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CLINICAL STUDY

Do neutrophil/lymphocyte, monocyte/lymphocyte, platelet/lymphocyte ratios affect prognosis and stage in avascular necrosis of the femoral head?

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ABSTRACT

INTRODUCTION: Avascular necrosis of the femoral head (AVNFH) is an osteonecrosis type caused by ischaemic osteocyte loss of femoral head, and its exact pathomechanism is still unknown. Neutrophil, lymphocyte, monocyte, platelet levels in complete blood count and ratios between these levels have been used by almost all medical disciplines as accesible and reliable biomarkers of immune response. Aim of this study is to identify the effects of neutrophil/lymphocyte (NL), monocyte/lymphocyte (ML), platelet/lymphocyte (PLT/L) ratios on prognosis and stage in patients with avascular necrosis of the femoral head (AVNFH).

MATERIALS AND METHODS: A total of 106 (30 female; 76 male) patients aged 18 and over diagnosed with avascular necrosis of femoral head between 2012–2022 years were retrospectively evaluated. Study was planned after a total of 106 (30 female, 76 male) healthy patients with consent to participate who were demographically equal to the study group were included in the control group. Patients in the study group were divided into 3 groups as Stage I, II and III according to the Ficat-Arlet classification.

RESULTS: In terms of neutrophil counts; neutrophil values of study and control groups were 4.94±1.89 and 4,21±1,17; respectively. There was statistically significant difference between counts ($p<0.05$). In terms of neutrophil/lymphocyte ratio, NL ratio was statistically significantly higher in study group (2.11±0.85) than control group (1.75±0.44). Cut-off value of NL ratio was 2.13 according to the ROC analysis (sensitivity 47.17% (95% CI (37.4–57.1)); specificity=84.91% 95% GA (76.6–91.1)). Sensitivity and specificity of cut-off value was statistically significant. There was no difference between groups created according to Ficat-Arlet in terms of hemogram parameters.

DISCUSSION: NL may indicate AVNFH; however, other parameters are considered as inadequate for identifying an independent marker in AVNFH due to ineffective immune response. Future studies with larger samples which allow standard and multi-dimensional analysis are needed *(Tab. 4, Fig. 5, Ref. 20)*. Text in PDF *www.elis.sk*

KEY WORDS: Femur avascular necrosis, NLR, PLR, MLR, Ficat-Arlet.

Introduction

Avascular necrosis (AN) or osteonecrosis is a process causing bone cell death due to impaired perfusion of the bone tissue with traumatic or non-traumatic causes (1). This process implicate the structural change causing secondary osteoarthritis in the femoral head occurring after osteocyte death. It is not directly related with a specific pathology; however, is a result of various pathologies with impaired blood flow of femoral head due to mechanical and biological factors. Avascular necrosis of femoral head may progress into different stages in 3–5 years and it is tend to progress without regression to previous stages (2).

This illness is thought to be triggering an inflammatory process, because it is known that physiological response of leucocytes to stress cause increased neutrophil count and decreased lymphocyte count. Therefore ratio between these two counts have been used as an inflammatory marker (3). There have been studies evaluating NLR levels in cardiovascular system diseases, chronic obstructive pulmonary disease (COPD), malignancy, rheumatologic diseases, and viral/bacterial infections (4, 5). It is widely accessible because it is cheap, easily applicable and calculable (6). Studies have demonstrated that monocyte/lymphocyte ratio is an inflammatory marker and a prognostic indicator (7, 8). MLR has been used as a prognostic indicator in diseases such as multiple myeloma, malignancy and lymphoma. MLR is more reliable and has more predicting value than a single value (9). Platelet/lymphocyte ratio is calculated by dividing platelet count to lymphocyte count in the routine complete blood count; and it has been reported that PLR levels are related with disease severity and inflammation in cardiovascular diseases as well as in diseases considered as systemic inflammatory diseases such as osteoarthritis, psoriatic arthritis (10, 11).

All of these indicators have not been studied in patients with AVNFH yet. Aim of this study is to evaluate the effect of these indicators on prognosis and stage.

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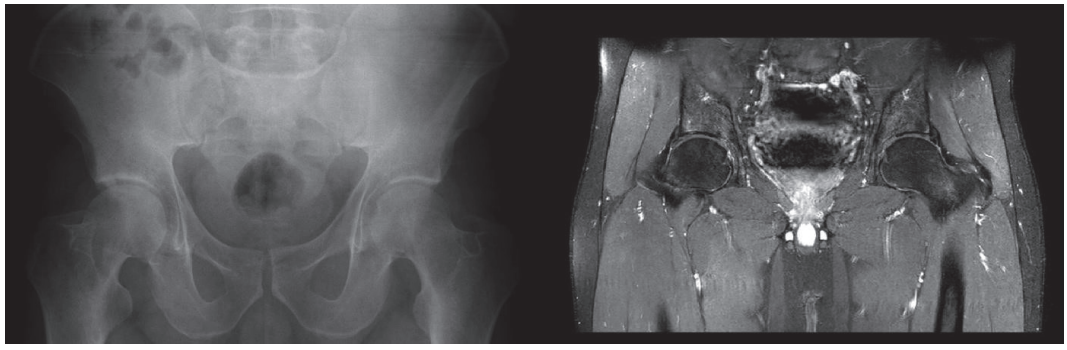

Fig. 1. X-ray and MRI images of Ficat-Arlet Stage I.

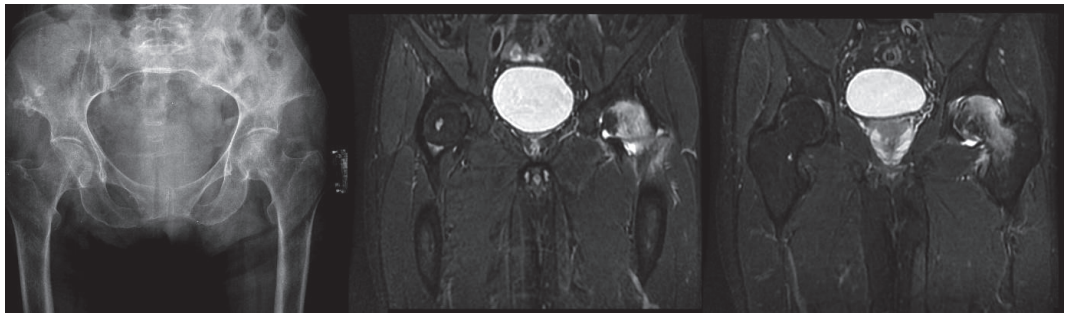

Fig. 2. X-ray and MRI images of Ficat-Arlet Stage II.

Materials and methods

A total of 106 (30 female; 76 male) patients aged 18 and over who were diagnosed with avascular necrosis of femoral head between 2012–2022 years in our clinic were retrospectively evaluated. Study was planned after including 106 (30 female, 76 male) individuals who were demographically equal to study group as control group (Tab. 1).

Inclusion criteria of study group

- Being diagnosed with avascular necrosis of femoral head
- Presence of all necessary data on the system for our study
- Being 18 year of age or older
- Willing to participate in the study
- Being at the Stage I, II, III according to the Ficat-Arlet Classification

Tab. 1. Demographics of participants.

		Study (n=106)	Control (n=106)	p
		n (%) Mean±Standard Deviation (Min–Max)	n (%) Mean±Standard Deviation (Min–Max)	
Gender	Male	76 (71.7)	76 (71.7)	1.000$^{\psi}$
	Female	30 (28.3)	30 (28.3)	
Age		44.61±13.66 (18–75)	45.19±7.31 (24–79)	0.703$^{\eta}$

p>0.05, $^{\eta}$t test;$^{\psi}$Chi-Square test

Exclusion criteria of study group

- Being at the Stage IV according to the Ficat-Arlet Classification
- History of any previous surgical operation
- History of previous malignancy diagnosis
- History of previous chemotherapotic medication
- Unwilling to participate in the study

Classification as Stage 1, 2 and 3 was made by examining X-ray and magnetic resonance imaging (MRI) images of patients (Tab. 2). According to the examination:

- 13 cases with normal direct radiography findings and positive MRI findings were Stage 1 (Fig. 1)
- 57 cases with sclerosis/subchondral cysts observed in direct radiography and geographic lesions observed in MRI were Stage 2 (Fig. 2)
- 36 cases with collapsing, cresent finding in direct radiography and coherent appearance in MRI were Stage 3 (Fig. 3)

Following classification; lymphocyte, monocyte, platelet counts and ratios between these counts were calculated and compared between study group, control group and stages.

Tab. 2. Classification of study group according to the Ficat-Arlet classification.

Ficat-Arlet	Number	Percentage (%)
Stage 1	13	6.1%
Stage 2	57	53.8%
Stage 3	36	34%

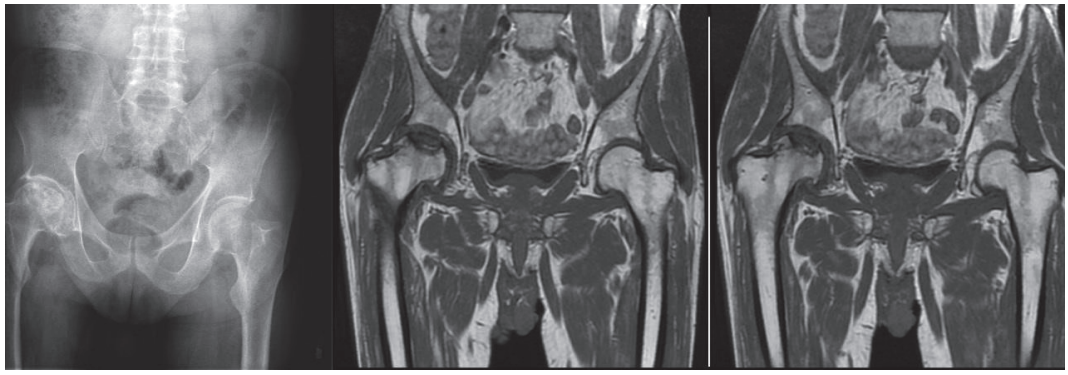

Fig. 3. X-ray and MRI images of Ficat-Arlet Stage III.

Statistical analysis

Descriptive statistics of obtained data in our study were presented with mean value and standard deviation for numeric variables whereas categorical variables were presented with frequency and percentage analysis. The suitability of biochemical measurements for normal distribution was examined with the Shapiro–Wilk test and it was determined that these variables were not normally distributed ($p<0.05$). Mann–Whitney U test was used to compare these variables according to study groups. Additionally, Kruskal–Wallis H test was used to compare the biochemical measurements of the patient group according to the Ficat-Arlet classification. Additionally, Chi-square analysis and t test were used to compare the study groups according to demographic characteristics. ROC analysis was used to determine cutoff points for NE and NL measurements. Analyzes were carried out with the help of SPSS 22.0 program. A significance level of $p<0.05$ was selected.

Results

There was no significant difference between groups in terms of Monocyte/Lymphocyte Ratio and Platelet/Lymphocyte Ratio values ($p>0.05$). However; there was a significant difference between groups in terms of Neutrophil/Lymphocyte Ratio values. NLR value was higher in study group (2.11±0.85) than in control group (1.75±0.44) (Tabs 3, 4).

ROC analysis was used for determining a cut-off value due to significantly higher neutrophil value in study group. Cut-off value of 4.85 was significant with 44.34% (95% CI (34.7–54.3))

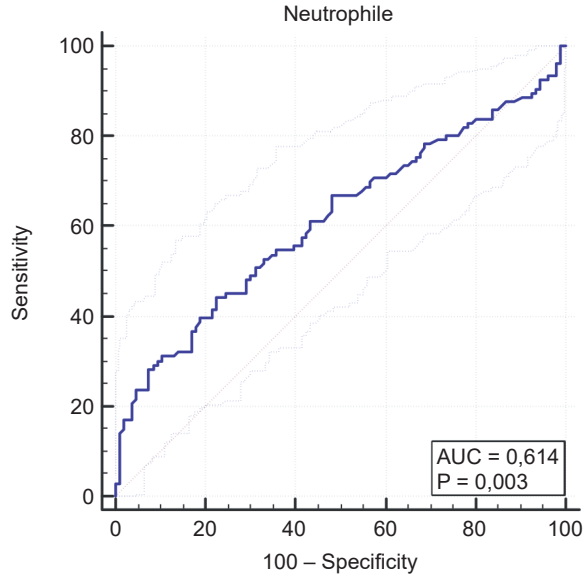

Fig. 4. Area under ROC analysis in prediction model of cut-off value of neutrophil count.

Tab. 3. Comparison between groups in terms of neutrophil, lymphocyte, monocyte, platelet, neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, platelet/lymphocyte ratio.

	Group				p
	Study		Control		
	Mean±SS	**Median (Q1-Q3)**	**Mean±SS**	**Median (Q1-Q3)**	
Neutrophil	4.94±1.89	4.66 (3.62–6.13)	4.21±1.17	3.94 (3.41–4.82)	**0.004***
Lymphocyte	2.49±0.74	2.5 (1.89–2.96)	2.47±0.64	2.39 (2.04–2.89)	0.719
Monocyte	0.68±0.25	0.6 (0.5–0.82)	0.6±0.17	0.58 (0.49–0.69)	0.051
Platelet	277.86±88.15	266 (215–322)	268.77±57.31	263 (231–299)	0.678
NLR	2.11±0.85	2.02 (1.47–2.59)	1.75±0.44	1.74 (1.47–1.99)	**0.002***
MLR	0.29±0.14	0.25 (0.21–0.33)	0.25±0.08	0.24 (0.21–0.28)	0.100
PLR	120.9±48.85	117.52 (86–143.75)	113.83±31.37	112.39 (93.95–131.35)	0.666

p>0.05, NLR: Neutrophil/Lymphocyte Ratio, MLR: Monocyte/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, p: statistical significance level, *Mann–Whitney U test

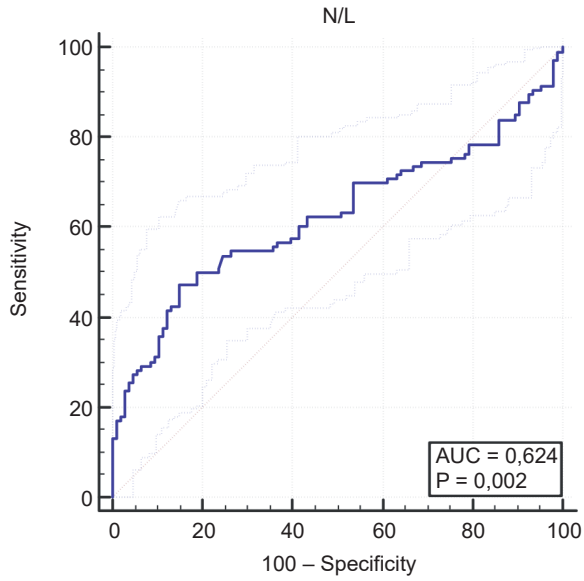

Fig. 5. Area under ROC analysis in prediction model of cut-off value of neutrophil/lymphocyte ratio.

sensitivity and 77.36% specifity. Area under the curve (AUC) was identified as 0.614 (p<0.05) (Fig. 4).

Cut-off value according to the ROC analysis of Neutrophil/Lymphocyte Ratio was 2.,13 (sensitivity) 47.17% (95% CI (37.4–57.1)); Specifity=84.91 95% GA (76.6–91.1)). Sensitivity and specifity of this cut-off value were statistically significant but low (AUC=0.624; p<0.05) (Fig. 5).

There was no statistically significant difference in terms of evaluated parameters between groups created according to Ficat-Arlet stages.

Tab. 4. Comparison between Ficat-Arlet groups in terms of Neutrophil, Lymphocyte, Monocyte, Platelet, Neutrophil/Lymphocyte Ratio, Monocyte/Lymphocyte Ratio, Platelet/Lymphocyte Ratio.

		Mean±SS	Median (Q1–Q3)	p
Neutrophil	Stage1	4.91±1.91	4.61 (3.47–6.27)	0.130
	Stage 2	5.23±1.84	4.87 (3.85–6.28)	
	Stage 3	4.5±1.93	4.18 (3.37–5.56)	
Lymphocyte	Stage 1	2.44±0.66	2.54 (1.73–2.91)	0.846
	Stage 2	2.53±0.75	2.49 (1.98–2.94)	
	Stage3	2.43±0.76	2.49 (1.85–2.98)	
Monocyte	Stage 1	0.67±0.28	0.61 (0.48–0.77)	0.950
	Stage2	0.68±0.25	0.6 (0.52–0.79)	
	Stage 3	0.68±0.25	0.62 (0.49–0.85)	
Platelet	Stage1	312±122	319 (242–348)	0.423
	Stage2	281±88	266 (227–324)	
	Stage 3	260±71	265 (213–315)	
NLR	Stage 1	2.12±0.88	2.03 (1.58–2.53)	0.739
	Stage2	2.19±0.84	2 (1.56–2.6)	
	Stage 3	1.99±0.85	2.08 (1.28–2.5)	
MLR	Stage1	0.28±0.1	0.29 (0.21–0.33)	0.882
	Stage 2	0.29±0.14	0.25 (0.21–0.31)	
	Stage 3	0.3±0.15	0.25 (0.22–0.34)	
PLR	Stage1	133.06±46.88	121.18 (102.12–167.26)	0.578
	Stage 2	120.31±50.49	116.86 (85–140.87)	
	Stage3	117.44±47.54	111.78 (87.82–140.84)	

p>0.05, NLR: Neutrophil/Lymphocyte Ratio, MLR: Monocyte/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, p: statistical significance level, * Kruskal–Wallis H test

Discussion

Biochemical parameters like NLR, MLR, PLR are easily accesible values and they can increase as a response to the acute inflammatory processes. Avascular necrosis of femoral head (AVNFH) is among diseases with high morbidity and necessity of early diagnosis for improving life quality of the patient. This study was planned as the first study to investigating the possible relationship of these parameters with diagnosis and staging in patients with AVNFH. Aim of this study was to investigate the effects of these biochemical parameters on patients with AVNFH as well as to evaluate their relations with prognosis.

Although there has been no large-scale study of this matter in our country; there has been around 15.000 AVN cases in America whom 18% of them require total hip prosthetic surgery (12). Risks causing development of AVNFH in adults are multifactorial. Therefore, interventions aiming prevention of AVNFH are insufficient. However, early diagnosis and staging may be possible with imaging modalities such as X-ray and MRI if clinical suspicion is present. Complete blood count is related with some of the inflammatory diseases; and cells like neutrophil, lymphocyte, platelet play a role in various stages of inflammation. Importance of blood cell ratios like NLR has been increasingly recognized as inflammation markers with remarkable skill for estimating the severity and/or prognosis of many different chronic inflammatory processes like ischemic heart and cerebral diseases, neurodegenerative diseases, metabolic syndrome, osteoporosis and autoimmune diseases as well as malignancies and chronic obstructive lung diseases (13).

Additionally, neutrophils may be related with occurrence of thrombocyte and leucocyte aggregations on intravascular lumen and therefore it may determine the increase in infarction progression area. Neutrophils may also precipitate plaque rupture by releasing proteolytic enzymes, arachidonic acid derivatives and superoxide radicals. N/L ratio is an easily accessible biomarker which may provide important information about complex inflammatory activity on the vascular bed during active phase of diseases (14, 15)

Although we couldn't find a study conducted on this issue in literature; there is a study of Wang et al demonstrating platelet/lymphocyte ratio as a diagnostic parameter in Perthes disease (16). However, there was no significant difference between two group in terms of PLR in our study.

There have been many studies about NLR in many orthopedic disorders in literature. Generally,

significant results have been obtained in studies about 1-year mortality of hip fractures in elders whereas it has also been considered as an indicator of an inflammatory process in other systemic disorders (17–19). In our study, a significant difference between groups in terms of Neutrophil/Lymphocyte ratio was observed. Neutrophil/Lymphocyte ratio was higher in study group (2.11±0.85) than control group (1.75±0.44). This may also be considered as an indicator of the inflammatory process.

Previous studies have shown that NLR increase in Legg-Calve-Perthes disease (20). In this study, significant NLR differences between stages according to Herring classification were also observed. In our study conducted with adults, there was no significant difference in biochemical parameters among Ficat-Arlet classification.

There are some limitations in our study. This study was designed to be retrospective. Number of patients in this study could be higher.

In conclusion, NLR which is an easily accessible biochemical parameter with significant difference may be a new adjuvant diagnostic parameter in patients with AVNFR.

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