Research Article

Isil Cakir* and Serkan Dogan

Association between systemic immune inflammation index and newly diagnosed adult celiac disease

Sistemik immün enflamasyon indeksi ve yeni tanı almış erişkin Çölyak Hastalığı ilişkisi

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Abstract

Objectives: The systemic immune inflammation index (SII) is a novel biomarker based on platelet, neutrophil and lymphocyte counts. SII serum levels have diagnostic, prognostic degrees and correlations with various immune, inflammatory diseases. Celiac disease (CD) is an immune-mediated chronic enteropathy with inflammatory situations. Here we aimed to evaluate clinical significance of SII and to compare SII with other inflammatory markers in CD.

Methods: 161 pathologically confirmed CD and 75 dyspeptic patients were enrolled. Hemogram, biochemical markers, SII, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), mean platelet volume-to-platelet ratio (MPR) and monocyte-to-high density lipoprotein cholesterol ratio (MHR) were evaluated.

Results: There was a statistically significant difference between groups for SII (p<0.001). SII was statistically correlated with and superior to inflammatory markers in relation with CD. There were also statistically significant differences between groups for hsCRP, PLR, NLR, MPR, haemoglobin, platelet count, platelet volume distribution width, plateletcrit, ferritin, total cholesterol and HDL cholesterol (p=0.034; 0.015; 0.032; <0.001; <0.001; <0.001; 0.030; 0.001; <0.001; <0.001; 0.048, respectively). Correlations between SII and NLR, PLR, MHR, hsCRP were statistically significant (p<0.001; <0.001; 0.033; 0.030, respectively). ROC analysis was used to determine the optimal cut-off value for CD by SII. A baseline SII level >560.0 was associated with CD with 64% specificity, 78% sensitivity (p<0.001).

Conclusions: To the best of our knowledge, this is the first study analyzed the diagnostic value of SII in CD. SII may serve as a beneficial marker for the diagnosis of inflammatory state superior to that of hsCRP, PLR, NLR, MHR, MPR and WBC.

Keywords: celiac disease; high sensitive C-reactive protein; inflammation based biomarkers; platelet derived biomarkers; systemic immune inflammation index.

*Corresponding author: Isil Cakir, Department of Clinical Biochemistry, Public Health Laboratory, 38010 Kayseri, Turkey, E-mail: isilsacakir@gmail.com. https://orcid.org/0000-0001-5728-4671
Serkan Dogan, Clinics of Endocrinology, Kayseri City Training and Research Hospital, Kayseri, Turkey. https://orcid.org/0000-0001-8511-8355

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Introduction

Celiac disease (CD) is a frequently seen immune mediated genetic disease. Until the last decades most of the believed opinion was that CD was a disease of children, but today lots of studies demonstrate important increase of CD prevalence in adults [1]. The precise and the gold standard diagnosis of CD is the biopsy of small bowel and CD can be presented by demonstrating villous atrophies in intestinal biopsies [2, 3]. Chronic inflammation caused by dietary gluten peptides of wheat or rye and barley reveals the disease in susceptible people [4]. These peptides are responsible for small intestinal epithelial inflammation, villous atrophy and mucosal damage so symptoms of malabsorption occur [5]. CD treatment is a lifelong strict gluten-free diet [6]. Patients with CD have some complications such as bone fractures, lung infections, hyposplenism, intestinal ulcers, collagenous enteritis and intestinal carcinoma [7].

There is a complicated CD pathogenesis that hasn’t been explained fully. But especially the immune-mediated theory plays an important role [7]. Latest studies have represented that newly diagnosed serum inflammatory markers are related with immune-mediated diseases like CD [8, 9]. The systemic immune inflammation index (SII) is a novel inflammatory biomarker based on platelet, neutrophil and lymphocyte counts. SII is an integrated marker that might be able to indicate immune and inflammatory status better than these markers alone [10]. This index was used to reflect inflammation status and as a prognostic marker of various diseases [11–13]. However, the relation between SII and patients with celiac disease remains unclear. Herein, in our study we aimed to investigate clinical significance of SII and other inflammation based biomarkers, their diagnostic abilities, and their relations and correlations in adult patients with CD before treatment.

Materials and methods

Study groups

Our study included a total of 236 patients who were admitted to gastroenterology outpatient clinic between January 2016 and January 2018. 161 patients with biopsy proven adult celiac disease (112 females and 49 males) included in patients group and 75 (54 females and 21 males) dyspeptic participants, with serological levels in reference normal upper gastrointestinal endoscopy or normal histological structures without CD, performed control group. We retrospectively examined their medical and laboratory records. The biochemical tests were studied at diagnosis before a gluten-free diet. We excluded patients with chronic liver disease, viral hepatitis, obstructive biliary diseases, cancer, Cushing Syndrome and pregnant women from the study. CD patients’ mucosal damage degrees were evaluated by using the Marsh classification [14, 15]. This study was performed in accordance with the Helsinki Declaration and The Ethical Committee of … University Medical Faculty approved the study protocol (2019/807).

Biochemical analyses

We retrospectively examined and recorded participants’ biochemical test results. Complete blood count parameters: haemoglobin (Hb), mean corpuscular volume (MCV), white blood cells (WBC), platelet (PLT) count, platelet volume distribution width (PDW), mean platelet volume (MPV), plateletcrit (PCT) were measured using Sysmex XN-1000 (Sysmex Corporation, Kobe, Japan) autoanalyser; ferritin, folate, free thyroxine (fT4), thyroid-stimulating hormone (TSH) levels were studied using chemiluminescent immunoassay by UniCel DxI 800 autoanalyser (Beckman Coulter Diagnostics, Miami, FL, USA); lipid parameters: triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c) and other biochemical analyses of high sensitive C-reactive protein (hsCRP), total protein (TP), albumin (ALB), fasting serum glucose (FSG) were done photometrically using AU680 autoanalyser (Beckman Coulter Diagnostics, Miami, FL, USA) using their original commercial kits. Novel inflammation parameters as platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR),...
mean platelet volume-to-platelet ratio (MPR) and monocyte-to-HDL-c (MHR) and SII (using the PLT × N/L formula) were calculated.

**Statistical analyses**

We analysed data using SPSS 23.0 (SPSS Inc., Chicago, IL, USA) software program. We used Student's t-test to compare variables with normal distribution. We compared non-normally distributed variables with Mann–Whitney U test. We presented normally distributed, continuous variables by mean ± standard deviation (SD), and non-normally distributed, continuous variables by median and interquartile range (25–75%). We performed correlation analysis using Spearman’s correlation coefficient. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic ability of SII and other inflammatory markers. p-Value <0.05 was considered as statistically significant.

**Results**

Clinical and demographic features and intestinal mucosal damage degrees of patients were presented in Table 1. In literature the incidence of CD is highest in females [16]. In accordance with the literature our study population mostly composed of female celiac patients. The mean age of CD and control groups were 38 ± 13.11 and 39 ± 11.94 years, respectively. There was no significant difference between mean levels of ages of both groups (p>0.05).

Celiac patients had some manifestations different from extraintestinal ones, as: 104 patients had anemia, 41 patients had autoimmune thyroid disease, 12 patients had vitiligo, 13 patients had osteoporosis, 20 patients had anxiety or depression, 3 patients had polyneuropathy, 10 patients had headache syndromes, 3 patients had myalgia, 14 patients had diabetes, 2 patients had Sjogren’s Syndrome, 10 patients had arthritis, 13 patients had asthma and 3 patients had obstructive pulmonary disease. According to Marsh classification, intestinal mucosal damage degrees of CD patients were shown in Table 1. Biochemical test results were presented in Table 2. Celiac patients had numerically higher WBC, MPV, TG, LDL-c and total protein, fasting serum glucose, NLR and MHR levels than controls'. Furthermore, statistically significant differences were found between two study groups for Hb, PLT, PDW, PCT, ferritin, TC, HDL-c, SII, hsCRP, PLR and MPR levels (Table 2).

Spearman’s correlation analyses were performed and statistically significant but not very strong correlations were found between celiac patients’ SII levels and other inflammation markers as NLR, PLR, MHR and hsCRP levels (Table 3).

We performed the ROC curve analysis of SII and other inflammatory parameters and decided optimal cut-off point for SII using the maximum value of Youden’s index (sensitivity + specificity – 1). We presented a baseline serum SII level >560.0 associated with adult CD with 64% specificity and 78% sensitivity (area under the curve [AUC], 0.732; 95% CI 0.630–0.834; p<0.001) (Figure 1).

**Discussion**

The whole immune system is known to be projected by venous markers. In inflammatory processes neutrophils are rapidly recruited from the blood stream into inflamed tissues. In order to attract to other inflammatory cells they release cytokines and proinflammatory chemokines. So, neutrophil recruitment is clearly critical for innate immunity. But excessive neutrophil recruitment can lead to tissue destruction and inflammatory disorders. Studies have shown that platelets are required for neutrophil recruitment in many acute and chronic inflammatory diseases [17, 18]. Neutrophils also need platelets for their important effector functions as phagocytosis, reactive oxygen species formation, and neutrophil extracellular traps (NETs) formation [19]. There is an important adhesion molecule called P-selectin on the platelet surface for neutrophil-platelet interactions. This molecule binds to another molecule called P-Selectin Glycoprotein Ligand 1 (PSGL-1) on the neutrophil surface [20].

**Table 1:** Clinical and demographic features and intestinal mucosal damage degrees of CD patients.

| Variables                  | Female CD patients (n=112) | Male CD patients (n=49) |
|----------------------------|---------------------------|------------------------|
| Age, year                  | 37 ± 12.4                 | 34 ± 12.8              |
| Anemia                     | 78                        | 26                     |
| Autoimmune thyroid disease | 41                        | 0                      |
| Vitiligo                   | 12                        | 0                      |
| Osteoporosis               | 13                        | 0                      |
| Anxiety or depression      | 20                        | 0                      |
| Polyneuropathy             | 0                         | 3                      |
| Headache syndromes         | 6                         | 4                      |
| Myalgia                    | 3                         | 0                      |
| Diabetes                   | 12                        | 2                      |
| Sjogren’s syndrome         | 2                         | 0                      |
| Arthritis                  | 10                        | 0                      |
| Asthma                     | 13                        | 0                      |
| Obstructive pulmonary disease | 0                         | 3                      |

**Marsh classification**

| Marsh classification | Female CD patients | Male CD patients |
|----------------------|--------------------|------------------|
| Marsh I              | 62                 | 12               |
| Marsh II             | 14                 | 5                |
| Marsh III            | 49                 | 19               |

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Studies have shown increased neutrophils in active CD [21, 22]. A 20-fold increase calculated neutrophils have been observed, so these cells may play a role in the early phase of gluten challenge [21, 22]. Their cytotoxic properties to

Table 2: Biochemical test results of study groups.

| Variables                      | CD patients (n=161) | Controls (n=77) | p-Value  |
|--------------------------------|---------------------|-----------------|----------|
| Hb, g/dL                        | 10.82 ± 1.90        | 13.86 ± 1.48    | <0.001a  |
| MCV, fl                         | 82.26 ± 10.70       | 84.50 ± 5.44    | 0.065    |
| WBC, 10^3/L                     | 7.41 ± 1.65         | 7.12 ± 1.41     | 0.191    |
| Neutrophil, mg/dL               | 4.06 ± 1.15         | 4.35 ± 1.22     | 0.118    |
| Lymphocyte, mg/dL               | 2.34 ± 0.72         | 2.35 ± 0.74     | 0.886    |
| PLT, 10^9/L                     | 321.98 ± 93.04      | 275.22 ± 74.81  | <0.001a  |
| PDW, %                          | 13.39 ± 2.23        | 12.66 ± 2.22    | 0.030a   |
| MPV, fl                         | 10.32 ± 0.94        | 10.09 ± 1.02    | 0.125    |
| PCT, %                          | 0.32 ± 0.08         | 0.29 ± 0.06     | 0.001a   |
| Ferritin, ng/mL                 | 7.80 (5.0–20.40)b   | 23.85 (10.75–85.85)b | <0.001a  |
| Folate, ng/mL                   | 6.94 ± 2.06         | 7.08 ± 2.65     | 0.803    |
| Triglycerides, mg/dL            | 136.58 ± 70.39      | 119.42 ± 54.11  | 0.129    |
| Total cholesterol, mg/dL        | 174.57 ± 49.02      | 84.50 ± 5.44    | <0.001a  |
| HDL cholesterol, mg/dL          | 44.60 ± 13.65       | 48.96 ± 10.81   | 0.048a   |
| LDL cholesterol, mg/dL          | 110.85 ± 39.66      | 106.16 ± 35.92  | 0.478    |
| Total protein, g/dL             | 7.45 ± 0.50         | 7.34 ± 0.62     | 0.314    |
| Albümin, g/dL                   | 4.37 ± 0.52         | 4.38 ± 0.36     | 0.862    |
| Fasting serum glucose, mg/dL    | 95.13 ± 15.59       | 94.29 ± 16.20   | 0.733    |
| SII                            | 698.61 ± 219.4      | 517.84 ± 183.69 | <0.001a  |
| hsCRP, mg/L                     | 4.15 ± 1.49         | 3.77 ± 1.01     | 0.034a   |
| NLR                            | 2.04 ± 0.83         | 1.82 ± 0.53     | 0.032a   |
| PLR                            | 148.54 ± 48.22      | 128.30 ± 39.40  | 0.015a   |
| MPR                            | 0.038 (0.032–0.045)b | 0.032 (0.025–0.041)b | <0.001a  |
| MHR                            | 0.0128 ± 0.0023     | 0.0113 ± 0.0011 | 0.114    |

SII, systemic immune inflammation index; hsCRP, high sensitive C-reactive protein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MPR, mean platelet volume to platelet ratio; MHR, monocyte to high density lipoprotein ratio. Student’s t-test was used, data were summarized as mean ± SD. *Statistically significant, p<0.05. **Mann–Whitney U test was used; data were summarized as median and interquartile range (25–75%).

Table 3: Spearman’s correlation analyses of systemic immune inflammation index with other inflammatory markers of patients with celiac disease.

| SII   | Correlation coefficient | p-Value  |
|-------|-------------------------|----------|
| NLR   | 0.553                   | <0.001a  |
| PLR   | 0.457                   | <0.001a  |
| MHR   | 0.261                   | 0.033a   |
| hsCRP | 0.208                   | 0.030a   |
| MPR   | −0.186                  | 0.057    |
| WBC   | 0.174                   | 0.076    |

SII, systemic immune inflammation index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MHR, monocyte to high density lipoprotein ratio; hsCRP, high sensitive C-reactive protein; MPR, mean platelet volume to platelet ratio; WBC, white blood cell. *Statistically significant, p<0.05.

Figure 1: Receiver operating characteristics curve analysis for SII, NLR, PLR, MPR, MHR, hsCRP and WBC levels of patients with celiac disease.
enterocytes were also shown [23]. CD and the relation with systemic inflammation have been demonstrated in previous studies [24]. Studies have shown the abnormal increases in inflammatory parameters of blood cells including PLR and NLR as simple markers of inflammation in CD [8, 9]. However these biomarkers involve only two types of inflammatory and immune cells and do not precisely reflect the inflammation status in CD. SII was appointed based on three types of circulating inflammatory and immune cells: platelets, neutrophils and lymphocytes [10]. The SII level serves as an easily detectable biomarker reflecting the inflammatory state and systemic inflammatory activity [10]. We evaluated clinical significance of SII in CD patients and compared the diagnostic abilities of SII, PLR, NLR, MPR, MHR, WBC and hsCRP. We represented that, compared to other inflammatory markers SII had statistically significant higher AUC by ROC curve analysis. According to our results we indicated that high SII is significantly associated with CD.

We approved some limitations of our study. Firstly, it is a retrospective single center study. Secondly, our patients were newly diagnosed without gluten free diet therapy, so evaluating SII levels before and after their therapy may be more informative.

To the best of our knowledge, this is the first study elaborately analyzed the diagnostic value of SII in adult CD patients. Our study also compared the relative diagnostic efficiency of SII, PLR, NLR, MHR, MPR, hsCRP and WBC. Our findings suggest that SII is significantly associated with adult CD and is superior to PLR, NLR, MHR, MPR, hsCRP and WBC. Therefore SII is worthy of further studies investigating prospectively as a hematologic parameter for adult CD patients.

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Informed consent: This is a retrospective study. Informed consent was not obtained from individuals included in this study.

Ethical approval: This study was performed in accordance with the Helsinki Declaration and The Ethical Committee of Erciyes University Medical Faculty approved the study protocol (2019/807).

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