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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Platelet Indices in Determination of Marsh Classification in New Diagnosed Celiac Patients

Yeni Tanı Çölyak Hastalarında Marsh Sınıflamasının Belirlenmesinde Trombosit İndeksleri

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Abstract

Objectives: Celiac disease is an autoimmune and inflammatory disease induced by dietary gluten in genetically susceptible individuals. The most important diagnostic method in celiac disease is histopathological examination, and Marsh classification. It is known that in some inflammatory diseases, systemic inflammatory response markers such as mean platelet volume (MPV), plateletcrit (PCT) and platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) are of diagnostic importance. Our aim in this study is to investigate the importance of systemic inflammatory response markers in determining the Marsh classification

Materials and Methods: Two hundred and fifty patients with gluten sensitive enteropathy were investigated by using MPV, PCT, PLR, and NLR. Patients were stratified into five groups; Group I: Marsh type 1, Group II: Marsh type 2, Group III: Marsh type 3, Group IV: increased intraepithelial lymphocytes, and also one group involving control group (Group V).

Results: 250 newly diagnosed celiac patients were divided into 3 groups as Group I (Marsh type 1, n=109), Group II (type 2, n=11) and Group III (type 3, n=130) according to the Marsh classification. Fifty patients with increased intraepithelial lymphocytes (Group IV) and 150 patients with normal duodenal biopsy were taken as the control group (Group V). Patients and control groups were compared in terms of MPV, PCT, PLR, and NLR values.

Conclusion: MPV (8.7±1.07 vs 8.7±1.2 fL, p=0.922), PCT (0.24±0.06 vs 0.22±0.07, p=0.145) and PLR (144.28±61.54 vs 148.59±89.71, p=0.711) values did not differ compared to the controls. As a result, it is not appropriate to use MPV, PCT, PLR, and NLR in determining the Marsh classification.

Key Words: Celiac Disease, Marsh Classification, Platelet Indices, Platelet/Lymphocyte Ratio

Öz

Amaç: Çölyak hastalığı, genetik olarak duyarlı bireylerde, diyetteki gluten tarafından uyarılan otoimmün ve enflamatuvar bir hastalıktır. Çölyak hastalığı tanısında en önemli tanı yöntemi histopatolojik inceleme ve Marsh sınıflamasıdır. Bazı enflamatuvar hastalıklarda ortalama trombosit hacmi (OTH), plateletkrit (PCT) ve trombosit/lenfosit oranı (TLO) ve nötrofil/lenfosit oranı (NLO) gibi sistemik enflamatuvar yanıt belirteçlerinin tanısal önemi olduğu bilinmektedir. Bu araştırmada amacımız, sistemik enflamatuvar yanıt belirteçlerinin Marsh sınıflamasını belirlemekteki önemini araştırmaktır.

Gereç ve Yöntem: Gluten sensitif enteropatisi olan 250 hasta OTH, PCT, TLO ve NLO kullanılarak değerlendirildi. Hastalar 5 gruba sınıflandırıldı. Grup I: Marsh tip 1, Grup II: Marsh tip 2, Grup III: Marsh tip 3, Grup IV: artmış intraepitelial lenfosit, ayrıca bir grup kontrol grubu olarak belirlendi (Grup: V).

Bulgular: Yeni tanı almış 250 çölyak hastası Marsh sınıflandırmasına göre Grup I (Marsh tip 1, n=109), Grup II (tip 2, n=11) ve Grup III (tip 3, n=130) olmak üzere 3 gruba ayrıldı. Ayrıca intraepitelyal lenfosit artışı olan 50 hasta (Grup IV) ile duodenum biyopsisi normal olan 150 hasta kontrol grubu olarak alındı (Grup V). Hastalar ve kontrol grubu OTH, PCT, TLO ve NLO değerleri yönünden karşılaştırıldı.

Sonuç: OTH (8,7±1,07 vs 8,7±1,2 fL, p=0,922), PCT (0,24±0,06 vs 0,22±0,07, p=0,145) ve TLO (144,28±61,54 vs 148,59±89,71, p=0,711) değerleri, kontrol grubu ile karşılaştırıldığında farklılık göstermemektedir. Bu araştırmanın sonuçlarına göre, OTH, PCT, TLO, NLO'nun Marsh sınıflandırmasının belirlenmesinde kullanılması uygun değildir.

Anahtar Kelimeler: Çölyak Hastalığı, Marsh Sınıflaması, Platelet İndeksleri, Platelet/Lenfosit Oranı

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Introduction

Celiac disease (CD) is a chronic, immune-mediated, small intestinal enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals who carry the HLA-DQ2 or DQ-8 alleles (1-3). The prevalence of gluten sensitive entheropathy varies between 1/130-260 worldwide. This ratio was found to be 1/22 in first-degree relatives of people with gluten sensitive entheropathy disease and 1/39 in second-degree relatives (4). The prevalence in Scandinavian and Great Britain ranges from 1/99 to 110, compared to 1/200-236 in African, Hispanic and African Americans (5). Gluten-sensitive enteropathy is a disease that affects the mucosa of the small intestine. The submucosa, muscularis propria, and serosa are usually not involved. Although genetic factors play an important role in the pathogenesis of the disease, environmental factors are also important (6). As long as up to 10 mg of gluten is not taken in the diet, the disease does not occur. For this reason, the incidence of CD has increased in societies where gluten-containing wheat, barley and rye have an important place in their diet. Gliadin in wheat, secalin in rye, hordein in barley cause toxic effects (6). Among these cereals, the toxic effect of the prolamine avenin in oats is controversial, but it is still not considered safe. Rice and corn, on the other hand, are completely safe cereals that contain zein and oryza prolamins but do not contain toxic prolamins, which these patients can consume (6).

The diagnosis of the disease is made by endoscopic findings of intraepithelial lymphocyte (IEL) increase in the small intestinal mucosa, crypt hyperplasia and villous atrophy (7). It is important to detect antigliadin antibody, anti-tissue transglutaminase antibody and/or anti-endomysium antibody, which is the first step in diagnosis, before small intestine biopsy is performed (8). CD is the final step in a complex biological pathway activated by inflammatory conditions, and this complex pathway may lead to changes in some inflammatory markers prior to CD. This can be used to prevent CD or to establish pre-celiac catching strategies and appropriate surveillance protocols. Currently, however, surveillance methods for pre-celiac duodenal lesions in clinical settings are variable and endoscopic surveillance intervals are unclear yet. Endoscopic and pathological examinations are not only expensive but also invasive methods and limit these methods in high-risk patients. In clinical settings, there are some biomarkers in the complete blood count, such as mean platelet volume (MPV) and plateletcrit (PCT). PCT is the volume percent of platelets in the blood, similar to hematocrit, while MPV represents the mean platelet size and platelet production rate (9). It has also been reported that simple markers of systemic inflammation such as platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) may have diagnostic importance in some clinical situations (10).

Our hypothesis was that conditions such as increased IEL are associated with chronic inflammation and that MPV, PCT, PLR and NLR values may play a role in the evaluation of the group with increased IEL but not yet celiac or who develop significant IEL increase and villous atrophy. Therefore, the aim of this study is to determine the difference between Marsh type 1, 2, 3 celiac patients using platelet indices and patients with increased IEL but not diagnosed with celiac and normal duodenal biopsy.

Materials and Methods

In this study, duodenal biopsy samples of patients who were referred to our endoscopy unit were analysed retrospectively by means of the presence of CD. Existing diseases such as malignant conditions, antiplatelet drug use, renal, heart and hepatic failure, active infection disease, diabetes mellitus, hypertension, hypothyroidism and patients whose data were lacking were also not included into the study. Four hundred and fifty patients were assigned into the study. We carried out a retrospective analysis of 250 patients diagnosed as having CD during the past 4 years. Fifty patients were patients with only intra-epithelial lymphocyte increase, and one hundred and fifty patients had normal duodenal biopsies. Only patients who had biopsy confirmed diagnosis were included into the study. Information retrieved from the hospital database and used in the present study included sex, age, date of CD diagnosis, initial symptoms prompting their diagnosis of CD, and laboratory parameters including, presence of anemia, serum ferritin, vitamin B12, folate, vitamin D. Histopathological examination of the duodenal biopsy specimens were also evaluated and classified according to the Marsh classification (11).

Ultimately, 450 patients were included into this study: Marsh type I (n=109), Marsh type II (n=11), Marsh type III (type 3, n=130), elevated IEL (n=50) and control groups (n=150). Based on histopathological findings patients with CD (n=250) were further stratified into 3 groups according to the classification of Marsh. In the final analysis, 5 groups were available:

1. Group I: Marsh type I (n=109)
2. Group II: Marsh type II (n=11)
3. Group III: Marsh type III (n=130)
4. Group IV: Elevated IEL (n=50)
5. Control group (n=150).

Demographic data, MPV (fl), PCT (%), platelet, lymphocyte and neutrophil counts ($x10^9$/L) were gathered from patients' files and PLR and NLR were calculated accordingly.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ankara City Hospital Ethics Committee (approval no: E2-22-1447).

Statistical Analysis

Statistical Package for the Social Sciences 16.0 was used for statistical analysis (SPSS Inc, Chicago, IL, USA) for Windows. We expressed results as percentage of patients, or mean ± standard deviation where appropriate. We performed analysis by using Shapiro-Wilk test, Mann-Whitney U and Kruskal-Wallis tests, and chi-squared where appropriate. While significant differences were detected, multiple comparison tests were used to know which groups differ from others. Receiver operating curve (ROC) analysis was performed in order to describe and compare the performance of diagnostic value of PLR and NLR, about determining CD.

Results

Four hundred and fifty patients were assigned into the study. Of the celiac patients included in the study, 186 (74.4%) were female and 64 (25.6%) were male. Of the patients with increased IEL, 36 (72%) were female and 14 (28%) were male. In the control group, 118 (78.7%) patients were female and 32 (21.3%) were male (p=0.2) The mean age of the patients was 33.58±11.54 in celiac patients, 35.62±11.6 in the group with increased IEL and 32.41±10.29 in the control group (p=0.09). As a result of the Sydney classification made as a result of the antrum and corpus biopsies of the patients, *Helicobacter pylori* positivity of the patients was 40 (36.6%), 4 (36.3%), 50 (38.5) in the celiac group, type 1, 2 and 3, respectively, 17 (34%) in the group with increased IEL, and 59 (39.3%) in the control group. This difference was not considered statistically significant (p=0.086). The analyzes of the subgroups of the whole group are given in Table 1. Platelet to lymphocyte ratio and NLR was lower in group V compared to groups I, II, III, IV (130.5±48.6 vs 131.2±57.3, 131.8±63.2, 131±76.132.17±59.9) but this difference was not statistically significant when compared between groups (p=0.06, 0.12, 0.31, 0.29,0.15, respectively). Neutrophil to lymphocyte ratio was also lower in group V compared to groups I, II, III, IV (2.3±1.64 vs 2.37±1.62, 2.41±1.9, 2.4±1.66). However, this difference was

Table 1: Demographic and clinical characteristics and investigated laboratory parameters of celiac, elevated IEL, control patients

	Total patients (n=450)	Marsh score type 1 (n=109)	Marsh score type 2 (n=11)	Marsh score type 3 (n=130)	Elevated IEL (n=50)	Control patients (n=150)	p-value
Age (years, SD)	32.94±11.54	33.21±10.9	36.15±62	33.71±10.3	35.62±11.6	32.41±10.29	0.3
Gender (F/M)	340/110 (75.6%/24.4%)	85/24 (77.9%/22.1%)	8/3 (72.7%/27.3%)	93/37 (71.5%28.5%)	36/14 (72%/28%)	118/32 (78.7%/21.3%)	0.12
Reason for investigation: upper GI symptoms/ iron and or vitamin B12 deficiency	195/255 (43.3%/56.7%)	44/65 (40.4%/59.6%)	6/5 (54.5%/45.5%)	108/22 (83.1%/16.9%)	11/39 (22%78%)	26/124 (17.3/82.7%)	<0.001
Anti-nuclear antibody (+/-)	63/387 (14%/86%)	12/97 (11%/89%)	2/9 (18.2%/81.8%)	29/101 (22.3%/77.7%)	7/43 (14%/86%)	13/137 (8.7%/91.3%)	<0.001
Hemoglobin (gr/dL)	12.2±1.8	12.1±1.5	11.2±1.8	10.4±1.7	13.1±1.9	13.9±2.1	<0.001
Vitamin D (nmol/L)	36.7±9.8	40.64±9.5	34.4±9.2	25.3±10.7	41.1±10.3	41.9±10.6	<0.001
Ferritin (ng/mL) [Median (Min.-Max.)]	24.3 (1-745)	24.5 (2-539)	17.5 (1-272)	12.2 (3-461)	30.6 (6-445)	34.6 (6-745)	<0.001
Vitamin B12 (pg/mL) [Median (Min.-Max.)]	202 (76-678)	201 (119-561)	189 (114-481)	168 (76-685)	221 (181-462)	234 (175-678)	0.002
PLT ($X10^3$/L)	257.18±78.7	254.33±81.39	247.21±68.7	266.48±79.86	268.29±81.9	261.78±79.5	0.08
WBC ($X10^3$/L)	8.29±3.8	8.41±4.12	7.78±3.49	7.22±3.57	8.21±4.35	8.2±3.9	0.14
Neutrophil	2.98±0.99	3.02±0.98	3.18±1	3.13±0.89	3.19±1.02	3.04±1.04	0.09
H. pylori (+/-)	170/280 (37.8%/62.2%)	40/69 (36.7%/63.3%)	4/7 (36.3%/63.7%)	50/80 (38.5%61.5%)	17/33 (34%/66%)	59/91 (39.3%/60.7%)	0.086
Intestinal metaplasia (+/-)	98/352 (21.8%/78.2%)	21/88 (19.3%/80.7%)	2/9 (18.2%/81.8%)	31/99 (23.8%/76.2%)	9/41 (18%/82%)	35/115 (23.3%/76.7%)	0.17
Activation (+/-)	189/261 (42%/58%)	40/69 (36.7%/63.3%)	5/6 (45.5%/54.5%)	53/77 (40.8/59.2%)	21/29 (42%/58%)	70/80 (46.7%/53.3)	0.43
Inflammation (+/-)	191/259 (42.4%/57.6%)	41/68 (37.6%/62.4%)	5/6 (45.5%/54.5%)	52/78 (40.8/59.2%)	21/29 (42%/58%)	72/78 (48%/52%)	0.57
Atrophy (+/-)	122/328 (27.1%/72.9%)	29/80 (26.6%/73.4%)	3/8 (27.3/72.7%)	35/95 (26.9%/73.1%)	13/37 (26%/74%)	42/108 (28%/72%)	0.3

SD: Standard deviation, F: Female, M: Male, IEL: Intraepithelial lymphocyte, Min.: Minimum, Max.: Maximum, GI: Gastrointestinal, PLT: Platelet, WBC: White blood cell

not statistically significant when compared between groups (p=0.11, 0.52, 0.14, 0.07, 0.13, respectively). PCT was lower in group V compared to group III (0.29±0.05 vs. 0.23±0.06, p=0.01). However, MPV was not different between groups. The laboratory features of the whole group and subgroups were illustrated in Table 1 and Table 2 in detail. The best platelet to lymphocyte ratio cut-off point was found to be 136.5 [area under the curve (AUC): 0.723] with a sensitivity and specifity of 0.65 and 0.68 respectively, and optimum NLR cut-off value was found to be 2.4 (AUC: 0.713) with a sensitivity and specifity of 0.69 and 0.63 respectively by using ROC analysis (Figure 1).

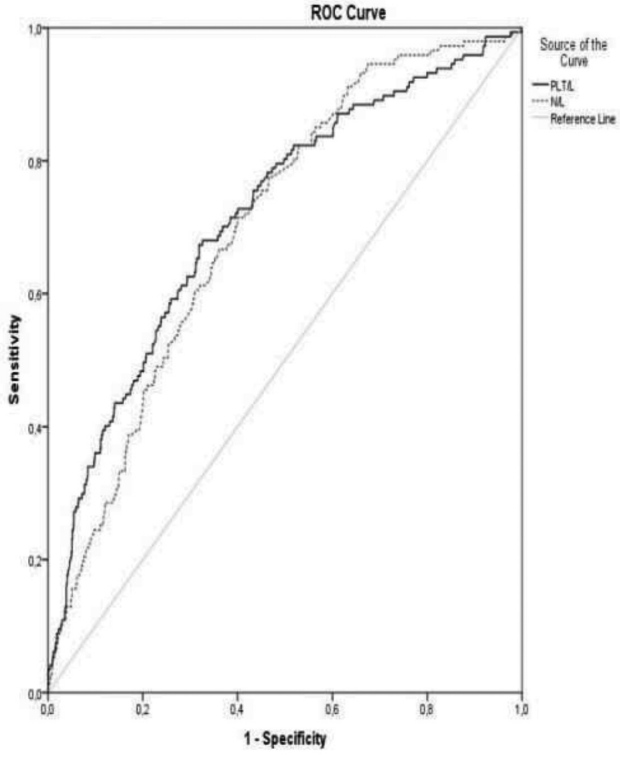

Figure 1: Receiver operating characteristic curve (ROC) curve analysis of PLR and NLR for the identification of Marsh type 3 patients and other groups. Receiver operating characteristic curve (ROC) analysis suggested that optimum PLR cut-off point was 136.5 (AUC: 0.723) with a sensitivity and specifity of 0.65 and 0.68, and optimum NLR cut-off point was 2.4 (AUC: 0.713) with a sensitivity and specifity of 0.69 and 0.63 respectively

PLT/L: Platelet/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, NLR: Neutrophil/lymphocyte ratio, AUC: Area under the curve

Discussion

CD is a genetic autoinflammatory disease that is caused by exposure to prolamins such as gliadin, secalin, hordein, especially in genetically predisposed individuals with HLA-B8, HLA-DR3, HLA-DQ2, whose prevalence varies between 1/130-260 worldwide. Loss of normal villus structure, infiltration of plasma cells and lymphocytes into the lamina propria, increase in the number of IEL and gamma/delta T-cells, decrease in epithelial surface in affected intestinal segments, disaccharidases, peptidases, alkaline phosphatase, ATPase and decreased esterase production are the main but not characteristic of CD. features (12-14). Neutrophils and platelets are involved in the production of cytokines that contribute to their activation. Any problem in neutrophil activation or lymphocyte apoptosis leads to autoimmunity and tissue damage, leading to the onset of autoinflammatory diseases (15). In our retrospective study, a total of 450 patients, 250 of whom were diagnosed with celiac, 50 with increased IEL, and 150 with normal duodenal biopsy were included. These patient groups were compared in terms of MPV, PCT, PLR and NLR. Previous studies have suggested that systemic inflammatory response markers might have an important role as predictive and prognostic markers in different inflammatory diseases populations (16,17). Sen et al. (18) investigated the relationship of NLR with inflammation in psoriasis, Qin et al. (19) investigated the relationship of PLO with inflammation in systemic lupus erythematosus, and Fu et al. (20) studied the predictive role of NLR during rheumatoid arthritis attacks.

In the current study, PLR was found to be higher in group III compared to other groups, this was statistically significant when only group 5 was compared (p=0.02). In our study, NLR was also higher in group III in comparison to other groups, this difference was evaluated as statistically significant when compared with group 5 (p=0.012) (18-20). Again, it has been investigated in the literature in autoinflammatory diseases such as MPV, RA, AS and IBD that MPV decreases with increasing inflammation (21). However, in our study, no significant difference was found between MPV and groups. It is known that PCT is a biomarker that can show the inflammatory response at an early stage and is used especially in the diagnosis of serious bacterial infections

Table 2: Laboratory parameters of the whole group and subgroups

	Total patients (n=450)	Marsh Type 1 (n=109)	Marsh Type 2 (n=11)	Marsh Type 3 (n=130)	Elevated IEL (N=50)	Control patients	p-value
MPV	8.62±1.11	8.65±1.01	8.65±1.07	8.75±1.01	8.71±1	8.44±1.13	0.292
PCT (%)	0.21±0.04	0.19±0.04	0.21±0.04	0.21±0.03	0.21±0.05	0.25±0.06	0.07
PLR	136.3±99.8	130.6±51.5	130±61.2	131.7±71	133±73	211.4±187	0.12, 0.02
NLR	2.41±2.23	2.2±1.41	2.34±1.63	2.47±1.86	2.35±1.55	3.71±3.33	0.15, 0.012

MPV: Mean platelet volume, PCT: Plateletcrit, PLR: Platelet/lymphocyte ratio, NLR: Neutrophil/lymphocyte ratio, IEL: Intraepithelial lymphocyte

(22). In our study, PCT was found to be significantly different between group III and group V.

Study Limitations

The main limitation of our study was its retrospective design. A future study should include more healthy subjects to verify the changes in the PCT, MPV, PLR and NLR in order to facilitate analysis in greater detail. Third, we did not have enough data regarding body mass index, smoking conditions, presence of metabolic syndrome and non-alcoholic steatohepatitis, because there are significant associations between MPV and above mentioned conditions.

Conclusion

In conclusion, although sensitivity and specifity are low, PLR and NLR may be useful tools in making clinical decision which patients need gastroscopic examination and biopsy in clinical practice during the follow-up of patients with at risk of developing CD.

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Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ankara City Hospital Ethics Committee (approval no: E2-22-1447).

Informed Consent: Retrospective study.

Peer-reviewed: Externally peer-reviewed.

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