

## THE ROLE OF PREOPERATIVE NEUTROFIL-LYMPHOCYTE RATIO AS A PREDICTOR OF PAIN IN DECOMPRESSION AND POSTERIOR STABILIZATION SURGERY PATIENTS (REVIEW OF INTERLEUKIN 6 LEVELS)

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### ABSTRACT

**Background:** Posterior decompression and stabilization on the vertebrae is a surgical procedure performed to treat the main cause of low back pain. NLR perioperative examination is very rarely used in determining the level of postoperative pain and can help in planning of postoperative analgesic drugs, even though this examination is certainly available as a perioperative assessment.

**Purpose:** This study aims to assess the relationship between NLR preoperative as a predictor of pain with pain intensity and IL-6 levels postoperative in patients undergoing posterior decompression and stabilization surgery.

**Methods:** This research is an analytical observational study with a prospective cohort design, which was carried out at Wahidin Sudirohusodo Hospital. The sample for this study was all patients who underwent elective surgical procedures for Decompression and Posterior Stabilization of the Lumbar Region at Dr. RSUP. Wahidin Sudirohusodo Makassar with 30 samples.

**Results:** There was a strong, significant correlation between the average NRS at rest and the NLR group, as well as the average NRS with movement,  $p$  value  $< 0.05$ ,  $r > 0.7$ . In IL-6 postoperative and delta-IL-6 levels, there was a statistically significant difference in IL-6 levels between the two groups with a  $p$  value  $< 0.05$ . There is a significant difference in the need for the opioid Fentanyl in the two groups with a  $p$  value  $< 0.05$ .

**Conclusion:** There was an increase in the pain intensity and IL-6 levels postoperative, as well as an increase in total opioids consumptions in patients undergoing decompression and posterior stabilization of the lumbar region with NLR preoperative  $\geq 2$  compared to NLR  $< 2$ . NLR can be used as a predictor of postoperative pain which is good, therefore it can be used as a reference for appropriate postoperative pain management.

**Keywords:** posterior decompression and stabilization, pain intensity, interleukin-6, numeric rating scale, neutrophil lymphocyte ratio

### INTRODUCTION

Posterior decompression and stabilization on the vertebrae is a surgical procedure performed to treat the main causes of low back pain, especially instability of the lumbar vertebrae due to compression in the body axis and/or excessive torsional load. Pain following spinal decompression and stabilization surgery can be caused by tissue damage that occurs during surgery and involves the activation of various pain mechanisms. Apart from tissue damage during surgery, postoperative pain can also be caused by mechanical irritation, compression or postoperative inflammation.<sup>1-4</sup> Acute post-operative pain that is not handled well can become chronic postoperative pain, thereby increasing morbidity and mortality rates, as well as reducing the patient's quality of life.<sup>5</sup> Patients often present clinically with low back pain. Stimulation of low back pain causes chronic lesions in the muscles which result in the release of various inflammatory mediators including bradykinin which triggers the release of 5-

hydroxytryptamine (5-HT) and prostaglandin E2 (PGE-2). It is known that PGE-2 contributes to the synthesis of interleukin-6 (IL-6) in macrophages and other nerve cells.<sup>6</sup>

There are several tests that can measure the stress response due to tissue damage during surgery. One examination that is easy and flexible to carry out is a complete blood examination, namely neutrophils and lymphocytes, which can describe the occurrence of an inflammatory process. The mechanism of using the neutrophil - lymphocyte ratio (NLR) as an inflammatory marker is reported to have quite good prognostic value and its use can be used to diagnose an acute condition.<sup>7-8</sup> Research by Hajibandeh S et al. in 2019 showed that NLR can predict the severity of appendicitis and this value can be used as a basis for surgical priorities, and can also be used for regular monitoring and evaluation of appendicitis patients with conservative therapy.<sup>9</sup> IL-6 plays a role in the mechanisms of pain and hypersensitivity associated with inflammation and neuropathy by interacting not only with

immune cells and glial cells but also neurons along the pain pathway.<sup>10</sup> Previous studies reported the effect of intraoperative infiltration anesthesia on inflammation after hip arthroplasty surgery with the result that postoperative increase in pro-inflammatory cytokines, which returned to normal levels after 3 days.

In patients undergoing surgery, there is a cellular immune response related to an increase in neutrophils and degradation of lymphocytes as part of an acute inflammatory response related to the formation of prostaglandin E2, thereby causing pain. IL-6 examination has been an accurate marker of inflammation, but the examination is quite expensive and not available in all institutions.<sup>6,9</sup> NLR preoperative examination is easy to carry out, because every patient who will undergo surgery will previously undergo a complete blood hematology examination. So, it is affordable to be used as a preoperative assessment parameter, especially in predicting postoperative pain and can help in planning the administration of postoperative analgesic drugs. Therefore, this study will look at whether there is a relationship between NLR preoperative as a predictor of pain and post-operative pain intensity and IL-6 levels in patients undergoing posterior decompression and stabilization surgery. This study aims to assess the relationship between NLR preoperative as a predictor of pain on pain intensity and post-operative IL-6 levels in patients undergoing posterior decompression and stabilization surgery.

**METHODS**

This research is an analytical observational study with a prospective cohort design, which was carried out at Wahidin Sudirohusodo Hospital, Makassar, Indonesia. The sample for this study was all patients who underwent elective surgical procedures for Decompression and Posterior Stabilization of the Lumbar Region at Dr. RSUP. Wahidin Sudirohusodo Makassar who met the inclusion criteria and agreed to take part in the research. This research was conducted on 30 patients who were divided into 2 groups, with 15 samples in each group. Patients who meet the research criteria undergo applicable elective surgical preparation procedures. All subjects underwent preoperative anesthesia examination and signed informed consent. Blood samples were taken

before surgery for routine blood tests and IL-6 levels. Given Paracetamol 1000 mg/orally 2 hours before surgery, Ranitidine 1 mg/kgBB/IV and Ondansetron 0.1 mg/kgBB/IV 30 minutes before surgery. Then a general anesthesia procedure was performed with Endotracheal Intubation according to the procedure. After the procedure, pain management was given with Fentanyl 0.5-1 mcg/kgBW/hour IV and paracetamol 1000 mg/6 hours/orally. Postoperative, pain intensity was observed when at rest and with movement after surgery at 2, 4, 6, 8, 12 and 24 hours using the Numeric Rating Scale (NRS) and the results were recorded on an observation sheet. Blood samples were taken 6 hours after surgery for routine blood tests and IL-6 levels. Postoperative pain relief opioids are given to patients if pain intensity is found with an NRS > 4 using fentanyl at a dose of 0.5 – 1 mcg/kg/IV titrated according to needs and the patient's total 1 x 24 hour opioid requirement is recorded.

The inclusion criteria in this study were patients who underwent elective decompression and posterior stabilization surgery in the lumbar region, physical status ASA I-II, aged 18-65 years, and agreed to take part in the study. Meanwhile, the exclusion criteria in this study were patients undergoing elective decompression and posterior stabilization surgery in the lumbar region due to infection or tumor, patients with previous corticosteroid treatment. Drop out criteria in this study were patients who experienced surgical complications that greatly affected hemodynamic status such as bleeding (>40% of total EBV), prolonged operation time (> 4 hours), ICU postoperative, patients withdrew from the study. After the research was completed, all data was recorded and statistical analysis was carried out using SPSS 25 for Windows.

**RESULTS**

Research on 30 patients undergoing decompression and posterior stabilization surgery in the lumbar region at RSUP Dr. Wahidin Sudirohusodo Makassar, obtained an overview of the characteristics of the research sample in the group with NLR < 2 and NLR ≥ 2 based on age group, gender and body mass index, the result was p > 0.05, which means the two groups had homogeneous data (Table 1).

**Table 1.** Characteristics of the Research Sample with Research Variables

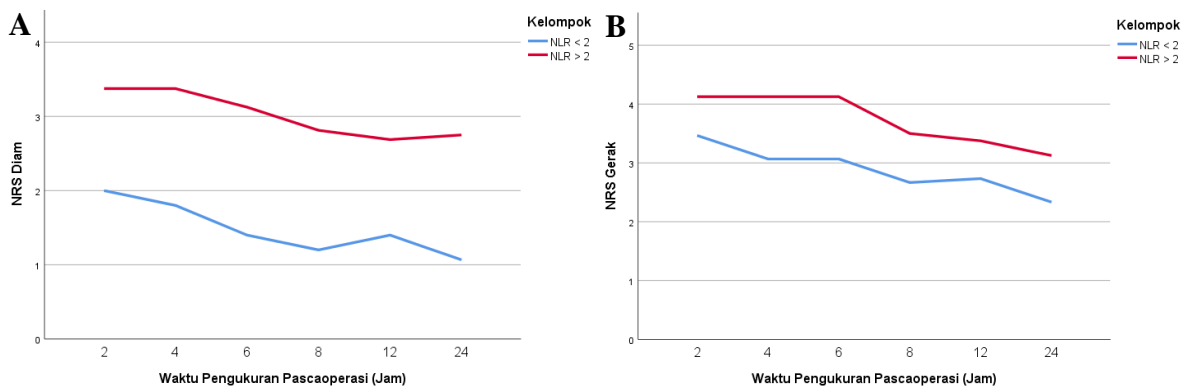
Characteristic	NLR < 2 (Mean±SD)	NLR ≥ 2 (Mean±SD)	p value
Age (years)	52±13.23	53±12.29	0.826 <sup>ns</sup>
Sex	Man (%)	8 (53)	0.853 <sup>ns</sup>
	Female (%)	7 (47)	
Body mass index (kg/m <sup>2</sup> )	24.89±3.21	23.39±2.35	0.169 <sup>ns</sup>

Gender: Chi Square test, Other variables: unpaired T test. ns: not significant (homogeneous data)

The difference in pain intensity assessed using NRS when at rest in the NLR < 2 and NLR ≥ 2 groups for 6 measurements over 24 hours was found to be a significant difference in the two groups with a p value <

0.05. Likewise, in the NRS with movement condition, significant differences were found in the two groups with a p value <0.05 (Figure 1).

THE ROLE OF PREOPERATIVE NEUTROFIL-LYMPHOCYTE RATIO AS A PREDICTOR OF PAIN IN



**Figure 1.** (A) Comparison between NRS at rest in the two NLR groups, (B) Comparison between NRS with movement in the two NLR groups

The correlation between NRS at rest and NRS with movement when compared with NLR levels was found. There was a significant correlation between the average NRS at rest and the NLR group, as well as the average

NRS with movement, p value < 0.05 was obtained in both groups, with an r value > 0.7 which means there is a strong correlation (Table 3).

**Table 2.** Correlation of NLR with NRS

Averages	NLR < 2 (Median (Min-Max))	NLR ≥ 2 (Median (Min-Max))	r value	p value
<b>NRS at rest</b>	1.5(1.17-1.83)	2.9(2.01-4.33)	0.870	0.001*
<b>NRS with movement</b>	2.83(2.50-3.17)	3.51(3.33-5.50)	0.714	0.001*

Uji Pearson Correlation; \*: significant

In preoperative conditions, there was no statistical difference in IL-6 levels between the two groups, with a p value > 0.05. Meanwhile, in postoperative conditions and

changes in IL-6 levels, there was a statistically significant difference in IL-6 levels between the two groups with a p value < 0.05 (Table 4).

**Table 3.** IL-6 levels in the NLR < 2 and High groups

IL-6 (pg/mL)	NLR < 2 (Median (Min-Max))	NLR ≥ 2 (Median (Min-Max))	p value
<b>Preoperative</b>	1.84(0.11-18.0)	1.62(0.11-11.29)	0.830 <sup>ns</sup>
<b>Postoperative</b>	20.51(7.24-131.10)	45.28(11.96-135.90)	0.017*
<b>delta-IL-6</b>	18.77(2.42-125.05)	42.15(11.69-126.33)	0.030*

Mann Whitney U Test; ns: not significant \*: significant

In terms of total opioid consumptions in the two NLR groups in posterior decompression and stabilization surgery, a significant difference was found in the need for

the opioid Fentanyl in the two groups with a p value < 0.05 (Table 5).

**Table 4.** Total Opioid Requirements in the NLR < 2 and NLR ≥ 2 Groups

Total opioid consumptions (mcg)	NLR < 2 (Median (Min-Max))	NLR ≥ 2 (Median (Min-Max))	p value
<b>Total opioid consumptions (mcg)</b>	1054 (850-1360)	1740 (1450-2030)	0.001*

Mann Whitney U Test; \*: significant

## DISCUSSION

In this study, significant differences were found between NRS at rest and movement NRS, respectively in the NLR < 2 and NLR ≥ 2 groups in 6 measurements over 24 hours. This shows that there is a significant difference between the pain intensity in the NLR preoperative group, namely low NLR preoperative are associated with lower pain intensity, as well as high NLR preoperative are associated with higher postoperative pain intensity. According to research conducted by Kerim et al, there is a

significant correlation between NLR preoperative in predicting postoperative pain in arthroscopic rotator cuff surgery. It was found that patients with NLR > 2 had higher NRS scores. NLR is a marker of subclinical inflammation and has been used in conjunction with other inflammatory markers to determine inflammation. The predictive role of NLR as a marker of inflammation in several diseases such as coronary heart disease, colorectal cancer and other inflammatory diseases suggests that NLR can be a useful predictive indicator for postoperative

pain due to secondary inflammatory pathways caused by surgical trauma and/or direct nerve trauma related to surgery.<sup>11</sup> In this study, there was also a significant correlation between the NRS at rest and the NLR group, as well as the NRS with movement, with a strong correlation. This shows that there is a significant correlation between NLR and pain intensity. Both NRS at rest and NRS with movement postoperative have a strong correlation with NLR preoperative of posterior decompression and stabilization patients. In accordance with previous research by Canbolat et al. who concluded that NLR is acceptable as a relatively objective method for the diagnosis of postoperative pain. Pathophysiologically, inflammatory cells (leukocytes and neutrophils) increase in the first 24 hours after surgical stress. This shows an inflammatory response triggered by surgery.<sup>12</sup> Turgut et al's research found that NLR preoperative can predict the need for postoperative analgesia in patients undergoing orthognathic surgery and thus postoperative pain control can be achieved by providing various kinds of treatments such as in the preoperative period preemptive analgesia can be given, administration of local anesthesia at the end of surgery or initial administration of analgesics.<sup>13</sup> This study established a significant correlation with high NLR with high pain scores indicating inflammation which can delay patient mobilization due to pain, which can trigger postoperative complications and prolong the duration of hospital stay.

This study also showed that in postoperative conditions and changes in IL-6 levels, there were significant differences between the two NLR groups. This shows that there is a significant difference in IL-6 levels postoperative in the NLR preoperative < 2 and NLR ≥ 2 groups. Not only IL-6 levels postoperative, delta-IL-6 levels also showed significant differences between the NLR preoperative < 2 and NLR ≥ 2 groups. The surgical incision is a traumatic stimulus that triggers a systemic neuroendocrine response and a local inflammatory response. Surgical trauma causes an acute phase response that allows the amount of injured tissue to be controlled, limiting infection and initiating the healing process. As a physiological response of circulating leukocytes to surgical stress, it causes an increase in the number of neutrophils and a decrease in the number of lymphocytes; the ratio of these two subgroups is used as an indicator of inflammation in intensive care practice. The study according to Akili et al divided 373 patients who came to the emergency department and required an intensive care unit, into 4 groups in their study which analyzed patient follow-up for 6 months prospectively in terms of mortality rates. Significant differences were found in the in-hospital and 6-month mortality ratios according to increasing NLR. Pro-inflammatory cytokines are generally produced by active macrophages and play a role in increasing inflammatory reactions. There is a lot of evidence that pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α play a role in the process of pain formation. Cytokines and prostaglandins are important inflammatory mediators that have an effect on pain receptors. These inflammatory

mediators can affect pain receptors directly or by releasing prostaglandins that activate pain receptors. The release of IL-1β and TNF-α causes the formation and release of other cytokines including IL-6. IL-6 is the main cytokine that causes the acute phase response. IL-6 reaches its peak 4 to 48 hours after surgery.<sup>14</sup> The total opioid requirements in both NLR groups in posterior decompression and stabilization surgery, found significant differences in opioid requirements in the two groups. The NLR < 2 group required a lower opioid dose compared to the NLR ≥ 2 with a p value < 0.05. This is in accordance with research conducted by Vildan et al who examined patients undergoing septorhinoplasty, where there were two groups, namely group 1 with NLR preoperative < 2 (1.46 + 0.29) and group 2 with NLR preoperative ≥ 2 (2.64 + 0.74). It was found that the total analgesic consumption in the first 24 hours after surgery in group 1 was 97.79 + 56.93 mg compared to group 2 which was statistically significantly higher, namely 130.21 + 65.83 mg.<sup>15</sup>

## CONCLUSIONS

There was an increase in postoperative pain intensity (NRS at rest and with movement), followed by an increase in post-operative IL-6 levels and changes in IL-6 levels in patients undergoing Decompression and Posterior Stabilization surgery of the Lumbar Region with a NLR preoperative ≥ 2 compared to NLR < 2. With an increase greater need for opioids in patients with NLR preoperative ≥ 2. Shows that NLR can be used as a good predictor of postoperative pain, therefore it can be used as a reference for appropriate postoperative pain management.

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