Relationship Between Systemic Immune-Inflammation Index and Irritable Bowel Syndrome

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Cite this article as: Güven İE, Başpınar B, Atalay R. Relationship between systemic immune-inflammation index and irritable bowel syndrome. *Turk J Gastroenterol.* 2022; 33(1): 30-34.

ABSTRACT

Background: *Irritable bowel syndrome is accepted as a functional disorder; however, there is growing evidence in favor of the inflammatory process contributing to its pathogenesis. We aimed to evaluate the role of the systemic immune-inflammation index as a marker of inflammation in patients with irritable bowel syndrome.*

Methods: *The study was conducted in the outpatient clinic of the Gastroenterology Department with patients having constipation-predominant irritable bowel syndrome diagnosis according to Rome IV criteria between March 1, 2019 and December 31, 2020. The systemic immune-inflammation index was calculated and compared with age- and sex-matched healthy controls.*

Results: *The study was performed with 214 participants, 107 patients and 107 control groups. Platelet and neutrophil counts ($P < .001$, for both) were higher, and lymphocyte count ($P = .003$) was lower in the irritable bowel syndrome group. The systemic immune-inflammation index was higher in irritable bowel syndrome patients ($P < .001$). Multivariate logistic regression analyses showed the role of the systemic immune-inflammation index as an independent predictor of the presence of IBS (odds ratio: 1.100, $P < .001$).*

Conclusion: *Systemic immune-inflammation index may be a cheap, universal, and reliable indicator of the inflammatory process in irritable bowel syndrome patients.*

Keywords: *Inflammation, irritable bowel syndrome, lymphocyte count, neutrophils, platelet count*

INTRODUCTION

Irritable bowel syndrome (IBS) is defined as a functional syndrome of the gastrointestinal (GI) system with symptoms predominantly abdominal discomfort and altered bowel habits in the absence of detectable organic GI disease.[1] It is a common condition that does not increase mortality but negatively affects the quality of life.[2] Despite the common acceptance of IBS as a functional disorder, recent studies have shown evidence that enteric inflammatory events have a significant role in IBS pathogenesis.[3] The underlying disease mechanisms include mucosal inflammation, mucosal immune activation, changes in intestinal permeability, alteration in the gut microbiome, and post-infection changes.[4,5]

In recent years, the platelet–lymphocyte ratio (PLR) and neutrophil–lymphocyte ratio (NLR) have been adapted as an indicator of inflammation. Platelet–lymphocyte ratio and NLR have been widely studied to define the severity of inflammation in rheumatic diseases, liver diseases, diabetes mellitus, arterial hypertension, several cardiovascular diseases, and malignancies.[6-9] Moreover, the systemic immune-inflammation index (SII; platelet count × NLR) has been proposed by Hu et al[10] as a valuable marker of inflammation and contains information about 3 cell types. Although the significance of SII has been demonstrated in many disease groups such as cancer and coronary artery disease, there is a lack of information considering its activity in IBS patients.[10-12] In this study, based on the role of inflammation in IBS pathogenesis, we aimed to evaluate the relationship between SII and IBS. To the best of our knowledge, this is the first study to evaluate the SII in IBS patients.

MATERIALS AND METHODS

Subjects

This study included all eligible patients who were diagnosed with constipation-predominant IBS (IBS-C) in the outpatient clinic of the Gastroenterology Department between March 1, 2019 and December 31, 2020. The IBS-C diagnosis was made according to the Rome IV criteria which are characterized by abdominal pain at least 1 day per week for the last 3 months with symptom onset at least 6 months prior to diagnosis, where the pain is associated with at least 2 of the following: (1) change in stool frequency toward infrequent bowel movements,

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Received: **April 11, 2021** Accepted: **August 18, 2021** Available Online Date: **January 10, 2022**

DOI: **10.5152/tjg.2021.21321**

(2) change in stool form toward harder stools, and (3) pain is related to defecation.[13] A total colonoscopy was performed in all IBS-C patients in order to rule out any organic colonic pathology. Patients with adequate bowel preparation (Boston bowel preparation score 3) and normal colonoscopic and anoscopic findings were recruited to the study. Sex- and age-matched healthy controls without any comorbidities or regular medication use have been employed from the subject who had been evaluated in the outpatient clinic for a routine check-up in our institute. For both IBS patients and healthy controls groups, exclusion criteria were age under 18 years, a history of major abdominal surgery, celiac disease, evidence of acute or chronic infection, systemic inflammatory or autoimmune disease, thyroid hormone abnormalities, severe liver or renal failure, diabetes mellitus, hematological diseases, inflammatory bowel diseases, malignancy, and psychiatric disorders. Previous health history, demographic characteristics, and laboratory and radiological results were obtained from hospital records.

Due to the retrospective design of the study, written informed consent from the participants could not be obtained. Our study was approved by the ethics committee in Ankara City Hospital, and its protocol conformed to the principles of the Declaration of Helsinki (Approval No: 1398/23.12.2020).

Biochemical Measurements

Laboratory parameters were obtained from the medical records of the patients. Complete blood count was measured with an autoanalyzer. Fasting blood glucose, liver and kidney function levels were additionally measured in all patients by using an automated chemistry analyzer. The NLR, PLR, and SII were calculated for each patient.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 22.0 software for Windows (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Continuous variables were shown as mean ± standard deviation or median (interquartile range), and categorical variables were given as numbers and percentages. In order to test the normality of distribution, the Kolmogorov–Smirnov test was used. Chi-square tests were used for categorical variables. Independent-samples *t*-test was used to compare unadjusted means between groups. Non-continuous numerical variables between groups were compared via Mann–Whitney *U* test. Logistic regression analysis was performed to examine the association between IBS-C and other variables. Variables with $P < .25$ in univariate logistic regression were included in a multivariate logistic regression model. Receiver operating characteristics curve analysis was used for the prediction of the presence of IBS-C. A two-tailed $P < .05$ was considered significant.

Main Points

- *Recent literature has shown evidence that enteric inflammatory events have a significant role in irritable bowel syndrome pathogenesis.*
- *Systemic immune-inflammation index was higher in patients with irritable bowel syndrome than age- and sex-matched healthy controls in the present study.*
- *Systemic immune-inflammation index may be an accessible, universal, and reliable indicator of the inflammatory process in IBS patients.*

RESULTS

The study included a total of 214 subjects, and the subjects were divided into the IBS-C patient group (n = 107) and the control group (n = 107). Table 1 shows the baseline characteristics and laboratory findings of the participants. Among IBS-C patients and the control group, the mean age was 46.6 (±15.2) and 45.3 (±13.3) years, with male sex accounting for 37% and 45%, respectively. No significant differences in age or sex were observed between both groups. Creatinine, hemoglobin, white blood cell count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and C-reactive protein levels were similar between the 2 groups. Platelet and neutrophil counts ($P < .001$, for both) were higher, and lymphocyte count ($P = .003$) was lower in the IBS-C group. Similarly, NLR, PLR, and SII levels were statistically higher in the IBS-C group ($P < .001$, all parameters).

Univariate and multivariate logistic regression analyses were performed to determine the independent predictors of the presence of IBS-C. Systemic immune-inflammation index was the independent predictor of the presence of IBS-C (odds ratio (OR): 1.100, CI: 1.072-1.129, $P < .001$) (Table 2). Receiver operator characteristic curve analysis revealed that the SII had the best predictive power for IBSC among the inflammatory parameters (Figure 1). An SII > 772 × 103 can predict the presence of IBS-C with an 84.1% sensitivity and an 84.1% specificity. It was also able to predict the presence of IBS-C with a sensitivity of 74.8% and a specificity of 74.8% with a cut-off value of NLR 2.0314 and PLR 0.1205.

Table 1. Baseline Clinical and Laboratory Parameters

	IBS (n = 107)	Control (n = 107)	*P*
Age (years), mean ± SD	46.6 ± 15.2	45.3 ± 13.3	.52
Gender (male), n (%)	40 (37)	49 (45)	.27
Smoking, n (%)	30 (28)	39 (36)	.25
FBG (mg/dL), mean ± SD	88.1 ± 8.4	87.0 ± 7.4	.30
Creatinine (mg/dL), mean ± SD	0.8 ± 0.2	0.8 ± 0.2	.54
Hemoglobin (g/dL), mean ± SD	14.0 ± 1.4	14.0 ± 1.2	.70
Platelet count (×10^3/mm^3), mean ± SD	311.5 ± 66.9	239.8 ± 50.4	**<.001**
WBC count (×10^3/mm^3), mean ± SD	6955.0 ± 1669.7	7014.6 ± 1426.5	.78
Neutrophil count (×10^3/mm^3), mean ± SD	5466.4 ± 1360.7	3946.5 ± 1040.6	**<.001**
Lymphocyte count (×10^3/mm^3), mean ± SD	2131.3 ± 590.7	2383.3 ± 630.3	**.003**
AST (U/L), mean ± SD	19.6 ± 5.7	20.5 ± 6.3	.28
ALT (U/L), mean ± SD	22.4 ± 9.7	23.6 ± 8.5	.32
NLR	2.7 ± 1.0	1.7 ± 0.6	**<.001**
PLR	155.8 ± 51.5	105.6 ± 29.0	**<.001**
SII (×10^3), mean ± SD	854.4 ± 376.1	411.9 ± 145.0	**<.001**
CRP (mg/L), median (IQR)	0.6 (0.3-1.2)	0.5 (0,3-0,8)	.12

CRP, C-reactive protein; FBG, fasting blood glucose; IBS, irritable bowel syndrome; IQR, interquartile range; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SD, standard deviation; SII, systemic immune-inflammation index; WBC, white blood cell.
Bold *P* values corresponds statistical significance.

Table 2. Univariate and Multivariate Logistic Regression Analysis Showing the Independent Predictors of the Presence of IBS

	Univariate				Multivariate			
	95% CI				95% CI			
	OR	Lower	Upper	*P*	OR	Lower	Upper	*P*
Age (years)	1.006	0.987	1.025	.52				
Gender	0.707	0.409	1.220	.21	1.221	0.556	2.680	.62
Smoking	0.688	0.386	1.226	.21	0.720	0.309	1.676	.45
FBG	1.018	0.984	1.054	.29				
Platelet count	1.022	1.016	1.029	**<.001**				
Neutrophil count	1.001	1.001	1.001	**<.001**				
Lymphocyte count	0.999	0.999	1.000	**.004**				
NLR	7.055	3.977	12.518	**<.001**				
PLR	1.159	2.049	6.551	**<.001**				
SII (×10^3)	1.101	1.073	1.130	**<.001**	1.100	1.072	1.129	**<.001**
CRP	1.220	0.945	1.574	.12	1.120	0.742	1.692	.59

CRP, C-reactive protein; FBG, fasting blood glucose; IBS, irritable bowel syndrome; NLR, neutrophil/lymphocyte ratio; OR, odds ratio; PLR, platelet/lymphocyte ratio; SII, systemic immune-inflammation index.
Bold *P* values corresponds statistical significance.

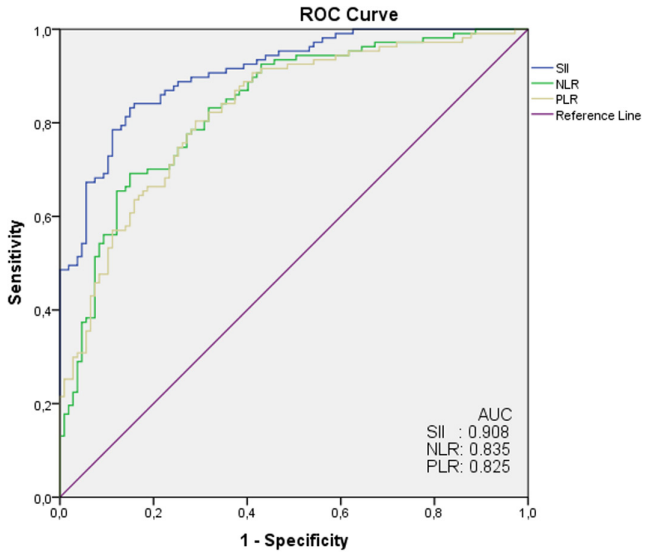

Figure 1. Receiver operating characteristic curve for systemic immune-inflammation index as a predictor of constipation-predominant irritable bowel syndrome.

DISCUSSION

In the present study, significantly higher SII, NLR, and PLR measurements were found in IBS-C patients compared to the control group. To the best of our knowledge, this is the first study demonstrating the relationship between increased SII with IBS. Although in the past it was thought that IBS had no underlying structural or biochemical abnormalities, recent studies have shown a significant role of inflammatory changes in the pathophysiology of IBS.[14] Current data revealed higher baseline tumor necrosis factor (TNF)-alpha, interleukin (IL)-1-beta, IL-6, and lipopolysaccharide (LPS)-induced IL-6 levels in IBS patients.[15] Besides, an increase in mast cells, higher levels of tryptase and histamine activity have been observed in the mucosal biopsy specimens from IBS patients.[16] Moreover, increased numbers of CD3+ T cells, CD25+ T cells, and neutrophils, which reflect an activated adaptive immune response, have been reported in biopsies from the intestinal mucosa.[17,18] Infectious gastroenteritis is also important in the development of IBS. The underlying mechanisms are increased intestinal permeability and persistent microscopic inflammation of the bowel that supports the role of low-grade inflammation in the pathogenesis of this disorder.[19,20]

There has been an increasing interest in the investigation of new biomarkers as an indicator of inflammation. Neutrophil, lymphocyte, and platelet cells participate in inflammatory processes.[21,22] Neutrophil–lymphocyte ratio and PLR calculated from the counts of these 3 cell types are widely used in this context, and higher NLR and PLR ratios are associated with poor clinical outcomes in malignancies, coronary artery diseases, and several rheumatic diseases.[23-25] A previous study that evaluates NLR in patients with IBS found a significantly higher NLR in patients with IBS than in controls.[26] In accordance with the literature, we have also shown a higher NLR ratio in IBS-C patients. In addition, PLR ratio was found higher in the IBS-C group.

The SII index has lately been defined as a new inflammatory index and has been argued to be more predictive than NLR and PLR.[27] Previously, it was demonstrated that a higher SII may be associated with poor clinical outcomes in various cancer types and cardiovascular diseases since increased values usually indicate a stronger inflammatory response.[28,29] In this study, we revealed that the predictive value of SII in IBS is much higher compared to NLR and PLR.

The study had some limitations. First of all, the study was conducted retrospectively. Secondly, the study had a relatively low number of patients and the population size, which precluded some IBS sub-groups. Thus, only patients diagnosed with IBS-C were recruited for the study. This situation makes it difficult to generalize the results of the study to all IBS patients.

In conclusion, SII which is a novel superior tool compared to other inflammatory markers may be a reliable, universal, and cheap indicator of inflammation in IBS patients. Systemic immune-inflammation index might show low-grade inflammation, which may be a part of the pathogenesis of IBS. Further studies are needed to determine whether the SII index can contribute to the diagnosis or serve as a potential marker of response to therapy in patients with IBS.

Ethics Committee Approval: This study was approved by the ethics committee of Ankara City Hospital, and its protocol conformed to the principles of the Declaration of Helsinki (Approval No: 1398/23.12.2020).

Informed Consent: Due to the retrospective design of the study, written informed consent from the patients could not be obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Consept – İ.E.G., B.B.; Design – İ.E.G., B.B.; Supervision – R.A.; Resources – İ.E.G., B.B., R.A.; Materials – İ.E.G., B.B., R.A.; Data Collection and/or Processing – İ.E.G., B.B.; Analysis and/or

Interpretation – İ.E.G., B.B., R.A.; Literature Search – İ.E.G., B.B., R.A.; Writing Manuscript – İ.E.G., B.B.; Critical Review – İ.E.G., B.B., R.A.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. N Engl J Med. 2017;376(26):2566-2578. [CrossRef]
2. El-Salhy M. Irritable bowel syndrome: diagnosis and pathogenesis. World J Gastroenterol. 2012;18(37):5151-5163. [CrossRef]
3. Sinagra E, Pompei G, Tomasello G, et al. Inflammation in irritable bowel syndrome: myth or new treatment target? World J Gastroenterol. 2016;22(7):2242-2255. [CrossRef]
4. Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. Lancet Gastroenterol Hepatol. 2016;1(2):133-146. [CrossRef]
5. Weston AP, Biddle WL, Bhatia PS, Miner PB Jr. Terminal ileal mucosal mast cells in irritable bowel syndrome. Dig Dis Sci. 1993;38(9):1590-1595. [CrossRef]
6. Qiang G, Liang C, Xiao F, et al. Prognostic significance of platelet-to-lymphocyte ratio in non-small-cell lung cancer: a meta-analysis. Onco Targets Ther. 2016;9:869-876. [CrossRef]
7. Liu W, Lou X, Zhang Z, Chai Y, Yu Q. Association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume with the risk of gestational diabetes mellitus. Gynecol Endocrinol. 2021;37(2):105-107. [CrossRef]
8. Sunbul M, Gerin F, Durmus E, et al. Neutrophil to lymphocyte and platelet to lymphocyte ratio in patients with dipper versus non-dipper hypertension. Clin Exp Hypertens. 2014;36(4):217-221. [CrossRef]
9. Chiriac S, Stanciu C, Singeap AM, Sfarti CV, Cuciureanu T, Trifan A. Prognostic value of neutrophil-to-lymphocyte ratio in cirrhotic patients with acute-on-chronic liver failure. Turk J Gastroenterol. 2020;31(12):868-876. [CrossRef]
10. Hu B, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20(23):6212-6222. [CrossRef]
11. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of Systemic immune-inflammation index in cancer: a meta-analysis. J Cancer. 2018;9(18):3295-3302. [CrossRef]
12. Tanacan E, Dincer D, Erdogan FG, Gurler A. A cutoff value for the systemic immune-inflammation index in determining activity of Behçet disease. Clin Exp Dermatol. 2021;46(2):286-291. [CrossRef]
13. Hellström PM, Benno P. The Rome IV: irritable bowel syndrome - a functional disorder. Best Pract Res Clin Gastroenterol. 2019;40-41:101634. [CrossRef]
14. Ford AC, Talley NJ. Mucosal inflammation as a potential etiological factor in irritable bowel syndrome: a systematic review. J Gastroenterol. 2011;46(4):421-431. [CrossRef]
15. Liebregts T, Adam B, Bredack C, et al. Immune activation in patients with irritable bowel syndrome. Gastroenterology. 2007;132(3):913-920. [CrossRef]
16. Barbara G, Cremon C, Carini G, et al. The immune system in irritable bowel syndrome. J Neurogastroenterol Motil. 2011;17(4):349-359. [CrossRef]
17. Törnblom H, Lindberg G, Nyberg B, Veress B. Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. Gastroenterology. 2002;123(6):1972-1979. [CrossRef]
18. Chadwick VS, Chen W, Shu D, et al. Activation of the mucosal immune system in irritable bowel syndrome. Gastroenterology. 2002;122(7):1778-1783. [CrossRef]
19. Lee YY, Annamalai C, Rao SSC. Post-infectious irritable bowel syndrome. Curr Gastroenterol Rep. 2017;19(11):56. [CrossRef]
20. Sadeghi A, Biglari M, Nasseri Moghaddam S. Post-infectious irritable bowel syndrome: a narrative review. Middle East J Dig Dis. 2019;11(2):69-75. [CrossRef]
21. Huang Z, Fu Z, Huang W, Huang K. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: a meta-analysis. Am J Emerg Med. 2020;38(3):641-647. [CrossRef]
22. Sari I, Sunbul M, Mammadov C, et al. Relation of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio with coronary artery disease severity in patients undergoing coronary angiography. Kardiol Pol. 2015;73(12):1310-1316. [CrossRef]
23. Hong X, Cui B, Wang M, Yang Z, Wang L, Xu Q. Systemic immune-inflammation index, based on platelet counts and neutrophil-lymphocyte ratio, is useful for predicting prognosis in small cell lung cancer. Tohoku J Exp Med. 2015;236(4):297-304. [CrossRef]
24. Park JJ, Jang HJ, Oh IY, et al. Prognostic value of neutrophil to lymphocyte ratio in patients presenting with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Am J Cardiol. 2013;111(5):636-642. [CrossRef]
25. Kawamura Y, Takeshita S, Kanai T, Yoshida Y, Nonoyama S. The combined usefulness of the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in predicting intravenous immunoglobulin resistance with Kawasaki disease. J Pediatr. 2016;178:281-284.e1. [CrossRef]
26. Güçlü M, Ağan AF. Relationship of peripheral blood neutrophil to lymphocyte ratio and irritable bowel syndrome. Turk J Med Sci. 2017;47(4):1067-1071. [CrossRef]
27. Fest J, Ruiter R, Ikram MA, Voortman T, van Eijck CHJ, Stricker BH. Reference values for white blood-cell-based inflammatory markers in the Rotterdam Study: a population-based prospective cohort study. Sci Rep. 2018;8(1):10566. [CrossRef]
28. Yang YL, Wu CH, Hsu PF, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clin Investig. 2020;50(5):e13230. [CrossRef]
29. Candemir M, Kiziltunç E, Nurkoç S, Şahinarslan A. Relationship between systemic immune-inflammation index (SII) and the severity of stable coronary artery disease. Angiology. 2021;72(6):575-581. [CrossRef]