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Systematic Review: The Effect of Preemptive Ketamine Administration on Post-Surgical Neutrophil to Lymphocyte Ratio And Interleukin-6 (Il-6) Levels

Muhammad Fakhri R[1], Muhammad Wirawan Harahap[1], Herawaty Baderu[1]

[1]*Faculty of Medicine, Universitas Muslim Indonesia*

**Corresponding Author: Muhammad Fakhri R*
E-mail: muhammadfakhrirasyidi@gmail.com

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Abstract

Surgical stress induces systemic inflammation characterized by increased neutrophil-to-lymphocyte ratio and interleukin-6 levels, which may contribute to postoperative pain, immune dysfunction, and complications. This systematic review aimed to evaluate the effects of preemptive ketamine administration on postoperative neutrophil-to-lymphocyte ratio and interleukin-6 levels. The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. Relevant studies were identified through PubMed, ScienceDirect, the Cochrane Central Register of Controlled Trials, Google Scholar, and ClinicalKey. Study selection was based on predefined population, intervention, comparison, outcome, and study-design criteria. Data were extracted using standardized tables, methodological quality was assessed using appropriate risk-of-bias instruments, and the findings were synthesized narratively according to ketamine dose, surgical procedure, biomarker measurement time, and clinical outcomes. Of 807 records identified, 17 studies were included in the final synthesis. Preemptive intravenous ketamine or S-ketamine generally reduced the early postoperative increase in the neutrophil-to-lymphocyte ratio and suppressed interleukin-6 secretion, particularly at subanesthetic doses of 0.3–0.75 milligrams per kilogram. These immunomodulatory effects were accompanied by lower postoperative pain scores, reduced opioid requirements, fewer episodes of postoperative nausea and vomiting, and a lower risk of chronic postsurgical pain. However, variations in dosage, surgical procedures, anesthetic techniques, and biomarker measurement times limited direct comparisons between studies. Preemptive ketamine appears to provide beneficial analgesic and immunomodulatory effects by attenuating postoperative systemic inflammation, although further standardized randomized trials are required to determine the optimal dosing regimen.

Introduction

Surgical stress is a complex, multidimensional neuroendocrine, metabolic, and immune system response resulting from mechanical tissue damage during surgical procedures.1 Tissue trauma triggers a local and systemic inflammatory response characterized by the massive release of proinflammatory cytokines, such as interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) (Yediyıldız et al., 2025; Ren et al., 2022). IL-6 is a key mediator of the acute-phase response, rapidly secreted by monocytes, macrophages, and endothelial cells, with a peak occurring 6 to 24 hours postoperatively (Yediyıldız et al., 2025; Tantri et al.,

2023). IL-6 levels are directly proportional to the degree of tissue trauma, the duration of surgery, the intensity of postoperative pain, and the risk of systemic complications (Yediyıldız et al., 2025; Ren et al., 2022). In addition to the humoral response, surgical trauma and anesthesia induce dynamic changes in peripheral immune cells, reflected in the neutrophil-to-lymphocyte ratio (NLR) (Shu et al., 2023; Domagalska et al., 2023). IL-6 is a key mediator of the acute-phase response. Surgery triggers an increase in neutrophils (neutrophilia) as an initial innate immune response to eliminate damaged tissue, but simultaneously induces T lymphocyte apoptosis (lymphopenia) due to the excessive release of cortisol and catecholamines (Rizvanović et al., 2023; Shu et al., 2023). Postoperative NLR elevation reflects the dominance of an uncontrolled systemic inflammatory response and suppression of adaptive immune function (immunosuppression). The dynamics or changes in postoperative NLR values (Δ"NLR") are now recognized as an inexpensive, sensitive, and reliable independent biomarker for predicting the risk of sepsis, surgical site infection, postoperative pulmonary complications, and the development of chronic postsurgical pain (CPSP) (Kriplani et al., 2022; Yao et al., 2023; Gigliotti et al., 2026; Lukaszewski et al., 2022; Perek et al., 2026; Jin et al., 2026).

Massive nociceptive stimulation during surgical incision and manipulation triggers a central sensitization process in the dorsal horn of the spinal cord, triggered by glutamate release (Viderman et al., 2024; Xuan et al., 2022; Krotov & Kopach, 2026; Gilbert et al., 2023; Tassou et al., 2025). This central sensitization amplifies the perception of postoperative pain, increases opioid requirements, and prolongs the inflammatory stress response (Viderman et al., 2024; Xuan et al., 2022). To prevent this phenomenon, the concept of preemptive analgesia is applied, namely administering analgesic interventions before the onset of nociceptive stimuli (before surgical incision) to prevent the formation of pain memory in the central nervous system and suppress the release of inflammatory mediators (Serden et al., 2025; Fiore et al., 2023; Xiong et al., 2024)

Ketamine, a non-competitive NMDA receptor antagonist (including its pure enantiomer S(+)-ketamine / S-ketamine), has proven efficacy in acute pain management and immunomodulation (Zhang et al., 2023; Ren et al., 2022). Preemptive administration of low-dose ketamine (sub-anesthetic, ≤0.5-0.75 mg/kg) not only reduces postoperative pain scores and suppresses opioid consumption by 14%–50%8, but has also been shown to suppress activation of the nuclear factor kappa B (NF-kB)1 pathway. This molecular inhibition reduces the formation of pro-inflammatory cytokines (IL-6), protects T lymphocytes (CD3+, CD4+), and stabilizes the postoperative NLR profile (Zhang et al., 2023; Hallikeri et al., 2024). Furthermore, ketamine has been shown to reduce perioperative complications such as postoperative nausea and vomiting (PONV), postoperative depression, and anxiety (Yao et al., 2023; Guo et al., 2023; Seo et al., 2025; Tang et al., 2026).

Although numerous studies have been published on analgesic interventions and the postoperative inflammatory response, 1-17, systematic evidence synthesis using the PRISMA 2020 Systematic Review methodology that simultaneously evaluates the impact of perioperative analgesia (specifically preemptive ketamine) on the dynamics of specific inflammatory biomarkers such as NLR and IL-6 remains limited. Most previous meta-analyses have focused solely on subjective pain scores (VAS/NPRS) or the efficiency of opioid consumption. Therefore, there is a gap in knowledge regarding the effect size and consistency of preemptive ketamine in reducing the dynamics of NLR elevation and IL-6 responses across various surgical procedures (ELSharkawy et al., 2025).

This systematic review is crucial for aggregating, critiquing, and synthesizing the latest clinical evidence in a transparent and objective manner. The results of this synthesis are expected to provide evidence-based medicine regarding the role of preemptive immunomodulation of ketamine in suppressing the post-surgical systemic inflammatory cascade.

Methods

Research Design

This study is a Systematic Review study that is compiled in detail and structured based on the PRISMA 2020 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The review was conducted to collect, critically evaluate, and synthesize the results of randomized clinical studies (Randomized Controlled Trials / RCTs) regarding the efficacy of preemptive ketamine/S-ketamine administration on the dynamics of postoperative NLR and IL-6 inflammatory biomarkers.

Literature Search Strategy

The literature search was conducted electronically through five primary scientific sources: PubMed/MEDLINE, ScienceDirect, the Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, and ClinicalKey. ClinicalKey was used as an additional source to obtain recent textbooks and clinical reviews relevant to the research topic. The search was limited to English-language studies published up to the end of the specified systematic search period.

Keywords and Search Strings

The search combined Medical Subject Headings (MeSH) terms and free-text keywords connected with Boolean operators (AND, OR).

Table 1. Literature Search Algorithm and Keywords

Database	Keywords
PubMed / MEDLINE	("Ketamine"[Mesh] OR "S-ketamine" OR "esketamine" OR "ketamine hydrochloride") AND ("Preemptive Analgesia"[Mesh] OR "preemptive" OR "pre-incisional" OR "preoperative") AND ("Neutrophil-to-Lymphocyte Ratio" OR "NLR" OR "Interleukin-6"[Mesh] OR "IL-6" OR "inflammatory markers") AND ("Postoperative Period"[Mesh] OR "postoperative" OR "post-surgical")
ScienceDirect / Cochrane	(Ketamine OR "S-ketamine" OR esketamine) AND ("preemptive analgesia" OR preoperative OR preincisional) AND (NLR OR "neutrophil to lymphocyte ratio" OR IL-6 OR "interleukin-6") AND postoperative

Inclusion and Exclusion Criteria (PICOS Framework)

Included studies were determined based on the PICOS (Population, Intervention, Comparison, Outcome, Study Design) eligibility criteria.

Table 2. Study Eligibility Criteria (PICOS Framework)

Elemen	Inclusion Criteria	Exclusion Criteria
Population (P)	Adult patients (≥18 years old) with ASA physical status I–III undergoing elective surgical procedures under general or regional anesthesia.	Pediatric patients, emergency surgery/massive trauma, patients with active preoperative infection, sepsis, autoimmune disease, or chronic immunosuppressant use.
Intervention (I)	Preemptive intravenous administration of ketamine or S-ketamine (before surgical incision/before induction of anesthesia).	Ketamine administered only in the postoperative period, non-intravenous routes without clear systemic data, or combination drug formulations where the ketamine effect cannot be isolated.

Comparison (C)	A control group received placebo (0.9% normal saline) or standard care without ketamine.	Studies without a valid placebo/control comparison group.
Outcome (O)	Postoperative Neutrophil-to-Lymphocyte Ratio (NLR) and/or postoperative serum Interleukin-6 (IL-6) levels (measured at 2, 6, 12, 24, or 48 hours postoperatively).	Studies that do not report quantitative postoperative NLR or IL-6 levels.
Study Design (S)	Randomized Controlled Trials (RCTs) published in peer-reviewed scientific journals.	Observational studies, case reports, animal/in vitro studies, narrative reviews, and draft abstracts without full-text articles.

Study Selection Procedure

Study selection was conducted following the steps in the PRISMA 2020 Flow Diagram. In the identification stage, all records obtained from various databases were collected, then duplicate articles were eliminated using reference management software. Next, the screening stage involved an initial screening based on the title and abstract by two independent reviewers to assess the relevance of each study to the research objectives. Articles that passed this stage then proceeded to the eligibility stage through a full-text evaluation to ensure their compliance with the established PICOS criteria. In the final stage, studies with randomized controlled trial designs that met all inclusion criteria were selected for further analysis and synthesis.

Study Quality Assessment / Critical Appraisal

The risk of bias assessment for each included randomized controlled trial (RCT) was conducted using the Cochrane Risk of Bias 2.0 (RoB 2) instrument (Tantri et al., 2023; Xuan et al., 2022) The assessment covered five domains: bias arising from the randomization process, bias due to deviations from the planned intervention, bias due to missing outcome data, bias in outcome measurement, and bias in the selection of reported outcomes. Based on the assessment results for each domain, each study was categorized into three levels of risk of bias: low risk, some concerns, or high risk (Tantri et al,, 2023; Viderman et al., 2024)

Data Extraction Process

Data extraction was performed in a structured manner using standard extraction tables. The data collected included study identifiers, such as the name of the primary author, year of publication, and country of study; subject characteristics, including the number of samples in each group, type of surgical procedure, mean age, and American Society of Anesthesiologists (ASA) status; and intervention protocols, including bolus or infusion doses of ketamine or s-ketamine, timing of preemptive administration, and primary anesthetic regimen. Primary outcome data included the mean and standard deviation (mean ± SD) or median and interquartile range (median [IQR]) of neutrophil-to-lymphocyte ratio (NLR) levels preoperatively and at 2, 12, 24, and 48 hours postoperatively (Zhang et al., 2023; Hallikeri et al., 2024). In addition, the mean and standard deviation of serum interleukin-6 (IL-6) levels in pg/mL were extracted preoperatively, at the end of surgery, and at 24 and 48 hours postoperatively (Yediyıldız et al., 2025). Secondary outcomes collected included pain scores based on the Visual Analog Scale (VAS) or Numeric Pain Rating Scale (NPRS), total postoperative opioid consumption, and the incidence of adverse events, such as postoperative nausea and vomiting (PONV), sedation, and psychotomimetic disorders.

Data Synthesis Method

Data synthesis was conducted using a narrative and structured approach (narrative synthesis). Data were grouped based on two primary outcome parameters, namely neutrophil-to-lymphocyte ratio (NLR) and interleukin-6 (IL-6), and then presented in comparative tables between primary studies. Subgroup analyses were conducted to evaluate variations in the immunomodulatory effects of ketamine based on dose and type of surgery. Based on dose, interventions were categorized into very low doses, namely 0.1–0.25 mg/kg, and medium to high doses, namely 0.3–0.75 mg/kg. Based on the type of surgery, studies were categorized into minor or minimally invasive surgeries, such as laparoscopy, and major surgeries, such as mastectomy, major orthopedic surgery, and laparotomy. Furthermore, the consistency of findings between studies was evaluated by comparing the direction and magnitude of postoperative changes in NLR and IL-6. Potential confounding factors that could influence the dynamics of these two biomarkers, such as patient characteristics, type and duration of surgery, anesthetic regimen, ketamine dose, opioid use, and sampling time, were also taken into account in the interpretation of the results.

Result and Discussion

Study Selection Flow

An electronic literature search was conducted across four major international scientific databases: PubMed/MEDLINE, ScienceDirect, the Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to “ketamine,” “S-ketamine,” “esketamine,” “preemptive analgesia,” “preoperative administration,” “Neutrophil-to-Lymphocyte Ratio,” “NLR,” “Interleukin-6,” “IL-6,” “inflammatory response,” and “postoperative pain.” Boolean operators (“AND” and “OR”) were used to combine the search terms and improve the sensitivity and specificity of the search. The reference lists of potentially relevant publications were also examined to identify additional eligible studies. The initial search yielded 807 records.

All retrieved records were imported into a reference-management database and checked for duplication based on the title, authors, publication year, journal, and digital object identifier. Following this process, 746 duplicate or overlapping records were removed, leaving 61 unique articles for screening. Two researchers independently screened the titles and abstracts of these articles. The screening focused on their relevance to perioperative ketamine or S-ketamine administration, preemptive analgesia, postoperative inflammatory responses, NLR or IL-6 outcomes, and human clinical research. Any disagreement between the researchers was resolved through discussion and consensus.

The full texts of all 61 potentially eligible articles were subsequently retrieved and assessed using predefined inclusion and exclusion criteria based on the PICOS framework. The population included adult patients undergoing surgical procedures. The intervention comprised ketamine or S-ketamine administered before surgical incision or before the initiation of significant nociceptive stimulation. Eligible comparators included placebo, saline, standard analgesic care, or another anesthetic or analgesic regimen. The primary outcomes were perioperative changes in NLR and IL-6, while secondary outcomes included postoperative pain intensity, opioid consumption, adverse events, and other inflammatory indicators. Eligible study designs included randomized controlled trials and relevant prospective or retrospective observational studies. Studies involving animals, pediatric populations, non-surgical settings, ketamine administered only after surgery, unavailable full texts, insufficient outcome data, duplicate datasets, conference abstracts, case reports, editorials, and non-English publications were excluded.

Following full-text assessment, 44 articles were excluded because they did not meet the population, intervention, outcome, or study-design criteria. Ultimately, 17 primary studies fulfilled all eligibility requirements and were included in the systematic synthesis. Data extracted from each study included the authors and publication year, country, study design, sample size, patient characteristics, type of surgery, ketamine formulation, dose, route and timing of administration, comparator, timing of biomarker measurement, NLR and IL-6 outcomes, pain scores, opioid consumption, adverse events, and principal conclusions. The study-selection process should be summarized in a PRISMA 2020 flow diagram, while the reasons for excluding the 44 full-text articles should be reported transparently. Meta-analyses and umbrella reviews may be used to support the background and discussion but should not be classified among the 17 primary studies included in the systematic synthesis.

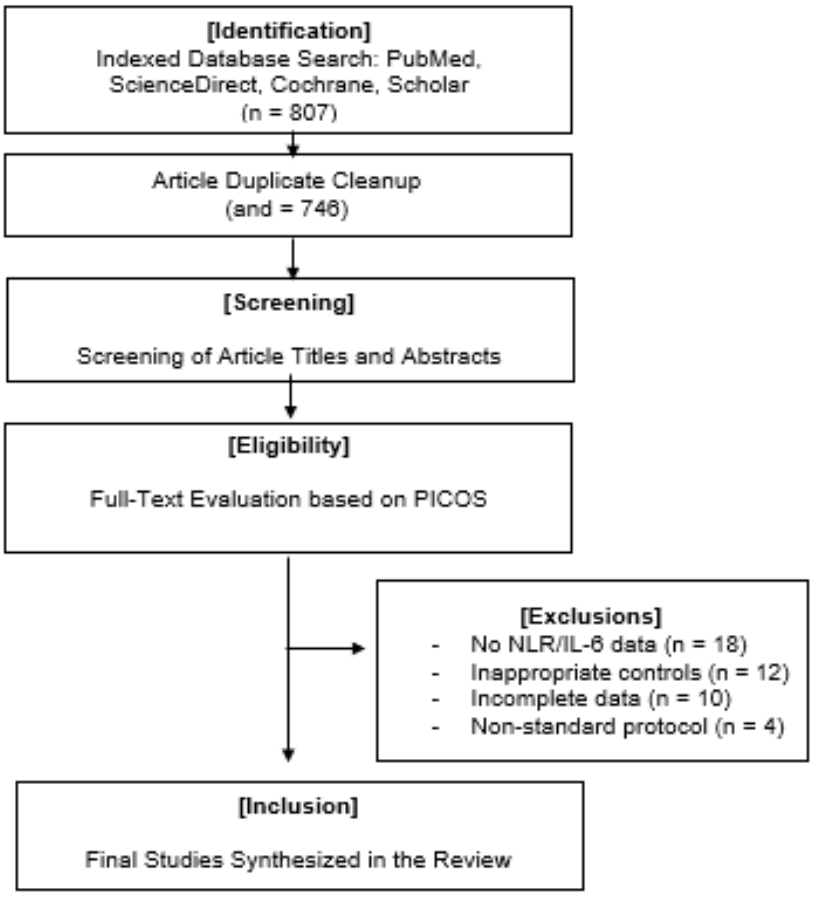

Figure 1. Study Selection Flowchart Based on the 2020 PRISMA Guidelines

Characteristics of Included Studies

Articles successfully included in this Systematic Review encompassed a diversity of study designs, patient populations, surgical procedures, and intervention dosing protocols. 1-17 Primary RCTs specifically examined the efficacy of racemic ketamine and its S(+)-ketamine enantiomer (S-ketamine/esketamine) administered preemptively or perioperatively in various surgical models. The surgical models studied included major oncology surgeries such as modified radical mastectomy (MRM) and colorectal cancer resections, laparoscopic procedures such as inguinal hernioplasty and cholecystectomy, orthopedic surgeries such as total knee/hip arthroplasty (TKA/THA), spine surgery (microdiscectomy and lumbar decompression), and thoracostomy.

The doses of ketamine and S-ketamine evaluated in randomized clinical trials ranged from subanesthetic, namely a pre-incision intravenous bolus of 0.1 mg/kg to 0.75 mg/kg, followed

in part by a continuous intraoperative infusion of 0.15 mg/kg/h to 0.75 mg/kg/h. The comparison group in the majority of primary RCTs was a control group that received a placebo infusion of 0.9% normal saline of identical volume and appearance. The control group also underwent a standardized general or regional anesthesia maintenance protocol that was uniform to the intervention group.

Table 3. Complete Characteristics of Studies Included in the Systematic Review

Author and Year of Publication	Research Design	Number of Samples (n) & Type of Surgery	Analgesia / Ketamine Intervention Protocol	Control / Comparison Group	Main Outcome Parameters Measured
Yediyıldız et al. (2025)	Prospective Double-Blind RCT	n = 40, lumbar microdiscectomy surgery	Total IV anesthesia (TIVA) with propofol	Sevoflurane inhalation anesthesia	Serum IL-6, CRP, PCT, and NLR levels preoperatively, intraoperatively, and 24 hours postoperatively
Rizvanović et al. (2023)	Prospective Parallel RCT	n = 60, open colorectal cancer surgery	Preoperative carbohydrate oral loading (CHO)	Conventional fasting protocol	NLR, delta NLR (ΔNLR), and Clavien-Dindo complications
Kriplani et al. (2022)	Prospective Observational	n = 517, percutaneous nephrolithotomy (PNL)	Pre-surgical biomarker evaluation	Patients without SIRS/sepsis	Predictive value of NLR, PLR, and LMR for the incidence of SIRS and postoperative urosepsis
Tantri et al. (2023)	Double-Blind RCT	n = 40, lumbar decompression and stabilization	Erector spinae plane block (ESPB) L3	Thoracolumbar interfascial plane (TLIP) block	Preoperative and 6-hour postoperative serum IL-6 and IL-10 levels, and 24-hour opioid consumption
Shu et al. (2023)	Ambispective Cohort	n = 968, elective abdominal surgery	Perioperative immune cell dynamics evaluation	Patients without chronic pain (non-CPSP)	NLR change ratio (NLRpost/NLRpre) > 5 and 1-year incidence of CPSP
Rahman et al. (2024)	Cross-Sectional Analytic	n = 51, appendectomy	Routine preoperative blood NLR evaluation	Uncomplicated appendicitis	Predictive ability of NLR in differentiating complicated vs. uncomplicated appendicitis
Domagalska et al. (2023a)	Double-Blind RCT	n = 366, total knee arthroplasty (TKA)	iPACK block combined with adductor canal block (ACB)	Sham block (control)	NLR and PLR levels at 12 and 24 hours postoperatively, pain scores, and functional recovery
Viderman et al. (2024)	Umbrella Review (20 SR/MA)	n = 8,341+, miscellaneous major and emergency department surgeries	IV ketamine (0.25–1 mg/kg bolus/infusion)	Placebo / standard opioid	Postoperative opioid consumption, VAS/NPRS pain scores, and PONV incidence
Zhang et al. (2023)	Prospective RCT	n = 120, modified radical mastectomy (MRM)	S-ketamine IV (0.25, 0.5, or 0.75 mg/kg)	Placebo (0.9% normal saline)	IL-6, hs-CRP, NLR, SIRI, SII, T-cell populations (CD3+, CD4+),

					VAS, and opioid consumption
Domagalska et al. (2023b)	Double-Blind RCT	n = 60, posterior lumbar decompression	Erector spinae plane block (ESPB) L4	Sham block (0.9% saline)	NLR and PLR values at 12 and 24 hours postoperatively, pain scores, and morphine consumption
Xuan et al. (2022)	Network Meta-Analysis (188 RCTs)	n = 13,769, various surgical procedures	19 preemptive analgesia regimens (including ketamine)	Placebo	VAS pain scores (6–48 hours), cumulative opioid consumption, PONV, and time to rescue analgesia
Ren et al. (2022)	Double-Blind RCT	n = 104, selective colorectal cancer surgery	Sub-anesthetic IV ketamine (0.1, 0.2, or 0.3 mg/kg)	Placebo (0.9% normal saline)	Serum IL-6, IL-8, TNF-α, HAD depression/anxiety scores, and QoR-40 questionnaire
Niu et al. (2024)	Systematic Review & Meta-Analysis	n = 1,447, various elective surgeries	Perioperative prophylactic esketamine	Placebo / no esketamine	Postoperative depression, anxiety, sleep quality, and risk of chronic postoperative pain
Serden Ay et al. (2025)	Double-Blind RCT	n = 73, laparoscopic cholecystectomy	Preemptive IV ibuprofen (400 mg)	Placebo (0.9% saline)	VAS pain scores and rescue analgesic requirements in NLR ≥ 2 vs. < 2 subgroups
Hallikeri et al. (2024)	Double-Blind RCT	n = 60, laparoscopic inguinal hernioplasty	IV ketamine (0.5 mg/kg bolus + 0.2 mg/kg/h)	Placebo (0.9% saline)	NLR and PLR ratios at 2 hours and POD 1, fentanyl requirements, and incidence of chronic pain at 3 months
Semerci et al. (2024)	Prospective RCT	n = 60, thoracotomy surgery	Preemptive epidural (pre-incision bupivacaine)	Control epidural (post-incision)	NRS pain score response and analgesic consumption based on preoperative NLR (≥ 2)
Yao et al. (2023)	Retrospective Cohort	n = 1,199, geriatric pelvic fracture surgery	Evaluation of admission inflammatory biomarkers	Patients without pneumonia	Predictive ability of NLR, PLR, and SII for the incidence of postoperative pneumonia (POP)

In addition to ketamine intervention studies, this review integrates observational studies and supporting meta-analyses that rigorously evaluate the predictive value of baseline NLR and IL-6 on postoperative clinical outcomes (Rizvanović et al., 2023). .These supporting studies provide a strong biological theoretical basis for the role of NLR and IL-6 as biomarkers for the degree of systemic inflammation, infectious complications, postoperative pneumonia, and the development of chronic postsurgical pain (CPSP) (Rizvanović et al., 2023; Kriplani et al., 2022). The characteristics matrix of all included studies is summarized in detail in Table 4.1.

Methodological Quality and Risk of Bias Assessment (Critical Appraisal)

The risk of bias assessment of all primary randomized controlled trials (RCTs) evaluated in this Systematic Review was conducted using the standard Cochrane Risk of Bias 2.0 (RoB 2) instrument (Tantri et al., 2023). The assessment covered five critical domains: randomization process bias, bias from the planned intervention, bias from missing outcome data, bias from outcome measurement, and bias from selecting reported outcomes (Viderman et al., 2024). The majority of primary RCTs examining ketamine and S-ketamine, such as those by Zhang et al. (2023), Ren et al. (2022), and Hallikeri et al. (2024), were categorized as having an overall low risk of bias.

In the randomization process domain, these primary studies used a computer-generated random sequence combined with allocation blinding techniques using sequentially numbered, opaque, sealed envelopes. Double-blinding was strictly implemented, with patients, the intraoperative anesthesia team, surgeons, and laboratory/clinical outcome assessors blinded to treatment group allocation. This effectively minimized the risk of performance bias and detection bias.

In the outcome measurement domain, the use of objective laboratory parameters, such as automated cell counts for calculating the NLR ratio and the Enzyme-Linked Immunosorbent Assay (ELISA) method for measuring serum IL-6 levels, ensured that the data collection process was free from subjective researcher intervention. Furthermore, the dropout rate was reported to be very low (<10%) and analyzed The included studies were either reviewed using the Intent-to-Treat (ITT) principle or transparently incorporated into the CONSORT flow diagram, thus minimizing attrition bias.

For secondary studies in the form of systematic reviews and meta-analyses (such as Viderman et al. (2024), Xuan et al. (2022), and Niu et al. (2024), methodological quality was assessed using the AMSTAR 2 (Assessing the Methodological Quality of Systematic Reviews) criteria. 8 In general, these meta-analyses met key critical components, including the development of a registered protocol (PROSPERO), a comprehensive literature search strategy across multiple databases, independent repeated data extraction, and a validated heterogeneity assessment.

The Effect of Preemptive Ketamine on Postoperative Neutrophil-to-Lymphocyte Ratio (NLR) Levels

Emphasis on Dynamics and Early Postoperative NLR Spike

A synthesis of quantitative evidence from randomized clinical studies showed that preemptive administration of ketamine or S-ketamine consistently and significantly reduced the spike in Neutrophil-to-Lymphocyte Ratio (NLR) levels in the early postoperative period compared to the control/placebo group.9,15 In a Randomized Clinical Trial by Hallikeri et al. (2024) involving laparoscopic inguinal hernioplasty patients, a pre-induction IV bolus of ketamine followed by a 0.2 mg/kg/hour infusion until the end of surgery was shown to significantly suppress the increase in NLR at 2 hours postoperatively (p=0.007).15 Specifically, Hallikeri et al. (2024) reported that the control group (0.9% saline) experienced a median NLR value jump of 4.63 times the pre-operative baseline value (from 2.07 [IQR 1.72-2.79] to 7.91 [IQR 5.74-14.7]). In contrast, in the group receiving preemptive ketamine, the median increase in NLR was significantly attenuated to only 2.53 times the baseline value (from 1.85 [IQR 1.4-2.61] to 5.45 [IQR 2.89-7.61]) with a p-value of 0.02.15 This suppression of the NLR ratio was driven by limiting the significant surge in neutrophil percentage in the ketamine group compared to the control group (77% vs. 84%, p=0.0005) and preventing an extreme decrease in lymphocyte percentage (14.5% vs. 11%, p=0.01) at 2 hours postoperatively.

This protective effect against immune cell shifts has high clinical urgency. As demonstrated by Shu et al. (2023) in a cohort study of 968 abdominal surgery patients, the magnitude of the postoperative NLR change ratio (〖"NLR" 〗_"post" / 〖"NLR" 〗_"pre") with a threshold

value of >5 was the main independent predictor of the onset of chronic postoperative pain (CPSP) and decreased quality of life 1 year after surgery (OR=1.068, p=0.011). By holding the increase in NLR below the critical threshold value in the acute postoperative phase, preemptive administration of ketamine directly interrupts the inflammatory stress cascade that has the potential to trigger long-term peripheral and central sensitization (Shu et al., 2025; Luetkemeier et al., 2026; Lullau et al., 2023).

Suppressive Effects Based on Ketamine Dose and Cellular Immune Preservation

A prospective clinical trial by Zhang et al. (2023) in 120 patients undergoing modified radical mastectomy (MRM) evaluated the immune modulation efficacy of three intravenous S-ketamine dose levels: low dose (0.25 mg/kg), medium dose (0.5 mg/kg), and high dose (0.75 mg/kg) administered at induction and continued intraoperatively. 9 The results showed that at 24 hours postoperatively (T2), the mean NLR values in the medium dose (0.5 mg/kg) and high dose (0.75 mg/kg) S-ketamine groups were significantly lower than those in the placebo control group ($p<0.05$).

In addition to suppressing NLR, Zhang et al. (2023) demonstrated that administration of S-ketamine at 0.5 mg/kg and 0.75 mg/kg significantly prevented postoperative cellular immune suppression commonly induced by surgical stress. The percentage of CD3+ and CD4+ T lymphocytes and the CD4+/CD8+ ratio in the medium and high-dose S-ketamine groups remained significantly higher both at the end of surgery and 24 hours postoperatively compared to the control group ($p<0.05$). Pairwise comparisons also confirmed that suppression of other cellular-based systemic inflammatory indices, namely the Systemic Inflammation Response Index (SIRI) and the Systemic Immune-Inflammation Index (SII), was superior in the S-ketamine groups at 0.5 mg/kg and 0.75 mg/kg compared to the 0.25 mg/kg dose ($p<0.05$).

These findings are consistent with evidence from the study by Domagalska et al. (2023a & 2023b) in major orthopedic surgery (TKA) and lumbar spinal decompression surgery.7,10 In that study, regional nerve block interventions that suppressed nociception and surgical stress responses resulted in significantly lower NLR and Platelet-to-Lymphocyte Ratio (PLR) values at 12 and 24 hours post-surgery compared to the control group ($p<0.0001$). This confirms the concept that preventing pre-incisional nociceptive signal conduction either through NMDA channel blockade by ketamine or regional block is a key factor in suppressing the peripheral inflammatory leukocyte shift.

Comparison of the Preemptive Effect of Ketamine with Other Intervention Modalities on NLR

The effect of preemptive analgesia on the NLR biomarker was also evaluated in the context of preoperative inflammatory risk stratification. Serden Ay et al. (2025) conducted a randomized clinical trial in laparoscopic cholecystectomy patients stratified by baseline NLR levels of ≥2 (high inflammation) and <2 (low inflammation). The study found that preemptive analgesic administration (400 mg IV ibuprofen) consistently reduced postoperative pain scores and the need for rescue analgesia in both high (NLR ≥2) and low (NLR <2) inflammatory patients compared to the placebo group ($p <0.001$).

Similar to these findings, Semerci et al. (2024) evaluated the timing of epidural analgesia administration in thoracotomy surgery based on preoperative NLR status. 16 The results showed that in the group of patients with a baseline "NLR" ≥ 2, preemptive epidural administration (before incision) resulted in a highly significant reduction in NRS pain scores at 2, 4, and 8 hours postoperatively and reduced additional analgesic consumption in the first 24 hours compared to post-incision epidural administration ($p < 0.05$). Conversely, in patients with a baseline "NLR" < 2, differences in epidural administration time did not show significant variations in analgesic outcomes. This proves that patients with a high baseline systemic

inflammation ("NLR" ≥ 2) receive the maximum clinical benefit from preemptive strategies (Semerci et al., 2024; Oriquat et al., 2026).

The role of NLR modulation is also evident in Enhanced Recovery After Surgery (ERAS) protocol interventions such as preoperative carbohydrate loading studied by Rizvanović et al. (2023), as well as the use of propofol-based Total Intravenous Anesthesia (TIVA) evaluated by Yediyıldız et al. (2025). Although these various perioperative modalities are capable of modulating the inflammatory cascade, preemptive ketamine/S-ketamine has a unique dual advantage because it works simultaneously as a central NMDA sensitizer in the dorsal horn and suppresses systemic humoral and cellular inflammatory reactions.

The Effect of Preemptive Ketamine on Postoperative Interleukin-6 (IL-6) Levels

Suppression of Serum IL-6 Secretion and Acute Phase Response

A synthesis of qualitative and quantitative data from primary RCTs confirmed that preemptive administration of ketamine or S-ketamine effectively suppresses the increase in serum levels of the pro-inflammatory cytokine Interleukin-6 (IL-6) in the postoperative period. Ren et al. (2022) evaluated the effect of a single subanesthetic intravenous dose of ketamine (0.1 mg/kg, 0.2 mg/kg, and 0.3 mg/kg) administered 5 minutes before surgical incision in 104 colorectal cancer patients.

ELISA laboratory test results in the Ren et al. study. (2022) showed that serum IL-6 levels in the control group (0.9% saline) experienced a massive spike post-surgery, reaching an average of 121.9±56.4" pg/mL" at the end of surgery (0 hours), 130.3±61.5" pg/mL" at 24 hours, and 131.5±55.3" pg/mL" at 48 hours post-surgery.12 In contrast, in the group receiving preemptive ketamine at a dose of 0.3" mg/kg", serum IL-6 levels were significantly suppressed at 80.8±40.8" pg/mL" (0 hours), 81.2±35.9" pg/mL" (24 hours), 79.2±33.3" pg/mL" (48 hours), and 79.1±38.8" pg/mL" (72 hours). postoperatively) with a significance value of $p<0.01$ compared to the control group.

This suppression of IL-6 secretion proves that the administration of subanesthetic ketamine at 0.3 mg/kg before tissue trauma directly suppresses the activation of the acute phase humoral inflammatory cascade. Conversely, in the lower-dose ketamine groups (0.1 mg/kg and 0.2 mg/kg), the suppression of serum IL-6 levels did not reach statistical significance compared to the control group ($p>0.05$).12 This indicates a dose-dependent threshold effect in ketamine's immunomodulatory ability on the IL-6 response.

Kinetics of Proinflammatory Cytokines (IL-6, IL-8, TNF-α, hs-CRP)

Suppression of the inflammatory response by preemptive ketamine is not limited to IL-6, but also includes a broad spectrum of proinflammatory cytokines and other acute-phase proteins. In a study by Ren et al. (2022), in addition to suppressing IL-6, pre-incision administration of 0.3 mg/kg ketamine simultaneously significantly reduced serum levels of Interleukin-8 (IL-8) and Tumor Necrosis Factor-alpha (TNF-α) at all postoperative observation points (0, 24, 48, and 72 hours) compared to the control group ($p<0.05$). TNF-α levels in the 0.3 mg/kg ketamine group remained low at 74.6-78.5 ng/mL, while in the control group they reached 102.7-113.2 ng/mL ($p=0.047$).

These findings were consistently confirmed by Zhang et al. (2023) in breast cancer surgery.9 Hypersensitive C-reactive protein (hs-CRP) levels—a major acute phase protein whose synthesis is directly stimulated by IL-6 in the liver—were shown to be significantly lower in all S-ketamine treatment groups (0.25 mg/kg, 0.5 mg/kg, and 0.75 mg/kg) at the end of surgery and 24 hours postoperatively compared to the control group ($p<0.05$).9 hs-CRP levels at 24 hours postoperatively were recorded at 16.7 mg/L in the control group, while in the 0.5 mg/kg and 0.75 mg/kg S-ketamine groups they ranged from 6.2-7.1 mg/L ($p<0.05$).

For comparison, the study by Yediyıldız et al. (2025) in microdiscectomy surgery showed that the selection of total IV anesthesia (TIVA) propofol technique was able to produce lower postoperative IL-6 (20.1" pg/mL") and CRP (15.3" mg/L") levels compared to sevoflurane inhalation anesthesia (54.8" pg/mL" and 25.3" mg/L", p<0.05).1 Similarly, the study of Tantri et al. (2023) noted that peripheral regional block techniques (ESPB and TLIP) were able to control postoperative IL-6 levels in the range of 29.6-40.3" pg/mL".4 However, the addition of preemptive intravenous ketamine/S-ketamine agents was shown to provide more comprehensive suppression of proinflammatory cytokines in systemic circulation because it works directly to inhibit signal transmission and the NF-κB transcription pathway in immune cells.

Secondary Clinical Outcomes: Pain Score, Opioid-Sparing, and Complication Prevention

Analgesic Effect and Opioid-Sparing Effect

Clinically, suppression of the inflammatory cascade (NLR and IL-6) by preemptive ketamine/S-ketamine is directly proportional to improved postoperative analgesia.8,9,11,12,15 Based on synthesized data from the Umbrella Review by Viderman et al. (2024) covering over 8,341 patients, and a Network Meta-Analysis by Xuan et al. (2022) of 13,769 patients, perioperative IV ketamine use has been shown to reduce cumulative postoperative opioid consumption by 14% to 50% in the first 24 and 48 hours postoperatively.

A randomized clinical trial by Hallikeri et al. (2024) confirmed this opioid-sparing effect, where the intraoperative fentanyl requirement in the ketamine group was significantly reduced to 7±15.2" " μ"g" compared to the saline control group of 26.6±28.3" " μ"g" (p=0.001).15 Postoperative fentanyl requirement was also shown to be significantly lower in the ketamine group (40.3±13.7" " μ"g" vs 57.7±24.4" " μ"g" , p=0.047).15 In line with this, Zhang et al. (2023) and Ren et al. (2022) reported that administration of S-ketamine and sub-anesthetic ketamine significantly reduced VAS pain scores at 4, 6, and 24 hours post-surgery, and significantly reduced the need for rescue analgesics (remedial analgesia).

Perioperative Side Effects, PONV, and Quality of Recovery

Reducing postoperative opioid consumption (opioid-sparing effect) through preemptive administration of ketamine/S-ketamine has a secondary impact in the form of a reduced incidence of opioid-related complications. Reviews by Viderman et al. (2024) and Xuan et al. (2022) confirmed that the group of patients receiving IV ketamine experienced a significant reduction in the incidence of postoperative nausea and vomiting (PONV) compared to the placebo group (OR=0.54-0.68, p<0.01).8,11 In the studies of Zhang et al. (2023) and Ren et al. (2022), the incidence of PONV in the ketamine/S-ketamine group was recorded at only 6.7%-10%, significantly lower than the control group at 33.3% (p=0.006).

Regarding the hemodynamic and neuropsychiatric safety profile, administration of subanesthetic doses of ketamine/S-ketamine (≤0.5-0.75 mg/kg) did not cause clinically significant prolongation of extubation time or delay recovery in the PACU. Ren et al. (2022) and Zhang et al. (2023) reported that there were no serious psychotomimetic side effects such as visual hallucinations, severe dizziness, or emergency delirium in the sub-anesthetic ketamine group. In contrast, S-ketamine at a dose of 0.3-0.5 mg/kg significantly increased patient satisfaction scores and postoperative quality of recovery (QoR-40) scores in the emotional status domain (p<0.001).

Prevention of Chronic Postoperative Pain (CPSP) and Long-Term Outcomes

The most important clinical benefit of preemptive ketamine's suppression of the inflammatory response (NLR and IL-6) and blocking of central NMDA receptor sensitization is the prevention of the development of chronic postsurgical pain (CPSP). 8,13,15 In a prospective, long-term evaluation 3 months postoperatively by Hallikeri et al. (2024), the incidence of

chronic inguinal pain was significantly lower in the ketamine group than in the control group (17.9% [5/28 patients] vs. 44.8% [13/29 patients], p=0.05). 15 The control group also had a higher proportion of patients experiencing radiating pain and discomfort during daily activities. 15

These findings are supported by a comprehensive meta-analysis review by Niu et al. (2024) in 1,447 surgical patients. This meta-analysis demonstrated that the use of perioperative prophylactic esketamine significantly reduced the risk of developing chronic postoperative pain (RR=0.556, 95%CI: 0.395-0.783, p=0.001).13 In addition to suppressing CPSP, the use of prophylactic esketamine was shown to significantly reduce postoperative depressive symptoms (SMD=-0.61, p=0.0008), reduce the incidence of anxiety (WMD=-0.695, p=0.021), and improve postoperative sleep quality (SMD=-0.587, p<0.001).

This synthesis of long-term outcomes confirms that the role of preemptive ketamine/S-ketamine is not limited to the acute recovery phase in the hospital, but provides a sustained neuro-immunological protective effect that improves the overall quality of life of patients.

Preemptive Immunomodulatory Effects of Ketamine on Postoperative NLR Dynamics

The systematic synthesis results in Chapter IV demonstrated that preemptive administration of ketamine or S-ketamine (before surgical incision) significantly reduced the spike in the Neutrophil-to-Lymphocyte Ratio (NLR) in the early postoperative period compared to the placebo control group. Physiologically, surgery induces a systemic leukocyte shift characterized by massive neutrophilia and transient lymphopenia. Neutrophilia results from the rapid mobilization of neutrophils from the bone marrow triggered by the release of granulocyte colony-stimulating factor (G-CSF) and proinflammatory cytokines following tissue trauma3, while lymphopenia is mediated by the release of cortisol and catecholamines that induce T-lymphocyte apoptosis.

Administration of subanesthetic doses of ketamine (such as a bolus of 0.5 mg/kg followed by an infusion of 0.2 mg/kg/hour) effectively inhibited the increase in the ratio. Postoperative NLR.15 In the study by Hallikeri et al. (2024), the control group experienced a 4.63-fold increase in NLR from baseline at 2 hours postoperatively, while in the ketamine group, the spike was reduced to only 2.53-fold (p=0.02). The molecular mechanism behind this suppression involves ketamine's ability to inhibit the chemotactic response and neutrophil activation, thereby limiting the release of tissue-damaging reactive oxygen species (ROS) and myeloperoxidase. On the other hand, ketamine simultaneously exerts a cytoprotective effect on the peripheral T lymphocyte population (CD3^+, CD4^+) by suppressing the apoptotic cascade triggered by surgical stress.

Suppression of the NLR spike in the acute phase has vital clinical implications for patient recovery. As demonstrated by Shu et al. (2023), the magnitude of the postoperative NLR change ratio (〖"NLR" 〗_"post" / 〖"NLR" 〗_"pre") with a threshold value of >5 is an independent predictor of the occurrence of chronic postoperative pain (CPSP) and decreased quality of life (OR=1.068, p=0.011). 5 Furthermore, high perioperative NLR values have also been shown to predict the onset of Systemic Inflammatory Response Syndrome (SIRS), urosepsis, surgical wound infections, and postoperative pneumonia (POP) in geriatric patients. By keeping postoperative NLR values controlled below the critical threshold, preemptive ketamine effectively cuts the chain of destructive inflammatory responses that have the potential to trigger systemic complications.

Mechanisms of Interleukin-6 (IL-6) Suppression and Humoral Immunomodulation by Ketamine

A synthesis of qualitative and quantitative evidence confirms that preemptive ketamine or S-ketamine consistently suppresses the postoperative rise in serum interleukin-6 (IL-6) levels.

IL-6 is a major pro-inflammatory cytokine synthesized massively by monocytes, macrophages, and endothelial cells immediately after mechanical tissue damage. Elevated serum IL-6 levels peak 6 to 24 hours postoperatively and act as a major inducer of acute-phase protein synthesis in the liver, such as C-reactive protein (CRP).

The main molecular mechanism underlying IL-6 suppression by ketamine is inhibition of the nuclear factor kappa B (NF-kB) signaling pathway. 1,12 During surgical trauma, activation of inflammatory receptors stimulates IkB phosphorylation and translocation of NF-kB subunits into the nucleus of immune cells, which triggers the transcription of proinflammatory genes. Ketamine and its enantiomer S-ketamine have been shown to directly suppress NF-kB activation, thereby inhibiting the synthesis and secretion of IL-6, IL-8, and TNF-α. This suppression has been shown to be dose-dependent, in the studies of Ren et al. (2022) and Zhang et al. (2023), a subanesthetic dose of 0.3-0.75 mg/kg significantly suppressed IL-6 and hs-CRP compared to a dose of 0.1 mg/kg ($p < 0.01$).

Clinically, suppressing the massive surge in serum IL-6 offers multiple benefits for patients undergoing surgery.1,12 Peripherally, reduced IL-6 levels reduce nociceptor sensitivity in the surgical wound area, contributing to decreased VAS/NPRS pain scores.1,9,12 Centrally, IL-6, which crosses the blood-brain barrier, is known to trigger neuroinflammatory activity in microglia, which underlies the onset of sickness behavior, postoperative depression, and anxiety. Suppression of IL-6 by S-ketamine has been shown to interrupt this neuroinflammatory chain, significantly reducing postoperative depression/anxiety scores and improving patient quality of recovery (QoR-40).

The Preemptive Role of Ketamine in Preventing Central Sensitization and Opioid Reduction

Ketamine's preemptive analgesic effect is rooted in its role as a non-competitive antagonist of NMDA receptors in the dorsal horn of the spinal cord. The trauma of a surgical incision triggers a massive release of glutamate from primary afferent nerve fibers, which occupies NMDA receptors and induces intracellular calcium influx. This process triggers the wind-up phenomenon, or central sensitization, responsible for secondary hyperalgesia and allodynia. Administering ketamine before the surgical incision occupies the ion channels of the NMDA receptor, effectively preventing the formation of pain memories in the central nervous system.

The immediate clinical impact of this prevention of central sensitization is its significant opioid-sparing effect. A synthesis of evidence from the Umbrella Review by Viderman et al. (2024) and the Network Meta-Analysis by Xuan et al. (2022) confirmed that perioperative intravenous ketamine use reduced cumulative postoperative opioid consumption by 14% to 50% in the first 24–48 hours. This reduction in opioid requirements not only benefits analgesic efficiency but also reduces the risk of opioid-induced postoperative complications, such as postoperative nausea and vomiting (PONV), respiratory depression, and paralytic ileus (Gan et al., 2020; Alvarez et al., 2014; Bohringer et al., 2020).

Furthermore, ketamine's reduction in opioid consumption also supports the preservation of patient immune function. High-dose opioid analgesics are known to have immunosuppressive properties that suppress adaptive immune cell proliferation and decrease Natural Killer (NK) cell activity (Plein et al., 2020; Moyano & Aguirre, 2019). By reducing the total perioperative fentanyl and morphine requirements, ketamine administration indirectly protects the patient's immune system from secondary opioid-induced suppression, which is particularly beneficial in oncological surgery.

The Relationship Between Acute Pain, Systemic Inflammation, and the Prevention of Chronic Postsurgical Pain (CPSP)

Acute postoperative pain and the systemic inflammatory response (NLR and IL-6) mutually reinforce each other in a positive feedback loop. Poorly managed acute pain triggers stimulation of the sympathetic nervous system and the HPA axis, which induces cortisol release and massive neutrophilia. Conversely, proinflammatory cytokines such as IL-6 stimulate peripheral nociceptor sensitization and exacerbate the central pain response. If this neuro-inflammatory cascade continues without preemptive intervention, permanent neuroplastic changes will occur in the dorsal horn, leading to the development of chronic postoperative pain (CPSP) (Fuller et al., 2023; Elsharkawy et al., 2025).

Preemptive administration of ketamine or S-ketamine has been shown to permanently interrupt this cycle. In a 3-month long-term evaluation study by Hallikeri et al. (2024), patients who received intraoperative ketamine infusion showed a significantly lower incidence of chronic pain compared to the control group (17.9% vs. 44.8%, p=0.05).15 These findings are supported by a meta-analysis by Niu et al. (2024), which demonstrated that prophylactic ketamine significantly reduced the risk of CPSP (RR=0.556, p=0.001), while also reducing the incidence of postoperative anxiety and sleep disturbances.

The integration of this evidence suggests that NLR and IL-6 biomarker values serve not only as indicators of acute inflammation in the hospital but also as biological predictors of long-term patient outcomes. The use of subanesthetic doses of ketamine before surgical incision provides broad neuro-immunological modulatory effects, which not only optimize acute analgesia but also protect patients' long-term quality of life.

Research Limitations

Although this Systematic Review was prepared using the rigorous PRISMA 2020 guidelines and synthesized high-quality studies, there are several methodological limitations that should be considered when interpreting the results: 1) Heterogeneity of Dosage Protocols and Administration Routes: There was variation in the ketamine/S-ketamine doses used between primary studies (ranging from 0.1 mg/kg to 0.75 mg/kg bolus, with or without continuous infusion). This diversity of regimens makes it difficult to determine a single optimal dose (golden standard dose) for immunomodulation purposes; 2) Variety of Surgical Procedures and Anesthetic Techniques: The included studies covered a wide range of surgeries with varying degrees of tissue trauma (ranging from minor laparoscopic surgery to major open orthopedic and oncology surgery). The use of different primary anesthetic regimens (TIVA propofol vs. sevoflurane inhalation) may also be a confounding factor in baseline and postoperative NLR and IL-61 levels.; 3) Variation in Blood Sampling Time: The time points of postoperative blood sampling for NLR and IL-6 measurements varied between studies (ranging from 2 hours, 6 hours, 12 hours, 24 hours, to 72 hours postoperatively). This presents challenges in uniformly mapping the peak kinetics of biomarker changes.

Conclusion

Based on the results of a systematic data synthesis (Systematic Review) based on the 2020 PRISMA guidelines of randomized controlled trials and a major meta-analysis on the effect of ketamine administration as preemptive analgesia on postoperative Neutrophil-to-Lymphocyte Ratio (NLR) and Interleukin-6 (IL-6) levels, the following conclusions can be drawn:

Effect on Postoperative Neutrophil-to-Lymphocyte Ratio (NLR) Levels: Preemptive administration of subanesthetic intravenous ketamine or S-ketamine (pre-incision bolus of 0.15-0.75 mg/kg with or without infusion followed by 0.15-0.75 mg/kg/hour) has been consistently and significantly shown to suppress the increase in NLR levels in the acute postoperative period (particularly during the 2- to 24-hour postoperative period) compared with the placebo control group. This suppression is mediated by ketamine's ability to suppress massive neutrophilia and protect T lymphocyte populations (CD3+, CD4+) from apoptosis due to surgical stress. Maintaining the NLR increase below a critical threshold has been shown to

be crucial for preventing excessive immunosuppression and reducing the risk of infectious complications and the transition to chronic postoperative pain (CPSP).

Effect on Postoperative Interleukin-6 (IL-6) Levels: Preemptive administration of subanesthetic intravenous ketamine or S-ketamine (especially at doses ≥ 0.3-0.75 mg/kg) significantly suppresses postoperative serum Interleukin-6 (IL-6) secretion and peak levels at 6, 24, 48, and 72 hours postoperatively compared to the placebo control group. The molecular mechanism of this suppression occurs through direct inhibition of the nuclear factor kappa B (NF-kB) transcription pathway in immune cells, which simultaneously suppresses other pro-inflammatory mediators such as IL-8, TNF-α, and the acute-phase protein hs-CRP.

Clinical Efficacy and Perioperative Safety: Preemptive ketamine administration provides comprehensive clinical benefits in the form of a reduction in acute postoperative pain scores (VAS/NPRS), a 14% to 50% reduction in cumulative postoperative opioid consumption (opioid-sparing effect), a prolongation of the time to first-rescue analgesic request, and a reduction in the incidence of postoperative nausea and vomiting (PONV). In the long term, neuro-immunological modulation by prophylactic ketamine/S-ketamine has been shown to reduce the risk of chronic postoperative pain (CPSP), reduce symptoms of postoperative depression and anxiety, and improve patient recovery (QoR) without causing severe psychotomimetic side effects at sub-anesthetic doses.

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