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Preoperative c-reactive protein predicts next-day pain after breast tumor surgery

Преоперативни С-реактивни протеин предвиђа бол првог постоперативног дана након операције тумора дојке

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SUMMARY

Introduction/Objective Subclinical inflammation is increasingly recognized as a driver of postoperative pain, yet its role in breast tumour surgery is not fully defined. The objective was to determine whether preoperative C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) predict acute postoperative pain (APSP); to examine how surgical extent influences the peri-operative inflammatory response; and to explore the relation between intra-operative fentanyl and pain intensity.

Methods In a prospective single-centre cohort, 101 adults scheduled for breast surgery were stratified into four groups: mastectomy (M, n = 25), tumourectomy (T, n = 28), tumourectomy plus axillary dissection (T+A, n = 20), and benign excision (C, n = 28). Venous blood was drawn on admission (T0) and at 24 h (T24) for CRP and ESR. Pain was assessed with an 11-point Numerical Rating Scale 30 min after recovery and at 24 h; the highest 24-h score (max-APSP) was the primary pain outcome.

Results Pre-operative CRP correlated with max-APSP (p = 0.043), whereas ESR did not (p = 0.11). Baseline CRP and ESR, and their 24-h increments, rose stepwise with surgical magnitude, peaking after mastectomy (baseline CRP 7.1 ± 1.9 mg/L; T24 27.5 ± 3.6 mg·L/¹; both p < 0.01 *vs.* other groups). Intra-operative fentanyl correlated with CRP at 24 h (r = 0.33, p = 0.001) and with max-APSP (r = 0.28, p = 0.005). Despite these biological gradients, mean max-APSP remained mild to moderate across groups.

Conclusion Pre-surgical systemic inflammation, reflected by CRP, independently predicts early pain after breast tumour surgery. Surgical magnitude amplifies inflammatory markers, and greater fentanyl exposure parallels both inflammation and pain. Routine perioperative CRP may help identify high-risk patients for targeted anti-inflammatory and opioid-sparing analgesic strategies to reduce acute pain and potentially mitigate chronic pain development.

Keywords: acute postoperative pain; breast tumor surgery; C-reactive protein; erythrocyte sedimentation rate

САЖЕТАК

Увод/Циљ Субклиничка инфламација је важан фактор у настанку постоперативног бола, њена улога у хирургији тумора дојке није разјашњена. Циљ рада је испитивање вредности преоперативнних *C*-реактивног протеина (*CRP*) или седиментације еритроцита (*SE*) у предикцији акутног постоперативног бола (*APSP*);утицај обима хируршке интервенције на периоперативни инфламаторни одговор; испитивање повезаности интраоперативне примене фентанила и интензитета бола.

Методе Проспективна, једноцентрична кохортна студија укључила је 101 одраслог болесника планираних за операцију дојке подељених у четири групе: мастектомија (*M*, *n* = 25), туморектомија (*T*, *n* = 28), туморектомија са аксиларном дисекцијом (*T* + *A*, *n* = 20) и ексцизија бенигних промена (*C*, *n* = 28). Венска крв је узимана при пријему (*T*0), након 24 сата (*T*24). Бол је процењиван помоћу нумеричке скале (0–10) 30 минута након буђења из анестезије и након 24 сата; највиша вредност бола у прва 24 сата (*max-APSP*) примарни је исход.

Резултати Преоперативни *CRP* био је у корелацији са *max-APSP* (*p* = 0,043), *SE* није показала значајну повезаност (*p* = 0,11). Почетне вредности *CRP* и *SE*, као и њихов пораст након 24 сата, расле су пропорционално обиму хируршке интервенције, највише вредности код мастектомије (почетни *CRP* 7,1 ± 1,9 *mg/L*; *T24* 27,5 ± 3,6 *mg/L*; оба *p* < 0,01 у односу на остале групе). Интраоперативна примена фентанила била је у корелацији са *CRP* након 24 сата (p = 0,33, *p* = 0,001) и са *max-APSP* (p = 0,28, *p* = 0,005).

Закључак Преоперативна системска инфламација, представља независтан предиктор раног постоперативног бола након хирургије тумора дојке. Обим интервенције појачава инфламаторни одговор, већа примена фентанила прати већи степен инфламације и интензитет бола. Рутинско одређивање *CRP* у периоперативном периоду може помоћи у идентификацији болесника са високим ризиком и омогућити примену циљаних антиинфламаторних и опиоид-штедљивих аналгетских стратегија ради смањења акутног бола и потенцијалне превенције хроничног бола.

Кључне речи: акутни постоперативни бол; хирургија тумора дојке; *C*-реактивни протеин; седиментација еритроцита

INTRODUCTION

Breast cancer surgery is among the most frequently performed oncological procedures worldwide. Each year, more than two million women are diagnosed with breast cancer, with surgery remaining a core treatment modality [1, 2]. Despite advances in anaesthetic and analgesic techniques, acute postoperative pain (APSP) remains common; observational data suggest that up to 60% of patients report severe pain within the first 24 h, and inadequate early control is associated with a higher risk of persistent postsurgical pain (PPSP) [3, 4]. Unrelieved APSP impairs shoulder mobility, delays hospital discharge, and independently predicts poorer health-related quality of life, reinforcing the need for early risk stratification and procedure-specific, opioid-sparing multimodal pathways [4].

A growing body of translational research links perioperative systemic inflammation to nociceptive sensitisation. Recent neurobiological evidence indicates that perioperative tissue injury can activate immune–neuronal and glial pathways, promoting proinflammatory mediator release, peripheral sensitisation and central sensitisation [5]. In parallel, experimental and clinical studies have associated circulating inflammatory markers, particularly C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR), with heightened pain sensitivity, although the strength and timescale of these associations vary across settings [6, 7]. CRP, an acute-phase reactant predominantly regulated by interleukin-6, is a pragmatic index of short-term inflammatory flux, whereas ESR, though widely available, is less specific and may reflect chronic processes [8]. In mastectomy cohorts, higher CRP on postoperative day 1, alongside acute pain severity, has been associated with later PPSP/CPSP, supporting the premise that early inflammatory load shapes pain trajectories [9, 10].

Breast surgery provides a clinically relevant model to explore these relationships. Thus, the procedures share local tissue characteristics yet differ markedly in surgical scope - from breast-conserving tumourectomy to mastectomy with axillary clearance, creating a natural gradient of tissue trauma and systemic inflammatory response [11]. Contemporary evidence supports regional analgesia as an important component of opioid-sparing postoperative pain management after breast cancer surgery [12]. Existing literature has extensively examined CRP in breast cancer, including its prognostic value across patient subgroups [13]. Moreover, prior reports seldom adjust for intra-operative opioid dose, although experimental and translational evidence suggests that opioid exposure may paradoxically amplify postoperative nociception through neuro-inflammatory mechanisms consistent with opioid-induced hyperalgesia [14].

To address these gaps, we conducted a prospective, single-centre observational study of patients undergoing breast tumour surgery. We tested three prespecified hypotheses: (i) higher pre-operative CRP and ESR are associated with greater APSP intensity at 24 h; (ii) postoperative inflammatory marker levels rise in proportion to surgical extent; and (iii) intra-operative fentanyl dose correlates positively with APSP intensity at 24 h. By clarifying how routine inflammatory biomarkers relate to early pain outcomes across different surgical magnitudes, our findings aim to inform risk-stratified analgesic

planning and to stimulate future interventional trials that target perioperative inflammation in breast cancer patients.

METHODS

Study design and participants

A prospective, single-centre observational study was conducted at the Department of Oncological Surgery, University Hospital Medical Center "Bežanijska kosa", Belgrade, Serbia, between 1 August and 30 November 2022. The study was approved by the Institutional Ethics Committee of Clinical Hospital Centre "Bežanijska kosa" (protocol No. 4831/1, 22.07.2022). All participants provided written informed consent. The investigation complied with the Declaration of Helsinki and followed GDPR-compliant data-protection procedures.

Consecutive adult patients (≥ 18 years) scheduled for elective breast tumour surgery were screened. Inclusion criteria were: histologically confirmed breast tumour (benign or malignant), physical status I–III, planned postoperative ward admission, and written informed consent. Exclusion criteria comprised incomplete medical records, pre-existing breast pain on the day of surgery, withdrawal of consent at any time, locally advanced or metastatic disease (stage IV), allergy to anaesthetic agents, or intra-/early postoperative complications requiring protocol deviation. After screening 142 patients, 101 met all criteria and were enrolled. According to surgical extent and final histology they were stratified into four predefined groups: 1) Mastectomy (M) – malignant, entire breast removed (n = 25); 2) Tumourectomy (T) – malignant, tumour excision only (n = 28); 3) Tumourectomy + axillary dissection (T + A) – malignant, tumour excision with axillary clearance (n = 20); 4) Benign excision (C) – benign lesion removed (n = 28).

Methods

General anesthesia was standardized in all study groups. Anesthesia was induced with propofol (1.5 mg/kg IV) and rocuronium bromide (0.9–1.2 mg/kg IV) to facilitate endotracheal intubation. Anesthesia was maintained with sevoflurane in an oxygen/air mixture, with the end-tidal concentration adjusted according to routine clinical practice to maintain an adequate depth of anesthesia. Intraoperative analgesia consisted of fentanyl administered intravenously and titrated according to the patient's clinical response and the extent of the surgical procedure. Additional fentanyl was titrated at the anaesthetist's discretion and the total intraoperative dose recorded (50 µg/mL solution).

Venous blood was drawn on admission (T_0) and at 24 h post-surgery (T_{24}). Erythrocyte sedimentation rate (ESR, mm/h) and C-reactive protein (CRP, mg/L) were analysed in the hospital laboratory using standardised turbidimetric assays.

Acute postoperative pain in the surgical breast was measured with an 11-point Numerical Rating Scale (NRS; 0 = no pain, 10 = worst imaginable) – a tool validated for postoperative settings. Scores were

obtained at T_0, 30 min after arrival in the recovery room ($T_{0.5}$), and at T_{24}. For analysis, the highest score within the first 24 h was designated the maximal acute postoperative pain. Between the scheduled pain assessments (30 minutes and 24 hours after surgery), postoperative analgesia consisted of non-steroidal anti-inflammatory drugs (NSAIDs), administered according to the institutional postoperative pain protocol and routine clinical assessment by the nursing staff. The same postoperative analgesic strategy was applied to all study groups.

Primary outcome: association between pre-operative CRP/ESR and max-APSP. Secondary outcomes: (i) relationship between surgical extent and postoperative CRP/ESR; (ii) correlation between intra-operative fentanyl dose and maximal acute postoperative pain.

Statistical analysis

Continuous variables are reported as mean ± SEM with ranges, and categorical variables as counts (percentages). Normality was assessed with the Shapiro–Wilk test and inspection of Q–Q plots; homogeneity of variances with Levene's test. Between-group comparisons used one-way ANOVA when assumptions were met; post-hoc tests were selected a priori according to variance diagnostics: LSD or Bonferroni when variances were homogeneous, and Games–Howell when they were not. Associations between continuous measures were examined using Pearson's correlation coefficient (r) after checking linearity and distributional assumptions. To assess whether preoperative CRP was independently associated with maximum 24 h APSP, a multivariable linear regression analysis within the general linear model framework was performed. Surgical group was entered as a fixed categorical factor, whereas preoperative CRP, preoperative ESR, intra-operative fentanyl dose, age and BMI were entered as covariates. All tests were two-sided with $\alpha = 0.05$. Analyses were performed in IBM SPSS Statistics v25.

RESULTS

Participant's baseline characteristics

The patients that met all eligibility criteria were enrolled (N = 101). Almost the entire cohort was female (100/101, 99 %). Mean age was 56.4 ± 1.7 years (range 19–88) and differed across surgical-extent strata: benign excision (C) patients were significantly younger than all malignancy groups (ANOVA $F = 25.622$, $p < 0.001$). The four predefined groups comprised 25 mastectomies (M) - mean age 61.96 ± 2.56 years (32–81); 28 tumourectomies (T) 65.93 ± 2.48 years (41–88); 20 tumourectomy + axillary dissections (T + A) 61.76 ± 2.43 years (38–76); and 28 benign excisions (C) 38.07 ± 2.79 years (19–71) (Figure 1A).

The mean tumour size across all patients was 23.45 ± 1.35 mm (range 8–98). By group, mean sizes were as follows: C, 21.42 ± 1.69 mm (10–47); M, 28.58 ± 3.82 mm (10–98); T, 21.11 ± 1.58 mm (8–40); and

T+A, 23.2 ± 3.56 mm (10–80). There was no statistically significant difference in tumour size between the groups (ANOVA: $F = 1.684$; $p > 0.05$) (Figure 1B).

The mean body mass index (BMI) for the cohort was 25.84 ± 0.46 kg/m² (range 15.92–38.54). By group, mean BMI values were as follows: C, 23.31 ± 0.88 kg/m² (15.92–34.89); M, 26.52 ± 0.87 kg/m² (20.2–36.25); T, 27.56 ± 0.91 kg/m² (18.29–38.54); and T+A, 26.11 ± 0.82 kg/m² (17.72–32.83). Patients with malignant breast tumours who underwent tumour excision (T) had a significantly higher BMI than those who underwent excision of a benign lesion (C) (ANOVA: $F = 4.634$; $p < 0.05$) (Figure 1C).

Primary outcome – association between preoperative inflammation and 24 h pain

In analyses of patients undergoing surgical excision of a breast tumour, a statistically significant correlation was observed between admission CRP and the maximum intensity of acute postoperative pain at 24 h (Pearson's $r = 0.246$; 95% CI 0.053 to 0.421; $p < 0.05$; Table 1). Admission CRP also correlated significantly with CRP at 24 h ($r = 0.574$; 95% CI 0.426 to 0.692; $p < 0.001$), with the ESR at admission ($r = 0.553$; 95% CI 0.401 to 0.675; $p < 0.001$) and at 24 h ($r = 0.539$; 95% CI 0.384 to 0.664; $p < 0.001$), as well as with the intraoperative fentanyl dose ($r = 0.232$; 95% CI 0.038 to 0.409; $p < 0.05$).

In addition to its positive correlation with admission CRP, the intraoperative fentanyl dose correlated significantly with CRP at 24 h ($r = 0.325$; 95% CI 0.138 to 0.489; $p = 0.001$), with ESR at admission ($r = 0.256$; 95% CI 0.064 to 0.430; $p = 0.01$), and with the maximum intensity of acute postoperative pain at 24 h ($r = 0.279$; 95% CI 0.088 to 0.450; $p < 0.01$) (Table 1).

To address potential confounding, a multivariable linear regression analysis within the general linear model framework was performed with maximum 24 h APSP as the dependent variable. Surgical group was entered as a fixed categorical factor, while preoperative CRP, preoperative ESR, intra-operative fentanyl dose, age and BMI were entered as covariates. The overall model was statistically significant ($F = 2.860$, $p = 0.007$; $R^2 = 0.199$; adjusted $R^2 = 0.130$). Preoperative CRP remained independently associated with maximum 24 h APSP after adjustment for surgical group, preoperative ESR, intra-operative fentanyl dose, age and BMI ($p = 0.014$). Intra-operative fentanyl dose was also independently associated with maximum 24 h APSP ($p = 0.007$), whereas preoperative ESR, age, BMI and surgical group were not independently associated with this outcome.

Inflammatory marker levels in relation to surgical extent in breast tumor surgery

The mean CRP on admission for the whole cohort was 3.75 ± 0.55 mg/L (range 0.6–36.2). By group, mean admission CRP values were as follows: C, 1.96 ± 0.37 mg/L (0.6–8.5); M, 7.08 ± 1.86 mg/L (0.6–36.2); T, 3.46 ± 0.73 mg/L (0.6–14.5); and T+A, 2.5 ± 0.39 mg/L (0.6–7.3). Between-group comparisons showed that patients undergoing mastectomy (M) had significantly higher circulating CRP on admission than those who underwent tumour excision (T) (ANOVA, post hoc LSD, $p < 0.05$), tumour excision with axillary dissection (T+A) (ANOVA, post hoc LSD, $p < 0.01$), and excision of a benign lesion (C) (ANOVA, post hoc LSD, $p < 0.01$) (Figure 2A).

The mean CRP at 24 h postoperatively for the whole cohort was 14.17 ± 1.41 mg/L (range 0.6–82.4). By group, mean postoperative CRP values were as follows: C, 5.22 ± 1.14 mg/L (0.6–23.4); M, 27.54 ± 3.61 mg/L (3.9–82.4); T, 11.96 ± 1.8 mg/L (0.9–34.9); and T+A, 13.11 ± 2.19 mg/L (0.9–43.6). Comparisons across groups, stratified by surgical extent, showed that patients who underwent mastectomy (M) had significantly higher circulating CRP at 24 h than those who underwent tumour excision (T) (ANOVA, post hoc Games–Howell, $p < 0.05$), tumour excision with axillary dissection (T+A) (ANOVA, post hoc Games–Howell, $p < 0.05$), and excision of a benign lesion (C) (ANOVA, post hoc Games–Howell, $p < 0.001$) (Figure 2B).

The mean ESR on admission was 23.62 ± 1.75 mm/h (range 2–75). By group, mean admission ESR values were as follows: C, 14.32 ± 2.32 mm/h (2–49); M, 33.48 ± 3.86 mm/h (9–75); T, 24.71 ± 3.06 mm/h (2–60); and T+A, 22.8 ± 3.98 mm/h (2–73). Between-group comparisons showed significantly higher ESR on admission in patients who underwent mastectomy (M) compared with those who had excision of a benign lesion (C) (ANOVA: $F = 6.050$; post hoc Bonferroni, $p < 0.001$) (Figure 3A).

At 24 h after surgery, the cohort's mean ESR was 20.09 ± 1.55 mm/h (range 2–64). Across groups, postoperative means were as follows: C, 11.46 ± 1.61 mm/h (2–31); M, 26.28 ± 3.48 mm/h (2–64); T, 24.71 ± 3.06 mm/h (2–60); and T+A, 18 ± 3.22 mm/h (2–55). Comparative analysis by surgical extent indicated significantly lower postoperative ESR in the benign excision group (C) than in the mastectomy group (M) (ANOVA, post hoc Games–Howell, $p < 0.01$) and the tumour excision group (T) (ANOVA: $F = 5.863$; post hoc Games–Howell, $p < 0.01$) (Figure 3B).

Intraoperative fentanyl dose and acute postoperative pain

There was a statistically significant positive correlation between intraoperative fentanyl dose and the maximum intensity of acute postoperative pain at 24 h (Pearson's $r = 0.279$; 95% CI 0.088 to 0.450; $p < 0.01$; Table 1). For the cohort overall, the mean intraoperative fentanyl volume was 5.47 ± 0.19 mL (range 0.5–10). By group, the means were as follows: C, 4.17 ± 0.24 mL (2–8); M, 7.28 ± 0.3 mL (5–10); T, 4.52 ± 0.32 mL (0.5–7); and T+A, 6.35 ± 0.27 mL (4–8). Patients in the benign excision group (C) received significantly less fentanyl than those who underwent mastectomy (M) (ANOVA, post hoc Games–Howell, $p < 0.001$) and those who had tumour excision with axillary dissection (T+A) (ANOVA: $F = 26.544$; post hoc Games–Howell, $p < 0.001$) (Figure 4).

The mean maximum postoperative pain intensity within 30 minutes ($T_{0.5}$) of surgery for the cohort was 2.56 ± 0.21 (range 0–8). By group, the means were as follows: C, 2.11 ± 0.37 (0–8); M, 1.92 ± 0.32 (0–5); T, 3.35 ± 0.48; and T+A, 2.9 ± 0.46 (0–8). Between-group comparison showed a significant difference at 30 minutes, with patients who underwent excision of a malignant tumour (T) reporting higher maximum pain intensity than those with excision of a benign lesion (C) (ANOVA: $F = 2.786$; post hoc least significant difference [LSD], $p < 0.05$) (Figure 5A).

The mean maximum postoperative pain intensity within 24 h (T_{24}) for the cohort was 2.17 ± 0.21 (range 0–8). By group, the means were: C, 1.5 ± 0.31 (0–5); M, 2.16 ± 0.39 (0–6); T, 2.35 ± 0.37 (0–5); and T+A, 2.85 ± 0.59 (0–8). There were no statistically significant differences between groups in maximum pain intensity within 24 h of surgery (ANOVA: F = 1.810; p = 0.150) (Figure 5B).

DISCUSSION

We set out to examine whether routine inflammatory markers and intraoperative opioid exposure relate to early pain after breast-tumour surgery across different procedures. In this single-centre prospective cohort we observed three robust signals. First, higher preoperative CRP predicted more intense pain 24 h after breast-tumour surgery, whereas ESR did not. Second, CRP and ESR rose in proportion to surgical magnitude. Thus, patients undergoing mastectomy exhibited the highest baseline and postoperative CRP and ESR values, followed by those receiving axillary dissection, tumourectomy, and benign excision. Third, the total intraoperative fentanyl dose correlated positively with both inflammatory load and 24 h pain intensity, suggesting a neuro-immune opioid–pain feedback loop. Although mean numeric-rating scores at 24 h were generally mild, up to 40 % of individuals still reported clinically relevant pain (NRS ≥ 4), confirming that breast surgery, even in the era of enhanced recovery, remains a procedure with substantial nociceptive burden.

Our findings align with growing evidence that low-grade systemic inflammation primes postoperative pain. Associations between perioperative CRP dynamics and acute postoperative pain have been demonstrated in other surgical populations, including total knee arthroplasty [15]. Evidence specific to breast surgery remains limited, with signals reported in mastectomy cohorts and studies linking systemic inflammation to early postoperative recovery [9, 10]. CRP generally outperforms ESR as a short-term index of inflammatory flux, consistent with its biology, while ESR is slower and more influenced by chronic processes (e.g., anaemia, age) [8]. Our mastectomy subgroup showed a four-fold higher mean CRP at 24 h than benign excision, reinforcing the concept that tissue load predicts systemic inflammation. The gradient we observed in inflammatory response across surgical extent mirrors prior evidence that postoperative CRP kinetics vary according to the type and magnitude of surgical trauma [16]. Despite such biological gradients, early pain scores did not differ between groups at 24 h. Two non-mutually exclusive explanations are plausible. First, that effective multimodal analgesia may have equalised pain perception, and the second, that the NRS, while valid and practical, captures only intensity, not qualitative dimensions such as movement-evoked pain [17]. Future studies incorporating quantitative sensory testing and breast surgery-specific patient-reported outcome measures may reveal more nuanced group differences [18].

Mechanistic insights

The breast-cancer micro-environment is characterised by tumour-associated macrophages, fibroblasts and cytokines that elevate circulating CRP and other acute-phase reactants [19]. High pre-operative CRP in mastectomy patients therefore likely reflects both tumour-driven inflammation and subclinical systemic inflammation secondary to comorbidities (obesity, metabolic syndrome) [20]. Tissue trauma may amplify this inflammatory state through the release of damage-associated molecular patterns and activation of inflammatory signalling pathways, including NF-κB, within the tumour and perioperative immune microenvironment [21].

Activated nociceptors express pattern-recognition receptors; IL-1β and TNF trigger ion-channel phosphorylation that lowers firing thresholds, while Fcγ-receptor signalling engaged by CRP–immune complexes at the neuro-immune interface can enhance excitability. Hence, patients entering theatre with high CRP may begin their postoperative course with a "primed" nociceptive system, explaining the correlation we observed.

Pre-clinical and translational data suggest that opioid exposure can interact with microglial and neuroinflammatory pathways, increasing pro-inflammatory signalling and potentially contributing to paradoxical postoperative pain amplification [22]. These mechanisms are concordant with experimental and translational evidence implicating neuro-inflammatory and inflammasome pathways in opioid-induced hyperalgesia and tolerance [14]. In our cohort, higher fentanyl requirements paralleled CRP and ESR elevations and predicted greater 24-h pain, supporting this paradigm and suggesting that opioid sparing may attenuate neuro-immune sensitisation.

Clinical implications

Routine peri-operative CRP measurement could be an inexpensive tool for risk stratification. Patients whose CRP exceeds a yet to be defined threshold might benefit from intensified, opioid-sparing multimodal analgesia, including regional techniques and non-opioid analgesic adjuncts where appropriate [23].

Persistent inflammation is strongly linked to chronic pain; after breast cancer treatment, clinically relevant shoulder or chest-wall pain remains common months after surgery [24]. Identifying a high-inflammation phenotype pre-operatively may offer an opportunity to intervene before the transition to chronic pain occurs. Longer-term follow-up of this cohort will determine whether baseline CRP adds prognostic value to existing chronic pain prediction models.

Our data also prompts re-evaluation of routine opioid dosing in breast surgery. Adoption of regional anaesthesia (paravertebral or pectoral nerve blocks) and adjuvants that reduce systemic opioid exposure may diminish both inflammation and hyperalgesic potential, ultimately improving short- and long-term outcomes [12, 14, 23].

Limitations

Strengths of this study include prospective design, simultaneous measurement of two biomarkers and inclusion of a benign-tumour control group, enabling separation of tumour-driven from surgery-driven inflammation. Limitations comprise single-centre scope, modest sample size per stratum and reliance on a unidimensional pain scale. The exclusion of regional blocks, while methodologically necessary to isolate the inflammation–pain axis, limits generalisability to settings where such analgesia is standard. Finally, we did not measure pro- and anti-inflammatory cytokines or genetic polymorphisms that might refine mechanistic understanding.

CONCLUSION

Proinflammatory status, captured by CRP but not ESR, is an independent determinant of early pain after breast-tumour surgery. Surgical magnitude and intraoperative opioid dose further modulate the inflammatory–pain axis. Routine CRP assessment may guide personalised analgesic strategies and offers a biomarker target for trials aimed at preventing persistent postsurgical pain.

Future studies should establish and externally validate simple, bedside CRP thresholds that predict clinically meaningful 24–48 h pain, and test whether dampening perioperative inflammation, via optimised multimodal care and selective anti-inflammatory strategies (e.g., peri-operative corticosteroids or IL-6 pathway modulation), reduces acute pain and subsequent persistence. Prediction models ought to incorporate psychophysical and psychosocial measures alongside biology to reflect the broader pain network. Finally, randomised trials comparing opioid-sparing *vs.* opioid-rich anaesthesia, with immune profiling and rigorous pain phenotyping, are needed to clarify the opioid–cytokine interface and its impact on short- and longer-term outcomes.

Ethics: This study was approved by the Institutional Ethics Committee of Clinical Hospital Centre "Bežanijska kosa" (protocol No. 4831/1, 22.07.2022). All participants provided written informed consent prior to enrolment. Consent for publication of anonymized study data was obtained.

Conflict of interest: None declared.

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Table 1. Correlations of CRP at admission and intra-operative fentanyl dose with inflammatory markers and pain outcomes

Variable	Admission CRP r (95% CI)	Admission CRP (p)	Intra-operative fentanyl r (95% CI)	Intra-operative fentanyl (p)
Admission CRP	–	–	0.232* (0.038–0.409)	0.019
CRP at 24 h (mg/l)	0.574** (0.426–0692)	< 0.001	0.325** (0.138–0.489)	0.001
ESR at admission (mm/h)	0.553** (0.401–0.675)	< 0.001	0.256** (0.064–0.430)	0.010
ESR at 24 h (mm/h)	0.539** (0.384–0.664)	< 0.001	0.160 (0.037–0.345)	0.109
APSP at 30 min (NRS 0–10)	0.062 (0.013–0.154)	0.536	0.150 (0.047–0.336)	0.133
APSP at 24 h (NRS 0–10)	0.246* (0.053–0.421)	0.043	0.279** (0.088–0.450)	0.005
Intra-operative fentanyl dose (mL; 50 µg/ml)	0.232* (0.038–0.409)	0.019	–	–

Pearson's correlation (two-tailed);

*p < 0.05;

**p < 0.01;

CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; APSP – acute postoperative pain; NRS – numerical rating scale

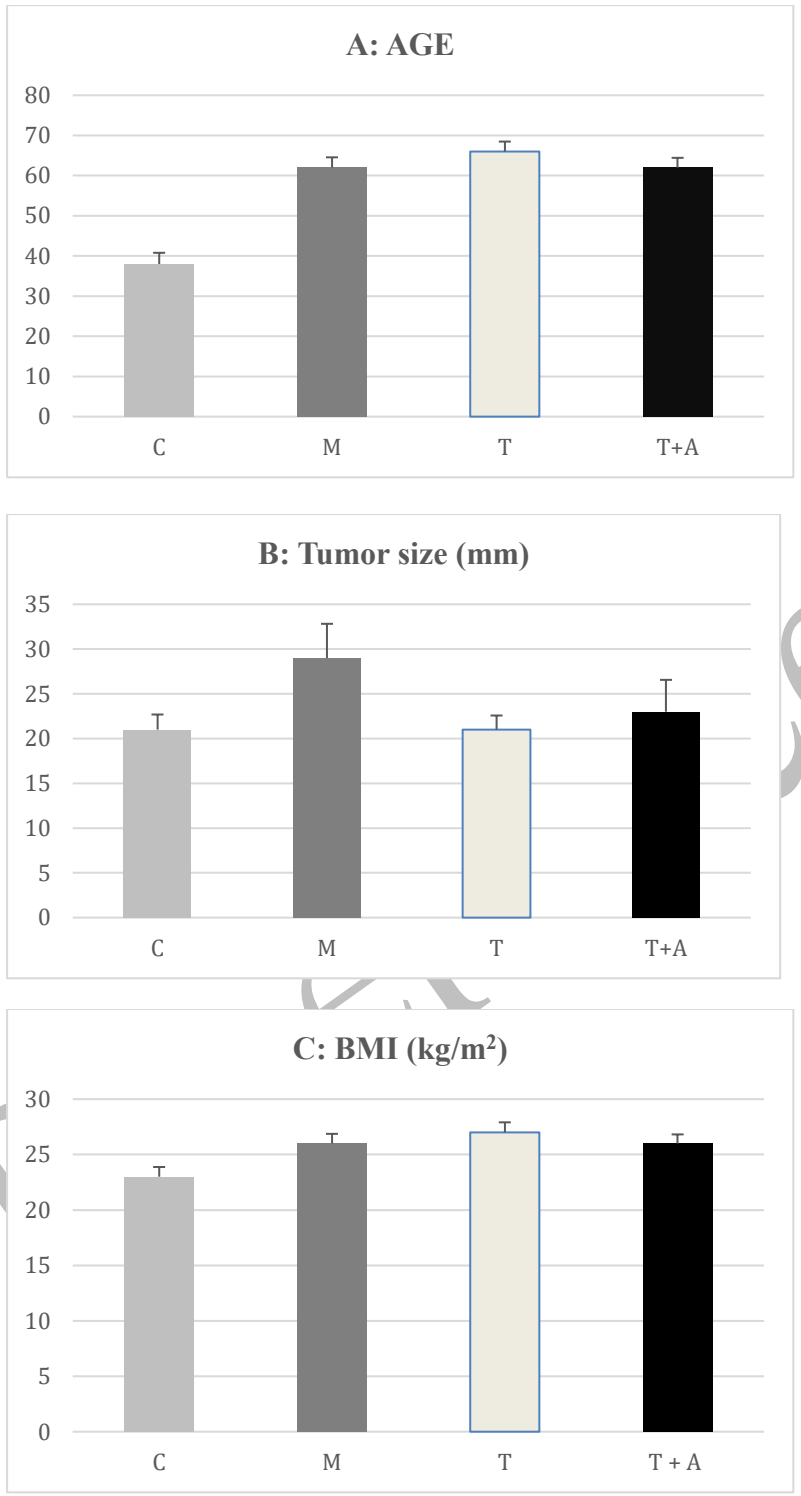
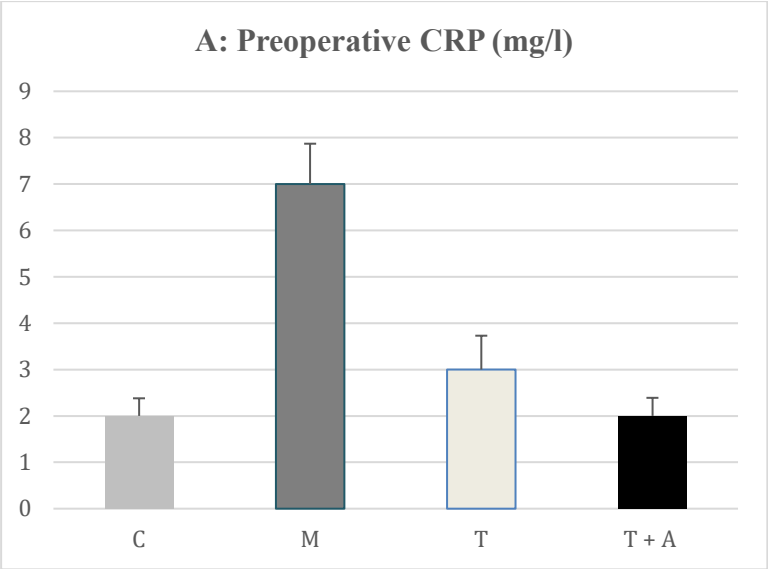


Figure 1. Baseline characteristics by surgical group; (A) age (years); one-way ANOVA with Bonferroni post hoc, $p < 0.01$; (B) tumor size (mm); one-way ANOVA, $F = 1.684$, $p > 0.05$; (C) body mass index (kg/m²); one-way ANOVA with Bonferroni post hoc, $p < 0.05$; data are mean ± SEM;

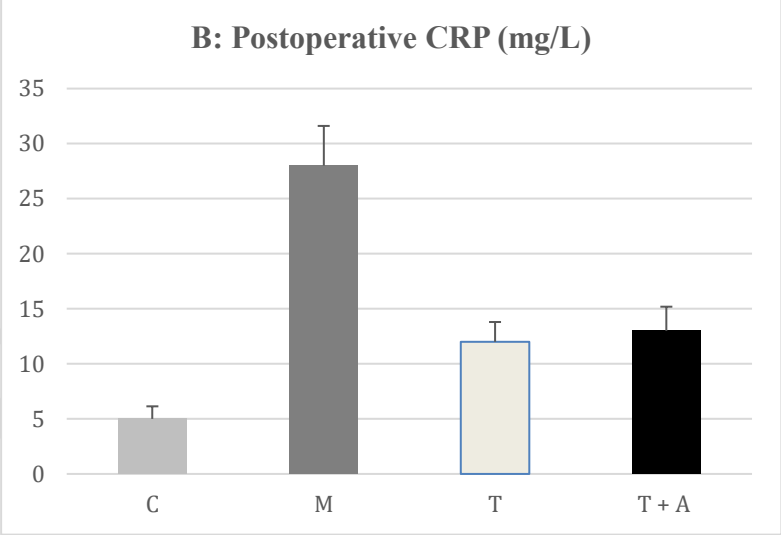
C – benign lesion excision; T – malignant tumorectomy; T + A – malignant tumorectomy with axillary dissection; M – mastectomy;

significance: $p < 0.05$



$p < 0.05$ (M *vs.* T);

$p < 0.01$ (M *vs.* C; M *vs.* T+A)



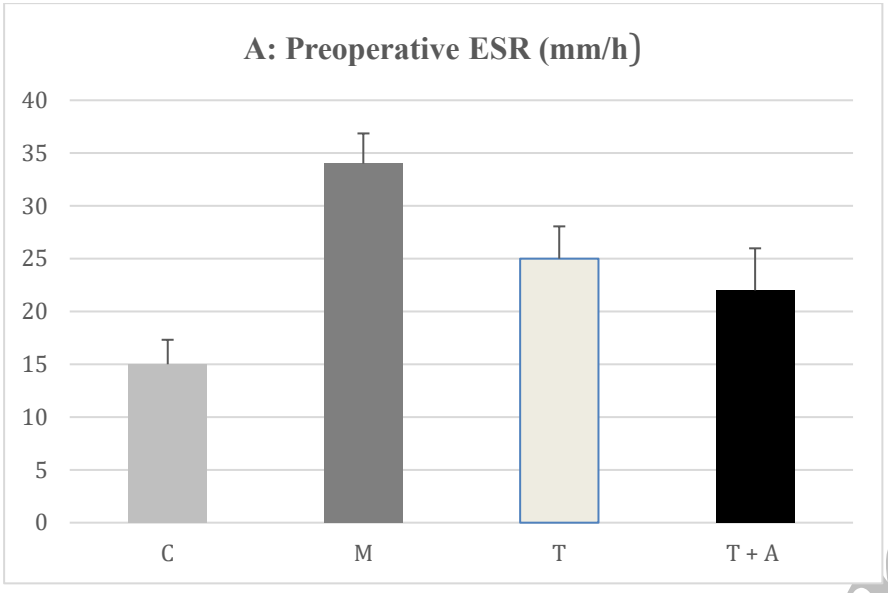
$p < 0.05$ (M *vs.* T; M *vs.* T+A);

$p < 0.001$ (M *vs.* C);

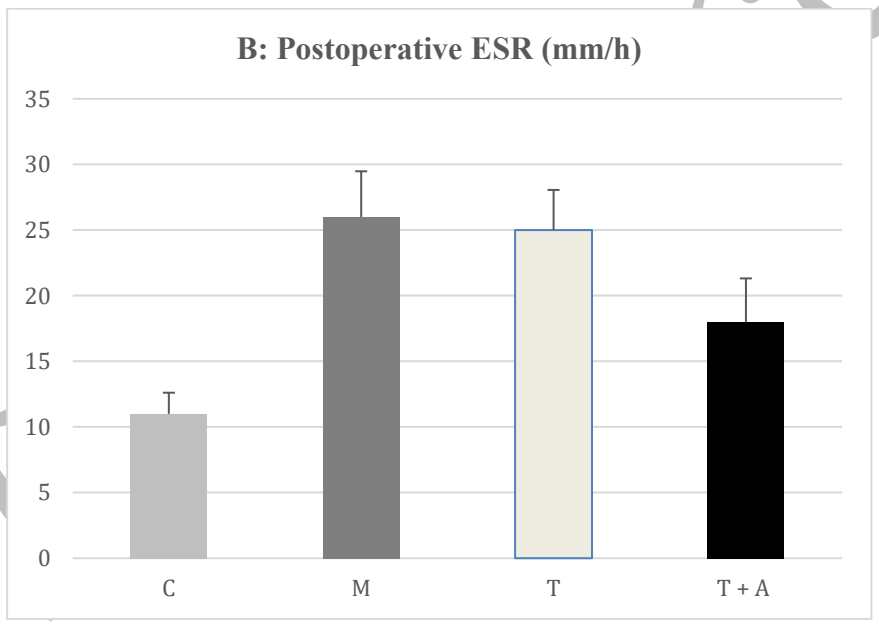
Figure 2. C-reactive protein (CRP) by surgical group; (A) admission CRP (mg/L); one-way ANOVA with LSD post hoc: $p < 0.05$ (M *vs.* T); $p < 0.01$ (M *vs.* C; M *vs.* T + A); (B) CRP at 24 h (mg/L); one-way ANOVA with Games–Howell post hoc: $p < 0.05$ (M *vs.* T; M *vs.* T+A); $p < 0.001$ (M *vs.* C); data are mean ± SEM;

C – benign lesion excision; T – malignant tumorectomy; T + A – malignant tumorectomy with axillary dissection; M – mastectomy;

significance: $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***)



$p < 0.001$ (M *vs*. C)

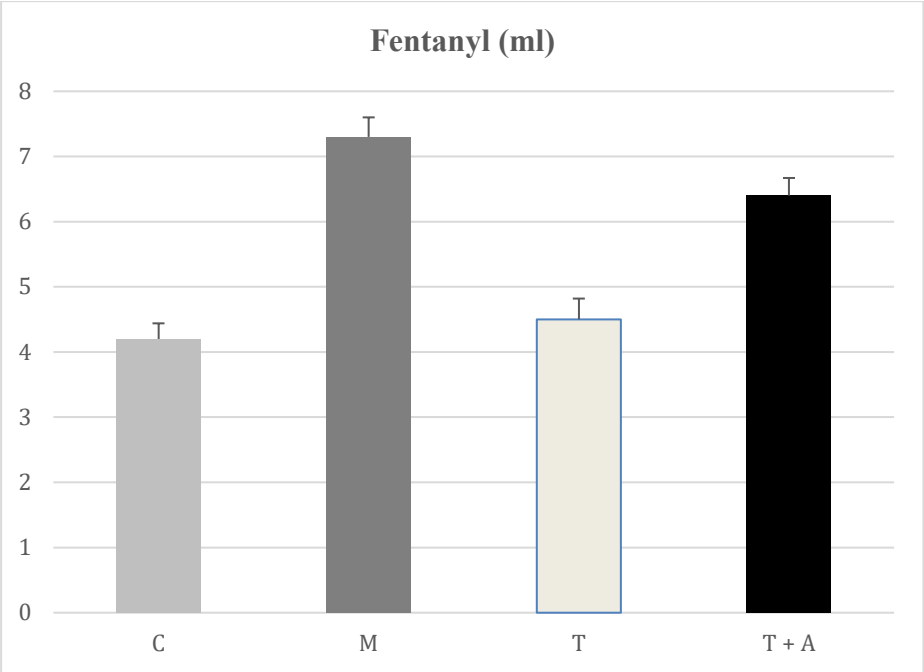


$p < 0.01$ (C *vs*. M; C *vs*. T)

Figure 3. Erythrocyte sedimentation rate (ESR) by surgical group; (A) admission ESR (mm/h); one-way ANOVA with Bonferroni post hoc: $p < 0.001$ (M *vs*. C); (B) ESR at 24 h (mm/h); one-way ANOVA with Games–Howell post hoc: $p < 0.01$ (C *vs*. M; C *vs*. T); data are mean ± SEM;

C – benign lesion excision; T – malignant tumorectomy; T + A – malignant tumorectomy with axillary dissection; M – mastectomy;

significance: $p < 0.01$ (**), $p < 0.001$ (***)

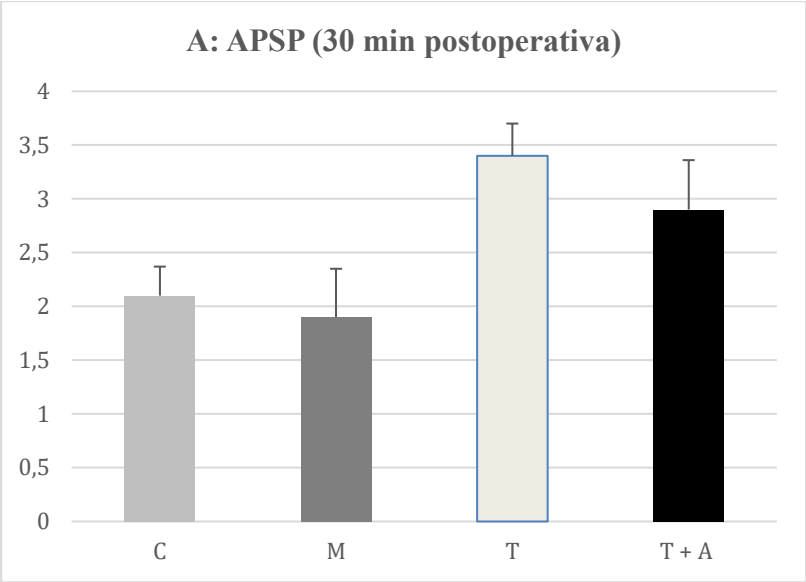


$p < 0.001$ (C *vs*. M; C *vs*. T+A)

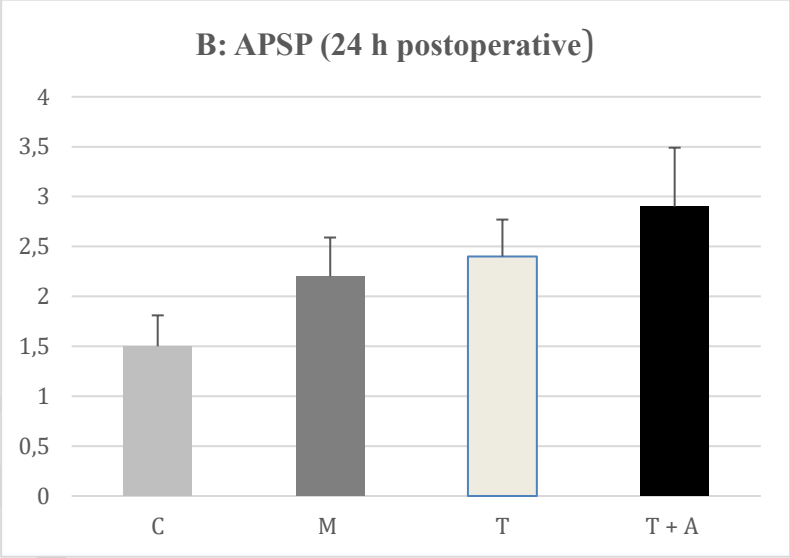
Figure 4. Intra-operative fentanyl by surgical group; mean intra-operative fentanyl volume (mL; 50 µg·mL^{-1} solution); one-way ANOVA with Games–Howell post hoc: $p < 0.001$ (C *vs*. M; C *vs*. T + A); data are mean ± SEM;

C – benign lesion excision; T – malignant tumorectomy; T + A – malignant tumorectomy with axillary dissection; M – mastectomy;

significance: $p < 0.001$ (***)



$p < 0.05$ (C *vs*. T)



$p = 0.150$

Figure 5. Maximum postoperative pain by surgical group; (A) maximum pain intensity at 30 min; (Numerical Rating Scale, 0–10); one-way ANOVA with LSD post hoc: $p < 0.05$ (C *vs*. T); (B) maximum pain intensity within 24 h (NRS, 0–10); no between-group differences (one-way ANOVA, $p = 0.150$); data are mean ± SEM;

C – benign lesion excision; T – malignant tumorectomy; T + A – malignant tumorectomy with axillary dissection; M – mastectomy;

significance: $p < 0.05$

