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Original Article

Could Hematologic Parameters Have a Predictive Role in Pediatric Hashimoto Thyroiditis?

Pediatrik Hashimoto Tiroiditinde Hematolojik Parametrelerin Prediktif Rolü Olabilir mi?

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ABSTRACT

Objective: Hashimoto thyroiditis (HT) is an autoimmune thyroid disease evolving as a result of lymphocyte infiltration and chronic inflammation. Although adult studies have shown that hematologic parameters, such as platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII) can be used as biomarkers of HT, knowledge is limited concerning the pediatric age group. The aim of our study is to investigate the potential of hematologic biomarkers in predicting HT in children.

Method: Children with HT (n=165) who were followed in the Pediatric Endocrinology Department of our hospital between July 2020 and July 2021, were enrolled in the present retrospective cross-sectional study. Hemogram values were compared with those of age-matched control group (n=122).

Results: The average leukocyte (p>0.05), platelet (p>0.05), and absolute neutrophil (p>0.05) counts, NLR (p>0.05) and SII (p>0.05) in the children with HT were not statistically different from those of the control group. Although PLR values were significantly higher in the HT group than the control group (p<0.05), in receiver operating characteristic curve analysis, PLR values had low specificity and sensitivity, in predicting HT.

Conclusion: Our study has shown that NLR and SII are not useful indicators in predicting HT in children. Although there is a statistically significant difference in PLR values, we think that PLR is not a useful marker due to its low specificity and sensitivity.

Keywords: Hashimoto thyroiditis, pediatric, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index

ÖZ

Amaç: Hashimoto tiroiditi (HT), lenfosit infiltrasyonu ve kronik enflamasyon sonucu gelişen otoimmün bir tiroid hastalığıdır. Erişkin hastalarda yapılan çalışmalarda trombosit-lenfosit oranı (PLR) ve nötrofil-lenfosit oranı (NLR) ve sistemik immün-enflamasyon indeksi (SII) gibi hematolojik parametrelerin HT'nin biyobelirteçleri olarak kullanılabileceği gösterilmiş olsada, pediatrik yaş grubunda bilgi sınırlıdır. Çalışmamızın amacı, çocuklarda HT'yi öngörmede hematolojik biyobelirteçlerin potansiyelini araştırmaktır.

Yöntem: Bu retrospektif kesitsel çalışmaya hastanemiz çocuk endokrinoloji bölümünde Temmuz 2020 ile Temmuz 2021 tarihleri arasında takip edilen HT'li çocuklar (n=165) ile aynı yaş ve cinsiyetteki kontrol grubu (n=122) karşılaştırıldı.

Bulgular: HT'li çocuklar ve kontrol grubu karşılaştırıldığında ortalama lökosit sayısı (p>0.05), trombosit sayısı (p>0,05), mutlak nötrofil sayısı (p>0,05), NLR (p>0,05) ve SII (p>0,05) istatistik olarak fark saptanmadı. HT grubunda PLR değerleri kontrol grubuna göre anlamlı olarak daha yüksek olmasına rağmen (p<0,05), alıcı işlem karakteristikleri (receiver operating characteristic curves) analizinde, PLR değerleri HT'yi öngörmede düşük özgüllük ve duyarlılığa sahipti.

Sonuç: Çalışmamız, NLR ve SII'nin çocuklarda HT'yi öngörmede yararlı göstergeler olmadığını göstermektedir. PLR değerinde istatistiksel olarak anlamlı bir fark olmasına rağmen, özgüllüğü ve duyarlılığının düşük olması nedeniyle yararlı bir belirteç olmadığını saptanmıştır.

Anahtar kelimeler: Hashimoto tiroiditi, pediatrik, nötrofil-lenfosit oranı, trombosit-lenfosit oranı, sistemik bağışıklık-enflamasyon indeksi

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INTRODUCTION

Hashimoto thyroiditis (HT), also known as chronic lymphocytic thyroiditis, is the most common cause of acquired thyroid diseases in children with or without goiter [1]. It is a thyroid gland specific autoimmune disease, characterized by autoimmune-mediated destruction [2]. The prevalence of HT in the pediatric population peaks at puberty. HT is more common in females and the presentation of the disease is rare before the age of 3 years. Strong female preponderance and also high prevalence in patients with Down and Turner syndrome have been reported. Clinical manifestations of HT are observed in the pediatric population in a spectrum ranging from completely normal, to severe thyroid dysfunction [3]. The pathology of HT is characterized with diffuse lymphocytic infiltration of thyroid gland with T-cells, fibrosis, parenchymal atrophy, evidence of goiter or thyroid glandular atrophy, elevated serum anti-thyroid antibodies and dysfunction to varying degrees [4].

Neutrophils (N) and platelets (P) play an active role in inflammation and have regulatory roles in the immune system. Recent studies have shown that the rates of various parameters such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in the hemogram have been used as effective predictive markers for the prognosis, survival and morbidity in a wide variety of diseases including autoimmune diseases such as psoriasis, ulcerative colitis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, Takayasu's arteritis, Behçet's disease and also various malignancies [5]. Another marker is systemic immune-inflammation index (SII) formulated by (N×P)/L where N, P and lymphocyte (L) represent N, P and lymphocyte counts, respectively. SII is associated with various diseases especially with malignancies, cardiovascular and infectious diseases [6].

In this study, we hypothesized that hemogram parameters may have a predictive value in pediatric patients with HT. To this end, NLR, PLR and SII levels were examined in 165 pediatric patients with HT and 122 patients in the control group.As far as we know, this is the first study that examines the predictive role of hematologic parameters (PLR, NLR ans SII) in pediatric patients with HT.

MATERIALS and METHODS

A total of 287 children (165 HT patients, and 122 healthy controls) were enrolled in this retrospective study. Patients data obtained from a retrospective scan of files of the patients who were admitted to our outpatient clinic between Janunary 2021 and December 2021. This study was approved by the University of Health Sciences Turkey İzmir Dr. Behçet Uz Pediatric Diseases and Surgery training and research Hospital Clinical Research Ethics Committee. (decision number: 2021/15-04, date: 07.10.2021)

Patients with other autoimmune diseases such as diabetes mellitus, chronic inflammatory disease, and patients with conditions that directly affect hematologic parameters such as, hematologic diseases, patients on anticoagulation therapy, hepatic or renal disorders, heart failure, myeloproliferative disorders, and acute or chronic infection were excluded from the study.

Hemogram parameters were determined using Sysmex NX1000 Automated Hematology System. All blood samples were obtained after 12 hours of fasting and analyzed within one hour after venipuncture. NLR and PLR values were calculated by dividing the N and P counts by absolute L counts, respectively. SII is calculated by (N×P)/L formula. Thyroid-stimulating hormone (TSH) and free thyroxine (fT_4) parameters were studied using Abbott Architect I 2000 SR® immunoassay analyzer.

Laboratory data were uploaded from computerized patient database. Demographic characteristics of the patients, and laboratory findings were reviewed from the files of the participants. Patients did not undergo any investigations other than those routinely requested. Hemoglobin (Hgb), hematocrit (Hct), leukocyte, N, L, P counts, C-reactive protein (CRP), serum TSH, fT_4, free triiodothyronine, and anti-thyroglobulin (anti-TG), anti-thyroid peroxidase (anti-TPO) values were recorded.

Statistical Analysis

Data obtained from this study were analyzed using GraphPad Prism (statistical software, version 8.0.0). Values are expressed as mean ± standard deviation. The statistical comparisons for mean values were performed using paired t-test for parametric, and Mann-Whitney test for nonparametric variables. Chi-square test was used to compare differences between categorical variables, and receiver operating characteristic (ROC) curve analysis was conducted to find out the cut-off values for PLR parameters. In the analyses, p=0.05 was accepted as the level of statistical significance.

RESULTS

One hundred and sixty- five HT patients [138 females (F) and 27 males (M)] and one hundred and twenty-two healthy controls (98 F and 24 M) were enrolled in this study. The mean ages of the patient, and the control

groups were was 13.5±3.3, and 12.6±2.8 years, respectively. F/M ratios of the HT patient and control groups were 5.1 and 4.0, respectively. NLR and SII were a little bit, but not statistically significantly higher in the HT group compared to the control group (1.65±1.09 and 1.42±0.49; p>0.05 for NLR, 512±373 and 450±275; p>0.05 for SII, respectively). However, PLR was significantly higher in HT patients to the control group (126.7±83.7, and 111.3±33.5; p=0.02, respectively). White blood cell (WBC), P, N, counts and CRP were not significantly different between HT patients and the control group. Whereas, L counts, levels of Hgb and Htc were statistically significantly lower in HT patients compared to the control group (2.74±0.91 and 2.99±0.92; p<0.05 for L, 12.8±0.99 and 13.3±1.2; p<0.05 for Hgb, 38.5±3 and 39.5±3.3; p<0.05 for hct, respectively). Laboratory characteristics of the two groups are presented in Table 1.

ROC curve analysis was performed for PLR parameter. The descriptive cut-off value of PLR was 112.8 with 61.7% sensitivity and 62.1% specificity. The area under curve for PLR was 0.596±0.04, and p=0.018) (Figure 1). In the correlation analysis, NLR and PLR values were not significantly correlated with anti-TPO and anti- TG values (p=0.33 r=0.07 for PLR-anti-TPO, p=0.15, r=0.11 for PLR-anti-TG, p=0.63 r=-0.03 for NLR-anti-TPO and p=0.33 r=0.07 for NLR-anti-TG).

DISCUSSION

HT is the most common cause of acquired hypothyroidism in childhood and adolescence.

Although the etiology of HT is still not fully understood, its pathogenesis reflects the combination of immunologic, genetic, and environmental factors [7,8]. As for the pathophysiology of disease, HT develops due to especially increased sensitized t-cell activation and cytokine levels. Ns and Ls are involved in the production of these cytokines. Hematologic parameters can be easily calculated from hemograms. Relationship with hematologic markers and HT disease have been reported in several studies [9-12].

Although WBC, N, and P counts were not statistically different between HT patients and the control group, L counts were lower in the HT group. Similarly, Bilge et al. [11] showed that L counts were lower in HT patients, while Cengiz et al. [13] showed that the number of Ls decreases in acute inflammatory phase of subacute granulomatous thyroiditis which can be explained with accumulation of Ls in the thyroid gland. In addition, hematocrit and hemoglobulin levels were lower in HT patients in comparison with control subjects. This fact may be accounted for the crucial effect of thyroid hormones on erythropoiesis via erythropoietin production enhancement and also proliferation of erythroid progenitors. However, iron-deficient anemia negatively affects thyroid hormone status [14].

Inflammatory conditions temporarly change N and L counts and abnormalities in the activation of Ns and Ls and defective apoptosis may lead to development of autoimmune disorders. NLR has been recently described as a simple and novel inflammatory marker in malignancy,

Table 1. Laboratory characteristics of the patient and control groups

	Patients group	Control group	p
Age (mean ± SD)	13.5±3.3	12.6±2.8	>0.05
TSH (mean ± SD)	10.4±19.5	2.1±1.0	<0.05
fT_4 (mean ± SD)	0.97±0.23	1.0±0.12	>0.05
Hb (mean ± SD)	12.8±0.99	13.3±1.2	<0.05
Hct (mean ± SD)	38.5±3	39.5±3.3	<0.05
Leukocyte ($10^3/mm^3$) (mean ± SD)	7.63±2.2	7.7±2.0	>0.05
Neutrophil ($10^3/mm^3$) (mean ± SD)	4.09±1.84	3.92±1.6	>0.05
Lymphocyte ($10^3/mm^3$) (mean ± SD)	2.74±0.91	2.99±0.92	<0.05
Platelet ($10^3/mm^3$) (mean ± SD)	306±75	315±81	>0.05
PLR (mean ± SD)	126.7±83.7	111.3±33.5	<0.05
NLR (mean ± SD)	1.65±1.09	1.42±0.49	>0.05
SII (mean ± SD)	512±373	450±275	>0.05
CRP (mg/dL) (mean ± SD)	0.3±0.2	0.3±0.2	>0.05

TSH : Thyroid stimulating hormone, fT_4 : Free thyroxine, Hb: Hemoglobulin, Hct: Hematocrit, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CRP: C-reactive protein

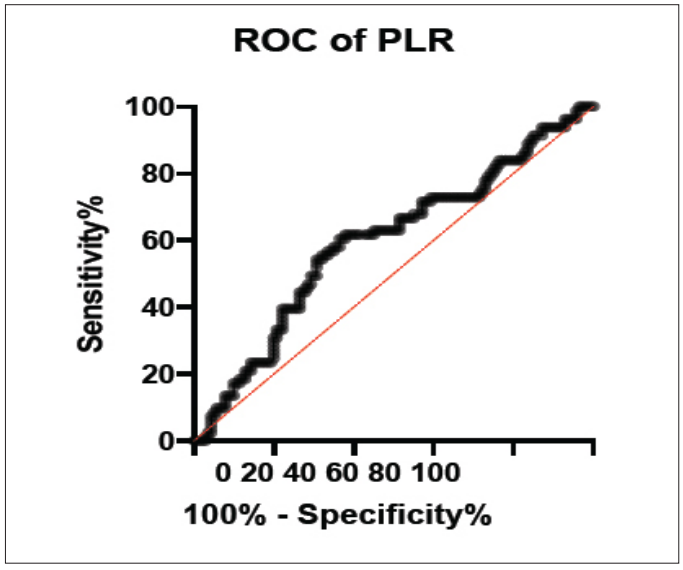

Figure 1. ROC curves for the PLR. For PLR, AUC was 0.596, with 61.7% sensitivity and 62.1% specificity

ROC: Receiver operating characteristic, PLR: Platelet-to-lymphocyte ratio, AUC: Area under curve

autoimmune inflammatory and cardiovascular diseases. In adult studies, NLR is statistically significantly higher in the HT group than the control group and higher NLR values reported might be a reliable predictive marker of the clinical course of the Hashimoto throiditis [9,11,12]. Moreover, Bilge et al. [11] showed that levothyroxine (LT_4) treatment decreases NLR and PLR. In the literature, some studies showed that LT_4 replacement therapy decreases inflammation and oxidative stress. In our study, although NLR was a little bit , but not significantly higher in the HT group which may be explained with changes in hemogram parameters during childhood. This study has demonstrated that NLR is not correlated with either thyroid antibodies or disease prognosis. Thus, we think that NLR is a nonspecific marker for all autoimmune diseases and is not a useful tool for the prediction of diagnosis and prognosis of HT.

Some literature stuides have shown that, PLR can provide valuable information about autoimmune and rheumatologic diseases and some malignancies. PLR values reflected shifts in P, L, N, or monocyte counts. Some authors have suggested that interpretation of PLR together with other hematologic markers have more accurate diagnostic value in inflammatory rheumatic diseases and also predicts related comorbidities [13]. Some literature studies have demonstrated the relationship between PLR values and diagnosis and disease activity in adult HT patients [9,11,12]. Ps interact with leukocytes in autoimmune diseases and are regarded as central players in the pathophysiology of especially vascular inflammation. In our study PLR was significantly higher in the HT group but ROC analysis revealed that sensitivity and specificity is not strong enough to use PLR values in predicting HT (Figure 1). In addition, PLR values were not correlated either with thyroid antibodies or with disease prognosis, as were NLR values.

The last marker, we compared between the two groups, was SII. It correlates positively with N and P counts, and negatively with L counts, and clinical significance of SII have been reported in inflammatory diseases and malignancies. In our study there were not significant differences between the HT and control groups in terms of SII values.

Study Limitations

This study was a retrospective basis and represented a single-center experience. The limited number of patients and, short follow-up period are major limitations of the study. Higher number of patients should be followed up for longer periods to achieve a higher statistical significance.

CONCLUSION

Our study suggested that NLR and SII are not useful indicators in predicting the course of HT. In addition, although there was a statistically significant difference between the HT, and the control groups in terms of PLR values we think that it is not a useful marker due to its low specificity and sensitivity.

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Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, İzmir Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee. (decision number: 2021/15-04, date: 07.10.2021)

Informed Consent: Retrospective study.

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Author Contributions

Surgical and Medical Practices: T.K., Concept: T.K., B.Ö., Design: T.K., B.Ö., Data Collection and/or Processing: T.K., Analysis and/or Interpretation: T.K., B.Ö., Literature Search: T.K., B.Ö., Writing: T.K., B.Ö.

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