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Evaluation of Systemic Immune-Inflammation Index and Systemic Inflammation Response Index in Children with Celiac Disease

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Abstract

Background: Celiac disease is an enteropathy characterized by intestinal inflammation and systemic immune activation. In recent years, there has been a rising focus on systemic inflammation markers obtained from complete blood count parameters, including the Systemic Immune-Inflammation Index (SII) and the Systemic Inflammation Response Index (SIRI), as readily available biomarkers reflecting inflammatory status. Nevertheless, their clinical significance in pediatric celiac disease remains incompletely understood. This study aimed to compare SII and SIRI levels between children with newly diagnosed celiac disease and healthy controls and to assess their relationships with laboratory parameters.

Methods: A retrospective case–control design was used, including pediatric patients with celiac disease and age-matched healthy controls. SII and SIRI values were calculated using routine complete blood count parameters. Laboratory markers, C-reactive protein (CRP), hemoglobin, ferritin, albumin were compared between groups.

Results: SII (507.55 ± 438.39 vs 738.15 ± 934.84; p=0.039) and SIRI (0.88 ± 1.14 vs 1.23 ± 1.30; p=0.022) levels were significantly lower in patients with CD than in controls. Compared with control groups, the celiac disease group showed significantly lower hemoglobin, ferritin, and albumin levels; however, there was no evidence of a significant difference in CRP levels between the groups. These findings suggest that systemic inflammatory indices in pediatric celiac disease may behave differently from those observed in other systemic inflammatory disorders.

Conclusion: Significantly lower SII and SIRI levels were observed in the newly diagnosed celiac disease group than in the control group. Collectively, these findings indicate that systemic inflammatory indices may not fully reflect localized intestinal inflammation in pediatric celiac disease and may be influenced by malabsorption-related hematological changes. Moreover, the clinical significance of these findings should be further investigated in prospective studies.

Keywords: Celiac disease; Child; Malabsorption Syndromes

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Çölyak hastalığı olan çocuklarda Sistemik İmmün-İnflamasyon İndeksi ve Sistemik İnflamasyon Yanıt İndeksinin değerlendirilmesi

Öz

Giriş: Çölyak hastalığı, bağırsak mukozasında inflamasyon ve sistemik immün aktivasyon ile karakterize bir enteropatidir. Son yıllarda tam kan sayımı parametrelerinden hesaplanan Sistemik İmmün-İnflamasyon İndeksi (SII) ve Sistemik İnflamasyon Yanıt İndeksi (SIRI) gibi sistemik inflamatuvar indeksler, inflamatuvar durumu yansıtan kolay erişilebilir biyobelirteçler olarak giderek daha fazla ilgi görmektedir. Bununla birlikte, pediatrik çölyak hastalığındaki klinik önemleri henüz tam olarak açıklığa kavuşturulmamıştır. Bu çalışmanın amacı, çölyak hastalığı tanısı yeni konulan çocuklar ile sağlıklı kontroller arasında tanı anındaki SII ve SIRI düzeylerini karşılaştırmak ve bu değerlerin laboratuvar parametreleriyle ilişkisini değerlendirmektir.

Yöntemler: Retrospektif bir vaka-kontrol tasarımı kullanılmış olup, çölyak hastalığı olan pediatrik hastalar ile yaş uyumlu sağlıklı kontrol grubu çalışmaya dahil edilmiştir. SII ve SIRI değerleri rutin tam kan sayımı parametreleri kullanılarak hesaplanmıştır. C-reaktif protein (CRP), hemoglobin, ferritin ve albümin gibi laboratuvar belirteçleri gruplar arasında karşılaştırılmıştır.

Bulgular: Çölyak hastalarında SII (507,55 ± 438,39 ve 738,15 ± 934,84; p=0,039) ve SIRI (0,88 ± 1,14 ve 1,23 ± 1,30; p=0,022) düzeyleri kontrollere göre anlamlı olarak daha düşüktü. Kontrol grubuna göre çölyak hastalığı grubunda hemoglobin, ferritin ve albümin düzeyleri de anlamlı olarak daha düşük saptanırken, CRP düzeyleri açısından gruplar arasında anlamlı bir fark izlenmemiştir. Bu bulgular, pediatrik çölyak hastalığında sistemik inflamatuvar indekslerin diğer sistemik inflamatuvar hastalıklarda gözlenenlerden farklı davranabileceğini düşündürmektedir.

Sonuç: Yeni tanı almış çölyak hastalığı grubunda SII ve SIRI düzeylerinin kontrol grubuna kıyasla anlamlı olarak daha düşük olduğu saptanmıştır. Bu bulgular, sistemik inflamatuvar indekslerin pediatrik çölyak hastalığında lokalize bağırsak inflamasyonunu tam olarak yansıtmayabileceğini ve malabsorpsiyona bağlı hematolojik değişikliklerden etkilenebileceğini düşündürmektedir. Ayrıca, bu bulguların klinik öneminin ileriye dönük prospektif çalışmalarla daha ayrıntılı olarak araştırılması gerekmektedir.

Anahtar kelimeler: Çölyak hastalığı, Çocuklar, Malabsorbsiyon sendromları.

INTRODUCTION

Celiac disease (CD) is a disorder of immune-mediated, chronic enteric disorder associated with gluten intake among genetically predisposed populations. It primarily affects the small intestine and is characterized by a wide spectrum of clinical manifestations, ranging from classical malabsorption symptoms to extraintestinal and even asymptomatic presentations[1]. The estimated prevalence of celiac disease (CD) in recent years has been reported as approximately 1%, with increasing recognition in pediatric populations[2,3]. Early identification of celiac disease in childhood is necessary to reduce the risk of late complications, including stunted growth, delayed puberty, and decreased bone density[4].

The underlying mechanisms of CD involve a complex relationship between genetic factors —most notably HLA-DQ2 and HLA-DQ8 haplotypes and triggers such as gluten exposure. This interaction leads to an inappropriate immune response characterized by both innate and adaptive immune activation. As a result, inflammatory pathways are activated, contributing to intestinal mucosal damage and systemic immune alterations[5,6]. Given this inflammatory background, there has been growing interest in identifying reliable, non-invasive biomarkers that reflect disease activity at the time of diagnosis.

Recently, Inflammatory scores derived from routine peripheral blood measurements have

become increasingly popular because of their accessibility and cost-efficiency. Among these, the Systemic Immune-Inflammation Index (SII), which is calculated from lymphocyte counts, platelet and neutrophil counts and the Systemic Inflammation Response Index (SIRI), based on lymphocyte, monocyte, and neutrophil counts, have been proposed as promising markers of immune-inflammatory status. These indices have been studied extensively in oncology, cardiovascular diseases, and various inflammatory conditions, demonstrating their potential prognostic and diagnostic value[7-9].

Despite increasing evidence supporting the clinical utility of SII and SIRI in systemic inflammatory conditions, their role in pediatric CD remains unclear[10]. While traditional inflammatory markers, including erythrocyte sedimentation rate and CRP, have been widely studied, they frequently demonstrate low sensitivity in CD, especially in pediatric cases where inflammation can be subtle or localized[11]. Therefore, novel indices reflecting subtle immune alterations could provide additional diagnostic or predictive value[10].

In this context, evaluating SII and SIRI at the time of diagnosis may offer insights into the inflammatory burden of pediatric CD and help identify patients with more pronounced immune activation. Such markers could potentially contribute to risk stratification and improve clinical decision-making. However, data on this subject are currently limited.

This study aimed to investigate differences in SII and SIRI values at the time of diagnosis between pediatric patients with celiac disease and healthy controls, as well as to examine the associations of these indices with relevant laboratory parameters.

METHODS

Study Design and Population

This research was conducted using a retrospective case–control methodology and based on the medical records of pediatric celiac disease patients treated at a training and research hospital between 1 September 2021-31 December 2025. The diagnosis of celiac disease was established in accordance with the 2020 European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) diagnostic guidelines. All patients were diagnosed based on duodenal biopsy findings, and children with histopathological findings consistent with Marsh type 3 classification were included in the study[12].

Healthy children without celiac disease were selected as the control group and matched with the patient group for age and sex who presented to the same institution during the same study period for non-inflammatory conditions and had no history of chronic, autoimmune, inflammatory, or hematological disease. Patients with acute infections or incomplete medical records were excluded from both groups.

Data Collection

Patient data were retrieved from the hospital's electronic medical records. Demographic characteristics, including age, sex, weight, height, body mass index (BMI), and standard deviation scores (SDS) for height, weight, and BMI, were recorded. Laboratory parameters obtained at the time of diagnosis included complete blood count indices such as neutrophil, lymphocyte, monocyte, hemoglobin, and platelet counts. In addition, serum albumin, ferritin, and C-reactive protein (CRP) levels were also collected for each participant.

Calculation of SII and SIRI

The following formulas were used to compute the inflammatory indices: SII, defined as neutrophils multiplied by platelets divided by lymphocytes, and SIRI, defined as neutrophils multiplied by monocytes divided by lymphocytes[7].

Statistical Analyses

Statistical evaluation was conducted in SPSS (version 16.0), and the Kolmogorov–Smirnov test was used to test data normality. Continuous data were summarized as mean ± SD, and categorical data as counts and percentages. Depending on normality, either the Student's t-test or the Mann–Whitney U test was applied for group comparisons. When appropriate, categorical variables were evaluated using the Chi-square test. A threshold of $p < 0.05$ was used to determine statistical significance.

The research was conducted following approval by the Human Research Ethics Committee. (No:811/2026).

RESULTS

Study Population

There were 126 pediatric cases of CD and an equal number of 126 healthy controls were enrolled.

The celiac disease cohort showed a mean diagnostic age of 10.16 ± 3.74 years, while the healthy controls had a mean age of 10.97 ± 4.14 years. Both groups showed similar age distributions, with no statistically significant difference (p = 0.327)

The gender distribution was 62.7% female in the celiac group and 61.1% female in the control group, with no significant difference (p = 0.896)

The mean body weight SDS, height SDS and BMI SDS values were significantly lower in the patient group compared to the control group (body weight SDS: -1.09±1.27 vs.-0.05±1.06, respectively=0.000, height SDS: -0.76±1.31vs 0.90±0.08, p=0.001 BMI SDS: -0.95±1.19 vs 0.59±2.77 p=0.000).

Laboratory Findings

The comparison of laboratory parameters between the groups is summarized in Table 1.

Table I: The comparison of laboratory parameters between the groups

Variables	Celiac group Mean±std deviaton	Control group Mean±std deviaton	*p* value
Hemoglobine (g/dL)	12.36±1.62	13.38±1.26	***0.006***
Ferritine ()	25.04±28.69	41.66±26.31	***<0.001***
CRP (mg/L)	0.54±0.72	0.62±0.98	*0.125*
Albumin (g/L)	4.61±0.24	4.81±0.20	***0.019***
SII index	**507.55 ±438.39**	**738.15 ± 934.84**	***0.039***
SIRI index	**0.88±1.14**	**1.23±1.30**	***0.022***

CRP; c-reactive protein, SII; Systemic Immune-Inflammation Index, SIRI; Systemic Inflammation Response Index

Patients with celiac disease had significantly decreased SII values compared to controls (507.55 ± 438.39 vs 738.15 ± 934.84; p = 0.039). Similarly, SIRI levels were lower in the celiac group (0.88±1.14 vs 1.23±1.30, p =0.022)

Hemoglobin levels were lower in the celiac group (p = 0.006). Ferritin levels levels were lower in the celiac group (p =0.000). CRP levels showed no significant difference between the groups (p = 0.240). Albumin levels were lower in the celiac group (p = 0.030)

DISCUSSION

The present study, we evaluated the potential diagnostic utility of SIRI and SII in pediatric patients newly diagnosed with CD. Our results demonstrated that both SIRI and SII values were significantly lower in patients with CD compared with the healthy control group. In addition, ferritin, hemoglobin, and albumin levels were significantly decreased in the patient group, whereas CRP levels were comparable between the groups. These findings suggest that, despite the chronic immune-mediated nature of CD, systemic inflammatory indices may exhibit a different profile in during the time of diagnosis in pediatric cases.

Celiac disease is defined by chronic inflammation of the small intestinal mucosa

following gluten exposure in genetically predisposed individuals[1,13]. Although inflammatory activation is central to disease pathogenesis, the inflammatory response in CD may not always be reflected by elevations in conventional systemic inflammatory markers[14]. In our study, CRP levels were comparable between patients and controls, supporting the concept that low-grade intestinal inflammation in CD may remain localized and may not induce a marked systemic acute-phase response. Similar findings have previously been reported in pediatric and adult studies evaluating inflammatory biomarkers in CD[15].

Previous studies investigating systemic inflammatory indices in CD have reported inconsistent findings. A recent adult study by Çakır and Doğan reported an association between SII and newly diagnosed CD, suggesting the potential utility of inflammatory indices in disease evaluation[16]. Similarly, Taştemur and Felek emphasized the possible relationship between systemic inflammatory parameters and CD activity[17]. However, our findings differed from these reports and may indicate that inflammatory indices behave differently in pediatric patients compared with adults.

Several mechanisms may explain the decreased SII and SIRI levels observed in our study. First, malabsorption-related nutritional deficiencies are common in newly diagnosed pediatric CD and may substantially affect hematological parameters[18]. Iron deficiency anemia, hypoalbuminemia, and micronutrient deficiencies frequently accompany untreated CD and may suppress bone marrow activity or alter peripheral blood cell distribution[19]. In our cohort, ferritin and hemoglobin levels were significantly lower in celiac patients, supporting the presence of iron deficiency and chronic malnutrition. Since SII and SIRI are calculated using neutrophil, lymphocyte, monocyte, and platelet counts, nutritional deficiencies affecting these cellular components may directly influence index values[7,20]. Therefore, decreased inflammatory indices in our patients may reflect impaired nutritional and hematological status rather than the absence of intestinal inflammation. Second, pediatric and adult CD may exhibit distinct clinical and immunological characteristics. Children are more likely to present with growth retardation, nutritional deficiencies, and overt malabsorption at diagnosis, whereas adult patients may demonstrate more subtle or atypical clinical manifestations[12,21]. Consequently, hematological suppression related to malnutrition may be more pronounced in pediatric populations and may directly influence inflammation-based indices[19,20].

Another possible explanation relates to the immunological mechanisms underlying CD. Although CD is characterized by chronic intestinal inflammation, the immune response is predominantly mediated through adaptive immunity involving T lymphocyte activation within the intestinal mucosa[5,13]. In contrast, SII and SIRI mainly reflect systemic innate inflammatory responses based on neutrophil, monocyte, and platelet activity[7]. As a result, these indices may not fully represent the localized and adaptive immune-mediated inflammatory process characteristic of CD[16]. In pediatric patients, where mucosal injury and malabsorption may dominate the clinical presentation, the relationship between systemic inflammatory indices and disease activity may be even weaker[22]. The lack of significant CRP elevation in our study further supports the hypothesis that systemic inflammation may remain relatively limited despite active intestinal disease.

Another important finding of our study was the significantly lower hemoglobin, ferritin, and albumin levels observed in the CD group. These results strongly suggest the presence of

malabsorption and nutritional impairment at diagnosis. Untreated pediatric CD is frequently associated with iron deficiency anemia, micronutrient deficiencies, hypoalbuminemia, and impaired nutritional status[21]. Such abnormalities may directly influence circulating neutrophil, monocyte, and platelet counts, which constitute the basis of SII and SIRI calculations[19]. Therefore, the lower SII and SIRI levels detected in our cohort may reflect the hematological consequences of chronic malabsorption rather than the absence of intestinal immune activation. This interpretation is further supported by the coexistence of low ferritin and albumin levels in the patient group.

In our study, female patients constituted the majority of the CD group. This finding is consistent with previous epidemiological data demonstrating a female predominance in CD and autoimmune disorders overall. Hormonal, genetic, and immunological differences between sexes have been proposed as contributing factors for the increased prevalence of autoimmune diseases among females[15]. In addition, females may exhibit different inflammatory and hematological responses, which could potentially influence systemic inflammatory indices such as SII and SIRI[23]. Therefore, sex distribution should be considered when interpreting inflammatory biomarkers in CD populations.

This study has several limitations that should be recognized. Primarily, it was conducted in a single center with a limited sample size. Second, due to its retrospective design, detailed evaluation of disease severity, histopathological grading, and dietary status could not be performed comprehensively. Third, longitudinal changes in SII and SIRI following initiation of a gluten-free diet were not assessed. Future prospective multicenter studies involving larger pediatric populations are needed to clarify the role of systemic inflammatory indices in CD and to determine their relationship with disease severity, mucosal recovery, and treatment response.

In conclusion, SII and SIRI values were significantly lower in children with newly diagnosed CD compared with healthy controls. These findings suggest that systemic inflammatory indices derived from peripheral blood cell counts may not adequately reflect localized intestinal inflammation in pediatric CD. Nutritional deficiencies and malabsorption-related hematological alterations appear to play an important role in shaping these indices at diagnosis. Future prospective pediatric studies with larger cohorts, detailed histopathological evaluation, and longitudinal follow-up after gluten-free diet initiation are needed to clarify the clinical significance of SII and SIRI in CD.

Ethics Committee Approval: The research was conducted following approval by the Human Research Ethics Committee. (No:811/2026).

Conflict of Interest: The author(s) declare that there is no financial conflict of interest related to this article.

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