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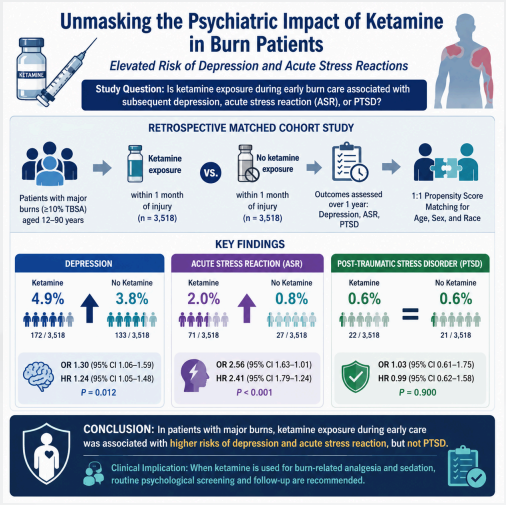

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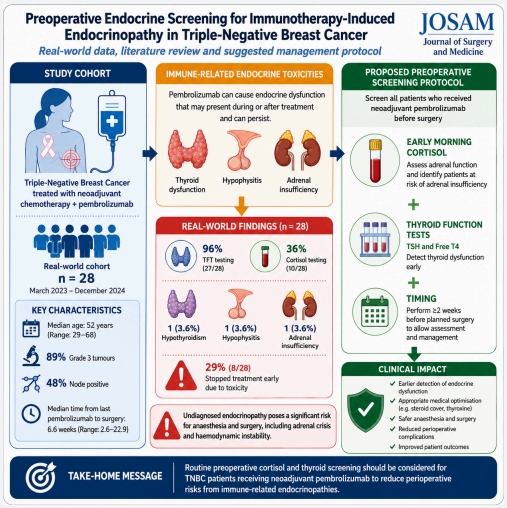

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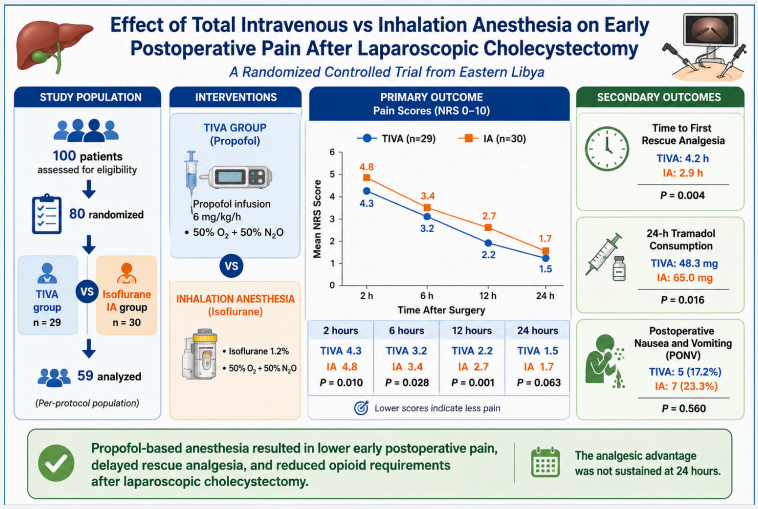

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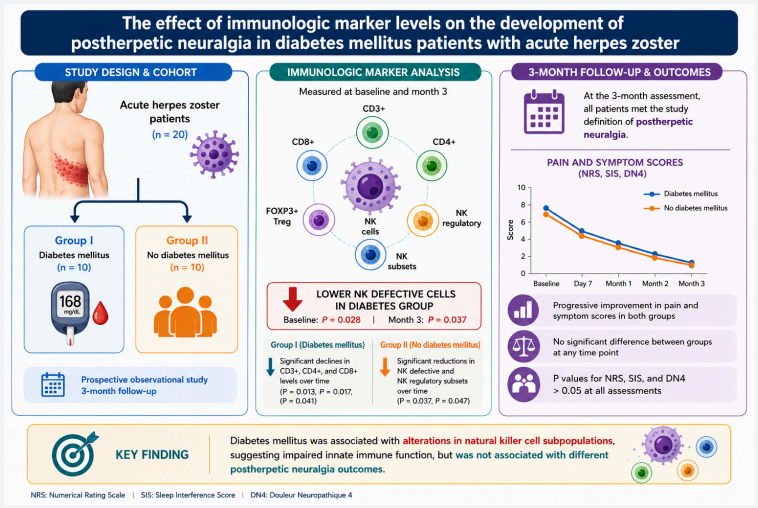

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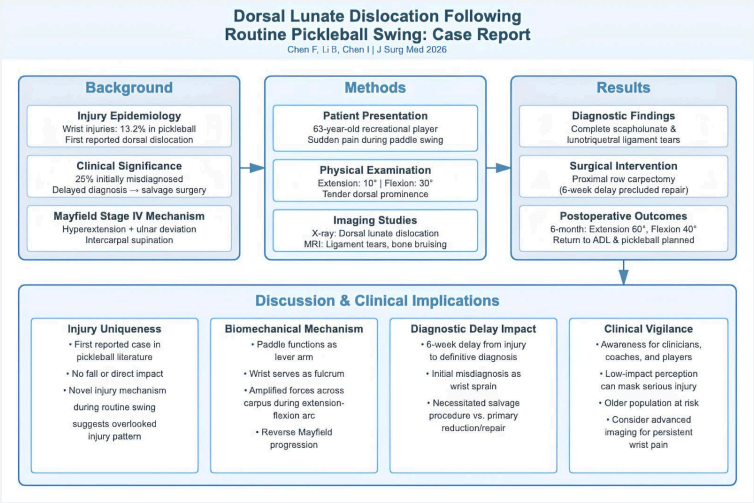

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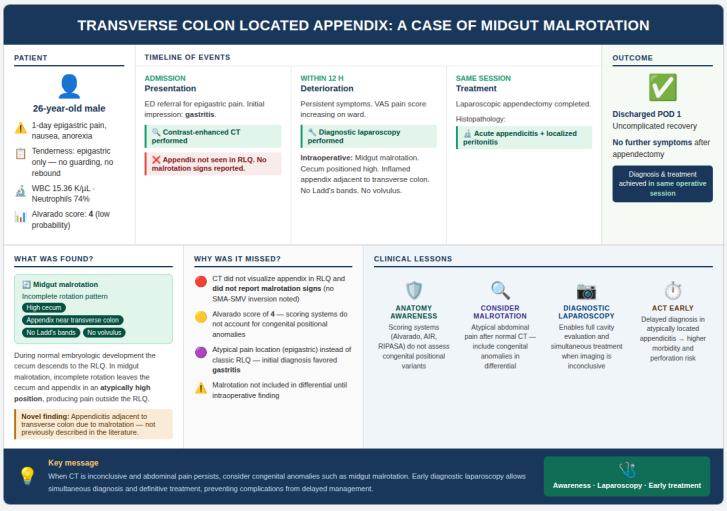

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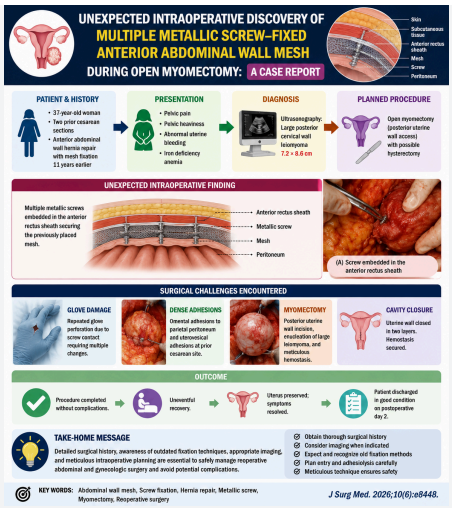

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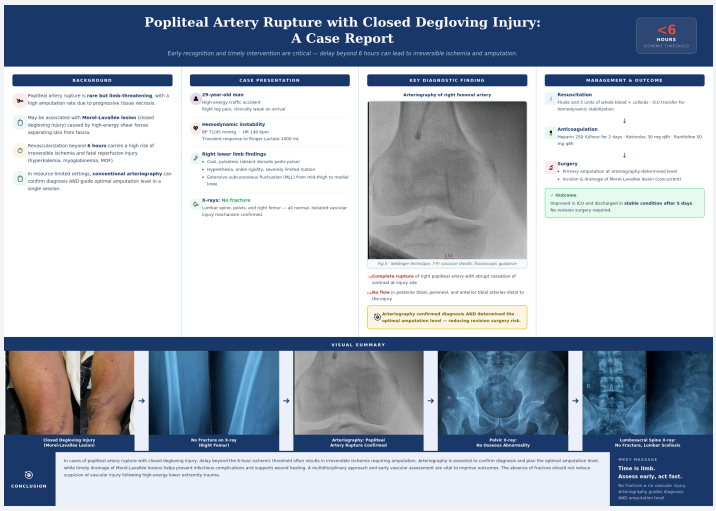

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Popliteal artery rupture with closed degloving injury

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The effect of total intravenous versus inhalation anesthesia on early postoperative pain after laparoscopic cholecystectomy: A randomized controlled trial from Eastern Libya

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Ethics Committee Approval
The study was approved by the Ethics Committee of the College of Medical Technology, Derna, Libya, on February 5, 2025 (CMTD 02-025). The research was conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
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Abstract

Background/Aim: Effective postoperative pain (POP) control remains a major determinant of recovery after laparoscopic cholecystectomy (LC), particularly in resource-limited healthcare settings such as Libya. Although propofol-based total intravenous anesthesia (TIVA) may improve early analgesia compared with isoflurane-based inhalation anesthesia (IA), comparative evidence from these settings is limited. This trial compared acute POP trajectories during the first 24 hours after LC under these two anesthetic techniques in Eastern Libya.

Methods: This prospective, double-blind, randomized controlled trial was conducted at two public hospitals in Eastern Libya between February and May 2025. Fifty-nine patients scheduled for elective LC were analyzed after randomization to propofol-based TIVA (n = 29) or isoflurane-based IA (n = 30). The primary outcome was pain intensity measured with the Numerical Rating Scale (NRS; 0-10) at 2, 6, 12, and 24 hours postoperatively. Data were analyzed using SPSS version 26.

Results: A significant anesthesia-by-time interaction was observed for postoperative pain scores ($F[2.92, 166.63] = 11.67$, $P < 0.001$). Pairwise comparisons showed lower mean pain scores in the TIVA group at 2 hours [4.3 (0.8) vs. 4.8 (0.8), $P = 0.010$] and 12 hours [2.2 (0.5) vs. 2.7 (0.6), $P = 0.001$]. The 6-hour difference was smaller [3.2 (0.6) vs. 3.4 (0.7), $P = 0.028$], and no significant difference was observed at 24 hours [1.5 (0.3) vs. 1.7 (0.4), $P = 0.063$]. The main effect of anesthetic type was not significant ($F[1, 57] = 2.21$, $P = 0.143$).

Conclusion: Propofol-based TIVA was associated with modestly lower early postoperative pain scores after LC compared with isoflurane-based IA, but this benefit was not sustained at 24 hours. Selection of anesthetic technique should consider whether early POP control is a clinical priority within the broader multimodal analgesia strategy.

Keywords: propofol, isoflurane, laparoscopic cholecystectomy, postoperative pain, Libya

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Introduction

Postoperative pain (POP) is a key determinant of patient satisfaction, quality of recovery, and healthcare utilization after surgery. Although laparoscopic cholecystectomy (LC) is considered minimally invasive, it is frequently associated with moderate to severe acute pain, particularly during the first 24 postoperative hours [1, 2]. In Libya, where healthcare resources have been constrained by ongoing instability, POP management remains suboptimal, and approximately 55% of patients experience significant pain on the first postoperative day [3].

Effective POP control requires multimodal strategies and may also be influenced by the choice of anesthetic maintenance technique. The two main approaches for maintaining general anesthesia are total intravenous anesthesia (TIVA) with propofol and inhalation anesthesia (IA) with volatile agents such as isoflurane [4]. Recent evidence suggests that these approaches may have different effects on postoperative nociception and inflammatory responses [5].

Beyond its hypnotic effects, propofol has anti-inflammatory and potential analgesic-sparing properties that may modulate early POP [6]. In contrast, volatile anesthetics may contribute to nociceptive sensitization through receptor-mediated pathways [7]. Clinical studies comparing these techniques have produced conflicting results. Some studies have reported lower early pain scores and reduced opioid consumption with propofol-based TIVA [8, 9], whereas others have found no significant differences in overall pain outcomes [10, 11]. These discrepancies may reflect differences in surgical procedures, analgesic protocols, and timing of pain assessment.

The analgesic efficacy of propofol-based TIVA may depend on several factors, including surgical technique and perioperative analgesic management [12]. Although the comparative effects of TIVA and IA on POP have been studied [13, 14], findings regarding the temporal pattern of analgesia remain inconsistent. Moreover, no study has evaluated this question in the Libyan healthcare context or in similar resource-constrained settings, where postoperative care pathways may differ. This randomized controlled trial (RCT) aimed to compare the trajectory of acute POP during the first 24 hours after LC in patients receiving either propofol-based TIVA or isoflurane-based IA in Eastern Libyan hospitals.

Materials and methods

Study design and setting

We conducted a prospective, double-blind, parallel-group RCT at two public hospitals in Eastern Libya, Derna and Shahat, between February and May 2025. The study protocol was approved by the Ethics Committee of the College of Medical Technology, Derna (CMTD 02-025), and was registered locally (The Libya Clinical Research Registry, LCRR/2025/02/003270). Written informed consent was obtained from all participants. The trial was reported in accordance with the CONSORT guidelines [15]. All study procedures complied with the Declaration of Helsinki.

Participants

Eligible participants were adults aged 18 years or older who were scheduled for elective LC and had an American Society of Anesthesiologists (ASA) physical status of I or II. Exclusion criteria were psychiatric disorders, known drug allergies, planned discharge within 24 hours, chronic pain conditions requiring regular analgesics, anticipated intensive care unit (ICU) admission, concomitant surgical procedures, pregnancy, and inability to provide informed consent. The primary outcome was the between-group difference in NRS pain score trajectories during the first 24 postoperative hours. A key secondary outcome was the 24-hour pain score. Rescue analgesic timing, 24-hour tramadol consumption, and postoperative nausea and vomiting (PONV) were also recorded.

Randomization and blinding

Eligible participants were randomly assigned in a 1:1 ratio using computer-generated block randomization with a block size of four. Sealed, opaque envelopes prepared by an independent statistician were opened immediately before induction by an anesthetist who was not involved in postoperative assessment. Participants, postoperative outcome assessors, and data analysts were blinded to group allocation.

Anesthesia protocol

All patients received intravenous atropine 0.5 mg and midazolam 0.03 mg/kg as premedication ten minutes before induction. Anesthesia was induced with fentanyl 1.5 micrograms/kg, propofol 1.5 mg/kg, and rocuronium 0.5 mg/kg, followed by tracheal intubation and orogastric tube insertion.

The intervention group received propofol-based intravenous anaesthesia maintained with a continuous propofol infusion (6 mg/kg/hour) together with a gas mixture of 50% oxygen and 50% nitrous oxide. No volatile anaesthetic agent was administered. The IA group received 1.2% isoflurane with the same gas mixture. Anesthetic depth was adjusted to maintain hemodynamic stability. All port sites were infiltrated with 0.25% bupivacaine before incision. Dexamethasone 8 mg intravenously was administered for PONV prophylaxis. Neuromuscular blockade was reversed with neostigmine 2.5 mg and atropine 0.5 mg, and patients were extubated after adequate recovery.

Postoperative analgesia

The standardized postoperative analgesic regimen consisted of intravenous paracetamol 1 g every 6 hours and ketorolac 30 mg every 8 hours for 24 hours. Rescue analgesia with intravenous tramadol 50 mg was available on patient request or when the NRS score was 4 or higher. Total rescue analgesic consumption was recorded.

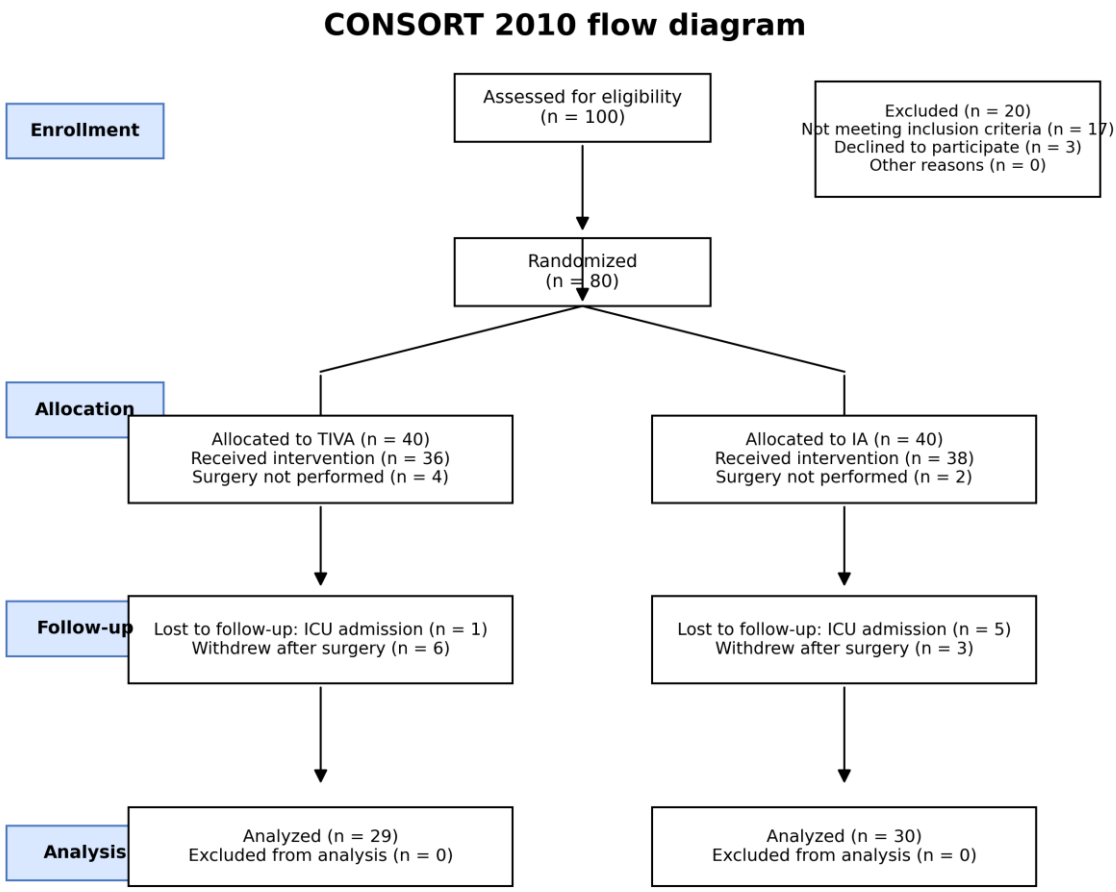
Sample size calculation

Based on data from Wong et al. [9], detecting a mean difference of 1.0 point on the NRS with an SD of 1.5, 80% power, and an alpha level of 0.05 required 36 patients per group. After allowing for a 15% attrition rate, the target recruitment was 80 patients, with 40 participants per group.

Statistical analysis

Data were analyzed using SPSS version 26. Normality was assessed with the Shapiro-Wilk test. Descriptive statistics are presented as mean (SD) or frequency (n). The primary analysis used repeated-measures analysis of variance to examine the interaction between anesthetic type and time on postoperative pain scores. When appropriate, Greenhouse-Geisser-corrected degrees of freedom were reported. Post hoc comparisons were performed using independent-samples t tests with Bonferroni correction. A

Figure 1. CONSORT flow diagram for the study



two-tailed *P*-value less than 0.05 was considered statistically significant, except where a Bonferroni-adjusted threshold was specified.

The primary analysis was conducted on a per-protocol basis, including participants who completed surgery and all scheduled postoperative pain assessments. Participants who were randomized but did not undergo surgery, required postoperative ICU admission, or withdrew before completion of follow-up were excluded from the final analysis.

Results

Participant flow and baseline characteristics

Of the 100 patients assessed for eligibility, 80 were randomized and 59 completed the study and were included in the final analysis (Figure 1). The main reasons for non-inclusion or postrandomization non-completion were failure to meet inclusion criteria (n = 17), declining participation (n = 3), surgery not performed after allocation (n = 6), postoperative ICU admission (n = 6), and withdrawal after surgery (n = 9).

Baseline demographic and clinical characteristics were comparable between the groups (Table 1). The mean age was 32.1 (11.5) years in the TIVA group and 29.9 (10.8) years in the IA group (*P* = 0.450). Overall, females comprised 57.6% of the sample and males comprised 42.4%. The distribution of anesthetic allocation was similar between groups, with 29 patients in the TIVA group and 30 patients in the IA group.

Table 1. Baseline characteristics of study participants

Characteristic	TIVA group (n = 29)	IA group (n = 30)	*P*-value
Female sex, n (%)	16 (55.2)	18 (60.0)	0.710
Age (years), mean (SD)	32.1 (11.5)	29.9 (10.8)	0.450
ASA score I/II, n (%)	20 (69.0)/9 (31.0)	22 (73.0)/8 (27.0)	0.790
Chronic pain history, n (%)	13 (44.8)	12 (40.0)	0.710
BMI (kg/m²), mean (SD)	26.8 (4.2)	27.1 (3.9)	0.770
Surgery duration (min), mean (SD)	68.5 (18.2)	71.3 (16.7)	0.530

ASA: American Society of Anesthesiologists, BMI: body mass index, IA: inhalation anesthesia, n: number, SD: standard deviation, TIVA: total intravenous anesthesia. *P* < 0.05 was considered statistically significant.

Primary repeated-measures analysis

There was no statistically significant main effect of anesthetic type on mean pain scores across the 24-hour assessment period. Mean pain scores across all time points were 5.2 (1.5) for TIVA and 5.5 (0.96) for IA (F[1, 57] = 2.21, *P* = 0.143, partial eta squared = 0.037), indicating a small effect size. However, the main effect of time and the time-by-anesthetic type interaction were statistically significant, indicating that pain scores changed over time and that the pattern of change differed between groups (Table 2).

Table 2. Repeated-measures analysis of pain scores by anesthetic group and time

Effect	df	F	*P*-value	Partial eta squared
Main effect of group	1, 57	2.21	0.143	0.037
Main effect of time	2.92, 166.63	32.52	<0.001	0.363
Time × group interaction	2.92, 166.63	11.67	<0.001	0.170

df: degrees of freedom. Greenhouse-Geisser-corrected degrees of freedom are shown for time and interaction effects. *P* < 0.05 was considered statistically significant.

Between-group comparisons by time point

Repeated-measures analysis of variance showed a significant interaction between anesthetic type and time (F[2.92, 66.63] = 11.67, *P* < 0.001, partial eta squared = 0.170). The main effect of time was also significant (F[2.92, 166.63] = 32.52, *P* <

0.001, partial eta squared = 0.363), whereas the main effect of group was not significant (F[1, 57] = 2.21, *P* = 0.143, partial eta squared = 0.037).

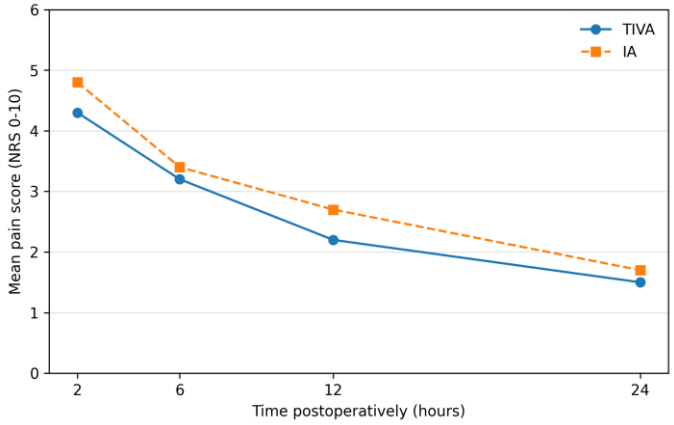
Mean pain scores were lower in the TIVA group at 2 hours [4.3 (0.8) vs. 4.8 (0.8), *P* = 0.010], 6 hours [3.2 (0.6) vs. 3.4 (0.7), *P* = 0.028], and 12 hours [2.2 (0.5) vs. 2.7 (0.6), *P* = 0.001]. At 24 hours, the difference between TIVA and IA was not statistically significant [1.5 (0.3) vs. 1.7 (0.4), *P* = 0.063]. With a Bonferroni-adjusted threshold of *P* < 0.0125 for four time-point comparisons, the 2-hour and 12-hour differences remained statistically significant, whereas the 6-hour and 24-hour differences did not (Table 3, Figure 2).

Table 3. Postoperative pain scores (NRS 0-10) by time point

Time point	TIVA group (n = 29) mean (SD)	IA group (n = 30) mean (SD)	Total (n = 59) mean (SD)	Mean difference (95% CI)	P-value
2 hours	4.3 (0.8)	4.8 (0.8)	4.6 (0.8)	-0.50 (-0.92 to -0.08)	0.010
6 hours	3.2 (0.6)	3.4 (0.7)	3.3 (0.7)	-0.20 (-0.54 to 0.14)	0.023
12 hours	2.2 (0.5)	2.7 (0.6)	2.5 (0.6)	-0.50 (-0.79 to -0.21)	0.001
24 hours	1.5 (0.3)	1.7 (0.4)	1.6 (0.4)	-0.20 (-0.38 to -0.02)	0.063

CI: confidence interval, IA: inhalation anesthesia, NRS: Numerical Rating Scale, SD: standard deviation, TIVA: total intravenous anesthesia. A Bonferroni-adjusted threshold of *P* < 0.0125 applies to the four time-point comparisons; unadjusted *P*-values are shown as reported.

Figure 2. Mean pain scores by anesthetic group over time



Rescue analgesia and postoperative nausea and vomiting

Secondary postoperative outcomes are summarized in Table 4. Patients in the TIVA group requested rescue analgesia significantly later than those in the IA group, with a mean difference of 1.3 hours (95% CI: 0.45 to 2.15; *P* = 0.004). Total tramadol consumption during the first 24 postoperative hours was significantly lower in the TIVA group, with a mean difference of -16.7 mg (95% CI: -29.9 to -3.5; *P* = 0.016). The incidence of postoperative nausea and vomiting was numerically lower in the TIVA group (17.2% vs. 23.3%), although the difference was not statistically significant (risk difference: -6.1%, 95% CI: -26.6% to 14.4%; *P* = 0.560).

Table 4. Secondary postoperative outcomes

Outcome	TIVA (n = 29)	IA (n = 30)	Mean Difference (95% CI)	*P*-value
Time to first rescue analgesia (hours), mean (SD)	4.2 (1.8)	2.9 (1.5)	+1.3 hours (0.45 to 2.15)	0.004
Total tramadol consumption in 24 hours (mg), mean (SD)	48.3 (22.5)	65.0 (28.1)	-16.7 mg (-29.9 to -3.5)	0.016
PONV, n (%)	5 (17.2)	7 (23.3)	-6.1% (-26.6% to 14.4%)	0.560

IA: inhalation anaesthesia, PONV: postoperative nausea and vomiting, SD: standard deviation; TIVA: total intravenous anaesthesia, CI: confidence interval

Discussion

This RCT evaluated the effect of propofol-based TIVA on early POP among Libyan patients undergoing LC. The findings suggest that TIVA was associated with lower early pain scores and reduced rescue opioid consumption compared with isoflurane-based IA; however, the between-group difference was not sustained at 24 hours.

Previous studies have reported inconsistent findings regarding differences in postoperative pain between TIVA and IA [9, 12]. In the present study, propofol-based TIVA was associated with modestly lower pain scores during the early postoperative period. The absence of a significant difference at 24 hours suggests that any analgesic benefit of propofol-based TIVA may be time-limited and most relevant during the immediate recovery phase.

Pain scores decreased over time in both groups, which is consistent with the expected postoperative recovery trajectory after LC under standardized multimodal analgesia. Adequate early POP control remains clinically important because poorly controlled pain can impair mobilization, reduce patient satisfaction, and delay recovery [16].

A relatively small proportion of patients in this Libyan cohort used opioid rescue analgesia, which is consistent with previous Libyan reports [3, 17]. The present findings are also broadly consistent with studies by Ortiz et al. [10] and Wong et al. [9], which did not demonstrate a sustained overall pain advantage for propofol-based anesthesia. Conversely, the early reduction in pain scores observed here aligns with reports suggesting an early analgesic benefit of propofol-based TIVA [12, 18].

Compared with an Iranian RCT [19] and an Indian observational study [20], patients in the present cohort appeared to report relatively higher postoperative pain levels. These differences may reflect variation in analgesic protocols, healthcare system resources, pain assessment practices, and cultural factors influencing pain reporting. Previous studies have reported broad ranges of acute POP prevalence across settings [21, 22], underscoring the importance of context-specific pain management research.

Limitations

Several limitations should be acknowledged. First, the final sample size of 59 patients was below the planned target, which may have limited the statistical power to detect smaller or sustained between-group differences. Second, recruitment from two centers in Eastern Libya may limit the generalizability of the findings to other regions and healthcare systems. Third, although the postoperative analgesic regimen was standardized, individual variation in pain perception and use of non-pharmacological pain-relief measures could not be fully controlled. Fourth, the study did not evaluate longer-term outcomes, such as chronic postsurgical pain, which may also be influenced by anesthetic technique.

Conclusion

Propofol-based TIVA was associated with lower early postoperative pain scores, delayed rescue analgesic request, and reduced 24-hour tramadol consumption after LC compared with isoflurane-based IA. However, the analgesic advantage was not sustained at 24 hours. These findings support selective use of propofol-based TIVA when early POP control is a priority, particularly within enhanced recovery or early-discharge pathways.

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Unmasking the psychiatric impact of ketamine in burn patients: Elevated risk of depression and acute stress reactions

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Ethical Approval
This study utilized secondary analysis of routinely collected, de-identified health records. As such, it did not involve direct patient contact and was exempt from informed consent requirements.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Ketamine is frequently administered for analgesia and sedation during burn dressing changes, but its potential psychological impact remains a concern. This study assessed whether ketamine exposure during early burn care is associated with subsequent depression, acute stress reaction (ASR), or post-traumatic stress disorder (PTSD) in patients with major burns.

Methods: A retrospective cohort study was conducted using the TriNetX global health research network. Patients aged 12 to 90 years with burn injuries involving ≥10% total body surface area were included. Two cohorts were defined according to ketamine exposure within one month of injury. Propensity score matching (1:1) was performed for age, sex, and race, yielding 3,518 patients per group. Outcomes were evaluated over one year using diagnostic codes for depression, ASR, and PTSD. Analyses included risk estimates, odds ratios, Kaplan-Meier methods, and hazard ratios.

Results: Ketamine exposure was associated with a higher risk of depression (4.9% vs. 3.8%; odds ratio 1.30; hazard ratio 1.24; $P = 0.012$) and ASR (2.0% vs. 0.8%; odds ratio 2.56; hazard ratio 2.41; $P < 0.001$). PTSD incidence was similar between cohorts (0.6% vs. 0.6%; odds ratio 1.03; hazard ratio 0.99; $P = 0.952$).

Conclusion: In patients with major burns, ketamine exposure during early care was associated with increased risks of depression and ASR, but not PTSD. These findings support routine psychological screening and follow-up when ketamine is used for burn-related analgesia and sedation.

Keywords: ketamine, burn injury, depression, acute stress reaction

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Introduction

Ketamine is widely used in clinical practice because of its anesthetic, analgesic, and dissociative properties [1]. It acts primarily through noncompetitive antagonism of the N-methyl-D-aspartate (NMDA) receptor [2]. Its favorable safety profile, including preservation of airway reflexes and cardiovascular stability, supports its use in pediatric anesthesia, procedural sedation, and trauma settings [3, 4].

Burn injuries are strongly associated with psychological morbidity, particularly depression and post-traumatic stress disorder (PTSD) [5]. The traumatic nature of the injury, severe pain, prolonged hospitalization, disfigurement, and functional limitations can contribute to persistent mental health challenges [6]. Depression is common among burn survivors and may emerge early in recovery, with symptoms that can persist beyond physical healing [6, 7]. Post-traumatic stress symptoms and broader psychological problems can also affect rehabilitation and quality of life after burn injury [8, 9].

Ketamine is commonly used for procedural analgesia and sedation because of its rapid onset and preservation of airway reflexes [3, 4]. Nevertheless, concern persists regarding potential psychological effects, including dissociation and psychotomimetic experiences, which may influence emotional processing after trauma [10, 11]. Clarifying psychiatric outcomes associated with ketamine in burn care is important to balance effective pain control with mental health risk mitigation.

This study evaluated depression, acute stress reaction, and PTSD in patients with burns involving ≥10% total body surface area, comparing those who received ketamine within one month of injury with those who did not.

Materials and methods

Study design and data source

This retrospective cohort study used TriNetX, a global federated health research network that provides access to de-identified electronic medical records from 93 healthcare organizations. The platform contains more than 134 million patient records and supports large-scale observational analyses across diverse populations.

A total of 29,184 patients with burn injuries were initially identified. Patients were categorized into two cohorts according to ketamine exposure within one month of injury. The exposed cohort comprised patients with burns involving ≥10% total body surface area who received ketamine within one month after injury. The unexposed cohort comprised patients with comparable burn extent who did not receive ketamine during the same timeframe.

Participants and eligibility criteria

Eligible patients were aged 12 to 90 years and had burn injuries involving ≥10% total body surface area. Patients were excluded if they had burns classified beyond third-degree severity or had a documented diagnosis of acute stress reaction, depression, or PTSD before the index event. The index event was defined as the first recorded ketamine administration for burn treatment or the corresponding matched date in the control cohort.

Outcomes

The primary outcomes were incident diagnoses of acute stress reaction, depression, and PTSD, identified using diagnostic codes recorded in electronic health records. Outcomes were assessed over one year after the index event to capture both early and later psychiatric sequelae.

Matching and covariates

To reduce confounding, propensity score matching was performed at a 1:1 ratio between cohorts based on age at index, sex, and race. After matching, each cohort included 3,518 patients. Before matching, the ketamine cohort included 3,607 patients, and the control cohort included 6,083 patients. Additional burn-related severity variables, intensive care exposure, pain burden, inhalation injury, comorbidities, and prior psychiatric medication use were not consistently available within the TriNetX network and therefore were not included in the matching process.

Statistical analysis

All analyses were conducted within the TriNetX platform. Risk analyses were performed to compute risk difference, risk ratio, and odds ratio for each outcome. Kaplan-Meier analyses were used to estimate time to onset, and the log-rank test assessed differences between survival curves. Hazard ratios were calculated to compare outcome incidence across the study period. Independent t-tests compared the mean number of outcome episodes between groups. Statistical significance was defined as $P < 0.05$.

Ethical considerations

This study involved secondary analysis of routinely collected, de-identified electronic health records and required no direct patient contact or informed consent. All data met HIPAA Privacy Rule standards for de-identification. TriNetX provides aggregated, de-identified clinical information and operates under a centralized IRB waiver for research using such data. Consistent with institutional policy at Howard University, the project underwent administrative review on June 02, 2025, and was designated exempt from IRB oversight because it involved analysis of fully de-identified secondary data with no interaction or intervention involving human participants.

Results

After matching, there were 3,518 patients in each cohort. Mean age was balanced between cohorts (42.4 (19.7) vs. 42.3 (19.8) years; $P = 0.866$). Sex distribution was similar after matching. Additional demographic characteristics are presented in Table 1.

Depression

Among patients with burns involving ≥10% total body surface area, those who received ketamine had a higher incidence of depression than those who did not (4.9% vs. 3.8%). The risk difference was 1.1% ($P = 0.012$). Risk estimates supported an increased likelihood of depression in the ketamine cohort (Figure 1). Kaplan-Meier analysis showed lower depression-free survival in the ketamine cohort (94.95% vs. 95.97%; $P = 0.012$), with a hazard ratio of 1.24 (95% CI, 1.05-1.48) (Table 2). The mean number of depressive episodes was higher in the ketamine cohort (1.69 vs. 1.35; $P = 0.011$).

Acute stress reaction

Acute stress reaction incidence was higher in the ketamine cohort (2.0% vs. 0.8%). The risk difference was 1.2% ($P < 0.001$), and risk estimates were consistent with increased ASR risk associated with ketamine exposure (Figure 1). Kaplan-Meier

Table 1. Baseline demographic characteristics before and after matching in ketamine and non-ketamine burn patients

Characteristic	Before match ketamine	Before match % cohort	Before match no-ketamine	Before match % cohort	Before match *P*	After match ketamine	After match no-ketamine	After match *P*
Age at index	42.2 (19.6) (n=3607)	100%	43.2 (21.6) (n=6083)	100%	0.035	42.4 (19.7) (n=3518)	42.3 (19.8) (n=3518)	0.866
Male	2648	73.4%	4198	69.1%	<0.001	2576	2577	0.979
Female	957	26.5%	1882	30.9%	<0.001	941	938	0.936
White	2307	63.9%	3588	58.9%	<0.001	2307	2354	0.236
Black/African American	659	18.2%	1026	16.8%	0.078	659	614	0.163
Asian	79	2.1%	152	2.5%	0.336	79	77	0.871
American Indian/Alaska Native	62	1.7%	42	0.7%	<0.001	45	40	0.585
Native Hawaiian/Pacific Islander	29	0.8%	52	0.8%	0.790	29	27	0.788
Other race	251	6.9%	199	3.2%	<0.001	179	184	0.788
Unknown race	220	6.01%	1024	16.8%	<0.001	220	222	0.922
Unknown gender	10	0.2%	10	0.1%	0.237	10	10	1.000

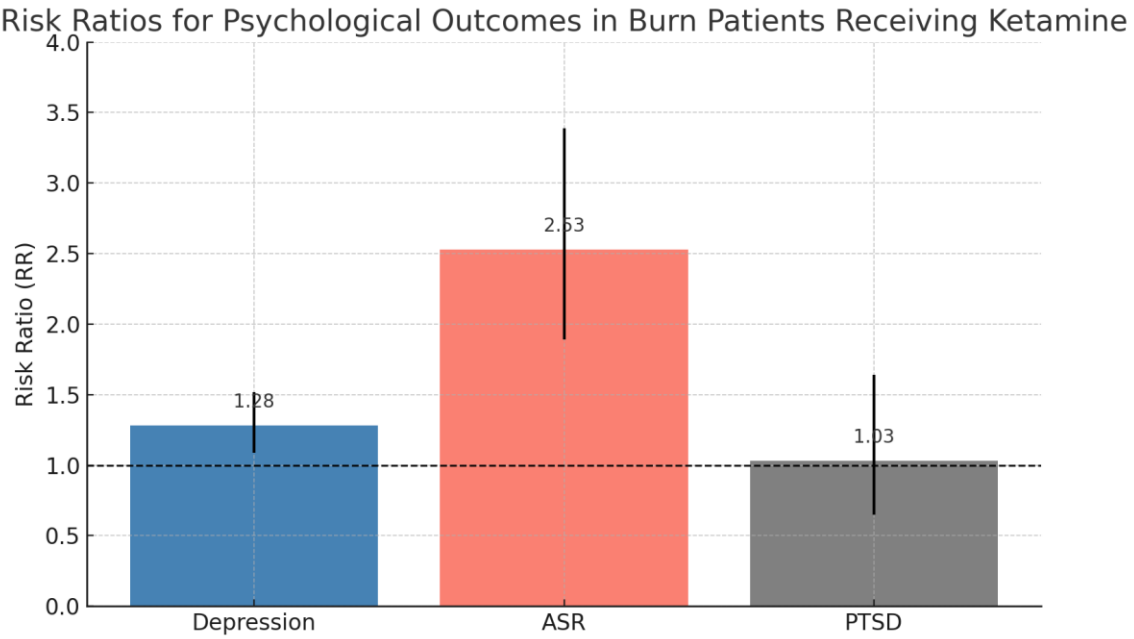
P: probability value. $P < 0.05$ was considered statistically significant.

Table 2. Summary of incidence, risk estimates with corresponding *P*-values, and survival outcomes for depression, acute stress reaction, and PTSD in ketamine vs. non-ketamine burn patients

Outcome	Incidence (%) ketamine vs. no-ketamine	Risk difference (%)	RR	OR	HR (95% CI)	*P*-value	Kaplan-Meier survival difference	Interpretation
Depression	4.9% vs. 3.8%	+1.1%	1.28	1.30	1.24 (1.05-1.48)	0.012	94.95% vs. 95.97% depression-free	Significant increased risk
Acute stress reaction	2.0% vs. 0.8%	+1.2%	2.53	2.56	2.41 (1.79-3.24)	<0.001	97.92% vs. 99.15% ASR-free	Significant increased risk
PTSD	0.6% vs. 0.6%	0.0%	1.03	1.03	0.99 (0.62-1.58)	0.900	99.35% vs. 99.33% PTSD-free	No difference

ASR: acute stress reaction, CI: confidence interval, HR: hazard ratio, KM: Kaplan-Meier, OR: odds ratio, PTSD: post-traumatic stress disorder, RR: risk ratio. $P < 0.05$ was considered statistically significant. *P*-values shown in Table 2 correspond to risk analysis comparisons between cohorts. Kaplan-Meier/log-rank *P*-values are reported separately in the text.

Figure 1. Risk ratios of psychological outcomes in burn patients receiving ketamine



This figure presents risk ratios with 95% confidence intervals for depression, acute stress reaction, and post-traumatic stress disorder in patients who received ketamine compared with those who did not. ASR: acute stress reaction, PTSD: post-traumatic stress disorder, RR: risk ratio.

curves showed reduced ASR-free survival in the ketamine cohort (97.92% vs. 99.15%; log-rank $P < 0.001$), with a hazard ratio of 2.41 (95% CI, 1.79-3.24) (Table 2). Among patients diagnosed with ASR, the mean number of episodes did not differ between cohorts (1.39 vs. 1.39; $P = 0.985$).

Post-traumatic stress disorder

Post-traumatic stress disorder incidence was similar between cohorts (0.6% vs. 0.6%). The risk difference was 0.0% ($P = 0.900$), with no evidence of association on odds ratio or hazard ratio analyses (Figure 1, Table 2). Kaplan-Meier analysis showed similarly high PTSD-free survival in both cohorts (99.35% vs. 99.33%; $P = 0.952$). The mean number of PTSD episodes was comparable (1.05 vs. 1.16; $P = 0.222$).

Discussion

In this retrospective, matched cohort of patients with major burns, ketamine exposure during early burn care was associated with increased risks of depression and acute stress reaction, whereas PTSD risk was not increased. Clinically, these findings support integrating mental health surveillance into burn care pathways when ketamine is used for analgesia and sedation.

Prior work in trauma and burn populations has produced mixed findings regarding ketamine and post-traumatic psychiatric outcomes. Some studies have raised concern that ketamine administered during acute injury care may be associated with greater early psychological distress, including acute stress symptoms and depressive features [10, 12]. The present findings align with the concept that psychiatric effects of ketamine may depend on clinical context, timing, and patient-level vulnerability, rather than being uniform across indications.

At the same time, clinical studies in psychiatric and perioperative settings have demonstrated antidepressant or preventive effects of ketamine and esketamine [13, 14]. The apparent contrast with the present findings supports a context-

dependent interpretation. Ketamine may have therapeutic psychiatric effects in controlled treatment settings, but its use during acute traumatic injury may carry different psychological implications, especially in patients experiencing severe pain, fear, disfigurement, or repeated procedures.

Mechanistically, ketamine's effects on glutamatergic signaling and dissociative experiences may plausibly influence memory consolidation and emotional processing after trauma [11, 15]. In burn care, this effect may interact with intense procedural pain, repeated dressing changes, prolonged hospitalization, and premorbid vulnerability. These mechanisms remain hypothetical in the present dataset because dose, route, timing, procedural context, and concurrent sedative or analgesic regimens were unavailable.

This study has several strengths, including a large, diverse population drawn from a global health research network, a matched design to reduce confounding by key demographic factors, and a one-year follow-up capturing both early and later outcomes. Limitations include the retrospective design and reliance on diagnostic codes, which may lead to under-ascertainment or misclassification. Detailed information on ketamine dose, route, timing relative to procedures, and concurrent analgesic or sedative regimens was not available, limiting causal inference and mechanistic interpretation. Residual confounding is possible, including factors related to burn severity beyond total body surface area, pain burden, intensive care exposure, and premorbid psychiatric risk.

Future research should prioritize prospective designs with granular exposure data and incorporate validated symptom scales alongside diagnostic outcomes. Identifying patient-level risk modifiers may enable tailored sedation strategies that optimize both analgesia and psychological recovery after burn injury.

Conclusion

Ketamine exposure during early care of patients with major burns was associated with increased risks of depression and acute stress reaction but not PTSD. When ketamine is used for burn-related analgesia and sedation, clinicians should consider proactive psychological screening and structured follow-up to detect early psychiatric sequelae and support recovery. Prospective studies with detailed exposure characterization are needed to clarify causality and to define safer, context-specific approaches to analgesia and sedation in burn care.

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The effect of immunologic marker levels on the development of postherpetic neuralgia in diabetes mellitus patients with acute herpes zoster

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Ethical Approval
Ethical approval was obtained from the Necmettin Erbakan University Clinical Research Ethics Committee (Decision No. 2021/491; April 14, 2021) and the Turkish Ministry of Health (Approval No. E.66175679-514.04.03-559105; October 6, 2021). Written informed consent was obtained from all participants.

Conflict of Interest
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Abstract

Background/Aim: Neuropathic pain is a complex condition with an incompletely understood pathogenesis, and immunologic mechanisms are increasingly recognized as important contributors. This study aimed to evaluate the association between immunologic marker levels and the development of postherpetic neuralgia in patients with acute herpes zoster, with a particular focus on the impact of diabetes mellitus.
Methods: In this prospective observational study, 20 patients with acute herpes zoster and a Douleur Neuropathique 4 score of 4 or higher were enrolled. Patients were categorized into two groups: those with diabetes mellitus (Group I, n = 10) and those without diabetes mellitus (Group II, n = 10). Routine laboratory parameters, including hemogram, C-reactive protein, erythrocyte sedimentation rate, fasting blood glucose, and hemoglobin A1c, were recorded. Immunologic markers, including CD3+, CD4+, CD8+, FOXP3+ regulatory T cells, natural killer cell subsets (regulatory, defective, cytotoxic, CD56 bright, and CD56 dim), and NK CD57, were analyzed at baseline and at month 3.
Results: NK defective subset levels were lower in Group I than in Group II at baseline and at month 3 (P = 0.028 and P = 0.037, respectively). During follow-up, significant reductions in CD3+, CD4+, and CD8+ levels were observed in Group I (P = 0.013, P = 0.017, and P = 0.041, respectively), whereas significant decreases in NK defective and NK regulatory subsets were identified in Group II (P = 0.037 and P = 0.047, respectively). At the 3-month assessment, all patients met the study definition of postherpetic neuralgia.
Conclusion: Diabetes mellitus was associated with alterations in natural killer cell subpopulations, suggesting impaired innate immune function in patients with acute herpes zoster. However, within the limitations of this small cohort, diabetes mellitus did not appear to independently increase the risk of postherpetic neuralgia. Larger, well-designed studies are needed to clarify the predictive role of immunologic markers in chronic neuropathic pain outcomes.

Keywords: diabetes mellitus, herpes zoster, immune system, natural killer cells, postherpetic neuralgia

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Introduction

Postherpetic neuralgia is a debilitating clinical condition characterized by persistent pain in the dermatomal distribution affected by acute herpes zoster [1]. As a form of neuropathic pain, postherpetic neuralgia arises from damage to the somatosensory system and represents a substantial clinical burden, particularly in aging populations. The incidence and severity of postherpetic neuralgia are influenced by multiple risk factors, among which diabetes mellitus has been identified as an important clinical comorbidity [2].

Diabetes mellitus is associated with impaired immune function, including alterations in cell-mediated immunity, phagocytosis, and opsonization [3]. These immune dysfunctions may not only predispose individuals to infections such as herpes zoster but also influence the subsequent development of chronic pain conditions such as postherpetic neuralgia. However, the precise mechanisms linking immune dysregulation to neuropathic pain remain incompletely understood.

In recent decades, growing evidence from both experimental and clinical studies has highlighted the critical role of the immune system in the pathogenesis of neuropathic pain [4]. Increasing attention has therefore focused on immunologic markers and cytokine profiles that may modulate pain pathways and treatment responses [5]. Despite these advances, the relationship between specific immune-cell subsets and the development of postherpetic neuralgia, especially in patients with comorbid diabetes mellitus, remains insufficiently defined.

The present study aimed to investigate changes in immunologic marker levels in patients with acute herpes zoster and to compare these patterns between patients with and without diabetes mellitus. By evaluating the potential association between immune profiles and postherpetic neuralgia status, this study sought to provide additional insight into the neuroimmune mechanisms underlying persistent neuropathic pain.

Materials and methods

This prospective observational study was conducted between April 2022 and March 2023 in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Necmettin Erbakan University Clinical Research Ethics Committee (Decision No. 2021/491; April 14, 2021) and the Turkish Ministry of Health (Approval No. E.66175679-514.04.03-559105; October 6, 2021). Written informed consent was obtained from all participants before enrollment. Patients aged 18 to 80 years presenting with acute herpes zoster and a Douleur Neuropathique 4 score of 4 or higher were eligible. Patients with cancer, chemotherapy, pregnancy, immune deficiency, immunosuppressive drug use, severe comorbid disease, or drug allergy were excluded. Participants were categorized into two groups according to diabetes mellitus status: Group I included patients with diabetes mellitus, and Group II included patients without diabetes mellitus.

At baseline, demographic data, including age, sex, body mass index, affected dermatome, medication use, Numerical Rating Scale score, Sleep Interference Score, and Douleur Neuropathique 4 questionnaire score, were recorded. All patients received standard clinical management with pregabalin or gabapentin, with dosing individualized according to age, comorbidities, concomitant medications, and overall clinical status. No experimental interventions were introduced for the purpose of the study.

Routine laboratory parameters, including white blood cell count, C-reactive protein, erythrocyte sedimentation rate, fasting blood glucose, and hemoglobin A1c, were measured at baseline and at month 3. Peripheral blood samples were collected for immunologic analysis. Peripheral blood mononuclear cells were isolated from EDTA-anticoagulated blood. Surface staining was performed using monoclonal antibodies against cluster of differentiation 3, 4, 8, 16, 56, and 57 (Becton Dickinson, USA). Cells were analyzed using a BD FACSCanto II flow cytometer. The evaluated immune-cell subsets included CD3+, CD4+, CD8+, FOXP3+ regulatory T cells, NK defective cells, NK regulatory cells, NK cytotoxic cells, NK CD56 bright cells, NK CD56 dim cells, and NK CD57 cells.

The primary outcomes were changes in immunologic marker levels and the association between diabetes mellitus and postherpetic neuralgia status at month 3. Secondary outcomes included relationships between changes in clinical scores and routine laboratory parameters and postherpetic neuralgia status.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Chicago, IL, USA). Continuous variables were summarized as mean (SD), median, minimum, and maximum values, and categorical variables were presented as counts and percentages. Normality was assessed with the Kolmogorov-Smirnov test. Between-group comparisons were performed using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Within-group comparisons were performed using the Wilcoxon signed-rank test. A *P*-value of less than 0.05 was considered statistically significant.

Results

A total of 20 patients were included in the study, with 10 patients in Group I and 10 patients in Group II (Figure 1). The cohort consisted of 15 women (75.0%) and 5 men (25.0%). All patients in Group I had type 2 diabetes mellitus. There were no significant between-group differences in age, sex distribution, or body mass index (P = 0.305, P = 0.606, and P = 0.850, respectively) (Table 1).

Table 1. Baseline demographic characteristics of the patients

Variable	Group I (n = 10)	Group II (n = 10)	*P* value
Age, years	70.4 (6.6)	63.2 (18.3)	0.305
Female sex, n (%)	8 (80.0)	7 (70.0)	0.606
Body mass index, kg/m²	28.65 (2.92)	28.92 (6.08)	0.850

Data are presented as mean (SD) unless otherwise stated. BMI: body mass index, Group I: patients with diabetes mellitus, Group II: patients without diabetes mellitus. $P < 0.05$ was considered statistically significant.

As shown in Table 2, fasting blood glucose and hemoglobin A1c levels were higher in Group I than in Group II at baseline (P = 0.028 and P = 0.006, respectively) and at month 3 (P = 0.021 and P = 0.014, respectively). Other routine laboratory parameters were comparable between the groups at both time points. Within-group analyses showed no significant temporal changes in Group I, whereas Group II demonstrated significant reductions in C-reactive protein (P = 0.005) and erythrocyte sedimentation rate (P = 0.036).

Figure 1. Flow diagram of patient enrollment, group allocation, follow-up, and analysis

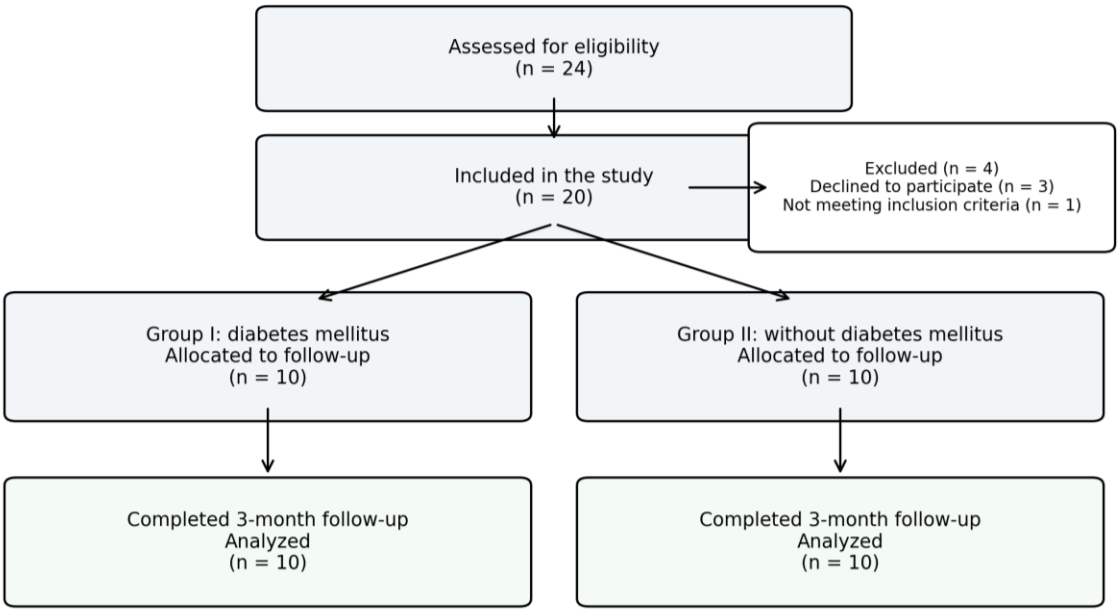


Table 2. Comparison of routine laboratory tests at baseline and month 3 between and within the groups

Variable	Time point	Group I (n = 10)	Group II (n = 10)	*P*-value
WBC, ×10³/µL	Baseline	7.88 (2.91)	8.01 (2.48)	0.734
	Month 3	7.51 (2.48)	6.70 (1.25)	0.520
	Within-group *P* value	0.646	0.093	
CRP, mg/dL	Baseline	12.38 (18.84)	7.05 (7.01)	0.970
	Month 3	10.63 (16.14)	3.45 (3.98)	0.850
	Within-group *P* value	0.386	0.005*	
ESR, mm/h	Baseline	16.30 (8.99)	15.40 (8.59)	0.733
	Month 3	14.80 (9.26)	8.60 (3.98)	0.052
	Within-group *P* value	0.683	0.036*	
FBG, mg/dL	Baseline	167.80 (77.81)	102.60 (20.70)	0.028*
	Month 3	162.42 (98.90)	101.30 (21.36)	0.021*
	Within-group *P* value	0.575	0.683	
HbA1c, %	Baseline	8.50 (2.48)	6.10 (0.59)	0.006*
	Month 3	7.85 (1.76)	6.08 (0.59)	0.014*
	Within-group *P* value	0.811	0.722	

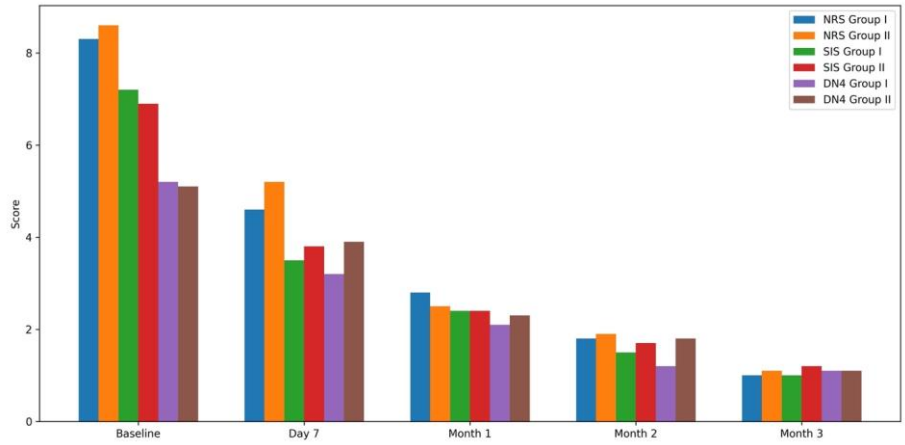
Data are presented as mean (SD). WBC: white blood cell count, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, FBG: fasting blood glucose, HbA1c: hemoglobin A1c. *$P < 0.05$ was considered statistically significant.

Table 3. Comparison of immunologic marker levels at baseline and month 3 between and within the groups

Variable	Time point	Group I (n = 10)	Group II (n = 10)	*P*-value
CD3+, %	Baseline	57.42 (11.34)	58.35 (11.06)	0.650
	Month 3	43.42 (9.65)	48.33 (17.75)	0.597
	Within-group *P* value	0.013*	0.059	
CD4+, %	Baseline	35.53 (7.16)	37.53 (10.75)	0.650
	Month 3	27.40 (8.57)	32.36 (14.58)	0.545
	Within-group *P* value	0.017*	0.074	
CD8+, %	Baseline	21.89 (8.36)	20.82 (8.67)	0.734
	Month 3	16.02 (2.86)	15.97 (6.45)	0.450
	Within-group *P* value	0.041*	0.059	
FOXP3+ (Treg), %	Baseline	7.84 (1.55)	6.84 (2.77)	0.723
	Month 3	7.84 (1.55)	7.25 (2.78)	0.705
	Within-group *P* value	0.074	0.386	
NK defective subset, %	Baseline	8.56 (9.24)	17.28 (11.42)	0.028*
	Month 3	3.49 (2.72)	7.53 (4.39)	0.037*
	Within-group *P* value	0.241	0.037*	
NK regulatory subset, %	Baseline	4.03 (2.93)	9.18 (7.21)	0.075
	Month 3	6.19 (7.28)	3.78 (2.63)	1.000
	Within-group *P* value	0.767	0.047*	
NK cytotoxic subset, %	Baseline	17.77 (12.37)	26.92 (15.07)	0.199
	Month 3	14.76 (10.10)	18.44 (11.84)	0.596
	Within-group *P* value	0.721	0.203	
NK CD57, %	Baseline	11.69 (7.69)	17.21 (12.01)	0.406
	Month 3	10.43 (7.46)	10.80 (5.67)	0.705
	Within-group *P* value	0.386	0.241	
NK CD56 bright, %	Baseline	2.71 (1.97)	3.63 (2.20)	0.427
	Month 3	3.65 (3.29)	3.23 (3.31)	0.705
	Within-group *P* value	0.445	0.441	
NK CD56 dim, %	Baseline	17.72 (12.40)	25.78 (11.22)	0.174
	Month 3	13.78 (9.55)	20.20 (15.79)	0.307
	Within-group *P* value	0.721	0.185	

Data are presented as mean (SD). FOXP3: forkhead box P3, Treg: regulatory T cell, NK: natural killer. *$P < 0.05$ was considered statistically significant.

Figure 2. Change in Numerical Rating Scale, Sleep Interference Score, and Douleur Neuropathique 4 scores during follow-up



DN4: Douleur Neuropathique 4, NRS: Numerical Rating Scale, SIS: Sleep Interference Score.

Immunologic assessment revealed significant differences in natural killer cell subsets between the groups (Table 3). The NK defective subset was lower in Group I than in Group II at baseline and at month 3 ($P = 0.028$ and $P = 0.037$, respectively). Over time, Group I showed significant declines in CD3+, CD4+, and CD8+ levels ($P = 0.013$, $P = 0.017$, and $P = 0.041$, respectively), whereas Group II showed significant reductions in NK defective and NK regulatory subsets ($P = 0.037$ and $P = 0.047$, respectively).

Pain-related outcomes did not differ significantly between the groups at any assessment point (Figure 2). For Numerical Rating Scale scores, between-group comparisons were not significant at baseline, day 7, month 1, month 2, or month 3 ($P = 0.614$, $P = 0.758$, $P = 0.531$, $P = 0.788$, and $P = 0.317$, respectively). Similarly, Sleep Interference Scores did not differ significantly between the groups at baseline, day 7, month 1, month 2, or month 3 (P = 0.810, $P = 0.759$, $P = 0.871$, $P = 0.675$, and $P = 0.453$, respectively). Douleur Neuropathique 4 questionnaire scores also showed no significant between-group differences at baseline, day 7, month 1, month 2, or month 3 ($P = 0.542$, $P = 0.197$, $P = 0.562$, $P = 0.066$, and $P = 0.317$, respectively). Both groups demonstrated progressive improvement in pain and symptom scores throughout follow-up. At the 3-month assessment, all patients met the study definition of postherpetic neuralgia.

Discussion

In this prospective observational study, patients with diabetes mellitus and acute herpes zoster exhibited lower natural killer defective subset levels than patients without diabetes mellitus, and immunologic markers changed dynamically during follow-up. However, all patients met the study definition of postherpetic neuralgia at month 3, and diabetes mellitus was not associated with a different postherpetic neuralgia outcome within this cohort.

Alterations in T-lymphocyte subsets have been inconsistently associated with postherpetic neuralgia in previous studies. In the present cohort, CD3+, CD4+, and CD8+ levels decreased over time in patients with diabetes mellitus, suggesting modulation of adaptive immune responses. Some studies have linked reduced T-cell counts to an increased risk of postherpetic neuralgia [6-8], whereas others have not confirmed this association [9]. Our findings are more consistent with the latter interpretation and may indicate that T-cell changes alone are insufficient to distinguish postherpetic neuralgia outcomes in a high-risk population.

Regulatory T cells are known to suppress neuroinflammation and may contribute to pain resolution [10]. In this study, FOXP3+ regulatory T-cell levels showed a modest, non-significant increase over time in both groups, while inflammatory markers declined more clearly in patients without diabetes mellitus. This pattern may reflect a more effective anti-inflammatory response in patients without diabetes mellitus. Nevertheless, the limited sample size requires cautious interpretation.

The findings also suggest differences in innate immune responses between the groups. Natural killer cell subsets were consistently lower in patients with diabetes mellitus, supporting the concept of diabetes-related impairment in innate immunity. In contrast, patients without diabetes mellitus showed more dynamic changes in NK-related subsets during follow-up. Previous studies have suggested a potentially protective role of natural killer cells in neuropathic pain conditions [11]. In this context, the attenuated NK-cell profile observed in patients with diabetes mellitus may reflect altered neuroimmune interactions after herpes zoster.

Routine inflammatory markers supported a similar pattern. C-reactive protein and erythrocyte sedimentation rate decreased significantly only in the group without diabetes mellitus, whereas patients with diabetes mellitus showed a less distinct inflammatory resolution profile. This observation is compatible with the recognized relevance of inflammatory markers in zoster-related outcomes and with clinical correlations reported in varicella-zoster infection [12, 13]. Because all patients received pregabalin or gabapentin as part of standard care, treatment-related immunomodulatory effects should also be considered when interpreting these laboratory changes [14].

An important contextual finding is that all patients in this cohort met the postherpetic neuralgia definition at month 3. This may be related to the selection criteria, because only patients with acute herpes zoster and clear neuropathic pain features were enrolled. Such a cohort likely represents a clinically high-risk subgroup in whom chronic pain mechanisms may already have been initiated during the acute phase. In addition, the small sample size and the absence of a comparator group without postherpetic neuralgia limited outcome variability.

This study has several limitations. The small sample size restricts generalizability and reduces the power to detect subtle between-group differences. The absence of a control group

without postherpetic neuralgia prevents direct comparison with patients who recover without chronic pain. Because all patients met the postherpetic neuralgia definition at month 3, subgroup analyses according to postherpetic neuralgia development were not possible. In addition, pregabalin or gabapentin treatment may have affected immune-cell dynamics, and cytokine profiling or functional immune assays were not performed.

In conclusion, diabetes mellitus may be associated with alterations in natural killer cell subpopulations in patients with acute herpes zoster, suggesting a potential impairment of innate immune responses. However, within the limitations of this small prospective cohort, diabetes mellitus was not identified as an independent determinant of postherpetic neuralgia status at month 3. Larger and methodologically broader studies are needed to clarify how immune dysregulation contributes to the pathogenesis of postherpetic neuralgia.

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Preoperative testing for immunotherapy-induced endocrinopathy in breast cancer: Real-world data, literature review, and suggested management protocol

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Ethics Committee Approval
This study was a retrospective review of previously collected, anonymized data. In accordance with UK Health Research Authority (HRA) guidance, formal research ethics approval was not required. The research was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with the UK General Data Protection Regulation (GDPR).

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Triple-negative breast cancer (TNBC) is an aggressive subtype for which pembrolizumab-based neoadjuvant therapy has demonstrated improved outcomes. However, immune checkpoint inhibitors, including pembrolizumab, are associated with endocrine toxicities such as hypothyroidism, hypophysitis, and adrenal insufficiency, which may significantly complicate perioperative care. This study aimed to evaluate real-world preoperative endocrine testing and propose a practical management protocol.
Methods: This retrospective study evaluated 28 patients with TNBC at Western General Hospital who received pembrolizumab before surgery between March 2023 and December 2024. Clinical data, endocrine function tests, surgical outcomes, and adverse events were analyzed.
Results: Endocrinopathies occurred in a subset of patients, including one case of hypothyroidism and two cases of adrenal insufficiency. Only 36% of patients underwent cortisol testing preoperatively.
Conclusion: We propose a protocol for routine preoperative endocrine screening in this population, including early-morning cortisol and thyroid function tests. Although the incidence is low, these complications may be severe, and implementing this protocol may reduce the risk of perioperative complications associated with immunotherapy-induced endocrinopathies.

Keywords: pembrolizumab, pre-assessment, endocrinopathy, breast cancer

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Introduction

Triple-negative breast cancer (TNBC) is considered an aggressive subtype of breast cancer because of its rapid growth, risk of recurrence, and risk of metastasis. In the United Kingdom, National Institute for Health and Care Excellence (NICE) guidance recommends considering chemotherapy regimens that include the immune checkpoint inhibitor pembrolizumab for high-risk, early-stage or locally advanced TNBC in the neoadjuvant setting. The KEYNOTE-522 trial demonstrated that this approach is associated with improved event-free survival and higher rates of pathological complete response [1-3].

The toxicity and side-effect profile of pembrolizumab is significant and complex. Adverse events of interest reported in the trial literature include endocrinopathies of moderate frequency, including pituitary, thyroid, and adrenal dysfunction [1, 4]. Endocrine deficiencies can occur during immunotherapy or up to six months after its completion and usually persist, requiring lifelong replacement therapy [4, 5].

Primary hypothyroidism is the most common endocrinopathy, occurring in 6%-9% of patients, whereas hyperthyroidism is less common [6]. Immunotherapy-induced hypophysitis occurs in approximately 1% of patients and is often observed later during treatment, with a median onset of six months [6]. Primary adrenal insufficiency is an increasingly recognized adverse event that can present acutely, with a reported incidence of 1%-2% [5, 6]. It has been associated with fatalities resulting from life-threatening adrenal crisis and vasodilatory shock [7]. The onset varies widely from a few days to more than 12 months [6]. In patients undergoing anesthesia and surgery, undiagnosed adrenal insufficiency poses a significant risk for perioperative blood pressure management and other physiological parameters [8, 9]. Therefore, these risks should be considered during the preoperative assessment of patients who have received neoadjuvant immunotherapy.

Materials and methods

This retrospective study analyzed patients treated at Western General Hospital, Edinburgh, United Kingdom, between March 2023 and December 2024. Patients included in the study were those diagnosed with TNBC who received neoadjuvant chemotherapy in combination with pembrolizumab according to the PEMBRO 3WK R1506 protocol. All patients subsequently underwent preoperative assessment followed by surgery. Patients with metastatic disease were excluded from the study. Data were collected on patient characteristics, clinical and histopathological breast cancer characteristics, treatment timing, preoperative assessment, surgery, blood test results, surgical intervention, postoperative complications, and adverse events. Baseline and clinical characteristics are summarized in Table 1.

Surgical intervention types included wide local excision (WLE), mastectomy, mammoplasty, and axillary surgery, including sentinel node biopsy (SNB), total axillary dissection (TAD), and axillary node clearance (ANC).

Blood work focused on renal function, including serum sodium, potassium, and creatinine; thyroid function, including thyroid-stimulating hormone (TSH) and free thyroxine (free T4); and adrenal function, including serum cortisol, as part of routine preoperative testing. The timing of blood test monitoring was also recorded and related to the completion dates of neoadjuvant pembrolizumab and surgery.

The duration of neoadjuvant pembrolizumab was recorded, including early termination due to adverse events or associated toxicity.

Statistical analysis

Data were analyzed descriptively. Continuous variables are presented as median and range where available, and categorical variables are presented as number and percentage. No hypothesis testing was performed because of the small single-center cohort and the protocol-development purpose of the study.

Table 1. Clinical and histopathological characteristics of the study cohort (n=28)

Characteristic	n	%
Histological subtype		
NST	24	86
Other	4	14
Histological grade		
1	0	0
2	3	11
3	25	89
Hereditary genes		
BRCA1	2	7
BRCA2	2	7
PALB2	1	4
TNM		
T1	3	11
T2	21	75
T3	3	11
T4	1	4
N0	15	54
N1	13	46
M0	28	100
M1	0	0
Immunotherapy-related toxicities		
None	20	71
Pneumonitis	2	7
Colitis	1	4
Skin toxicity, grade 1	0	0
Skin toxicity, grade 2	0	0
Skin toxicity, grade 3	2	7
Hepatitis	1	4
Hypophysitis	1	4
Adrenal insufficiency	1	4
Pre-existing thyroid dysfunction		
Hypothyroid on levothyroxine replacement	5	18
None known	23	82
Preoperative endocrine assessment		
Thyroid function tests between neoadjuvant treatment and surgery	17	61
Cortisol test in immediate preoperative window	1	4
Surgical intervention		
WLE + SNB	18	64
WLE + TAD/ANC	4	14
Mastectomy + SNB/TAD/ANC	6	21
Postoperative surgical complications		
None	25	89
Seroma	2	7
Hematoma	1	4

ANC: axillary node clearance, NST: no special type, SNB: sentinel node biopsy, TAD: total axillary dissection, TNM: tumor-node-metastasis, WLE: wide local excision.

Results

Cohort characteristics

A total of 30 patients with TNBC received neoadjuvant treatment with chemotherapy plus pembrolizumab during the study window from March 2023 through December 2024. Two patients with metastatic disease were excluded, resulting in a final study cohort of 28 patients. The age range of the study cohort was 29-68 years, with a median age of 52 years.

Histological assessment showed that 86% (24/28) of tumors were of no special type (NST), whereas 14% (4/28) comprised other histological subtypes. Histological tumor grade was predominantly grade 3 (89%, 25/28), with three tumors (11%)

classified as grade 2. Five patients had germline mutations, including BRCA1 (n=2), BRCA2 (n=2), or PALB2 (n=1).

TNM classification was reviewed. Most patients (75%, 21/28) had T2 cancer, three patients had T1 disease, three had T3 disease, and one had T4d disease. Involved lymph nodes were observed in 46% (13/28) of patients.

Surgery and postoperative complications

The interval from completion of neoadjuvant treatment, defined as the date of the last cycle, to surgery varied from six to nine weeks. Surgical interventions varied, but most patients underwent breast-conserving surgery.

Length of stay ranged from zero to four days, with a median of one day. Postoperative complications occurred in five patients, including two cases of seroma, one case of hematoma, and one case with postoperative thyroid function test (TFT) derangement.

Immunotherapy treatment and toxicities

A total of 75% of patients completed full neoadjuvant pembrolizumab treatment according to the PEMBRO 3WK R1506 protocol. Overall, 46% (13/28) of patients achieved a pathological complete response (pCR). Eight of 28 patients (29%) discontinued pembrolizumab because of toxicity. Toxicities potentially associated with pembrolizumab included pneumonitis (two cases), colitis (one case), grade 3 skin toxicity (two cases), hypophysitis (one case), hepatitis (one case), hypothyroidism (one case), and adrenal insufficiency (one case).

Preoperative assessment

Presurgical blood testing showed that all patients had preoperative urea and electrolytes (U&E) measured, demonstrating normal serum sodium, potassium, and creatinine levels. Thyroid function was assessed in 96% (27/28) of patients within three months before surgery, with 61% (17/28) having tests between the end of neoadjuvant pembrolizumab/chemotherapy and surgery. Only one patient was diagnosed with hyperthyroidism. Five patients were already receiving thyroxine treatment. Finally, only 36% (10/28) of patients had serum cortisol checked before surgery, one to three months before the final cycle of neoadjuvant treatment, with only one patient (3.5%) having cortisol measured in the immediate preoperative window between the end of neoadjuvant treatment and surgery.

Discussion

Following the results of the KEYNOTE-522 trial, NICE guidance in the United Kingdom has been updated to support consideration of neoadjuvant chemotherapy regimens containing the checkpoint inhibitor pembrolizumab for patients with higher-risk TNBC. This approach has improved both event-free survival and rates of pathological complete response. Despite these benefits, immunotherapies such as pembrolizumab may be associated with significant toxicities and adverse events. The toxicity profile of pembrolizumab is wide-ranging and complex and includes immunosuppression, skin reactions, rheumatological problems, hepatic, pulmonary, pancreatic, cardiovascular, renal, gastrointestinal, ophthalmic, and hematological manifestations, and endocrinopathies. Endocrinopathies are the focus of this study and most commonly manifest as hypophysitis, thyroid dysfunction, or adrenal insufficiency.

These complications are particularly important in patients with early TNBC who undergo surgery under general anesthesia within weeks of completing neoadjuvant treatment. The concern arises from well-documented complications that may occur when these conditions are undiagnosed at the time of anesthesia induction and surgery. These conditions have been linked to several anesthesia-related risks, including difficult blood pressure management and, in some cases, fatal outcomes. Furthermore, the physiological impact of surgery can exacerbate undiagnosed endocrinopathies and perpetuate hemodynamic instability.

Given the risk of these complications after immunotherapy and the increased risk of proceeding to anesthesia and surgery in patients with potentially undiagnosed endocrinopathies, we propose a practical screening protocol. This approach is designed to initiate thyroid and adrenal testing preoperatively and to provide guidance on appropriate management.

In our cohort, 61% of patients had appropriate thyroid function testing at the time of preoperative assessment, whereas only one patient had cortisol measured in the immediate preoperative window. A total of 36% of patients had cortisol levels checked during neoadjuvant treatment as part of routine admission blood tests when they presented to the Cancer Admissions Unit (CAU) with unrelated symptoms while on treatment. The most common reason for admission was pyrexia and other infective symptoms. Overall, two patients were diagnosed with adrenal axis deficiency. On both occasions, these diagnoses were made incidentally when the patients attended the CAU with pyrexia. These patients could otherwise have proceeded to surgery and anesthesia with potentially dangerous undiagnosed endocrinopathies. Implementing a protocol to identify these complications may help reduce risk in this patient group.

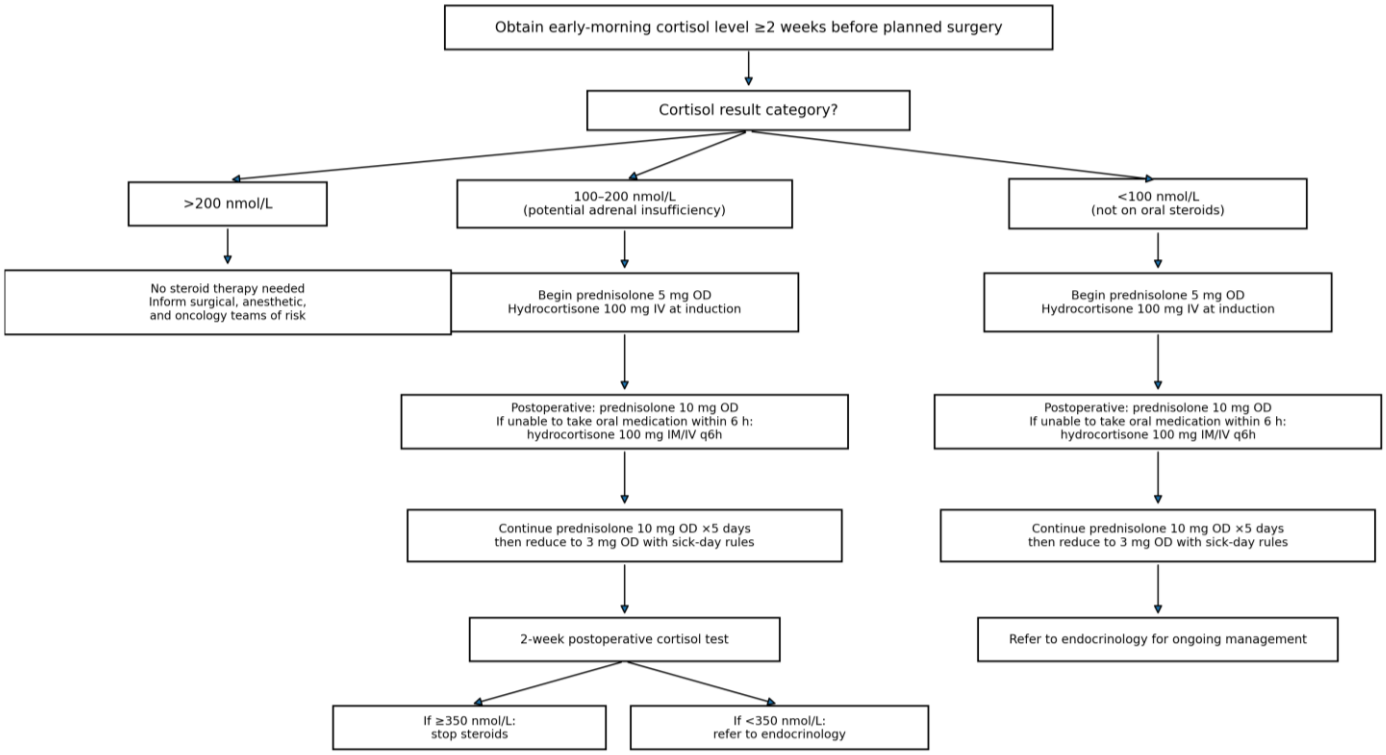
Limitations of this study include its single-center design, which may limit generalizability, and its retrospective nature, which precluded standardized clinical evaluation and may introduce observer bias. The small sample size limits statistical power, and the absence of standardized timing for endocrine testing introduces potential detection bias. Future work should consider prospective data collection, a control group, and assessment of confounding variables.

Review of literature

Thyroid disorders

Hypothyroidism is important to identify in the perioperative period because thyroid hormone homeostasis is closely linked to cardiovascular, respiratory, renal, and gastrointestinal function [4]. With respect to cardiovascular effects, evidence suggests that patients with hypothyroidism may exhibit a 30%-50% reduction in cardiac output, which may contribute substantially to intraoperative and postoperative hypotension [4, 10, 13]. Gastrointestinal complications are also a concern because patients with hypothyroidism frequently have reduced gastrointestinal motility, which poses postoperative challenges and may contribute to ileus, particularly when compounded by opioid use. Reduced motility may also be a concern during anesthetic induction [4, 10, 11]. From a respiratory standpoint, low thyroid function has been associated with

Figure 1. Protocol flowchart for preoperative cortisol assessment



diminished spontaneous ventilation and blunted hypoxic and hypercapnic drive, thereby increasing the risk of postoperative atelectasis and respiratory infections [10, 12-14]. Although direct evidence linking hypothyroidism to increased infection rates in breast surgery is limited, other surgical fields have demonstrated impaired wound healing in patients with hypothyroidism. Finally, although rare, myxedema remains a critical consideration because it is potentially life-threatening [15].

Adrenal dysfunction

A recent large-scale retrospective cohort study of patients with adrenal insufficiency demonstrated an increased risk of all-cause mortality, with risk ratios of 2.19 for men and 2.86 for women. The risk was more strongly associated with primary adrenal insufficiency; although cardiovascular disease was the major cause of mortality, adrenal crisis was also identified as a common cause. The authors concluded that avoidance of adrenal crisis is essential to reducing mortality [16]. Studies have reported that up to 8% of patients with known adrenal insufficiency experience adrenal crisis during inpatient stays [17]. Adrenal crisis can lead to loss of vasomotor tone, hypotension, and profound hyponatremia [9, 18, 19].

Primary adrenal insufficiency is an increasingly recognized adverse event that can present acutely, with a reported incidence of 1%-2% [5, 6]. It has been associated with fatalities resulting from life-threatening adrenal crisis and vasodilatory shock [7]. Onset varies widely from a few days to more than 12 months [6]. In patients undergoing anesthesia, undiagnosed adrenal insufficiency poses a significant risk in terms of blood pressure management and other physiological parameters [8, 9]. Furthermore, surgical stress is known to exacerbate this physiology [20].

Suggested protocol for preoperative management of patients receiving pembrolizumab

An early-morning serum cortisol test should be performed at least two weeks before surgery. If the cortisol level is greater than 200 nmol/L, no steroid replacement is required. Surgical, anesthetic, and oncology teams should be aware of pembrolizumab use and the associated adrenal insufficiency risk on the day of surgery.

If the cortisol level is between 100 and 200 nmol/L, indicating potential adrenal insufficiency, prednisolone 5 mg once daily should be initiated. Perioperatively, hydrocortisone 100 mg should be administered intravenously at induction, followed by a switch to prednisolone 10 mg once daily when the patient is able to eat and drink. If the patient is unable to take oral medication within six hours of induction, hydrocortisone 100 mg should be administered intramuscularly or intravenously every six hours. Prednisolone 10 mg once daily should be continued for five days after surgery and extended if recovery is delayed; it should then be reduced to prednisolone 3 mg once daily with sick-day rules. At two weeks postoperatively, steroids should be stopped if the cortisol level is greater than 350 nmol/L, whereas a cortisol level below 350 nmol/L should prompt referral to endocrinology.

If the cortisol level is less than 100 nmol/L and the patient is not on oral steroids, adrenal insufficiency is likely, and prednisolone 5 mg once daily should be initiated. Perioperative management in this group consists of hydrocortisone 100 mg intravenously at induction, followed by prednisolone 10 mg once daily when oral intake is possible, or hydrocortisone 100 mg intramuscularly or intravenously every six hours if oral medication cannot be taken within six hours of induction. Prednisolone 10 mg once daily should be continued for five days after surgery and extended if recovery is delayed; it should then be reduced to prednisolone 3 mg once daily with sick-day rules,

and the patient should be referred to endocrinology for ongoing management.

If thyroid function tests are abnormal at any stage, urgent referral to endocrinology should be made, and specialist advice should be awaited before proceeding with surgery. Subsequently, long-term thyroid monitoring should be arranged through endocrine follow-up. The protocol is summarized in Figure 1.

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Unexpected intraoperative discovery of multiple metallic screw-fixed anterior abdominal wall mesh during open myomectomy: A case report

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Ethics
The Institutional Review Board of Al Emadi Hospital, Doha, Qatar approved the procedure (IRB No. PAT0268548).

Informed Consent
Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

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No conflict of interest was declared by the authors.

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Abstract

Mesh repair is the standard approach for anterior abdominal wall hernias because it provides durable reinforcement and low recurrence rates. Over time, fixation techniques have evolved toward safer and less invasive methods, and metallic screw fixation has largely become obsolete. Nevertheless, older fixation techniques may still be encountered and may complicate subsequent abdominal or pelvic surgery. We report the case of a 37-year-old woman with a history of two prior cesarean sections and hernia repair with mesh fixation 11 years earlier. She presented with pelvic pain, pelvic heaviness, and abnormal uterine bleeding. Ultrasonography revealed a large posterior cervical wall leiomyoma. During open myomectomy, multiple metallic screws securing the anterior abdominal wall mesh were unexpectedly identified, requiring careful dissection, adhesiolysis, and modification of the abdominal entry technique to safely access the peritoneal cavity. The procedure was completed without complications, and the patient recovered uneventfully. This case highlights the importance of obtaining a detailed surgical history, recognizing outdated fixation techniques, using preoperative imaging when appropriate, and performing meticulous intraoperative planning to minimize risk during reoperative abdominal and gynecologic surgery.

Keywords: abdominal wall mesh, screw fixation, hernia repair, metallic screw, myomectomy, reoperative surgery

Introduction

Mesh reinforcement is widely accepted as the standard technique for anterior abdominal wall hernia repair because it provides strong and durable support [1]. Over time, several fixation methods have been developed to improve mesh stability and reduce complications. Currently, absorbable or non-absorbable sutures, tacks, and self-gripping meshes are preferred because of their safety and effectiveness [2]. In contrast, metallic screw fixation has largely become obsolete, as it may lead to chronic pain, infection, or technical difficulties during reoperation [3]. We report a rare case of incidentally encountered screw-fixed anterior abdominal wall mesh during open myomectomy in a woman with prior hernia repair, highlighting the surgical implications of outdated fixation techniques in reoperative pelvic surgery.

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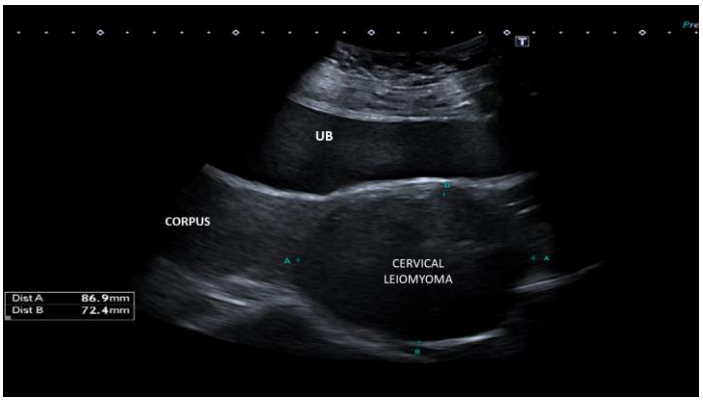
Case presentation

A 37-year-old woman with a history of two prior cesarean sections had undergone anterior abdominal wall hernia repair with mesh fixation 11 years earlier. Several years later, she developed progressive pelvic pain, constipation, dyschezia, persistent pelvic heaviness, severe congestive dysmenorrhea, and menorrhagia associated with iron deficiency anemia. As shown in Figure 1, pelvic ultrasonography confirmed a large posterior cervical wall leiomyoma measuring 7.2 x 8.6 cm, supporting the decision to proceed with posterior uterine wall access during cervical myomectomy.

Figure 1. Ultrasonographic image of a cervical leiomyoma.



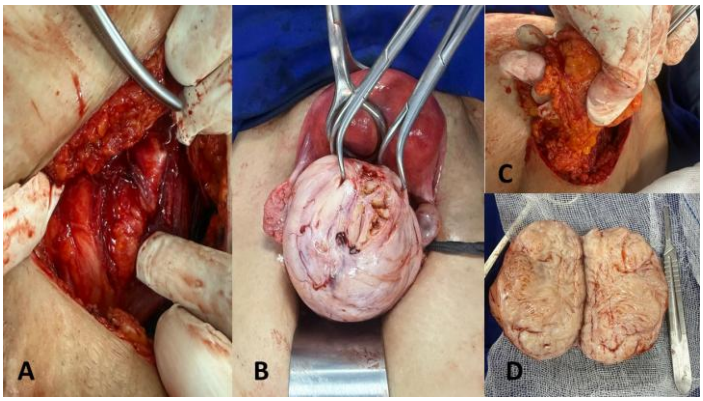
After informed consent and Institutional Review Board approval (PAT0268548) were obtained, the patient was scheduled for open myomectomy with possible hysterectomy. During dissection of the skin and subcutaneous tissue, multiple metallic screws embedded in the anterior rectus sheath were palpated (Figure 2A), securing the previously placed mesh. Contact with these screws repeatedly damaged the double-layered surgical gloves, necessitating multiple changes. With careful dissection, the lower portion of the mesh was incised, and the peritoneal cavity was entered. As anticipated preoperatively, dense omental adhesions to the parietal peritoneum (Figure 2C) and uterovesical adhesions at the prior repeat cesarean section site were identified. Extensive adhesiolysis and meticulous hemostasis were performed. The uterus was elevated using a uterine manipulator.

The large cervical myoma bulged posteriorly, away from the dense uterovesical adhesions. A longitudinal posterior uterine wall incision was made, and the leiomyoma was successfully enucleated (Figures 2B and 2D). The intraoperative images (Figure 2) demonstrate the rigid screw fixation of the mesh to the anterior rectus sheath and the dense omental and uterovesical adhesions encountered at peritoneal entry, underscoring the technical difficulty and increased risk associated with abdominal entry.

Hemostasis was achieved, and the hysterotomy site was securely closed in two layers using 0 Vicryl sutures. The myoma bed was carefully sutured to reduce the risk of postoperative hematoma. After thorough peritoneal lavage, an intraperitoneal suction drain was inserted. The rectus sheath was closed with a No. 1 Vicryl suture, with reinforcement at the mesh incision site. The subcutaneous adipose layer was closed with interrupted sutures, followed by skin closure using 3-0 Monocryl.

The postoperative course was uneventful, and the patient was discharged in good condition after drain removal on postoperative day 2. Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Figure 2. Intraoperative findings: (A) metallic screw embedded in the anterior rectus sheath, removed with long artery forceps; (B) cervical myoma protruding through a longitudinal posterior uterine wall incision; (C) dense omental adhesions at peritoneal entry; and (D) bisected leiomyoma following myomectomy.



Discussion

In this case, the unexpected presence of metallic screws securing the anterior abdominal wall mesh created significant technical challenges during abdominal entry and adhesiolysis. This finding underscores the risks associated with older mesh fixation techniques that are rarely encountered in contemporary surgical practice.

Modern mesh fixation typically relies on sutures, tacks, or self-gripping materials, which provide adequate stability while minimizing postoperative pain and tissue trauma [4]. In contrast, metallic screw fixation in soft tissue is mechanically inappropriate and clinically suboptimal. It is associated with complications, including chronic pain from rigid anchorage, foreign-body reaction, infection, and difficulty during re-entry laparotomy [5], as observed in the present case.

Although metallic screws may be used selectively in reconstructive procedures requiring fixation to bone, their use in standard soft-tissue hernia repair has largely been abandoned [6]. In a previous study, we used screws to anchor mesh to the anterior longitudinal ligament of the sacrum, with the opposite end fixed to the cervix and uterosacral ligaments in cases of apical pelvic organ prolapse repair [7]. This approach clearly demonstrates the distinction between fixation to bony structures and fixation to soft tissues, highlighting that metallic screws may be appropriate in selected procedures requiring osseous anchorage but are generally unsuitable for routine soft-tissue hernia repair.

In the present case, the metallic screws were firmly embedded in the anterior rectus sheath and caused multiple perforations of the surgical gloves, necessitating careful dissection to safely access the peritoneal cavity. Difficult entry also carried the risk of dislodging metallic fragments into the peritoneal cavity. The presence of rigid foreign material may have contributed to adhesion formation, as evidenced by the extensive omental adhesions observed after peritoneal entry.

This case emphasizes the importance of thorough documentation of previous abdominal wall reconstruction techniques, particularly in women of reproductive age who may require future pelvic or gynecologic surgery. No operative report from the previous hernia repair was available, which contributed to the unexpected discovery of metallic screws. From a technical standpoint, prior mesh repairs involving metallic hardware may

prolong operative time, obscure tissue planes, and increase the risk of visceral injury due to dense adhesions. In addition, hand injuries among surgical staff and the potential transmission of blood-borne infections represent additional risks.

When metallic hardware is suspected, surgical teams should rely on appropriate metal instruments rather than manual palpation to minimize contact with sharp objects. Careful review of surgical history and appropriate use of preoperative imaging are therefore essential for safe surgical planning. This rare case contributes to the limited literature on screw fixation of abdominal wall mesh and reinforces the importance of recognizing older surgical techniques that may influence future operative outcomes.

This report highlights the need to anticipate unexpected intraoperative findings in patients with a history of abdominal wall reconstruction. The incidental discovery of screw-fixed mesh, an outdated fixation method, illustrates how earlier surgical practices can complicate modern procedures. Surgeons and healthcare institutions share responsibility for providing detailed operative notes to patients undergoing surgical interventions. Comprehensive preoperative assessment and cautious surgical maneuvers are essential to ensure surgeon and patient safety and to optimize outcomes in reoperative abdominal and gynecologic surgery.

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Transverse colon located appendix: A case of midgut malrotation

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Abstract

Acute appendicitis is the most common cause of abdominal pain requiring general surgical intervention in emergency departments. Its pathogenesis typically involves obstruction of the appendiceal lumen, followed by inflammation, ischemia, and potentially perforation or diffuse peritonitis. The Alvarado score is practical for bedside assessment; however, it does not account for anatomical variations of the vermiform appendix, which may delay diagnosis and increase complication rates. Midgut malrotation results from abnormal or incomplete rotation of the midgut during embryogenesis and may cause an atypically high position of the cecum and appendix. Appendicitis outside the right lower quadrant is associated with higher morbidity and mortality because clinical manifestations are variable and imaging may be inconclusive. We present a 26-year-old male patient admitted with one day of epigastric abdominal pain, nausea, and loss of appetite. Physical examination showed tenderness confined to the epigastrium, and laboratory evaluation revealed leukocytosis. Contrast-enhanced computed tomography did not visualize the appendix in the right lower quadrant and did not report signs suggestive of intestinal malrotation. Because symptoms persisted and pain increased during follow-up, diagnostic laparoscopy was performed within 12 hours of admission. Laparoscopy demonstrated midgut malrotation and an inflamed appendix located adjacent to the transverse colon; laparoscopic appendectomy was completed in the same session. The patient recovered uneventfully and was discharged 24 hours postoperatively, and histopathology confirmed acute appendicitis with localized peritonitis. Diagnostic laparoscopy is a valuable tool in atypical cases when clinical and radiological findings are insufficient, as it enables comprehensive evaluation of the abdominal cavity and allows definitive treatment without delay. In patients with atypical abdominal pain who cannot be diagnosed using conventional pathways, early consideration of congenital anomalies such as midgut malrotation and timely diagnostic laparoscopy are critical to prevent complications.

Keywords: acute appendicitis, midgut malrotation, transverse colon, atypical appendicitis

Introduction

Acute appendicitis is the most common cause of abdominal pain requiring general surgical attention in emergency departments. Several scoring systems have been developed to support diagnosis and operative decision-making, and the Alvarado score is the most widely used. Although practical, these scoring systems do not account for anatomical variations of the vermiform appendix, which may lead to diagnostic difficulty and delayed treatment. The appendix demonstrates substantial anatomical variability, and the most common location, regardless of sex, is the retrocecal position. This rate has been reported as 25.4% to 71.0% in the literature [1, 2].

Midgut malrotation is a congenital anomaly caused by incomplete or abnormal rotation of the midgut around the superior mesenteric artery during embryogenesis [3, 4]. This condition may result in abnormal positioning of the cecum and appendix, producing atypical clinical manifestations of appendicitis outside the right lower quadrant.

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Acute appendicitis remains one of the leading causes of acute abdominal surgery. Although the classic clinical course is well described, variations in appendiceal anatomy can significantly alter pain localization and delay diagnosis. In atypically located appendicitis, classical findings may be absent and standard diagnostic pathways may be insufficient.

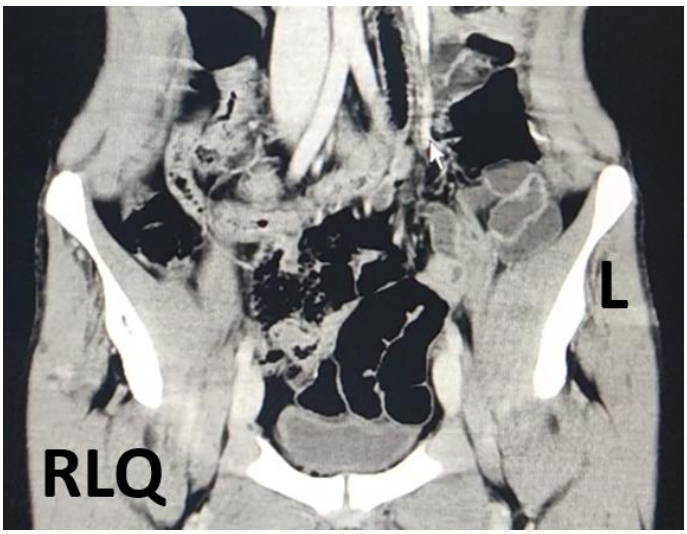
Imaging modalities such as ultrasonography and computed tomography have a central role in the diagnostic work-up, particularly in atypical presentations. Nevertheless, radiological assessment may be inconclusive when anatomical variations or congenital anomalies are present. Because delayed diagnosis in atypically located appendicitis is associated with increased morbidity, awareness of anatomical diversity is essential. In this context, we report a rare case of acute appendicitis located adjacent to the transverse colon due to midgut malrotation.

Case presentation

A 26-year-old male patient presented to the emergency department with one day of epigastric abdominal pain accompanied by nausea and loss of appetite. He had no known comorbidities. On physical examination, tenderness was limited to the epigastric region, without guarding or rebound. Examination of the remaining abdominal quadrants was unremarkable. Laboratory findings were as follows: C-reactive protein 1.6 mg/L (0–5), white blood cell count 15.36 K/µL (4–11), and neutrophils 74% (40–75).

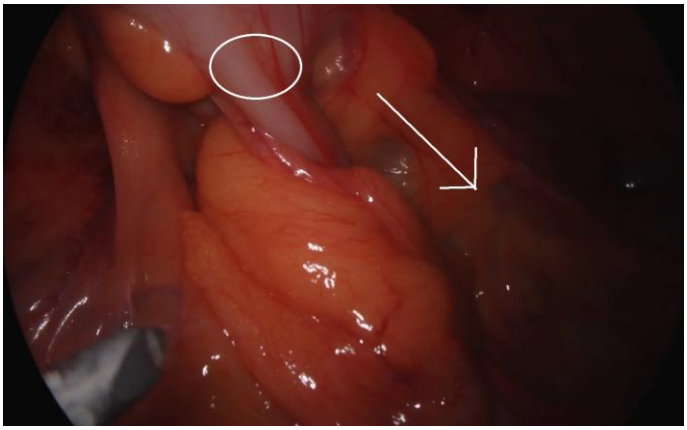
Contrast-enhanced computed tomography was performed for differential diagnosis. The radiology report stated that the appendix was not visualized in the right lower quadrant, and no radiological findings suggestive of intestinal malrotation, including an abnormal superior mesenteric artery–vein relationship, were reported (Figure 1).

Figure 1: Contrast-enhanced computed tomography image in the coronal plane demonstrating the right lower quadrant (RLQ), where the appendix could not be visualized. The left side of the patient is indicated (L). No radiological findings suggestive of intestinal malrotation were identified.



During follow-up after admission to the ward, symptoms persisted and the visual analog scale pain score increased. Diagnostic laparoscopy was performed within 12 hours of admission. Laparoscopic evaluation demonstrated midgut malrotation, with the appendix located adjacent to the transverse colon (Figure 2). Laparoscopic appendectomy was performed. The postoperative course was uncomplicated; the patient tolerated oral intake, mobilized without difficulty, and was discharged after 24 hours of observation. Histopathological examination confirmed acute appendicitis with localized peritonitis. Written informed consent was obtained from the patient for publication of this case and the accompanying images.

Figure 2: Laparoscopic view demonstrating the inflamed appendix (encircled) located adjacent to the transverse colon (arrow) in a patient with midgut malrotation.



Discussion

In patients presenting with non-localized or atypical abdominal pain, the underlying pathology may be an atypically located vermiform appendix rather than classic right lower quadrant appendicitis. Delayed diagnosis in such cases increases the risk of complications, including perforation and diffuse peritonitis [5, 6]. In the present case, early clinical reassessment and diagnostic laparoscopy within 12 hours of ward admission likely contributed to the favorable outcome by limiting disease progression.

Morbidity and mortality increase when acute appendicitis occurs outside the right lower quadrant [7]. Atypical presentations and diagnostic uncertainty can delay appropriate management. In our patient, the initial evaluation favored gastritis; however, persistent symptoms and abnormal laboratory findings prompted further assessment. Because contrast-enhanced computed tomography did not establish a definitive diagnosis and did not identify alternative common causes of acute abdomen, diagnostic laparoscopy was performed.

During normal embryologic development, the cecum and appendix settle in the right lower quadrant. In midgut malrotation, abnormal positioning of the cecum can relocate the appendix, resulting in non-classical symptoms. Acute appendicitis associated with malrotation has been reported with left lower quadrant or right upper quadrant pain, including presentations extending toward the hepatic flexure [8, 9]. Epigastric tenderness may also occur in conditions such as mobile cecum syndrome or in patients with a long appendix crossing the midline [7, 10].

In our case, intraoperative findings were most consistent with an incomplete rotation pattern rather than complete non-rotation. The cecum was positioned abnormally high, and the inflamed appendix was located adjacent to the transverse colon. No Ladd's bands or midgut volvulus were identified. Although transverse colon diverticulitis mimicking acute appendicitis has been reported, to our knowledge, acute appendicitis adjacent to the transverse colon associated with midgut malrotation, as observed here, has not been previously described [11].

Diagnostic laparoscopy is particularly valuable when clinical and radiological findings do not clarify the diagnosis. Di Buono et al. [12] emphasized the importance of a laparoscopic approach in anatomically atypical presentations such as situs inversus. Laparoscopy enables evaluation of the entire abdominal cavity and is associated with lower rates of incisional hernia and wound infection compared with laparotomy [13]. In this case, the primary rationale for laparoscopy was comprehensive intra-abdominal evaluation, which allowed diagnosis and treatment to be achieved in the same session.

The Alvarado score in our patient was 4, based on nausea (1 point), leukocytosis (2 points), and neutrophil shift (1 point). Although alternative scoring systems such as the Appendicitis Inflammatory Response score and the Raja Isteri Pengiran Anak Saleha Appendicitis score have been developed, these tools similarly do not evaluate congenital or positional anomalies that may underlie atypically located appendicitis [14].

In patients with atypical abdominal pain who cannot be diagnosed using conventional investigations, congenital anomalies such as midgut malrotation should be considered, and diagnostic laparoscopy should be considered early to prevent complications and establish the correct diagnosis.

Anatomical diversity is an essential consideration for surgeons. Atypical presentations, such as acute appendicitis located adjacent to the transverse colon due to midgut malrotation, can increase diagnostic uncertainty and delay treatment. In such situations, diagnostic laparoscopy can be highly useful when clinical and radiological evaluation is inconclusive, as it allows direct visualization of anomalies and enables definitive treatment without delay. This case highlights the importance of considering rare anatomical variations in the differential diagnosis of patients presenting with unusual abdominal pain in order to prevent complications.

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Dorsal lunate dislocation following a routine pickleball swing: A case report

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Abstract

Pickleball has gained substantial popularity across diverse age groups, and the increasing number of participants has been accompanied by more frequently reported injuries. Upper extremity conditions related to pickleball range from overuse tendinitis to fractures after falls. More serious injuries, including wrist fractures and dislocations, are typically associated with significant trauma. We present the case of a recreational pickleball player who sustained a dorsal lunate dislocation during a routine paddle swing, without a fall or direct impact. The injury was recognized after a delay, ultimately requiring treatment with a salvage procedure.

Keywords: pickleball, perilunate injury, lunate dislocation

Introduction

Dorsal lunate dislocation is a rare injury that results from disruption of the intercarpal and radiocarpal ligaments. In the Mayfield classification, lunate dislocation represents a later stage in the progression of perilunate injuries and is generally associated with substantial force [1]. In pickleball, the presumed mechanism would most commonly involve a fall onto an outstretched hand. The rarity of this injury pattern likely contributes to delayed diagnosis, and traumatic lunate dislocation is reported to be missed at initial assessment in a considerable proportion of cases [2]. Recognition is clinically important because the wrist is among the most frequently injured anatomic locations in pickleball [3, 4].

In this case report, a middle-aged recreational pickleball player sustained a dorsal lunate dislocation during a routine swing, without an associated fall or direct impact. A six-week delay in recognition resulted in the need for a salvage operation.

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Case presentation

A 63-year-old left-hand-dominant recreational pickleball player developed sudden, severe pain in the left wrist while swinging to return a serve. The pain was immediate and prompted him to stop playing. Despite rest and icing, symptoms persisted, and he was evaluated by a local physician. He was diagnosed with a wrist sprain and treated with anti-inflammatory medication. Because his symptoms did not improve, he presented to our orthopedic office five weeks after symptom onset.

His primary complaint was persistent throbbing pain with limited mobility, which led him to avoid using the left hand. He was particularly concerned about impaired ability to write, which affected his work as an attorney. He reported no prior injury or underlying wrist problems, including inflammatory conditions.

Physical examination demonstrated limited wrist extension and flexion, with full forearm supination and pronation. Goniometer measurements showed extension limited to 10 degrees and flexion to 30 degrees. There was no clinical evidence of generalized ligamentous laxity in the upper extremities. A tender dorsal bony prominence was apparent over the wrist. Digital range of motion was full, and the neurovascular examination was intact. Guarding was noted during attempted radial stress testing and weight-bearing maneuvers.

A dorsal lunate dislocation was suspected and confirmed on radiographs (Figure 1). Magnetic resonance imaging demonstrated complete tears of the scapholunate and lunotriquetral ligaments. Localized bone bruising was present without evidence of fracture.

Given the chronicity of the injury, primary reduction and ligament repair were considered unlikely to yield a satisfactory outcome. The patient therefore underwent proximal row carpectomy. Postoperative management included several months of formal physical therapy. At the final follow-up 6 months after surgery, he reported good functional recovery and return to activities of daily living. Goniometer measurements showed wrist extension of 60 degrees and flexion of 40 degrees, which were nearly equivalent to the contralateral side. Final radiographs demonstrated a well-maintained radiocapitate articulation (Figure 2). The patient intended to return to recreational pickleball.

Figure 1. Preoperative radiographs (anteroposterior and lateral views).

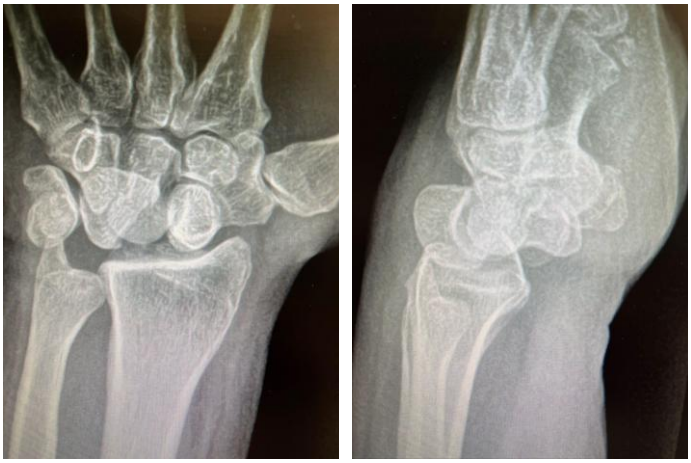
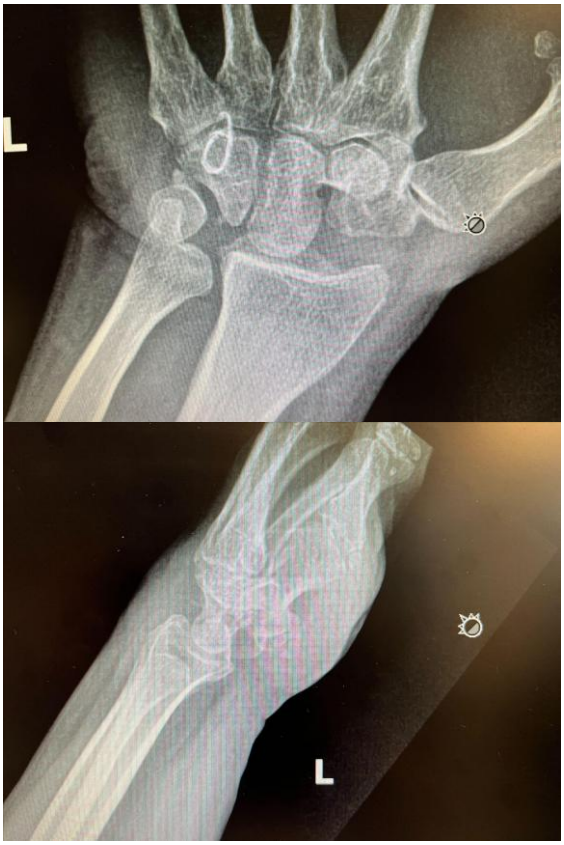


Figure 2. Six-month postoperative radiographs after proximal row carpectomy.



Discussion

Pickleball participation has increased markedly, with a parallel rise in sports-related injuries. Using National Electronic Injury Surveillance System data, Forrester reported that pickleball injuries involved the lower extremity in 32% and the upper extremity in 25.4% of cases [5]. Wrist injuries in pickleball have been reported at an incidence of 13.2% [3]. Recent reports emphasize that severe wrist injuries in pickleball are most commonly associated with a fall onto an outstretched hand, often resulting in distal radius fractures [6]. To our knowledge, dorsal lunate dislocation has not previously been reported as a pickleball-related injury.

Dorsal lunate dislocation is typically associated with high-energy trauma and is generally considered a Mayfield stage IV injury, reflecting severe carpal disruption [1]. Because this injury is uncommon, it may be overlooked during initial evaluation. Prior work suggests that approximately 25% of lunate dislocations are initially misdiagnosed, leading to treatment delays [2, 7].

In the present case, the absence of a perceived traumatic event contributed to an initial diagnosis of wrist sprain, followed by a six-week delay before definitive management. In acute and selected subacute settings, lunate reduction with primary ligamentous repair is generally recommended. With delayed presentation, salvage procedures such as proximal row carpectomy are more commonly considered. After discussion of treatment options, proximal row carpectomy was performed. Beyond chronic settings, this procedure may also be appropriate in acute cases complicated by vascular compromise and extensive ligamentous disruption [8, 9].

This case expands awareness of a potentially overlooked injury pattern in pickleball and raises questions regarding injury

mechanisms for dorsal lunate dislocation. Mayfield proposed that perilunate injuries occur because of force applied to a hyperextended wrist in ulnar deviation and intercarpal supination [1]. A reverse mechanism has also been described, in which injury progression occurs from the ulnar to the radial direction, producing a volar intercalated segmental instability pattern as an extended wrist undergoes intercarpal pronation [10]. Although dorsal lunate dislocation is generally attributed to high-energy trauma, isolated cases have been reported after comparatively minor mechanisms. Siddiqui and Sarkar described an isolated dorsal lunate dislocation after a sudden traction force when a dog pulled a patient's wrist, which they characterized as a trivial mechanism; that case was recognized early and treated with closed reduction and percutaneous pinning [11].

In the present case, given the lack of direct impact, it is plausible that an overzealous swing taking the wrist through a rapid extension-to-flexion arc contributed to the injury. Biomechanically, the pickleball paddle functions as a lever arm during the swing, with the wrist serving as a fulcrum and potentially amplifying forces across the carpus. Technique recommendations commonly emphasize maintaining a rigid wrist at ball contact to improve control [12]. Awareness of this potential injury may therefore be relevant not only for clinicians but also for coaches and players.

Sports participation can lead to clinically significant injuries, and timely diagnosis is critical for prompt treatment. This report describes a rare but consequential dorsal lunate dislocation that occurred during a routine pickleball swing and was recognized late, requiring a salvage procedure. Although proximal row carpectomy may still have been an appropriate treatment choice even with earlier presentation, delayed diagnosis prolonged pain and functional limitation until surgery. As pickleball is widely perceived as a low-impact sport and is particularly popular among recreational and older individuals, clinicians should remain vigilant for serious wrist injuries even after seemingly minor mechanisms.

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Popliteal artery rupture with closed degloving injury: A case report

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Ethical approval
This case report was approved by the Health Research Ethics Committee of Sultan Agung Islamic Hospital on June 16, 2025 (No. 99/KEPK-RSISA/VI/2025). All patient-related procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent
Verbal and written informed consent was obtained from the patient for publication of this case report and all accompanying images without personal identifiers.

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Abstract

Popliteal artery rupture is a rare but limb-threatening vascular injury, particularly when it occurs with a Morel-Lavallée lesion (closed degloving injury). The concurrent presence of complete arterial disruption and extensive soft-tissue damage substantially increases the risk of irreversible distal ischemia and amputation, especially when definitive intervention is delayed beyond the critical six-hour ischemic threshold. We report the case of a 29-year-old man who presented after a high-energy traffic accident with hemodynamic instability, absent distal arterial pulsation, and extensive subcutaneous fluctuation extending from the right thigh to the medial knee. Initial radiologic assessment revealed no fracture. Arteriography of the right femoral artery confirmed complete rupture of the right popliteal artery with nonvisualization of the posterior tibial, peroneal, and distal anterior tibial arteries beyond the injury site. Arteriographic delineation of the vascular occlusion level was used to determine the optimal amputation level. The patient underwent fluid resuscitation, transfusion of three units of whole blood, intravenous heparin therapy, surgical drainage of the closed degloving cavity, and primary amputation of the right lower extremity. Amputation was required because delayed presentation beyond the golden period had resulted in irreversible ischemia. He was discharged in stable condition after five days of hospitalization. This case underscores the need for early recognition and timely intervention in popliteal artery injuries. Delay beyond the ischemic threshold substantially increases the risk of amputation. A multidisciplinary approach and awareness of the narrow window for limb salvage are essential in complex lower extremity trauma.

Keywords: closed degloving injury, popliteal artery rupture, morel-lavallée lesion, arteriography, irreversible ischemia, amputation

Introduction

The popliteal artery is a continuation of the femoral artery that traverses the popliteal fossa and branches into the anterior tibial, posterior tibial, and peroneal arteries [1]. This artery plays a crucial role in supplying blood to the lower extremity below the knee, including the gastrocnemius, soleus, and plantaris muscles and the muscles of the foot [2]. Although the popliteal artery is protected by surrounding osseous and muscular structures, sufficiently high-energy trauma can cause serious injury. Popliteal artery injuries typically occur after blunt trauma, such as traffic accidents. Blunt trauma may damage the vessel wall, resulting in thrombus formation, contusion, or complete vascular rupture [3]. This condition is often accompanied by severe soft-tissue injury, including closed degloving injuries caused by substantial shear forces acting on the skin and subcutaneous tissue [4, 5]. Popliteal artery rupture is a severe vascular injury associated with a high lower-limb amputation rate because of tissue damage, circulatory compromise, and progressive tissue necrosis [5]. Complete rupture of the popliteal artery carries a high risk of irreversible distal ischemia when revascularization is not performed within six hours of injury [6, 7].

Closed degloving injury, also known as internal degloving injury or a Morel-Lavallée lesion (MLL), is a rare soft-tissue injury. It is usually caused by significant shear forces applied to the skin surface, which separate the skin and subcutaneous tissue from the underlying fascia. This process creates a potential space filled with blood, lymphatic fluid, and necrotic fat, resulting in a subcutaneous hematoma with varying degrees of tissue damage [8, 9]. MLLs may occur in the thigh, pelvis, knee, or lumbar region and are often not recognized at the initial trauma assessment, making diagnosis challenging in resource-limited settings. Despite their low incidence, serious complications such as infection, skin necrosis, and extremity dysfunction may occur if these lesions are not identified and managed in a timely manner. Diagnosis may be suggested by physical examination, while adjunctive imaging modalities such as ultrasonography and magnetic resonance imaging can support early detection and guide optimal management [9-11].

When ischemia is already irreversible on patient arrival, amputation becomes necessary to prevent life-threatening systemic complications of reperfusion injury, including hyperkalemia, myoglobinemia, and multiple organ failure [12, 13]. In such cases, arteriography has a dual role: it confirms the diagnosis and accurately defines the extent of vascular occlusion to guide the optimal amputation level, thereby reducing the risk of revision surgery at a more proximal level [13, 14]. This report describes the case and discusses the diagnostic approach, the role of arteriography in surgical planning, and relevant lessons for clinicians managing high-energy lower extremity trauma in resource-limited settings.

Case presentation

A 29-year-old man presented to the Emergency Department with right-leg pain after a traffic accident. The patient appeared clinically weak but had no altered consciousness on arrival. Primary survey examination showed a patent airway. Breathing assessment revealed dyspnea with a respiratory rate of 25 breaths per minute, without tracheal deviation or jugular venous distension. During circulatory evaluation, his blood pressure was 71/45 mmHg and his pulse rate was 140 beats per minute. Immediate resuscitation was initiated with 1000 mL of Ringer lactate, after which the patient showed a transient favorable response.

Examination of the right lower limb revealed erythema, edema, and extensive hematoma without visible deformity or open wound. On palpation, the limb was tender and markedly cool distally, with hypesthesia throughout the foot and complete absence of the right dorsalis pedis pulse. Extensive subcutaneous fluctuation was detected from the mid-thigh to the medial aspect of the knee, consistent with a large subfascial fluid collection. Active range of motion of the right lower extremity was markedly restricted, and passive ankle dorsiflexion was met with rigidity, suggesting advanced muscular ischemia (Figure 1).

Radiographic evaluation of the lumbosacral spine revealed lumbar scoliosis without fracture or dislocation. Anteroposterior pelvic radiography demonstrated no osseous abnormality, and plain radiographs of the right femur in anteroposterior and lateral projections similarly showed no fracture or dislocation (Figures 2-4).

Figure 1. Closed degloving injury involving the medial aspect of the right thigh and knee, demonstrating characteristic ecchymosis and subcutaneous fluctuation overlying a large Morel-Lavallée fluid collection. The absence of an open wound is consistent with the closed degloving mechanism.

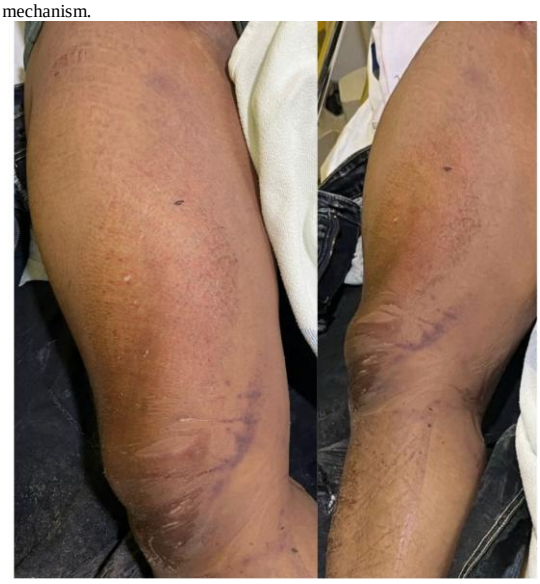


Figure 2. Lumbosacral spine X-ray. (A) Anteroposterior and (B) lateral views showing no dislocation but the presence of lumbar scoliosis. The absence of spinal injury directed clinical focus toward a vascular etiology for the patient's hemodynamic compromise.

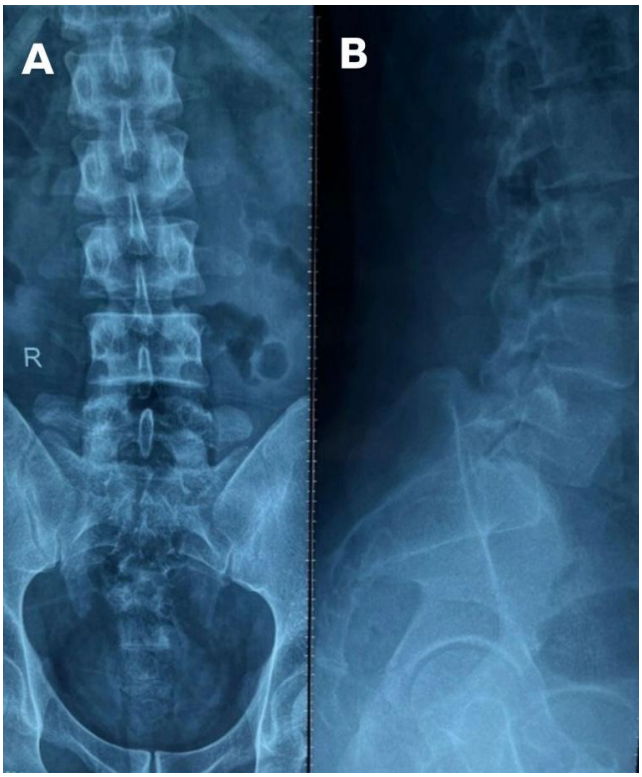


Figure 3. Pelvic X-ray, anteroposterior view, showing no fracture, dislocation, or bony abnormality. This finding, together with the femoral radiographs, confirmed the absence of skeletal injury and reinforced the suspicion of isolated vascular injury as the cause of distal ischemia.

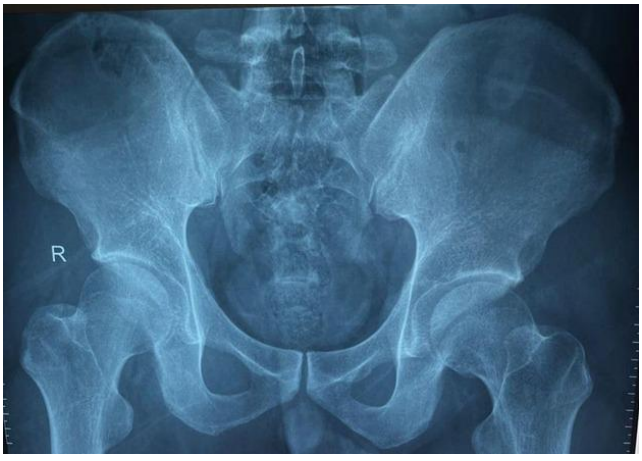
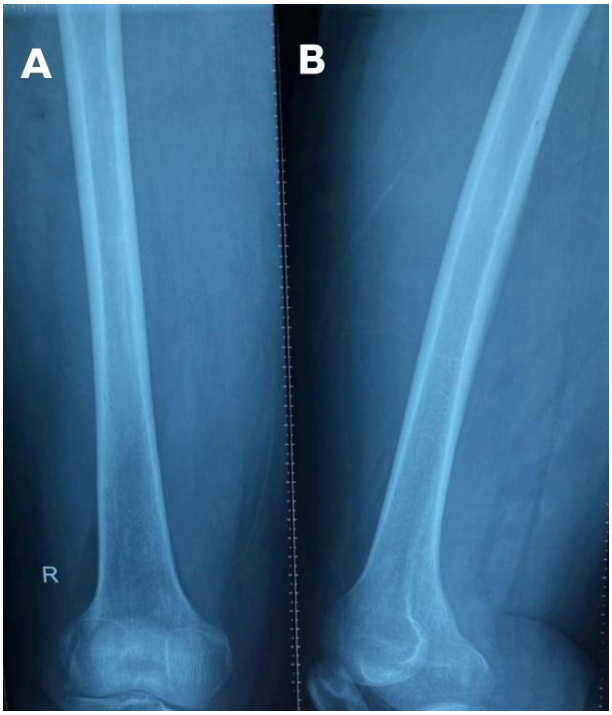
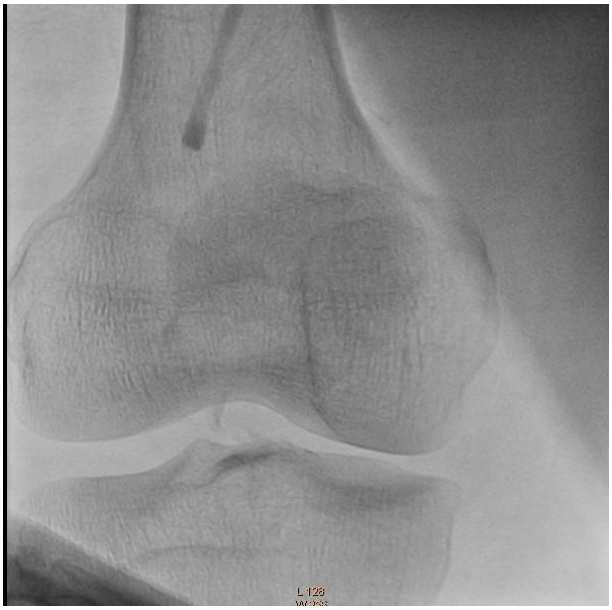


Figure 4. Right femur X-rays. (A) Anteroposterior and (B) lateral views confirming the absence of fracture, dislocation, or other osseous injury. The lack of skeletal injury, together with clinical signs of distal ischemia, confirmed an isolated vascular injury mechanism.



Arteriography of the right femoral artery was performed using the Seldinger technique with insertion of a 7-French vascular sheath, followed by catheter-guided contrast injection under fluoroscopic guidance. The study demonstrated complete transection of the right popliteal artery, with abrupt cessation of contrast opacification at the level of injury. The posterior tibial, peroneal, and distal anterior tibial arteries were entirely nonvisualized beyond the lesion, confirming total vascular occlusion without demonstrable collateral reconstitution. Considering the patient's hemodynamic instability and the unavailability of computed tomography angiography, conventional arteriography was selected as the most appropriate imaging method. The arteriographic finding of absent distal vessels was used to determine the appropriate level for primary amputation (Figure 5).

Figure 5. Arteriography of the right femoral artery demonstrating complete rupture of the right popliteal artery, accompanied by absence of blood flow in the posterior tibial, peroneal, and anterior tibial arteries distal to the injury site.



Following arteriography, the patient was admitted for inpatient care. Complete blood laboratory testing revealed low hemoglobin levels with hemodynamic instability. Resuscitation was therefore performed with three units of whole blood and colloids, and the patient was transferred to the Intensive Care Unit for further stabilization. Pharmacologic therapy included heparin at 250 IU per hour for two days, ketorolac 30 mg every eight hours, and ranitidine 50 mg every eight hours. Surgical management was performed after hemodynamic parameters had been adequately stabilized through resuscitation. The operation included primary above-knee (transfemoral) amputation of the right lower extremity at the level determined by arteriographic findings and confirmed intraoperatively based on the proximal extent of non-viable tissue. The patient was closely monitored in the Intensive Care Unit after surgery. He gradually improved clinically and was discharged in stable condition after a total hospital stay of five days.

Discussion

This case illustrates the diagnostic and therapeutic complexity encountered when complete popliteal artery rupture occurs in combination with an MLL in the absence of associated fracture. The interval between injury and arrival, combined with the time required for resuscitation and imaging, resulted in ischemia that exceeded the six-hour threshold described for extremity vascular injury [6, 7, 15]. Clinical findings, including an absent dorsalis pedis pulse, poikilothermia, hypesthesia, ankle rigidity, and severe restriction of active movement, precluded an attempt at limb salvage. Revascularization of a nonviable limb may cause fatal reperfusion injury due to systemic release of potassium, myoglobin, and reactive oxygen species [12, 16].

Conventional arteriography is useful for assessing distal blood vessels before amputation. The degree of occlusion and the patency of distal flow correlate with the likelihood of wound healing and can therefore help predict the appropriate amputation level [13, 16]. In this patient, the complete absence of all three infrapopliteal arteries indicated the absence of a viable vascular territory below the popliteal injury, supporting amputation above the zone of occlusion. This approach is consistent with guidance recommending preoperative vascular imaging before major lower extremity amputation to reduce the risk of subsequent revision at a more proximal level [17]. In resource-limited settings where computed tomography angiography is unavailable, conventional arteriography can fulfill this role effectively by providing high-resolution anatomic mapping and potential interventional access in a single session [18].

The concurrent MLL added further complexity to the surgical management. The most common causes of MLL are high-energy trauma, compressive injuries, and blunt trauma, including traffic accidents [4, 9]. MLLs predominantly occur in areas where mobile overlying skin overlies rigid fascia, such as the quadriceps fascia above the knee and the iliotibial fascia of the proximal lateral thigh [9]. In the present case, the lesion extended from the mid-thigh to the medial knee, consistent with commonly affected periarticular regions. Degloving injuries can be assessed clinically by skin examination, which may reveal ecchymosis, edema, fluctuation, skin hypermobility, and decreased skin sensation. As

the injury evolves, the overlying skin may become hardened and painful, indicating encapsulation of fluid collections [19].

When an MLL accompanies irreversible limb ischemia requiring amputation, management of the degloving component remains critical. If left untreated, fluid accumulation can lead to wound infection, delayed stump healing, and increased risk of revision amputation [20, 21]. Surgical drainage performed concurrently with amputation may reduce this risk. This approach is consistent with evidence supporting surgical management for extensive MLLs [9, 22].

Overall, this case highlights three principles that distinguish its management from the standard algorithm for popliteal artery injuries. First, the absence of fracture should not reduce clinical suspicion of vascular injury after high-energy lower extremity trauma. Second, when a patient presents beyond the golden period and arteriography confirms irreversible ischemia without distal blood flow, primary amputation is an appropriate life-saving intervention, and arteriographic findings can guide the optimal amputation level. Third, concomitant MLL must be actively identified and surgically treated during the same operative session to prevent infectious complications and support healing in patients undergoing amputation.

Conclusion

Popliteal artery rupture with concurrent MLL after blunt trauma is an exceptionally rare and clinically challenging combination. These conditions carry a high risk of irreversible limb loss, particularly when presentation is delayed beyond the six-hour ischemic threshold. Arteriography serves two purposes: confirming the diagnosis and defining the extent of vascular occlusion to establish the optimal level of amputation, thereby reducing the risk of revision surgery. Concomitant surgical drainage of MLLs is crucial for preventing infectious complications and promoting healing. A multidisciplinary approach is essential to optimize outcomes in these complex cases and underscores the life-saving value of systematic clinical protocols and early vascular assessment in all patients with high-energy lower extremity trauma.

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