Research Square

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Effects of esketamine combined with parecoxib sodium on early postoperative pain and inflammatory biomarkers after video-assisted thoracoscopic lung resection: a single-center, four-arm randomized controlled trial

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Research Article

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Abstract

Background

Postoperative pain and inflammation associated with one-lung ventilation may impair recovery after video-assisted thoracoscopic lung resection. We evaluated esketamine combined with parecoxib sodium for early analgesia and systemic postoperative inflammation.

Methods

In this single-center, four-arm randomized controlled trial in Chongqing, China, 100 patients undergoing video-assisted thoracoscopic lobectomy or segmentectomy were assigned 1:1:1:1 to parecoxib sodium (P group), esketamine (S group), both agents (PS group), or saline control (N group). The P group received intravenous parecoxib sodium 0.5 mg/kg 20 min before incision; the S group received an esketamine infusion of 0.25 mg/kg/h from anesthesia induction until 30 min before surgery ended; and the PS group received both interventions. The primary outcome was resting visual analog scale (VAS) score 30 min after extubation and at 6, 12, 24, and 48 h. Secondary outcomes included interleukin-6 (IL-6), C-reactive protein (CRP), hemodynamics, adverse events, and pulmonary complications.

Results

Of 100 randomized participants, 92 (23 per group) were included in the complete-case analysis. Exploratory overall comparisons showed between-group differences in resting VAS scores at 6 and 12 h ($P < 0.001$ and $P = 0.012$), but not at 30 min, 24 h, or 48 h. The PS group had the lowest mean VAS scores at 6, 12, 24, and 48 h. IL-6 and CRP differed among groups on postoperative days 1, 3, and 6, with the lowest means in the PS group. Systolic and diastolic blood pressure and heart rate differed at incision, with the highest means in the S group. Adverse events and pulmonary complications were infrequent.

Conclusions

The combined regimen was associated with lower mean resting pain scores and inflammatory biomarker levels at several early postoperative time points. These exploratory findings support further evaluation of esketamine plus parecoxib sodium as a multimodal perioperative regimen.

Trial registration:

Chinese Clinical Trial Registry, ChiCTR2500095107. Registered 2 January 2025.

Background

Video-assisted thoracoscopic surgery (VATS) lobectomy and segmentectomy are widely performed for the surgical management of pulmonary diseases. Although VATS is less invasive than conventional thoracotomy, substantial acute postoperative pain may still result from surgical incisions, pleural and intercostal nerve irritation, chest tube placement, and airway instrumentation [1, 2]. Inadequately

controlled postoperative pain may exacerbate the surgical stress response and impair effective coughing, deep breathing, and early mobilization [3, 4].

Thoracoscopic lung resection commonly requires one-lung ventilation. The ventilated lung is exposed to mechanical and oxidative stress, whereas the collapsed lung undergoes ischemia, hypoxia, and surgical manipulation. These processes may disrupt the alveolar–capillary barrier and trigger an inflammatory response [5]. Interleukin-6 (IL-6) is a proinflammatory cytokine that rises early after tissue injury, whereas C-reactive protein (CRP) is a widely used acute-phase marker; together, they may reflect the systemic inflammatory burden during the perioperative period [6, 7].

Multimodal analgesia combines agents with distinct mechanisms of action to improve pain control while reducing the dose requirements of individual drugs and minimizing opioid-related adverse effects [8, 9]. Esketamine is a noncompetitive N-methyl-D-aspartate receptor antagonist with analgesic, antihyperalgesic, and sympathomimetic properties [10–13]. Parecoxib sodium is a selective cyclooxygenase-2 inhibitor that reduces prostaglandin synthesis and exerts both analgesic and anti-inflammatory effects [14–16]. Their combined use may provide complementary effects on central sensitization, peripheral inflammation, and the perioperative stress response; however, evidence supporting this combination in thoracoscopic lung resection remains limited.

This study compared the effects of esketamine, parecoxib sodium, their combination, and placebo control on resting postoperative pain, inflammatory biomarkers, hemodynamic variables, and safety outcomes in patients undergoing thoracoscopic lung resection. We hypothesized that the combined regimen would reduce early postoperative resting VAS scores and serum IL-6 and CRP levels compared with either monotherapy or placebo control.

Methods

Study design, ethics, and registration

This single-center, four-arm, parallel-group randomized controlled trial was conducted at Yongchuan Hospital of Chongqing Medical University between January and June 2025. The study protocol was approved by the Ethics Committee of Yongchuan Hospital of Chongqing Medical University (approval no. 2024EC0090), and written informed consent was obtained from all participants. The trial was registered with the Chinese Clinical Trial Registry on 2 January 2025 (ChiCTR2500095107). This trial is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement. The full trial protocol is available from the corresponding author upon reasonable request.

Changes from trial registration. The initial trial registration specified a planned sample size of 80 participants (20 per group), based on the preliminary design assumptions available at the time of registration. During protocol refinement, the sample size was reassessed after the schedule of five postoperative VAS assessments and the anticipated attrition rate had been finalized. The revised calculation indicated a recruitment target of 96 participants (24 per group). A small additional

recruitment margin was then applied to account for potentially nonevaluable participants due to intraoperative conversion to thoracotomy or loss to follow-up, resulting in a final recruitment target of 100 participants (25 per group). This reassessment was completed before the final outcome analysis, was not based on observed between-group treatment effects, and was not contemporaneously reflected in the initial registry entry; the discrepancy is reported here for transparency. No changes were made to the prespecified primary or secondary outcomes after trial commencement.

Participants

The inclusion criteria were as follows: age 50–80 years; American Society of Anesthesiologists (ASA) physical status I or II; and scheduled elective video-assisted thoracoscopic lobectomy or segmentectomy under general anesthesia.

The exclusion criteria were as follows: known allergy to any study medication; clinically significant psychiatric disorders or a previous diagnosis of anxiety or depression; substantial hepatic or renal dysfunction, defined as transaminase or serum creatinine levels exceeding twice the upper limit of normal; a history of gastrointestinal bleeding or a high risk of bleeding; an increased risk of elevated intracranial pressure; uncontrolled hypertension, defined as a resting blood pressure > 180/100 mmHg; untreated or poorly controlled hyperthyroidism; severe coexisting pulmonary disease, such as bronchiectasis or pulmonary tuberculosis; or a preoperative 4AT score ≥ 1.

Prespecified criteria for withdrawal or study discontinuation included withdrawal requested by the participant or their legally authorized representative, loss to follow-up, intraoperative oxygen saturation (SpO_2) < 90%, conversion to thoracotomy, severe bleeding or any other serious event precluding continuation of the study, postoperative admission to the intensive care unit, or the need for reoperation.

Randomization and blinding

Participants were randomly assigned in a 1:1:1:1 ratio to the P, S, PS, or N group using simple randomization based on a random number table, with 25 participants initially allocated to each group. Jingnan Li generated the random allocation sequence and recruited and enrolled participants. After generation, the randomization list was retained by Jing Zhang, who was not involved in recruitment or enrollment, and allocation information was released only after a participant had been enrolled. Jing Zhang then assigned participants to groups according to the allocation sequence. Participants, outcome assessors, and data analysts were blinded to group allocation, whereas the attending anesthesiologist responsible for administering the study interventions was not blinded.

Interventions and perioperative management

Patients in the P group received intravenous parecoxib sodium at 0.5 mg/kg 20 min before skin incision. Patients in the S group received a continuous intravenous infusion of esketamine at 0.25 mg/kg/h from after induction of anesthesia until 30 min before the end of surgery. Patients in the PS group received both interventions, whereas those in the N group received corresponding volume-matched normal saline placebos.

All patients underwent a standardized balanced general anesthetic technique. Anesthesia was induced with midazolam 0.05 mg/kg, penehyclidine hydrochloride 0.01 mg/kg, sufentanil 0.4–0.5 μg/kg, etomidate 0.2–0.3 mg/kg, and rocuronium 0.6–0.8 mg/kg. After placement of a double-lumen endobronchial tube, one-lung ventilation was initiated with a tidal volume of 6–8 mL/kg and a respiratory rate of 16–18 breaths/min. Anesthesia was maintained with propofol, remifentanil, and sevoflurane. The bispectral index was maintained between 40 and 60, and blood pressure was maintained, whenever possible, within 20% of the baseline value.

At the end of surgery, all patients received postoperative analgesia using a nonelectronic patient-controlled intravenous analgesia (PCIA) pump. The pump contained sufentanil 2 μg/kg diluted with 0.9% sodium chloride solution to a total volume of 100 mL. The background infusion rate was 2 mL/h, the patient-controlled bolus dose was 2 mL, and the lockout interval was 15 min. After return to the ward, patients with a resting VAS score > 5 received intramuscular tramadol 100 mg as rescue analgesia.

Outcome measures

The primary pain outcome was the resting visual analog scale (VAS) score within the first 48 h after surgery, assessed 30 min after extubation and at 6, 12, 24, and 48 h postoperatively. VAS scores ranged from 0 to 10, with 0 indicating no pain and 10 indicating the worst imaginable pain.

Resting postoperative pain was designated as the primary outcome because pain is a clinically important determinant of early recovery after thoracic surgery. Serum IL-6 and CRP were evaluated as secondary outcomes because perioperative inflammation may contribute to pain and provide complementary biological information. The overall objective was to explore whether the combined regimen could support early postoperative recovery through improved analgesia and attenuation of the inflammatory response.

Secondary outcomes included: (1) serum interleukin-6 (IL-6) and C-reactive protein (CRP) levels measured preoperatively and on postoperative days 1, 3, and 6; at each time point, 5 mL of venous blood was collected, and biomarker concentrations were determined using enzyme-linked immunosorbent assays; (2) systolic blood pressure, diastolic blood pressure, and heart rate recorded on arrival in the operating room, at skin incision, 10 min after skin incision, before extubation, 30 min after extubation, 30 min after return to the ward, and on postoperative days 1 and 2; (3) postoperative nausea and vomiting, somnolence, respiratory depression, depression, and delirium within 48 h after surgery; and (4) pulmonary infection, atelectasis, pneumothorax, and respiratory failure occurring during hospitalization.

Sample size estimation

The initial trial registration specified a planned sample size of 80 participants (20 per group), based on preliminary design assumptions. After the final schedule of five postoperative VAS assessments had been established, a sensitivity calculation was performed using G*Power. Assuming an effect size of f = 0.25, a two-sided significance level of α = 0.05, a statistical power of 1 − β = 0.80, four study groups, a correlation of 0.50 among repeated measurements, a nonsphericity correction of ε = 0.25, and the group-by-time interaction as the target effect, the theoretical minimum sample size was 74 participants. This value was rounded up to 76 participants (19 per group) to permit equal allocation. After allowing for an anticipated 20% attrition rate, the revised recruitment target was 96 participants (24 per group). A small additional recruitment margin was applied to account for potentially nonevaluable participants resulting from intraoperative conversion to thoracotomy or loss to follow-up; therefore, the final recruitment target was set at 100 participants (25 per group). This reassessment was completed before the final outcome analysis and was not based on observed between-group treatment effects. Of the 100 randomized participants, 4 underwent intraoperative conversion to thoracotomy and 4 were lost to follow-up; consequently, 92 participants (23 per group) were included in the complete-case analysis.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, version 27.0. The analysis population comprised the 92 participants with complete follow-up data (23 per group). Participants who underwent conversion to thoracotomy or were lost to follow-up were excluded from the complete-case analysis, and no missing-data imputation was performed. Continuous variables are presented as the mean ± standard deviation or median with interquartile range, as appropriate according to their distribution, whereas categorical variables are summarized as counts and percentages. Baseline characteristics were summarized descriptively without significance testing. In the original analysis, longitudinal continuous outcomes were evaluated using repeated-measures analysis of variance, and overall differences among the four groups at each time point were assessed using one-way analysis of variance. All tests were two-sided, and a P value < 0.05 was considered statistically significant. One interim analysis was performed during the trial; no formal stopping guidelines were prespecified. No subgroup or adjusted analyses were prespecified or performed.

Use of artificial intelligence tools

OpenAI ChatGPT was used solely to assist with manuscript formatting and language editing. The authors reviewed and verified the resulting text and take full responsibility for the final content.

Results

Participant disposition and baseline characteristics

A total of 100 patients were assessed for eligibility and randomized, with 25 participants allocated to each of the S, P, PS, and N groups. No patients were excluded before randomization. After randomization, 4 participants underwent intraoperative conversion to thoracotomy and 4 were lost to follow-up. Consequently, 92 participants (23 per group) were included in the complete-case analysis (Fig. 1). Baseline characteristics of the analyzed participants are summarized descriptively in Table 1. Recruitment was completed as planned, and the trial was not stopped early.

Table 1
Baseline characteristics of the four groups.

Variable	**S group (*n* = 23)**	**P group (*n* = 23)**	**PS group (*n* = 23)**	**N group (*n* = 23)**
Sex, male/female	15/8	14/9	14/9	13/10
ASA physical status, I/II	10/13	11/12	9/14	11/12
Age, years	67.00 ± 4.58	65.25 ± 4.63	66.20 ± 4.27	64.75 ± 4.83
Lesion side, left/right	11/12	10/13	11/12	12/11
Operative duration, h	2.88 ± 0.64	3.06 ± 0.53	2.70 ± 0.69	2.86 ± 0.66

Data are presented as mean ± standard deviation or number of patients. ASA, American Society of Anesthesiologists. Baseline characteristics are presented descriptively; no significance tests were performed.

Primary pain outcome: postoperative resting VAS scores

Resting VAS scores in all four groups initially increased and subsequently decreased over time, reaching relatively high levels at 12 h postoperatively. Exploratory overall comparisons at individual time points showed significant differences among the four groups at 6 and 12 h postoperatively ($P < 0.001$ and $P = 0.012$, respectively). No significant between-group differences were observed 30 min after extubation or at 24 and 48 h postoperatively ($P = 0.889$, $P = 0.320$, and $P = 0.149$, respectively). The PS group had the lowest mean VAS score among the four groups at 6, 12, 24, and 48 h postoperatively (Table 2; Fig. 2).

Table 2
Resting visual analog scale scores at different postoperative time points in the four groups.

Time point	S group (*n* = 23)	P group (*n* = 23)	PS group (*n* = 23)	N group (*n* = 23)	Exploratory overall *P* value
30 min after extubation	0.95 ± 0.94	0.80 ± 0.95	0.75 ± 0.72	0.75 ± 0.91	0.889
6 h postoperatively	3.70 ± 0.80	2.70 ± 1.03	2.60 ± 0.68	3.55 ± 0.83	< 0.001
12 h postoperatively	3.85 ± 0.67	3.40 ± 1.10	3.20 ± 0.52	3.90 ± 0.97	0.012
24 h postoperatively	2.45 ± 0.46	2.40 ± 1.10	2.20 ± 0.41	2.45 ± 0.51	0.320
48 h postoperatively	0.65 ± 0.81	1.00 ± 0.65	0.55 ± 0.69	0.85 ± 0.81	0.149

Data are presented as mean ± standard deviation. VAS, visual analog scale. *P* values are from exploratory overall comparisons among the four groups at each time point and were not adjusted for multiplicity across time points.

Inflammatory biomarkers

Postoperative IL-6 and CRP levels increased from baseline in all four groups. Exploratory overall comparisons at individual time points showed significant between-group differences in IL-6 levels on postoperative days 1, 3, and 6 (P = 0.002, P < 0.001, and P < 0.001, respectively). The corresponding mean IL-6 levels in the PS group were 36.76 ± 17.43, 24.29 ± 14.64, and 7.68 ± 7.16 pg/mL, which were the lowest among the four groups at each time point.

Significant between-group differences in CRP levels were also observed on postoperative days 1, 3, and 6 (P = 0.041, P < 0.001, and P = 0.015, respectively). The corresponding mean CRP levels in the PS group were 34.51 ± 13.47, 65.29 ± 22.27, and 26.20 ± 11.91 mg/L (Table 3; Figs. 3, 4).

Table 3
Perioperative serum interleukin-6 and C-reactive protein levels in the four groups.

Biomarker	Time point	S group (n = 23)	P group (n = 23)	PS group (n = 23)	N group (n = 23)	Exploratory overall P value
IL-6, pg/mL	Preoperative	1.51 ± 0.21	1.38 ± 0.27	1.52 ± 0.47	1.73 ± 0.56	0.085
IL-6, pg/mL	Postoperative day 1	69.05 ± 49.14	56.76 ± 37.86	36.76 ± 17.43	85.39 ± 48.20	0.002
IL-6, pg/mL	Postoperative day 3	66.46 ± 40.37	60.03 ± 48.03	24.29 ± 14.64	64.10 ± 41.96	< 0.001
IL-6, pg/mL	Postoperative day 6	18.26 ± 8.41	22.19 ± 15.56	7.68 ± 7.16	22.99 ± 12.70	< 0.001
CRP, mg/L	Preoperative	1.68 ± 0.86	1.96 ± 0.98	1.75 ± 1.05	1.65 ± 0.72	0.527
CRP, mg/L	Postoperative day 1	38.69 ± 22.78	49.37 ± 23.34	34.51 ± 13.47	56.09 ± 27.39	0.041
CRP, mg/L	Postoperative day 3	88.73 ± 29.61	114.92 ± 41.28	65.29 ± 22.27	125.08 ± 27.57	< 0.001
CRP, mg/L	Postoperative day 6	38.70 ± 13.64	36.32 ± 27.94	26.20 ± 11.91	41.39 ± 15.29	0.015

Data are presented as mean ± standard deviation. IL-6, interleukin-6; CRP, C-reactive protein. *P* values are from exploratory overall comparisons among the four groups at each time point.

Hemodynamic variables

Exploratory overall comparisons at individual time points showed significant between-group differences in systolic blood pressure, diastolic blood pressure, and heart rate at skin incision (P < 0.001, P = 0.005, and P = 0.019, respectively). In the S group, mean systolic blood pressure, diastolic blood pressure, and heart rate at skin incision were 124.80 ± 11.51 mmHg, 67.85 ± 8.73 mmHg, and 65.75 ± 6.50 beats/min, respectively. The corresponding values in the N group were 107.80 ± 12.83 mmHg, 57.90 ± 14.65 mmHg, and 59.50 ± 4.60 beats/min.

Adverse events and pulmonary complications

Within 48 h after surgery, postoperative nausea and vomiting occurred in 1 patient (4.3%) in the S group, 3 patients (13.0%) in the P group, 1 patient (4.3%) in the PS group, and 2 patients (8.7%) in the N group. No cases of somnolence, respiratory depression, depression, or delirium were documented in the study records. During hospitalization, 1 case of atelectasis was recorded in the S group and 1 case of

pulmonary infection in the N group, whereas no pulmonary complications were recorded in the P or PS groups (Table 4).

Table 4
Adverse events within 48 h after surgery and pulmonary complications during hospitalization.

Event	S group (*n* = 23)	P group (*n* = 23)	PS group (*n* = 23)	N group (*n* = 23)
Postoperative nausea and vomiting	1 (4.3)	3 (13.0)	1 (4.3)	2 (8.7)
Somnolence	0	0	0	0
Respiratory depression	0	0	0	0
Depression	0	0	0	0
Delirium	0	0	0	0
Pulmonary infection	0	0	0	1 (4.3)
Atelectasis	1 (4.3)	0	0	0
Pneumothorax	0	0	0	0
Respiratory failure	0	0	0	0

Data are presented as *n* (%). Owing to the low event counts, outcomes are reported descriptively; no inferential between-group comparisons were performed.

Discussion

In this study, exploratory overall comparisons showed between-group differences in resting VAS scores at 6 and 12 h postoperatively, with lower mean scores observed in the PS group at several time points. The PS group also had the lowest mean IL-6 and CRP levels on postoperative days 1, 3, and 6. By contrast, no significant overall between-group differences in VAS scores were observed 30 min after extubation or at 24 and 48 h postoperatively.

Pain after thoracic surgery is multifactorial and may arise from surgical incisions, pleural irritation, intercostal nerve injury, chest tube placement, and airway instrumentation [1, 2]. Esketamine attenuates central sensitization through N-methyl-D-aspartate receptor blockade, whereas parecoxib sodium reduces peripheral inflammation and nociceptive signaling by inhibiting cyclooxygenase-2 and prostaglandin synthesis. These distinct mechanisms provide a theoretical basis for complementary analgesic effects when the two agents are combined [8–16]. The absence of a significant between-group difference 30 min after extubation may be attributable to the standardized opioid-based PCIA regimen administered to all patients at the end of surgery [17].

One-lung ventilation and surgical trauma may trigger a systemic inflammatory response [5, 6]. The consistently lower mean IL-6 and CRP levels observed in the combined-treatment group suggest that this regimen may be associated with a reduced postoperative systemic inflammatory burden. Previous systematic evidence has likewise suggested that perioperative ketamine may attenuate certain components of the postoperative inflammatory response [18]. Nevertheless, the IL-6 and CRP measurements showed considerable variability. Both are nonspecific systemic inflammatory biomarkers and, therefore, cannot independently establish a lung-protective effect or substitute for imaging findings, oxygenation indices, or lung-specific injury biomarkers [6, 7].

Esketamine has sympathomimetic properties and may influence noradrenergic neurotransmission [12, 13, 19]. In the present study, blood pressure and heart rate at skin incision were higher in the S group than in the N group, which may reflect the cardiovascular stimulatory effects of esketamine.

Regarding safety, only a small number of episodes of postoperative nausea and vomiting were recorded, and pulmonary complications were uncommon across all groups. These findings should be interpreted cautiously because the study was not powered to detect differences in infrequent adverse events.

The strengths of this study include its four-arm randomized design, relatively standardized perioperative anesthetic management, and repeated assessment of both pain and inflammatory outcomes. Several limitations should also be acknowledged. First, this was a single-center study with a relatively small sample size. Second, IL-6 and CRP lack pulmonary specificity. Third, the follow-up period was short, and the study had insufficient statistical power to evaluate rare adverse events or pulmonary complications. Larger, adequately powered multicenter studies with longer follow-up are therefore warranted to determine the durability and long-term clinical relevance of the observed effects.

Overall, the combined regimen was associated with lower mean pain scores and inflammatory biomarker levels at several early postoperative time points.

Conclusions

In patients undergoing video-assisted thoracoscopic lobectomy or segmentectomy, the combined regimen showed the lowest mean resting VAS scores at several early postoperative time points and the lowest mean postoperative IL-6 and CRP levels. These exploratory findings support further evaluation of esketamine plus parecoxib sodium as a multimodal perioperative regimen.

Abbreviations

ASA
American Society of Anesthesiologists
BIS
bispectral index
CRP

C-reactive protein
DBP
diastolic blood pressure
HR
heart rate
IL-6
interleukin-6
OLV
one-lung ventilation
PACU
post-anesthesia care unit
PCIA
patient-controlled intravenous analgesia
PONV
postoperative nausea and vomiting
SBP
systolic blood pressure
VAS
visual analog scale
VATS
video-assisted thoracoscopic surgery.

Declarations

Ethics approval and consent to participate

The study involving human participants was reviewed and approved by the Ethics Committee of Yongchuan Hospital of Chongqing Medical University (approval no. 2024EC0090). All procedures involving human participants were performed in accordance with the Declaration of Helsinki and with relevant institutional and national guidelines and regulations. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

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Author Contribution

Jingnan Li and Jing Zhang conducted the investigation, curated the data, and wrote the original draft. DY conceptualized the study, developed the methodology, and supervised the work. JNL, JZ, and DY reviewed and edited the manuscript. All authors read and approved the final manuscript. JNL and JZ contributed equally to this work.

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This article is based in part on a master's thesis completed by one of the authors at Chongqing Medical University. The content has been substantially reorganized and revised in accordance with the structure and reporting requirements of a clinical trial manuscript.

Data Availability

The de-identified data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to applicable ethical, privacy, and institutional requirements.

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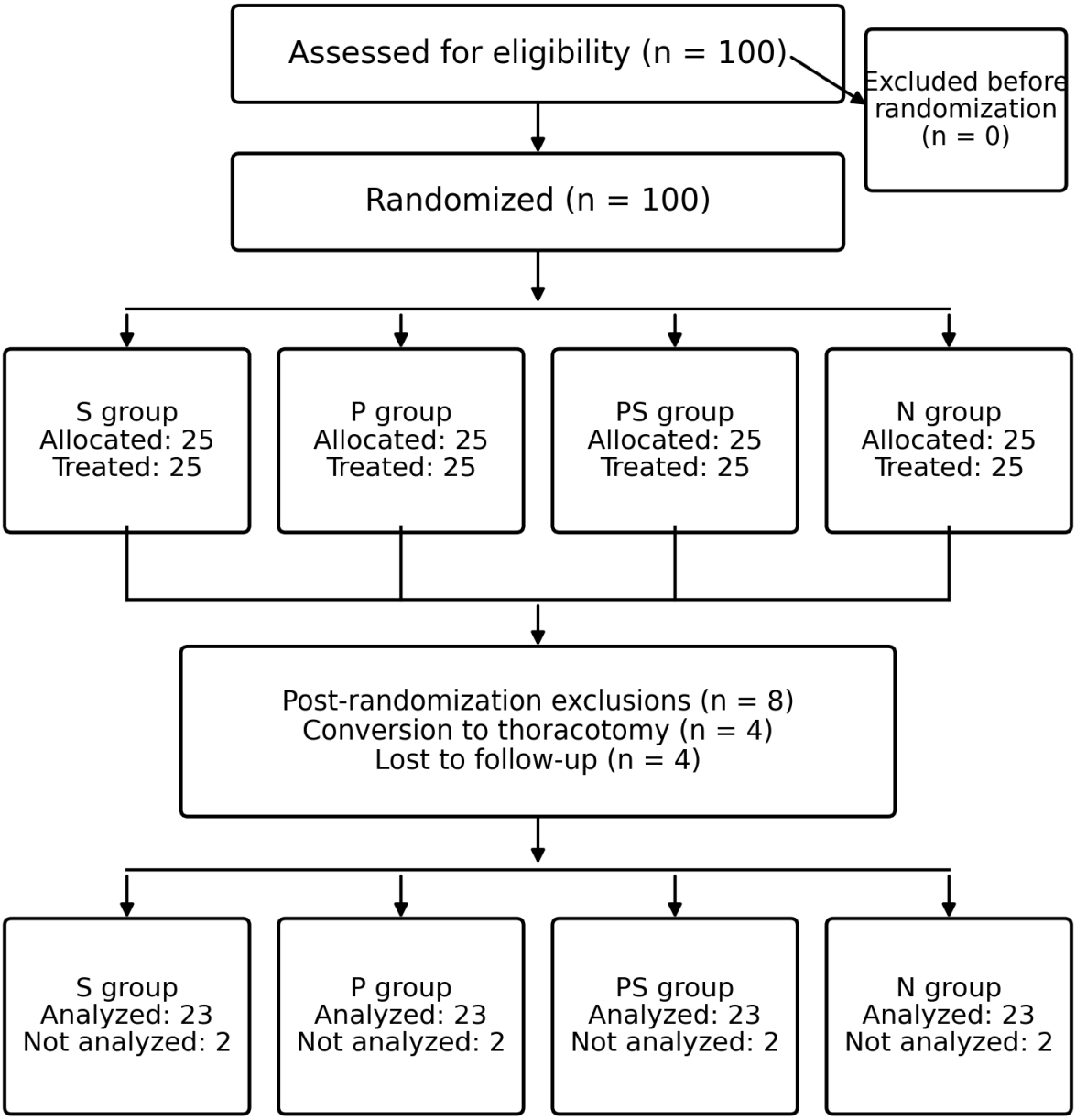
Figures



Reasons for post-randomization exclusion are reported in aggregate.

Figure 1

CONSORT flow diagram. Participant enrollment, randomization, post-randomization exclusions, and analysis.

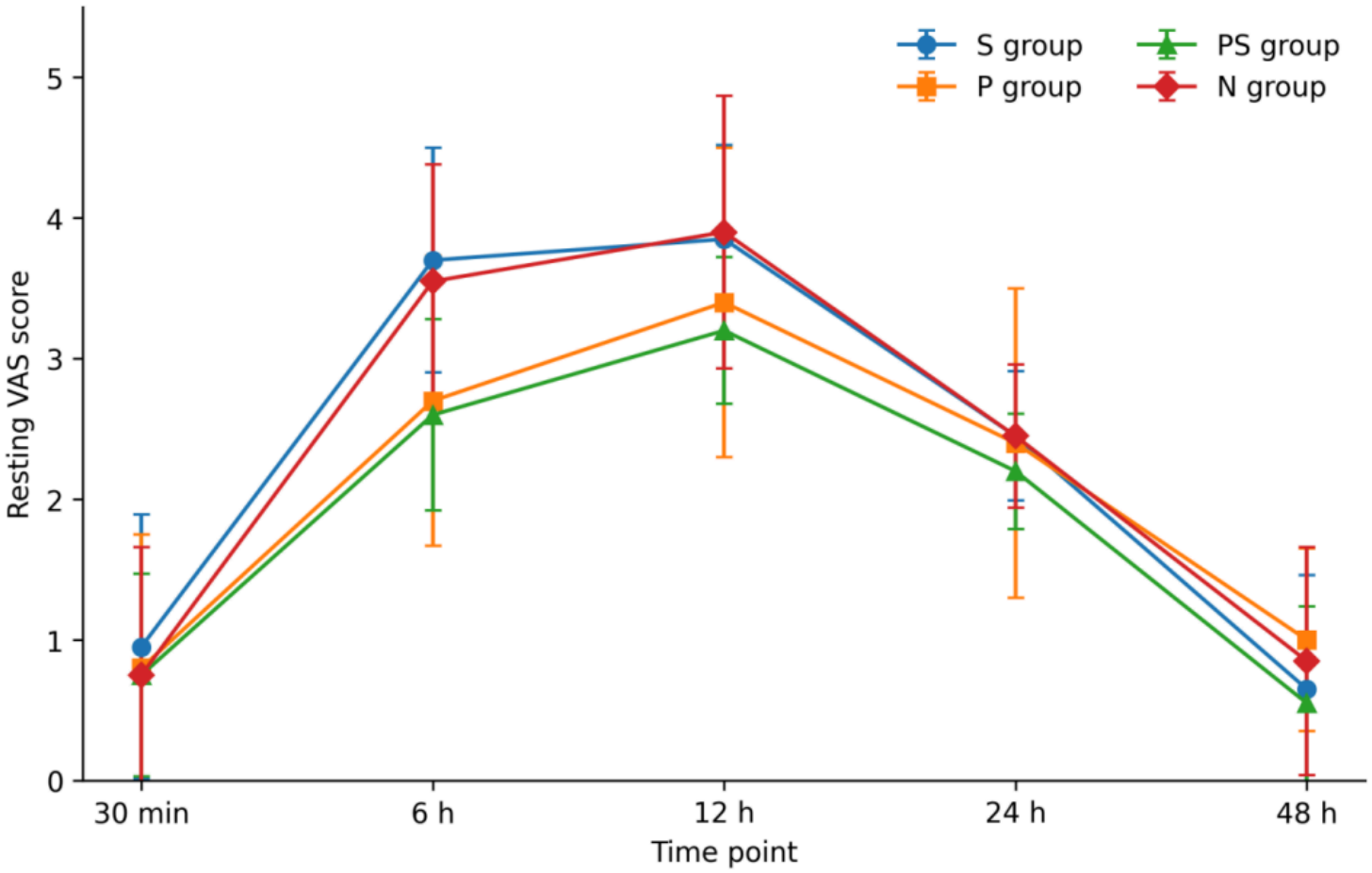


Figure 2

Resting visual analog scale scores during the first 48 postoperative hours. Values are means; error bars indicate standard deviations.

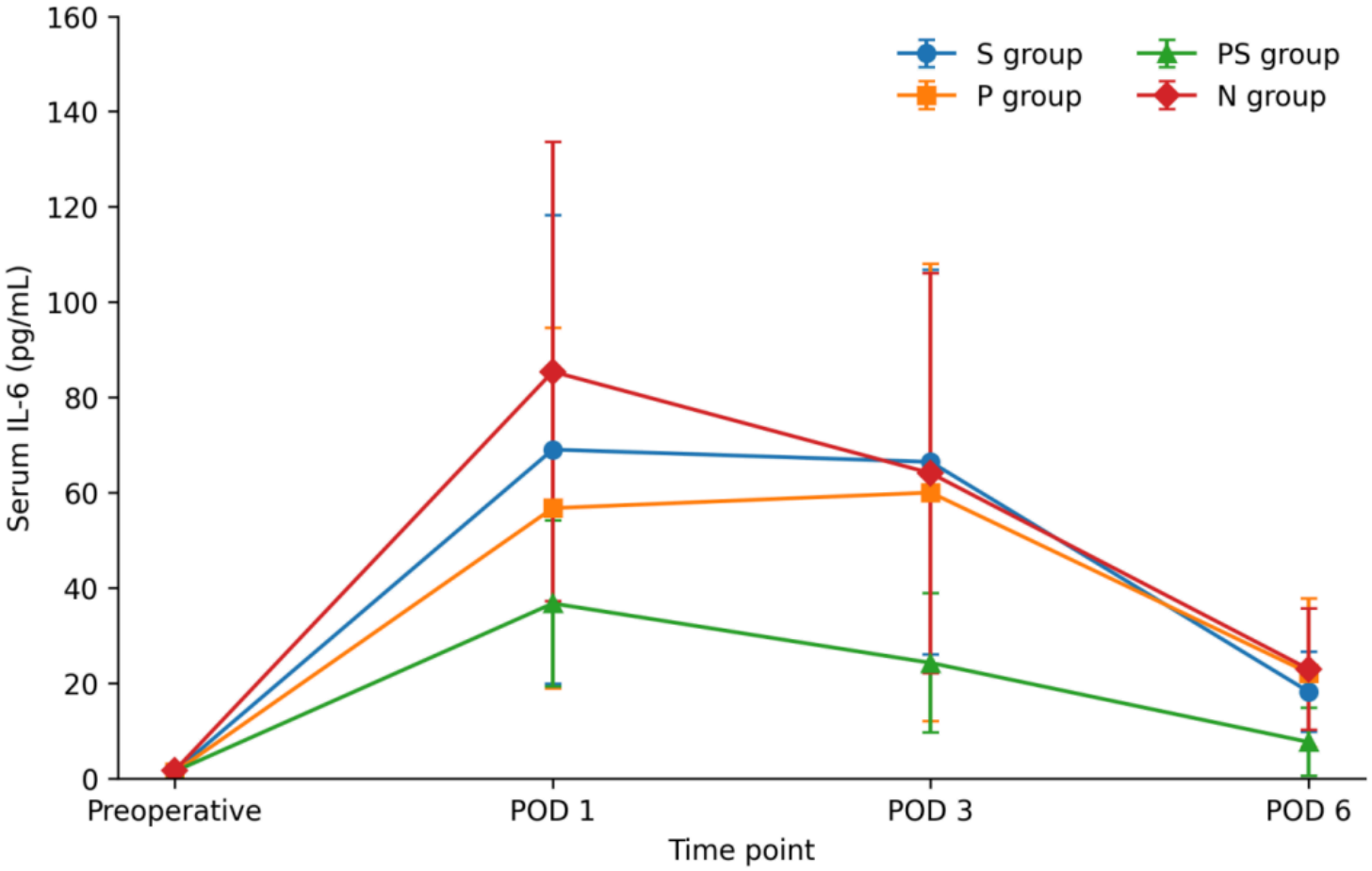


Figure 3

Perioperative serum interleukin-6 levels. Values are means; error bars indicate standard deviations. IL-6, interleukin-6; POD, postoperative day.

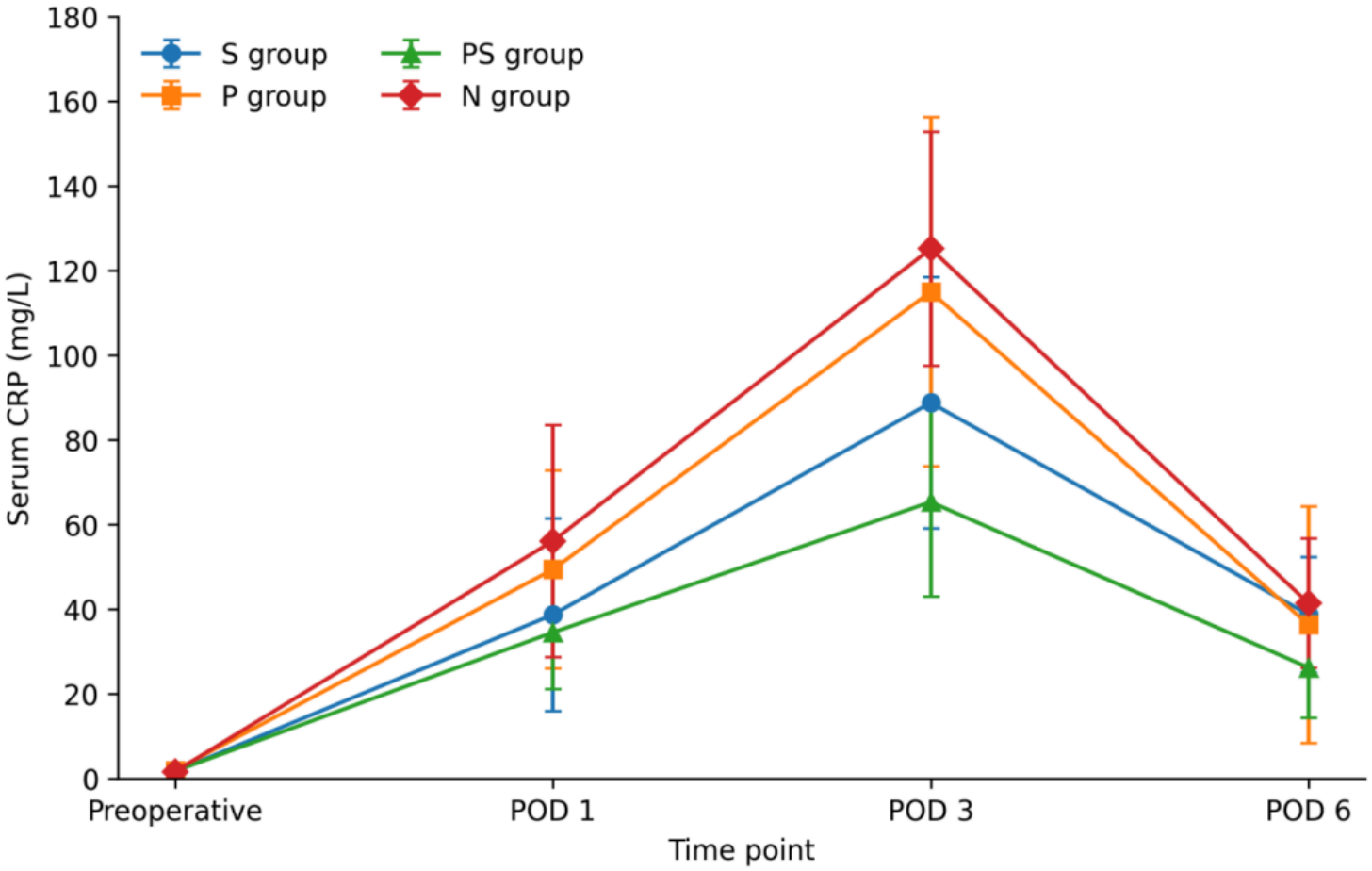


Figure 4

Perioperative serum C-reactive protein levels. Values are means; error bars indicate standard deviations. CRP, C-reactive protein; POD, postoperative day.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010checklistcompleted.docx