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Neutrophil Lymphocyte Ratio as a Predictor of Chronic Low Back Pain Severity

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ABSTRACT

Low back pain is a frequently seen problem in the society and causes loss of productivity. In recent studies, inflammatory mediators and inflammation itself has an efficient role in pain mechanism. We aimed to investigate the association between the neutrophil to lymphocyte ratio level as an inflammatory biomarker with pain severity patients with chronic low back pain. A retrospective analysis was conducted on medical records of low back pain patients between Januari until December 2024 in Neurology Department of Bhakti Rahayu Denpasar Hospital. Seventy-three medical record patients between 27-81 years old were included in the study. The neutrophil-to-lymphocyte ratio (NLR) is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count based on blood samples. The patients were divided into two groups based on pain severity. The average age of the participants was 56,63 years (±15,56) (p= 0,077), with 40 males (54,85) and 33 females (45,2%) with average neutrophil count 5,99 x 10^9/L (±1,45) (p= 0,200) and lymphocyte count 1,75x 10^9/L (±0,39) (p= 0,093). NLR cut-off was 3,55 (±0,72) (p= 0,200). Higher NLR correlated with age (r = 0.243, p = 0.038) and pain score (r = 0.394 p < 0.001). High NLR increased the risk of 33, 43 LBP patients experiencing moderate pain (p= <0.001). NLR may be used as a simple and reliable premise independent predictor of pain severity in patients with chronic low back pain

Keywords: Neutrophil to Lymphocyte Ratio, Low Back Pain, Numerical Pain Rating Scale, Lumbar Disc Herniation

Introduction

Low back pain (LBP) is significant global health issue that affects millions of people each year. Low back pain is a frequently seen problem in the society and causes loss of labor and significant burden on both the healthcare system and the economy(1). The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) systematically quantifies health loss due to diseases and injuries by age, sex, year, and geographical location, and allows for the comparison of burden across disparate diseases(2). Previous GBD low back pain estimate confirmed that low back pain is the leading cause of disability in most countries (3–5). It is expected that both the total disability burden and disease-related costs will further increase in the coming decades(6)

Lumbar disc herniation occurs as a result of tear of annulus fibrosus not resisting to

torsional forces and nucleus becomes herniated (7). In addition to mechanical effects on lumbar disc degeneration and herniation, extended inflammation and inflammatory cytokine (such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β) has had efficient role for lumbar disc degeneration and herniation (8,9)

Clinically, inflammation is identified by five main signs: redness (rubor), heat (calor), swelling (tumor), pain (dolor), and loss of function (functio laesa). Acute inflammation is a protective mechanism that involves immune cells, blood vessels, and inflammatory mediators. The purpose of inflammation is to remove the initial cause of cell damage and to start the healing process. Acute pain, often referred to as nociceptive pain, is a key characteristic of inflammation. Most known inflammatory mediators induce pain by interacting with receptors on nociceptive primary sensory neurons in the peripheral nervous system (nociceptors) that are responsible for sensing injury in skin, muscle, and joint tissues)(10)

Unlike acute inflammation, chronic inflammation can be harmful and is associated with various diseases, including periodontitis, atherosclerosis, rheumatoid arthritis, and even cancer. It remains uncertain whether chronic inflammation is as pivotal in causing chronic pain as acute inflammation is for acute pain. Research over the past few decades has shown that neuronal plasticity is a crucial mechanism in the onset and persistence of chronic pain. Peripheral sensitization in nociceptors plays a vital role in the development of chronic pain and the transition from acute to chronic pain. Additionally, central sensitization—enhanced responses of pain pathways in the spinal cord and brain—affects the persistence of pain, promotes the spread of pain beyond the injury site, and influences emotional and affective responses to pain.(10)

Neuroinflammation is localized inflammation occurring in both the peripheral and central nervous systems in response to trauma, neurodegeneration, infections, autoimmunity, and toxins. Key indicators of neuroinflammation include the activation and infiltration of leukocytes, glial cell activation, and increased production of inflammatory mediators. It is also associated with vascular changes that facilitate leukocyte entry. Compared to general inflammation, neuroinflammation is more persistent in chronic pain conditions, making it more significant in maintaining chronic pain.(10,11)

The relationship between inflammation and pain is bidirectional. Nociceptive sensory neurons not only react to immune signals but also actively modulate inflammation. Nociceptors have receptors for cytokines and chemokines and can produce these inflammatory mediators. Furthermore, the activation of pain signaling pathways influences neuroinflammation in the central nervous system, a process referred to as neurogenic neuroinflammation in cases of chronic pain and neurodegenerative diseases.(10,11)

Previously, Neutrophil-to-lymphocyte ratio (NLR), known to be a systemic inflammatory marker, has been shown to play a role in the progression of many diseases and it was shown that it has a prognostic value in many acute and chronic diseases. NLR is measured by proportioning 2 inflammatory markers (neutrophil and lymphocyte), it has a stronger predictive value (12).

Although it was shown that predictive value of increased NLR in many diseases, the relationship between NLR as marker of inflammation and pain severity level in low back pain or

lumbar disc herniation has not been investigated comprehensively. Therefore, in this particular study, we aimed to investigate the association between the NLR level and pain severity level in patients with chronic low back pain.

Research Methods

STUDY POPULATION

This was an observational analytic retrospective cohort study analyzed medical record patients presenting with low back pain attributable to lumbar disc herniation or lumbar spinal stenosis of Neurology Department Bhakti Rahayu Hospital between January until December 2024. 362 medical record patients with multiple physical measurements were taken from participants and a blood sample was collected at the time of admission.

Inclusion criteria were age between 18-81 years old, chronic back pain (onset more than 3 months or 12 weeks), diagnosed with lumbar disc herniation or lumbar spinal stenosis accompanied by severe back pain and radicular pain, presence of radicular symptoms, including pain, sensory abnormalities, and positive straight leg raising test, imaging data consistent with disc herniation or spinal stenosis at the symptomatic segment as per MRI findings. Exclusion criteria included incomplete medical record, history of lumbar infections, injuries or tumors, previous history of lumbar spine surgery, patients with cauda equina syndrome, patients with a history of chronic diseases such as lung, kidney, and liver diseases, systemic infectious diseases such as osteomyelitis, systemic lupus erythematosus, ankylosing spondylitis, rheumatoid arthritis, etc., history of analgetic and steroid therapy patients within last 6 months, and pregnancy.

Seventy three medical record patients were included in the study between 27-81 years old with general information were age, gender, numerical pain rating scale (NPRS) range between 1-10, MRI imaging with herniated disc result, neutrophil count, and lymphocyte count. The neutrophil-to-lymphocyte ratio (NLR) is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Blood samples were taken from patients that were admitted to our Neurology Department with the complaint of low back pain for the whole blood count and the biochemistry parameter measurement. Blood samples were collected by puncture the antecubital vein and were sent to the laboratory for analysis within 1 hour after collection. Neutrophils, lymphocytes, and Neutrophil Lymphocyte Ratio (NLR) were determined by an automated blood cell counter Coulter LH 780 Hematology Analyzer (Beckman Coulter IrelandInc Mervue, Galway, Ireland). Biochemical parameters were measured during the Abbott Architect C16000 autoanalyzer (Abbott Laboratories, Abbott park, IL, USA).

STATISTICAL ANALYSIS

The data analysis was conducted using SPSS (version 29.0.0, SPSS Inc., Chicago, IL, USA). Continuous variables data are expressed as the average ± standard deviation. Categorical variables were compared using Chi-square or Fisher's exact tests and summarized as percentages. The Kolmogorov–Smirnov test was used to evaluate the distribution of the continuous variables. Normally distributed data were represented as average ± standard

deviation (SD), nonnormally distributed data were expressed as median [interquartile range], and categorical variables were presented as frequency and n (%). Receiver operating characteristic (ROC) curves were used to predict the cut-off value of NLR. Logistic regression analysis was conducted to identify risk factors for severe disc degeneration. Four multivariate logistic regression models were developed for various indicators, including neutrophils, lymphocyte, NPRS, and the NLR. Statistical significance was determined at a two-tailed p-value of <0.05 were included in the multiple logistic analyses..

Results and Discussion

This study was attended by 73 research subjects who met the inclusion and exclusion criteria. The basic characteristics of the research subject are presented in table 1 below

Table 1. Characteristics of subject

Variable		**Number (n)**	**P value**
Age (years)	Average	56,63 (±15,56)	0,077
Sex (n, %)	Male	40 (54,8%)	
	Female	33 (45,2%)	
NPRS	0-10	3,22 (±1,14)	0,000
Neutrophil Value (10^9/L)	Average	5,99 (±1,45)	0,200
Lymphocyte Value (10^9/L)	Average	1,75 (±0,39)	0,093
NLR	Average	3,55 (±0,72)	0,200

Detailed patient characteristics and group comparisons are summarized in table 1. The average age of the participants was 56,63 years (±15,56)(p= 0,077), with 40 males (54,85) and 33 females (45,2%). The average of NPRS was mild-moderate pain 3,22 (±1,14) (p= 0,000) with average neutrophil count 5,99 x 10^9/L (±1,45) (p= 0,200) and lymphocyte count 1,75x 10^9/L (±0,39) (p= 0,093). Neutrophil-Lymphocyte Ratio (NLR) was 3,55 (±0,72) (p= 0,200). Test of normality distribution data showed age, neutrophil, lymphocyte, and NLR were normally distributed.

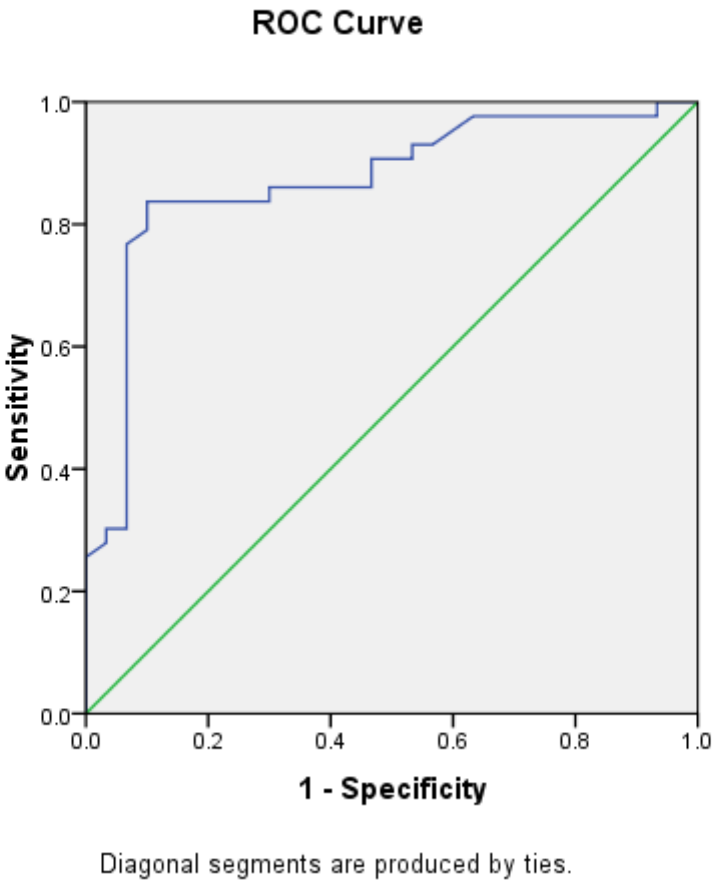
Table 2 Correlation between NLR and patients' characteristics

Item	**r**	**P**
Age	0,243	0,038
Sex	0,261	0,609
NPRS	0,394	<0,001

The analysis of correlations between NLR and patient characteristics (Table 2) revealed significant associations with several factors. NPRS demonstrated a strong positive correlation (r

= 0.394 p < 0.001), indicating that moderate pain score patients tend to have higher NLR inflammation.

Additionally, age (r = 0.243, p = 0.038) were positively correlated with higher NLR. In contrast, sex (r = 0,261, p = 0609) was not significantly correlated with NLR.



Receiver Operating Characteristic (ROC) curve was then generated to evaluate the predictive capability of NLR for pain severity. As shown in Figure 1, the Area Under the Curve (AUC) for NLR was 0.871 (95%CI 0,784-0,957; p = 0,000). The optimal cut-off value for NLR was 3,53, yielding Youden's index with a maximum sensitivity of 0,837 and specificity of 0.900, indicating that patients with NLR >3,53 had a significantly higher likelihood of pain score.

NLR data then categorized into high NLR (≥ 3,53) and normal NLR (<3,53), NPRS categorized into mild pain (0-3) and moderate-severe pain (4-10), age categorized into ≥ 65 years and < 65 years. Characteristic participants based on NLR cut-off value 3,53 showed in table 3.

Table 3. Characteristics subject on high and normal NLR

Variable		**High NLR(40)**	**Normal NLR (33)**	**P value**
Age (years)	Average,	59,02 (54,44-63,61)	53,20 (47,13-59,27)	

	Standard deviation	(p= 0,200)*	(p=0,169)*	
	Age ≥ 65 years	18 (45,0%)	8 (24,2%)	0,065
	Age < 65 years	22 (55,0%)	25 (75,8%)	
Sex (n, %)	Male	23 (57,5%)	17(51,5%)	0,609
	Female	17 (42,5%)	16 (48,5%)	
NPRS	Moderate (4-6)	36 (90,0%)	7 (21,2%)	<0,001
	Mild (1-3)	4 (10,0%)	26 (78,8%)	
Neutrophil count (10^9/L)	Average	6,54 (4,32-8,61) (p= 0,117)*	5,32 (3,01-8,10) (p=0,200)*	
Lymphocytes count (10^9/L)	Average	1,70 (1,10-2,81) (p=0,200)*	1,81 (1,12-2,65) (p=0,200)*	

**= test of Normality Kolmogorov-Smirnov*

The age in the high NLR group had a average data of 59,02 (54.44-63.61) years with normal data distribution (p= 0,200) while the average in the normal NLR group was 53,20 (47.13-59.27) and normal distributed data (p=0,169). Most of the high NLR groups are < 65 years old. The gender in the NLR group was high, mostly males, 23 males (55,0%) and 17 females (42,5%). The same was also found in normal NLR, with more participants 17 males (51.1%) and 16 females (48.5%). Both sex data were normally distributed (p= 0.609). The NPRS pain scale was felt by 36 patients with high NLR (90%), only 4 patients with high NLR felt moderate pain. The average value of neutrophils in the high NLR group was 6.54 (4.32-8.61), higher than the average value of normal NLR of 5.32 (3.01-8.10). The average value of lymphocytes in high NLR was 1.70 (1.10-2.81), lower than the normal NLR group of 1.81 (1.12-2.65). Neutrophil (p= 0.200) and lymphocyte (p= 0.200) data were normally distributed.

Table 4

Bivariate and Multivariate analysis of independent predictors of NPRS

Variables	**Moderate NPRS**	**Mild NPRS**	**Bivariate RR 95%CI(p)**	**Multivariate RR 95%CI(p)**
Age (years)				
Age ≥ 65 years	16 (37,2%)	10 (33,3%)	1,18 (0,44-3,15) (p= 0,734)	
Age < 65 years	27 (62,8%)	20 (66,7%)		
Sex (n, %)				
Male	24 (55,8%)	16 (53,3%)	1,10 (0,43-2,82) (p= 0,834)	
Female	19 (44,2%)	14 (46,7%)		
NLR				
High NLR	36 (83,7%)	4 (13,3%)	33,43 (8,86-126,14) (p< 0,001)**	
Normal NLR	7 (16,3%)	26 (86,7%)		
Neutrophil count (10^9/L)				
≥7,00	16 (37,2%)	3 (10,0%)	5,33 (1,39-20,44)	

< 7,00	27 (62,8%)	27 (90,0%)	(p= 0,009)***	
Lymphocyte count (10^9/L)				
< 1,70	27 (62,8%)	11 (36,7%)	2,91 (1.11-7.66) (p= 0,028)***	
≥1,70	16 (37,2%)	19 (63,3%)		

**Multivariate Logistic Regression Test

*** Chi-Square bivariate analysis

The results of the Chi-Square bivariate analysis between NPRS and the independent factor are presented in table 4 above. Age had no significant effect on the degree of pain (RR 1,18; p= 0,734). Similarly, sex also did not show an effect on pain (RR 1,10; p= 0,834). NLR had the most significant effect, namely high NLR increased the risk of 33, 43 LBP patients experiencing moderate pain (p= <0.001). Neutrophil values of 7, 00 x 10^9/L out of 5,33 times were also proven to increase the risk of moderate pain (p= 0, 009). A lymphocyte value < 1,70 x 10^9/L indicates a 2, 91 risk of experiencing moderate pain (p= 0, 028).

Based on the results of the multivariate analysis, it was found that the independent risk factor that was meaningful to pain was NLR. LBP patients with high NLR had a 33,43 times greater risk of moderate pain than LBP patients with normal NLR (RR=33.43; IK 95%=8.86-126.143; p< 0.001). Other independent risk factors, namely neutrophil and leucocyte, showed insignificant results on the outcome of treatment for patients with acute ischemic stroke, with a p> value of 0.05.

DISCUSSION

Our findings suggest that a high Neutrophil-to-Lymphocyte Ratio (NLR) is linked to moderate pain in low back pain. Multivariate analyses have confirmed that a high NLR is an independent risk factor for this condition. This connection is due to the pro-inflammatory state, which is a significant driver of disc degeneration, potentially speeding up both its onset and progression. Inflammatory cytokines prompt disc cells to produce chemokines, which attract macrophages, neutrophils, and T cells. Studies on disc degeneration and herniation have shown increased levels of specific chemokines, such as monocyte chemotactic protein-1 (MCP-1), CCL3, CCL4, MCP-3, C-X-C motif chemokine 10 (CXCL10), and IL-8. The release of cytokines draws immune cells, starts an inflammatory cascade, and worsens disc degeneration. Research has also found that higher levels of inflammatory cytokines are linked to discogenic low back pain. Additionally, systemic inflammation can affect treatment outcomes and postoperative results in patients with lumbar spine diseases. These findings highlight the crucial role of inflammatory cytokines and chemokines in attracting immune cells to the disc and surrounding tissues, which is a key step in the pain generation process. (10,11,13,14)

The inflammatory response involves various cell types, including immune cells like neutrophils and lymphocytes. Recent research has focused on the response of disc cell-produced cytokines to different environmental stressors and the importance of leukocyte ratios in various inflammatory conditions, such as smoking, abnormal mechanical load, cancer, diabetes, injury, and infection. Inflammatory indices, like the NLR and the Lymphocyte-to-

Monocyte Ratio (LMR), are calculated based on the counts of neutrophils, lymphocytes, and monocytes. Neutrophils are a primary cell type in the inflammatory response, capable of releasing inflammatory mediators and enzymes like interleukin-1b, tumor necrosis factor-a, and matrix metalloproteinases. Lymphocytes also participate in the inflammatory response and disc degeneration process, secreting cytokines such as interleukin-6 and tumor necrosis factor-a. (7,8,15)

Chi-Square bivariate analysis in this study showed that high neutrophil count and low lymphocyte count were independent risk factors for moderate pain. Elevated neutrophil counts and reduced lymphocyte counts emphasize the potential of NLR as a prognostic biomarker, with higher NLR values indicating greater systemic inflammation. According to the ROC curve predicting pain severity based on NLR, we found that patients with NLR >3,53 had more pain intensity. This existing correlation is clinically significant to a certain extent. The results also revealed a significant correlation between the severity of pain with age and NLR. Identifying risk factors for disc degeneration and its progression can help mitigate long-term prognosis and reduce the economic burden on patients, offering significant value for future medical practice.

NLR can reflect the inflammatory state in the body and is associated with low back pain, showing significant relations with age. With the progression of degeneration, the levels of inflammatory cytokines will increase, degradation of glycosaminoglycans and collagen will intensify, and changes in the phenotype of intervertebral disc cells will occur (16). This finding further emphasizes the importance of age factors in the prevention and management of disc degeneration.

Growing evidence indicates that the pathophysiology of chronic pain entails a complicated interaction between the neurological and immune systems, facilitated by both neuronal and non-neuronal cells (17). Circulating immune cells, including neutrophils, monocytes, and T cells, are attracted to areas of tissue injury and or inflammation and frequently infiltrate both the peripheral and central nervous systems (18,19). The activation of these cells leads to the synthesis of several inflammatory mediators, such as cytokines, chemokines, lipids, and proteases, which exert effects directly on peripheral sensory or central second-order neurons and indirectly on other immune or local cells to modulate pain. Microglia and astrocytes in the central nervous system act in a similar fashion, contributing to central sensitization and pain (20–23). The presence of these activated immune cells and glia, peripherally or centrally, is thought to contribute to the transition from acute to chronic pain(24–26).

Conclusion

This study's findings indicate a correlation between NLR and the severity of intervertebral disc degeneration, proposing NLR as a potential biomarker for the early detection of lumbar disc degeneration. This study's findings indicate a correlation between NLR and the severity of intervertebral disc degeneration, proposing NLR as a potential biomarker for the early detection of lumbar disc degeneration.

Nonetheless, it is crucial to recognise the constraints of this study. First, the retrospective design may introduce selection bias, as only patients with complete records were included, and information bias, as we relied on preexisting data. This limits our ability to control for all

confounding variables that could influence the results. Additionally, the cross-sectional nature of the data prevents us from evaluating the progression of lumbar disc degeneration and NLR changes over time. A longitudinal cohort prospective study would provide more insight into the dynamic relationship between NLR and disc degeneration and other pro-inflammatory variables such as body mass index (BMI), Diabetes Mellitus (DM), and others which can help determine whether NLR predicts future degeneration.

Despite these limitations, based on the results of this study, we can still posit that a single NLR test could be a reliable predictive marker for pain severity in chronic low back pain cases. More research is needed in the future to further validate our findings and ascertain their practical clinical implications that could help us better understand the role of inflammation in disc degeneration and provide new research directions for the prevention and treatment of related diseases.

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