Jurnal Internasional Ilmu Kesehatan & Penelitian Medis

Vol 5. No. 1 (2026) : Februari

EFFECT OF EPIDURAL AND GENERAL ANESTHESIA ON PERIOPERATIVE NEUTROPHIL LYMPHOCYTE RATIO CHANGES IN MASTECTOMY PATIENTS

Fina Damayanti[1], Muhammad Wirawan Harahap[2], Abdul Mubdi Ardiansar Arifuddin Karim[3], Faisal Sommeng[4], Tirta Swarga[5]
Medical Education Study Program, Faculty of Medicine,
Indonesian Muslim University, Indonesia
e-mail: finad42003ynti@gmail.com

Abstract

Mastectomy induces a systemic inflammatory response that may be influenced by the anesthetic technique, as reflected by changes in the neutrophil–lymphocyte ratio (NLR). Unlike previous studies that assessed mixed breast surgeries, broadly evaluated regional anesthesia, or focused on combined general–epidural techniques and cytokine markers, this study uniquely compares perioperative pre–post changes in NLR (ΔNLR) between epidural anesthesia alone and general anesthesia alone in mastectomy patients using a routinely available biomarker. This quantitative experimental study was conducted at Ibnu Sina YW-UMI Hospital, Makassar, from August 2025, involving 30 mastectomy patients recruited consecutively and allocated into two independent groups (15 epidural, 15 general anesthesia). Venous blood samples were collected preoperatively and 24 hours postoperatively to calculate NLR, with ΔNLR as the primary outcome. Within-group analysis using the Wilcoxon test showed significant postoperative increases in NLR in both the epidural group (5.13 ± 5.42 to 7.65 ± 5.99; $p<0.001$) and the general anesthesia group (4.12 ± 4.59 to 14.72 ± 8.43; $p<0.001$). Between-group comparison using the Mann–Whitney test demonstrated that ΔNLR was significantly higher in the general anesthesia group (10.60 ± 7.23) than in the epidural group (2.52 ± 2.36; $p<0.001$). These findings indicate that epidural anesthesia is associated with a smaller postoperative increase in NLR, suggesting better attenuation of the systemic inflammatory response after mastectomy. Further randomized studies with larger samples, additional inflammatory biomarkers, and clinical outcomes are recommended to enhance evidence strength and generalisability.

Keywords: Epidural anesthesia; General anesthesia; NLR; Mastectomy postoperative inflammation.

Received: January 5th, 2026; 1st Revised January 14st, 2026;
Accepted for Publication: January 30th, 2026

INTRODUCTION

Mastectomy is a surgical procedure in the form of a thorough breast removal that aims to treat breast cancer, but this procedure often has significant physical and psychological impacts on the patient (1). The loss of one or both breasts not only leaves extensive scars, but can also trigger psychological trauma, impaired body image, as well as affect the psychosocial aspects and sexual life of the patient (2,3). Mastectomy procedures are generally performed under balanced inhalation general anesthesia, given the long duration of surgery, the breadth of the surgical area, and the need for intensive tissue manipulation for patient comfort and stability of vital signs during surgery (4). Nevertheless, general anesthesia is known to cause loss of the airway protective reflex as well as increase the risk of pulmonary complications, especially in patients with poor lung function or pulmonary metastases, which can have an impact on increased perioperative morbidity and mortality (5,6). This condition raises the need for alternative anesthesia techniques that are able to suppress postoperative stress and inflammatory responses without increasing the risk of systemic complications.

Epidural anesthesia is one of the neuroaxial anesthesia techniques that works by blocking the transmission of sensory and motor nerve impulses through the injection of local anesthesia into the epidural space, making it effective in controlling intraoperative and postoperative pain. This technique has long been widely used in obstetric anesthesia, particularly in labor and sectio caesaria, as it allows patients to remain conscious with minimal pain as well as shows an increasing trend in its use (7). In the context of oncological surgery, attention to the impact of anesthesia techniques on systemic inflammatory responses is increasing. Neutrophil to Lymphocyte Ratio (NLR) is known as an inflammatory biomarker that reflects the balance between innate and adaptive immune responses, and plays a role in systemic inflammatory response syndrome (SIRS) through neutrophil activation and lymphocyte suppression (8). Research shows that anesthesia techniques in breast cancer surgery affect postoperative NLR and PLR changes (9). Another study found that postoperative NLR values were higher in patients with general anesthesia than in regional anesthesia (10). Meta-analyses also reported that the combination of general anesthesia and epidural was associated with decreased inflammatory mediators such as IL-6, TNF-α, and CRP (11). However, there have been no studies that specifically compare pre- and postoperative NLR changes in mastectomy patients with epidural anesthesia compared to general anesthesia, so there are scientific gaps that need to be studied further.

Based on the background and findings of previous studies, this study hypothesizes that there is a difference in effectiveness between epidural anesthesia and general anesthesia on the post-mastectomy inflammatory response as reflected by changes in the Neutrophil to Lymphocyte Ratio (NLR), whereby epidural anesthesia is expected to suppress the inflammatory response more optimally than general anesthesia. NLR was chosen as the main parameter because it is an inflammatory biomarker that is easily obtained from routine blood tests, is fast, relatively inexpensive, and has been widely used to describe the balance between innate (neutrophil) and adaptive (lymphocyte) immune responses in surgical stress conditions. However, the authors recognize that systemic inflammation is complex, so a single biomarker does not fully represent the entire inflammatory response. Combination with other biomarkers such as C-reactive protein (CRP) or proinflammatory cytokines such as interleukin-6 (IL-6) has the potential to provide a more comprehensive picture. However, this study focused its analysis on NLR due to its more consistent availability in perioperative clinical practice and ease of application as a routine monitoring indicator, while CRP/IL-6 testing is not always uniformly available, requires additional costs, and is not part of the standard protocol in some facilities. Therefore, NLR is used as a practical indicator to compare the effects of the two anesthetic techniques, with the recommendation that future studies may consider combining NLR with CRP and/or IL-6 to improve the accuracy of assessing postoperative inflammatory responses.

RESEARCH METHODS

This quantitative experimental study used a pre–post design with two independent groups to compare the effects of general and epidural anesthesia on changes in Neutrophil to Lymphocyte Ratio (ΔNLR) in mastectomy patients. Conducted at Ibnu Sina YW-UMI Makassar Hospital from August 2025, the study involved 30 patients selected by consecutive sampling (15 per group), based on inclusion criteria of age 30–60 years, BMI 18.5–29.9 kg/m², and ASA I–II. Venous blood samples were taken preoperatively and 24 hours postoperatively to measure neutrophil and lymphocyte counts, and NLR was calculated accordingly. The independent variable was the type of anesthesia, and the dependent variable was ΔNLR. Data were analyzed using an independent t-test or

Mann–Whitney test as appropriate. Ethical approval was obtained from the Health Research Ethics Committee (No. 453/A.1/KEP-UMI/VII/2025), and the study was conducted in accordance with research ethics principles.

RESULT AND DISCUSSION

Results

Table 1. Distribution of Respondent Characteristics

Respondents Charateristics	**General Anesthesia**		**Epidural Anesthesia**	
	n	**%**	**n**	**%**
Age Category (Years)				
Productive : 14–45	4	26,7	4	26,7
Elderly: >45	11	73,3	11	73,3
Total	**15**	**100**	**15**	**100**
IMT Category				
Underweight (<18,5)	2	13,3	4	26,7
Normal (18,5–24,9)	8	53,3	7	46,7
Overweight (25,0–29,9)	2	13,3	2	13,3
Obesity I (30,0 – 34,9)	3	20,0	2	13,3
Obesity II (35,0 – 39,9)	0	0	0	0
Total	**15**	**100**	**15**	**100**

Source: Data Processing, 2025

Table 1 shows the distribution of the frequency characteristics of mastectomy patient respondents based on the type of anesthesia given, general anesthesia and epidural anesthesia. In both groups, the age distribution was relatively similar, where most of the respondents were in the age category >45 years (elderly), which was 73.3% in each group, while the productive age group (14–45 years) was only 26.7%. Based on the body mass index (BMI) category, most of the respondents in both groups were in the normal BMI category, namely 53.3% in the general anesthesia group and 46.7% in the epidural anesthesia group. The underweight category was more common in the epidural anesthesia group (26.7%) than in general anesthesia (13.3%). Meanwhile, the proportion of respondents who were overweight was relatively similar in both groups (13.3%), and only a small percentage of respondents were included in the obesity I category, with no respondents in the obesity II category. The distribution of these characteristics suggests that the two research groups have relatively comparable basic characteristics.

Table 2. Results of Comparison of Neutrophil to Lymphocyte Ratio Preoperative and Postoperative Levels in the General Anesthesia and Epidural Anesthesia Groups

Group	Measurement Time	n	Mean ± SD	*p-value*
Epidural	Pre-Surgery	15	5.13 ± 5.42	0.000*
Anesthesia	Post-Surgery	15	7.65 ± 5.99	
General	Pre-Surgery	15	4.12 ± 4.59	
Anesthesia	Post-Surgery	15	14.72 ± 8.43	

Source: Data Processing, 2025

Table 2 shows a comparison of Neutrophil to Lymphocyte Ratio (NLR) levels before and after mastectomy surgery in the epidural anesthesia and general anesthesia groups. In the epidural anesthesia group, the mean NLR level increased from 5.13 ± 5.42 at pre-surgery to 7.65 ± 5.99 at postoperatively, with a statistically significant difference ($p = 0.000$). A larger improvement was seen in the general anesthesia group, where the average NLR increased sharply from 4.12 ± 4.59 in pre-surgery to 14.72 ± 8.43 in post-surgery. These findings suggest that mastectomy surgery was accompanied by a postoperative inflammatory response in both groups, but the increase in NLR appeared to be more pronounced in patients undergoing general anesthesia compared to epidural anesthesia.

Table 3. Comparison Results Average change in Neutrophil to Lymphocyte Ratio between General Anesthesia and Epidural Anesthesia Groups

Group	Average Change in Neutrophil to Lymphocyte Ratio	*p-value*
	Mean ± SD	
Epidural Anesthesia	10.60 ± 7.23	0.000*
General Anesthesia	2.52 ± 2.36	

Source: Data Processing, 2025

Table 3 shows the comparison of the average change in NLR (ΔNLR) levels between the general anesthesia and epidural anesthesia groups. The results of the analysis showed that the average increase in NLR in the general anesthesia group was 10.60 ± 7.23, while in the epidural anesthesia group it was only 2.52 ± 2.36. The difference in the change in the mean NLR between the two groups was statistically significant ($p = 0.000$). This indicates that general anesthesia is associated with a higher postoperative inflammatory response than epidural anesthesia, as reflected by a greater increase in NLR values.

Discussion

Differences in NLR Values by Type of Epidural Anesthesia

The results showed that in the group of patients undergoing epidural anesthesia, there was a statistically significant increase in the Neutrophil to Lymphocyte Ratio (NLR) value after surgery compared to before surgery (p <

0.05). These findings reflect the presence of a physiological inflammatory response due to the unavoidable trauma of mastectomy surgery. However, the degree of increase in NLR in the epidural anesthesia group was relatively smaller than in the general anesthesia group, indicating that epidural anesthesia was able to better modulate the postoperative systemic inflammatory response.

Physiologically, the antiinflammatory effect of epidural anesthesia is related to the blockade of nocisceptive afferent impulses from the surgical area to the central nervous system, thereby suppressing the activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis. Suppression of this pathway leads to a decrease in the secretion of stress hormones such as cortisol and catecholamines, which play an important role in neutrophil mobilization and lymphocyte suppression. In addition, epidural anesthesia improves tissue perfusion through the effects of local vasodilation, improves microcirculation, as well as accelerates the elimination of inflammatory mediators. This mechanism contributes to hemodynamic stability and a decrease in postoperative systemic inflammatory stress.

The findings of this study are in line with various previous studies that have shown the immunomodulatory effects of regional anesthesia. Ahmed reported that the combination of general anesthesia and thoracic epidural significantly lowered IL-6 and NLR levels compared to a single general anesthesia (7). Surhonne also showed that the postoperative NLR increase was lower in patients undergoing spinal or epidural anesthesia compared to general anesthesia (8). Similar results were reported in breast cancer patients with paravertebral blocks and reinforced by meta-analyses concluding that the epidural component consistently lowers systemic inflammation, CRP, and NLR (12,13).

Differences in NLR Values by Type of General Anesthesia

In the group of patients undergoing general anesthesia, this study showed a significant increase in NLR values after surgery compared to before surgery ($p < 0.05$). This increase describes a stronger systemic inflammatory response due to surgical stress. Although general anesthesia is effective in creating optimal surgical conditions through involuntary induction, amnesia, and muscle relaxation, this technique does not completely inhibit the transmission of peripheral nociceptive impulses, so systemic stress responses persist.

Physiologically, general anesthesia triggers the activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, which is characterized by increased secretion of ACTH, cortisol, and catecholamines. Cortisol plays a role in suppressing lymphocyte proliferation and adaptive immunity, while catecholamines increase the recruitment and adhesion of neutrophils to the vascular endothelium. This combination of processes led to an increase in postoperative NLR ratios. In addition, some inhalation anesthetic agents have been reported to increase oxidative stress and free radical production, which exacerbates an imbalance of the immune response (Buonacera).

These results are in line with various previous studies. Surhonne reported a higher spike in NLR in general anesthesia patients compared to regional anesthesia (14), more significant increase in NLR in breast cancer patients with general anesthesia compared to regional blocks (15). General anesthesia consistently increased IL-6, CRP, and NLR compared to regional or combination techniques (16). Although some studies showed insignificant results in surgery with minimal trauma (17).

Comparison of ΔNLR between General Anesthesia and Epidural

The results of the analysis showed a significant difference in the ΔNLR value between the general anesthesia and epidural anesthesia groups, with a p-value <0.001 based on the Mann–Whitney test. The general anesthesia group showed a much higher increase in ΔNLR than the epidural group. These findings indicate that the anesthesia technique is associated with different magnitudes of systemic inflammatory response after mastectomy, as reflected by changes in NLR.

The observed difference in ΔNLR may be explained by neuroimmunological mechanisms that have been described in previous studies. Neuraxial blockade with epidural anesthesia can attenuate afferent nociceptive transmission and reduce sympathetic outflow, which is proposed to lower perioperative stress responses and thereby reduce neutrophil mobilisation and lymphocyte suppression. In contrast, general anesthesia may not fully blunt neuroendocrine stress activation related to surgical trauma, potentially resulting in a higher postoperative inflammatory signal, reflected in higher ΔNLR. However, it is important to note that the present study did not directly measure stress hormones, cytokines (e.g., IL-6), or other neuroendocrine markers; therefore, these mechanisms should be interpreted as theoretical explanations supported by the literature rather than conclusions derived directly from our data.

The results of this study are consistent with reports showing lower postoperative inflammatory changes when neuraxial or regional techniques are used as part of the anesthetic approach, including studies reporting lower ΔNLR in techniques involving epidural compared with general anesthesia alone (18). Nevertheless, some studies have reported non-significant findings, possibly due to differences in surgical procedures, anesthetic agents, perioperative analgesia, and timing of postoperative sampling (19).

The results of the analysis showed a significant difference in the ΔNLR value between the general anesthesia and epidural anesthesia groups, with a p< value of 0.001 based on the Mann–Whitney test. The general anesthesia group showed a much higher increase in ΔNLR than the epidural group. These findings confirm that this type of anesthesia technique has a significant influence on the degree of systemic inflammation after mastectomy.

Applicability of Study Findings to Very Elderly Patients and Those with Severe Comorbidities

This study showed that epidural anesthesia was associated with a smaller postoperative increase in NLR compared with general anesthesia, suggesting a potential benefit in attenuating the systemic inflammatory response after mastectomy. However, applying these findings to patients of very advanced age or those with severe comorbidities should be done with caution. High-risk patients often have reduced physiological reserve and greater frailty, which may lead to inflammatory and surgical stress responses that differ from those seen in patients with more stable baseline conditions. In addition, in very elderly populations, age-related immune changes (immunosenescence) may alter baseline neutrophil and lymphocyte profiles; therefore, preoperative NLR values and postoperative trajectories may not fully reflect the effect of the anesthetic technique alone.

In patients with severe comorbidities such as severe chronic obstructive pulmonary disease (COPD), heart failure, advanced chronic kidney disease, uncontrolled diabetes, active infection, steroid therapy, or advanced-stage malignancy baseline NLR is often higher and more variable. These factors can act as confounders because they independently influence neutrophil mobilisation and lymphocyte suppression; consequently, postoperative ΔNLR may not be solely attributable to differences in anesthetic technique. Moreover, while epidural anesthesia may reduce sympathetic activation and the stress response through neuraxial blockade, neuraxial techniques also have specific safety considerations in certain high-risk patients (e.g., more pronounced hypotension, coagulopathy, or anticoagulant use). Therefore, anesthetic selection in these populations should remain individualised based on comprehensive clinical assessment.

Accordingly, the findings of this study are best interpreted as preliminary evidence supporting the potential immunomodulatory advantage of epidural anesthesia in the studied cohort, while generalisability to very elderly patients or those with severe comorbidities remains limited. Future research should adopt stronger designs (e.g., randomised studies), include larger samples, and stratify participants by comorbidity burden (e.g., ASA or Charlson index) and frailty status. Combining NLR with additional biomarkers (CRP/IL-6) and incorporating clinical outcomes (pulmonary complications, length of stay, pain, and functional recovery) would also provide a more comprehensive assessment of epidural benefits in high-risk groups.

CONCLUSION AND RECOMMENDATION

This study concluded that both epidural anesthesia and general anesthesia led to an increase in NLR values after mastectomy surgery, but the degree of the increase was significantly different. The general anesthesia group showed a higher increase in postoperative NLR and ΔNLR than the epidural anesthesia group, suggesting that epidural anesthesia may be more effective in attenuating the postoperative systemic inflammatory response. However, the recommendation to use epidural anesthesia must be made ethically and contextually, because its safe implementation depends on the availability of trained anaesthesia providers, appropriate monitoring, sterile technique, and institutional readiness to manage potential complications. Therefore, epidural anesthesia should be considered only when resources and expertise are adequate, and decisions should follow local protocols, clinician competence, and patient-specific risk–benefit assessment. Regarding applicability, the findings remain clinically relevant for hospitals with limited facilities as they highlight the potential inflammatory differences between techniques; nevertheless, translation into practice may be constrained where epidural equipment, monitoring, or specialist expertise is unavailable. In such settings, the results should be interpreted as supportive evidence for optimising perioperative care rather than as a universal directive. Alternative strategies (e.g., multimodal analgesia and other feasible regional techniques) may be prioritised according to local capacity. Finally, follow-up research with randomised designs, larger and more diverse samples, inclusion of additional biomarkers (e.g., CRP/IL-6), and clinical outcomes is needed to strengthen the evidence and improve generalisability across different hospital settings.

ACKNOWLEDGE

The authors would like to express their sincere gratitude to the management and medical staff of Ibnu Sina YW-UMI Makassar Hospital for their support and cooperation during data collection. Special thanks are extended to all patients who voluntarily participated in this study. The authors also acknowledge the Health Research Ethics Committee for granting ethical approval and ensuring that this study was conducted in accordance with ethical research principles. Appreciation is further given to colleagues and laboratory staff who assisted in data processing and hematological analysis. Finally, the authors thank all parties who contributed directly or indirectly to the completion of this research.

REFFERENCES

1. Goethals A, Menon G, Rose J. Mastectomy. StatPearls [Internet]: StatPearls Publishing; 2024.
2. Apridawati L, Antoro B, Maryuni S. Pengaruh Teknik Relaksasi Autogenik Terhadap Skala Nyeri Pasien Post Operasi Mastektomi di RSUD DR. H. Abdul Moeloek Provinsi Lampung. Malahayati Nursing Journal. 2025 Jan 1;7(1):426–46.
3. Avila Hernandez AN, Hendrix JM. Epidural Anesthesia. StatPearls. 2025.
4. Jilani TL, Banjar AS, alhazmi EM, Khojah SA, Maimani ASM, Ageel O, et al. Anesthesia And Recovery: Comparing Methods To Minimize Drug Effects On Emergence Time. Diabetic Studies. 2024;20(S5):201–24.
5. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to Lymphocyte Ratio: An Emerging Marker of the Relationships between the Immune System and Diseases. International Journal of Molecular Sciences. 2022 Mar 26;23(7):3636.
6. Hewson DW, Tedore TR, Hardman JG. Impact of Spinal or Epidural Anaesthesia on Perioperative Outcomes in Adult Noncardiac Surgery: A Narrative Review of Recent Evidence. British Journal of Anaesthesia. 2024 Aug;133(2):380–99.
7. Zhang Y, Jiang W, Luo X. Remifentanil Combined with Dexmedetomidine on The Analgesic Effect of Breast Cancer Patients Undergoing Modified Radical Mastectomy and The Influence of Perioperative T Lymphocyte Subsets. Frontiers in Surgery. 2022;9(November):1–8.
8. Lee S, Pyo DH, Sim WS, Lee WY, Park M. Early and Long-Term Outcomes after Propofol-and Sevoflurane-Based Anesthesia in Colorectal Cancer Surgery: A

Retrospective Study. Journal of Clinical Medicine. 2022;11(9).

9. Brescia F, Favero A, Segatto I, Massarut S, Zanier C, Fabiani F, et al. Impact of opioid-free general anesthesia with locoregional blocks during breast cancer surgery on systemic inflammatory response: results from a randomized controlled trial. Reg Anesth Pain Med. 2025 Jun 25;rapm-2025-106504.
10. Köksal BG, Bollucuoğlu K, Şahin E, Bayram MG, Küçükosman G, Ayoğlu H. The effect of anesthesia methods on the neutrophil–lymphocyte ratio in patients undergoing forearm surgery: A monocentric and retrospective study. Medicine. 2024 Oct 25;103(43):e40290.
11. Lin EJ, Prost S, Lin HJ, Shah S, Li R. Combined General/Epidural Anesthesia vs. General Anesthesia on Postoperative Cytokines: A Review and Meta-Analysis. Cancers. 2025 May 15;17(10):1667.
12. Su J, Li Y, Tan S, Cheng T, Luo Y, Zhang L. Pretreatment Neutrophil-to-Lymphocyte Ratio is Associated with Immunotherapy Efficacy in Patients with Advanced Cancer: A Systematic Review and Meta-Analysis. Scientific Reports. 2025 Jan 2;15(1):446.
13. Kenzi IA, Hartawan IU, Sidemen IS, Agung Senapathi TG, Gede Widnyana IM. Comparison of Inflammation, Pain, and Recovery in Colorectal Cancer Patients Undergoing Surgery with General Anesthesia and Combined Epidural. Journal La Medihealtico. 2025 Mar 13;6(2):379–89.
14. She H, Wu B, Mao S, Gao T. Effects of Different Anesthesia Methods on Perioperative Immune Function and Long-Term Regression of Patients Undergoing Thoracoscopic Radical Esophagectomy For Esophageal Cancer. Heliyon. 2023 Dec;9(12):e22822.
15. Nindya P, Rahadi K, Made I, Ruma W, Made Wihandani D, Gede I, et al. Hubungan neutrophil lymphocyte ratio dan tumor infiltrating lymphocyte dengan karakteristik klinikopatologi pasien kanker payudara di Rumah Sakit Umum Pusat Prof. Dr. I Goesti Ngoerah Gde Ngoerah Denpasar. MEDICINA. 2023;54(3):179–85.
16. Zhu K, Zheng F, Wang C, Ding L. Effect of Ultrasound-Guided Fascia Iliac Compartment Block on Serum NLRP3 and Inflammatory Factors in Patients with Femoral Intertrochanteric Fracture. Comput Math Methods Med. 2022 May 17;2022:1–6.

17. Reysner T, Kowalski G, Mularski A, Grochowicka M, Daroszewski P, Reysner M. Modulation of postoperative inflammatory response in total knee arthroplasty: Impact of iPACK block on neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in a randomized controlled trial. Trends in Anaesthesia and Critical Care. 2025 Jun;62:101551.

18. Müller SD, Both CP, Sponholz C, Voelker MT, Christiansen H, Niggli F, et al. Association between Intraoperative Blood Transfusion, Regional Anesthesia and Outcome after Pediatric Tumor Surgery for Nephroblastoma. Cancers. 2022 Nov 14;14(22):5585.

19. Yediyıldız MB, Durmuş İ, Ak HY, Taşkın K, Ceylan MAD, Yüce Y, et al. Comparison of inhalation and total intravenous anesthesia on inflammatory markers in microdiscectomy: a double-blind study. BMC Anesthesiol. 2025 May 10;25(1):238.