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ORIGINAL ARTICLE

The Importance of Biomarkers in the Diagnosis and Follow-Up of Celiac Disease

Çölyak Hastalığının Tanı ve Takibinde Biyobelirteçlerin Önemi

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ABSTRACT

Aim: In the present study, the purpose is to investigate the clinical significance, diagnostic capabilities, relationships, and correlations of inflammation-based biomarkers before and after treatment in children with Celiac Disease.
Methods: The study was conducted by retrospectively evaluating the files of patients who were diagnosed and followed up in the Department of Pediatric Gastroenterology of Selcuk University between January 2011 and January 2023. The study was completed with 202 Celiac Disease patients who were diagnosed according to the criteria of the European Pediatric Gastroenterology, Hepatology, and Nutrition Community and 160 healthy follow-ups. In case of clinical or laboratory suspicion, serological tests such as positive Tissue Transglutaminase Antibody and Anti-Endomysium values and the histopathological examination of the endoscopic tissue sample findings consistent with Celiac Disease were evaluated.
Results: There were 122 (56.7%) girls and 80 (54.4%) boys in the patient group and 93 (43.3%) girls and 67 (45.6%) boys in the control group. The most common intestinal complaint was abdominal pain in 49 (22.3%) patients. Gluten-free diet treatment was started after the diagnosis. The values of the patients at the time of diagnosis, in the 6th month after the diet, and the values of healthy control patients were compared. A weak and positive correlation was found between NLR, RPR, RLR levels, and age, body weight, and height in the correlation analysis. The ROC curve for hematological biomarkers was used to evaluate the level of additional diagnostic support in Celiac Disease patients.
Conclusion: After a gluten-free diet, symptoms regress, and the development of more serious celiac-related damage can be prevented. This suggests that NLR, RLR, PLR, SII, HRR, and PNI formulas, which are used in many inflammatory conditions and obtained from routine hemogram parameters, can be used to determine dietary compliance in Celiac Disease patients during their follow-ups.

Keywords: Celiac disease, Children, Biomarker, Gluten-free diet

ÖZ

Amaç: Çalışmamızda çölyak hastalığı tanılı çocuklarda tedavi öncesi ve sonrası inflamasyon temelli biyobelirteçlerin klinik önemi, tanısal yetenekleri, ilişkileri ve korelasyonlarını araştırmayı amaçladık.
Yöntemler: Bu çalışma, Ocak 2011- Ocak 2023 tarihleri arasında Selçuk Üniversitesi Çocuk Gastroenteroloji bölümünde tanı alan ve takip edilen hasta dosyalarının retrospektif olarak değerlendirilmesi ile gerçekleştirilmiştir. Avrupa Pediatrik Gastroenteroloji, Hepatoloji ve Beslenme topluluğunun kriterlerine göre tanı konulan 202 Çölyak hastası ve 160 sağlıklı kontrol grubu ile çalışma tamamlanmıştır. Hastaların tamamında klinik ve laboratuvar olarak şüphe duyulması halinde bakılan Doku Transglutaminaz Antikor dTG ve Anti Endomisyum (EMA) düzeyi gibi serolojik testlerinde pozitiflik olan ve endoskopik doku örneğinin histopatolojik incelemesinde ÇH ile uyumlu bulgular olma şartı arandı.
Bulgular: Hasta grubunda 122 (%56.7) kız, 80 (%54.4) erkek ve kontrol grubunda ise 93 kız (%43.3), 67 erkek (%45.6) idi. En sık karşılaşılan intestinal başvuru yakınması 49 (%22,3) idi. Hastalara tanı sonrası glutensiz diyet tedavisi başlandı. Hastaların tanı anı, diyet sonrası 6. ay kontrol değerleri ve sağlıklı kontrol hastaların değerleri karşılaştırıldı. Yapılan korelasyon analizinde NLR, RPR, RLR seviyeleri ile yaş, vücut ağırlığı ve boy arasında zayıf pozitif korelasyon tespit edildi. Çölyak hastalarının tanısal ek destek düzeyini değerlendirmek amacı ile Hematolojik biyobelirteçler için ROC eğrisi kullanılmıştır.
Sonuç: Glutensiz diyet sonrası semptomlar gerilemekte ve daha ciddi çölyak ilişkili hasarların gelişmesi önlenebilmektedir. Çölyak hastaların takipte diyet uyumunu belirlemek için birçok inflamatuar durumda kullanılan ve rutin hemogram parametrelerinden elde edilen NLR, RLR, PLR, Sİİ, HRR ve PNİ formüllerinin kullanılabileceğini düşündürmektedir.

Anahtar Sözcükler: Çölyak hastalığı, Çocuklar, Biyobelirteç, Glutensiz diyet

Introduction

Celiac Disease (CD) is an autoimmune enteropathy characterized by persistent sensitivity to gluten, occurring after ingestion of foods with gluten in genetically susceptible individuals (1,2). Its diagnosis is increasing all over the world in parallel with the development of easy and fast diagnostic methods with an incidence of 0.05-0.1% in the world and 0.3-0.9% in our country (3,4). In children, the classic triad is abdominal distension, diarrhea, and growth retardation. Other common symptoms can be listed as abdominal pain, weakness, vomiting and nausea. Although gastrointestinal symptoms are more common in children under the age of 3, extra-intestinal symptoms such as iron deficiency anemia and short stature are common in older children (5). The diagnosis is made based on clinical, serological, genetic, and histopathological examination results. Serological tests are the most valuable methods used for screening. It was shown in standardization studies that anti-Endomysium Antibody (EMA) and anti-Tissue

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Transglutaminase (dTG) IgA-G type antibodies are superior to Antigliadin (AGA) IgA-G type antibodies (6). Increased Intraepithelial Lymphocyte (IEL), crypt hyperplasia, and villus atrophy in the intestine mucosa make the definitive diagnosis of CD (7). Treatment is a lifelong gluten-free diet. Delayed diagnosis can lead to increase in treatment costs and cause patients to be unnecessarily hospitalized many times(8, 9).

Serological tests are used to monitor dietary compliance. However, these tests can be difficult to follow because of their high cost and difficulty in access. Systemic immune inflammation indices derived from peripheral blood cells are used frequently in recent years since they are fast and can be easily calculated in any center. Neutrophil/Lymphocyte Ratio (NLR), Platelet/Lymphocyte Ratio (PLR), Erythrocyte distribution width (RDW) and RDW/Lymphocyte Ratio (RLR) are calculated as adjunct laboratory tests at the time of diagnosis of CD and to evaluate adherence to a gluten free diet and the severity of histo-pathological findings (3, 4). The Systemic Immune Inflammation Index (SII) is a novel marker based on lymphocyte, neutrophil, and platelet counts that can show inflammation and immune status better than these alone (10). This index is used to assess the inflammatory status of various diseases and to evaluate the course and prognostic status (11). However, the relationship between biomarkers and patients remains unclear. In this study, the purpose was to investigate the clinical significance, diagnostic capabilities, relationships, and correlations of inflammation-based biomarkers before and after treatment in children with CD.

Material and Methods

Selection of Patient:

This study was conducted by retrospectively evaluating the files of patients who were diagnosed and monitored up in the Department of Pediatric Gastroenterology of Selcuk University between January 2011 and January 2023. The study was completed with 202 CD patients who were diagnosed according to the criteria of the European Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Community and 160 healthy follow-ups (12). In case of clinical or laboratory suspicion, serological tests such as positive Tissue Transglutaminase Antibody (Anti-dTG) and Anti-Endomysium (EMA) values and the histopathological examination of the endoscopic tissue sample findings consistent with CD were evaluated. Volunteering patients with CD under the age of 18 who came to regular follow-ups, had complete data, and signed an Informed Consent Form for the study were included in the study. Those who discontinued their follow-ups, whose data could not be accessed, or whose data were missing were not included. The patient files and laboratory records were examined in diagnosis and at the 6th-month follow-ups by using the Selcuk University Patient Database. The patients were compared in 3 groups (those aged <48 months, 49-120 months, and >121 months).

Evaluation of Demographic and Clinical Characteristics: Gender, age, presenting complaints, anthropometric measurements, physical examinations and laboratory values of the patients who were diagnosed with CD were recorded. Measured weight, height values, and calculated Body Mass Index (BMI) values were assessed according to gender and age by using the Neyzi Growth Curves (13). BMI was calculated with the formula Weight/Height^2.

Laboratory Analysis: Complete blood counts of the patients were performed with the Beckman Coulter LH780 device in Selçuk University Medical Faculty Hospital Biochemistry Laboratory and the samples were studied with Beckman Coulter AU5800 and Beckman Coulter AU680 devices in Selçuk University Medical Faculty Hospital Biochemistry Laboratory.

Hemogram, Ferritin, Folic acid, Vitamin B12, iron, iron-binding capacity, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), ferritin, folic acid, vitamin B12, phosphorus (P), calcium (Ca), albumin, total protein, endomysium antibodies, tissue transglutaminase results, and histopathology reports were recorded from the hospital database. Laboratory and clinical findings of the patients were evaluated at the 6th-month follow-up after starting a gluten free diet.

Hemoglobin (Hb), RDW, Mean Corpuscular Volume (MCV), Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), leukocyte, lymphocyte, neutrophil, platelet and erythrocyte, count were recorded from the routine hemogram analysis at the diagnosis. Then, Platelet/Lymphocyte Ratio (PLR), Neutrophil/Lymphocyte Ratio (NLR), Lymphocyte/Monocyte Ratio (LMR), Hemoglobin/RDW (HRR), RDW/Lymphocyte Ratio (RLR). RDW/Platelet Ratio (RPR) and MPV/Platelet Ratio (MPR) were calculated and recorded. The Prognostic Nutritional Index (PNI) was measured as [10 x serum albumin (g/dl)] + [0.005 x total lymphocyte count]. The (SII) values of the patients were calculated by using the neutrophil, thrombocyte, and lymphocyte values according to the formula (SII=N×P/L).

Since the normal reference range for EMA, which is one of the serological tests, is 0-20 U/mL, values above 20 U/mL and values above 200 U/ml for dTG IgA were considered positive.

Endoscopic and Histopathological Evaluation: Multiple biopsies were taken from the duodenum by using Fujinon EG-530 NP and EG-530 FP Gastroscope from patients who had positive serological test results. All biopsies were examined by expert pathologists and histopathology was examined according to the Modified Marsh Classification that was published in 1999 (7). Re-biopsy was taken from the patients whose biopsy results could not be evaluated clearly, and histopathological examination was performed again. Patients who were diagnosed with CD as a result of histopathological examination were included by dividing into groups with the Marsh Classification according to the pathology results in the study. Marsh-1 (infiltrative) was evaluated as more than

30 intraepithelial lymphocytes per 100 enterocytes, Marsh-2 (infiltrative-hyperplastic) was evaluated as more than 30 intraepithelial lymphocytes per 100 enterocytes, normal villi, and crypt hyperplasia, and Marsh-3 was evaluated as Villosis Crypt Hyperplasia and intraepithelial lymphocytosis accompanied by atrophy (a: Partial Villous Atrophy, b: Subtotal Villous Atrophy, c: Total Villous Atrophy). Modified Marsh Stage ≥2 was considered significant for CD.

The examinations performed at the admission of the patients to the hospital were accepted as pre-diagnosis (pre-diet), and the examinations 6 months after for follow-up purposes were accepted as the 6th-month follow-up (post-diagnosis, post-diet).

Ethical approval was obtained by Clinical Research Ethics Committee of Selçuk University on 09.05.2023 with decision no 2023/E-70632468-050.01.04-503485.

Statistical Analysis

The SPSS 23.0 Package Program was used for statistical analysis of the data in this study. The categorical data are shown with number percent values and numerical data with prevalence criteria such as mean, standard deviation, minimum and maximum value. When comparing the categorical data, Pearson's Chi-Square Test was used for independent groups, and the Mc Nemar Test was used for comparing dependent groups. The conformity of the continuous numerical data to normal distribution was evaluated statistically with the Kolmogorov-Smirnov Test and visually with histogram graphs. Whether there was a difference between the groups in terms of the variables indicated by the measurement was evaluated with the t-test in independent groups and with the Mann-Whitney U-Test when the necessary assumptions could not be met. The Kruskal-Wallis Analysis of Variance was used for the comparisons of three or more groups. The Wilcoxon Signed-Rank Test was used in dependent groups in the comparison of the continuous numerical data. The Spearman Correlation Test was used to test the relationships between the variables. The ROC curves were generated in the CD group and the Area Under the Curve (AUC) was calculated for each marker. The sensitivity and specificity were calculated relative to the cutoff point that was determined by the ROC curves and a $p<0.05$ was accepted as the statistical significance level.

Results

A total of 202 Celiac child patients, there were 80 (54.4%) boys, 122 (56.7%) girls in the patient group and 93 (43.3%) girls and 67 (45.6%) boys in the control patient group. No statistically significant differences were detected between the groups in terms of gender in the comparison of the groups (p:0.371). The demographic data of the patients who participated are shown in Table 1.

When the presenting symptoms of the patients were examined, it was found that 33 (15.0%) of the CD patients presented without symptoms. The most common intestinal complaint was abdominal pain in 49 (22.3%) patients, and the non-intestinal symptom was growth retardation in 20 (9.1%) patients.

When the histopathological results of the 135 patients who were included in the present study were assessed according to the Modified Marsh Staging, 8 (4.5%) of them were Type 2, 39 (21.9%) Type 3a, 88 (49.4%) Type 3b, and 43 (24.2%) were Type 3c.

When genetic tests of the CD patients were examined, it was found that HLA DQ2 was negative in 10 (6.8%) patients and positive in 138 (93.2%) of the 148 patients. Although HLA DQ8 was positive in 79 (54.1%) of the 146 patients, it was negative in 67 (45.9%) patients.

Gluten-free diet treatment was started after the diagnosis. The values of the patients at diagnosis, in the 6th month after the diet, and the values of healthy control patients were compared. Although the mean total leukocyte count of CD patients at the time of in their diagnosis was found as 7.903±2.808, it was 7.372±2.194 in the 6th-month follow-up of the patients. The total leukocyte count was 8.358 ± 2.355 in the healthy control group. When the total leukocyte count of the patients was compared statistically, no statistical significance was detected between the diagnosis and the 6th-month follow-up after the diet, but there were significantly higher values in the healthy control group of children (p:<0.001). The comparison of hemogram and biochemical values of CD patients in diagnosis, 6 months after the diet, and in the healthy control group of children is given in Table 2.

The prognostic factors of CD patients at the time of diagnosis, in the 6th-month follow-up after the diet, and the values of healthy control patients were also compared. Although the mean NLR values of CD patients were 1.408 ± 0.939 at the time of admission to the hospital, it was 1.518 ± 0.894 in the 6th-month follow-up. The NLR value was 1.173 ± 0.736 in the healthy control group. When the NLR values of the patients were compared statistically, no statistically significant differences were detected between the diagnosis and the 6th month follow-up, but it was found significantly lower in the healthy control group (p:<0.001). The comparison of the Prognostic Index Values of CD patients at the diagnosis in the 6th-month follow-up and control group is given in Table 3.

When the Prognostic Indices of CD patients were examined according to the Modified Marsh Staging, it was not statistically significant (Table 4).

When the diagnosis and 6th-month follow-up serological test results of the CD patients were examined, although dTGIgA A was positive in 160 (93.6%) of the 171 patients at the diagnosis, it was negative in 127 (79.4%) patients in the 6th month after the diet, and positivity persisted in 33 (20.6%) patients.

A weak and positive correlation was found between NLR, RPR, RLR levels, and age, body weight, and height in the correlation analysis. The correlation analysis of inflammation biomarkers with other parameters in CD patients is given in Table 5.

Table 1: The demographic data of the patients who participated in the study are given

		Patient Group n (%)	Control Group n (%)	Total n (%)	p
Gender	Female	122 (56.7)	93 (43.3)	215 (59.4)	0.371
	Male	80 (54.4)	67 (45.6)	147 (40.6)	
Age group	< 48 ay	37 (67.3)	18 (32.7)	55 (15.2)	0.143
	49-120 ay	81 (51.9)	75 (48.1)	156 (43.1)	
	>121 ay	84 (55.6)	67 (44.4)	151 (41.7)	
Body Weight Percentile	<3	56[a] (98.2)	1[b] (7.8)	57 (19.9)	<0.001
	4-97	139[a] (60.4)	91[b] (39.6)	230 (80.1)	
Height Percentile	<3	54[a] (94.7)	3[b] (5.3)	57 (20.1)	<0.001
	4-96	140[a] (62.2)	85[b] (37.8)	225 (79.2)	
	>97	2[a] (50.0)	2[a] (50.0)	2 (0.7)	
BMI	<18.5	155[a] (83.8)	30[b] (16.2)	185 (65.2)	<0.001
	18.6-24.5	35[a] (39.3)	54[b] (60.7)	89 (31.3)	
	>24.6	2[a] (20.0)	8[b] (80.0)	10 (3.5)	
	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	
Age (month)	105.99 ± 51.49	109.5 (15 - 206)	107.08 ± 39.83	105.0 (39 - 176)	<0.001
Body Weight Percentile	23.57 ± 27.29	9.50 (1 - 96)	47.39 ± 30.66	41 (2 - 97)	<0.001
Height Percentile	28.70 ± 28.38	20.5 (1 - 98)	45.48 ± 28.19	46.5 (2 - 99)	<0.001
BMI	16.21 ±2.77	16.0 (11 - 27)	19.86 ± 3.39	20.0 (11 - 28)	<0.001

a-c: There is no statistical difference between values with the same letter.

Table 2: The comparison of hemogram and biochemical values of CD patients at the time of diagnosis, 6 months after the diet, and in the healthy control group

	At the time of diagnosis		6 months after the diet		Healthy control group		
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	p
WBC	7.86±2.75[a]	7.3 (3.4 - 19)	8.43±2.27[b]	8.34 (4. -14.83)	7.30±2.03[c]	7.1 (3.6 - 15.4)	<0.001
Hgb	12.47 ± 1.28[a]	12.7 (7.8 - 15.7)	13.06±1.23[b]	13.2 (9.2 - 16)	13.16±1.31[b]	13.1 (9.1-17.5)	<0.001
RBC	4.78 ± 0.44	4.75 (3.7 - 6.8)	4.76 ± 0.36	4.8 (3.8 - 5.9)	4.86 ± 0.44	4.8 (3.8 - 6.4)	0.091
MCV	77.97 ± 6.47[a]	79 (56 - 91)	78.97 ± 5.80[a]	78.55 (53.6 - 96)	80.20 ± 5.89[b]	81 (60 - 98)	0.002
RDW	14.66 ± 3.25[a]	14 (11 - 33)	13.77± 1.49[b]	13.3 (11 - 21)	13.96 ± 3.89[b]	13 (11 - 60)	0.011
NC	3.80 ± 1.86	3.4 (1.1 - 13)	3.75 ± 1.53	3.48 (1.2 - 9.79)	3.74 ± 1.53	3.4 (1.4 - 8.7)	0.957
LC	3.11 ± 1.32[a]	2.8 (0.9 - 9.2)	3.69 ± 1.46[b]	3.45 (1.1 - 8)	2.73 ± 0.91[c]	2.5 (1.1 - 6.1)	<0.001
MC	0.57 ± 0.25[a]	0.5 (0.15 - 2.2)	0.67 ± 0.88[a]	0.5 (0 - 8)	0.52 ± 0.19[b]	0.5 (0.1 - 1.7)	0.253
PC	348.25±99.63	343 (151-773)	337.99±87.66	331 (147-639)	328.74±91.94	310 (107 - 690)	0.098
PDW	14.64 ± 2.72[a]	16.0 (8.0 – 23.0)	14.67 ± 2.68[a]	16.0 (7.0 – 22.0)	13.31 ± 2.99[b]	14.9 (7.40 – 17.50)	<0.001
MPV	8.25 ± 1.39	8.0 (4.9 - 14.0)	8.39 ± 1.20	8.30 (4.0 - 12.0)	8.13 ± 1.12	8.0 (6.0 - 11.0)	0.176
Na	138.15 ± 2.61	138 (130 - 144.2)	137.86 ± 2.2	138 (132 - 144)	138.72 ± 2.23	139 (131 - 144)	0.123
K	4.33 ± 0.37	4.3 (3.1 - 5.6)	4.41 ± 0.33	4.3 (3.7 - 5.2)	4.41 ± 0.36	4.4 (3.6 - 6)	0.138
ALT	19.81 ± 12.64[a]	17 (6 - 132)	14.46 ± 4.80[b]	14 (6 - 35)	16.98 ± 6.97[b]	15 (7 - 61)	<0.001
AST	30.97 ± 14.92[a]	29 (10 - 136)	28.39 ± 8.97[b]	27 (12 - 56)	27.07 ± 8.165[b]	26 (8 - 62)	0.017
Ca	9.66 ± 0.47[a]	9.7 (8.1 - 11)	10.05 ± 0.56[b]	10 (9 - 12)	9.84 ± 0.41[c]	9.9 (8.8 - 11)	<0.001
T.P.	6.87 ± 0.603	7 (4.6 - 8.6)	6.92 ± 0.50	6.95 (4.4 - 7.9)	7.02 ± 0.39	7 (6 - 8.6)	0.087
Albumin	4.33 ± 0.44[a]	4.3 (2.4 - 5.3)	4.48 ± 0.40[b]	4.45 (4 - 7.3)	4.47± 0.29[b]	4.4 (3.2 - 5.3)	0.005
Fe	61.48 ± 34.96	55.5 (11 - 198)	74.01 ± 34.12	70.5 (13 - 169)	79.92 ± 36.67	74 (22 - 196)	<0.001
Ferritin	15.03 ± 10.56[a]	12 (2 - 66)	41.82 ± 19.04[b]	37 (13 - 97)	31.85 ± 19.88[b]	28 (1 - 141)	<0.001
IBC	320.67 ± 75.38[a]	315.5 (61 - 483)	297.14± 68.37[b]	286.5 (137 - 495)	298.31 ± 76.58[b]	300 (116 - 455)	0.012
B12	410.92 ± 236.78	359 (83 - 1800)	396.41 ± 171.28	371.5 (100 - 1006)	393.77 ± 198.68	355.5 (107 - 1500)	0.845
Folic acid	9.89 ± 5.37[a]	9 (2 - 23)	9.62 ± 4.39[a]	9 (2 - 20)	13.26 ± 5.50[b]	12 (2 - 26)	<0.001

WBC: White blood cell; Hgb: Hemoglobin; RBC: Red blood cell; MCV: Mean Corpuscular Volume; RDW: Red cell distribution width; NC: Neutrophil Count; LC: Lymphocyte Count; MC: Monocytes Count; PC: Platelet Count; PDW: Platelet Distribution Width; MPV: Mean Platelet Volume; Na: Sodium; K: Potassium; ALT: Alanin Aminotransferaz; AST: Aspartat Aminotransferaz; Ca: Calcium; TP: Total Protein; Fe: Iron level; IBC: Iron binding capacity.

a-c: There is no statistical difference between values with the same letter.

WBC:mcL. Hgb: g/L. RBC: milion cell/mcL. MCV: mm³. RDW: fL. PDW: fL. MPV: fL. Na: mEq/L . K: mmol/L . ALT: U/L . AST: U/L . Ca: mg/dL . T.P: g/dL. Albumin: g/dL. Fe: mg/ng . Ferritin: ml/mg .IBC: ug/dL. B12: pg/mL. Folic Acid: mcg.

Table 3: The comparison of the Prognostic Index Values of CD patients at the time of diagnosis, in the 6th-month follow-up and control group

	At the time of diagnosis		6 months after the diet		Healthy control group		
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	p
CRP	2.063 ± 2.774	1 (0.1 - 26)	2.958 ± 4.571	1 (0.1 - 26)	1.876 ± 1.84	1 (0.1 - 12)	0.338
Sedim	6.214 ± 7.539	4 (1 - 60)	4.86 ± 4.542	3 (1 - 23)	4.687 ± 4.847	3 (1 - 27)	0.068
PDW	14.64 ± 2.72[a]	16 (8 - 23)	13.31 ± 2.99[b]	14.95 (7.4 - 17.5)	14.67 ± 2.68[a]	16 (7 - 22)	<0.001
MPV	8.25 ± 1.39	8 (4.9 - 14)	8.13 ± 1.12	8 (6 - 11)	8.39 ± 1.20	8.3 (4.1 - 12)	0.176
Mentzer	16.516 ± 2.464	16.522 (8.824-24.595)	17.202±1.868	16.948 (12.6-22.368)	16.649±2.165	16.735 (10.323-22.105)	0.083
NLR	1.372 ± 0.777[a]	1.232 (0.202 - 5.5)	1.19 ± 0.729[b]	0.972 (0.234 - 4.92)	1.514 ± 0.868[a]	1.318 (0.357 - 7.636)	<0.001
LMR	5.893 ± 2.579	5.458 (1.818 - 19.333)	6.583 ± 5.697	5.571 (0.438 - 44)	5.932 ± 4.23	5.333 (1.545 - 46)	0.378
PLR	125.214±51.786[a]	117.778 (36.067-482.222)	102.817±37.857[b]	102.655 (34.431-209.489)	130.503±49.45[a]	121.818 (32.623-399.091)	<0.001
RPR	0.045 ± 0.015	0.042 (0.017 - 0.122)	0.044 ± 0.012	0.042 (0.024 - 0.101)	0.046 ± 0.025	0.044 (0.021 - 0.337)	0.820
MPR	0.026 ± 0.009	0.025 (0.008 - 0.061)	0.026 ± 0.007	0.025 (0.011 - 0.05)	0.028 ± 0.01	0.027 (0.011 - 0.072)	0.067
RLR	5.467 ± 2.584[a]	4.828 (1.413 - 20)	4.459 ± 1.95[b]	4.031 (1.463 - 11.818)	5.808 ± 3.629[a]	5.417 (1.897 - 46.154)	<0.001
HRR	0.89 ± 0.202[a]	0.914 (0.252 - 1.427)	0.957 ± 0.145[b]	0.969 (0.5 - 1.283)	0.976 ± 0.184[b]	1 (0.228 - 1.346)	<0.001
SII	484.655±342.936[a]	403.848 (44.892-2950)	393.277±240.64[b]	336.684 (63.516-1268.286)	499.75±360.626[a]	408.387 (92.143-3352.364)	<0.001
PNI	43.402 ±4.405[a]	43.02 (24.022 - 53.019)	44.823 ± 4.083[b]	44.516 (40.007 - 73.02)	44.725 ± 2.933[b]	44.021 (32.008 - 53.017)	0.010
ALT/AST	0.657 ± 0.276[a]	0.607 (0.28 - 2.357)	0.541 ± 0.193[b]	0.5 (0.209 - 1.333)	0.646 ± 0.228[a]	0.6 (0.321 - 2.103)	<0.001

Sedim: Sedimentation; Meintzer: MCV/RBC; NLR: Neutrophil-Lymphocyte ratio; LMR: Lymphocyte-Monocyte Ratio; PLR: Platelet-Lymphocyte Ratio; RPR:RDW-Platelet Ratio; MPR: MPV-Platelet Ratio; RLR: RDW-Lymphocyte Ratio; HRR: Hemoglobin/RDW Ratio; SII: Systemic inflammatory index; PNI: Prognostic Nutritional Index; a-c: There is no statistical difference between values with the same letter; CRP:mg/L; Sedimentation:mm/h

Table 4: The Comparison of the prognostic indices of celiac disease according to Modified Marsh staging

Marsh Classification	Type 2 n:8 (%4.5)	Type 3a n:39 (%21.9)	Type 3b n:88 (%49.4)	Type 3c n:43 (%24.2)	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	p
WBC	7.45 ± 2.227	7.767 ± 2.375	7.768 ± 2.795	7.747 ± 2.34	0.985
NC	3.713 ± 1.629	3.456 ± 1.41	3.894 ± 2.03	3.681 ± 1.438	0.718
LC	2.938 ± 0.67	3.231 ± 1.305	3.011 ± 1.277	3.026 ± 1.157	0.567
MC	0.538 ± 0.262	0.543 ± 0.178	0.573 ± 0.263	0.57 ± 0.253	0.932
PC	320 ± 64.673	342.718 ± 88.644	340.443 ± 90.145	339.093 ± 87.273	0.952
RDW	13.329 ± 1.106	14.231 ± 2.476	14.938 ± 3.643	14.512 ± 2.738	0.632
PDW	14.286 ± 2.498	14.495 ± 2.568	14.655 ± 2.764	14.276 ± 3.216	0.955
MPV	8.114 ± 1.325	8.534 ± 1.273	8.201 ± 1.292	8.529 ± 1.694	0.594
MEİNTZER	16.864 ± 1.209	16.754 ± 1.797	16.536 ± 2.709	16.339 ± 2.629	0.901
NLR	1.303 ± 0.537	1.217 ± 0.651	1.442 ± 0.838	1.347 ± 0.585	0.520
LMR	6.3 ± 2.463	6.599 ± 3.3	5.705 ± 2.482	5.711 ± 2.17	0.296
PLR	114.312 ± 35.103	116.756 ± 41.704	127.656 ± 59.035	126.175 ± 52.495	0.803
RPR	0.045 ± 0.011	0.044 ± 0.012	0.047 ± 0.018	0.045 ± 0.012	0.932
RLR	4.992 ± 1.642	4.971 ± 2.002	5.749 ± 2.825	5.564 ± 2.826	0.438
HRR	0.942 ± 0.13	0.912 ± 0.2	0.885 ± 0.216	0.884 ± 0.197	0.849
SII	430.07 ± 202.126	425.035 ± 263.222	510.205 ± 407.799	449.88 ± 215.941	0.815
PNI	43.515 ± 3.069	43.227 ± 4.02	43.582 ± 4.653	43.634 ± 4.842	0.866
MPR	0.027 ± 0.006	0.027 ± 0.009	0.026 ± 0.009	0.027 ± 0.011	0.860
ALT/AST	0.594 ± 0.228	0.727 ± 0.42	0.626 ± 0.241	0.656 ± 0.211	0.795

WBC:mcL; RDW: fL; PDW: fL; MPV: fL.

Table 5: The correlation analysis of inflammation biomarkers with other parameters in CD patients is given

	NLR		LMR		PLR		RPR		RLR		HRR		SII		PNI		MPI		ALT/AST	
	R	P	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	P
Age	0.293	0.000	-0.260	0.000	0.334	0.000	0.159	0.025	0.424	0.000	0.134	0.058	0.115	0.103	0.328	0.000	0.266	0.000	0.205	0.004
BW	0.275	0.000	-0.272	0.000	0.261	0.000	0.184	0.010	0.375	0.000	0.099	0.171	0.101	0.160	0.293	0.000	0.285	0.000	0.149	0.039
BW Percentile	0.073	0.311	-0.039	0.587	-0.015	0.839	0.028	0.695	0.000	0.996	0.052	0.469	0.037	0.606	0.066	0.372	0.098	0.177	-0.030	0.683
Height	0.312	0.000	-0.253	0.000	0.292	0.000	0.197	0.006	0.409	0.000	0.177	0.014	0.124	0.085	0.383	0.000	0.300	0.000	0.166	0.022
Height Percentile	0.082	0.257	-0.041	0.566	0.025	0.731	0.036	0.621	0.039	0.588	0.059	0.412	0.051	0.481	0.098	0.180	0.110	0.133	-0.010	0.895
BMI	0.227	0.002	-0.186	0.010	0.131	0.070	0.154	0.033	0.241	0.001	0.102	0.162	0.086	0.237	0.213	0.003	0.264	0.000	0.097	0.183
WBC			0.077	0.277			-0.359	0.000			-0.098	0.169			-0.073	0.309	-0.351	0.000	-0.148	0.036
Hgb	-0.010	0.891	0.040	0.577	-0.093	0.188	-0.224	0.001	-0.227	0.001			-0.123	0.083	0.168	0.019	0.086	0.233	0.125	0.078
RDW	-0.036	0.611	-0.073	0.301	0.132	0.062							0.018	0.794	-0.284	0.000	-0.052	0.472	-0.019	0.790
NC					0.086	0.226	-0.319	0.000			-0.008	0.908			0.018	0.798	-0.247	0.000	-0.097	0.173
LC							-0.219	0.002			-0.103	0.146			-0.142	0.047	-0.246	0.001	-0.100	0.160
MC	0.018	0.799			-0.208	0.003	-0.091	0.199	-0.246	0.000	-0.206	0.003	0.140	0.047	-0.149	0.037	-0.190	0.007	-0.184	0.009
PC	0.088	0.215	0.117	0.096					-0.169	0.016	-0.205	0.004			-0.190	0.008	-0.811	0.000	0.046	0.515
MPV	0.113	0.115	-0.032	0.654	-0.019	0.787	0.223	0.002	0.154	0.032	0.014	0.844	-0.015	0.834	0.133	0.067			0.117	0.104
PDW	0.143	0.044	-0.067	0.349	0.102	0.151	0.138	0.052	0.178	0.012	-0.117	0.101	0.087	0.223	-0.146	0.044	-0.091	0.204	-0.101	0.157
CRP	0.016	0.838	-0.189	0.016	0.101	0.201	0.007	0.933	0.100	0.205	-0.075	0.344	0.023	0.773	0.063	0.435	-0.018	0.823	-0.029	0.720
Sedim	0.049	0.529	-0.082	0.291	-0.011	0.892	0.074	0.338	0.063	0.420	-0.298	0.000	0.046	0.555	0.179	0.021	-0.045	0.564	-0.024	0.759
Mentzer	0.062	0.382	-0.056	0.426	-0.040	0.573	-0.062	0.378	-0.073	0.305	0.274	0.000	-0.012	0.863	0.037	0.603	0.126	0.080	-0.077	0.277
NLR							-0.102	0.149			0.023	0.749			0.102	0.156	-0.027	0.702	-0.012	0.872
LMR							-0.129	0.067			0.032	0.656			-0.058	0.423	-0.093	0.196	0.131	0.064
PLR											-0.140	0.048			-0.021	0.765			0.126	0.076
RPR	-0.102	0.149	-0.129	0.067											-0.041	0.566			-0.069	0.330
RLR															-0.034	0.637	0.189	0.008	0.071	0.318
HRR	0.023	0.749	0.032	0.656	-0.140	0.048	-0.414	0.000					-0.073	0.302	0.287	0.000	0.114	0.113	0.080	0.261
SII											-0.073	0.302			0.000	0.999	-0.345	0.000	-0.009	0.896
PNI	0.102	0.156	-0.058	0.423	-0.021	0.765	-0.041	0.566	-0.034	0.637	0.287	0.000	0.000	0.999			0.191	0.008	-0.098	0.173
MPI	-0.027	0.702	-0.093	0.196					0.189	0.008	0.114	0.113	-0.345	0.000	0.191	0.008			-0.005	0.947
ALT	-0.168	0.018	0.128	0.072	0.023	0.743	-0.053	0.459	-0.015	0.838	-0.244	0.001	-0.065	0.359	-0.381	0.000	-0.190	0.008		
AST	-0.216	0.002	0.047	0.510	-0.081	0.257	-0.027	0.700	-0.100	0.161	-0.317	0.000	-0.075	0.294	-0.421	0.000	-0.226	0.002		
ALT/AST	-0.012	0.872	0.131	0.064	0.126	0.076	-0.069	0.330	0.071	0.318	0.080	0.261	-0.009	0.896	-0.098	0.173	-0.005	0.947		
T.P.	0.221	0.004	-0.194	0.012	0.180	0.019	-0.087	0.260	0.132	0.087	0.192	0.013	0.127	0.099	0.652	0.000	0.084	0.284	-0.139	0.073
Albumin	0.102	0.154	-0.058	0.418	-0.021	0.774	-0.041	0.569	-0.033	0.647	0.287	0.000	0.000	0.995	1.000	0.000	0.192	0.008	-0.098	0.173
Ferritin	-0.076	0.293	0.091	0.209	-0.196	0.006	-0.102	0.158	-0.230	0.001	0.381	0.000	-0.127	0.079	0.151	0.039	0.105	0.150	0.050	0.494
Fe	0.077	0.357	-0.057	0.495	-0.010	0.902	-0.111	0.184	-0.066	0.432	0.150	0.072	0.072	0.388	0.220	0.008	-0.066	0.435	0.048	0.570
IBC	-0.017	0.839	0.013	0.877	0.104	0.218	0.109	0.196	0.132	0.118	-0.190	0.024	0.000	0.999	0.143	0.093	0.048	0.575	-0.069	0.413

BW: Body Weight Percentile

WBC:mcL; Hgb: g/L; RBC: milion cell/mcL; MCV: mm³; RDW: fL; MPV: fL; PDW: fL; CRP:mg/L; Sedimentation:mm/h; ALT: U/L; AST: U/L; Ca: mg/dL; T.P: g/dL; Albumin: g/dL; Ferritin: ml/mg; Fe: ml/ng; IBC: ug/dL.

Table 6: The ROC analysis results

	AUC	%95 CI	Cut-off Value	p	+LR	Sensitivite (%)	Spesifisite (%)
CRP	0.461	0.382-0.539	1.8	0.328		40.50	63.30
Sedim	0.555	0.477-0.632	10.5	0.173		17.10	87.10
PDW	0.614	0.552-0.675	13.55	<0.001	1.43	74.70	47.90
NLR	0.598	0.530-0.648	0.81	0.004	1.24	78.70	36.90
LMR	0.479	0.400-0.558	7.29	0.591		19.80	80.10
PLR	0.631	0.573-0.688	162.32	<0.001	4.15	20.80	95.50
RPR	0.506	0.443-0568	0.049	0.891		32.80	74.80
RLR	0.629	0.569-0.689	4.095	<0.001	1.45	69.70	52.10
HRR	0.407	0.347-0.467	1.199	0.003	1.4	40.00	97.10
SII	0.588	0.529-0.646	436.94	<0.001	1.51	45.50	70.00
PNI	0.423	0.355-0.492	47.01	0.040	1.32	25.50	80.80
MPR	0.491	0.430-0551	0.032	0.758		22.40	85.60
ALT/AST	0.661	0.594-0.728	0.52	<0.001	1.75	71.50	59.20

AUC: Area under the curve; 95%CI: %95 Confidence Interval; +LR: pozitivite likelihood ratio; CRP:mg/L; Sedimentation:mm/h; *PDW:fL.*

The ROC curve for hematological biomarkers was used to evaluate the level of additional diagnostic support in CD patients. The Area Under the Curve obtained for NLR was 0.598 (95% CI: 0.538-0.656). When the cut-off value of the NLR level was taken as 1.58, the sensitivity was calculated as 61.10% and the specificity as 81.25% (p<0.001). The ROC analysis are given in Table 6. According to the ROC analysis results of the study, the researchers found that PDW, NLR, PLR, RLR, HRR, SII, PNI, and ALT/AST values were statistically high in diagnosing.

Discussion

CD is defined as immune-mediated enteropathy of the intestine as a result of exposure to gluten in genetically susceptible people (14-17) It is already known that the immune system is reflected by the biomarkers in the blood. Neutrophils are rapidly released into inflamed tissues in an inflammatory process, secreting cytokines and proinflammatory chemokines to attract other inflammatory cells. For this reason, neutrophil release is critical for innate immunity. However, excessive neutrophil secretion can cause tissue breakdown and inflammatory disorders. Previous studies reported that platelets are necessary for neutrophil release in a lot of acute and/or chronic inflammatory diseases (18). Neutrophils also require platelets for important effector functions such as phagocytosis, generation of reactive oxygen species formation and neutrophil extracellular traps (19).

Many recent studies have been conducted on biomarkers for diagnosis and prognosis. The data from these studies support the effect of inflammation on the advencement and progression of various diseases. It has been demonstrated in studies that the changes in the number of cells calculated from peripheral blood samples and their differences relative to each other indicate the inflammatory response in various diseases (20). These cells also play roles in the early phase of the gluten challenge because the number of neutrophils increases up to 20-fold (20). In the present study, it was considered that routine hemogram and biochemical biomarkers could be used in the prognosis of the disease as well as the serological tests used in the follow-up because the patient group included mostly adolescents and the gluten free diet compliance of the patients was not complete. These biomarkers used in acute inflammation were compared at the diagnosis of the disease and 6 months after the start of the gluten free diet.

Lymphocytes and neutrophils are part of the adaptive and natural immune system, playing significant roles in the initiation and maintenance of immune processes. They are also effective in chronic inflammation with the neutrophil elastase enzyme they secrete (22). The increased neutrophil activity and the increased formation of reactive oxygen radicals and nitric oxide may lead to the development of many metabolic conditions. NLR is a simple parameter to calculate, indicating the inflammatory state. It has been reported in previous studies that it was useful in determining mortality in major cardiac events, predicting prognosis in various cancer types, and determining postoperative complications and inflammatory responses in the presence of various pathogens (21).

In a study that was conducted by Uslu et al., NLR was reported high in the patient group compared to the control group. A significant difference was reported between the groups that followed the diet and those that did not in the post-diet follow-ups of CD (23). In Palmacci et al.'s study, which evaluated the effects of a gluten-free diet on NLR retrospectively along with the relationship between NLR and adherence to the Mediterranean Diet and selected food groups (i.e., fruits, vegetables, red meat, potatoes, and unrefined and refined grains), no relationships were detected

between the Modified Marsh Staging and Anemia NLR and NLR was found higher in patients with osteoporosis when compared with normal bone mineral densityand osteopenia (24). In the study conducted by Sarıkaya et al., NLR was found significantly higher in patients with CD compared to the control group (25). In their study, Karaceer et al. reported that the difference in NLR height was significant between patients who followed and did not follow a gluten free diet (26). In the present study, although no significant differences were detected between the groups after the gluten free diet, the NLR value was significantly low in the healthy control group. When the NLR cutoff point of 1.58 was taken in the study, the sensitivity was determined as 61.10% and the specificity as 81.25%. This result emphasized that the signs of inflammation after a gluten free diet continue in CD patients and NLR values can be available to use in the treatment, follow-up and prognosis of these patients.

Mean Platelet Volume (MPV) is a marker of plateletes activation and function, and is influenced by inflammation. The correlation between changes in MPV and CD was first reported by O'Grady et al. (27). Purnak et al. and O'Grady et al. reported that MPV was higher in individuals with CD than the control group values and Demirezer et al. reported that MPV was similar in the control and CD patients groups (27-29). It has been reported in both studies that MPV is a useful biomarker for monitoring dietary compliance in the 3 months after starting a gluten free diet. Demirezer et al. reported that MPV was not useful either in the diagnosis of CD and/or in monitoring adherence to diet (in a 1-year follow-up) (29). In the present study, MPV values were similar in patients with CD at the diagnosis and in the healthy control group after a gluten free diet. The platelet count was not statistically significant in all three groups. This may be explained by the fact that similar MPV levels before and after a gluten-free diet in CD patients differ from other inflammatory diseases, and histological inflammation persists for years in CD patients despite a good clinical response. In conclusion, the study shows that MPV cannot be used as an inflammatory marker to predict adherence to diet in CD patients. If future studies are conducted with more patients with CD and if the follow-up period is longer, better results can be obtained.

In another present study, although no statistically significant differences were detected between the CD patient and follow-up group after the gluten free diet, it was found significantly low in the healthy control group compared with both groups. When the relationship of PLR was examined between CD patients and the healthy control group, it was determined that the increase above the PLR cut-off point of 91.21 in the study had a specificity of 56.20% and a sensitivity of 77.20% in the diagnosis of celiac. Based on this result, we think that inflammation findings continue after a gluten free diet in CD patients and that PLR values can be used in the follow up, treatment, and prognosis of pediatric patients.

Previous studies show that the PLR and NLR indices have high diagnostic power for CD, and the diagnostic power of RLR is better than PLR and NLR (25, 30). Uslu et al. showed that the neutrophil count was higher, the lymphocyte count was low, and the NLR was high in CD patients at the time of diagnosis, the neutrophil counts and NLR values of the patients who did not follow the diet after one year of the gluten-free diet remained high, and the neutrophil count and NLR values of the patients who followed a full diet were similar to the control group (23). They also showed that NLR is useful for predicting patients who did not comply with a gluten free diet (23). It is considered that changes in the leukocyte formula in active CD may be associated with lymphocytic infiltration in the gastrointestinal tract and inflammation and cytokines that play roles in the pathogenesis of the disease (25). In the present study, the RLR values that were measured 6 months after the gluten free diet with the CD group were not found statistically significant. Yet, it was low in the healthy control group compared to the other two groups. We believe that the reason for this was that the patients did not fully comply with the gluten-free diet and the inflammation continued.

However, biomarkers such as NLR and PLR do not reflect the inflammatory state in CD fully because they contain only two types of immune and inflammatory cells. For this reason, biomarkers that include other inflammatory cells are needed. One of these is SII in which all three types of immune and inflammatory cells (neutrophils, lymphocytes and platelets) are present (10). A decreased number of lymphocytes can be considered a deterioration in the cellular immune response, and an increased number of neutrophils and platelets can be considered a response to systemic inflammation. Level SII acts as an easily detectable biomarker to reflect the inflammatory status and systemic inflammatory activity and inflammatory status. It has been demonstrated that SII can show systemic inflammation better than NLR and PLR alone (10). In the present study, the clinical significance of SII in pediatric CD patients was also evaluated and its diagnostic capabilities were compared with other parameters. When compared with other inflammatory markers, it was shown that SII has a statistically significantly higher AUC area in the ROC curve analysis. Based on the results, it was shown in the present study that high SII was significantly associated with NLR and PLR in CD patients.

No studies were detected in the literature review on the biomarkers such as RLR, HRR, and PNI in children with CD. In the present study, although no statistically significant differences were detected between the patient group at the time of admission and the healthy control group, significantly lower values were detected in the control patient group after a gluten-free diet compared to both groups. When the relationship between RLR was examined between CD patients and the healthy control group, it was determined that the increase above the RLR cut-off point of 4.095 with a specificity of 26.10% and a sensitivity of 69.70% in the diagnosis of celiac. Based on this result, we think that

RLR values can be used in the follow-up, treatment, and prognosis of CD patients.

In the present study, no statistically significant differences were detected between the control patient group and the healthy control group after the gluten-free diet in terms of HRO values, but the HRR values at the time of admission of the CD patients were significantly lower than the other groups. When the relationship between HRR and CD patients in the healthy control group was examined, it was determined that the increase above the HRR cut-off point of 1.199 had 97.10% specificity and 40.00% sensitivity in the diagnosis of celiac. Based on this result, we think that HRR values can be used in the follow up, treatment, and prognosis of CD patients.

Also, no statistically significant differences were detected between the control patient group and the healthy control group after the gluten free diet, but the PNI values at the time of admission of the CD patients were found to be significantly lower than both groups. When the relationship between PNI was examined between CD patients and the healthy control group, it was determined that the increase above the PNI cut-off point of 47.01 in the study had a specificity of 80.80% and a sensitivity of 25.50% in the diagnosis of CD. We think that PNI values can be used in the follow up, treatment, and prognosis of CD patients.

The limitations of the study were that it had a retrospective design, it had a relatively small sample size that could confirm the results, and it had a single-center structure. The strengths of the study were that there were no similar studies in the literature, the control group in the study consisted of CD patients, and gluten-free diet compliance was determined objectively with hematological parameters.

Conclusion

Early diagnosis and treatment of CD are very important. After a gluten free diet, symptoms regress, and the development of more serious celiac-related damage can be prevented. This suggests that NLR, RLR, PLR, SII, HRR, and PNI formulas, which are used in many inflammatory conditions and obtained from routine hemogram parameters, can be used to determine dietary compliance in CD patients during their follow-ups. Larger prospective randomized controlled trials are required to confirm these findings.

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