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Original Article

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Effects of Kinesio Taping in Carpal Tunnel Syndrome Treatment: A Randomized Controlled Trial

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Abstract

Aim: The effectiveness of kinesio taping (KT) on carpal tunnel syndrome (CTS) remains controversial. Therefore, we aimed to investigate the clinical effectiveness of KT compared to sham taping and exercises in patients with CTS.

Methods: The study was conducted between July 2020 and February 2022. Patients were randomly divided into three groups: group 1 (KT plus tendon and nerve gliding exercises), group 2 (sham-taping plus exercises), and group 3 (exercises alone). Kinesio taping was applied three times with 5-day intervals, with the "neural technique" for median and ulnar nerves and the "area correction technique" for carpal tunnel releasing. The primary outcome was the visual analog scale (VAS), while secondary outcomes included hand grip strength, the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ), and the Short Form-12 (SF-12).

Results: The study was completed with 44 patients. Significant improvement was observed in all parameters in the KT group ($p<0.05$). In both the sham taping and control groups, significant improvement was observed in all parameters except SF-12. The decrease in VAS and the improvement in the BCTQ score and hand grip strength were the highest in the KT group and were found to be significantly greater compared to the other groups ($p<0.001$, $p=0.046$, and $p=0.004$, respectively).

Conclusion: Kinesio taping in addition to exercises is more effective in improving pain, symptom severity, and hand grip strength in patients with CTS.

Keywords: Carpal tunnel syndrome, kinesio tape, pain

Introduction

Carpal tunnel syndrome (CTS) represents the most frequently encountered peripheral nerve entrapment, arising from median nerve compression as it traverses the carpal tunnel in the wrist (1). Depending on the diagnostic criteria used, its prevalence ranges between 5% and 16%, with middle-aged individuals and women being more commonly affected (2). Patients with CTS report pain, numbness, and tingling in the first three radial fingers and the radial side of the fourth finger. Diagnosis is primarily established through clinical evaluation, with electrodiagnostic studies providing additional confirmation when necessary (3). Furthermore, ultrasonography is utilized in evaluating peripheral nerve entrapments, with the most reliable ultrasonographic indicator being the nerve cross-sectional area (4).

For mild and moderate CTS, several conservative treatment methods are available, including corrective splints, local steroid injections, oral medications, physical therapy agents (ultrasound, paraffin, laser), and tendon and nerve gliding exercises (5-7). Kinesio taping (KT) is a relatively new technique for managing upper arm and hand pain. Studies suggest that its use in CTS improves symptoms (8-12). Application of KT with specific methods and tension facilitates decompression of the median nerve through extension of the transverse carpal ligament. It also regulates subcutaneous edema, enhances lymphatic and blood circulation, reduces muscle spasms, facilitates

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tendon and fascia movement, and reduces pain through neurological suppression (13). We hypothesized that KT combined with exercises would result in greater improvements in pain, symptom severity, hand grip strength, and quality of life compared to sham taping or exercises alone.

Materials and Methods

Compliance with Ethical Standards

This study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the Karadeniz Technical University Scientific Research Ethics Committee (approval no.: 9, date: 24.02.2020). The clinical trial registration number is NCT06710041.

Study Design

A priori sample size calculation was performed using G*Power software (version 3.1.9.7, Universität Düsseldorf, Germany). Assuming a large effect size (f=0.50) based on prior research on pain reduction with KT in musculoskeletal conditions, an alpha level of 0.05, and a power of 80%, the minimum sample requirement was 42 participants (14 per group) for a One-Way Analysis of Variance (ANOVA) across three groups.

A sample of 60 patients (aged between 18 and 65 years) diagnosed with mild to moderate CTS and experiencing symptoms for at least 6 weeks was enrolled in the study between July 2020 and February 2022. The study was designed as a prospective, randomized, placebo-controlled trial. Study procedures were explained to patients and written informed consent was obtained. To maintain blinding, patients received separate informed consent forms.

Exclusion criteria included electrophysiological evidence of severe CTS; presence of thenar atrophy; history of local corticosteroid injection or physiotherapy for CTS within the past three months; secondary metabolic causes of CTS such as diabetes mellitus, thyroid disease, pregnancy, rheumatoid arthritis, or sarcoidosis; coexisting conditions associated with neck or arm pain (e.g., cervical disc herniation, arthritis, or epicondylitis); history of wrist fracture; and prior CTS surgery.

Demographic variables such as age, gender, body mass index, symptom duration, smoking status, occupation, and dominant hand were recorded. For patients with bilateral CTS, only the side with more prominent symptoms was analyzed. If symptoms were equal on both sides, only the dominant hand was considered. Patients were randomly assigned to three groups via the sealed envelope method: group 1 (KT combined with tendon and nerve gliding exercises), group 2 (sham taping combined with tendon and nerve gliding exercises), and group 3 (tendon and nerve gliding exercises alone, control group). Randomization was conducted by an independent researcher uninvolved in other aspects of the study. Patients and assessors were blinded to treatment allocation, with taping and evaluations conducted by separate researchers. Patient evaluations were conducted after removing kinesiotape to ensure blinded assessments.

All three groups underwent physical, musculoskeletal, and neurological examinations, including Tinel, Phalen, and carpal compression tests. Hand grip strength was assessed using a digital dynamometer with the patient seated, forearm neutral, and elbow flexed at 90°. The highest of three measurements was recorded.

The primary outcome measurement was pain level, assessed using a visual analog scale (VAS). Secondary outcome measurements were hand-grip strength, the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ), and the Short Form-12 (SF-12) Health Survey. The BCTQ is a disease-specific questionnaire to evaluate symptom severity and functional capacity (14). A validity and reliability study of the Turkish version of the scale was conducted (15). Higher scores indicate increased symptom severity and reduced functional capacity. Short form-12 assesses health-related quality of life, with lower scores indicating poorer physical and mental health (16).

Kinesio taping was applied three times at five-day intervals. The KT application was performed three times at five-day intervals. The "neural technique" was applied along the median and ulnar nerves, while the "area correction technique" was used for carpal tunnel release. The skin was cleaned with alcohol before taping. The patient was positioned with the wrist at 30° extension and the elbow fully extended and supinated. One of the two I-bands, prepared for the neural technique, was applied along the median nerve from the second and third metacarpophalangeal joints to 5 cm below the medial epicondyle, with medium stretching. For the ulnar nerve, the same procedure was applied from the fourth and fifth metacarpophalangeal joints to 5 cm below the medial epicondyle. For the area correction technique, a tape of half the length of the wrist circumference was prepared. It was applied to the volar face of the wrist with a 50-75% stretch at the middle third. Sham taping was performed with no stretch, without the area-correction technique, and with suboptimal joint positioning to minimize biomechanical and neurophysiological effects (e.g., on transverse carpal ligament tension, lymphatic flow, or cutaneous mechanoreceptor input). This was done to maintain blinding and procedural credibility.

Tendon and nerve gliding exercises were performed three times daily (15 repetitions per session) for 6 weeks. Instructions were given in person and supplemented with brochures. Evaluations were conducted at baseline, 3 weeks, and 6 weeks.

Statistical Analysis

Data analysis was performed using SPSS version 20. Normality was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation (SD) or median (range), while categorical data were expressed as frequencies and percentages. One-Way Analysis of Variance, Kruskal-Wallis, Mann-Whitney U, and chi-squared tests were used as appropriate. Comparisons across three time points were evaluated using the Friedman test, followed by post-hoc tests when significant differences were found. Statistical significance was set at $p<0.05$. In addition to conventional significance testing, effect sizes were calculated to quantify the magnitude of between-group differences. Cohen's d was computed for change scores (baseline to 6 weeks) using pooled SD. Cohen's thresholds were adopted for interpretation, with 0.2, 0.5, and 0.8 corresponding to small, moderate, and large effects. Reporting effect sizes provides a clinically meaningful interpretation of the results beyond p-values.

Results

Forty-four patients completed the study, which still exceeded the calculated minimum sample size, ensuring sufficient statistical power for the primary outcome. No adverse effects related to KT or exercises were reported. The study flowchart is shown in Figure 1.

Baseline demographic and clinical characteristics were found comparable among groups (Table 1). The mean age of the patients was 50.02±9.07 years, and 86.4% were women. Only Boston-Functional Status Scale (FSS) and SF-12-M scores were better in group 3 compared to other groups. At three and six weeks, significant improvement was observed in all measured parameters for the KT group ($p<0.05$). The sham taping group showed improvement in all parameters except SF-12 mental health. The control group improved in all parameters except SF-12 physical and mental health. Detailed results and p-values are shown in Table 2.

The amount of change between baseline and 6 weeks was compared between the groups. Hand grip strength

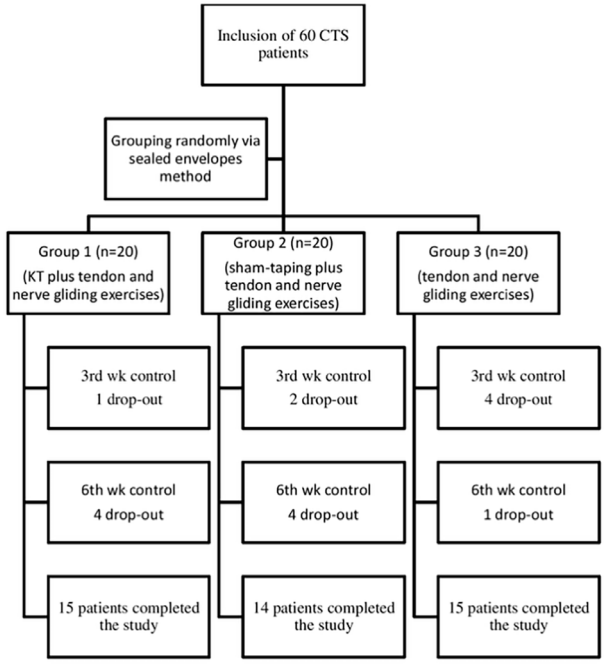

Figure 1. Flowchart
CTS: Carpal tunnel syndrome, KT: Kinesio taping

Table 1. Baseline characteristics of the patients

	Group 1	Group 2	Group 3	p-value
Age (mean ± SD)	53.20±9.78	50±7.72	46.87±8.90	0.16
Sex (female) n (%)	12 (80)	13 (92)	13 (86)	0.60
BMI (mean ± SD)	31.50±4.26	30.47±7.21	29.86±5.30	0.72
Disease duration, wk	14.13 (6-48)	33.8(6-100)	32.93 (6-100)	0.18
Median (min-max)				
Former or current smoker, n (%)	14 (93)	11 (78)	14 (93)	0.35
Number of hands affected (mean ± SD)	1.93±0.25	1.93±0.26	1.87±0.35	0.79
Hand grip strength, right, kg	25.40±6.95	23.16±8.74	22.72±10.62	0.68
Hand grip strength, left, kg	23.30±7.34	21.11±9.30	19.80±9.78	0.55
VAS at rest, cm	7.67±2.40	7.29±2	5.80±2.40	0.08
Boston-SSS	35.67±11.6	33.07±11.90	29±10.6	0.34
Boston-FSS	26.33±11.08	23.86±9.66	14.93±10	**0.011'**
SF-12-physical health	34.93±10.58	36.09±11.3	44.05±10.2	0.07
SF-12-mental health	36.63±11.04	44.55±15.2	51.73±10.1	**0.011"**

': Statistically significant difference between groups 1 and 3 and groups 2 and 3, ": Statistically significant difference between groups 1 and 3
SD: Standard deviation, BMI: Body mass index, VAS: Visual analog scale, SSS: Symptom severity scale, FSS: Functional status scale, SF-12: Short form-12

Table 2. Baseline 3rd week, and 6th week data for all three groups and in-group comparison

	Group 1				Group 2				Group 3			
	1st visit	3rd wk	6th wk	p-value	1st visit	3rd wk	6th wk	p-value	1st visit	3rd wk	6th wk	p-value
Hand grip strength, right, kg	25.4±6.9	31.7±8.3	33.8±7.2	**<0.001**	23.1±8.7	25.0±9.0	25.4±8.8	**0.001**	22.7±10.6	24.2±11.0	24.8±10.6	**<0.001**
Hand grip strength, left, kg	23.3±7.3	29.1±7.3	30.9±8.2	**<0.001**	21.1±9.3	23.4±8.9	23.8±8.8	**0.004**	19.8±9.7	20.8±9.5	21.4±9.7	**<0.001**
VAS at rest, cm	7.6±2.4	4.5±2.3	3.8±2.0	**<0.001**	7.2±2.0	5.6±1.4	5.2±1.4	**<0.001**	5.8±2.4	4.7±2.0	4.6±2.2	**0.001**
Boston-SSS	35.6±11.6	23.0±8.3	20.4±9.3	**<0.001**	33.0±11.9	25.4±8.0	25.7±8.2	**<0.001**	29±10.6	26.6±9.9	25.1±10.1	**<0.001**
Boston-FSS	26.6±11.0	17.3±7.0	16.2±7.3	**<0.001**	23.8±9.6	18.0±5.8	17.2±5.5	**0.001**	14.9±10.2	14.2±8.9	14.0±9.2	**0.015**
SF-12-physical	34.9±10.5	42.2±12.0	42.0±12.2	**0.014**	36.0±11.3	42.1±9.8	42.7±10.6	**<0.001**	44.0±10.2	45.9±9.4	48.2±9.1	0.10
SF-12-mental	36.6±11.0	51.6±11.6	52.1±10.8	**0.001**	44.5±15.2	52.4±9.8	53.1±9.4	0.11	51.7±10.1	53.1±8.6	53.2±10.0	0.53

VAS: Visual analog scale, SSS: Symptom severity scale, FSS: Functional status scale, SF-12: Short form-12

increased most in the KT group, showing significant differences compared to the other groups (p<0.001; Cohen's d for KT vs sham =2.54; KT vs control =3.05). There was no significant difference between the second and third groups in terms of the increase in hand grip strength. Pain reduction (VAS) was also greatest in the KT group (p=0.046; d=-1.81 vs sham; d=-2.14 vs. control). There was no significant difference between the second and third groups in terms of the change in VAS (p=0.425). BCTQ symptom severity improved most in the KT group (d=-1.80 vs sham; d=-2.04 vs. control). Boston Carpal Tunnel Syndrome Questionnaire-FSS showed a moderate effect compared with sham (d=-1.47) and a very large effect compared with control (d=-1.82). Detailed results are shown in Table 3 and Figure 2.

Discussion

This randomized controlled trial demonstrated that KT combined with tendon and nerve gliding exercises was more effective than sham taping or exercises alone in reducing pain and symptom severity and improving hand grip strength in patients with mild-to-moderate CTS. While improvements were also observed in the sham taping and exercise groups, the magnitude of benefit was consistently greater in the KT group, suggesting a specific therapeutic effect beyond placebo or exercise-related mechanisms. These results support the clinical utility of KT as an adjunctive conservative treatment modality in CTS management.

Our findings align with recent trials reporting significant short-term benefits of KT on CTS-related outcomes. Güvener et al. (11) showed immediate symptomatic

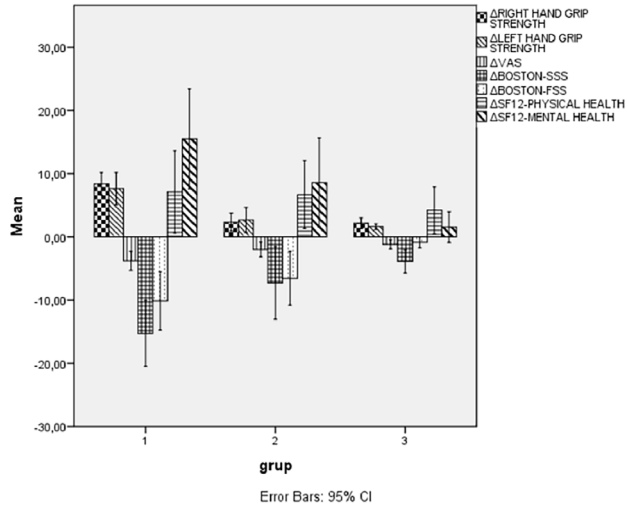

Figure 2. The amount of change in clinical parameters for all three groups

CI: Confidence interval, VAS: Visual analog scale, SSS: Symptom severity scale, FSS: Functional status scale, SF-12: Short form-12

Table 3. Comparison of the amount of change between baseline and 6th week data for all three groups				
	Group 1	**Group 2**	**Group 3**	**p-value**
Δ Hand grip strength, right, kg	8.40±3.23	2.32±2.46	2.16±1.54	**<0.001***
Mean ± SD				**<0.001****
				0.91***
Δ Hand grip strength, left, kg	7.60±4.66	2.69±3.40	1.61±0.78	**0.003***
Mean ± SD				**<0.001****
				0.81***
Δ VAS	-3.80±2.67	-2.00±2.00	-1.20±1.26	**0.046***
Mean ± SD				**0.004****
				0.42***
Δ Boston-SSS	-15.26±9.46	-7.28±9.95	-3.86±3.33	**0.004***
Mean ± SD				**0.005****
				0.18***
Δ Boston-FSS	-10.13±8.37	-6.57±7.37	-0.86±1.55	0.20*
Mean ± SD				**<0.001****
				0.033***
Δ SF-12-P	-18.15-27.50	-4.02-24.69	-3.00-18.00	**0.004***
Min-max				**0.001****
				0.66***
Δ SF-12-M	-16.70-33.17	-2.37-29.01	-5.00-13.00	0.12*
Min-max				**0.001****
				0.20***

*: Difference between group 1 and 2, **: Difference between group 1 and 3, ***: Difference between group 2 and 3
SD: Standard deviation, VAS: Visual analog scale, SSS: Symptom severity scale, FSS: Functional status scale, SF-12: Short form-12

improvements with KT, while Chen et al. (12) confirmed reductions in pain and functional limitations after KT application. Similarly, Sahin et al. (17) and Karpuz et al. (18) demonstrated that KT provided superior functional recovery compared with exercise or splinting. The present study extends these observations by confirming not only statistically significant improvements but also clinically meaningful ones, as reflected in the large effect sizes across multiple outcomes.

Interestingly, the sham taping group also showed moderate improvements in pain and symptom severity. Previous research is limited. A systematic review examining the effects of KT versus sham taping in individuals with musculoskeletal conditions found inconclusive and low-quality evidence supporting the superiority of KT over sham taping in patients with low back pain (19). Similarly, a study by Giray et al. (20) reported that KT was more effective than sham taping in alleviating pain and disability caused by lateral epicondylitis. However, studies specifically comparing KT and sham taping in CTS patients are scarce. Geler Külcü et al. (21) found no significant difference in pain reduction between KT and sham taping in CTS patients. They suggested that pain relief in the sham taping group might have been due to increased patient awareness, leading to better ergonomic practices and reduced repetitive wrist movements. Conversely, another study, similar to the present findings, showed that KT significantly improved pain and function in CTS patients compared to sham taping (22).

Although KT was superior, the sham taping group also exhibited significant pain reduction at six weeks, raising the question of whether the specific KT application technique plays a crucial role. Geler Külcü et al. (21) proposed that sham taping may provide pain relief through direct mechanical stimulation of nociceptors or mechanoreceptors. Further research is needed to explore this mechanism.

A key contribution of this study is the demonstration of substantial improvement in hand grip strength with KT. This result is consistent with prior experimental and clinical studies reporting enhanced motor performance following KT application (23,24). Notably, our findings showed large effect sizes for grip strength, suggesting that KT may not only alleviate symptoms but also improve functional capacity, which is critical for daily living and work-related activities. de Sire et al. (25) also reported improved hand

functioning with KT, although they did not observe significant changes in quality of life measures. In contrast, our study found a trend toward better physical health scores in the KT group, though no significant differences were observed in mental health outcomes, possibly due to the short follow-up or insensitivity of the SF-12 tool in this population.

Recent high-quality trials and systematic reviews further corroborate the benefits of KT in CTS. Sahin et al. (17) compared two KT techniques and confirmed significant reductions in pain and improvements in functional status. Karpuz et al. (18) showed that KT and splinting both improved functional outcomes and sleep quality, with KT demonstrating comparable or superior effects. Zainab et al. (26) found additional benefit when KT was combined with active release techniques, while Li et al. (27), in a 2025 meta-analysis, concluded that KT provides meaningful symptom relief and functional gains in mild-to-moderate CTS. These contemporary findings strengthen the external validity of our results and position KT as a relevant option within the spectrum of non-surgical CTS management.

The use of two comparators strengthens interpretation. Compared to exercises alone, KT demonstrated an incremental, clinically relevant benefit, supporting its pragmatic use as an adjunct to standard care. Compared to sham taping, KT outperformed a credible placebo that controls for attention, touch, and expectancy, indicating that the observed effects are unlikely to be explained by non-specific mechanisms. Together, these findings enhance both internal validity (specific efficacy beyond placebo) and external validity (added value over routine exercise-based management).

Study Limitations

This study has several limitations. First, the relatively small sample size and the dropout of participants may have reduced the statistical power, although the study still met the minimum sample size determined by a priori power analysis. Second, the follow-up duration was limited to six weeks, which precludes conclusions about the long-term sustainability of KT effects in chronic CTS. Third, subgroup analyses according to age, sex, symptom duration, or baseline severity were not performed, but such analyses could have provided insights into which patient groups benefit most from kinesiotaping. Fourth, although only exercise interventions were included as a control to reflect standard conservative management, the absence of an untreated control arm prevents differentiation between natural history and treatment effects. Fifth, hand dominance was not analyzed separately, which might have influenced grip strength outcomes. Finally, the use of the SF-12, although validated, may not have been sensitive enough to detect subtle changes in mental health-related quality of life in this population.

Despite these limitations, the study has notable strengths, including its randomized controlled design, blinded assessments, and use of both disease-specific and generic outcome measures, which enhance the validity and generalizability of the findings.

Conclusion

Kinesio taping plus exercises is more effective than sham taping plus exercises and exercises alone for improving pain, symptom severity, and hand grip strength in patients with CTS at the early stage. Applying KT with neural and area correction techniques at five-day intervals could enhance treatment outcomes for mild and moderate CTS. However, considering the chronic nature of CTS, further studies are needed to examine its long-term effects.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the Karadeniz Technical University Scientific Research Ethics Committee (approval no.: 9, date: 24.02.2020). The clinical trial registration number is NCT06710041.

Informed Consent: Study procedures were explained to patients and written informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.K., E.C., Concept: H.B.S., G.S.A., Design: H.B.S., G.S.A., Data Collection or Processing: F.K., E.C., Analysis or Interpretation: H.B.S., G.S.A., Literature Search: H.B.S., F.K., E.C., G.S.A., Writing: H.B.S.

Conflict of interests: No conflict of interest were declared by the authors.

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Original Article

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Comparison of the Postoperative Analgesic Efficacy of Adjuvant Anterior Quadratus Lumborum Block in Laparoscopic Cholecystectomies: A Prospective Randomized Double-blind Study

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Abstract

Aim: The quadratus lumborum block (QLB) is frequently used for postoperative pain relief in laparoscopic cholecystectomies (LC). When added as an adjuvant to local anesthetics, dexamethasone may improve and extend the analgesic effect. This prospective study aimed to assess the efficacy of dexamethasone as an adjuvant in anterior QLB for LC.

Methods: Eighty-three patients undergoing LC were randomly assigned to two groups. Group anterior (A)-QLB (n=39) received bilateral anterior QLB with 20 mL of 0.25% bupivacaine plus 4 mg of dexamethasone. Group QLB (n=44) received the same volume and concentration of bupivacaine without dexamethasone. Dermatomal spread was evaluated after the block. Intraoperative remifentanil consumption, 24-hour postoperative tramadol use, time to first rescue analgesic, numeric rating scale (NRS) pain scores, and side effects were recorded.

Results: Total tramadol consumption within the first 24 postoperative hours was comparable between the groups. However, NRS scores at 4, 8, 12, and 24 hours were significantly lower in the A-QLB group. Dermatomal spread was broader in the A-QLB group. No significant differences were observed between the groups regarding the time to first rescue analgesic and intraoperative remifentanil consumption.

Conclusion: In LC, anterior QLB used for postoperative pain relief showed that patients receiving dexamethasone with local anesthetic via the interfascial route had lower postoperative NRS scores and broader dermatomal spread compared to those receiving only local anesthetic, indicating that interfascial dexamethasone provides superior analgesic effects.

Keywords: Adjuvant, dexamethasone, postoperative analgesia, laparoscopic cholecystectomy

Introduction

Among surgical interventions, laparoscopic cholecystectomy (LC) ranks as one of the most frequently conducted procedures. The pain intensity following LC is typically lower than in open procedures, but patients may still report moderate to severe levels. This pain can originate from somatic nerves at the trocar entry sites, visceral discomfort due to gallbladder manipulation, or visceral discomfort caused by CO_2 insufflation of the abdomen (1).

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Postoperative analgesia often requires the use of opioid analgesics. However, due to undesirable side effects—such as nausea, vomiting, itching, dependency, and prolonged hospital stays—the use of truncal blocks as part of multimodal analgesia has increased in recent years (2,3). Quadratus lumborum blocks (QLB) are among the techniques used for postoperative analgesia in abdominal surgical procedures. Studies have shown that analgesia can be achieved in the T7-L2 dermatomal regions (4).

Dexamethasone is a glucocorticoid known for its ability to prolong the effects of local anesthetics and suppress inflammation when used as an adjuvant (5,6). Its efficacy in pain management has been shown in caudal, brachial plexus, epidural, and perineural blocks without associated adverse effects (7,8). The exact mechanism is not fully understood, but several pathways have been proposed. Glucocorticoids have been reported to produce a membrane-stabilizing effect on nerve cells, similar to local anesthetics; this effect reduces nerve conduction. In addition, they suppress proinflammatory transcription factors such as nuclear factor kappa B (NF-κB) at the spinal level, thus inhibiting central sensitization (9,10). These properties make dexamethasone a safe and effective adjuvant for enhancing postoperative analgesia.

We hypothesized that using perineural (interfascial) dexamethasone as an adjuvant in the anterior QLB, would improve postoperative analgesic efficacy compared to local anesthetics without adjuvants in LC cases. We also considered that analyzing dermatomal spread in the adjuvant QLB group would offer important information regarding dexamethasone's contribution to overall analgesic efficacy.

This study aimed to determine whether the addition of dexamethasone to local anesthetics in the interfascial plane of the anterior QLB improves postoperative analgesia in patients undergoing LC. Specifically, we assessed total tramadol consumption within the first 24 hours postoperatively, numeric rating scale (NRS) scores (at rest and during movement), intraoperative remifentanil consumption, time to first rescue analgesic administration, dermatomal spread, and adverse effects. By analyzing these outcomes, this study aims to clarify the impact of dexamethasone on multimodal analgesia strategies, particularly regarding opioid consumption and postoperative pain management. Given its anti-inflammatory and analgesic-prolonging effects, dexamethasone may enhance these outcomes as an adjuvant in the interfascial plane.

Materials and Methods

Compliance with Ethical Standards

Ethical approval was obtained from the University of Health Sciences Türkiye, Gaziosmanpasa Training and Research Hospital Clinical Research Ethics Committee under the registration number (approval no.: 40, date: 10.05.2023). The study was registered in the Clinical Trials database with the number NCT06028061.

The study was conducted at the general surgery OR of University of Health Sciences Türkiye, Gaziosmanpasa Training and Research Hospital between September 1, 2023, and February 15, 2024. It adhered to the Declaration of Helsinki. Only patients who gave signed informed consent prior to participation were included.

Study Design and Patients

The present research was double-blind, randomized, and prospective. Participants were American Society of Anesthesiologists (ASA) class I-II patients, aged 18-65, scheduled for elective LC. Exclusion criteria were infection at the block site, previous abdominal surgery, allergy to local anesthetics, coagulation disorders, chronic analgesic or opioid use, neurological or psychological disorders, communication difficulties, body mass index >35 kg/m², absent dermatomal involvement at 30 minutes, non-adherence to the analgesia protocol, major perioperative complications, or operative time over 90 minutes.

Grouping and Randomization

A computer-based system created the randomization list. This list was placed in sealed envelopes labeled with sequential numbers. Group allocation was determined by opening the next envelope for each patient. Participants were divided into two groups: Group A-QLB (adjuvant) and Group QLB (non-adjuvant).

Block Procedure

The local anesthetic solutions were prepared by a blinded anesthetist who was not involved in either block administration or patient follow-up. All block procedures were performed by the same experienced anesthesiologist, who was also blinded to the prepared medication. The patients were blinded as well. All blocks were administered 30 minutes prior to surgery.

The block procedures were performed after standard monitoring was established, with the patients placed in the lateral position and appropriate aseptic conditions ensured. A convex ultrasound (USG) probe (2-6 MHz) (MyLabseven; Esaote Europe, Netherlands) was used. The probe was positioned in the subcostal area, above the iliac crest, and along the mid-axillary line to visualize the quadratus lumborum muscle, psoas major muscle, and the L4 vertebra. Using the in-plane technique, a 22G 100 mm peripheral block needle (Stimuplex® Ultra; B. Braun, Melsungen, Germany) was advanced toward the anterior aspect of the quadratus lumborum muscle, targeting the subfascial space between the quadratus lumborum and psoas major muscles. Hydrodissection was performed with 1-2 mL of 0.9% saline to confirm correct needle placement,

after which the local anesthetic was administered (Figure 1). In Group A-QLB, patients received 20 mL of a solution containing 10 mL of 0.5% bupivacaine, 9 mL of saline, and 1 mL (4 mg) of dexamethasone per side. In contrast, patients in Group QLB received 10 mL of 0.5% bupivacaine diluted with 10 mL of saline to yield a final concentration of 0.25%, and 20 mL was administered on each side.

Dermatomal Analyses

After the block procedure, a blinded anesthesiologist performed cold sensation testing at 30 minutes using an ice pack. A healthcare professional applied the ice pack to the deltoid muscle area of the shoulder to help patients recognize the sensation of cold before assessing the dermatomal regions. Each dermatome, from T4 to L2 along the midclavicular line, was assessed sequentially. The right side was tested first, then the left, to evaluate cold perception.

To prevent local warming after skin contact, the orientation of the ice pack was changed after testing each dermatome. The ice pack was applied for 2 seconds at each dermatome level. Absence of cold sensation, or a significant reduction in perception, was interpreted as sensory cutaneous blockade and was documented as dermatomal involvement. Patients whose dermatomal involvement was confirmed at 30 minutes were transferred to the operating room for surgery.

General Anesthesia Application

All patients underwent a standardized general anesthesia protocol. Induction was performed with intravenous midazolam, lidocaine, propofol, fentanyl, and rocuronium. Maintenance was performed with sevoflurane and remifentanil infusion, titrated to maintain hemodynamic stability. All LC procedures were performed by the same surgical team, using the conventional four-port method with carbon dioxide pneumoperitoneum. Intra-abdominal pressure was kept below 12 mmHg. At the end of surgery, patients received intravenous paracetamol, tramadol, and ondansetron. Neuromuscular blockade was antagonized with neostigmine and atropine. Total intraoperative remifentanil consumption was recorded. Patients were transferred to the post-anesthesia care unit for monitoring before discharge to the ward.

Postoperative Analgesia Regimen and Outcomes

All patients routinely received 1 g of paracetamol four times daily. If the resting NRS (rNRS) was ≥4, 100 mg of intravenous tramadol was given as rescue analgesia. Postoperative visits were conducted at 1, 4, 8, 12, and 24 hours by a blinded anesthesiologist, who recorded tramadol usage, time to first rescue analgesic, NRS scores at rest and during movement, dermatomal involvement, and adverse effects such as nausea, vomiting, and shoulder pain. Patients with no dermatomal involvement at 30 minutes, non-compliance with the analgesia protocol, major perioperative complications, or an operative time longer than 90 minutes were excluded. The primary outcome was total tramadol consumption within the first 24 hours, while secondary outcomes included postoperative NRS scores, time to first rescue analgesic, intraoperative remifentanil consumption, dermatomal spread, and side effects.

Sample Size and Statistical Analyses

A priori power analysis was performed using G*Power software (Version 3.1, Brunsbüttel, Germany) (11). Preliminary data indicated 24-hour tramadol consumption was 146.80±74.60 mg in the QLB group (non-adjuvant) and 113.40±65.60 mg in the A-QLB group (adjuvant). With a significance level (α) of 0.05, 80% power, and an effect size of 0.63, the study's estimated sample size was 39 per group. To account for potential conversions to open surgery and patient attrition during follow-up, 45 patients were planned for each group.

All statistical analyses were conducted using IBM SPSS Statistics 26 and IBM SPSS Amos 21. Categorical variables were summarized as counts and percentages. Continuous variables were expressed as mean ± standard deviation or median with range [median (min-max)], depending on data distribution. Normality was assessed with the Kolmogorov-Smirnov test. Parametric variables were compared using the independent samples t-test. Non-parametric data were evaluated with the Mann-Whitney U test. The chi-square or Fisher's exact test was used for categorical variables. For intragroup comparisons across repeated measures, such as postoperative pain scores, the Friedman test was used. When applicable, Bonferroni correction was applied in post-hoc analyses to determine specific time points with significant differences. Statistical significance was defined as $p<0.05$.

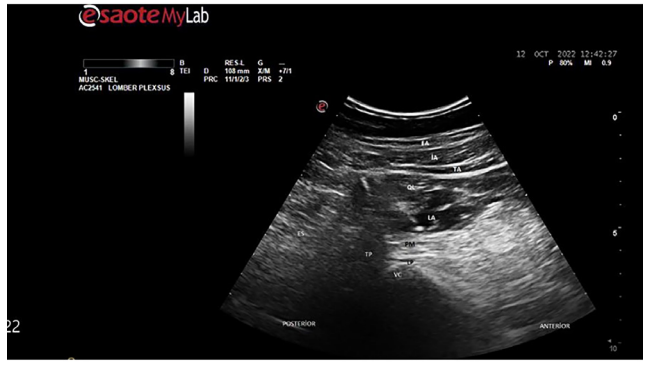

Figure 1. Ultrasound image of anterior quadratus lumborum block

Results

Patient Characteristics

In total, 83 patients were included in the final analysis (Figure 2). The groups were found to be comparable in terms of demographic variables, with no meaningful differences observed (Table 1).

Analgesic Consumption

The total tramadol consumption within the first 24 postoperative hours was similar between the adjuvant QLB group (58.97±54.86 mg, 95% CI: 41.19-76.76) and the standard QLB group (79.55±92.96 mg, 95% CI: 51.28-107.81), with no statistically significant difference (p=0.539, Cohen's d=0.122) (Table 2).

The time to first rescue analgesic was comparable between the adjuvant QLB group (4.59±3.62 h, 95% CI: 2.99-6.19) and the non-adjuvant QLB group (3.79±4.60 h, 95% CI: 1.85-5.73), with no statistically significant difference (p=0.305, Cohen's d=0.302) (Table 1).

Pain Scores

When comparing rNRS and dynamic NRS (dNRS) scores between the groups, rNRS and dNRS values at 4, 8, 12, and 24 hours were significantly lower in the A-QLB group than in the QLB group (Table 3).

Time-Dependent Tramadol Consumption

Across all recorded postoperative intervals (0-1 hours, 1-4 hours, 4-8 hours, 8-12 hours, and 12-24 hours), there were no statistically significant variations in tramadol usage between the groups (Table 4).

Dermatomal Spread

In terms of dermatomal involvement, the A-QLB group showed a significantly greater bilateral involvement in the T9, T10, and L1 dermatomes on both the right and left sides at 30 minutes compared to the QLB group (Table 5).

Postoperative Side Effects

Regarding postoperative complications, including nausea, vomiting, and shoulder pain within 24 hours, both groups demonstrated similar outcomes without any significant intergroup differences (Table 6).

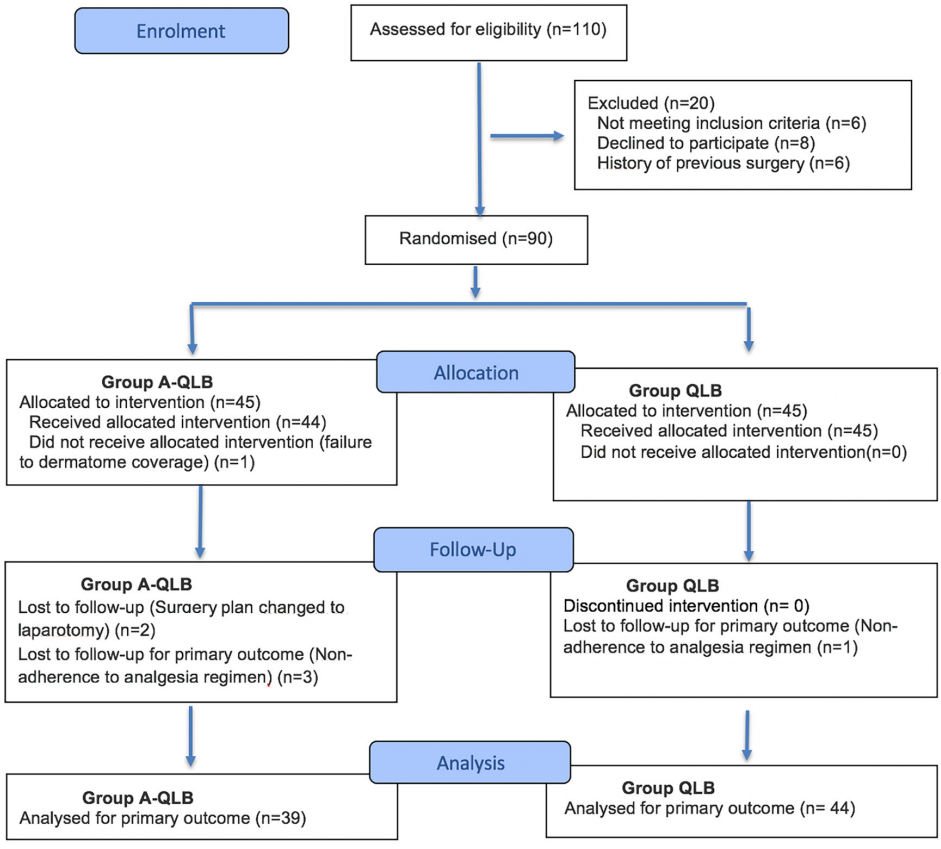

Figure 2. Consort flow diagram

OLB: Quadratus lumborum block

Table 1. Comparison of demographic data and operational durations among groups			
	Group A-QLB (n=39)	**Group QLB (n=44)**	**p**
	n (%)	**n (%)**	
Gender			
Female	31 (79.5)	33 (75)	0.6
Male	8 (20.5)	11 (25)	
	Mean ± SD	**Mean ± SD**	**p**
Age (year)	45.41±9.7	42.9±12.4	0.3
BMI (kg/m^2)	27.97±5.1	27.8±4	0.9
Operation time (minute)	55.5±18.9	57.3±15.2	0.5
Intraoperative Remifentanil Consumption (mcg/kg)	4.10±2.92	4.13±3.84	0.488
Values are presented as Mean ± SD QLB: Quadratus lumborum block, A-QLB: Anterior quadratus lumborum block, SD: Standard deviation			

Table 2. Comparison of analgesic usage between groups						
	Group A-QLB (n=39)		**Group QLB (n=44)**			
	Mean ± SD	**95% CI**	**Mean ± SD**	**95% CI**	**p**	**Effect size(d)**
Time to first rescue analgesic (hour)	4.59±3.62	2.99-6.19	3.79±4.6	1.85-5.73	0.305	0.302
Postoperative total tramadol consumption (mg/day)	58.97±54.86	41.19-76.76	79.55±92.96	51.28-107.81	0.539	0.122
Values are presented as mean ± SD and 95% QLB: Quadratus lumborum block, A-QLB: Anterior quadratus lumborum block, SD: Standard deviation, CI: Confidence interval						

Table 3. Comparison of rNRS and dNRS values between groups						
	Group A-QLB (n=39)		**Group QLB (n=44)**		**p**	**Effect size (d)**
	Mean ± SD	**95% CI**	**Mean ± SD**	**95% CI**		
rNRS 1st hour	2.59±1.52	2.10-3.08	3.59±2.35	2.88-4.30	0.060	0.412
rNRS 4th hour	1.92±1.51	1.43-2.41	2.80±1.91	2.21-3.38	**0.021***	0.508
rNRS 8th hour	1.54±0.94	1.23-1.84	2.18±1.35	1.77-2.59	**0.029***	0.470
rNRS 12th hour	1.13±1.06	0.79-1.47	1.82±1.17	1.46-2.17	**0.005***	0.616
rNRS 24th hour	0.69±0.73	0.46-0.93	1.55±1.56	1.07-2.02	**0.003***	0.637
Fr; p-value	65.345; 0.000*		65.345; 0.000*			
Difference	24<1,4,8 12<1,4 8<1		24<1,4 12<1 8<1			
dNRS 1st hour	3.69±1.73	3.13-4.25	4.61±2.46	3.87-5.36	0.096	0.365
dNRS 4th hour	3.08±1.58	2.57-3.59	4.20±2.22	3.53-4.88	**0.021***	0.515
dNRS 8th hour	2.64±1.22	2.24-3.04	3.61±1.91	3.03-4.19	**0.011***	0.566
dNRS 12th hour	2.13±1.38	1.68-2.58	3.18±1.74	2.65-3.71	**0.006***	0.616
dNRS 24th hour	1.64±1.16	1.27-2.02	2.64±2.07	2.01-3.27	**0.040***	0.450
Fr;p	57.065; 0.000*		45.634; 0.000*			
Difference	24<1,4,8 12<1,4		24<1,4 12<1			
Values are presented as mean ± SD and 95%, *=p<0.05 rNRS: Resting numeric rating scale, dNRS: Dynamic numeric rating scale, CI:Confidence interval, SD: Standard deviation						

Table 4. Comparison of tramadol usage between groups				
Tramadol usage by time interval (mg)	**Group A-QLB (n=39)**	**Group QLB (n=44)**		
	Mean ± SD 95% CI	**Mean ± SD 95% CI**	**p**	**Effect size (d)**
0-1 Hours	15.38±36.55 95% CI (3.54-27.23)	18.18±39.02 95% CI (6.32-30.04)	0.73	0.048
1-4 Hours	10.26±30.74 95% CI (0.29-20.22)	15.91±37 95% CI (4.66-27.16)	0.45	0.097
4-8 Hours	17.95±38.88 95% CI (5.35-30.55)	18.18±39.02 95% CI (6.32-30.04)	0.98	0.004
8-12 Hours	12.82±33.87 95% CI (1.84-23.80)	9.09±29.08 95% CI (0.25-17.93)	0.59	0.001
12-24 Hours	2.56±16.01 95% CI (-2.63-7.75)	13.64±34.71 95% CI (3.08-24.19)	0.07	0.064
Fr;p	4.711; 0.318	2.196; 0.700		
Values are presented as mean ± SD (95% confidence interval) QLB: Quadratus lumborum block, A-QLB: Anterior quadratus lumborum block, SD: Standard deviation, CI: Confidence interval				

Table 5. Comparison of dermatomal involvement at the 30th minutes after block application			
	Group A-QLB (n=39)	**Group QLB (n=44)**	**p**
	n (%)	**n (%)**	
Right side, 30th minute			
T7	2 (5.1)	0 (0)	-
T8	12 (30.8)	12 (27.3)	0.726
T9	27 (69.2)	21 (47.7)	**0.048***
T10	33 (84.6)	28 (63.6)	**0.031***
T11	36 (92.3)	36 (81.8)	0.16
T12	36 (92.3)	40 (90.9)	0.82
L1	33 (84.6)	28 (63.6)	**0.031***
L2	9 (23.1)	10 (22.7)	0.97
Left side, 30th minute			
T7	1 (2.6)	0 (0)	**-**
T8	12 (30.8)	12 (27.3)	0.726
T9	27 (69.2)	21 (47.7)	**0.048***
T10	34 (87.2)	25 (56.8)	**0.002***
T11	36 (92.3)	36 (81.8)	0.16
T12	36 (92.3)	42 (95.5)	0.55
L1	33 (84.6)	28 (63.6)	**0.031***
L2	9 (23.1)	9 (20.5)	0.77
Values are presented as number and percentage (n, %), *=p<0.05 QLB: Quadratus lumborum block, A-QLB: Anterior quadratus lumborum block			

Table 6. Comparison of postoperative side effects between the groups			
	Group A-QLB (n=39)	**Group QLB (n=44)**	**p**
	n (%)	**n (%)**	
Nouse	16 (41)	22 (50)	0.4
Vomiting	3 (7.7)	8 (18.2)	0.2
Shoulder pain	12 (30.8)	12 (27.3)	0.7
Values are presented as number and percentage (n, %)			

Discussion

This study found that interfascial dexamethasone combined with local anesthetics in anterior QLB blocks for LC resulted in significantly lower postoperative NRS scores. The dexamethasone group showed a broader dermatomal spread, especially at T9, T10, and L1. However, total tramadol use, intraoperative remifentanil, and time to first rescue analgesic were similar between groups.

Quadratus lumborum blocks blocks are used for postoperative pain relief in surgeries involving the lower thoracic, abdominal, retroperitoneal, and inguinal regions (12,13).

Based on the idea that the rich mechanoreceptor content in the anterior thoracolumbar fascia may offer more effective analgesia, we selected anterior QLB in this study (4,14). The anterior QLB technique was first described by Børglum (15).

Effective and long-lasting postoperative pain relief is essential for patient comfort, early discharge, and reduced hospital expenses. Adding adjuvants to local anesthetics is a promising approach to enhance the duration and effectiveness of analgesia. Many studies, including randomized trials on QLB, pectoral nerve block, and erector spinae blocks, demonstrate that adjuvants like dexamethasone or dexmedetomidine can decrease postoperative analgesic consumption, lower pain scores, and prolong the time until the first rescue

analgesia (6,16-22). However, evidence regarding the effectiveness of adjuvants in fascial plane blocks remains limited, and few studies have examined dexamethasone use with dermatomal spread. We believe our inclusion of dermatomal analysis provides a new contribution and an innovative perspective in evaluating analgesic effectiveness.

In our study, the total tramadol consumption within 24 hours was 58.97±54.86 mg in the adjuvant group and 79.55±92.96 mg in the non-adjuvant group, with no statistically significant difference between the groups. However, the consumption values showed a trend favoring the adjuvant group. Similarly, the time to first rescue analgesia was 3.79±4.6 hours in the non-adjuvant group and 4.59±3.62 hours in the adjuvant group. Although the difference was not statistically significant, it was longer in the adjuvant group. We believe that the differences between our findings and those reported in the literature may be partly related to sample size. Furthermore, while most previous studies primarily focused on analgesic consumption as the main indicator of efficacy, our study differed by including NRS scores and dermatomal analysis in the evaluation. This methodological difference offers additional insight into the analgesic effects of adjuvant dexamethasone and could explain the variability seen across studies.

Although dexamethasone is widely used, its perineural application is considered off-label by both the US. Food and Drug Administration and the European Medicines Agency, which raises concerns among some practitioners. As a result, intravenous administration has become more common in recent years. When reviewing the literature on whether adjuvants should be given intravenously or added directly to local anesthetics, we noted concerns about precipitation and crystallization that may occur due to the alkalinization of local anesthetic solutions (23). However, relevant publications show that precipitation is more likely with ropivacaine (more acidic than bupivacaine), especially when combined with more alkaline steroids like betamethasone (23,24). In our study, we used bupivacaine and dexamethasone. Previous research indicates that precipitation is more often seen in alkaline environments and is rare with bupivacaine. We did not observe any turbidity or signs of precipitation in our local anesthetic mixture.

In recent years, the intravenous administration of dexamethasone as an adjuvant has been widely discussed. However, studies by Abdellatif et al. (25) and Arafa et al. (26) showed that interfascial administration of dexamethasone is more effective than intravenous use. Two meta-analyses further confirmed that perineural dexamethasone extends analgesia more effectively than intravenous administration, without evidence of neurological complications, infection risk, or significant hyperglycemia (27,28). Dexamethasone is thought to improve the quality and duration of peripheral nerve blocks by reducing the release of inflammatory mediators, suppressing ectopic neuronal discharge, and inhibiting potassium channel-mediated depolarization in nociceptive C-fibers (29-31). In our study, we specifically chose the interfascial route because of the relatively poor vascularity of this anatomical plane, which we expected would lead to a longer duration of action. If systemic absorption had been predominant in this setting, a lower incidence of postoperative nausea and vomiting (PONV) would have been expected in patients receiving dexamethasone; however, the similar rates of PONV between groups suggest otherwise. This interpretation is further supported by previous reports consistently showing the strong antiemetic effect of intravenous dexamethasone (32).

In this study, patients who received dexamethasone showed significantly lower rNRS and dNRS scores at the 4^{th}, 8^{th}, 12^{th}, and 24^{th} postoperative hours, indicating that dexamethasone improved the analgesic effectiveness of the local anesthetic. These results align with previous studies on adjuvant use and match the observation that dermatomal involvement was more common in the adjuvant group.

Furthermore, analgesic consumption during the 12-24 hours period was lower in the A-QLB group than in the QLB group (2.56±16.01 vs. 13.64±34.71, respectively). Although this difference did not achieve statistical significance, the lower tramadol requirement in the adjuvant group during this period was viewed as an indication of dexamethasone's effectiveness. This result, along with decreased NRS scores and more widespread dermatomal spread, suggests that dexamethasone may extend the duration of local anesthetic effects in interfascial plane blocks and thus enhance effective and longer-lasting postoperative pain relief.

There have been no documented cases of dexamethasone-related neuronal damage so far. Conversely, cell-level studies in mice indicate that dexamethasone might reduce the neurotoxic effects of bupivacaine (33-35). Additionally, concerns about the potential for dexamethasone to increase surgical site infection risk have led some clinicians to restrict its use. However, Jones et al. (36) reported in their meta-analysis that perioperative dexamethasone use in diabetic patients does not raise the risk of infection. While the current data support its early safety, long-term prospective studies are limited. Therefore, more research is needed to understand long-term outcomes.

Dermatomal involvement at 30 minutes was broader in the adjuvant group compared to the non-adjuvant group. In QLB blocks, dermatomal involvement typically occurs

within the T7-L1 range, although the literature has reported extensions into both higher and lower dermatomal levels. In this study, cutaneous sensory blockade was primarily observed in the T9-L1 dermatomes.

At the 30th minute, involvement of the T9, T10, and L1 dermatomes on both the right and left sides was significantly greater in the adjuvant group. The involvement of the T11-T12 dermatomes was similar between the two groups. In both groups, bilateral sensory cutaneous blockade in the T11-T12 dermatomes was observed in 80-95% of patients. Sensory cutaneous blockade was most frequently noted in the T10-L1 dermatomes in both groups. These findings are consistent with the literature (37).

The difference in dermatomal involvement between the groups was linked to the lower NRS scores seen in the adjuvant group. Since previous studies have not examined dermatomal involvement, we could not compare our findings on the relationship between dermatomal spread and pain relief with those studies. The greater dermatomal spread in the adjuvant group, especially in the T9, T10, and L2 dermatomes, may be related to how dexamethasone works and how anterior QLB blocks might extend into the paravertebral space. A key strength of our study is the inclusion of dermatomal analysis, which allowed us to show the connection between dermatomal spread and pain relief-a new contribution that sets our work apart from previous research and could guide clinical practice.

Although QLB primarily targets the lower thoracic and upper lumbar dermatomes (T9-L1), our study involving patients undergoing LC showed cutaneous sensory involvement in the T8-L2 range. Since LC procedures involve both somatic pain from trocar incisions and visceral pain related to CO_2 insufflation and gallbladder manipulation, we believe that QLB can significantly contribute to multimodal analgesia protocols. While transversus abdominis plane blocks generally provide only somatic analgesia and may be inadequate for complete sensory blockade of the abdominal wall, erector spinae plane blocks—although effective against visceral pain—are more technically difficult to perform. Visualizing the spread of local anesthetic using an in-plane approach in ESP blocks is not always possible. In contrast, anterior QLB is easier to perform under USG guidance. The lower NRS scores observed in our study further support the potential usefulness of QLB, especially when combined with dexamethasone as an adjuvant, for postoperative pain management in LC.

In this study, dexamethasone was administered via the interfascial route rather than intravenously. Beyond the reduced vascularization in the interfascial area, which limits systemic absorption and prolongs local action, this route also provides additional advantages. The anterior QLB has the potential to spread to the paravertebral and epidural spaces, enabling dexamethasone to exert analgesic effects through the inhibition of NF-κB, a transcription factor involved in central sensitization and pathological pain (9,10). In addition, the vasoconstrictive properties of steroids may further decrease systemic uptake and contribute to extending the duration of analgesia. Collectively, these anatomical and pharmacological mechanisms support the use of dexamethasone as an effective adjuvant to enhance and prolong postoperative analgesia, particularly in inflammatory and incisional pain.

Study Limitations

A major limitation of our study was the inability to analyze postoperative dermatomal areas. Patients were sedated and under the influence of analgesic medications following general anesthesia, which could compromise data reliability. In addition, dermatomal testing at thoracic entry sites carries a potential risk of cutaneous nerve injury, further limiting its feasibility. Another limitation was the relatively short follow-up period (24 hours), since patients were routinely discharged within this timeframe. This prevented the evaluation of prolonged analgesic effects, even though the duration of action of interfascial dexamethasone may be longer due to reduced vascularization and delayed absorption. In addition, the lack of long-term follow-up restricted the ability to definitively evaluate the clinical outcomes of dexamethasone administration. Furthermore, the single-center design and relatively young ASA I–II population may restrict the generalizability of the findings and the study might also be underpowered for some secondary outcomes.

Despite these limitations, this study has several strengths. Its prospective, randomized, and double-blinded design enhances methodological rigor, and the use of standardized anesthesia and surgical protocols ensures homogeneity across groups. Moreover, the analysis of dermatomal spread in the adjuvant anterior QLB group represents a unique and original contribution to the literature, offering clearer insights into the role of dexamethasone in enhancing analgesic efficacy.

Conclusion

These findings demonstrate that the addition of dexamethasone to QLB may provide clinical advantages in terms of both more effective pain control and broader dermatomal spread. Moreover, the administration of dexamethasone into the interfascial plane, unlike dexamethasone's use in extremity blocks, may offer additional benefits due to reduced vascularization. Taken together, these results highlight the need for further studies to evaluate the efficacy of adjuvants in fascial plane blocks.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye Gaziosmanpasa Training and Research Hospital Clinical Research Ethics Committee under the registration number (approval no.: 40, date: 10.05.2023).

Informed Consent: Only patients who gave signed informed consent prior to participation were included.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S., D.G.M., B.B., Concept: S.S., D.G.M., V.D., Design: S.S., D.G.M., V.D., Data Collection or Processing: S.S., O.O., B.B., V.D., Analysis or Interpretation: S.S., O.O., B.B., Literature Search: S.S., O.O., D.G.M., Writing: S.S.

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Original Article

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Evaluating Cervical Cancer Risk Using Machine Learning

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Abstract

Aim: Cervical cancer development is influenced by a complex interaction of socio-demographic, behavioral, and clinical factors, which can be systematically analyzed using large datasets. Therefore, this study aimed to evaluate the effectiveness of machine learning (ML) models applied to the University of California, Irvine (UCI), cervical cancer risk factors dataset in predicting cervical health outcomes and supporting early detection strategies.

Methods: This study was designed as a retrospective data analysis covering a random sampling of patients between 2012 and 2013 who attended the gynecology service at Hospital Universitario de Caracas in Caracas, Venezuela. The publicly available UCI cervical cancer risk factors dataset was utilized for the analysis. A correlation heatmap was generated to explore the relationships among various risk factors. To address the class imbalance present in the dataset, the synthetic minority over-sampling technique (SMOTE) was applied. Subsequently, different ML classifiers were trained and evaluated to predict cervical cancer outcomes with improved accuracy.

Results: The correlation analysis revealed strong correlations among smoking-related measures and diagnostic variables, indicating internal consistency. After applying SMOTE, the dataset achieved a balanced distribution of healthy and diseased individuals. The ensemble classifiers demonstrated high accuracy, up to 97%, and precision, with random forest and light gradient boosting machine performing particularly well. However, the recall for cancer detection was lower: 0.80, indicating potential missed diagnoses.

Conclusion: The findings support the integration of ML in clinical diagnostics for cervical cancer, highlighting its potential for improving early detection and patient outcomes while also emphasizing the need for ongoing refinement in model performance.

Keywords: Cervical cancer, risk factors, machine learning, gynecology, diagnosis

Introduction

Cervical cancer remains one of the most significant global health concerns among women, especially in developing regions (1). Cervical cancer accounts for approximately 6.5% of all malignancies in women. Despite advances in screening and vaccination programs, the high incidence and mortality rates highlight the urgent need for improved strategies in prevention and early detection (2,3). Infection with human papillomavirus (HPV), primarily transmitted through sexual contact, is the leading cause of cervical cancer, and vaccination against HPV has become an essential preventive measure supported by global health authorities (4-6).

Early detection is critical to reducing mortality, yet asymptomatic progression in the early stages makes timely diagnosis (Dx) challenging (7). Traditional screening methods such as Pap smears and HPV tests, while effective, may be limited in sensitivity, accessibility, or cost in certain healthcare settings. For example, Pap smears may yield false-negative results in up to 50% of cases, leading to delayed diagnosis (8). In addition, in many low- and middle-income countries, limited access to trained

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personnel and laboratory infrastructure further reduces the effectiveness of routine screening programs (9). Advances in artificial intelligence and machine learning (ML) offer opportunities to improve prediction and stratification of high-risk individuals (10).

We hypothesized that the integration of socio-demographic, behavioral, and medical data into ML based models would enhance the accuracy of cervical cancer risk prediction compared to traditional screening methods alone. Therefore, the aim of this study was to evaluate multiple ML algorithms on the University of California, Irvine (UCI) cervical cancer risk factors dataset (11), addressing class imbalance through the use of the synthetic minority over-sampling technique (SMOTE) (12). This approach is expected to contribute to clinical practice by supporting earlier identification of high-risk patients, thereby enabling timely interventions and ultimately reducing cervical cancer-related morbidity and mortality.

Materials and Methods

Dataset Description

Ethics committee approval was not required for this study, as the data used does not contain personally identifiable information. Therefore, ethics committee approval was not obtained. The dataset used in this study was obtained from a publicly available cervical cancer screening database, containing clinical and behavioral attributes of female patients. The dataset, sourced from the UCI ML repository, includes 858 instances with 32 attributes capturing demographic, sexual, and clinical risk factors.

- Age
- Number of sexual partners
- First sexual intercourse age
- Number of pregnancies
- Smoking status and history
- Smokes (packs/year)
- Sexually transmitted diseases (STDs) and HPV infection status
- Diagnostic test results (Hinselmann, Schiller, cytology, biopsy)

The target variable was a binary classification indicating the presence or absence of cervical cancer or precancerous conditions such as cervical intraepithelial neoplasia (CIN) and HPV-positive status. Missing values were handled by imputing missing values. Categorical variables were encoded using one-hot encoding (13).

A snapshot of the dataset used in this study is presented in Figure 1.

Handling Imbalanced Data

Given the rarity of positive biopsy cases in the dataset, the class distribution was heavily skewed. We applied SMOTE to synthetically balance the classes and ensure fair model evaluation. synthetic minority over-sampling technique works by generating synthetic samples of the minority class rather than simply duplicating existing instances. It achieves this by selecting a minority class sample and interpolating it with one of its k-nearest neighbors in the feature space (14). This process introduces new, plausible samples and helps the model learn a more generalized decision boundary, thereby reducing the bias toward the majority class and improving the classifier's ability to detect minority class instances. synthetic minority over-sampling technique is particularly beneficial when used prior to training classification models, as it provides a balanced dataset without introducing exact duplicates, which could otherwise lead to overfitting (15).

Exploratory Data Analysis

Exploratory data analysis (EDA) was conducted using Python's data visualization libraries seaborn and matplotlib to visualize the distributions of patient groups or characteristics, including those pertaining to patients (16). Histograms were generated to assess the normality of the distribution of variables in the dataset. In this study, we conducted an EDA to investigate the relationships between cervical cancer Dx and HPV status using a heatmap visualization. This approach allows us to visualize the interactions and correlations between these critical variables.

Age	Num.	Fir.	Num.	Smokes	Smo.	Smo.	STD.	Dx:Cance	Dx:CIN	Dx:HPV	Dx	Hinselmar	Schiller	Citology	Biopsy
18	4.0	15.0	1.0	0.0	0.0	0.0	0	0	0	0	0	0	0	0	0
15	1.0	14.0	1.0	0.0	0.0	0.0	0	0	0	0	0	0	0	0	0
34	1.0	?	1.0	0.0	0.0	0.0	0	0	0	0	0	0	0	0	0
52	5.0	16.0	4.0	1.0	37.0	37.0	0	1	0	1	0	0	0	0	0
46	3.0	21.0	4.0	0.0	0.0	0.0	0	0	0	0	0	0	0	0	0

Age → Age, Num. → Number of sexual partners, Fir. → First sexual intercourse, Num. → Num of pregnancies, Smokes → Smokes, Smo. → Smokes (years), Smo. → Smokes (packs/year), STD. → STDs: Number of diagnosis, Dx:Cancer → Dx:Cancer, Dx:CIN → Dx:CIN, Dx:HPV → Dx:HPV, Dx → Dx, Hinselmann → Hinselmann, Schiller → Schiller, Citology → Citology, Biopsy → Biopsy

Figure 1. A snapshot of the dataset for this study, filtered data with first 5 rows

Machine Learning Model Training and Evaluation

For predictive modeling, the dataset was split into training and testing subsets using an 80/20 split ratio. The LazyPredict library was employed to facilitate the comparison of multiple regression models, including multi-layer perceptron regressor, extreme gradient boosting (XGBoost), elastic net with cross-validation, and Lasso, using Python and scikit-learn (17).

Software and Tools

All analyses were conducted using Python 3.10 within a Jupyter Notebook environment. The primary libraries utilized were pandas and NumPy for data manipulation, as well as matplotlib (18) and seaborn for visualization. For model development and evaluation, scikit-learn, XGBoost, and Light Gradient Boosting Machine (LightGBM) were employed, providing robust tools for building and assessing ML models (19).

Statistical Analysis

Model performance metrics were calculated to comprehensively assess the predictive ability and efficiency of each algorithm. Each model was evaluated in terms of accuracy, which reflects the overall correctness of predictions; sensitivity (recall), which measures the ability to correctly identify positive cases; specificity, which quantifies the correct identification of negative cases; precision, which reflects the proportion of true positives among predicted positives; F1-score, which balances precision and recall; and receiver operating characteristic (ROC) area under curve (AUC), which provides a global measure of model discrimination capability (20). In addition, the computational efficiency of each model was assessed by recording the time taken (in seconds) to complete both training and prediction phases. This was particularly important in evaluating the scalability of the models for real-world applications where rapid decision-making may be required.

Results

Exploratory Data Analysis

A correlation heatmap (Figure 2) illustrated both weak and strong relationships among variables, emphasizing the multifactorial nature of cervical cancer risk.

- Smokes, smokes (years), and smokes (packs/year) show strong correlations ($r \approx 0.69$-0.72), indicating internal consistency across these smoking-related measures.
- Diagnostic variables (Dx: Cancer, Dx: HPV, Dx: CIN, and overall Dx) are also strongly correlated ($r > 0.68$), reflecting overlapping diagnostic criteria or comorbidity.
- Visual inspection outcomes (Hinselmann, Schiller, cytology) are moderately to strongly correlated with biopsy, with Schiller showing the strongest correlation ($r = 0.74$), suggesting predictive value for biopsy-confirmed cases.
- Age correlates moderately with number of pregnancies ($r = 0.56$) and first sexual intercourse ($r = 0.37$), consistent with expected life course patterns. Several variables, including STDs, number of diagnoses, and number of sexual partners, display very weak correlations with most other variables ($r < 0.1$), implying limited linear association in this sample.

The distribution indicates that HPV diagnosis (Dx: HPV) is the most frequently observed condition, slightly surpassing cancer diagnoses (Dx: Cancer), while CIN (Dx: CIN) is relatively less common (Figure 3).

A significant class imbalance is evident. The number of healthy individuals greatly outnumbers diseased individuals, indicating a highly skewed dataset. This imbalance in class frequencies may necessitate data augmentation techniques to mitigate class bias and enhance model learning. After applying SMOTE, a balancing technique, the classes are now evenly distributed, with almost equal numbers of healthy and diseased individuals (Figure 4).

Machine Learning on SMOTE Balanced Data

Table 1 below shows the performance of various classification models used to predict cervical cancer based on raw data. The highest accuracy and ROC-AUC scores (97%) were achieved by both the RandomForestClassifier and LGBMClassifier. RandomForestClassifier delivered this high performance with a training time of just 0.74 seconds, while LGBMClassifier achieved similar results even faster (0.33 seconds), making both models efficient and effective. Other strong performers include XGBClassifier, DecisionTreeClassifier, BaggingClassifier, and ExtraTreesClassifier, each achieving 96% accuracy and ROC-AUC, with DecisionTreeClassifier standing out for its extremely low training time (0.02 seconds).

Model Performance of Categorized Data

The ML model demonstrated strong classification performance in predicting cervical health outcomes across four categories: Healthy, Cancer, CIN, and HPV infection. The overall accuracy achieved was 93%, with particularly high precision in detecting cancer (1.00) and high recall for HPV (0.93). However, the recall for the cancer class was slightly lower (0.80), suggesting an increase in false negatives, while CIN prediction maintained balanced precision and recall (Table 2).

A precision of 1.00 for the cancer class indicates no false positives. While this is desirable, the recall is only 0.80, implying that 20% of true cancer cases were missing.

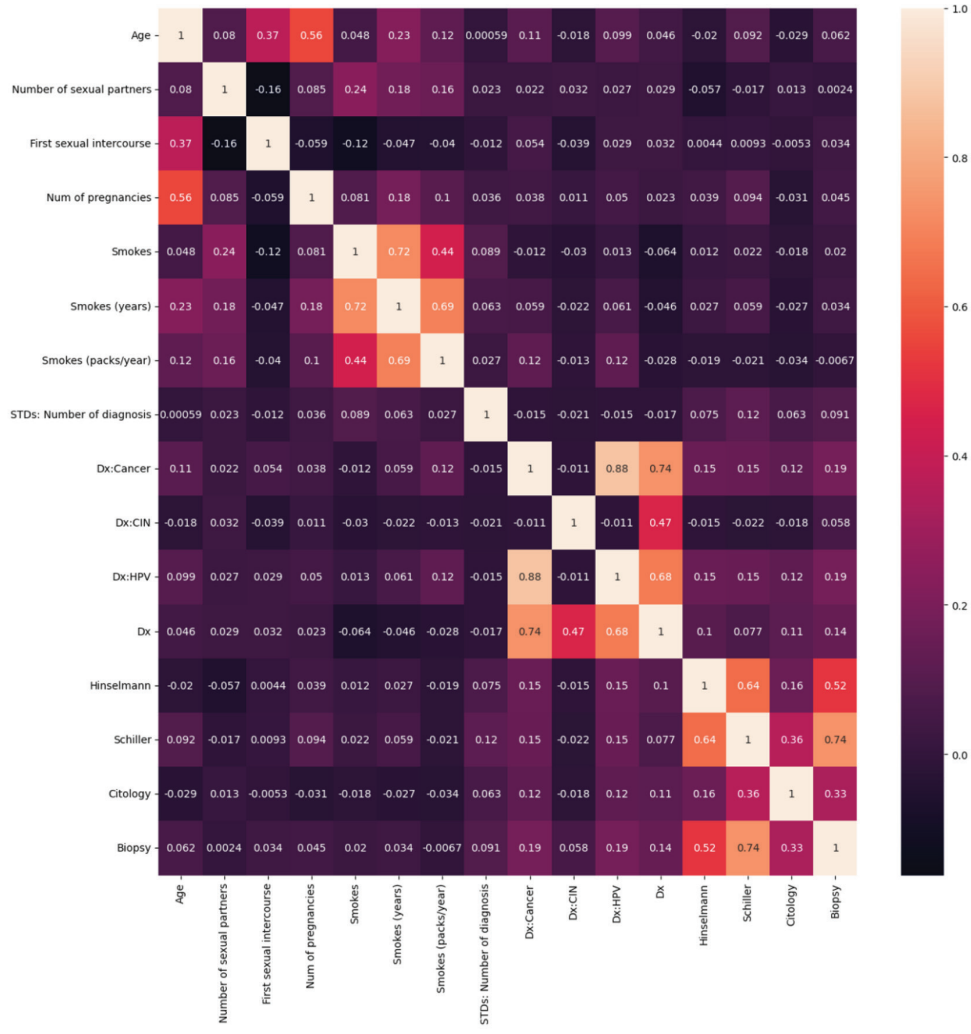

Figure 2. Multivariate correlation structure of risk factors associated with cervical cancer diagnosis

Dx: Diagnosis, CIN: Cervical intraepithelial neoplasia, HPV: Human papillomavirus, STDs: Sexually transmitted diseases

In clinical diagnostics, false negatives for cancer can have severe implications, leading to delayed Dx and treatment. For HPV, the recall of 0.93 is excellent; however, a precision of 0.78 means there's a relatively higher false positive rate.

Discussion

This study provides a detailed evaluation of ML approaches for predicting cervical cancer risk based on clinical and lifestyle data. Our analysis revealed strong internal consistency among smoking-related variables, confirming their collective importance as predictive features. This finding emphasizes that integrating multiple related behavioral factors can enhance the discriminatory power of ML models, supporting targeted risk assessment strategies.

Interestingly, reproductive variables such as high parity and early age at first sexual intercourse did not show a direct association with cervical cancer in our dataset, despite being reported as risk factors in previous epidemiological studies (21,22). There are several possible explanations for the lack of observed association between reproductive factors and cervical cancer risk in our analysis. First, the relationship may not be detectable in smaller or demographically homogeneous samples. Second, unmeasured confounders such as HPV infection, socio-economic status, smoking habits, contraceptive use, or access to cervical cancer screening may influence or obscure the true relationship between reproductive behaviors and cancer risk. Lastly, issues related to data quality, such as self-reported information, missing values,

or inaccuracies in key variables like age at first intercourse, could contribute to the attenuation of expected associations. This discrepancy suggests that contextual variables such as HPV status, socio-economic conditions, screening access, and smoking habits may modulate the impact of reproductive behaviors. It also highlights the importance of considering dataset-specific characteristics and potential confounders when applying ML models to real-world clinical data.

The evaluation of different ML classifiers demonstrated that ensemble methods, particularly RandomForestClassifier and LightGBMClassifier, outperformed simpler probabilistic models. The superior accuracy and ROC-AUC of these methods indicate that capturing complex, non-linear relationships between clinical features is crucial for reliable prediction. While the high precision for cancer detection minimizes false positives, the relatively lower recall underscores the need for caution in clinical interpretation, as some true cases may still be missed. In contrast, models such as DecisionTreeClassifier and ExtraTreeClassifier provide a balance between performance and computational efficiency, suggesting potential utility for rapid or mobile-based screening tools. These results are in line with existing literature that highlights the efficacy of ML in improving early detection of cervical cancer and HPV-related abnormalities (23).

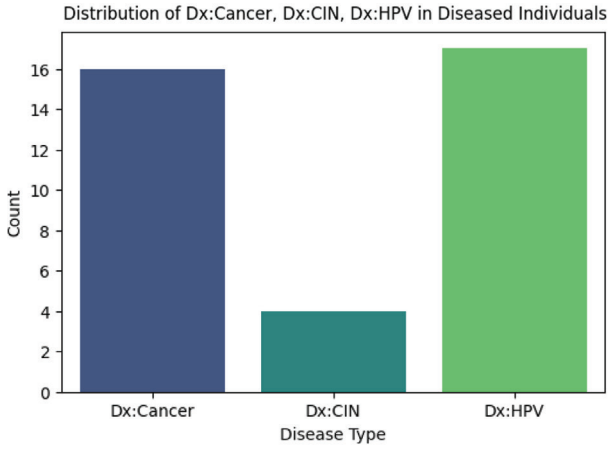

Figure 3. Distribution of diagnoses: Cancer, CIN and HPV among diseased individuals

Dx: Diagnosis, CIN: Cervical intraepithelial neoplasia, HPV: Human papillomavirus

Furthermore, the application of SMOTE to address class imbalance proved essential for ensuring adequate representation of minority cases. Our findings reinforce that data preprocessing techniques directly impact model reliability and generalizability, particularly in medical datasets, where diseased cases are often underrepresented (24). This supports the broader integration of ML pipelines into digital health solutions, potentially improving early detection in resource-limited settings and complementing existing clinical workflows.

The high precision in the cancer class (1.00) indicates that the model effectively minimizes false positives, which is crucial in avoiding unnecessary psychological and medical interventions. Conversely, the lower recall for cancer (0.80) implies a potential risk of missed cancer diagnoses, which is critical in a clinical setting. The model's strong performance in HPV prediction is also consistent with research indicating that behavioral and screening features are highly predictive of HPV status. According to Schiffman et al. (25), the integration of HPV typing into

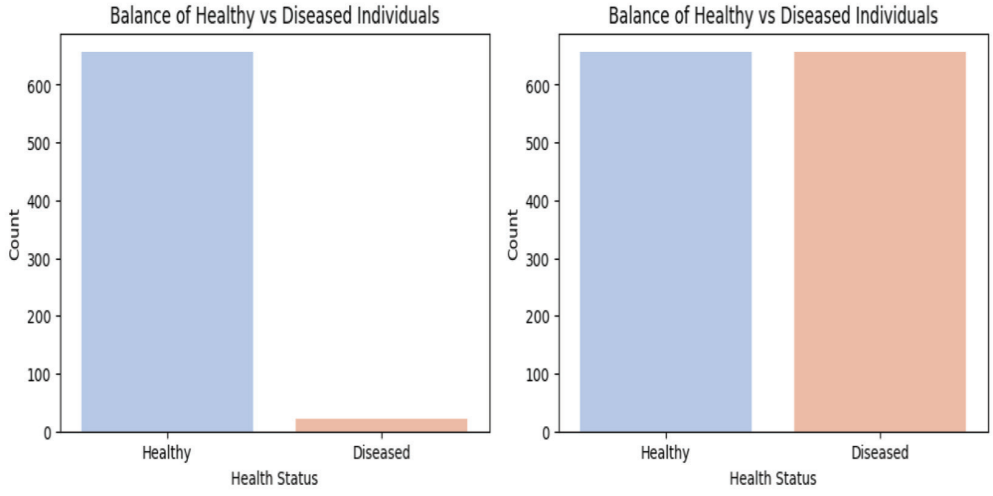

Figure 4. Distribution of Healthy vs. Diseased individuals in the dataset before SMOTE (left) after SMOTE(right)

SMOTE: Synthetic minority over-sampling technique

Table 1. Comparative analysis of classifier efficacy in cervical cancer prediction

Model	Accuracy	ROC-AUC	Time taken
XGBClassifier	0.96	0.96	1.06
RandomForestClassifier	0.97	0.97	0.74
DecisionTreeClassifier	0.96	0.96	0.02
BaggingClassifier	0.96	0.96	0.06
ExtraTreesClassifier	0.96	0.96	0.18
LightGBMClassifier	0.97	0.97	0.33
LabelPropagation	0.95	0.95	0.23
LabelSpreading	0.95	0.95	0.36
ExtraTreeClassifier	0.95	0.95	0.02
AdaBoostClassifier	0.87	0.87	0.17
K-NeighborsClassifier	0.91	0.91	0.06
BernoulliNB	0.86	0.87	0.02
GaussianNB	0.69	0.75	0.02

LightGBM: Light Gradient Boosting Machine, XGBClassifier: Extreme gradient boosting, BernoulliNB: Bernoulli Naïve Bayes

Table 2. Classification performance metrics of the cervical cancer prediction model

	Precision	Recall	f1-score
Healthy	0.96	0.95	0.94
Cancer	1.00	0.80	0.84
CIN	0.88	0.84	0.81
HPV	0.78	0.93	0.94

CIN: Cervical intraepithelial neoplasia, HPV: Human papillomavirus

screening strategies significantly enhances early detection of precancerous changes.

Finally, the balance between CIN classification metrics (precision: 0.88, recall: 0.84) indicates that the model can reasonably detect intermediate lesion stages, which are crucial for preventive interventions before progression to invasive cancer.

Overall, the study highlights that a careful combination of data preprocessing, feature selection, and ensemble learning can produce predictive models with both high accuracy and practical applicability. These results contribute to ongoing efforts to optimize automated screening tools and provide clinicians with evidence-based decision support in cervical cancer prevention and management.

Study Limitations

The potentially limited and non-diverse sample size may affect the generalizability of the findings. Data quality issues, such as missing information, could introduce bias, and additionally, important risk factors may have been overlooked in feature selection. Additionally, the complexity of the models may hinder interpretability, and the lack of external validation on independent datasets limits the applicability of the results in real-world settings. Despite these limitations, our findings indicate the integration of ML into clinical diagnostics to enhance early detection and treatment of cervical cancer, while recognizing the need for further research to address these limitations.

Conclusion

The study highlights the multifactorial nature of cervical cancer risk, revealing significant correlations among variables through a heatmap analysis. While addressing class imbalance with SMOTE improved model performance, particularly with ensemble classifiers like random forest and LightGBM, the lower recall for cancer detection emphasizes the need for further investigation to avoid missing true cases.

Ethics

Ethics Committee Approval: Ethics committee approval was not required for this study, as the data used does not contain public, anonymous, or personally identifiable information. Therefore, ethics committee approval was not obtained.

Informed Consent: This study was designed as a retrospective study.

Footnotes

Authorship Contributions

Concept: M.K., Design: T.M.O., M.K., Data Collection or Processing: T.M.O., M.K., Analysis or Interpretation: I.Y., M.K., Literature Search: T.M.O., M.K., Writing: T.M.O., I.Y., M.K.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Serum Interleukin-6 as a Potential Biomarker in Absence Epilepsy

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Abstract

Aim: The role of inflammation in absence epilepsy remains a subject of debate. The present study aims to assess the role of interleukin-6 (IL-6) in absence epilepsy by determining serum IL-6 levels of children with absence epilepsy and the association with anti-seizure medications, seizure frequency, and semiology by comparing to a control group.

Methods: Fifteen children aged 3-17 years who were followed up with the diagnosis of absence epilepsy and 30 healthy controls were included in this cross-sectional observational study between November 2020 and April 2021. Serum IL-6 levels of subjects were measured by the chemiluminescence method.

Results: Serum IL-6 levels in the patient group were significantly lower (2.98±1.02 pg/mL) than in the controls (5.35±0.87 pg/mL) ($p<0.001$). The patients receiving valproic acid monotherapy had significantly lower serum IL-6 levels than both the patients receiving other anti-seizure medications and healthy controls ($p=0.04$). Patients with active seizures had higher serum IL-6 levels than seizure-free patients (3.52±0.54 pg/mL, 2.72±1.12 pg/mL; $p=0.01$, respectively). Moreover, there was a moderate to strong positive correlation between the presence of active seizures and serum IL-6 levels (Spearman's $p=0.629$, $p=0.0069$).

Conclusion: Our study is the first clinical investigation of IL-6 concentrations in absence epilepsy patients and possible relations between IL-6 and patient characteristics.

Keywords: Absence, epilepsy, interleukin-6, seizures, valproic acid

Introduction

The role of immunity in epilepsy was first proposed in the 1960s (1). Today, an increasing amount of evidence from both preclinical animal models and human studies indicates that brain inflammation is associated with epilepsy (2). Besides, it remains uncertain whether the inflammatory alterations in the central nervous system (CNS) contribute to epileptogenesis, or these alterations occur as a consequence of epileptic activity.

Cytokines, which are soluble signaling peptides secreted by numerous cell types including macrophages (e.g., microglia), T and B lymphocytes, mast cells, endothelial cells, and fibroblasts, play a crucial role in not only the proper function and development of CNS, but also in CNS disorders (3). In previous studies, it has been demonstrated that cytokines, including interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), and IL-8 may enhance the permeability of the blood-brain barrier (BBB) (4). Leakage through the BBB is thought to induce

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seizures and lead to progression of epileptogenesis (4). Moreover, pro-inflammatory cytokines, notably IL-6, can increase the extracellular glutamate level that results in glutamate neurotoxicity and excitatory transmission in the brain (5). Neurotoxic effects of IL-6 are also associated with suppression of γ-aminobutyric acid (GABA)-ergic inhibition via endocytosis of $GABA_A$ receptors (5). Recent studies with epilepsy patients have addressed the function of IL-6 in both peri-ictal and chronic neuroinflammation. Serum and cerebrospinal fluid concentrations of IL-6, as a pleiotropic cytokine, have been reported to fluctuate in both ictal and interictal periods in patients with epilepsy (6). Elevated IL-6 levels were mostly associated with generalized tonic-clonic seizures, refractory seizures, or temporal lobe epilepsy (TLE) in previous studies (7). Absence epilepsy (AE) is characterized predominantly by non-motor seizures that cause a brief loss of awareness of abrupt onset and offset with generalized 3 Hz spike-and-wave discharges (SWDs) electrographically (8). Both childhood and juvenile forms of AE are polygenic syndromes involving the genes that encode GABA receptors, T-type calcium channels, and glucose transporter type 1 (9). However, the role of inflammation in the modulation of AE is still unclear. In some animal models, administration of bacterial endotoxin lipopolysaccharide (LPS) has been shown to increase cytokine levels, including IL-6, and enhance SWDs and absence seizures (10).

Despite the supportive results of animal studies, there are no data about the levels of IL-6 in children with AE. To address this issue, we investigated serum IL-6 concentrations of children with AE and their association with anti-seizure medications (ASMs), seizure semiology, and frequency of seizures by comparing them with control subjects. Through investigating the association between IL-6 and AE, we also suggest a possible role for immunomodulatory therapies in future clinical management.

Materials and Methods

Compliance with Ethical Standards

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the University of Health Sciences Türkiye, Izmir Tepecik Training and Research Hospital Clinical Research Ethical Committee (approval no.: 01 date: 08.10.2020). Written informed consent was obtained from the children and/or children's parents or legal guardians following a detailed explanation.

Study Design

This is a cross-sectional observational case-control study conducted on fifteen children aged 3 to 17 years with a diagnosis of AE in the pediatric neurology outpatient clinics and 30 healthy controls between November 2020 and April 2021. Patients' clinical data were evaluated and those meeting the following criteria were included: Patients followed for at least six months with a clinical diagnosis of AE based on seizure semiology and electroencephalogram (EEG) findings, according to the criteria of the International League of Epilepsy (ILAE) current guidelines (8). The exclusion criteria consisted of having an immunologic disease or an acute/chronic infectious disease and receiving an immune-related treatment in the last six months. A detailed neurological examination, an EEG record according to the 10-20 international system of electrode placement, and a brain magnetic resonance imaging (MRI) were performed on all the patients. A flow diagram illustrating the enrollment of patients, application of exclusion criteria, and final study groups is presented in Figure 1.

Measurement of serum IL-6 levels: samples from participants were collected in a clot-activating tube containing a gel separator (BD Vacutainer® SST II Advance tube, 5 mL, 13 x 100 mm, NJ, USA). Each tube was centrifuged at 1500 × g for 10 minutes. The samples were stored at -80 °C. Serum IL-6 concentrations were measured by the chemiluminescence method using the Immulite 2000 autoanalyzer (Siemens Healthcare Diagnostics, Marburg, Germany).

Statistical Analysis

Data were analyzed using the SPSS software (Statistical Package for Social Science), version 29. Percentage and frequency (n) were calculated for the categorical data, whereas mean and standard deviation values were calculated for the continuous variables. The normality of data distribution was assessed using the Shapiro-Wilk test. For group comparisons, the chi-square test was applied to categorical variables, Student's t-test was used for normally distributed continuous variables, and the Mann-Whitney U test was applied for non-normally distributed continuous variables. P-values of less than 0.05 were considered to be significant.

Results

The study was conducted on a patient group consisting of fifteen children (8 girls and 7 boys) with AE and a control group consisting of 30 healthy subjects (16 girls and 14 boys). Demographic characteristics and IL-6 levels of the patients and the control group were summarized in Table 1. Serum IL-6 levels in the patient group were significantly lower (2.98±1.02) than in the control group (5.35±0.87) ($p<0.001$).

Among the patient group, ten patients were receiving valproic acid (VPA) monotherapy; one patient was receiving ethosuximide (ETH) monotherapy; one patient was receiving oxcarbazepine (OXC) and lamotrigine

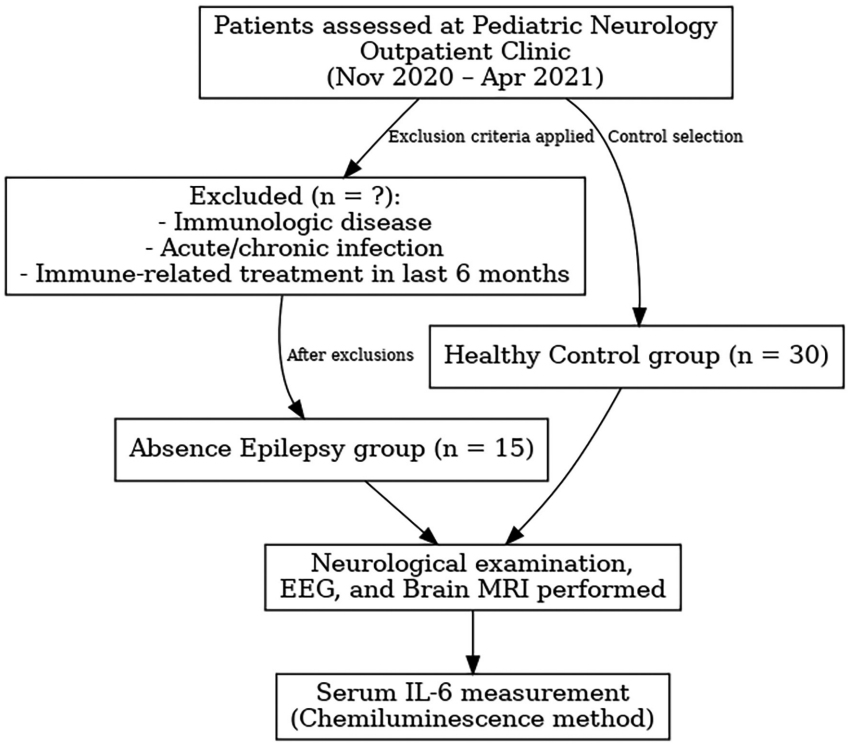

Figure 1. Flow diagram of the study
IL: Interleukin, MRI: Magnetic resonance imaging

Table 1. Demographic characteristics and IL-6 levels of the study population

		Patient group (n=15)	Control group (n=30)	p
Age (year)	Mean ± SD	10.5±3.6	11.2±3.8	0.46[a]
	Range	3-16	3-17	
Male/Female	Male (%)	7 (46.7)	14 (46.7)	1.00[b]
	Female (%)	8 (53.3)	16 (53.3)	
IL-6 (pg/mL)	Mean ± SD	2.98±1.02	5.35±0.87	**<0.001**[a]
	Range	2.08-5.81	3.5-6.78	

[a]:Mann-Whitney U test was used. [b]:Chi-square test was used, p-values <0.05 are shown in bold
IL: Interleukin, n: Number, SD: Standard deviation, pg/mL: Picogram/milliliters

(LTG); one patient was receiving ETH, VPA, LTG and clobazam; one patient was receiving levetiracetam (LEV) and topiramate (TPR); and one patient was receiving ETH, VPA, and LEV. The patients receiving only VPA treatment had significantly lower serum IL-6 values when compared to the patients receiving other ASMs or polytherapy for treatment (p=0.04). Twelve patients had normal brain MRI findings, whereas one of the patients had mild cerebellar atrophy. All the patients had generalized 3 Hz SWDs on EEG before anti-seizure treatment. However, EEG records of nine patients were normal under the anti-seizure treatment during the period of sample collection, while six patients still had SWDs on EEG. Brain MRI and EEG findings had no effect on serum IL-6 levels of the patients (p=0.57, p=0.14, respectively). We found a moderate-to-strong positive correlation between the presence of active seizures and serum IL-6 levels (Spearman's p=0.629, p=0.0069). Assessment of serum IL-6 levels according to seizure types, seizure control, brain MRI and EEG findings, and ASMs received is given in Table 2.

Discussion

Patients with AE had significantly reduced serum IL-6 concentrations compared to sex- and age-matched healthy controls in our study. (p<0.001). This finding suggests that AE may be characterized by a distinct immune profile compared with some other epilepsy syndromes in which elevated IL-6 levels have frequently been reported. One

Table 2. Assessment of serum IL-6 concentrations according to the patient characteristics				
		n	IL-6 (pg/mL) Mean ± SD	p
Type of seizures	Absence	12	2.96±1.09	0.54[a]
	Absence and GTCs	3	3.08±0.95	
Seizure control	Seizure-free	10	2.72±1.12	**0.01**[a]
	Non-seizure free	5	3.52±0.54	
Brain MRI findings	Normal	12	3.02±1.06	0.61[a]
	Abnormal	1	2.24	
EEG findings	Normal	9	2.89±1.26	0.14[a]
	Abnormal	6	3.12±0.6	
Anti-seizure medication	VPA monotherapy	10	2.55±0.51	**0.04**[a]
	Other ASMs/Polytherapy	5	3.86±1.28	

[a]:Mann-Whitney U test was used, p values <0.05 are shown in bold
ASM: Anti-seizure medication, EEG: Electroencephalography, GTCs: Generalized tonic-clonic seizures, IL: Interleukin, MRI: Magnetic resonance imaging, n: Number, pg/mL: Picogram/milliliters, SD: Standard deviation, VPA: Valproic acid

potential explanation for this phenomenon is that reduced IL-6 levels reflect a compensatory mechanism aimed at limiting chronic neuroinflammation in AE. Alternatively, the reduced IL-6 levels observed in our cohort may at least partly be attributable to the widespread use of VPA, which has been shown to suppress cytokine production through nuclear factor kappa B (NF-κB) inhibition (11). At present, there is a lack of data about the role of cytokines in AE. Despite the existence of numerous clinical studies examining the function of various cytokines in other forms of epilepsy, there is a paucity of research that focuses on the potential role of cytokines in the epileptogenesis of AE patients. Moreover, the results of clinical studies on patients with other epilepsies are conflicting. Similar to our results, Alvim et al. (12) recently showed that several plasma cytokine levels, including IL-6, are lower in the patient group independent of the underlying etiology in a cohort study with 446 epilepsy patients and 166 healthy controls. In contrast, a previous meta-analysis of 66 studies involving 1934 patients reported elevated serum IL-6 levels in epilepsy patients with several etiologies, including TLE, West syndrome, and refractory epilepsy, as well as in acute seizures (7). A recent study has demonstrated that interictal elevations of IL-6 and TNF-α are associated with an increased risk of seizure recurrence (13). Furthermore, the study found a negative correlation between IL-6 levels and time to seizure recurrence (13).

Despite the much evidence supporting the crucial role of inflammatory cytokines in both the course and pathogenesis of epilepsy, the exact mechanism remains unclear. Most studies have focused on pro-inflammatory cytokines involving IL-1β, TNF-α, and IL-6. Epileptic seizures have been shown to not only affect the expression of these pro-inflammatory cytokines in the brain but also alter their serum concentrations (14-16). A recent Mendelian randomization analysis revealed that genetically simulating IL-6R blockade was associated with a modest but significant reduction in overall epilepsy risk [odds ratio (OR) 0.827, 95% confidence interval (CI) 0.685-1.000, p=0.05], suggesting a tentative causal role for IL-6 signaling in epileptogenesis (17). Although their study supports our results and suggests IL-6R inhibition as a potential therapeutic strategy in epilepsy, the subtype analysis demonstrated that the effect of IL-6R blockade was not statistically significant in AE (17).

Almost all of the existing data on the role of cytokines in AE come from animal studies. A previous study with the Wistar Albino Glaxo/Rijswijk (WAG/Rij) strain, an animal model of AE, showed that an increase in thalamic NF-κB and IL-6 levels results in a decrease in the SWDs and seizure activity (18). Another study with WAG/Rij rats showed that rapamycin treatment (a specific mechanistic target of rapamycin inhibitor) decreases the development of absence seizures and provides about a 52% reduction of SWDs by preventing the release of inflammatory cytokines (19). Leo et al. (20) demonstrated that administration of tocilizumab, a monoclonal antibody against the IL-6 receptor, resulted in a substantial decrease in absence seizures in the WAG/Rij rats with AE. In line with our findings suggesting an immunological component in AE, a very recent experimental study demonstrated that long-term treatment with low doses of edaravone, a free radical scavenger, reduced the incidence of SWDs in WAG/Rij rats by attenuating oxidative stress and neuroinflammation (21). Accumulating experimental evidence from animal studies leads us to speculate about alterations in the serum IL-6 concentrations of AE patients.

Furthermore, we detected elevated serum IL-6 levels in patients with uncontrolled seizures compared to seizure-free patients (p=0.01). A moderate-to-strong positive

correlation was identified between the existence of active seizures and serum IL-6 levels (Spearman's p=0.629, p=0.0069), indicating that patients with ongoing seizures tend to have higher IL-6 levels. These results indicate significant clinical implications, namely that serum IL-6 levels may serve as a reliable indicator of seizure activity in patients with AE. Previous studies comparing the interictal and postictal serum IL-6 levels in patients with active seizures have conflicting results (22-25). A previous study comparing patients with refractory and well-controlled epilepsy indicated that serum IL-6 and oxidative stress markers were significantly higher in refractory epilepsy patients than in well-controlled epilepsy patients (26). In a previous study, Alapirtti et al. (23) revealed that IL-6 concentrations remained unchanged following a single seizure in patients with frequent seizures, whereas increased IL-6 concentrations were detected in patients with infrequent seizures. Moreover, they emphasized that the patients with frequent seizures had chronically elevated IL-6 levels, whereas baseline IL-6 concentrations were reduced in patients with infrequent seizures (23).

Another factor altering the serum cytokine concentrations in epilepsy patients is the modulatory effect of ASMs on the immune system. Our study indicated that the patients receiving VPA monotherapy had significantly reduced serum IL-6 concentrations compared to both the patients receiving other ASMs and healthy controls (p=0.04). These results underscore the immunomodulatory properties of VPA, which extend beyond the realm of seizure suppression. Steinborn et al. (27) revealed a significant decrease in serum IL-6 levels following a period of four to six months of VPA treatment in patients with generalized epilepsy (p<0.001). A previous in vitro study also demonstrated the production of both TNF-α and IL-6 to be inhibited by VPA through the suppression of NF-κB activation (11). A more recent study showed that VPA combined with LEV lowers the serum IL-6 levels and improves the EEG findings in pediatric epilepsy patients (28). In contrast, another study comparing patients receiving VPA or LEV treatment found that both ASMs have no effect on interictal serum levels of IL-1β, IL-6, and TNF-α (29). Abu-Rish et al. (30) showed that LTG significantly inhibits IL-1β, IL-6, and TNF-α excretion in vivo and in vitro, specifically in LPS-treated RAW264.7 cells. The reducing effect of TPR on the LPS-activated excretion of these three cytokines has also been shown in rat cortical microglial cells (31). However, in a study of patients with focal and generalized epilepsy, no significant alteration was detected in serum concentrations of these cytokines after 12 months of TPR or VPA treatment (32). Another study demonstrated that six months of OXC therapy resulted in a significant decrease in IL-2, TNF-α, and IL-6 concentrations (33). Carbamazepine has been shown to elevate serum IL-1α, IL-1β, IL-2, and IL-6 levels after 1 year of therapy (34).

Normal EEG findings did not affect the patients in our study. Unlike our results, a previous study demonstrated that decreased serum IL-6 levels were accompanied by improvement in EEG patterns in patients with electrical status epilepticus in sleep (35). Another study of 75 children with idiopathic epilepsy indicated that serum concentrations of IL-2, TNF-α, and IL-6 in epilepsy patients with epileptic discharges and slow waves on EEG were significantly higher than those with normal EEG (36).

Study Limitations

Our study presents several limitations. The results must be interpreted with caution due to the relatively small number of patients and the heterogeneity of patient characteristics such as ASM dosage and duration of drug treatment. An important limitation of our study is that we studied only one type of serum cytokine level. Despite these limitations, the main strength of this study is that it represents the first clinical investigation specifically evaluating serum IL-6 levels in children with AE. The inclusion of a well-defined patient group diagnosed according to standardized ILAE criteria and age- and sex-matched healthy controls enhances both the validity and the clinical relevance of the findings. Moreover, by highlighting a potential immunological mechanism, this study provides a basis for larger cohorts.

Conclusion

Although evidence from other epilepsy syndromes is conflicting, our data provide the first direct clinical evidence that serum IL-6 is altered in AE and related to both seizure control and ASM type. This adds a novel dimension to the understanding of AE pathogenesis, suggesting that immune mechanisms may play a role. Notably, serum IL-6 concentrations were significantly lower in patients with AE receiving VPA monotherapy than in patients receiving other ASMs or healthy controls, supporting the immunomodulatory effect of VPA. Taken together, our findings indicate that IL-6 may serve as a biomarker reflecting disease activity and treatment response in AE. To our knowledge, this is the first clinical study to explore the role of the immune system in AE and to demonstrate associations between serum IL-6 concentrations and patient characteristics influencing the disease course. Future studies with larger cohorts and longitudinal designs are needed to validate these results and to further investigate the neuromodulatory role of IL-6 as a biomarker in AE.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical principles

stated in the Declaration of Helsinki and approved by the University of Health Sciences Türkiye, Izmir Tepecik Training and Research Hospital Clinical Research Ethical Committee (approval no.: 01 date: 08.10.2020).

Informed Consent: Written informed consent was obtained from the children and/or children's parents or legal guardians following a detailed explanation.

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Footnotes

Authorship Contributions

Concept: G.B., A.B., S.B.Y., A.C., N.O.D., P.G., Design: G.B., A.B., S.B.Y., A.C., N.O.D., P.G., Data Collection or Processing: G.B., A.B., S.B.Y., Analysis or Interpretation: A.C., N.O.D., P.G., Literature Search: G.B., A.C., N.O.D., P.G., Writing: G.B.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Evaluation of Urine Drug Screening for Substance Use Based on Medical Laboratory Data from a Tertiary Hospital in Istanbul

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Abstract

Aim: Substance use is a significant public health concern, and early detection is essential for prevention and intervention. The study aimed to assess the prevalence and demographic patterns of substance use, including polysubstance use, based on five years of urine drug screening data.

Methods: This retrospective descriptive study analyzed urine drug screening results from 8,051 individuals tested between January 1, 2020, and June 31, 2024, at University of Health Sciences Türkiye, Basaksehir Cam and Sakura City Hospital. The panel included amphetamines, cannabis, opiates, cocaine, benzodiazepines, K2-3 synthetic cannabinoids, barbiturates, buprenorphine, and ethyl glucuronide. Statistical analyses used SPSS v26.0 ($p<0.05$).

Results: Among 6,006 valid tests, 25.2% were positive for at least one substance, most commonly benzodiazepines, amphetamines, and cannabis. Females had slightly higher positivity than males; however, this difference was without statistical significance. Benzodiazepine use was significantly higher in females [odds ratio (OR)=21.4; 95% confidence interval (CI): 16.55-27.75], while amphetamines were more common in males (OR=1.609; 95% CI: 1.22-2.11). Positivity in individuals under 18, was 27.1%, which was not statistically significant (p=0.560). Polysubstance use occurred in 15.8% of positive cases.

Conclusion: The findings reveal urgent, gender-specific risks in benzodiazepine and polysubstance use, underscoring the need for targeted prevention, improved outpatient care, updated clinical guidelines, and comprehensive monitoring systems.

Keywords: Amphetamines, benzodiazepines, public health, retrospective studies, substance-related disorders

Introduction

Substance abuse is a significant public health concern, affecting millions of individuals worldwide. According to the World Drug Report, global drug use increased by approximately 20% in 2022 compared to the previous decade (1). Similarly, the 2024 European Drug Report highlighted a rise in illicit drug use across all sectors of society, noting that nearly all psychoactive substances have the potential for misuse (2). Recent studies continue to confirm these trends, emphasizing the ongoing global challenge of substance abuse (3,4). According to the World Drug Report, global drug use increased by approximately 20% in 2022 compared to the previous decade (1). Similarly, the 2024 European Drug Report highlighted a rise in illicit drug use across all sectors of society; it noted that nearly all psychoactive substances have the potential for misuse. Recent studies continue to confirm these trends, emphasizing the ongoing global challenge of substance abuse. The misuse of psychoactive substances, including alcohol and illicit drugs, poses serious physical, psychological and social risks. Addressing substance abuse is thus vital not only for individual health but also for safeguarding public well-being. Early diagnosis and timely intervention are critical in mitigating the adverse effects

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of addiction, with substance screening recognised as an essential component of the treatment process (2).

We hypothesized that analyzing urine drug screening data from our laboratory would provide valuable insights into substance use prevalence, testing patterns, and the demographic characteristics of individuals undergoing screening. In Türkiye, the Ministry of Health's Medical Laboratories Regulation mandates that all licensed laboratories conducting substance analyses comply with established standards and report their findings accordingly. The standard screening panel includes amphetamines, benzodiazepines, cannabis, cocaine, and opiates, with confirmatory testing performed only after a positive screening result (5,6). Urine testing protocols developed by the Substance Abuse and Mental Health Services Administration (SAMHSA) have long been considered the gold standard in this field (7-9). Furthermore, in accordance with the Medical Laboratories Regulation (10) and the relevant circular (5), appropriate laboratory infrastructures, including designated specimen collection areas, have been established to support the detection of both emerging and commonly used narcotic and stimulant substances. Our laboratory conducts urine substance screening analyses in full compliance with these regulatory requirements.

This study aims to enhance awareness of substance use by analysing urine screening data collected in our laboratory. It investigates substance prevalence, patterns of test requests, and the influence of demographic factors—particularly age and gender—on positivity rates and polysubstance use. This, in turn, contributes to clinical practice by supporting early detection strategies, informing preventive health policies, and providing evidence-based data for the optimization of substance abuse management.

Materials and Methods

Compliance with Ethical Standards

Ethical approval for this study was obtained from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Basaksehir Cam and Sakura City Hospital (approval no.: KAEK/24.07.2024.135, date: 19.08.2024). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Study Design and Participants

This retrospective study analysed urine drug screening results from 8,051 individuals tested between 1 January 2020 and 30 June 2024 at the Medical Biochemistry Laboratory of University of Health Sciences Türkiye, Basaksehir Cam and Sakura City Hospital, Türkiye. The data were extracted from the hospital's information management system. Out of the total, 6,006 individuals had valid urine drug screening results, and they were included in demographic evaluations. Among them, 1,516 (25.2%) tested positive, and 4,490 (74.8%) tested negative. 2,045 samples (25.4%) were excluded due to the following reasons:

- Integrity test failure (70.3%, n=1,438)
- Improper transfer/storage conditions (12.8%, n=262)
- Procedural non-compliance (10.1%, n=207)

There were no inclusion or exclusion criteria based on age or gender. The final study population included both inpatients and outpatients, with a wide age range (1-89 years). No personally identifiable information or biological samples were used. Informed consent was obtained from all participants, and chain of custody protocols were strictly applied (Figure 1).

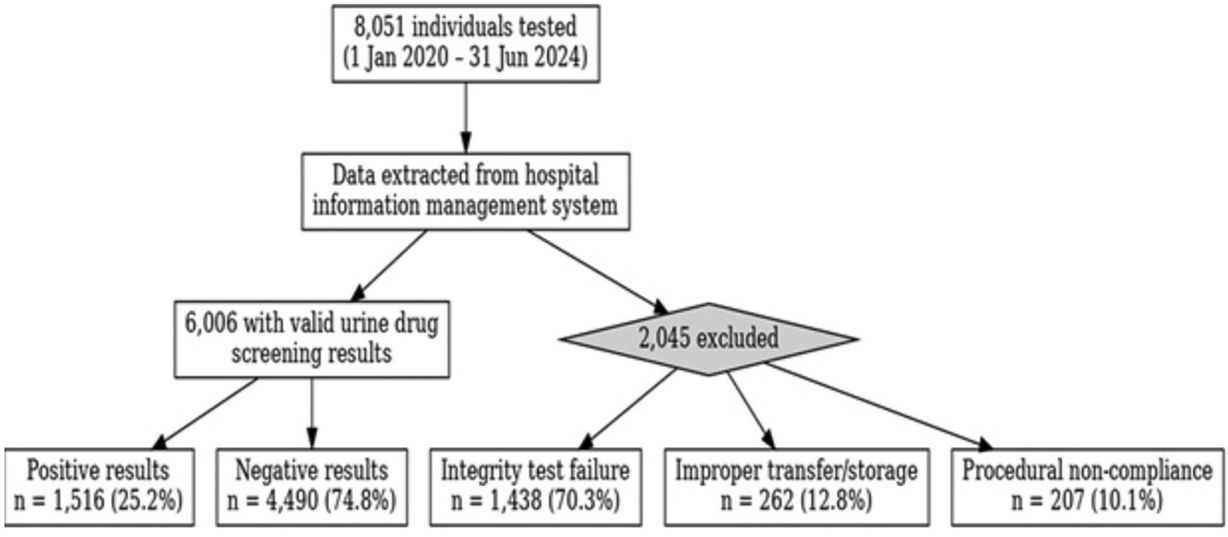

Figure 1. Flow diagram of the retrospective descriptive urine drug screening study

Measures and Procedure

Urine drug analyses targeted both standard panel substances and additional compounds, as follows:

- Standard panel: Amphetamines, cannabis (tetrahydrocannabino), opiates, cocaine and benzodiazepines
- Expanded panel: Synthetic cannabinoids (K2 and K3), barbiturates, buprenorphine and ethyl glucuronide

Testing was performed using a cloned enzyme donor immunoassay with Thermo Scientific kits on the Indiko Plus automated analyser (Thermo Fisher Scientific, Finland). Synthetic cannabinoid analyses were performed using ARK Diagnostics kits.

The cut-off concentrations for the screening analyses were as follows: 500 ng/mL for amphetamines, 50 ng/mL for cannabis, 300 ng/mL for opiates, 300 ng/mL for cocaine, 50 ng/mL for benzodiazepines, 5 ng/mL for synthetic cannabinoids, 200 ng/mL for barbiturates, 5 ng/mL for buprenorphine, and 500 ng/mL for ethyl glucuronide. Results exceeding these thresholds were considered positive, while values below them were considered negative. Outcomes were reported both qualitatively and quantitatively.

All the analyses underwent daily dual-level internal quality control and external proficiency testing. The coefficients of variation for both normal and pathological levels were as follows: amphetamines, 7.8% and 5.2%, respectively; cannabis, 5.2% and 4.5%; opiates, 5.3% and 4.7%; cocaine, 4.8% and 4.4%; benzodiazepines, 3.1% and 3.7%; synthetic cannabinoids, 11.1% and 7.8%; barbiturates, 6.3% and 5.2%; buprenorphine, 10.4% and 14.5%; and ethyl glucuronide, 5.7% and 4.5%.

Urine specimens were collected in designated collection areas. Sample integrity was verified within four minutes of collection via temperature measurement (accepted range: 32°C-37°C). Samples outside this range were excluded. Additional integrity tests included creatinine levels, pH, and oxidant screening.

Statistical Analysis

Categorical variables were summarised using frequencies and percentages, while continuous variables were presented as mean ± standard deviation and median, (minimum-maximum) values. The normality of the continuous variables is determined by using the Kolmogorov-Smirnov test. Comparisons between groups were made using the chi-square test. A p-value below 0.05 was considered statistically significant. All the statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). No artificial intelligence tools were used for data collection or analysis.

Results

The demographic and clinical characteristics of the patients are presented in Table 1. A total of 6,006 individuals underwent urine substance testing, with a mean age of 31.9±11.7 years (median: 29.0; range: 1-89). Of these, 1,516 patients (25.2%) tested positive for at least one substance.

Table 1. Basic descriptive characteristics of patients and distribution of urine drug screening applications by demographics, clinical departments, and test purpose (n=6006)

	n	%
Year of application		
2020	144	2.4
2021	1026	7.1
2022	1188	19.8
2023	2390	39.8
2024*	1258*	20.9*
Gender		
Male	4705	78.3
Female	1301	21.7
Age group		
<10 years	14	0.2
10-17 years	167	2.8
≥18 years	5825	97.0
Requesting department		
Psychiatry outpatient clinic	2242	37.3
Psychiatry service (male)	1432	23.8
Psychiatry service (female)	831	13.8
EPOC	631	10.5
Psychiatry consultation	441	7.3
Pediatric emergency	134	2.2
Adult emergency	102	1.7
Intensive care	30	0.5
Pediatric service	30	0.5
PEM	18	0.3
Pediatric intensive care	12	0.2
Pediatric psychiatry consultation	12	0.2
Pediatric psychiatry	7	0.1
OAOCS	84	1.4
Inpatient/outpatient		
Inpatient	2329	38.8
Outpatient	3677	61.2
Test request (forensic and medical)		
Forensic	1089	18.1
Medical	4917	81.9

*The data is up to June 31 2024
n: Number of individuals, %: Percentage, EPOC: Emergency psychiatry outpatient clinic, PEM: Pediatric endocrinology and metabolism, OAOCS: Other adult outpatient clinics and services

The distribution of substance-positive cases by requesting departments is shown in Table 2. The highest positivity rates were observed in psychiatry services, psychiatry consultations, and emergency psychiatry outpatient clinics, whereas paediatric departments accounted for the lowest proportion.

According to Table 3, benzodiazepine positivity was significantly higher in females (14.5%) compared with males (7.2%) odds ratio (OR)=21.4; 95% confidence interval (CI): 16.55-27.75), while amphetamine positivity was significantly higher in males (7.8%) compared with females (5.0%) (OR=1.609; 95% CI: 1.22-2.11). No statistically significant difference was observed in overall positivity between genders (p=0.103).

The bar chart shown in Figure 2 illustrates the distribution of the detected substances categorized by gender (female and male) and overall percentage. Benzodiazepines were the most frequently detected substance, with the risk of use being 21.4 times higher in females compared to males (OR=21.4; 95% CI: 16.55-27.75). Conversely, the likelihood of amphetamine use was significantly higher in males than in females, with an odds ratio of 1,609 (95% CI=1.22-2.11) (Figure 2).

The comparison between adolescents and adults is summarised in Table 4. No significant difference in overall positivity rates was observed (27.1% vs. 25.2%; p=0.560). Benzodiazepine use was more prevalent among adolescents, whereas amphetamines, opiates, and cocaine were more common among adults.

Benzodiazepine use was observed in both age groups, but it was more prevalent among adolescents, whereas positivity for amphetamines, opiates, and cocaine was more common in adults. Certain substances, such as buprenorphine and opiates, were not detected in the adolescent group (Figure 3).

Finally, Table 5 demonstrates the distribution of polysubstance use. Polysubstance use was identified in 239 patients, corresponding to 3.97% of the total sample and 15.8% of substance-positive cases. Most cases involved two substances, while a smaller proportion involved three or more. There was no significant difference in polysubstance use between adolescents and adults (p=0.110).

Table 2. Distribution of positive urine drug screening results by requesting department

Department	n	(%)*
Psychiatry service (male)	508	33.5
Psychiatry consultation	271	17.9
EPOC	266	17.5
Psychiatry service (female)	213	14.1
Psychiatry outpatient clinic	110	7.3
Adult emergency	74	4.9
Pediatric emergency	42	2.8
Other clinics and services	11	0.7
Intensive care	9	0.6
PEM	4	0.2
Pediatric intensive care	4	0.2
Pediatric service	3	0.2
Pediatric psychiatry consultation	1	0.1
Pediatric psychiatry	0	0

*Percentages were calculated based on 1.516 positive tests
n: Number of individuals, %: Percentage, EPOC: Emergency psychiatry outpatient clinic, PEM: Pediatric endocrinology and metabolism

Table 3. Distribution of positive urine drug screening results by substance type and gender (n=6006)

	Total (n=6006) n (%)	Male (n=4705) n (%)	Female (n=1301) n (%)
Substance Positive*	1516 (25.2)	1165 (24.8)	351 (27.0)
Benzodiazepine	527 (8.8)	339 (7.2)	188 (14.5)
Amphetamine	432 (7.2)	367 (7.8)	65 (5.0)
Cannabinoid-THC	232 (3.9)	189 (4.0)	43 (3.3)
Synthetic Cannabinoid K2-3	88 (1.5)	74 (1.6)	14 (1.1)
Ethyl Glucuronide	64 (1.1)	52 (1.1)	12 (0.9)
Opiate	63 (1.0)	55 (1.2)	8 (0.6)
Cocaine	51 (0.8)	49 (1.0)	7 (0.5)
Buprenorphine	33 (0.5)	25 (0.5)	8 (0.6)
Barbiturate	9 (0.1)	7 (0.1)	2 (0.2)

*Indicate the most frequently detected substance in each gender group
n: Number of individuals, %: Percentage, THC: Tetrahidrokannabinol
K2-3: Spice

Discussion

This study analysed data from 6,006 patients who underwent urine drug screening. The majority of patients were male (78.3%); 97% of them were aged 18 or older, and the mean age was 31.9 years. These findings underscore the ongoing public health challenge of substance use, particularly among adults. The results align with the 2022 National Survey on Drug Use and Health (NSDUH) by SAMHSA, which reported that 48.7 million individuals (17.3%) aged 12 or older experienced substance use disorders, including 29.5 million with alcohol use disorder and 27.2 million with drug use disorder (11,12). These statistics highlight the widespread prevalence of substance use and the urgent need for targeted treatment interventions.

In this study, a five-year analysis was conducted on test requests. The findings show fluctuating numbers, with a marked increase in 2023 (39.8%) and the lowest in 2020 (2.4%). This rising trend suggests increasing demand

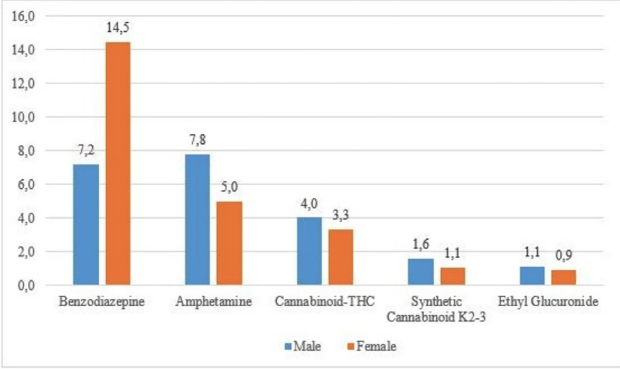

Figure 2. Gender-based comparison of the five most frequently detected substances in urine drug screening

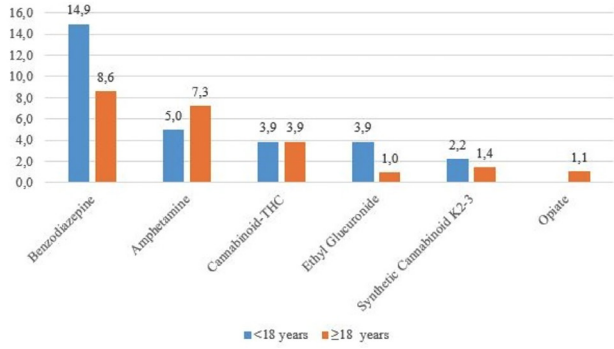

Figure 3. Substance positivity in urine drug screening by age group: adolescents vs. adults

Table 4. Comparison of substance positivity rates in urine drug screening between adolescents and adults

	<18 age (n=181) n (%)	≥18 age (n=5825) n (%)
Substance Positive*	**49 (27.1)**	**1467 (25.2)**
Benzodiazepine	27 (14.9)	500 (8.6)
Amphetamine	9 (5.0)	423 (7.3)
Cannabinoid-THC	7 (3.9)	225 (3.9)
Synthetic Cannabinoid K2-3	4 (2.2)	84 (1.4)
Opiate	-	63 (1.1)
Ethyl Glucuronide	7 (3.9)	57 (1.0)
Cocaine	1 (0.6)	50 (0.9)
Buprenorphine	-	33 (0.6)
Barbiturate	1 (0.6)	8 (0.1)

*Indicates the overall positivity rate for any tested substance within each age group.
n: Number of individuals, %: Percentage, THC: Tetrahidrokannabinol
K2-3: Spice

Table 5. Distribution of polysubstance use by age, gender, and number of substances detected

	n	(%)
Polysubstance Use	239	4%*/15.8%#
Gender Distribution		
Male	189	4%+/16.2%ᵣ
Female	50	3.8%⊥/14.3%&⊥
Age Distribution		
<18	4	2.1%ᵡ/1.4%ᵑ
≥18 years	235	4.0%ᵚ/3%ᵝ
Age & Gender		
<18 years Female	4	1.7%
<18 years Male	-	-
≥18 years Female	46	19.3%
≥18 years Male	189	79.1%
Number of Substances Used		
Dual	196	82.0%
Triple	38	15.9%
Quadruple	4	1.67%
Quintuple	1	0.42%

n: Number of İndividuals, (%): Percentage, #Substance-Positive Patients, +All Males, ᵣSubstance-Positive Males, ⊥All Females, &Substance-Positive Females, ᵡSubstance-positive patients under 18, ᵑ of all patients under 18, ᵚsubstance-positive patients aged 18 and over, ᵝall patients aged 18 and over

for psychiatric care, possibly influenced by the long-term psychological effects of the coronavirus disease-2019 pandemic, economic stressors, and growing mental health awareness. The significant rise from 2020 to 2022 aligns with studies documenting the pandemic's impact on mental health (13). The low case numbers in 2020 may also reflect the recent implementation of screening in our laboratory, which had yet to gain widespread recognition in healthcare settings.

The majority of test requests originated from the psychiatry outpatient clinic (37.3%) and the male psychiatry service (23.8%). The predominance of male patients in test requests may suggest a higher clinical detection rate of substance use among men. Additionally, 61.2% of the patients were outpatients, indicating a substantial demand for outpatient treatment services. These results are consistent with a study conducted in Jordan, which also reported a higher prevalence of substance use disorders among male patients receiving outpatient psychiatric care (14).

An important finding of this study is that 18.1% of the substance screening tests were conducted for forensic purposes, while 81.9% were done for medical reasons. This highlights the predominant role of clinical evaluations in identifying substance use and points to the need for health policies that prioritise medical intervention over legal processing.

These results are consistent with SAMHSA's 2022 NSDUH report, which emphasized the need for accessible outpatient treatment services (5). Similarly, the 2023 European Drug Report by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) identified outpatient services as the primary mode of treatment for substance use disorders across Europe. Expanding access to outpatient care has been shown to ease the burden on inpatient facilities (2), and our findings further support the development of comprehensive outpatient programmes.

Notably, 10.5% of our cases involved emergency psychiatric services, underscoring the need for crisis intervention strategies and enhanced community-based mental health programmes to reduce dependency on emergency care. Recent studies support this interpretation and contain similar recommendations (15,16).

A noteworthy gender-related finding of the present study is that the rate of substance positivity was slightly higher among women (27%) than men (24.8%). Benzodiazepines were the most frequently detected substances in women, whereas amphetamines were more common in men. The higher prevalence of benzodiazepine use among women may be influenced by their longer life expectancy and greater engagement with healthcare services (17,18). Several scholars have reported a female-to-male ratio of 3:1 for benzodiazepine misuse in primary healthcare settings (19). In a study conducted in Porto, the authors found that older women, particularly those who were divorced or widowed, were at higher risk of benzodiazepine misuse (20).

According to our findings, benzodiazepine positivity was higher in women, while amphetamine positivity was higher in men; these results are also consistent with other studies conducted in Türkiye.

At Ankara Bilkent City Hospital, benzodiazepines, cannabinoids, and amphetamines were reported as the most frequent substances, with clear gender- and age-related differences (21). Similarly, Öğüt and Yıldırım (22) found that benzodiazepine and amphetamine use was more common among women, while cannabinoids were more prevalent among men.

Our findings are consistent with these studies, but the lower cannabinoid rate in our cohort may reflect regional differences in substance availability or testing practices. Overall, these results emphasise the importance of gender-sensitive prevention and treatment strategies.

Amphetamine use appears to be more prevalent among men, which is consistent with our findings. According to the 2024 European Drug Report, approximately two million adults used amphetamines in the year preceding the report's data collection, with a higher incidence among men (2). Paz-Ramos et al. (23) also reported widespread misuse of amphetamine-type stimulants, particularly among male users.

In our study, substance positivity was slightly higher among individuals under 18 (27.1%) compared to adults (25.2%); however, this difference was not statistically significant (p=0.560). Benzodiazepines were the most commonly detected substances across both age groups, possibly reflecting prescribing practices and potential misuse. The 2021 NSDUH reported the highest rates of substance use disorders among young adults aged 18-25, which emphasizes the need for targeted prevention strategies. Bushnell et al. (24) noted a rising trend in diagnoses of sedative, hypnotic, or anxiolytic use disorders among both prescribed and non-prescribed users, especially young adults. These results underscore the need for improved prescription monitoring and public education regarding the risks of misuse.

In addition, our data showed that substance positivity was slightly higher in adolescents compared to adults, with benzodiazepines being the most frequently occurring substances in this age group. In adults, however, amphetamines, opiates, and cocaine were more common. Survey-based studies in Türkiye have reported a growing use of amphetamine-type stimulants among young people, particularly in metropolitan areas (25). This pattern suggests that adolescents may often initiate substance use with sedatives, while with increasing age, there is a shift toward stimulants and opiates, which carry higher risks of dependence.

A key finding of our study is that 239 patients (3.97%) engaged in polysubstance use, which accounted for 15.8% of the substance-positive individuals. Although polysubstance use was more prevalent among males, a notable number of female and underage patients also exhibited it. This warrants further attention to gender- and age-specific risk factors. Data from recent studies support our results as they show that approximately 72.7% of women use two or more substances on a daily basis, including cocaine, opioids, cannabis, alcohol, benzodiazepines and nicotine (26). These results highlight the need for tailored interventions that address women's unique risks and usage patterns.

While men generally have higher rates of substance use, women often progress more quickly from initial use to dependence and may experience more severe consequences. This phenomenon, known as the telescoping effect, underscores the necessity for gender-sensitive prevention and treatment strategies (27).

Polysubstance use, which involves the concurrent use of illicit drugs, alcohol and prescription medications, is now the predominant pattern of substance use in Europe, especially among younger populations (28). In the United States (US), SAMHSA and NSDUH data indicate that 81% of individuals misusing opioids also consume other substances (29). This complexity presents significant challenges for diagnosis and treatment.

Polysubstance use patterns differ across regions. According to the EMCDDA, opioids, benzodiazepines, and stimulants are commonly co-used in Europe, while NSDUH data from the US identify alcohol, cannabis, and cocaine as substances typically co-used with opioids (29). These regional differences highlight the importance of locally relevant harm reduction and treatment strategies.

In our cohort, polysubstance use was identified in 15.8% of substance-positive individuals, most frequently involving the concurrent use of two substances. Recent evidence also indicates that polysubstance users are at higher risk of psychiatric comorbidities and treatment resistance (30). This highlights the necessity of early recognition of polysubstance use in clinical practice and the adaptation of treatment plans accordingly.

Study Limitations

Despite offering valuable insights into urine drug screening, this study has several limitations. First, the study was conducted in a single healthcare institution; hence, the generalizability of the findings to wider populations may be limited. Second, while urine drug screening tests are effective for the initial detection of substance use, they do not differentiate between acute and chronic use, nor do they precisely determine the timing of substance intake. Additionally, the study did not include a detailed assessment of the patients' clinical histories or psychosocial factors, which limited our ability to fully explore the underlying causes and contexts of substance use. Despite these limitations, this study is strengthened as one of the few large-scale investigations in this field, through the use of standardized laboratory methods in accordance with national regulations and circulars, and because such studies are very limited in number but provide highly valuable contributions.

Conclusion

This retrospective analysis of urine drug screenings at University of Health Sciences Türkiye, Basaksehir Cam and Sakura City Hospital documents critical trends in substance use, including higher positivity rates among females, particularly for benzodiazepines, and a notable prevalence of polysubstance use, predominantly among adults. Most of the test requests originated from psychiatric services, reflecting the integral role of mental health care in substance use detection and management. While medical screenings made up the majority of the tests, forensic evaluations also played a meaningful role.

The findings emphasise the importance of regulatory-compliant laboratory practices, effective prescription monitoring and widespread public awareness in shaping health policy, updating clinical guidelines and improving prevention, screening and treatment approaches. Given the growing prevalence of polysubstance use and distinct gender-related risks—especially among young adults and women—tailored, gender-sensitive interventions are essential to mitigate the rising burden of substance use disorders.

Ethics

Ethics Committee Approval: The Clinical Research Ethics Committee University of Health Sciences Türkiye, Basaksehir Cam and Sakura City Hospital, provided the necessary ethical permissions for the investigation with (approval no.: KAEK/24.07.2024.135, date: 19.08.2024).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Financial Disclosure: This study received no financial support.

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Original Article

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Follow-up of Fertility, Contraception, and Pregnancy Outcomes After Pelvic Organ Prolapse Surgery

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Abstract

Aim: Pelvic organ prolapse (POP) is a common condition among parous and aging women. While surgical repair is effective, little is known about fertility, contraception, and pregnancy outcomes postoperatively. This study evaluates these aspects to inform preoperative counseling and reproductive planning.

Methods: This retrospective observational study included 122 sexually active women aged 18-45 years with negative preoperative pregnancy tests who underwent POP surgery between January 2019 and September 2023. Data were collected from hospital records and follow-up calls and analyzed using SPSS.

Results: The mean patient age was 39.9±4.4 years. The most frequent prolapse types were rectocele (68.9%) and cystocele (54.1%). Preoperatively, 54.1% of patients used no contraception, while 21.3% used intrauterine devices and 9.8% underwent bilateral tubal ligation (BTL) or bilateral salpingectomy (BS). Postoperatively, the percentage of individuals not using contraception dropped to 40.2%, and BTL/BS use rose to 20.5%. Two patients conceived postoperatively, both with favorable short-term outcomes. Postoperative complications were rare, with pelvic pain (8.2%) as the most common.

Conclusion: Findings highlight a shift toward permanent contraception post-surgery, influenced by completed fertility and cancer prevention. Pelvic organ prolapse surgery, particularly uterine-sparing approaches, can preserve fertility in selected cases. However, early menopause or ovarian failure remains a risk. Pelvic organ prolapse surgery in reproductive-aged women requires individualized counseling on fertility and contraception. Surgical planning should include discussion of reproductive goals, and long-term follow-up is essential to monitor outcomes and support informed choices.

Keywords: Pelvic organ prolapse, urogynecologic surgery, contraception, fertility

Introduction

Pelvic organ prolapse (POP) is a prevalent condition among parous and aging women, with a lifetime risk of undergoing a surgical intervention for prolapse or urinary incontinence (UI) estimated at 11.1% by the age of 80 (1). Since the 1900's, anterior colporrhaphy (CA) and posterior colporrhaphy (CP) have been widely used in POP surgery (2). Over the past 30 years, procedures such as tension-free vaginal tape (TVT) (3), transobturator tape (TOT) (4), and, more recently, suspension and ligament surgeries have gained popularity (5). Pelvic organ prolapse surgery utilizes various techniques, with organ-preserving approaches becoming increasingly popular (6-8). Patients planning pregnancy can be reassured about their ability to conceive and deliver vaginally (9). Boyd et al. (10) confirmed the safety and durability of

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POP surgery during and after pregnancy, aligning with previous case series.

Due to the risk of UI recurrence during and after pregnancy, it is advisable to delay suburethral sling surgery until family planning is complete (11). The literature on pregnancy after surgical treatment of UI is limited, with no clear recommendations for management (11-14). The 2006 French national survey found no clear guidance on the optimal delay between suburethral sling placement and pregnancy (15). However, patients should be informed about potential pregnancy and the risk of UI recurrence postpartum (11).

Various studies have examined the outcomes of planned and unplanned pregnancies following these surgeries, the necessity of pre- and postoperative contraceptive counseling, contraceptive method preferences and failure rates, and the impact of fertility desire. Research in this area is ongoing and will likely continue.

We hypothesized that in reproductive-aged women undergoing POP surgery-particularly in those scheduled for incontinence procedures-appropriate contraceptive counseling would optimize surgical timing and support decision-making regarding the mode of delivery in potential postoperative pregnancies.

This study aims to provide patients with a comprehensive understanding of the diagnostic and treatment spectrum before POP surgery. Additionally, it seeks to enhance awareness of contraception options and improve patients' knowledge and health literacy regarding unintended pregnancies following prolapse surgery.

Materials and Methods

Compliance with Ethical Standards

Approval was obtained from the University of Health Sciences Türkiye, Istanbul Training and Research Hospital Clinical Research Ethics Committee (approval no.: 276, date: 13.10.2023). All authors fully complied with the Declaration of Helsinki during the course of the study. Due to its status as a research hospital, informed consent is obtained from all patients admitted.

Study Design

This study was planned as a retrospective case-control study. The flowchart of the study is summarized in Figure 1.

Sample and Setting

This study is a retrospective case-control study conducted between January 2019 and September 2023 at the University of Health Sciences Türkiye, Istanbul Training and Research Hospital in Istanbul, Türkiye. A total of 122 patients who met the inclusion criteria were included in the study. The inclusion criteria were sexually active women aged 18 to 45 years with a negative pregnancy test during the preoperative evaluation.

Data Collection Tools

The study data were collected using the "Personal Information Form". This was prepared by the researcher by scanning the relevant literature (1-6,8,9) and consists of questions about the socio-demographic characteristics of the patients participating in the study and obstetric and operation-related features.

Data Collection

Patient data covering the specified period were retrospectively reviewed using the hospital's electronic database and archived files. A total of 289 patient records were evaluated. After excluding those who did not meet the inclusion criteria, those who did not attend routine postoperative follow-up visits, those who could not be reached by phone for follow-up and research purposes, and those with incomplete or insufficient data, the study was continued with 122 patients who met all the criteria.

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences (IBM SPSS Statistics, version 27). Demographics and clinical characteristics of the participants were expressed as frequency (percentage) or as mean ± standard deviation. Number, percentage calculation, and average (minimum and maximum) criteria were used to evaluate the data. To evaluate differences between preoperative and postoperative contraceptive preferences, McNemar's test was applied to paired categorical data (Supplementary Table 1). Contraceptive methods of very low frequency and distinct clinical implications-such as hysterectomy, depot medroxyprogesterone acetate, early menopause, and premature ovarian insufficiency (POI) were excluded from the comparative analysis to ensure statistical validity and interpretative clarity. These methods were observed in 3 patients preoperatively and 9 patients postoperatively but were not included in the McNemar test.

Results

The study included 122 women with a mean age of 39.9±4.4 years (Table 1). Table 2 summarizes patients' medical history and risk factors, highlighting that most women had prior abdominopelvic surgery (particularly cesarean section) and notable rates of smoking and chronic comorbidities such as hypertension and diabetes. Postoperative complications were infrequent, with pelvic pain being the most common (8.2%) (Table 3).

Regarding contraceptive use, the proportion of patients reporting no contraception significantly decreased after surgery (from 54.1% to 40.2%), while the use of permanent methods BTL/BS significantly

increased (from 9.8% to 20.5%) (Bonferroni-corrected p<0.01) (Table 3). No significant changes were observed for reversible methods. Among the subgroup of women who underwent postoperative BTL/BS, all had shifted to a permanent contraceptive method (p=0.031).

Two women conceived after POP surgery, and both had favorable short-term outcomes. Additionally, the incidence of hysterectomy increased from 1.6% preoperatively to 4.9% postoperatively, and a small number of patients experienced endocrine conditions negatively affecting fertility (early menopause 1.6%, POI 0.8%).

Overall, the results demonstrate a significant shift toward permanent contraception after POP surgery, with fertility preserved in selected cases.

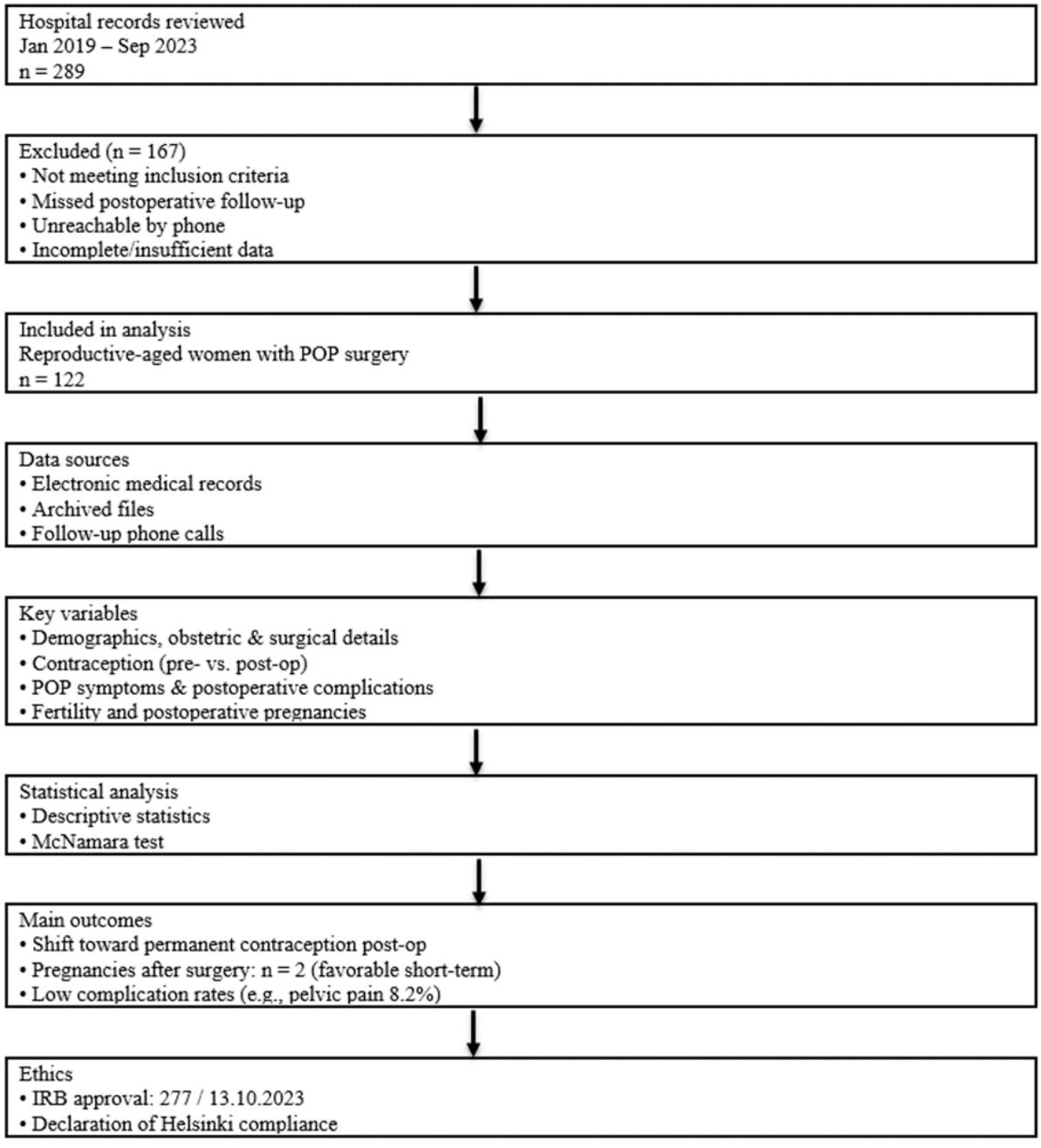


Figure 1. Flowchart of the study
POP: Pelvic organ prolapse

Discussion

Pelvic floor dysfunction is common among older women and often requires surgical treatment, with a significant risk of reoperation (1). In our cohort, the mean age was 39.9 years, and the majority of patients had a history of vaginal delivery, which is consistent with known risk factors such as parity and age (16). The high preoperative prevalence of rectocele (68.9%) and cystocele (54.1%) observed in our population underscores the dominance of anterior and posterior compartment defects, whereas apical prolapse remained relatively rare (10.7%) (Table 2). This distribution aligns with the literature, where anterior and posterior prolapse are more frequently reported as primary indications for surgical intervention (17).

Our study provides specific insights into reproductive health outcomes in women of childbearing age undergoing POP surgery, an area where the literature remains scarce. The most striking finding was the significant increase in contraception use postoperatively, with a concomitant rise in permanent methods such as BTL/BS (18,19). This change suggests that POP surgery often coincides with the end of fertility and reflects clinicians' increasing emphasis on opportunistic salpingectomy as a cancer-preventive strategy (7,20).

Fertility preservation is another key observation. In our cohort, two patients conceived postoperatively, both resulting in favorable outcomes. Although the numbers are small, these pregnancies demonstrate that uterine-sparing POP procedures do not preclude future fertility. This is consistent with prior reports indicating that pregnancy, while uncommon, can occur following uterine-preserving prolapse surgery (7,8,21,22). These results highlight the importance of comprehensive preoperative counseling, stressing that women who do not desire pregnancy must still use effective contraception after surgery. Notably, a small percentage of patients experienced early menopause (1.6%) and premature ovarian failure (0.8%), which are critical factors when evaluating postoperative fertility potential.

Urinary incontinence was present in a substantial proportion of our cohort, with 32% reporting stress UI and 17.2% mixed UI preoperatively (Graphic 1). In cases

Table 1. Mean and standard deviation values of sociodemographic continuous variables (n=122)

Variables	Mean ± SD	Min.	Max.
Age (years)	39.92±4.43	27	45
Number of vaginal deliveries	2.98±1.68	0	9
Body mass index	28.05±4.69	18	43
Time since surgery (months)	18.93±14.90	1	52
Patient satisfaction score (0-5)	3.48±0.97	0	5

Min.: Minimum, Max.: Maximum, SD: Standard deviation

Table 2. Patients' medical history and risk factors (n=122)

Variables	n	%
Educational status		
Illiterate	7	5.7
Primary school	69	56.6
Middle school	17	13.9
High school	21	17.2
University	8	6.6
Infertilite history		
Yes	6	4.9
No	116	95.1
Smoking history		
Yes	37	30.3
No	85	69.7
History of abdominopelvic surgery		
None	82	67.2
TOT	1	0.8
C/S	31	25.4
Sacrohysteropexy	2	1.6
Hysterectomy	4	3.3
CA	1	0,8
History of heavy physical activity		
Yes	9	7.4
No	113	92.6
History of difficult delivery		
Yes	5	4.1
No	117	95.9
History of asthma/COPD		
Yes	12	9.8
No	110	90.2
History of diabetes mellitus		
Yes	7	5.7
No	115	94.3
History of hypertension		
Yes	9	7.4
No	113	92.6
History of cardiac disease		
Yes	6	4.9
No	116	95.1
Other risk factors		
Yes	3	2.5
No	119	97.5
Total	122	100

C/S: Cesarean section, TOT: Transobturator tape, CA: Anterior colporrhaphy, COPD: Chronic obstructive pulmonary disease

Table 3. Surgical procedures, contraceptive use, and postoperative complications (n=122)					
Surgical procedures	**n**	**%**	**Preoperative contraceptive methods**	**n**	**%**
TOT	27	22.1	None	66	54.1
TOT+CAP	7	5.7	Withdrawal	9	7.4
CP	25	20.5	IUD	26	21.3
CA	6	4.9	Condom	3	2.5
TVT	6	4.9	BTL/BS	12	9.8
TVT+CAP	1	0.8	Oral contraceptive pills	3	2.5
CAP	39	32.0	DMPA	1	0.8
TOT+CP	4	3.3	Hysterectomized	2	1.6
TOT+CA	1	0.8			
CP+Burch colposuspension	2	1.6			
Sacropexy	3	2.5			
McCall culdoplasty+CA	1	0.8			
Postoperative complications	**n**	**%**	**Postoperative contraceptive methods**	**n**	**%**
None	100	82.0	None	49	40.2
Pain	10	8.2	Withdrawal	6	4.9
Dyspareunia	2	1.6	IUD	25	20.5
Surgical site complication	4	3.3	Condom	4	3.3
Recurrent UTI	2	1.6	BTL/BS	25	20.5
Mesh erosion	2	1.6	Oral contraceptive pills	4	3.3
Recurrence of symptoms	1	0.8	Hysterectomized	6	4.9
Cuff prolapse	1	0.8	Early menopause	2	1.6
			Premature ovarian insufficiency	1	0.8
Total	122	100	Total	122	100

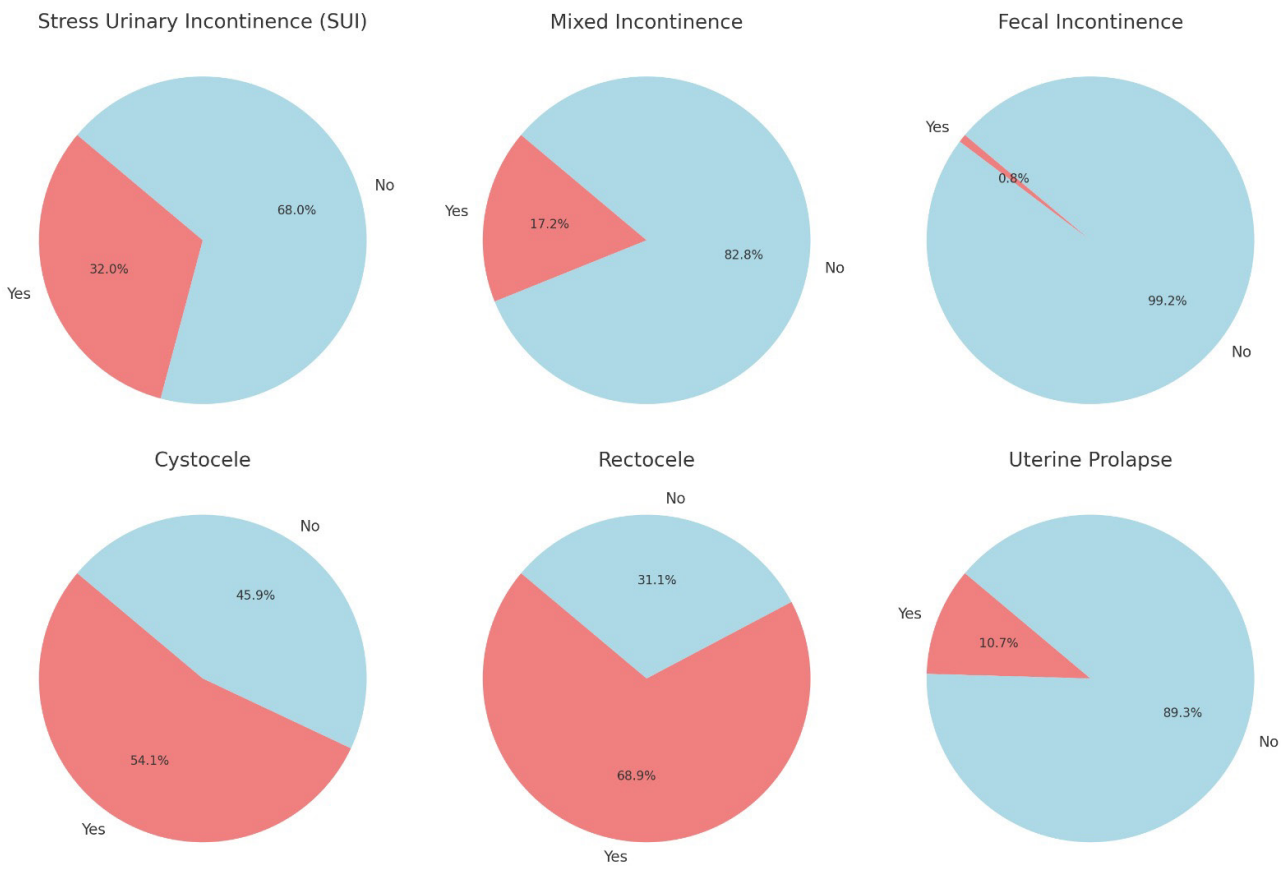
TOT: Transobturator tape, CAP: Anterior and posterior colporrhaphy, CP: Posterior colporrhaphy, CA: Anterior colporrhaphy, TVT: Tension-free vaginal tape, IUD: Intrauterine device, BTL: Bilateral tubal ligation, BS: Bilateral salpingectomy, DMPA: Depot medroxyprogesterone acetate, UTI: Urinary tract infection

where conservative management (rehabilitation) fails and delaying surgery is not feasible, suburethral sling placement may be considered (11). In our cohort, 38.5% of patients underwent surgery for stress UI; among these, 83.0% received TOT and 14.9% TVT, highlighting a clear preference for TOT in routine practice. Notably, one 36-year-old multigravida (G6) patient conceived during the 18-month postoperative follow-up period and subsequently delivered by cesarean section, a mode of delivery often favored due to patient or physician concerns, as similarly reported in the literature (10,15).

Evidence on pregnancy outcomes after POP or UI surgery remains mixed, and the lack of randomized studies due to ethical constraints complicates clinical decision-making (12,15,23). With regard to CP, Esercan and Demir (9) reported effective correction of symptomatic rectocele, reassuring patients planning pregnancy about their ability to conceive and deliver vaginally. In our study, classic CP alone was performed in 25 patients (20.5%), while a total of 79 patients (64.8%), including those who had classic CP alone, underwent CP as part of their surgical management. In the subgroup of patients who chose postoperative BTL/BS, (Supplementary Table 2), 12 had CP, 9 underwent combined CAP, and 1 underwent CA. The high rate of definitive contraception in this subgroup suggests that patients undergoing reconstructive pelvic surgery received effective contraceptive counseling, reflecting a proactive approach to long-term reproductive planning in the context of pelvic floor reconstruction (24).

Regarding McCall culdoplasty, one study discouraged its use in patients with a history of vaginal delivery of macrosomic infants because of significantly higher surgical failure rates (25). In line with this, only one patient in our cohort underwent McCall culdoplasty, reflecting a cautious and selective application of this technique.

Complication rates in our study were low. Pelvic pain was the most frequently reported issue (8.2%), while mesh erosion, recurrence, or cuff prolapse were rare.



Graphic 1. Distribution of symptoms and clinical findings

These findings support the safety and durability of POP surgery in younger women, as previously published series indicate (22,24).

Our data emphasize the need to standardize preoperative reproductive counseling, aligning surgical planning with women's long-term fertility goals.

Study Limitations

This research carries inherent constraints that merit consideration. The retrospective methodology, while practical, depends heavily on the precision and completeness of archived patient records and subjective follow-up responses, which may introduce potential biases. Being a single-center study conducted in a tertiary care institution, the findings may not be broadly applicable across diverse healthcare settings or populations. The rarity of postoperative pregnancies in this cohort limits the capacity to draw definitive conclusions about fertility preservation and gestational outcomes following prolapse repair. Some patients were unreachable or had insufficient data, which may have limited the robustness of the dataset. Moreover, variations in the delivery and documentation of contraceptive and fertility counseling were not assessed, despite their likely impact on patient choices. The follow-up period, though adequate for short-term assessment, may be insufficient to fully capture long-term outcomes such as delayed prolapse recurrence or evolving reproductive health concerns.

Nevertheless, this study offers a valuable perspective by specifically addressing a relatively understudied group-women of reproductive age undergoing POP surgery. It presents a detailed examination of contraceptive use patterns, surgical decisions, and reproductive outcomes in a real-world clinical context. The inclusion of a sizable patient group and the focus on both pre- and postoperative reproductive behavior make it a meaningful contribution to current urogynecological knowledge. Its findings emphasize the need for proactive, personalized counseling and may guide clinicians in shaping informed, patient-centered care strategies for women balancing pelvic floor health with fertility considerations.

Despite these limitations, this study is one of the few to specifically address reproductive-aged women undergoing POP surgery. The relatively large cohort, the focus on both pre- and postoperative contraceptive

behavior, and the integration of real-world clinical data provide valuable insights. The results emphasize the importance of individualized counseling and contribute to the development of evidence-based reproductive planning strategies in women with POP.

Conclusion

Pelvic organ prolapse surgery in reproductive-aged women requires a delicate balance between anatomical correction and reproductive planning. Our findings indicate a postoperative shift toward permanent contraceptive methods and highlight that fertility can be preserved in selected cases. Nevertheless, this study has certain limitations: its retrospective design, reliance on a single-center sample, and the limited number of postoperative pregnancies restrict the generalizability and depth of the conclusions. Despite these constraints, the study underscores the importance of individualized, preoperative fertility and contraceptive counseling, as well as long-term follow-up. Future prospective, multicenter studies are warranted to establish standardized guidelines for reproductive counseling and postoperative care in this patient population.

Ethics

Ethics Committee Approval: Approval was obtained from the University of Health Sciences Türkiye, Istanbul Training and Research Hospital Clinical Research Ethics Committee (approval no.: 276, date: 13.10.2023). All authors fully complied with the Declaration of Helsinki during the course of the study.

Informed Consent: Due to its status as a research hospital, informed consent is obtained from all patients admitted.

Footnotes

Authorship Contributions

Surgicial and Medical Practices: T.I., N.U., A.F., Concept: T.I., N.U., A.F., Design: T.I., O.K., N.U., A.F., Data Collection or Processing: T.I., O.K., N.U., A.F., Analysis or Interpretation: T.I., O.K., Literature Search: T.I., Writing: T.I., O.K.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Supplementary Tables 1, 2: https://d2v96fxpocvxx.cloudfront.net/6548c443-00ef-4a8c-a306-c0848f02b51f/content-images/7d393c5c-616a-466f-af63-06b194090873.pdf

Original Article

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Effects of Sentinel Lymph Node Dissection on Sexual Function After Endometrial Cancer Surgery

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Abstract

Aim: The purpose of this research was to determine whether endometrial cancer (EC) patients' sexual function (SF) and quality of life (QoL) were affected by sentinel lymph node dissection (SLND). The effects on SF of SLND and pelvic and paraaortic lymph node dissection (LND) in the surgical treatment of EC were compared.

Methods: This prospective, single-center research comprised 82 individuals who had LND for endometrial cancer. Patients were categorized into two groups based on the extent of LND: Group A SLND and Group B (pelvic and/or para-aortic lymphadenectomy). The Female Sexual Function Index (FSFI) and the Functional Assessment of Cancer Therapy (FACT-G) were used to measure SF and QoL, respectively, six months after surgery.

Results: Among the 82 patients, 14 (17%) retained normal SF (FSFI ≥26.55), while 68 (83%) experienced sexual dysfunction. While no substantial difference was seen in overall FSFI scores among the groups, patients in the SLN group had significantly higher ratings in the desire (p=0.036) and orgasm (p=0.042) subdomains compared to the other groups. Quality of life, as assessed by the FACT-G, was negatively impacted by lower SF scores, particularly among highly educated patients (p=0.013).

Conclusion: Sentinel lymph node dissection may preserve aspects of female SF in patients undergoing surgery for endometrial carcinoma, especially in younger and more educated patients.

Keywords: Sentinel lymph node, endometrial neoplasms, sexual dysfunction, quality of life

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Introduction

In affluent nations, endometrial cancer (EC) is the predominant gynecological malignancy, impacting both young nulliparous and postmenopausal women (1). The median age for EC diagnosis is 61 years; however, the incidence rate has recently increased in women under 40, representing 4.2% of low-grade ECs detected in the United States (2). The majority of cases are identified early and exhibit a favorable prognosis (3). Prognosis is often positive after an EC diagnosis, with 81% of women surviving five years post-diagnosis (4). Enhancing the quality of care for patients undergoing treatment for EC would positively influence their sexual functioning (SF) and quality of life (QoL) metrics (5).

The mainstay of therapy in endometrial carcinoma is complete hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy (6). Accurate nodal evaluation is essential for identifying lymphatic metastases, which are critical factors for prognosis and treatment planning (6). Sentinel lymph node dissection (SLND) is the recommended intervention compared to total lymphadenectomy when the illness is confined to the uterus. This is attributable to the reduced incidence of problems and the capability to perform lymph node assessment using ultrastaging (7,8).

Sexual engagement is an essential aspect of total well-being. Sexual dysfunction (SDF), a frequently neglected consequence of gynecological cancer therapies, pertains to challenges encountered at any phase of the sexual response cycle (9). Most cancer patients prioritize anticancer therapy and associated challenges, rendering sexuality less relevant. In EC, women have surgical menopause concurrent with surgery, adversely affecting their QoL (10). Despite the considerable frequency of SDF among patients with gynecologic malignancies, healthcare practitioners frequently lack awareness of the illness (11). The assessment of the effects of lymph node dissection (LND) on postoperative survival outcomes was conducted on individuals who received surgery for ovarian cancer in the literature review (11).

We hypothesized that this investigation of LND, especially SLND, would examine its impact on the social functions of patients with EC undergoing surgical intervention. In this context, we aimed to compare the SF and QoL scale scores in individuals from whom lymph nodes were removed during sentinel, pelvic, and pelvic para-aortic surgeries.

Materials and Methods

From March 2022 to December 2023, we operated on patients who had been diagnosed with EC. We assessed the sexual well-being of our patients using the Female Sexual Function Index (FSFI) and rated their QoL with the Functional Assessment of Cancer Therapy (FACT-G). All patients participating in the clinical investigation provided signed voluntary permission forms after being verbally informed about the study and reviewing the form.

Compliance with Ethical Standards

The study was carried out in conformity with the Good Clinical Practice Guidelines and the Declaration of Helsinki. Ethical approval was obtained from the University of Health Sciences Türkiye, Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no.: 2022-04-12, date: 21.02.2022).

Study Design

This study is an observational, prospective, single-center investigation. Our patients were categorized into two groups: Those who underwent SLND (Group A) and those who underwent only pelvic or pelvic and para-aortic LND (Group B). The extent of LND was determined according to the current guidelines (12,13). As molecular studies were not feasible, we designated tumors without lymphovascular invasion, endometrioid type, and grade 1 and 2 tumors up to Stage 2A as early stage (6). Before the surgery, we refrained from assessing SF and scoring the QoL scale due to the assumption that the patient's new diagnosis would induce anxiety. Patients above the age of 18 were included if they had operable EC and no other malignancies, did not have any systemic or local diseases that could affect their SFs, had a spouse or partner, agreed to participate in interviews, and signed voluntary consent forms. Patients who were under the age of 18, had a malignancy other than EC and were undergoing therapy, had a systemic condition affecting SF, or did not have a sexual relationship were eliminated.

Six months postoperatively, patients responded to questions on the FSFI and FACT-G scales. Questions were explained if participants did not understand them. Scores for the FSFI's arousal, lubrication, orgasm, and pain components vary from 0 to 5, while the desire and pleasure sections run from 1 to 5. To get the overall section scores, we multiplied the section scores by the following coefficients: 3.0 for stimulation and lubrication, 0.6 for desire, and 0.4 for pleasure, agony, and orgasm. The overall FSFI score was derived by aggregating the scores from these sections. The FSFI scores were categorized as follows: Normal SF (total FSFI score ≥26.55), mild risk for female SDF (total FSFI score 18-26.55), moderate risk for female SDF (total FSFI score 11-17), and severe risk for female SDF (total FSFI score <10). The SDF of individuals was evaluated when their FSFI score fell below 26.55 (14). The FACT-G (version 4) is a validated 27-item questionnaire specific to cancer that evaluates overall QoL and is categorized into four primary subscales: Physical, social, emotional, and functional well-being. Numbers vary from zero to 108, with greater numbers signifying superior QoL. In our study, the median FACT-G score at six months served as the threshold to indicate poor or good QoL. Figure 1 presents a concise depiction of the study's flow diagram.

Statistical Analysis

The power study was carried out using the G*Power 3.1 Manual for macOS, which was developed by the Heinrich-Heine-Universität Dusseldorf in Dusseldorf, Germany. Following Cohen's instructions and the research of Datta, Datta et al. (3), we determined the effect size and accepted 1 beta at 0.95 to preserve the greater power of the study. The minimum required number of research participants was determined to be 32 patients for each group. The analyses were performed using version 25.0 of the statistical package for social sciences software, with a significance level of $p<0.05$. The independent samples t-test was used for continuous variables, [age, body mass index (BMI)] since the assumption of normal distribution was satisfied. Categorical factors (menopausal status, education, SF, kind of surgery, stage): The chi-square test was utilized. The FSFI scale scores were compared with LND operation types by using non-parametric tests (Mann-Whitney U test). The independent factors were identified using multivariable linear regression analysis [age, BMI, education level, International Federation of Gynecology and Obstetrics (FIGO) stage, FACT-G score] of the FSFI total score.

Results

Eighty-two patients with EC were stratified by type of LND. At six months postoperatively, 14 (17%) demonstrated normal SF (FSFI >26.55), while 68 (83%) had dysfunction. Sexual function did not differ significantly between groups (p=0.244). The mean age and BMI were 54±8.7 years and 34.5±6.5, respectively, with 63% having primary/secondary education. Age, BMI, education, disease stage, menopausal status, and surgical approach showed no significant association with postoperative SF. Postoperatively, 12% of patients in Group A and 5% in Group B remained sexually active, with no significant difference in FSFI scores. As shown in Table 1, following surgery, 10 (12%) patients in Group A and 4 (5%) patients in Group B were sexually active. In evaluating SF among both groups in the study, it was observed there was no statistical difference between the FSFI total scores.

Furthermore, as seen in Table 2, when the FSFI subcategories were evaluated independently, patients who had SLN dissection exhibited substantially elevated ratings in sexual desire (p=0.036) and orgasm (p=0.042) relative to the other cohort. The postoperative SF rates of patients in Group A were found to be higher than those of Group B. The patients underwent independent assessment utilizing FSFI subcategories (arousal, lubrication, desire, orgasm, pleasure, and pain) based on their age, BMI, cancer stage, and educational attainment. A reduction in patient age (p=0.002) and an enhancement in educational

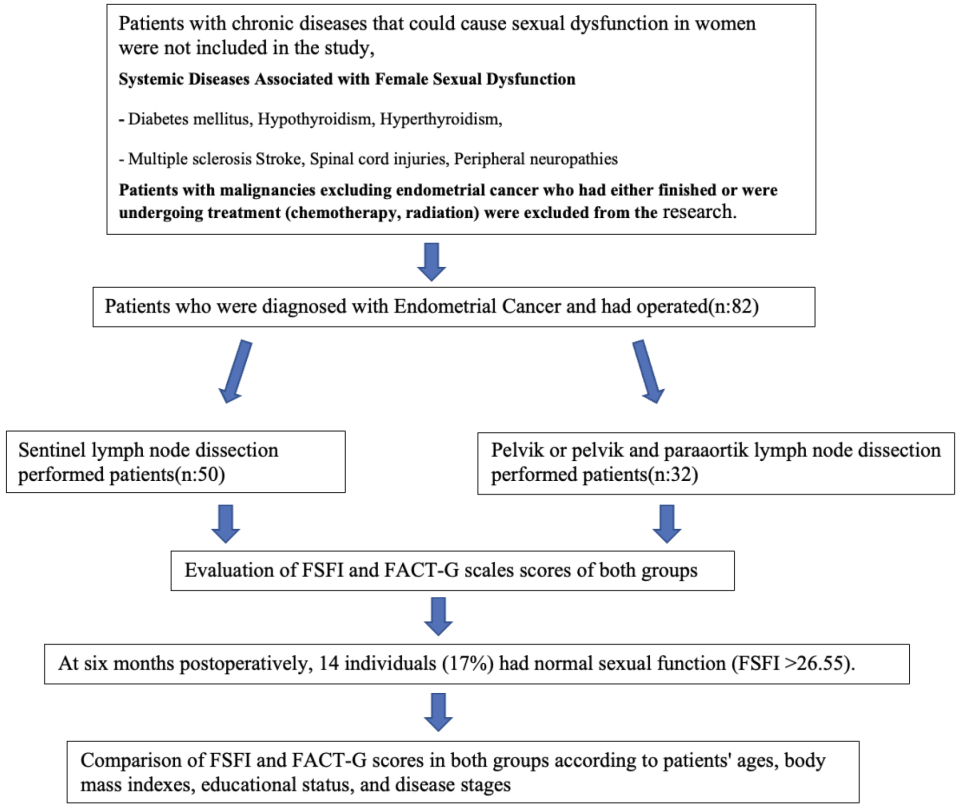

Figure 1. Presents a concise depiction of the study's flow diagram

Table 1. Demographic characteristics of patients treated for endometrial cancer			
	Total (n=82)		**p-value**
Variables	**Group A: Sentinel lymph node dissecsition (n=50)**	**Group B: Pelvic/pelvic+paraaortic lymph node dissection lymph node dissection (n=32)**	
Sexually active	10 (20%)	4 (13%)	0.244
Age (years)	54±8.7	56.4±9.3	0.188
BMI (kg/m^2)	34.5±6.5	34.6±8.5	0.741
Menopousal status (%)			0.373
Premenopausal	14 (21.5%)	7 (30.4%)	
Postmenopausal	51 (78.5%)	16 (69.6)	
Educational status			0.756
Primary school	31 (47.7%)	10 (43.5%)	
Secondary school	12 (18.5%)	3 (13%)	
Tertiary school	17 (26.2%)	6 (26.1%)	
High school	3 (4.6%)	3 (13%)	
University	2 (2%)	1 (4.3%)	
Type of surgery			0.376
Laparotomy	0	3 (12%)	
Laparoscopy	14 (21.5%)	17 (68%)	
Robotic surgery	51 (78.5%)	5 (20%)	
FIGO stage†			0.491
Early stage (1A-1B-2A)	42 (84%)	-	
Advanced stages (2B and over)	12 (16%)	32 (100%)	

†FIGO Stage: FIGO endometrial cancer staging 2023
BMI: Body mass index

Table 2. Comparisons of FSFI and FACT-G scores between groups			
	Group A: Sentinel lymph node dissecsition (n=50)	**Group B: Pelvic/pelvic+paraaortic lymph node dissection lymph node dissection (n=32)**	**p-value†**
FSFI desire	4.8 (1.8-6.0)	2.0 (1.8-3.6)	**0.036**
FSFI arousal	2.2 (1.2-4.8)	1.9 (1.2-4.2)	0.226
FSFI lubrication	2.3 (1.8-4.6)	1.8 (1.8-3.6)	0.641
FSFI orgasm	3.9 (1.2-4.8)	1.9 (1.2-4.8)	**0.042**
FSFI satisfaction	2.2 (1.6-4.8)	2.4 (1.6-4.2)	0.745
FSFI pain	2.2 (1.2-4.2)	3.9 (1.2-4.2)	0.037
FSFI total	15.6 (29.8-11.7)	12.8 (26.6-9.4)	0.255
FACT-G total	91 (65-104)	91 (60-104)	0.642

†: p-value of <0.05 was considered significant for all bold values
FSFI: Female sexual function index, FACT-G: Functional assessment of cancer therapy, FIGO: International Federation of Gynecology and Obstetrics

achievement (p=0.003) were associated with a statistically significant increase in sexual desire. In patients whose SF was active after surgery, there was no statistically significant variation between the assessment of SF and the stage of the disease, even if the disease was still in its early stages (p=0.466). When SF and education level were compared, it was found that college and university graduates had higher SF scores than other patients. In the multivariate analysis of the FSFI total score and its subgroups, alongside the patients' education level and FACT-G QoL scores in Group A patients who underwent SLND, an inverse correlation was observed between education level and SF, which significantly reduced the FACT-G scores (p=0.013). Table 3 presents an overview of the aforementioned explanations.

Table 3. Correlation between FSFI[¥] (total and subscores) and variables in patients with sentinel lymph node dissection Group A														
	FSFI total		FSFI arousal		FSFI desire		FSFI satisfaction		FSFI orgasm		FSFI pain		FSFI lubrication	
Variables	**r**	**P***	**r**	**P**	**r**	**P***	**r**	**P**	**r**	**P**	**r**	**P**	**r**	**P**
Age (years)	-0.380	0.282	-0.312	**0.018**	-0.321	0.002	-0.204	0.072	-0.541	0.753	-0.625	0.243	0.591	0.453
BMI (kg/m²)	-0.423	0.242	-0.036	0.563	-0.064	0.423	0.056	0.242	-0.034	0.341	-0.043	0.672	-0.078	0.212
Education status	0.032	**0.004**	-0.199	0.243	-0.043	0.112	0.216	0.651	0.024	0.411	-0.025	0.342	-0.244	0.211
FIGO stage[†]	0.366	0.212	-0.213	0.221	0.013	0.131	-0.214	0.314	0.145	0.141	0.156	0.284	0.272	0.116
FACT-G score	-0.360	**0.013**	0.206	0.113	0.014	0.183	-0.167	0.192	0.154	0.916	0.141	0.711	0.145	0.214

¥: Female sexual function index, †:FIGO Stage: FIGO endometrial cancer staging 2023, *: P-value of <0.05 was considered significant for all bold values
BMI: Body mass index, FSFI: Female sexual function index, FACT-G: Functional assessment of cancer therapy, FIGO: International Federation of Gynecology and Obstetrics

Discussion

The study's results indicate that SLND may mitigate the loss of SF in patients with EC, particularly in younger individuals.

This study is the first in the literature to examine the impact of SLND on SF after EC surgery. Sexual dysfunction is expected as a result of surgical and natural menopause, as mentioned in the literature (15,16). Upon evaluation of the FSFI subheadings, the orgasm and desire ratings in patients who underwent SLND were shown to be statistically significantly elevated compared to other groups. Consistent with our findings, it has been documented that the preservation of sympathetic and parasympathetic nerves following surgery leads to a diminished effect on SF (17). The investigation demonstrated, as previously shown in the literature (18,19), that the average age and menopausal state of patients in both groups did not affect postoperative SF.

After a cancer diagnosis, people frequently abstain from sexual intercourse with their partners throughout and after treatment, concentrating exclusively on illness care and dreading recurrence following intercourse. Several patients indicated that they participated in sexual intercourse due to a perceived responsibility to their partners. It has been shown that the QoL of these individuals, together with their SFs, is markedly impacted, resulting in heightened social isolation (3,9,15,16). Our findings about the influence of age on SF in patients post-EC surgery align with a meta-analysis (4). In accordance with the literature, we observed that BMI did not affect SF in patients with increased BMI who underwent surgery for EC (20). However, contrary to our findings, evidence suggests that obesity adversely affects SF and QoL assessments in patients with EC (10). No association was seen between disease stage and SF in the FIGO staging of patients following surgery. Furthermore, in accordance with the literature, patients with SF were noted to be in the initial stage (21,22). The data we acquired about the impact of EC stage and postoperative SF aligns with existing research (3). Literature indicates that SF scores and QoL metrics are diminished in EC, irrespective of disease stage (23).

The study concluded that a diminished or low SF score impacts QoL measures more significantly in patients with higher education levels, underscoring the increased relevance of SF in assessing QoL within this population. Comparable findings have been documented in the contemporary literature for the assessment of educational attainment, SF, and QoL scale metrics (2,24).

Study Limitations

The fact that the patients were evaluated only at 6 months after surgery and not evaluated at later times, that depression and body image evaluations were not made before and after treatment, and that the patients' spouses or partners were excluded from the study introduces limitations to our study. Despite these limitations, our study was conducted as a prospective single-center investigation. This study is the first in the literature evaluating the effect of SLND on SF in the management of EC.

Conclusion

Sentinel lymph node dissection positively influences SF in the management of EC. Furthermore, health practitioners should foster understanding to enhance patients' SFs and elevate their QoL following EC surgery.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no.: 2022-04-12, date: 21.02.2022).

Informed Consent: Patients above the age of 18 were included if they had operable EC and no other malignancies, did not have any systemic or local diseases that could affect their SFs, had a spouse or partner, agreed to participate in interviews, and signed voluntary consent forms.

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Footnotes

Authorship Contributions

Surgicial and Medical Practices: E.S., S.K., Concept: E.S., S.Y., S.K., S.G., O.A.Y., Design: E.S., S.Y., S.K., C.C., L.Y., Data Collection or Processing: E.S., S.G., O.A.Y., N.K., Analysis or Interpretation: S.Y., O.K., Literature Search: E.S., Writing: E.S., C.C., L.Y.

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Original Article

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Comparison of the Effectiveness of Laboratory Parameters in Predicting Lymph Node Positivity in Patients with Gastric Cancer

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Abstract

Aim: We proposed that inflammation and nutrition-based laboratory indices measured at the time of initial diagnosis could predict lymph node positivity in patients with gastric adenocarcinoma. In this context, this study aimed to evaluate and compare the predictive performance of the C-reactive protein (CRP) -to-albumin ratio (CAR), CRP-to-lactate dehydrogenase ratio (CLDR), lymphocyte-to-CRP ratio (LCR), and CRP-albumin-lymphocyte index (CALLY).

Methods: This retrospective, single-center observational study included 215 consecutive patients who underwent gastrectomy for histologically confirmed gastric adenocarcinoma between January 2014 and May 2024. Preoperative laboratory parameters were used to calculate CAR, CLDR, LCR, and CALLY. Receiver operating characteristic (ROC) curve analysis assessed discriminative ability, and multivariable logistic regression was performed to identify independent predictors of lymph node positivity, adjusting for age, sex, and neoadjuvant therapy status.

Results: Lymph node metastasis was present in 173 patients (80%). CAR and CLDR were significantly higher in patients with nodal involvement (p=0.014 and p=0.017, respectively), whereas LCR and CALLY showed borderline associations (p=0.056 and p=0.052). ROC analysis revealed modest predictive ability, with area under the curve values of 0.622 for CAR and 0.618 for CLDR. In multivariable analysis, both CAR [odds ratio (OR): 1.36, p=0.026] and CLDR (OR: 19.93, p=0.018) remained independent predictors of lymph node positivity.

Conclusion: CAR and CLDR are inexpensive and widely accessible indices that independently predict lymph node metastasis in gastric cancer at diagnosis. Although their discriminative performance is modest, they may provide complementary value when combined with imaging and clinicopathological data to improve preoperative risk stratification.

Keywords: Gastric cancer, lymph node metastasis, C-reactive protein, albumin, lymphocytes, lactate dehydrogenase, biomarkers

Introduction

Gastric cancer remains a major global health challenge, ranking as the fifth most common malignancy and the third leading cause of cancer-related mortality worldwide (1). Its prevalence is particularly high in East Asian countries, including China, Japan, and South Korea. The disease is most frequently diagnosed between the ages of 40 and 65 and occurs nearly twice as often in men as in women (2).

Lymph node metastasis is one of the most critical prognostic factors in gastric cancer, as it strongly influences tumor, node, metastasis staging, surgical strategies, and the selection of neoadjuvant or adjuvant therapy (3). Accurate prediction of nodal involvement

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at the time of initial diagnosis is therefore essential for guiding treatment planning and improving outcomes. Despite the widespread use of computed tomography, magnetic resonance imaging, and endoscopic ultrasound for preoperative staging, these modalities have limited sensitivity in distinguishing reactive from metastatic lymph nodes (4,5). Recently, systemic inflammation has been recognized as a key driver of tumor progression and metastasis. Several inflammation-based and nutrition-based indices derived from routine blood tests, such as the C-reactive protein (CRP) -to-albumin ratio (CAR), lymphocyte-to-CRP ratio (LCR), and systemic immune-inflammation index, have been extensively investigated for their prognostic significance (6,7). However, newer indices, including the CRP-to-lactate dehydrogenase (LDH) ratio (CLDR) and the CRP-albumin-lymphocyte index (CALLY), remain underexplored, particularly in relation to predicting lymph node metastasis in gastric cancer (8-10).

We hypothesized that preoperative inflammation and nutrition-based indices measured at the time of diagnosis could predict lymph node positivity in patients with gastric adenocarcinoma. Accordingly, this single-center study aimed to evaluate and compare the predictive performance of four indices-CAR, CLDR, LCR, and CALLY-in estimating lymph node status at baseline. By identifying cost-effective and widely available biomarkers, this approach may provide additional value in clinical practice by supporting more accurate preoperative risk stratification and personalized treatment planning.

Materials and Methods

Compliance with Ethical Standards

This retrospective, single-center observational study was conducted in accordance with the principles of the Declaration of Helsinki and its later amendments. Approval was obtained from the Bolu Abant Izzet Baysal University Non-Interventional Clinical Research Ethics Committee (approval no.: 2024/300; date: 19.11.2024).

Study Design

Medical records of consecutive adult patients who underwent gastrectomy for histologically confirmed gastric adenocarcinoma between January 2014 and May 2024 were reviewed. Of 270 initially screened patients, 43 who underwent emergency surgery for complications (e.g., perforation or bleeding) and 12 with incomplete records were excluded. The final cohort consisted of 215 patients.

Demographic characteristics (age, sex), clinical information, preoperative laboratory results, operative notes, and postoperative histopathological findings were collected. All blood samples were obtained at the time of initial diagnosis, before any treatment, after at least 8 hours of fasting, and within 7 days prior to surgery. Patients who subsequently received neoadjuvant therapy were not excluded; however, their laboratory results reflected pretreatment baseline status, and neoadjuvant therapy was prespecified as an adjustment covariate in the analyses.

Laboratory Assessment

Based on routine laboratory measurements, four preoperative indices were calculated:

- C-reactive protein-to-albumin ratio: CRP/Albumin
- CRP-to-lactate dehydrogenase ratio: CRP/LDH
- Lymphocyte-to-CRP ratio: Lymphocyte/CRP
- CRP-albumin-lymphocyte index: (Albumin × Lymphocyte)/(CRP × 10^4)

No additional composite scores were analyzed to maintain focus on these a priori selected indices.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 27.0 (Armonk, NY, USA). Normality of continuous variables was tested using the Kolmogorov-Smirnov test. Group comparisons between lymph node-negative and lymph node-positive patients were performed using the Independent Samples t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables.

Diagnostic performance of the indices was assessed using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC), 95% confidence intervals (CIs), and optimal cut-off values determined by the Youden index were reported, along with corresponding sensitivity and specificity.

Independent predictors of lymph node positivity were identified using multivariable logistic regression, which included age, sex, neoadjuvant therapy status, and the four indices (CAR, CLDR, LCR, CALLY). Odds ratios (ORs) with 95% CIs were calculated. A two-tailed p-value <0.05 was considered statistically significant.

Results

A total of 215 patients met the inclusion criteria and were included in the final analysis. The mean age of the cohort was 65.8±12.3 years, and 160 patients (74.4%) were male. Lymph node metastasis was confirmed in 173 patients (80%) based on postoperative histopathological examination.

Comparison of inflammation and nutrition-based indices between patients with and without lymph node metastasis revealed significant differences (Table 1). CAR and CLDR values were significantly higher in the lymph node positive group (p=0.014 and p=0.017, respectively), whereas LCR (p=0.056) and CALLY (p=0.052) demonstrated borderline significance. These findings

suggest that patients with nodal involvement exhibit a heightened systemic inflammatory response and impaired nutritional status compared with those without lymph node metastasis.

Receiver operating characteristic curve analysis demonstrated modest diagnostic performance for all indices (Table 2, Figure 1). CAR had the highest discriminative ability (AUC: 0.622, 95% CI: 0.540-0.704, p=0.014), followed closely by CLDR (AUC: 0.618, 95% CI: 0.535-0.698, p=0.017). LCR (AUC: 0.585, p=0.056) and CALLY (AUC: 0.573, p=0.052) exhibited only borderline predictive performance.

Multivariable logistic regression was performed to identify independent predictors of lymph node metastasis (Table 3). After adjusting for age, sex, and neoadjuvant therapy status, both CAR (OR: 1.36, 95% CI: 1.04-1.78, p=0.026) and CLDR (OR: 19.93, 95% CI: 1.69-235.31, p=0.018) remained statistically significant. In contrast, LCR and CALLY were not significant (p>0.05). Importantly, inclusion of neoadjuvant therapy status in the regression model did not alter the predictive value of CAR and CLDR, indicating that their associations reflect baseline inflammatory and metabolic status rather than treatment-related effects.

Overall, CAR and CLDR emerged as statistically significant and independent predictors of lymph node positivity. However, their modest AUC values indicate that these indices should not be used as standalone diagnostic tools. Instead, they may serve as complementary markers alongside imaging and clinicopathological parameters to improve preoperative risk stratification.

Discussion

Neoadjuvant therapy has become an established strategy for patients with locally advanced gastric carcinoma, as it can reduce primary tumor burden and lymph node involvement, occasionally achieving pathological downstaging before surgery (11). Reliable preoperative prediction of nodal status remains essential because it strongly influences the surgical approach, the extent of lymphadenectomy, and the overall oncological treatment plan (12). Previous studies have also shown that successful downstaging correlates with improved long-term survival (13), underscoring the importance of cost-effective and widely accessible tools to complement imaging techniques.

Although D2 lymphadenectomy remains the standard surgical approach, it is associated with increased morbidity compared with less extensive procedures (14). In selected early-stage cases, limited lymphadenectomy or endoscopic resection may be appropriate alternatives (15,16). Therefore, accurate risk stratification before surgery is critical for tailoring operative strategies and optimizing treatment outcomes. Despite advances in cross-sectional imaging and endoscopic ultrasonography, these modalities still show limited sensitivity and specificity in identifying metastatic lymph nodes during initial staging, and restaging accuracy after neoadjuvant therapy also remains suboptimal (17,18). This diagnostic gap has driven growing interest in inflammation and nutrition-based biomarkers, which are inexpensive, reproducible, and reflect tumor biology at baseline.

Table 1. Comparison of inflammation and nutrition-based indices between patients with and without lymph node metastasis

Index	LN Negative (Median, IQR)	LN Positive (Median, IQR)	p-value
CAR	0.33 (0.20-0.51)	0.56 (0.34-0.88)	**0.014**
CLDR	0.057 (0.041-0.069)	0.084 (0.062-0.110)	**0.017**
LCR	0.117 (0.085-0.146)	0.068 (0.042-0.098)	0.056
CALLY	0.487 (0.310-0.682)	0.221 (0.150-0.362)	0.052

The Mann-Whitney U test was applied. Significant p-values are shown in bold.
CAR: C-reactive protein-to-albumin ratio, CLDR: C-reactive protein-to-lactate dehydrogenase ratio, LCR: Lymphocyte-to-C-reactive protein ratio, CALLY: C-reactive protein-albumin-lymphocyte index

Table 2. ROC analysis of laboratory indices for predicting lymph node positivity

Index	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	p-value
CAR	0.622 (0.540-0.704)	0.375	58.0	58.0	0.014
CLDR	0.618 (0.535-0.698)	0.064	57.0	58.0	0.017
LCR	0.585 (0.502-0.662)	3.20	55.0	56.0	0.056
CALLY	0.573 (0.489-0.651)	4.10	55.0	54.0	0.052

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, CAR: C-reactive protein-to-albumin ratio, CLDR: C-reactive protein-to-lactate dehydrogenase ratio, LCR: Lymphocyte-to-C-reactive protein ratio, CALLY: C-reactive protein-albumin-lymphocyte index

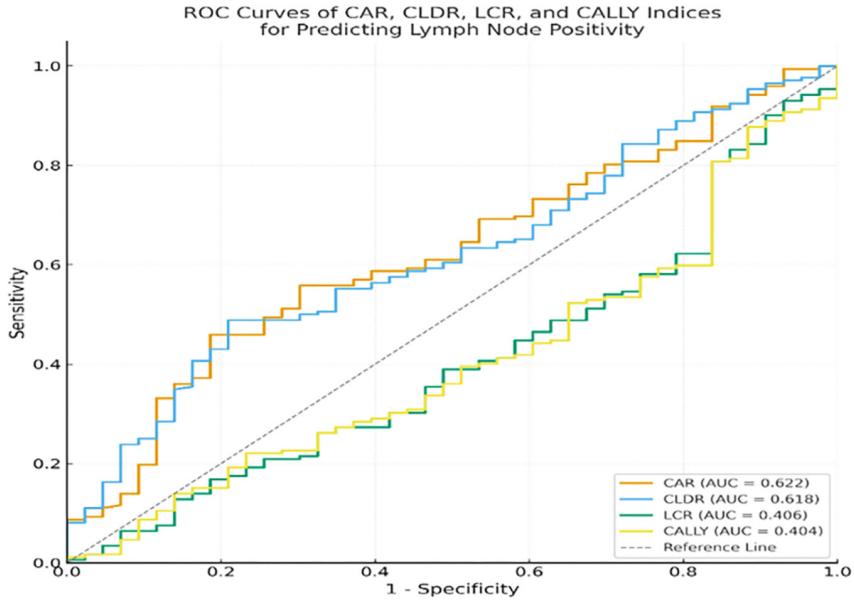

Figure 1. ROC curves of CAR, CLDR, LCR, and CALLY indices for predicting lymph node positivity
ROC: Receiver operating characteristic, CAR: C-reactive protein-to-albumin ratio, CLDR: C-reactive protein-to-lactate dehydrogenase ratio, LCR: Lymphocyte-to-C-reactive protein ratio, CALLY: C-reactive protein- albumin-lymphocyte index, AUC: Area under the curve

Table 3. Multivariate logistic regression analysis of predictors for lymph node positivity				
Variable		**OR**	**95% CI**	**p-value**
Age	-0.027	0.973	0.944-1.004	0.084
Sex (male)	0.051	1.052	0.467-2.370	0.903
Neoadjuvant therapy	-1.566	0.209	0.070-0.619	0.005
CAR	0.306	1.358	1.037-1.778	0.026
CLDR	2.992	19.931	1.688-235.309	0.018
LCR	0.054	1.055	0.824-1.351	0.634
CALLY	0.084	1.087	0.913-1.285	0.351
Model summary: χ^2=18.72, df=7, p<0.01, Nagelkerke R^2=0.286 OR: Odds ratio, CI: Confidence interval, CAR: C-reactive protein-to-albumin ratio, CLDR: C-reactive protein-to-lactate dehydrogenase ratio, LCR: Lymphocyte-to-C-reactive protein ratio, CALLY: C-reactive protein-albumin-lymphocyte index				

In the present study, four such indices were evaluated preoperatively to predict lymph node positivity. Among these, CAR and CLDR showed significant associations with nodal metastasis and remained independent predictors in multivariable analysis, even after adjusting for age, sex, and neoadjuvant therapy status. These findings highlight the importance of systemic inflammation and metabolic alterations in lymphatic spread. In contrast, LCR and CALLY demonstrated only borderline associations, suggesting weaker utility for preoperative assessment.

Our ROC analysis showed that CAR (AUC: 0.622) and CLDR (AUC: 0.618) had statistically significant but modest discriminative ability, with sensitivity and specificity around 58%. These results indicate that neither index alone is sufficient for reliable diagnosis, but that they may provide incremental value when combined with imaging and clinicopathological parameters.

The prognostic role of CAR has been consistently reported in gastric cancer, where it correlates with advanced stage, nodal involvement, and poor survival outcomes (18,19). As CRP reflects systemic inflammation and albumin indicates nutritional and functional status, CAR integrates two clinically relevant dimensions of host response. Importantly, our findings expand the evidence by identifying CLDR-a novel index incorporating CRP and LDH-as an independent predictor of nodal metastasis. LDH reflects tissue injury and tumor metabolism, and its integration with CRP may enhance risk stratification. To the best of our knowledge, this is one of the first studies to demonstrate the clinical relevance of CLDR in predicting lymph node involvement

in gastric cancer. These findings expand the current evidence by identifying CLDR as a promising biomarker and supporting its potential integration into predictive models for individualized clinical decision-making.

In contrast, prior research has suggested possible roles for LCR and CALLY in predicting prognosis and treatment response in gastrointestinal malignancies (20-22). However, our study indicates limited value for these indices in preoperative nodal assessment. Further large-scale, multicenter studies are warranted to confirm whether LCR and CALLY retain clinical significance in specific subgroups or when integrated into multi-parameter models.

Another strength of this study is that all laboratory parameters were obtained at diagnosis, before any therapy was initiated. This minimized the potential confounding effect of neoadjuvant treatment on biomarker levels. Subgroup analyses confirmed that including neoadjuvant therapy status in regression models did not alter the predictive significance of CAR and CLDR, reinforcing their role as baseline markers of disease biology.

Overall, our results demonstrate that CAR and CLDR are practical, inexpensive, and widely available biomarkers that can complement existing staging modalities. However, due to their modest accuracy, they should not be regarded as standalone diagnostic tools. Instead, integration of these indices into multimodal predictive strategies that combine imaging, histopathology, and clinical variables may offer improved accuracy and clinical applicability.

Study Limitations

This study has several limitations. First, its retrospective and single-center design may limit the generalizability of the findings. Although 215 patients were included, the sample size may still be insufficient to fully capture population heterogeneity, and larger multicenter cohorts are needed for validation. Second, while multivariable models adjusted for age, sex, and neoadjuvant therapy, other potentially relevant clinicopathological factors-such as tumor size, histology, or lymphovascular invasion-were unavailable and could not be included. Third, the diagnostic performance of the evaluated indices was modest, with AUC values below 0.70, restricting their role as standalone diagnostic tools. Finally, although some patients received neoadjuvant therapy, all laboratory measurements were obtained prior to treatment, minimizing confounding.

Despite these limitations, the study has notable strengths. It evaluated four easily obtainable, cost-effective laboratory indices in a relatively homogeneous cohort, and all measurements were performed before any therapy, ensuring reflection of baseline disease biology. Moreover, by demonstrating that both CAR and the novel CLDR independently predict lymph node positivity, this work contributes original evidence that may support the development of integrated predictive models in gastric cancer.

Conclusion

In this retrospective study, four inflammation- and nutrition-based indices were evaluated for their ability to predict lymph node positivity at the time of initial diagnosis in patients with gastric cancer. Among these, the CAR and the CLDR emerged as independent predictors, even after adjustment for age, sex, and neoadjuvant therapy. However, their modest diagnostic accuracy indicates that they should not be used as standalone tools. Instead, CAR and CLDR may provide complementary value when integrated with imaging and clinicopathological assessments to refine preoperative risk stratification.

As both indices are inexpensive, widely available, and based on routine laboratory parameters, their use may support more individualized surgical and treatment planning. Nevertheless, prospective multicenter studies with larger cohorts are required to validate these findings and to incorporate such biomarkers into clinically applicable predictive models.

Ethics

Ethics Committee Approval: Approval was obtained from the Bolu Abant Izzet Baysal University Non-Interventional Clinical Research Ethics Committee (approval no.: 2024/300, date: 19.11.2024).

Informed Consent: Retrospective, single-center observational study.

Footnotes

Authorship Contributions

Concept: M.F.K., F.B., M.S., Design: M.F.K., F.B., S.P.O., Data Collection or Processing: M.F.K., F.B., O.C., Analysis or Interpretation: M.F.K., F.B., B.O., Literature Search: M.F.K., F.B., S.P.O., M.S., Writing: M.F.K., F.B.

Conflicts of Interest: No conflict of interest were declared by the authors.

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Case Report

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Is Subcutaneous Seeding Possible Following PAIR Treatment of a Hydatid Cyst? A Case Report and Current Literature Review

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Abstract

Cystic echinococcosis (CE) is a widespread endemic helminthic disease caused by infection with the metacestodes of *Echinococcus granulosus*. This article reports the case of a 30-year-old woman who presented with a cystic lesion in the lumbar region. On the physical examination, cystic structures were palpated in the left gluteus maximus and posterior to the paravertebral muscles. Following a puncture, aspiration, injection, reaspiration (PAIR) procedure, an magnetic resonance imaging revealed a hyperintense cyst consistent with a newly developed CE1 hydatid cyst, likely resulting from subcutaneous seeding during the intervention. Various treatment modalities for hydatid disease have been described in the literature, including medical therapy, surgical approaches (laparoscopic, open, and robotic), and percutaneous techniques. In the majority of the articles, it has been indicated that PAIR treatment is associated with several risks and therefore should be recommended only for selected patients. This case demonstrates the effectiveness of PAIR therapy in reducing the number of daughter vesicles within hydatid cysts but also emphasizes the need for close follow-up due to the potential risk of new cyst formation caused by seeding during the procedure, particularly in atypical sites such as subcutaneous tissue. To the best of our knowledge, this is the first case described in the literature with this presentation.

Keywords: Echinococcus granulosus, subcutaneous tissue, physical examination, cysts, lumbosacral region

Introduction

Cystic Echinococcosis (CE) is a parasitic disease caused by *Echinococcus granulosus* and remains a major public health problem in endemic regions (1-3). Diagnosis is established through a combination of clinical examination, serological tests, imaging, and patient history (1,2). Currently, various treatment options are available, including medical therapy, surgery (laparoscopic, open, or robotic), and percutaneous approaches (1,4). Among these, the puncture, aspiration, injection, reaspiration (PAIR) technique is a percutaneous method used in the management of hydatid cysts and is primarily recommended for World Health Organization (WHO) type CE1 and CE3a cysts smaller than 10 cm in diameter (3).

This article reports the case of a 30-year-old woman who presented to the hospital with a cystic lesion in the lumbar region. Following PAIR treatment, the patient developed a newly formed subcutaneous cyst on the dorsal

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side, possibly due to seeding during the procedure. To the best of our knowledge, this is the first case described in the literature with such a presentation. Current literature lacks sufficient data regarding the seeding potential of PAIR therapy.

Case Report

Our case involves a 30-year-old female refugee patient who presented to the hospital in 2021 with a cystic lesion in the lumbar region. All necessary informed consent was obtained from the patient prior to the procedures. Her ultrasonography revealed a 12 cm cystic lesion with septal components. A lumbar magnetic resonance imaging (MRI) was subsequently performed, which demonstrated a CE3b hydatid cyst located paravertebrally in a T2-weighted sagittal section (Figure 1). In addition, a 7 cm renal hydatid cyst was identified. On physical examination, cystic structures were palpable posterior to the paravertebral muscles and within the left gluteus maximus.

After undergoing abscess drainage at another public hospital, the patient subsequently presented to our hospital. Her prior medical history was reviewed, and follow-up MRI scans were requested. Post-drainage imaging revealed a CE3b hydatid cyst located paravertebrally, with a markedly reduced number of hyperintense daughter vesicles in the T2-weighted sagittal MR scan. Additionally, an increase in heterogeneous hypointense fragments (germinative membranes, dead scolices, etc.) was noted on T2A images compared to pre-treatment (Figure 2). In T2-weighted axial section MRI, dead scolices and remnants of the germinative membrane appeared hypointense within the paravertebral hydatid cyst (Figure 3). Cardiac MRI further demonstrated a 3 cm lesion, presumed to be a hydatid cyst, located on the right ventricular side of the septum. Left ventricular systolic function was normal. The patient received albendazole therapy with a dosage of two doses of 400 mg.

Following albendazole treatment, the patient was referred to the interventional radiology department for PAIR therapy. During the subsequent physical examination, newly developed cystic structures were palpable posterior to the paravertebral muscles. Post-therapeutic control computed tomography (CT) scans demonstrated a hyperintense cyst, located within the muscle plane beneath the skin (Figure 4), consistent with a newly formed CE1 hydatid cyst, likely resulting from seeding into the subcutaneous tissue during PAIR therapy.

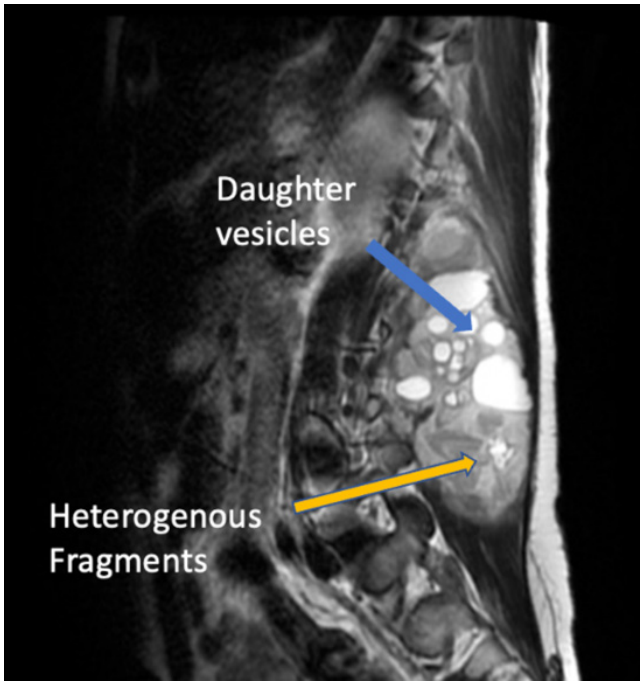

Figure 1. The CE3b hydatid cyst, which is situated in the paravertebral region on T2-weighted sagittal section MRI, contains daughter vesicles that are clearly hyperintense on T2A and contain heterogeneous hypointense fragments in the lower part of the cyst
CE: Cystic echinococcosis, MRI: Magnetic resonance imaging

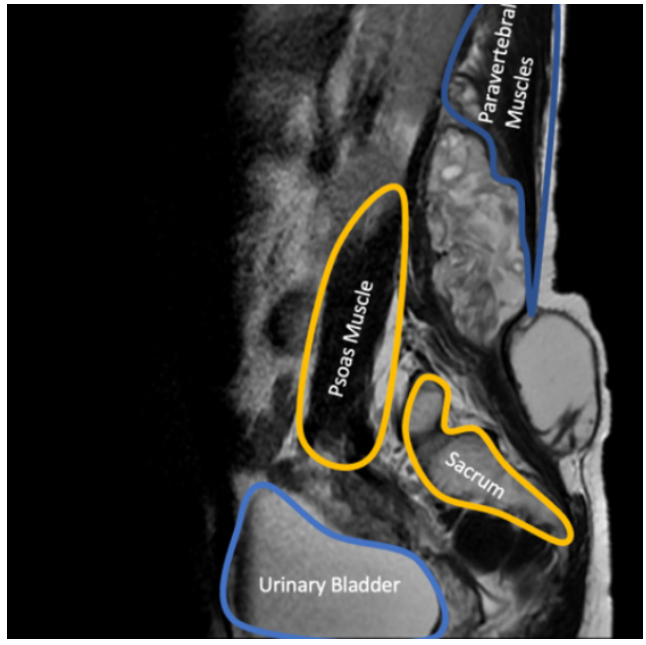

Figure 2. The T2-weighted sagittal section MRI demonstrates a CE3b hydatid cyst located paravertebrally. The cyst contains fewer daughter vesicles, which are visibly hyperintense on T2A, and an increase in heterogeneous hypointense fragments on T2A (germinative membranes, dead scolices, etc.) compared to before treatment
CE: Cystic echinococcosis, MRI: Magnetic resonance imaging

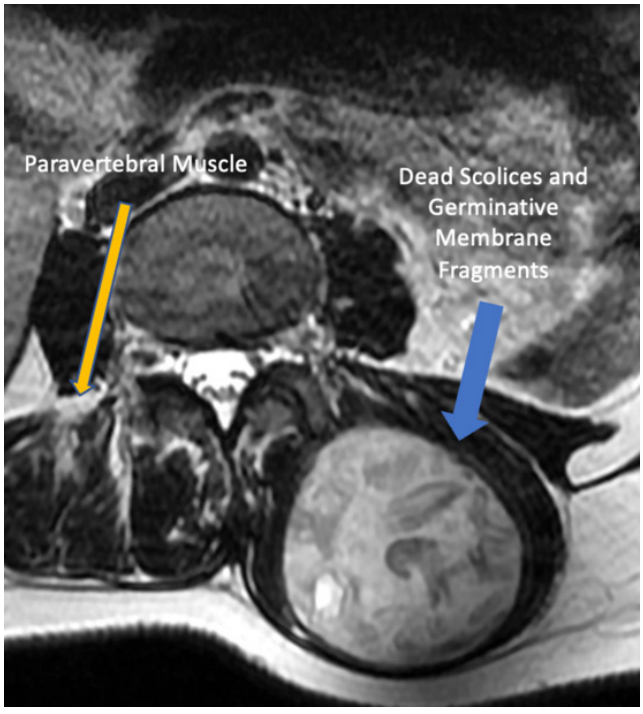

Figure 3. On T2-weighted axial section MRI, dead scolexes and germinative membrane fragments are observed as hypointense in the paravertebral muscle hydatid cyst

MRI: Magnetic resonance imaging

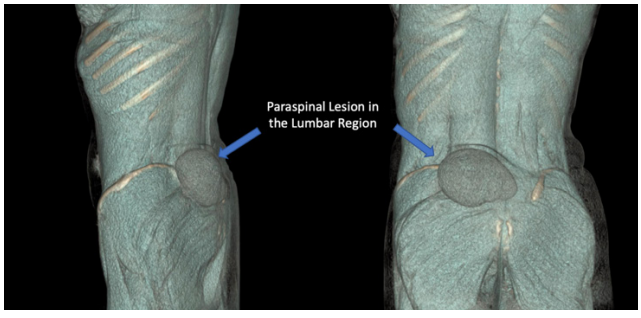

Figure 4. The 3D image produced by abdomen CT reveals a paraspinal lesion resulting in swelling of the skin in the lumbar region, achieved by volume rendering techniques

3D: Three-dimensional, CT: Computed tomography

Control imaging revealed hydatid cysts in the liver, left kidney, paravertebral muscles at the L4-L5 and S1 levels, and in the gluteus maximus muscle, all identified on the abdominal CT scan. The patient also underwent the modified catheterization technique (MoCaT) procedure, and a cytological analysis was conducted, confirming the diagnosis of a hydatid cyst. After this treatment, however, the patient did not continue with the planned management, and therefore her current status remains unknown.

Discussion

Cystic Echinococcosis is a helminthic disease that is widely endemic and is primarily caused by infection with Echinococcus granulosus (1,2,5-7). In 70% of cases, the liver is the primary site of involvement, though the lungs and other organs can also be affected (1,4,5,8-10). Case reports in the literature rarely document muscle involvement in hydatid cysts. It is considered unusual due to lactic acid levels and muscle contractions (7).

There is no single optimal medical treatment for hydatid cysts, as noted by Bhalla et al. (1) however, albendazole has shown therapeutic potential. In selected patients for whom surgery is not feasible, the PAIR technique may be applied. Bhalla et al. (1) also suggested that PAIR is indicated for cysts classified as WHO CE1, CE2, and CE3; for infected cysts; for pregnant women or patients refusing surgery; for recurrent cases unresponsive to medical therapy alone; and for multiple cysts that are accessible to puncture. In addition, Theodossis emphasized that guided interventional approaches should be considered for patients refusing surgery while also highlighting that surgical management remains the most effective treatment modality (11).

Although surgery remains the most effective treatment according to the literature, Aziz et al. (3), in their 2025 article, emphasized that each patient should be individually assessed to determine an appropriate treatment plan. In our case, after abscess drainage, the patient was given albendazole treatment by the infectious disease department, followed by PAIR therapy, which is consistent with the indications described in the literature for patients unsuitable for surgery.

Puncture, aspiration, injection, reaspiration has been reported to have a high recurrence rate and spillage risk, according to Mihetiu et al. (5). Eckert and Deplazes (2) indicate that the PAIR technique should always be performed by experienced physicians to minimize complications. In another retrospective analysis published in 2024, Mihetiu et al. (8) further indicated that although PAIR treatment is minimally invasive, shortens hospital stay, can be performed under local anesthesia, and is applicable in patients refusing surgery, it is also associated with a higher recurrence rate and contamination risk. Although numerous articles in the literature highlight the potential complications of this procedure, such as spillage, the present case provides imaging evidence of these complications and raises awareness of the issue. Finally, in our case, the MoCaT procedure—described by Akhan (12) in the early 2000s and used for the treatment of WHO CE2 and CE3b type cysts—was applied as the final treatment modality (4).

Our case is distinctive because of the unusual sites of the hydatid cysts' involvement and, to the best of our knowledge, represents the first documented instance of subcutaneous seeding following PAIR treatment of hydatid cysts. This case highlights the potential for the formation of new cysts due to seeding during treatment, particularly in atypical locations such as subcutaneous tissue. In managing such cases, close monitoring and careful follow-up are imperative.

Ethics

Informed Consent: All necessary informed consent was obtained from the patient prior to the procedures

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.C., M.B.A., Z.O.E., V.E., F.S., Concept: K.C., M.B.A., Z.O.E., V.E., F.S., Design: K.C., M.B.A., Data Collection or Processing: K.C., M.B.A., Z.O.E., V.E., F.S., Analysis or Interpretation: K.C., M.B.A., Literature Search: K.C., Writing: K.C., M.B.A., Z.O.E., V.E., F.S., Concept: K.C., M.B.A., Z.O.E., V.E., F.S.

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Letter to the Editor

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Management of a Rare and Unusual Case of Sebaceous Carcinoma in a Kidney Transplant Patient

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To the Editor,

Sebaceous carcinoma (SC) is a rare malignant adnexal neoplasm that shows sebocytic differentiation. It usually involves sun-exposed areas, particularly the head and neck. However, immunosuppression, such as that seen in organ transplant recipients, increases the likelihood of atypical and aggressive cutaneous malignancies, including SC (1). This report presents a rare case of rapidly growing SC in a non-ultraviolet (UV) exposed area in a kidney transplant patient under chronic immunosuppression.

A 60-year-old fair-skinned male presented with a rapidly enlarging skin lesion on the left upper trunk, which had developed over the previous 6 months. Eleven years earlier, he had undergone a kidney transplant and was receiving oral prednisone, tacrolimus, and azathioprine for immunosuppression.

Dermatological examination revealed a 2 cm, exophytic, non-pedunculated nodule with yellow and pink hues on an erythematous base, accompanied by signs of inflammation (Figure 1). Excisional biopsy was performed with primary closure. Histopathological analysis confirmed SC (Figure 2). Although no tumor was observed at the surgical margins, the lesion was within 1 mm of the closest margin.

Postoperative staging included full-body computed tomography and ultrasonographic evaluation of the left axillary region. No metastatic or pathological lymph nodes were detected. Due to the close margin, a wider re-excision was carried out. Immunosuppressive therapy continued unchanged. The patient was followed for one year without recurrence or metastasis.

Sebaceous carcinoma is a rare but aggressive tumor with metastatic potential, particularly in immunocompromised hosts. The presented case is notable for its trunk localization, which is atypical due to the limited exposure to UV radiation. Immunosuppressive agents—particularly calcineurin inhibitors such as tacrolimus—are known to increase cancer susceptibility (2).

Surgical excision remains the primary treatment approach for SC, and lymph node dissection or adjuvant therapies may be considered depending on the stage and metastatic involvement. In our case, the absence of lymphovascular invasion or metastatic disease justified treatment with surgical excision alone. Given the reported aggressive nature of SC, close clinical surveillance was maintained for one year, during which no adverse findings were observed (3).

Sebaceous carcinoma should be considered in the differential diagnosis of rapidly growing skin lesions in immunosuppressed individuals, even when located in non–sun exposed regions. Early diagnosis and adequate surgical intervention are essential. This case underscores the importance of vigilant skin examination and monitoring in kidney transplant recipients under chronic immunosuppressive therapy.

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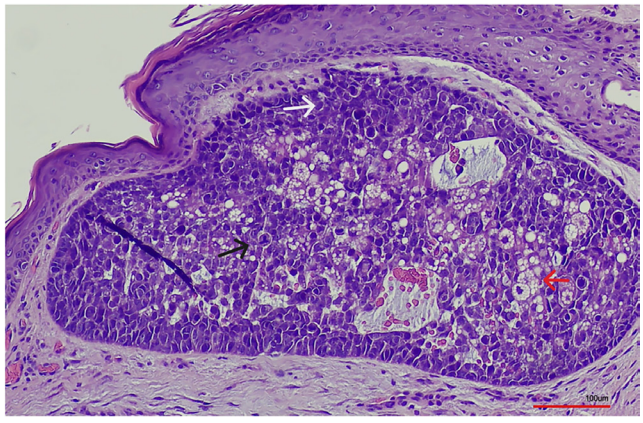

Figure 1. Two cm, exophytic, non-pedunculated nodule with yellow and pink hues on an erythematous base, accompanied by signs of inflammation
Black arrow: atypical mitosis; red arrow: multivacuolated sebaceous cells; white arrow: basaloid cells (HE, 10X10)

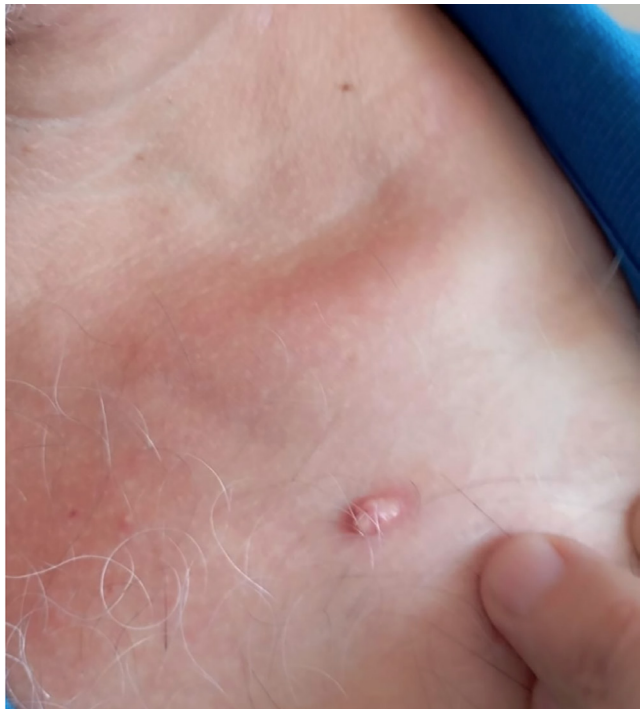

Figure 2. Atypical mitose and numerous mitoses are observed in the atypical basaloid cells

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.A., I.C., T.K., Concept: B.A., I.C., T.K., Design: B.A., I.C., T.K., Data Collection or Processing: B.A., I.C., T.K., Analysis or Interpretation: B.A., I.C., T.K., Literature Search: B.A., I.C., T.K., Writing: B.A., I.C., T.K.

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