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ÇÖLYAK HASTALARINDA NÖTROFİL/LENFOSİT VE PLATELET/LENFOSİT ORANI

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Öz

Çölyak hastalığı, genetik yatkınlığı olan kişilerde, diyetle alınan glutenin tetiklediği kronik inflamatuar ince bağırsak enteropatisidir. Bu çalışmada; nötrofil-lenfosit oranı ve platelet-lenfosit oranı ile sistemik inflamatuar bir hastalık olan çölyak hastalığı arasındaki ilişkinin ortaya konulması ve bu değerlerin Marsh skoru ile karşılaştırılması amaçlanmıştır. Çalışmaya çölyak tanısı konulan 132 hasta ve sağlıklı 55 kontrol dahil edildi. Hastaların ve kontrol gurubunun sonuçları, hastane otomasyon sistemi ve hasta dosyalarından retrospektif olarak taranarak kaydedildi ve istatistiksel analizi yapıldı. Ayrıca daha önce yapılan biyopsilerin patoloji raporlarında yer alan march skorları ile elde edilen veriler karşılaştırıldı. Çölyak hastalarının %60.0'ında demir, %63.3'ünde ferritin, %78.0'ında D vitamini, %30.0'ında folat düşük bulunurken, %51.8'inde demir bağlama yüksek bulundu. Hasta gurubunda nötrofil-lenfosit oranı ve platelet-lenfosit oranı kontrol gurubuna göre anlamlı yüksek bulundu (sırasıyla, p:0.000, p:0.002). Yapılan ROC analizinde eğri altı alan HGB için 0.708, PLT için 0.687, RDW için 0.674, nötrofil için 0.606, nötrofil-lenfosit oranı için 0.706, platelet-lenfosit oranı için 0.644 olarak bulundu. Sonuç olarak nötrofil-lenfosit oranı ve platelet-lenfosit oranı tam kan sayımı ile hesaplanabilen ve yaygın olarak kullanılan ucuz testlerdir. Hem nötrofil-lenfosit oranı hem de platelet-lenfosit oranı sistemik inflamasyonun önemli bir ölçüsü olarak çölyak hastalığında kullanılabilir.

Anahtar kelimeler: Çölyak hastalığı, Nötrofil lenfosit oranı, Platelet lenfosit oranı, ROC

NEUTROPHIL/LYMPHOCYTE AND PLATELET/LYMPHOCYTE RATIO IN PATIENTS WITH CELIAC

Abstract

Celiac disease is a chronic inflammatory small intestine enteropathy triggered by dietary gluten in people with genetic predisposition. In this study; It was aimed to reveal the relationship between neutrophil-lymphocyte ratio and platelet-lymphocyte ratio and celiac disease, which is a systemic inflammatory disease, and to compare these values with Marsh score. 132 patients diagnosed with celiac disease and 55 healthy controls were included in the study. The results of the patients and the control group were scanned retrospectively from the hospital automation system and patient files, and statistical analysis was performed. In addition, the data obtained with the march scores in the pathology reports of the previous biopsies were compared. While 60.0% of celiac patients had low iron, 63.3% ferritin, 78.0% vitamin D, 30.0% folate, 51.8% iron binding was found to be high. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio were significantly higher in the patient group compared to the control group (p: 0.000, p: 0.002, respectively). In the ROC analysis, the area under the curve was 0.708 for HGB, 0.687 for PLT, 0.674 for RDW, 0.606 for neutrophil, 0.706 for neutrophil-lymphocyte ratio, and 0.644 for platelet-lymphocyte ratio. In conclusion, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio are widely used cheap tests that can be calculated by complete blood count. Both the neutrophil-lymphocyte ratio and the platelet-lymphocyte ratio can be used in celiac disease as an important measure of systemic inflammation.

Keywords: Celiac disease, Neutrophil lymphocyte ratio, Platelet lymphocyte ratio, ROC

1. INTRODUCTION

Celiac Disease (CD) is a chronic inflammatory enteropathy of the small intestine triggered by dietary gluten in people with a genetic predisposition. The disease appears with the interaction of genetic, environmental, and immunological factors (1, 2). The pathogenesis of CD involves the immune-mediated damage to the mucosa of the small intestine, and results in the malabsorption of the small intestine if gluten intake is not limited. In general, the prevalence of CD was reported as between 0.5% and 1%, although it varies among different societies, and the prevalence of it is increasing gradually in developed countries being higher in women than in men, and higher in children than in adults (1, 3, 4).

Celiac Disease shows common clinical diversity. Patients may admit with complaints about the gastrointestinal system or extraintestinal findings, or it may be completely asymptomatic. The symptoms of the disease result from the damage in the small intestinal enterocytes (3, 5). Although serological and genetic tests are employed for its diagnosis, small bowel biopsy is considered as the gold standard. In serological terms, the presence of antibodies e.g. anti-endomysium antibody (EMA), anti-tissue transglutaminase antibody (anti-tTG), and anti-gliadin antibodies (AGA) is important for its diagnosis. Since only HLA (Human Leucocyte Antigen) DQ2, DQ7, or DQ8 molecules present it to the immune system after binding to gluten, people who carry these HLA types genetically are affected by the disease. The definitive diagnosis is made with the histopathological evaluation of the biopsy samples taken from the duodenum by using the Marsh Classification (intraepithelial lymphocytes, villus atrophy, and crypt hyperplasia) (6-8).

Hematological variations are very common and important in CD because of the systemic inflammatory response. There are various biochemical and hematological markers to measure systemic inflammation. Complete blood count is among these easily accessible tests, and is an inexpensive test yielding fast results. The white blood cell count (WBC), neutrophil, lymphocyte, platelet count (PLT), and mean platelet volume (MPV) values that are examined in this test, and the rates of these values to each other are employed as inflammatory markers (9-11).

Neutrophil, platelet, and lymphocyte cells play important roles in inflammatory processes. Lymphopenia generally reflects the weakness of cellular immunity, and neutrophilia is a parameter showing the response to systemic inflammation. The rate of these two values to each other can be interpreted as showing the adequacy of cellular immune response despite the dimension of the systemic inflammation, and neutrophil and lymphocyte counts change temporarily in inflammation (9, 12, 13). In recent years, neutrophil-to-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) are introduced as useful indices in the diagnosis or prognosis of different diseases. Also, there are many studies that examine the clinical importance of NLR in hypertension, diabetes, metabolic syndrome, kidney diseases, inflammatory diseases, cancer and rheumatological diseases. Elevated preoperative NLR levels are considered as a poor prognostic factor in gastric, pancreatic, non-small cell lung cancer, and ovarian cancer (14-19).

The question of whether these simple data on the immune reaction and the response to it will be significant for other diseases is at the forefront especially in recent years. Its use as an indicator of acute inflammation in gastrointestinal system (GIS) diseases is also being discussed (13, 14, 16). In this respect, leukocyte count, neutrophil percentage, PLT, NLR, PLR, MPV, RDW, and PDW parameters were investigated for use in the diagnosis and estimation of complex CD. The strengths of our study are that we did not find any studies in the literature evaluating the relations between NLR and PLR values and CD, and comparing the hematological parameters with a control group. In

the present study, the purpose was to uncover the relations between NLR and PLR and CD, which is a systemic inflammatory disease, and to compare resulting values with the Marsh Score.

2. MATERIALS AND METHODS

Patients who were followed up in Konya Training and Research Hospital, Gastroenterology Clinic for 5 years between 01/09/2015 and 01/09/2020 were included in the present study. The study group included 132 patients who were diagnosed with CD as a result of specific image in endoscopic examinations performed upon clinical suspicion in examinations and laboratory findings and pathological examinations of biopsies taken during endoscopy. In the Control Group, 55 patients who did not have any chronic inflammatory diseases, but were examined because of clinical suspicion, who were serologically negative (antiendomysium IgA and tissue transglutaminase IgA), and who underwent endoscopic examination due to the same suspicion, and who had excluded CD in endoscopic examination and/or biopsy results. Patient files were evaluated retrospectively; and no new examinations or tests were performed in the study.

The anti-endomysium IgA and anti-tissue transglutaminase IgA levels of all patients who were included in the study were evaluated. All of the patients in the study group had positive HLA-DQ2 and/or DQ8 test results, and upper GI endoscopy was carried out following clinical and laboratory examinations. A total of six biopsies, three from the second part of the duodenum and three from the bulbous, were taken from all of the patients included in the study group by using standard endoscopic biopsy forceps, and the specimens were evaluated according to the Modified Marsh Classification, and those who met the criteria were diagnosed with CD. There were no appearances that were compatible with CD in the endoscopic examinations of the patients who were included in the Control Group, and tissue transglutaminase IgA and antiendomysium IgA test results were negative.

The age, gender, biochemistry, serology and complete blood count results (WBC, HGB, PLT, MPV, PDW, RDW, neutrophil, lymphocyte), and NLR and PLR values of the patients obtained from the results were recorded retrospectively from the hospital automation system and patient files. The Sysmex XN-1000 Device was used to examine the complete blood counts. The NLR values were calculated by dividing the neutrophil count by the lymphocyte number in the complete blood count reports, and the PLR value was calculated by dividing the platelet count by the lymphocyte number. These data were compared with Marsh Scores that were included in patient files which were reported after pathological examinations of previous biopsies.

The patients who were under the age of 18 and over the age of 65, pregnant women, those who did not undergo serological examinations and endoscopic evaluations, and those who did not have complete blood count results were not included in the study. Those with systemic and/or other inflammatory diseases (e.g. diabetes, hypertension, malignancy, cerebrovascular disease, coronary artery disease, infectious diseases, liver and kidney failure, and rheumatic diseases), which might affect NLR and PLR values other than CD, those who received hormone replacement and antiplatelet therapies, those who had a history of recent blood transfusion were excluded from the study. In addition, patients who were diagnosed with CD but whose marsh score could not be reached were also excluded from the study.

2.1. Statistical analysis

The data that were obtained as a result of the data collection step were transferred to the computer medium and were analyzed. The data analysis was performed by using the Package for Social Sciences (SPSS) Software. The conformity of the data to normal distribution was examined with visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk Tests). Arithmetic mean values, standard deviation, minimum and maximum values were used in the evaluation of numerical data, and the frequency distributions and

percentages were used to summarize the categorical data. The Chi-Square Test ($\chi 2$) was used to compare the categorical data. The relations between non-normally distributed numerical data and categorical data was evaluated with the Man-Whitney U Test; and the Kruskal Wallis Test was used to evaluate three or more groups that exhibited numerical data. The Posthoc Man-Whitney U Test and Bonferroni Correction were used for pairwise comparisons between the groups that had significant Kruskal Wallis test results. The correlations of non-normally distributed numerical variables were analyzed with the Spearman Correlation Coefficient. The diagnostic decision-making characteristics of HGB, PLT, RDW, neutrophil, NLR, PLR levels in predicting the disease severity were analyzed with the ROC (Receiver Operating Characteristics) Curve Analysis. Type-1 Error Level was accepted as 5% for statistical significance. In the evaluation of Spearman Correlation Coefficients, 0.05-0.30 was considered to be low or not significant, 0.30-0.40 as low-moderate, 0.40-0.60 as moderate, 0.60-0.70 as good, 0.70-0.75 as very good, and 0.75-1.00 was considered as excellent. The correlation coefficients that had positive signs showed that the variables increased and decreased together, and the correlation coefficients that had negative signs show that as one variable increased, the other decreased or vice versa.

2.2. Ethical Approval

For this study, approval was obtained from the Ethics Committee of KTO Karatay University, Faculty of Medicine, Non-Pharmaceutical and Medical Device Research, and research and publication ethics were followed in the article (No: 2020/004, Date: 19.06.2020). Care was taken to ensure that the study complies with the Declaration of Helsinki.

3. RESULTS

A total of 132 patients (98 women, 34 men) who were diagnosed with Celiac Disease, and 55 healthy controls (31 women, 24 men) were included in the present study. The patients were between the ages of 19-65 (42.16±16.01), and the control group was between the ages of 21-52 (31.50±7.31). Significant differences were detected in terms of age and gender in the statistics made between the patient and control groups because of the high mean age of the patient group and the high rate of women patients ($p<0.001$, p:0.016, respectively).

The levels of Fe were found to be low in 60.0% of celiac patients along with ferritin in 63.3%, Vitamin D in 78%, and folate in 30.0%, and high Fe binding was detected in 51.8%. Some laboratory parameters of the patient group are given in Table 1.

Table 1. Basic laboratory findings of celiac patients

Parameters	The reference range	Patient (medyan ± SD)	n
Fe (µg/dL)	70-180	55 ± 43.3	85
Fe binding (µg/dL)	155-355	310 ± 100.7	85
Ferritin (mmol/L)	18.5-306.5	12.05 ± 75.87	90
Vitamin D (mg/dL)	>20	13.80 ± 11.45	59
Vitamin B12 (µg/L)	185-914	354± 215.43	91
Folate (µg/L)	>5.38	7.27± 5.16	76

The anti-endomysium IgA and anti-tissue transglutaminase IgA levels of all celiac patients who were included in the study were examined, and the results were found to be positive.

As a result of the evaluation of the patients according to the Marsh Classification in endoscopic biopsy results, it was found that the majority of them were Class III (54.5%). When the laboratory parameters of the groups were compared according to the Marsh Scores of 132 patients, no statistically significant differences were detected ($p>0.05$). Laboratory findings according to Marsh score grouping of celiac patients are given in Table 2.

Table 2. Comparison of laboratory findings according to Marsh score grouping of celiac patients

Parameters	Marsh I (n: 47)	Marsh II (n: 13)	Marsh III (n: 72)	p
Age	39.36±13.22	42.36±13.45	46.50±17.70	0.58
WBC ($10^3/mm^3$)	7.09 ±1.86	6.91± 1.19	6.91± 1.19	0.76
HGB (g/dL)	13.20±2.30	12.1±2.48	12.85±12.80	0.71
PLT ($10^3/mm^3$)	311±67.55	307±76.83	282±101.42	0.61
MPV (fL)	10.60±0.91	10.30±0.50	10.05±1.05	0.12
PDW (fL)	12.60±5.18	11.10±1.59	11.85± 14.75	0.24
RDW (%)	13.80±2.29	15±4.49	14.30±3.15	0.16
Lymphocyte ($10^3/mm^3$)	2.20±0.76	2.27±0.37	1.97±0.75	0.38
Neutrophil ($10^3/mm^3$)	4.43±1.24	3.98±1.06	4.93± 1.67	0.17
NLR	1.94±0.82	1.55±0.64	2.22± 1.36	0.07
PLR	134.52±45.99	128.02±42.38	135.52±57.54	0.77
Fe (µg/dL)	50±49.20	32±36.18	56±30.60	0.74
Fe binding (µg/dL)	317±99.78	358±81.56	302±30.60	0.43
Ferritin (mmol/L)	11.70±42.12	11.10±26.98	12.10±86.37	0.97
Vitamin D (mg/dL)	12.99±16.08	7.40±13.77	14.98±6.54	0.78
Folate (µg/L)	8.03±4.96	6.61±3.67	7.63±5.24	0.77
Vitamin B12 (µg/L)	348±101.81	342±94.84	359.50±137.82	0.78

$p<0.05$: statistically significant

When a comparison was made between the patient group and the control group for hemogram parameters, significant differences were detected between the groups in terms of HGB, PLT, PDW, RDW, lymphocyte, neutrophil, NLR, and PLR ($p<0.05$) (Table 3).

Table 3. Comparison of hemogram parameters of celiac patients and control group

Parameters	Patient (medyan ± SD) (n: 132)	Control (medyan ± SD) (n: 55)	p
WBC ($10^3/mm^3$)	7.08 ± 2.15	7.31± 1.79	0.829
HGB (g/dL)	13.15± 8.48	14.5± 1.64	0.000*
PLT ($10^3/mm^3$)	295.50± 88.83	246±59.95	0.000*
MPV (fL)	10.30±0.95	10.10±1.07	0.676
PDW (fL)	12.20±10.23	16.10±0.30	0.000*
RDW (%)	14.00±2.88	13.40±0.78	0.000*
Lymphocyte ($10^3/mm^3$)	2.10±0.72	2.19±0.71	0.049*
Neutrophil ($10^3/mm^3$)	4.99±1.70	4.00±1.02	0.045*
NLR	2.38±1.73	1.82±0.91	0.000*
PLR	140.71±49	112.55±53.89	0.002*

$p<0.05$: statistically significant, SD: Standard deviation

When the correlation parameters of the patient group were examined, a high correlation was detected between HGB-RDW and MPW-PDW. Some correlation values are given in Table 4.

Table 4. Correlation parameters of the patient group

Parameters	Correlation coefficient (r)	p	Grade
HGB-RDW	-0.690	0.000	High level
MPV-PDW	+0.687	0.000	High level
HGB-Ferritin	+0.538	0.000	Intermediate
WBC- Lymphocyte	+0.417	0.000	Intermediate
NLR/PLR	+0.447	0.000	Intermediate
PLT- Lymphocyte	+0.343	0.000	Weak level

In the ROC analysis, the area under the curve was 0.708 for HGB, 0.687 for PLT, 0.674 for RDW, 0.606 for neutrophils, 0.706 for NLR, and 0.644 for PLR. The NLR, PLR ROC graphics and PLT, RDW ROC graphics are given in Figures 1 and 2.

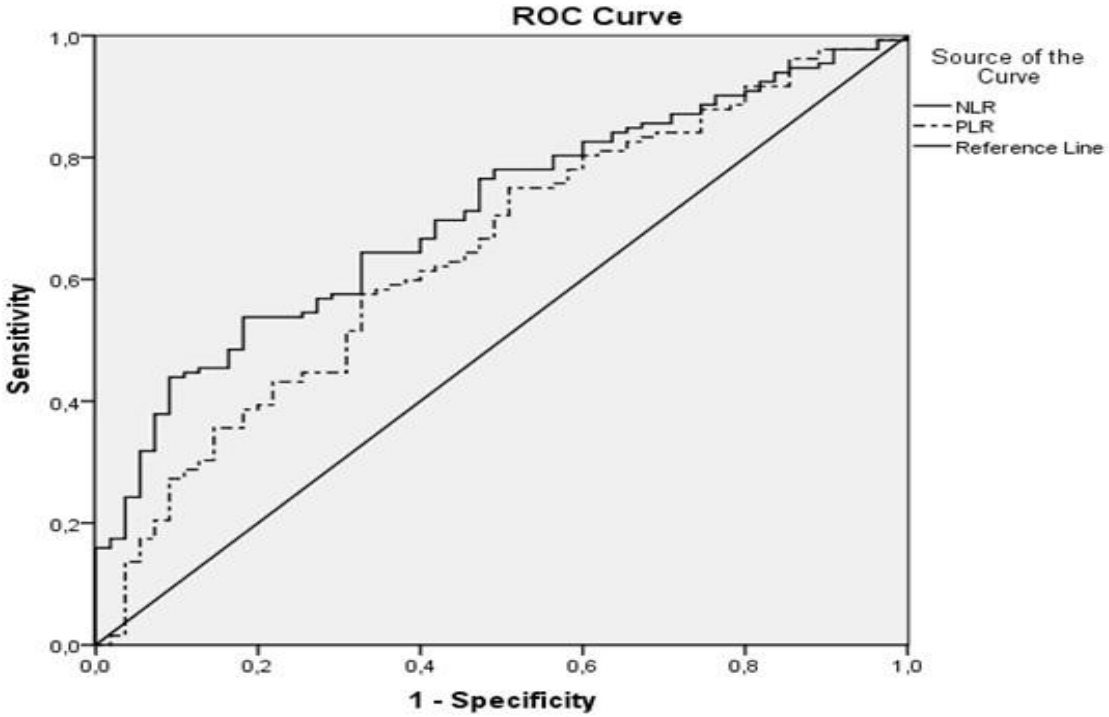

Figure 1. ROC plot of NLR and PLR

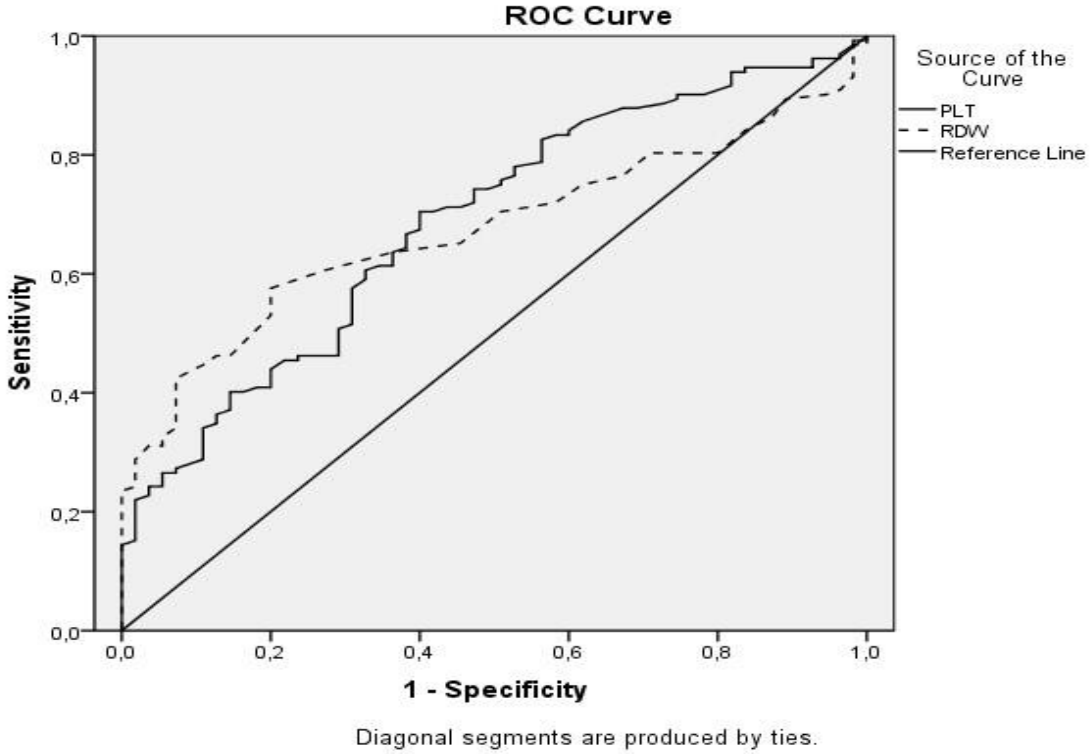

Figure 2. ROC plot of PLT and RDW

4. DISCUSSION

A total of 132 patients (98 female, 34 male) who were aged 19-65 years and 55 healthy controls (31 female, 24 male) who were aged 21-52 years were included in the present study. The fact that the number of women was higher in the patient group than that of men was similar to the data in other studies (13, 20, 21).

The Fe, vitamin D, folate, and vitamin B12 deficiency are common in celiac patients because of malabsorption. In the study conducted by Wierdsma NS et al. with 80 newly diagnosed celiac patients, folate was found to be deficient in 20.0% and vitamin B12 in 19.0% of patients. It was also reported in the same study that decreased ferritin was found in 46.0% of the patients and anemia was found in 32.0% (22).

In a study that was conducted by Ciğerli et al. in 2013 with 2131 patients, the mean vitamin D level was found to be 17.4 mg/dL and vitamin D deficiency was reported in 66.3% of patients (23). In another study that was conducted in 2017, it was reported that vitamin D deficiency was most common in 69.4% of patients. It was reported in the same study that 11.5% of the patients had Fe deficiency and 34.4% had subnormal ferritin levels (24). In a study that consisted of 24 celiac patients and 50 children in the control group conducted in 2012, it was reported that there were no differences in terms of vitamin D levels between the patient and control group (25). In the study conducted by Erdem T et al. conducted with 52 children with celiac disease in 2015, 51.9% of patients were found to have low vitamin D levels (26). In our study, Fe binding was found to be low in 60.0% of the patients, ferritin in 63.3%, vitamin D in 78.0%, folate in 30.0%, and high Fe binding in 51.8%. The results were below the reference values in only one patient in terms of vitamin B12. Malabsorption is a known fact in celiac patients. We believe that the differences between the studies may be because of the number of patients, lack of knowledge on vitamin and mineral supplements taken by patients, and methodological differences. The fact that the vitamin B12 values were within the normal range may be due to the absorption of this vitamin, especially from the ileum, and/or the initiation of parenteral B12 replacement therapy before the patients were referred to tertiary hospital after being diagnosed with the disease.

Significant differences were detected in the comparison of hemogram parameters between the patient group and the control group because of the low HGB values in the patient group. We believe that this difference may be caused by Fe deficiency. In our study, significant differences were detected in the PLT value depending on the elevated values in the patient group. Terlemez S et al. reported in 2018 that thrombocytosis was found in 57.5% of the patients in their study conducted with 66 celiac patients, and this value decreased after the treatment (27). We see that increased platelet amounts in inflammation were increased in our celiac patient group when compared to the control group, and it was found that the area under the curve was 0.687 in the ROC analysis.

Mean platelet volume value also reflects inflammation, and it was shown that its amount increases in chronic inflammatory diseases. In a study that was conducted by Purnak T. et al. in 2011 with 67 newly diagnosed celiac patients and 40 control group people, it was found that the MPV and PLT values were significantly higher in the patient group, suggesting that the MPV value may be an early indicator of intestinal inflammation (28). In our study, it was found that PDW value was significantly lower in the patient group, unlike the high PLT value, and although it was high in the patient group in terms of MPW value, no significant differences were detected between our groups.

Regarding RDW, it was reported in previous studies that it is a sensitive marker for CD (9, 10). Balaban DV et al. compared 34 newly diagnosed and 16 treated celiac patients in 2018. It is

well known that RDW value can be an indicator of Fe, folate, and B12 deficiency for celiac patients. The findings in our study are consistent with these studies (9, 29, 30).

Neutrophils and lymphocytes play important roles in inflammatory process, and their number changes temporarily. Cellular immunity also plays important roles in intestinal damage in CD. NLR and PLR are among the parameters which attract attention in recent years. Elevated NLR shows more serious pathology, especially in clinically intermittent cases. In a study that was conducted by Uslu AU et al. in 2016 with 37 celiac patients and 37 healthy control people, it was reported that the NLR was significantly higher in the patient group, lymphocyte amount was significantly lower, and the area under the curve was 0.819 for NLR in the ROC analysis (13). In a study that was conducted by Sarıkaya M et al. in 2014 with 76 celiac patients and 86 control group people, it was reported that NLR was significantly higher in the patient group, and the area under the curve was 0.607 in their ROC analysis (31). In the study conducted by Palmacci F et al. in 2019 that investigated the relations between NLR and eating habits and osteoporosis in celiac patients, it was found that NLR was higher in patients with osteoporosis (20). The findings of our study are similar to the studies in the literature, emphasizing NLR once again. We obtained significant differences in NLR because of the significantly high neutrophil and low lymphocyte count in the patient group. In the ROC analysis, it was found that the area under the curve was 0.706.

Platelet-lymphocyte ratio is an inexpensive and easily accessible marker showing systemic inflammation like NLR. Although there are studies conducted on NLR for CD, articles on PLR are limited. Balaban DV et al. compared 34 newly diagnosed celiac patients and 16 treated celiac patients in 2018 ($p<0.001$). The area under the curve obtained in the same study was found to be 0.754 (9). However, in our study, the PLR was found to be significantly different depending on the elevated values in the patient group, and the area under the curve was 0.644 in the ROC analysis.

Limitations

Our important limitations are the retrospective design of our study, the small number of patients and single center data, and the lack of clear information on the use of vitamin and mineral supplements that may affect the parameters studied. One of the shortcomings of our study is that the number of participants in the control group was lower than the patient group.

Conclusion

In conclusion, NLR and PLR are inexpensive tests that can be measured by complete blood count and are widely used. Both NLR and PLR can be used in CD as an important measure of systemic inflammation. In addition, new indices that will be created by taking into account parameters such as RDW and PDW can guide the determination of disease severity. More extensive studies will shed more light on the role of these parameters.

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