

Relationship between neutrophil lymphocyte ratio and interleukin-17A levels with pain intensity and degree of herniated nucleus pulposus in low back pain patients

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Relationship between neutrophil lymphocyte ratio and interleukin-17A levels with pain intensity and degree of herniated nucleus pulposus in low back pain patients

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ABSTRACT

Background and Objectives. Low back pain (LBP) affects 80% of individuals globally and causes significant disability. Intervertebral disc disorders (IDDs), a major LBP contributor, result in chronic pain, impaired function, and economic challenges. Degenerative processes, inflammatory cytokines, and disrupted extracellular matrix play key roles in IDD pathology. This study aims to investigate the relationship between serum neutrophil-lymphocyte ratio (NLR) and interleukin-17A (IL-17A) levels in patients with LBP due to herniated nucleus pulposus (HNP), neuropathic, and nociceptive pain intensity.

Materials and Methods. This observational cross-sectional study was conducted in patients with HNP. HNP diagnosis is based on radiological findings. NRS assessment tool used to measure pain intensity. NLR was calculated from routine blood tests, and IL-17A levels were measured with an ELISA method.

Results. This study included 62 HNP patients, predominantly male (51.6%), with a mean age of 45.5 years. HNP severity showed extrusion (40.3%), protrusion (38.7%), and bulging (21.0%). Median NLR was 2.34, and IL-17A was 129.65 pg/mL. NLR correlated positively with nociceptive ($r = 0.472$) and neuropathic NRS ($r = 0.345$), while IL-17A correlated with nociceptive ($r = 0.518$)



and neuropathic NRS ($r = 0.390$). NLR significantly differed across HNP degrees ($p = 0.010$). However, IL-17A showed no significant result ($p = 0.144$).

Conclusions. Significant correlations were found between NLR levels and nociceptive/neuropathic pain NRS in HNP patients, and IL-17A levels. NLR varied significantly across HNP severity, suggesting its potential as a biomarker. However, IL-17A showed no significant relationship with HNP severity, indicating its role in inflammation rather than disease progression.

Keywords: Herniated nucleus pulposus, low back pain, neutrophil-lymphocyte ratio, interleukin-17A.

Abbreviations:

LBP – Low back pain,

IDDs – Intervertebral disc disorders,

NLR – Neutrophil-lymphocyte ratio,

HNP – Herniated nucleus pulposus,

CRP – C-reactive protein,

NP – Nucleus pulposus,

ESR – Erythrocyte sedimentation rates,

IL-17A – Interleukin-17A,

MRI – Magnetic resonance imaging,

BMI – Body Mass Index,

LDL-C – Low-density lipoprotein cholesterol,

HDL-C – High-density lipoprotein cholesterol,

AF – Annulus fibrosus,

NRS – Numeric Rating Scale,

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INTRODUCTION

Low back pain (LBP) is a prevalent condition affecting approximately 80% of the global population at some point in their lives. Despite an incidence rate of less than 1%, LBP has a prevalence of about 8% in primary healthcare settings worldwide and is the sixth leading cause of disability globally. Its incidence increases with age, peaking between 40 and 50 years and reaching the highest disability levels among individuals aged 80–84 years. Sex differences have also been observed, with females experiencing LBP more frequently than males [1,2].

Intervertebral disc disorders (IDDs), a primary contributor to LBP, significantly affect quality of life through chronic pain, functional limitations, and economic burdens. These disorders disrupt daily living and work efficiency, resulting in substantial economic challenges [3,4].



can cause chronic spinal instability by altering disc height and spinal mechanics, further intensifying pain and functional impairments [5]. Degenerative intervertebral disc processes, one of the leading causes of LBP, have an incidence rate of 26–49%. The degeneration begins in young adulthood and progresses with age, exacerbated by pathological injuries and changes in extracellular matrix (ECM) composition. Dysregulated ECM functions, mechanical loading, poor nutrient supply, genetics, smoking, obesity, diabetes, and atherosclerosis are significant contributors to this degeneration [6–8].

Pain in IDD is complex, involving structural abnormalities, mechanical deformities, and inflammatory mediator activity. Chronic pain often results from compressed spinal nerve roots, the proliferation of nociceptive nerve endings within degenerated discs, and continuous inflammatory mediator release. A critical factor in IDD development is the increased synthesis of pro-inflammatory cytokines. Cytokines released by nucleus pulposus (NP) cells, macrophages, neutrophils, and lymphocytes trigger degeneration, oxidative stress, autophagy, cellular senescence, and apoptosis. Imbalances in cytokine production and receptor expression exacerbate IDD pathology [9].

Recent studies have explored inflammatory biomarkers associated with IDD. For instance, Yilmaz et al. [10] identified the neutrophil-lymphocyte ratio (NLR) as an independent predictor of lumbar disc herniation. Similarly, Ethemoglu and Erkoç [11] reported elevated neutrophil counts, NLR, and C-reactive protein (CRP) levels in patients with cervical disc herniation compared to controls. Özcan-Eksi et al. [12] demonstrated that chronic LBP patients exhibited increased serum monocytes, basophils, and erythrocyte sedimentation rates (ESR). Furthermore, Xue et al. [13] found elevated interleukin-17A (IL-17A) levels in serum and intervertebral disc tissues correlated positively with LBP severity. Another study also revealed higher IL-17A expression in ruptured annulus fibrosus tissues than in intact ones [14]. These studies showed a relationship between NLR, IL-17A, pain intensity, and severity of herniated nucleus pulposus (HNP). However, studies showing a relationship between IL-17A, NLR, and herniated discs that relate to the severity of HNP, LBP exacerbation, and its relationship to nociceptive and neuropathic pain have not been available. This study aims to investigate the relationship between serum NLR and IL-17A levels in patients with LBP due to HNP, neuropathic, and nociceptive pain intensity, enhancing understanding of inflammation and its association with disease severity.

MATERIALS AND METHODS

This study employed an analytical observational approach with a cross-sectional design. Data collection was conducted from November 2024 until the required sample size is achieved. Samples were patients diagnosed with HNP at Wahidin Sudirohusodo General Hospital and its



affiliated hospitals. Sampling were collected with purposive sampling, in line with the study objectives, over the designated period.

Inclusion criteria include patients diagnosed with LBP due to HNP, confirmed through magnetic resonance imaging (MRI) examinations, who provide informed consent to participate. Exclusion criteria encompass LBP patients with underlying infectious, neoplastic, or autoimmune conditions; those consuming alcohol for pain relief; and individuals who have received NSAID or steroid therapy within the past 24 hours.

Body mass index (BMI)

The Body Mass Index (BMI) serves as a commonly used equation for evaluating obesity, determined by dividing weight in kilograms by the square of height in meters ($BMI = \text{weight}/\text{height}^2$) [15]. The BMI classification utilized in this research is based on the BMI categories set forth by the Indonesian Ministry of Health: obese ($BMI \geq 27.0 \text{ kg/m}^2$), overweight ($BMI \geq 25.0 - < 27 \text{ kg/m}^2$), normal weight ($BMI \geq 18.5 - < 24.9 \text{ kg/m}^2$), and underweight ($BMI < 18.5 \text{ kg/m}^2$) [16–18].

Herniated nucleus pulposus (HNP) Degree

HNP diagnosis is based on radiological findings, specifically identifying bulging, protrusion, extrusion, or sequestration of intervertebral discs. A radiological examination was performed using a General Electric Signa Pioneer 3.0 Tesla MRI (Illinois, USA). The results of the MRI examination were read by a radiology specialist, and then the diagnosis was made by a neurology specialist. Identification of the degree of HNP is following lumbar disc nomenclature 2.0 recommendations by the working group of the American Society of Spine Radiology, American Society of Neuroradiology, and North American Spine Society [19].

Heavy lifting

The patient had a history of lifting heavy loads while in a bent position, twisting, and subsequently experiencing back pain.

Smoking

Detailed medical history was obtained from the patient and their family to ascertain their exposure to cigarette smoke and to determine if they are smokers.

Hypertension

A diagnosis of hypertension is confirmed when the systolic blood pressure is equal to or greater than 140 mmHg and/or the diastolic blood pressure is equal to or greater than 90 mmHg [20], ongoing use of antihypertensive medication, or a prior diagnosis of hypertension made by a healthcare professional.

Diabetes mellitus (DM)

A diagnosis of diabetes is confirmed when a fasting blood glucose level reaches 126 mg/dL or higher following an 8-hour fasting period, a 2-hour postprandial blood glucose measurement is



200 mg/dL or above, a glycated hemoglobin level is 6.5% or greater, a random blood glucose test shows 200 mg/dL or more in conjunction with symptoms of hyperglycemia, the patient has a documented history of diabetes in the hospital's medical records, has received a prior diagnosis of diabetes from a healthcare professional, or is currently taking antidiabetic medications [21,22].

Hyperlipidaemia

Hyperlipidaemia is diagnosed by increased low-density lipoprotein cholesterol (LDL-C) at or above 130 mg/dL, increased triglyceride concentrations equal to or greater than 150 mg/dL, or decreased high-density lipoprotein cholesterol (HDL-C) levels below 40 mg/dL [23].

Numeric Rating Scale (NRS)

NRS is a validated pain assessment tool used to measure pain intensity, as reported by patients. It evaluates two primary pain components: (1) Nociceptive pain described as a dull, aching discomfort localized to the lower back; (2) Neuropathic pain (Radiculopathy) characterized as burning, electric-like, tingling, or sharp pain radiating along a spinal nerve dermatome. The scale ranges from 1 to 10, with higher scores indicating greater pain intensity [24–26].

Neutrophil-Lymphocyte Ratio (NLR)

NLR is calculated from routine blood test results performed using the Sysmex XN1000 (Hyogo, Japan) flow cytometry method. The device determines the levels of neutrophils and lymphocytes, and the ratio is derived by dividing the neutrophil count by the lymphocyte count.

Interleukin-17A (IL-17A)

IL-17A levels are measured from patient plasma samples using Thermo Scientific equipment and the ELISA (Enzyme-Linked Immunosorbent Assay) technique. The study utilized reagents from the Human Interleukin 17A ELISA Kit from Bioassay Technology Laboratory (Shanghai, China), catalog number E0047Hu.

Statistical Analysis

Data were analyzed using SPSS version 27.0. Categorical variables were presented as frequency (n) and percentage (%), while numerical data were summarized as mean±SD or median (min–max). Data normality was assessed with the Kolmogorov-Smirnov test. Spearman correlation analysis was used to examine relationships between variables, while group differences were analyzed using the Kruskal-Wallis test, followed by post-hoc Dunn's tests for multivariate analysis. Statistical significance was set at a p-value < 0.05.

RESULTS

A total of 62 patients with low back pain due to HNP met the inclusion criteria for this study. The sample included a slightly higher proportion of males (51.6%) compared to females (48.4%). The mean patient age was 45.5 years, with the largest age group being 26–45 years (46.8%). The BMI distribution among participants was predominantly normal (41.9%), followed

by pre-obesity (22.6%), obesity I (21.0%), and obesity II (9.0%). Regarding the degree of HNP, the majority of patients presented with extrusion (40.3%), followed by protrusion (38.7%) and bulging (21.0%), while no cases of sequestration were observed. Comorbid conditions among the subjects included hypertension (30.6%), hyperlipidemia (17.7%), diabetes mellitus (6.5%), smoking (16.1%), and a history of heavy lifting (88%) (Table 1).

Median NLR value was 2.34, with a range of 0.60 to 9.61. Median IL-17A level was 129.65 pg/mL, with a range of 32.5 to 808.11 pg/mL. For the NRS assessments, the median nociceptive NRS was 4 (range: 1–9), and the median neuropathic NRS was 6 (range: 0–9) (Table 2).

A significant positive correlation between NLR and nociceptive NRS ($r = 0.472$; $p = 0.000$) (Figure 1A) as well as neuropathic NRS ($r = 0.345$; $p = 0.006$) (Figure 1B). Similarly, IL-17A levels showed a significant positive correlation with nociceptive NRS ($r = 0.518$; $p = 0.000$) (Figure 2A) and neuropathic NRS ($r = 0.390$; $p = 0.002$) (Figure 2B).

NLR values stratified by HNP severity were as follows: bulging (median: 2.15; range: 0.60–3.99), protrusion (median: 2.06; range: 0.81–4.15), and extrusion (median: 3.00; range: 1.33–9.61) (Table 3). A multivariate test revealed significant differences between the protrusion and extrusion groups ($p = 0.0149$), while no significant differences were found between bulging and protrusion ($p > 0.9999$) or bulging and extrusion ($p = 0.0853$) (Figure 3A). The overall change in NLR across HNP categories was statistically significant ($p = 0.010$), indicating a relationship between NLR and HNP severity, particularly between protrusion and extrusion groups ($p = 0.0149$) (Figure 3A).

Analysis of IL-17A levels across HNP severity revealed no statistically significant relationship ($p = 0.144$). Median IL-17A values were as follows: bulging (114.06 pg/mL; range: 85.05–238.81), protrusion (129.65 pg/mL; range: 32.50–458.21), and extrusion (139.77 pg/mL; range: 94.67–808.11) (Table 3). Multivariate comparisons of IL-17A levels among HNP degrees yielded non-significant results: bulging vs. protrusion ($p = 0.541$), protrusion vs. extrusion ($p > 0.9999$), and bulging vs. extrusion ($p = 0.1475$) (Figure 5B).

DISCUSSION

The majority of patients presented with extrusion HNP, and the most common comorbid conditions were hypertension and hyperlipidemia. The study found a significant positive correlation between NLR and IL-17A levels with NRS assessments. NLR values were significantly different between protrusion and extrusion groups, indicating a relationship between NLR and HNP severity. This study had a slightly higher proportion of males (51.6%) than females (48.4%). This aligns with findings from the World Federation of Neurosurgical Societies, identifying male as a risk factor for HNP [27]. However, other studies suggest a higher prevalence of HNP-related back pain in females [1,2]. The mean age of participants was 45.5 years, with the majority aged 26–45 years. This is consistent with prior research, which indicates that HNP frequently affects



individuals aged 40–50 years [1,2]. BMI in this study was predominantly within the normal range (41.9%). Most patients (88%) reported a history of heavy lifting, a known risk factor for HNP due to repetitive mechanical loading and flexion-twisting movements [27,28]. Comorbidities among participants included hypertension (30.6%), hypercholesterolemia (17.7%), smoking (16.1%), and diabetes mellitus (6.5%). Smoking has been linked to increased pro-inflammatory stress responses in nucleus pulposus (NP) and annulus fibrosus (AF) tissues, promoting intervertebral disc degeneration [29]. Similarly, diabetes alters intervertebral disc proteoglycan content and slows AF tissue healing, which are predictors of recurrent HNP [30]. Hyperlipidemia, characterized by low HDL and elevated LDL/triglyceride levels, correlates with the severity of HNP [31].

This study observed significant correlations between NLR and both nociceptive and neuropathic NRS scores. NLR, derived from the neutrophil-to-lymphocyte ratio in blood, serves as a biomarker of systemic inflammation [32]. IL-17A, a pro-inflammatory cytokine, also correlated with NRS scores. IL-17A has been implicated in enhancing nociceptive excitability and contributing to hyperalgesia through inflammatory processes, as well as promoting neuropathic pain via astrocyte activation and cytokine secretion [33–36].

NLR levels varied across HNP severity categories: bulging [2.15 (0.60–3.88)], protrusion [2.06 (0.81–4.15)], and extrusion [3.00 (1.33–9.61)]. These findings are consistent with studies demonstrating increased NLR in severe disc degeneration and suggest its potential as a biomarker for assessing HNP severity [10,37]. Conversely, no significant relationship was found between serum IL-17A levels and HNP severity. Prior research has identified elevated IL-17A in local disc tissues of HNP patients, suggesting its role in the inflammatory processes associated with low back pain rather than the direct development of HNP [13,35,38].

The study's strengths include the balanced gender distribution of the samples, which reduces the risk of bias. During the examination, we differentiated between nociceptive and neuropathic pain complaints to assess the relationship between NLR, IL-17A, and nociceptive and neuropathic pain. The limitation of this study is that the routine blood tests were performed at different times, which may have introduced variability in the results. Additionally, the absence of sequestered HNP samples in our study limited our ability to compare NLR, IL17A levels, and the severity of HNP.

CONCLUSION

This study demonstrates a significant relationship between NLR levels and both nociceptive pain and neuropathic pain NRS in patients with low back pain attributable to HNP. Similarly, IL-17A levels are correlated with nociceptive and neuropathic pain NRS in the same patient population. Notably, there are significant differences in NLR levels across varying degrees of HNP



severity, suggesting its potential as a biomarker for assessing disease progression. However, no significant relationship was identified between IL-17A levels and the degree of HNP, indicating that IL-17A may play a more prominent role in the inflammatory processes associated with pain rather than directly influencing HNP severity.

CONFLICT OF INTEREST: none declared

AUTHOR'S CONTRIBUTIONS: FR (Concept, Design, Resources, Materials, Data Collection and Processing, Analysis and Interpretation, Literature Search, Writing Manuscript). JT (Concept, Design, Supervision, Analysis and Interpretation, Literature Search). SA (Concept, Design, Supervision, Analysis and Interpretation, Literature Search). ADW (Concept, Design, Critical Review). MIB (Concept, Design, Analysis and Interpretation, Critical Review). MYA (Concept, Design, Analysis and Interpretation, Critical Review). AAZ (Concept, Design, Analysis and Interpretation, Critical Review).

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INFORMED CONSENT: informed consent was obtained from all participants in the study.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: The study was approved by the Ethics Review Committee of the Dr. Wahidin Sudirohusodo, Makassar, Indonesia under reference number 31076/UN4.6.8/PT.01.04/2024.



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TABLES

Table 1. Study characteristics

Variables	n (%)
Sex	
Males	32 (51.6)
Females	30 (48.4)
Age (years)	
12-25	5 (8.1)
26-45	29 (46.8)
46-59	17 (27.4)
≥60	11 (17.7)
BMI	
Normal	26 (41.9)
Pre-obesity	14 (22.6)
Obesity I	13 (21.0)
Obesity II	9 (14.5)
HNP Degree	
Bulging	13 (21.0)
Protrusion	24 (38.7)
Extrusion	25 (40.3)
Heavy lifting	
Yes	55 (88.0)
No	7 (12.0)
Smoking	
Yes	10 (16.1)
No	52 (83.9)
Hypertension	
Yes	19 (30.6)
No	43 (69.4)
Diabetes mellitus	
Yes	4 (6.5)
No	58 (93.5)
Hyperlipidaemia	
Yes	11 (17.7)
No	51 (82.3)



Note: HNP, Herniated nucleus pulposus; BMI, Body Mass Index,



Table 2. Baseline characteristics of NRS scale, NLR, IL-17A

Variables	Mean \pm SD	Median (min-max)
NRS Nociceptive	4.18 \pm 1.66	4.00 (1.00-9.00)
NRS Neuropathic	4.79 \pm 2.57	6.00 (0.00-9.00)
NLR	2.67 \pm 1.63	2.34 (0.60-9.61)
IL-17A	173.87 \pm 130.42	129.65 (32.50-808.11)

Note: NRS, Numeric Rating Scale; NLR, Neutrophil-lymphocyte ratio; IL-17A, interleukin-17A.



Table 3. Comparison of NLR and IL-17A with HNP Degree

Variable	Degree of HNP median (min-max)			p-value
	Bulging	Protrusion	Extrusion	
NLR	2.15 (0.60-3.99)	2.06 (0.81-4.15)	3.00 (1.33-9.61)	0.010
IL-17A	114.06 (85.05-238.81)	129.65 (32.50-458.21)	139.77 (94.67-808.11)	0.144

Note: NLR, Neutrophil-lymphocyte ratio; IL-17A, interleukin-17A; HNP, Herniated nucleus pulposus.



FIGURES

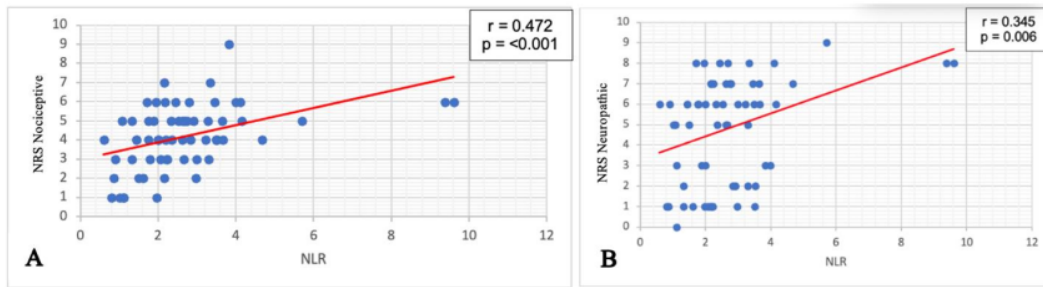


Figure 1. Distribution of NLR to NRS Nociceptive (A) and Neuropathic (B).

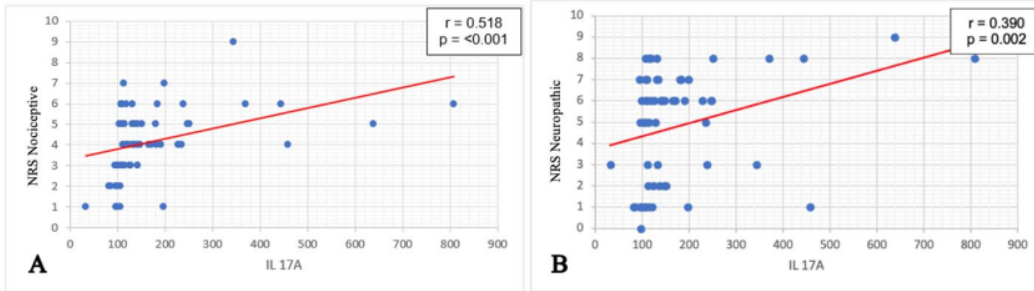


Figure 2. Distribution of IL-17A to NRS Nociceptive (A) and Neuropathic (B).

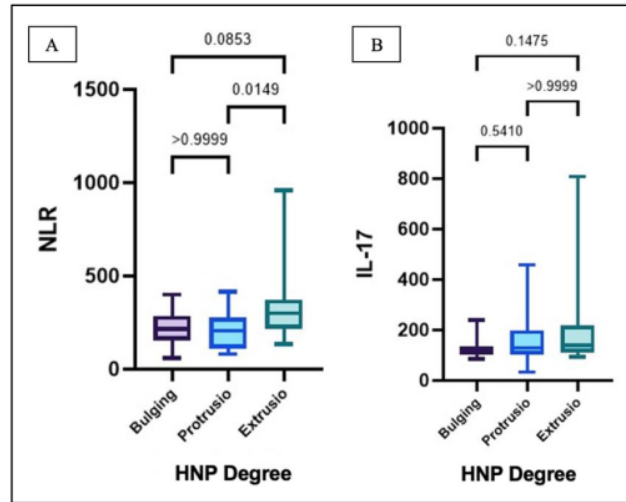


Figure 3. Comparison between NLR (A) and IL-17A (B) with HNP Degree.