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Original Article *Özgün Araştırma*

PLATELET TO LYMPHOCYTE RATIO AS A PREDICTIVE BIOMARKER FOR PREOPERATIVE DIAGNOSIS OF PARATHYROID ADENOMA

Paratiroid Adenomunun Ameliyat Öncesi Tanısında Öngörücü Bir Biyobelirteç Olarak Trombosit/Lenfosit Oranı

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ABSTRACT

Objective: There is a significant increase in studies concerning the use of platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) for diagnosis and prognosis in many inflammatory and malignant diseases. The idea that PLR and NLR can be used as a biomarker attracts many researchers to this area. The aim of this retrospective case control study was to investigate the role of PLR and NLR values in diagnosis of the parathyroid adenoma.

Material and Methods: In this study, 17 patients with parathyroid adenoma (PAD group) were included and the PLR and NLR values of these patients were compared with control group (15 participants) consisted of healthy subjects.

Results: The lymphocyte count values of the PAD group were significantly higher than those of the CONTROL group. The platelet count and NLR values were not different between the groups. The PLR values of the PAD group were significantly lower than those of the CONTROL groups. ROC-Curve analysis results showed that if platelet to lymphocyte ratio value was <125, it could be a specific and sensitive biomarker in discrimination of patients with parathyroid adenoma from healthy individuals.

Conclusion: In conclusion, low PLR values measured in patients with primary hyperparathyroidism could be a new preoperative diagnostic biomarker for parathyroid adenoma.

***Keywords**: Primary hyperparathyroidism, parathyroid adenoma, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio*

ÖZ

Amaç: Trombosit lenfosit oranı (PLR) ve nötrofilin lenfosit oranı (NLR) değerlerinin pekçok inflamatuvar ve malign hastalığın prognoz ve tanısında kullanımına yönelik çalışmalar her geçen gün artarak devam etmektedir. PLR ve NLR nin bir biyobelirteç olarak kullanılabilirliği fikri pek çok araştırmacının ilgisini bu alana çekmektedir. Bu retrospektif vaka kontrol çalışmasının amacı, PLR ve NLR değerlerinin paratiroid adenomu tanısındaki rolünü araştırmaktır.

Gereç ve Yöntemler: Bu çalışmaya paratiroid adenomu olan 17 hasta (PAD grubu) dahil edildi ve bu hastalara ait PLR ve NLR değerleri sağlıklı bireylerden oluşan Kontrol grubu (15 katılımcı) değerleri ile karşılaştırıldı.

Bulgular: PAD grubunun lenfosit sayım değerleri CONTROL grubundan anlamlı derecede yüksekti. Trombosit sayısı ve NLR değerleri gruplar arasında farklı değildi. PAD grubunun PLR değerleri Kontrol grubundakilerden anlamlı derecede düşüktü. ROC-Curve analizi sonuçları, trombosit lenfosit oranı değeri <125 olduğunda, paratiroid adenomlu hastaların sağlıklı bireylerden ayrılmasında spesifik ve hassas bir biyobelirteç olabileceğini göstermiştir.

Sonuç: Sonuç olarak, primer hiperparatiroidizm hastalarında ölçülen düşük trombosit lenfosit oranı değerleri paratiroid adenomu tanısı için preoperatif yeni bir biyobelirteç olabilir.

***Anahtar Kelimeler**: Primer hiperparatiroidizm, paratiroid adenomu, nötrofil lenfosit oranı, trombosit lenfosit oranı*

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INTRODUCTION

Parathyroid hormone (PTH) regulates calcium and phosphorus metabolism through the modulation of osteoblastic and osteoclastic activities, renal tubular calcium reabsorption, vitamin D absorption, and hydroxylation (1,2). Primary hyperparathyroidism (PHPT) is most commonly associated with parathyroid adenoma while parathyroid hyperplasia and carcinoma are two other less common etiological entities (3). While PTH induces the production of interleukin 6 (IL-6) (4,5), vitamin D decreases pro-inflammatory markers such as IL- 6 and C-reactive protein (CRP) (6). It has been reported that high serum PTH levels are associated with increased CRP and platelet to lymphocyte ratio (PLR) (1). Furthermore, the neutrophil to lymphocyte ratio (NLR) and PLR have been found to decrease after parathyroidectomy in patients with secondary hyperparathyroidism (7). To date, a limited number of studies have focused on the relationship between PLR, NLR, parathyroid adenoma size and PTH level in patients who have undergone parathyroidectomy (2,8). To the best of our knowledge, the possible associations of PLR and NLR values with the parathyroid adenoma have not been previously studied.

The aim of this retrospective case-control study was to explore the possible association of NLR and PLR values with the parathyroid adenoma in patients who underwent parathyroidectomy.

MATERIALS AND METHODS

Patient Groups

The study protocol was approved by the Local Ethics Committee. Since the study was conducted retrospectively, written informed consent was not required.

This study included patients with primary hyperparathyroidism who underwent parathyroidectomy between January 2014 and December 2017. The demographic characteristics of the patients, surgical details, and histopathological examination results were recorded. In order to compare the results of the patients with PHPT to the results of the healthy individuals, a control group consisting of 15 individuals who had normal serum calcium level, without active infectious disease over 18 years of age and without systemic or malignant disease was formed. The study groups were described as below:

CONTROL group comprising healthy individuals (n=15)

PAD group comprising patients with parathyroid adenoma (n=17)

Patients with incomplete data, active infectious diseases, history of other malignancies, systemic inflammatory or autoimmune diseases, or hematological disorders were excluded from the study. Any patients diagnosed with parathyroid or thyroid carcinoma were also excluded from the study.

Methods

The age and gender of all participants included in the study were recorded.

Preoperative values of the serum calcium level, blood leukocyte count, neutrophil count, lymphocyte count, platelet count, NLR and PLR were evaluated. Preoperative and postoperative serum calcium and PTH level values and postoperative histopathological examination results of the parathyroid glands were evaluated in all patients. Parathyroid glands of all patients were evaluated by ultrasonography (USG) preoperatively to show the presence and localization of parathyroid gland lesions. If the lesion could not be identified on USG, magnetic resonance imaging (MRI) was performed. If both radiological methods could not demonstrate the lesion, technetium 99-MIBI scintigraphy was applied to the patients.

Surgical Procedure

All patients underwent standard parathyroidectomy. The PTH level was measured in a venous blood sample 10 minutes after the removal of the pathological

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parathyroid tissue and the operation was terminated when the measured PTH level value was confirmed to be less than 50% compared to the preoperative value (9).

Biochemical Analysis

Serum calcium (reference range 8.8-10.6 mg/dL) and PTH (reference range 15-65 pg/mL) levels obtained preoperatively and at 24h postoperatively were studied in the biochemistry laboratory using the original commercial kits (Roche) (Roche Diagnostic COBAS c501). Serum PTH levels were measured using the "immunoturbidimetric" method. Serum calcium levels were determined with the ISE (ion selective electrode) method. Blood platelet count (reference range: 150,000-500,000/uL), leukocyte count (reference range: 4,400-11,300/uL), neutrophil count (reference range: 1,100-9,600/uL) and lymphocyte count (reference range: 500-6,000/uL) values were determined using an automatic analyzer (Mindray BC-6800, Shenzen, China).

Statistical Analysis

Non-parametric data were analyzed using the *Mann-Whitney U* test. Parametric data were analyzed using the *Independent Samples t* test Parametric data of the repeated measures were analysed for each group using the *Paired Samples t* test. Non-parametric data of the repeated measures were analysed for each group using the *Wilcoxon Signed Ranks* test. *ROC-Curve* test was applied to determine the predictive properties of the parameters of the disease and the sensitivity and specificity ratios were determined by setting "cut-off" values. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

The Control group was consisted of 5 male and 10 female. The PAD group contained 4 male and 13 female. No difference was found between the groups in terms of age and gender.

When the preoperative findings of the PAD group were compared with the Control group findings, serum calcium levels ($p<0.001$) and lymphocyte count values ($p=0.012$) in the PAD groups were higher than those of the CONTROL group. However, PLR values of the PAD group were lower than Control group's values ($p=0.010$) (Table 1).

When the postopreative findings of the PAD group were compared with the Control group findings, the neutrophil count ($p=0.011$), serum calcium level ($p=0.001$) and PLR level ($p=0.005$) values were found to be statistically different between the Control and PAD groups. These results revealed that calcium levels and PLR values in the PAD group was lower than those of the CONTROL group, but neutrophil count values were higher than those of the CONTROL group (Table 2).

Statistical analysis of the repeated measures of the variables in the patients of the PAD group demonstrated that postoperative serum PTH levels ($p=0.001$), calcium levels ($p<0.001$) and platelet count values ($p=0.002$) were significantly decreased compared to the preoperative level values (Table 3).

The ROC-Curve analysis results demonstrated that if the PLR value was <125.00, it could be 80% sensitive and 76.5% specific in discriminating the patients with parathyroid adenoma from the healthy subjects (area=0.824, $p=0.002$, cut-off value=125.00). (Table 4, Figure 1).

Table 1: The table demonstrates the findings of the Control group and preoperative findings of the PAD group. *Independent Samples t test, p<0.05* (Min: minimum, Max: maximum, SD: standart deviation, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio)

	CONTROL				**PAD**				
Variable	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	p
Age	48.93	15.89	20.00	75.00	56.05	10.79	37.00	71.00	0.144
Neutrophil count	4.52	1.40	2.47	7.05	5.26	1.65	2.45	8.15	0.187
Lymphocyte count	1.88	0.48	1.02	2.82	2.62	0.96	1.45	4.73	0.012
Platelet count	279.93	56.84	210.00	413.00	282.47	102.24	168.00	474.00	0.933
NLR	2.44	0.68	1.46	3.75	2.12	0.73	1.38	3.84	0.206
PLR	158.79	64.21	100.00	374.00	111.28	29.11	74.57	180.25	0.010
Serum calcium	9.34	0.26	8.80	9.74	11.43	0.96	9.36	12.89	<0.001

Table 2: The table demonstrates the findings of the Control group and postoperative findings of the PAD group. *Independent Samples T Test,* p<0.05 (Min: minimum, Max: maximum, SD: standart deviation, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio).

	CONTROL				**PAD**				
Variable	Mean	SD.	Min.	Max.	Mean	SD	Min.	Max.	p
Neutrophil count	4.52	1.40	2.47	7.05	6.37	2.23	2.24	9.96	0.011
Lymphocyte count	1.88	0.48	1.02	2.82	2.42	0.93	1.40	4.74	0.055
Platelet count	279.93	56.84	210.00	413.00	234.00	73.23	156.00	359.00	0.065
NLR	2.44	0.68	1.46	3.75	2.88	1.31	1.23	5.53	0.262
PLR	158.79	64.21	100.00	374.00	102.61	29.91	56.50	154.76	0.005
Serum calcium	9.34	0.26	8.80	9.74	8.77	0.56	7.98	9.89	0.001

Table 3: The table demonstrates the preoperative and postoperative findings of the PAD group. *Wilcoxon Signed Ranks Test and Paired Samples T Test,* p<0.05 (Min: minimum, Max: maximum, SD: standart deviation, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, PTH: parathyroid hormon)

	PREOPERATIVE					**POSTOPERATIVE**					
Variable	Mean	Median	SD	Min.	Max.	Mean	Median	SD	Min.	Max.	p
Neutrophil count	5.26	5.33	1.65	2.45	8.15	6.37	6.14	2.23	2.24	9.96	0.065[1]
Lymphocyte count	2.62	2.51	0.96	1.45	4.73	2.42	2.21	0.93	1.40	4.74	0.406[1]
Platelet count	282.47	251.00	102.24	168.00	474.00	234.00	209.00	73.23	156.00	359.00	0.002[1]
NLR	2.12	1.90	0.73	1.38	3.84	2.88	2.63	1.31	1.23	5.53	0.050[1]
PLR	111.28	110.55	29.11	74.57	180.25	102.61	100.00	29.91	56.50	154.76	0.491[1]
Serum calcium	11.43	11.33	0.96	9.36	12.89	8.77	8.80	0.56	7.98	9.89	<0.001[1]
PTH	184.40	139.85	141.52	62.90	637.00	40.35	26.81	42.65	5.07	196.72	0.001

[1]t test

Table 4: The table demonstrates the ROC-Curve test result for platelet to lymphocyte ratio. (PLR: platelet to lymphocyte ratio)

Variable	**Area**	**p**	**Cut-off value**	**Sensivity**	**Specificity**
PLR	0.824	0.002	<125	80%	76.5%

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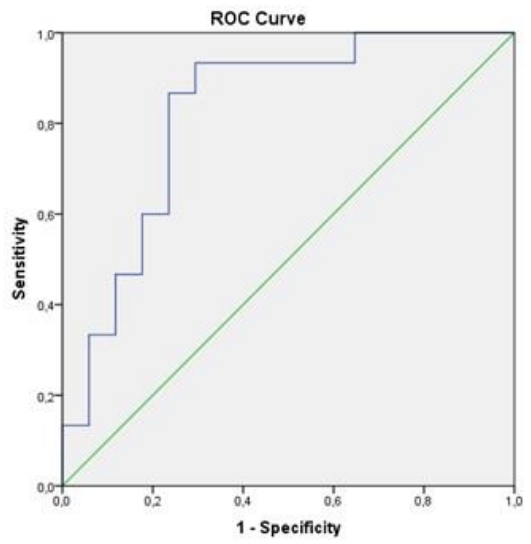

Figure 1: Figure shows the ROC-Curve analysis result of the platelet to lymphocyte ratio

DISCUSSION

There have been an increasing number of investigations about the PLR and NLR, which are blood-based laboratory parameters used regularly as diagnostic and prognostic biomarkers in several malignant diseases. Systemic inflammation has been found to have a role in tumor progression and recurrence in various solid malignancies (2,7,8,10,11,12). As a result of this process, the neutrophil and platelet counts increase, while the lymphocyte count decreases. Accordingly, PLR and NLR values are expected to increase. In the current study, the lymphocyte count results were high and PLR values were low in patients with parathyroid adenoma. However, NLR values and neutrophil and platelet count values were similar in all the patients and healthy participants. It was thought with these results that the decreasing of PLR values in patients with parathyroid adenoma could be due to higher lymphocyte count values rather than thrombocytosis. Therefore, it could be said that parathyroid adenoma may induce a systemic inflammatory response and increase circulating lymphocytes as mentioned above.

Cheng et al observed a trend but not a significant association between serum PTH and PLR values (1). PLR and NLR have also been studied in patients with secondary hyperparathyroidism who underwent parathyroidectomy. After successful surgery, the PLR and NLR values and platelet count values were observed to have significantly decreased, although NLR and PLR did not change in patients with recurrent or persistent hyperparathyroidism. However, a causal relationship between PTH levels and PLR or NLR values has not yet been identified (13). In literature, a few studies have reported an association of preoperative PTH with PLR and NLR in secondary hyperparathyroidism, but no such association has been previously demonstrated in primary hyperparathyroidism. However, Kamani et al demonstrated a significant positive correlation between serum PTH and calcium levels and adenoma size and weight (2). In the present study, no correlation was found between the PTH and PLR level values measured preoperatively in patients with parathyroid adenoma. Nevertheless, no association was found between preoperative PTH level value and adenoma size in the present study. As the aim of this study was to determine the etiological cause using simple laboratory tests in patients with PHPT diagnosed using radiological methods, the results of this study could not identify which molecular mechanisms (Such as cytokines, kemokines) could increase circulating lymphocytes while decreasing the PLR value in patients with parathyroid adenoma. On the other hand, platelet count results, serum calcium levels and PTH levels decreased and NLR values were slightly increased after parathyroidectomy in patients with parathyroid adenoma. However, neutrophil count, lymphocyte count and PLR values did not change after surgery. With these results, it could be said that PLR value is the predictive biomarker for distinguishing the patients with parathyroid adenoma from the healthy individuals. Moreover, the ROC-Curve analysis results

which supported this hypothesis demonstrated that when the PLR value was <125, it could be 80% sensitive and 76.5% specific in differentiating patients with parathyroid adenoma from healthy individuals. Therefore, it can be concluded with these findings that the PLR value could be used as a predictive biomarker for the preoperative diagnosis of parathyroid adenoma in patients with PHPT.

Finally, it was concluded from the results of this preliminary study that the lymphocyte count value was high and PLR level value was low in patients with parathyroid adenoma. Therefore, there is a need for those mechanisms to be investigated in more advanced studies with wider sampling.

Limitations

There are some limitations to the current study. *First*, as the study was a retrospective analysis, there could have been selection bias. *Second*, this study was a single center analysis including a limited number of patients because of the relatively rare incidence of PHPT and this small sample size may limit the generalization of the results. However, its findings were unexpected and therefore there is a clear need for more studies to confirm and/or generalize these findings. Finally, systemic inflammatory processes at the molecular level (such as chemokine and/or cytokine release) were not analyzed, because this study was performed using only the radiological, clinical and simple laboratory findings of the patients. In fact, these inflammatory processes may have a predictive effect on the etiological cause, but molecular analysis was far from the aim of this study. Therefore, it could be recommended that the predictive effects of these and other biochemical parameters should be investigated in more advanced studies with wider sampling and long-term follow-up findings.

It was thought at the end of this study that low PLR values measured in patients with PHPT could be a diagnostic biomarker for parathyroid adenoma, preoperatively. Therefore, the findings of this study could provide a base for further investigations of PLR changes in parathyroid diseases.

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Conflict of Interests: The authors have no conflict of interests to declare.

Ethical approval: The study protocol was approved by the Local Ethics Committee (Approval date: 29.05.2018 and Approval number: 13/03).

Informed consent: Since the study was conducted retrospectively, written informed consent was not required.

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