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Original Research

Evaluating the clinical application of the immune cells' ratios and inflammatory markers in the diagnosis of inflammatory bowel disease

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Abstract

Objective: Inflammatory Bowel Diseases (IBDs) are chronic inflammatory conditions of the gastrointestinal tract, including Crohn's disease (CD) and ulcerative colitis (UC). Developing methods for effective screening and diagnosis is extremely needed. Accordingly, this study aims to evaluate the potential of immune cells ratios in the diagnosis of IBD. **Methods:** This case-control study includes data from Jordan University Hospital (JUH) medical records for IBD patients with age- and gender-matched healthy controls. **Results:** This study included 46 participants, of which 56.52% had IBD, 54.35% were males, with insignificant differences in sex, age, and body mass index (BMI) between IBD patients and controls ($p>0.05$). In the CD group, the variables with the highest sensitivity and specificity (HSS) were neutrophil-to-lymphocyte (NLR) (75%, 80%) and platelet-to-lymphocytes (PLR) (75%, 90%), in UC group; mean corpuscular hemoglobin (MCH) (80%, 80%). In CD group, the combinations giving the HSS were PLR+NLR (76%, 90.9%), C-reactive protein (CRP)+PLR (76%, 90.9%), and CRP+NLR (73.07%, 90%). In UC group, the combinations giving the HSS were erythrocyte sedimentation rate (ESR)+PLR (76.9%, 100%), PLR+MCH (74.07%, 100%), PLR+CRP (71.42%, 100%), and PLR+NLR (71.42%, 100%). Regression analysis identified five different combinations of significance in the diagnosis of CD and UC. Higher Youden's index was used and defined the most beneficial clinical combinations as NLR+PLR and CRP+PLR for CD, whereas ESR+PLR for UC. **Conclusion:** Implications to our study include the clinical application of immune cell ratios, inflammatory markers, and their different combinations along with patients' history and physical examination findings for easier, faster, and more cost-effective diagnosis of IBDs.

Keywords: IBD; Crohn's disease; ulcerative colitis; immune cells; inflammation; biomarkers; neutrophil-to-lymphocyte; platelet-to-lymphocytes

INTRODUCTION

Inflammatory bowel diseases (IBDs) are idiopathic chronic inflammatory conditions of the gastrointestinal tract, that include Crohn's disease (CD) and ulcerative colitis (UC). IBDs affected 6.8 million people in 2017 with years lived with disability (YLD) that doubled between 1990 and 2017.[1] These diseases are relapsing-remitting in nature with symptoms of abdominal pain and bloody diarrhea emerging in flare-ups. Moreover. IBDs predispose affected patients to a higher risk of developing colorectal cancer, small bowel adenocarcinoma, intestinal lymphoma, anal cancer, and cholangiocarcinoma.[2] The pathogeny of these diseases is a complex process that involves genetic predispositions, gut microbiome, and environmental factors.[3] Many immunological facets are involved in IBD, including innate immune system Toll-like receptors (TLRs), NLRP3 gene, complement components, neutrophils, and macrophages along with the adaptive immune system lymphocytes, plasma cells, and antibodies.[4-10] Accordingly, agents with anti-inflammatory and immunosuppressive functions are used to induce and maintain remission in IBD patients.[11] However, these agents are not completely effective and have adverse effects. For instance, long-term daily treatment with the first-line drug, Mesalazine in UC, was more effective than short-term treatment, but 30% of the cases relapsed in four years. However, these results may be overestimated as the study was an unrandomized retrospective investigation that only included patients who had clinical improvements.[12] Moreover, anti-tumor necrosis factor (TNF)-alpha antibody, infliximab, is ineffective after induction in 30% of patients and is discontinued by 50% of patients due to secondary loss of response or serious adverse effects, such as infusion reactions, infections, in addition to lymphoproliferative and skin malignancies.[2,13] These statistics are only worsened by the fact that 70% to 90% of CD patients require surgery in their lifetime.[14] Accordingly, an extreme need is there to develop effective screening and diagnostic methods.

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Regarding diagnostic and prognostic factors, a 2014 review by Billiet et. al reported the absence of any serological or clinical markers that exceeded the diagnostic and prognostic value of careful clinical phenotyping and endoscopic features.[15] These included certain p-ANCA types, C-reactive protein (CRP), immune cells ratios, disease phenotype at diagnosis, perianal involvement, and the initial use of corticosteroids.15 Of interest to us are immune cells ratios, which include neutrophil-to-lymphocyte (NLR), platelet-to-lymphocytes (PLR), lymphocytes-to-monocytes (LMR), and the systemic immune-inflammatory index (SII, platelets*neutrophils/ lymphocytes). These were implicated in numerous diseases, including breast and gastric cancer stage, breast, pancreatic, and colorectal cancer mortality, IBDs activity, *H. pylori* gastritis, septic shock, Influenza, and COVID-19 severities.[16-24]

In IBDs, these immune cells ratios were repeatedly correlated with disease activity, endoscopic features, and loss of response to biological treatments.[2-4,6-8,11,14-17,25,26] Considering disease activity, values of NLR, SII, PLR, and LMR were found higher in IBD patients with active disease (both CD and UC) when compared to inactive disease counterparts and non-IBD controls.27-29 For instance, significantly higher NLR and PLR, along with lower LMR differentiated were found in CD patients compared to non-IBD controls.[27] Similarly, in a study of 104 UC patients and 105 healthy controls, Akpinar et. al. reported higher NLR and PLR in the former when compared to the latter.25 These studies among others point to a diagnostic value for these immune cells ratios that when combined with clinical suspicion may be sensitive and specific for IBDs. The cut-off values, sensitivities, and specificities of these ratios were highly variable in the literature. For example, Okba et. al. disclosed a cut-off value of 1.91 for NLR, in which higher scores are 90% sensitive and specific in diagnosing UC.30 However, a cut-off value of 2.26 had similar specificity but a 54.2% sensitivity in a different population of UC patients 31. The optimal NLR may even differ between CD and UC, as a cut-off value of 2.72 produced a 68.3% and 75.9 % sensitivity and specificity, respectively, in one study of CD patients.26 Moreover, Hanafi et. al established a scoring system, consisting of lactoferrin at a cutoff of 148.5 µg/mL, neutrophil-lymphocyte ratio at a cutoff of 2.35, erythrocyte sedimentation rate (ESR) at the first hour at a cutoff of 29.5 mm/h, C-reactive protein at a cutoff of 3.85 mg/L, mean platelet volume at a cutoff of 8.8 fL, fecal white blood cells at a cutoff of 9 cells/HPF, and fecal red blood cells at a cutoff of 6 cells/HPF. Interestingly, a score ≥5 can detect 94% of cases of UC with a sensitivity of 94% and a specificity 100%.32 Accordingly, our study aims to be the first regional and Jordanian study to evaluate the potential of immune cells ratios in the diagnosis of IBD patients and correlate that with the global population's indices.

MATERIALS AND METHODS

Study design

This case-control study includes data from Jordan University Hospital (JUH) medical records. The targeted population included IBD patients, and age- and gender-matched healthy controls. The CD group was made up of 16 samples, 11 of which were males and 5 of which were females. The UC group was made up of 10 samples, 5 of which were males and 5 of which were females. In total, the IBD group was made of up 26 samples, which included 16 males and 10 females. The control group was made up of 20 samples, 9 of which were males, and 11 of which were females. Exclusion criteria included recurring infections with *H. pylori*, recurring or invasive amoebiasis, infection with cytomegalovirus, diagnosis with Familial Mediterranean Fever, chronic obstructive pulmonary disease (COPD), colorectal cancer, or celiac disease, stomach infections, stomach ulcers, diverticulosis, and current use of Infliximab or Humira. Acquired data include patients' age, gender, diagnosis, body mass index (BMI), and clinical laboratory results (CRP, ESR levels, CBC, and WBC).

Ethical statement

Ethical approval was obtained from the institutional review board (IRB) at Jordan University Hospital (10-2021-15559). Moreover, written consent was obtained from participants.

Statistical analysis

The principal component analysis (PCA) was carried out on the values of the following blood tests for both the Control and IBD group: Age, BMI, WBC, RBC, Hematocrit, Hemoglobin, MCV, RDW, MCH, MCHC, Neutrophil%, Basophil%, Lymphocyte%, Platelet's count, and MPV. The PCA, T-test, simple logistic regression, and multiple logistic regression were carried out using GraphPad Prism 9.3.1 software. The variables with a loading score lower than .3 were excluded from further analysis. In cases when two variables had correlation scores higher than .7, either the variable with the lower score was excluded, or the two variables were extracted to create a new variable (e.g., Neutrophil% and Lymphocyte% were extracted into the Neutrophil-to-Lymphocyte ratio variable).

The following blood tests that were incorporated into the multiple regression model based on their loadings in the previous PCA and their significance in the IBD population: CRP, ESR, NLR, PLR, and MCH. Two separate models were used for the CD and UC groups, due to the differing rates of correlation to serum biomarkers in each group. Simple logistic regression was carried out on each of the following variables: Age, BMI, ESR, CRP, NLR, PLR, and MCH. Multiple logistic regression for both groups was also carried on the same variables listed above. Two multiple logistic regression models were made: one excluding NLR and one excluding PLR, due to the high multicollinearity between them (variance inflation factor>5). ROC curve analysis was carried out for both groups using the MedCalc software, in order to determine the optimal cut-off, point for each blood test. The validity of the cut-off point selected was assessed using the Youden's index, which is calculated using the following formula: Sensitivity% + specificity% - 100 at the cut-off point that was selected. Blood tests that gave Youden's index values lower than .50 were considered non-significant. For assessing the precision of using a combination of two blood tests together, the samples that exceeded the cut-off

values for both variables were given a "true" value, and the other samples were given a "false" value. The formula used for calculating sensitivity was (true positive)/ (true positive + false negative) and the formula used for calculating specificity was (true negative)/ (true negative + false positive). The validity of each biomarker's efficiency was further assessed by calculating the number of samples from each group that fell into the range shared by the Control and IBD groups for each biomarker.

RESULTS

Demographic characteristics of participants

This study included 46 participants, of which 56.52% had IBD. Among total participants, 54.35% were males, with insignificant difference in sex between patients and controls (P=0.207). Regarding age, mean age and standard deviations were 40.75±8.83 and 35.31±11.34 for controls and IBD patients, respectively (P=0.074). Age difference was also insignificant when comparing UC patients to controls and CD patients to controls (P=0.440 and P=0.066, respectively). Concerning body mass index (BMI), the average for the total sample, controls and IBD patients were 25.46±5.38, 25.91±4.59, and 25.12**±5·98, respectively· Independent T-test analysis revealed insignificant BMI difference between IBD patients and controls (P=0·614). Additionally, marital status was not statistically different between IBD patients and controls, and between CD and UC patients (P=0·080 and P=0·126, respectively) (Table 1).** The descriptive statistics for the blood tests for the CD and UC groups are found in Figure 1.

Single blood test results and IBD

In the CD group, the only variables that had B-coefficients significantly different from zero were NLR (P-value =0.026) and PLR (P-value =0.022). The odds ratio (OR) for each variable was 6.521 and 1.441, respectively. All the P-values generated for the B-coefficients in the UC group were non-significant.

Table 1. Demographic Characteristics for the CD, UC, and Control groups

Demographic Characteristic	Controls n (%)	IBD n (%)	P-value	CD n (%)	UC n (%)	P-value
Sex			0.264			0.339 (OR=0.455)
Male	11 (55.00)	16 (61.54)		11 (68.75)	5 (50.00)	
Female	9 (45.00)	10 (38.46)		5 (31.25)	5 (50.00)	
Age (mean±S.D.)	40.75±8.83	35.31±11.34	.074	33.56±12.72	38.10±8.58	0.289
BMI	25.91±4.59	25.12±5.98	.614	25.67±7.10	24.23±3.72	0.505
Marital Status			.080 (OR=.282)			0.126 (OR=0.250)
Married	17 (85.00%)	16 (61.54)		17 (85.00%)	8 (80.00%)	
Single	3 (15.00%)	10 (38.46)		3 (15.00%)	2 (20.00%)	

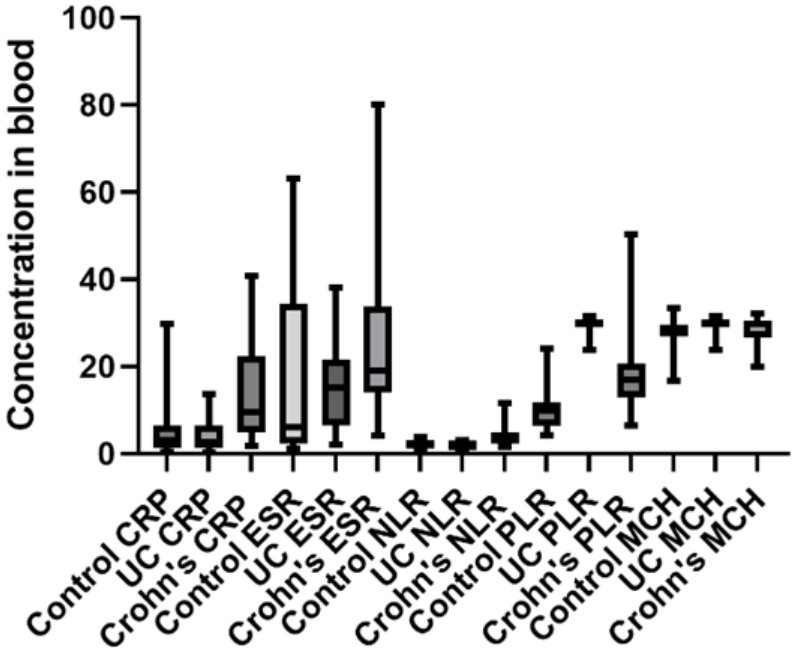

Figure 1. Descriptive statistics for each variable in the Control, CD, and UC

The P-value generated through the Mann-Whitney U-test proved to be significant in CRP, NLR, and PLR values in the CD group (0.009, 0.001, and <0.0005, respectively). However, the P-values generated through the Mann-Whitney U-test for the UC group were significant only for PLR values (p<0.0001).

The ROC curves for each of the variables in the CD and UC group are found in Figures 2 and 3, respectively. In the CD group, the variables with the highest sensitivity and specificity were NLR (75%, 80%) and PLR (75%, 90%), while in the UC group, the variable with the highest sensitivity and specificity was MCH (80%, 80%).

The Venn diagrams in Figure 4 show the index number for IBD samples (in red) and Control samples (in green) for each biomarker. The samples present in the shared area between the two Venn diagrams are the samples that had values that were included in the range shared by both groups.

Combined blood tests result and IBD

The sensitivity and specificity of two combined variables for each group are found in Table 2. In the CD group, the combinations that gave the highest sensitivity and specificity were PLR + NLR (76%, 90.9%), CRP + PLR (76%, 90.9%), and CRP + NLR (73.07%, 90%). In the UC group, the combinations that gave the highest sensitivity and specificity were ESR + PLR (76.9%, 100%), PLR + MCH (74.07%, 100%), PLR + CRP (71.42%, 100%), and PLR + NLR (71.42%, 100%).

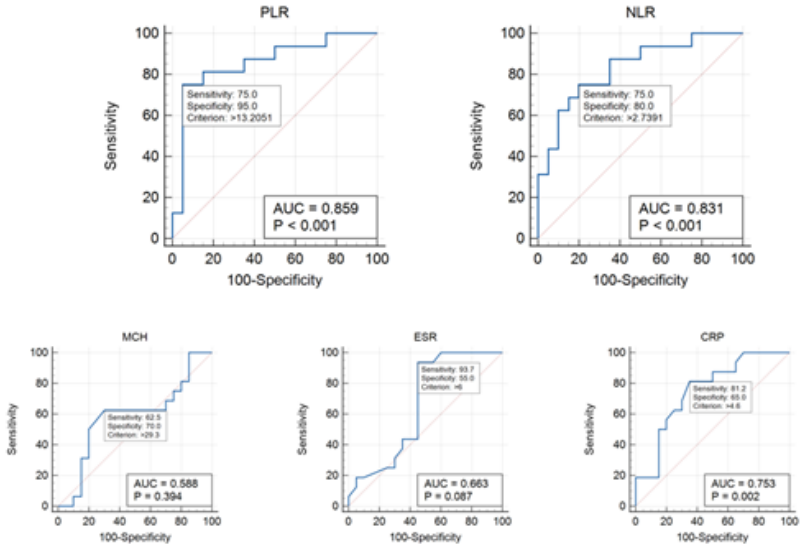

Figure 2. ROC curve analysis results for the CD and control group

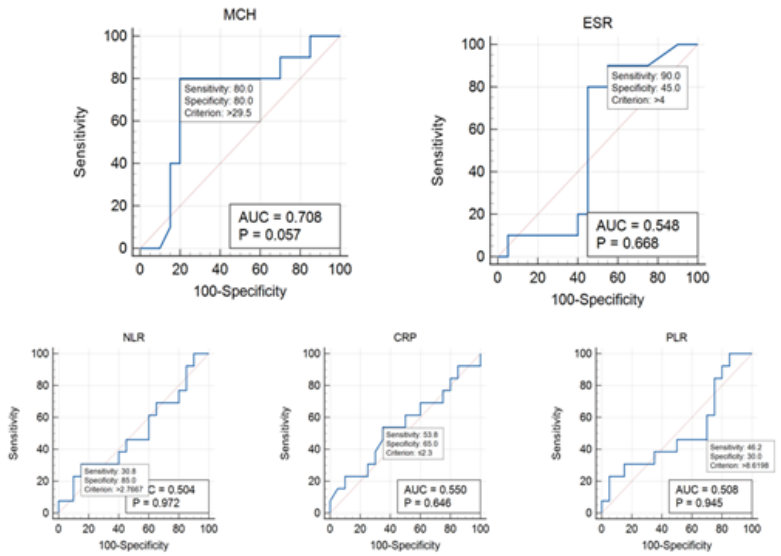

Figure 3. ROC curve analysis results for the UC and control group

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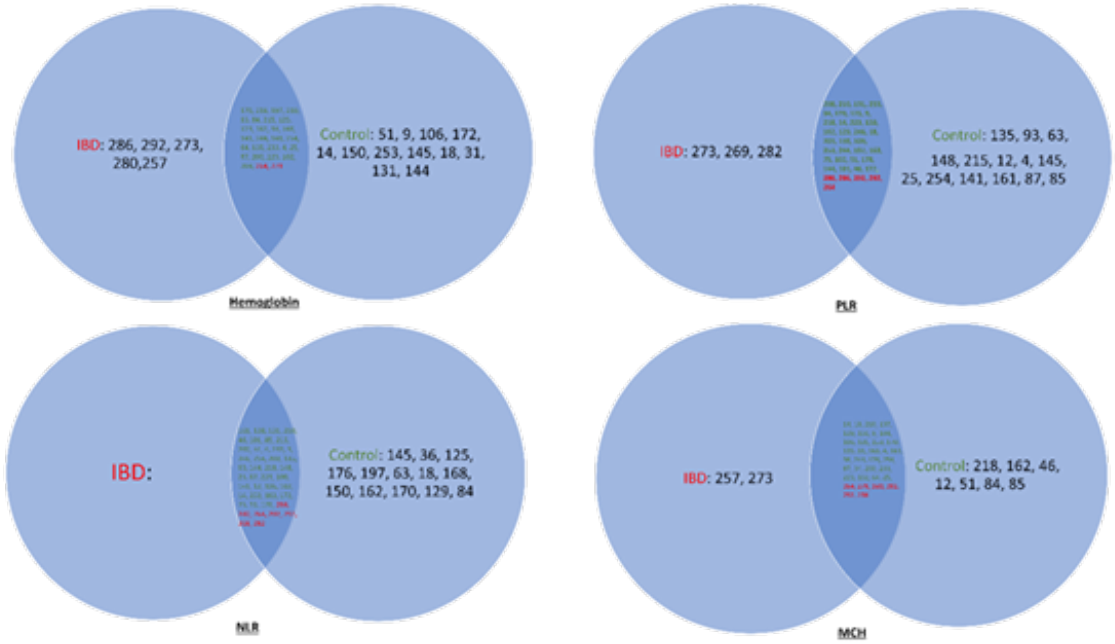

Figure 4. Venn diagrams containing the index number of each sample shared by each respective group

Table 2. Sensitivity, specificity and Youden's index for the combination of two variables for the CD, UC, and Control group

IBD vs Control	Sensitivity (CD)	Sensitivity (UC)	Specificity (CD)	Specificity (UC)	Youden's index (CD)	Youden's index (UC)
PLR + NLR	76	71.42	90.9	100	66.9	71.42
CRP + PLR	76	71.42	90.9	100	66.9	71.42
CRP + ESR	77.7	75	66.6	42.85	44.44	17.85
ESR + NLR	80.9	70.83	80	50	60.9	20.83
CRP + NLR	73.07	69.23	90	50	63.07	19.23
ESR + PLR	78.2	76.9	84.6	100	62.87	76.9
MCH + PLR	62	74.07	71.4	100	33.49	74.07
MCH + NLR	60	66.66	66.6	33.33	26.6	0
MCH + ESR	54.5	85.71	42.85	77.77	-2.59	63.49
MCH + CRP	56	77.27	45.45	62.5	1.45	39.77

DISCUSSION

An initial aim of our study was to identify IBD diagnostic biomarkers based on simple tests such as CBC, ESR, and CRP. Mann-Whitney analysis revealed a significant association between patients' CRP, NLR, and PLR, and CD. This lines with previous findings on higher CRP, NLR, and PLR.[27] Except for PLR, none of the aforementioned parameters was found significant in Mann-Whitney analysis in patients with UC (UC). This finding contradicts previous literature which had shown a consistent correlation between UC and NLR.[28] However, this could be attributed to a lack of distinction based on disease activity status, which has been previously found to associate with NLR, in our report.[17,24,33-35]

Based on the proposed methodology, variables with loading scores lower than 0.3 were excluded, and only CRP, ESR, NLR, PLR, and MCH were included in the regression analysis. Both ROC curves and Youden's index were utilized to determine the optimal cut-off for these variables. Significance, defined for as Youden's index higher than 0.5, was observed for NLR and PLR in CD patients when compared to controls (cut-off 2.73; sensitivity 75%; specificity 80%, and sensitivity 75%; cut-off 13.2; specificity 95%, respectively). Our findings demonstrated a cut-off closely similar to those produced by Feng et al.[26] Consistently, the specificity of PLR was superior to that of NLR while possessing similar or higher sensitivity.[26] Other studies in CD showed a possible correlation between NLR and CD patients' response to infliximab.36 In UC, unexpectedly, MCH was significant in ROC curve analysis (cut-off 29.5; sensitivity 80%; specificity 80%), but neither NLR nor PLR were. This association contradicts UC manifestations, such as bloody diarrhea and malabsorption, all of which cause reduction MCH and anemia.37 Moreover, it is worth mentioning that UC-related parameters were not compared to CRP/albumin ratio

due to lack of studies addressing its accuracy in the diagnosis but rather its accuracy in predicting the prognosis of the disease.

Our investigation also targeted the combination of the above-mentioned parameters and found a significant association between five different combinations and the risk of CD. These included PLR + NLR, CRP + PLR, CRP + NLR, ESR + NLR, and ESR + PLR. The highest sensitivity for CD was attributed to ESR + NLR, whereas higher specificity was found in PLR + NLR and CRP + PLR. Based on Youden's index, both NLR + PLR and CRP + PLR were the most beneficial combinations in diagnosing CD. However, it is worth mentioning that when not combined, PLR had the highest Youden's index.

Similar to CD, five different combinations were associated with the risk of UC. These included PLR + NLR, CRP + PLR, MCH + ESR, MCH + PLR, and ESR + PLR. The highest sensitivity for UC was attributed to MCH + ESR, whereas highest specificity (100%) was found for PLR + NLR, CRP + PLR, MCH + PLR, and ESR + PLR. Based on Youden's index, ESR + PLR was the most beneficial combination in diagnosing UC.

Implications to our study include the clinical application of immune cell ratios, inflammatory markers, and their different combinations along with patients' history and physical examination findings for easier, faster, and cost-effective diagnosis of IBDs. However, our findings must be interpreted with caution due to our small sample size, the lack of control for patients' comorbidities, and diet. Correspondingly, recommendations for future researchers include investigating immune cell ratios and inflammatory markers in the light of different confounding factors, in a longitudinal design, and with larger sample sizes included.

CONCLUSION

Following the completion of a regression analysis, it was determined that five distinct combinations contributed significantly to the accurate diagnosis of CD and UC. NLR+PLR and CRP+PLR were found to have the greatest Youden's index for CD, whereas ESR+PLR had the highest Youden's index for UC. The most beneficial combinations for CD were found to be CRP+PLR and NLR+PLR. Implications of our research include the clinical application of immune cell ratios, inflammatory markers, and their various combinations, in addition to the findings of patients' histories and physical examinations, for the purpose of making the diagnosis of inflammatory bowel diseases (IBDs) simpler, more efficient, and less costly.

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