CLINICAL STUDY

# Value of neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio and red blood cell distribution width in distinguishing between reactive lymphadenopathy and lymphoma in children

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**ABSTRACT**

OBJECTIVES: The aim of our study was to assess the diagnostic value of neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and red blood cell distribution width (RDW) in children with lymphadenopathy (LAP).

METHODS: Between January, 2009 and December, 2018, 190 children who underwent excisional lymph node biopsy due to enlarged lymph nodes were included. The clinical and laboratory features of pediatric patients with lymph node enlargement, histopathological examination of the lymph node, and the role of complete blood count parameters in the differentiation of reactive and malignant LAP were analyzed retrospectively.

RESULTS: In total, 139 (73.2 %) children had pathologically confirmed reactive LAP and 51 (26.8 %) were diagnosed with lymphoma. Compared with the reactive LAP group, median values for NLR, MLR, PLR, and RDW were significantly higher in children with lymphoma (p < 0.01). According to receiver operating characteristic curve analysis performed for distinguishing between reactive LAP and lymphomas, the area under curves of NLR, MLR, PLR, and RDW were 0.75, 0.76, 0.71, and 0.61, respectively.

CONCLUSIONS: Children with histologically proven lymphoma have higher NLR, MLR, PLR, and RDW values than children with reactive LAP. NLR, MLR, PLR, and RDW tests, which can be performed even in primary health care centers, may be useful markers to determine which patients with LAP should be referred to the advanced center at an early stage for biopsy *(Tab. 4, Fig. 2, Ref. 26)*. Text in PDF *www.elis.sk*.

KEY WORDS: lymphadenopathy, lymphoma, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, red blood cell distribution width.

## Introduction

Because children's immune systems are constantly stimulated by environmental antigens and microorganisms, their lymph nodes are often palpable. The prevalence of lymphadenopathy (LAP) varies according to age and regional location of lymph node (1, 2). Small occipital and postauricular lymph nodes are common in infants, but not in older children. Cervical and inguinal lymph nodes are more common after 2 years of age than in the first six months of life (2). Epitrochlear and supraclavicular adenopathy are rarely seen at any age. LAP was reported in 44 % of healthy children younger than 5 years and 64 % of children evaluated for

disease (2, 3). LAP can be classified as either localized or generalized depending on whether it occurs in a single region (such as cervical, axillary, or inguinal), or if there are many in more than one non-adjacent region. LAP can occur during the course of various infectious diseases and may develop due to immunological, endocrine, lymphoproliferative, or malignant diseases as well as in consequence of some drug use (3, 4).

Unexplained LAPs are a cause for concern to patients and clinicians because of the possibility of malignancy (5). Peripheral LAP in children is usually benign and self-limiting. However, since LAP may also be a manifestation of malignant and autoinflammatory diseases, it is necessary to define the underlying etiology in each patient. The etiology of peripheral lymphadenopathy can often be determined after a full history and physical examination. If the diagnosis remains unclear after clinical evaluation, additional evaluations should be performed (5, 6). The urgency and scope of the evaluation is determined by the extent of the patient's appearance and presence of clinical features suggestive of malignancy. Yet, there is no biomarker that can be applied in clinical practice.

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In addition to clinical and physical examination findings, the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and red blood cell distribution width (RDW) values which can be calculated automatically from a complete blood count have been reported in recent years to be used separately or together in the differential diagnosis and prognosis of inflammatory and malignant diseases (7–9). No study has investigated the role of NLR, MLR, PLR, and RDW in children with LAP. In this study, we evaluated the value of NLR, MLR, PLR, and RDW in distinguishing between reactive LAP and lymphoma in children.

**Materials and methods**

In our retrospective study we assessed data from children who underwent excisional lymph node biopsy due to enlarged lymph nodes at the Department of Pediatrics of our tertiary university hospital from January 2009 to December 2018. The approval for the study was obtained from local ethics committee (MEU 2018/314).

The inclusion criteria were: pathologically confirmed reactive LAP or lymphoma after biopsy. The exclusion criteria were: necrotizing granulomatosis, non-necrotizing granulomatosis, other granulomatous diseases, metastatic involvement, autoimmune diseases, lymphoproliferative disorders, or histiocytic disorders. Besides these, the history of antibiotic use within 2 weeks before biopsy was accepted as an exclusion criterion for reactive LAP (Fig. 1).

Clinical and laboratory data were obtained by patient file researching. All of the study children received physical examination before biopsy. Fever history, duration, size, extension of lymph nodes, and biopsy location were determined by reviewing medical records. The size of the lymph node was classified as < 1 cm, 1–3 cm, or > 3 cm. The extension of lymph nodes was classified as localized LAP (a single or multiple but adjacent lymph node involvement) and generalized LAP (more than two non-adjacent

**Tab. 1. Demographic and clinical characteristics by study group.**

| Characteristics | Reactive LAP (n=139, 73.2%) | Lymphoma (n=51, 26.8%) | p |
|---|---|---|---|
| Age, years | 6.75 (0.25-18) | 14.00 (0.5-18) | **<0.001** |
| Males | 89 (64.0) | 32 (62.7) | 0.870 |
| Fever | 37 (26.6) | 25 (49.0) | **0.004** |
| Duration | | | |
|   Acute | 54 (38.8) | 31 (60.8) | **0.021** |
|   Chronic | 85 (61.2) | 20 (39.2) | |
| Size | | | |
|   <1cm | 34 (24.5) | 5 (9.8) | |
|   1–3 cm | 68 (48.9) | 20 (39.2) | **0.004** |
|   >3 cm | 37 (26.6) | 26 (51.0) | |
| Extension | | | |
|   Generalized | 18 (12.9) | 30 (58.8) | **<0.001** |
|   Localized | 121 (87.1) | 21 (41.2) | |
| Biopsy location, % | | | |
|   Cervical | 61.9 | 56.9 | |
|   Submandibular | 17.3 | 7.8 | |
|   Abdominal | 9.4 | 11.8 | |
|   Axillary | 4.3 | 2.0 | |
|   Supraclavicular | 2.9 | 7.8 | — |
|   Inguinal | 2.2 | 7.8 | |
|   Suboccipital | 2.2 | 0 | |
|   Mediasten | 0 | 5.9 | |

LAP – lymphadenopathy, Data are shown as median (min–max), number (%) as appropriate

lymph node involvements). The duration of LAP was classified as acute (≤ 4 weeks), or chronic (> 4 weeks).

Complete blood count (CBC) parameters, including leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts (PC) as well as mean platelet volume (MPV), RDW, and hemoglobin values were measured up to 2 days before biopsy. NLR, MLR, and PLR were calculated.

All biopsies were performed by experienced pediatric surgeons; pathologic examinations were performed by experienced
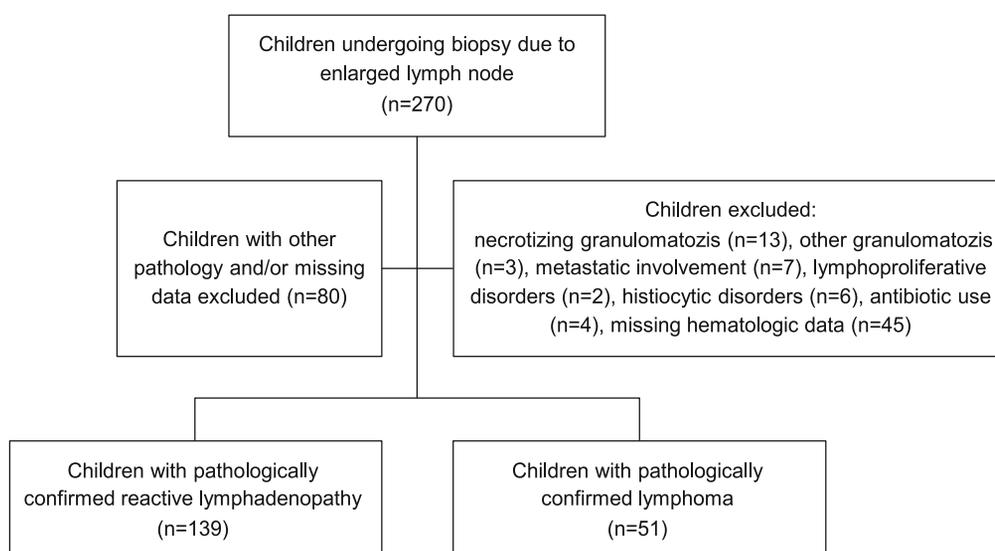


**Fig. 1. Selection of the study population.**

**Tab. 2. Hematologic biomarkers in reactive LAP and lymphoma groups.**

| Biomarker | Reactive LAP (n=139, 73.2%) | Lymphoma (n=51, 26.8%) | p |
|---|---|---|---|
| Hemoglobin, g/dL | 12.1 (7.7–15.2) | 11.1 (6.7–13.4) | **<0.001** |
| RDW, % | 13.9 (11.8–25.1) | 14.6 (12.2–22.4) | **0.017** |
| Leucocyte, 10³/μL | 8.93 (2.83–33.54) | 10.31 (1.06–28.82) | 0.996 |
| Neutrophil, 10³/μL | 4.15 (0.46–30.61) | 6.07 (0.50–20.44) | **0.019** |
| Lymphocyte, 10³/μL | 3.18 (0.53–14.61) | 1.75 (0.29–7.99) | **<0.001** |
| Monocyte, 10³/μL | 0.69 (0.13–3.26) | 0.75 (0.10–3.09) | 0.412 |
| Platelet, 10³/μL | 338 (58–1141) | 322 (40–775) | 0.232 |
| MPV, fL | 9.50±1.13 | 9.58±1.14 | 0.657 |
| MPV/PC ratio | 2.87 (0.68–14.66) | 2.92 (1.17–27) | 0.196 |
| NLR | 1.24 (0.14–23.55) | 4.28 (0.17–14.26) | **<0.001** |
| MLR | 0.20 (0.06–1.45) | 0.41 (0.12–1.63) | **<0.001** |
| PLR | 105.55 (12.94–570.50) | 192.94 (8.39–775) | **<0.001** |

LAP – lymphadenopathy; RDW – red cell distribution width; MPV – mean platelet volume; PC – platelet count; NLR – neutrophil-to-lymphocyte ratio; MLR – monocyte-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio
Data are shown as median (min–max): mean±SD as appropriate

**Tab. 3. Multivariate odd ratios of variables for predicting malignancy in all children.**

| Variables | B | Wald | OR | (95% CI) | p |
|---|---|---|---|---|---|
| Age | 0.214 | 9.398 | 1.239 | (1.080–1.420) | **0.002** |
| Duration (acute) | 0.822 | 1.782 | 2.276 | (0.680–7.613) | 0.182 |
| Fever (presence) | 0.851 | 2.007 | 2.341 | (0.722–7,597) | 0.157 |
| Size | | | | | |
| 1–3 cm vs 1 cm | –0.462 | 0.267 | 0.630 | (0.109–3.631) | 0.605 |
| > 3 cm vs 1 cm | 0.385 | 0.213 | 1.470 | (0.286–7.547) | 0.645 |
| Extension (generalized) | 2.679 | 16.027 | 14.576 | (3.926–54.120) | **<0.001** |
| Hemoglobin | –0.409 | 4.395 | 0.664 | (0.453–0.974) | **0.036** |
| RDW | 0.064 | 0.178 | 1.066 | (0.792–1.436) | 0.673 |
| NLR | –0.034 | 0.086 | 0.966 | (0.768–1.215) | 0.770 |
| MLR | 2.659 | 4.883 | 14.280 | (1.351–150,965) | **0.027** |
| PLR | 0.000 | 0.005 | 1.000 | (0.995–1.006) | 0.946 |

OR – odds ratio; CI – confidence interval; RDW – red cell distribution width; NLR – neutrophil-to-lymphocyte ratio; MLR – monocyte-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio

**Tab. 4. Sensitivity and specificity of potential hematologic biomarkers for diagnosis of lymphoma.**

| Biomarker | Cut-off value | Sensitivity % | Specificity % | PPV % | NPV % | AUC (95% CI) |
|---|---|---|---|---|---|---|
| RDW | 15.1 | 43.1 | 77.0 | 40.7 | 78.7 | 0.61 (0.54–0.68) |
| NLR | 3.17 | 60.8 | 85.6 | 60.8 | 85.6 | 0.75 (0.68–0.81) |
| MLR | 0.29 | 70.6 | 73.4 | 49.3 | 87.2 | 0.76 (0.69–0.82) |
| PLR | 180 | 56.9 | 87.8 | 63.0 | 84.7 | 0.71 (0.64–0.77) |

PPV – positive predictive value; NPV – negative predictive value; AUC – area under the curve; CI – confidence interval; RDW – red cell distribution width; NLR – neutrophil-to-lymphocyte ratio; MLR – monocyte-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio

pathologists. According to biopsy results, patients with reactive LAP or lymphomas were grouped as cases with benign or malignant disorder, respectively.

*Statistical analysis*

SPSS 21 and MedCalc packages were used for statistical analysis. Continuous variables are statistically described as mean ± standard deviation or median (min–max) values; categorical variables, are given as numbers (n) and percentages (%). Shapiro–Wilk test and histogram were used to test for normality. Independent groups were compared with student t-test, Mann–Whitney U test or Pearson Chi-square test.

Receiver operator curves (ROC) were plotted, and the area under the curve (AUC), 95% confidence interval (CI), and cut-off values were calculated for NLR, MLR, PLR, and RDW. Sensitivity, specificity, as well as positive and negative predictive values were used to describe predictive properties. The most promising independent variables (univariate analysis) were incorporated into a multivariate analysis as single risk factors, while the binary logistic regression analysis was conducted by calculating the odds ratio to establish the risk for malignancy. The statistical significance level was accepted when p < 0.05.

**Results**

A total of 190 lymph node biopsy and complete blood count results were included in the study. In total, 139 (73.2 %) children had pathologically confirmed reactive LAP and 51 (26.8 %) were diagnosed with lymphoma. The median age was significantly different between benign and malignant disorder groups (6.75 (0.25–18.00) and 14.00 (0.5–18.00), respectively; p < 0.001). In the malignant disorder group, 31 children (60.8 %) had Hodgkin, and 20 children (39.2 %) had non-Hodgkin lymphoma. The demographic and clinical characteristics of the study children are shown in Table 1.

As compared with the reactive LAP group, the lymphoma group had a significantly higher median value for neutrophil count (p = 0.030), and median values for RDW (p = 0.017), NLR, MLR, and PLR (all p < 0.001), but a lower median value for lymphocyte count and median value for hemoglobin (both p < 0.001). No significant differences were found in leukocyte, monocyte, PC, MPV value, and MPV/PC ratio (p > 0.05) between the two groups (Tab. 2).

In logistic regression analysis, the overall percent of cases that are correctly predicted by the model was 85.6 %. The associations between risk factors and malignancy outcome are shown in Table 3.

The AUCs for RDW, NLR, MLR, PLR, as well as sensitivity, and specificity, and positive and negative predictive values are shown in Table 4. According to pairwise comparisons of ROC curves, the differences between RDW~NLR areas and
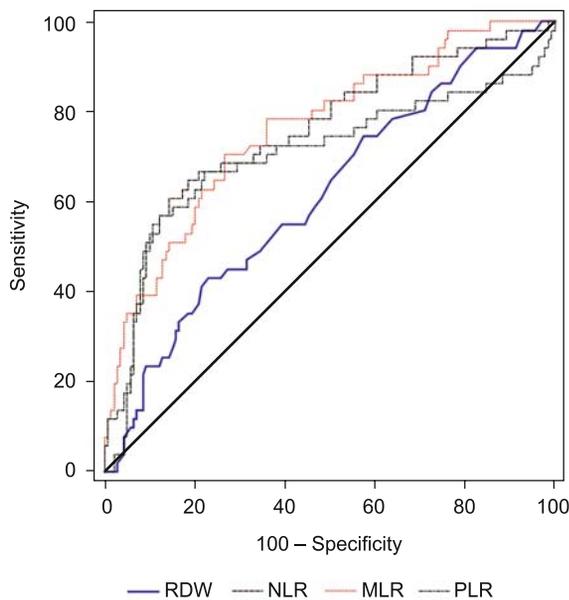
**Fig. 2. Receiver operating characteristics (ROC) curves of RDW, NLR, MLR, and PLR in diagnosing lymphoma.**

RDW~MLR areas were statistically significant (p = 0.031 and p = 0.017, respectively); the differences between RDW~PLR, NLR~MLR, NLR~PLR, and MLR~PLR areas were statistically insignificant (p = 0.147, p = 0.744, p = 0.206, p = 0.183, respectively). The sensitivity, specificity, and positive and negative predictive values for the combination of RDW, NLR, MLR, and PLR biomarkers were 23.5 %, 97.1 %, 75.0 %, and 77.6 %, respectively. The ROC curves for RDW, NLR, MLR, and PLR are shown in Figure 2.

**Discussion**

To our knowledge, this is the first study that has been focused on the role of whole blood parameters in children with LAP. We showed that children in the lymphoma group had significantly higher levels of NLR, MLR, PLR, and RDW than those in the reactive LAP group. On the other hand, we found that there was no difference in the levels of leukocytes, monocytes, PC, MPV, and MPV/PC ratio between the children with lymphoma and reactive LAP.

Peripheral LAP in children may occur during the course of many infectious diseases such as viral, bacterial, fungal, protozoal, and spirochetal (3, 5). All patients should have a detailed history and completed systemic examination in order to ascertain facts such as the duration of LAP, whether there was an increase in size, previous history of febrile illness, symptoms of B seen in lymphoma (fever, night sweats, weight loss), animal contact, travel history, vaccinations, medications, and chronic disease history. Further facts and circumstances should be investigated, such as the size of the lymph gland, whether it is mobile or painful, whether there is redness and local heat increase on the skin, localization,

and number, as well as additional pathological examination findings such as concomitant organomegaly (10).

The evaluation of the child with LAP should be carried out in steps of approximately four weeks. In cases with localized LAP, the etiology is often determined by history and physical examination. In generalized LAP, some laboratory tests are needed to determine the etiology. Several diagnostic tests have been used in the evaluation of lymph nodes (2, 4). The attempt to administer antimicrobial therapy after the initial evaluation has an important role in the diagnosis and treatment. Further investigation should be performed in cases that cannot be explained by antimicrobial therapy and initial tests. Chest X-ray and abdominal ultrasonography, tuberculin skin test, HIV serology, autoantibodies, toxoplasmosis and serological tests for cat scratch disease may be requested (2, 3). Biopsy should be requested in cases of LAP the cause of which could not be revealed despite these tests and which persist for more than three weeks. Biopsy can be performed in the early period in patients who have the possibility of malignancy according to physical examination and tests (4). The timing and sequence of tests and the trial of antibiotic therapy vary depending on the localization, distribution, size and accompanying clinical features of the lymph node.

Neutrophils and lymphocytes are essential cellular components of human host defense. The distribution and number of leukocytes depend on the immunological status of the patient and etiology of the infection. Neutrophils are the first line of cellular defense of the innate immune system against infections while lymphocytes play a role in adaptive immunity. The physiological immune response to bacterial infections promotes an increase in neutrophil counts and a decrease in lymphocyte counts (11). Systemic inflammation responses have been associated with cancer development and progression.

Complete blood count, acute phase reactants such as ESR and CRP, and radiological examinations may support or rule out some diagnoses. However, they are not determinative in distinguishing infection from other inflammatory diseases in patients with LAP. Also, they cannot determine the necessity of biopsy for the differentiation of benign and malignant disease (5,6). Therefore, there is a need for a new biomarker that is specific, precise, inexpensive, fast and easy to measure and applicable at every step.

Changes in the distribution of blood cells that develop during the course of infection, inflammation or malignant diseases have led to the idea that blood parameters which are calculated from CBC may be new biomarkers that can be used in the diagnosis and course of diseases. The role of these biomarkers in different diseases has been reported (7–9). Previous studies on whole blood parameters led us to assess whether NLR, MLR, PLR, and RDW may have a value in distinguishing between reactive LAP and lymphoma in children.

NLR is a marker of general inflammation that can be calculated from complete blood counts. The published studies indicate that increased NLR is valuable in the diagnosis and prognosis of some diseases including cancer and inflammation (7, 8, 11). NLR has been shown to be a new biomarker of bacterial infections, and increased NLR has been shown to be superior to con-

ventional infection markers in the early detection of bacteremia (12). In critically ill patients with sepsis and/or trauma, NLR was found to be significantly higher in those with higher risk of mortality determined by clinically applied scores compared to those not at risk (7, 13). In our study, the NLR levels were significantly higher in children with lymphoma when compared with the reactive LAP.

*In vivo* studies have shown that activated platelets can bind to normal endothelium, and secrete potent inflammatory, mitogenic, and chemotactic mediators to promote monocyte migration and inflammatory response. NLR, PLR and MLR are increased by secreted cytokines in systemic inflammation (7). When inflammation is prolonged, the apoptotic cascade is activated in lymphocytes and the lymphocyte count decreases. Based on these changes in inflammation, Chen et al. investigated the diagnostic value of blood parameters as biomarkers in patients with rheumatoid arthritis (RA) and rheumatoid arthritis-associated interstitial lung disease (RA-ILD) (14). They found that PLR may be applied as a new biomarker for predicting and diagnosing RA and RA-ILD and for distinguishing RA-ILD patients from RA patients and healthy subjects. PLR has also been shown to be useful in monitoring vascular system disorders and malignancies (15, 16). High levels of PLT which are shown to serve as a new systemic inflammatory marker, have been shown to be associated with increased mortality risk at the onset of the disease in patients with sepsis (17). We showed that PLT levels in children with lymphoma were significantly higher than in children with the reactive LAP.

*In vivo* studies showed that monocytes induce tumorigenesis and angiogenesis and inhibit antitumoral immune response. Therefore, it is thought that increased monocyte and decreased lymphocyte counts may be related to tumor processes and so far, the studies investigating the relationship between tumors and MLR support it (18, 19). Other studies have shown that MLR is a more useful marker than WBC, neutrophil count and CRP for differentiating patients with bacteremia from those who do not have bacterial infection (7, 20). In our study, the mean levels of MLR in children were significantly higher in the lymphoma group than in the reactive LAP group.

RDW is a measure of variation in the size of circulating erythrocytes, which is routinely reported in a standard automated CBC (9). Recently, an extensive research has been done on RDW, and several studies have demonstrated the role of RDW in various forms of inflammatory disease and pathophysiological conditions. RDW has been recently identified as a prognostic factor in various types of cancer (21). It has been found that as for hematologic malignancies, the prognosis in patients with higher RDW is more likely to be poorer than in those with lower RDW (22). We found that RDW levels in children with lymphoma were significantly higher than those in children with the reactive LAP.

We found that 139 (73.2 %) children had pathologically confirmed reactive LAP and 51 (26.8%) were diagnosed with lymphoma. The majority of cases with LAP first apply to the family doctor. The prevalence of malignancy in primary care patients is relatively low (23, 24). Biopsy is performed in 2–3 % of patients who apply to pediatrician, and the rate of malignancy in these cases is only 1–2 %. The prevalence of malignancy in lymph node biopsies was reported to be 13–27 % in cases referred to advanced centers (25, 26).

This study is mainly limited by its retrospective nature. On the other hand, our study has several strengths. This is the first study to examine the values of NLR, MLR, PLR, and RDW in children with lymphoma and reactive LAP.

## Conclusions

Children with histologically proven lymphoma have higher NLR, MLR, PLR, and RDW than children with reactive LAP. When combined with clinical physical examination findings, these markers, which can be calculated automatically from simple blood counts, may be useful for clinicians in referring suspected cases to further centers. This applies especially for the clinicians in centers of primary and secondary levels of care where the serological tests are limited.

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