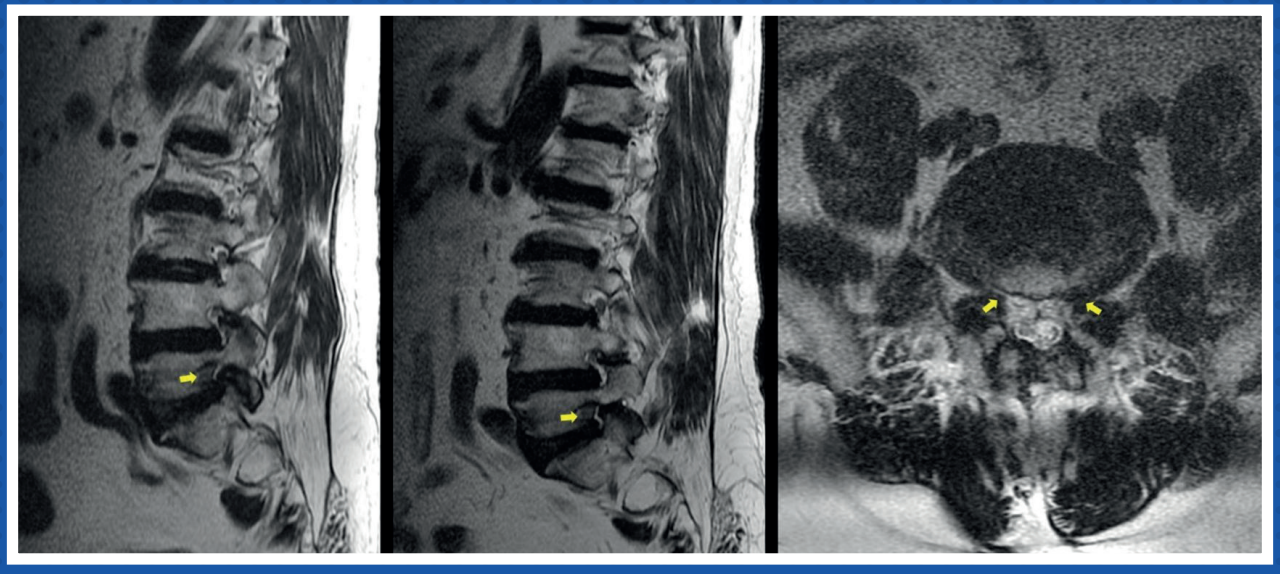

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Editorial

Dear colleagues and distinguished readers,

We are pleased to launch the first issue of 2026 of the Northwestern Medical Journal. We find ourselves living through a time where scientific advancements are constantly occurring, the role of artificial intelligence continues to integrate itself into the practice of medicine, and the best practices of surgery are continually being improved upon. The current issue contains a variety of articles ranging from genetics through the effects on psychology, emergency responses related to the nervous system through the treatment of diabetes.

This journal contains 10 high-quality original articles, a review, and a case report tackling important issues in different fields of medicine:

Afreen et al. compared l-gel insertion using propofol-fentanyl vs propofol-dexmedetomidine in pediatric day surgery. Memiş reports on an experience with mechanical thrombectomy in ischemic stroke with valuable observations on the role of stroke units. On the other hand, testing of novel CpG chromatin fragments as UCOE candidates for improved gene therapy vectors is presented by Anakök et al.

In surgical practice, Kendir et al. report a retrospective study on bipolar cauterization of the orbicularis oculi muscle. Saygı Uysal et al. assessed the accuracy of ChatGPT-generated information in the field of general audiology. Çobanoğlu et al. presented their results with 329 benign laryngeal lesions from a single center.

Özde investigates the association between hematochemical values, micronutrient levels, and glycemic control in patients with Type 1 diabetes, while focusing on adolescents.

The article by Toprak et al. also highlights an aspect which is usually ignored. They evaluate sexual dysfunction in patients with vertigo using ASEX Scale.

Another article by Lochana et al. discusses how radiation safety standards affect nursing staff.

Başdemirci et al., presented a rare case of lumbosacral radiculopathy and denervation pseudohypertrohy of bilateral calf muscles.

As the Northwestern Medical Journal, we are not only promoters of knowledge generation but also believers in the dissemination of that knowledge according to high academic standards. This issue once again displays the diversity that exists within the field of medicine.

I would like to extend my most sincere thanks to all authors who provided these precious works, to all reviewers who ensure the high quality of our journal by carefully reviewing articles, and, of course, to all of you, our honorable readers, whom I wish a healthy and successful year illuminated by the light of science.

Sincerely,
Prof. Ahmet Ural, M.D.
Editor-in-chief

NORTHWESTERN MEDICAL JOURNAL

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RESEARCH ARTICLES

Comparison of I-gel insertion using propofol-fentanyl vs propofol-dexmedetomidine in pediatric day surgery

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ABSTRACT

Objective: Supraglottic airway devices are pivotal tools for airway management in anesthesia. The I-gel, a widely used second-generation airway device, is recognized for ease of insertion and low complication rate. This study aims to compare the ease of insertion of I-gel and associated insertion conditions when used with Fentanyl and Dexmedetomidine in combination with Propofol.

Methods: After obtaining approval of ethical committee, a total of 60 patients were enrolled a tertiary care hospital and divided into two groups. Group F received 2 mcg/kg of intravenous fentanyl and propofol; Group D received 1 mcg/kg of intravenous dexmedetomidine infusion in 10 minutes and propofol. The ease of I-gel insertion and jaw relaxation was assessed using the modified Lund and Stovener criteria and Young's criteria, respectively. The physiologic variables, adverse events like apnea, desaturation, cough, jaw movement; and additional requirement of propofol bolus doses were recorded at baseline, first, third, fifth and tenth minutes after insertion.

Results: No significant differences were observed in jaw relaxation, ease of I-gel insertion, and adverse events. The apnea duration was shorter in Group D (12.1±2.3 min vs 15.1±2.8, $p<0.001$). Respiratory rate was significantly lower in Group F. It was easier to insert I-gel in Group D ($p=0.213$). Ramsay Score was higher and Aldrete score was lower in Group D ($p<0.001$).

Conclusion: Dexmedetomidine as an adjuvant to propofol is a safe alternative to combination of propofol and fentanyl in pediatric surgeries. Although both drugs maintain a stable hemodynamic profile, dexmedetomidine demonstrates superior efficacy in preserving respiratory stimulus.

Keywords: I-gel, supraglottic airway device, hemodynamic, upper airway reflexes, dexmedetomidine, fentanyl

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INTRODUCTION

Airway management in patients receiving general anesthesia is an essential skill. Failure to secure the airway can lead to catastrophic outcomes (1). Among anesthetic agents, propofol is the most used agent, especially in the placement of supraglottic airway devices (SGADs) such as the I-gel, classic laryngeal mask airway proseal LMA, and others (2,3). Second-generation SGADs like the I-gel are single-use devices equipped with an integrated biting block, a narrow-bore gastric drain tube, and a soft gel-like cuffless mask. Prior studies have demonstrated that I-gel is a reliable device and has a low morbidity rate (4).

The design of SGADs vary among different types, influencing the pressure exerted on the pharynx and larynx and the ease of insertion (5). For non-paralyzed patients, achieving adequate depth of anesthesia is crucial for jaw relaxation during I-gel insertion. Care must be taken to avoid complications such as coughing, head or limb movements, and laryngospasm. Propofol is effective in suppressing pharyngeal and laryngeal reflexes but may cause dose-dependent cardiorespiratory depression (6). To address these concerns, propofol is commonly combined with opioids, which may help mitigate associated adverse effects.

The I-gel insertion rate improves with the use of opioids. However, they also pose some disadvantages like delayed anesthetic recovery, inhibition of respiratory stimulus, , and muscle rigidity (7). Dexmedetomidine, a chemically active dextro-isomer of medetomidine, is commonly used as an intravenous anesthetic adjunct due to its anesthetic and analgesic effects at lower doses of 0.5–2 mcg/kg. It also allows dose reduction of propofol during induction and maintenance (8,9,10). Dexmedetomidine is an alpha-2 agonist with anxiolytic, sympatholytic, sedative, analgesic, and hypnotic properties (11). Recent literature reports that dexmedetomidine, when used as an adjuvant to propofol, improves insertion conditions and reduces pressor response during SGAD insertion (12,13).

We hypothesized that dexmedetomidine in combination with propofol may provide better responses for I-gel insertion conditions compared to fentanyl. Thus, we aimed to compare the optimal combination of propofol with dexmedetomidine and fentanyl. The primary objective is to evaluate jaw relaxation and I-gel insertion conditions using the Modified Scheme of Lund and Stovener criteria. The secondary objective is to monitor hemodynamic parameters, including heart rate, mean arterial pressure, duration of apnea, and the total requirement of propofol.

MATERIALS AND METHODS

This was a cross-sectional comparative study conducted prospectively at a tertiary care hospital over a period of two years (January 2020 to December 2022). Ethical committee approval was obtained prior to patient recruitment (ECR/300/Inst/AP/2013/RR-16).

The inclusion criteria comprised patients aged 2–10 years with ASA physical status I or II, whose parents or guardians provided written informed consent. Eligible children were scheduled for elective short surgical procedures, defined as operations lasting less than 60 minutes. Exclusion criteria were ASA grade III or higher, age below 2 or above 10 years, lack of parental/guardian consent, presence of cardiac disorders, emergency surgeries, and patients with a full stomach.

Patients were randomly assigned into two groups using computer-generated single-sequence randomization (Figure 1):

1) Group F received 2.5 mg/kg of intravenous (iv) propofol and 2 mcg/kg of iv fentanyl, followed by I-gel insertion.

2) Group D received 1 mcg/kg of iv dexmedetomidine infused over 10 minutes, followed by 2.5 mg/kg of iv propofol, and then I-gel insertion.

All patients received premedication with 0.01 mg/kg of iv atropine, and 10 mg/kg of iv paracetamol during the intraoperative period. The ease of I-gel insertion was assessed based on the level of jaw relaxation using "Young's criteria" (I-Absolutely relaxed jaw, II-Moderately relaxed jaw, III-Poorly relaxed jaw) and the Modified Scheme of Lund and Stovener criteria (Excellent: No gagging or coughing, no laryngospasm, no patient movement; Good: Mild to moderate gagging

or coughing, no laryngospasm, mild to moderate patient movement; Poor: Moderate to severe gagging or coughing, no laryngospasm, moderate to severe patient movement; Unacceptable: Severe gagging or coughing, laryngospasm, severe patient movement). If any of the conditions occurred during the initial attempt at I-gel insertion, an additional dose of 0.5 mg/kg of iv propofol was administered, and the number of boluses was recorded.

The study also measured the respiratory rate and apnea time. Apnea time was defined as the interval between the last spontaneous breath following propofol administration and the first spontaneous breath observed thereafter, using the 8-level Modified Ramsay Sedation Scale.

Changes in heart rate and blood pressure during I-gel insertion were documented at baseline (before any medication, at the operating table), after the infusion of the study drug, after propofol induction, and at 1, 3, 5, and 10 minutes following I-gel insertion.

Patients were evaluated postoperatively using Aldrete Score. Recovery from anesthesia was evaluated with five clinically relevant parameters: muscle activity, respiration, circulation, consciousness, and color. Each category is assigned a score of 0, 1, or 2, with a maximum total score of 10. A score of 8 or higher indicates that a patient is suitable for discharge.

After surgery, the I-gel was removed once the patient could open their mouth upon command. It was then examined for any bloodstains. Both the front and back of the I-gel cuff were inspected for regurgitation of gastric contents using litmus paper, which changes color in the presence of acidic pH. Any adverse events, such as bradycardia, hypotension, coughing, laryngospasm, bronchospasm, or desaturation, were documented and addressed appropriately. Postoperative measurements included recovery time, sedation status, respiratory rate, heart rate, and non-invasive blood pressure.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 25 (SPSS Inc., Chicago, IL). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as counts and percentages. Normality of data distribution was assessed prior to analysis. Between-group comparisons of continuous variables were performed using independent samples t-test for normally distributed data, and Mann–Whitney U test for non-normally distributed variables. Categorical variables

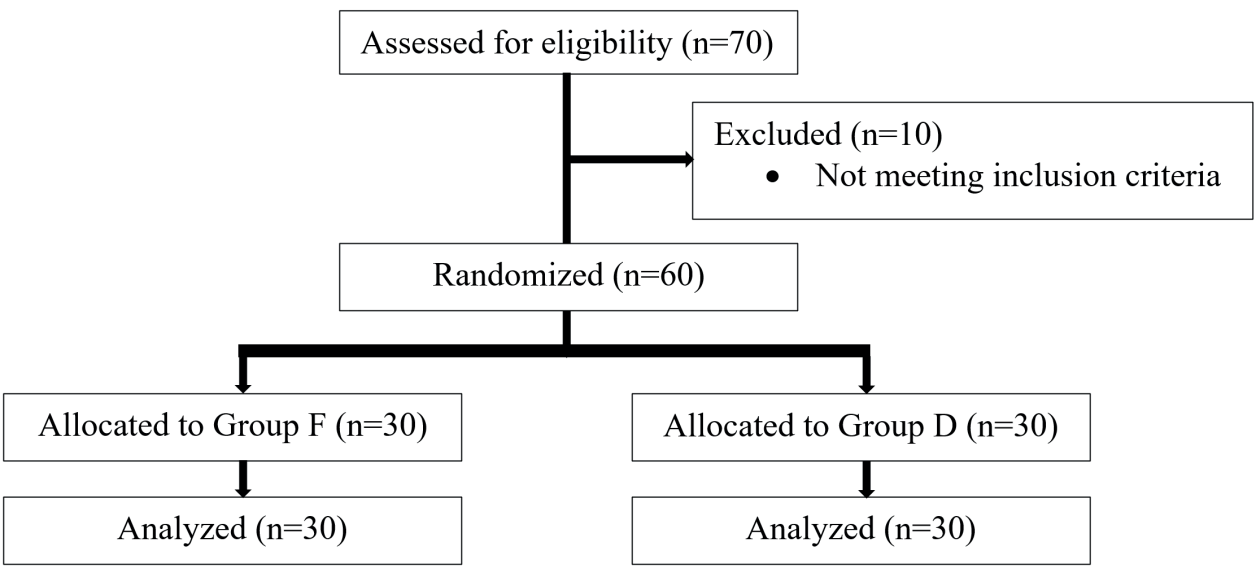

Figure 1. Flow diagram of the study.

were analyzed using the Fisher's exact test. Timepoint-specific comparisons of heart rate, mean arterial pressure, and respiratory rate at each timepoint (T1–T5) were compared with independent samples t-tests. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 60 patients were enrolled in this study. Baseline demographics were similar. Briefly, Group D was slightly older (5.08±0.5 vs 4.5±2.4 years; mean difference 0.58 years, 95% CI −0.33 to 1.49; Welch's p=0.20), and the gender proportion did not differ significantly (26/30 vs 24/30; Fisher's p=0.73). The mean surgical duration was 42 ± 8 minutes for Group D and 45 ± 10 minutes for Group F. Procedures included herniotomy, circumcision, hydrocele repair, and superficial soft tissue excisions. None of the patients exhibited poorly relaxed jaws (Table 1).

Lund and Stovener Criteria was statistically similar (Table 2). However, numerically, a higher percentage of patients had excellent insertion conditions in Group D compared to Group F. In one patient in Group F, the insertion condition was evaluated as unacceptable.

I-gel size, duration of I-gel insertion, and number of attempts were similar (Table 3).

Number of propoofl bolus doses were lower in Group D (Fisher's exact test, 4×2: p = 0.009; Table 4). When dichotomized as any vs none, Group F required more often boluses (50% vs 10%; odds ratio 9.0, 95% CI 2.24–36.17; absolute risk difference 40%, 95% CI 19–61%) (Table 4).

Apnea duration was 2.9 min shorter in Group D (mean difference −2.94, 95% CI −4.06 to −1.82; p<0.001). The incidence of desaturation, laryngospasm, and cough was similar in both groups (Table 5).

Table 1. Comparison of jaw relaxation prior to I-gel insertion based on Young's criteria

Jaw relaxation	Group F (n = 30)	Group D (n = 30)	Total	p-value
Excellent	17 (56.6%)	18 (60%)	35	0.720*
Good	13 (43.3%)	10 (33.3%)	23	
Poor	0 (0%)	2 (6.0%)	2	

*Fisher's exact test.

Table 2. Comparison of I-gel insertion conditions based on Modified Lund and Stovener criteria

Ease of insertion	Group F (n = 30)	Group D (n = 30)	p-value
Excellent	25 (83.3%)	29 (96.7%)	0.213*
Good	4 (13.3%)	1 (3.3%)	
Poor	-	-	
Unacceptable	1 (3.3%)	-	

*Fisher's exact test.

Table 3. Insertion metrics for i-gel airway—groupwise comparison of size, insertion time, and attempts

	Group F (n = 30)	Group D (n = 30)	p-value*
I-gel size	2.06 ± 0.4	1.9 ± 0.2	0.169
Insertion time (seconds)	12.03 ± 2.9	11.73 ± 2.2	0.659
Number of attempts	1.07 ± 0.25	1.17 ± 0.46	0.302

*Fisher's exact test.

Table 4. Number of additional propofol bolus doses required throughout the surgery

# of propofol bolus doses	Group F (n = 30)	Group D (n = 30)	p-value
None	15 (50%)	27 (90%)	0.009*
1	8 (26.7%)	2 (6.7%)	
2	6 (20%)	1 (3.3%)	
3	1 (3.3%)	0	

*Fisher's exact test.

Table 5. Intraoperative adverse events

	Group F (n = 30)	Group D (n = 30)	p-value*
Duration of apnea (minutes)	15.07 ± 2.82	12.13 ± 2.28	<0.001
Desaturation	1 (3.3%)	-	0.313
Laryngospasm	1 (3.3%)	-	0.313
Cough	5 (16.7%)	1 (3.3%)	0.085

*Fisher's exact test.

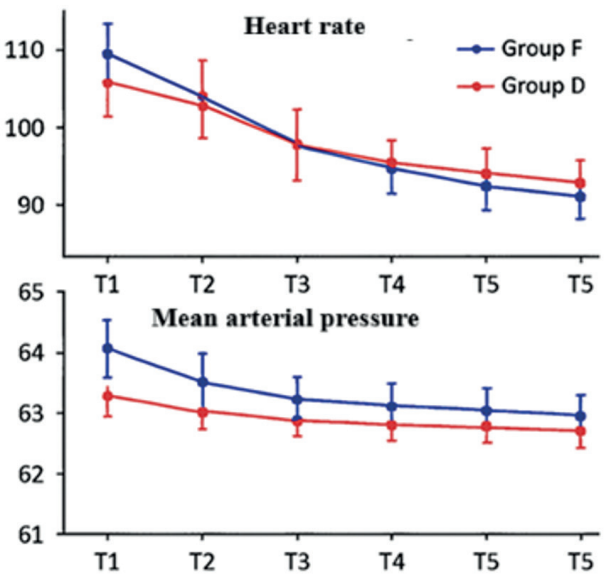

Figure 2. Comparison of heart rate and mean arterial pressure.

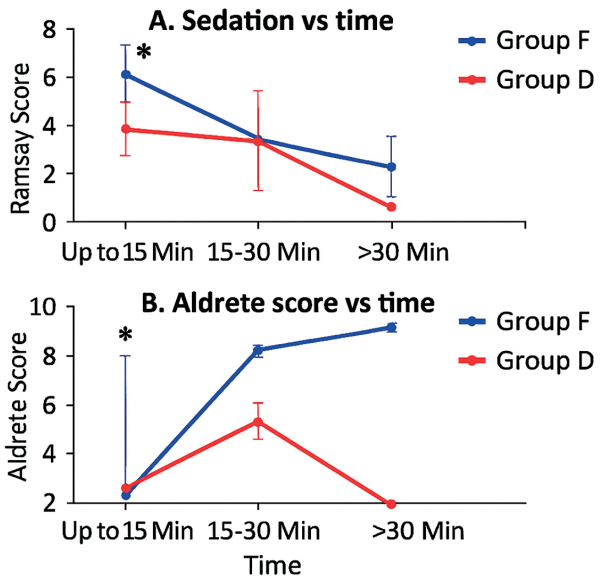

Figure 3. Comparative differences in Ramsay sedation scores and Aldrete recovery.

Trends of heart rate and mean arterial pressure were similar in both groups (Figure 2). SpO_2 remained ≥99% in both groups at all timepoints (all p≥ 0.09).

Respiratory rate was lower in Group F at every timepoint (all p<0.001; Table 6), with between-group mean differences of 7.5–8.6 breaths/min across T1–T5.

Significant differences were observed in both Ramsay Sedation Scores and Aldrete Recovery Scores between Group F and Group D during the early postoperative period (Figure 3).

Table 6. Trend of respiratory rate

Timepoint	Respiratory rate		p-value*
	Group F (n = 30)	Group D (n = 30)	
T1	11.23 ± 0.093	19.38 ± 0.521	<0.001
T2	10.02 ± 0.12	18.23 ± 0.801	<0.001
T3	9.21 ± 0.352	17.83 ± 0.675	<0.001
T4	9.48 ± 1.174	17.02 ± 0.140	<0.001
T5	8.32 ± 1.815	16.50 ± 1.21	<0.001

Data are presented as mean ± standard deviation.
*Independent samples t-test.

Sedation Scores (Ramsay)

At <15 minutes, Group D demonstrated deeper sedation (mean ± SD: 7.37 ± 0.49) compared to Group F (6.33 ± 1.18) with a mean difference of 1.04 (95% CI: 0.58 to 1.50); p < 0.001. Between 15–30 minutes, sedation remained higher in Group D (5.50 ± 0.51) than in Group F (2.93 ± 2.27), with a mean difference of 2.57 (95% CI: 1.65 to 3.49). At >30 minutes, both groups recovered fully with minimal sedation levels (1.00 ± 0.00, Figure 3A).

Recovery Scores (Aldrete)

Group F recovered faster, with significantly higher Aldrete Scores at <15 minutes (6.47 ± 0.51) compared to Group D (4.43 ± 0.50), with a mean difference of 2.04 (95% CI: 1.61 to 2.47); p < 0.001. Between 15–30 minutes, Group F fully recovered (10.00 ± 0.00), while some patients did not recover in Group D (6.47 ± 0.51), with a mean difference of 3.53 (95% CI: 3.23 to 3.83). At >30 minutes, both groups recovered completely (10.00 ± 0.00) (Figure 3B).

DISCUSSION

This study demonstrated that the insertion conditions of the I-gel with either fentanyl or dexmedetomidine as an adjunct to propofol showed no significant difference. However, a numerically higher percentage of patients who received dexmedetomidine had excellent insertion conditions compared to patients who received fentanyl. One patient in Group F experienced unacceptable insertion conditions.

Dexmedetomidine was initially approved by the FDA in 1999 for sedation in intubated and mechanically ventilated adult patients in intensive care settings. In 2008, its approval was expanded to include non-intubated adults undergoing procedural sedation. However, its use in pediatric patients has been under evaluation. While studies have been conducted to assess its efficacy and safety in children, the FDA has not yet granted full approval for pediatric procedural sedation. A recent submission proposed its use for sedation in non-intubated pediatric patients aged 1 month to 16 years undergoing non-invasive procedures. The FDA has required further studies to ensure its safety and efficacy in this population.

Given that dexmedetomidine's pediatric approval process is still under review, this study contributes valuable clinical insights into its airway tolerance and sedation efficacy in children. If further regulatory evaluations align with our findings, this study could support its inclusion in pediatric sedation protocols and assist in refining dosing recommendations for optimized patient outcomes.

Rustagi et al. (14) evaluated I-gel insertion conditions following propofol induction with dexmedetomidine or fentanyl premedication. They used modified scheme of Lund and Stovener criteria to assess overall insertion conditions. Similar insertion conditions were observed between the two groups.

Moderately relaxed jaw, coughing, and movement were observed more frequently in patients from Group F in this study. Also, the incidence of coughing and movement was notably higher in Group F, with

a statistically significant difference in occurrence of coughing between the two groups. Rustagi et al. reported a higher incidence of apnea with fentanyl (18/40) compared to dexmedetomidine (3/40). In this study, the duration of apnea also differed significantly between the groups.

Dexmedetomidine demonstrated better maintenance of oxygen saturation compared to fentanyl, despite inducing deeper sedation. Fentanyl was associated with more cases of oxygen desaturation, likely due to its opioid-induced respiratory depression, which differs pharmacologically from dexmedetomidine. Although fentanyl had a shorter duration of action, resulting in less impact on apnea time beyond the initial sedation phase, patients receiving fentanyl-propofol should be closely monitored for oxygen desaturation, particularly in high-risk populations.

Rustagi et al. also observed that emergence times were shorter in patients receiving fentanyl compared to patients receiving dexmedetomidine, with more propofol bolus doses required in the former group. Similarly, this study also showed that the number of propofol boluses required in Group F was significantly higher compared to Group D. This can be attributed to the effects of dexmedetomidine, which prolongs sedation and lowers the overall propofol requirement.

Rustagi et al. also observed that the respiratory rate was higher in patients receiving dexmedetomidine. This finding aligns with the findings of Ramaswamy et al. (15). Similarly, this study indicated that the respiratory rate was significantly higher in Group D compared to Group F. Hanci et al. (16) compared the effects of fentanyl and dexmedetomidine when combined with propofol and lidocaine for tracheal intubation. Their study found that heart rate was significantly lower in patients receiving dexmedetomidine, while mean arterial pressure was significantly lower in patients receiving fentanyl.

Uzumcugil et al. (13) observed greater reductions in systolic and mean arterial blood pressure in patients receiving fentanyl. In contrast, this study did not observe any significant differences in heart rate or mean arterial pressure at different time intervals. This finding is consistent with the findings of Choudhary et al. (17), which examined the insertion of Proseal LMA (a supraglottic device like classical LMA, with a second bore for gastric access) and reported hemodynamic stability in both groups. This study also found no significant differences in terms of I-gel size or number of insertion attempts. Based on these results, it is recommended that either protocol can be used without major concerns for hemodynamic instability.

This study found no significant difference in desaturation and laryngospasm, but a significant difference in the Ramsay Score. The mean Ramsay Score within the first 30 minutes was significantly higher in Group D. Prolonged sedation in Group D suggests improved patient comfort and reduced movement, both of which are advantageous for procedures requiring minimal patient response.

This study found a significantly lower Aldrete Score in Group D within the first 30 minutes. This indicates prolonged post-anesthesia effects, necessitating extended monitoring before discharge. Clinically, this suggests that dexmedetomidine-propofol patients may require additional monitoring time before discharge, whereas fentanyl-propofol patients can be discharged sooner, especially in outpatient settings.

Limitations

The findings of this study are limited by the small sample size, single-center design, subjective anesthesia assessment, lack of patient-reported comfort, and the absence of continuous capnography as an objective measure of apnea. Future research should aim to integrate objective sedation monitoring devices including capnography, larger and more diverse populations; and comprehensive evaluations of patient factors to improve the clinical applicability of findings.

CONCLUSIONS

This study compared I-gel insertion conditions using propofol–fentanyl versus propofol–dexmedetomidine in pediatric daycare surgeries at a tertiary care hospital. Jaw relaxation was similar between groups, and overall insertion conditions were statistically comparable. However, Group D demonstrated a higher rate of excellent placement and no unacceptable

scores. Group D required significantly fewer propofol boluses but exhibited higher Ramsay Sedation Scores and lower Aldrete Scores, consistent with deeper sedation and delayed recovery. With no significant differences in hemodynamic or respiratory parameters, dexmedetomidine as an adjunct to propofol appears to be a promising alternative to fentanyl in this setting.

Ethical approval

Ethical committee approval was obtained prior to patient recruitment (ECR/300/Inst/AP/2013/RR-16).

Author contribution

Surgical and Medical Practices: NA, JH; Concept: SP; Design: NA, HJ; Data Collection or Processing: NA, JH; Analysis or Interpretation: NA, JH; Literature Search: NA; Writing: NA, SP. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLES

Mechanical thrombectomy in acute ischaemic stroke: 1 year stroke centre experience

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ABSTRACT

Aim: Although successful recanalization is frequently achieved in acute ischemic stroke, favorable clinical outcomes are not universal. Multiple independent factors influence post-thrombectomy prognosis. This study aimed to identify the determinants of good clinical outcomes following mechanical thrombectomy (MT) in patients with acute ischemic stroke.

Methods: We retrospectively reviewed patients who underwent MT and/or intravenous thrombolytic therapy at our comprehensive stroke center between 2022 and 2023. Patients were classified by occlusion site: Group 1—middle cerebral artery (MCA, M1–M2) and anterior cerebral artery (ACA, A1); Group 2—internal carotid artery (ICA, cervical/distal) and tandem occlusions; Group 3—posterior circulation (distal vertebral, basilar, posterior cerebral artery (PCA) P1). Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and collateral circulation was graded with the TAN score for MCA occlusions. The modified Rankin Scale (mRS) score at 3 months was recorded in patients achieving successful recanalization (modified Thrombolysis in Cerebral Infarction (mTICI) 2b–3). Independent predictors of mRS were analyzed.

Results: Among 140 patients (57.9% male; median age, 69.5 years), successful recanalization was achieved in 85%. Poor outcome (mRS ≥3) was associated with older age, higher baseline NIHSS, elevated glucose, and higher 24-hour hemorrhage rates. Good outcome (mRS ≤2) correlated with higher mTICI and TAN scores.

Conclusion: Baseline and 24-hour NIHSS scores, collateral circulation, glucose level, and early intracranial hemorrhage are independent predictors of clinical outcome following MT in acute ischemic stroke.

Keywords: ischemic stroke, mechanical thrombectomy, clinical outcomes

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INTRODUCTION

Stroke ranks second among the leading causes of death worldwide and is the most common cause of disability (1). Cerebral angiography performed immediately after the onset of stroke shows arterial occlusions in 80% of acute infarcts (2,3). In a meta-analysis conducted by Goyal and colleagues, evaluating five randomized controlled trials, it was reported that clinical outcomes were better in patients with acute ischemic stroke (AIS) who underwent mechanical thrombectomy (4). According to the DAWN study, the rate of functional independence, defined by a score of 0 to 2 on the mRS at 90 days, was higher in the thrombectomy group compared to the control group (5). There is compelling evidence that good clinical outcomes are strongly associated with successful recanalization (6). In the Hermes meta-analysis, 71% of patients were successfully recanalized after mechanical thrombectomy (MT), but only 46% achieved good clinical outcomes (4). This discrepancy has led to investigations into factors influencing MT success. Studies have found that the absence of a history of diabetes, younger age, successful recanalization, a shorter time from symptom onset to recanalization, fewer passes with a stent retriever, and the absence of symptomatic hemorrhage are associated with good clinical outcomes (7). In our study, we examined the factors affecting clinical outcomes in patients who underwent mechanical thrombectomy.

METHODS

The medical records of patients who were treated with mechanical thrombectomy (MT) and/or intravenous (IV) tissue plasminogen activator (tPA) at the stroke center between 2022 and 2023 were retrospectively reviewed. Demographic data, cerebral angiography results, hospital admission and imaging times, medical history, medication use, and neurological examination findings at admission, 24 hours, and at 3 months were obtained from the hospital information management system (HIMS). Large vessel occlusions were examined in three groups: the first group included the middle cerebral artery (MCA) M1 and M2 segments and the anterior cerebral artery (ACA) A1 segment; the second group included the internal carotid artery (ICA) cervical segment, distal segment, and tandem occlusions; the third group included distal vertebral artery, basilar artery, and posterior cerebral artery (PCA) P1 occlusions. Patients who achieved successful recanalization (modified treatment in cerebral infarction (TICI) score: 2b-3) were evaluated using the modified Rankin Scale (mRS) at 3 months and divided into three groups for functional independence (0-II, III-V, and VI). TAN scoring was assessed only in patients with MCA occlusions.

This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences, Sultangazi Haseki Training and Research Hospital (Decision no: 259-2023) and was conducted in accordance with the ethical standards of the Helsinki Declaration. All patients were evaluated by an interventional neurologist and a stroke neurologist. All patients underwent non-contrast brain computed tomography (CT) and contrast-enhanced cervical + brain CT angiography (CTA). Early infarct signs on brain CT were evaluated using the Alberta Stroke Program Early Computed Tomography (ASPECT) score. Alteplase at a dose of 0.9 mg/kg was administered in the emergency department to patients who presented within 4.5 hours after symptom onset, or who presented within 16 hours and had no ischemic lesion on FLAIR sequence in magnetic resonance imaging (MRI) and had no contraindications. These patients were then taken to the angiography unit for MT. MT was performed on patients aged ≥18 years, with a pre-stroke mRS score of 0 or 1, with MCA M1-M2 and ACA A1 occlusions, ICA cervical, tandem, distal ICA T, L, or I occlusions, vertebral artery, basilar artery, or PCA P1 occlusions, with an NIHSS score of ≥6 points, and an ASPECT score of ≥6 within 16 hours of symptom onset (8).

Endovascular treatment

Mechanical thrombectomy was performed on a monoplane angiography device under conscious sedation or general anesthesia. The femoral artery was used as the entry site for the procedure. A 6 French (F)

guiding catheter (Destination, Terumo, Tokyo, Japan) was then placed in the subclavian artery, vertebral artery, common carotid artery, or cervical segment of the internal carotid artery. A distal access catheter (Catalist 5F-6F, Stryker, Kalamazoo, Michigan), microcatheter (Rebar, Medtronic, Minneapolis, USA), and 0.014-inch microguidewire (Syncroo, Stryker) were used. Mechanical thrombectomy was performed using one of the stent-retriever thrombectomy techniques (isolated stent retriever, ARTS, SAVE, Solumbra) or aspiration (ADAPT). For stent-retriever MT, appropriately sized stent retrievers (Trevo, Stryker, Kalamazoo, Michigan, USA; Thrombite, Zylox-Tonbridge, Hangzhou, China; Solitaire X, Medtronic, Minneapolis, USA) were deployed in the occluded segment. If the procedure failed after two attempts, a technical change was made. If success could not be achieved after seven thrombectomy attempts, the procedure was terminated. In tandem occlusions, direct aspiration was performed first, and if unsuccessful, balloon angioplasty was performed on the internal carotid artery (ICA) origin. If reocclusion of the ICA origin occurred despite balloon angioplasty, carotid artery stenting was performed following a loading dose of 300 mg acetylsalicylic acid and 300 mg clopidogrel. Patients who underwent MT were monitored in the intensive care unit post-procedure. Blood pressure and neurological examination were monitored every 30 minutes for the first 2 hours and then every hour thereafter. A brain CT scan was performed 24 hours after MT. If no hemorrhage was detected on brain CT, antiplatelet or anticoagulant therapy was initiated based on the underlying etiology.

Clinical evaluation and outcome measures

The severity of the initial clinical findings was assessed using the National Institutes of Health Stroke Scale (NIHSS) score. Early infarct signs of AIS on brain CT were evaluated using the ASPECT score. Collateral levels on CTA in MCA occlusions were assessed according to the Tan scale. The level of recanalization was classified using the modified Treatment in Cerebral Ischemia (mTICI) classification (9). According to the classification: mTICI 0 was defined as no antegrade flow or perfusion beyond the occlusion; mTICI 1 as penetration beyond the occlusion but no perfusion; mTICI 2a as perfusion with less than 50% distal branch filling of the MCA territory; mTICI 2b as perfusion with more than 50% distal branch filling of the MCA territory; mTICI 2c as near-complete perfusion except for slow flow or small distal cortical emboli in a few distal cortical vessels; and mTICI 3 as full perfusion of the MCA territory.

Statistical analysis

In the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used. The distribution of variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For the analysis of independent quantitative data, ANOVA (Tukey test), Kruskal-Wallis, and Mann-Whitney U tests were used. For the analysis of independent qualitative data, the Chi-square test was used, and when the conditions for the Chi-square test were not met, the Fisher's test was applied. The analyses were performed using the SPSS 28.0 program.

RESULTS

A total of 140 patients were treated with mechanical thrombectomy (MT) for acute ischemic stroke. Of these, 57.9% were male and 42.1% were female, with a median age of 69.5 years (range: 21–96). Successful recanalization (mTICI 2b–3) was achieved in 119 patients (85%). Intravenous thrombolysis (IV tPA) was administered to 60% of patients. Among the cohort, 39.3% were smokers, 57.9% had hypertension (HT), 45.7% had atrial fibrillation (AF), 40% had coronary artery disease (CAD), 25.7% had diabetes mellitus (DM), and 24.3% were obese. Anticoagulant use was noted in 7.1% (warfarin) and 11.4% (NOAC). A previous history of stroke was present in 17.1%.

The median ASPECTS score at presentation was 9 (range: 6–10), and the median baseline NIHSS score was 9 (range: 3–22). Occlusion sites included MCA-M1 (49.3%), MCA-M2 (14.3%), ICA (19.3%), tandem lesions (7.1%), and posterior circulation (PCA/basilar artery, 10%) (Table 1).

Table 1. Demographic data and clinical characteristics								
		Min-Max			**Median**	**Mean±sd/n-%**		
Age		21.0	-	96.0	69.5	67.6	±	14.7
Sex	Women					81		57.9%
	Man					59		42.1%
Cigarette Usage	(-)					85		60.7%
	(+)					55		39.3%
Comorbid Disease								
Hypertension						81		57.9%
Atrial Fibrillation						64		45.7%
Coronary artery disease						56		40.0%
Diabetes mellitus						36		25.7%
Obesity						34		24.3%
Stroke History	(-)					116		82.9%
	(+)					24		17.1%
Application Aspect Score		6.0	-	10.0	9.0	9.1	±	1.1
Occluded Vessel	MCA M1					69		49.3%
	MCA M2					20		14.3%
	ICA DISTAL					27		19.3%
	ICA TANDEM					10		7.1%
	BA,VA,PCA P1					14		10.0%
Warfarin Usage	(-)					130		92.9%
	(+)					10		7.1%
NOAK Usage	(-)					124		88.6%
	(+)					16		11.4%
IV TPA	(-)					56		40.0%
	(+)					84		60.0%
Symptom Puncture Duration		15.0	-	795.0	180.0	250.6	±	174.3
Symptom Recanalisation Time		75.0	-	815.0	237.5	308.3	±	181.2
Puncture Recanalisation		10.0	-	190.0	55.0	56.8	±	24.0
Door Imaging		2.0	-	120.0	15.0	19.0	±	15.8
Door TPA		20.0	-	120.0	45.0	51.2	±	20.9
Door Puncture		15.0	-	110.0	60.0	56.5	±	17.5
TICI	0					13		9.3%
	2A					8		5.7%
	2B					35		25.0%
	2C					22		15.7%
	3					62		44.3%
Application NIHSS		3.0	-	22.0	9.0	9.7	±	3.5
24th Hour NIHSS		0.0	-	25.0	5.0	6.2	±	4.9
3rd Month MRS		0.0	-	6.0	2.0	2.4	±	2.0
Glucose		76.0	-	608.0	125.0	148.8	±	75.7
HB		5.1	-	16.9	12.5	12.4	±	2.3
PLT		61.0	-	996.0	225.0	248.4	±	104.3
Lymphocyte		0.3	-	7.0	2.0	2.2	±	1.2
Leukocyte		4.3	-	32.0	8.5	9.3	±	3.4
RDW		4.1	-	28.9	14.0	14.5	±	2.2

MCA: Middle cerebral artery; ACA: Anterior cerebral artery; ICA: Internal carotid artery; BA: Basilar artery; VA: Vertebral artery; PCA: Posterior cerebral artery; HT: Hypertension; AF: Atrial fibrillation; CAD: Coronary artery disease; DM: Diabetes mellitus; NOAC: Novel oral anticoagulant; IV tPA: Intravenous tissue plasminogen activator; ASPECTS: Alberta Stroke Program Early CT Score; NIHSS: National Institutes of Health Stroke Scale; TICI: Thrombolysis in Cerebral Infarction; mTICI: Modified Thrombolysis in Cerebral Infarction; mRS: Modified Rankin Scale; Hb: Hemoglobin; PLT: Platelet; RDW: Red cell distribution width.

Table 1. Continued

		Min-Max	Median	Mean±sd/n-%
First Pass Recanalisation	First Pass			99 - 70,7%
	Repeating			41 - 29.3%
Use of Stent Retriver	(-)			38 - 27.1%
	(+)			102 - 72.9%
Distal Embolism	(-)			75 - 53.6%
	(+)			65 46.4%
Bleeding in 24 hours	(-)			97 69.3%
	(+)			43 30.7%
Antiaggregant Therapy	(-)			82 58.6%
	(+)			58 41.4%
Rescue Therapy	(-)			116 82.9%
	(+)			24 17.1%

MCA: Middle cerebral artery; ACA: Anterior cerebral artery; ICA: Internal carotid artery; BA: Basilar artery; VA: Vertebral artery; PCA: Posterior cerebral artery; HT: Hypertension; AF: Atrial fibrillation; CAD: Coronary artery disease; DM: Diabetes mellitus; NOAC: Novel oral anticoagulant; IV tPA: Intravenous tissue plasminogen activator; ASPECTS: Alberta Stroke Program Early CT Score; NIHSS: National Institutes of Health Stroke Scale; TICI: Thrombolysis in Cerebral Infarction; mTICI: Modified Thrombolysis in Cerebral Infarction; mRS: Modified Rankin Scale; Hb: Hemoglobin; PLT: Platelet; RDW: Red cell distribution width.

Patients with MCA/ACA occlusions had significantly higher age (p=0.039), AF prevalence (p=0.003), and NIHSS scores at presentation (p=0.001) compared to those with ICA and tandem occlusions. Door-to-imaging time was significantly longer in posterior circulation strokes (p=0.015), and rescue therapy was more frequently required in PCA/basilar artery occlusions than in MCA/ACA occlusions (p<0.05) (Table 2).

Clinical outcome groups

At three months, patients were categorized into three clinical outcome groups according to the modified Rankin Scale (mRS):

- Good clinical outcome group: mRS 0–2
- Dependent clinical outcome group: mRS 3–5
- Mortality group: mRS 6

Good clinical outcome group (mRS 0–2)

Patients with good clinical outcomes (mRS 0–2) were younger (p = 0.025) and had significantly higher mTICI and TAN collateral scores (p < 0.05), along with lower NIHSS scores at presentation and at 24 hours (both p < 0.001). Glucose levels were lower (p = 0.026), and the rate of intracranial hemorrhage within 24 hours was reduced compared to other outcome groups (p = 0.006).

Dependent clinical outcome group (mRS 3–5)

In the dependent clinical outcome group (mRS 3–5), patients were older (p = 0.025) and had higher NIHSS scores at presentation and at 24 hours compared to those with good outcomes (both p < 0.001). This group also exhibited higher glucose levels (p = 0.026) and an increased rate of intracranial hemorrhage within the first 24 hours (p = 0.006).

Mortality group (mRS 6)

Patients in the mortality group (mRS 6) demonstrated the highest NIHSS scores at presentation and at 24 hours (both p < 0.001), significantly elevated platelet counts (p = 0.018), and the highest frequency of intracranial hemorrhage. TAN collateral scores were significantly lower in this group than in both the good and dependent outcome groups (p < 0.05) (Table 3).

DISCUSSION

In this study, we retrospectively evaluated 140 patients who underwent mechanical thrombectomy (MT) for acute ischemic stroke due to large vessel occlusion (LVO). Successful recanalization (mTICI 2b–3) was achieved in 85% of patients. Based on 3-month outcomes, patients were stratified into three categories: good clinical outcome (mRS 0–2), dependent clinical outcome (mRS 3–5), and mortality (mRS 6). Favorable outcomes were associated with

Table 2. Comparison of patients according to vessel occlusion sites

			[2] Group-I (MCA M1-M2, ACA A1)	[3] Group-II (ICA ve Tandem)	[4] Group-III (BA, VA, PCA P1)	p	
Age	Mean±sd		69.5 ± 16.7	63.4 ± 12.5	65.6 ± 8.8	**0.039**	K
	Median		75	65.0 [2]	64.5		
Sex							
Women		n-%	55 - 61.8%	20 - 54.10%	6 - 42.90%	0.16	X^2
Man		n-%	34 - 38.2%	17 - 45.90%	8 - 57.10%		
Cigarette Use	(-)	n-%	60 - 67.4%	18 - 48.60%	7 - 50.00%	0.056	X^2
	(+)	n-%	29 - 32.60%	19 - 51.40%	7 - 50.00%		
Comorbid Disease				-	-		
Hypertension		n-%	56 - 62.90%	18 - 48.60%	7 - 50.00%	0.456	X^2
Atrial Fibrillation		n-%	48 - 53.90%	9 [2] - 24.30%	7 - 50.00%	**0.003**	X^2
Coronary artery disease		n-%	35 - 39.30%	14 - 37.80%	7 - 50.00%	0.759	X^2
Diabetes mellitus		n-%	19 - 21.30%	11 - 29.70%	6 - 42.90%	0.173	X^2
Obesity		n-%	24 - 27.00%	7 - 18.90%	3 - 21.40%	0.655	X^2
Stroke History	(-)	n-%	77 - 86.50%	29 - 78.40%	10 - 71.40%	0.217	X^2
	(+)	n-%	12 - 13.50%	8 - 21.60%	4 - 28.60%		
Warfarin Usage	(-)	n-%	83 - 93.30%	36 - 97.30%	11 - 78.60%	**p<0.05**	X^2
	(+)	n-%	6 - 6.70%	1 - 2.70%	3 - 21.40%		
NOAK Usage	(-)	n-%	78 - 87.60%	33 - 89.20%	13 - 92.90%	p>0.05	X^2
	(+)	n-%	11 - 12.40%	4 - 10.80%	1 - 7.10%		
IV TPA	(-)	n-%	52 - 58.40%	21 - 56.80%	11 - 78.60%	**0.000**	X^2
	(+)	n-%	37 [1] - 41.60%	16 [1] - 43.20%	3 [1] - 21.40%		
Symptom Puncture Duration	Mean±sd		248.9 ± 166.6	235.5 ± 167.3	304.9 ± 239.9	0.886	K
	Median		202.5	170	180		
Symptom Recanalisation Time	Mean±sd		303.1 ± 171.8	297.1 ± 176.1	375.2 ± 249.5	0.876	K
	Median		252.5	220	265		
Puncture Recanalisation	Mean±sd		53.3±17.9	61.3 ± 26.9	67.9 ± 42.6	0.192	K
	Median		50	60	60		
Door Imaging	Mean±sd		18.8±16.6	16.2 ± 9.1	32.4 ± 24.1	**0.015**	K
	Median		15.0 [4]	15.0 [4]	26		
Door TPA	Mean±sd		48.7±20.7	49.8 ± 20.3	58.8 ± 23.2	0.646	A
	Median		45	42.5	62.5		
Door Puncture	Mean±sd		55.4±17	57.1 ± 17.8	61.5 ± 20	0.56	K
	Median		56	60	70		
TICI	0	n-%	6 - 6.70%	5 - 13.20%	2 - 15.40%	p>0.05	X^2
	2A	n-%	4 - 4.50%	4 - 10.50%	0 - 0.00%		
	2B	n-%	25 - 28.10%	9 - 23.70%	1 - 7.70%		
	2C	n-%	15 - 16.90%	5 - 13.20%	2 - 15.40%		
	3	n-%	39 - 43.80%	15 - 39.40%	8 - 61.50%		
Application NIHSS	Mean±sd		10.4±3.3	9.4 ± 3.6	10.1 ± 4.9	**0.001**	K
	Median		10	8.0 [2]	10.5		
24th Hour NIHSS	Mean±sd		6.2±5	6.4 ± 4.8	6.9 ± 6.1	0.934	K
	Median		4	6	5		
3rd Month MRS	Mean±sd		2.2±2.1	2.3 ± 2	2.3 ±2	0.16	K
	Median		2	2	1.5		
Glucose	Mean±sd		134.5±54.9	160.6 ± 102.7	162.2 ± 75.2	**0.049**	K
	Median		119.0 [1]	125	143		
HB	Mean±sd		12.2±2.1	12.5 ± 2.5	12.2 ± 2.2	0.395	K
	Median		12.2	12.7	12.9		
First Pass Recanalisation		n-%	59 - 66.30%	31 - 81.60%	9 - 69.20%	p>0.05	X^2
Repeating		n-%	30 - 33.70%	7 - 18.40%	4 - 30.80%		
Use of Stent Retriver	(-)	n-%	27 - 30.30%	8 - 21.10%	3 - 23.10%	p>0.05	X^2
	(+)	n-%	62 - 69.70%	30 - 78.90%	10 - 76.90%		
Distal Embolism	(-)	n-%	51 - 57.30%	15 - 39.50%	9 - 69.20%	p>0.05	X^2
	(+)	n-%	38 - 42.70%	23 - 60.50%	4 - 30.80%		
Bleeding in 24 hours	(-)	n-%	62 - 69.70%	24 - 63.20%	11 - 84.60%	0.08	X^2
	(+)	n-%	27 - 30.30%	14 - 36.80%	2 - 15.40%		
Antiaggregant Therapy	(-)	n-%	54 - 60.70%	22 - 57.90%	6 - 46.20%	0.703	X^2
	(+)	n-%	35 - 39.30%	16 - 42.10%	7 - 53.80%		
Rescue Therapy	(-)	n-%	81 - 91.00%	27 - 71.10%	8 - 61.50%	**p<0.05**	X^2
	(+)	n-%	8 - 9.00%	11 - 28.90%	5 - 38.50%		

[A] ANOVA / K Kruskal-wallis (Mann-whitney u test) / X^2 Chi-square test (Fischer test).
[1] Difference with Group I p<0.05, [2] Difference with Group II p<0.05, [3] Difference with Group III p<0.05,[4] Difference with Group-IV p<0.05.
MCA – Middle cerebral artery; ACA – Anterior cerebral artery; ICA – Internal carotid artery; BA – Basilar artery; VA – Vertebral artery; PCA – Posterior cerebral artery; AF – Atrial fibrillation; CAD – Coronary artery disease; DM – Diabetes mellitus; NOAC – Novel oral anticoagulant; IV tPA – Intravenous tissue plasminogen activator; NIHSS – National Institutes of Health Stroke Scale; TICI – Thrombolysis in Cerebral Infarction; mRS – Modified Rankin Scale; Hb – Hemoglobin; PLT – Platelet; DAPT – Dual antiplatelet therapy.

Table 3. Comparison of MRS groups

			[1] 3rd Month MRS Score 0-I-II	[2] 3rd Month MRS Score III-IV-V	[3] 3rd Month MRS Score VI	p	
Age	Mean±sd		66.3 ± 14.7	76.5 ± 12	71.6 ± 13.7	**0.025**	A
	Median		66.5	79.0 [1]	76.5		
Sex	Women	n-%	46 - 52.30%	9 - 60.00%	12 - 75.00%	0.23	X^2
	Man	n-%	42 - 47.70%	6 - 40.00%	4 - 25.00%		
Cigarette Use	(-)	n-%	47 - 53.40%	11 - 73.30%	12 - 75.00%	0.129	X^2
	(+)	n-%	41 - 46.60%	4 - 26.70%	4 - 25.00%		
Comorbid Disease							
Hypertension		n-%	48 - 54.50%	10 - 66.70%	11 - 68.80%	0.438	X^2
Atrial Fibrillation		n-%	36 - 40.90%	8 - 53.30%	11 - 68.80%	0.102	X^2
Coronary artery disease		n-%	39 - 44.30%	3 - 20.00%	7 - 43.80%	0.204	X^2
Diabetes mellitus		n-%	25 - 28.40%	2 - 13.30%	3 - 18.80%	0.376	X^2
Obesity		n-%	23 - 26.10%	4 - 26.70%	3 - 18.80%	0.814	X^2
Stroke History	(-)	n-%	78 - 88.60%	10 - 66.70%	11 - 68.80%	**0.028**	X^2
	(+)	n-%	10[23] - 11.40%	5 - 33.30%	5 - 31.30%		
Application Aspect	Mean±sd		9.3 ± 0.8	9.1 ± 1.1	8.6 ± 1.5	0.155	K
	Median		10	9	9		
LVO	(-)	n-%	1 - 1.10%	0 - 0.00%	0 - 0.00%	p>0.05	X^2
	(+)	n-%	87 - 98.90%	15 - 100.00%	16 - 100.00%		
IV TPA	(-)	n-%	52 - 59.10%	10 - 66.70%	10 - 62.50%	0.844	X^2
	(+)	n-%	36 - 40.90%	5 - 33.30%	6 - 37.50%		
Symptom Puncture Duration	Mean±sd		254.4 ± 182.3	232 ± 168.7	220.3 ± 160.4	0.85	K
	Median		180	180	167.5		
Symptom Recanalisation Time	Mean±sd		308.7 ± 186.5	296.5 ± 176.7	277.2 ± 185.1	0.876	K
	Median		220	220	225		
Puncture Recanalisation	Mean±sd		54 ± 18.8	64.5 ± 29.6	51.3 ± 19.5	0.299	K
	Median		51	60	45		
Door Imaging	Mean±sd		19.9 ± 18.3	19.5 ± 14.2	16.9 ± 13.6	0.761	K
	Median		15	15	14.5		
Door TPA	Mean±sd		49.2 ± 20.2	65.8 ± 14.3	30 ± 8.4	**0.004**	K
	Median		45	70.0 [1]	30.0 [12]		
Door Puncture	Mean±sd		54.7 ± 16.7	63.8 ± 14.4	55.3 ± 17.5	0.16	K
	Median		57	60	50		
TICI	2B	n-%	22 - 25.00%	6 - 40.00%	7 - 43.80%	**0.01**	X^2
	2C	n-%	12 - 13.60%	6 - 40.00%	4 - 25.00%		
	3	n-%	54 - 61.40%	3 [1] - 20.00%	5 - 31.30%		
NIHSS Score							
Application	Mean±sd		9.1 ± 2.9	13.2 ± 3.9	13.7 ± 2.7	**0**	K
	Median		9.0 [23]	14	13		
24th hour	Mean±sd		3.4 ± 2.2	10.9 ± 3.6	13.8 ± 2.9	**0**	K
	Median		3.0 [23]	10.0 [3]	13.5		
Glucose	Mean±sd		138.3 ± 78.9	146.4 ± 35.3	164.6 ± 82.6	**0.026**	K
	Median		115.0 [2]	145	148		
HB	Mean±sd		12.2 ± 2.3	13.2 ± 1.9	12.1 ± 2	0.214	A
	Median		12.4	13.2	11.7		
PLT	Mean±sd		246.9 ± 91.9	207.1 ± 63.9	320.5 ± 194.5	**0.018**	K
	Median		224.5 [3]	211.0 [3]	302.5		
Lymphocyte	Mean±sd		2.29 ± 1.2	2.02 ± 1.12	2.44 ± 1.9	0.615	K
	Median		2.03	1.71	1.52		
Leukocyte	Mean±sd		9 ± 3	8.9 ± 3.8	10.2 ± 3.2	0.249	K
	Median		8.4	7.9	10.1		
RDW	Mean±sd		14.6 ± 1.8	13.9 ± 1	15 ± 2.3	0.511	K
	Median		14	14	14.2		
First Pass Recanalisation	First Pass	n-%	57 - 64.80%	14 - 93.30%	11 - 68.80%	0.087	X^2
	Repeating	n-%	31 - 35.20%	1 - 6.70%	5 - 31.30%		
Use of Stent Retriver	(-)	n-%	25 - 28.40%	2 - 13.30%	4 - 25.00%	0.467	X^2
	(+)	n-%	63 - 71.60%	13 - 86.70%	12 - 75.00%		
Distal Embolism	(-)	n-%	53 - 60.20%	7 - 46.70%	8 - 50.00%	0.51	X^2
	(+)	n-%	35 - 39.80%	8 - 53.30%	8 - 50.00%		
Bleeding in 24 hours	(-)	n-%	69 - 78.40%	8 - 53.30%	7 - 43.80%	**0.006**	X^2
	(+)	n-%	19 [23] - 21.60%	7 - 46.70%	9 - 56.30%		
TAN Score	0	n-%	7 - 11.30%	4 - 33.30%	10[1] - 66.60%	**p<0.05**	X^2
	1	n-%	16 - 25.80%	6 - 50.00%	3 - 20.00%		
	2	n-%	28 - 45.20%	2 - 16.70%	1 - 6.70%		
	3	n-%	11 - 17.70%	0 - 0.00%	1 - 6.70%		
Rescue Therapy	(-)	n-%	78 - 88.60%	13 - 86.70%	11 - 68.80%	0.112	X^2
	(+)	n-%	10 - 11.40%	2 - 13.30%	5 - 31.30%		

[A] ANOVA / K Kruskal-wallis (Mann-whitney u test) / X^2 Chi-square test (Fischer test).

[1] 3rd Month MRS Score difference with 0-I-II group<0.05, [2] 3rd Month MRS Score difference with III-IV-V group p<0.05, [3] 3rd Month MRS Score difference with VI group p<0.05.

mRS – Modified Rankin Scale; MCA – Middle cerebral artery; ACA – Anterior cerebral artery; ICA – Internal carotid artery; PCA – Posterior cerebral artery; NIHSS – National Institutes of Health Stroke Scale; TICI – Thrombolysis in Cerebral Infarction; TAN – Tan collateral grading score; Hb – Hemoglobin; PLT – Platelet; RDW – Red cell distribution width; IV tPA – Intravenous tissue plasminogen activator; DAPT – Dual antiplatelet therapy.

younger age, higher mTICI and TAN collateral scores, and lower NIHSS and glucose levels. Conversely, poor outcomes were associated with older age, higher baseline and 24-hour NIHSS scores, elevated glucose levels, intracranial hemorrhage, and lower TAN scores. Increased platelet levels were associated with mortality. Posterior circulation strokes had longer door-to-imaging times and higher rates of rescue therapy compared to anterior circulation strokes.

Mechanical thrombectomy is the standard therapeutic approach for acute ischemic stroke caused by LVO (10,11). The DAWN and DEFUSE-3 trials expanded the treatment window to 24 hours and highlighted the importance of imaging-based selection (5,12). The 2019 AHA/ASA and European Stroke Organization guidelines support thrombectomy for selected LVOs within 24 hours of last known well time (10). Consistent with prior findings, our study demonstrated longer door-to-imaging times in posterior circulation strokes and higher NIHSS scores in MCA/ACA infarctions (13).

Patients with underlying intracranial atherosclerosis have been shown to experience longer procedural times, lower recanalization rates, and higher reocclusion rates (14,15). In such cases, rescue strategies such as dual antiplatelet therapy (DAPT), intra-arterial glycoprotein IIb/IIIa inhibitors, angioplasty, and stenting may improve outcomes (16-18). In our cohort, rescue therapy was more frequently applied in posterior circulation strokes.

Multiple studies have identified age, baseline NIHSS, glucose level, and collateral circulation as independent predictors of outcome after MT (6,19-23). Our findings confirm these associations. Higher NIHSS scores at admission and at 24 hours predicted worse outcomes, while successful recanalization was significantly associated with good clinical outcomes, in agreement with Yoo et al. and others (6,21-23).

Hyperglycemia at admission is a known indicator of disease severity and has been linked to worse neurological recovery (24,25). In our study, elevated glucose levels were associated with poor functional outcomes, supporting this relationship.

Elevated platelet counts have been linked to increased mortality and recurrent stroke (26); our study similarly found an association between higher platelet levels and mortality. Intracranial hemorrhage (ICH) remains a major determinant of poor outcomes after MT, often related to arterial injury or reperfusion damage (27,28). In our cohort, ICH was associated with higher mRS scores, consistent with prior literature.

Finally, collateral circulation plays a pivotal role in post-thrombectomy prognosis. The TAN collateral score, which reflects the adequacy of leptomeningeal collaterals in MCA occlusions, has been validated as a prognostic tool in MT candidates beyond the 6-hour window (29,30). In agreement with these studies, higher TAN scores were observed in patients with good clinical outcomes, highlighting the prognostic significance of collateral status in achieving favorable recovery after MT.

Study limitations

The first limitation of our study is its retrospective nature. When grouping large vessels in the study, MCA M1, MCA M2, and ACA were grouped together; all segments of the ICA and ICA tandem occlusions were grouped together; and basilar, PCA, and vertebral arteries were grouped together. This resulted in a lack of vessel-specific analysis. Although the table evaluating factors affecting mRS scores included only patients who achieved successful recanalization, which does not provide data on the impact of unsuccessful recanalizations on mRS scores, it is thought to provide more specific data on the evaluation of other variables. Another limitation is the small sample size, due to the stroke center being in its first year of operation. Different results may be obtained with larger study groups.

CONCLUSION

Although numerous independent factors influence the clinical outcome of acute cerebral infarction, the NIHSS score at admission and at 24 hours, the collateral circulation score, glucose level, and the presence of intracranial hemorrhage are particularly significant predictors of functional outcomes following mechanical thrombectomy. Future studies involving

larger cohorts are warranted to evaluate these independent variables individually and to better delineate their specific contributions within distinct patient subgroups.

Ethical approval

This study has been approved by the Clinical Research Ethics Committee of the University of Health Sciences, Sultangazi Haseki Training and Research Hospital (approval date 27/12/2023, number 259-2023).

Author contribution

Surgical and Medical Practices: ZM, Bİ; Concept: ZM, Bİ; Design: ZM, Bİ; Data Collection or Processing: ZM, Bİ; Analysis or Interpretation: ZM, Bİ; Literature Search: ZM, Bİ; Writing: ZM, Bİ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLES

Testing of novel CpG chromatin fragments as UCOE candidates for improved gene therapy vectors

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ABSTRACT

Aim: The A2UCOE sequence, positioned between the HNRPA2B1 and CBX3 gene promoters in the human genome, supports durable and consistent expression of integrated transgenes, even within compact heterochromatin domains such as centromeres. This project focuses on evaluating the dual-component hypothesis of A2UCOE function by analyzing alternative DNA elements that possess CpG-rich content and divergent promoter features.

Method: To investigate expression stability, lentiviral vectors carrying eGFP reporter constructs driven by novel UCOE candidates and various A2UCOE subregions were introduced into P19 and F9 mouse embryonal carcinoma cells. Expression was tracked over time, both before and after lineage-specific differentiation toward neuroectoderm and endoderm. To examine the proposed bipartite model of UCOE function, we employed two types of CpG-rich, bidirectionally transcribed elements: the endogenous *SETD3–CCNK* housekeeping gene pair, and a synthetically arranged divergent configuration composed of *RPS11* and *HNRPA2B1* promoters.

Results: Placing these regulatory elements in either orientation upstream of the SFFV-eGFP reporter gene—known for its susceptibility to transcriptional silencing—conferred a noticeable, though incomplete, resistance to silencing when compared to the full activity of the reference 1.5A2UCOE-SFFV-eGFP construct. This partial protective effect was consistently observed in both P19 and F9 cell lines, prior to and following their differentiation. In conclusion, we successfully identified a naturally occurring (*SETD3–CCNK*) and synthetically engineered (*RPS11–HNRPA2B1*) pair of divergent promoters that exhibited measurable but incomplete UCOE-like activity relative to the established HNRPA2B1–CBX3 core element.

Conclusion: This study demonstrates that natural and synthetic divergent promoter pairs confer significant, though partial, resistance to transgene silencing. This finding directly supports the A2UCOE's dual-component hypothesis, confirming that CpG-rich bidirectional architecture is key for sustaining stable expression through differentiation and in challenging genomic contexts.

Keywords: chromatin remodelling, gene silencing, lentiviral vector, neuroectodermal and endodermal differentiation, UCOE

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INTRODUCTION

Gene therapy is an emerging method that is used to treat genetic diseases, both inherited and acquired. It is applied by inserting therapeutic nucleic acids into living cells. These nucleic acid molecules either correct faulty genes or alter how genes function (1). For the delivery of these nucleic acid molecules, there are mainly two types of systems: viral and non-6viral. Viral vectors operate by using viruses' natural ability to enter cells and non-viral delivery methods involve carriers like DNA-lipid complexes (e.g., liposomes) (2,3).

Recent advancements in molecular genetics have made it possible for researchers to develop virus-based delivery systems for both research and clinical use (4,5). These include lentiviral vectors (LVs), which are derived from HIV-1, and are significantly advantageous because they can efficiently transduce both proliferating and non-proliferating cells. This feature makes them favorable for treating tissues with low cell renewal activity, such as the central nervous system and some types of stem cells (6).

Lentiviral vectors are widely used because they can carry large genetic inserts (up to ~8 kb) and can be modified by altering their envelope proteins, which enables targeting of specific cell types (7). However, the use of these vectors comes with potential safety risks such as the risk of recombination or unwanted gene activation caused by random integration into the genome. To be able to reduce these risks, researchers have developed self-inactivating (SIN) systems. These minimize promoter interference and decrease the likelihood of insertional mutagenesis (8).

Challenges in gene silencing and transgene expression

A significant concern in gene therapy is maintaining stable and long-term expression of the introduced gene, referred to as a transgene. Retroviral vectors can integrate the transgene into the host genome, which is important for ensuring persistent expression (9,10). However, over time, this expression may decrease or stop altogether due to epigenetic silencing. This process of epigenetic silencing may be triggered by DNA methylation at CpG sites or it may be mediated by histone modifications which cause the chromatin to become more compact and make it harder for the molecular components involved in transcription to access the gene. As a result, the therapeutic effect may weaken or be lost (11,12).

To address this problem, vector systems have been optimized through the incorporation of ubiquitous chromatin-opening elements (UCOEs). These regulatory DNA sequences prevent heterochromatin-mediated silencing and promote stable and long-term gene expression in mammalian cells (13,14). A well-characterized example is A2UCOE, which is derived from the HNRPA2B1-CBX3 locus. This element encompasses two promoter regions and contains a naturally unmethylated CpG island, which helps secure an open chromatin structure and supports active transcription that includes transcriptionally repressive regions like centromeric DNA (13,15).

Functional role and applications of A2UCOE

There are two pathways for the A2UCOE element to function. The first one is a dual-promoter system (HNRPA2B1 and CBX3), and the second is a CpG island that shows natural resistance to DNA methylation (1,2). This unique structure supports an open chromatin configuration and enables consistent and long-term gene expression. It has proven to be a reliable regulatory element in lentiviral vector systems, which support stable transgene expression in both in vitro cell cultures and in vivo models, such as murine hematopoietic stem cells (16). Similarly, A2UCOE is widely used to overcome the issues of epigenetic silencing in gene therapy applications.

Recent studies have explored new CpG-rich DNA regions and other dual-promoter designs to develop improved versions of ubiquitous chromatin-opening elements (UCOEs). The goal of these efforts was to create next-generation vector systems that are more resistant to gene silencing and more effective in delivering therapeutic genes. In summary, incorporating regulatory elements such as A2UCOE into lentiviral vectors has been shown to optimize gene expression for stability, reliability, and reduced risk, which makes them more suitable for gene therapy applications.

MATERIALS AND METHODS

Luria-bertani (LB) medium preparation

To prepare LB broth, 10 g of tryptone, 5 g of yeast extract, and 10 g of sodium chloride were added to one liter of deionized water. The mixture was sterilized in an autoclave at 15 psi for 20 minutes and then cooled to about 55°C. To enable antibiotic selection, ampicillin was added at the final concentration of 50 µg/mL. To make LB agar plates, 20 g of agar was added per liter of LB broth. For selective growth, both plates and broths were supplemented with 100 µg/mL ampicillin.

Competent E. coli DH5α transformation

Chemically competent DH5α *Escherichia coli* cells (sourced from Life Technologies) were transformed following the supplier's instructions. Plasmid-containing bacterial colonies were cultured on ampicillin plates (100 µg/mL) for a duration of approximately 16 hours at 37°C. Selected bacterial colonies were subsequently cultivated in LB broth supplemented with 100 µg/mL ampicillin, using either small (5 mL) or larger volumes (200–500 mL), depending on the experimental scale. Plasmids were isolated using Qiagen kits and eluted in TE buffer.

Cell culture

HEK293T cells were maintained in high-glucose DMEM enriched with 10% bovine serum, L-glutamine (2 mM), and antibiotics (penicillin and streptomycin, 10 µg/mL), and incubated at 37°C in a humidified atmosphere containing 5% carbon dioxide. A total of 2×10^7 cells were plated into T162 flasks and cultured under standard conditions until reaching approximately 80–90% cell density prior to transfection. Medium was collected 48 hours after transfection, replaced with fresh DMEM, and harvested again at 72 hours. For viral titration, $1–2 \times 10^5$ cells were plated individually into separate compartments of a 24-well tissue culture dish and transduced with serially diluted virus stocks, achieving a multiplicity of infection (MOI) ranging from 1 to 10^{-5} per µL. Detached cells were treated with PBS and Tryple Red reagent, and neutralized with serum-based medium. For flow cytometry, cells were fixed in 4% formaldehyde-PBS, shaken, and placed at 4°C in darkness until they were analyzed.

Mouse embryonic carcinoma cells culture

P19 cells were maintained in Dulbecco's Modified Eagle Medium supplemented with 2 mM glutamine, 1% non-essential amino acids, 10% FBS, and antibiotics (penicillin and streptomycin, 10 µg/mL), under standard incubation conditions (37°C, 5% CO_2). Neuronal differentiation was initiated by culturing embryoid bodies in suspension using DMEM supplemented with 5% FBS and a final concentration of 1 micromolar retinoic acid, applied at a cell density of 1×10^5 per milliliter. F9 cells were cultured in gelatin-coated flasks using DMEM supplemented with fetal bovine serum, antibiotics to prevent contamination, and L-glutamine to support cell metabolism. Differentiation toward extraembryonic endodermal lineage was induced by culturing cell aggregates in DMEM/F12 supplemented with 5% FBS and 50 nM retinoic acid at a density of 1×10^5 cells per milliliter.

Reporter gene analysis

Within the lentiviral system, UCOE and A2UCOE-driven eGFP reporter constructs were introduced into P19 and F9 cells, and the persistence of gene activity was assessed before differentiation as well as during their development into neural and endodermal cell types. Differentiated embryoid bodies were transferred to laminin-coated coverslips in 6-well plates. Immunofluorescence staining was performed post-differentiation to assess the expression of reporter genes.

A minimum of 2×10^5 preserved cells were examined for green fluorescent protein expression using a BD FACSymphony™ flow cytometer. Viable cells were identified by assessing their size and granularity through forward and side scatter measurements. Subsequently, GFP+ cells were distinguished by detecting fluorescence emission at 525 nm relative to 575 nm, with non-transduced cells serving as controls to accurately define positive gating. This approach estimates the proportion of live cells within the sample that are actively expressing GFP. The fraction of GFP+ cells was correlated with the amount of virus applied to each sample and extrapolated to determine the number of cells infected by the viral preparation, allowing for the calculation of the multiplicity of infection (MOI) based on mean fluorescence intensity.

For accuracy, values between 1% and 20% GFP-positive cells were selected. Higher percentages likely indicate multiple viral integrations per cell, which can lead to an underestimation of viral titre, while lower percentages may be unreliable due to background fluorescence interference.

Statistical analyses

Statistical analyses were conducted using Prism version 7. Statistical analysis of eGFP+ flow cytometry, MFI, and vector copy number estimation results of transduced cell cultures was performed using Student's t-test. A threshold of $p < 0.05$ was used to determine statistical significance.

RESULTS

The experimental approach aimed at testing the UCOE two-component model involved the use of unmethylated CpG islands and dual transcribed regions, including the SETD3-CCNK gene duo—commonly involved in basic cellular functions—and an engineered combination of RPS11 with HNRPA2B1 regulatory sequences. These sequences were connected in both directions to the silencing-prone SFFV-eGFP reporter to assess their potential for preventing gene expression repression (Figure 1). Although partial protection was noted when compared to the benchmark 1.5A2UCOE-SFFV-eGFP construct, the observed effectiveness remained modest, especially in P19 and F9 cells, throughout the undifferentiated as well as the differentiated conditions. Testing A2UCOE fragments (450–950 bp) positioned before the SFFV-eGFP sequence, regardless of promoter presence, did not preserve the complete UCOE activity. Sequences originating within the initial intronic region of *CBX3*, characterized by a high density of CpG sites but lacking promoter function, showed minimal ability to prevent gene silencing. However, a 0.9-kb subcore fragment of the 1.5-kb A2UCOE, encompassing the transcriptional start sites of CBX3 and HNRPA2B1, provided partial resistance to silencing. These findings suggest that both natural (SETD3-CCNK) and artificial (RPS11-HNRPA2B1) dual promoters exhibit partial UCOE activity, but their protective effects are weaker than the HNRPA2B1-CBX3 prototype.

To further explore the impact of these UCOEs, test vectors were generated using a lentiviral system engineered for reduced self-activation, incorporating the SFFV regulatory sequence to control eGFP expression, along with the WPRE element (SEW). The 1.5 kb 1.5A2UCOE element derived from the HNRPA2B1-CBX3 locus was cloned upstream of the SFFV promoter via a polylinker (PL), generating the 1.5A2UCOE-SEW construct. To broaden the panel of candidate UCOEs, the endogenous SETD3–CCNK locus and an engineered divergent promoter segment combining RPS11 with HNRPA2B1 were bidirectionally cloned into the PL vector, producing constructs named SET-CCN-SEW/CCN-SET-SEW and B1-RPS-SEW/RPS-B1-SEW (Figure 1).

A self-inactivating LV containing an SFFV promoter responsible for initiating eGFP production (SEW) was employed to generate test UCOE vectors that include the WPRE regulatory sequence. A 1.5 kb segment of the HNRPA2B1-CBX3 UCOE (1.5A2UCOE) was introduced before the SFFV promoter via a polylinker, generating the 1.5A2UCOE-SEW plasmid. Promoter regions derived from the human *SETD3–CCNK* locus and the engineered *RPS11–HNRPA2B1* sequence were cloned in both orientations within the PL vector, resulting in the creation of constructs named SET-CCN-SEW/CCN-SET-SEW and B1-RPS-SEW/RPS-B1-SEW. (LTR refers to the long terminal repeat).

The efficiency of lentiviral transduction in the P19 cell line (at an MOI of 3, see Figure 2) was evaluated by assessing cells via flow cytometry at 72 hours following transduction (Figure 3). Cells lacking GFP expression are indicated in red, whereas GFP-expressing cells appear in green. Panels represent the following groups: (A) non-transduced control; (B) cells transduced with SEW; (C) cells transduced with 1.5A2UCOE-SEW; (D) cells transduced with SET-CCN-SEW; (E) cells transduced with CCN-SET-SEW; (F) cells transduced with B1-RPS-SEW; and (G) cells transduced with RPS-B1-SEW.

P19 cells were subjected to transduction using candidate UCOE vectors (SET-CCN-SEW, CCN-SET-SEW, B1-RPS-SEW, RPS-B1-SEW) alongside control vectors as illustrated in Figure 1. The analysis included

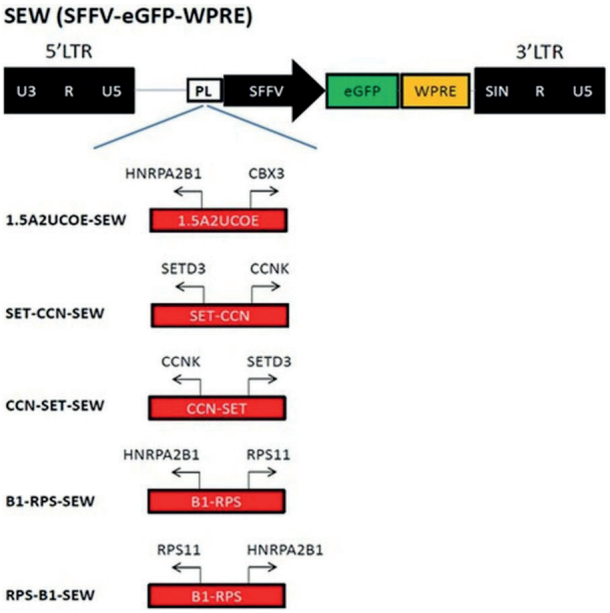

Figure 1. Representation of novel candidate UCOE and control lentiviral vectors.

the percentage of eGFP+ cells, their MFI, and the quantification of integrated vector sequences per cell. The data shown combine findings from three separate transduction experiments per vector and the NEG, collected over a period ranging from 3 to 52 days after transduction. (A) Percentage of eGFP+ cells tracked over the course of the experiment ($p<0.01$). (B) Changes in mean fluorescence intensity recorded across time points ($p<0.01$). (C) Average VCN per cell monitored longitudinally ($p<0.01$).

The transduction of F9 cells was performed using both experimental UCOE constructs (SET-CCN-SEW, CCN-SET-SEW, B1-RPS-SEW, RPS-B1-SEW) and control vectors (SEW and 1.5A2UCOE-SEW), as illustrated in Figure 1. Flow cytometry was used to assess eGFP+ cell percentage, MFI, and VCN. The results combine findings from three independent transduction experiments for each vector and NEG, tracked from day 3 to day 52 post-transduction. (A) Timeline of the percentage of eGFP+ cells (mean ± SEM, based on four samples; **$p<0.01$). (B) Changes in mean fluorescence intensity over time (mean ± SEM, based on four samples; $p<0.01$). (C) Average vector copy number per cell throughout the study period (mean ± SEM), based on four samples; $p<0.01$).

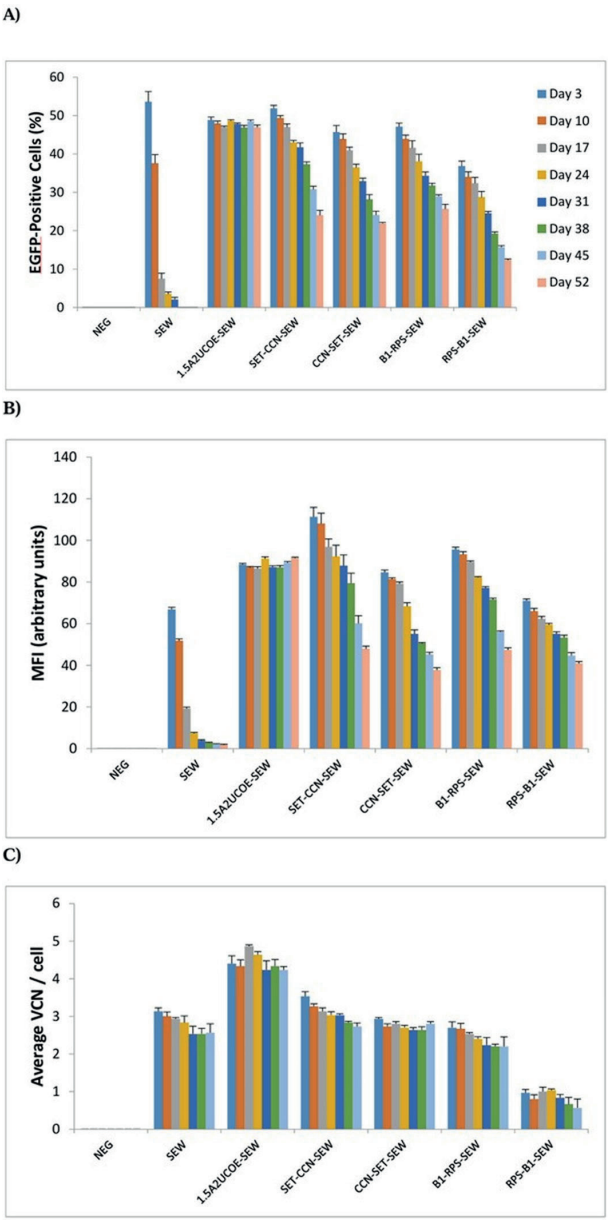

Figure 2. Novel candidate UCOEs provide only partial protection against silencing in undifferentiated P19 cells. (A) Percentage of eGFP+ cells tracked over the course of the experiment, (B) Changes in mean fluorescence intensity recorded across time points, (C) Average VCN per cell monitored longitudinally.

P19 cells underwent genetic transduction with potential UCOE vectors alongside control vectors (SEW and 1.5A2UCOE-SEW), as illustrated in Figure 1, and were induced to differentiate into the neuroectodermal lineage 72 hours following transduction. Flow

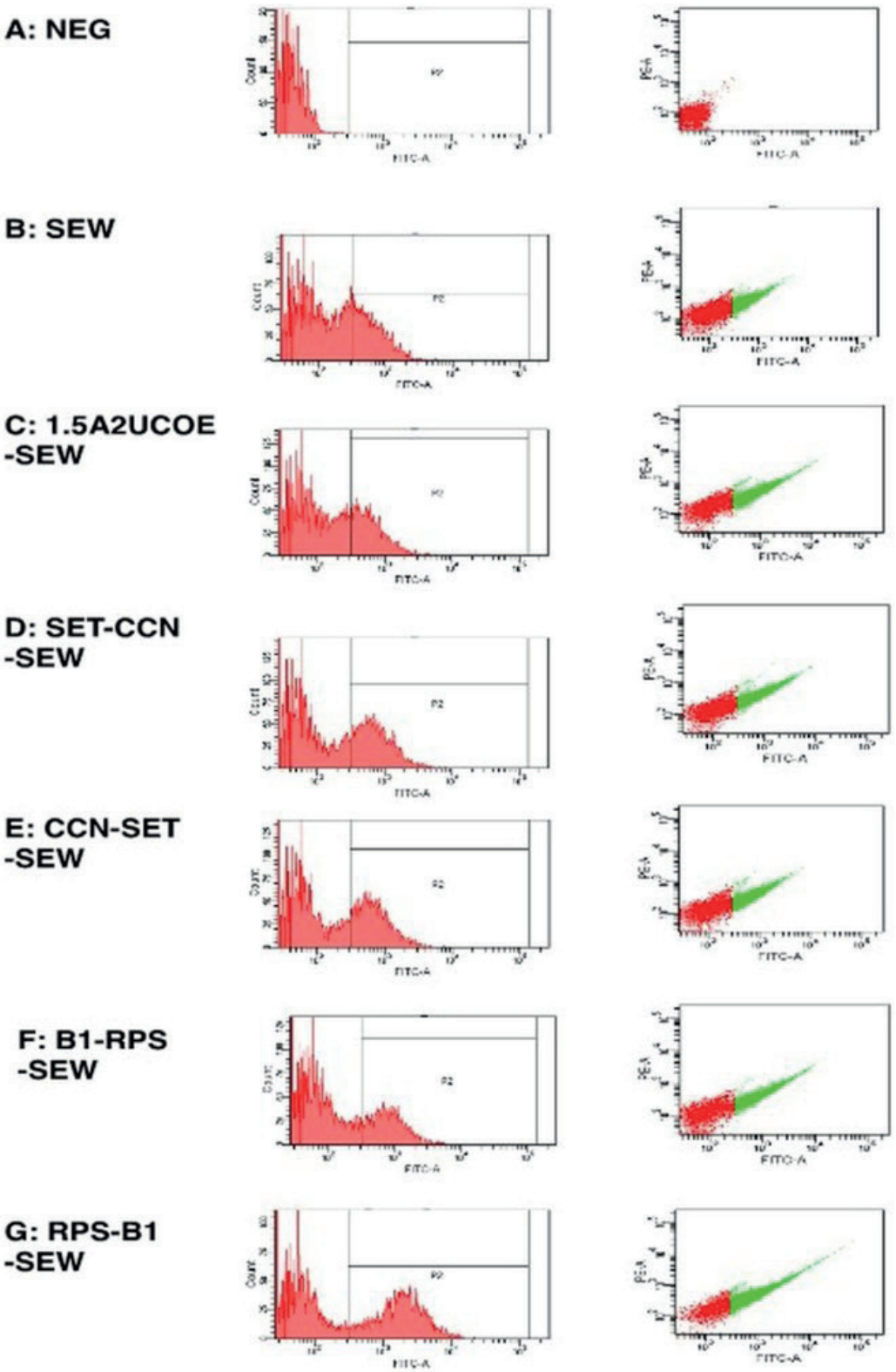

Figure 3. Untransduced and transduced P19 array flow cytometry plots.

cytometry was used to analyze eGFP+ cell percentage and MFI, while VCN was assessed using real-time qPCR at various time points post-differentiation. Data are presented as the aggregate of three separate transduction experiments conducted for each vector, including NEG, monitored from day 3 to day 45 after transduction. (A) eGFP+ cell percentage timeline; ($p<0.01$). (B) MFI timeline ($p<0.01$). (C) Mean VCN/cell timeline ($p<0.01$).

Selected UCOE vectors (SET-CCN-SEW, CCN-SET-SEW, B1-RPS-SEW, RPS-B1-SEW), along with control vectors (SEW and 1.5A2UCOE-SEW), were used to transduce F9 cells (Figure 1). Seventy-two hours after transduction, cells were stimulated to differentiate toward the endodermal lineage. Flow cytometry was performed to measure the percentage of eGFP+ cells and MFI, while VCN was assessed using real-time qPCR at multiple intervals. The data represent combined results from three independent transduction experiments per vector, including NEG, collected between day 3 and day 41 after transduction. (A) eGFP+ cell percentage timeline ($p<0.01$). (B) MFI timeline ($p<0.01$). (C) Mean VCN/cell timeline ($p<0.01$). The findings at 3 days post-transduction reflect the undifferentiated state of the cells.

To confirm the flow cytometry findings (Figures 2-6), P19 and F9 cells that had differentiated into neuroectodermal and endodermal lineages, respectively, were labeled with specific markers and examined using fluorescence-based immunostaining techniques (Figures 7, 8).

P19 and F9 cells were transduced with newly developed UCOE vectors alongside control vectors (Figure 1), and were induced to differentiate along the neuronal and endodermal lineages 3 days post-transduction. Cultures were then analyzed by flow cytometry according to eGFP fluorescence reference points. The results showed that novel UCOE candidates indicated partially stable activity after differentiation compared to the A2UCOE control vector (Figure 9, 10).

P19 cells were transduced with novel UCOE vectors (SET-CCN-SEW, CCN-SET-SEW, B1-RPS-SEW, RPS-B1-SEW) and control vectors (SEW, 1.5A2UCOE-SEW)

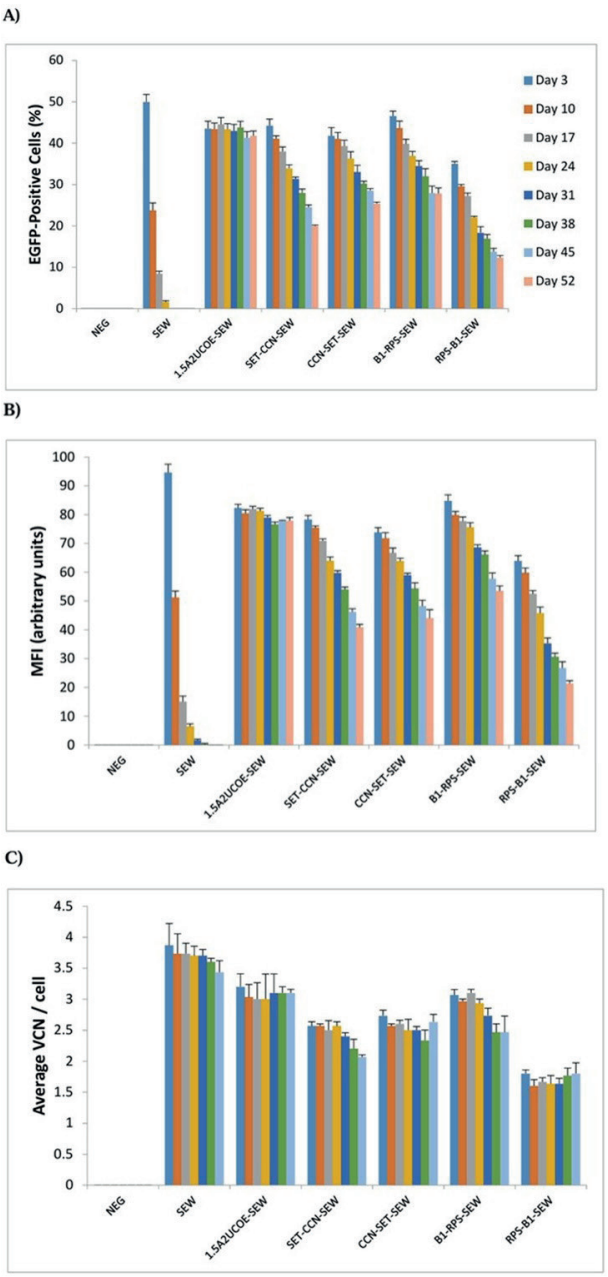

Figure 4. Novel candidate UCOEs provide only partial protection against silencing in undifferentiated F9 cells. (A) Timeline of the percentage of eGFP+ cells, (B) Changes in MFI over time, (C) Average VCN per cell throughout the study period.

(Figure 1). The cells were subsequently induced to differentiate toward the neural ectodermal pathway three days after vector delivery. Fluorescence

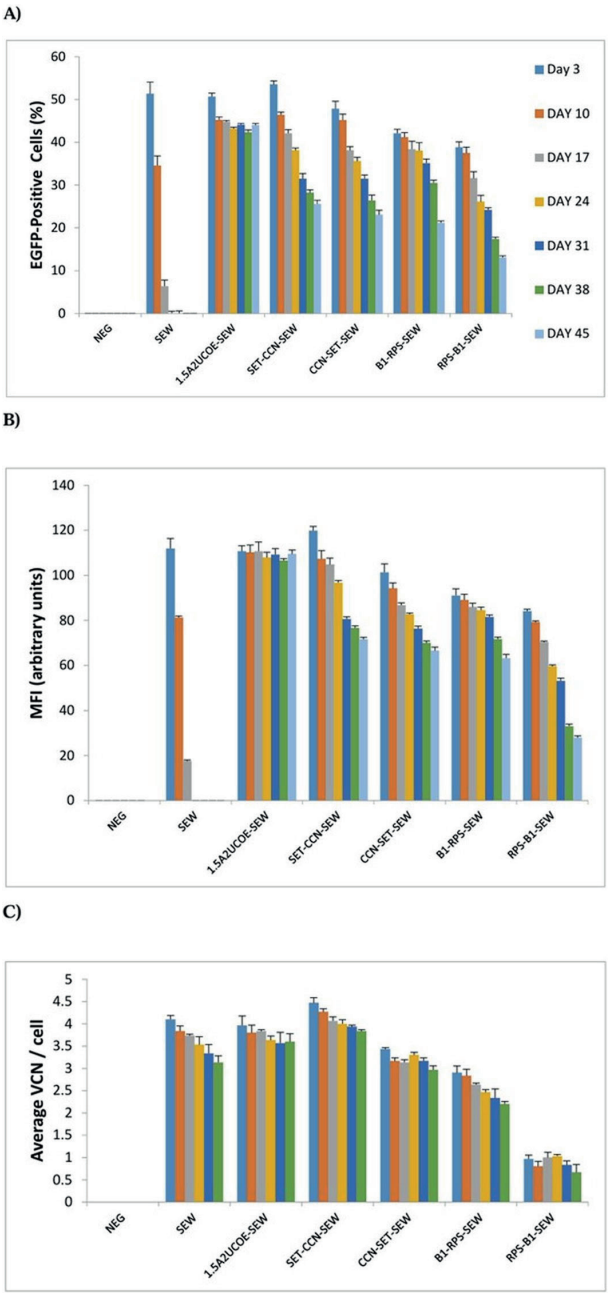

Figure 5. Novel candidate UCOEs provide only partial protection against silencing in differentiated P19 cells. (A) eGFP+ cell percentage timeline. (B) MFI timeline, (C) Mean VCN/cell timeline.

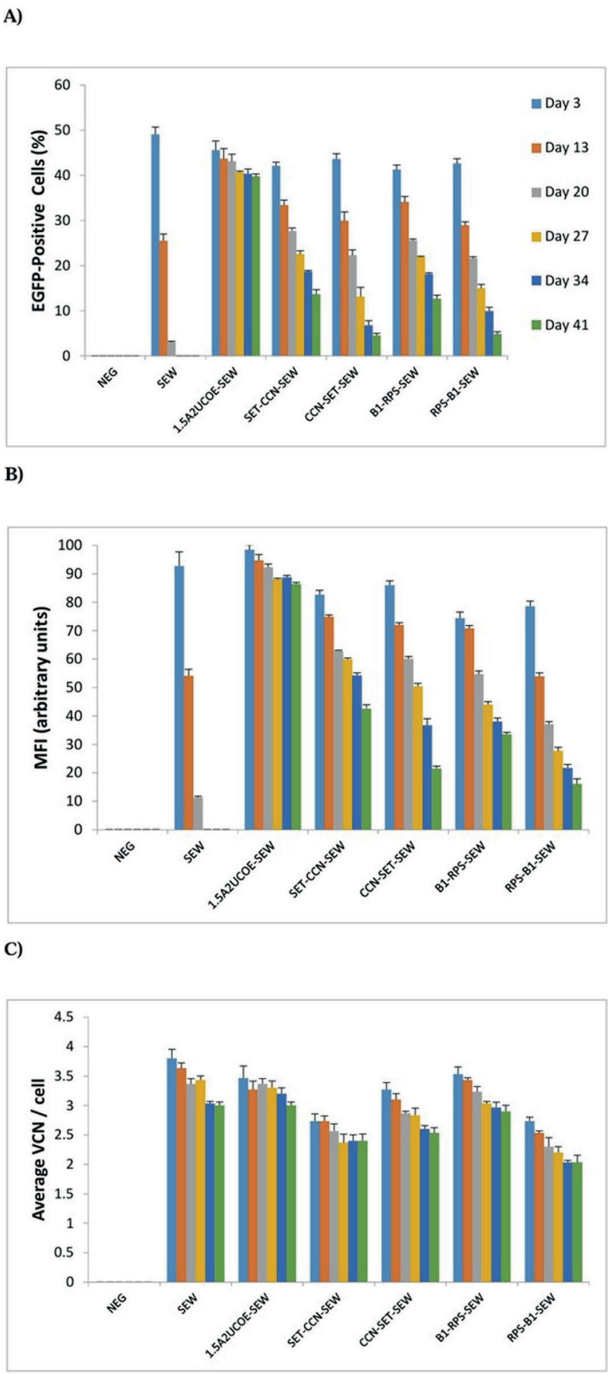

Figure 6. Novel candidate UCOEs provide only partial protection against silencing in differentiated F9 cells. (A) eGFP+ cell percentage timeline, (B) MFI timeline, (C) Mean VCN/cell timeline.

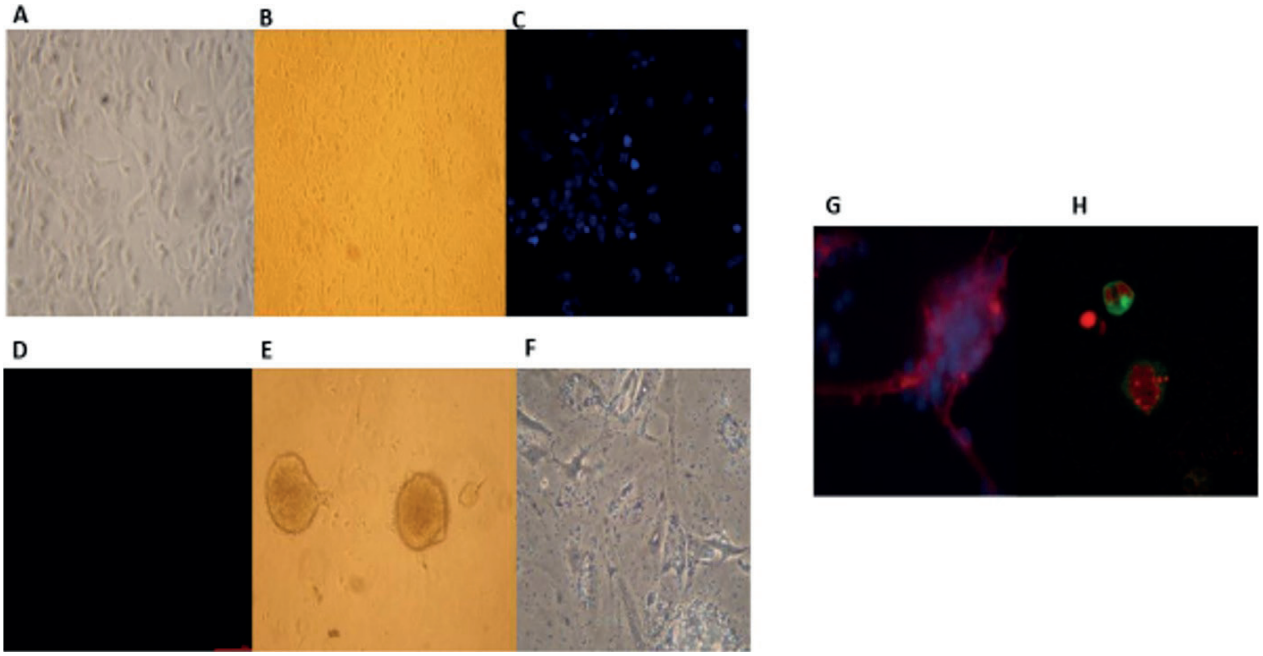

Figure 7. Microscopic Visualization of Undifferentiated and Differentiated P19 Cells

A–B: Phase-contrast microscopy images of undifferentiated and non-transduced P19 cells captured at 40× magnification.

C–D: Fluorescent labeling of the same cell population using DAPI (C) and anti-β-III tubulin (D), visualized at 40× and 100× magnifications, respectively. Cells exhibit positive nuclear staining with DAPI (blue), while showing no detectable expression of neuronal marker β-III tubulin (red) or GFP signal (green).

E–F: Formation of embryoid-like aggregates after 48 hours of culture in non-adherent conditions (E; 40× magnification). Differentiating cells were subsequently replated onto adherent surfaces and imaged after four days of neuroectodermal induction (F; 100× magnification).

G–H: Dual immunofluorescence analysis of P19 cells transduced with UCOE-eGFP vector following neuroectodermal differentiation. Panel G shows co-localization of DAPI (blue) and β-III tubulin (red), while Panel H displays β-III tubulin (red) alongside eGFP signal (green); both at 100× magnification.

microscopy was used at selected intervals to assess cells co-expressing eGFP and β-tubulin III. The findings are based on the pooled outcomes of three separate transduction experiments conducted for each vector and the negative control group, spanning a 3 to 24-day observation period. Analysis revealed statistically meaningful differences ($p < 0.01$)

F9 cells were transduced with novel UCOE vectors and control vectors (Figure 1), then induced to differentiate along the endodermal lineage 3 days post-transduction. Cells were analyzed by fluorescence microscopy at various time points, scoring for eGFP and anti-Oct3-4 double-positive cells. Data represent combined results from three independent transductions for each vector and the NEG over 3–24 days ($p<0.01$).

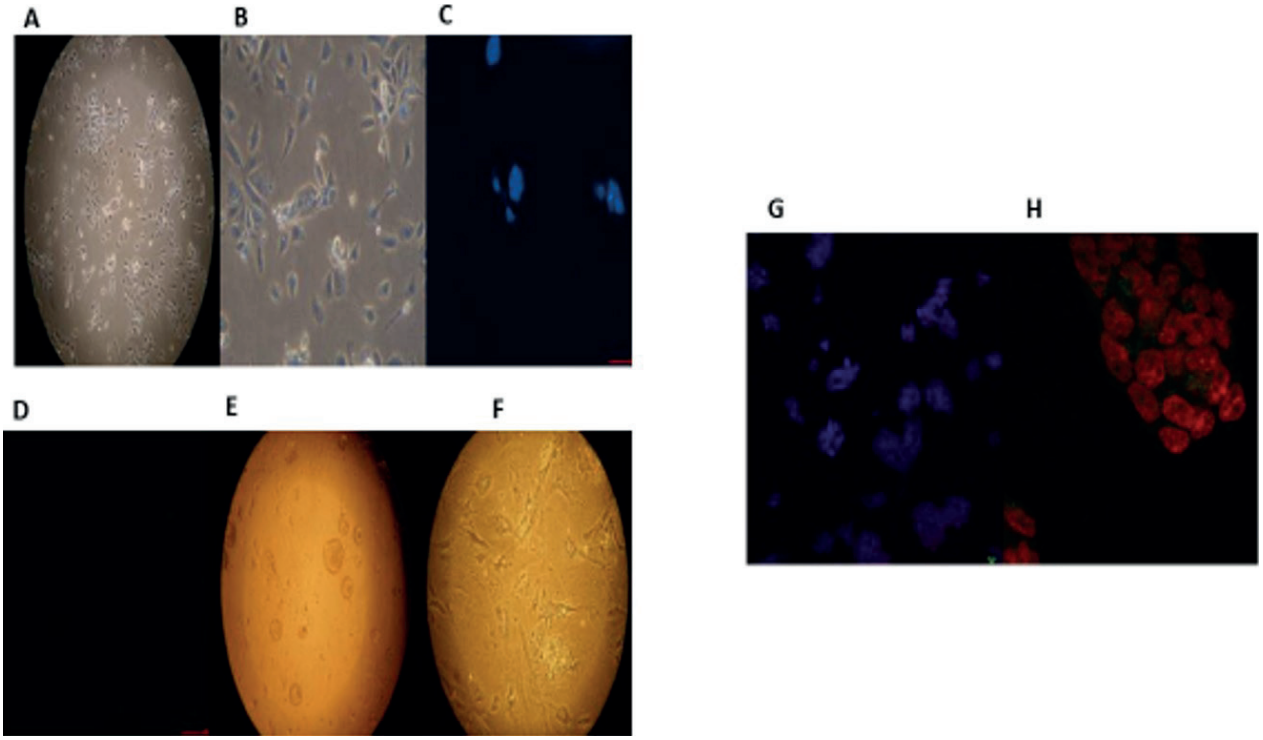

Figure 8. Morphological Examination of F9 Cells Prior to and Following Differentiation.

A-B: Phase contrast images illustrating the morphology of undifferentiated and non-transduced F9 cells at 20x (A) and 40x (B) magnifications.

C-D: Immunofluorescent labeling of undifferentiated F9 cells with nuclear stain DAPI (C) and anti-Oct3/4 antibody (D), both captured at 40x magnification. Cells exhibit DAPI-positive nuclei (blue), but no detectable Oct3/4 (red) or eGFP (green) signal.

E-F: Formation of embryoid bodies following 2-day suspension culture on non-adherent bacterial-grade dishes (E; 40x) and differentiated F9 cells after 5 days of endodermal induction, subsequently plated on adherent tissue culture surfaces (F; 100x).

G-H: Immunofluorescence analysis of F9 cells following endodermal differentiation and lentiviral transduction with UCOE-eGFP constructs. G: Nuclear (DAPI, blue) and Oct3/4 (red) staining shown at 20x magnification. H: Co-localization of Oct3/4 (red) and eGFP expression (green) visualized at 100x magnification.

DISCUSSION

This stage of the study focused on determining whether the newly designed UCOEs operate in accordance with the bidirectional transcriptional mechanism previously attributed to A2UCOE elements (17-19). Additionally, the experiments were designed to assess whether these UCOEs could ensure sustained gene expression when positioned adjacent to a non-native promoter, regardless of the DNA strand orientation in which they were inserted. The A2UCOE has been demonstrated to stabilize gene expression at linked promoters, both ubiquitous(16,18) and tissue-specific(20,21), generally requiring a specific alignment, especially when the CBX3 terminus lies adjacent to the linked promoter. The hypothesis of this study proposed that the two promoters within each chosen gene pair would exhibit comparable expression levels across various tissues, aiming to address the problem related to orientation dependency.

Integrating gammaretroviral and lentiviral vector classes remain the most effective approach to ensure consistent maintenance and expression of a therapeutic gene. This is particularly applicable when focusing on mitotically active stem cell populations. In fact, over the past 15 years, clinical trials employing an ex vivo strategy targeting HSCs with these vector types have consistently demonstrated successful outcomes (4). However, the use of these integrase classes involves two critical challenges that must always be considered.

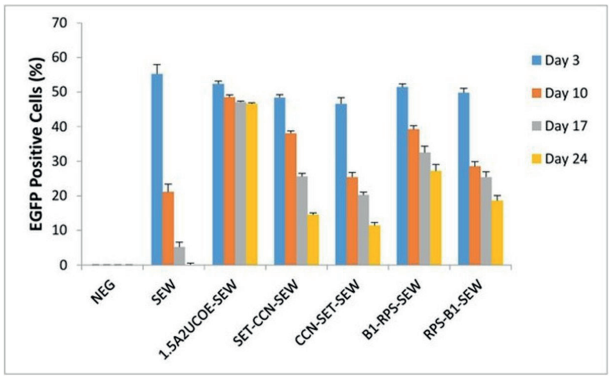

Figure 9. Novel candidate UCOEs provide only partial protection against silencing in differentiated P19 cells.

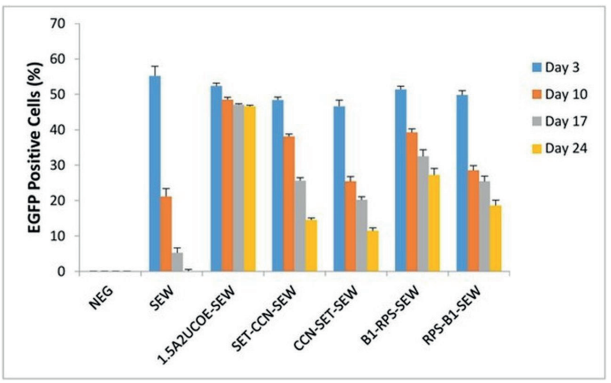

Figure 10. Novel candidate UCOEs provide only partial protection against silencing in differentiated F9 cells.

The first is insertional mutagenesis, and the second concerns therapeutic gene inactivation mediated by epigenetic mechanisms (3). Notably, gammaretroviral integration caused insertional mutagenesis in 5 out of 20 SCID-X1 patients, which led to unintended activation of host proto-oncogenes and subsequent oncogenesis (22). Additionally, therapeutic gene inactivation caused by methylation of promoter DNA eventually led to the loss of therapeutic efficacy in two individuals treated for CGD (23).

The findings were encouraging, as stable expression driven by the SFFV promoter was preserved in both configurations of the SETD3-CCNK element as well as the synthetic HNRPA2B1-RPS11 pair, independent of their orientation (Figures 3 and 10). This observation supports the hypothesis that orientation might not be as critical if both promoters exhibit similar expression profiles. The stability of the new candidate UCOE vectors and controls was evaluated in both undifferentiated and differentiated P19 and F9 cells (representing neuroectodermal and endodermal lineages, respectively). This study extends previous work by examining not only undifferentiated P19 cells but also differentiated cells, which have been less frequently studied in prior research (16,24).

The results showed that while both SETD3-CCNK and HNRPA2B1-RPS11 elements contributed to maintaining expression from the SFFV promoter, they were less effective than the positive control UCOE vector in preventing gene inactivation. Specifically, expression from the RPS-B1-SEW LV vector decreased the most rapidly, indicating less stability. In contrast, the positive control UCOE vector provided excellent, stable expression not only in undifferentiated P19 and F9 cells but also in differentiated neuroectodermal and endodermal lineages. These results confirm the robustness of the 1.5A2UCOE-SEW vector in preserving stable transgene expression during both cell types' differentiation, which aligns with findings from Zhang, Frost et al. (16).

The underlying mechanism enabling the A2UCOE to ensure both consistent and stable gene expression, independent of the transgene's integration site, involves two key elements: a prolonged CpG-free region resistant to methylation, alongside the inherent chromatin-opening properties of the HNRPA2B1 and CBX3 promoters (25,26). Consequently, the goal was to discover a compact yet fully active A2UCOE variant suitable for integration into lentiviral vectors, thus allowing for greater capacity to accommodate therapeutic genes. Previous studies have shown that positioning the core 1.5 kb or 1.2 kb A2UCOE sequence upstream of various heterologous promoters enhances expression stability in an orientation-dependent fashion. Specifically, this stability is achieved when the CBX3 end of the A2UCOE is adjacent to heterologous ubiquitous promoters such as SFFV (16) and EF1α (25), or the tissue-specific MRP8 promoter (27).

The orientational dependence observed in A2UCOE functionality has been attributed to the comparatively lower transcriptional strength of the CBX3 promoter relative to HNRPA2B1 (28). Consequently, the stronger activity of the HNRPA2B1 promoter in a divergent transcriptional arrangement is thought to create a more effective barrier, preventing the spread of repressive epigenetic modifications such as DNA methylation and histone changes to the transgene region, thereby maintaining gene expression (29). To evaluate this theory, our initial experimental series was designed with the goal of identifying UCOEs that possess a bidirectional transcriptional architecture and can operate effectively in either orientation when linked to heterologous promoters. We hypothesized that directional preference issues in UCOE-heterologous promoter combinations might be overcome if both promoters within selected gene pairs exhibited comparable expression levels and variability across different tissues.

In conclusion, while the new candidate UCOEs demonstrated some protective ability, they did not perform as well as the original A2UCOE, particularly in preventing silencing. Therefore, further investigation will focus on dissecting the 1.5A2UCOE structure to identify specific subregions critical to its function. These insights will guide future developments of more effective UCOE elements for gene therapy applications, aiming to enhance the stability and reproducibility of transgene expression.

CONCLUSION

This study supports the dual-component hypothesis of A2UCOE function, highlighting the key role of CpG-rich, bidirectional promoter architecture in maintaining stable transgene expression. Both the natural SETD3–CCNK and synthetic RPS11–HNRPA2B1 pairs exhibited partial UCOE-like activity, providing orientation-independent resistance to silencing in undifferentiated and differentiated P19 and F9 cells. However, the canonical 1.5A2UCOE element performed superiorly, indicating additional sequence-specific features are required for full potency. The HNRPA2B1–CBX3 promoter asymmetry likely enhances chromatin opening and transcriptional stability. These findings validate simplified UCOE-like elements and guide future research toward identifying minimal subregions for optimized, reliable therapeutic gene expression.

Ethical approval

In this study, ethical approval is not required.

Author contribution

Surgical and Medical Practices: ÖFA; Concept: ÖFA; Design: ÖFA, AOA; Data Collection or Processing: ÖFA; Analysis or Interpretation: AOA; Literature Search: ÖFA, AOA; Writing: ÖFA, AOA. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLES

Evaluation of the efficacy and safety of bipolar cauterization of the orbicularis oculi muscle for the purpose of reshaping: A retrospective, controlled, clinical study

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ABSTRACT

Aim: We aimed to compare the aesthetic results and safety profile of bipolar coagulation of muscle during blepharoplasty with those of blepharoplasty with muscle resection.

Materials and Methods: This retrospective study included patients who underwent isolated upper eyelid blepharoplasty. The patients were divided into two groups according to the blepharoplasty technique: patients who had muscle resection (Group A) and patients who had muscle contraction with bipolar cautery (Group B). The data were obtained from patient files and photograph archives. The photographs of the patients were evaluated by two independent plastic surgeons. The Visual Analysis Scale/Score (VAS) was used to evaluate the safety profile, And the Global Aesthetic Improvement Scale (GAI) was used to evaluate the aesthetic results. The scores were compared between the two groups.

Results: The mean VAS scores of Group A were 5.21 for edema, 4.95 for bruising, 0.91 for scar, 0.67 for fold loss, and 0.86 for asymmetry. Same scores for Group B were 5.43 for edema, 4.83 for bruising, 0.87 for scar, 0.63 for fold loss, and 0.79 for asymmetry. The mean GAI scores were 3.82 at 3 months and 3.76 at 12 months for Group A, and 4.19 at 3 months and 4.12 at 12 months for Group B. There was no statistically significant difference between the groups for VAS ($p>0.05$), but there was a statistically significant difference for GAI ($p<0.05$).

Conclusion: We state that in the upper lid blepharoplasty, bipolar cautery coagulation technique could be applied as an alternative to muscle and soft tissue resection.

Keywords: blepharoplasty, bipolar cautery, eye aesthetics, orbicularis oculi muscle, periorbital rejuvenation

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INTRODUCTION

Upper blepharoplasty is the gold standard procedure for the management of dermatochalasis and for restoring youthful contours to the periorbita (1). It is among plastic surgery's most common procedures in the US and ranks third in surveys (2). It might be predicted that the number of blepharoplasty operations performed in today's society, which is trying to prevent the undesirable effects of normal aging, will probably increase in the coming years.

In aged individuals the supratarsal fold tends to degenerate, which can cause elevation of the crease, lid ptosis, and skin laxity of the upper lid (3). During upper lid blepharoplasty, excess skin resection for the purpose of skin laxity treatment is applied to almost every patient today as a gold-standard technique. However, no consensus has yet been reached on the management of herniated muscle and periorbital soft tissue or on the actions that should be taken to replace the palpebral crease (4).

It is obvious that laxity in the upper eyelid soft tissue, which appears as a result of periorbital aging, affects the aesthetic appearance of patients. However, no gold-standard technique for the management of the deformity in question has yet been established.

In this study, we aimed to compare the aesthetic results and safety profile of bipolar coagulation blepharoplasty (BCB) technique, which is based on the principle of coagulating periorbital muscle and soft tissue with bipolar cautery, with those of blepharoplasty with muscle resection (MRB). Additionally, we aimed to share our department's 10 years of experience with the BCB technique.

MATERIALS AND METHODS

Patients who underwent isolated upper eyelid blepharoplasty in our clinic between the years 2013 and 2022 were analyzed retrospectively. Patients who had simultaneous lower eyelid surgery, patients who had additional interventions other than blepharoplasty on the upper eyelid such as brow lift or ptosis correction surgery, patients who previously underwent upper eyelid surgery, patients who were not followed up regularly for at least 1 year, and patients whose photos of the operative period could not be accessed appropriately were excluded from this study.

The patients included in the study were divided into two groups according to the blepharoplasty technique applied: those who had orbicularis oculi muscle resection (MRB) and those who had muscle contraction with bipolar cautery coagulation (BCB). Patients who could not be included in either of these two groups were excluded from the study.

All surgical procedures were performed by the senior author.

Surgical technique

Surgical markings were performed while the patients were sitting. In patients with frontal hyperactivity, drawings were done after blocking the frontal muscle manually. The lower border of the skin excision was marked at least 7 mm above the orbital fissure, with care taken to preserve the upper tarsus. While the patients' eyes were in open and closed positions, the excess skin amount was determined using the pinch technique, and the upper excision border was marked. The surgical marking was designed so that the skin excision did not extend beyond the medial canthus in all the patients. The lateral border was adjusted according to the excess skin amount of the patient. The final scar was designed to remain within the eyelid crease (Figure 1).

The operations were performed under local anesthesia (20mg/ml lidocaine hydrochloride + 0.0125mg/ml epinephrine). The local anesthetic solution was infiltrated under the skin to be excised to provide hydrodissection.

After local infiltration, the starting incision was made with a surgical blade in accordance with the drawings. The skin to be excised within the incision was resected with a scalpel using a technique similar to full-thickness skin graft harvesting. Even if the muscle tissue was unveiled, it was left intact in all patients during the skin resection (Figure 2).

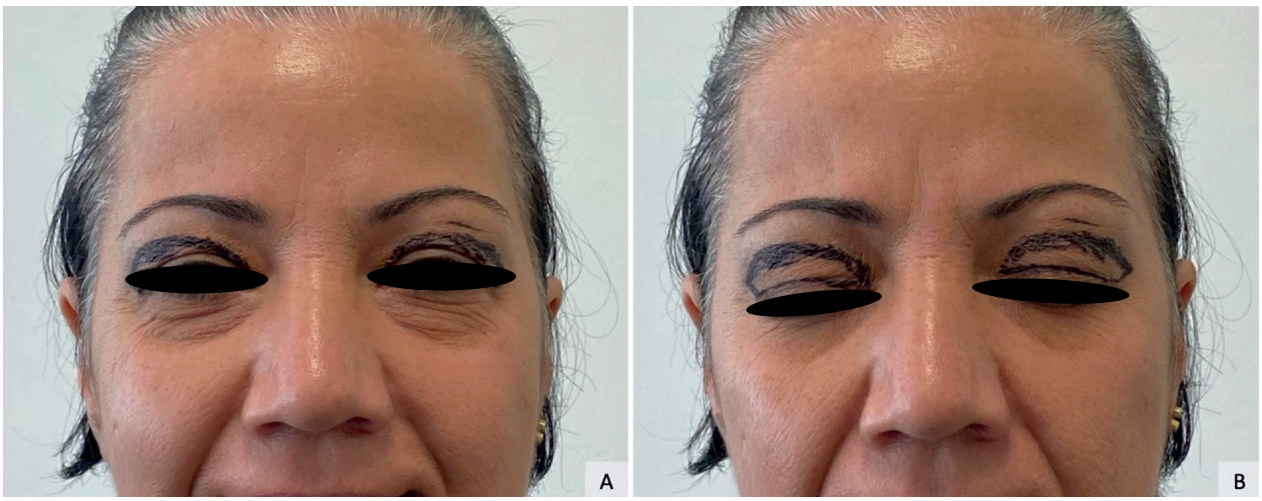

Figure 1. 47 years old, female patient. Surgical markings have been just performed. Excess skin was determined by pinch test. A-) eyes are open. B-) eyes are closed. Patient consent about using the photographs in scientific publications has been obtained

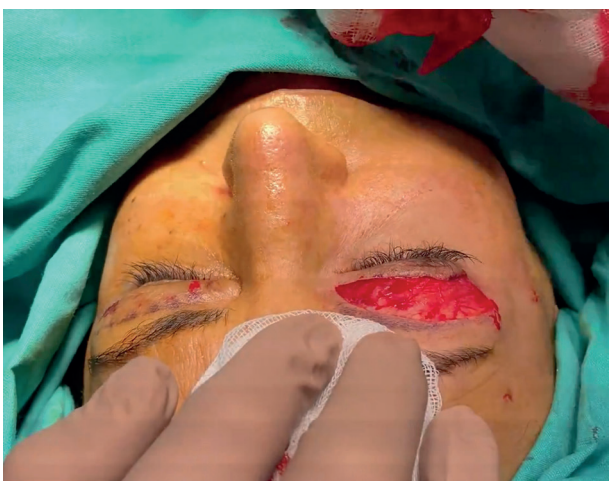

Figure 2. 43 years old, female patient. Intra-operative view of orbicularis oculi muscle. The muscle is completely exposed. Patient consent about using the photographs in scientific publications has been obtained.

In the BCB technique, after exposure of the muscular layer, linear bipolar coagulation was applied on the muscle to create the newly designed eyelid crease line, for the management of excess soft tissue under the skin (Video 1). As a result of coagulation, shrinkage of the orbicularis oculi muscle, the orbital septum, and the fatty tissue below the septum was observed. Due to this shrinkage, the distance between the upper and lower incision edges decreased.

In the MRB group, the excess amount of muscle was resected using scissors (Figure 3). Bipolar cautery was used only for hemostasis in this group, if necessary. After muscular resection, muscle incision lines were sutured with 5-0 vicryl sutures.

In patients deemed necessary, after a 5 mm length incision, only the medial fat pad was excised with the pull-through technique, limited to those patients in both groups for whom fat excision was considered necessary. Fat pads were left intact in all other patients. After bleeding control, the skin was closed using primary 6-0 polypropylene suture.

Sterile strips were applied to upper eyelids at the end of the operation. The patients were discharged with prescriptions for antibiotics and anti-inflammatory treatment. On the 7th day post-op, the sterile strips were opened and the sutures were removed.

All patients were followed up regularly at the first week, second week, first month, third month, sixth month and first year after the operation. During follow-ups, standard photographs were taken (Figure 4, Figure 5).

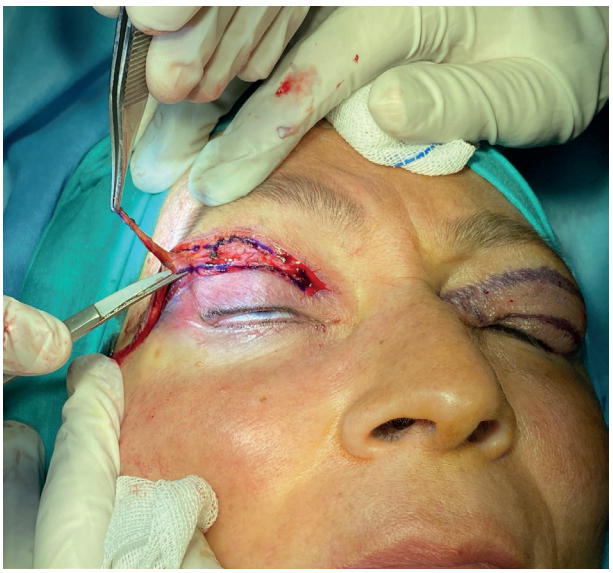

Figure 3. 41 years old, female patient. Intra-operative view during the resection of orbicularis oculi muscle. Patient consent about using the photographs in scientific publications has been obtained

All patient data were obtained from patient files and photographic archives. Patient photos were evaluated by two independent plastic surgeons who had no knowledge of the groups and patients.

The Visual Analysis Scale/Score (VAS), which is a line marked from 0 to 10 points, was used to evaluate the safety and side effect profile of the surgery (5). Bruising and edema were evaluated in photographs taken on the 7th day post-op to assess early side effects. For the late period side effects, scarring, palpebral asymmetry and fold loss were evaluated in the photographs taken at the 12th month post-op. The scores were compared between the two groups. In addition, other major and minor complications not included in this scale were also noted.

The Global Aesthetic Improvement Scale (GAI) was used to evaluate the aesthetic results (5). According to this scale, the photographs of the patients taken at the third and 12th months were rated by two independent, blinded plastic surgeons. The score range was between

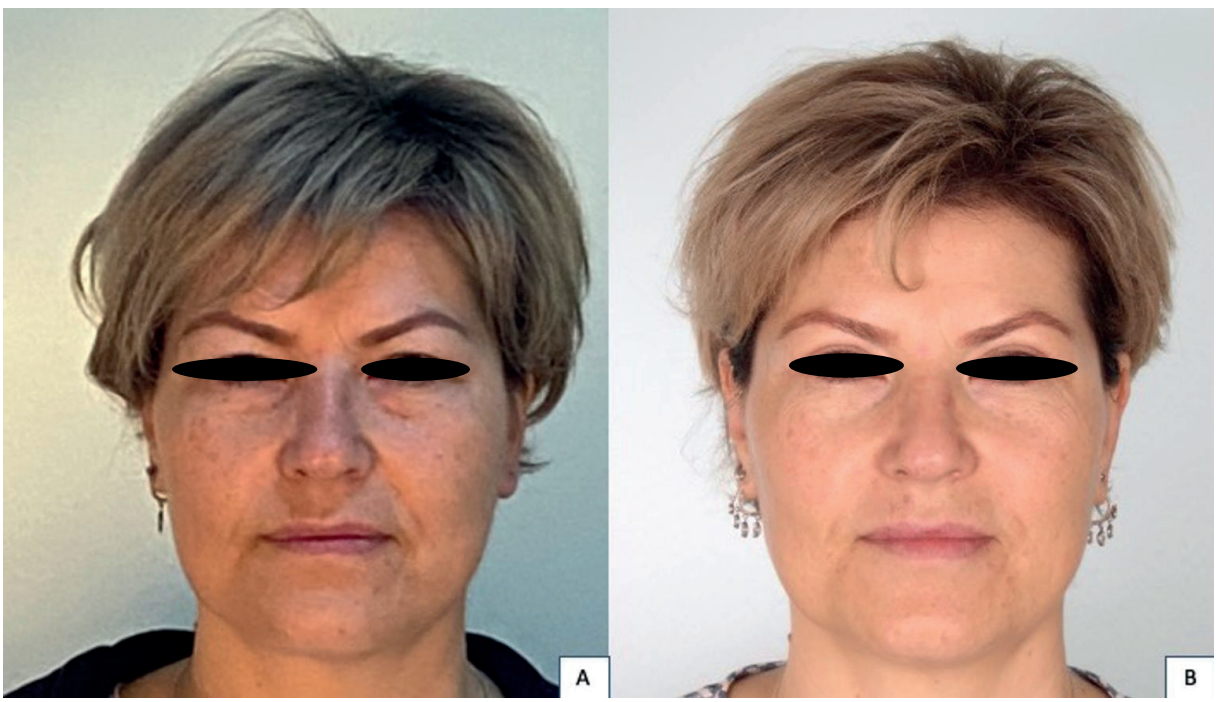

Figure 4. 49 years old, female patient who underwent blepharoplasty with bipolar coagulation of orbicularis oculi muscle A-) pre-operative view of upper eyelids. B-) 12th month post-op view. In post-operative view, upper eyelid fullness and newly designed palpebral creases are seen clearly. Patient consent about using the photographs in scientific publications has been obtained

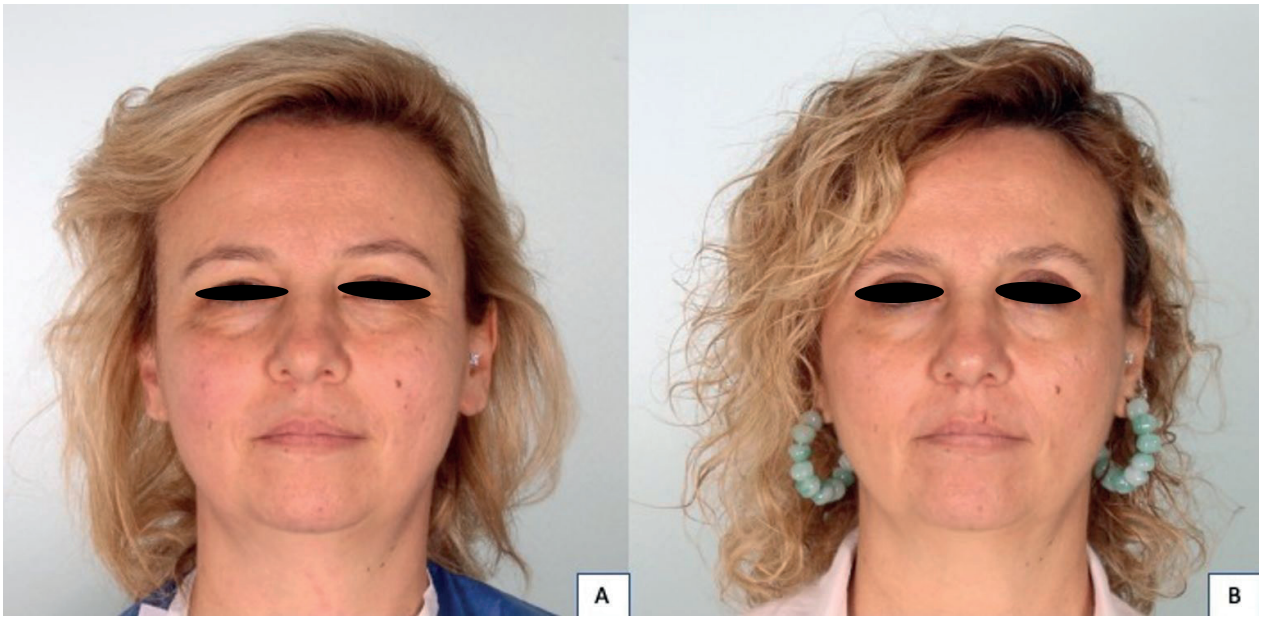

Figure 5. 52 years old, female patient who underwent blepharoplasty with only skin resection A-) pre-operative view of upper eyelids. B-) 12th month post-op view. Patient consent about using the photographs in scientific publications has been obtained

1 and 5. Details of the scale can be seen in Table 1. The scores were compared between the two groups.

Consent for the use of patient data in scientific studies was taken from all participants of the study. Signed confirmation for the publication of their photographs was taken from the patients whose photographs were used in this paper.

Statistical analysis

The statistical significance of the differences between the mean values was analyzed using SPSS 27.0 (USA) statistical software. An independent sample t test was used to compare the VAS and GAI scores between the groups, and paired t test was used to compare the VAS and GAI score changes for each group between sessions. P values < 0.05 were considered statistically significant.

RESULTS

A total of 322 patients, 237 women and 85 men, were included in this study. The mean age of the patients was 53.68 (min 38-max 74). The mean follow-up duration was 14.5 months (min 12 – max 38). Group A consisted

Table 1. Global Aesthetic Improvement Scale scoring system of groups

Score	Situation	Comment
1	Very much improved	Optimal cosmetic result in this patient
2	Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this patient
3	Improved	Obvious improvement in appearance from the initial condition, but a small corrective surgery is suggested
4	No change	The appearance is essentially the same as the original condition
5	Worst	The appearance is worse than the original condition

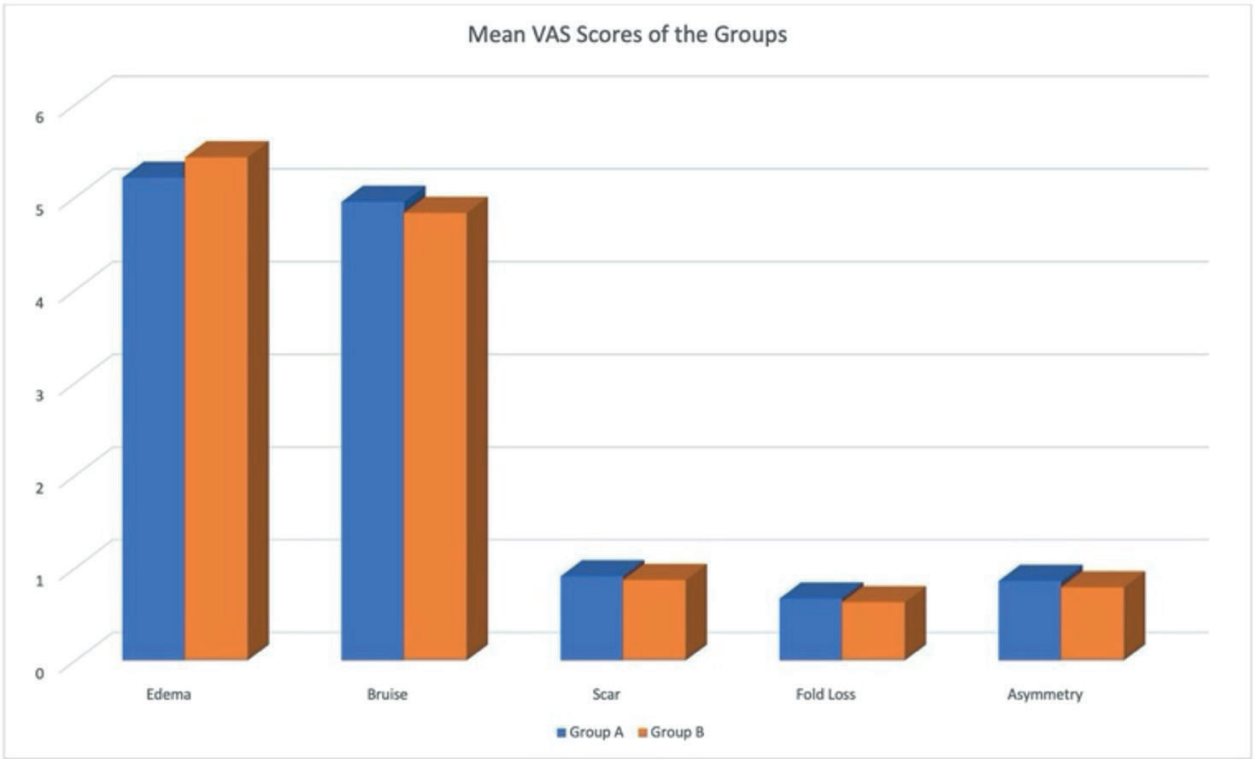

Figure 6. The graphic shows Mean Visual Assessment Scores (VAS) of the groups

of 143 patients who underwent MRB, while Group B consisted of 179 patients who underwent BCB.

The mean VAS scores of Group A were 5.21 (min 1 - max 8) for edema, 4.95 (min 2. - max 7) for bruising, 0.91 (min 0 - max 2) for scar, 0.67 (min 0 – max 3) for fold loss, and 0.86 (min 0 -max 5) for asymmetry. The corresponding scores for Group B were 5.43 (min 2 - max 8) for edema, 4.83 (min 2 - max 8) for bruising, 0.87 (min 0 - max 2) for scar, 0.63 (min 0 - max 2) for fold loss, and 0.79 (min 0 - max 4) for asymmetry (Figure 6). There was no statistically significant difference between the groups for VAS scores ($p>0.05$).

When we analyzed other complications that occurred in the groups, no major complication was observed in any patient in either group. Postoperative prolonged edema (more than 6 weeks) was observed in two patients in Group B and in one patient in Group A. In addition, one patient in Group A had unilateral incomplete closure of the eyelid, which was thought to have developed due to muscle skin removal. However, complete recovery without additional surgical intervention was observed at post-operative 6th week control. There wasn't any complaints about orbicularis oculi functions or dry eye in any patient.

The mean GAI scores were 3.82 (min 3 – max 5) at three months and 3.76 (min 2 - max 5) at 12 months for Group A, and 4.19 (min 3 – max 5) at three months and 4.12 (min 3 – max 5) at 12 months for Group B. When the data obtained were analyzed statistically, it was seen that Group B had superior aesthetic results compared with Group A, at both the third and 12th months ($p<0.05$).

DISCUSSION

The treatment of excess soft tissue in the upper blepharoplasty has not yet been clearly standardized. In recent studies, new techniques are being tried and recommended in this regard. For upper blepharoplasty, it is known that the complication rate and aesthetic results are at an acceptable level, even when one of

the techniques that has been used for many years is applied (6). The search for new techniques is not aimed at reducing complications, but rather at achieving better aesthetic results while preserving the existing physio-anatomy and functions.

Skin excess and laxity are seen in almost every blepharoplasty patient. For this reason, skin resection is a method preferred by nearly all surgeons who perform upper lid blepharoplasty. However, it is impossible to talk about a similar consensus for subcutaneous tissues. The fact that this consensus has not been formed suggests that the ideal method has not yet been defined.

While various authors have suggested the excision of excess muscle and periorbital adipose tissue, some authors have argued that this procedure should not be performed (1,4,7,8). Proponents of resection and excision state that, as a result of these procedures, the crease is regenerated gracefully and the supratarsal definition increases (4), whereas the opposing authors argue that such resection reduces eyelid fullness, which provides a youthful appearance (7). The rationale for performing both muscle and skin resection, or skin resection alone preserving the muscle, remains uncertain (1).

It is known that the amount of periorbital adipose tissue decreases with aging (9). In fact, fat excision during blepharoplasty accelerates this component of aging. However, laxity of the orbicularis oculi muscle and the orbital septum can be considered the cause of prolapsus of the adipose tissue, rather than excess fat (10). For this reason, the desired result can be obtained by preventing laxity in the covering tissues instead of performing fat resection (11).

Muscle resection is a safe and reliable technique in blepharoplasty patients. However, the side effects of coagulation and contraction of muscle with bipolar cautery are not well known. In our study, there was no statistical difference between the two groups, either in the VAS scores for side effects and safety or in the number of other major complications. Consequently, it can be thought that the BCB technique is as reliable as blepharoplasty with muscle resection, which has been used for years.

We have been using BCB technique for about 10 years as a method to treat laxity of the periorbital soft tissue. We have also performed muscle resection on many patients. Our observation over time was that patients who underwent bipolar cautery tightening showed higher aesthetic satisfaction. Therefore, we investigated this retrospectively. The results of our study also showed a statistically significant difference in this regard. Accordingly, we can say that while bipolar coagulation is no different from muscle resection in terms of safety, it is more successful in terms of aesthetic results.

Our purpose in evaluating the third month and 12th month scores of the patients in the study was to compare the short-term and long-term results of blepharoplasty. There was no difference in aesthetic results between the third and 12th months. According to our findings, the effects of contraction achieved with the BCB method continued for at least one year.

In a previous study, only one strip of orbital muscle was resected, and then the orbital septum and soft tissue behind the muscle were coagulated with bipolar cautery (8). In that study, it was reported that the aesthetic results were at a satisfactory level. Nevertheless, the absence of a control group was a limitation of that study. In our study, it was shown that it is possible to treat excess and laxity in the orbicularis muscle with a similar method, without muscle resection. Longitudinal cauterization of the orbicularis muscle in the palpebral crease region results in fibrosis over time, and it strengthens the orbital septum by providing support to it.

The VAS and GAI scales used in our study provide subjective data. However, the reason these scales were preferred in this study is that evaluations made with standardized measurements in eyelid evaluation do not fully reflect the aesthetic result. Therefore using other methods such as questionnaires or photographic evaluations has been recommended to researchers (12).

Muscle resection performed during blepharoplasty does not result in functional problems with blinking, closing eyes, tear production and distribution (13,14). Similarly, none of these complications related to

orbicular muscle function were observed in our direct coagulation method. This may be explained by the fact that the orbicularis muscle is innervated by the facial nerve branches that enter the muscle laterally and are oriented in a horizontal direction. Thus, horizontally directed coagulation does not damage the structural and functional integrity of other muscle fibers and motor units, while only affecting the coagulated muscle fibers.

One of the disadvantages of our study is that, as it was a retrospective study, we didn't have standardized criteria regarding the management of the muscles. However, the senior surgeon applied bipolar cauterization if she needed to reduce the soft tissue amount intraoperatively. If clear standardized criteria for the approach to the muscular layer had existed, our study would have been more scientifically valuable.

Considering the data obtained from our study, it can be thought that the contraction occurring after bipolar coagulation has an effective function in the restructuring of the orbicularis muscle. In addition, bipolar coagulation causes shrinkage of the orbital septum and muscle, resulting in the immediate desired disappearance of bulging. In this context, coagulation with bipolar cautery could be considered as a method that might be applied to patients with muscle laxity and bulging in soft tissue.

In conclusion, we state that in the upper lid blepharoplasty, muscle and soft tissue management with the bipolar cautery coagulation technique could be applied as an alternative to muscle and soft tissue resection in patients with orbital muscle and orbital septum laxity and related soft tissue herniation.

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Ethical approval

This study has been approved by Necmettin Erbakan University Clinic Research Ethical Commitee (approval date 20/09/2024, number 2024/5193). Written informed consent was obtained from the participants.

Author contribution

Surgical and medical practices: MSK, ZKA; Concept: MSK, ZKA; Design: MSK; Datacollection or Processing: MSK; Analysis or Interpretation: MSK, ZKA; Literature Search: MSK; Writing: MSK, ZKA. Aşş authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLES

Evaluation of the accuracy of ChatGPT-generated information in the field of general audiology

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ABSTRACT

Aim: This study evaluates the accuracy and reliability of ChatGPT's responses to open-ended questions in otology and audiology, focusing on its potential use in training ear, nose, and throat (ENT) professionals. As artificial intelligence (AI) applications like ChatGPT become more accessible to healthcare professionals and the public, ensuring that the information provided is reliable, accurate, and reproducible is crucial, especially in the medical field.

Materials and Methods: In March 2024, 60 audiology-related questions, categorized as 'general audiology,' 'hearing,' and 'balance,' were posed twice using ChatGPT (version 4) on the same computer to assess reproducibility. The responses were recorded as the '1st' and '2nd' answers. Three ENT specialists independently evaluated the answers to ensure accuracy, with a third reviewer specializing in audiology assessing the agreement between the responses. Answers were categorized as 1 (completely correct), 2 (partially correct), 3 (mixed accuracy), or 4 (incorrect). Analyses were conducted separately for each subgroup.

Results: Statistically significant difference was found between the two responses in general audiology questions ($p = 0.008$) and across all responses collectively ($p = 0.002$), while no significant difference was observed in hearing and balance questions ($p > 0.05$). The second responses had higher accuracy rates, with 65%, 80%, and 70% accuracy for general audiology, hearing, and balance areas, respectively.

Conclusion: ChatGPT's second responses were more accurate and reliable, making it a valuable resource for clinicians despite occasional misleading answers. With continued advancements, AI is expected to become a more reliable tool in audiology.

Keywords: answer, artificial intelligence, audiology, Chat-GPT, head and neck surgery

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INTRODUCTION

Artificial intelligence applications have recently developed rapidly and have become available in the field of health and medical sciences as well as in many other fields. Since these applications can be accessed by health professionals and all segments of the society, it is thought that they may indirectly affect human health. Therefore, it is very important that the information provided by such applications is reliable, accurate and reproducible for its applicability in medical fields.

One of the most recent artificial intelligence applications is the Chat Generative Pre-trained Transformer (ChatGPT) program.

ChatGPT is a new artificial intelligence model designed to generate human-like conversational dialog and can generate answers to textual inputs/questions from a large database of information (websites, books and recent articles) (1-3). ChatGPT, which has a large language model trained by Open AI (Artificial Intelligence) on internet-sourced data and a very large information source, has a highly developed ability to answer questions and translate between languages, as well as the ability to create conversations on various topics. Thanks to this feature, it can be used in both medical and non-medical fields (1-4).

Since applications in the medical field and the information sources accessed require high responsibility and reliability, it is of great importance to develop an artificial intelligence model with accurate and reliable medical knowledge (5). There are studies evaluating the ChatGPT application in terms of medical exams, clinical evaluation and diagnosis, and article writing (6-9).

While some researchers consider the medical information provided by ChatGPT to be valuable, others have distanced themselves from this issue due to misuse during medical writing, security, plagiarism, inability to ensure the accuracy of the information and legal problems that may arise (10-12).

When the studies in the field of Ear, Nose and Throat Diseases (ENT) are reviewed; artificial intelligence studies have been reported in clinical grading systems, evaluation of cochlear implant function, clinical management of parathyroid gland diseases, prediction of clinical prognosis of some diseases, and determination of accuracy and reliability of information about head and neck cancers (4,6,13). In the field of audiology, there are a limited number of studies on ChatGPT (14,15).

Our aim in this study is to determine the accuracy and reliability of ChatGPT's answers to open-ended questions posed in the field of otology and audiology and subdivided into subgroups within the field and to determine whether this artificial intelligence application can be used in the training of ENT professionals.

MATERIAL AND METHOD

In March 2024, 60 questions related to the field of audiology were asked to ChatGPT (Chat GPT version 4) in 3 sub-headings.

The questions to be used in the study were categorized in 3 basic areas: 'general audiology', 'hearing' and 'balance'. The questions were adapted from general ENT and audiology reference books and questions used in board examinations. A total of 60 questions were prepared, 20 open-ended questions in English in each field.

An example question for each subheading area is provided below:

1. What is the concept of audiometric zero? Please explain.
2. Please explain the clinical signs and symptoms of vestibular neuritis.
3. What are the current treatment modalities for sudden hearing loss?

The questions were asked twice, one after the other, from the same computer, each time with a 'new chat' function to assess reproducibility. The answers were recorded as '1st and 2nd answer' (shown in the Supplementary File).

All answers from the ChatGPT were evaluated by 3 different, active, ENT specialists (reviewers) who were not in contact with each other during the evaluation phase. All questions were checked simultaneously by 3 different reviewers to exclude individual factors, to minimize the margin of error of the examiners and to ensure that the answers were evaluated accurately. The agreement between the 1st and 2nd answers was assessed by the 3rd reviewer (an expert with specific studies in audiology).

In order to ensure standardization in the evaluation of the answers, the answer categorization determined in a previous study by Kuşcu et al. was used (4). According to this scheme, answers were categorized as 1 (Completely correct), 2 (Partially correct), 3 (A mix of accurate and inaccurate/misleading), 4 (Completely incorrect/ irrelevant). All analyses were performed separately for all questions according to the subheadings in each of the three groups.

Statistical analysis

The analysis of the data included in the study was performed with SPSS (Statistical Program in Social Sciences) 27 program. Descriptive statistics were calculated as number, percentage, mean, standard deviation, median and min-max.

Inter-measurement consistencies and analyses were determined by intraclass correlation coefficient (ICC, intraclass correlation coefficient: 0.80-1.0 very high correlation) and Kruskall Wallis H Test and Wilcoxon Sign Test (p; statistical significance, $p<0.05$; there is a statistically significant difference between groups).

RESULTS

Harmonization between reviewers

When the responses received from ChatGPT were analyzed by three reviewers, the intra-group ICC was used to examine the consistency of the reviewers' decisions. For answer 1, the ICC is 0.994, while for answer 2, the ICC is 0.991, indicating that the raters are highly consistent in their decisions for both answers. (Table 1)

Table 1 presents the classification of responses to questions by three independent reviewers,. Both the first and second responses were evaluated separately, and inter-reviewer agreement was analyzed using p-values and intraclass correlation coefficients (ICC).

For the first responses, the proportion of responses deemed *completely correct* ranged from 65.0% to 66.7% across reviewers. *Partially correct* responses accounted for 26.7% to 28.3%, while *mixed* responses were minimal (1.7%), and *completely incorrect* responses were only 5.0%. The p-value was calculated as 0.918, indicating no statistically significant differences among reviewers' classifications. Furthermore, the ICC value of 0.994 demonstrates an exceptionally high level of inter-rater reliability for the first responses.

Table 1. Harmonization between reviewers

Questions			Completely correct, n%	Partially correct, n%	Mix of accurate - inaccurate/ misleading, n%	Completely incorrect/ irrelevant, n%	p	ICC
Total	1. Answer	1	39(65.0)	17(28.3)	1(%1.7)	3(5.0)	.918	.994
		2	40(66.7)	16(26.7)	1(%1.7)	3(5.0)		
		3	40(66.7)	16(26.7)	1(%1.7)	3(5.0)		
	2. Answer	1	43(71.7)	13(21.7)	4(6.7)		.980	.991
		2	43(71.7)	12(20.0)	5(8.3)			
		3	43(71.7)	12(20.0)	5(8.3)			

ICC: intraclass correlation coefficients.

Similarly, for the second responses, *completely correct* answers were consistently rated at 71.7% by all reviewers. *Partially correct* classifications ranged between 20.0% and 21.7%, while *mixed* responses varied slightly from 6.7% to 8.3%. Notably, *completely incorrect or irrelevant* responses were absent in this round. The p-value of 0.980 again indicates no statistically significant differences between reviewers, and the ICC value of 0.991 reflects a strong level of agreement.

Repeatability

The questions were asked twice to the Chat GPT and it was examined whether the 1st and 2nd answers were compatible with each other, in other words, the repeatability of the application. This evaluation was done separately for each question category. The Wilcoxon sign test was used to compare whether there was a statistically significant difference between the 1st and 2nd answers in all areas. The rates of agreement in the answers to the questions asked in each of the three fields were 65% (13 compatible, 7 incompatible answers), 90% (18 compatible, 2 incompatible) and 80% (16 compatible, 4 incompatible answers) for general audiology, hearing and balance fields, respectively.

When evaluated in terms of all categorized answers, a statistically significant difference was found between the 1st and 2nd answers (p=0.002). When analyzed according to the sub-headings, a statistically significant difference was found between both answers, especially in general audiology questions (p=0.008). No significant difference was found in the other two sub-headings (p>0.05) details are shown in table 2.

Table 2 illustrates the concordance between ChatGPT's first and second answers (harmony) and the accuracy rates of those answers according to expert evaluations (controller compliance). For each subheading (General Audiology, Hearing, and Balance), it reports both the number and percentage of concordant answers, the accuracy of each answer, and the p values for their comparison.

Concordance Rates (1st vs. 2nd answers):

- General Audiology: 65% concordance (13/20), p = 0.008 → Significant difference
- Hearing: 90% concordance (18/20), p = 0.157 → Not significant
- Balance: 80% concordance (16/20), p = 0.083 → Not significant
- Total: 78% concordance (47/60), p = 0.002 → Overall significant difference

Accuracy According to Expert Evaluations (1st & 2nd answers):

- The 1st answers were found to be 95–100% accurate across all areas.
- The 2nd answers showed similarly high accuracy rates (97–100%).

Table 2. Concordance analysis of 1st and 2nd answers from ChatGPT

Subject	Harmony	Controller Compliance	
	n(%)	1. Answer, n(%)	2. Answer, n(%)
General Audiology	13(%65)	20(%100)	19(%95)
P	.008*	1.00	.992
Hearing	18(%90)	20(%100)	20(%100)
P	.157	1.00	1.00
Balance	16(%80)	19(%95)	20(%100)
P	.083	.950	1.00
Total	47(%78)	59(%98)	58(%97)
P	.002*	.979	.998

- No significant differences were detected between these accuracy rates ($p > 0.9$).

Overall, ChatGPT's first and second answers exhibit a high level of concordance (78%). However, in the General Audiology domain there is a statistically significant difference between the two rounds of answers ($p = 0.008$), suggesting slightly lower repeatability in this area. Expert evaluations confirm that both sets of answers are largely accurate, underscoring the high quality of content. In conclusion, ChatGPT's responses are generally consistent and reliable, though some subdomains—especially General Audiology—may require closer attention to repeatability.

Evaluation of answers according to categorization - accuracy rates

All three reviewers evaluated 2 answers each as completely wrong (4) for the 1st answers in the general audiology domain, no completely wrong (4) evaluation was made for the 2nd answers. In the field of hearing, no completely wrong (4) assessment was made for answers 1 and 2. In the field of balance, 1 answer was evaluated as completely wrong (4) by all 3 controllers for the 1st answers (5%). In the 2nd answers, no completely wrong (4) assessment was made.

It was observed that the accuracy rates of the 2nd answers were higher for all subheadings. Based on the 2nd answers, the accuracy rates were 65%, 80% and 70% for general audiology, hearing and balance areas, respectively.

Details are shown in Table 3.

Commentary on Table 3:

- **General Audiology:**
  - In the 1st answers, 65% were completely correct (category 1) and 10% were completely incorrect (category 4).
  - In the 2nd answers, the completely correct rate remained at 65%, while completely incorrect responses dropped to 0%.
  - This suggests that critical errors present in the first round were corrected in the second.
  - ICC = 0.985 and p = 0.944 confirm high inter rater consistency and no significant change in category distribution.
- **Hearing:**
  - In the 1st answers, 75% were completely correct and none were completely incorrect.
  - In the 2nd answers, the completely correct rate rose to 80%, with 0% completely incorrect.
  - ICC = 1.00 and p = 1.00 indicate perfect agreement and no distributional differences between rounds.
- **Balance:**
  - In the 1st answers, 55% were completely correct and 5% completely incorrect.
  - In the 2nd answers, the completely correct rate increased to 70%, and completely incorrect responses were eliminated.
  - ICC = 0.992 and p = 0.950 again demonstrate very high agreement and stable category distributions.

The elimination of completely incorrect responses and the stable or improved rates of completely correct answers in the second round indicate that ChatGPT's likelihood of critical errors decreases on repeat questioning. The consistently high ICC values across all fields further underscore strong inter rater reliability. In sum, Table 3 shows that the second answers are at least as accurate—and often more accurate—than the first ones, with a significantly reduced error rate.

DISCUSSION

Artificial intelligence applications have started to be used in many fields such as technology, industry, software and health. The use of artificial intelligence applications in the field of health constitutes an area where not only health professionals who are trained and serve in this field, but also individuals from all segments of society can easily access information because it is easily accessible and can be concluded quickly. Fast

Table 3. Evaluation of ChatGPT's responses by category in each field

Questions			1 n(%)	2 n(%)	3 n(%)	4 n(%)	p	ICC
General Audiology	1. Answer	1	13(65.0)	5(25.0)		2(10.0)	1.00	1.00
		2	13(40.0)	5(26.7)		2(13.3)		
		3	13(40.0)	5(26.7)		2(13.3)		
	2. Answer	1	13(65.0)	4(20.0)	3(15.0)		.944	.985
		2	13(65.0)	3(15.0)	4(20.0)			
		3	13(65.0)	3(15.0)	4(20.0)			
Hearing	1. Answer	1	15(75.0)	5(25.0)			1.00	1.00
		2	15(75.0)	5(25.0)				
		3	15(75.0)	5(25.0)				
	2. Answer	1	16(80.0)	3(15.0)	1(5.0)		1.00	1.00
		2	16(80.0)	3(15.0)	1(5.0)			
		3	16(80.0)	3(15.0)	1(5.0)			
Balance	1. Answer	1	11(55.0)	7(35.0)	1(5.0)	1(5.0)	.950	.992
		2	12(60.0)	6(30.0)	1(5.0)	1(5.0)		
		3	12(60.0)	6(30.0)	1(5.0)	1(5.0)		
	2. Answer	1	14(70.0)	6(30.0)			1.00	1.00
		2	14(70.0)	6(30.0)				
		3	14(70.0)	6(30.0)				

ICC: Intraclass Correlation Coefficient, p; Kruskall Wallis H Test p value.

and easy access to this summary information may also bring along misguidance of patients / patient relatives and possible ethical problems.

In the literature, there are studies on whether ChatGPT application can be a source of information for clinicians in different medical fields, health professionals in the learning process and patients / patient relatives, and in the study of Ayoub et al. It was noted that ChatGPT may contradict basic knowledge when giving medical advice, and this may create problems in terms of patient safety (16).

In the field of ENT, there are studies on the applicability of Chat GPT in different areas such as evaluation of clinical prognosis, staging of the disease, and diagnosis (1-6,13,17 -20).

It has the potential to provide rapid access to topics related to their fields for professionals receiving ENT specialty training and to be a resource for exams. For this reason, the study by Park et al. demonstrated that the interest in ChatGPT has increased in ENT education as in other medical fields (21). In this study, the effectiveness of ChatGPT in supporting clinical decisions, patient education, assisting in research and literature review was investigated and it was concluded that ChatGPT provides important information in clinical applications, but it has disadvantages such as data reliability, inability to perform physical examination and inaccurate information (21).

In the study of Qu et al. (6), it was reported that ChatGPT was inadequate as a diagnostic tool, in the study of Brennan et al. (22) it was reported to be a good supplementary source in ENT education, but in the study of Hoch et al. (8) it was reported to have

low accuracy rates in multiple-choice questions in ENT board exams. As a result, it has been reported in various studies that Chat GPT as a diagnostic tool shows a lower accuracy rate in diagnosis and triage compared to clinicians (6,8,23,24).

In the literature, there are studies evaluating the accuracy of answers by posing questions to artificial intelligence, as well as studies comparing different search engines (24,25).

In a study on balance, benign paroxysmal positional vertigo (BPPV) patient education materials obtained from traditional search engines (Google) and ChatGPT were compared and as a result it was found that the information in ChatGPT was harder to read, of lower quality, and more difficult to understand compared to the information in Google searches (25).

In another study comparing chatbots, Bellinger et al. (26) asked ChatGPT, ChatGPT Plus, Google Bard and Microsoft Bing questions about six rhinology topics such as epistaxis, chronic sinusitis, sinus infections, allergic rhinitis, allergies and nasal polyps and evaluated the answers with criteria such as readability, quality, understandability and applicability. As a result of this study, Bard and Bing provided higher readability, while ChatGPT Plus stood out in terms of quality and accuracy. Both chatbots showed advantages in providing understandable and actionable information for patients (25,26).

There are few studies on hearing and more have evaluated whether the Chat GPT can be a suitable source of patient information in this area (14,15). For example, one study reported that it could be used as an aid to medical documentation in cases of eustachian tube dysfunction (15).

In an article discussing the future applications of chatbots in hearing health, the possible use of these tools by patients, clinicians and researchers was discussed, and from the perspective of patients, Swanepoel et al. stated that chatbots can be used for initial screening, making recommendations for interventions, patient education and support, but the accuracy of the information should be ensured (27).

Patel et al. evaluated the performance of ChatGPT 3.5 and 4.0 on ENT (Rhinology) Standardized Board Examination questions in comparison with residents. They stated that ChatGPT4, which is a higher version, performed much better and that artificial intelligence applications may be useful in ENT education (28).

Chiesa-Estomba et al. stated that ChatGPT can guide the clinician in decision-making processes (planning of cialoendoscopy) (7).

In their study, Sireci et al. stated that Chat-GPT can guide the choice of optimal treatment (29).

Ayoub et al. compared whether ChatGPT and Google Search engine can be a resource for the rules and instructions that patients and their relatives should follow after pediatric ENT surgeries. It was emphasized that ChatGPT was inferior to Google Search engine, but it could be advantageous for both patients and clinicians when alternative sources of information are limited (16).

In their study, Riestra-Ayora et al. (GPT-3.5) employed a question-based evaluation approach to assess the accuracy and reliability of responses generated by ChatGPT on rhinologic pathologies. Their findings suggest that ChatGPT can serve as a valuable information source for health professionals (30). Kuşçu et al. examined the accuracy and reproducibility of ChatGPT's answers to the questions asked in the field of head and neck cancers and stated that the answers were largely accurate and reproducible (4).

Workman et al. stated that, in general, the ChatGPT answered more than 80% of the questions correctly and could be a resource (31).

In our study, ChatGPT was asked detailed, open-ended, interpretative and specific knowledge-based questions in the field of audiology to investigate whether this application can help in the education process or exam preparations in the field of ENT and audiology.

In the evaluation of the responses, the response categorization determined in the study by Kuşcu et al. (4).

Another scale that can be used in such studies is the Likert scale (32). However, we preferred to use the categorization of Kusçu et al.

In the Likert scale, which is another classification similar to this classification, the responses are categorized as (1 = extremely unsatisfactory, 2 = unsatisfactory, 3 = neutral, 4 = satisfactory and 5 = extremely satisfactory) (32).

As in our study, it is thought that a new ChatGPT evaluation scale can be created by basing future studies on this or similar classifications. For example, (33-35) evaluated the accuracy and reproducibility of ChatGPT's responses to a series of questions about tinnitus. Three open-ended questions (divided into two groups, comprising basic and more comprehensive information) were posed again at three and six months. It was found that the majority of responses received at three months were of a higher quality, and no change was observed in the responses at six months compared to those at three months.

In our study, the evaluation of the accuracy and reproducibility of ChatGPT's answers to the questions asked in the field of audiology was investigated by asking the questions 2 times in a row. Similar to the study of Jedrzejczak WW et al. it was observed that the accuracy rates of the answers to the questions asked for the second time were higher. This result is consistent with the result we found in our study. The advantage of our study is that we have more questions (35).

Since the accuracy rate was higher in the second answers to the questions asked twice to the ChatGPT, it can be concluded that the questions should be asked repeatedly to the ChatGPT to reach the correct answer. It was observed that the correct answers were higher in hearing and balance than in general audiology. This may be due to data overload or it may be interpreted as inadequacy in terms of repeatability and reliability.

Chat-GPT repeatability for hearing and balance questions was found to be high (90% and 80%, respectively). In the study conducted by Kuşcu et al. (4), the repeatability was 94.1%, which is comparable to the results observed in the hearing and balance domain in our study. The reproducibility in the general audiology domain was found to be 65% in our study, which was lower than that reported by Kuşcu et al (4).

This result may support that more objective data can be obtained by grouping the questions even within the field and this can be considered as another positive aspect of our study.

Another strength of our study is that there is no previous study specific to the field of audiology and the number of questions is the highest in this field. However, the preference for open-ended questions instead of multiple-choice questions may be a disadvantage since it requires interpretation and knowledge. This may negatively affect the accuracy rates of the answers to the questions.

For example, in the general audiology category, the 13th question;

"What do you think about a patient who underwent surgery due to middle ear pathology in the right ear, showing lateralization of Weber test to the left and bilateral positive Rinne tests on postoperative examination?" was evaluated as "Completely incorrect/irrelevant (4)" for the 1st answer and "Mix of accurate - inaccurate/ misleading (3)" for the 2nd answer.

Open ended questions, which do not specify a single correct answer and require interpretation and creativity, expand the model's probabilistic generation space. This increases the likelihood that, rather than reproducing high probability patterns from its training data, the model will deviate from context and introduce incomplete, misleading, or fabricated details ("hallucinations"). Moreover, because open ended prompts can admit many valid approaches, the model's outputs are harder to verify rigorously and lack clear source grounding, further raising error risk. Finally, higher sampling temperature and similar hyperparameter settings amplify response diversity at the expense of consistency, thereby increasing the chance of incorrect or incoherent answers.

In the literature, studies with open-ended and case discussion questions were found. This makes the

results of our study supportable with the literatüre (31,36).

Riestra-Ayora et al. (30) used 65 questions (rhinology questions), Habib G. Zalzal et al. (37) used 30 questions (pediatric ENT questions to inform patients and their relatives) and Ziya Karimov et al. (36) used 25 questions (case presentation). In our study, a total of 60 open-ended questions, 20 questions in each of the 3 areas, were used.

In the study of Zalzal et al. (37), it was observed that while the rate of complete accuracy was 56.7% in the first answers to open-ended questions, it increased to 96.7% in the answers received for the second time, and at the same time, it was stated that asking the questions twice enabled reaching the correct answer, and this result is similar to our study.

Hoch et al. reported that 57% of 2576 questions (479 multiple-choice and 2097 single-choice) were answered correctly and that single-choice questions were associated with a significantly higher rate of correct answers than multiple-choice questions. It was also emphasized that accuracy rates were lower for questions in audiology (71% incorrect answers) compared to other fields (8).

In our study, we found that the accuracy rate for questions in the field of general audiology was lower than in other fields.

CONCLUSION

While providing access to basic information in a specialized field such as audiology, caution may be required as accurate information may be confused with errors that non-expert users may find difficult to recognize. This information can be used for educational purposes, under the control of experts in the field.

It is indisputable that artificial intelligence will become an increasingly reliable source with the developments in technology and the studies to be carried out especially in the field of audiology. In addition to being a potential source of information for the time being, further studies are needed for it to become a useful tool in the decision-making process of clinicians in diagnosis and treatment.

Limitations

This study focuses on a specific version of ChatGPT, called GPT-4, and the responses it provided during a specific period. It is important to note that the results may vary with model updates. Comparative studies with different AI models may also be conducted in the future.

The responses were categorized based on accuracy, but the study did not analyze critical factors such as incorrect diagnosis and treatment due to the potential clinical consequences of inaccurate information.

The questions posed were open-ended, resulting in lengthy answers, and the study had a limited number of questions for ease of evaluation. Future studies with more diverse questions could be beneficial.

It is also important to highlight that this study specifically provides guidance for healthcare professionals, and further research with guiding questions for patients and their relatives would contribute to the literature.

Ethical approval

In this study, since no patient or experimental animal data were used, ethical committee approval was not required.

Author contribution

Concept: GSU; Design: GSU, AÖ; Data Collection or Processing: GSU, AÖ, ZK, EA; Analysis or Interpretation: GSU, ZK; EA; Literature Search: GSU; Writing: GSU, AÖ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLES

Benign laryngeal lesions: review of 329 cases in a single center

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ABSTRACT

Aim: Benign laryngeal lesions are non-neoplastic growths of abnormal tissue on the laryngeal mucosa. They are significant because they can affect the laryngeal functions of voice production, respiration, and deglutition. This study aims to present the histopathological and clinical data of patients diagnosed with benign vocal cord lesions who were followed up and underwent surgical treatment in our tertiary referral center, evaluate the distribution percentages, and assess the pathological findings in relation to age and gender.

Materials and Methods: This retrospective study was conducted by evaluating the medical records of patients who were diagnosed with benign vocal cord lesions between October 2014 and May 2019 at the Department of Otorhinolaryngology, Faculty of Medicine, Karadeniz Technical University.

Results: Of the 329 patients included in the study, 235 (71.4%) were male, and 94 (28.6%) were female. The mean age of the patients was 48.6 (±13.62) years. Histopathological evaluation revealed that the most common diagnosis was vocal cord polyp in 223 patients (67.8%). The second most common pathology was vocal cord nodule, observed in 23 patients (7.0%). This was followed by Reinke's edema in 21 patients (6.4%) and intracordal cyst in 20 patients (6.1%). No significant relationship was found between gender and the distribution of vocal cord biopsy results. However, a significant relationship was found between age groups and pathology distribution ($p < 0.001$). In particular, Reinke's edema and active chronic inflammation were more frequently observed in patients aged 49 and above.

Conclusion: Among patients with benign vocal cord lesions, vocal cord polyps are the most frequently encountered pathology. With increasing age, the diagnostic diversity of benign lesions also increases. Reinke's edema and inflammatory lesions are more frequently observed in older individuals.

Keywords: benign lesions, microlaryngeal surgery, nodule, polyp, vocal cords

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INTRODUCTION

Benign lesions of the larynx are defined histopathologically as non-malignant abnormal growth or inflammation of laryngeal tissue. These lesions are of clinical significance due to their high prevalence and potential to negatively impact the quality of life. Treatment options include medical therapy and voice therapy; however, surgical intervention remains the primary approach, especially when conservative treatments fail (1).

The most common presenting symptom of benign vocal cord pathologies is dysphonia (2,3). More than half of patients presenting with hoarseness exhibit benign changes in the laryngeal epithelium. In patients undergoing surgery for diagnostic or therapeutic purposes, the main goals are to improve phonatory function and/or establish a definitive histopathological diagnosis via biopsy (4). Histopathological confirmation is essential since malignant lesions can mimic benign ones during laryngoscopic examination.

Smoking, improper or excessive voice use, chronic laryngitis, various vitamin and mineral deficiencies, and gastroesophageal reflux are among the primary etiological factors (5,6). Benign laryngeal lesions are more commonly seen in individuals using their voice professionally, such as singers, actors, and teachers. These lesions may present with mild dysphonia or with life-threatening stridor requiring emergency intervention in cases such as extensive laryngeal papillomatosis (7). Therefore, accurate histopathological diagnosis is extremely important for appropriate management.

This study analyzed the clinical characteristics and histopathological results of patients who were diagnosed with benign vocal cord lesions over five years following direct microlaryngoscopic surgery performed in our clinic.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Otorhinolaryngology in Karadeniz Technical University. This study included patients diagnosed with benign vocal cord lesions between October 2014 and May 2019. Prior approval was obtained from the Karadeniz Technical University Faculty of Medicine Clinical Research Ethics Committee on 31.05.2019 with decision number 2019/189.

Histopathological specimens which were obtained from mucosal lesions, benign laryngeal pathologies, and benign tumors which were excised for diagnostic or therapeutic purposes were included. Patients who had undergone surgery for laryngeal malignancy or had received chemotherapy or radiotherapy for malignant conditions were excluded. In addition, revision surgeries and blind biopsies which were performed only to rule out malignancy were not included.

Demographic data of age, gender, and postoperative pathological diagnoses were recorded. Patients were categorized by gender (male/female) and age group ("48 years and under" and "49 years and above"). Histopathological findings were compared accordingly.

No artificial intelligence–assisted technologies were used for data collection, statistical analysis, or figure generation.

An artificial intelligence–assisted language model (ChatGPT, OpenAI, USA) was used only to improve grammar, clarity, and readability of the manuscript text. All scientific content, analyses, and interpretations were created and verified by the authors.

Statistical analysis

Statistical analysis was performed using the SPSS software. Descriptive statistics were given as numbers and percentages for categorical variables and as means for numerical variables. The relationship between pathological findings and age/gender was analyzed by using the chi-square test. $P < 0.05$ was considered the statistical significance level.

RESULTS

This study included 329 patients; 235 (71.4%) were male, and 94 (28.6%) were female, with a male-to-female ratio of 2.5:1. The mean age of the patients was 48.6 ± 13.62 years, ranging from 11 to 88 years.

Histopathological examination showed that the most common lesion was vocal cord polyp in 223 patients (67.8%). The second most common diagnosis was vocal cord nodule which was observed in 23 patients (7.0%), followed by Reinke's edema in 21 patients (6.4%) and intracordal cyst in 20 patients (6.1%).

The histopathological results are shown in Table 1. There is no significant association between gender and biopsy results. However, a significant relationship was found between age group and pathology distribution ($p < 0.001$). In particular, Reinke's edema and active chronic inflammation were more prevalent in patients aged 49 years and older.

In the chi-square analysis, no significant association was found between gender and vocal cord biopsy results ($p = 0.939$). This finding indicates that the distribution of vocal cord lesions is similar in male and female patients, suggesting that gender does not have a significant impact on the type of lesion.

However, a significant relationship was observed when evaluated according to age groups ($p < 0.001$). In particular, diagnoses such as Reinke's edema and active chronic inflammation were more frequently observed in patients aged 49 years and older.

Table 1. Distribution of vocal cord pathologies by number and percentage

Diagnosis	Number (n)	Percentage (%)
Vocal cord polyp	223	67.8
Vocal cord nodule	23	7.0
Reinke's edema	21	6.4
Intracordal cyst	20	6.1
Papilloma	9	2.7
Vocal cord cyst	6	1.8
Active chronic inflammation	6	1.8
Fibrin-exudate mass	3	0.9
Inflammatory granulation tissue	3	0.9
Laryngeal epithelial cyst	2	0.6
Laryngocele	2	0.6
Hemangioma	1	0.3
Hemorrhagic polyp	1	0.3
Candidal lesion	1	0.3
Cavernous hemangioma	1	0.3
Chronic inflammation	1	0.3
Laryngeal amyloidosis	1	0.3
Fungal hyphae	1	0.3
Oncocytic cystadenoma	1	0.3
Oncocytic papillary cystadenoma	1	0.3
Telangiectatic polyp	1	0.3
Vallecular cyst	1	0.3
Total	329	100

Table 2. Distribution of vocal cord biopsy results by gender and age group

Diagnosis	Male	Female	Total	≤48 years	≥49 years	Total
Vocal cord nodule	14	9	23	15	8	23
Vocal cord polyp	162	61	223	125	98	223
Vocal cord cyst	4	2	6	2	4	6
Reinke's edema	15	6	21	6	15	21
Papilloma	7	2	9	4	5	9
Intracordal cyst	14	6	20	8	12	20
Active chronic inflammation	5	1	6	0	6	6
Others	14	7	21	4	17	21
Total	235	94	329	164	165	329

DISCUSSION

Benign vocal cord lesions are one of the most common pathological causes of hoarseness following infectious etiologies. Although hoarseness is the primary complaint, patients may also present with symptoms such as cough, foreign body sensation in the throat, sore throat, dysphagia, and dyspnea (8). Benign laryngeal lesions generally do not pose a life-threatening risk except for rare obstructive conditions such as laryngeal papillomatosis. Their primary clinical significance lies in their impact on vocal function, vocal identity, and, indirectly, the individual's self-identity (9,10). These lesions usually do not spread or impair the function of vital organs since they are non-malignant. However, the clinical diagnosis of benign laryngeal lesions such as nodules, polyps, or cysts must always consider the potential for malignancy unless the lesion regresses with treatment or a benign nature is confirmed histopathologically.

Several studies in the literature report different findings regarding gender predominance in benign vocal cord lesions. Some of them have suggested that these lesions are more common in females, with female-to-male ratios reported as high as 3.2:1. It has been proposed that this female predominance may be related to greater awareness of voice changes among women, leading to earlier and more frequent clinical consultations. In addition, the higher proportion of female teachers, a profession associated with vocal strain, may contribute to this trend (11).

In contrast, many other studies have reported a male predominance in benign vocal cord lesions (3,7,12). Our study similarly observed a higher prevalence in males, with a male-to-female ratio of 2.5:1. This male predominance may be attributed to higher rates of smoking among the male population in the region where the study was conducted. In addition, no significant association was found between gender and the distribution of vocal cord biopsy results. The lesion distribution was similar between male and female patients, suggesting that benign vocal cord lesions occur independently of gender and that gender does not play a significant role in the diagnostic spectrum.

The most common benign lesions of the vocal cords include nodules, polyps, papillomas, polypoid degeneration (Reinke's edema), and cysts. Literature reports are inconsistent regarding which lesion is most common. While some studies cite vocal polyps as the most frequent benign lesion, others report nodules as the leading pathology (13,14).

Although vocal cord nodules causing hoarseness can be detected by indirect laryngoscopy or stroboscopy, most cases are treated conservatively or pharmacologically (15). In particular, non-surgical management is the preferred treatment for vocal cord nodules in the pediatric population. In our study, the relatively low number of histopathologically confirmed nodules may be due to the lower rate of microlaryngeal surgery performed for such cases.

Although benign laryngeal lesions can be seen at any age, they are most commonly diagnosed in individuals between the third and fifth decades of life, with an average age of presentation between 34 and 43 years (16). In a study by Zhukhovitskaya et al., certain benign laryngeal lesions were reported to be strongly associated with both age and gender. Variations in lesion distribution based on age and gender have been linked to differences in laryngeal anatomy, phonatory physiology, and the vibratory properties of the membranous vocal fold during phonotrauma (17).

In our study, lesions such as Reinke's edema and active chronic inflammation were more frequently observed in patients aged 49 and above. Similar to the findings of our study, previous literature has also reported that Reinke's edema is more frequently observed in a similar age group. In addition, it has been presented that the severity of Reinke's edema tends to increase with advancing age (18). Some diagnoses, such as "active chronic inflammation," were seen exclusively in this age group. These findings suggest that with increasing age, the diversity of vocal cord pathologies broadens, and the diagnostic process may become more complex. In addition, the diagnosis of malignancy in laryngeal lesions increases with advancing age (19). This situation further enhances diagnostic diversity and complexity in older individuals.

Limitations

This study has several limitations. Due to its retrospective design, detailed information on potentially relevant variables—such as occupation, smoking history, and reflux history—was not consistently available in the medical records. Consequently, subgroup analyses for these factors could not be performed, and their possible influence on the distribution of benign vocal cord lesions could not be fully evaluated. In addition, the inclusion of only histopathologically confirmed cases may have led to underrepresentation of certain lesion types that are typically managed conservatively without surgical intervention. Despite these limitations, the large sample size and comprehensive histopathological assessment strengthen the validity and clinical relevance of the study.

CONCLUSION

Vocal cord polyps were the most frequently encountered pathology in patients with benign vocal cord lesions. There was no significant association between gender and the diagnostic distribution of benign vocal cord pathologies, and lesion distribution was similar between male and female patients. However, diagnostic diversity increased with age. Reinke's edema and inflammatory lesions were more frequently observed in older individuals. These findings suggest that the increased diagnostic diversity of vocal cord lesions in older patients may complicate the diagnostic process and potentially delay the initiation of appropriate treatment. Although patients with malignancy were excluded from our study, it is well established that the incidence of malignant lesions rises with age, further contributing to diagnostic complexity. Therefore, older patients should be evaluated with greater caution, and a broader spectrum of differential diagnoses should be considered in this population to ensure accurate diagnosis and timely management.

Ethical approval

This study has been approved by the Karadeniz Technical University Faculty of Medicine Clinical Research Ethics Committee (approval date 31.05.2019, number 2019/189).

Author contribution

Surgical and Medical Practices: HBC, KK, ERK; Concept: HBC; Design: HTS; Data Collection or Processing: ERK; Analysis or Interpretation: HBC; Literature Search: ERK, HTS; Writing: KK. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLES

Changes in hematological and micronutrient parameters and their relationship with glycemic control in pediatric patients with type 1 diabetes

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ABSTRACT

Aim: Disturbances in hematological indices and micronutrient status are frequently encountered during the routine follow-up of children with type 1 diabetes mellitus (T1DM). In clinical practice, these alterations often parallel poor glycemic control. Therefore, this study was designed to evaluate hematological parameters and micronutrient levels in pediatric patients with T1DM and to investigate their relationship with metabolic control.

Materials and Methods: This retrospective analysis included 159 children and adolescents with T1DM followed at the Pediatric Endocrinology Clinic of Düzce University Faculty of Medicine, alongside 160 age- and sex-matched healthy controls. Laboratory data were obtained from medical records and included complete blood count parameters, lipid profile, ferritin, vitamin B_{12}, and vitamin D levels. Glycemic control was classified as "good" for HbA1c <8.5% and "poor" for HbA1c ≥8.5%. Statistical analyses were performed using SPSS version 22.0, with $p<0.05$ considered statistically significant.

Results: In the study cohort, children with T1DM exhibited significantly higher mean platelet volume (MPV), white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI). In contrast, platelet count and vitamin B_{12} levels were significantly lower. Multivariate analysis demonstrated that MPV, hemoglobin, hematocrit, high-density lipoprotein (HDL) cholesterol, vitamin B_{12}, SIRI, and NLR were independently associated with the presence of T1DM. In the ROC analysis, the area under the curve (AUC) for NLR was 0.791 (95% CI: 0.742-0.839), with a sensitivity of 71.1% and a specificity of 72.5% at a cutoff value of 1.46. When patients were stratified according to metabolic control, those with HbA1c ≥8.5% were older, had higher glucose levels, and had a higher proportion of females, whereas hematocrit levels were lower.

Conclusion: Hematological alterations and inflammatory indices appear to be closely associated with metabolic control in pediatric T1DM. Elevated MPV, SIRI, and NLR values suggest that hyperglycemia, particularly during adolescence, disrupts hematological homeostasis. In this context, the combined evaluation of hematological and inflammatory parameters may be clinically meaningful for identifying the presence of T1DM and delineating the burden of chronic low-grade inflammation. Supported by prospective studies, these findings may help guide individualized treatment strategies.

Keywords: Type 1 diabetes, pediatric patients, HbA1c, hematological parameters, inflammation, biomarkers

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is one of the most common endocrine disorders encountered during childhood and adolescence (1,2). It results from the immune-mediated destruction of pancreatic beta cells triggered by environmental factors in genetically susceptible individuals (3,4). Although the disease often manifests early in life, its consequences extend beyond childhood, leading to an increased risk of microvascular complications, macrovascular disease, and long-term cardiovascular morbidity.

The clinical course and severity of diabetes-related complications in children are shaped by multiple interacting factors, including disease duration, the level of metabolic control, genetic predisposition, and environmental exposures. In clinical practice, T1DM imposes a substantial psychosocial and economic burden not only on pediatric patients but also on their families and healthcare systems. This burden is particularly evident in developing regions where regular follow-up is limited.

Routine hematological parameters obtained from complete blood count analysis provide practical and readily accessible means for evaluating inflammatory activity and endothelial dysfunction associated with diabetic complications. Alterations in erythrocyte indices, white blood cell counts, and platelet morphology have been associated with metabolic syndrome, insulin resistance, and vascular risk in adult diabetic populations (5-14). Whether similar patterns occur in children with T1DM remains a focus of interest in pediatric research.

In pediatric populations, anemia most commonly occurs in the setting of iron, vitamin B_{12}, or folate deficiency, as these micronutrients are essential for effective hemoglobin synthesis. In patients with T1DM, nutritional insufficiency represents an important cause, but it is rarely the sole factor. Acute metabolic disturbances, dietary restrictions, coexisting autoimmune diseases, and socioeconomic challenges may further increase the risk. In poorly controlled diabetes, chronic hyperglycemia can sustain a low-grade inflammatory state that disrupts hematological homeostasis (15).

Early recognition of iron deficiency is of major clinical importance. Timely correction of anemia in children with diabetes contributes not only to reduced morbidity but also to improved physical performance, cognitive function, and psychosocial development (16). Nevertheless, data regarding iron, vitamin B_{12}, folate, and vitamin D status in pediatric populations with T1DM remain limited. This may partly reflect the assumption that children with diabetes who receive regular medical follow-up and nutritional counseling are protected against anemia.

Within this context, the present study was designed to comprehensively evaluate hematological parameters and micronutrient levels in pediatric patients with T1DM, to determine the prevalence and potential causes of anemia, and to examine the relationship between these variables and glycemic control.

MATERIALS AND METHODS

Study Design and Ethical Approval

This retrospective study was conducted to evaluate the epidemiological and laboratory data of pediatric patients with T1DM followed in the Pediatric Endocrinology Department of XXXX University Faculty of Medicine. Participant information was obtained retrospectively from the hospital's electronic database. The study was approved by the Ethics Committee of XXXX University Faculty of Medicine (approval number: 2025/284; date: November 10, 2025).

Sample Selection and Inclusion Criteria

The study included adolescent patients diagnosed with T1DM who regularly attended their three-month and annual follow-up visits and had received education on diabetes management and nutrition. Patients with systemic diseases that could cause anemia or micronutrient deficiencies, malnutrition, gastrointestinal malabsorption, or abnormal uterine bleeding, as well as those with uncontrolled hypothyroidism or adrenal insufficiency, were excluded from the study.

Data Collection and Laboratory Measurements

Data from annual follow-up examinations were used to record complete blood count parameters [hemoglobin, hematocrit, red blood cells (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), white blood cells (WBC), and platelet count], along with serum iron, total iron-binding capacity (TIBC), ferritin, folic acid, vitamin B_{12}, and vitamin D levels. Hemoglobin and MCV values were evaluated based on age-specific reference ranges (6). Anemia was defined according to age- and sex-specific hemoglobin reference ranges, in accordance with World Health Organization (WHO) criteria (11,13,15). Vitamin B_{12} deficiency was defined as serum B_{12} <200 pg/mL (16-19). All reference ranges used in this study were consistent with the standards of the institutional laboratory.

Calculation of Inflammatory Indices

Hemogram-based inflammatory markers were calculated using the following formulas:

- NLR (Neutrophil-to-Lymphocyte Ratio) = Neutrophil / Lymphocyte
- SII (Systemic Immune-Inflammation Index) = (Platelet × Neutrophil) / Lymphocyte
- SIRI (Systemic Inflammatory Response Index) = (Neutrophil × Monocyte) / Lymphocyte

These indices are considered reliable markers that reflect the peripheral inflammatory response and are widely used in clinical research.

Classification and Statistical Analysis

Age, sex, disease duration, and metabolic control are key variables influencing both hematological and biochemical profiles in children with type 1 diabetes. Therefore, participants in our study were stratified according to age (10-14.9 years and 15-18.9 years), sex (female/male), duration of diabetes (<3 years or ≥3 years), and level of glycemic control.

Glycemic control was defined as "good" for HbA1c <8.5% and "poor" for HbA1c ≥8.5%. This cutoff value was deliberately selected. In clinical practice, standard HbA1c categories (<7.0%, 7.0-8.5%, and >8.5%) often result in uneven subgroup sizes, particularly in adolescent populations. Because HbA1c values in our study cohort were not homogeneously distributed across these categories, an HbA1c cutoff of 8.5% was used to achieve balanced subgroup sizes and adequate statistical power. Hematological and biochemical parameters were compared according to this classification.

Correlation analyses were performed to examine the relationship between HbA1c, as a marker of long-term glycemic exposure, and other clinical and laboratory variables. Pediatric patients were evaluated within two glycemic control subgroups, allowing for the analysis of both categorical differences and continuous associations.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 22.0. The normality of distribution was assessed using the Shapiro-Wilk test. For descriptive statistics, normally distributed variables were expressed as mean ± standard deviation, whereas non-normally distributed variables were presented as median and interquartile range (IQR).

Categorical variables were compared using the chi-square test, with Fisher's exact test applied when expected cell counts were low. For comparisons of continuous variables between groups, the independent-samples t-test was used for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. When more than two independent groups were compared, one-way ANOVA was applied for normally distributed variables, and the Kruskal-Wallis test was used for non-normally distributed variables.

Associations between continuous variables were assessed using Pearson's correlation coefficient for normally distributed parameters and Spearman's rank correlation coefficient for non-normally distributed parameters. A two-sided p-value of <0.05 was considered statistically significant for all analyses.

RESULTS

A total of 319 pediatric patients were included in this study, comprising 159 patients with T1DM and 160 healthy controls. The mean age of the T1DM group was significantly higher than that of the control group ($p<0.05$). No significant difference was found between the groups in terms of sex distribution ($p>0.05$). The demographic, hematological, and biochemical characteristics of the study population are presented in Table 1.

In the comparative analysis of hematological and biochemical parameters, patients with T1DM demonstrated significantly higher levels of mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), systemic inflammatory indices (SII and SIRI), white blood cell count (WBC), hemoglobin, hematocrit, red blood cell count (RBC), triglycerides, high-density lipoprotein (HDL), and total cholesterol compared with healthy controls (all $p<0.05$). In contrast, platelet count and vitamin B_{12} levels were significantly lower in the T1DM group ($p<0.05$). No statistically significant

Table 1. Demographic, hematological, and biochemical characteristics of the study population

Characteristic	Min-Max	Median	Mean ± SD or n (%)
Age	5.0 - 21.0	15	14.4 ± 2.9
Gender	Female		177 (55.5%)
	Male		142 (44.5%)
BMI kg/m²	13.8 - 38.6	20.3	20.8 ± 3.6
HbA1c %	5.0 - 16.3	5	7.3 ± 2.7
Platelets (10^3/µL)	125.0 - 779.0	313	313.9 ± 83.1
MPV (fL)	6.9 - 11.1	8.8	8.8 ± 0.9
Glucose (mg/dL)	21.6 - 632	98.6	150.0 ± 95.2
RBC (10^3/µL)	3.9 - 6.5	4.8	4.8 ± 0.4
Hemoglobin (g/dL)	8.8 - 17.5	13	13.1 ± 1.4
Hematocrit (%)	31 - 51.3	38.2	38.8 ± 4.2
WBC (10^3/µL)	3.4 - 24.1	6.6	6.8 ± 1.9
Triglyceride (mg/dl)	28.0 - 1112.0	82.9	105.1 ± 97.1
LDL (mg/dl)	31.5 - 220.3	85	89.7 ± 28.3
HDL (mg/dl)	30.9 - 107.1	51	54.3 ± 13.2
TSH (mIU/L)	0.3 - 9.5	2.1	2.3 ± 1.3
Total Cholesterol (mg/dl)	100 - 759.4	153.4	159.9 ± 49.3
D Vitamin (ng/mL)	2.0 - 56.7	16.2	18.0 ± 9.1
B12 Vitamin (pg/mL)	120.2 - 1553.0	334.8	395.0 ± 201.9
NLR	0.4 - 13.6	1.4	1.8 ± 1.6
SII	82.3 - 5515.9	431.5	564.7 ± 520
SIRI	0.1 - 22.5	0.8	1.2 ± 1.8
Group	Healthy Controls		177 (55.5%)
	Type 1 Diabetes		142 (44.5%)

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as number and percentage [n (%)].

differences were observed between the groups with respect to low-density lipoprotein cholesterol (LDL), thyroid-stimulating hormone (TSH), or vitamin D levels (p>0.05; Table 2).

As shown in Table 3, univariate analysis indicated that age, MPV, RBC count, hemoglobin, hematocrit, WBC count, triglyceride, HDL, total cholesterol, vitamin B_{12}, NLR, SIRI, and SII were significantly associated with T1DM (p<0.05). Among these variables, NLR (OR=5.057; 95% CI: 3.299-7.754; p<0.001) and SIRI (OR=7.299; 95% CI: 4.039-13.190; p<0.001) demonstrated the strongest associations with the presence of T1DM.

In the multivariate forward logistic regression (LR) model, MPV, hemoglobin, hematocrit, HDL, vitamin B_{12}, NLR, and SIRI remained independently associated with T1DM (p<0.05). Increased MPV (OR=1.509; 95% CI: 1.021-2.232; p=0.039), hemoglobin (OR=2.041; 95% CI: 1.506-2.767; p<0.001), HDL (OR=1.046; 95% CI: 1.014-1.078; p=0.004), NLR (OR=5.158; 95% CI: 2.980-8.926; p<0.001), and SIRI (OR=6.438; 95% CI: 1.269-32.660; p=0.025) were identified as independent risk factors, whereas hematocrit exhibited a protective association (OR=0.437; 95% CI: 0.308-0.621; p<0.001). SII did not retain statistical significance in the multivariate model (p=0.680).

Table 2. Comparison of hematological and biochemical parameters between children and adolescents with T1DM and healthy controls

		Healthy Controls Group (n:160)		Type 1 Diabetes Group (n:159)		p	
		Mean±sd / n (%)	Median	Mean±sd / n (%)	Median		
Age		13.9 ± 2.9	14	14.9 ± 2.7	15	**0.003**	m
Gender	Female	86 (53.8%)		91 (57.2%)		0.531	X^2
	Male	74 (46.3%)		68 (42.8%)			
BMI kg/m²		20.4 ± 3.5	20	21.2 ± 3.7	20.4	0.063	m
HbA1c %		5.0 ± 0.0	5	9.5 ± 2.1	9.3	**0.000**	m
Platelets (10^3/µL)		322.5 ± 82.0	316.5	305.2 ± 83.5	306	**0.037**	m
MPV (fL)		8.7 ± 0.9	8.7	9.0 ± 0.9	9	**0.007**	m
RBC (10^6/µL)		4.7 ± 0.4	4.7	4.8 ± 0.4	4.8	**0.037**	m
Hemoglobin (g/dL)		12.8 ± 1.3	12.8	13.5 ± 1.4	13.4	**0.000**	m
Hematocrit %		37.8 ± 3.2	37.8	39.92 ± 4.09	39.6	**0.000**	m
WBC (10^3/µL)		6.3 ± 1.5	6	7.4 ± 2.2	7.1	**0.000**	m
Triglyceride mg/dl		92.2 ± 56.0	79.5	118.1 ± 124.3	89.6	**0.019**	m
LDL (mg/dl)		91.4 ± 32.1	90	87.8 ± 29.6	81	0.167	m
HDL (mg/dl)		50.0 ± 11.2	50	56.8 ± 15.8	55	**0.000**	m
TSH (mIU/L)		2.4 ± 1.2	2.1	2.3 ± 1.3	2.1	0.696	m
Total Cholesterol (mg/dl)		146.9 ± 27.4	145	172.0 ± 62.8	160	**0.000**	m
D Vitamin (ng/mL)		17.4 ± 8.4	16	18.6 ± 9.8	16.9	0.293	m
B12 Vitamin (pg/mL)		429.9 ± 246.1	352.8	359.8 ± 136.4	323.8	**0.034**	m
NLR		1.2 ± 0.5	1.1	2.4 ± 2.0	2	**0.000**	m
SIRI		0.67 ± 0.35	0.59	1.81 ± 1.76	1.12	**<0.001**	m
SII		389.06 ± 207.13	315.2	741.54 ± 662.02	576.2	**<0.001**	m

Table 3. Presents the results of univariate and multivariate logistic regression analyses evaluating hematological, biochemical, and inflammatory parameters associated with the presence of T1DM in pediatric patients

	Univariate Model			Multivariate Model		
	OR	**%95 GA**	**p**	**OR**	**%95 GA**	**p**
Age	1.14	1.049 - 1.231	0.002			
Platelets (10^3/μL)	1	0.995 - 1.000	0.064			
MPV (fL)	1.44	1.111 - 1.863	0.006	1.51	1.021 - 2.232	0.039
RBC (10^6/μL)	1.68	1.006 - 2.812	0.048			
Hemoglobin (g/dL)	1.5	1.249 - 1.792	0.000	2.04	1.506 - 2.767	0.000
Hematocrit %	0.78	0.706 - 0.857	0.000	0.44	0.308 - 0.621	0.000
WBC (10^3/μL)	1.43	1.235 - 1.660	0.000			
Triglyceride (mg/dl)	1	1.000 - 1.008	0.028			
HDL (mg/dl)	1.04	1.020 - 1.058	0.000	1.05	1.014 - 1.078	0.004
Total Cholesterol (mg/dl)	1	0.997 - 0.999	0.003			
B12 Vitamin (pg/mL)	1.02	1.012 - 1.028	0.000	1	0.995 - 1.000	0.021
NLR	5.06	3.299 - 7.754	0.000	5.16	2.980 - 8.926	0.000
SIRI	7.3	4.039 - 13.190	<0.001	6.44	1.269 - 32.660	0.025
SII	1	1.002 - 1.004	<0.001	1	0.995 - 1.003	0.68

Univariate and multivariate logistic regression analyses were performed using the forward likelihood ratio (Forward LR) method. Variables with p<0.05 in univariate analysis were entered into the multivariate model. Odds ratios are presented with 95% confidence intervals. A p-value <0.05 was considered statistically significant.

Table 4. ROC analysis of hemogram-based inflammatory indices for distinguishing pediatric patients with Type 1 diabetes mellitus from healthy controls

Parameter	**AUC**	**95% CI**	**Cut-off value**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**p-value**
NLR	0.791	0.742-0.839	1.46	71.1	72.5	72.0	71.6	<0.001
SIRI	0.768	0.716-0.820	0.97	60.4	83.8	78.7	68.0	<0.001

AUC: Area Under the Curve; CI: Confidence Interval; NLR: Neutrophil-to-Lymphocyte Ratio; SIRI: Systemic Inflammatory Response Index; PPV: Positive Predictive Value; NPV: Negative Predictive Value; ROC: Receiver Operating Characteristic.

The discriminative power of the NLR parameter between pediatric patients with T1DM and healthy controls was statistically significant (AUC=0.791; 95% CI: 0.742-0.839; p<0.001). The cutoff value of 1.46 for NLR yielded a sensitivity of 71.1%, specificity of 72.5%, positive predictive value of 72.0%, and negative predictive value of 71.6%, indicating moderate diagnostic performance. Similarly, the systemic inflammatory response index (SIRI) showed significant discriminatory performance, with an AUC of 0.768 (95% CI: 0.716-0.820; p<0.001). At a cutoff value of 0.97, SIRI provided a sensitivity of 60.4%, specificity of 83.8%, positive predictive value of 78.7%, and negative predictive value of 68.0%.

Overall, both NLR and SIRI exhibited moderate diagnostic accuracy in differentiating pediatric patients with T1DM from healthy controls, as summarized in Table 4.

The discriminative performance of hemogram-based inflammatory indices was further evaluated using receiver operating characteristic (ROC) curve analysis. The ROC-derived parameters for NLR and SIRI are summarized in Table 4, while the corresponding ROC curves are illustrated in Figure 1. The optimal cutoff value for the neutrophil-to-lymphocyte ratio (NLR) is illustrated in Figure 2.

In Table 5, demographic, hematological, and biochemical parameters were compared according to glycemic control status (HbA1c <8.5% vs. ≥8.5%) in pediatric patients with Type 1 diabetes mellitus. The group with HbA1c ≥8.5% had a significantly higher mean age and a higher proportion of female patients ($p<0.05$). In the same group, fasting blood glucose levels were significantly higher, while hematocrit values were significantly lower ($p<0.05$). No significant differences were observed between the groups in terms of body mass index, MPV, hemoglobin, WBC count, lipid profile, TSH, vitamin B_{12}, vitamin D, NLR, SII, or SIRI ($p>0.05$).

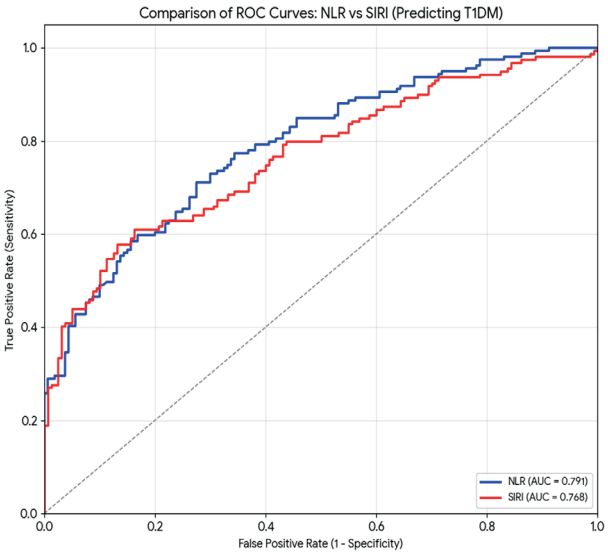

Figure 1. Receiver operating characteristic (ROC) curve analysis comparing the neutrophil-to-lymphocyte ratio (NLR) and systemic inflammatory response index (SIRI) for distinguishing pediatric patients with T1DM.

DISCUSSION

Evidence linking hematological alterations with metabolic control in type 1 diabetes mellitus (T1DM) remains limited. In our study cohort, distinct differences in hematological profiles were identified between children with T1DM and their healthy peers. We believe these differences are not incidental but convey important clinical information; they parallel glycemic control and suggest that hematological balance in pediatric diabetes is closely related to metabolic status.

In our clinical practice, persistently elevated HbA1c levels are often accompanied by changes in blood parameters. In the present study, increased MPV, WBC, NLR, SII, and SIRI values, together with decreased platelet count and vitamin B_{12} levels, indicate a disruption of hematological homeostasis under chronic hyperglycemic conditions. Similar findings have been reported by Tihić Kapidžić et al. in Bosnian children with T1DM (20), supporting both our observations and the notion that these alterations may be present across different ethnic pediatric populations.

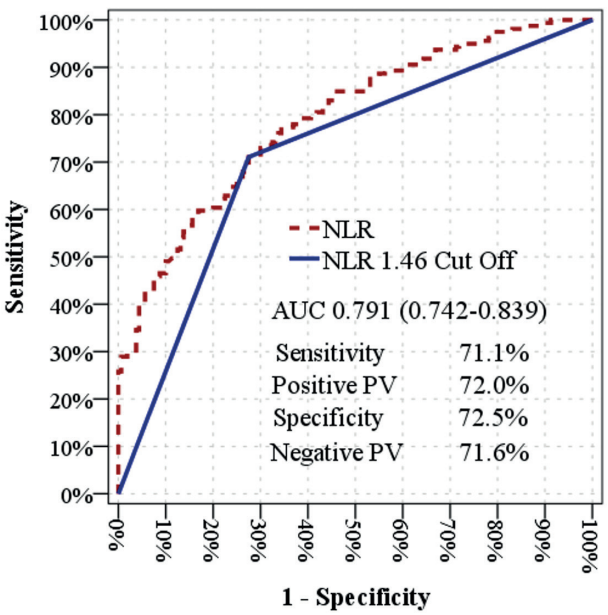

Figure 2. ROC curve of neutrophil-to-lymphocyte ratio (NLR) showing the optimal cut-off value of 1.46 with corresponding sensitivity and specificity for distinguishing children with Type 1 diabetes mellitus from healthy controls.

Tablo 5. Comparison of demographic, hematological, and biochemical parameters according to glycemic control (HbA1c <8.5% vs ≥8.5%) in children and adolescents with T1DM

Type 1 Diabetes		HbA1c<8.5 (n:61)		HbA1c≥8.5 (n:98)		p	
		Mean±sd / n (%)	Median	Mean±sd / n (%)	Median		
Age		14.2 ± 2.8	14	15.4 ± 2.6	16	0.009	m
Gender	Female	26 (42.6%)		65 (66.3%)		**0.003**	X^2
	Male	35 (57.4%)		33 (33.7%)			
BMI kg/m²		21.1 ± 4.3	20.1	21.2 ± 3.2	21	0.271	m
Platelets (10^3/μL)		307.6 ± 90.9	307	303.7 ± 79.1	305	0.911	m
MPV (fL)		9.1 ± 0.8	9.1	8.9 ± 0.9	8.9	0.2	m
Glucose (mg/dL)		194.0 ± 170.6	190	301.5 ± 235.6	243	0.003	m
RBC (10^6/μL)		4.9 ± 0.4	4.9	4.8 ± 0.4	4.8	0.24	m
Hemoglobin (g/dL)		13.6 ± 1.3	13.6	13.4 ± 1.5	13.3	0.598	t
Hematocrit %		40.22 ± 3.86	39.8	39.76 ± 4.22	39.4	0.493	t
WBC (10^3/μL)		7.4 ± 2.7	6.9	7.4 ± 1.8	7.2	0.559	m
Triglyceride (mg/dl)		105.55 ± 63.47	92	125.10 ± 147.71	88.7	0.991	m
LDL (mg/dl)		89.1 ± 27.2	81	87.0 ± 31.1	80.5	0.581	m
HDL (mg/dl)		55.6 ± 17.6	52.7	57.6 ± 14.6	55.6	0.321	m
TSH		2.5 ± 1.4	2.2	2.2 ± 1.3	2	0.161	m
Total Cholesterol (mg/dl)		181.3 ± 87.4	159	166.2 ± 40.2	162.5	0.745	m
D Vitamin (ng/mL)		18.7 ± 8.7	17.6	18.6 ± 10.5	16.4	0.586	m
B12 Vitamin (pg/mL)		371.1 ± 147.1	346.2	352.7 ± 129.5	320.5	0.568	m
NLR		2.6 ± 2.4	2	2.3 ± 1.8	2	0.791	m
SIRI		2.05 ± 3.48	1.16	1.73 ± 2.57	1.1	0.936	m
SII			581.6	704.83 ± 505.04	573.9	0.772	m

t: Independent Samples t test; m: Mann-whitney u test; X^2: Chi-square test.
Pediatric patients were categorized according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines. HbA1c <8.5% represents suboptimal but stable control for this cohort's distribution, while HbA1c ≥8.5% represents high-risk glycemic control.

Mean platelet volume (MPV) is of particular importance. Elevated MPV reflects increased platelet activation and is associated with a higher risk of microvascular complications (21,22). The higher MPV values observed in our diabetic group suggest that chronic hyperglycemia adversely affects platelet morphology and function. This finding is consistent with the results of Çoban et al. (23), who associated increased MPV with vascular involvement in pediatric diabetes. Hyperglycemia enhances non-enzymatic glycation and platelet membrane reactivity, exerting a prothrombotic effect that leads to an increase in MPV (24).

In multivariate analysis, MPV, hemoglobin, hematocrit, HDL, vitamin B_{12}, SIRI, and NLR emerged as independent factors distinguishing children with T1DM from healthy controls. When considered together, these findings demonstrate that the disease is not confined to disturbances in glucose metabolism alone but exerts broader systemic effects (25,26).

Inflammatory indices derived from the hemogram provide clinicians with an additional perspective. The elevated NLR, SII, and SIRI values observed in our study reflect the autoimmune and inflammatory nature of T1DM. These indices should not be regarded as primary

diagnostic tools; rather, they should be interpreted as indicators of chronic low-grade inflammation accompanying autoimmune beta-cell destruction and metabolic dysregulation. Previous studies have shown that such indices may reflect subclinical immune activation even before overt vascular complications develop (27,28). From this viewpoint, increased NLR, SII, and SIRI values are not diagnostic per se but are informative markers of inflammatory burden.

Age-related effects were also clinically relevant. Children in the HbA1c ≥8.5% group were relatively older, indicating that glycemic control becomes increasingly difficult during adolescence. Rising levels of growth hormone and sex steroids during puberty contribute to increased insulin resistance (29-33). Adolescence itself represents a physiological period characterized by changes that may influence hematological parameters and should therefore be considered a potential confounding factor. The higher proportion of females in the poor glycemic control group is consistent with the literature reporting lower insulin sensitivity and higher HbA1c levels in adolescent girls compared with boys (34,35).

Treatment adherence represents another important consideration. Adolescence is frequently associated with irregular insulin use, dietary non-adherence, increased fast-food consumption, and psychosocial stressors, all of which complicate glycemic regulation (31-33). Current ADA guidelines recommend targeting an HbA1c level below 7.5% in pediatric patients; however, achieving this goal under real-life conditions is often challenging (36).

The lower vitamin B_{12} levels observed in children with T1DM in our study are consistent with previous reports indicating an increased risk of deficiency in this population. Potential contributing factors include coexisting autoimmune conditions such as autoimmune gastritis and celiac disease, inadequate dietary intake, malabsorption, and diabetes-related gastrointestinal motility disorders (37,38). These findings support the need for routine monitoring of vitamin B_{12} levels, particularly in children with longer disease duration or suboptimal metabolic control. Regular nutritional counseling and support for treatment adherence constitute essential components of comprehensive diabetes care.

In our ROC analysis, NLR differed significantly between diabetic and healthy groups but demonstrated only moderate discriminative power. Although a cutoff value of 1.46 provided acceptable sensitivity and specificity, these values do not support its use as a standalone diagnostic marker. Rather, NLR should be considered a biomarker reflecting inflammatory activity associated with T1DM, without directly predicting clinical outcomes or complications (39-41). Details of its diagnostic performance are presented in Figure 2.

Our study has several limitations. Its retrospective design precludes causal inference, and its single-center nature limits generalizability. In addition, detailed data on dietary intake and physical activity were unavailable, and long-term complications were not assessed prospectively. Nevertheless, the inclusion of a well-matched control group and the evaluation of emerging indices such as SII and SIRI enhance the clinical relevance of our findings.

CONCLUSION

Hematological alterations, inflammatory indices, and micronutrient status are closely associated with metabolic regulation in children with T1DM. Elevated MPV, NLR, SII, and SIRI values, together with reduced vitamin B_{12} levels, demonstrate the detrimental effects of hyperglycemia on hematological balance.

Poor glycemic control, increasing age, and puberty-related hormonal changes—particularly in females—further accentuate metabolic deterioration during adolescence. These observations highlight the importance of age- and sex-specific, individualized treatment and nutritional strategies in pediatric diabetes management.

We believe that readily accessible hematological parameters such as MPV and NLR can provide useful insights into subclinical inflammatory activity in T1DM. In addition, regular assessment of vitamin B_{12} levels and continuous nutritional education are important for long-term metabolic control.

In conclusion, the combined evaluation of hematological and metabolic parameters may offer clinicians a practical and informative approach for assessing inflammatory burden and for planning individualized treatment strategies in pediatric patients with type 1 diabetes mellitus.

Ethical approval

This study has been approved by the Düzce University Non-Interventional Health Research Ethics Committee (approval date 10.11.2025, number 2025/284). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: ŞÖ; Concept: ŞÖ; Design: ŞÖ, İlknur Arslanoğlu; Data Collection or Processing: ŞÖ; Analysis or Interpretation: ŞÖ, İA; Literature Search: ŞÖ; Writing: ŞÖ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLES

Sexual dysfunction in vertigo patients: a clinical assessment using Arizona Sexual Experiences Scale

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ABSTRACT

Objective: Vertigo represents a chronic and disabling disorder that is often associated with anxiety, depressive symptoms, sleep disturbances, and prolonged medication use, factors that may collectively contribute to impaired sexual function. Sexual health is rarely addressed in vestibular clinics. We aimed to quantify sexual dysfunction in adults with chronic vertigo using the Arizona Sexual Experiences Scale (ASEX) and to compare outcomes with healthy controls.

Methods: We performed a prospective case–control study of 30 consecutive outpatients with chronic vertigo (mean age 37.8 years; 57% female) and 30 age- and sex-matched volunteers. Participants completed the ASEX, Dizziness Handicap Inventory (DHI), Patient Health Questionnaire-9 (PHQ-9), Generalised Anxiety Disorder-7 (GAD-7), and Pittsburgh Sleep Quality Index (PSQI). Between-group differences in ASEX total and item scores were analysed with t-tests or Mann–Whitney U tests. Sexual dysfunction was defined as ASEX ≥19. Multivariable logistic regression tested whether vertigo status predicted sexual dysfunction after adjustment for depressive symptoms and sleep quality.

Results: Vertigo patients showed significantly worse global sexual function than controls (ASEX total 16.9±5.1 vs 11.8±3.7; $p<0.001$). Clinical sexual dysfunction occurred in 43% of patients and 13% of controls ($p=0.007$). The five domains of ASEX: drive, arousal, lubrication/erection, ability to reach orgasm and satisfaction were significantly worse in the group with vertigo (all $p\leq0.005$). Patients had higher PHQ-9and GAD-7 scores (both $p<0.001$). Vertigo was an independent predictor of sexual dysfunction (adjusted odds ratio ≈ 4.0; $p<0.01$).

Conclusion: Adults with chronic vertigo suffer from a significantly increased burden of SD. The ASEX is a usefulscreening instrument. Health care professionals should seek information about sexual health and modifiablecontributors such as mood, sleep, and medications.

Keywords: Arizona Sexual Experience Scale, dizziness, sexual dysfunction, quality of life, vertigo

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INTRODUCTION

Vertigo, the false sense of movement within stable surroundings, is a common and disabling disorder that severely compromises quality of life. Patients with chronic vertigo often develop anxiety and depression, and accordingly, they are frequentlytreated with vestibular suppressants or antidepressants. Emotional stress and drug side effects are known contributingfactors for sexual dysfunction (1). Sexual dysfunction, defined as difficulty in any stage of the sexual response cycle, is widespread among healthy individuals, affecting approximately 40% of women and30% men reporting one or more sexual problems. It is much higher incases with other chronic medical conditions. Large-scale surveys and meta-analyses have shown that chronic diseases, such as diabetes, hypertension, and depression, increase the likelihood of having SD by2–6 fold when compared to age-matched normal men (2). Clinicians frequently neglect sexual health in non-sexual fields.

Vestibular illnesses exhibit increasing evidence of widespread comorbidity with mood and cognitive alterations that may impact intimacy. Zapata and López-Escámez (2011) examined 48 individuals with Menière's illness, a chronic vestibular ailment. They discovered that men exhibited twice the national rate of erectile dysfunction, whereas women reported markedly diminished sexual satisfaction and increased dyspareunia. In both genders, these sexual issues were significantly associated with diminished emotional well-being (3). A link between tinnitus, another inner-ear ailment, and erectile dysfunction has been documented (4). Moreover, numerous people with vertigo experience secondary psychological disorders, with 50–60% of individuals suffering from persistent vestibular issues reporting clinically significant anxiety or sadness (5). Anxiety and depression themselves are well-known causes of sexual dysfunction (e.g., up to 75% of women with severe depression fulfil ASEX criteria for sexual dysfunction (6). Sleep disturbance, frequent in chronic disease, also predicts erectile dysfunction (7).

These findings imply a biopsychosocial model: chronic vertigo imposes physical constraints (e.g., activity avoidance, weariness) and emotional loads that presumably impair libido and arousal. Many vertigo drugs (antihistamines, benzodiazepines, SSRIs) have sedating or serotonergic side effects that diminish sexual response. Indeed, vestibular suppressants (e.g., meclizine, diazepam) can cause sleepiness and, in consequence, diminished sexual drive, whereas SSRIs are connected with anorgasmia and erectile difficulties. Thus, the impact of vertigo on sexual function is likely complex.

Arizona Sexual Experience Scale (ASEX). To study sexual function in this context, we employed the 5-item ASEX questionnaire. ASEX quantifies essential domains: drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm. Each item is graded on a scale of 1 (ideal) to 6 (worst), generating a total score of 5–30. Higher scores suggest more dysfunction. A total ≥19 or any item ≥5 is usually used as a criterion for clinically severe impairment. The ASEX has demonstrated excellent reliability and validity across various patient groups. For example, Elnazer and Baldwin's structured review indicated that ASEX had strong internal consistency (Cronbach's α ~0.9) and reliably distinguished between patients and controls (1). It is also gender-neutral in design, making it practical for mixed cohorts (2). However, ASEX has not been previously applied to patients with vertigo.

Study aims and hypotheses. We thus conducted a prospective case–control research to examine sexual function in vertigo patients. Our primary aim was to compare overall ASEX scores between patients with chronic vertigo and healthy controls. We expected that vertigo patients would have considerably higher (worse) ASEX ratings and a higher prevalence of ASEX-defined sexual dysfunction than controls, indicating the burden of sickness and its psychosocial repercussions. Secondary aims were to study specific ASEX dimensions and to explore correlates of sexual dysfunction (demographics, diagnosis, concomitant anxiety/depression, sleep quality). We also investigated the viability of ASEX in an ENT clinical context. Subgroup analyses by gender and by usage of vestibular medicines were planned.

MATERIALS AND METHODS

This case-control study was approved by the Ethics Committee of Gazi Yaşargil Education and Research Hospital (Approval No: 459) and conducted in accordance with the Declaration of Helsinki. We selected 30 adults (18–55 years old) from our university hospital's outpatient otology/vestibular clinic who had a clinical diagnosis of chronic vertigo. For this study, chronic vertigo was operationally defined as persistent or recurrent vestibular symptoms for at least 3 months, consistent with commonly used definitions of chronic vestibular symptomatology. This definition encompassed both disorders characterised by continuous symptoms (e.g., persistent postural–perceptual dizziness) and episodic vestibular disorders with a chronic course (e.g., vestibular migraine, Ménière's disease, or recurrent benign paroxysmal positional vertigo), provided that patients experienced ongoing functional impairment, symptom-related anxiety, or activity restriction beyond acute attacks. Although several of the vestibular disorders evaluated in this study are characteristically episodic, patient inclusion was restricted to individuals whose condition resulted in a sustained impact on daily functioning.

Disorders such as vestibular migraine, Ménière's disease, and recurrent benign paroxysmal positional vertigo were therefore considered eligible only when vestibular symptoms were recurrent or persistent for a minimum duration of three months. They were associated with ongoing functional or psychological consequences. These consequences included residual balance disturbances between attacks, anticipatory anxiety related to symptom recurrence, activity avoidance, and long-term limitations in everyday life. Accordingly, patient recruitment was based not on isolated acute vertigo episodes but on the presence of a clinically meaningful chronic vestibular disease burden, regardless of attack periodicity.

All patients were evaluated by an experienced otologist using a standardised diagnostic approach. Diagnoses were established in accordance with internationally recognised criteria, supported by detailed clinical assessments and, when indicated, vestibular function testing. Vestibular migraine was diagnosed according to the diagnostic criteria of the International Headache Society (IHS). In contrast, Ménière's disease was diagnosed according to established clinical guidelines, particularly those of the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS). Persistent postural–perceptual dizziness (PPPD) was diagnosed in accordance with the 2017 Bárány Society criteria, which require persistent non-spinning dizziness or unsteadiness for at least 3 months, exacerbated by upright posture, active or passive motion, or exposure to complex visual stimuli.

All patients underwent a comprehensive neurotologic examination, including bedside head impulse testing. When clinically warranted, vestibular function was further assessed using objective measures such as caloric testing, cervical and ocular vestibular-evoked myogenic potentials (cVEMP and oVEMP), and pure-tone audiometry. These investigations were performed to support the clinical diagnosis and to characterise vestibular system function. Notably, bilateral vestibulopathy was systematically excluded by both clinical evaluation and vestibular testing, as none of the patients demonstrated evidence of bilateral vestibular hypofunction, including diminished vestibulo-ocular reflex responses on head-impulse or caloric testing. This integrated diagnostic approach enabled reliable differentiation among overlapping chronic vestibular syndromes.

Key exclusion criteria included the use of medications known to substantially reduce sexual desire, such as specific antipsychotic agents or high-dose selective serotonin reuptake inhibitors; uncontrolled metabolic or endocrine disorders, including diabetes mellitus or hormonal abnormalities; identifiable neurological conditions with an independent impact on sexual function, such as multiple sclerosis; and the presence of major psychiatric disorders requiring ongoing pharmacological treatment known to affect sexual function (e.g., severe depressive disorders treated with potent antidepressants or schizophrenia). Individuals already diagnosed with primary mental health conditions that could significantly change sexual function, like major depression being treated, intense anxiety, psychosis, or somatoform issues, were not included. A complete mental health diagnosis was not done for everyone; instead, we used the Patient Health Questionnaire-9 (PHQ-9) and the Generalised Anxiety

Disorder-7 (GAD-7) to check how bad their depression and anxiety were. We used these tools to see how many symptoms people had at that moment, but not to make any official diagnoses. Patients with bilateral vestibulopathy were excluded a priori. Bilateral vestibular failure is characterised by persistent oscillopsia, severe gait instability, and continuous postural imbalance, which may influence sexual activity predominantly through profound physical limitations rather than through mechanisms related to episodic vertigo or vestibular symptom–related anxiety. Inclusion of such patients could therefore introduce a qualitatively distinct pathophysiological subgroup and confound interpretation of sexual function outcomes. Importantly, no patient in the screened population met diagnostic criteria for bilateral vestibulopathy; thus, this exclusion criterion did not alter the final study sample but was implemented as a predefined methodological safeguard.

A comparative group of 30 healthy volunteers (mean age, 36.5 years; 60% female) was recruited through community advertisements. Controls were age- and sex-matched, and screened to have no history of chronic vertigo, no significant neurological or psychiatric condition, and not using drugs with recognised sexual side effects. Mild common conditions (e.g., hypertension with ACE medications) were allowed. All participants provided informed consent.

Demographics and clinical variables: We collected age, sex, relationship status (married/cohabiting vs. not), and body mass index (BMI). In vertigo patients, we noted the diagnosis, symptom duration (in years), and current medications (including vestibular suppressants, SSRIs, etc.).

The patient and control groups were intentionally matched for sex distribution in order to minimise sex-related confounding. The proportion of female participants was comparable between groups (patients: 57%, 17/30; controls: 60%, 18/30), with no statistically significant difference in sex distribution.

Dizziness Impairment Inventory (DHI): Patients with vertigo completed the 25-item DHI to quantify their reported vestibular impairment. The DHI is commonly used in patients with dizziness to assess the impact of vertigo on daily activities (8,9). It produces a total score (0–100) with subscales for functional, emotional, and physical effects. Higher DHI indicates higher impairment. (The DHI has shown good reliability) (9). Controls were not administered the DHI.

Arizona Sexual Experiences Scale (ASEX): ASEX consists of 5 Likert-scaled items (see Introduction). Total scores range from 5 to 30, with higher scores implying worse function. We applied ASEX consistently to both patients and controls. We utilised established cutoff criteria (total ≥19 or any item ≥5) to diagnose "clinically significant sexual dysfunction (10). ASEX was administered in private by a physician during a face-to-face interview.

Mental health and sleep questionnaires: All participants completed the Patient Health Questionnaire-9 (PHQ-9) for depression (11), the Generalised Anxiety Disorder 7-item scale (GAD-7) (12), and the Pittsburgh Sleep Quality Index (PSQI) (10). The PHQ-9 and GAD-7 are brief, validated measures for depression and anxiety severity (11,12). The PSQI assesses subjective sleep quality (global score 0–21; >5 indicates poor sleep) (10). These tools permitted assessment of mood and sleep status, which are potential correlates of sexual function.

We summarised continuous data as mean ± SD (or median and IQR if skewed) and categorical variables as counts (%). Group comparisons (vertigo vs. control) used two-sample t-tests or Mann–Whitney U tests for continuous data and chi-square or Fisher's exact tests for categorical data. ASEX overall and domain scores were compared by t-test/Mann–Whitney as applicable. We also provide the proportion meeting the ASEX dysfunction criterion and evaluate this with a chi-square test.

To adjust for potential confounders, we ran multivariable logistic regression with sexual dysfunction (ASEX ≥ 19) as the outcome, including group (vertigo versus control), age, gender, and significant covariates (e.g., PHQ-9, GAD-7) as predictors. Adjusted odds ratios (aOR) with 95% confidence intervals were computed. Finally, subgroup analyses stratified by sex and by use

of vestibular medications were undertaken to evaluate the robustness of the findings. Statistical tests were two-tailed with α=0.05. Analyses were conducted in SPSS v.25 (IBM Corp., Armonk, NY).

RESULTS

Participant characteristics are reported in Table 1. Vertigo patients (n = 30) and controls (n = 30) were well-matched for age (37.8 ± 10.2 vs. 36.5 ± 11.0 years, p = 0.62) and sex (57% vs. 60% female, p = 0.79). Most were in a long-term relationship (87% vs. 83%, p = 0.74). In the vertigo group, the median symptom duration was 1.8 years (inter-quartile range, IQR, 1.0–3.5 years). The most prevalent diagnoses were vestibular migraine (40%), Menière's disease (30%), and PPPD/other (30%). Twenty patients (67%) were taking at least one vestibular suppressor or anxiolytic drug; none of the controls were on such meds.

Compared to controls, vertigo patients had significantly higher mean scores on the PHQ-9 (8.2±2.9 vs 3.1±1.1, p<0.001) and GAD-7 (7.5±3.0 vs 2.4±1.2, p<0.001), indicating more depressive and anxiety symptoms in the patient group. Sleep quality was also worse in patients (PSQI 8.5±2.5 vs. 4.9±1.3, p < 0.001). The mean DHI score in patients was 52.0±14.8, reflecting moderate handicap. These additional results (not shown in tables) confirm that vertigo patients had greater psychiatric distress and worse perceived dizziness than controls.

Sexual function data are summarised in Table 2. Vertigo sufferers got significantly worse ASEX ratings. The mean total ASEX score was 16.9±5.1 in the sick

Table 1. Demographics and baseline characteristics of vertigo patients versus controls

Characteristic	Vertigo (n=30)	Control (n=30)	p-value
Age, mean ± SD (years)	37.8 ± 10.2	36.5 ± 11.0	0.62
Female, n (%)	17 (56.7%)	18 (60.0%)	0.79
In relationship (yes), n (%)	26 (86.7%)	25 (83.3%)	0.74
Body Mass Index, mean ± SD	25.9 ± 3.4	25.1 ± 3.1	0.45
Symptom duration, median (IQR)	1.8 (1.0–3.5) years	–	–
Vestibular suppressants, n (%)	20 (66.7%)	0 (0%)	<0.001
PHQ-9 score, mean ± SD	8.2 ± 2.9	3.1 ± 1.1	<0.001
GAD-7 score, mean ± SD	7.5 ± 3.0	2.4 ± 1.2	<0.001
PSQI (sleep) score, mean ± SD	8.5 ± 2.5	4.9 ± 1.3	<0.001

PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalized Anxiety Disorder 7; PSQI: Pittsburgh Sleep Quality Index (PSQI).

Table 2. ASEX scores in vertigo patients and controls

ASEX Outcome	Vertigo (n=30)	Control (n=30)	p-value
Total ASEX score, mean ± SD	16.9 ± 5.1	11.8 ± 3.7	<0.001
ASEX score, median (IQR)	17.0 (13.0–21.0)	12.0 (9.0–14.0)	<0.001
Sex drive, mean ± SD	3.8 ± 1.1	2.5 ± 0.8	0.002
Arousal, mean ± SD	3.6 ± 1.2	2.4 ± 0.9	<0.001
Erection/Lubrication, mean ± SD	3.3 ± 1.1	2.2 ± 0.7	0.005
Orgasm ability, mean ± SD	3.7 ± 1.3	2.3 ± 0.8	<0.001
Orgasm satisfaction, mean ± SD	3.5 ± 1.2	2.0 ± 0.7	<0.001
ASEX dysfunction (n, %)	13 (43.3%)	4 (13.3%)	0.007

ASEX: Arizona Sexual Experiences Scale.

group, compared to 11.8±3.7 in the controls (t-test, p<0.001). The median ASEX score was considerably higher in patients (17.0 (IQR 13–21) vs 12.0 (9–14), p<0.001). By domain, vertigo patients scored lower than controls on all five ASEX measures (all p≤0.005): sex drive, arousal, penile erection/vaginal lubrication, orgasm ability, and orgasm satisfaction. For example, average arousal levels were 3.6 vs. 2.4 (out of 6) in patients compared to controls (p < 0.001). As shown in Figure 1 and Figure 2, the distributions differ significantly between groups.

Clinically severe dysfunction (ASEX≥19 or any item ≥5) was found in 13 of 30 vertigo patients (43.3%) compared to 4 of 30 controls (13.3%, χ^2=7.40, p = 0.007). In other words, vertigo patients were over three times as likely to screen positive for sexual dysfunction. Logistic regression supported this finding: after adjusting for age, sex, PHQ-9, and GAD-7 scores, the adjusted odds ratio for dysfunction in vertigo versus control was ~4.0 (95% CI, 1.4–11.5, p = 0.008). Sleep quality (PSQI) was associated with ASEX in univariate analysis (greater PSQI scores were associated with dysfunction, p = 0.02), but this association did not remain significant in the multivariable model.

By gender: When stratified, both men and women showed the same pattern. Among the 17 female vertigo patients, the average ASEX total was 17.2 (SD 4.9) vs 2/18 (11.1±3.5) in female controls (p=0.001). Among males, patients averaged 16.4±5.3 years, compared to 12.6±3.8 years in male controls (p=0.009). The prevalence of dysfunction (ASEX ≥ 19) was 41% in female patients and 46% in male patients, compared with 11% and 17% in female and male controls, respectively (differences not statistically significant by gender subgroup due to small sample sizes). There was no significant interaction by gender – vertigo status predicted dysfunction similarly in men and women.

To explore potential sex-related effects, sexual dysfunction prevalence was additionally analysed separately for female and male participants. Among women, 39% (7/18) of vertigo patients met criteria for sexual dysfunction compared with 11% (2/18) of female controls. Among men, sexual dysfunction was present in 42% (5/12) of male vertigo patients versus 8% (1/12) of male controls. The study, while not designed to find sex-specific differences, found higher rates of sexual dysfunction in vertigo patients of both sexes when compared to controls of the same sex.

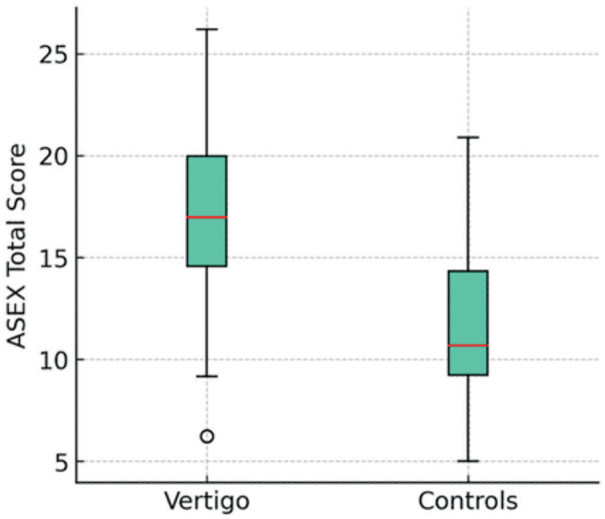

Figure 1. Distribution of total ASEX scores. Boxplots of total ASEX score in vertigo patients (left) and healthy controls (right). The vertigo group shows significantly higher ASEX scores (worse sexual function) than controls. Median values (horizontal lines) and interquartile ranges are indicated.

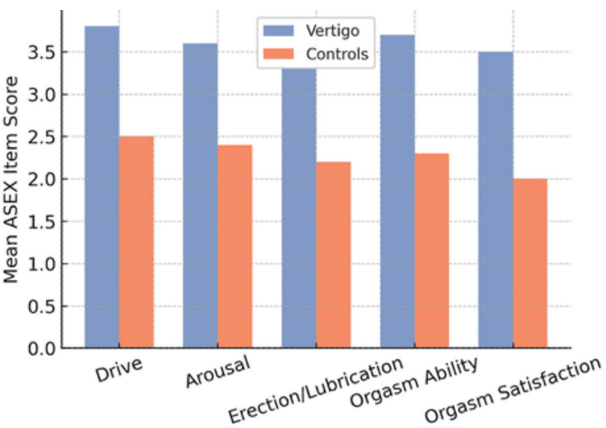

Figure 2. ASEX domain scores by group. Bar chart of mean scores (±SE) for each ASEX domain in vertigo patients (dark bars) versus controls (light bars). Higher scores indicate worse function. All five domains are significantly higher (worse) in the vertigo group (p<0.01 by t-test).

Table 3. Multivariable logistic regression for sexual dysfunction (ASEX≥19). Adjusted for age, sex, PHQ-9 and GAD-7

Predictor	Adjusted OR (95% CI)	p-value
Vertigo patient (yes)	4.20 (1.44 – 12.2)	0.008
PHQ-9 (per point)	1.15 (0.99 – 1.34)	0.056
GAD-7 (per point)	1.08 (0.94 – 1.25)	0.28
Age (per year)	0.97 (0.91 – 1.04)	0.40
Female sex (M=0, F=1)	1.02 (0.30 – 3.42)	0.98

PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalized Anxiety Disorder 7.

Looking at diagnosis and medication within the vertigo group, ASEX scores did not differ much across vestibular diagnoses (e.g., Menière's, vestibular migraine, or PPPD), even though the numbers in each group were small. Patients on daily vestibular suppressants (n = 20) exhibited somewhat higher mean ASEX scores (17.5 vs. 15.2) and a higher dysfunction rate (50% vs. 29%), although these differences were not statistically significant (p = 0.18). Excluding patients on SSRIs or benzodiazepines (n=8) did not dramatically impact results — the vertigo group still exhibited a 3.5-point higher ASEX mean than controls. Thus, medication use did not fully explain the group difference.

Correlations: In the vertigo group, total ASEX score linked modestly with DHI total (r≈0.45, p=0.01) and with PHQ-9 (r≈0.43, p=0.02) and GAD-7 (r≈0.41, p=0.03). These relationships persisted after correcting for age and sex. This shows that severe dizziness handicap and higher mood symptoms were associated with lower sexual function. However, in the logistic model, only vertigo status remained a strong independent predictor (see Table 3).

Regression model: We conducted a multivariable logistic regression with sexual dysfunction (ASEX≥19) as the outcome (Table 3). After controlling for age and sex, vertigo status was very significant (adjusted OR 4.2; 95% CI 1.44–12.2; p=0.008). Depression score (PHQ-9) exhibited a borderline influence (aOR 1.15 per point; p=0.056), and anxiety (GAD-7) was not significant. Sleep quality (as measured by the PSQI) was not significant after correction. These data reveal that, despite accounting for psychological considerations, vertigo patients had considerably higher probabilities of sexual dysfunction than controls.

DISCUSSION

In this study, patients with persistent vertigo reported considerably lower sexual performance than healthy volunteers. Patients with vertigo exhibited significantly higher ASEX total scores and a substantially higher rate of ASEX-defined impairment (43% vs 13%). All areas measured by the ASEX were impacted, with arousal and orgasm showing the most change. Our results support the idea that the difficulties caused by vertigo can lead to sexual problems. This study is, to the best of our knowledge, the first to systematically examine sexual function in people with vestibular disorders. These results parallel findings in other chronic illness groups. For instance, in an extensive US study, Wu et al. (2022) found that psychological variables (depression and poor sleep) strongly predicted erectile dysfunction (7). In our population, patients exhibited higher PHQ-9 and PSQI scores, consistent with these observations. Similarly, Liu et al. (2023) observed that women with severe depression had considerably higher ASEX scores than men (6). In our study, both sexes in the vertigo group exhibited higher ASEX scores, without a significant gender difference, and mood aspects appeared to contribute. In inflammatory disorders, Yan et al. (2024) recently reported that men with osteoarthritis or rheumatoid arthritis had a markedly higher incidence of ED compared to the general population (2). Our observation of higher ASEX dysfunction in vertigo patients shows that vestibular diseases should be recognised among systemic illnesses where sexual health is affected.

Potential reasons explaining our findings include both psychological and physiological routes. Vertigo typically leads to anticipatory worry and avoidance behaviour; some patients fear generating dizziness by exertion or particular motions, which may extend to sexual engagement. Emotional anxiety from unpredictable vertigo attacks might reduce libido and

orgasmic function. The literature corroborates this: distress and mental health issues are consistently associated with sexual function in patient groups (1-3). Our findings indicated a moderate connection between ASEX scores and both depression and anxiety scales, suggesting mood symptoms partly explain the link.

Many vertigo sufferers take sedating medicines or SSRIs for comorbid anxiety. Although our subgroup analysis did not uncover a significant impact of medication on ASEX (perhaps because of the restricted sample size), we note that vestibular sedatives and serotonergic antidepressants can decrease sexual drive and orgasm. For example, SSRIs are well-known to produce erectile and orgasmic issues. Thus, some of the observed dysfunction may be iatrogenic.

Another consideration is the vestibular-autonomic connection. Vertigo and imbalance can trigger the autonomic nervous system, potentially altering genital blood flow or arousal. However, this link is not widely investigated. The DHI-association findings (worse ASEX with higher DHI) imply that more severe dizziness may be directly linked to sexual issues. Dizziness handicaps have been demonstrated to connect with autonomic and emotional dysregulation, which could indirectly influence sexual function (8).

Our findings have practical value. Sexual health is a crucial component of overall well-being; however, it is rarely assessed during ENT or neurology consultations. Many chronically sick people prefer more talk of sexuality with their caregivers. Vertigo sufferers may not reveal sexual difficulties unless asked, due to shame or the belief that it is irrelevant. The ASEX is quick and easy to use. Our work indicates that it is a good way to detect problems in dizzy patients. Doctors should ask dizzy patients about their sexual function, especially if patients seem anxious or sad, or say that their lives are restricted. Spotting problems can mean patients get advice, changes to their drugs, or treatments that could really improve their lives. For example, PDE5 inhibitors can be given to men.

The limits of our study should be considered. This study has several limitations that should be considered when interpreting the findings. First, the relatively small sample size and single-centre design may limit the generalizability of the results to broader populations. In addition, the study cohort included patients with heterogeneous vestibular diagnoses, reflecting real-world clinical practice; however, different vertigo etiologies may influence sexual function through distinct mechanisms. Factors such as partner status and menopause in female participants, which are known to affect sexual function, were not systematically evaluated and may therefore represent unmeasured confounders.

Furthermore, given the observational nature of the study, causal relationships between vertigo and sexual dysfunction cannot be established. Another limitation relates to diagnostic grouping. The chronic vertigo group comprised patients with various underlying vestibular disorders. Although all participants met predefined criteria for symptom chronicity and functional impairment, the diagnostic heterogeneity within this group may have introduced variability and potentially obscured disorder-specific effects on sexual function. Consequently, the present findings likely reflect the overall burden of chronic vertigo rather than the impact of any single vestibular disorder. Future studies with larger sample sizes should aim to include more homogeneous diagnostic groups or perform robust subgroup analyses to delineate better the relationship between specific vertigo etiologies and sexual dysfunction.

Excluding patients with bilateral vestibulopathy is an additional limitation of this study. Although bilateral vestibulopathy constitutes a prototypical form of chronic vestibular dysfunction, its characteristic symptoms—such as persistent imbalance and oscillopsia—may influence sexual function through mechanisms that differ from those observed in episodic or fluctuating vestibular disorders. Consequently, the present findings may not be directly generalizable to individuals with bilateral vestibulopathy. Further research is warranted to determine whether the prevalence, severity, and underlying mechanisms of sexual dysfunction in this population differ from those observed in other chronic vestibular conditions.

Moreover, the study cohort comprised patients with a range of vestibular disorders, including both persistent and episodic conditions, who experienced

long-standing symptoms with a sustained impact on daily functioning. While this approach reflects real-world clinical practice, the heterogeneity of diagnoses may have limited the ability to detect disorder-specific effects on sexual function. As a result, the findings likely represent the overall burden of chronic vestibular dysfunction rather than the influence of individual etiologies. Accordingly, this study should be regarded as exploratory. Future investigations with larger sample sizes should prioritise homogeneous diagnostic cohorts—such as patients with persistent postural–perceptual dizziness or bilateral vestibular hypofunction—or perform disorder-specific subgroup analyses to characterise the relationship between vestibular pathology and sexual function more precisely.

An additional limitation of this study is the absence of a comprehensive psychiatric evaluation. Although individuals with known psychiatric diagnoses were excluded and depressive and anxiety symptoms were screened using the PHQ-9 and GAD-7, these self-report instruments do not replace formal psychiatric assessment. Undiagnosed or subclinical mood and anxiety disorders may therefore have been present and could have contributed to the observed sexual dysfunction, partly confounding the association between chronic vertigo and sexual outcomes. Furthermore, despite matching patients and controls by sex, female-specific factors known to influence sexual function—such as menopausal status, hormonal abnormalities, use of hormonal contraception, and gynaecological conditions—were not systematically assessed. As a result, the potential impact of these sex-specific confounders cannot be excluded, and they may have contributed to variability in sexual function measures. Future studies should incorporate structured psychiatric evaluations and detailed assessment of sex-specific clinical factors to clarify these relationships better.

Future studies should seek to replicate and extend these findings in larger, multicenter cohorts. Such studies may benefit from stratifying participants by specific vertigo diagnoses and incorporating objective measures, including hormonal assessments and partner-reported outcomes. Longitudinal designs could help determine whether improvements in vertigo symptoms or associated anxiety and depression lead to meaningful changes in sexual function. In addition, qualitative research may provide valuable insights into patients' perceptions of how vertigo affects intimacy and interpersonal relationships. Given the high prevalence of sexual dysfunction observed, interventional trials integrating vestibular rehabilitation with targeted sexual or psychosocial counselling may also be warranted.

CONCLUSIONS

Sexual dysfunction is a frequently ignored condition in vertigo patients. Our ASEX-based assessment found that individuals with persistent vestibular illnesses have considerably lower sexual performance than healthy controls, even after accounting for mood symptoms. These findings underline the need for routine sexual health screening in vertigo care. By including brief screening and open discourse about sexuality, physicians can address a crucial component of patient well-being that is often neglected in general practice.

Ethical approval

This study has been approved by the Ethics Committee of Gazi Yaşargil Education and Research Hospital (approval date 09/05/2025, number 459). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: SD, SFT, ES, SUD; Concept: SD, SFT, ES, SUD; Design: SD, SFT, ES; Data Collection or Processing: SD, SFT, ES, SUD; Analysis or Interpretation: SD, SFT, ES, SUD; Literature Search: SD, SFT, ES, SUD; Writing: SD, SFT, ES, SUD. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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REVIEW

Management of psychological impacts of radiation safety protocols on nursing staff in radiotherapy departments

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ABSTRACT

Objective: Ionizing radiation, which is utilized in radiation therapy, is one of the mainstays of cancer treatment. It is used to eliminate cancer cells while causing the least possible harm to surrounding healthy tissues. Exposure to ionizing radiation poses significant hazards to healthcare workers, including nursing staff in radiotherapy departments. In order to reduce risks and safeguard both patients and employees, radiation safety procedures such as the use of protective equipment, shielding, and monitoring must be implemented. Despite these safeguards, psychological issues such as stress, anxiety, and burnout are common among nursing staff.

Methods: A systematic review was conducted to explore the psychological impacts of radiation safety protocols on nursing staff. PRISMA guidelines were followed, with a literature search across Google Scholar, PubMed, and Web of Science from 2000 to 2024. Studies included impacts on mental health such as anxiety, stress, and burnout. Data extraction focused on psychological impacts, safety measures, and coping strategies.

Results: Out of the 602 initial records, 58 studies met the inclusion criteria, highlighting common psychological challenges such as stress, anxiety, and exhaustion associated with radiation safety protocols. Both short-term and long-term exposure to radiation significantly contribute to heightened anxiety levels. Furthermore, organizational culture and the quality of staff training serve as critical determinants of psychological well-being.

Conclusion: Nursing staff in radiotherapy are concerned about the psychological strain brought on by radiation safety procedures. Institutions should consider mental health support to build a resilient workforce in radiotherapy departments. Modern safety technologies, organizational support, and appropriate training are essential for reducing anxiety and enhancing the well-being of staff.

Keywords: radiation safety procedures, psychological effects, stress, anxiety, radiation treatment, nursing staff

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INTRODUCTION

High-energy radiation to target and eliminate malignant cells while conserving healthy tissue as much as possible is the principle of radiation therapy, which plays a notable role in cancer treatment (1). Radiation therapy treatments are frequently applied as a single treatment in a curative manner or in co-occurrence with surgery and chemotherapy to improve treatment outcomes and patient survival rates (2). Besides being beneficial as a treatment technique, exposure to ionizing radiation instigates intrinsic danger to the healthcare workforce specifically dealing with patients.

Nursing staff of radiotherapy departments are engaged in versatile roles in patient surveillance, treatment delivery, and assuring the straightforward operation of therapeutic approaches. Patient evaluation and instructions during complex treatment plans under radiation oncologists are accounted for by nurses, who also rely on certain radiation safety protocols to protect patients and personnel from ionizing radiation (3,4).

Efficacious radiation safety protocols are crucial in radiotherapy departments, as personal protective equipment (PPE), proper shielding, adherence to safety guidelines, and consistent radiation level monitoring are utilized to achieve effective radiation safety (5). Mitigation of prospective long-term health risks correlated with cumulative radiation exposure can cause the development of malignancies and further unfavorable health repercussions (6).

METHOD

The psychological impacts of safety protocols related to occupational radiation exposure on the nursing workforce in radiotherapy departments are appraised in this systematic review. Publications from 2000 to 2024 in Google Scholar, PubMed, and Web of Science were used to conduct the search using keywords such as "nursing staff," "radiation safety," "psychological impact," and "radiotherapy departments," with related terms. The PRISMA guidelines were also followed to ensure a comprehensive assessment of the literature.

Peer-reviewed English-language studies with a specific focus on nursing employees in radiotherapy departments that have been published between 2000 and 2024 were included in the review. These studies investigated the ways in which radiation security measures influenced psychological outcomes consisting of anxiety, stress, burnout, or fear. Review papers were included in addition to original research (qualitative, quantitative, or mixed methods). Studies that neglected psychological consequences, were not peer-reviewed, did not have full-text availability, or concentrated on other healthcare providers were excluded. Two researchers performed the study process of selection independently to minimize bias. In accordance with the PRISMA flow diagram, abstracts and titles were screened first, and then full-text assessment was conducted using the inclusion and exclusion criteria (Figure 1).

A standardized form was utilized to extract data from each study, such as information about the author, year, country, design, sample size, psychological consequences, radiation precautions, and coping strategies. This procedure ensured that each significant variable for analysis was explained in great detail. Since study designs and results varied widely, the data synthesis was performed narratively. Common psychological issues, such as increased stress and anxiety from exposure to radiation and exhaustion from long-term risks, were identified through thematic analysis, in addition to coping strategies such as training, peer support, and organizational tactics. No new data collection or ethical approval was required because the review investigated previously published studies. However, each investigation was evaluated for compliance with ethical guidelines, including acquiring adequate consent from those who participated. The exclusion of non-English studies, possible publication bias due to the review's reliance on previously published research, and the inability to perform a meta-analysis caused by disparities in study designs and conclusions were some of its limitations.

RESULTS

The database search turned up 602 records in total, which included 305 from PubMed, 154 from Google Scholar, and 143 from ScienceDirect. Following a

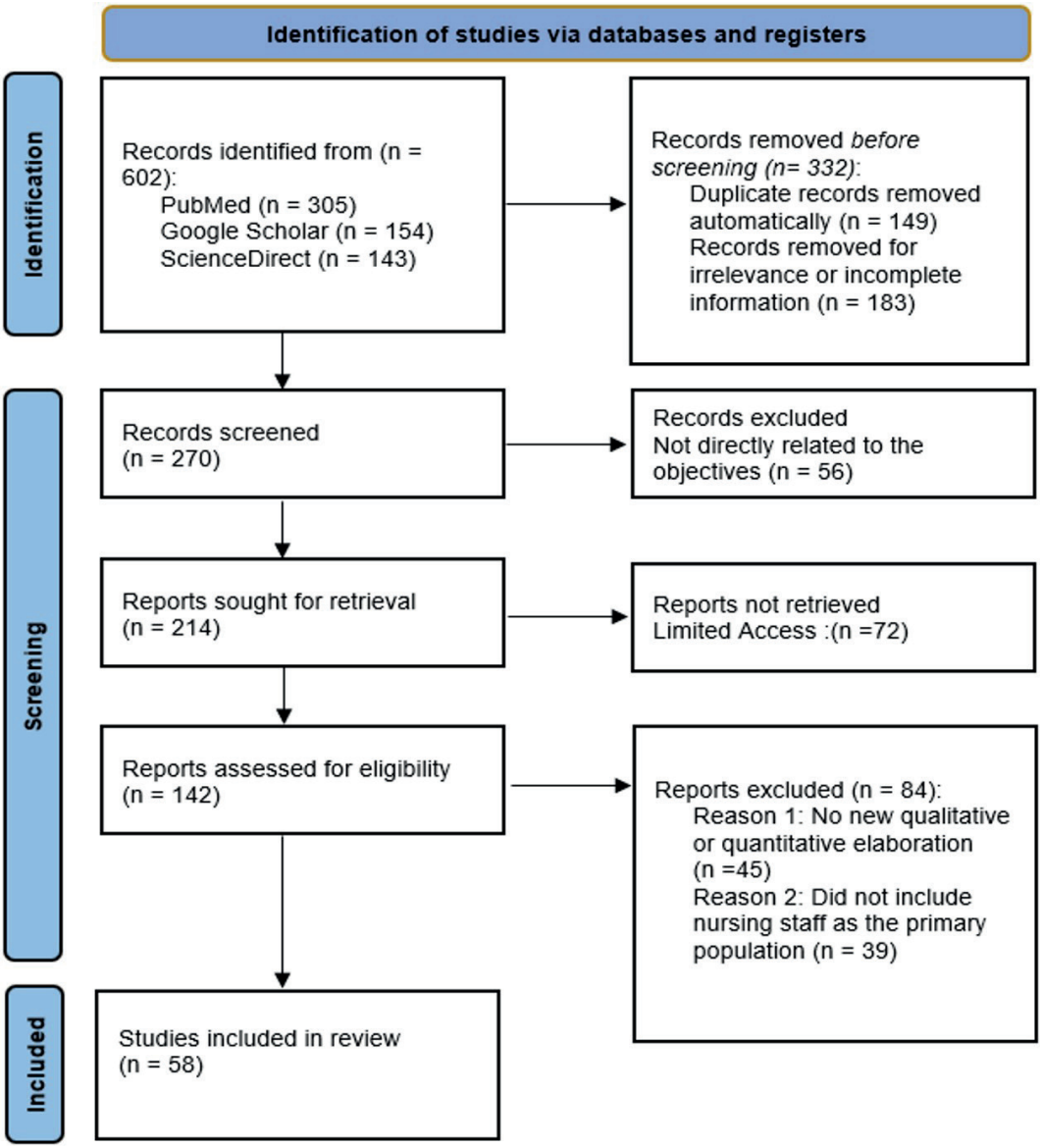

Figure 1. PRISMA 2020 flow diagram.

preliminary assessment, 332 records were eliminated: 183 were considered to be irrelevant, and 149 duplicates were removed with automation tools. Two hundred seventy studies remained for further assessment. Fifty-six records were eliminated during the preliminary screening, allowing 214 reports for full-text assessment. However, 72 reports were unable to be obtained due to access restrictions, leaving 142 studies for assessment. Eighty-four of these were disqualified for a variety of reasons: 39 were not focused on nursing staff, and 45 offered no novel perspectives on the psychological effects of radiation security protocols. In summary, 58 studies were evaluated, offering instructive insights into the mental health problems—such as anxiety, stress, burnout, and mechanisms for coping—of nursing professionals in radiotherapy.

Psychological challenges faced by nursing staff

Radiation safety protocols in radiotherapy departments are essential to ensure the protection of both patients

and staff; nevertheless, nursing staff have to work closely with radiation-emitting equipment and sources, and these protocols cause significant psychological impacts on patients as well (7). Even when stringent safety measures are in place, constant adjacency to radiation sources can lead to heightened stress and anxiety (8). Research has shown that elevated stress during procedures involving radiation has been frequently reported by nurses, with concerns provoked by the potential for accidental exposure (9). This stress stems not only from immediate risks but also from the long-term effects of radiation exposure, even within regulatory constraints. Insomnia, irritability, and hypervigilance can be caused by persistent stress, impacting both professional performance and personal well-being (10).

Although safety limits have been assured, worries about the cumulative effects of radiation exposure persist, and nursing staff in radiotherapy experience a great deal of mental strain due to the fear of long-term health effects (11). Long-term exposure to ionizing radiation has been associated with a number of health hazards, including genetic mutations and cancer, justifying this fear (12). Chronic stress and anxiety due to the uncertainty surrounding potential long-term effects have an impact on their overall quality of life and job satisfaction (13).

The cumulative effects of anxiety, stress, concerns about risks to long-term health, compassion fatigue, and burnout can have a substantial impact on the emotional and physical well-being of nursing professionals in radiotherapy (14). Nurses often experience emotional depersonalization and fatigue due to the continual attention to detail required to comply with safety procedures (15). In addition, the psychological implications of this strain can impact lifestyle contentment and interpersonal interactions outside of the work environment (16).

In radiotherapy departments, organizational culture has an important effect on whether these psychological effects are mitigated or worsened. Stress levels can be substantially reduced in supportive work environments that place a high priority on employee training, offer adequate radiation safety resources, and promote open discussion (17). On the other hand, an absence of organizational support or a perceived neglect for the well-being of employees may exacerbate feelings of isolation and anxiety among nurses (18).

Factors influencing psychological impact

For the purpose of delivering therapeutic doses to cancerous tissues while limiting exposure to healthy cells, radiation therapy involves the use of ionizing radiation, such as photons (X-rays) and particles (protons and electrons) (19). Safety profiles for different kinds of radiation vary significantly, which has consequences for healthcare providers' occupational safety along with patient outcomes. Since it allows for deep tissue penetration, photon-based therapies are frequently employed; and they require careful monitoring and shielding to avoid unintentional exposure (20). Particle therapies, such as proton therapy, offer accurate targeting but necessitate rigorous adherence to safety protocols to prevent operational mistakes and minimize the effects on employees (21).

Workload pressures, institutional safety culture, equipment reliability, and the sophisticated nature of safety protocols are among the numerous variables that influence adherence. These procedures present specific challenges for oncology nursing staff in radiotherapy departments, which may influence their stress levels and mental health (22). Procedural compliance and psychological resilience in radiation treatment settings are emphasized by the fact that noncompliance, whether as a consequence of human error or equipment malfunctions, may increase anxiety and lower confidence (23).

An abundance of support systems and tools have been established to assist nurses in radiotherapy departments in managing occupational stress caused by the emotional burden that their position places on them. These systems and tools, which comprise both internal and external aid, include peer support, counselling, radiation safety training, and alterations that reduce physical strain (24). Additionally, comprehensive support frameworks might assist radiotherapy departments in establishing healthier workplaces through improved psychological resilience and job satisfaction (25).

Coping mechanisms and support strategies

Radiation safety education and training are necessary to mitigate the psychological impact on nursing staff in radiation therapy departments. Those who obtain thorough and continuous instructions become more capable of understanding radiation risks and carrying out security measures (26).

Nurses' anxiety and fears about potential hazards can be mitigated by well-designed training programs while simultaneously improving their confidence when performing radiation-related duties. Nurses also feel more empowered and in charge of their work environment when they have become familiar with safety regulations and radiation protection strategies. Maintaining higher awareness reduces the psychological impact of working in a high-risk environment, and this encourages adherence to procedures (27). Ongoing education, which keeps nurses up to date on the recent advancements in radiation safety, improves their competence and adaptability which are required for maintaining vigilance and guaranteeing adherence to the evolving safety regulations (28). Frequent training, psychological support programs and counselling services strengthen nurses' ability to manage the anxiety and stress of their profession, resulting in advantages when dealing with the overall emotional strain caused by their profession (29,30).

Research has shown that access to counselling services allows nurses to process their feelings in a secure atmosphere (31). Nurses can mitigate emotional distress and exhaustion by addressing issues related to radiation exposure and exploring coping mechanisms. Moreover, counselling helps individuals develop adaptive coping strategies and resilience, which enable them to better handle stress at work (32). Nursing staff members also feel more united and supported when they engage in psychological support programs designed specifically for healthcare professionals (33). Nurses can share their experiences, coping mechanisms, and encouragement with one another in peer support groups and debriefing sessions (34). These initiatives help create a welcoming environment where nurses in radiotherapy feel appreciated, understood, and less isolated. Establishing resilient environments for nursing staff necessitates strong team dynamics as well as assistance from fellow employees and superiors. A supportive environment where nurses feel valued and respected is established by cooperative teamwork and positive interpersonal relationships (35). Cohesive team dynamics have been shown to reduce the psychological effects of radiation safety procedures. Effective teamwork and open communication allow fellow employees to share duties, assist one another through difficulties, and offer emotional support, which enhances job satisfaction and lowers anxiety and isolation among nursing staff (36).

In addition, supportive supervision is necessary for encouraging nurses' well-being and growth as professionals. Compassionate supervisors who concentrate on staff welfare, offer constructive feedback, and appreciate nurses' efforts encourage a positive work culture. By addressing nurses' concerns rapidly and acknowledging their efforts, supervisors develop confidence and trust within the team, which improves the overall work environment in radiotherapy departments (37).

Case studies and experiences

The psychological challenges faced by nursing staff in radiotherapy departments can be better understood with case studies. Strict radiation safety procedures have a bearing on nursing staff, according to a significant study from a large US hospital. The study found that strict adherence to safety standards for the protection of both patients and staff frequently caused nurses to experience more stress and anxiety. Concerns regarding radiation exposure remained despite precautions, which had an adverse effect on well-being and work performance. Increased exhaustion among nursing staff was linked to this persistent fear (38).

Improving psychological health, treatment adherence, quality of life, and the well-being of patients and healthcare providers all rely on effective communication in oncology. Oncology nurses, however, face challenges in this regard. A total of 121 inpatient oncology nurses participated in a survey between November 2012 and March 2014, which revealed common challenges including stress management,

empathetic communication, and handling end-of-life conversations (39).

Different approaches to dealing with the psychological impacts of radiation safety protocols on nursing staff have been highlighted by experiences from radiotherapy departments around the world. Nurses at Japanese hospitals, which are known for their strict security standards, emphasized the significance of continuing education and training in reducing radiation exposure anxiety. According to these nurses, staff confidence was strengthened through methodical training programs and simulations, which helped them follow procedures successfully while safeguarding their psychological well-being (40).

The case report highlights two emergency department visits of patients that had undergone iodine-125 seed brachytherapy implanted in the abdominal wall in oncologic management. The unavailability of documented or communicated information on radiation therapy exposed the medical personnel on duty to a lot of occupational exposure. These occurrences highlight the intrinsic risks posed to the frontline clinicians due to lack of awareness and lack of documentation of the procedure of brachytherapy. To this effect, this report recommends that strong surveillance systems, specialized employee training programs, and well-defined working guidelines should be adopted to reduce this risk eventuality amid an incident (41).

In a recent study, the occupational radiation exposure of intensive care unit (ICU) nurses, who might be at risk from regular chest X-rays, was monitored. Five nurses wore film badge dosimeters for eight weeks, and three badges recorded levels beneath detection limits, while two measured 0.05 mSv each. ICU nurses would remain within recommended dose limits, according to extrapolated annual exposure. In accordance with the study's outcomes, nurses may deliver patient care without worrying about serious medical problems, as standard radiation protection measures effectively minimize exposure risks (42).

The knowledge and attitudes of final-year nursing students in the United Arab Emirates about radiation protection were studied in a 2022 online cross-sectional survey. The outcomes demonstrated that 52% of the participants were not aware of radiation protection courses and had significant knowledge gaps. Many students acknowledged the importance of radiation safety, even though they were deficient in practical knowledge about radiation risks and the ALARA (As Low As Reasonably Achievable) principle. The research emphasized the necessity for broadened educational initiatives that prepare nursing students for expected radiation safety challenges (43).

Impact of technology and innovation

Radiation oncology nurses are currently employed in a much safer environment as a result of advances in safety equipment and techniques. Radiation handling is usually dangerous for patients and medical personnel, specifically those who give treatments. Protocols have evolved as a result of the implementation of advanced safety measures such as automated shielding systems, remote-controlled devices, and real-time dosimeters. By lowering direct radiation exposure and associated anxiety, these innovations enhance patient safety while minimizing the emotional burden on nursing staff (44,45).

During treatments, automated shielding systems minimize the necessity for manual adjustments by nursing staff by enabling efficient and precise manipulation of radiation barriers. Nurses may utilize treatment equipment remotely by utilizing the benefits of novel interfaces that provide thorough monitoring and control capabilities. By mitigating physical proximity to radiation sources, this remote functionality not only enhances safety but also preserves nurses' self-reliance when performing treatments from safer areas within the department (46).

Subsequently, technological advancements have mitigated stress among nurses by improving patient care, safety, and workflow efficiency. Fear of radiation exposure and its adverse health consequences is a major source of stress for nursing staff. Cone-beam CT and MRI-guided radiation therapy are examples of modern imaging systems that enable more precise tumor targeting, minimize the need for repeated procedures and extended exposure, and shorten the duration of treatment (47).

Additionally, new planning simulation tools and software have made it feasible for medical professionals to design customized radiation treatment plans that are suitable for each patient's distinctive anatomical and clinical requirements (48). By streamlining the treatment process, these tools free up nurses' time from administrative duties and enable them to concentrate more on offering direct patient care. By transitioning from manual to automated systems, nursing staff may offer higher-quality care with fewer administrative burdens, improve efficiency, and enhance job satisfaction (49). In conclusion, the psychological health of nursing staff in radiotherapy departments has benefited from incorporating technology into safety procedures. In addition to providing devices that enhance control, efficiency, and precision in patient care, advanced safety equipment and procedures have reduced exposure risks (50).

DISCUSSION

Improving safety procedures in radiotherapy departments and decreasing the psychological stress on nursing staff require resilient policy recommendations. Prioritizing the well-being of patients and employees also requires straightforward, comprehensive, and frequently revised regulations that integrate the most recent developments in radiation safety technology and industry best practices. To ensure that nursing staff members are adequately trained to employ safety equipment and comply with established protocols, regular workshops and training sessions should be put in place (51).

A system that enables employees to report security concerns or incidents without fear of reprisals ought to be implemented. Transparency and continuous organizational improvement can be encouraged by an anonymous evaluation procedure (52). In addition, collaboration between medical physicists, safety officers, radiation oncologists, and nursing staff is necessary (53). To assess security protocols, evaluate incidents, and define areas for improvement, regular multidisciplinary discussions should be conducted (54). By incorporating a variety of opinions into the establishment of policies, a collaborative approach encourages a team-based safety culture. Adequate funding ensures the advancement and maintenance of safety equipment, while adequate staffing levels minimize workload pressures that can result in errors. Furthermore, using technology to decrease human error and automate safety checks strengthens the efficacy of safety procedures (55).

To reduce the mental impact of working in a highly stressful environment, it is essential that nursing professionals in radiotherapy departments receive better psychological support. Detecting stress, anxiety, or exhaustion in nursing staff requires proactive steps such as routine psychological assessments. These issues can be reduced through early interventions such as counseling, support groups, and communication with mental health professionals (56). Peer support programs, in which skilled nurses offer emotional support and mentoring, foster consistency, and reduce anxiety and isolation (57).

To provide nurses with the resources they require for dealing with challenging circumstances, training programs that include stress management, resilience building, and coping strategies should be implemented on a regular basis (58). Promoting a balance between work and life is also essential, and policies that prevent excessive overtime, provide flexible scheduling, and ensure appropriate rest periods can all help minimize burnout while improving overall well-being (59). To minimize stigma, leaders must prioritize open communication, address staff concerns, and encourage open conversations about mental health to establish a supportive organizational environment. Programs that recognize the accomplishments and contributions of nursing staff can also boost morale and job satisfaction (60).

Future studies should concentrate on significant subjects for enhancing the mental health of radiotherapy nursing staff. In order to evaluate the long-term consequences of radiation exposure and safety policies, such as cumulative anxiety, burnout, and retention rates, longitudinal studies are necessary (61). The application of automation and technology to reduce stress while enhancing safety is another intriguing field of study. Research should investigate the methods by which modern technologies, including robotics, artificial intelligence, and remote surveillance systems, may help nursing staff in fulfilling their

responsibilities and reducing psychological stress (62). To further address specific challenges encountered by diverse nursing populations, attention is required to develop culturally relevant interventions. These approaches should consider factors such as socioeconomic status, gender, and ethnicity, as well as their impact on coping strategies and psychological well-being (63). Collaborative research projects by multidisciplinary teams are crucial for the beneficial development and implementation of scientifically supported treatments that strengthen psychological well-being and safety in radiotherapy departments (64).

CONCLUSION

The psychological effects of radiation security measures on radiotherapy department nursing staff highlight the serious mental health issues that these staff members encounter. As a result of close proximity to sources of radiation and stringent safety regulations, 58 studies were selected from a total of 602 records, which demonstrate the stress, anxiety, and burnout that healthcare workers endure.

The need to preserve the lives of patients and healthcare specialists promotes the need to ensure that the safety measures are directed at reducing the physical and psychological suffering. These precautions must address the issues on the short-term exposure and the possible longer-run health risks. This reiterates the important role of providing access to psychological resources, continuous training as well as conducive organizational settings. This support is necessary in order to curb the long-term anxiety that negatively influences the job satisfaction.

Technological applications, such as remote-controlled devices and automated shielding systems, may reduce radiation exposure for nursing staff and decrease psychological stress. A healthier workplace, elevated job satisfaction, and the well-being of nursing professionals in radiotherapy depend upon a multifaceted strategy that involves training, support networks, and modern technology.

Author contribution

Surgical and Medical Practices: SL; Concept: SL; Design: SL; Data Collection or Processing: SNH; Analysis or Interpretation: SL, SNH; Literature Search: SNH; Writing: SL, SNH. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

A rare clinical presentation of lumbosacral radiculopathy: Denervation pseudohypertrophy of bilateral calf muscles

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ABSTRACT

Denervation from various conditions typically results in muscular atrophy; in contrast, a paradoxical volumetric increase can also rarely occur in affected muscles, which is called denervation pseudohypertrophy. Although this condition may potentially affect any muscle group, it is most commonly seen in the calf muscles. When evaluating patients with painless calf muscle enlargement, denervation pseudohypertrophy is an important differential diagnosis that should be considered. Radiological imaging methods and electromyography (EMG) are useful for differentiating pseudohypertrophy from muscular hypertrophy. Identifying denervation pseudohypertrophy requires multidisciplinary evaluation. Alongside radiological imaging and EMG findings, patient's detailed medical history and physical examination remain essential components of the diagnostic process. In this case report, we aim to present a 73-year-old man with bilateral calf muscle denervation pseudohypertrophy due to S1 radiculopathy, along with the relevant literature.

Keywords: magnetic resonance imaging, denervation, pseudohypertrophy, calf muscles, radiculopathy

INTRODUCTION

Muscle denervation may occur due to various conditions, ranging from trauma and metabolic neuropathies to autoimmune and infectious causes, and radiculopathy (1,2). Denervation in muscle tissue typically leads to atrophy in muscle fibers and reduction in overall muscle volume. In some cases, it can conversely cause volumetric increase due to fat deposition among muscle fibers. Denervation pseudohypertrophy is a paradoxical increase in muscle volume attributable to adipose tissue accumulation rather than atrophy following denervation (3). To distinguish between hypertrophy and pseudohypertrophy in muscle tissue, radiological and electrophysiological imaging techniques are used. In this article, we aimed to present a patient with bilateral calf muscle denervation pseudohypertrophy secondary to S1 radiculopathy, along with previous findings in the literature.

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CASE REPORT

A 75-year-old man presented with complaints of swelling in his lower legs for approximately one year. He also had concerns about bilateral intermittent pain radiating from the waist to the legs, along with weakness, more pronounced on the left side, that has been present for the past three years. The patient's medical history included lumbar disk herniation surgery (ten years ago), hypertension, and coronary artery disease. There was no previous history of trauma or fracture. There was no palpable focal swelling on physical examination, but a diffuse volumetric increase was observed at the level of both calf muscles, more prominent on the left. Peripheral pulses could be felt, and there was no pain with palpation.

Ultrasonography (US) images showed increased volume and diffuse echogenicity with fibrillary pattern in the bilateral soleus and gastrocnemius muscles (Figure 1). Magnetic Resonance Imaging (MRI) examination revealed a volume increase in the soleus and gastrocnemius muscles on both sides, hyperintensity similar to adipose tissue on T1WI and T2WI, and signal suppression on fat-suppressed images. No pathological contrast enhancement was detected on post-contrast images (Figure 2).

When the patient's previous tests were reviewed, an electromyography (EMG) examination revealed a prolonged latency in both tibial nerves, more on the left, and a decrease in the amplitude of the motor response, while no motor response was obtained in the left peroneal nerve. H reflex could not be obtained in either soleus muscle. Chronic neurogenic involvement was detected in muscles innervated by the bilateral S1 root and segment, which was moderate to severe on the left and moderate on the right. Bilateral S1 root compression was observed as an underlying cause in the lumbar MRI (Figure 3). When the patient's imaging findings, history, and EMG results were evaluated together, the findings were considered consistent with denervation pseudohypertrophy.

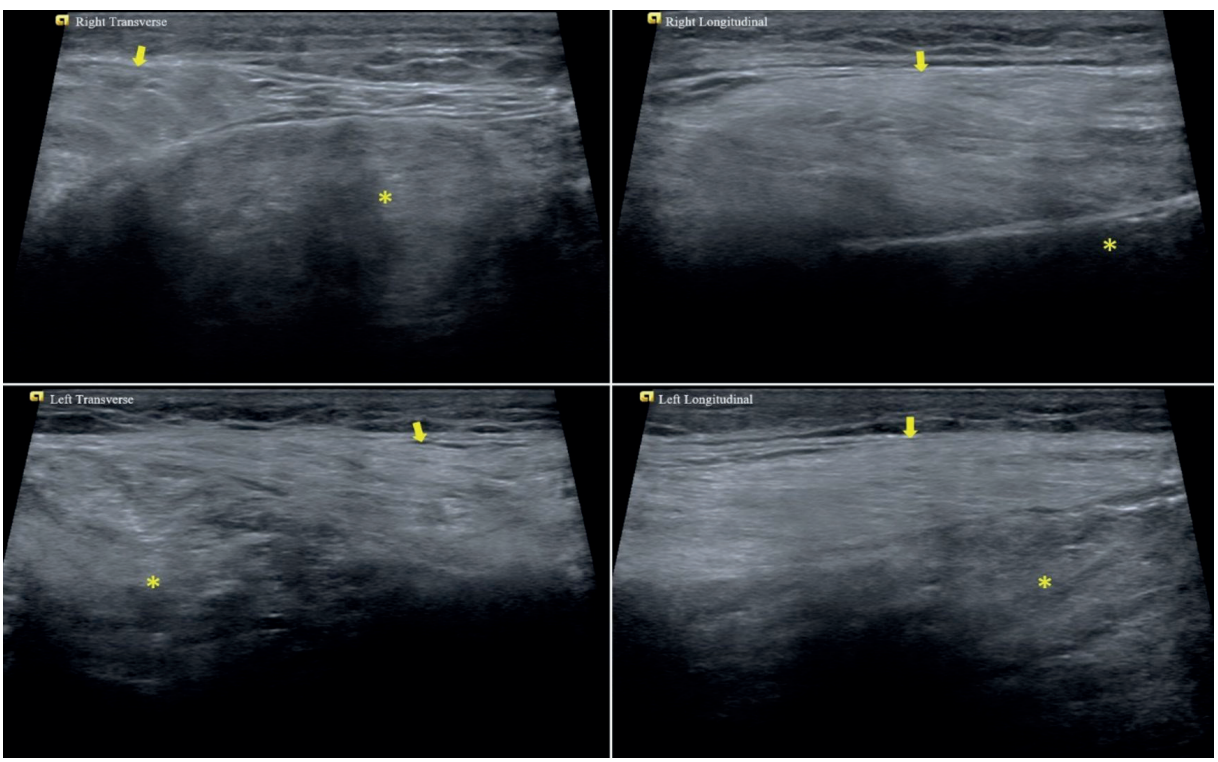

Figure 1. Ultrasonography images show an increase in volume and diffusely increased echogenicity with fibrillary pattern in the bilateral soleus (asterisks) and gastrocnemius muscles (arrows).

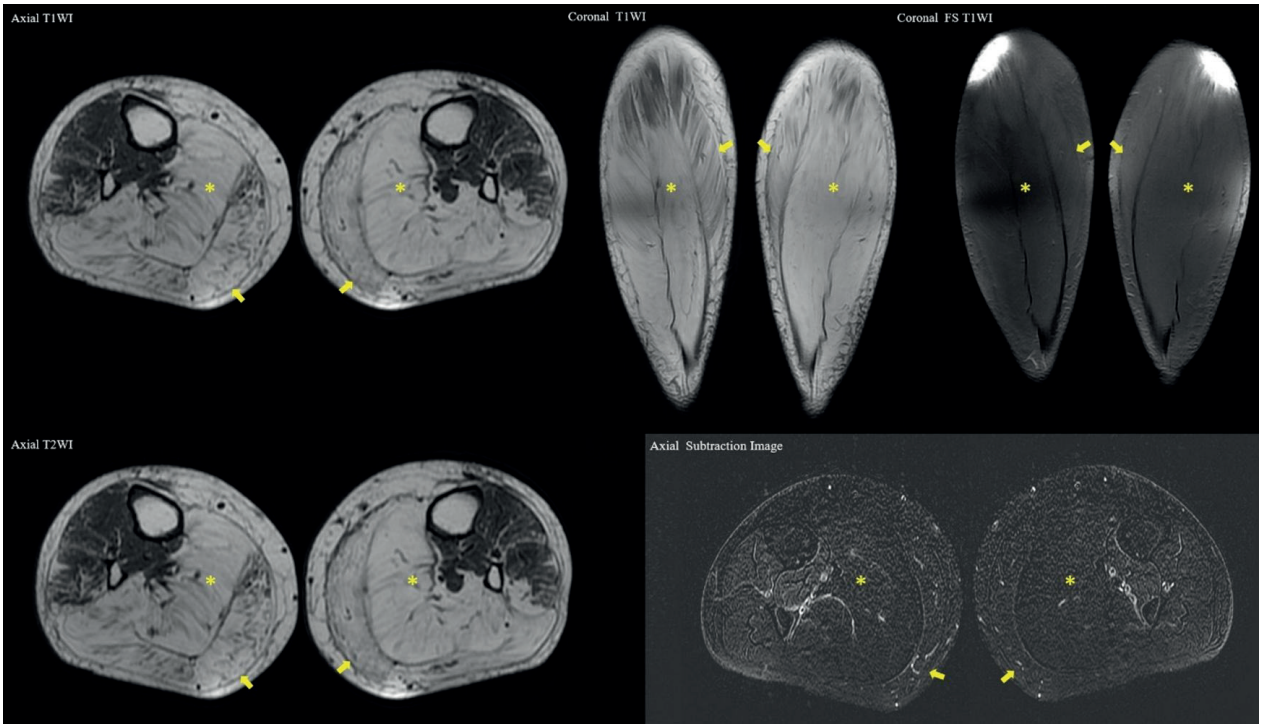

Figure 2. MRI images show hyperintensity and increased volume in the soleus (asterisks) and gastrocnemius muscles (arrows) on both axial and coronal T1W and T2W images, and signal suppression on coronal fat-suppressed T1W images. No pathologic contrast enhancement was observed on axial subtraction images.

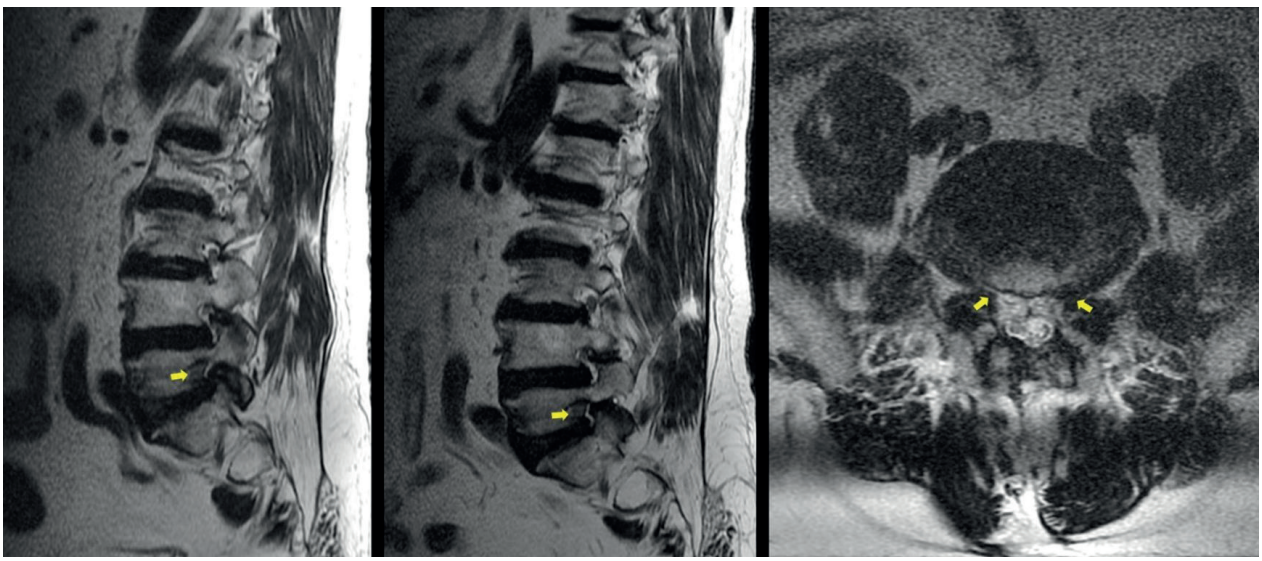

Figure 3. Sagittal and axial T2W lumbar MRI images show compression of bilateral S1 roots (arrows).

DISCUSSION

Conditions that cause damage to nervous tissue characteristically result in muscle atrophy due to denervation. However, pseudohypertrophy may also be observed in response to denervation, although much less frequently (2). De Beuckeleer et al. reported the pathophysiology of fatty infiltration in denervation pseudohypertrophy (4). While muscle fiber dimensions decrease after nerve damage, pluripotent mesodermal cells form lipocytes, causing fatty infiltration. Cases of denervation pseudohypertrophy resulting from various causes have been reported in the literature. Reported causes include trauma, poliomyelitis (5), muscular dystrophy (6), diabetic neuropathy (7), and radiculopathy (8). As in our case, the literature indicates that the most commonly affected muscle group is the calf muscles, and the most frequently reported cause is S1 radiculopathy (9).

Patients often present with a clinical picture of painless swelling in the muscles accompanied by muscle weakness or asymmetrical increase in the circumference of the legs. Although less common, patients may also experience fasciculations and muscle pain (9). In the literature, denervation pseudohypertrophy has usually been reported as unilateral (10). In unilateral cases, deep infiltrating intramuscular lipoma is an important differential diagnosis. Although the patient's clinical history and presentation are important guides for differentiation, histopathological evaluation may be required to make distinctions in some cases (11). In our case, unlike what is mostly reported in the literature, there was bilateral pseudohypertrophy due to bilateral chronic compression at the S1 level. In cases of bilateral pseudohypertrophy, Duchenne Muscular Dystrophy (DMD) is included in the differential diagnosis. DMD is an X-linked genetic disease, which is the most common type of muscular dystrophy in children. DMD is a progressive disorder that can affect not only skeletal muscles, but also the heart and respiratory muscles over time. This progression can cause serious complications involving the circulatory and respiratory systems, such as cardiac impairment and respiratory insufficiency, which are the major causes of death in this group of patients during early adulthood (12). In patients with DMD, the onset of symptoms during childhood and the progressive involvement of additional muscle groups are helpful findings for differential diagnosis from denervation pseudohypertrophy (3).

The main imaging finding is an increase in the size of the affected muscles and an increase in the amount of fat within the muscle, while the normal muscular fibrillar pattern is preserved. On US, this presents as an increase in volume and echogenicity, along with preservation of the linear and feather-like fibrillar structure (4). In computed tomography, it is observed as an increase in volume and a decrease in density in the affected muscles, with preservation of its feather-like fibrillar pattern. On MRI, along with increased muscle size, high signal areas that are isointense with fat tissue on T1WI are observed within the fibrillar structure. In these areas, signal suppression occurs in fat-suppressed sequences (13). The general approach to demonstrating muscle denervation is clinical and EMG-based, but besides its diagnostic assistance, radiological imaging may also help demonstrate underlying pathologies (14).

There are no established treatment guidelines for denervation pseudohypertrophy. Although spontaneous recovery has been reported in the literature, treatment methods may include decompression surgery for the underlying cause, cortisone treatment, anticonvulsants, and botulinum toxin (9,15).

In conclusion, denervation hypertrophy is an important differential diagnosis to consider in patients presenting with painless enlargement of the lower leg muscles. The diagnosis of denervation pseudohypertrophy necessitates a comprehensive approach that incorporates clinical history, thorough physical examination, EMG, and radiological findings. MRI plays a crucial role not only in diagnostic imaging but also in revealing the underlying cause.

Ethical approval

Written informed consent was obtained from the participant.

Author contribution

Surgical and Medical Practices: ED; Concept: MB, ED; Design: MB, ED; Data Collection or Processing: OB; Analysis or Interpretation: OB, ED; Literature Search: OB, MB; Writing: OB, MB. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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