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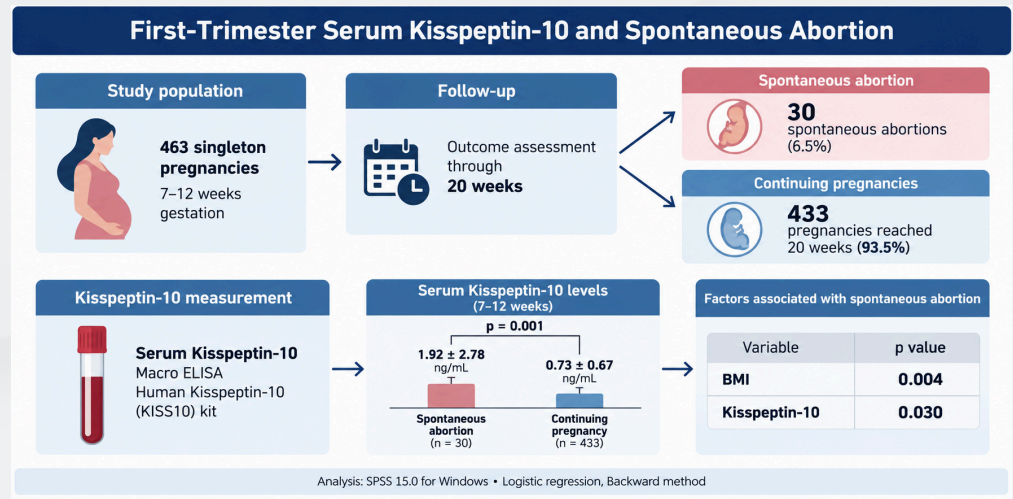


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Published: 2026-10-31

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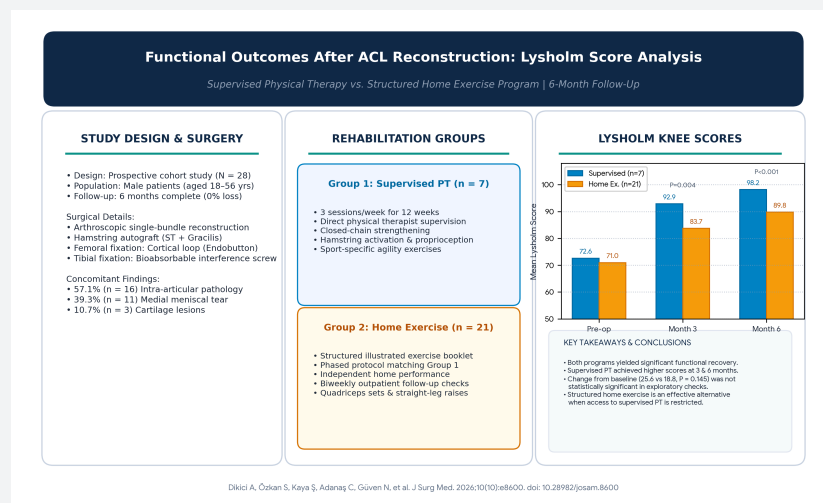


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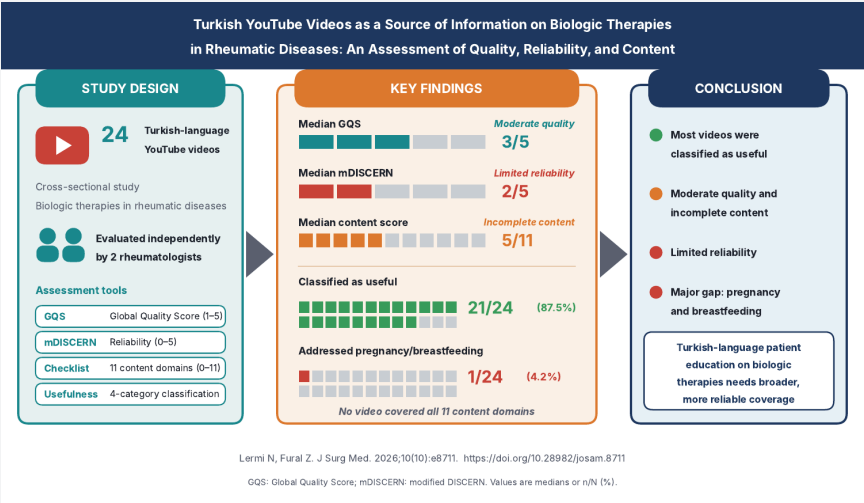
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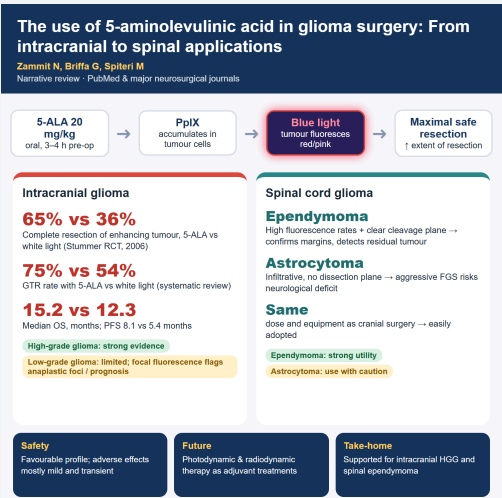
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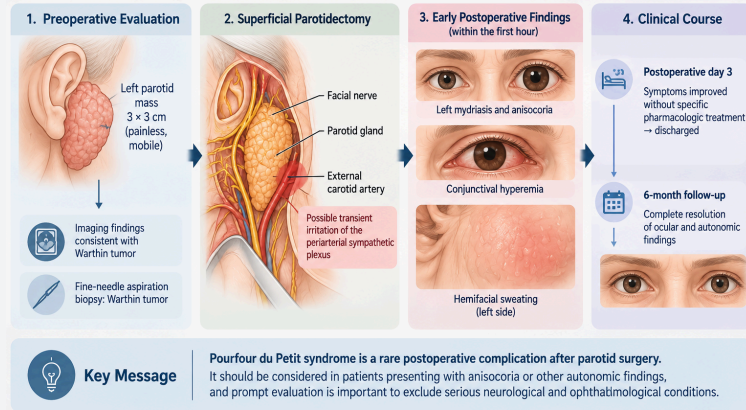
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First-Trimester Serum Kisspeptin-10 Levels as a Predictor of Spontaneous Abortion: A Prospective Cohort Study

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Ethical Approval

The study was approved by the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital, Health Sciences University (Approval No. 2011-KAEK-25 2016/12-01; June 22, 2016).

Informed Consent

Written informed consent was obtained from the participants after they were informed about the study.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

The authors declared that this study received no financial support.

CRedit Author Statement

Bilal Efe: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft.
Emin Üstünyurt: Supervision, Writing – Review & Editing, Tayfur Çift: Supervision, Investigation, Writing – Review & Editing, Muzaffer Temur: Supervision, Investigation, Writing – Review & Editing, Engin Korkmaz: Supervision, Investigation, Writing – Review & Editing.

Use of AI Statement

No generative AI or AI-assisted tools were used in the preparation of the manuscript.

Data Availability

The data are not publicly available because they contain clinical information obtained from human participants and are subject to ethical and institutional restrictions. De-identified data may be available from the corresponding author upon reasonable request, subject to institutional and ethical requirements.

Published

2026 October 8

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Abstract

Background/Aim: Spontaneous abortion remains a common complication of early pregnancy, and biomarkers reflecting placental function may improve risk assessment after fetal cardiac activity has been confirmed. This study aimed to evaluate the predictive value of first-trimester serum kisspeptin-10 levels for spontaneous abortion in pregnancies with confirmed fetal cardiac activity.

Methods: This prospective observational study included singleton pregnancies between 7 and 12 weeks of gestation with documented fetal cardiac activity. Serum kisspeptin-10 concentrations were measured using an enzyme-linked immunosorbent assay. Pregnancies resulting in spontaneous abortion before 20 weeks were compared with randomly selected controls whose pregnancies progressed beyond 20 weeks. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of spontaneous abortion.

Results: Among 463 eligible pregnancies, 30 resulted in spontaneous abortion, and 60 controls were selected from pregnancies progressing beyond 20 weeks. Mean serum kisspeptin-10 levels were significantly lower in the spontaneous abortion group than in controls (0.73 (0.67) ng/mL vs. 1.92 (2.78) ng/mL, $P = 0.001$). Multivariate analysis demonstrated that lower serum kisspeptin-10 levels ($P = 0.030$) and higher body mass index ($P = 0.004$) were independently associated with spontaneous abortion.

Conclusion: Lower first-trimester serum kisspeptin-10 levels are associated with an increased risk of spontaneous abortion in pregnancies with confirmed fetal cardiac activity. Kisspeptin-10 may serve as a supplementary biomarker for early pregnancy risk stratification.

Keywords: spontaneous abortion, kisspeptin-10, early pregnancy, biomarker

Introduction

Spontaneous abortion is the most common complication of early pregnancy and affects approximately 10–15% of clinically recognized gestations. Despite improvements in antenatal care and diagnostic modalities, most pregnancy losses occur during the first trimester, often without an identifiable cause [1, 2]. Importantly, even in pregnancies with confirmed fetal cardiac activity, the risk of subsequent pregnancy loss remains clinically significant and poses challenges in patient counseling and management [2, 3].

Current strategies for predicting early pregnancy loss rely primarily on ultrasonographic findings and biochemical markers such as serum β -human chorionic gonadotropin (β -hCG) and progesterone levels. However, once fetal viability has been established, the predictive performance of these markers is limited because they primarily reflect embryonic development rather than placental function [4]. Consequently, there is increasing interest in identifying biomarkers that reflect early placentation and trophoblastic activity, which play a central role in pregnancy maintenance.

Kisspeptins are a family of peptides encoded by the KISS1 gene and are well recognized for their role in regulating the hypothalamic-pituitary-gonadal axis [5-7]. Beyond their central effects, kisspeptins are highly expressed in the placenta, particularly in trophoblastic tissue during pregnancy [8]. Placental trophoblasts represent the primary source of circulating kisspeptins in pregnant women, with serum concentrations rising progressively throughout gestation and declining rapidly following delivery [8, 9].

Experimental data indicate that kisspeptins regulate trophoblast invasion, angiogenesis, and implantation through autocrine and paracrine mechanisms [10, 11]. By limiting excessive trophoblastic invasion, kisspeptins contribute to controlled placental development and stability of the maternal-fetal interface. Dysregulation of these processes has been implicated in adverse pregnancy outcomes, including spontaneous abortion, preeclampsia, and fetal growth restriction [8].

Clinical studies evaluating circulating kisspeptin levels in early pregnancy have suggested an association between reduced kisspeptin concentrations and adverse pregnancy outcomes. Lower plasma or serum kisspeptin levels have been reported in women presenting with threatened miscarriage and in those who subsequently experienced early pregnancy loss [12, 13]. However, existing studies are heterogeneous with respect to study design, gestational age at sampling, and inclusion criteria. Importantly, many studies have included pregnancies without confirmed fetal cardiac activity, limiting their applicability to clinically viable pregnancies.

Therefore, the predictive value of serum kisspeptin-10 levels in pregnancies with documented fetal cardiac activity remains insufficiently defined. The present study aimed to evaluate whether first-trimester serum kisspeptin-10 levels are associated with spontaneous abortion in singleton pregnancies between 7 and 12 weeks of gestation with confirmed fetal cardiac activity and to assess the independent predictive value of kisspeptin-10 alongside established clinical factors.

Materials and methods

Study Design and Population

This prospective observational cohort study with a nested case-control analysis was conducted at the Department of Obstetrics and Gynecology, Bursa Yüksek İhtisas Training and Research Hospital, between June 2016 and September 2016. The study was approved by the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital, Health Sciences University (Approval No. 2011-KAEK-25 2016/12-01; June 22, 2016). The study was conducted and reported in accordance with the STROBE guidelines.

Singleton pregnancies between 7 and 12 weeks of gestation with documented fetal cardiac activity on ultrasonography were eligible for inclusion.

Exclusion criteria included multiple pregnancy, known fetal chromosomal or structural abnormalities at enrollment, ectopic or molar pregnancy, chronic systemic disease requiring medical treatment, and use of hormonal medication during early pregnancy.

Study Groups

A total of 463 eligible pregnant women were enrolled. Pregnancies resulting in spontaneous abortion before 20 weeks of gestation constituted the study group. A control group was randomly selected from pregnancies that progressed beyond 20 weeks without complications. The final analysis included 30 pregnancies in the spontaneous abortion group and 60 pregnancies in the control group.

Data Collection

Maternal age, obstetric history, body mass index (BMI), gestational age at blood sampling, and pregnancy outcomes were recorded prospectively. All participants underwent standardized ultrasonographic evaluation confirming fetal cardiac activity at enrollment.

Measurement of Serum Kisspeptin-10

Venous blood samples were obtained at enrollment. Serum samples were separated and stored in accordance with the manufacturer's instructions. Serum kisspeptin-10 concentrations were measured using a commercial human kisspeptin-10 enzyme-linked immunosorbent assay kit. Measurements were performed using a microplate washer and reader system, and results were expressed in ng/mL.

Statistical Analysis

Statistical analyses were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean (standard deviation) or median (range), as appropriate, and categorical variables as frequencies and percentages. Normality was assessed before selection of the statistical test. Normally distributed continuous variables were compared using Student's *t*-test, whereas non-normally distributed variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using the chi-square test. Univariate logistic regression analysis was used to identify potential predictors of spontaneous abortion. Variables with $P < 0.10$ in univariate analysis were included in multivariate logistic regression models. $P < 0.05$ was considered statistically significant.

Results

Of the 463 enrolled pregnancies, 30 resulted in spontaneous abortion before 20 weeks and were included in the study group, while 60 ongoing pregnancies served as controls.

Baseline demographic and clinical characteristics are presented in Table 1. There were no significant differences between the groups in maternal age, gestational age at sampling, gravidity, parity, or smoking status ($P = 0.480$, $P = 0.620$, $P = 0.710$, $P = 0.830$, and $P = 0.690$, respectively). However, body mass index was significantly higher in the spontaneous abortion group ($P = 0.004$).

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population

Variable	Spontaneous Abortion (n = 30)	Control Group (n = 60)	P-value
Maternal age (years)	28.6 (5.1)	27.9 (4.8)	0.480
Gestational age at sampling (weeks)	9.4 (1.6)	9.6 (1.5)	0.620
Body mass index (kg/m ²)	28.3 (3.9)	24.9 (3.6)	0.004
Gravidity	2 (1-4)	2 (1-5)	0.710
Parity	1 (0-3)	1 (0-3)	0.830
Smoking status, n (%)	6 (20.0%)	10 (16.7%)	0.690

Data are presented as mean (standard deviation) or median (range), as appropriate. Group comparisons were performed using Student's t-test or the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Abbreviations: BMI: body mass index, SD: standard deviation. * $P < 0.05$ was considered statistically significant.

Serum kisspeptin-10 levels were significantly lower in pregnancies that resulted in spontaneous abortion than in ongoing pregnancies ($P = 0.001$) (Table 2).

In univariate logistic regression analysis, higher body mass index and lower serum kisspeptin-10 levels were identified as significant predictors of spontaneous abortion (Table 3). In the multivariate model, both variables remained independently associated with spontaneous abortion (Table 4).

Table 2. Serum Kisspeptin-10 Levels According to Pregnancy Outcome

Parameter	Spontaneous Abortion (n = 30)	Control Group (n = 60)	P-value
Serum kisspeptin-10 (ng/mL)	0.73 (0.67)	1.92 (2.78)	0.001

Serum kisspeptin-10 concentrations were measured between 7 and 12 weeks of gestation using an enzyme-linked immunosorbent assay. Comparisons were performed using the Mann-Whitney U test. * $P < 0.05$ was considered statistically significant.

Table 3. Univariate Logistic Regression Analysis for Predictors of Spontaneous Abortion

Variable	OR	95% CI	P-value
Maternal age (per year)	1.03	0.95-1.11	0.460
Gestational age (per week)	0.92	0.74-1.14	0.440
Body mass index (per kg/m ²)	1.18	1.05-1.33	0.004
Serum kisspeptin-10 (per ng/mL)	0.54	0.31-0.94	0.030

Univariate logistic regression analysis was performed to evaluate potential predictors of spontaneous abortion. Abbreviations: OR: odds ratio, CI: confidence interval. * $P < 0.05$ was considered statistically significant.

Table 4. Multivariate Logistic Regression Analysis of Independent Predictors of Spontaneous Abortion

Variable	Adjusted OR	95% CI	P-value
Body mass index (per kg/m ²)	1.21	1.06-1.38	0.004
Serum kisspeptin-10 (per ng/mL)	0.57	0.33-0.98	0.030

Multivariate logistic regression analysis adjusted for maternal age and gestational age at blood sampling. Abbreviations: OR: odds ratio, CI: confidence interval. * $P < 0.05$ was considered statistically significant.

Discussion

The present study demonstrates that reduced first-trimester serum kisspeptin-10 levels are associated with subsequent spontaneous abortion in pregnancies with confirmed fetal cardiac activity. By focusing specifically on clinically viable pregnancies, these findings provide evidence that biomarkers reflecting placental function may offer additional prognostic value beyond conventional embryonic markers.

Early pregnancy maintenance depends on tightly regulated trophoblastic invasion and placental development. Kisspeptins, primarily produced by placental trophoblasts, are known to modulate these processes through autocrine and

paracrine signaling pathways [14]. While β -hCG and progesterone measurements have limited predictive value after fetal cardiac activity is established, placental biomarkers such as kisspeptin offer a biologically plausible alternative [15].

The placenta represents the principal source of circulating kisspeptins during pregnancy [12, 16, 17]. Experimental studies have shown that kisspeptin signaling limits excessive trophoblast invasion while supporting angiogenesis and implantation. Therefore, reduced circulating kisspeptin levels may reflect impaired placentation and instability at the maternal-fetal interface, which are key mechanisms underlying early pregnancy loss. Previous clinical studies have consistently reported lower circulating kisspeptin levels in women with threatened miscarriage or early pregnancy loss [12, 18-20]. However, many of these studies included heterogeneous populations without confirmed fetal cardiac activity, limiting their clinical applicability. By restricting the study population to pregnancies with documented fetal viability, the present study addresses a more specific and clinically relevant scenario in which traditional biomarkers such as β -hCG and progesterone are less informative. In this context, kisspeptin may serve as a surrogate marker of placental integrity rather than embryonic development.

An additional important finding of this study is the independent association between increased maternal body mass index and spontaneous abortion. Maternal adiposity is associated with chronic low-grade inflammation, altered adipokine secretion, and metabolic dysregulation, all of which may adversely affect placental development and function. These pathways may influence trophoblastic activity and potentially modulate placental peptide secretion, including kisspeptin. This interaction suggests a biologically plausible link between obesity and impaired placental signaling, further contributing to pregnancy loss risk [21].

The findings of this study support the concept that placental biomarkers can enhance early pregnancy risk stratification. Unlike traditional markers that primarily reflect embryonic viability, kisspeptin appears to provide insight into placental function, which plays a central role in pregnancy maintenance. Integration of such biomarkers into clinical assessment may improve individualized counseling and monitoring strategies in early pregnancy.

Several limitations should be considered. The number of spontaneous abortion cases was relatively limited, and serum kisspeptin-10 levels were assessed at a single time point. Longitudinal measurements could provide a more comprehensive understanding of dynamic changes in placental function. In addition, correlation with placental histopathology was not available. Future studies with larger cohorts and serial measurements are needed to establish clinically applicable thresholds and to further elucidate the mechanistic role of kisspeptin in early pregnancy.

Conclusion

Lower first-trimester serum kisspeptin-10 levels were associated with an increased risk of spontaneous abortion in pregnancies with confirmed fetal cardiac activity. Serum kisspeptin-10 may serve as a supplementary biomarker for early pregnancy risk stratification; however, larger prospective studies

are needed to establish clinically applicable thresholds and validate its predictive performance.

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Turkish YouTube Videos as a Source of Information on Biologic Therapies in Rheumatic Diseases: An Assessment of Quality, Reliability, and Content

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Ethical Approval

Ethics committee approval was not required for this study because it involved publicly available YouTube videos and did not include human participants or identifiable personal data. The Declaration of Helsinki was not applicable because no human participants were involved.

Informed Consent

Not applicable.

Conflict of Interest

No conflict of interest was declared by the authors.

Financial Disclosure

The authors declared that this study received no financial support.

CRediT Author Statement

Nihal Lermi: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision.
Zeynep Fural: Investigation, Writing – review & editing.

Use of AI Statement

AI-assisted tools were used to support English language editing, improve the clarity and readability of the manuscript, and assist with table formatting and presentation. All AI-assisted modifications were reviewed and verified by the authors, who take full responsibility for the accuracy and integrity of the manuscript.

Data Availability

The dataset generated and analyzed during the current study is available from the corresponding author upon reasonable request.

Published

2026 October 17

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Abstract

Background/Aim: YouTube is increasingly used as a source of health-related information; however, the quality and reliability of Turkish-language content on biologic therapies in rheumatic diseases remain unclear. This study aimed to evaluate the quality, reliability, usefulness, and content completeness of Turkish-language YouTube videos on biologic therapies.

Methods: In this cross-sectional study, 24 eligible videos were independently evaluated by two rheumatologists using the modified DISCERN (mDISCERN), Global Quality Score (GQS), usefulness classification, and an 11-item content checklist.

Results: Twenty videos (83.3%) were physician-presented. The median content score was 5 (range, 1–10), and no video addressed all 11 domains. Indications for biologic therapy were the most frequently covered domain (79.2%), whereas pregnancy/breastfeeding was the least frequently addressed (4.2%). The median mDISCERN and GQS scores were 2 (range, 1–4) and 3 (range, 1–5), respectively, and 21 videos (87.5%) were classified as useful. GQS correlated with mDISCERN ($\rho = 0.452$, $P = 0.026$) and content score ($\rho = 0.436$, $P = 0.033$). Video duration correlated strongly with content score ($\rho = 0.801$, $P < 0.001$) and moderately with GQS ($\rho = 0.474$, $P = 0.019$), whereas views and likes were not associated with quality, reliability, or content completeness.

Conclusion: Turkish-language YouTube videos on biologic therapies were generally useful but showed limited reliability and incomplete content. The marked lack of information on pregnancy and breastfeeding highlights an important gap in patient-oriented educational content.

Keywords: biologic therapy, patient education, rheumatic diseases, reliability, youtube

Introduction

The Internet has become one of the principal sources of health-related information for patients, and among the many platforms available online, YouTube has emerged as one of the most influential video-sharing sites for the dissemination of medical content, with hundreds of hours of new material uploaded every minute [1, 2]. Its free access, ease of use, and capacity to convey complex information through visual and narrative formats have made it an increasingly common resource for patients seeking to understand their diagnosis and treatment, often as a supplement to, rather than a substitute for, information obtained during clinical encounters [3, 4].

Biologic therapies have transformed the management of numerous rheumatic diseases, and patients with high disease activity despite conventional treatment are increasingly offered these agents [5]. Nevertheless, considerable uncertainty persists among patients regarding response variability, administration, and the long-term safety of biologic agents [3]. Because consultation time is limited, video-based platforms are increasingly used by patients to supplement counseling on issues such as the mechanism of action, route and frequency of administration, pre-treatment infection screening, adverse events, monitoring during treatment, and safety considerations in special populations, including pregnancy and breastfeeding [5, 6].

However, YouTube content is not subject to independent editorial or peer review before publication, and the diversity of its contributors, together with the absence of a formal quality-control mechanism, creates a considerable risk that patients will encounter incomplete, outdated, or misleading information [3, 7, 8]. A growing number of studies have accordingly evaluated the quality and reliability of YouTube videos on rheumatological topics—including secukinumab [5], the side effects of biologic therapy [3], musculoskeletal ultrasound [2], anakinra self-injection [9], self-administered subcutaneous anti-TNF injections [10], spondyloarthritis [11], systemic lupus erythematosus [12], and Sjögren's syndrome [13]—generally using validated instruments such as the Global Quality Score (GQS) [14] and a modified DISCERN (mDISCERN) tool adapted from the original written-health-information instrument of Charnock et al. [15]. These studies have consistently reported wide variability in video quality and reliability, and several have shown that videos uploaded or presented by physicians and professional/academic organizations tend to be of higher quality and reliability than those uploaded by patients or independent users [4, 5, 6, 16].

Most of this literature has focused on English-language videos, and Turkish-language YouTube content specific to rheumatology remains comparatively underexplored. Turkish-language videos have been examined for ankylosing spondylitis [6] and, outside rheumatology, for immunotherapy in oncology [17], both of which found that content produced by specialists was of substantially higher quality and reliability than content from non-expert or unidentified sources. However, to our knowledge, no prior study has specifically evaluated Turkish-language YouTube videos addressing biologic therapies used across the spectrum of rheumatic diseases. In addition, whereas most previous studies in this field have concentrated on overall quality and reliability scores, comparatively few have systematically

assessed which specific clinical content domains are actually covered within individual videos, and none, to our knowledge, has done so for biologic therapies in rheumatology using a dedicated, multi-domain checklist.

The present study was therefore designed to evaluate the quality, reliability, and content of Turkish-language YouTube videos providing information on biologic therapies in rheumatic diseases. In addition to the GQS and mDISCERN instruments used in prior research, we developed an 11-item content checklist specifically to assess the completeness of information on biologic therapies, spanning domains from indications and mechanism of action to administration, infection screening, monitoring, adverse events, and pregnancy/breastfeeding. We further examined the relationships between video popularity and engagement, presenter type, video duration, and these quality, reliability, and content measures.

Materials and methods

Study Design and Search Strategy

This cross-sectional study evaluated the quality, reliability, and content of Turkish-language YouTube videos providing information on biologic therapies in rheumatic diseases. As the study involved only publicly available online content and did not include human participants or personal data, ethics committee approval was not required. No identifiable user comments, usernames, or other personal information were collected or analyzed; only aggregate comment counts were recorded.

The YouTube searches were conducted between the evening of August 19 and the early morning of August 20, 2026. YouTube searches were performed using Microsoft Edge in InPrivate browsing mode without logging into a personal account to minimize the potential influence of previous search history and personalized recommendations. All searches were conducted using the same search strategy. No predefined limit was applied to the number of videos screened for each search term. For each search, the results page was continuously scrolled until no additional results were displayed, and all videos retrieved under the selected search settings were screened. The ‘Popularity’ sorting option was selected to prioritize videos with greater user visibility, consistent with previous YouTube-based health information studies that prioritized highly viewed content to capture videos with greater potential public impact [1, 5].

Initially, six combinations of Turkish search terms related to rheumatic diseases and biologic therapies were used: “romatolojik hastalıklar biyolojik tedavi,” “romatizmal hastalıklar biyolojik tedavi,” “romatizma biyolojik tedavi,” “romatolojik hastalıklar biyolojik ajanlar,” “romatizmal hastalıklar biyolojik ajanlar,” and “romatizma biyolojik ajanlar.” During pilot screening of the initial search results, the initial search terms yielded a limited number of relevant videos, and it was observed that relevant Turkish-language content frequently used the term “anti-TNF” rather than the broader terms “biologic therapy” or “biologic agents.” Therefore, to improve the comprehensiveness of the search, three supplementary anti-TNF searches were added. This refinement was introduced after inspection of the pilot search results but before formal video screening and evaluation. The initial six searches yielded 17, 13, 14, 4, 3, and 4 results,

respectively, corresponding to 55 search results before duplicate removal. Duplicate videos were identified using their unique YouTube video IDs, leaving 22 unique videos.

The supplementary searches used the terms “romatolojik hastalıklar anti-TNF,” “romatizmal hastalıklar anti-TNF,” and “romatizma anti-TNF.” These searches yielded 31, 26, and 34 results, respectively. After duplicate removal, 52 unique videos were identified from the anti-TNF searches. Most of these videos were not in Turkish. Nine additional Turkish-language candidate videos not represented in the initial search set were identified, of which eight met the eligibility criteria and were included.

After removal of duplicates and application of the eligibility criteria, 24 videos constituted the final study sample.

Eligibility Criteria

Videos were eligible if they were in Turkish and contained substantive information on biologic therapy in rheumatic diseases. Videos in which biologic therapy constituted the main topic were included. Videos addressing a broader rheumatologic topic were also considered eligible when biologic therapy was discussed in sufficient detail to allow meaningful assessment.

Videos were excluded if they were not in Turkish, were duplicates, referred to biologic therapy only incidentally without providing substantive information, focused on biologic drugs without sufficient relevance to rheumatic diseases, or consisted primarily of unrelated or promotional content. Patient-generated videos were not excluded solely on the basis of their source, as patient experiences and opinions regarding biologic therapies may also represent health information encountered by YouTube users.

Video Characteristics

For each included video, the video title, URL, upload date, duration, number of views, number of likes, number of comments, and presenter type were recorded. Videos were categorized according to the person presenting the information as physician-presented or patient/individual-user-presented.

Video characteristics were recorded independently of the subjective quality assessments and were therefore not considered rater-dependent variables. For videos in which comments were disabled, the number of comments was considered unavailable rather than being recorded as zero.

Content Assessment

To evaluate the completeness of information specifically related to biologic therapies in rheumatic diseases, a study-specific 11-item content assessment checklist was developed before video evaluation. The domains were selected by the two rheumatologist investigators based on clinically relevant information considered important for patients receiving biologic therapies and on content domains evaluated in previous YouTube-based studies of rheumatic diseases and biologic treatments [1, 3, 5, 9, 10]. The checklist was intended as a predefined framework for assessing the breadth of biologic-therapy information provided in each video rather than as a validated measurement instrument. The checklist evaluated the presence of the following information: (1) definition/general characteristics of biologic therapy; (2) mechanism of action; (3) indications/rheumatic diseases in which biologic therapies are used; (4) criteria for treatment initiation/patient selection; (5) route and/or frequency of administration; (6) pre-treatment infection screening/evaluation

and/or vaccination recommendations; (7) risk of infection; (8) other adverse events; (9) contraindications, precautions, and/or concomitant use with other rheumatologic treatments; (10) monitoring/follow-up during treatment; and (11) pregnancy/breastfeeding.

Each item was scored as present (1) or absent (0). The individual scores were summed to obtain a total content score ranging from 0 to 11, with higher scores indicating more comprehensive coverage of information related to biologic therapy.

Reliability and Quality Assessment

The reliability of the videos was assessed using the modified DISCERN (mDISCERN) instrument. The instrument consists of five yes/no questions. Each positive response receives 1 point and each negative response 0 points, resulting in a total score ranging from 0 to 5, with higher scores indicating greater reliability.

Overall video quality was evaluated using the Global Quality Score (GQS), a five-point scale ranging from 1 (poor quality) to 5 (excellent quality). GQS was assessed according to the overall flow, clarity, and usefulness of the information within the intended scope of each video rather than solely according to the number of content domains addressed. Consistent with previously used GQS categorizations in YouTube-based health information studies [16], scores of 1–2 were categorized as low quality, 3 as moderate quality, and 4–5 as high quality.

Usefulness Assessment

Videos were additionally classified according to their overall usefulness into one of four mutually exclusive categories, adapted from classifications used in previous YouTube-based health information studies [10, 16]: (1) useful medical information, defined as accurate and informative medical content; (2) misleading medical information, defined as inaccurate, incomplete, or potentially misleading medical content; (3) useful patient experience/opinion, defined as personal experience or opinion that provided relevant and potentially helpful information from the patient perspective; and (4) misleading patient experience/opinion, defined as personal experience or opinion containing inaccurate or potentially misleading medical claims. Videos containing both useful and misleading medical information were classified in the misleading category.

Evaluation Process and Inter-rater Agreement

All eligible videos were independently evaluated by two rheumatologists using the same standardized assessment form. The reviewers independently assessed the 11 content items, the five mDISCERN items, GQS, and usefulness without access to each other's ratings.

After completion of the independent assessments, all disagreements were reviewed and resolved by consensus. Consensus ratings were used for the final analyses, whereas the original independent ratings were retained for assessment of inter-rater reliability.

For the 11-item content checklist and the five individual mDISCERN items, inter-rater agreement was assessed using percentage agreement and pooled Cohen's kappa coefficients, calculated by combining item-level ratings across all videos. To account for the clustering of multiple item ratings within the same video, 95% confidence intervals (CIs) for the pooled kappa

estimates were obtained using cluster bootstrap resampling at the video level. Agreement for the total mDISCERN score was assessed using a two-way random-effects, single-measure, absolute-agreement intraclass correlation coefficient [ICC(2,1)]. Agreement for GQS was assessed using quadratic-weighted Cohen's kappa, and agreement for usefulness classification was assessed using unweighted Cohen's kappa. Ninety-five percent CIs were reported for the ICC and kappa estimates.

Statistical Analysis

Continuous variables were summarized using medians, interquartile ranges (IQRs), and minimum–maximum values, as appropriate, and categorical variables were presented as numbers and percentages. Frequencies of the individual content domains were calculated, and the total content score was determined for each video. Given the small sample size and distributional characteristics of the data, non-parametric tests were used for group comparisons. Physician-presented and patient/individual-user-presented videos were compared using the Mann–Whitney U test for continuous and ordinal variables. Given the small and markedly unequal group sizes (20 physician-presented vs. 4 patient/individual-user-presented videos), these between-group comparisons were considered exploratory. Associations between video characteristics, GQS, mDISCERN, and total content scores were assessed using Spearman rank correlation coefficient. Comment-related analyses included only videos for which comment counts were available. A two-sided $P < 0.05$ was considered statistically significant. Statistical analyses were performed using Python version 3.13.5 (Python Software Foundation, Wilmington, DE, USA), with SciPy version 1.17.0.

Results

Search Results and Video Characteristics

The initial six YouTube searches yielded 55 results before duplicate removal. After duplicates were identified and removed using unique YouTube video IDs, 22 unique videos remained. Six videos were excluded during eligibility screening, leaving 16 eligible videos from the initial search strategy.

The three additional anti-TNF searches yielded 91 search results in total (31, 26, and 34, respectively), corresponding to 52 unique videos after duplicate removal. Most were non-Turkish-language videos. Nine additional Turkish-language candidate videos were identified, of which eight met the eligibility criteria. Consequently, a total of 24 Turkish-language YouTube videos were included in the final analysis.

Of the included videos, 20 (83.3%) were physician-presented and 4 (16.7%) were presented by patients or individual users.

The median video duration was 1.93 minutes (IQR, 1.38–6.51; range, 0.90–67.13 minutes). The median number of views was 8,650 (IQR, 5,850–17,000; range, 15–100,000), and the median number of likes was 42 (IQR, 15.25–143.25; range, 0–442). Comment counts were available for 11 videos; among these, the median number of comments was 13 (IQR, 2.5–43; range, 0–289) (Table 1).

Content Assessment

The median total content score was 5 (range, 1–10), and none of the videos addressed all 11 predefined content domains. Indications/rheumatic diseases in which biologic therapies are

used was the most frequently addressed domain (19/24, 79.2%), whereas pregnancy/breastfeeding was the least frequently addressed (1/24, 4.2%). Detailed coverage of the individual content domains is presented in Table 2.

Table 1. General Characteristics, Quality, Reliability, and Usefulness of the Included YouTube Videos (N = 24)

Variable	Value
Presenter type	
Physician-presented	20 (83.3%)
Patient/individual-user-presented	4 (16.7%)
Video duration (minutes)	1.93 (1.38–6.51; 0.90–67.13)
Views	8,650 (5,850–17,000; 15–100,000)
Likes	42 (15.25–143.25; 0–442)
Comments (n = 11)	13 (2.5–43; 0–289)
Total content score (range 0–11)	5 (1–10)
mDISCERN score (range 0–5)	2 (1–4)
Score 1	2 (8.3%)
Score 2	12 (50.0%)
Score 3	8 (33.3%)
Score 4	2 (8.3%)
Score 5	0 (0.0%)
GQS (range 1–5)	3 (1–5)
Low quality (GQS 1–2)	1 (4.2%)
Moderate quality (GQS 3)	15 (62.5%)
High quality (GQS 4–5)	8 (33.3%)
Usefulness classification	
Useful medical information	18 (75.0%)
Misleading medical information	2 (8.3%)
Useful patient experience/opinion	3 (12.5%)
Misleading patient experience/opinion	1 (4.2%)

Data are presented as median (IQR; range) or n (%), as applicable. IQR is not reported for total content score, mDISCERN score, or GQS, for which only the median (range) was given. Comment counts were available for 11 of the 24 videos. Abbreviations: IQR: interquartile range, mDISCERN: modified DISCERN, GQS: Global Quality Score.

Table 2. Coverage of the 11-Item Biologic Therapy Content Checklist Across the Included Videos (N = 24)

Content domain	Videos addressing domain, n (%)
1. Definition/general characteristics of biologic therapy	9 (37.5%)
2. Mechanism of action	12 (50.0%)
3. Indications/rheumatic diseases in which biologic therapies are used	19 (79.2%)
4. Criteria for treatment initiation/patient selection	14 (58.3%)
5. Route and/or frequency of administration	8 (33.3%)
6. Pre-treatment infection screening/evaluation and/or vaccination recommendations	14 (58.3%)
7. Risk of infection	17 (70.8%)
8. Other adverse events	9 (37.5%)
9. Contraindications, precautions, and/or concomitant use with other rheumatologic treatments	10 (41.7%)
10. Monitoring/follow-up during treatment	10 (41.7%)
11. Pregnancy/breastfeeding	1 (4.2%)

Data are presented as n (%). The total content score (range, 0–11) was calculated as the sum of the 11 binary domain scores (present = 1, absent = 0). No video addressed all 11 domains.

Data are presented as n (%). The total content score (range, 0–11) was calculated as the sum of the 11 binary domain scores (present = 1, absent = 0). No video addressed all 11 domains.

Video Quality and Reliability

The median mDISCERN score was 2 (range, 1–4), and no video achieved the maximum score of 5. The median GQS was 3 (range, 1–5), indicating moderate overall quality. Detailed score distributions are presented in Table 1.

Usefulness Classification

According to the overall usefulness classification, 18 of the 24 videos (75.0%) were categorized as useful medical information, two (8.3%) as misleading medical information, three (12.5%) as useful patient experience/opinion, and one (4.2%) as misleading patient experience/opinion.

Overall, 21 videos (87.5%) were therefore classified as providing useful medical information or useful patient experiences/opinions, whereas three (12.5%) were classified as misleading.

Table 3. Correlations Among Video Characteristics and Quality, Reliability, and Content Measures; Comparison by Presenter Type; and Inter-Rater Agreement

Analysis	Physician-presented (n = 20), median (IQR)	Patient/individual-user-presented (n = 4), median (IQR)	Statistic	P-value
Correlations (Spearman's ρ)				
GQS vs. mDISCERN score	—	—	$\rho = 0.452$	$P = 0.026$
GQS vs. total content score	—	—	$\rho = 0.436$	$P = 0.033$
mDISCERN score vs. total content score	—	—	$\rho = 0.375$	$P = 0.071$
Video duration vs. total content score	—	—	$\rho = 0.801$	$P < 0.001$
Video duration vs. GQS	—	—	$\rho = 0.474$	$P = 0.019$
Video duration vs. mDISCERN score	—	—	$\rho = 0.237$	$P = 0.264$
Views vs. GQS	—	—	$\rho = -0.185$	$P = 0.387$
Views vs. mDISCERN score	—	—	$\rho = 0.120$	$P = 0.577$
Views vs. total content score	—	—	$\rho = -0.241$	$P = 0.257$
Likes vs. GQS	—	—	$\rho = 0.076$	$P = 0.724$
Likes vs. mDISCERN score	—	—	$\rho = 0.300$	$P = 0.155$
Likes vs. total content score	—	—	$\rho = 0.136$	$P = 0.527$
Comments (n = 11) vs. total content score	—	—	$\rho = -0.608$	$P = 0.047$
Comments (n = 11) vs. GQS	—	—	$\rho = -0.354$	$P = 0.286$
Comments (n = 11) vs. mDISCERN score	—	—	$\rho = -0.177$	$P = 0.603$
Presenter-type comparison				
Total content score	5.00 (3.00–6.25)	4.50 (3.50–5.50)	U = 46.5	$P = 0.637$
mDISCERN score	2.00 (2.00–3.00)	2.00 (1.75–2.25)	U = 53.0	$P = 0.290$
GQS	3.00 (3.00–4.00)	3.50 (2.50–4.00)	U = 41.0	$P = 0.964$
Number of views	8,650 (5,850–13,500)	31,400 (6,003.25–66,250)	U = 29.0	$P = 0.416$
Number of likes	33 (15.25–73)	215 (154.75–280)	U = 20.5	$P = 0.141$
Video duration, min	1.81 (1.29–5.75)	5.32 (2.37–15.04)	U = 23.0	$P = 0.201$
Inter-rater agreement				
11-item content checklist, % observed agreement	—	—	87.1%	—
11-item content checklist, pooled Cohen's κ	—	—	$\kappa = 0.735$ (95% CI 0.655–0.809)	—
Individual mDISCERN items, % observed agreement	—	—	80.8%	—
Individual mDISCERN items, pooled Cohen's κ	—	—	$\kappa = 0.618$ (95% CI 0.487–0.746)	—
Total mDISCERN score, ICC(2,1)	—	—	ICC = 0.525 (95% CI -0.316–0.868)	—
GQS, quadratic-weighted Cohen's κ	—	—	$\kappa = 0.412$ (95% CI 0.149–0.606)	—
Usefulness classification, Cohen's κ	—	—	$\kappa = 0.679$ (95% CI 0.371–1.000)	—

Data are Spearman rank correlation coefficients (ρ), Mann–Whitney U statistics, Cohen's κ , or the intraclass correlation coefficient (ICC), with exact P-values where applicable. Presenter-type data are presented as median (IQR), and these comparisons were considered exploratory because of the small and markedly unequal group sizes. Comment-related analyses included only videos for which comment counts were available (n = 11). For the 11-item content checklist and five individual mDISCERN items, pooled Cohen's κ was calculated by combining item-level ratings across all videos; 95% CIs were obtained using cluster bootstrap resampling at the video level. The ICC for the total mDISCERN score was based on a two-way random-effects, single-measure, absolute-agreement model [ICC(2,1)]. GQS agreement was assessed using quadratic-weighted Cohen's κ . Abbreviations: CI: confidence interval, GQS: Global Quality Score, mDISCERN: modified DISCERN, ICC: intraclass correlation coefficient, IQR: interquartile range. $P < 0.05$ was considered statistically significant.

Inter-Rater Agreement

For the 11-item content assessment, the overall observed agreement between the two reviewers was 87.1%, with a pooled Cohen's κ of 0.735 (95% CI 0.655–0.809). For the five individual mDISCERN items, the overall observed agreement was 80.8%, with a pooled Cohen's κ of 0.618 (95% CI 0.487–0.746).

The ICC for the total mDISCERN score was 0.525 (95% CI -0.316–0.868). Agreement for GQS was moderate (quadratic-weighted Cohen's $\kappa = 0.412$ [95% CI 0.149–0.606]), whereas agreement for usefulness classification was substantial (Cohen's $\kappa = 0.679$ [95% CI 0.371–1.000]). All disagreements were subsequently resolved by consensus, and consensus ratings were used for the final analyses.

Associations Between Quality, Reliability, and Content

GQS showed a moderate positive correlation with both the mDISCERN score (Spearman's $\rho = 0.452$, $P = 0.026$) and the total 11-item content score ($\rho = 0.436$, $P = 0.033$).

A positive correlation was also observed between the mDISCERN score and the total content score; however, this association did not reach statistical significance ($\rho = 0.375$, $P = 0.071$).

Video duration showed a strong positive correlation with the total content score ($\rho = 0.801$, $P < 0.001$) and a moderate positive correlation with GQS ($\rho = 0.474$, $P = 0.019$). In contrast, video duration was not significantly correlated with the mDISCERN score ($\rho = 0.237$, $P = 0.264$).

Associations With Video Popularity and Engagement

The number of views was not significantly correlated with GQS ($\rho = -0.185$, $P = 0.387$), mDISCERN score ($\rho = 0.120$, $P = 0.577$), or total content score ($\rho = -0.241$, $P = 0.257$).

Similarly, the number of likes was not significantly correlated with GQS ($\rho = 0.076$, $P = 0.724$), mDISCERN score ($\rho = 0.300$, $P = 0.155$), or total content score ($\rho = 0.136$, $P = 0.527$). Among videos for which comment counts were available (n = 11), the number of comments was negatively correlated with the total content score ($\rho = -0.608$, $P = 0.047$), whereas correlations with GQS ($\rho = -0.354$, $P = 0.286$) and mDISCERN score ($\rho = -0.177$, $P = 0.603$) were not statistically significant. Given the limited number of videos with available comment data, this finding was considered exploratory.

Comparison According to Presenter Type

When videos were compared according to presenter type, no statistically significant differences were detected between physician-presented (n = 20) and patient/individual-user-presented videos in terms of total content score ($P = 0.637$), mDISCERN score ($P = 0.290$), GQS ($P = 0.964$), number of views ($P = 0.416$), number of likes ($P = 0.141$), or video duration ($P = 0.201$).

Given the small and markedly unequal group sizes, these between-group comparisons were considered exploratory and should be interpreted cautiously. These results are summarized in Table 3.

Discussion

In this cross-sectional study of 24 Turkish-language YouTube videos on biologic therapies in rheumatic diseases, we found that most videos were physician-presented and were generally classified as useful, yet overall quality was moderate, reliability was limited, and information content was frequently incomplete. To our knowledge, this is the first study to evaluate Turkish-language YouTube content specifically addressing

biologic therapies across the spectrum of rheumatic diseases, and the first in this specific area to systematically quantify content completeness using a dedicated multi-domain checklist rather than relying on quality and reliability scores alone.

The median GQS of 3 indicates moderate overall video quality, consistent with the variable and generally moderate quality reported in previous YouTube-based evaluations of rheumatology-related content [2, 3, 4, 5, 6, 16]. Importantly, although most videos in our sample were physician-presented, overall quality was not consistently high, suggesting that physician presentation alone does not ensure high-quality educational content.

The median mDISCERN score of 2 (of a possible 5), with no video achieving the maximum score, indicates limited reliability and is broadly consistent with the generally low mDISCERN scores reported in previous YouTube-based evaluations [2, 3, 4, 6, 17], although higher scores have also been reported [16]. Because mDISCERN specifically captures the transparency of information sources and the balance of the material presented rather than independently verifying the clinical accuracy or completeness of all medical statements, a video may be classified as useful while still receiving a low mDISCERN score. This distinction may explain why most videos in our sample were classified as useful despite generally low mDISCERN scores.

In our sample, 87.5% of videos were classified as useful, a finding broadly consistent with previous YouTube-based studies in related areas [4, 16, 17]. However, usefulness classification should not be interpreted as evidence of comprehensive content or high reliability, as demonstrated by the limited mDISCERN scores and uneven coverage of the predefined content domains in our study.

Most videos in our sample were physician-presented (83.3%), consistent with previous rheumatology-focused YouTube studies [3, 4, 5, 6, 16]. However, we found no statistically significant differences between physician-presented and patient/individual-user-presented videos in the evaluated measures. Given the small and markedly unequal group sizes (20 vs. 4), these exploratory comparisons are inconclusive and should not be interpreted as evidence of equivalence or as indicating that presenter type does not influence video quality or reliability.

Neither the number of views nor the number of likes was significantly associated with GQS, mDISCERN, or total content score in our sample. A similar absence of association between popularity metrics and video quality has been reported by Kocyigit and Akaltun [5] and by Zengin and Onder [3], suggesting that viewer engagement, as measured by views and likes, does not reliably signal educational quality on this topic. Other studies, however, have described weak or even paradoxical relationships between engagement metrics and quality indicators [2, 16, 18], underscoring that popularity should not be used as a proxy for the accuracy or completeness of medical information on YouTube. Among the subset of videos with available comment data ($n = 11$), comment count was negatively correlated with total content score; however, given the small sample and the multiple correlation analyses performed, this finding should be considered exploratory and interpreted cautiously.

Video duration was strongly correlated with the total content score and moderately correlated with GQS, but was not significantly correlated with mDISCERN. This pattern indicates that longer videos tended to cover more of the predefined clinical domains and were judged somewhat higher in overall quality, but were not thereby more transparent about their sources or more balanced in their presentation. This association may partly reflect the greater opportunity for longer videos to address a larger number of predefined content domains and should not be interpreted as evidence that increasing video duration itself improves educational quality. In other words, duration appears to track content comprehensiveness rather than information reliability, and the two should not be conflated: a longer video is not necessarily a more reliable one, even though it is more likely to be a more complete one.

A distinguishing feature of the present study is the use of an 11-item checklist to characterize which specific clinical domains were addressed, rather than relying solely on aggregate quality and reliability scores. This approach showed that no video addressed all 11 domains and that coverage was highly uneven: indications for biologic therapy and infection risk were the most frequently discussed domains, whereas route/frequency of administration, monitoring during treatment, and, most strikingly, pregnancy and breastfeeding were addressed only infrequently. Pregnancy/breastfeeding was discussed in only a single video (4.2%). Reproductive health is a clinically important consideration in the use of antirheumatic therapies, as reflected in contemporary rheumatology guidance on reproduction, pregnancy, and lactation [19, 20]. However, these guidelines are cited here to establish the clinical relevance of this topic rather than to imply that every patient-facing video should reproduce the scope or content of professional guidance. This gap is consistent with the pregnancy-specific focus of Yagiz et al. and Yerlanova et al., both of whom highlighted substantial deficiencies in the availability and quality of pregnancy-related rheumatology content on YouTube [4, 18]. These findings suggest that Turkish-language YouTube content on biologic therapies, while broadly informative regarding indications and infection-related risk, leaves clinically relevant gaps that could be particularly consequential for patients of reproductive age.

Inter-rater agreement varied across the assessment measures, with higher agreement estimates for the content checklist and individual mDISCERN items and more moderate agreement for the total mDISCERN score and GQS.

Overall, these findings should be interpreted in light of the small final sample size ($n = 24$), which limits statistical power, particularly for subgroup comparisons such as that between physician- and patient/individual-user-presented videos, and precludes firm causal or generalizable conclusions. As in other single-language, single-platform assessments of this kind [1, 2, 3, 4, 6, 16, 17, 18], our results describe a specific and time-limited snapshot of the Turkish-language YouTube landscape for this topic rather than a definitive characterization of it, and should be interpreted accordingly.

This study has several limitations. First, the study-specific content checklist was not a validated instrument, and all domains contributed equally to the total content score despite potential differences in their clinical importance. Therefore, the

total content score should be interpreted as a measure of the breadth of predefined topic coverage rather than as a weighted measure of clinical completeness. Second, the final sample comprised only 24 videos, and the patient/individual-user-presented subgroup consisted of only 4 videos; the resulting limited statistical power means that non-significant comparisons, particularly by presenter type, cannot be interpreted as evidence of no difference. Third, YouTube content, along with view counts, like counts, and comment counts, is inherently dynamic, and videos may be added, removed, edited, or re-ranked over time; our findings therefore reflect a single cross-sectional snapshot at the time of the search rather than a stable or permanent state of the platform. Fourth, search results on YouTube may vary depending on the search date, the device or browser used, region, and the platform's proprietary ranking algorithm, even when steps are taken to minimize personalization, such as searching in a private browsing mode without an active account; our results may not be fully reproducible with a different search date or configuration. Fifth, the study was restricted to Turkish-language videos identified using a predefined set of Turkish search terms; videos using alternative terminology, dialectal variation, or content behind different keywords may have been missed, and the findings cannot be generalized to other languages or platforms. Sixth, comment counts were available for only 11 of the 24 videos, limiting the statistical power and generalizability of comment-related analyses, which should accordingly be regarded as exploratory. Finally, although the content checklist, mDISCERN, and GQS were applied independently by two rheumatologists with disagreements resolved by consensus, quality and reliability assessment inherently retains a subjective component, and some degree of rater-dependent variability, particularly given the variation in inter-rater agreement across measures, cannot be entirely excluded.

Conclusion

In this study of Turkish-language YouTube videos on biologic therapies in rheumatic diseases, most videos were physician-presented and were generally classified as useful, but overall quality was moderate, reliability was limited, and information content was frequently incomplete, most notably with respect to pregnancy and breastfeeding. Video duration was strongly associated with content comprehensiveness but not with reliability, and neither views nor likes were associated with quality or reliability, indicating that popularity is not a reliable proxy for educational value on this topic. Because the sample was small and the patient/individual-user subgroup limited to 4 videos, these findings should be regarded as preliminary and hypothesis-generating rather than conclusive, and should not be extrapolated causally or to other languages, platforms, or time periods. Notably, although most videos were physician-presented, physician presentation alone did not ensure high reliability or broad coverage of the predefined content domains. These findings highlight the need for Turkish-language educational content on biologic therapies that provides broader coverage of clinically relevant topics, particularly reproductive health, administration, and treatment monitoring.

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Functional Outcomes After Anterior Cruciate Ligament Reconstruction: Lysholm Score Analysis

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Ethical Approval

This study was approved by the Clinical Research Ethics Committee of Yüzüncü Yıl University Faculty of Medicine on February 13, 2019 (decision no. 06). The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent

Written informed consent was obtained from all participants.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Financial Disclosure

This study received no financial support.

CRediT Author Statement

AD: conceptualization, methodology, formal analysis; SÖ: conceptualization, methodology, formal analysis, writing – original draft; ŞK: data curation; CA: data curation; NG: data curation; TT: supervision; AA: writing – original draft, supervision; BE: supervision; YCÜ: methodology, data curation, writing – original draft. All authors approved the final manuscript.

Use of AI Statement

AI-assisted tools were used for language editing of the original manuscript. The authors are responsible for the accuracy and integrity of the final content.

Data Availability

The patient-level data are not publicly available due to patient confidentiality.

Published

2026 October 18

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Abstract

Background/Aim: Anterior cruciate ligament reconstruction is followed by a prolonged rehabilitation period, and the relative effectiveness of supervised clinical physical therapy versus a structured home exercise program remains clinically relevant. This study evaluated postoperative functional recovery using the Lysholm knee scoring system after arthroscopic anterior cruciate ligament reconstruction with autologous hamstring grafts and compared outcomes between patients who received supervised clinical physical therapy and those who followed an independent home exercise program.

Methods: In this prospective cohort study conducted from May 2019 through May 2021, 28 male patients with complete anterior cruciate ligament tears underwent arthroscopic single-bundle reconstruction using hamstring autografts, with femoral Endobutton fixation and tibial bioabsorbable interference screw fixation. Mean age was 33.03 (8.53) years (range, 18-56 years). Group 1 (n = 7) received supervised clinical physical therapy three times weekly for 12 weeks, whereas Group 2 (n = 21) followed a structured home exercise program. Lysholm scores were assessed preoperatively and at 3 and 6 months. Between-group comparisons were exploratory and used two-sided Welch t-tests calculated from reported summary statistics. Longitudinal changes were described without inferential testing.

Results: Preoperative Lysholm scores were 72.57 (10.21) in Group 1 and 70.95 (11.45) in Group 2 ($P = 0.731$). Mean scores increased over time in both groups. At 3 months, scores were 92.86 (5.14) and 83.71 (8.92), respectively ($P = 0.004$); at 6 months, they were 98.17 (2.36) and 89.76 (7.41), respectively ($P < 0.001$). The between-group comparison of change from baseline to 6 months was not statistically significant ($P = 0.145$). These P -values are unadjusted exploratory comparisons calculated from rounded summary statistics. Medial meniscal tears were present in 11 patients (39.3%).

Conclusion: Arthroscopic anterior cruciate ligament reconstruction with autologous hamstring grafts was associated with higher mean Lysholm scores at follow-up. The supervised physical therapy group had higher 6-month scores, but the between-group difference in baseline-to-6-month change was not statistically significant in exploratory unadjusted comparisons. Small, unequal, nonrandomized groups limit causal interpretation.

Keywords: anterior cruciate ligament reconstruction, lysholm score, hamstring autograft, rehabilitation, physical therapy

Introduction

Anterior cruciate ligament (ACL) rupture is a common and potentially disabling knee injury among physically active individuals [1]. These injuries often occur through noncontact pivoting or sudden deceleration during athletic activity [1, 2]. In patients with symptomatic instability, surgical reconstruction is commonly performed to restore joint stability, reduce the risk of secondary meniscal and chondral injury, and facilitate return to activity [2, 3].

Autologous hamstring tendon grafts, typically comprising the semitendinosus and gracilis tendons, are widely used in arthroscopic ACL reconstruction because they provide high tensile strength, limited donor-site morbidity, and favorable clinical outcomes [3, 4]. However, technically successful graft placement alone does not ensure full recovery. Functional restoration also depends on postoperative rehabilitation, recovery of muscle strength, and confidence in knee stability [4, 5].

Postoperative outcomes are commonly assessed using validated patient-reported measures. The Lysholm knee scoring system is widely used because it is practical, responsive to clinical change, and focused on symptoms related to knee instability [5, 6]. Although supervised physical therapy is generally recommended after ACL reconstruction, access to and adherence with formal rehabilitation programs vary.

This study evaluated short-term functional recovery using the Lysholm knee score in patients who underwent arthroscopic ACL reconstruction with autologous hamstring grafts and compared outcomes between supervised clinical physical therapy and a structured independent home exercise program during 6 months of follow-up.

Materials and methods

Study Design and Participants

This prospective, single-center cohort study included consecutive male patients who underwent primary arthroscopic single-bundle ACL reconstruction using autologous hamstring tendon grafts between May 2019 and May 2020. The study was approved by the Clinical Research Ethics Committee of Yüzüncü Yıl University Faculty of Medicine on February 13, 2019 (decision no. 06), before enrollment began in May 2019. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

Eligible patients were men aged 18-60 years with a complete ACL rupture confirmed by clinical examination and magnetic resonance imaging, primary single-bundle reconstruction using a hamstring autograft, at least 6 months of follow-up, and complete preoperative and postoperative functional assessments. Patients were excluded if they had revision ACL reconstruction or previous surgery on the ipsilateral knee, a multiligamentous injury requiring concurrent ligament reconstruction, advanced knee osteoarthritis (Kellgren-Lawrence grade > 2), meniscal repair performed either before or concurrently with the index ACL reconstruction, or visual, hearing, neurologic, or psychiatric impairment that could prevent adherence to the protocol. Patients who underwent meniscectomy were eligible.

A total of 28 consecutive patients met the eligibility criteria during the study period and completed the 6-month protocol, with no loss to follow-up. No a priori sample-size or power calculation was performed; the sample comprised all available eligible patients with complete follow-up, and between-group comparisons were exploratory. Rehabilitation exposure depended on transportation access to supervised treatment and was not randomized. Group 1 comprised 7 patients who could attend supervised clinical physical therapy, and Group 2 comprised 21 patients who followed a structured independent home exercise program because transportation access limited attendance.

Surgical Procedure

All procedures were performed by senior orthopedic surgeons using a standardized arthroscopic technique under spinal or general anesthesia. Diagnostic arthroscopy was first performed to confirm complete ACL rupture and identify concomitant intra-articular abnormalities, including meniscal tears and chondral lesions. Meniscal tears that were not amenable to repair were treated with partial meniscectomy.

The semitendinosus and gracilis tendons were harvested through a 3-cm anteromedial incision over the pes anserinus. The tendons were stripped, debrided, folded into a quadrupled graft, and pretensioned. The femoral tunnel was prepared through an anteromedial portal. Femoral fixation was achieved using a cortical suspensory loop device (Endobutton, Smith & Nephew), and tibial fixation was achieved using a bioabsorbable interference screw with the knee in full extension after manual precycling.

Rehabilitation Protocols

All patients received standard perioperative care, including prophylactic antibiotics, analgesia, and a postoperative hinged knee brace locked in extension during ambulation for the first 2 weeks.

Patients in Group 1 attended outpatient physical therapy three times weekly for 12 weeks under the direct supervision of a physical therapist. The program included progressive patellar mobilization, active-assisted range-of-motion exercises, progressive closed-kinetic-chain quadriceps strengthening, hamstring activation, proprioceptive training, and sport-specific agility exercises.

Patients in Group 2 received a structured, illustrated home exercise booklet describing the same phased rehabilitation timeline, including quadriceps sets, straight-leg raises, progressive range-of-motion exercises, and closed-chain exercises. Patients performed the exercises independently at home and attended outpatient clinic assessments every 2 weeks.

Full weight-bearing was permitted at week 4 in both groups once adequate quadriceps control had been achieved. Bracing was discontinued at week 5. Straight-line running was permitted at 3 months, and pivoting sports were permitted at 6 months based on clinical stability.

Outcome Assessment

Functional outcomes were assessed preoperatively and at 3 and 6 months after surgery using the Lysholm knee scoring system. Scores range from 0 to 100 and are categorized as poor (< 65), fair (65-83), good (84-94), or excellent (95-100) [6]. Physical examination findings, including the anterior drawer, Lachman,

and pivot-shift tests, and standard anteroposterior and lateral radiographs were recorded.

Statistical Analysis

Continuous variables are presented as mean (standard deviation), and categorical variables as number and percentage. At proof correction, between-group comparisons were recalculated from reported group sizes, rounded means and standard deviations using two-sided Welch independent-samples t-tests; categorical comparisons used two-sided Fisher exact tests based on reported counts. Calculations were performed using Python and SciPy. *P*-values are approximate, unadjusted for multiple comparisons, and exploratory; a nominal threshold of 0.05 was used. Change-score comparisons use the reported means and standard deviations of individual change scores. Patient-level repeated-measures data and original model outputs were unavailable for these checks. Consequently, longitudinal change is described descriptively; no time-effect or group-by-time interaction *P*-value, sphericity result, Greenhouse-Geisser correction, or Bonferroni-adjusted result is claimed.

Results

Baseline Characteristics and Intra-Articular Pathologies

The cohort comprised 28 male patients with a mean age of 33.03 (8.53) years (range, 18-56 years). The right knee was involved in 7 patients (25.0%) and the left knee in 21 patients (75.0%). The injury mechanism was sports-related in 27 patients (96.4%). Spinal anesthesia was administered to 27 patients (96.4%), and general anesthesia was administered to 1 patient (3.6%).

Baseline characteristics, including age [33.28 (8.12) years in Group 1 vs. 32.95 (8.86) years in Group 2; *P* = 0.929] and side distribution (*P* = 1.000), did not differ significantly between the groups in exploratory comparisons (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Total cohort (N = 28)	Group 1: supervised PT (n = 7)	Group 2: home exercise (n = 21)	P-value
Age, mean (SD), years	33.03 (8.53)	33.28 (8.12)	32.95 (8.86)	0.929*
Age range, years	18-56	21-48	18-56	-
Male sex, n (%)	28 (100)	7 (100)	21 (100)	-
Involved side n (%) Right / left	7 (25.0) / 21 (75.0)	2 (28.6) / 5 (71.4)	5 (23.8) / 16 (76.2)	1.000**
Injury mechanism n (%) Sports / other trauma	27 (96.4) / 1 (3.6)	7 (100) / 0	20 (95.2) / 1 (4.8)	1.000**
Preoperative Lysholm score, mean (SD)	71.36 (11.02)	72.57 (10.21)	70.95 (11.45)	0.731*

Abbreviations: PT: physical therapy, SD: standard deviation. *Two-sided Welch independent-samples t-test recalculated from reported group sizes and rounded summary statistics. **Two-sided Fisher exact test based on reported counts. *P*-values are exploratory and unadjusted for multiplicity; nominal *P* < 0.05.

Diagnostic arthroscopy identified an isolated ACL tear in 12 patients (42.9%). Concomitant intra-articular pathologies were present in 16 patients (57.1%). Medial meniscal tears were the most common finding and occurred in 11 patients (39.3%), including 3 patients with coexisting cartilage damage. Isolated cartilage lesions were identified in 3 patients (10.7%) (Table 2).

Table 2. Intra-Articular Pathologies Identified During Arthroscopy

Intra-articular pathology	Patients n	Percentage %
Isolated ACL tear (no additional pathology)	12	42.9
Isolated medial meniscal tear	8	28.6
Medial meniscal tear with cartilage damage	3	10.7
Isolated cartilage damage	3	10.7
Isolated lateral meniscal tear	1	3.6
Multiligamentous injury managed conservatively except for ACL reconstruction	1	3.6

Abbreviations: ACL: anterior cruciate ligament.

Functional Outcome Analysis

Preoperative examination showed a positive anterior drawer test in 26 patients (92.8%), a positive Lachman test in 23 patients (82.1%), and a positive pivot-shift test in 10 patients (35.7%). At the complete 6-month clinical assessment of all 28 patients, no graft failure or persistent grade 2 or greater instability was recorded. These are recorded clinical findings; formal outcome definitions were not confirmed as prespecified.

Mean Lysholm scores increased over time in the overall cohort. Preoperative scores were 72.57 (10.21) in Group 1 and 70.95 (11.45) in Group 2 (*P* = 0.731). At 3 months, scores were 92.86 (5.14) and 83.71 (8.92), respectively (*P* = 0.004). At 6 months, scores were 98.17 (2.36) and 89.76 (7.41), respectively (*P* < 0.001). These unadjusted exploratory between-group comparisons were calculated from rounded summary statistics using two-sided Welch t-tests; longitudinal significance was not re-estimated.

The mean change from the preoperative assessment to 6 months was 25.60 (9.80) in Group 1 and 18.81 (10.15) in Group 2. The exploratory between-group Welch comparison of change scores, calculated from the reported means and SDs, was not statistically significant (*P* = 0.145; Table 3). At the final 6-month assessment, all 28 patients had clinically documented full knee range of motion, including flexion > 130 degrees.

Table 3. Lysholm Scores by Rehabilitation Group and Follow-Up Time

Follow-up time point	Group 1: supervised PT (n = 7) mean (SD)	Group 2: home exercise (n = 21) mean (SD)	Total cohort (N = 28) mean (SD)	Between-group P-value*
Preoperative	72.57 (10.21)	70.95 (11.45)	71.36 (11.02)	0.731
Postoperative month 3	92.86 (5.14)	83.71 (8.92)	86.00 (8.98)	0.004
Postoperative month 6	98.17 (2.36)	89.76 (7.41)	91.86 (7.48)	< 0.001
Change from preoperative to month 6	25.60 (9.80)	18.81 (10.15)	20.50 (10.35)	0.145

Abbreviations: PT: physical therapy, SD: standard deviation. *Two-sided Welch independent-samples t-tests between rehabilitation groups, recalculated from reported group sizes and rounded summary statistics. The change-score row compares individual baseline-to-6-month changes using their reported mean and SD; it is not a group-by-time interaction. All *P*-values are exploratory and unadjusted for multiple comparisons; nominal *P* < 0.05. No inferential longitudinal model is reported.

Discussion

This prospective cohort study showed substantial short-term improvement in patient-reported knee function after arthroscopic single-bundle ACL reconstruction with autologous hamstring grafts. Both rehabilitation groups improved during follow-up. The supervised physical therapy group had higher 6-month scores in an exploratory unadjusted comparison, but the between-group difference in baseline-to-6-month change was not statistically significant. Small, unequal groups and allocation based on transportation access limit causal interpretation.

The overall degree of functional recovery was consistent with previous reports. Türkoğlu [7] described favorable postoperative Lysholm scores after ACL reconstruction with a hamstring autograft, and Dalyaman [8] reported a marked postoperative increase in Lysholm scores. Favorable midterm

stability has also been reported after hamstring ACL reconstruction using Endobutton fixation [9].

Rehabilitation is central to recovery after ACL reconstruction [10, 11]. Supervised treatment may improve exercise technique, progression, quadriceps activation, and adherence. In the present study, supervised rehabilitation was associated with higher follow-up Lysholm scores, but the exploratory comparison of baseline-to-6-month change did not demonstrate a statistically significant between-group difference. Nevertheless, patients who followed the structured home program also achieved good functional scores, suggesting that a clearly defined home-based program may be a practical alternative when regular supervised therapy is unavailable [10-12]. Because the rehabilitation strategy was not randomized and potential confounders were not adjusted for, this comparison should be considered exploratory.

Concomitant intra-articular injuries are common in ACL-deficient knees. Medial meniscal tears were the most frequent secondary finding in this cohort, consistent with evidence that recurrent instability increases meniscal loading [13]. Chondral lesions were also observed at rates broadly consistent with previous reports of injuries associated with ACL insufficiency [14-16].

At 6 months, full knee range of motion was clinically documented in all 28 patients, and no arthrofibrosis was reported. Early controlled mobilization, an emphasis on full extension in the immediate postoperative period, and close follow-up may have contributed to this finding.

Study Limitations

This study has several limitations. The overall sample and supervised physical therapy group were small, reducing the precision of between-group estimates. Rehabilitation exposure depended on transportation access, was not randomized, and the groups were unequal; therefore, selection bias and unmeasured confounding cannot be excluded. The exploratory comparisons were unadjusted for confounders and multiplicity and do not establish a causal benefit of supervised treatment. The inclusion of only male patients limits generalizability to female patients. The 6-month follow-up period describes early functional recovery but does not address long-term return to sport, graft failure, or osteoarthritis. Muscle strength was assessed clinically rather than with objective isokinetic testing. No a priori sample-size or power calculation was performed. The available sample determined the cohort size. Between-group comparisons are exploratory. Summary-statistic checks do not verify individual observations, distributional assumptions, or longitudinal effects.

Conclusion

Arthroscopic single-bundle ACL reconstruction with autologous hamstring grafts was associated with higher mean Lysholm scores at follow-up, with no graft failure or persistent grade 2 or greater instability recorded at 6 months. The supervised physical therapy group had higher 6-month scores in exploratory unadjusted comparisons, but the between-group difference in baseline-to-6-month change was not statistically significant. Small, nonrandomized and imbalanced groups, allocation based on transportation access, and unadjusted comparisons limit causal interpretation.

Acknowledgments

The authors thank Prof. Mehmet Ata Gökalp.

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The Use of 5-Aminolevulinic Acid in Glioma Surgery: From Intracranial to Spinal Applications

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Abstract

Fluorescence-guided surgery (FGS) with 5-aminolevulinic acid (5-ALA) has become an important adjunct in glioma surgery, with the aim of maximizing the extent of resection while preserving neurological function. After oral or intravenous administration, 5-ALA is metabolized to protoporphyrin IX (PpIX), which preferentially accumulates in tumor cells and fluoresces under blue light, thereby improving intraoperative visualization of malignant tissue. This narrative review summarizes the current indications, evidence, challenges, and future directions of 5-ALA in intracranial and spinal cord glioma surgery. Randomized and observational studies have demonstrated that 5-ALA FGS increases gross total resection rates and improves progression-free and overall survival in intracranial high-grade glioma. Although its role in low-grade glioma is less established, focal fluorescence may identify anaplastic foci and serve as a prognostic marker. In spinal cord gliomas, 5-ALA appears particularly useful for ependymomas, in which high fluorescence rates and favorable resection outcomes have been reported. Its application in spinal astrocytomas requires caution because robust evidence of benefit remains limited and over-resection may cause substantial neurological harm. Overall, 5-ALA has a favorable safety profile, with mostly mild and transient adverse effects. Beyond resection guidance, 5-ALA-based photodynamic and radiodynamic approaches are being explored as adjuvant therapies. Current evidence strongly supports its use in high-grade intracranial gliomas and selected spinal ependymomas, while emerging theranostic applications may further expand its role in multimodal neuro-oncology.

Keywords: 5-aminolevulinic acid, fluorescence-guided surgery, glioma, glioblastoma, spinal cord tumors, ependymoma, extent of resection, photodynamic therapy, radiodynamic therapy

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Ethical Approval

Not required because this manuscript is a narrative review based on previously published literature and does not involve direct human participants, identifiable patient-level data, or animal experiments.

Conflict of Interest

No conflict of interest was declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Published

2026 October 5

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Introduction

Gliomas are primary central nervous system tumors arising from glial cells and include a spectrum of entities ranging from indolent lesions to highly aggressive malignancies in both intracranial and spinal compartments. Fluorescence-guided surgery (FGS) using 5-aminolevulinic acid (5-ALA) was first introduced by Dr. Walter Stummer, who demonstrated its benefit in the resection of malignant intracranial gliomas in a human cohort [1]. Evidence supporting the use of 5-ALA in spinal glioma resection has also emerged in recent years [2, 3]. Intracranial gliomas, particularly glioblastoma multiforme (GBM), have a poor prognosis, with a median survival of 12 to 15 months and fewer than 10% of patients surviving beyond five years [4]. Spinal cord gliomas, although less common, present distinctive surgical challenges because of the eloquent nature of spinal cord tissue and the potentially catastrophic consequences of over-resection.

Maximal safe surgical resection has long been the mainstay of treatment for both intracranial and spinal gliomas, with gross total resection (GTR) as a central objective. More recently, supratotal resection has also been advocated in selected intracranial cases [5]. Extent of resection (EOR) has shown a strong positive association with patient outcomes, including progression-free survival (PFS) and overall survival (OS), in intracranial gliomas [6, 7]. Although complete tumor excision is desirable, postoperative functional outcomes must be carefully considered. Given the infiltrative nature of high-grade gliomas and the eloquent anatomy of both brain and spinal cord tissue, the risk of disrupting adjacent critical areas must be weighed against the impact of subtotal resection on OS and recurrence. This balance forms the basis of maximal safe resection (MSR) [8].

This narrative review provides a clinically oriented overview of the current indications, evidence, and complications associated with the use of 5-ALA in intracranial and spinal cord glioma resection and explores emerging applications of this technology.

Materials and methods

This work is a narrative review intended to provide a clinically oriented synthesis for readers. The review was based on current literature that included key clinical and experimental studies on 5-ALA in glioma surgery. Relevant studies were identified through targeted searches of PubMed and major neurosurgical and neuro-oncology journals using terms such as "5-ALA," "fluorescence-guided surgery," "glioma," "glioblastoma," "spinal cord tumors," "ependymoma," "astrocytoma," "low-grade glioma," "photodynamic therapy," and "radiodynamic therapy."

Pharmacological basis and current indications for 5-ALA

5-ALA is an endogenous amino acid used in the porphyrin synthesis pathway as a precursor of heme production in mammals. After administration, it is metabolized to PpIX, which acts as a fluorescent marker and preferentially accumulates in tumor cells because of altered tumor metabolism [1, 9]. PpIX fluorescence becomes visible under blue light, enabling the surgeon to distinguish malignant tissue from normal parenchyma in both brain and spinal cord.

The fluorescent property of 5-ALA has been used to support intraoperative MSR, particularly in high-grade gliomas (HGGs) of the cranial vault (World Health Organization grades III and IV). It has been approved for use in Europe, Asia, Australia, and the United States, and the standard dose is 20 mg/kg, administered orally 3 to 4 hours before the start of surgery [10]. After craniotomy or laminectomy and dural opening, the surgeon can switch between white-light and blue-light modes to delineate fluorescent tumor margins and guide resection.

Evidence supporting 5-ALA use in intracranial high-grade gliomas

Studies have shown that 5-ALA FGS significantly improves EOR in intracranial glioma resection, and several landmark trials have confirmed that 5-ALA reliably differentiates normal brain from malignant tissue. Stummer et al. [11] conducted a randomized controlled trial showing that 5-ALA FGS nearly doubled the rate of complete resection of contrast-enhancing tumor compared with conventional white-light surgery (65% vs. 36%; between-group difference, 29%; 95% CI, 17 to 40; $P < 0.001$) and improved 6-month PFS (41.0% vs. 21.1%; $P < 0.001$). Coburger et al. [12] also demonstrated that EOR increased with the addition of 5-ALA to intraoperative MRI (iMRI) compared with iMRI alone, with GTR achieved significantly more often (100% vs. 82%; $P = 0.010$) and a higher mean EOR (99.7% vs. 97.4%; $P = 0.004$), without an increase in complications ($P = 0.518$). Su et al. [13] conducted a systematic review and meta-analysis that quantified the benefits of 5-ALA FGS, demonstrating higher rates of complete resection and improved PFS compared with conventional surgery. Schuppper et al. [14] subsequently conducted a prospective multicenter study that demonstrated enhanced surgical visualization without increased neurological morbidity.

A recent systematic review showed that 5-ALA increased GTR rates from 54.3% with white light alone to 75.4% with 5-ALA ($P < 0.001$), accompanied by a corresponding reduction in residual contrast-enhancing volume on early postoperative MRI [15]. The same review also reported improvements in 6-month PFS (median, 8.1 vs. 5.4 months; $P = 0.002$) and OS (median, 15.2 vs. 12.3 months; $P = 0.008$) with 5-ALA FGS. Ryskeldiyev et al. [16] also reported improved survival with 5-ALA-guided resections, attributable to increased GTR, although multivariable models indicated that EOR itself, rather than 5-ALA per se, is the primary driver of the survival benefit.

The benefit of 5-ALA appears most pronounced in newly diagnosed HGG, whereas its impact in recurrent tumors is less consistent. A systematic review of 5-ALA in recurrent malignant gliomas suggested that although fluorescence facilitates resection and modestly prolongs OS, there is no clear effect on PFS in this setting. Nevertheless, 5-ALA remains a useful and safe adjunct to consider when planning resection of recurrent malignant gliomas [17].

5-ALA in low-grade and intermediate-grade gliomas

Although the literature provides strong evidence supporting 5-ALA in HGG, its use in low-grade gliomas (LGGs) is less established. LGGs have a cytoarchitecture that more closely resembles normal tissue and show less malignant tracer uptake than higher-grade tumors. 5-ALA has therefore been less effective in LGG, with Ishihara et al. [18] reporting limited and inconsistent

uptake in gliomas below central nervous system grade III [18-20]. Suero Molina et al. [21] suggested that doubling the 5-ALA dose from 20 mg/kg to 40 mg/kg may increase fluorescence rates in LGG by improving blood-brain barrier penetration; however, this approach remains investigational and must be balanced against theoretical toxicity concerns.

Widhalm et al. [20] showed promise for the future use of 5-ALA in LGG because of its ability to identify anaplastic foci within these tumors. Focal 5-ALA fluorescence in lesions preoperatively classified as low grade or indeterminate was shown to highlight areas of anaplastic transformation, thereby guiding targeted sampling and influencing grading. Hosmann et al. [22] evaluated 5-ALA fluorescence in World Health Organization grade II LGGs at two specialized centers and found that intraoperative fluorescence was associated with less favorable clinical and molecular characteristics, poorer PFS (2.3 (0.7) vs. 5.0 (0.4) years; $P = 0.010$), and shorter OS (5.4 (1.0) vs. 10.3 (0.5) years; $P = 0.010$), suggesting that fluorescence may serve as a prognostic marker. This association is most likely related to blood-brain barrier breakdown at anaplastic foci, which increases permeability. Muther et al. [23] showed that increased preoperative MRI contrast enhancement was associated with fluorescence uptake in intermediate-grade gliomas, indicating increased permeability of the tumor focus to both contrast and 5-ALA. Bianconi et al. [24] also showed a link between MRI contrast uptake and 5-ALA fluorescence in more aggressive foci, and reported that 5-ALA fluorescence was significantly associated with shorter OS and PFS.

5-ALA in spinal cord gliomas

Although most published experience with 5-ALA relates to intracranial gliomas, evidence increasingly supports its use in selected intramedullary spinal cord tumors, particularly ependymomas and, to a lesser extent, astrocytomas. Spinal cord gliomas present distinctive surgical challenges because even minor injury to eloquent spinal cord tissue can result in permanent neurological deficit. In this context, 5-ALA fluorescence guidance may help maximize tumor resection while minimizing functional morbidity.

Ependymomas are the most common primary intramedullary tumors in adults, and surgical resection remains the treatment of choice. GTR is a realistic objective in many cases because a well-defined cleavage plane usually exists between a benign ependymoma and the surrounding normal spinal cord. This tissue boundary allows the tumor to be dissected free of the cord. 5-ALA fluorescence works in tandem with this anatomical plane by helping the surgeon confirm the margin and detect residual tumor foci at the tumor-cord interface. Several series have demonstrated that spinal ependymomas exhibit strong 5-ALA-induced fluorescence, with positive fluorescence rates ranging from 50% to 100% [2, 3, 25]. In a series of 14 patients with spinal cord ependymomas undergoing 5-ALA-guided resection, Moreno et al. [2] reported strong fluorescence in 85.71% of patients (12 of 14) and achieved GTR in 79% of cases. Importantly, 10 of 14 patients (71%) experienced clinical improvement according to the modified McCormick scale, with only two patients showing postoperative deterioration, a lower rate than typically reported in non-fluorescence-guided series.

The role of 5-ALA in intramedullary astrocytomas is less established and requires a more cautious approach. Unlike ependymomas, spinal astrocytomas lack a clear dissection plane and actively infiltrate surrounding cord tissue. This infiltrative growth pattern explains why aggressive fluorescence-guided resection may be dangerous in this setting. Although some spinal astrocytomas demonstrate positive fluorescence, chasing every fluorescent focus may be hazardous because of the intimate relationship between tumor and eloquent spinal cord tissue. Unlike cerebral gliomas, increased EOR in spinal astrocytomas has not been conclusively shown to improve outcomes, and the risk of permanent myelopathy from over-resection based on fluorescence may outweigh any potential oncological benefit [25].

The comprehensive review of 5-ALA in spinal tumor surgery by Wainwright et al. [25] emphasized that the technique is particularly suited to ependymomas because of their well-defined margins and consistent PpIX accumulation. Intraoperative visualization of residual tumor foci may reduce the need for repeat surgery and potentially improve long-term tumor control. For spinal astrocytomas, however, 5-ALA may assist in tumor identification and biopsy guidance, but routine use for aggressive resection should be approached cautiously because of the unique anatomical and functional constraints of the spinal cord.

Overall, 5-ALA FGS appears to be a safe and valuable adjunct for spinal cord ependymoma resection, facilitating more complete tumor removal and potentially reducing postoperative neurological deterioration [2, 3, 25]. The technique requires the same equipment and dosing protocols used for intracranial procedures, making it readily adoptable in centers already performing 5-ALA-guided cranial surgery. A direct comparison between the two anatomical compartments is clinically instructive. The brain may tolerate a degree of manipulation, and in selected non-eloquent areas, supratotal resection beyond the contrast-enhancing margin can be a reasonable survival-oriented goal. The spinal cord allows no such margin for error. Within the cord, pursuing every fluorescent focus of an infiltrative astrocytoma can result in irreversible paraplegia. Therefore, the surgeon must continuously balance oncological ambition against functional preservation. In this unforgiving compartment, fluorescence should inform the extent of resection without dictating it.

Safety profile and current challenges

Several studies have documented a favorable safety profile for 5-ALA. In general, adverse effects are minimal, transient, and self-limited [11, 12, 26]. Reported adverse effects include photosensitivity caused by PpIX accumulation in the skin. Clinicians should therefore warn patients to avoid strong light sources for at least 24 hours postoperatively. The Food and Drug Administration warns against concomitant use of phototoxic drugs, such as St. John's wort, griseofulvin, thiazide diuretics, sulfonyleureas, phenothiazines, sulfonamides, quinolones, tetracyclines, and topical preparations containing ALA, for 24 hours before and after 5-ALA administration [10]. Other reported adverse effects include gastrointestinal symptoms, nausea, transient neurological symptoms, and mild liver enzyme abnormalities. In large clinical series and the pivotal randomized controlled trial, serious 5-ALA-related complications were rare and comparable to those observed with standard surgery [11].

Despite its benefits, 5-ALA FGS has several practical challenges, including the need for specialized equipment and operator training to interpret fluorescence accurately. The technique requires access to microscopes equipped with appropriate excitation and detection modules, as well as training in recognizing and interpreting fluorescence patterns. The qualitative nature of standard fluorescence assessment introduces subjectivity, and interobserver variability may influence decisions at the resection margin. False-negative and false-positive fluorescence can occur. Nonfluorescent tumor regions, particularly in LGG or at infiltrative margins, may limit complete resection if the surgeon relies solely on fluorescence. Conversely, fluorescence in areas of treatment-related change, inflammation, or reactive tissue could lead to unnecessary resection if not contextualized with imaging and functional information. Experienced users generally advocate treating fluorescence as an adjunct to, rather than a replacement for, neuronavigation, tractography, and awake mapping when appropriate [27].

Beyond resection: emerging therapeutic applications

An emerging application of 5-ALA is photodynamic tumor targeting, in which 5-ALA is used as a cytotoxic agent activated by specific wavelengths of light. Several studies have tested this property to target the tumor bed and address residual tumor after resection [28-30]. 5-ALA serves as a photosensitizer for photodynamic therapy (PDT), in which activated PpIX generates reactive oxygen species that lead to tumor cell death upon exposure to light at specific wavelengths. For 5-ALA-mediated PDT, relevant wavelengths excite PpIX absorption peaks, especially in the blue (approximately 405 to 410 nm) and red (approximately 630 to 635 nm) regions. Preclinical and early clinical studies have explored intraoperative or postoperative PDT to treat residual microscopic disease in the resection cavity, with some reports suggesting delayed tumor progression and acceptable safety [29].

Studies are also investigating the combination of 5-ALA's photodynamic properties with radiotherapy. A recent *in vivo* study in mouse models treated with 5-ALA before radiotherapy showed slower tumor growth and regression compared with radiotherapy alone [31]. Similarly, Nordmann and Michael [32] reviewed 11 *in vitro* and *in vivo* studies on 5-ALA radiodynamic therapy (RDT) and showed promise for this form of adjuvant therapy in HGG. Building on PDT concepts, RDT uses radiation to activate PpIX-mediated cytotoxic effects and may synergize with conventional radiotherapy in glioblastoma, although clinical data remain limited.

Future directions

Future work is likely to focus on several key areas. First, refinement of quantitative fluorescence techniques and integration with intraoperative imaging and artificial intelligence may improve margin assessment and reduce subjectivity in fluorescence interpretation. Emerging work on PpIX fluorescence spectroscopy and quantitative imaging aims to move beyond purely qualitative assessment toward objective maps of fluorophore concentration at the resection margin. Early clinical studies demonstrate that spectrally resolved techniques can detect tumor-associated PpIX at concentrations below visual thresholds, strongly correlate with histopathology, and may reduce false-

negative margins in both HGG and the infiltrative components of LGG [33].

Second, improved predictive models for 5-ALA fluorescence in diffuse gliomas, incorporating imaging and molecular features, could help tailor 5-ALA use to patients most likely to benefit. Coupling these methods with machine-learning-based prediction of fluorescence from preoperative MRI could ultimately support a more personalized and data-driven paradigm for 5-ALA-guided glioma surgery [34].

Third, ongoing translational and early-phase clinical studies in 5-ALA-based PDT and RDT will clarify the potential of these adjuvant modalities to improve local control and survival in glioblastoma and other aggressive tumors [32]. Future clinical studies should evaluate the potential synergy between radiotherapy and the photodynamic capabilities of 5-ALA demonstrated in preclinical models.

Finally, comparative studies of 5-ALA and other fluorescent agents, including fluorescein and novel targeted probes, will further define the role of 5-ALA within the evolving landscape of fluorescence-guided neurosurgery [35]. In addition, the application of 5-ALA in central nervous system tumors beyond gliomas and ependymomas warrants further investigation, particularly to determine which tumor types benefit most from fluorescence guidance and how resection aggressiveness should be balanced against functional preservation in eloquent anatomical locations [36].

Conclusion

5-ALA has transformed glioma surgery across intracranial and spinal compartments by enabling more complete MSR. Current evidence strongly supports its use in intracranial HGG, where it increases GTR rates and improves short-term PFS without an excess of major neurological morbidity [11, 12]. In spinal cord surgery, 5-ALA has demonstrated particular utility in ependymoma resection, with high fluorescence rates and improved detection of residual tumor foci; however, caution is warranted in spinal astrocytomas because of the eloquent nature of spinal cord tissue [2, 3, 25]. In LGG, 5-ALA can highlight anaplastic foci and may provide prognostic information, although its sensitivity is limited and the absence of fluorescence does not exclude higher-grade components [19, 22]. The safety profile of 5-ALA is generally favorable across both intracranial and spinal applications, and practical limitations primarily relate to equipment, training, and interpretation.

Emerging photodynamic and radiodynamic applications, together with expanding use in non-glioma tumors, suggest that 5-ALA will continue to play an important role in neurosurgical oncology [29-32]. Research has identified new horizons for this dye, moving it from a purely diagnostic tool toward a theranostic platform. Further clinical and translational research will determine how best to integrate these modalities into comprehensive, multimodal care pathways for patients with gliomas across all anatomical locations.

Acknowledgments

The authors would like to acknowledge the contributions of researchers and clinicians worldwide who have advanced the field of fluorescence-guided surgery.

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Pourfour du Petit Syndrome Following Superficial Parotidectomy: A Case Report

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Ethical Approval

Ethics committee approval was not required for this case report in accordance with our institutional policies and local ethics committee guidelines.

Informed Consent

Written informed consent was obtained from the patient for publication of the case report and associated clinical photographs.

Conflict of Interest

The authors declared no conflicts of interest.

Financial Disclosure

The authors declared that this case received no financial support.

CRedit Author Statement

Deniz Baklacı (Conceptualization, Supervision, Writing – Review & Editing), Özlem Özdemir (Writing – Original Draft, Investigation, Data Curation, Writing – Review & Editing), İnara Bashirova (Writing – Original Draft, Investigation, Data Curation), Gökhan Furkan Kılıç (Supervision, Validation, Writing – Review & Editing).

Use of AI Statement

Generative AI tools were used solely for language editing, grammar refinement, and improving the readability of the manuscript during preparation. The authors reviewed, edited, and verified all content and take full responsibility for the final manuscript.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. All clinical data relevant to the case report are included within the published article.

Published

2026 October 14

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Abstract

Pourfour du Petit syndrome (PDPS) is a rare oculosympathetic hyperactivity disorder and is considered the clinical counterpart of Horner syndrome, resulting from irritation of the cervical sympathetic pathway. We report a 62-year-old man with no significant medical history who developed PDPS in the early postoperative period after left superficial parotidectomy for a painless, mobile 3 × 3 cm mass. Preoperative imaging and fine-needle aspiration biopsy were consistent with a Warthin tumor. Within the first postoperative hour, the patient developed left-sided anisocoria with mydriasis, conjunctival hyperemia, and hemifacial sweating. Neurological and ophthalmological evaluations excluded acute central and ocular causes. Given the lesion's anatomical proximity to the external carotid artery, the findings were attributed to transient irritation of the periarterial sympathetic plexus secondary to surgical manipulation. The patient improved clinically without specific pharmacologic treatment, was discharged on postoperative day 3, and showed complete resolution of symptoms at the 6-month follow-up. PDPS is a rare postoperative complication that should be considered after head and neck surgery in patients presenting with anisocoria or other autonomic findings. Prompt evaluation is important to exclude serious neurological and ophthalmological conditions.

Keywords: pourfour du petit syndrome, parotid neoplasms, parotidectomy, anisocoria, mydriasis, hyperhidrosis

Introduction

Pourfour du Petit syndrome (PDPS) is a rare oculosympathetic hyperactivity disorder resulting from hyperstimulation of the cervical sympathetic pathway [1, 2]. Clinically, it represents the reverse of Horner syndrome and may occur after irritation of preganglionic fibers emerging from the upper thoracic segments or the cervical sympathetic chain [2]. Although several surgical and interventional procedures in the neck region, including regional anesthesia, carotid surgery, and maxillofacial operations, have been associated with PDPS [3-5], tumor-related compression and other cervical or traumatic conditions have also been reported [6-10].

Although facial nerve injury and Frey syndrome are recognized complications of parotid surgery, PDPS is exceedingly rare. This report describes PDPS developing after superficial parotidectomy for a Warthin tumor extending toward the external carotid artery, with emphasis on diagnosis, clinical course, and spontaneous resolution.

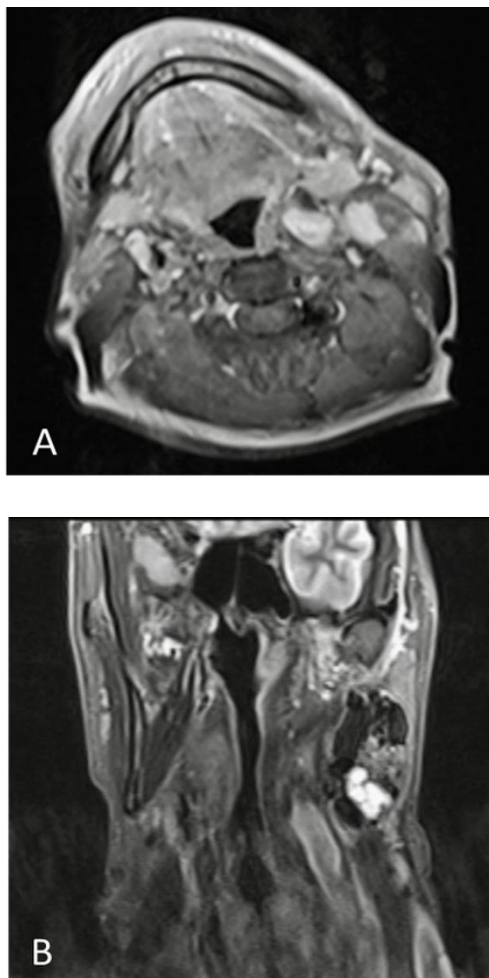
Case presentation

A 62-year-old man presented with a painless, gradually enlarging swelling in the left parotid region that had first been noticed 2 years earlier. His medical history was unremarkable, with no known systemic diseases or prior surgical interventions. Fine-needle aspiration biopsy performed at an external facility was consistent with a Warthin tumor. Baseline neurological and ophthalmological examinations were normal.

Neck ultrasonography and contrast-enhanced facial magnetic resonance imaging demonstrated a 30 × 35 mm heterogeneous mass extending toward the deep lobe of the left parotid gland (Figure 1). The lesion was located in close proximity to the carotid space.

The patient subsequently underwent superficial parotidectomy with continuous intraoperative facial nerve monitoring. During dissection, the lesion was observed to extend toward the deep lobe of the parotid gland in close proximity to the external carotid artery. No intraoperative complications occurred, and facial nerve integrity was preserved.

Figure 1. Preoperative contrast-enhanced MRI demonstrating a heterogeneous mass located within the deep lobe of the left parotid gland. (A) Axial and (B) coronal images show the lesion's proximity to the carotid space.



Within the first postoperative hour, the patient developed acute left-sided oculosympathetic hyperactivity characterized by anisocoria with mydriasis, conjunctival hyperemia, and hemifacial sweating (Figure 2). Urgent neurological and ophthalmological consultations were obtained. Brain computed tomography and diffusion-weighted magnetic resonance imaging showed no evidence of an acute central cause, including brainstem ischemia or postoperative hemorrhage. Detailed ophthalmological

evaluation, including a pilocarpine test, tonometry, and slit-lamp examination, excluded pharmacologic mydriasis, traumatic iris sphincter injury, Adie pupil, acute angle-closure glaucoma, and anterior uveitis.

Figure 2. Postoperative clinical photograph at 1 hour showing marked left-sided mydriasis and conjunctival hyperemia.



Given the temporal relationship with surgery and the anatomical proximity of the lesion to the sympathetic plexus surrounding the external carotid artery, PDPS was diagnosed. No specific pharmacologic treatment was administered. The patient's symptoms improved rapidly, and he was discharged on postoperative day 3. At the 6-month follow-up, all ocular and autonomic findings had completely resolved (Figure 3). Written informed consent was obtained from the patient for publication of this case report and the associated clinical photographs.

Figure 3. Clinical appearance at the 6-month follow-up showing complete resolution of the ocular findings.



Discussion

Pourfour du Petit syndrome is a rare clinical entity caused by hyperstimulation of the oculosympathetic pathway [1, 2]. Historically, PDPS was described as a manifestation of sympathetic pathway irritation and was named after François Pourfour du Petit, who experimentally demonstrated these effects in the early 18th century [2]. In contrast to Horner syndrome, which reflects interruption of sympathetic input, PDPS represents an excitatory state and can create a diagnostic challenge in the acute postoperative setting [3, 4].

The anatomical basis of PDPS after parotid surgery may be related to the close relationship between the superior cervical ganglion and the external carotid artery (ECA). Postganglionic sympathetic fibers arising from the superior cervical ganglion form a plexus around the ECA [4]. During surgery involving the deep lobe of the parotid gland, manipulation adjacent to the ECA may therefore cause transient irritation of the periarterial sympathetic plexus. In the present case, traction during deep-lobe dissection was considered the most likely contributing factor, although thermal irritation from bipolar cautery could not be excluded.

A clinically important feature of postoperative PDPS is its generally favorable course. Unlike permanent sympathetic nerve injury, many reported postoperative cases are self-limiting and improve spontaneously with supportive care [5]. Complete resolution within 6 months in our patient supports a transient and reversible neural irritation rather than structural damage.

Although our patient recovered without specific medication, topical alpha-2 adrenergic agonists such as brimonidine or clonidine have been discussed as potential symptomatic treatments. Their presynaptic alpha-2 activity reduces norepinephrine release from sympathetic nerve terminals and may therefore counter excessive adrenergic activity [6]. However, evidence for pharmacologic treatment of PDPS remains limited, and observation may be appropriate when serious central and ocular causes have been excluded.

PDPS should be considered in the differential diagnosis of new-onset postoperative anisocoria when there has been manipulation near the cervical sympathetic pathway or ECA [5]. Early recognition, together with neurological and ophthalmological assessment, is important to distinguish this uncommon syndrome from urgent central or ocular disorders and to avoid unnecessary invasive interventions.

Pourfour du Petit syndrome is a rare but important differential diagnosis in patients who develop new-onset anisocoria and facial autonomic findings after head and neck surgery. Awareness of this condition may facilitate early recognition and help distinguish it from more serious central or ocular disorders. Although PDPS is often self-limiting, prompt multidisciplinary evaluation remains important to exclude urgent causes and guide appropriate follow-up.

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