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Predictive Value of Neutrophil-to-Lymphocyte Ratio for the Assessment of Remission in Cushing's Disease

Cushing Hastalığı Remisyon Değerlendirmesinde Nötrofil Lenfosit Oranının Yeri

Özgün Araştırma
Research Article

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ABSTRACT

Objective: *In recent years neutrophil-to-lymphocyte ratio is defined as one of the new and early prognostic markers for many carcinomas including some types of intracranial tumors. The aim of the present study is to assess the association between preoperative and postoperative neutrophil-to-lymphocyte ratios and remissions in patients with Cushing's disease.*
Method: *The present study was carried out using the data of 162 consecutive patients operated for Cushing's disease by a single surgeon (NG) between 1997 and 2017. Clinical records were analyzed retrospectively. Neutrophil-to-lymphocyte ratios calculated from complete blood counts recorded preoperatively, on postoperative 1st day and at postoperative 3rd month in 24 patients in early, and 3rd month remissions and correlations among them were investigated.*
Results: *A statistically significant difference was observed between preoperative, postoperative 1st day and postoperative 3rd month NLRs in patients who were in early stage emission (p=0.001) or not (p=0.002). Any statistically significant difference was not found between patients who were in remission or not at 3rd months in terms of NLRs measured at different time points. There was a statistically significant difference between preoperative, postoperative first day and postoperative 3rd month NLRs in patients in remission (p=0.001) or not (p=0.005) during long-term follow-up. No statistically significant difference was found between NLRs measured at different times among those who were remission or not during long-term follow-up.*
Conclusion: *Cushing's disease is a disease directly associated with stress hormones and its effects on NLR is inevitable. New studies with larger patient series will shed light on this issue.*

Keywords: *Neutrophil lymphocyte ratio, cushing's disease, remission*

ÖZ

Amaç: *Son yıllarda nötrofil lenfosit oranı bazı beyin tümörü tiplerini de içeren pek çok kanser için erken prognostik faktörlerden biri olarak tanımlanmıştır. Çalışmanın amacı Cushing hastalarında operasyon öncesi ve sonrası nötrofil lenfosit oranları ile remisyon arası ilişkiyi araştırmaktır.*
Yöntem: *Çalışma Cushing hastalığı tanısıyla 1997 ila 2017 yılları arasında tek bir cerrah (NG) tarafından opere edilmiş ardışık 162 hastanın bilgileri retrospektif olarak araştırılarak gerçekleştirilmiştir. Çalışma kriterlerini karşılayan 24 hastanın operasyon öncesi, postoperatif 1. gün ve postoperatif 3. ay tam kan sayımı değerlerinden hesaplanan nötrofil lenfosit oranları ile erken remisyon ve 3. ay remisyona girmiş olma durumları karşılaştırılarak arasındaki ilişki araştırıldı.*
Bulgular: *Preoperatif, postoperatif 1.gün ve postoperatif 3. ay nötrofil lenfosit oranının erken remisyona giren hasta grubunda (p=0,001) ve erken remisyona girmeyen grup hastalarda da (p=0,002) anlamlı farklı olduğu gözlendi. Ancak 3. ay remisyona giren grupta ve remisyona girmeyen grupta ölçülen nötrofil lenfosit oranları arası fark anlamlı bulunmadı. Uzun dönem takipte olup remisyonda olan ve remisyona girmemiş olguların operasyon öncesi, postoperatif 1. gün ve postoperatif 3. ayda bakılan nötrofil lenfosit oranları arasında anlamlı bir fark bulundu. Ancak uzun dönem takiplerinde remisyonda olan hastalar (p=0,001) ile remisyona girmemiş hastaların (p=0,005) oranları arasında anlamlı bir fark bulunmamıştır.*
Sonuç: *Cushing hastalığı stres hormonları ile direkt bağlantılı bir hastalıktır ve bunun nötrofil lenfosit oranlarına etkisi kaçınılmazdır. Daha geniş serilerle yapılacak çalışmalar bu konuya ışık tutacaktır.*

Anahtar kelimeler: *Nötrofil lenfosit oranı, cushing hastalığı, remisyon*

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INTRODUCTION

About 15% of brain tumors are pituitary adenomas [1]. Cushing's disease (CD) is a rare type of pituitary adenoma characterized by uncontrolled release of adrenocorticotrophic hormone (ACTH) and cortisol. The clinical manifestations of CD may be variable including centripetal obesity, moonface, cutaneous striae, and hirsutism. High cortisol levels for many years have been shown to be associated with a number of comorbidities and an increased rate of mortality [2,3]. Of course these complications occur due to chronic exposure. However the benefits of corticosteroids are inevitable. Glucocorticoids have anti-inflammatory effects by supressing the production of acute phase reactants. As is known, neutrophils are one of the most important components of acute inflammation and they play an important role in the fight against pathogens [4].

In recent years, several articles on the relationship between chronic inflammation and cancer have been published. The inflammatory response triggered by the tumor microenvironment causes the release of acute phase reactants followed by changes in the serum neutrophil and lymphocyte counts. This change is often in the form of neutrophilia and lymphopenia, which leads to an elevation in neutrophil-to-ymphocyte ratio (NLR). NLR is an emerging inflammatory marker and it has been shown in the literature that the increase in NLR affects the course of the disease and the survey in various types of cancer [5].

In Cushing's disease increased levels of proinflammatory cytokines are found both in remission and active disease period. Although glucocorticoid levels increase with antiinflammatory activity in Cushing's disease patients, inflammation-related complications such as obesity, cardiovascular disease are frequently observed [6]. In the present study we aimed to test the predictive value of NLR for remission in Cushing's disease.

MATERIALS AND METHODS

A total of 162 consecutive patients who underwent surgery for Cushing's disease by a single surgeon (NG) between 1997 and 2017 were evaluated retrospectively. Approval of the Ethics Committee of University of Health Sciences Izmir Tepecik Education and Research Hospital was obtained for our study (approval number/date 2019/15-11/24.10.2019). Medical records of patients were investigated. Patients who had inflammatory disease, metabolic syndrome, diabetes mellitus, other intracranial pathologies, hematologic diseases and also patients whose preoperative and postoperative 1st day and 3rd month complete blood count (CBC) results were not available were excluded from the study. Twenty-four patients who had preoperative and postoperative follow-up CBC results and meeting the criteria for the study were included in the study. The preoperative, early postoperative and postoperative third month CBC values of the patients were recorded. NLRs were calculated as the ratio between absolute neutrophil and lymphocyte counts.

Remission was defined as: normalization of circadian rthym and ACTH and postoperative baseline cortisol of <3,5 µg/dl; serum cortisol of <1,8 µg/dl after 1 mg dexamethasone suppression test.

Statistical analysis

Descriptive statistics were reported as median and IQRs. The variables were investigated using analytical methods (Kolmogorov-Simirnov test) to determine whether they are normally distributed or not. Freidman tests were used for statistical comparison of data between the related groups. The Wilcoxon test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. Mann-Whitney U tests were used for statistical comparison of data between the independent groups. A p value <0.05 was considered to be statistically significant within the 95% confidence interval. Statistical analyses were

performed using SPSS v21.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

There was a female predominancy (%79,1; n:19) The median age of the patients was 37.5 (range, 24-71) years with an average follow-up of 103 months (range, 12-247 months). Sixteen patients were in remission at 3rd month while 8 of them were not. Sixteen patients were in remission, while 7 patients were not at final follow-up visit. There was a statistically significant difference between preoperative, postoperative 1st day and postoperative 3rd month NLRs in patients in remission at 3rd months (p=0.001). In posthoc binary analysis, postoperative 1st day values were higher than other groups. In the non-remission group, there was a statistically significant difference between preoperative, postoperative 1st day and postoperative 3rd month NLRs (p=0.002). In post-hoc binary analysis, postoperative 3rd month values were lower than other groups (Table 1). Any statistically significant difference was not found in 3rd month patients in remission or not in terms of NLR measured at different time points (Figure 1).

There was a statistically significant difference between preoperative, postoperative first day and postoperative 3rd month NLRs in patients who were in remission or not at final follow-up visit p=0.005). In post-hoc binary analyzes, NLR values of postoperative 3rd month were lower than other groups. There

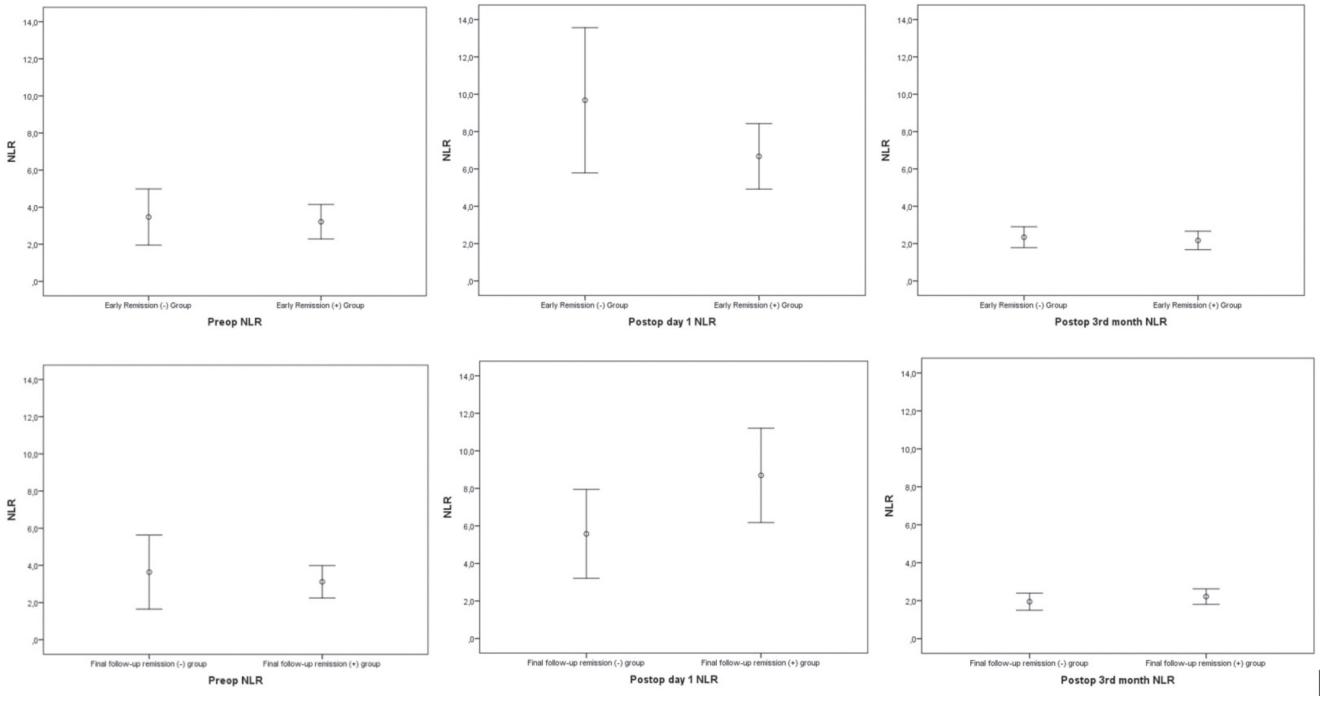


Figure 1. Statistical analysis results of remission and non-remission groups' NLRs measured at different time points.

Table 1. Statistical results of the groups.

	Preop NLR	Postop 1st day	Postop 3rd moth	p*	Group 1-2	Group 1-3	Group 2-3
3rd month remission (16 patients)	3.0 (2.4)	6.7 (5.5)	2.0 (1.3)	0.001	0.014	1	0.001
3rd month non-remission (8 patients)	3.5 (3.4)	8.8 (6.5)	2.0 (1.4)	0.002	1	0.018	0.003
Final follow-up remission (16 patients)	3.2 (2.4)	6.9 (5.3)	2.0 (1.1)	0.001	0.024	0.867	0.001
Final follow-up non-remission (7 patients)	2.9 (2.1)	5.1 (6.3)	1.8 (0.4)	0.005	1	0.023	0.01

**FreidmanTest*
***Post-hoc p value was calculated as adjusted value for pairwise comparisons.*

was a statistically significant difference between preoperative, postoperative first day and postoperative 3rd month NLRs in patients in remission at final follow-up visit (p=0.001). In post-hoc binary analysis, postop 1st day values were higher than other groups (Table 1).

No statistically significant difference was found between NLRs measured at different time points among those who were or were not in remission at final follow-up visit (Figure 1).

DISCUSSION

In recent years, articles investigating the relationship between NLR and many types of cancers are noteworthy. It has been also shown that NLR can be used as a prognostic factor for some types of cancer, such as lung, colorectal and renal carcinomas [7]. Our study is the first study to date investigating the relationship between NLR and remission in Cushing's disease. CD is directly associated with cortisol levels and the effects of cortisol on peripheral blood cells are well known. In this context, lthough there were significant differences between the preoperative, postoperative 1st day and postoperative 3rd month NLR values, when we evaluated the relationship between the disease and NLR, we could not find any evidence that NLR values could be significant predictors for remission.

Inflammation is one of the factors responsible for both the development and the progression of various cancers [8]. As a well known fact hypoxic areas in tumor tissues secrete lactic acid. Some molecules are expressed by tumor-associated macrophages accumulating in these areas and then angiogenesis is triggered. Also this areas trigger the proinflammatory pathways. Two main pathways have been identified that activate leukocytes. The first is the intrinsic pathway, which is driven by genetic factors and causes inflammation leading to neoplasia. Another is the extrinsic pathway where cancer is triggered directly by inflammatory agents [8]. Although the cause is not fully understood there may be an increase in neutrophil counts in cases with cancer. The cytokines that are effective in the pathways mentioned above are thought to trigger increases in neutrophil counts [7]. Increased neutrophil count is also one of the reasons for lymphocytes to undergo apoptosis and eventually number of lymphocytes is reduced.

The following result can be deduced; decreased lymphocyte counts may show progression of tumor and poor prognosis. In this context, many studies have reported that NLR can be used to determine the prognosis and recurrence of many tumors [5,9-11].

Corticosteroids are known to increase lymphocyte counts and reduce lymphocyte ratios [12]. In the literature, there are studies in which NLR's are examined without considering the use of corticosteroids. These studies are reported as pitfalls in studies with NLR in the literature [13]. The circulating lymphocytes in the peripheral blood are affected by the secretions of adrenal cortex. In studies conducted with experimental animals and human beings in the 1940s, adrenocorticotropic hormone-treated subjects had decreased lymphocyte counts and increased neutrophil counts, and the researchers stated that the pituitary adrenal mechanism is an important control center affecting the number of peripheral leukocyte, and neutrophil counts [14]. So it is not difficult to predict that there will be a change in NLR rates when the levels of stress hormones increase in Cushing's disease. In our study there was a statistically significant difference between the preoperative, postoperative day 0 and third month NLRs in patients with early onset remission (p=0.004). Determining remission in patients with Cushing's disease may not always be easy. Some of the patients who were operated had not immediately reach remission so the hormone levels were normalized over time during follow-up. Some may enter remission in the early postoperative period, some in months

later on, or additional treatments may be required.

We have analyzed NLRs in our patients for, which we think may be a criterion that can help in monitoring this difficult treatment and follow-up process. When we examine the NLR in operated patients in remission or not for preop, postop 1st day and postop 3rd month, values were statistically different. Patients with 3rd month remission or final follow-up remission were found to have higher NLR values on the postoperative first day. These results excited us at first sight. However, no statistically significant difference was found between 3rd month remission and non-remission groups in terms of NLR and N/L (%) rates measured at different time points Also there was no significant difference in follow-up remission and non-remission groups. As a result, we think that there may be a difference between groups with larger patient populations, and perhaps even NLR may be used as an early predictor for remission.

There are limitations to our study design. In our routine, we check CBC in preoperative and postoperative 1st day for the patients we operated for Cushing's disease. We rarely check CBC in 3rd month control. This situation led us to investigate only 24 of 162 patients. Although we could not find statistically significant results in patients with 3rd month remission or at final follow-up, we found have higher NLR values on the postoperative first day. Perhaps these results will be able to shed light on the confusion in the literature regarding remission by re-working with larger series.

In conclusion, we hypotized that NLR might be a predictive factor for remission in Cushing's disease. Although we have found various clues, we did not find any evidence to support our hypothesis among patients who were in remission or not. We think that our study is the first in literature to test the relation between NLR and remission in Cushing's disease. New studies with larger patient series will shed light on this issue.

Ethics Committee Approval: İzmir Tepecik Training and Research Hospital Local Ethics Committee approval was obtained (approval number/date 2019/15-11/24.10.2019).
Conflict of Interest: None.
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Informed Consent: None (retrospective study)

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