

The evaluation of extraintestinal manifestations in children diagnosed with inflammatory bowel disease: A single-center experience

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ABSTRACT

Objective: We aimed to examine the relationship between the disease activity index rates at the time of diagnosis and the development of extraintestinal manifestations (EIMs) in children and adolescents with inflammatory bowel disease (IBD).

Material and Methods: Our study was conducted with 57 children and adolescent patients diagnosed with IBD between 2018 and 2022. The records of the patients were reviewed retrospectively. For the evaluation of IBD activity, Pediatric Crohn's Disease Activity Index and Pediatric Ulcerative Colitis Activity Index measurements were made.

Results: Fifty-seven patients with a diagnosis of IBD were included in the study. When the activity status of the disease was classified as mild, moderate, and severe, there were 11, 14, and 32 patients, respectively. The most common EIM was arthralgia, and it was shown to occur in 23 (40.4%) patients. The presence of EIM was analyzed in 2 (18.2%) patients in mild disease, in 5 (35.7%) patients in moderate disease, and in 17 (53.1%) patients in severe disease, and there was no significant difference between the groups ($p=0.110$). The area under curve value was found to be 0.623 in the receiver operating characteristic curve to detect the presence of EIM for ulcerative colitis patients ($p=0.242$). The ideal cutoff value was determined as 67.5, the sensitivity was calculated as 61.5%, and the specificity was calculated as 42.1%.

Conclusion: It was found that the presence of EIM at the time of diagnosis was more common in the presence of severe disease, but the result was not significant.

Keywords: Extraintestinal manifestations, inflammatory bowel disease, Crohn's disease, ulcerative colitis.

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INTRODUCTION

Today, it is known that the risk of inflammatory bowel disease (IBD) increases in the adolescent and childhood age groups.^[1] This group of diseases is known to be of multifactorial origin; it can occur in three different clinical forms such as Crohn's disease (CD), ulcerative colitis (UC), and unclassifiable colitis.^[1] The diagnosis of IBD is performed with a combination of symptoms, examination findings, laboratory tests, radiological imaging results, endoscopy, and histological findings.

In the literature, there are many activity indices developed to evaluate disease activity and response to treatment for use in clinical studies.^[2–5] The scoring of the Pediatric Crohn's Disease Activity Index (PCDAI) is divided into four main headings. This index has high reliability in the assessment of disease activity by the physician and is global.^[2] The Pediatric Ulcerative Colitis Activity Index (PUCAI) is a six-item non-invasive tool used to assess the severity of the disease.^[6]

Since IBD is a multisystemic disease, patients often also have extraintestinal manifestations (EIMs).^[6] In the pediatric age group, rates of EIMs at diagnosis (28%) are higher than in adults.^[7,8] It is known that EIMs are more common in CD than in UC and are generally correlated with disease activity.^[9] Although EIMs are known to be common in patients with pediatric-onset IBD, few studies have examined EIM rates and their association with other disease-related factors.^[10] Therefore, in our study, we aimed to examine the relationship between the disease activity index rates at the time of diagnosis and the development of EIM in children and adolescents with IBD.

MATERIAL AND METHODS

Our study was conducted with 57 children and adolescent patients diagnosed with IBD. The files of the patients who were followed up with the diagnosis of IBD between September 2017 and January 2021 were retrospectively reviewed and recorded between February 2021 and March 2021. The gender, age, albumin, iron and hemoglobin levels, neutrophil, lymphocyte, platelet count, erythrocyte sedimentation rate (ESR), and C-reactive protein values of the patients were noted. Endoscopy was performed in all patients to evaluate the upper gastrointestinal system findings for control purposes. Stomach and duodenal endoscopy findings and presence of *Helicobacter pylori* were investigated. All patients underwent colonoscopy, and the diagnosis of the disease was confirmed histopathologically. Patients whose diagnosis of IBD could not be confirmed pathologically (cytomegalovirus colitis and ileal ulcer due to non-steroidal anti-inflammatory use), patients whose activity index could not be evaluated clearly because of mental retardation, and patients whose EIM findings may be due to another systemic disease (arthritis associated with acute rheumatic fever patient) were excluded. Ethics committee approval was obtained for the study from our local ethics committee (meeting number: 75, date: January 27, 2021, approval number: 1291).

EIMs were recorded at the time of diagnosis and afterward. We included and defined the EIM as follows: joint manifestations (arthritis with objective signs of inflammation), eyes (uveitis or scleritis), and skin (erythema nodosum or pyoderma gangrenosum). Liver findings

(primary sclerosing cholangitis) and autoimmune hepatitis were not detected in any of the patients. All patients with EIM in the joints and eyes were followed up by a specialist physician (pediatric rheumatologist or an ophthalmologist). EIM symptoms that occur before the diagnosis of IBD are also called EIM.

For the evaluation of IBD activity, PCDAI,^[2] PUCAI,^[11] and ESR measurements were made. This PCDAI included (a) subjective reporting of the degree of abdominal pain, stool pattern, and general well-being; (b) presence of EIMs, such as fever, arthritis, rash, and uveitis; (c) physical examination findings; (d) weight and height; and (e) hematocrit, ESR, and serum albumin. PUCAI is a non-invasive tool for the assessment of UC disease severity consisting of six clinical items: daily abdominal pain, rectal bleeding, stool consistency, number of stools, nocturnal stools, and activity level for a maximum score of 85. PCDAI scores were classified as 0–10 score means remission, the scores of 11–29 is mild, the scores of 30–39 is moderate, and ≥ 40 score is severe disease. PUCAI scores of 0–9 were classified as remission, scores of 10–34 as mild, scores between 35 and 64 as moderate, and scores ≥ 65 as severe.

Statistical analysis of the study is the normal distribution of variables was examined using Kolmogorov–Smirnov tests. χ^2 and Fisher's tests were used to compare categorical variables (used noun and %). Student's t-tests were used to compare normally distributed (used mean \pm standard deviation) continuous variables, and Mann–Whitney U tests were used to compare variables that were not normally distributed (used median [minimum–maximum]). Receiver operating characteristic (ROC) curve analysis was performed to determine the cutoff values of SUVmax for predicting clinical parameters. The area under the ROC curve (AUC) is presented as a measure of discrimination. In determining the optimal cutoff values, the Youden index was used. Data record and statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) software (version 17, SPSS, Inc., Chicago, IL). $p < 0.05$ was considered statistically significant.

RESULTS

Fifty-seven patients with a diagnosis of IBD were included in the study. The mean age at which they were diagnosed was 153 ± 51 months. When the activity status of the disease was classified as mild, moderate, and severe, there were 11, 14, and 32 patients, respectively. Of the patients, 32 (56.1%) were male and 25 (43.9%) were female. Fifty-two (92.1%) patients were Turkish. There were UC in 32 (56.1%) patients and CH in 25 (43.9%) patients. The most common EIM was arthralgia, and it was shown to occur in 23 (40.4%) patients. Arthritis was seen in 1 (1.8%) patient, oral aphtha in 5 (8.8%) patients, and erythema nodosum in 1 (1.8%) patient. EIM was analyzed in a total of 24 (42.1%) patients. Eighteen (75%) patients had a single EIM and 6 (25%) had two EIMs at the same time. The mean PCDAI score in CD patients was 38.0 ± 15.9 , and the mean PUCAI score in UC patients was 62.5 ± 18.9 . Eight (32.0%) CD patients had mild disease activity, 4 (16.0%) had moderate disease activity, and 13 (52.0%) patients had severe disease activity. In UC patients, 3 (9.4%) patients had mild, 10 (31.3%) moderate, and 19 (59.4%) severe activity values.

The clinical and demographic characteristics according to the severity of the disease are given in Table 1. Considering the se-

Table 1: Clinical and demographic characteristics according to the severity of the disease

	Mild (n=11)	Moderate (n=14)	Severe (n=32)	p
Gender, n (%)			16 (50.0)	0.422
Male	8 (72.7)	8 (57.1)		
Female	3 (27.3)	6 (42.9)	16 (50.0)	
Ethnic, n (%)				0.448
Turkish	11 (100)	12 (85.7)	29 (90.6)	
Others	–	2 (14.3)	3 (9.4)	
Type of disease, n (%)				0.075
UC	3 (27.3)	10 (71.4)	19 (59.4)	
CD	8 (72.7)	4 (28.6)	13 (40.6)	
Age, month; mean±SD	159±43	181±29	140±57	0.039
Albumin, mean±SD	4.0±0.7	3.8±0.8	3.4±0.6	0.044
Vitamin B12, mean±SD	309±140	241±146	301±186	0.490
Iron, mean±SD	58±49	53±40	52±62	0.949
Hemoglobin, mean±SD	13.1±1.7	12.0±2.8	10.9±2.3	0.035
MCV, mean±SD	78±6	77±8	73±10	0.318
Platelet, mean±SD	337±182	363±122	384±142	0.636
MPV, mean±SD	8.7±1.4	8.5±1.2	8.1±1.3	0.353
Neutrophil, mean±SD	5909±2834	5400±2245	4969±2453	0.542
Lymphocyte, mean±SD	2127±631	2328±1223	2608±1393	0.504
NLR, mean±SD	2.9±1.3	2.8±1.8	2.4±2.1	0.689
Sedimentation, mean±SD	9.1±8.2	16.9±19.3	16.4±19.8	0.479
CRP, mean±SD	12.0±24.9	13.3±37.5	20.5±33.8	0.684
Calprotectin, mean±SD	642±824	1065±803	1335±677	0.088
Pathology at upper GIS, n (%)	7 (63.6)	10 (71.4)	25 (78.1)	0.150
Presence of helicobacter, n (%)	3 (27.3)	4 (28.6)	11 (34.4)	0.506
Additional illness				
EIM, n (%)	2 (18.2)	5 (35.7)	17 (53.1)	0.110

UC: Ulcerative colitis; CD: Crohn's disease; SD: Standard deviation; MCV: Mean corpuscular volume; MPV: Mean platelet volume; NLR: Neutrophils lymphocytes ratio; CRP: C-reactive protein; EIM: Extraintestinal manifestation.

verity of the disease, there was no significant difference between the groups in terms of gender ($p=0.422$). Although the potential for severe disease in UC patients was higher than in CD patients, no significant difference was analyzed between the groups ($p=0.075$). Severe disease was calculated to be more common in younger patients ($p=0.003$). It was shown that hemoglobin values decreased as the severity of the disease increased (13.1±1.7 for mild, 12.0±2.8 for moderate, and 10.9±2.3 for severe disease; $p=0.035$). The presence of EIM was analyzed in 2 (18.2%) patients in mild disease, in 5 (35.7%) patients in moderate disease, and in 17 (53.1%) patients in severe disease, and there was no significant difference between the groups ($p=0.110$).

The demographic data and disease activity status according to the presence of EIM are given in Table 2. It was shown that there

was no difference between patients with and without EIM in terms of gender ($p=0.054$) and disease type ($p=0.505$). It was shown that there was no difference between age and hemoglobin values in patients with and without EIM. The incidence of upper gastrointestinal tract findings on endoscopy was similar between patients with and without EIM ($p=0.725$).

The AUC value was found to be 0.623 in the ROC curve to detect the presence of EIM for UC patients ($p=0.242$) (Fig. 1a). The ideal cutoff value was determined as 67.5, the sensitivity was calculated as 61.5%, and the specificity was calculated as 42.1%. ROC curve analysis found an AUC value of 0.708 to detect the presence of EIM in CD patients ($p=0.080$) (Fig. 1b). The ideal cut-off value was found to be 32.5, the sensitivity was 90.9%, and the specificity was 57.1%.

Table 2: Demographic data and disease activity status according to the presence of EIM

	No EIM (n=33)	EIM positive (n=24)	p
Gender, n (%)			0.054
Male	22 (66.7)	10 (41.7)	
Female	11 (33.3)	14 (58.3)	
Ethnic, n (%)			0.920
Turkish	30 (90.9)	22 (91.7)	
Others	3 (9.1)	2 (8.3)	
Type of disease, n (%)			0.505
UC	19 (57.6)	13 (54.2)	
CD	14 (42.4)	11 (45.8)	
Age, month; mean±SD	161±42	143±60	0.205
Albumin, mean±SD	3.8±0.6	3.5±0.8	0.135
Vitamin B12, mean±SD	260±147	326±191	0.150
Iron, mean±SD	63±62	41±39	0.142
Hemoglobin, mean±SD	12.1±2.5	10.9±2.3	0.081
MCV, mean±SD	77±9	72±9	0.082
Platelet, mean±SD	333±143	421±134	0.023
MPV, mean±SD	8.6±1.3	7.9±1.3	0.073
Neutrophil, mean±SD	5682±2795	4671±1816	0.127
Lymphocyte, mean±SD	2339±1063	2594±1455	0.448
NLR, mean±SD	2.9±2.2	2.2±1.4	0.165
Sedimentation, mean±SD	9.2±8.6	22.3±23.3	0.008
CRP, mean±SD	10.2±22.8	25.7±41.5	0.085
Calprotectin, mean±SD	1086±794	1269±708	0.441
Pathology at upper GIS, n (%)	23 (69.7)	19 (79.2)	0.725
Presence of Helicobacter, n (%)	6 (18.2)	12 (50.0)	0.038
Additional illness			0.110
Severity of activity, n (%)			
Mild	9 (27.3)	2 (8.3)	
Moderate	9 (27.3)	5 (20.8)	
Severe	15 (45.5)	17 (70.8)	

UC: Ulcerative colitis; CD: Crohn's disease; SD: Standard deviation; MCV: Mean corpuscular volume; MPV: Mean platelet volume; NLR: Neutrophils lymphocytes ratio; CRP: C-reactive protein; EIM: Extraintestinal manifestation.

DISCUSSION

In our study, it was determined that the presence of EIM at the time of diagnosis did not show a significant relationship with the severity of the disease. In children with IBD, the incidence of EIM is higher in patients with CD than in UC (59–73% vs. 24–32%).^[12,13] The mean age at diagnosis was around 11.6±3.1 years, and it was more common in males (57.5%).^[14] In our cohort, there were UC in 32 (56.1%)

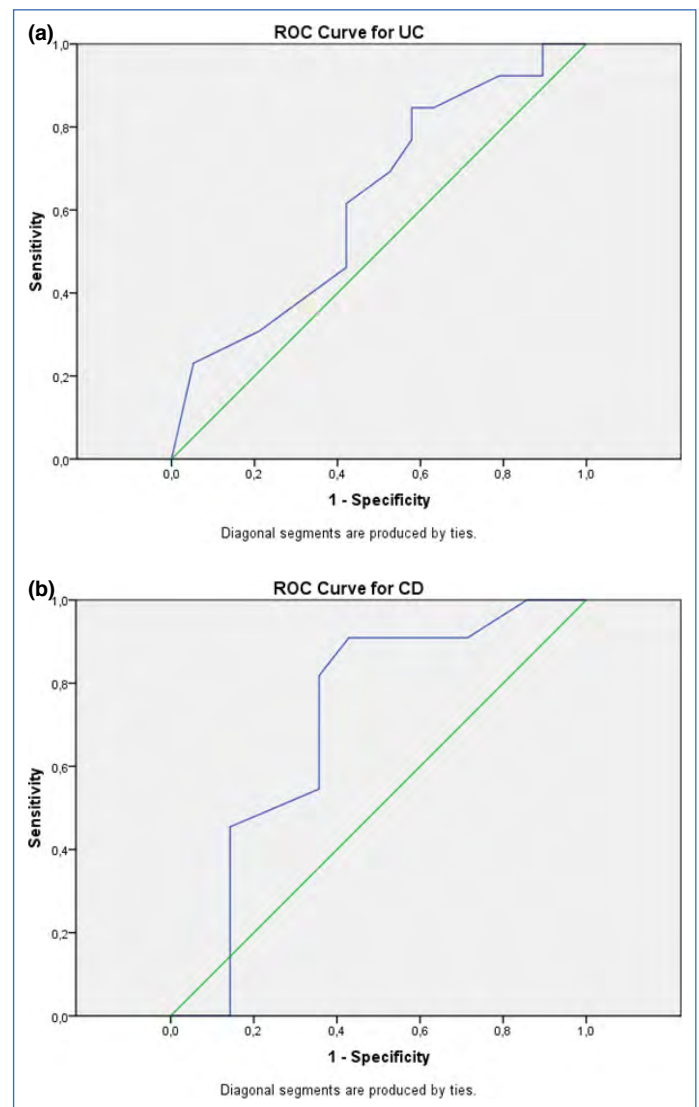


Figure 1: Disease activity index value in patients with ulcerative colitis (a) and Crohn's disease (b) was evaluated by receiver operating characteristic analysis to assess the extraintestinal manifestations.

patients and CD in 25 (43.9%) patients. The mean age at which the patients were diagnosed was 153±51 months. In our study, of the patients, 32 (56.1%) were male and 25 (43.9%) were female.

The incidence of EIM in IBD patients is around 11–28%.^[6,10,13] EIMs are more common in women than men.^[15] CD (14–24%) patients have more EIM than UC (11–22%) patients.^[6,10,13,14] EIM was found to be 23.5% at diagnosis and 29.8% during follow-up in pediatric IBD patients.^[16] In our study, the incidence of EIM was found to be 42.1% at the time of diagnosis. In our study, the incidence of EIM was found to be higher than in the literature. We think that this may be due to racial differences or the low level of education of the patients. In IBD patients presenting with a single EIM is 60–66% percentage of the patients, the occurrence of two EIMs in patients is 24–28% of the cases, and the occurrence of three EIMs in patients is 9–12% of the cases.^[17] In our study, 75% of patients had a single EIM and 25% had two EIMs at the same time. This finding was

found at similar rates with the literature. The reason for the slightly higher rate of single EIM may be that the EIM findings at the time of diagnosis were evaluated. It was found to be the most common EIM joint finding (arthritis) in IBD patients (12–21%).^[6,10,12,13,16,17] In a study designed by Rahmani et al.^[12] in CD and UC patient groups, the incidence of EIM related with joint was found to be 21.2% and 12.5%, respectively. Oral aphtha was seen in 15% of CD patients, but not in UC patients.^[12] The incidence of erythema nodosum in CD and UC patients was between 6% and 0%.^[12] In our study group, arthralgia was detected in 40.4%, arthritis 1.8%, oral aphthae 8.8%, and erythema nodosum 1.8%. Gallstones, primary sclerosing cholangitis, and uveitis were not detected in any of the patients.

The mean values of PCDAI and PUCAI were found to be between 43–60 and 35–50 in CD and UC patients, and these values were found to decrease significantly with treatment.^[12,18] 12.1% of CD patients were found to be mild, 21.2% moderate, and 66.6% severe.^[1] Totally 37.5% of the UC patients were found in the mildly active group, 60.0% of the UC patients were in moderately active group, and 2.5% of them were in severely active group.^[12] Esophagitis was 57.5% and 22.5%, gastritis 72.7% and 37.5%, and duodenitis findings 27.2% and 7.5% in CD and UC patients, respectively.^[12] Ulcers were found in 15.1% in CD and 12.5% in UC patients.^[12] In our cohort, the mean PCDAI score in CD patients was 38.0±15.9, and the mean PUCAI score in UC patients was 62.5±18.9. Eight (32.0%) CD patients had mild disease activity, 4 (16.0%) had moderate disease activity, and 13 (52.0%) patients had severe disease activity. In UC patients, 3 (9.4%) patients had mild, 10 (31.3%) moderate, and 19 (59.4%) severe activity values. As a result of endoscopic evaluation, finding in the upper gastrointestinal tract was detected in 23 (69.7%) patients in the group without EIM, while it was detected in 19 (79.2%) patients in the group with EIM ($p=0.725$).

There are studies evaluating EIM and disease activity in the literature. Some of the extraintestinal manifestations (i.e., erythema nodosum, peripheral arthritis, and orofacial lesions) were clearly associated with bowel disease activity.^[19] In other studies, there was consistency between the recurrence of IBD and the presence/absence of EIM at follow-up.^[14,20,21] Jansson et al.^[20] found that UC patients with EIMs are non-responsive to steroid regimens and need biological agents for the treatment, and CD patients with EIM are at increased risk of requiring escalation of therapy due to uncontrolled disease activity compared with those without. However, contrary to these findings, PUCAI and PCDAI scores at diagnosis did not differ significantly between EIM-positive and EIM-negative patients.^[10] Regression analysis also revealed no significant relationship between the development of EIM and PUCAI.^[10] Yu et al.^[6] found a relationship between the severity of the disease at diagnosis and the development of EIM. In one study, the presence of severe disease at baseline was associated with any EIM ($p<0.001$), arthralgia ($p=0.024$), aphthous stomatitis ($p=0.001$), and erythema nodosum ($p=0.009$).^[14] In our study, the presence of EIM at the time of diagnosis was analyzed in 2 (18.2%) patients in mild disease, in 5 (35.7%) patients in moderate disease, and in 17 (53.1%) patients in severe disease, and there was no significant difference between the groups ($p=0.110$). Cutoff PCDAI and PUCAI scores were evaluated to detect the presence of EIM at the time of diagnosis. The

ideal cutoff PUCAI value was determined as 67.5, the sensitivity was calculated as 61.5%, and the specificity was calculated as 42.1%. The ideal cutoff PCDAI value was found to be 32.5, the sensitivity was 90.9%, and the specificity was 57.1%. The specificity and sensitivity of PCDAI to detect EIM are probably higher than PUCAI because it also includes laboratory parameters.

Limitations

Our study has some shortcomings. First, the retrospective nature of the study may cause some recall difficulties and bias. In spite of these restrictions, the demographic characteristics of the two groups were similar. Second, the small size of the sample group is also a limitation.

CONCLUSION

In conclusion, it was found that the presence of EIM at the time of diagnosis was more common in the presence of severe disease, but the result was not significant. The subject should continue to be investigated with larger number of patients and prospective studies.

Statement

Ethics Committee Approval: The Adana City Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 27.01.2021, number: 1291).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – DGT, AG; Design – DGT, AG; Supervision – DGT, AG; Resource – DGT, AG; Materials – DGT, AG; Data Collection and/or Processing – DGT, AG; Analysis and/or Interpretation – DGT; Literature Search – DGT; Writing – AG; Critical Reviews – DGT, AG.

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