Journal of Pain Research

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CLINICAL TRIAL REPORT

# Neutrophil-to-Lymphocyte Ratio as an Indicator of Opioid-Induced Immunosuppression After Thoracoscopic Surgery: A Randomized Controlled Trial

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**Purpose:** The neutrophil-to-lymphocyte ratio (NLR) is a useful prognostic marker for various diseases and surgery-induced immunosuppression. While opioids are important in general anesthesia, the association between immediate perioperative immune monitoring and opioid consumption for postoperative analgesia after video-assisted thoracoscopic surgery (VATS) is unknown. We aimed to investigate the effect of analgesic techniques on opioid-induced immune perturbation, and the feasibility of NLR as an indicator of opioid-induced immune changes.

**Patients and Methods:** Patients were randomly assigned to two groups: Group P (n=40) or Group C (n=40). Patients in group P received ultrasound-guided paravertebral block (PVB) before surgery, and followed by sufentanil patient-controlled intravenous analgesia (PCIA) after surgery, and group C received sufentanil PCIA only. The total and differential white blood cell counts, including CD4+ T lymphocyte counts, CD8+ T lymphocyte were recorded before surgery and at 24 and 72 hours after surgery. NLR was determined using the frequencies of lymphocyte subpopulations. The cumulative dose of sufentanil were recorded at 24 and 24h after surgery while the 40-item quality of recovery questionnaire (QoR-40) score were assessed at 48h after the surgery.

**Results:** At 24 and 48 hours after surgery, a lower sufentanil consumption, and higher QoR-40 recovery scores were found in group P than in group C (P<0.05). In biochemical analyses, the values of NLR were lower in group P compared to group C ($p$<0.0001) and ratio of CD4/CD8 were higher in group P compared to group C ($p$<0.05) on day three after surgery. NLR showed excellent predictive capability for immunosuppression, with an area under the curve (AUC) of 0.92 [95% confidence interval (CI), 0.86–0.98, P < 0.0001].

**Conclusion:** Opioid-sparing pain management strategies may affect postoperative immunosuppression and NLR could be a reliable indicator of opioid-related immunosuppression. Moreover, opioid-sparing pain management strategies could improve patient's satisfaction in VATS.

**Keywords:** neutrophil-to-lymphocyte ratio, immunosuppression, paravertebral block, opioid, analgesia

## Introduction

Inflammation seems to be one of the most important perioperative factors for cancer recurrence, especially in kidney, lung, and breast tissues.[1,2] Animal models and retrospective clinical data suggest that regional anesthesia, particularly central blocks, can attenuate immunosuppression and minimize inflammation after cancer surgery.[3,4] Various inflammatory markers have been widely used in cancer patients, such as prognostic index (PI), prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), CD4+ T lymphocyte counts, modified Glasgow prognostic

Received: 16 April 2022
Accepted: 27 June 2022
Published: 30 June 2022

score (mGPS).[5,6] Meanwhile, mGPS and NLR have the moderate predictive ability in overall survival and disease-free survival of oesophageal cancer.[7] In the absence of pain, opioids induce a decrease in natural killer (NK) cell activity and may be responsible for opioid-induced immunosuppression.[8] Data on synthetic opioids have revealed a phenomenon similar to that of fentanyl and sufentanil.[9] Neutrophils are critical in surveilling circulating tumor cells to enable cell cycle progression and anti-tumor immune response.[10] NLR is a useful marker to predict inflammation and surgery-induced immunosuppression which reflects trends in both neutrophils and lymphocytes, combining the strengths of both systems rather than a single one.[11,12] Whether it is associated with opioid-related immunosuppression after thoracoscopic surgery is unknown. We investigated the effect of analgesic techniques on opioid-induced immune perturbation in patients undergoing video-assisted thoracoscopic surgery (VATS), and the feasibility of NLR as an indicator of opioid-induced immune changes.

# Materials and Methods

## Study Design

Eighty patients in the age range of 18–65 years, with American Society of Anesthesiologists (ASA) class I–III status and body mass index (BMI) of 18.5–28.0, who received thoracoscopic lobectomy were enrolled finally. All surgeries were performed using a lateral chest wall incision with unilaterally inserted drainage tube. Patients with infection at the injection site, bleeding diathesis, opioid dependence, neuropathies, or psychiatric illnesses which could distracted perception and pain assessment were excluded from the study (Figure 1). Preoperative guidance on QoR-40 questionnaire evaluation was provided by the same anesthesiologist. The patients were randomly allocated to one of the two study groups using random numbers in a one-to-one ratio. The numbers for group allocation were concealed in sealed opaque envelopes and investigator opened the envelopes after anesthesia induction.

## Anesthesia Procedure

General anesthesia with tracheal intubation were taken after 1–2 mg midazolam and 0.3–0.4 μg/kg sufentanil along with target-controlled infusion of 3–4 ng/min propofol and 0.8 mg/kg rocuronium.

After the onset of muscle relaxation, the left-side double-lumen endotracheal tube (32–35 Fr for women and 35–37 Fr for men) was inserted under video laryngoscopy. The appropriate depth of double-lumen endotracheal tube was checked immediately after intubation using an Olympus BF 3C30-type fibreoptic bronchoscope (FOB). After anesthesia induction, the patients were placed carefully in the lateral decubitus position and thoracic paravertebral nerve block (TPVB) with ultrasound guidance was performed in all patients in group P by the same investigator. Under sterile conditions, the costal space corresponding to the surgical incision was located using ultrasound probe (Mindray M9 super, Shenzhen, China; linear high-frequency probe, 6–13 MHz). The ultrasound probe was placed on the midline in the craniocaudal direction, showing an image of the spinous process. The probe could be moved laterally to identify the hyperechoic transverse process, slidable parietal pleura and superior costotransverse ligament. The space between the pleura and the superior costotransverse ligament was injected with 20 mL of 0.3% ropivacaine (AstraZeneca AB, Sodertalje, Sweden). General anesthesia was maintained with sevoflurane and remifentanil in conjunction with intermittent cisatracurium, which maintained a minimum alveolar concentration of 1–1.5. According to the grouping results, anesthesiologists used different analgesic strategies during the operation. In group C, sufentanil was administered intermittently according to the condition of the patients during the operation. The total dose of sufentanil was maintained at 0.8–0.9 μg/kg. In group P, sufentanil was administered only before the end of the operation. Its total dose was maintained below 0.5 μg/kg. The neuromuscular block was antagonized with 0.04 mg/kg neostigmine and 0.01 mg/kg atropine if needed. The trachea was extubated when the patients were fully awake and breathing adequately in the postanesthesia care unit (PACU). Once the VAS scores expressed by the patients were ≥3, patient-controlled intravenous anesthesia (PCIA) was programmed to deliver 2 μg of sufentanil boluses with a lockout interval of 10 minutes. No background infusion was allowed in both groups. If the patient's VAS score> 4, additional flurbiprofen axetil 50mg will be given.

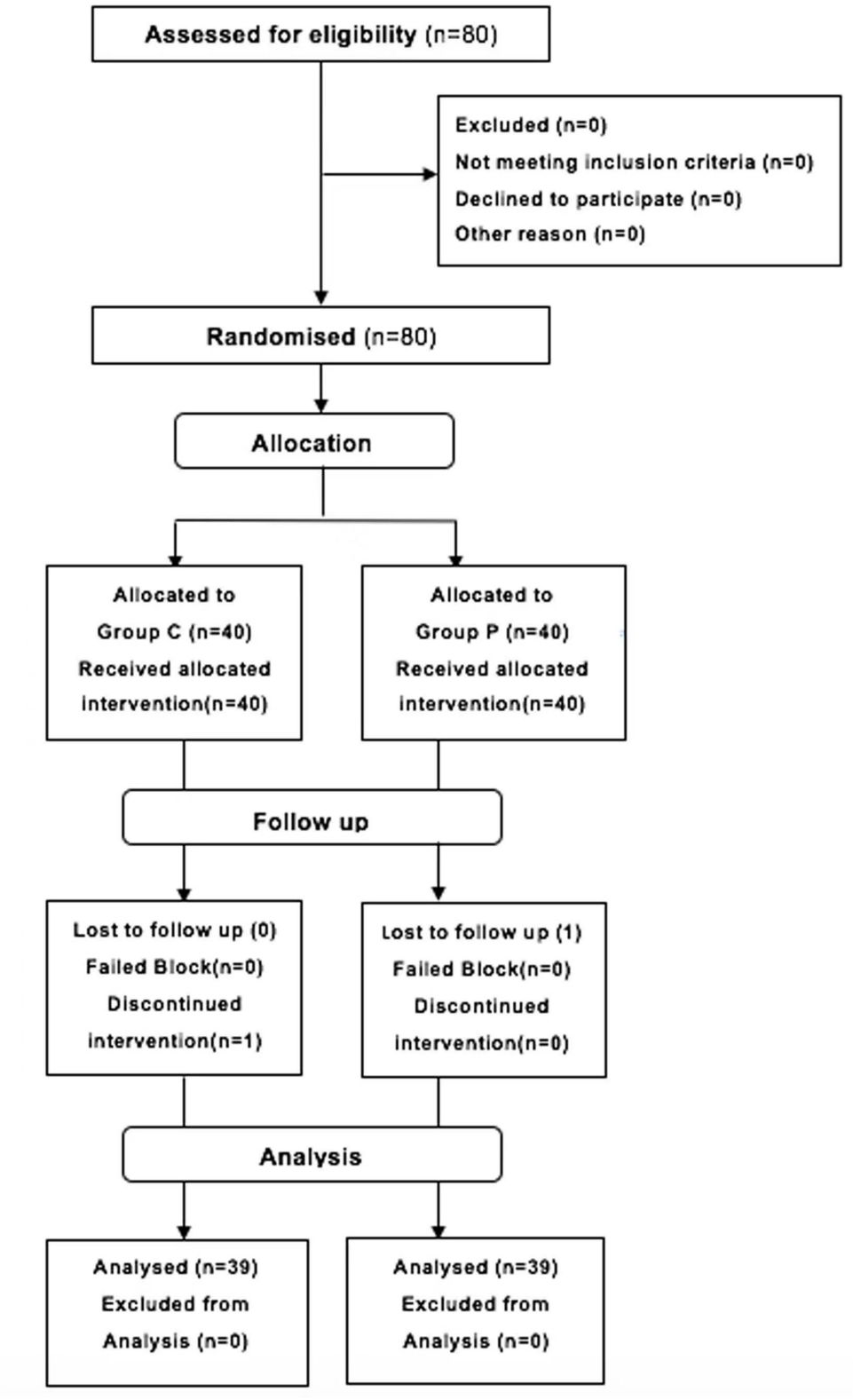


**Figure 1** CONSORT flow diagram showing the number of patients at each phase of the study.

## Outcome Measures

The primary outcome measures of the study were NLR three days before surgery, one day and three days after surgery, and the dose of remedial analgesics at 24 and 48h postoperatively. The secondary outcome measures were ratio of CD4/CD8 one day and three days after surgery and the QoR-40 scores at 48h postoperatively.

## Blood Sample Analysis

All complete blood cell (CBC) counts, CD4+T lymphocyte counts and CD8+T lymphocyte counts were recorded three days prior to surgery and one day and three days after surgery. Automated hematology analyzer XE- 5000 (SYSMEX K1000 hematology analyzer; Medical Electronics, Kobe, Japan) were used for measuring the CBC in ethylenediamine-tetraacetic acid-treated blood. Peripheral blood lymphocytes were counted using Sysmex. Flow cytometry (FACSCanto, BD) was used to determine the proportion of CD4+ T lymphocytes and CD8+ T lymphocytes.

## Statistical Analysis

SPSS (version 21.0; IBM Corporation, Armonk, NY, USA) was used statistical analysis. Normally, distributed interval data (age, weight, height, BMI, time of surgery and QoR-40 scores) were reported as means ± standard deviations (SDs) and analyzed by the Student's unpaired t-tests. Non-normally distributed interval and ordinal data (cumulative of remedial sufentanil) were reported as median values with interquartile and analyzed by the Mann–Whitney *U*-tests. Biochemical indicators at different times were compared with baseline using repeated-measures ANOVA, followed by the Student's paired t-tests. Post-hoc analysis with Bonferroni correction was applied for multiple comparisons. Statistical significance threshold was set at $p < 0.05$.

The sample size was calculated from a pilot study.[13] Given the mean sufentanil consumption of 20.4 μg with SD of 5.9 μg, for a 50% difference in the 24-hour postoperative sufentanil consumption at a significance level of 0.05 and power of 0.8, a minimum of 35 patients were required in each group. To account for possible dropouts, 80 patients were recruited for this randomized study.

# Results

Two study groups were comparable in terms of age, height, weight, ASA physical status, smoking history, and duration of surgery (Table 1). One patients were excluded from the study due to refused to continue participating in the trial after surgery in group C while one patients were excluded from the study due to acute coronary syndrome occurred after operation and entered ICU for treatment in group P. Total sufentanil consumption in group P was significantly reduced in comparison to that of group C at 24 hours (14 μg vs 26 μg) and 48 hours (52 μg vs 68 μg) after surgery (Table 2). The ratio of CD4/CD8 were decreased significantly in both groups one day after operation when compared with preoperation, but the postoperative ratio of CD4/CD8 in group P were higher than those in group C three days after operation ($p<0.05$). Meanwhile, NLR were increased significantly in

**Table 1** Characteristic of Participants

| Variable | Group C | Group P | P |
|---|---|---|---|
| Cases(male/female) | 39 (27/12) | 39 (24/14) | 0.617 |
| Ages, yrs | 60.3±7.7 | 59.4±7.5 | 0.238 |
| Weight, kg | 62.4±8.5 | 63.6±9.2, | 0.532 |
| Height, cm | 165.3±16.1 | 166.1±15.2 | 0.591 |
| ASA (I/II/III) | 5/23/11 | 7/24/7 | 0.163 |
| Smoking history | 24 | 19 | 0.332 |
| Duration of surgery, min | 82.5±19.3 | 84.9±17.9 | 0.274 |

**Notes**: all values are presented as mean ± SD or number of patients. There were no significant differences in parameters between groups.
**Abbreviation**: ASA, American Society of Anesthesiologists.

**Table 2** Total Analgesic Requirement After Surgery

| Variable | Group C | Group P | *P* |
|---|---|---|---|
| 24h sufentanil consumption, ug | 26 (12) | 14 (8) | <0.0001 |
| 48h sufentanil consumption, ug | 68 (36) | 52 (24) | <0.0001 |

**Notes**: Analgesic requirement reported as median values with interquartile and analyzed by the Mann–Whitney *U*-tests. *P*<0.05 shows statistical significance.

**Table 3** Perioperative Changes of Immunocyte in Patients

| Variable | Group C | Group P | *P* |
|---|---|---|---|
| CD4/CD8 | | | |
| Preoperation | 1.72±0.20 | 1.74±0.19 | 0.602 |
| Postoperation 1d | 1.21±0.15 | 1.30+0.13 | 0.130 |
| Postoperation 3d | 1.27±0.16 | 1.44±0.15[a] | 0.0018 |
| NLR | | | |
| Preoperation | 2.15±1.02 | 2.21±1.10 | 0.590 |
| Postoperation 1d | 11.25±3.41 | 10.23±3.27 | 0.204 |
| Postoperation 3d | 6.63±1.73 | 5.06±1.64[a] | <0.0001 |

**Notes**: Differences in biochemical indicators were analyzed repeated-measures ANOVA, followed by the Student's paired t-tests. Post-hoc analysis with Bonferroni correction was applied for multiple comparisons. [a]Statistical significance when compared with Group C.
**Abbreviations**: CD4, Cluster of Differentiation 4 receptors; CD8, Cluster of Differentiation 8 receptors; NLR, Neutrophil–Lymphocyte Ratio.

both groups one day after operation but were significantly decreased in group P when compared to those in group C on day three after surgery ($p$<0.0001) (Table 3). Using ratio of CD4/CD8 as the gold standard for immunosuppression, the ROC curve of NLR and immunosuppression is shown in Figure 2). NLR showed excellent predictive capability for immunosuppression, with an area under the curve (AUC) of 0.92 [95% confidence interval (CI), 0.86–0.98, P < 0.0001].

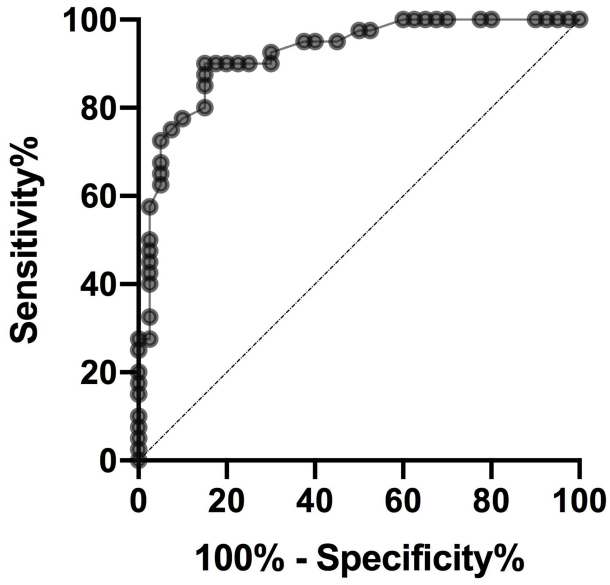


**Figure 2** The ROC of neutrophil-to-lymphocyte ratio to predictive capability for immunosuppression after thoracoscopic surgery; area under the ROC curve appears in cartouche with 95% confidence interval.

**Table 4** QoR-40 Questionnaire Scores

| Variable | Group C | Group P | *P* |
|---|---|---|---|
| Comfort | 46.18±1.93 | 53.78±2.33 | <0.0001 |
| Emotions | 40.42±1.34 | 40.58±1.42 | 0.476 |
| Physical independence | 20.24±1.02 | 20.86±1.22 | 0.389 |
| Patient support | 33.20±1.16 | 32.62±1.31 | 0.332 |
| Pain | 28.15±1.34 | 32.29±1.16 | <0.05 |
| Global | 168.19±2.94 | 180.54±3.32 | <0.0001 |

**Notes**: Differences in the QoR-40 scores were analyzed using Student's unpaired t-tests. $P<0.05$ shows statistical significance.

The assessment of recovery after surgery shows that patients in group P had better QoR-40 scores than those in group C on day two after surgery (Table 4, $P<0.05$). The incidence of postoperative nausea and vomiting (PONV) was recorded and assessed using a QoR-40 questionnaire. As noted, we did not observe any obvious delay in the discharge of the patients from the PACU and no patients used flurbiprofen axetil as rescue analgesia postoperatively in either group.

## Discussion

In this study, we evaluated the effects of perioperative opioid use on immunological functions by using the NLR value. NLR is regarded as a reliable indicator of opioid-induced immune changes. We confirmed that the reduction in perioperative opioids by regional block may have a positive effect on the reduction of immunosuppression and improve the quality of postoperative recovery.

Opioids have been a major focus of medical research because of their critical role in pain management, especially in anesthesia during perioperation.[14,15] Opioids can produce powerful analgesia, which is effective in treating severe pain. However, it has some common adverse effects, one of which is related to immune function.[16,17] While it is believed that most opioids suppress the immune system, recent research indicates that they may have various effects on immune function.[18,19] However, the mechanisms by which opioids and opioid receptors regulate immune responses are still not clearly. Recent literature suggests that morphine-induced inhibition of NK cell activity may be a consequence of opioid receptor activation in the central nervous system. This impact on NK cell activity seems to be related to the dose of opioids.[20,21] In our study, regional anesthesia was used to ensure adequate analgesia while reducing the use of opioids to observe the effect of different doses of opioids on postoperative immunity.

CD4+ regulatory T cells and NK cells play important roles in the immune system.[22] In our study, although the ratio of CD4/CD8 were decreased significantly in both groups one day after operation when compared with preoperation, the postoperative ratio of CD4/CD8 in group P were higher than those in group C three days after operation. These findings suggest that reducing the use of opioids may alleviate immunosuppression in the body. At the same time, NLR in group P also decreased significantly three days after the operation, suggesting that NLR can also be used as an indicator of opioid-induced immune changes. Frequencies of leukocytes and their subtypes are well-known inflammatory markers.[23] In recent years, some studies have investigated the potential diagnostic role of NLR in the inflammatory processes of different chronic diseases.[24,25] NLR is a readily available and inexpensive marker of systemic inflammation. This indicator is driven by elevated concentrations of circulating cytokines. It has been shown to modulate myocardial injury and used for risk stratification in different diseases. This is the first study to investigate the relationship between NLR and opioid immunosuppression. It also demonstrated the effect of multimodal analgesia for opioid-sparing in reducing perioperative immunosuppression.

Our study has several limitations. First, we observed only the acute immunosuppressive period. Therefore, the long-term impact of opioids on immune function remains to be determined. Second, the relationship between postoperative opioid-induced immunosuppression and the incidence of related complications has not been recorded and requires further investigation.

## Conclusion

NLR might be a reliable indicator of opioid-related immunosuppression after surgery with its advantage of rapid, easy and cost-effective. Meanwhile, opioid-sparing pain management strategies may affect postoperative immunosuppression and improve patient's satisfaction in thoracoscopic surgery.

## Abbreviations

ASA, American Society of Anesthesiologists; BMI, body mass index; CBC, complete blood count; mGPS, modified Glasgow prognostic score (mGPS); NK, natural killer; NLR, neutrophil to lymphocyte ratio; PACU, postanesthesia care unit; PCIA, patient-controlled intravenous analgesia; PI, prognostic index (PI); PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; PONV, postoperative nausea and vomiting; PVB, paravertebral block; QoR-40, 40-item quality of recovery questionnaire; SD, standard deviation; TPVB, thoracic paravertebral block; VATS, video-assisted thoracoscopy.

## Data Sharing Statement

When needed, we can provide our original data, such as dose of sufentanil, values of NLR, CD4 and CD8. The data will be available for anyone who wishes to access them for academic purpose. The data will be accessible from immediately following publication to 6 months after publication by sending email to corresponding author via qqyc2005@163.com.

## Ethics Approval and Informed Consent

This prospective, randomized, double-blind clinical trial was approved by the Ethics Committee of Chongqing University Cancer Hospital China (2019-177). The study was conducted in accordance with the Declaration of Helsinki and implemented from January 2020 to August 2020. It was also registered at www.clinicaltrials.gov (ChiCTR1900027208). Participants who underwent elective thoracoscopic surgery were provided with written informed consent prior to surgery.

## Consent for Publication

Written consent was obtained from each of three patients for all procedures and publication.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was supported by Laboratory Open Fund of Chongqing University Cancer Hospital (2021); High-Level Medical Personnel Training Project of Chongqing (2019GDRC017); Basic science and advanced technology foundation of Chongqing Science and Technology Commission (cstc2018jcyjAX0775).

## Disclosure

The authors declare no conflicts of interest.

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