Original Article

Cukurova Anestezi ve Cerrahi Bilimler Dergisi

Clinical and Hematological Factors Associated with Propofol Injection Pain: A Prospective Observational Study

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Abstract

Aim: This study investigated whether systemic inflammatory indices, including SII, NLR, and PLR, were associated with propofol injection pain and explored associations between clinical characteristics and pain occurrence. **Methods:** This prospective observational study included 84 adults with American Society of Anesthesiologists Physical Status I–II who underwent elective surgery. Propofol injection pain was assessed using the McCrirrick–Hunter four-point scale and dichotomized as pain absent (no pain) or pain present (mild, moderate, or severe pain). Demographic and anthropometric characteristics, preoperative anxiety, and hematological inflammatory indices were recorded. Multivariable logistic regression and exploratory ROC analyses were performed. **Results:** Propofol injection pain occurred in 53 participants (63.1%). SII, NLR, and PLR did not differ significantly between the pain-present and pain-absent groups. Female participants were more frequent, and height and body weight were lower, in the pain-present group. In a multivariable model adjusted for age, BMI, and SII, female sex was associated with higher odds of injection pain. However, the observed association may have been affected by residual confounding related to body size. Female sex alone showed an apparent AUC of 0.638 (95% CI: 0.533–0.743), and adding BMI increased the AUC only marginally, to 0.659 (95% CI: 0.524–0.793). The combined model therefore provides little discriminative advantage over sex alone. **Conclusions:** No significant association was detected between routine hematological inflammatory indices and propofol injection pain at the present sample size. The observed relationships with sex and anthropometric characteristics should be considered hypothesis-generating. The exploratory model does not currently support clinical risk stratification and requires validation in larger independent cohorts.

Keywords: Propofol; Injection Pain; Systemic Immune-Inflammation Index; Neutrophil-to-Lymphocyte Ratio; Body Mass Index; Sex Differences.

1. Introduction

Propofol is among the most frequently administered intravenous anesthetic agents for the induction of general anesthesia and procedural sedation because of its rapid onset, brief duration of action, and smooth recovery characteristics.[1] Nevertheless, propofol injection pain remains a common adverse effect, with reported incidence rates reaching 28% to 90% in patients who receive no preventive intervention.[2] Although this complication is not life-threatening, it is often the first unpleasant stimulus experienced during anesthetic induction and may adversely influence the patient's overall perioperative experience. Several pharmacological and non-pharmacological approaches have been evaluated to mitigate this pain; however, their efficacy has varied across studies, and no single strategy has become universally accepted.[3]

The mechanisms underlying propofol injection pain have not been completely clarified. Vascular endothelial irritation, activation of peripheral nociceptors, and the release of local inflammatory mediators are thought to contribute to its development.[4] In particular, bradykinin-mediated vasodilation induced through activation of the kallikrein-kinin system may increase the interaction between propofol and free nerve endings within the vessel wall, thereby triggering pain.[4] These data suggest that interindividual variation in inflammatory responsiveness may affect susceptibility to propofol injection pain.

Pain is no longer regarded as a purely sensory response to tissue injury, but rather as a complex biopsychosocial phenomenon shaped by immune-neural interactions. Proinflammatory cytokines, including tumor necrosis factor alpha, interleukin 1 beta (IL-1β), and interleukin 6 (IL-6), can sensitize peripheral nociceptors and amplify pain processing through central sensitization at spinal and supraspinal levels.[5,6] Therefore, differences in systemic inflammatory status may influence how intensely an individual perceives a given painful stimulus. In recent years, hematological indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have been linked to a variety of acute and chronic pain conditions.[7,8] This body of evidence supports the hypothesis that systemic inflammation may also contribute to acute pain phenomena such as propofol injection pain.

Beyond being a transient discomfort, propofol injection pain may adversely affect the perioperative experience.[2] Several preventive measures have been proposed, including lidocaine pretreatment, lidocaine–propofol admixture, venous occlusion, and altered injection techniques.[2] Procedural factors such as intravenous access site, propofol formulation, drug temperature, and injection rate can influence the occurrence and severity of injection pain.[2,9] Accordingly, these factors should be standardized and reported when clinical or biological associations are examined.

Although numerous studies have focused on the prevention of propofol injection pain, comparatively few have examined the clinical and biological characteristics associated with its occurrence. In particular, the relationship between routine hematological inflammatory indices and propofol injection pain remains uncertain. Therefore, the primary aim of the present study was to evaluate the associations of SII, NLR, and PLR with the occurrence of propofol injection pain. A secondary, exploratory aim was to examine the associations of demographic and anthropometric characteristics with pain occurrence and to estimate their apparent discriminative performance.

2. Methods

Study Design and Participants

This single-center prospective observational study was conducted at Istanbul Atlas University Hospital. All 84 participants were recruited and all clinical procedures and data collection were performed at this institution. Recruitment began only after approval

had been obtained from the Ethics Committee of Istanbul Atlas University Faculty of Medicine (E-22686390-050.99-96238; Approval No. 23.03.2026-03/34), and written informed consent was obtained before enrollment. Recruitment was prospective: consecutive eligible patients scheduled for elective surgery were enrolled during the preanesthetic evaluation, and all predictor and outcome data were recorded before the pain outcome was determined. Enrolment began in May 2026 and was completed in June 2026. All 84 participants in the source dataset had complete primary pain-scale data and were included in the analysis; the numbers screened and excluded before inclusion were not retained in the source records. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[10] Patients aged 18–65 years who were scheduled for elective surgery and classified as American Society of Anesthesiologists Physical Status (ASA) I or II were eligible. Exclusion criteria were emergency surgery, ASA classification III or higher, active malignancy, nonsteroidal anti-inflammatory drug use within the preceding three days, chronic steroid therapy, and incomplete laboratory data. Age, sex, height, weight, body mass index (BMI), ASA class, surgical procedure, and preoperative anxiety were recorded. Standardized variables for smoking, alcohol use, specific chronic pain or rheumatologic disorders, active infection, psychiatric diagnoses, and regular analgesic, psychotropic, anticonvulsant, or opioid use were not available for analysis.

Anesthesia Protocol and Assessment of Propofol Injection Pain

All participants received the same standardized anesthesia and propofol administration protocol. A 20-gauge peripheral intravenous cannula was inserted into a vein on the dorsum of the hand. PROPOFOL-PF MCT 1% (200 mg/20 mL; Polifarma İlaç San. ve Tic. A.Ş., Ergene, Tekirdağ, Türkiye) was stored and administered under routine operating-room conditions. The ambient operating-room temperature was maintained at approximately 22–24 °C, although the exact temperature of the preparation was not measured for each participant. No premedication or opioid was administered before pain assessment. The calculated propofol induction dose was 2.5 mg/kg, and approximately one-quarter of this dose was administered over 5 seconds. Immediately thereafter, 0.9% sodium chloride was allowed to run freely by gravity with the roller clamp fully open to flush the propofol through the intravenous line; the exact saline flow rate was not measured. Pain was assessed before the remaining propofol or any opioid was given. After pain assessment, the remaining propofol was administered to complete the induction dose, followed by fentanyl 2 μg/kg. Preoperative anxiety was assessed during the preanesthetic evaluation using a locally used five-category verbal rating scale (none, mild, moderate, high, or very severe). Anxiety was treated as an ordinal variable and was not entered into the multivariable model.

Propofol injection pain was assessed using the McCrirrick–Hunter four-point scale.[11] Participants were asked about pain at the injection site, and verbal and behavioral responses were observed. The categories were 0 = no pain; 1 = mild pain (pain reported only in response to questioning and without behavioral signs); 2 = moderate pain (pain reported spontaneously or accompanied by behavioral signs); and 3 = severe pain (a strong vocal response or a response accompanied by facial grimacing, arm withdrawal, or tears). This verbal and behavioral approach is consistent with commonly used pain-rating methods and prior propofol injection studies.[12,13] The assessment was performed by an anesthesiologist who was blinded to the study hypothesis and the participants' hematological results. The primary outcome was the occurrence of any propofol injection pain: score 0 was classified as pain absent, whereas scores 1–3 were classified as pain present. Severity-specific analyses were not prespecified.

Calculation of Inflammatory Markers

Preoperative complete blood count results obtained routinely before surgery were used to calculate inflammatory indices. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count, the platelet-to-lymphocyte ratio (PLR) by dividing the platelet count by the lymphocyte count, and the systemic immune-inflammation index (SII) using the formula: platelet count × neutrophil count / lymphocyte count.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). Distributions of continuous variables were assessed using histograms, Q–Q plots, and the Shapiro–Wilk test. Continuous variables are presented as median (25th–75th percentile) and were compared between pain-present and pain-absent groups using the Mann–Whitney U test. The preoperative anxiety rating was treated as an ordinal variable and analyzed using the same test. Categorical variables are presented as n (%) and were compared using the Pearson chi-square test or Fisher's exact test, as appropriate; sex was compared using the Pearson chi-square test without continuity correction because all expected cell counts exceeded five. The primary outcome was any propofol injection pain; analyses of clinical, anthropometric, and hematological variables were secondary and exploratory. Multivariable logistic regression was used to estimate adjusted associations with pain. Height and weight were excluded because of collinearity with BMI. Because height ($p = 0.021$) and weight ($p = 0.018$) showed significant univariate associations with pain occurrence, the multivariable estimate for female sex was not adjusted for these body-size variables; the sex association should therefore be interpreted as unadjusted for the significant body-size signal. Because SII is calculated from platelet count and NLR, SII and NLR are mathematically dependent and were not entered simultaneously. SII was selected as the representative complete blood count-derived inflammatory index; NLR and PLR were retained for secondary between-group analyses but were not entered into the multivariable model to preserve parsimony. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. SII was expressed per 100-unit increase in the logistic model. Exploratory ROC analyses estimated apparent discrimination for SII, BMI (with lower values treated as positive), female sex alone, and predicted probabilities from a model combining sex and BMI. AUCs with 95% CIs were calculated, and the optimal cutoff was selected using the Youden index. No direct statistical comparison of ROC curves, calibration assessment, or internal or external validation was performed. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

3. Results

All 84 participants were included in the analysis; 53 (63.1%) had propofol injection pain and 31 (36.9%) did not. Participants in the pain-present group were shorter and had lower body weight than those in the pain-absent group ($p = 0.021$ and $p = 0.018$, respectively). Female participants were more frequent in the pain-present group (79.2% vs. 51.6%; $p = 0.008$). Age, BMI, ASA class, and preoperative anxiety did not differ significantly between groups ($p = 0.714$, $p = 0.155$, $p = 0.451$, and $p = 0.423$, respectively). Anxiety data were available for 80 participants and were summarized as median (25th–75th percentile): 2 (1–3) in the pain-present group and 2 (1–2) in the pain-absent group (Table 1).

The hematological inflammatory indices were comparable between the groups. No statistically significant differences were detected for SII ($p = 0.926$), NLR ($p = 0.835$), or PLR ($p = 0.774$) (Table 2).

Table 1. Comparison of demographic and clinical characteristics according to propofol injection pain status

Variable	Pain absent (n=31)	Pain present (n=53)	p
Age, years	41 (29–45)	41 (31–48)	0.714
Female sex, n (%)	16 (51.6)	42 (79.2)	0.008
ASA Physical Status I, n (%)	19 (61.3)	28 (52.8)	0.451
ASA Physical Status II, n (%)	12 (38.7)	25 (47.2)	—
Height, cm	169 (163–180)	163 (160–170)	0.021
Weight, kg	80.0 (67.5–97.5)	71.0 (63.0–80.0)	0.018
BMI, kg/m²	26.4 (25.2–31.2)	26.1 (22.9–28.6)	0.155
Preoperative anxiety score (VRS)	2 (1–2)	2 (1–3)	0.423

Data are presented as median (25th–75th percentile) or n (%). Continuous variables and the ordinal anxiety rating were compared using the Mann–Whitney U test. Sex and ASA class were compared using the Pearson chi-square test without continuity correction. Anxiety data were available for 80 participants (pain absent, n = 30; pain present, n = 50). BMI, body mass index; VRS, verbal rating scale.

Table 2. Comparison of hematological inflammatory indices according to propofol injection pain status

Variable	Pain absent (n=31)	Pain present (n=53)	p
SII	440.4 (358.8–740.4)	491.6 (347.8–657.7)	0.926
NLR	1.76 (1.35–2.44)	1.76 (1.29–2.76)	0.835
PLR	108.9 (90.1–149.8)	119.9 (91.1–151.7)	0.774

Data are presented as median (25th–75th percentile) and compared using the Mann–Whitney U test. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

ROC analysis showed no apparent discrimination for SII (AUC = 0.494, 95% CI: 0.362–0.625; p = 0.924) and limited discrimination for lower BMI values (AUC = 0.594, 95% CI: 0.464–0.724; p = 0.157). Female sex alone showed an apparent AUC of 0.638 (95% CI: 0.533–0.743; p = 0.010). The exploratory model combining sex and BMI yielded an apparent AUC of 0.659 (95% CI: 0.524–0.793; p = 0.021). At the Youden-derived probability cutoff of 0.487, sensitivity was 86.8% and specificity was 51.6%. The p values compare each AUC with 0.5 and do not represent pairwise comparisons between curves (Table 3 and Figure 1).

Table 3. Exploratory receiver operating characteristic analysis of apparent discrimination for propofol injection pain

Variable / Model	AUC	95% CI	p
SII	0.494	0.362–0.625	0.924
BMI	0.594	0.464–0.724	0.157
Female sex	0.638	0.533–0.743	0.010
Combined model (sex + BMI)	0.659	0.524–0.793	0.021

For BMI, lower values were treated as positive. For the combined model, the Youden-derived probability cutoff was 0.487, with sensitivity of 86.8% and specificity of 51.6%. The model and cutoff were developed and evaluated in the same dataset; p values compare each AUC with 0.5 and are not pairwise curve comparisons. AUC, area under the curve; BMI, body mass index; CI, confidence interval; SII, systemic immune-inflammation index.

In the multivariable logistic regression model, female sex was associated with higher odds of propofol injection pain (OR = 3.25, 95% CI: 1.20–8.76; p = 0.020). BMI showed a nonsignificant inverse association (OR = 0.93, 95% CI: 0.86–1.01; p = 0.080). Age and SII were not significantly associated with pain; the OR for SII per 100-unit increase was 1.003 (95% CI: 0.953–1.055; p = 0.908) (Table 4).

Table 4. Exploratory multivariable logistic regression analysis of factors associated with propofol injection pain

Variable	OR	95% CI	P
Female sex (vs. male)	3.25	1.20–8.76	0.020
BMI	0.93	0.86–1.01	0.080
Age	1.01	0.97–1.05	0.549
SII (per 100-unit increase)	1.003	0.953–1.055	0.908

SII was selected as the representative complete blood count-derived inflammatory index. NLR and PLR were evaluated in secondary between-group analyses but were not entered into the multivariable model to preserve parsimony and avoid redundant representation of shared components. ORs are adjusted for the other variables shown; the SII OR is reported per 100-unit increase. BMI, body mass index; CI, confidence interval; OR, odds ratio; SII, systemic immune-inflammation index.

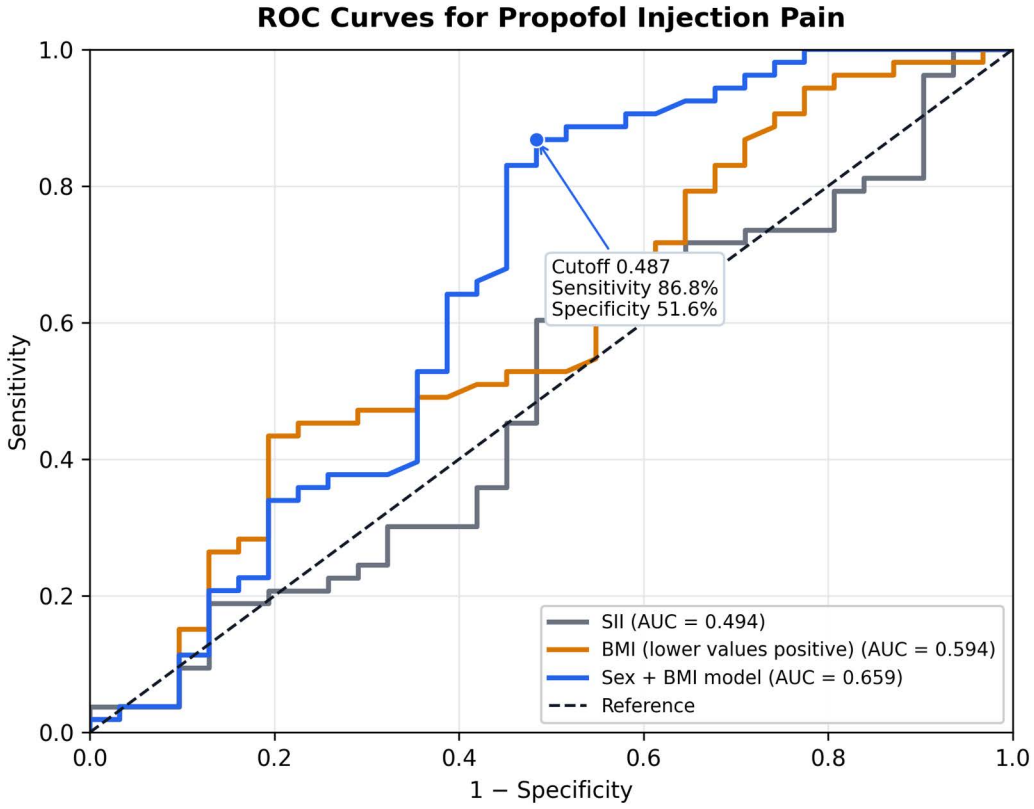

Figure 1. Receiver operating characteristic curves for SII (AUC = 0.494, 95% CI: 0.362–0.625), BMI with lower values treated as positive (AUC = 0.594, 95% CI: 0.464–0.724), female sex alone (AUC = 0.638, 95% CI: 0.533–0.743), and the exploratory model combining sex and BMI (AUC = 0.659, 95% CI: 0.524–0.793). *The reference line is shown as a dashed diagonal. For the combined model, the Youden-derived probability cutoff was 0.487, with sensitivity of 86.8% and specificity of 51.6%. The model and cutoff were developed and evaluated in the same dataset. AUC, area under the curve; BMI, body mass index; CI, confidence interval; SII, systemic immune-inflammation index.*

4. Discussion

This prospective observational study examined clinical and hematological factors associated with propofol injection pain. No significant association was detected between SII, NLR, or PLR and pain at the present sample size. Female sex was associated with higher odds of pain in the adjusted model, whereas BMI showed a nonsignificant inverse association. Because the pain-present group was also shorter and lighter, the sex association may be affected by residual confounding related to body size. The sex-and-BMI model showed only modest apparent discrimination and should be regarded as exploratory.

The lack of a significant association between propofol injection pain and SII, NLR, or PLR may appear inconsistent with the established contribution of immune and neuroimmune pathways to pain.[5,6] Propofol injection pain, however, is thought to arise predominantly from local vascular endothelial irritation, activation of the kallikrein–kinin system, and bradykinin-mediated vasodilation.[4] These localized mechanisms may not be adequately reflected by systemic complete blood count-derived indices, which may explain the null findings in this cohort.

Our findings differ from those of Tasargol[14] who reported higher NLR, PLR, and SII values among 79 young adult men, 54 of whom experienced injection pain. By contrast, Taşargol and Kose[15] studied 80 women divided into reproductive-age and postmenopausal groups and found no significant association between these indices and injection pain; only 22 participants experienced pain. Differences in sex composition, age and hormonal status, pain-event distribution, subgrouping, perioperative procedures, and statistical power may explain the inconsistent results. Together with the present findings, the available evidence does not support complete blood count-derived inflammatory indices as reproducible standalone markers of propofol injection pain.

Female participants were more frequent in the pain-present group, and female sex was associated with higher odds of pain after adjustment for age, BMI, and SII. This is broadly consistent with reports of sex-related differences in pain sensitivity and propofol injection pain.[16-19] However, the pain-present group was also shorter and lighter. Because these anthropometric differences may partly reflect the higher proportion of women, adjustment for BMI alone may not fully account for confounding by body size. Height, weight, venous anatomy, and vessel calibre may contribute to the observed association. The finding should therefore not be interpreted as evidence that female sex is an independent causal risk factor.

Although BMI showed an inverse association with propofol injection pain, it did not reach statistical significance. Prior studies have suggested that patient characteristics and body composition may influence injection pain,[18] but the present data do not establish BMI as an independent factor. Larger studies with prespecified models and more detailed measures of body size and venous anatomy are needed.

The sex-and-BMI model yielded an AUC of 0.659, while sex alone yielded an AUC of 0.638; the incremental discriminative contribution of BMI was therefore limited. The sex-and-BMI model had a lower confidence bound close to 0.5 and specificity of only 51.6% at the Youden-derived cutoff. No formal pairwise ROC comparison was performed, and the model and cutoff were developed and evaluated in the same dataset without calibration or validation. Its apparent performance is therefore likely to be optimistic. These findings do not support clinical risk stratification or selective preventive intervention; they are hypothesis-generating and require confirmation in larger independent cohorts.

Limitations

Several limitations should be acknowledged. The sample was modest, no a priori sample-size calculation was documented, and weak associations may therefore have gone undetected. Recruitment and data collection were conducted prospectively, with consecutive enrolment between May and June 2026, and all 84 participants with complete primary pain-scale data were analyzed. However, the numbers of patients screened or excluded before inclusion were not retained in the source records; the sampling ratio therefore cannot be reported with certainty. The available records did not support a reliable retrospective assessment of chronic pain syndromes, neuropathic or rheumatologic disease, migraine, active infection, psychiatric diagnoses, or regular analgesic, psychotropic, anticonvulsant, and opioid use; sensitivity analyses excluding such conditions were therefore not feasible. Smoking and alcohol-use data were also unavailable. These unmeasured

factors may have confounded associations with both pain perception and hematological indices. Free-text surgical procedure entries could not be converted into sufficiently reliable specialty categories for adjusted analysis.

The multivariable and ROC analyses were exploratory. The smaller outcome group comprised 31 participants, providing approximately 7.8 observations per model variable and increasing the risk of overfitting and unstable estimates. The model and Youden cut-off were derived and evaluated in the same sample; no calibration, internal validation, or external validation was performed. The multivariable estimate for female sex was not adjusted for height or weight, both of which showed significant univariate associations with pain ($p = 0.021$ and $p = 0.018$). The observed sex association may therefore partly reflect differences in body size rather than an independent biological effect. Residual confounding related to venous anatomy or vessel calibre cannot be excluded. All injections were administered through a dorsal hand vein, which limits generalizability to larger forearm or antecubital veins. Exact propofol temperature and gravity-driven saline flow rate were not measured for each participant. Preoperative anxiety was assessed with a nonvalidated five-category verbal scale, and data were missing for four participants. Finally, dichotomizing the McCrirrick–Hunter scale as no pain versus any pain may have influenced the estimated incidence and precluded severity-specific analyses. These limitations warrant cautious interpretation.

5. Conclusion

At the present sample size, no significant association was detected between propofol injection pain and SII, NLR, or PLR. Female sex was associated with higher odds of pain in the adjusted model, while the pain-present group was also shorter and lighter; residual confounding between sex and body size cannot be excluded. The exploratory sex-and-BMI model showed only modest apparent discrimination and is not suitable for clinical risk stratification. Larger, adequately powered studies with prespecified analyses, careful control of procedural and clinical confounders, calibration assessment, and internal and external validation are required.

Statement of Ethics: The study was approved by the Ethics Committee of Istanbul Atlas University Faculty of Medicine (E-22686390-050.99-96238; Approval No. 23.03.2026-03/34) and conducted in accordance with the Declaration of Helsinki. Participant recruitment began after ethics approval, and written informed consent was obtained from all participants before enrollment. All participant recruitment, written informed consent, and clinical data collection were performed exclusively at Istanbul Atlas University Hospital, the single study site covered by the ethics approval (E-22686390-050.99-96238; Approval No. 23.03.2026-03/34). No participant recruitment or data collection was conducted at any other institution.

AI: Generative artificial intelligence was not used for study design, data collection, statistical analysis, or scientific interpretation. During revision, an AI-assisted tool was used for language editing and organization of responses to reviewers. All scientific content, numerical results, interpretations, and final wording were critically reviewed and approved by all authors, who take full responsibility for the manuscript.

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Conflict of Interest Statement: The authors declare that they have no conflict of interest.

Availability of Data and Materials: De-identified McCrirrick–Hunter pain-scale data for all 84 participants, on which the primary outcome (53 pain-present, 31 pain-absent) is based, are available from the corresponding author upon reasonable request.

Author Contributions: EG, SA, ID and MS conceptualized the study and contributed to the design. ANY, ANS, YAT performed the literature search. EG, SA and MS were responsible for data collection and processing. EG, SA and ID contributed to the analysis and interpretation of the data. EG, SA and MS drafted the manuscript. All authors read and approved the final version of the manuscript. ID's affiliation with Necmettin Erbakan University reflects contribution to the study design only; this author had no role in participant recruitment, clinical procedures, data collection, or the ethics application at any other site.

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