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ORIGINAL ARTICLE

Does the preoperative neutrophil-to-lymphocyte ratio have a prognostic value in aneurysmal bone cysts?

İbrahim Kaya, MD, Batuhan Ayhan, MD, Coşkun Ulucaköy, MD, Güray Toğral, MD, Bedii Şafak Güngör, MD

Department of Orthopedics and Traumatology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye

ABSTRACT

Objectives: The aim of this study was to evaluate the prognostic value of neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) in aneurysmal bone cysts (ABCs).

Patients and methods: Between February 2001 and August 2019, a total of 86 patients (44 males, 42 females; mean age: 21.5±15.2 years; range, 2 to 73 years) with a histologically confirmed diagnosis of ABCs who did not receive cancer treatment previously and had a minimum follow-up period of 24 months were retrospectively analyzed. Data including age, sex, side, tumor location, pre-treatment complete blood count analysis results, preferred surgical method, follow-up period, presence of recurrence, and date of recurrence were recorded. Preoperative NLR, LMR and PLR values were calculated in all patients.

Results: The mean follow-up was 56.7±13.5 (range, 24 to 179) months. Forty-one (47.7%) ABCs were located in the lower extremities, 36 (41.8%) in the upper extremities, and nine (10.4%) in the pelvic girdle. A statistically significant difference was detected in the NLR values according to recurrence status (p=0.023). The PLR and LMR values were not significant for area under the curve, while NLR values were significant for recurrence. The cut-off value was determined as 2.054. Those with an NLR of ≥2.054 were found to have a 4.561-fold higher risk of recurrence than those with an NLR of <2.054 (odds ratio [OR]=4.561).

Conclusion: Our study results suggest that NLR, which is the pre-treatment inflammatory index, is a prognostic factor in patients with ABCs. Although NLR alone is not decisive in patients with elevated NLR, it can be used to evaluate the clinical prognosis and recommend an appropriate treatment strategy.

Keywords: Aneurysmal bone cyst, neutrophil-to-lymphocyte ratio, prognostic value.

Aneurysmal bone cysts (ABCs) are uncommon, benign, potentially locally aggressive bone lesions. The main features are prompt growth and a localized bone destruction that can endanger bone integrity and stability, thereby leading to secondary fractures.[1,2] Preoperative histopathological confirmation is required, as the age and location of the patient and the radiographic characteristics of the lesions may be similar to telangiectatic osteosarcoma or other malignant cystic lesions.[3] The traditional treatment of ABCs is intralesional curettage, sometimes with the addition of adjuvant techniques such as cauterization, phenol, argon bean coagulation, and cryotherapy. In case of extensive periarticular bone destruction or tumors in less important bones such as the fibula and clavicle, extended resection is rarely considered.[4]

Recurrence is the most common within 24 months of treatment and ranges from 10 to 59% after various surgical procedures.[5] Several risk factors have been associated with tumor recurrence, including young age, particularly children younger than five years, open growth plates, male sex, and location of the lesion close to the axial skeleton and physis.[5-7] In a study examining the histopathology of ABCs, Dabska and Buraczewski[8] defined ABC as a cavernous

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Correspondence: İbrahim Kaya, MD. Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim ve Araştırma Hastanesi, Ortopedi ve Travmatoloji Kliniği, 06200 Yenimahalle, Ankara, Türkiye.

E-mail: ibrahimkaya_97@hotmail.com

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vascular tumor composed of hemorrhagic tissue and microscopic analysis of the lesion was found to consist of spindle cells, giant cells, and inflammatory cells.

Inflammation is understood to be a vital hallmark of cancer, contributory to tumor cell proliferation and genomic instability.[9] It has been shown that prognostic markers calculated on the premise of inflammatory cells would contribute to diagnostic and prognostic analysis in certain types of cancer. In studies on bone tumors, hematological parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been used to evaluate musculoskeletal tumors, such as osteosarcoma and giant cell tumors.[10-13]

However, to the best of our knowledge, there is no study in the literature evaluating the prognostic value of NLR, PLR, and LMR values on ABCs. In the present study, we hypothesized that these hematological parameters associated with numerous tumors could be prognostic markers of a tumor-like lesion with vascular processes such as ABCs. We, therefore, aimed to investigate the effect of pre-treatment inflammatory markers on prognosis in patients with ABCs.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Orthopedics and Traumatology between February 2001 and August 2019. Patients who were operated and followed in our clinic with the diagnosis of an ABC were included. Data of the patients were retrieved from the medical records in the hospital database, and no additional interventional procedures were performed. Data including age, sex, side, tumor location, pre-treatment complete blood count analysis results, preferred surgical method, follow-up period, presence of recurrence, and date of recurrence were recorded. Only patients with a histologically confirmed diagnosis of ABCs, who did not receive cancer treatment before and any treatment that could change their blood values, who had a medical record and had a follow-up period of a minimum 24 months were included to study. Patients with a pre-existing hematological disease, high acute phase reactants, diabetes mellitus, infectious, rheumatological and another inflammatory disease, incomplete medical records, and those previously treated with anti-inflammatory drugs which may affect the blood tests were excluded from the study. Finally, a total of 86 patients (44 males, 42 females; mean age: 21.5±15.2 years; range, 2 to 73 years) were included.

The NLR and PLR were calculated as the absolute count of neutrophils and platelets divided by the absolute number of lymphocytes, respectively. The LMR was estimated as the absolute number of lymphocytes divided by the absolute number of monocytes.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. Parametric methods were used to measurement values appropriate for normal distribution. In conformity with parametric methods, the independent samples t-test was used to compare the measurement values of two different groups. Non-parametric methods were used for the measurement values that did not conform to the normal distribution. The Mann-Whitney U test was used to compare the measurement values of two independent groups. The Pearson chi-square test was carried out to examine the relationships between two qualitative variables. The Kaplan-Meier and Cox regression analysis were used to analyze follow-up duration based on the recurrence status. The log-rank (Mantel-Cox) analysis was used to estimate the mean time to recurrence according to the NLR classes. The receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value for NLR, LMR, and PLR in predicting recurrence. In the *post-hoc* power analysis, the study power was 82%. A p value of <0.05 was considered statistically significant.

RESULTS

The mean follow-up was 56.7±13.5 (range, 24 to 179) months. Forty-one (47.7%) ABCs were located in the lower extremities, 36 (41.8%) in the upper extremities, and nine (10.4%) in the pelvic girdle. While 56 patients were treated with curettage+grafting+adjuvants, 30 patients underwent additional internal fixation. Baseline characteristics of the patients are summarized in Table I.

The patients were further divided into two groups based on recurrence (Table II). According to overall recurrence rate, 16.3% (n=14) of the patients had recurrence. The mean time to relapse in relapsed cases was 24.0±10.0 (range, 6 to 48) months.

TABLE I
Baseline characteristics of patients

Variables	Results				
	n	%	Mean±SD	Median	Min-Max
Age (year)			21.5±15.2	16.0	2.0-73.0
Sex					
Male	44	51.2			
Female	42	48.8			
Side					
Right	53	61.6			
Left	33	38.4			
Location					
Hand	6	7.0			
Femur	14	16.2			
Fibula	13	15.1			
Humerus	17	19.7			
Calcaneus	1	1.2			
Clavicle	4	4.7			
Cuboid	1	1.2			
Pelvic ring	9	10.5			
Radius	4	4.7			
Scapula	3	3.5			
Talus	1	1.2			
Tibia	11	12.7			
Ulna	2	2.3			
Operation					
Curettage + grafting + adjuvant	56	65.1			
Curettage + grafting + adjuvant + internal fixation	30	34.9			
Follow-up time (months)			56.7±13.5	46.0	24-179.0

SD: Standard deviation.

TABLE II
Classification of patients according to recurrence status

Recurrence	No (n=72)			Yes (n=14)			Statistical analysis* Possibility	
Variables	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Z	*p*
Age (year)	21.2±15.6	16.0	2.0-73.0	23.1±14.1	18.0	9.0-53.0	-0.568	0.570
MPV	9.04±1.10	9.0	6.4-11.2	9.17±0.87	9.1	7.6-10.6	-0.564	0.573
PLT	303.90±92.51	278.0	197.0-612.0	293.64±80.86	262.0	222.0-504.0	-0.457	0.648
High	13.67±1.62	13.6	9.6-16.8	13.52±1.84	13.3	9.6-16.2	-0.515	0.606
WBC	7.34±1.82	7.4	4.6-12.1	7.83±1.67	8.2	5.3-11.2	-1.383	0.167
LMR	0.32±0.11	0.32	0.16-0.51	0.26±0.07	0.25	0.17-0.45	t=2.535	0.017
NLR	2.16±1.17	1.7	0.8-4.8	2.68±0.78	2.5	1.7-4.7	-2.276	0.023
PLR	143.61±45.57	141.9	68.1-241.5	153.72±52.85	145.7	77.8-265.3	-0.480	0.631

SD: Standard deviation; MPV: Mean platelet volume; PLT: Platelet count; WBC: White blood cell; LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; * "Independent Sample-t" test (t-table value) statistics were used to compare the measurement values of two independent groups in data with a normal distribution. The "Mann-Whitney U" test (Z-table value) statistics were used to compare the measurement values of two independent groups in the data that did not have a normal distribution.

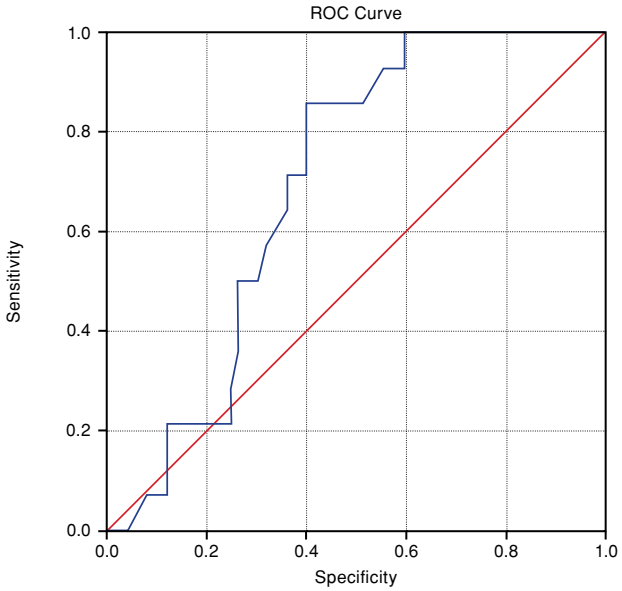


FIGURE 1. Neutrophil-to-lymphocyte ratio values according to recurrence status.
ROC: Receiver operating characteristic.

There was no statistically significant relationship between recurrence status and sex, side, and location of the tumor (p>0.05). There was no statistically significant difference in terms of age, mean platelet volume, platelet count, hemoglobin, white blood cell count, and PLR according to recurrence status (p>0.05).

On the other hand, a statistically significant difference was found in terms of LMR according to recurrence status (p=0.017). The LMR values of the patients without recurrence were significantly higher than those with recurrence. A statistically significant difference was also observed in the NLR values according to recurrence status (p=0.023). The NLR values of those with recurrence were found to be significantly higher than those without recurrence.

The ROC curve analysis revealed that PLR and LMR values were not significant in terms of area under the curve (AUC), and only NLR values had significance for recurrence. For NLR, the sensitivity was 85.7% and the specificity was 59.7%, and the cut-off value was determined as 2.054 (Figure 1, Table III).

The Cox regression analysis also revealed that an NLR of ≥2.054 was associated with a 4.561-fold higher risk of recurrence than those with an NLR of <2.054 (odds ratio [OR]=4.561) (Table IV).

There was a significant difference in recurrence times according to the NLR classes (p=0.002). The mean duration of recurrence was 100.3 months in patients with an NLR of ≥2.054 and 171.8 months in patients with an NLR of <2.054. Recurrence was seen

TABLE III
Preoperative NLR values for predicting recurrence

Variable	Area (AUC)	*p*	Sensitivity (%)	Specificity (%)	Cut-off
NLR	0.693	0.023	85.7	59.7	2.054

NLR: Neutrophil-to-lymphocyte ratio; AUC: Area under the curve.

TABLE IV
Cox regression model for NLR for recurrence during follow-up

Variable	β	SE	Wald	SD	*p*	OR	95% CI Upper	95% CI Lower
NLR*	1.518	0.778	22.875	1	0.000	4.561	1.874	9.884

NLR: Neutrophil-to-lymphocyte ratio; CI: Confidence interval; SE: Standard error; SD: Standard deviation; OR: Odds ratio; * Reference category: <2.054.

TABLE V
Log-rank (Mantel-Cox) analysis for the mean time to recurrence according to NLR classes

Variable	Log-rank χ^2	*p*	NLR <2.054	NLR Lower-upper (95%)	NLR ≥2.054	NLR Lower-upper (95%)
Follow-up time (months)	9.455	0.002	171.0	160.0-181.8	100.3	76.9-123.6

NLR: Neutrophil-to-lymphocyte ratio.

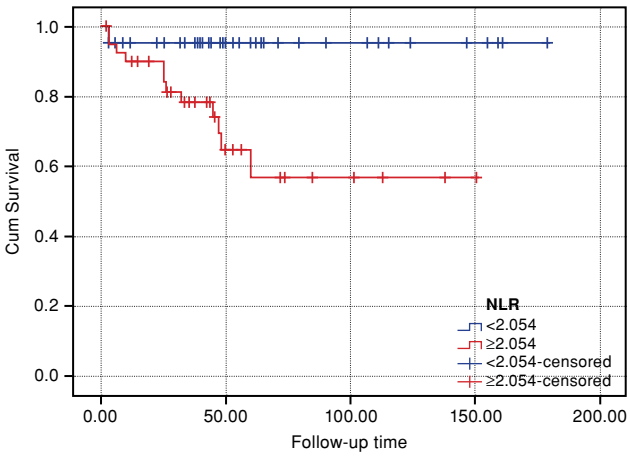


FIGURE 2. Time to recurrence in terms of NLR according to recurrence status.
NLR: Neutrophil-to-lymphocyte ratio.

in a shorter time in patients with an NLR of ≥2.054. (Figure 2, Table V).

DISCUSSION

Aneurysmal bone cysts are benign, but locally aggressive bone lesions without a specific treatment option, and the pathophysiology of which remains unclear. The main finding of this study was that preoperative NLR in the peripheral blood of patients with ABC patients was considerably associated with postoperative recurrence. In the ROC analysis, the AUC of NLR was adequate level in patients with recurrence, and those with an NLR of ≥2.054 were found to have a 4.561-fold greater risk of recurrence than those with an NLR of <2.054 (OR=4.561). The NLR was found to provide a more accurate prognostic prediction for ABC. However, the prognostic value of LMR and PLR was inadequate to predict recurrence.

Hematological parameters such as NLR, PLR, and LMR have been shown to be altered by systemic inflammatory response and are not only being used comprehensively in musculoskeletal tumors, but also in the diagnosis and evaluation of prognosis in hip fractures and many other tumors.[14-18] Recently, these hematological parameters have also been used as prognostic factors in musculoskeletal tumors such as soft tissue sarcomas,[19] pigmented villonodular synovitis,[20] and osteosarcoma.[10,11,21,22] In a study including patients with osteosarcoma, pre-treatment NLR and PLR values were related to survival and, particularly, NLR was concluded to be a good predictor of overall survival and progression-free survival.[23] Yapar et al.[13] reported that NLR was a promising prognostic factor in patients with giant cell tumors, and a pre-treatment NLR value of more than 2.25 was associated with a poor prognosis. Giant cell tumors and ABCs are bone tumors rich in giant cells and have similar histological features.[24,25] According to the 2020 World Health Organization (WHO) Classification of Tumors of Bone, ABC is currently classified as a benign osteoclastic giant cell-rich tumor.[26] In the current study, NLR was found to be a marker in predicting prognosis in patients with ABC, as in giant cell tumors.

In their series, Dormans et al.[27] reported that 51.1% of ABC cases were in the lower extremities and 24.4% were in the upper extremities and trunk. In this study, the most frequently involved bone was the humerus (19.7%), followed by the femur (16.2%).

Controversy still exists regarding optimal treatment, and recurrence rates vary, regardless of the reported techniques. The reported recurrence rates of ABCs after surgical treatment vary and usually range between 10 and 59%.[5,6,27,28] It has been shown that local recurrence rates vary from 0 to 5% in resection procedures, 22% in curettage with adjuvant treatment, and 50% in curettage procedures alone.[28,29] In the current study, the recurrence rate was 16.3%. The discrepancy in recurrence rates may be due to different treatment modalities, use of different adjuvants and different surgical experience. To date, few studies have reported factors affecting the risk of recurrence after ABC treatment. In the literature, studies have usually associated younger age, open growth plates, and male sex with an increased risk of local recurrence.[6,30] Conversely, Dormans et al.[27] reported that there was no relationship between age and recurrence, but that the ABC location close to the physis increased the risk of recurrence. In our study, we found no statistically significant correlation between age, sex, location of the lesion, and recurrence.

Nonetheless, this study has some limitations, such as its single-center and retrospective design. Another limitation is that blood cell counts are rapidly changing parameters that can be affected by multiple factors, and only pre-treatment values were used in this study. The long-term prognosis of ABC can be affected by many factors, and their impact was unable to be determined due to the lack of a prospective, randomized-controlled study design. Finally, there was heterogeneity for treating these patients, which could have caused bias.

However, this study has a number of strengths. First, inflammatory markers were assessed and their effect on inflammatory markers was avoided

by excluding patients who were considered to be infected, and had pre-existing hematological disease and rheumatological disease. The NLR is a simple, reproducible, and low-cost prognostic biomarker, as complete blood count testing is routinely performed in all patients before surgery. This study is the initial attempt to assess the prognosis of patients with ABC based on inflammatory biomarkers in peripheral blood and to build a prediction model to improve prediction accuracy. Further multi-center, large-scale, well-designed studies are warranted.

In conclusion, our study results suggest that NLR, which is the pre-treatment inflammatory index, is a prognostic factor in patients with ABCs. Therefore, although NLR alone is not decisive in patients with elevated NLR, it can be used to evaluate the clinical prognosis and recommend an appropriate treatment strategy. The NLR is only one of many factors that can predict the prognosis of neoplastic diseases. The present study confirms the value of NLR as an accessible, non-invasive, and low-cost biomarker that can be used as a routine tool in clinical practice in patients with ABC. However, multi-center, prospective studies are needed to confirm these findings.

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Dr. Abdurrahman Yurtaslan Oncology Health Practice and Research Center Clinical Research Ethics Committee (date: 09.062021, no: 2021-06/1152). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient and/or the parents of the patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept and design: İ.K., C.U.; Data collection and/or processing: İ.K., B.A.; Analysis and/or interpretation and control/supervision: İ.K., G.T., B.S.G.; Literature review: B.A., İ.K.; Writing the article: İ.K., C.U., B.A.; Critical review: G.T., B.S.G.; References and fundings: İ.K., C.U., B.A.; Materials: G.T., C.U.

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