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THE ROLE OF NEUTROPHIL TO LYMPHOCYTE RATIO AND PLATELET TO LYMPHOCYTE RATIO IN THE DIAGNOSIS OF SUBACUTE THYROIDITIS

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Abstract

Patients with subacute thyroiditis (SAT) usually apply to clinics with thyrotoxicosis and neck pain. Hemogram is frequently applied tests in primary health care services, and it can warn physicians for SAT in a thyrotoxic patient. In our study, the role and usability of neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in the diagnosis of SAT were evaluated.

Between January 2015 and January 2020, 192 SAT patients who applied to endocrinology clinics and 85 healthy control were included in the study. Neutrophil, lymphocyte, platelet leves were recorded.

The median NLR and PLR values of SAT patients before treatment were 2.78 (0.91-11.33) and 168.3 (25.7-818.3), respectively, and were significantly higher than the control group ($p<0.001$). The optimum cut-off values for NLR and PLR for SAT were 1.84 (specificity 85.9% and sensitivity 90.1%; $p<0.001$; AUC=0.934; 95% CI: 0.905-0.964) and 140.2 (specificity 83.5% and sensitivity 77.1%, $p<0.001$, AUC=0.821 95% CI: 0.767-0.874), respectively. Pretreatment NLR, PLR, CRP, and ESR levels were significantly higher than the posttreatment levels (all $p<0.001$). Correlation

analysis revealed positive linear relations between pretreatment PLR and CRP (p=0.002, r=0.220), pretreatment PLR and ESR (p=0.018, r=0.171), pretreatment NLR and CRP (p<0.001, r=0.330), and pretreatment NLR and ESR (p=0.001, r=0.242). Multiple linear regression analysis revealed a 0.008 unit of increment of NLR per 1 unit increase in CRP levels (B=0.008; p<0.001; %95 CI=0.004-0.012).

High NLR and PLR values accompanying thyrotoxicosis are both warning and helpful parameters for the diagnosis of SAT.

Key Words: Neutrophil to lymphocyte ratio, NLR, Painless subacute thyroiditis, Platelet to lymphocyte ratio, PLR, Subacute thyroiditis

Özet

Subakut tiroiditi (SAT) olan hastalar genellikle tirotoksikoz ve boyun ağrısı şikayetleriyle kliniklere başvururlar. Hemogram birinci basamak sağlık hizmetlerinde sıklıkla uygulanan testler olup, tirotoksik bir hastada hekimleri SAT konusunda uyarabilmektedir. Çalışmamızda nötrofil lenfosit oranı (NLO) ve trombosit lenfosit oranının (PLO) SAT tanısındaki rolü ve kullanılabilirliği değerlendirildi.

Ocak 2015 ile Ocak 2020 tarihleri arasında endokrinoloji kliniğine başvuran 192 SAT hastası ve 85 sağlıklı kontrol çalışmaya dahil edildi. Nötrofil, lenfosit, trombosit seviyeleri kaydedildi.

SAT hastalarının tedavi öncesi medyan NLO ve PLO değerleri sırasıyla 2,78 (0,91-11,33) ve 168,3 (25,7-818,3) idi ve kontrol grubundan anlamlı derecede yüksekti (p<0,001). SAT için NLO ve PLO için optimum cut-off değerleri sırasıyla 1,84 (özgüllük %85,9 ve duyarlılık %90,1; p<0.001; AUC=0.934; %95 CI: 0,905-0,964) ve 140,2 (özgüllük %83.5 ve duyarlılık %77,1, p<0,001, AUC=0.821 %95 CI: 0.767-0.874) idi. Tedavi öncesi NLO, PLO, CRP ve sedimentasyon seviyeleri tedavi sonrası seviyelere göre anlamlı derecede yüksekti (tümü p<0,001). Korelasyon analizinde, tedavi öncesi PLO ve CRP (p=0,002, r=0,220), tedavi öncesi PLO ve sedimetasyon (p=0,018, r=0,171), tedavi öncesi NLO ve CRP (p<0,001, r=0,330) ve tedavi öncesi NLO ve sedimetasyon (p=0,001, r=0,242) arasında pozitif doğrusal ilişki vardı. Çoklu lineer regresyon analizinde, CRP seviyelerinde 1 birimlik artış başına 0.008 birimlik bir NLO artışı olduğu görüldü (B=0.008; p<0.001; %95 CI=0.004-0.012).

Tirotoksikoza eşlik eden yüksek NLO ve PLO değerleri SAT tanısında hem uyarıcı hem de yardımcı parametrelerdir.

Anahtar Kelimeler: Ağrısız subakut tiroidit, NLO, Nötrofil/Lenfosit Oranı, PLO, Subakut Tiroidit, Trombosit/Lenfosit Oranı

1. Introduction

Subacute granulomatous thyroiditis (SAT) is a self-limiting disease. T cell-mediated hypersensitivity reaction is seen against follicular epithelial cells carrying viral antigen (Desailloud & Hober, 2009; Kojima et al., 2002; Nishihara et al., 2008). It usually occurs following a viral infection and is characterized by neck pain that can spread to the jaw and ear, symptoms of thyrotoxicosis, increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels (Mizukoshi et al., 2001). In addition, neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) increase as well as inflammatory acute phase reactants (Benbassat et al., 2007; Calapkulu et al., 2020; Cengiz et al., 2020; Gabay & Kushner, 1999; Harrison, 2015; Kilinc et al., 2018; Mizukoshi et al., 2001; Sproston & Ashworth, 2018) In the treatment, prednisolone is used for its anti-inflammatory effects (Mizukoshi et al., 2001). SAT patients with thyrotoxicosis who are not accompanied by neck pain in daily practice can also apply to clinics. These painless admissions may delay diagnosis and subsequent treatment. NLR and PLR may be useful tests for physicians to refer patients with SAT, one of the differential diagnoses of thyrotoxicosis, to relevant specialists.

Hemogram is a basic and easily available test for general practitioners (GPs) to evaluate patients admitting with nonspecific symptoms. NLR and PLR is an indicator of immune response and systematic inflammation (Ahsen et al., 2013; Azab et al., 2011; Gasparyan et al., 2019; Imtiaz et al., 2012; Luo et al., 2019; Qin et al., 2016; Stefaniuk et al., 2020; Zahorec, 2001). Recent studies found that NLR and PLR are elevated in SAT (Calapkulu et al., 2020; Cengiz et al., 2020; GU et al., 2017; Kilinc et al., 2018; Taşkaldiran et al., 2019). It is cost-effective, readily available, and could be calculated easily (Imtiaz et al., 2012).

In our study, usability of neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) in detecting of SAT patients was evaluated.

2. Material and Methods

Materials and Methods used in the study should be given under this heading. If subheading would be given, it should be numbered with main heading number (for example 2.1.) and written in italic. A clear description of current, new or modified methods should be given to provide sufficient information and to allow someone to repeat the work. If a previously published method is used, relevant literature should be cited.

Local ethics committee approval was obtained from the Ondokuz Mayıs University Ethics Committee with NoB.30.2.ODM.0.20.08/242. The study was conducted in accordance with the Declaration of Helsinki. Between January 2015 and January 2020, 192 SAT patients over the age of 18 who applied to our endocrinology clinic and 85 healthy controls were included in the study. Infectious or inflammatory disease, severe renal, pulmonary, or liver disease, malignancy, pregnancy and those with missing data were excluded. Data were obtained from computerized patient databases of participating centers.

Having neck, jaw or ear pain, fever, painless swelling in the neck and thyrotoxic symptoms; thyrotoxicosis, increased ESR and CRP; with avascular blurred margin and hypoechoic areas in thyroid ultrasonography were diagnosed SAT. According to clinical symptoms, physical examination, ESR, CRP and ultrasonography findings, patients were treated with NSAID or steroid therapy. Propranolol treatment was started in patients with symptoms of thyrotoxicosis. Propranolol was given at a dose of 40 mg/day. As a non-steroidal anti-inflammatory drug (NSAID) treatment, ibuprofen was given in divided doses of 800-1200 mg/day. As steroid treatment, 32 mg/day methylprednisolone was given for the first 10 days, and it was reduced by 4 mg every week and stopped in 8 weeks. The treatment was discontinued when clinical symptoms, thyroid function tests, ultrasonography findings improved and ESR and CRP levels returned to normal after at least 8 weeks of appropriate therapy.

Neutrophil (Neu), lymphocyte (Lym), platelet (PLT), ESR, CRP values were recorded. NLR was calculated by dividing the total neutrophil count by the total lymphocyte count. Platelet to lymphocyte ratio (PLR) was calculated by dividing the total platelet count by the total lymphocyte count.

CRP, ESR, NLR and PLR levels in acute phase (pre-treatment) and recovery phase (post-treatment) were compared with each other. NLR and PLR cut-off values were calculated for SAT. The relationship between NLR, PLR, ESR and CRP were evaluated.

Hemograms were determined with an autoanalyzer (Sysmex-XN haematology system). Reference ranges were defined as ESR: 0–20 mm/h, CRP: 0–5 mg/L, Neu: 1650–4970 cell/μL, Lym: 1170–3170 cell/μL, PLT: 170000-360000 cell/μL.

2.1. Statistical analysis

Data analysis was performed using the SPSS 18 (Statistical Package for Social Sciences) program. The distribution of continuous parameters was evaluated by Kolmogorov-Smirnov tests. Descriptive statistics were expressed as mean ± standard deviation and median (minimum-maximum) for numerical parameters, number of observations and percentages for nominal variables. The difference between pre- and post-treatment values was evaluated by the Wilcoxon test. Correlation between NLR and PLR with continuous variables were evaluated by determining Spearman'ın "rho" coefficient and level of significance (p). The combined effect of risk factors associated with change in NLR and PLR was studied by multiple linear regression analysis. For each risk factor, the regression coefficient was determined with a 95% confidence interval and level of significance. For diagnostic purposes, the NLR and PLR cut-off values with the highest sensitivity and specificity were determined by ROC analysis. Statistical significance was accepted at $p<0.05$.

3. Results

A total of 192 SAT patients and 85 healthy controls were included in the study. Patients' median age was 42 (range 27-68) years, the median age of the control group was 42 (range 18-78) years (p=0.836). 68.8% of SAT patients were female, 72.9% of the control group were female (p=0.483). The percentages of the patients that received steroid and NSAID treatment were 46.4% (n=89) and 53.6% (n=103), respectively. Demographic and laboratory data are summarized in Table 1.

Median values for CRP, ESR, NLR and PLR was 52.9 mg/l (range 6.4-273), 73 mm/h (range 7-130), 2.78 (range 0.91-11.33), and 168.3 (range 25.7-818.3), respectively. The median NLR value of the control group was 1.56 (range 0.88-3.07) and the PLR value was 116 (range 6.1-253.5). Pre-treatment NLR, PLR, CRP, and ESR levels were significantly higher than those after the treatment (all $p<0.001$) (Table 2). Pre-treatment NLR and PLR values of SAT patients were significantly higher than the control group ($p<0.001$ in all) (Table 1).

Table 1. Demographic data and laboratory results of the patients

Parameters	SAT patients (n=192)	Control group (n=85)	p
Age (years)	42 (27-68)	42 (18-78)	0.836
Sex			0.483
• **Female**	132 (68.8%)	62 (72.9%)	
• **Male**	60 (31.3%)	23 (27.1%)	
Neu (cell/µl)	5765 (2600-15310)	3550 (2090-5000)	<0.001
Lym (cell/µl)	2015 (600-4610)	2300 (1250-3670)	0.001
PLT (cell/µl)	359125± 95178	265835± 95178	<0.001
NLR	2,78 (0.91-11.33)	1,56 (0.88-3.07)	<0.001
PLR	168.3 (25.7-818.3)	116 (6.1-253.5)	<0.001

*Neu: Neutrophil; Lym: Lymphocyte; PLT: Platelet; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio

*To convert from ng/dL to pmol/L, multiply the fT4 value by 12.87

*To convert from pg/mL to pmol/L, the fT3 value is multiplied by 1.53

*Data are expressed as median (range) or number (percent) or mean (±SD)

Table 2. Comparison of pre- and post-treatment laboratory values

	Pre-treatment levels	Post-treatment levels	p
ESR (mm/h)	73 (7-130)	16.5 (1-42)	<0.001
CRP (mg/L)	52.9 (6.4-273)	3 (0.1-9)	<0.001
NLR	2.78 (0.91-11.33)	1.65 (0.51-5.51)	<0.001
PLR	168.3 (25.7-818.3)	117.3 (50-295.5)	<0.001

*ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio

*To convert from ng / dL to pmol / L, multiply by 12.87 for FT4

*To convert from pg / mL to pmol / L, multiply by 1.53 for FT3

*Data are expressed as median (interquartile range), p<0.05

The NLR and PLR optimum cut-off values for SAT patients were 1.84 (specificity 85.9% and sensitivity 90.1%; p<0.001; AUC=0.934; 95% CI: 0.905-0.964) and 140.2 (specificity 83.5% and sensitivity 77.1%; p<0.001; AUC=0.821 95% CI: 0.767-0.874) respectively (Figures 1 and 2). For higher specificity and lower sensitivity, the cut-off value for NLR increased to 2.4 (with 98% specificity and 67% sensitivity), and the PLR cut-off value increased to 212.1 (98% specificity and 21% sensitivity).

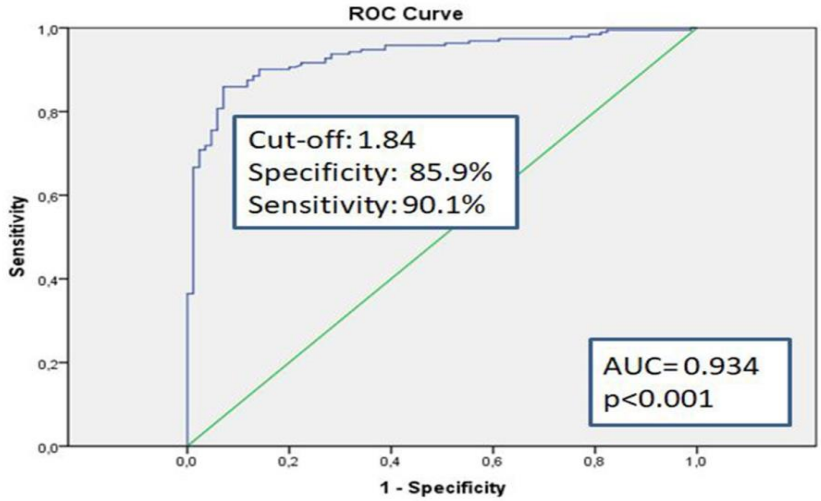

Figure 1. ROC curve for NLR in SAT diagnosis

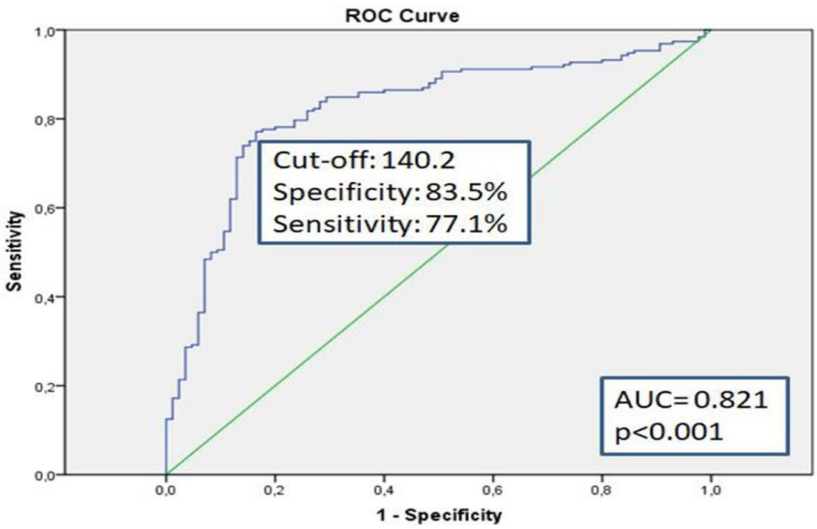

Figure 2. ROC Curve for PLR in SAT diagnosis

Correlation analysis revealed positive linear relations between pre-treatment PLR and CRP (p=0.002, r=0.220), pre-treatment PLR and ESR (p=0.018, r=0.171), pre-treatment NLR and CRP (p<0.001, r=0.330), and pre-treatment NLR and ESR (p=0.001, r=0.242). Multiple linear regression analysis revealed a 0.008 unit of increment of NLR per 1 unit increase in CRP levels (B=0.008; p<0.001; %95 CI=0.004-0.012).

4. Conclusion

The main finding of our study is that NLR and PLR can be helpful test for detecting SAT. Elevated NLR and PLR in the presence of thyrotoxicosis is a warning sign regarding SAT for the general practitioners. Pre-treatment NLR, PLR values, and CRP levels significantly decreased when patients improved. It shows that NLR and PLR can be a useful parameter to assess disease activity.

It has also been shown in other studies conducted in our country that NLR and PLR values increase in SAT (Table 3) (Calapkulu et al., 2020; Cengiz et al., 2020; Kilinc et al., 2018). In the study of Cengiz et al (n=71), the cut-off value for NLR was 2.4 (51% specificity and 80% sensitivity), and the cut-off value for PLR was 146.84 (54% specificity and 83% sensitivity). In our study (n=192), the optimum cut-off values for NLR and PLR were detected 1.84 (specificity 85.9% and sensitivity 90.1%) and 140.2 (specificity 83.5% and sensitivity 77.1%), respectively. In another study conducted in China (n=169), the cut-off value for NLR was 2.0 (specificity 76.9%, sensitivity 80.5%), and the cut-off value for PLR was 150 (specificity 84.2%, sensitivity 64.3%) was determined (GU et al., 2017). Differences in cut-off values may be due to patient numbers and racial differences. For this reason, it may be more appropriate to use cut-off values adapted to breeds. The high specificity feature sought in diagnostic tests, when used for cut-off values, may be more beneficial for physicians in terms of guiding the diagnosis. When high specificity values were used in our study, the cut-off values increased to 2.4 (98% specificity, 67% sensitivity) for NLR and 212.1 (98% specificity, 21% sensitivity) for PLR.

Table 3. NLR and PLR values of SAT patients in studies conducted in our country

	NLR	**PLR**
Kılınç et al., [11]	3.56 ± 2.64[a]	-
Cengiz et al., [10]	2.78 ± 1.52[a]	173.04 ±74[a]
Calapkulu et al., [9]	3.49 ± 2.1[a]	199.6±105.7[a]
Our study	2.78 (0.91-11.33)[b]	168.3 (25.7-818.3)[b]

*NLR: Neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; [a]mean ± SD; [b]median (range)

It can be said that the neck pain may alert the endocrinologist who usually has easy access to CRP. On the other hand, patients may not have typical symptoms and they may admit to general

practitioners with thyrotoxicosis symptoms. Since hemogram is one of the fundamental and easily accessible laboratory tests for general practitioners, In the presence of thyrotoxicosis, an elevated NLR and PLR may warn the physician regarding SAT.

Regarding evaluating disease activity, NLR can be used especially in patients who were being treated with NSAID. But since steroid therapy may increase the neutrophil count, it would be a more accurate approach to evaluate the ESR and CRP values as inflammatory markers to evaluate the disease activity after treatment in patients who were given steroids. However, further studies are needed for disease activity assessment with NLR and PLR.

Besides, there are some opposing reports against NLR increase in autoimmune and inflammatory diseases. Turan et al., found lower NLR in Graves' disease (GD) with overt hyperthyroidism and a significant increase following treatment. These results may probably be due to increase in lymphocytes in GD (Turan, 2019). GD, unlike other inflammatory diseases, may exhibit a wide variety of distribution of white blood cells, including leukopenia, absolute and relative neutropenia, relative lymphocytosis (Irvine et al., 1977). High NLR in SAT patients and low NLR in GD may be a helpful test in the differential diagnosis of thyrotoxicosis seen in both diseases, especially in SAT patients with painless presentation. NLR can assist general practitioners in the differential diagnosis of painless SAT from GD.

There are some limitations to this study. First, this is a retrospective study where we did not have control on parameters that may affect the results. Second, though there are studies to determine NLR mean and cut-off value for differential diagnosis of SAT (Cengiz et al., 2020; GU et al., 2017), there is no widely accepted value.

In conclusion, NLR and PLR are useful additional test in diagnosing SAT patients and referring them to relevant specialists. With further disease-specific cut-off studies, its use may be increased.

Conflicts of interest

The authors declare that there are no potential conflicts of interest relevant to this article.

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