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Original Article / *Özgün Makale*

How does allergen-specific immunotherapy affect mean platelet volume and complete blood inflammation markers?

Alerjen spesifik immünoterapi ortalama trombosit hacmini ve tam kan inflamasyon belirteçlerini nasıl etkiler?

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ABSTRACT

Objectives: This study aims to investigate how allergen-specific immunotherapy (ASI) affected mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), eosinophil-to-lymphocyte ratio (ELR), basophil-to-lymphocyte ratio (BLR), and lymphocyte-to-monocyte ratio (LMR), which are essential indicators of systemic inflammation.

Patients and Methods: Medical records of a total of 19 patients (7 males, 12 females; mean age: 33 years; range, 18 to 45 years) who received ASI for medical treatment-resistant seasonal or perennial allergic rhinitis (AR) and 24 healthy individuals (12 males, 12 females; mean age: 34 years; range, 18 to 45 years) were retrospectively analyzed between January 2015 and January 2020. The patients were divided into three groups as follows: control group including healthy individuals (Group 1, n=24); pre-immunotherapy (PreIT) treatment (Group 2, n=19); and post-immunotherapy (PostIT) treatment group (Group 3, n=19). The prespecified markers were calculated from the routine complete blood count analyses and the results were compared among the PreIT, PostIT, and control groups.

Results: The MPV after ASI significantly increased in the PostIT group, compared to the PreIT group ($p<0.05$). The platelet, neutrophil, eosinophil, lymphocyte, and monocyte counts and PLR, NLR, ELR, and LMR values of the PostIT group did not significantly differ, compared to the PreIT group ($p>0.05$). Basophil and BLR values of the PostIT group significantly decreased, compared to the PreIT group ($p<0.05$).

Conclusion: Based on these results, it can be concluded that not only local inflammation, but also systemic inflammation contribute to the pathogenesis of AR, and not only local inflammation, but also systemic inflammation can be suppressed with ASI.

Keywords: Allergen specific immunotherapy, allergic rhinitis, basophil, basophil-to-lymphocyte ratio, complete blood inflammation markers, mean platelet volume.

ÖZ

Amaç: Bu çalışmada alerjen spesifik immünoterapinin (SİT) sistemik inflamasyonun temel göstergeleri olan ortalama trombosit hacmi (MPV), trombosit-lenfosit oranı (PLR), nötrofil-lenfosit oranı (NLR), eozinofil-lenfosit oranı (ELR), bazofil-lenfosit oranı (BLR) ve lenfosit-monosit oranını (LMR) ne yönde etkilediği araştırıldı.

Hastalar ve Yöntemler: Ocak 2015 - Ocak 2020 tarihleri arasında medikal tedaviye dirençli mevsimsel veya yıl boyu devam eden alerjik rinit (AR) nedeniyle SİT uygulanan toplam 19 hasta (7 erkek, 12 kadın; ort. yaş: 33 yıl; dağılım, 18-45 yıl) ile 24 sağlıklı bireyin (12 erkek, 12 kadın; ort. yaş: 34 yıl; dağılım, 18-45 yıl) tıbbi kayıtları retrospektif olarak incelendi. Hastalar şu şekilde üç gruba ayrıldı: sağlıklı bireylerden oluşan kontrol grubu (Grup 1, n=24), immünoterapi öncesi (PreIT) grup (Grup 2, n=19) ve immünoterapi sonrası (PostIT) grup (Grup 3, n=19). Önceden belirlenen belirteçler, rutin tam kan sayımı analizlerinden hesaplandı ve sonuçlar PreIT, PostIT ve kontrol grupları arasında karşılaştırıldı.

Bulgular: PreIT grubuna kıyasla, PostIT grubunda SİT sonrası MPV anlamlı düzeyde arttı ($p<0.05$). PreIT grubuna kıyasla, PostIT grubunda trombosit, nötrofil, eozinofil, lenfosit ve monosit sayıları ve PLR, NLR, ELR ve LMR değerleri anlamlı düzeyde farklılık göstermedi ($p>0.05$). PostIT grubunun bazofil ve BLR değerleri, PreIT grubuna kıyasla anlamlı düzeyde azaldı ($p<0.05$).

Sonuç: Bu sonuçlara göre, yalnızca lokal inflamasyonun değil, aynı zamanda sistemik inflamasyonun da AR patogenezine katkıda bulunduğu ve yalnızca lokal inflamasyonun değil, sistemik inflamasyonun da SİT ile baskılanabileceği sonucuna varılabilir.

Anahtar sözcükler: Alerjen spesifik immünoterapi, alerjik rinit, bazofil, bazofil-lenfosit oranı tam kan inflamasyon belirteçleri, ortalama trombosit hacmi.

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Allergic rhinitis (AR) is the most common cause of nasal mucosal inflammation characterized by reduced quality of life, work and home performance, affecting one in six individuals.[1] Since pharmacotherapy may provide a partial improvement, particularly in the control of systemic symptoms (e.g., tiredness or headache) of considerable amount of patients, both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) have been increasingly considered for the treatment of this patient group.[2]

The increased eosinophils, mast cells, and type 2 helper T cells (Th2) are responsible for AR immunopathology. There is also systemic inflammation in addition to nasal inflammation in patients with AR, which is associated with an immunoglobulin (Ig) E-mediated immune response to allergens. It has been previously shown that there is a relationship between systemic inflammation and AR.[3] Suppression of immediate and late-phase reactions in the nasal mucosa, and a decrease in the number of eosinophils and allergen-specific CD4+T lymphocytes in nasal secretions have been demonstrated after allergen administration in allergen-specific immunotherapy (ASI).[4]

The ASI causes numerous cellular and molecular events to occur and can be divided into four main topics. After initial exposure to therapeutic allergen doses, the early phase reaction develops, which is observed as a decrease in mast cell and basophil activity. Afterwards, interleukin (IL)-10 secretion increases with the regulatory T (T_{reg}) and B (B_{reg}) cell activation.[5] Transforming growth factor-beta (TGF-β) and IL-10, secreted by T_{reg} and B_{reg} cells, suppress total and specific IgE by encouraging B cells to switch types.[6] Late phase responses in allergic reactions are characterized by the accumulation, activation, and persistence of eosinophils and T cells in the area exposed to the allergen.[5] The immunotherapy has been demonstrated to cause a shift from Th2 lymphocyte production to Th1 lymphocytes by suppressing the production of primary eosinophil agents and increasing the production of primary neutrophil agents.[7] Therefore, it is evident that ASI affects regional inflammation components, leading to an increase in some factors, and suppresses others.

The platelet size has been shown to affect the platelet activity and has been accepted as a useful predictor and prognostic biomarker of cardiovascular events.[8] The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been investigated in recent years as important indicators of systemic inflammation, and several studies have reported that NLR and PLR have a prognostic value in many diseases, including cardiovascular diseases and cancer.[9,10] The high NLR, along with the high eosinophil/lymphocyte ratio (ELR), is a new inflammation marker which can be easily calculated from complete blood count.[11,12] Additionally, it has been shown that the high basophil/lymphocyte ratio (BLR), together with the high ELR, can be used as an inflammation marker to predict recurrence in recurrent nasal polyps.[13] Similarly, the high lymphocyte-monocyte ratio (LMR) has been accepted as an indicator of systemic inflammation and poor prognosis in malignancies.[14]

To the best of our knowledge, there is no study in the literature investigating the effects of immunotherapy on systemic inflammation markers, i.e., NLR, PLR, ELR, BLR, and LMR, and post-immunotherapy changes in these inflammation markers have not been revealed, yet. In the present study, we aimed to investigate how the ASI affected mean platelet volume (MPV), PLR, NLR, ELR, BLR, and LMR, which are essential indicators of systemic inflammation.

PATIENTS AND METHODS

Study design and study population

This single center, retrospective study was conducted at Istanbul Training and Research Hospital, internal medicine allergy and immunology clinic and otorhinolaryngology-head and neck surgery clinic between January 2015 and January 2020. Medical records of a total of 19 patients (7 males, 12 females; mean age: 33 years; range, 18 to 45 years) who received ASI for medical treatment-resistant seasonal or perennial AR and 24 healthy individuals (12 males, 12 females; mean age: 34 years; range, 18 to 45 years) who were admitted to the otolaryngology outpatient clinic with symptoms other than AR, asthma, any chronic systemic and atopic disease were reviewed. The control group was selected from the patients with available complete blood count results in the hospital data entry system. Using the medical records, comorbidities of the patients were documented. The patients were also contacted by phone and the presence of comorbid diseases and medications used were questioned. Those aged between 18 and 45 with chronic or systemic diseases were excluded from the study. An informed consent was waived due to the retrospective nature of the study and the analysis used anonymous clinical data. The study protocol was approved by the Clinical Research Ethics Committee of Istanbul Training and Research Hospital (No: 2553-Date: 16.10.2020). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients were divided into three groups in the study as follows: control group including healthy

individuals (Group 1, n=24); pre-immunotherapy (PreIT) treatment (Group 2, n=19); and post-immunotherapy (PostIT) treatment group (Group 3, n=19). Except for data analyst masking, no randomization and blinding were applied.

Twenty patients aged from 18 to 45 years with a confirmed diagnosis of moderate or severe AR were included in the study. The diagnosis of AR was made by evaluating the presence of typical symptoms for at least two years in the medical history, typical examination findings, and allergy prick test results together. The prick test was done with extracts supplied from the ALK company (ALK-Abelló A/S, Hørsholm, Denmark). The patients who had AR allergic symptoms for less than two years, those with respiratory tract diseases such as asthma, infectious diseases, chronic obstructive respiratory diseases, nasal polyposis, and with anatomical pathologies accompanying AR in ear, nose and throat examination, who had medical treatment or underwent surgical intervention (including plastic and reconstructive surgery) two months before the study or during the study, who were pregnant or breastfeeding, and with immunodeficiency or hematological diseases, who had obstructive sleep apnea, cardiovascular, infectious and rheumatological diseases and who had diabetes mellitus, hypertension, and malignancy were excluded from the study. In the hospital database, there are no available data before 2015. Since patients without any comorbid diseases and infections were included in this study, a change in the inflammation parameters of the complete blood count is not expected. Therefore, the results of complete blood count before 2015 were not analyzed.

Type of treatment

The patients underwent SCIT with grass pollen or mite extracts (ALK-Abelló A/S, Hørsholm, Denmark) for five years. The treatment was followed in accordance with the manufacturer's recommendations and taking into account the patient's local and systemic reactions to the injections.

Determining cell proportions

For the calculation of NLR, PLR, ELR, BLR, and LMR, the results of complete pre-immunotherapy and post-immunotherapy one-month blood count in the healthy control group and patients who received ASI were used. Before and after immunotherapy, these two groups and the healthy control group were compared in terms of NLR, PLR, ELR, LMR, and BLR and MPV values. The Sysmex XT-2100 hematology analyzer (Sysmex Corp., Kobe, Japan) was used to analyze blood samples.

Statistical analysis

Statistical analysis was performed using the 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. The distribution of variables was measured using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to analyze independent quantitative data. The Wilcoxon test was used to analyze dependent quantitative data, while the chi-square test was carried out to analyze independent qualitative data. A p value of <0.05 was considered statistically significant.

RESULTS

No significant difference was observed in the sex between the study and control groups (p>0.05). The platelet count, neutrophil count, eosinophil count, lymphocyte count, PLR, NLR, and LMR ratio did not significantly differ between the study and control groups (p>0.05). However, the MPV value in the study group was significantly lower than the control group (p<0.05). The basophil count was significantly higher in the study group than the control group (p<0.05). The monocyte count in the study group was significantly lower than the control group (p<0.05). The ELR and BLR values were significantly higher in the study group than the control group (p<0.05), (Table 1).

The MPV value after ASI significantly increased (p<0.05), compared to pre-immunotherapy values. However, the platelet, neutrophil, eosinophil, lymphocyte, and monocyte counts and PLR, NLR, ELR, and LMR of post-immunotherapy did not change significantly (p>0.05), compared to pre-immunotherapy values. In addition, post-immunotherapy basophil count and BLR significantly decreased (p<0.05), compared to pre-immunotherapy values (Table 1).

DISCUSSION

In the present study, we investigated how the ASI affected essential indicators of systemic inflammation. The most important findings of our study were that ELR, BLR, and basophil values were significantly higher in the pre-immunotherapy AR group than the control group. On the other hand, the monocyte count was significantly lower than the control group. Post-immunotherapy MPV value significantly increased, while the BLR and basophil values significantly decreased, compared to pre-immunotherapy values. The post-immunotherapy PLR and NLR did not differ significantly, compared to pre-immunotherapy values. To the best of our knowledge, there is no study showing

Table 1
Comparison of control, pre-immunotherapy, and post-immunotherapy groups

	Control group				Pre-immunotherapy group					Post-immunotherapy group		
	n	%	Mean±SD	Median	n	%	Mean±SD	Median	*p**	Mean±SD	Median	*p***
Sex									0.388¶			
Female	12	50.0			12	63.2						
Male	12	50.0			7	36.8						
Mean platelet volume			10.1±0.9	9.80			8.5±1.2	8.4	0.000†	9.5±1.3	9.8	0.002‡
Platelet			271±49	277			265±49	259	0.427†	273.4±53.4	279.0	0.446‡
Neutrophil			4.1±0.9	4.03			4.7±1.6	4.53	0.231†	4.5±0.7	4.60	0.744‡
Eosinophil			0.2±0.2	0.11			0.3±0.2	0.20	0.084†	0.3±0.2	0.20	0.670‡
Basophil			0.0±0.0	0.04			0.1±0.0	0.10	0.000†	0.1±0.0	0.03	0.006‡
Lymphocyte			2.4±0.6	2.22			2.2±0.8	2.30	0.723†	2.3±0.5	2.20	0.931‡
Monocyte			0.6±0.2	0.63			0.5±0.1	0.50	0.011†	0.5±0.2	0.47	0.744‡
Platelet-lymphocyte ratio			121.5±38.5	110.5			144.1±106.1	118.8	0.961†	122.9±22.8	121.9	0.525‡
Neutrophil-lymphocyte ratio			1.8±0.5	1.80			3.0±3.5	1.9	0.434†	2.0±0.5	2.00	0.528‡
Eosinophil-lymphocyte ratio			0.1±0.1	0.04			0.1±0.1	0.1	0.019†	0.1±0.1	0.10	0.231‡
Basophil-lymphocyte ratio			0.0±0.0	0.01			0.0±0.0	0.0	0.000†	0.0±0.0	0.01	0.010‡
Lymphocyte-monocyte ratio			4.1±1.4	3.75			4.8±1.6	4.6	0.139†	6.2±6.0	4.76	0.845‡

SD: Standard deviation; * Difference with the control group; ** Pre-/Post-immunotherapy difference; † Mann-Whitney u test; ‡ Wilcoxon test; ¶ Chi-Square test.

possible changes in MPV, PLR, NLR, ELR, BLR, and LMR, new blood inflammation markers, after ASI. Thus, this is the first study investigating how these new blood inflammation parameters change after ASI.

The NLR, PLR, and MPV are important, cost-effective, and easily calculated markers of complete blood count in the follow-up of systemic inflammation.[15,16] The association of NLR and PLR with several diseases such as heart diseases, chronic diseases, and malignancies has been shown in the literature.[8,10,16] Both NLR and PLR are useful markers for the diagnosis of persistent AR. It has been demonstrated that clinicians can use these markers to evaluate the severity of the disease at the beginning of the diagnosis process.[3] A clinical study including children diagnosed with pediatric AR revealed that NLR was significantly higher in moderate-to-severe AR than mild AR.[17] High NLR was found to be associated with the severity of AR in children. Therefore, the authors concluded that NLR could be used as an indicator of inflammation in AR. The NLR was also found to be significantly higher in children with asthma, compared to the control group; therefore, it was suggested that NLR could be used as an indicator of systemic inflammation in pediatric patients with asthma.[18] Similarly, in another clinical study conducted in adult AR patients, both NLR and PLR were found to be higher in moderate-to-severe AR.[3] Unlike these studies, in our study, NLR and PLR values were not significantly different between the control and AR groups.

Our study revealed that post-immunotherapy MPV value increased significantly ($p<0.05$), compared to pre-immunotherapy values. Previous studies have shown that MPV can provide important information about the course and prognosis in many pathological conditions.[8,19] It has been demonstrated that MPV, an important indicator of inflammation, can vary from disease to disease and the increased MPV can be seen in cardiovascular diseases, stroke, respiratory tract diseases, chronic renal failure, intestinal diseases, rheumatological diseases, diabetes, and various cancers, while decreased MPV can be found in patients with tuberculosis exacerbation, ulcerative colitis, adult systemic lupus erythematosus, and different neoplastic diseases.[8]

In our study, the MPV values before ASI were significantly lower than the control group. In the clinical study conducted by Akgedik and Yağız[19] in patients with allergic airway disease (asthma and AR), the MPV values of the study groups were significantly lower than the control group and that MPV was negatively correlated with white blood cell count, neutrophil count, platelet count, and IgE levels. The lowest MPV value was measured in asthma + AR group with the highest airway involvement, while the highest MPV value was found in the AR without asthma group with the least airway involvement. In the aforementioned study, even if the MPV level was within the normal range (below 8.18 fL), it was found to be associated with an increased risk of allergic airway disease.[19] From this point of view, the MPV value of patients with AR, compared to the control group, is consistent with the literature.

Furthermore, the ELR value was significantly higher in the pre-immunotherapy AR group than the control group. Post-immunotherapy ELR did not significantly differ, compared to pre-immunotherapy. Post-immunotherapy BLR and basophil value decreased significantly ($p<0.05$), compared to pre-immunotherapy. The ELR and BLR are other ratios which reveal the inflammatory state and can be easily calculated. Eosinophils and basophils are closely related to allergic conditions and parasitic infections.[20,21] Eosinophils, basophils, and monocytes are also essential components of the blood associated with inflammation and immune response. The NLR, as well as ELR, BLR, and LMR, are indicators of systemic inflammation.[11,12] Brescia et al.[13] found that high ELR and BLR levels were closely associated with nasal polyp recurrence. Kökoğlu et al.[22] also investigated the relationship between patient satisfaction and ELR and BLR after septoplasty, and they reported high ELR and BLR values in patients with low patient satisfaction. In addition, the study of Yenigün et al.[11] including pediatric patients diagnosed with AR found a correlation between ELR and AR in patients with positive skin prick test results. The authors found that ELR values were significantly higher in the sensitized asymptomatic and sensitized symptomatic groups than the non-sensitized asymptomatic and non-sensitized symptomatic groups. Therefore, they concluded that ELR was associated with more atopic sensitization than rhinitis symptomatology, including itchy and runny nose, sneezing, and watery nasal discharge.

In our study, either the baseline LMR value in the study and the control groups or post-immunotherapy LMR values, compared to pre-immunotherapy, did not significantly differ. In many malignant diseases and heart diseases, low pre-treatment LMR values were found to be closely associated with poor prognosis and low overall survival rates.[23,24] A meta-analysis conducted in patients with head and neck cancer showed that the patients with increased LMR values had better prognosis and survival.[24]

It has been shown that these new blood systemic inflammation markers are promising indicators of

prognosis and treatment response in many diseases. Immunotherapy can change the course of systemic inflammation markers. From this perspective, our study is the first to reveal how immunotherapy affects systemic inflammation in terms of cell ratios. Nevertheless, one of the main limitations of this study is that immunotherapy was not covered by health insurance and a small number of patients were treated and followed in the long-term, since it is a costly treatment. In addition, patients with incomplete ASI were excluded from the study. On the other hand, although the sample size is relatively high in AR studies, the number of patients may be lower in studies including patients undergoing ASI.[25] Since ASI is a very long and costly treatment, not all patients who start ASI can complete three to five years of treatment. Another limitation is that, according to the ASI response, it was not evaluated whether there was a change in these full blood count inflammation markers, and the possible relationship between the symptom scores was not investigated, either. Also, almost all patients used additional drugs such as nasal steroids, mast cell stabilizers (e.g., montelukast) and antihistamines and these drugs can affect the cell numbers and rates in the blood count.

In the study conducted by Wilson et al.,[26] there was an increase in basophils and eosinophils in the nasal epithelium in patients with grass pollen allergy, but not in mast cells and neutrophils at the same rate. With the post-immunotherapy success of the treatment, a decrease in basophils and eosinophils in the nasal mucosa was observed, compared to pre-treatment values. However, in this study, blood cells were not analyzed in the nasal mucosa and the study investigated only systemic influence of ASI, but not symptom scores or the changes in the nasal mucosa, or even failure of immunotherapy in controlling the AR.

The failure to research possible subgroup changes in terms of the mentioned inflammation parameters, which was the most common ASI indication in our study on pollen allergy with house dust mite, is another limitation. Further prospective and large-scale studies are needed to investigate the possible relationship between these complete blood inflammation markers with subgroup analyses using symptom scores obtained according to the ASI response.

In conclusion, MPV, basophil count, and BLR, among the MPV, NLR, PLR, ELR, BLR, and LMR values, which have been suggested in the pathogenesis of inflammation currently, may show variability in the evaluation of complete blood count of patients after ASI, compared to before ASI. In our study, the MPV value after ASI was found to be significantly higher than before ASI, and BLR and basophil values were found to be significantly lower. Based on these results, it can be concluded that not only local inflammation, but also systemic inflammation contribute to the pathogenesis of AR, and not only local inflammation, but also systemic inflammation can be suppressed with ASI, showing a possible association with each other.

Declaration of conflicting interests

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REFERENCES

1. Kakli HA, Riley TD. Allergic rhinitis. Prim Care 2016;43:465-75.
2. Walker SM, Durham SR, Till SJ, Roberts G, Corrigan CJ, Leech SC, et al. Immunotherapy for allergic rhinitis. Clin Exp Allergy 2011;41:1177-200.
3. Göker AE, Ekincioglu E, Alagöz MH, Hummatov R, Arkan ME, Baskadem Yilmazer A, et al. The association of allergic rhinitis severity with neutrophil-lymphocyte and platelet-lymphocyte ratio in adults. Eur Arch Otorhinolaryngol 2019;276:3383-8.
4. Şahin E, Bafaqeeh SA, Güven SG, Çetinkaya EA, Muluk NB, Coşkun ZO, et al. Mechanism of action of allergen immunotherapy. Am J Rhinol Allergy 2016;30:1-3.
5. Zhang W, Lin C, Sampath V, Nadeau K. Impact of allergen immunotherapy in allergic asthma. Immunotherapy 2018;10:579-93.
6. Wang W, Yin J. Is it worthy to take full-course immunotherapy for allergic rhinitis? About efficacy biomarker of allergen immunotherapy. Scand J Immunol 2020;91:e12817.
7. Håkansson L, Heinrich C, Rak S, Venge P. Priming of eosinophil adhesion in patients with birch pollen allergy during pollen season: effect of immunotherapy. J Allergy Clin Immunol 1997;99:551-62.
8. Korniluk A, Koper-Lenkiewicz OM, Kamińska J, Kemona H, Dymicka-Piekarska V. Mean Platelet Volume (MPV): New Perspectives for an Old Marker in the Course and Prognosis of Inflammatory Conditions. Mediators Inflamm 2019;2019:9213074.
9. Larmann J, Handke J, Scholz AS, Dehne S, Arens C, Gillmann HJ, et al. Preoperative neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are associated with major adverse cardiovascular and cerebrovascular events in coronary heart disease patients undergoing non-cardiac surgery. BMC Cardiovasc Disord 2020;20:230.
10. Bojaxhiu B, Templeton AJ, Elicin O, Shelan M, Zaugg K, Walser M, et al. Relation of baseline neutrophil-to-lymphocyte ratio to survival and toxicity in head and neck cancer patients treated with (chemo-) radiation. Radiat Oncol 2018;13:216.

11. Yenigun A, Sezen S, Calim OF, Ozturan O. Evaluation of the eosinophil-to-lymphocyte ratio in pediatric patients with allergic rhinitis. Am J Rhinol Allergy 2016;30:e21-5.
12. Çekici Y, Yılmaz M, Seçen Ö. New inflammatory indicators: association of high eosinophil-to-lymphocyte ratio and low lymphocyte-to-monocyte ratio with smoking. J Int Med Res 2019;47:4292-303.
13. Brescia G, Pedruzzi B, Barion U, Cinetto F, Giacomelli L, Martini A, et al. Are neutrophil-, eosinophil-, and basophil-to-lymphocyte ratios useful markers for pinpointing patients at higher risk of recurrent sinonasal polyps? Am J Otolaryngol 2016;37:339-45.
14. Tan D, Fu Y, Tong W, Li F. Prognostic significance of lymphocyte to monocyte ratio in colorectal cancer: A meta-analysis. Int J Surg 2018;55:128-38.
15. Stojkovic Lalosevic M, Pavlovic Markovic A, Stankovic S, Stojkovic M, Dimitrijevic I, Radoman Vujacic I, et al. Combined Diagnostic Efficacy of Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Mean Platelet Volume (MPV) as Biomarkers of Systemic Inflammation in the Diagnosis of Colorectal Cancer. Dis Markers 2019;2019:6036979.
16. Wu Y, Chen Y, Yang X, Chen L, Yang Y. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were associated with disease activity in patients with systemic lupus erythematosus. Int Immunopharmacol 2016;36:94-9.
17. Dogru M, Evcimik MF, Cirik AA. Is neutrophil-lymphocyte ratio associated with the severity of allergic rhinitis in children? Eur Arch Otorhinolaryngol 2016;273:3175-8.
18. Dogru M, Yesiltepe Mutlu RG. The evaluation of neutrophil-lymphocyte ratio in children with asthma. Allergol Immunopathol (Madr) 2016;44:292-6.
19. Akgedik R, Yağız Y. Is Decreased Mean Platelet Volume in Allergic Airway Diseases Associated With Extent of the Inflammation Area? Am J Med Sci 2017;354:33-8.
20. Metcalfe DD, Pawankar R, Ackerman SJ, Akin C, Clayton F, Falcone FH, et al. Biomarkers of the involvement of mast cells, basophils and eosinophils in asthma and allergic diseases. World Allergy Organ J 2016;9:7.
21. Motran CC, Silvane L, Chiapello LS, Theumer MG, Ambrosio LF, Volpini X, et al. Helminth infections: Recognition and modulation of the immune response by innate immune cells. Front Immunol 2018;9:664.
22. Kökoğlu K, Şahin MI. Use of neutrophil, eosinophil, basophil, and platelet to lymphocyte ratio to predict patient satisfaction after septoplasty plus inferior turbinate reduction. J Craniofac Surg 2019;30:1022-6.
23. Gong S, Gao X, Xu F, Shang Z, Li S, Chen W, et al. Association of lymphocyte to monocyte ratio with severity of coronary artery disease. Medicine (Baltimore) 2018;97:e12813.
24. Tham T, Olson C, Khaymovich J, Herman SW, Costantino PD. The lymphocyte-to-monocyte ratio as a prognostic indicator in head and neck cancer: a systematic review and meta-analysis. Eur Arch Otorhinolaryngol 2018;275:1663-70.
25. Bahçeciler NN, Işik U, Barlan IB, Başaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. Pediatr Pulmonol 2001;32:49-55.
26. Wilson DR, Irani AM, Walker SM, Jacobson MR, Mackay IS, Schwartz LB, et al. Grass pollen immunotherapy inhibits seasonal increases in basophils and eosinophils in the nasal epithelium. Clin Exp Allergy 2001;31:1705-13.