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Original Article

Association between perioperative opioid consumption and postoperative outcomes in lung cancer surgery: evidence from a retrospective study with inflammatory and immune biomarker analysis

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Abstract: Opioids are crucial for lung cancer postoperative analgesia, but perioperative dosage-inflammation/immunity associations remain unclear. This study explores perioperative opioid use and inflammation/immunity biomarker changes in lung cancer surgery patients. This retrospective study enrolled 412 patients who underwent lung cancer surgery (Jan 2022 - Jan 2025), with clinical data extracted from medical records. Primary outcomes include perioperative opioid morphine equivalent doses, postoperative 72-h C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and immunoglobulin (Ig) A, IgG, IgM, CD4+/CD8+, natural killer (NK) cells; postoperative clinical outcomes include postoperative hospital stay duration, pain score at 72 hours postoperatively, first postoperative ambulation time, gastrointestinal function recovery time, and complications within 30 days postoperatively. Spearman's rho analyzed opioid-biomarker relationships; multivariate regression identified independent risk factors. Among 412 patients, the perioperative opioid morphine equivalent dose was 81.5 (52.15, 116.78) mg. Patients were stratified into four groups (n=103 each), low-dose (≤52.15 mg), low-medium dose (52.15-81.5 mg), medium-high dose (81.5-116.78 mg), and high-dose (>116.78 mg). With increasing opioid dosage, CRP, IL-6, TNF-α significantly elevated; IgA, IgG, IgM, CD4+/CD8+, NK cells significantly decreased (all $P<0.001$). Clinically, postoperative hospital stay duration prolonged, first postoperative ambulation and gastrointestinal function recovery time delayed, complication rates increased (all $P<0.001$), while 72-h postoperative pain scores significantly reduced ($P<0.001$). Pulmonary infection ($P=0.009$) and nausea/vomiting ($P=0.020$) showed significant intergroup differences. Spearman's rho analysis revealed morphine equivalent dose was positively correlated with CRP, IL-6, TNF-α (all $P<0.001$) and negatively correlated with IgA, IgG, IgM, CD4+/CD8+, NK cells (all $P<0.001$). Multivariate regression identified morphine equivalent dose as an independent risk factor for elevated CRP, IL-6, TNF-α and reduced CD4+/CD8+, NK cells at 72 h postoperatively. Perioperative opioid dosage correlates with inflammation/immunity biomarkers in lung cancer surgery. Clinicians should adjust perioperative opioids to reduce dependence and improve outcomes.

Keywords: Lung cancer surgery, opioids, postoperative outcomes, inflammatory biomarkers, immune biomarkers

Introduction

Lung cancer, a malignant tumor characterized by both high incidence and mortality worldwide, is imposing an increasingly heavy disease burden at an alarming rate [1]. In China, the epidemiological situation of lung cancer is equally grim. In 2022, there were around 828,000 new lung cancer cases and 657,000 deaths in the country, meaning roughly 1 out of every 4 cancer deaths was caused by lung cancer [2]. Surgical resection serves as the preferred curative therapeutic regimen for early-stage and regionally advanced lung carcinoma, offering patients a chance of cure or significantly prolonging their survival. Nevertheless, postoperative pain remains one of the core issues plaguing patients [3].

Postoperative pain not only directly impairs patients' quality of life but also hinders the postoperative rehabilitation process through

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multiple pathways. Opioids, a class of drugs that exert analgesic effects by activating opioid receptors in the central nervous system (CNS), have become the cornerstone for managing moderate to severe perioperative pain in lung cancer surgery due to their potent analgesic efficacy and well-defined mechanism of action [4, 5]. Clinically, opioids encompass various formulations such as morphine, fentanyl, sufentanil, and oxycodone, which can be administered via multiple routes including intravenous injection, epidural administration, and patient-controlled analgesia (PCA) during the perioperative period, catering to analgesic needs across different surgical scenarios and pain intensities. However, the clinical application of opioids has always been confronted with the dilemma of balancing efficacy and risks. On one hand, their analgesic effect is unquestionable; on the other hand, optimizing their dosage remains a challenging issue in clinical practice [6]. Currently, the dosage of opioids used during lung cancer surgery is mainly determined based on anesthesiologists' clinical experience, combined with estimates derived from factors such as patient age, body weight, and surgical type, lacking unified and precise quantitative standards. This experience-based medication pattern leads to significant variations in clinical opioid dosages: some patients may suffer from inadequate analgesia due to insufficient dosage, while others may experience a series of adverse reactions caused by excessive dosage. Moreover, life-threatening complications like respiratory depression may occur, particularly in elderly, debilitated lung cancer patients or those with comorbid chronic obstructive pulmonary disease [7]. More importantly, a growing body of research in recent years has suggested that opioids may exert profound impacts on the postoperative outcomes of cancer patients by regulating the body's inflammatory response and immune function - this finding has brought new insights into the clinical application of opioids [8].

The elevation of inflammatory markers is not caused by a single factor; its core driving mechanism is that opioids regulate immune cell functions and inflammatory signaling pathways through both central and peripheral pathways, ultimately disrupting the body's inflammatory balance. From a structural perspective, opioid receptors (μ, δ, and κ types) are not only distributed in the central nervous system but also widely expressed in immune cells such as macrophages, neutrophils, and T lymphocytes, as well as vascular endothelial cells. This provides molecular targets for drugs to directly regulate peripheral inflammatory responses [9]. When opioids bind to μ receptors on the surface of immune cells, they activate the G protein-adenylyl cyclase-cyclic adenosine monophosphate (G protein-AC-cAMP) signaling pathway, thereby altering the polarization direction of immune cells and their cytokine secretion profiles. Specifically, high-dose opioids can significantly promote the polarization of macrophages toward the M1 phenotype. As classic pro-inflammatory effector cells, activated M1 macrophages secrete large amounts of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β through pathways including nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) [10]. Meanwhile, these drugs inhibit the differentiation and activation of M2 macrophages. M2 macrophages exert anti-inflammatory effects by secreting anti-inflammatory cytokines such as transforming growth factor-β (TGF-β) and IL-10, and the suppression of their function further exacerbates inflammatory imbalance [11, 12]. Studies on the impact of opioids on postoperative prognosis of lung cancer have confirmed this conclusion [13], when the morphine equivalent dose exceeds 80 mg, the proportion of M1 macrophages in the peripheral blood of patients increases by 42% compared with the group with a dose lower than 50 mg, and the expression level of IL-6 is upregulated by 3.1 times. In addition, opioids can also inhibit the release of nitric oxide (NO) from vascular endothelial cells, increase vascular permeability, lead to the infiltration of inflammatory cells into tissue spaces, further amplify the inflammatory response, and ultimately result in a significant elevation of inflammatory markers in peripheral blood [14].

The immune system serves as a crucial defense line against the growth and metastasis of tumor cells. For lung cancer patients undergoing surgery, in particular, the integrity of postoperative immune function is directly linked to the risk of tumor recurrence and metastasis. Surgical trauma itself can induce a certain degree of immunosuppression, and the administration of opioids may further aggravate this immunosuppressive effect through complex

mechanisms involving multiple immune cell subsets. Humoral immunity and cellular immunity constitute the two core components of the body's immune function, and opioids may affect both aspects [15]. In terms of humoral immunity, immunoglobulins are key immunologically active substances secreted by B lymphocytes. Existing studies have demonstrated that high-dose opioids can restrain the proliferative activity and differentiative potential of B lymphocytes, thereby reducing the synthesis and secretion of immunoglobulins [16]. Regarding cellular immunity, the balance of T lymphocyte subsets is a critical indicator for evaluating cellular immune function. The impact of opioids on T lymphocyte subsets has been widely verified: studies indicate that opioids can suppress the activation and proliferation of T lymphocytes through both central and peripheral pathways [17].

The innovative value of the correlation between immunosuppression and elevated inflammatory markers is mainly reflected in three core aspects. First, it fills the theoretical gap in the interaction between inflammation and immunity, and improves the application of the opioid-mediated immunometabolic theory in lung cancer surgery patients. Second, it provides a new direction for postoperative outcome intervention, changes the previous symptomatic treatment mode for opioid-related adverse reactions, and guides the clinical establishment of a combined strategy of anti-inflammation and immune regulation. Third, it promotes the precise transformation of analgesic regimens, enabling the establishment of a dual-dimensional medication guidance system based on pain scores and biomarkers, which addresses the current dilemma of relying solely on empirical medication and improves the safety and effectiveness of analgesic therapy.

In summary, the mechanisms by which perioperative opioids influence the rehabilitation process of lung cancer patients by regulating inflammatory responses and immune function remain to be clearly elucidated. Through a large-sample retrospective analysis, this study intends to explore the association between opioid dosage and inflammation- as well as immunity-related biomarkers. The findings of this research are expected to provide important clinical guidance and scientific value for optimizing perioperative analgesic regimens in lung cancer surgery and improving patient outcomes.

Patients and methods

Patient selection

Clinical data of 463 potential subjects were initially retrieved from the First Affiliated Hospital of Guangzhou University of Chinese Medicine Electronic Medical Record (EMR) system between January 2022 and January 2025. These initially identified cases were screened one by one in accordance with the inclusion and exclusion criteria, resulting in 438 eligible cases. For these 438 preliminarily qualified cases, special attention was paid to reviewing the records of opioid dosage and key postoperative indicators. A total of 26 cases with incomplete data were excluded, and the remaining 412 cases were included in the final analysis. These patients were divided into four groups based on the morphine equivalent doses of opioid drugs: low-dose group, low-medium dose group, medium-high dose group, and high-dose group, with 103 patients in each group (**Figure 1**).

Inclusion criteria: (1) Definitive diagnosis of primary bronchogenic carcinoma confirmed by postoperative pathological examination; preoperative tumor staging was determined by chest enhanced computed tomography (CT), positron emission tomography-CT, and fiberoptic bronchoscopy, which conformed to the Ninth Edition of Lung Cancer Staging Standards by the International Association for the Study of Lung Cancer [18]; (2) Underwent radical lung cancer surgery in our hospital, including video-assisted thoracoscopic radical lung cancer surgery, robot-assisted radical lung cancer surgery, and traditional open radical lung cancer surgery; (3) The analgesic contribution ratio of opioids in the perioperative analgesic regimen (from the initiation of anesthesia induction to 72 hours postoperatively) was ≥70%, including perioperative intravenous sufentanil administration and postoperative patient-controlled intravenous analgesia (PCIA) with morphine or oxycodone; (4) Surgery was performed between January 2022 and January 2025.

Exclusion criteria: (1) History of other malignant tumors; (2) Preoperative severe infectious dis-

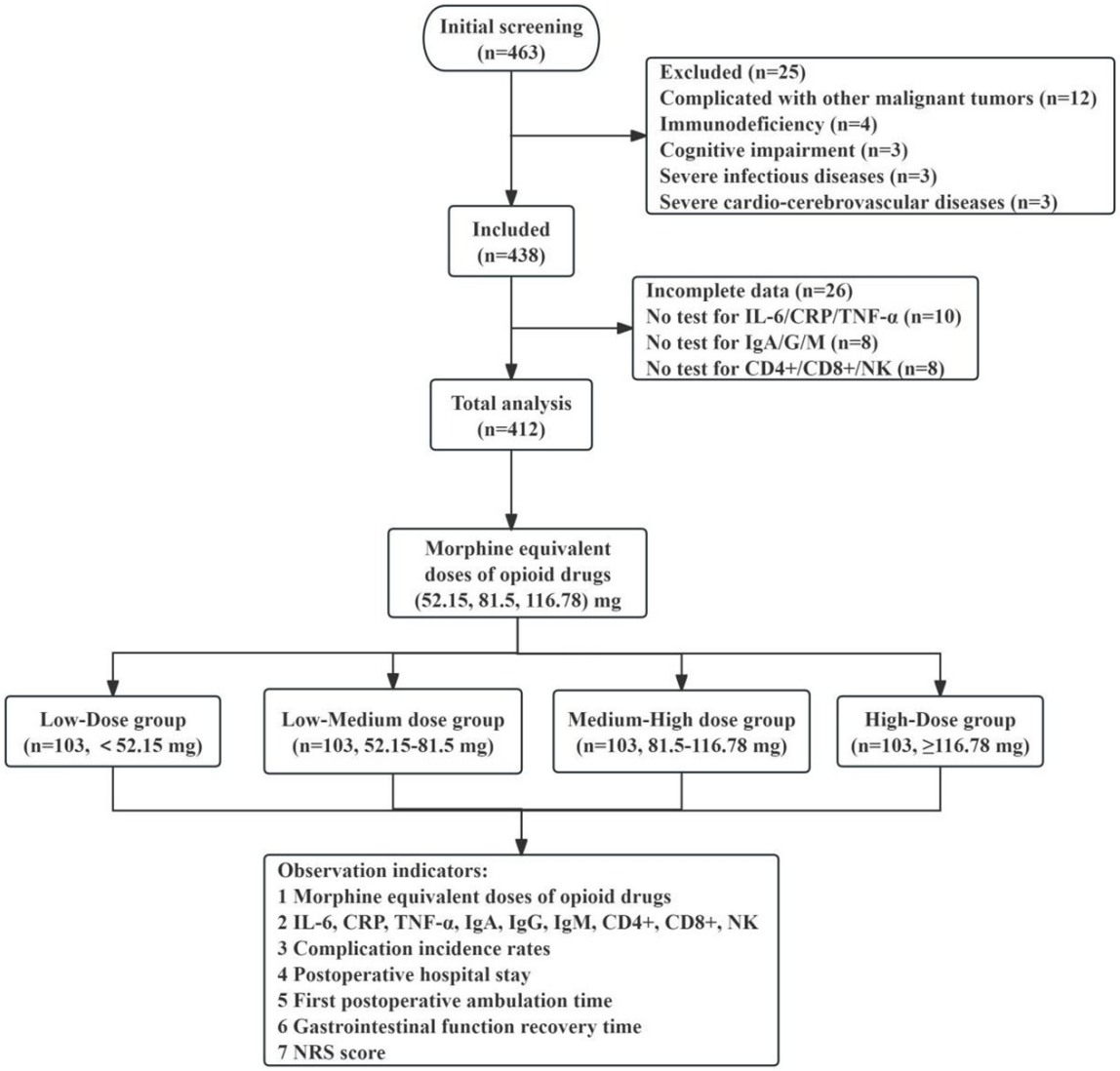

Figure 1. Research flowchart. Note: Overall, 463 patients with lung cancer who underwent surgical intervention were initially screened. Guided by the inclusion and exclusion criteria, 25 cases were excluded, and 438 patients were enrolled. During the subsequent data review, 26 cases were further excluded due to incomplete information, leaving 412 patients for the final analysis. These 412 patients were divided into four groups based on the perioperative opioid morphine equivalent dose, with 103 patients in each group. CRP, C-reactive Protein; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M; CD4+, CD4 Positive T Cells; CD8+, CD8 Positive T Cells; NK, Natural Killer; NRS, Numerical Rating Scale.

eases; (3) Immunodeficiency or long-term use of immunosuppressants; (4) Severe liver or renal dysfunction; (5) Preoperative severe cardiovascular and cerebrovascular diseases; (6) Mental illness or cognitive impairment; (7) Transfer to another department or death within 72 hours postoperatively [19].

Data collection

In this study, data of the 412 enrolled patients were collected through multiple hospital information systems to ensure comprehensiveness and accuracy. Specifically, demographic characteristics, clinicopathological information, and postoperative clinical events (including postoperative hospital stay duration, first postoperative ambulation time, gastrointestinal function recovery time, type and occurrence time of complications within 30 days after surgery, and pain score at 72 hours postoperatively) were extracted from EMR system. Perioperative opioid use information (including drug type, administration route, single dose, and total dose) was

accurately retrieved from the Clinical Anesthesia Information System, and all doses were converted into morphine equivalent dose according to standard conversion criteria. Peripheral venous blood test data before surgery and at 72 hours postoperatively - including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), immunoglobulin (Ig) A, IgG, IgM, CD4+ cell count, CD8+ cell count, CD4+/CD8+, and natural killer (NK) cell percentage - were obtained from the Laboratory Information System, venous blood samples were collected after fasting at 1 day before surgery (24±2 hours) and within 72 hours (±2 hours) after surgery. All the detected blood indicators are routine mandatory items for lung cancer patients after surgery. These indicators can dynamically monitor inflammatory responses and immune status, providing a core basis for adjusting postoperative analgesic regimens and preventing complications, which is consistent with clinical diagnosis and treatment standards. All data were independently extracted by two researchers. For items with inconsistent extraction results, the original medical records, anesthesia records, and laboratory reports were reviewed to confirm the accurate data, thereby ensuring the integrity and reliability of the collected data. For continuous data, the intraclass correlation coefficient (ICC) was used to test inter-rater consistency, with an ICC value of 0.92, indicating good consistency. For categorical data, the Kappa coefficient was adopted for consistency evaluation, with a Kappa value of 0.85, demonstrating good consistency.

Outcome measures

Primary outcome measures: (1) Perioperative morphine equivalent doses of opioid drugs: A universally accepted international conversion standard was adopted for unified quantification. The conversion ratios between different opioids and morphine were as follows: 10 μg sufentanil = 1 mg morphine, 100 μg fentanyl = 1 mg morphine, and 1 mg oxycodone = 1.5 mg morphine [20]. Based on perioperative medication records and postoperative PCA data, the opioid dosages used perioperatively and within 72 hours postoperatively were calculated separately, converted into morphine equivalent doses, and summed to obtain the total perioperative dosage [21]. (2) Postoperative detection of inflammatory biomarkers: Five milliliters of peripheral venous blood was collected using an anticoagulant tube. After centrifugation to separate serum, the levels of relevant indicators were measured using corresponding detection methods. Specifically, CRP was detected by immunoturbidimetry [22] using an automatic biochemical analyzer (Model: XPT, Manufacturer: Siemens Healthineers, Origin: Germany); IL-6 and TNF-α were detected by enzyme-linked immunosorbent assay [22] using a microplate reader (Model: Multiskan FC, Manufacturer: Thermo Fisher Scientific Inc., Origin: USA). (3) Postoperative detection of immune biomarkers: Five milliliters of peripheral venous blood was collected using an anticoagulant tube, and serum was separated by centrifugation. IgA, IgG, and IgM were detected by immunoturbidimetry [23] using the same instrument as that for CRP detection; the CD4+/CD8+ and NK cell percentage were detected by flow cytometry [24] using a flow cytometer (Model: CytoFLEX, Manufacturer: Beckman Coulter, Inc., Origin: USA). For the quality control of IgA, IgG, and IgM, the intra-batch coefficient of variation (CV) ranged from 1.5% to 2.8%, and the inter-batch CV ranged from 3.1% to 4.5%. For the CD4+/CD8+, the intra-batch CV ranged from 2.1% to 3.5%, and the inter-batch CV ranged from 4.2% to 5.8%. For the percentage of NK cells, the intra-batch CV ranged from 1.8% to 2.9%, and the inter-batch CV ranged from 3.9% to 5.2%.

Postoperative clinical events: (1) Postoperative hospital stay duration: Calculated as the number of days from the end of surgery to the date of discharge, which was verified through cross-checking with the hospital's inpatient charging management system and discharge records in the EMR system [25]. (2) Pain score at 72 hours postoperatively: Evaluated utilizing the Numerical Rating Scale (NRS), with scores spanning from 0 to 10; higher scores indicated more severe pain [26]. (3) First postoperative ambulation time: Defined as the time when the patient first got out of bed independently, stood, and maintained the posture for at least 5 minutes after surgery, which was determined based on postoperative medical records and nursing records [27]. (4) Gastrointestinal function recovery time: Judged by the time of the patient's first flatus after surgery, which was confirmed based on postoperative medical

records and nursing records [27]. (5) Complications within 30 days postoperatively: Information on complications was extracted from postoperative medical records, examination reports, and laboratory test results in the EMR system, including pulmonary infection, nausea and vomiting, constipation, urinary retention, poor incision healing, and others [28].

Analgesia protocol

All lung cancer surgery patients enrolled in this retrospective study received a standardized whole-process analgesia protocol, which was specified as follows:

Preoperatively, celecoxib 200 mg was administered orally at 12 hours and 2 hours before surgery for preemptive analgesia. Thirty minutes after induction of general anesthesia, perioperative thoracic paravertebral block (TPVB) was performed, with 20 ml of 0.375% ropivacaine injected (for unilateral lung cancer surgery, the corresponding thoracic level was blocked; for bilateral surgery, 10 ml was injected bilaterally). During the induction of general anesthesia, sufentanil was slowly injected via a peripheral vein (dosage calculated based on patient weight, injection rate controlled at 1 μg every 10 seconds to avoid severe hemodynamic fluctuations); during the maintenance phase, remifentanil was continuously infused, and the infusion rate was adjusted according to the patient's perioperative vital signs (heart rate, blood pressure, respiratory entropy). Thirty minutes before the end of surgery, tropisetron 5 mg was injected and remifentanil infusion was discontinued. Once the patient was awake and able to follow medical instructions postoperatively, patient-controlled intravenous analgesia (PCIA) was initiated immediately. The PCIA pump contained sufentanil (dosage calculated based on patient weight) combined with tropisetron 10 mg, diluted to 100 ml with 0.9% normal saline, and infused continuously at a rate of 2 ml/h. Additionally, parecoxib sodium 40 mg was intravenously injected at 24, 48, and 72 hours postoperatively. If the Numerical Rating Scale (NRS) score >3, flurbiprofen axetil 50 mg was administered as a rescue analgesic; if breakthrough pain occurred with NRS score ≥5, sufentanil 5 μg was slowly injected intravenously (injection time >30 seconds). PCIA was routinely used for 72 hours postoperatively. During this period, respiratory rate and blood oxygen saturation were monitored hourly (respiratory function was a key focus for patients undergoing lung cancer surgery), and blood pressure, heart rate, and NRS scores (resting pain and pain during coughing were recorded separately) were evaluated every 4 hours to ensure medication safety and analgesic efficacy [29].

Ethical statement

This study strictly adhered to the Declaration of Helsinki [30]. All research procedures were fully reviewed and approved by the The First Affiliated Hospital of Guangzhou University of Chinese Medicine Medical Ethics Committee, with the ethical approval number [NO. GZ-K-20250612]. As a retrospective study, all data were derived from existing clinical data and laboratory test results in the hospital's standardized information systems, without additional interventions on patients. Therefore, the ethics committee approved the exemption of informed consent from patients, while the principle of patient privacy protection was strictly implemented.

Sample size calculation

Based on the findings of previous similar studies [22], the median doses of remifentanil administered to the three patient groups during video-assisted thoracoscopic lobectomy were 8.74 μg/kg/h, 8.56 μg/kg/h, and 7.59 μg/kg/h, respectively. At 48 hours postoperatively, the serum IL-6 levels were 42.27 (26.29, 91.31) pg/mL, 25.99 (16.79, 34.65) pg/mL, and 19.36 (10.98, 33.66) pg/mL, respectively. The effect size (η^2) was calculated as 0.46 using the corresponding formula. With a preset significance level α=0.05 (two-tailed test) and statistical power (1-β) = 0.95, G*Power 3.1.9.7 software estimated that 84 cases were required for each group. Additionally, taking into account the potential data loss inherent in retrospective studies, a total of 412 patients with analyzable data were actually enrolled in this study. The sample size exceeded the estimated requirement, which ensured the study had sufficient statistical power and guaranteed the reliability of the research conclusions.

A post-hoc power analysis was performed based on the large effect size (d=0.980) between the total morphine equivalent dose

and IL-6 levels at 72 hours postoperatively, which was calculated from the actual data of this study. The two-tailed significance level was set at α=0.05 and the target statistical power at 1-β=90%. The results showed that the statistical power corresponding to the 412 cases actually included in this study was as high as 99.9%, far exceeding the preset target. Furthermore, the prospectively estimated minimum required sample size was only 56 cases, and the actual sample size was 1.8 times this value. These findings fully confirm that the sample size based on the total morphine equivalent dose has sufficient statistical power, which can effectively support the reliability of the study conclusions.

Statistical analysis

All data in this study were collated and analyzed using SPSS 27.0 statistical software. Quantitative data were first subjected to normality test (Kolmogorov-Smirnov test) and homogeneity of variance test (Levene test). Quantitative data conforming to normal distribution and homogeneous variance were expressed as mean ± standard deviation (mean ± SD), and intergroup comparison was performed using analysis of covariance (ANCOVA), Bonferroni test was used for post-hoc analysis. Quantitative data not conforming to normal distribution were expressed as median (interquartile range) [M (Q1, Q3)], and intergroup comparison was conducted using Kruskal-Wallis H test. Categorical data were presented as case number (percentage) [n (%)], and intergroup comparison was carried out using chi-square test. For correlations between quantitative data, Pearson correlation analysis was used if all data conformed to normal distribution; otherwise, Spearman's rho correlation analysis was adopted. Multivariate linear regression analysis was employed to screen for independent risk factors.

Results

Perioperative morphine equivalent doses of opioid drugs

The median morphine equivalent dose of opioids in the 412 patients was 81.5 mg, with an interquartile range of 52.15-116.78 mg. Based on the distribution of morphine equivalent dose among all patients, they were divided into four groups: low-dose group (≤52.15 mg), low-medium dose group (52.15-81.5 mg), medium-high dose group (81.5-116.78 mg), and high-dose group (>116.78 mg), with 103 patients in each group (**Table 1**).

Baseline characteristics of patients

No statistically significant differences (all $P>0.05$) were observed among the four groups in terms of demographic characteristics, clinicopathological features, and surgery-related characteristics. Additionally, the effect size indicated that the actual differences between groups were extremely small (**Table 2**). Confounding factors were adjusted using logistic regression analysis, and no significant difference (all $P>0.05$, $R^2=0.042$) was observed between the groups (**Table 3**). These results demonstrate that the opioid dose grouping in this study has good baseline balance, which provides a fundamental guarantee for the reliability of the research conclusions.

Changes in outcome measures

This study compared the core outcome measures among the four groups after adjusting for all the baseline confounding factors using ANCOVA. Compared with before surgery, at 72 hours postoperatively, the levels of CRP, IL-6 and TNF-α were increased, while the levels of IgA, IgG and IgM, the CD4+/CD8+, the NK cell percentage and the NRS score were decreased (all $P<0.05$). The core indicators of postoperative inflammatory response (CRP, IL-6, TNF-α) showed a stepwise increase with the elevation of opioid dosage, with significant differences between groups (all $P<0.001$). The immune function-related indicators (IgA, IgG, IgM, CD4+/CD8+, NK cell percentage) exhibited varying degrees of decreasing trends as the opioid dosage increased (all $P<0.001$). The clinical recovery indicators (postoperative hospital stay duration, first postoperative ambulation time, gastrointestinal function recovery time) were characterized by delayed recovery with the increase of opioid dosage (all $P<0.001$) (**Table 4**). Although the 72-hour postoperative NRS pain scores were relatively low across all groups and the between-group differences were statistically significant ($P<0.001$), the score differences were minimal and did not reach the threshold for clinically meaningful pain differences.

Table 1. Morphine equivalent doses of opioid drugs [M (Q1, Q3)]

Indicators	Total (n=412)	Low-Dose Group (n=103)	Low-Medium Dose Group (n=103)	Medium-High Dose Group (n=103)	High-Dose Group (n=103)
Morphine equivalent doses of opioid drugs (mg)	81.5 (52.15, 116.78)	37.1 (29.4, 44.9)	68.8 (62.5, 75.6)	98.1 (91.2, 106.4)	137.6 (128.5, 146.7)

Table 2. Baseline data [mean ± SD, n (%)]

Indicators	Low-Dose Group (n=103)	Low-Medium Dose Group (n=103)	Medium-High Dose Group (n=103)	High-Dose Group (n=103)	*P*	Effect size
Age (years)	62.56±2.64	62.74±1.95	62.41±1.59	62.84±1.60	0.409	η^2=0.007
BMI (kg/m^2)	23.63±0.57	23.73±0.57	23.75±0.67	23.66±0.64	0.633	η^2=0.007
Gender (n%)						
Male	58 (56.3)	59 (57.3)	57 (55.3)	58 (56.3)	0.994	Cramer's V=0.014
Female	45 (43.7)	44 (42.7)	46 (44.7)	45 (43.7)		
Smoking history (n%)	46 (44.7)	49 (57.3)	52 (50.5)	51 (49.5)	0.845	Cramer's V=0.045
Pathological type (n%)						
Adenocarcinoma	65 (63.1)	64 (62.1)	66 (64.1)	63 (61.2)	0.996	Cramer's V=0.027
SCC	33 (32.0)	32 (31.1)	31 (30.1)	33 (32.0)		
Others	5 (4.9)	7 (6.8)	6 (5.8)	7 (6.8)		
Tumor staging (n%)						
I	49 (47.6)	46 (44.6)	45 (43.7)	45 (43.7)	0.995	Cramer's V=0.029
II	35 (34.0)	36 (35.0)	36 (35.0)	35 (34.0)		
III	19 (18.4)	21 (20.4)	22 (21.3)	23 (22.3)		
Maximum tumor diameter (cm)	3.09±0.25	3.11±0.24	3.12±0.24	3.08±0.27	0.767	η^2=0.003
Lymph node metastasis (n%)	36 (35.0)	38 (36.9)	41 (39.8)	41 (39.8)	0.863	Cramer's V=0.042
Surgical method (n%)						
Thoracoscopy	58 (56.3)	57 (55.3)	52 (50.5)	51 (49.5)	0.457	Cramer's V=0.083
Robot-Assisted	25 (24.3)	26 (25.3)	24 (23.3)	20 (19.4)		
Thoracotomy	20 (19.4)	20 (19.4)	27 (26.2)	32 (31.1)		
Postoperative PCIA bolus (n%)	28 (27.2)	25 (24.3)	20 (19.4)	18 (17.5)	0.316	Cramer's V=0.093
Postoperative supplementary administration of flurbiprofen axetil/sufentanil (n%)	40 (38.8)	38 (36.9)	31 (30.1)	25 (24.3)	0.101	Cramer's V=0.123
Postoperative rescue dose of flurbiprofen axetil (mg)	93.20±35.04	94.17±35.22	93.20±35.04	91.75±35.07	0.969	η^2=0.001
Postoperative rescue dose of sufentanil (μg)	4.32±3.50	4.42±3.52	4.27±3.46	4.27±3.39	0.989	η^2<0.001
Combined use of celecoxib (mg/d)	198.06±12.99	198.25±12.87	198.45±13.04	198.45±13.04	0.996	η^2<0.001
Combined use of ropivacaine (mg)	119.22±6.52	119.32±6.46	119.42±6.54	118.84±6.61	0.925	η^2=0.001
Combined use of parecoxib sodium (mg)	40.85±0.78	40.84±0.80	40.86±0.79	40.83±0.79	0.987	η^2<0.001

Severity of surgical trauma (n%)						
Mild	42 (40.8)	40 (38.8)	38 (36.9)	37 (35.9)	0.995	Cramer's V=0.028
Moderate	48 (46.6)	50 (48.6)	52 (50.5)	53 (51.5)		
Severe	13 (12.6)	13 (12.6)	13 (12.6)	13 (12.6)		
Perioperative blood loss (mL)	185.90±2.29	185.85±2.28	185.83±2.23	185.84±2.25	0.996	η^2<0.001
Perioperative fluid infusion (mL)	1253.98±10.79	1254.27±10.81	1253.79±10.86	1254.17±10.89	0.989	η^2<0.001
Perioperative blood transfusion (n%)	15 (14.6)	16 (15.5)	17 (16.5)	18 (17.5)	0.948	Cramer's V=0.030
Actual dosage of postoperative adjuvant analgesics (mg, morphine equivalent)	45.40±1.08	45.43±1.08	45.38±1.09	45.42±1.09	0.989	η^2<0.001

Note: BMI, Body Mass Index; SCC, Squamous Cell Carcinoma; PCIA, Patient-Controlled Intravenous Analgesia.

Table 3. Baseline data

Indicators	*B*	P	OR	95% CI for OR
Age	0.028	0.472	1.028	0.941, 1.123
BMI	0.032	0.451	1.033	0.955, 1.118
Gender	0.075	0.416	1.078	0.892, 1.304
Smoking history	0.069	0.443	1.071	0.885, 1.295
Pathological type	0.058	0.492	1.060	0.881, 1.276
Tumor staging	0.082	0.385	1.085	0.899, 1.311
Maximum tumor diameter	0.071	0.422	1.074	0.893, 1.292
Lymph node metastasis	0.094	0.351	1.099	0.908, 1.327
Surgical method	0.066	0.457	1.068	0.888, 1.285
Postoperative PCIA bolus	0.081	0.391	1.084	0.898, 1.309
Postoperative supplementary administration of flurbiprofen axetil/sufentanil	0.074	0.419	1.077	0.894, 1.298
Postoperative rescue dose of flurbiprofen axetil	0.029	0.468	1.029	0.944, 1.122
Postoperative rescue dose of sufentanil	0.035	0.447	1.036	0.951, 1.129
Combined use of celecoxib	0.055	0.498	1.057	0.879, 1.272
Combined use of ropivacaine	0.062	0.475	1.064	0.884, 1.280
Combined use of parecoxib sodium	0.059	0.489	1.061	0.882, 1.277
Severity of surgical trauma	0.102	0.326	1.107	0.915, 1.338
Perioperative blood loss	0.091	0.362	1.095	0.905, 1.322
Perioperative fluid infusion	0.087	0.376	1.091	0.902, 1.317
Perioperative blood transfusion	0.113	0.301	1.120	0.926, 1.355
Actual dosage of postoperative adjuvant analgesics (morphine equivalent)	0.098	0.339	1.103	0.912, 1.333
R^2			0.042	
Adjusted R^2			0.038	

Note: OR, Odds Ratio; 95% CI, 95% Confidence Interval.

Table 4. Changes in observation indicators

Indicators	Time	Low-Dose Group (n=103)	Low-Medium Dose Group (n=103)	Medium-High Dose Group (n=103)	High-Dose Group (n=103)	*P*	Effect size
CRP (mg/L)	Before surgery	2.34±0.40	2.27±0.29	2.30±0.25	2.34±0.29	0.328	0.008
	72 hours after surgery	9.92±3.67*	12.67±2.62*	16.93±2.70*	20.51±2.57*	<0.001	0.658
IL-6 (pg/mL)	Before surgery	3.21±0.36	3.20±0.25	3.22±0.29	3.21±0.38	0.970	0.001
	72 hours after surgery	19.55±12.23*	22.84±2.96*	31.39±5.89*	38.11±1.44*	<0.001	0.532
TNF-α (pg/mL)	Before surgery	2.08±0.28	2.10±0.19	2.12±0.22	2.13±0.29	0.433	0.007
	72 hours after surgery	9.58±9.13*	12.19±8.30*	15.11±8.17*	17.17±1.36*	<0.001	0.132
IgA (g/L)	Before surgery	1.84±0.25	1.83±0.18	1.83±0.06	1.84±0.12	0.991	<0.001
	72 hours after surgery	1.70±0.13*	1.67±0.06*	1.60±0.06*	1.53±0.06*	<0.001	0.348
IgG (g/L)	Before surgery	12.43±0.55	12.49±0.31	12.48±0.53	12.49±0.96	0.860	0.002
	72 hours after surgery	11.48±0.54*	10.98±0.48*	10.44±0.69*	10.00±0.34*	<0.001	0.529
IgM (g/L)	Before surgery	1.31±0.26	1.31±0.24	1.31±0.20	1.30±0.03	0.989	<0.001
	72 hours after surgery	1.21±0.04*	1.18±0.04*	1.16±0.04*	1.14±0.04*	<0.001	0.305
CD4+/CD8+	Before surgery	1.77±0.09	1.76±0.19	1.75±0.28	1.73±0.34	0.751	0.003
	72 hours after surgery	1.67±0.14*	1.57±0.20*	1.53±0.06*	1.41±0.06*	<0.001	0.350
NK (%)	Before surgery	18.33±0.71	18.13±2.68	17.90±4.22	17.68±4.74	0.565	0.005
	72 hours after surgery	15.84±1.98*	15.19±1.37*	14.50±0.76*	12.96±0.86*	<0.001	0.393
Postoperative hospital stay duration (days)	-	6.94±0.34	8.16±0.39	9.91±0.37	11.50±0.40	<0.001	0.956
First postoperative ambulation time (days)	-	1.70±0.14	2.21±0.15	2.81±0.15	3.40±0.13	<0.001	0.948
Gastrointestinal function recovery time (days)	-	2.01±0.16	2.61±0.15	3.21±0.16	3.81±0.15	<0.001	0.951
NRS (scores)	Before surgery	4.35±0.84	4.35±0.22	4.37±0.77	4.53±1.04	0.257	0.010
	72 hours after surgery	1.34±0.21*	1.63±0.21*	2.04±0.22*	2.33±0.20*	<0.001	0.994

Note: *$P<0.05$ vs. Before surgery; CRP, C-reactive Protein; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M; CD4+, CD4 Positive T Cells; CD8+, CD8 Positive T Cells; NK, Natural Killer; NRS, Numerical Rating Scale.

Incidence of postoperative complications

A further analysis was conducted on the occurrence of various postoperative complications among patients in different opioid dosage groups. Pulmonary infection showed the most prominent dose-dependent pattern. The incidence was the lowest in the low-dose group, only 6.8%. It then increased to 10.7% in the low-medium dose group and 15.5% in the medium-high dose group with the elevation of opioid dosage, and reached 22.3% in the high-dose group. There existed a prominent difference between the study groups (P=0.009), which suggests that high-dose opioids may increase the risk of pulmonary infection by impairing the body's anti-infective capacity. As a common gastrointestinal side effect of opioids, nausea and vomiting also showed a clear dose-dependent relationship. The incidence was 4.9% in the low-dose group and increased to 17.5% in the high-dose group, with a statistically significant difference between groups (P=0.020). This result is associated with the inhibitory effect of opioids on gastrointestinal function. Although the incidences of constipation, urinary retention, poor incision healing, and other complications slightly increased with the increase of opioid dosage, no statistically significant differences were observed between groups (all P>0.05). In terms of the total incidence of complications, it was only 17.5% in the low-dose group, 29.1% in the low-medium dose group, 42.7% in the medium-high dose group, and as high as 62.1% in the high-dose group. A significant difference was found between groups (P<0.001) (**Table 5**). These results further confirm that high-dose opioids are associated with an increased risk of postoperative complications by exacerbating inflammatory responses and suppressing immune function.

Correlation analysis between opioid dosage and inflammation- and immunity-related biomarkers

Correlation analysis was performed to explore the association between opioid dosage and inflammation- as well as immunity-related biomarkers (**Table 6**). The morphine equivalent dose of opioids showed a positive correlation with the core postoperative inflammatory biomarkers (CRP, IL-6, TNF-α). The correlation coefficients were 0.754, 0.787, and 0.695 respectively, with all P values <0.001. Among these, the correlation with IL-6 was the strongest, indicating that for each 1 mg increase in opioid dosage, the increase in IL-6 level was slightly higher than that in CRP and TNF-α levels. Regarding immunity-related biomarkers, the morphine equivalent dose of opioids exhibited the strongest negative correlation with IgG level (r=-0.766, P<0.001), followed by NK cell percentage (r=-0.673, P<0.001) and CD4+/CD8+ (r=-0.690, P<0.001). The correlations with IgA (r=-0.661, P<0.001) and IgM (r=-0.548, P<0.001) levels were negative correlations. The results of the multicollinearity analysis showed that all VIF values were less than 5, indicating low multicollinearity among the indicators and that the results of the correlation analysis were acceptable.

Independent risk factors for postoperative inflammatory and immune biomarkers

After adjusting for confounding factors in **Table 2**, linear regression analysis revealed that the morphine equivalent dose of opioids exerted an independent promoting effect on inflammatory biomarkers. It was identified as an independent risk factor for elevated levels of CRP, IL-6, and TNF-α (all P<0.05). Among these, its independent impact on IL-6 was the strongest. Both the regression coefficient (B=4.803) and t-value (10.726) were the highest. This indicates that after controlling for other confounding factors, each 1 mg increase in the morphine equivalent dose of opioids was correlated with an average upturn of 4.803 pg/mL in IL-6 level. Its independent promoting effects on CRP and TNF-α were slightly weaker, with B values of 0.570 and 1.314, and t-values of 3.133 and 7.041 respectively. These results further confirm that the activating effect of opioid dosage on postoperative inflammatory response is independent and not interfered by baseline confounding factors. The morphine equivalent dose of opioids was an independent risk factor for decreased IgG level, reduced CD4+/CD8+, and lower NK cell percentage (all P<0.001). It showed no significant independent impact on IgA and IgM levels (P=0.371, 0.637). In terms of the strength of independent influence, its inhibitory effect on NK cells was the strongest (B=-0.153, t=-5.129), followed by IgG (B=-0.883, t=-4.135) and CD4+/CD8+ (B=-0.419, t=-3.578). This suggests that after excluding other interfering factors, each 1 mg increase in opioid dosage was associated with an average

Table 5. Comparison of complication incidence rates

Indicators	Low-Dose Group (n=103)	Low-Medium Dose Group (n=103)	Medium-High Dose Group (n=103)	High-Dose Group (n=103)	*P*	Effect size
Pulmonary infection	7 (6.8)	11 (10.7)	16 (15.5)	23 (22.3)	0.009	0.168
Nausea and vomiting	5 (4.9)	8 (7.8)	12 (11.7)	18 (17.5)	0.020	0.155
Constipation	3 (2.9)	5 (4.9)	7 (6.8)	9 (8.7)	0.316	0.093
Urinary retention	2 (1.9)	3 (2.9)	4 (3.9)	6 (5.8)	0.490	0.077
Poor incision healing	1 (1.0)	2 (1.9)	3 (2.9)	5 (4.9)	0.352	0.089
Others	0 (0.0)	1 (1.0)	2 (1.9)	3 (2.9)	0.336	0.091
Total	18 (17.5)	30 (29.1)	44 (42.7)	64 (62.1)	<0.001	0.343

Table 6. Correlation analysis

Indicators	Morphine Equivalent Doses of Opioid Drugs		
	Spearman's rho	*P*	VIF
CRP	0.754	<0.001	4.838
IL-6	0.787	<0.001	3.261
TNF-α	0.695	<0.001	2.133
IgA	-0.661	<0.001	4.133
IgG	-0.766	<0.001	3.971
IgM	-0.548	<0.001	3.557
CD4+/CD8+	-0.690	<0.001	3.647
NK	-0.673	<0.001	3.967

decrease of 0.153% in NK cell percentage, 0.883 g/L in IgG level, and 0.419 in CD4+/CD8+ (**Table 7**). The overall linear regression model showed good fitness (R^2=0.721).

Discussion

The results of this study suggested a positive correlation between opioid dosage and the levels of CRP, IL-6, and TNF-α at 72 hours postoperatively. Multivariate regression analysis further confirmed that opioid dosage is an independent risk factor for the elevation of these inflammatory indicators. In a single-center prospective randomized study [31], reducing opioid use was found to decrease fluctuations in perioperative inflammatory response-related markers. Although this study focused on patients undergoing cardiac surgery, its findings are consistent with the core conclusion of the present study that "opioid dosage is positively correlated with inflammatory markers", further supporting that the regulatory effect of opioids on postoperative inflammatory response is universal across different surgical procedures. Mechanistically, opioids may activate inflammatory responses through both CNS and peripheral tissue pathways. At the central level, after binding to μ receptors in the dorsal horn of the spinal cord, opioids can promote the transcription of pro-inflammatory factors by activating the nuclear factor kappa-B signaling pathway [22, 32]. At the peripheral level, they may inhibit the apoptosis of monocytes, prolong the survival time of inflammatory cells, and lead to the continuous release of inflammatory factors.

Immune function analysis revealed a negative correlation between opioid dosage and the levels of IgG, CD4+/CD8+, and NK cells. Opioid dosage was also identified as an independent risk factor for the reduction of these indicators. A study using the South Korean National Health Insurance Database as the data source [33] indicated that long-term opioid use may enhance tumor-promoting activity by inducing immunosuppression. This is consistent with the finding in the present study that "excessive opioid dosage is associated with impaired immune function". Furthermore, that study focused on patients after lung cancer surgery, which is consistent with the study population of the present research, further supporting the reliability of our results. A decrease in Ig G level may impair the body's anti-infective and anti-tumor capabilities [34]. NK cells can directly kill tumor cells and pathogenic microorganisms. The decrease in NK percentage in the high-dose group further may increase the risks of postoperative infection and tumor recurrence [35]. Opioids had a weaker impact on IgA and IgM. This may be attributed to the fact that these two types of immunoglobulins are mainly synthesized by mucosa-associated lymphoid tissue and are less affected by central immune regulation [36]. Studies have indicated that mucosal B cells secrete large quantities of immunoglobulins through multiple follicular

Table 7. Analysis of independent risk factors

Indicators		*B*	*t*	*P*
Morphine equivalent doses of opioid drugs	CRP	0.570	3.133	0.002
	IL-6	4.803	10.726	<0.001
	TNF-α	1.314	7.041	<0.001
	IgA	17.395	0.896	0.371
	IgG	-0.883	-4.135	<0.001
	IgM	-5.762	-0.473	0.637
	CD4+/CD8+	-0.419	-3.578	<0.001
	NK	-0.153	-5.129	<0.001
	Age	0.082	1.215	0.225
	BMI	-0.156	-1.428	0.154
	Gender	0.214	1.189	0.235
	Smoking history	-0.198	-1.345	0.179
	Pathological type	0.276	1.561	0.119
	Tumor staging	-0.245	-1.672	0.095
	Maximum tumor diameter	0.189	1.721	0.085
	Lymph node metastasis	-0.211	-1.812	0.070
	Surgical method	0.167	1.321	0.187
	Postoperative PCIA bolus	-0.134	-1.123	0.262
	Postoperative supplementary administration of flurbiprofen axetil/sufentanil	0.178	1.456	0.146
	Postoperative rescue dose of flurbiprofen axetil	-0.121	-1.098	0.273
	Postoperative rescue dose of sufentanil	0.145	1.234	0.218
	Combined use of celecoxib	-0.112	-0.987	0.324
	Combined use of ropivacaine	0.098	0.876	0.381
	Combined use of parecoxib sodium	-0.109	-0.954	0.340
	Severity of surgical trauma	0.223	1.654	0.098
	Perioperative blood loss	-0.087	-0.765	0.444
	Perioperative fluid infusion	0.076	0.654	0.513
	Perioperative blood transfusion	-0.091	-0.812	0.417
	Actual dosage of postoperative adjuvant analgesics (morphine equivalent)	0.123	1.012	0.312
R^2			0.042	
Adjusted R^2			0.038	

and extrafollicular pathways, among which IgA is the most abundant antibody subtype in mucosal secretions. Epithelial cells can not only transport IgA to the mucosal surface but also guide B cells to initiate IgA responses by sensing the status of intestinal flora. This close collaboration between local mucosal cells forms an independent regulatory system for antibody synthesis, which is minimally interfered with by central immune signals. These findings confirm that IgA synthesized in the mucosa is not susceptible to the effects of opioids [37]. A retrospective clinical study [38] found that advanced lung cancer patients treated with opioid analgesics had significantly shortened progression-free survival (PFS) and overall survival (OS). These findings confirm that opioid use exerts an adverse effect on the prognosis of lung cancer patients, indirectly reflecting that opioids may increase the risk of recurrence by interfering with immune function.

Clinical recovery indicators showed that increased opioid dosage not only prolonged postoperative hospital stay duration but also first postoperative ambulation time. A meta-analysis mentioned that longer hospital stays are associated with a higher probability of continuous opioid use [25]. Another study reported that reduced morphine use in patients after lung resection was accompanied by lower pain scores. These findings are consistent with the results of this study [39]. In addition, the incidence of nausea and vomiting in the high-dose group reached 17.5%, which was 3.6 times higher than that in the low-dose group. This is directly related to the pharmacological effect of opioids in stimulating the chemoreceptor trigger zone of the medulla oblongata. The dose-

dependent increase in the total incidence of complications is the ultimate manifestation of the dual effects of opioids in activating inflammation and suppressing immunity [40]. The significant differences in pulmonary infection and nausea and vomiting suggest that these two complications can serve as clinical early warning indicators for monitoring excessive opioid dosage, providing references for the dynamic adjustment of postoperative analgesic regimens.

The innovation and necessity of this study lie in the establishment of clinical evidence linking opioid dosage to inflammatory and immune biomarkers. It quantifies the strength of the association between opioid dosage and core indicators such as inflammation and immunity, providing quantitative indicators and new approaches for individualized clinical adjustments. The study reveals the mechanism by which high-dose opioids exacerbate inflammation-immune disorders, providing a biological basis for relevant strategies. It makes up for the deficiency in mechanism exploration and addresses the pain point of experience-based medication in clinical practice, thus possessing important practical and disciplinary value.

Study limitations

Although this study has obtained valuable results, it still has the following limitations. First, the retrospective study design itself has selection bias. Although ANCOVA has been used and adjustments have been made through multivariate regression, it cannot be completely excluded. Second, the differences in opioid administration routes were not considered. Different administration routes may lead to differences in drug effects by affecting bioavailability [41]. Third, biomarker detection was only performed once at 72 hours postoperatively. The lack of dynamic monitoring data makes it impossible to clarify the duration of the impact of opioids. Fourth, long-term outcome indicators such as postoperative tumor recurrence and long-term survival rate were not included. This prevents the evaluation of the impact of opioid dosage on the long-term prognosis of patients. Fifth, this study did not perform a stratified analysis based on lung cancer subtypes and surgical method. Some patients were excluded from this study due to missing data on the primary observation indicators, which may lead to selection bias and thus limit the extrapolation of the research conclusions.

Conclusion

This study clarifies the close association between opioid dosage and postoperative inflammatory and immune biomarkers. Future studies need to verify the correlation between opioid dosage and long-term outcomes through prospective research, and explore the differences in the efficacy of different opioids, thereby contributing to the realization of individualized analgesia.

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Disclosure of conflict of interest

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