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Research Article

THE UTILITY OF HEMATOLOGICAL INDICES AT THE INITIAL ADMISSION TO THE NEUROSURGERY CLINIC IN CERVICAL DISC HERNIATION

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ABSTRACT

Objective: This study aimed to investigate hematological indices to predict spontaneous regression in patients with cervical disc herniation (CDH) during the initial visit to outpatient clinics.

Materials and Methods: This retrospective study was carried out at a single center by reviewing laboratory parameters to assess the outcomes of CDH patients. The cohort consisted of patients with CDH who had undergone surgery, those who had undergone conservative treatment and achieved spontaneous regression, and a control group without CDH. The laboratory data consisted of the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune-inflammatory index (SIII).

Results: Differences in the NLR, MLR, and SIII were statistically significant across groups ($p<0.001$). Compared with the spontaneous regression and control groups, the surgical intervention group presented significantly greater NLR, MLR, and SIII values. According to the comparison of the patients with CDH in terms of the level of herniation, there were no significant differences at the C4-C5 and upper levels, whereas there was a statistically significant increase in the NLR, MLR, and SIII in the surgical intervention group compared with the spontaneous regression group at the C6-C7 level ($p = 0.015$, $p<0.001$, and $p = 0.003$, respectively).

Conclusion: This study provides valuable insights into the use of hematological indices to predict the need for surgical intervention in CDH patients. The observed associations emphasize their practical use, providing a way for further research and their inclusion in routine diagnostic protocols for CDH management.

Keywords: cervical disc herniation, inflammation, systemic immune-inflammatory index, neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio

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INTRODUCTION

Cervical radiculopathy refers to functional impairment in a specific area of the upper extremity caused by irritation or compression of the cervical spinal nerve root. Cervical disc herniation (CDH), or cervical disc disease, is the disturbance and displacement of the gel-like disc structure located between the cervical vertebrae, causing compression in the spinal canal and foramina. There are 85 cases of cervical radiculopathy per 100,000 people worldwide, and 20–25% of these cases are caused by CDH (1). Cervical radiculopathy is more commonly observed in males, peaking between 50 and 54 years of age. Patients who have chronic pain that is resistant to medical treatment for longer than six weeks and who also experience weakness in their arms and legs as a result of the involvement of arm-extending nerves necessitate surgery (2). Although spontaneous regression is a common occurrence in the lumbar area, it has also been noted to occur in the cervical region, with a rate of approximately 40% for improving CDH (3, 4). Three mechanisms for spontaneous regression have been described in the literature. First, the herniated portion progressively loses water content, contracts, and withdraws into the intervertebral space. Second, the herniation is helped to retract by the posterior longitudinal ligament, which is situated between the cartilaginous tissue and the spinal canal. Third, when the herniation advances into the epidural region, an inflammatory reaction results in enzymatic breakdown and phagocytosis, which slow cartilaginous tissue absorption and encourage neovascularization. According to several recent articles, the third mechanism is more likely to be the dominant process (5-8). The intriguing interaction of inflammatory responses resulting in enzymatic breakdown and neovascularization are some of the proposed mechanisms that hold great promise for further investigation in the field of spinal health research. Understanding the intricate underpinnings of these systems may provide new insights into therapeutic targets and treatment approaches for people with such diseases.

The subparameters of the hemogram, such as the neutrophil, lymphocyte, monocyte, and platelet counts, can be used to determine a variety of different ratios that can be used to assess inflammation and the immune response. Hematologically calculated indices depict a wide range of immune pathways and cell functions (9, 10). These calculated indices offer important information about the inflammatory and immunological conditions of patients. These ratios may help with the diagnosis, prognosis, and follow-up of

various diseases and conditions marked by altered immune responses and inflammation by revealing the balance and interactions between various immune cell populations. As a result, the hemogram and the ratios derived from it are extremely important in clinical practice, helping medical professionals make wise decisions and provide individualized patient care (11, 12). The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammatory index (SIII) are all signs of systemic inflammation in a number of diseases (13, 14).

The goal of this study was to ascertain whether the NLR, MLR, PLR, and SIII parameters might be used to predict spontaneous regression in patients with CDH at the time of their initial admission to the neurosurgical clinic.

MATERIALS AND METHODS

This study was designed retrospectively and conducted in a single center at Çanakkale Onsekiz Mart University Hospital. The scientific ethics committee of Çanakkale Onsekiz Mart University approved the study with a decision dated May 4, 2023, and numbered 06/16, and it was then carried out under the principles of the Helsinki Declaration.

Patient selection

Patients with CDH who attended the neurosurgery outpatient clinics at Çanakkale Onsekiz Mart University Hospital between April 1, 2020, and April 1, 2023, made up all of the study participants over the age of 18. Three groups of patients were formed by scanning hospital archive records. The first group consisted of patients who underwent single-level anterior microdiscectomy due to CDH. Patients with CDH who were eligible for single-level surgery but were unable to undergo surgery were included in the second group. During normal follow-up, however, they exhibited spontaneous regression with medical treatment. The control group included patients who complained of neck pain at the time of admission, had routine blood tests, and had no evidence of CDH on cervical magnetic resonance imaging (MRI). The exclusion criteria for

the study included those with cervical spondylosis, those with a history of previous spinal surgery, multilevel CDH, diabetes mellitus, active infections, rheumatological conditions, cervical spondylotic myelopathy, chronic obstructive pulmonary disease, osteoporosis, malignancy, hypertension, and cardiovascular disease. The control group was subjected to the same exclusion criteria. The demographic details of the patients, including age, sex, clinical findings, cause of surgery, type of surgery, and hemogram parameters, were retrieved from the hospital's medical records.

Laboratory analysis

For the surgical intervention, spontaneous regression, and control groups, laboratory data were gathered at the time of the patient's initial admission to the outpatient clinic without the use of any analgesics, anti-inflammatory medications, or muscle relaxants for the management and treatment of pain. The complete blood cells were analyzed on a Mindray BC6200 automated hematology analyzer (Mindray Biomedical Electronics, Shenzhen, China). To determine the NLR, MLR, and PLR, the absolute neutrophil count was divided by the absolute lymphocyte count. The same was done for the absolute monocyte cell counts by the absolute lymphocyte cell counts, and so on for the absolute platelet cell counts by the absolute lymphocyte cell counts. The SIII was calculated with the following formula: platelet count × neutrophil count/lymphocyte count.

Statistical analysis

The total sample size needed to reach 80% power with a 95% confidence interval and a 0.25 effect size was 159 cases, according to the G*Power program (v3.1.9.7). SPSS v17.0 (SPSS for Windows, Chicago, IL, USA) and Jamovi Project v2.3 (2022) were used to carry out the statistical analyses. The Shapiro–Wilk test was used to check whether the data distribution was normal. The median (1st quartile-3rd quartile) was used to represent continuous data without a normal distribution, and the mean ± standard deviation (SD) was used to represent data with a normal distribution. Numbers (percentages) were used to summarize categorical variables, and the chi-square test or Fischer's exact test was used to compare them. One-way analysis of

variance for parametric data was used to compare the differences between groups. The homogeneity of variances was tested with Levene's test. Tukey's test or the Games-Howell test was used for post hoc analysis. Kruskal–Wallis and Dwass–Steel–Critchlow–Fligner pairwise comparisons were used for nonparametric data. Independent sample t tests or Mann–Whitney U tests were used to compare the surgical intervention and spontaneous regression groups according to the level of herniation. The cutoff values of the NLR, MLR, and SIII were detected via receiver operating characteristic (ROC) analysis, and the area under the curve (AUC) values were calculated. The effect size was calculated for the identified differences in the analyses and interpreted according to Cohen's (1988) classification. A p value of less than 0.05 was used to indicate statistical significance.

RESULTS

Table 1. Demographic results of participants

Variable	Surgical intervention (n=64)	Spontaneous regression (n=64)	Control (n=65)	p-value*
Age, years	47 (42-57)	44 (39-50)	43 (38-52)	0.054
Gender				0.851
Female, n (%)	31 (48.4%)	34 (53.1%)	32 (49.2%)	
Male, n (%)	33 (51.6%)	30 (46.9%)	33 (50.8%)	
Level of herniation				0.741
C3-C5, n (%)**	11 (17.2%)	12 (18.8%)		
C5-C6, n (%)	32 (50.0%)	35 (54.7%)		
C6-C7, n (%)	21 (32.8%)	17 (26.6%)		

*p<0.05 was considered significant. **C3-C5 represents C3-C4 and C4-C5 levels of herniation. Continuous data was expressed as the median (1st quartile-3rd quartile). Categorical data was expressed as number (percentage).

There were 64 (33.2%) patients who underwent surgery for CDH in the surgical intervention group, and the same quantity was true in the spontaneous regression group. The control group consisted of 65 (33.6%) patients. Among the participants, 96 (49.7%) were male. Among the males, 33 (51.6%) were in the surgical intervention group, 30 (46.9%) were in the spontaneous regression group, and 33 (50.8%) were in the control group. All the patients with CDH presented with single-level herniation. Tables 1 and 2 present participant demographics along with laboratory findings.

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Table 2. Test results of participants in surgical treatment, spontaneous regression, and control groups

Parameters	Surgical intervention (n=64)	Spontaneous regression (n=64)	Control (n=65)	p value*	Effect size**
NLR	2.42±0.79	1.95±0.57	1.93±0.44	<0.001	0.120
MLR	0.27 (0.21-0.34)	0.20 (0.17-0.23)	0.19 (0.17-0.22)	<0.001	0.274
PLR	126 (103-159)	123 (105-148)	130 (106-157)	0.574	0.009
SIII	630±156	541±193	522±159	<0.001	0.073

*p<0.05 was considered significant. ** η^2 was used for effect size. η^2 results represented 0.14 large, 0.06 medium and 0.01 small effects. Normally distributed data was expressed as the mean ± standard deviation. Non-normally distributed data were expressed as the median (1st quartile-3rd quartile). NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SIII, systemic immune-inflammatory index

The NLR, MLR, and SIII were significantly different (p<0.001) between the groups, whereas the PLR did not differ between the groups (p=0.574). A moderate effect size was observed for the NLR and SIII, whereas a large effect size was observed for the MLR. The differences in the NLR, MLR, and SIII between the spontaneous regression group and the control group were not statistically significant (p=0.971, p=0.831, and p=0.804, respectively). Compared with those in the spontaneous regression group, the NLR, MLR, and SIII in the surgical intervention group were significantly greater (p<0.001, p<0.001, and p=0.009, respectively). The NLR, MLR, and SIII were significantly greater in the surgical intervention group than in the control group (p<0.001) (Figure 1a-c).

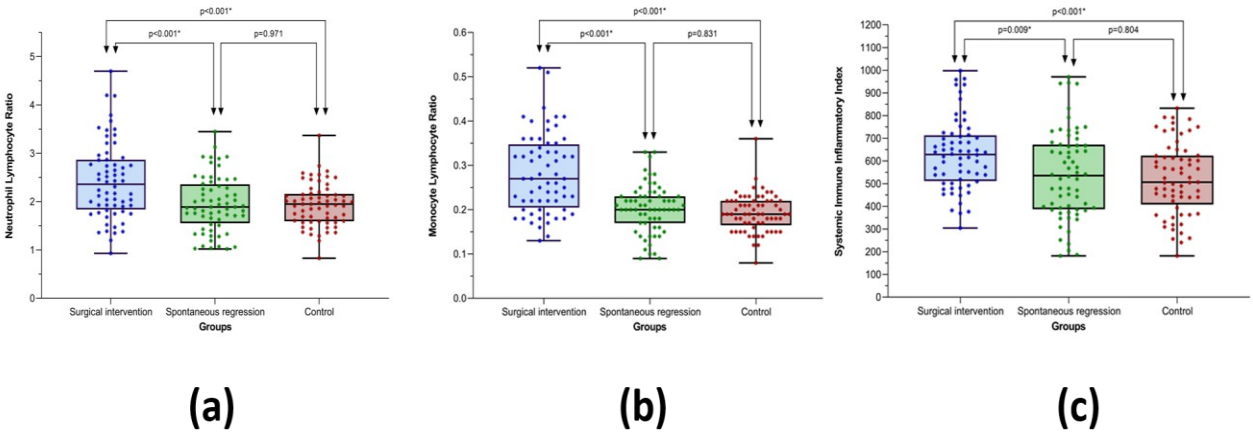

Figure 1. (a)Neutrophil-to-lymphocyte ratios in the surgical treatment, spontaneous regression and control groups, (b) Monocyte-to-lymphocyte ratios in the surgical treatment, spontaneous regression and control groups, (c) Systemic immune inflammatory index in the surgical treatment, spontaneous regression and control groups

When the surgical intervention and spontaneous regression groups were compared according to the level of herniation, no statistically significant difference was observed in any parameter at the C4-C5 and upper levels ($p<0.05$). When the two groups were compared at the C5-C6 level, the surgical intervention group had significantly greater NLRs and MLRs ($p=0.002$, and $p<0.001$, respectively). At the C6-C7 level, compared with those in the spontaneous regression group, the NLR, MLR, and SIII in the surgical intervention group were significantly greater ($p=0.015$, $p<0.001$, and $p=0.003$, respectively) (Table 3). The ROC analysis revealed that the NLR cutoff value for predicting surgery was 2.51, with an AUC of 0.683 (95% CI 0.600–0.767) and values of 43.8% for sensitivity, 87.6% for specificity, 63.6% for positive predictive value (PPV), and 75.8% for negative predictive value (NPV). The MLR had a cutoff value of 0.25 and an AUC of 0.778 (95% CI 0.704- 0.852), with a sensitivity of 57.8%, a specificity of 89.9%, a PPV of 74%, and an NPV of 81.1%. A cutoff value of 447 with a sensitivity of 92.2%, a specificity of 35.7%, a PPV of 41.5%, and an NPV of 90.2% was found for SIII (AUC=0.658, 95% CI 0.581- 0.736). The findings of the ROC curve analysis are summarized in Table 4, and Figure 1(c) illustrates the ROC curve analysis of the NLR, MLR and SIII for predicting surgical intervention.

Table 3. Test results of the patients in surgical treatment and spontaneous regression groups according to herniation level

Parameters	Herniation level	Surgical intervention	Spontaneous regression	p value*
NLR	*C3-C5***	2.05 (1.79-2.30)	2.09 (1.80-2.31)	1.000
	C5-C6	2.40±0.59	1.97±0.54	0.002
	C6-C7	2.52 (1.75-3.48)	1.76 (1.33-2.15)	0.015
MLR	*C3-C5***	0.22 (0.19-0.25)	0.22 (0.17-0.26)	1.000
	C5-C6	0.28±0.08	0.19±0.05	<0.001
	C6-C7	0.32 (0.22-0.36)	0.21 (0.20-0.23)	<0.001
PLR	*C3-C5***	124 (108-136)	111 (105-136)	0.712
	C5-C6	121 (103-150)	122 (103-145)	0.821
	C6-C7	138 (109-169)	126 (107-156)	0.411
SIII	*C3-C5***	615 (511-685)	595 (516-668)	0.880
	C5-C6	628±162	551±199	0.087
	C6-C7	647 (552-720)	453 (346-672)	0.003

*p<0.05 was considered significant. **C3-C5 represents C3-C4 and C4-C5 levels of herniation. Normally distributed data was expressed as the mean ± standard deviation. Non-normally distributed data were expressed as the median (1st quartile-3rd quartile). NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SIII, systemic immune-inflammatory index

Table 4. ROC analysis of NLR, MLR and SIII to predict the surgery indication at first admission

Parameters	Cutoff	AUC	95% CI	Sensitivity	Specificity	PPV	NPV	p value
NLR	2.51	0.683	0.600-0.767	43.8%	87.6%	63.6%	75.8%	<0.001
MLR	0.25	0.778	0.704-0.852	57.8%	89.9%	74.0%	81.1%	<0.001
SIII	447	0.658	0.581-0.736	92.2%	35.7%	41.5%	90.2%	<0.001

ROC, reciever operating characteristics; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SIII, systemic immune-inflammatory index; AUC, area under curve; CI, confidence intervals; PPV, positive predictive value; NPV, negative predictive value

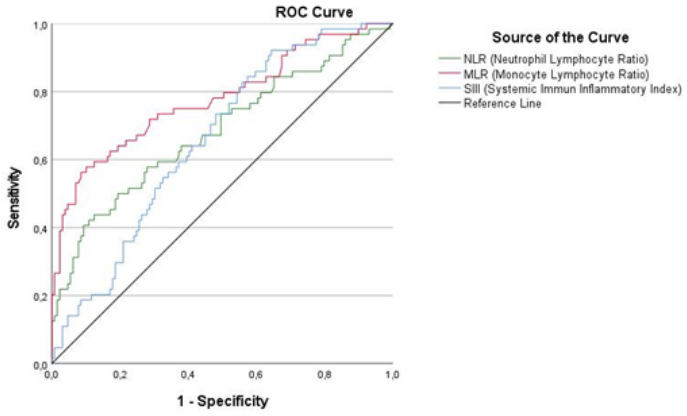

Figure 2 Receiver operating characteristic curves of the neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and systemic immune-inflammatory index

DISCUSSION

This study provides valuable insights into the potential clinical usefulness of inflammatory markers, particularly the NLR, MLR, and SIII, in determining the most suitable treatment approach for CDH. This study aimed to investigate noninvasive and easily accessible biomarkers that could assist in predicting the clinical outcomes of CDH, particularly in determining the necessity of surgical intervention or the option of medical follow-up. In accordance with the currently available literature, this study is the first to investigate hematological indices to predict spontaneous regression in CDH patients.

The pathogenesis of numerous spinal disorders involves inflammation to varying degrees. Although previously believed to be primarily mechanical or degenerative, inflammation is also present in conditions such as disc herniation (15). Although inflammation has historically been thought of predominantly as detrimental and linked to the evolution of the disease, it is still unclear whether it is a cause or an effect of

intervertebral disc degeneration and herniation. As recently proposed for other tissues, restoring intervertebral disc degeneration function may necessitate a balanced inflammatory response (16, 17). Induced degenerative discs release proinflammatory chemokines, chemokine ligand 5, and chemokine ligand 6. Chemokine ligand 5 has been associated with discogenic back pain (18). Xue et al. compared 34 patients with lumbar disc herniation (LDH) and 20 healthy controls and reported that LDH patients had significantly elevated serum levels of interleukin (IL)-21 and IL-17 compared with healthy controls. Disc tissues from individuals with LDH exhibited elevated expression levels of IL-21, IL-17, and cyclooxygenase-2 (19). Kang et al. revealed that the levels of nitric oxide, IL-1, IL-6, and tumor necrosis factor alpha were significantly greater in the cervical disc tissues of patients suffering from discogenic neck pain than in those of symptomatic and healthy controls (20).

However, the process of testing these markers is more complex, costly, and uncommon for use daily. In contrast, we used SIII, NLR, and MLR values calculated from hemogram tests in our study to measure inflammation in CDH patients. The distinct patient groups presented significant differences in the NLR, MLR, and SIII, indicating the potential value of these inflammatory markers in identifying CDH-related variations. The effect size analyses, which range from moderate to high, highlight the robustness of these associations and emphasize their clinical importance. Group comparisons between surgical intervention and spontaneous regression, as well as between surgical intervention and control groups, revealed specific patterns in these inflammatory markers. In contrast to the spontaneous regression and control groups, the surgical intervention group presented notable increases in the NLR, MLR, and SIII. Upon eliminating potential inflammatory diseases, the NLR and MLR had specificities of over 87% for both indices at the optimal cutoff values for predicting surgical intervention, as determined by ROC analysis. Despite the low specificity of SIII, it exhibited a sensitivity of 92.2%. These results imply that these markers may serve as indicators necessitating surgical intervention, offering clinical decision-makers useful information at initial patient admission.

Several studies have investigated the relationships between inflammatory biomarkers and LDH in the literature. Yılmaz et al. recently reported that the NLR was a standalone predictor in patients with LDH and low back pain (21). Similarly, a study by Bozkurt et al. revealed that patients with LDH had more pain before

and after surgery, especially when their NLRs were higher, which is a known sign of inflammation (22). In contrast to controls, Sugimori et al. reported that patients with LDH had significantly higher mean levels of high-sensitivity CRP. Notably, they reported no discernible association between the level of herniation in question and high-sensitivity CRP levels (23).

Studies examining CDH and inflammation, however, are relatively uncommon. Previously, 126 individuals with neck pain were examined, and particular characteristics were identified in patients with CDH. The CDH group presented significantly greater leucocyte counts, neutrophil counts, NLRs, and C-reactive protein (CRP) levels than did the normal cervical MRI patients with neck pain and healthy controls. Notably, multilevel CDH patients had a significantly greater NLR than controls did. These results suggest a link between the development of CDH and the inflammatory response. Higher NLRs and CRP levels may act as warning signs and prompt early protective measures against disc degeneration and CDH. The importance of these inflammatory markers in understanding and perhaps lowering the risk of CDH is emphasized by the few comparable studies that have been carried out (24). Our study differs from other previously published studies in that it makes comparisons on the basis of the CDH level. The lack of significant differences at the C4-C5 and upper levels and the distinct variations at the C5-C6 and C6-C7 levels highlight the importance of considering specific anatomical locations in the assessment of CDH. These results suggest that herniation at C4-C5 and upper levels is most likely related to a mechanical or degenerative etiology, whereas herniation at lower levels is likely to have an inflammatory etiology.

The study's limited sample size and retrospective approach were the primary limitations. Even though we excluded patients with acute and chronic inflammatory diseases from the study during the patient selection process, the study's findings might have been impacted by an inflammatory condition that the patient may have had but did not disclose in the archived records. Another drawback of this study was the lack of access to postoperative follow-up tests to examine the status of systemic inflammatory responses in CDH patients in the surgical intervention and spontaneous regression groups.

CONCLUSION

This study offers critical new understanding of the diagnostic potential of inflammatory markers, particularly the NLR, MLR, and SIII, in determining whether surgical intervention in CDH patients is likely. These markers are candidates to become helpful parameters in clinical decision-making and provide clinicians with more tools to customize patient care in the context of CDH. Although more research is necessary to validate and improve these findings, the observed associations highlight their clinical relevance and suggest potential integration into routine diagnostic protocols for CDH management.

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Authorship contributions

Surgical and medical practices: AA, ÜAM; Concept: HYÇ, AA; Design: HYÇ, AA; Data collection and processing: HYÇ, ÜAM, SA; Analysis and interpretation: HYÇ; Literature search: AA, ÜAM, SA; Writing: HYÇ, SA, AA

Data availibity statement

The data of the study will be provided by the corresponding author upon request.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Ethics

The scientific ethics committee of Çanakkale Onsekiz Mart University approved the study, with the decision dated 04.05.2023 and numbered 06/16.

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