ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Role of Prognostic Nutritional Index and Systemic Immune-Inflammation Index in Determining Ulcerative Colitis Severity

Prognostik Nutrisyonel İndeksin ve Sistemik İmmün-İnflamasyon İndeksin Ülseratif Kolit Hastalık Şiddetinin Belirlenmesindeki Rolü

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ABSTRACT

Aim: *Ulcerative colitis (UC) is a chronic, idiopathic, relapsing inflammatory disease of the gastrointestinal tract. In recent years, biochemical parameters have been widely used to determine the disease activity of UC. The present study aimed to determine the relationship between the prognostic nutritional index (PNI), systemic immune-inflammation index (SII), and disease activity.*

Material and Method: *All adult patients followed in the IBD unit of the Ankara City Hospital Gastroenterology Department between March 1st, 2019, and March 31st, 2021, were included in this retrospective study. We analyzed the relationship between the SII, PNI, and the endoscopic severity of UC. In addition, PNI and SII were compared between the active and remission group. Disease activity was described by the Rachmilewitz endoscopic activity index (EAI).*

Results: *The study group consisted of 402 patients. One hundred sixty-five of these patients were in the endoscopic remission group, and 237 were in the endoscopically active group. SII, NLR, and PLR values were significantly higher in the active UC group, and PNI values exhibited a lower mean than inactive UC patients ($p<0.05$ for all parameters). In addition, the NLR, PLR, and SII were positively, and PNI was negatively correlated with the endoscopic activity index (respectively, R=0.29, R=0.24, R=0.38, R=-0.32; and for all parameters, $p<0.001$).*

Conclusion: *PNI and SII were significantly associated with UC activity. PNI and SII may be useful tools for assessing disease activity in UC.*

Key words: *ulcerative colitis; disease activity; nutrition*

ÖZET

Amaç: *Ülseratif kolit (ÜK) gastrointestinal sistemin kronik, idiyopatik, tekrarlayan inflamatuar bir hastalığıdır. Son yıllarda ÜK'in hastalık aktivitesini belirlemek için biyokimyasal parametreler yaygın olarak kullanılmaktadır. Bu çalışmada, prognostik nutrisyonel indeksi (PNİ) ve sistemik immün-inflamasyon indeksi (SII) ile hastalık aktivitesi arasındaki ilişkinin belirlenmesi amaçlanmıştır.*

Materyal ve Metot: *Bu retrospektif çalışmaya Ankara Şehir Hastanesi Gastroenteroloji Bölümü İBH ünitesinde 1 Mart 2019 ile 31 Mart 2021 tarihleri arasında takip edilen tüm erişkin hastalar dahil edildi. PNİ ve SII ile ÜK'in endoskopik aktivite şiddeti arasındaki ilişki analiz edildi. Ek olarak PNİ ve SII aktif ve remisyondaki hasta grupları arasında karşılaştırıldı. Hastalık aktivitesinin belirlenmesinde Rachmilewitz endoskopik aktivite indeksi (EAİ) kullanıldı.*

Bulgular: *Çalışma grubu 402 hastadan oluşuyordu. Bu hastaların 165'i endoskopik olarak remisyon grubunda, 237'si endoskopik olarak aktif gruptaydı. Aktif ÜK grubunda, SII, NLR ve PLR değerleri, inaktif ÜK hastalarına kıyasla anlamlı olarak daha yüksekti ve PNI değerleri daha düşük saptandı ($p<0,05$ tüm parametreler için). Ek olarak, NLR, PLR, SII pozitif olarak ve PNİ negatif olarak endoskopik aktivite indeksi ile korele saptandı (sırasıyla, R=0,29, R=0,24, R=0,38, R=-0,32; ve tüm parametreler için $p<0,001$).*

Sonuç: *PNİ ve SII, ÜK aktivitesi ile önemli ölçüde ilişkiliydi. PNİ ve SII, ÜK'de hastalık aktivitesinin değerlendirilmesi için faydalı bir araç olabilir.*

Anahtar kelimeler: *ülseratif kolit; hastalık aktivitesi; nutrisyon*

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Introduction

Ulcerative colitis (UC) is an immune-mediated bowel disorder characterized by chronic and recurrent inflammation of colonic mucosa[1]. There is often rectal involvement, and the inflammation spreads from the rectum to the proximal colon[2]. The natural course of the disease is characterized by relapse and remission periods[3]. During exacerbations, the main symptoms are bleeding, fever, and abdominal pain[4]. Early detection of the disease activity is important for both treatment success and prevention of complications that can affect the quality of life[5].

Colonoscopy is the most sensitive and specific diagnostic step for diagnosing and determining the disease activity and severity. However, the assessment of disease activity by colonoscopy is an invasive procedure and not easily accessible[6]. Therefore, noninvasive inflammatory biomarkers are needed for early detection of the disease activity.

White blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are frequently evaluated to assess inflammation severity in UC. However, an optimal test has not yet been developed, and the currently used biomarkers are nonspecific[7]. In recent years, the prognostic nutritional index (PNI), the systemic immune-inflammation index (SII), the platelet-lymphocyte ratio (PLR), and neutrophil-lymphocyte ratio (NLR) have been adapted as an indicator of inflammation and have been widely studied to define the severity of inflammation in rheumatic diseases, diabetes mellitus, arterial hypertension, several cardiovascular diseases, and malignancies[8–11].

Herein, we aimed to evaluate the relationship between SII, PNI, and endoscopic activity in patients with UC.

Material and Methods

Patients

All adult patients followed in the Inflammatory Bowel Disease Unit of the Ankara City Hospital Gastroenterology Department between March 1st, 2019, and March 31st, 2021, was employed in this retrospective study. The UC diagnosis was made based on clinical, radiological, laboratory, endoscopic, and histological findings. The patient's demographic characteristics, disease duration, medication history, endoscopic activity score, disease localization, and laboratory test results were obtained from hospital records. Exclusion criteria were hematological disease and malignancy, acute bacterial or viral infection or chronic infectious diseases, autoimmune diseases, steroid usage within the previous week, neoplastic disorders, chronic liver disease, or chronic renal failure. This study was approved by Ankara City Hospital Scientific Research Assessment and Ethics Committee (Approval No: E1/1753/2021).

Laboratory Values

NLR, PLR, SII, and PNI were calculated by the formulas mentioned below:

- NLR: neutrophil count/lymphocyte count
- PLR: platelet count/lymphocyte count
- SII: platelet count × NLR
- PNI: 10 × albumin (g/dL) +0.005 × lymphocyte count

Disease Activity

The endoscopic disease activity and severity in patients with UC were determined by the Rachmilewitz endoscopic activity index (EAI) based on colonoscopy findings. The EAI score is <4 points for the remission group. Based on the severity of inflammation, the EAI score is regarded as 4–9 points for the mild/moderate active group and 10–12 points for the severe active group.

Statistical Analysis

Statistical analysis was performed with SPSS 23.0 for Windows (SPSS Inc., Chicago, IL, USA). The normality of distribution was tested using the Kolmogorov-Smirnov test for continuous variables. The results were presented as mean ± standard deviation (SD) for variables with normal distribution and median (interquartile range, IQR 25%–75%) for variables with the abnormal distribution. Statistical comparisons of continuous variables were performed using the independent samples t-test or Mann-Whitney U test regarding the distribution pattern. Comparisons of categorical variables were performed using the chi-square test. Spearman's or Pearson's test was used for the correlation analysis. A two-tailed $p<0.05$ was considered statistically significant.

Results

A total of 402 UC patients were enrolled in the presented study. One hundred sixty-five of these patients

were in the endoscopic remission group, and 237 were in the endoscopically active group. No significant difference was found in group comparisons regarding age, gender, and lymphocyte counts. The median disease duration of UC patients after diagnosis was 84.0 (48.0–141.0) months. The medication history and disease location of all patients are presented in Table 1.

Platelet, WBC, neutrophil, CRP, and sedimentation values were higher in the active disease group. The mean hemoglobin and albumin values were lower than the remission group ($p<0.05$ for all parameters). SII, NLR, and PLR values were significantly increased in the active UC group, and PNI values exhibited a lower mean than the remission group ($p<0.05$ for all parameters).

According to the severity of the disease, the active patient group was also separated into two groups mild/moderate and severe. While no significant difference was observed in age, gender, and disease duration between the two groups, there was a significant difference between hemoglobin, platelet, WBC, neutrophil, albumin, CRP, and sedimentation values ($p<0.05$ for all parameters). SII, NLR, and PLR values were significantly higher, and PNI values were significantly lower in patients in the severe UC group versus the mild to moderate UC group ($p<0.05$ for all parameters) (Table 2).

In addition, the NLR, PLR, and SII were positively, and PNI was negatively correlated with EAI (respectively, R=0.29, R=0.24, R=0.38, R=-0.32; and for all parameters $p<0.001$) (Table 3).

Discussion

This retrospective study revealed significantly higher SII, NLR, PLR values, and lower PNI values in the

Table 1. *Baseline clinical and laboratory parameters of study population*

	Total (n=402)	Active (n=237)	Remission (n=165)	P value
Age, (years)	47.4±13.7	47.6±13.7	47.2±13.7	0.75
Gender male, n (%)	238 (59)	148 (62)	90 (55)	0.12
Disease duration, month	84.0 (48.0–141.0)	84.0 (36.0–142.0)	84.0 (48.0–132.0)	0.80
Endoscopic activity index	5.5±3.8	8.3±2.3	1.6±1.4	**<0.001**
Hemoglobin, g/dl	13.4±1.7	13.2±1.8	13.8±1.6	**0.01**
Platelet, $x10^3/mm^3$	300.5±96.4	320.1±109.3	272.4±64.7	**<0.001**
WBC, $x10^3/mm^3$	7.4±1.9	7.9±2.0	6.7±1.5	**<0.001**
Neutrophil, $x10^3/mm^3$	4.6±1.6	5.0±1.8	4.0±1.1	**<0.001**
Lymphocyte, $x10^3/mm^3$	1.9±0.7	2.0±0.7	1.9±0.6	0.67
Albumin, gr/dL	4.4±0.4	4.3±0.4	4.6±0.2	**<0.001**
CRP, mg/dL	2.0 (0.6–10.0)	7.0 (2.1–16.0)	0.6 (0.3–0.9)	<0.001
Sedimentation, mm/hour	11.0 (6.0–20.0)	15.0 (7.0–23.0)	8.0 (5.0–12.0)	**<0.001**
NLR	2.6±1.5	2.9±1.8	2.2±0.8	**<0.001**
PLR	152.6 (117.9–187.7)	159.4 (122.5–205.8)	148.0 (114.8–173.0)	**<0.001**
SII x 10^3	672.2 (468.0–910.6)	768.3 (525.5–1045.2)	596.8 (419.0–726.5)	**<0.001**
PNI	54.8±5.5	53.8±6.2	56.2±4.0	**<0.001**
Medication history, n (%)				
5-ASA	291 (72)	156 (66)	135 (82)	**0.001**
5-ASA + AZA	48 (12)	38 (16)	10 (6)	**0.002**
5-ASA + anti-TNF	51 (13)	37 (16)	14 (9)	**0.03**
5-ASA + AZA + anti-TNF	11 (3)	5 (2)	6 (4)	0.36
Localization, n (%)				
Proctitis	76 (19)	28 (12)	48 (29)	**<0.001**
Left-sided colitis	231 (58)	141 (60)	90 (55)	0.30
Pan-colitis	94 (23)	67 (28)	27 (16)	**0.005**

Results are expressed as: mean ± SD or median (IQR) or frequency (%), WBC: white blood cell, CRP: C-reactive protein, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, SII: systemic immune-inflammation index, PNI: prognostic nutritional index, 5-ASA: 5-aminosalicylic acid, AZA: azathioprine, TNF: tumor necrosis factor

Table 2. *Baseline clinical and laboratory parameters according to the severity of the disease*

	Mild/Moderate (n=137)	Severe (n=100)	P value
Age, (years)	47.0±13.7	48.5±13.6	0.39
Gender male, n (%)	84 (61)	64 (64)	0.68
Disease duration, month	84.0 (48.0–145.0)	72.0 (24.0–120.0)	0.16
Endoscopic activity index	6.6±1.5	10.5±0.9	**<0.001**
Hemoglobin, g/dl	13.7±1.6	12.6±1.89	**<0.001**
Platelet, x10^3/mm^3	308.6±110.6	335.9±105.9	**0.027**
WBC, x10^3/mm^3	7.5±1.7	8.3±2.3	**0.006**
Neutrophil, x10^3/mm^3	4.7±1.5	5.5±2.0	**0.001**
Lymphocyte, x10^3/mm^3	2.0±0.6	1.9±0.8	0.38
Albumin, gr/dL	4.5±0.3	4.2±0.5	**<0.001**
CRP, mg/dL	3.1 (0.9–8.3)	15.5 (7.5–32.0)	**<0.001**
Sedimentation, mm/hour	11.0 (6.0–18.0)	20.0 (10.2–29.7)	**<0.001**
NLR	2.6±1.7	3.2±1.7	**0.006**
PLR	154.4 (115.6–191.5)	170.4 (133.5–244.2)	**0.007**
SII x 10^3	704.2 (480.1–954.3)	863.4 (650.8–1386.5)	**<0.001**
PNI	55.2±4.8	51.7±7.2	**<0.001**
Medication history, n (%)			
5-ASA	97 (71)	59 (59)	**0.048**
5-ASA + AZA	18 (13)	20 (20)	0.16
5-ASA + anti-TNF	19 (14)	18 (18)	0.40
5-ASA + AZA + anti-TNF	2 (2)	3 (3)	0.65
Localization, n (%)			
Proctitis	21 (15)	7 (7)	**0.048**
Left-sided colitis	79 (58)	62 (62)	0.55
Pan-colitis	36 (26)	31 (31)	0.45

Results are expressed as: mean ± SD or median (IQR) or frequency (%), WBC: white blood cell, CRP: C-reactive protein, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, SII: systemic immune-inflammation index, PNI: prognostic nutritional index, 5-ASA: 5-aminosalicylic acid, AZA: azathioprine, TNF: tumor necrosis factor

Table 3. *Correlation between Endoscopic activity index and different inflammatory variables in study population*

	Rho	p
NLR	0.294	<0.001
PLR	0.245	<0.001
SII	0.385	<0.001
PNI	-0.328	<0.001

NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, SII: systemic immune-inflammation index, PNI: prognostic nutritional index.

active UC group compared to the inactive UC group. Also, NLR, PLR, and SII were significantly higher, and PNI was significantly lower in patients in the severe UC group versus the mild to moderate UC group. In addition, the NLR, PLR, and SII were positively, and PNI was negatively correlated with the endoscopic activity index.

UC is a chronic inflammatory disease of the colonic mucosa, and the clinical course of the disease is characterized by remission and relapse[12]. Early activation diagnosis is important as it reduces the need for surgery and enables early treatment modification[13]. Clinical evaluation of disease activation is determined by evaluating the radiological, endoscopic, and pathological findings[14]. Colonoscopy is the standard gold method for assessing the disease activity, allowing direct visibility of the mucosa and biopsy. However, there are some limitations, such as the increased risk of complications and lack of accessibility of the process[15]. Therefore, non-invasive methods to evaluate disease activation have attracted more attention in recent years[16]. In this concept, calprotectine is frequently used as a non-invasive inflammatory marker. However, lack of availability in all clinics and high cost limits the routine use of calprotectine[17].

In routine clinical practice, WBC count, CRP, and ESR have been widely used in the follow-up of UC[18]. However, due to their low sensitivity and specificity, they don't accurately reflect the activity of the disease[19]. In recent years, NLR and PLR values have been widely used to determine the disease activity of UC, and it has been shown that there is a significant relationship between the disease activity index and high NLR and PLR values[20]. Moreover, the SII index has been proposed by Hu et al. as a valuable marker of inflammation and contains information about three cell types[21]. The significance of SII has been demonstrated in many disease groups such as cancer and coronary artery disease[22,23]. By the literature, we have also shown higher NLR, PLR, and SII values in the active UC patient group, and they are correlated with the endoscopic activity index.

Albumin synthesis is negatively affected by the systemic inflammation process[24]. The catabolic state activated by inflammatory cytokines has suppressed the negative acute-phase reactants synthesis. Additionally, active gastrointestinal involvement in UC patients can lead to hypoalbuminemia by causing malabsorption and protein loss[25]. Moreover, functional inflammatory changes can decrease lymphocyte production due to dysregulation of apoptosis of the lymphocytes[26]. In the light of the above, the PNI index, which is calculated by albumin and lymphocyte values, has been more sensitive since it combines two components. In this concept, the PNI index was widely used to assess disease activity in rheumatic diseases such as Behçet's disease and systemic lupus erythematosus[27,28]. Our study revealed that UC activity was negatively correlated with PNI value.

In conclusion, this study demonstrates that SII, PNI, NLR, and PLR values were strongly associated with disease activity and endoscopic severity in UC, which can help determine the disease's endoscopic severity.

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