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Diagnostic Values of Blood and Serum Markers for Active Disease in Children with Ulcerative Colitis

Ülseratif Kolitli Çocuklarda Kanve Serum Belirteçlerinin Aktif Hastalık İçin Tanısal Değerleri

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Abstract

Background: Ulcerative colitis is a chronic inflammatory bowel disease characterized by colonic mucosal ulceration. The search for noninvasive tests can reduce the use of endoscopy in the diagnosis and treatment monitoring of ulcerative colitis is ongoing. This study aimed to find noninvasive biomarkers for endoscopically diagnosed ulcerative colitis that adequately reflect histologic disease activity.

Materials and Methods: This study is based on the retrospective comparison of the data of pediatric patients between the ages of 0-18 years who were followed up with a diagnosis of ulcerative colitis and healthy children who were constituted the control group. Pre- and post-treatment values of these parameters in the patient group and control group parameters were compared separately.

Results: The present study was conducted with a total of 72 children, including 36 ulcerative colitis and 36 healthy controls. Following a comparative analysis of four parameters (ESR, CRP, MCV, and albumin) were identified as exhibiting similar characteristics across the high and low levels. The logistic regression analysis of these parameters revealed that ESR and CRP were associated with a high ulcerative colitis diagnosis, while MCV and albumin were associated with a low diagnosis. In the ROC analysis, whereas 8.5 mm/h for ESR and 1.89 mg/L for CRP were found as cut-off values.

Conclusions: In cases where there is suspicion of inflammatory bowel disease, it would be appropriate to refer patients to procedures involving simple blood tests. This approach is preferable to reaching a diagnosis with costly, difficult-to-access noninvasive tests or invasive procedures. The presence of ESR and CRP elevation, as well as low levels of MCV and albumin, can serve as a triage tool.

Keywords: Biomarker, cut-off value, inflammatory bowel disease, noninvasive test, ulcerative colitis.

ÖZ

Amaç: Ülseratif kolit, kolonik mukozal ülserasyon ile karakterize kronik bir inflamatuvar bağırsak hastalığıdır. Ülseratif kolit tanı ve tedavi izleminde endoskopi kullanımını azaltabilecek testlerin arayışı devam etmektedir. Bu çalışmanın amacı, endoskopi yoluyla teşhis edilen ülseratif kolit için, histolojik hastalık aktivitesini yeterince yansıtan noninvazif biyobelirteçler bulmaktır.

Gereç ve Yöntem: Bu çalışma ülseratif kolit tanısı alarak izlenen, 0-18 yaş arasındaki çocuk hastalar ile; sağlıklı olarak izlenen çocukların kontrol grubunu oluşturup retrospektif olarak verilerinin karşılaştırılması esasına dayanır. Bu parametrelerden kontrol grubu ile hasta grubunun tedavi öncesi ve sonrası değerleri ayrı ayrı karşılaştırıldı.

Bulgular: Çalışma 36 ülseratif kolit hastası ve 36 sağlıklı olmak üzere 72 çocuk ile gerçekleştirilmiştir. Sonuçlarımızda yüksekliği ve düşüklüğü ile benzer özellikte, anlamlı ortak dört parametre bulundu (ESR, CRP, MCV ve albümin). Bu parametrelerin lojistik regresyon analizinde ESR ve CRP yüksekliği ile; MCV ve albümin ise düşüklüğü ile ülseratif kolit tanısında ayrı ayrı bağımsız birer risk olduğu saptandı. ROC analizinde ESR için 8.5 mm/h ve CRP için 1.89 mg/L sınır değerler olarak bulundu.

Sonuç: Çalışma sonuçlarımıza göre inflamatuvar bağırsak hastalığı şüphesi varlığında yüksek maliyetli, zor ulaşılabilen noninvazif testlerle ya da invazif işlemlerle tanıya ulaşmak yerine, kolay, ucuz ve ulaşılabilir olan basit kan testleriyle hastayı bu işlemlere yönlendirmenin uygun olacağı; ESR ile CRP yüksekliği ve MCV ile albümin düşüklüğünün tamamı ya da birinin varlığını bir triyaj aracı olarak kullanıp hastayı histolojik tanıya yönlendirmenin uygun olacağı kanaatindeyiz.

Anahtar kelimeler: Biyobelirteç, inflamatuvar bağırsak hastalığı, noninvaziv test, sınır değer, ülseratif kolit.

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Highlights

- Pediatric patients with ulcerative colitis and healthy children were analyzed comparatively.
- Biomarkers that may reflect the histologic diagnosis of ulcerative colitis were investigated.
- Cut-off value research was conducted for the biomarkers found.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by colonic mucosal ulceration and bloody diarrhea during relapses. The prevalence of IBD is increasing in both adult and pediatric populations, and this increase parallels industrialization (1). The etiology of IBD appears to be associated with changes in the environment and diet that can lead to alterations in the microbiota, which, in genetically susceptible individuals, result in the development of IBD (2). The symptoms associated with UC are typically mild and clinically difficult to distinguish from functional disorders such as irritable bowel syndrome (IBS), in which diarrhea predominates. The manifestation of both conditions may include altered bowel habits and abdominal pain. The absence of specific biomarkers further complicates diagnosis, as it often leads to prolonged diagnostic delays (3). Early diagnosis is therefore paramount in UC patients, as it can prevent long-term complications, including delayed puberty, nutritional and growth retardation, inadequate response to treatment, and the need for surgery.

The diagnosis of ulcerative colitis is determined through a series of evaluations, including invasive procedures such as colonoscopy. There is no gold standard diagnosis for UC. In recent years, there has been an ongoing search for noninvasive tests, such as blood-stool markers and ultrasonography, which could reduce the use of endoscopy in UC diagnosis and treatment monitoring. The rationale behind this is twofold: first, the procedure is invasive, and second, it is performed under general anesthesia. Consequently, the development of noninvasive tests for UC can assist clinicians in addressing this diagnostic challenge. These tests can function as a triage tool, safely ruling out existing UC and directing patients for further investigations (4).Currently, fecal calprotectin (FCal) and C-reactive protein (CRP) are most widely used biomarkers; however, they lack specificity for UC because they are present in high concentrations in a wide range of inflammatory diseases of the lower gastrointestinal tract (5-7). FCal plays a crucial role in differentiating between IBD and IBS but CRP can't do that either. Circulating microRNAs and exosomes have shown promise in monitoring disease activity and predicting exacerbations without requiring invasive procedures. Receptor inhibitors such as Janus kinases, interleukin 23 and Smad7, and fatty acid modulators are under investigation and have the potential for clinical efficacy. But the use of none of them is widespread and clear (8).

The utilization of specific laboratory parameters has the potential to facilitate the diagnosis of CUC, particularly in cases where children present with symptoms of severe disease, such as rectal bleeding, weight loss, abdominal tenderness, or milder symptoms, including occasional abdominal discomfort and intermittent episodes of loose stools. However, a comprehensive evaluation of the diagnostic accuracy of the disease when combining all symptoms and noninvasive tests other than FFCal is currently unavailable. Furthermore, the optimal combination of tests or the superiority or cut-off value of a single test over other tests has rarely or never been examined. Consequently, the objective of this study was to identify cost-effective, readily accessible, noninvasive biomarkers for UC diagnosed by endoscopy in children presenting with diverse gastrointestinal symptoms that accurately reflect histologic disease activity. The objective of this study was twofold: first, to determine the association of UC with the single or combined use of these biomarkers, and second, to provide cut-off values for disease prediction with these biomarkers.

Material and Methods

Study design

The present study was based on a comparison of pediatric patients between 0-18 years of age who were followed up with a diagnosis of Ulcerative Colitis (UC) in the Department of Pediatric Gastroenterology of Selçuk University Faculty of Medicine with healthy children who were followed up in the same period by the Department of Pediatric Infectious Diseases as the control group. The control group comprised children between the ages of 0-18 years, whose treatment was completed due to upper respiratory tract infection, who had the necessary data for the study after treatment, and who were determined after simple random selection in order to ensure numerical homogenization between the groups. The data of both groups was retrospectively recorded and

analyzed in the hospital automation system.

The patient group consisted of 36 patients with newly diagnosed UC between September 2012 and July 2020. The diagnosis was made in accordance with the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition guidelines, incorporating both endoscopic and histological criteria. Patients with Crohn's disease and indeterminate colitis were excluded from the study. Disease activity was calculated according to the Pediatric Ulcerative Colitis Index (PUCAI) and graded as remission (<10 points), mild or inactive (<35 points), moderate (35-64 points), or severe (>64 points) (9). Patients were not receiving treatment at the time of diagnosis and sampling for tests. The control group consisted of 36 healthy children with excluded gastrointestinal inflammatory disease.

The demographic and clinical characteristics of the study participants, including their age, gender, and PUCAI scores, were documented. Additionally, the following laboratory parameters were recorded: Erythrocyte sedimentation rate (ESR), CRP, mean corpuscular volume (MCV), hemoglobin (Hb), leukocyte (WBC), and platelet counts from venous blood, as well as mean corpuscular volume (MCV), hemoglobin (Hb), leukocyte (WBC), and platelet counts from complete blood count components. Neutrophil, lymphocyte, eosinophil, basophil, monocyte counts and ratios, red blood cell distribution width (RDW), RDW to platelet ratio (RPR), and albumin values were recorded.

Statistical analysis

The data obtained in the study were subjected to descriptive statistics, which included the calculation of the mean and standard deviation. The distribution of the data was then examined to determine its conformity to the normal distribution using the Kolmogorov-Smirnov test. The results indicated that the data did not conform to a normal distribution ($p < 0.05$). Following this observation, the Mann-Whitney U test and Wilcox test were employed to conduct a comparative analysis between the patient and control groups. The chi-square test was employed to compare categorical data. For the study, $p<0.05$ was considered statistically significant. All statistical analyses were conducted using the SPSS 25.0 program (SPSS Inc., Chicago, IL, USA).

Ethical Approval

This study approval was obtained from the Selçuk University Faculty of Medicine, Ethics Committee (number: 2020/318. date: 27.07.2020). The data of both groups was retrospectively recorded and analyzed in the hospital automation system. This study was conducted retrospectively. Therefore, no consent form was obtained. All procedures were carried out in accordance with the Declaration of Helsinki.

Results

The present study was conducted with a total of 72 children, including 36 patients with UC who met the exclusion criteria and 36 participants who served as the control group. The mean age of the study population was 13.16 years (range 4/16 years for the control group and 7/17 years for the patient group) and included 28 boys (15 patients/13 controls) and 44 girls (21 patients/23 controls). The study's findings were derived from a comparative analysis of the medical records of the control group with the patient group's data at the time of diagnosis and the patient group's post-treatment data. The statistical analysis revealed that factors such as age (p=0.001), PUCAI (p=0.001), ESR (p=0.001), CRP (p=0.001), WBC count (p=0.007), neutrophil count (p=0.001), and percentage (p=0.001), platelet count (p=0.001), monocyte count (p=0.001), RDW (p=0.001), neutrophil/lymphocyte ratio (NLR) (p=0.001) and platelet/lymphocyte ratio (PLR) (p=0.001) were significantly higher in the patient group, while MCV (p=0.001), Hb (p=0.001), lymphocyte count (p=0.008) and ratio (p=0.001), lymphocyte/monocyte ratio (LMR) (p=0.001) and albumin value (p=0.001) were significantly lower in the patient group compared to the control group (Table 1).

A comparative analysis of the post-treatment data from the patient group and the control group revealed that the levels of CRP (p=0.026), neutrophil count (p=0.012), and percentage (p=0.001), platelet count (p=0.041), monocyte count (p=0.001), RDW (p=0.001), and NLR (p=0.001). Conversely, the patient group exhibited significantly elevated CRP (p=0.026), neutrophil count (p=0.012), percentage (p=0.001), platelet count (p=0.041), monocyte count (p=0.001), RDW (p=0.001), NLR (p=0.001), and PLR (p=0.001) ratios, while Hb (p=0.001), lymphocyte count (p=0.006), and ratio (p=0.001), LMR ratio (p=0.001), and albumin value (p=0.001) were significantly lower in the patient group after treatment **(Table 1)**.

A comparative analysis of the patient group's data at the time of diagnosis and the post-treatment data set revealed that ESR (p=0.001), CRP (p=0.001), and eosinophil percentage (p=0.046) exhibited significant increases, while MCV

(p=0.039) and albumin value (p=0.001) demonstrated significant decreases **(Table 1)**.
After the comparison of three different data sets, four parameters (ESR, CRP, MCV, and albumin) were found to be statistically significant with similar characteristics of high and low levels. Logistic regression analysis of these parameters revealed that ESR (Odds 1.148 and p=0.023) and CRP (Odds 1.632 and p=0.041) were significantly independent risk factors for UC diagnosis with high levels, while MCV (Odds 0.891 and p=0.018) and albumin (Odds 0.022 and p=0.001) were significantly independent risk factors for UC diagnosis with low levels **(Table 2)**. According to ROC analysis; ESR>8.5 mm/h cut-off value with 72.2% sensitivity and 27.8% specificity (p= 0.001; AUC 0.807); CRP>1.89 mg/L cut-off value with 69.4% sensitivity and 30.6% specificity (p= 0.001; AUC 0.764) support the diagnosis of UC. According to these results, no cut-off value could be determined for albumin and MCV because AUC<0.5 **(Table 2, Figure 1)**.

Table 1. Comparison of the values of the patient group pre-post treatment and the control group.

Variables	A	B	C	*A / B p*	*A / C p*	*B / C p*
Age, (years)	10.64 ± 3.97	14.28 ± 2.75	14.58 ± 2.78	0.001	0.001	0.002
Gender, (%) (Boy/Girl)	13 (36.1) / 23 (63.9)	15 (41.7) / 21 (58.3)	15 (41.7) / 21 58.3)	0.765		
PUCAI Score				0.001		
Remission (<10)	36(100)		35(97.2)			
Mild activity (10 – 34)		5(13.9)	1(2.8)			
Moderate activity (35 – 64)		22(61.1)				
Severe activity (65 – 85)		9(25)				
ESR	6.67 ± 5.11 (2-17)	28.25 ± 27.8 (2-111)	9.28 ± 8.28 (2-44)	0.001	0.134	0.001
CRP	1.67 ± 1.32 (0.60-5.99)	28.87 ± 47.67 (0.20-165)	2.72 ± 3.64 (0.11-23)	0.001	0.026	0.001
MCV	82.54±6.27 (58-92.2)	74.95 ± 8.50 (60-92)	80.13±10.45 (62-108)	0.001	0.111	0.039
Hb	13.4±1.18 (10.7-16)	10.95 ± 2.52 (5.8-14.8)	11.8±2.05 (7.5-14.9)	0.001	0.001	0.232
WBC	7.07 ± 2.06 (2.8-12.2)	9.72 ± 5.29 (1.90-31)	8.08±4.0 (1.6-24.4)	0.007	0.322	0.093
Neutrophile (%)	51.53 ± 10.24 (30.2-71)	64.02 ± 11.16 (44-84)	62.38-13.37 (30-85.1)	0.001	0.001	0.857
Lymphocyte (%)	37.74 ± 9.61 (21-57.7)	23.73 ± 9.05 (6.30-43)	27.46 ± 11.69 (9.8-59)	0.001	0.001	0.238
Eosinophils (%)	2.43 ± 2.36 (0.30-10.90)	3.04-2.98 (0-12.30)	1.81-1.61 (0-6.79)	0.562	0.169	0.046
Basophile (%)	0.38±0.27 (0-1.10)	0.43±0.34 (0-2.10)	0.54±0.72 (0.10-4.5)	0.444	0.257	0.312
Monocyte (%)	7.52 ± 1.66 (4-11.8)	8.06 ± 3.21 (0.90-15.9)	7.45 ± 2.44 (4.06-16.0)	0.608	0.414	0.338
Platelet ($\times10^{-3}$)	305.67 ± 66.17 (176-453)	396.58 ± 120.35 (113-709)	364.03 ± 110.361 (189-625)	0.001	0.041	0.056
Neutrophile count	3.75 ± 1.56 (0.90-8)	6.78±4.55 (2.20-25)	5.34 ± 3.51 (1.60-20.8)	0.001	0.012	0.144
Lymphocyte count	2.61 ± 0.89 (1.10-4.80)	2.11±0.74 (0.70-4.0)	2.10 ± 1.04 (0.98-6.47)	0.008	0.006	0.184
Monocyte count	391.39 ± 258.52 (50-1000)	781.6 ± 563.99 (88-2600)	745.56 ± 951.12 (200-6100)	0.001	0.001	0.160
Eosinophils count	132.5 ± 173.44 (0-700)	209±271.13 (0-1310)	176.94 ± 338.8 (0-2000)	0.225	0.544	0.112
Basophile count	202.78 ± 277.16 (0-990)	30.42 ± 43.10 (0-200)	35.03 ± 67.86 (0-400)	0.092	0.213	0.939
RDW	13.51 ± 1.09 (11.9-17.2)	16.55 ± 4.45 (12.6-32)	16.74 ± 3.62 (12.2-25.6)	0.001	0.001	0.604
NLR	1.57 ± 0.73 (0.56-3.32)	3.72 ± 3.09 (1.06-14.14)	2.93 ± 1.88 (0.51-8.67)	0.001	0.001	0.481
LMR	12.15 ± 12.33 (2.7-47)	4.41 ± 5.17 (0.59-28.07)	3.7 ± 1.87 (0.49-8.94)	0.001	0.001	0.540
PLR	129.41 ± 55.03 (53.48-329.09)	219.77 ±128.21 (59.47-665.71)	200.43 ± 82.95 (67.08-373.15)	0.001	0.001	0.925
Albumin	4.24 ± 0.43 (3.5-5.20)	3.22 ± 0.77 (1.5-4.6)	3.92 ± 0.43 (3.10-4.60)	0.001	0.010	0.001
RPR ($\times10^{6}$)	6.67 ± 5.12 (2-17)	28.25 ± 27.29 (2-111)	9.28 ± 8.28 (2-44)	0.253	0.648	0.090

Abbreviations: **A**-Control group mean±sd (min-max); **B**-Patient pretreatment mean±sd (min-max); **C**-Patient posttreatment mean±sd, (min-max); CRP:C-Reaktive Protein; ESR: Erythrocyte Sedimentation Rate; Hb:Haemoglobin; LMR:Lymphocyte Monocyte Ratio; MCV:Mean Corpuscular Volume; NLR:Neutrophile Lymphocyte Ratio; PUCAI: Pediatric Ulcerative Colitis Activity Index; RDW:Red Cell Distribution Width; PLR: Platelet Lymphocyte Ratio; RPR: RDW Platelet Ratio; WBC: White Blood Cell)

Table 2. LRA and ROC analysis of four common parameters.

	LRA		ROC			
	Odds ratio	**p**	**Area**	**p**	**Sensitivity**	**Specificity**
ESR	1.148	0.023	0.807	0.001	0.722	0.278
CRP	1.632	0.041	0.764	0.001	0.694	0.306
MCV	0.891	0.018	0.230	0.001	-	-
Albumin	0.022	0.001	0.105	0.001	-	-

Abbreviations: CRP:C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; LRA:Logistic regression analysis; MCV: Mean Corpuscular Volume; ROC: Receiver Operating Characteristic)

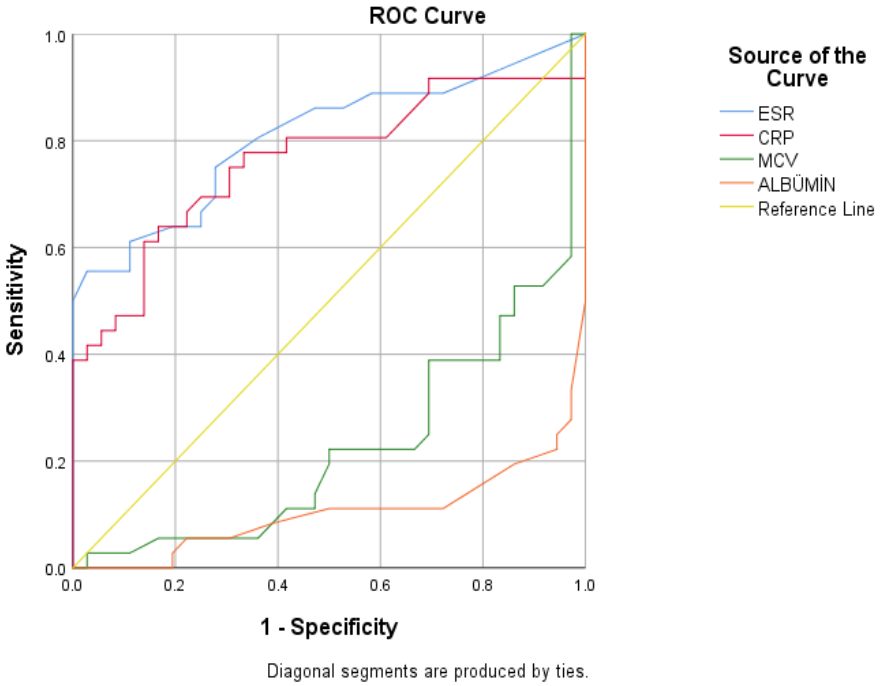

Figure 1. ROC curve analysis of four common parameters

Discussion

Mucosal healing is associated with long-term clinical remission following treatment and has been shown to improve long-term prognosis by reducing the risk of hospitalization and surgical intervention (10). Mucosal healing is identified through endoscopic procedures; however, colonoscopy is a highly invasive examination, and frequent examinations are challenging due to their significant medical cost. Consequently, there is a clinical need for noninvasive, cost-effective diagnostic tools for mucosal healing using biomarkers that are useful in the diagnosis, treatment, and monitoring of UC. This is particularly salient in the pediatric population, where hospitalization is often necessary to ensure adequate bowel cleansing for endoscopies and biopsies and to provide sedation or anesthesia of sufficient quality in a child-friendly environment. It is imperative to acknowledge that these procedures are not only associated with significant risks and complications for the patient but also result in the utilization of valuable healthcare system resources (11,12). Therefore, there is a need for noninvasive measurement tools to minimize the invasiveness, discomfort, potential complications, and cost associated with these procedures.

One approach is to look at the patient's FCal serum amyloid A (SAA) parameters, but due to the lack of comprehensive analysis, availability, and high cost, a decrease in ESR and CRP or an increase in albumin and MCV from our study results can be used as a marker of mucosal healing.

Weinstein et al. analyzed the laboratory test results of 71 children with newly diagnosed UC. The researchers reported that the absolute laboratory values for ESR and platelet count were higher, whereas the absolute values for hemoglobin and albumin levels were lower at the time of presentation. The researchers also identified a substantial overlap in laboratory values among children with mild to moderate disease (13). Conversely, our results demonstrate that ESR and platelet counts were significantly higher, while hemoglobin and albumin levels were significantly lower in children with UC at the time of diagnosis compared to the control group. However, the study did not incorporate a grading system based on disease severity.

The pathogenesis of ulcerative colitis involves complex dysregulation of mucosal immune cells (14) and concomitant invasion by neutrophils, leading to the formation of crypt abscesses and dysfunction of the colonic epithelial barrier (15). Neutrophils reach the colonic lumen during transmigration and can be detected in the stool (16), similar to the mediators they secrete (17,18), such as polymorphonuclear elastase, Cal or Cathepsin G. Therefore, biomarkers reflecting neutrophil activation seem promising in UC (18,19). It can be expected that the concentration of inflammatory cells in the blood will increase during neutrophil activation that occurs in active inflammatory processes of UC. The proven importance of platelet count as a biomarker in UC, PLR (20), and neutrophil-to-platelet ratio (21) in predicting disease activity may also increase the informative value of other cellular markers. In light of this information, the significantly higher WBC, neutrophil, platelet, NLR, RDW, PLR, and RPR results of UC patients compared to the control group in our study support the literature.

Anemia can result from iron deficiency due to reduced iron uptake from enterocytes, chronic diseases that inhibit erythropoiesis, or chronic blood loss from the gastrointestinal tract. In all three cases, it is difficult to treat, and for these reasons, anemia persists in many patients with UC even after one year of treatment. In the management of UC patients with anemia, it is important and useful to determine the type of anemia since treatment options depend on the type of anemia (22). The results of our patients with UC were similar to the literature; RDW values were high, Hb values were significantly lower and anemic compared to the control group, and although Hb values increased slightly after treatment, they continued to be anemic.

Among the various biochemical laboratory markers, serum CRP has received the most extensive study. A review evaluating biomarkers in children suggests that CRP is the most effective blood marker to differentiate IBD from IBS (23). The increase in CRP in the diagnosis or recurrence of UC is usually associated with a moderate increase in CRP, although this varies depending on the extent of the area involved (24). In the present study, we observed a significant increase in CRP levels in patients with UC, consistent with the findings reported in the literature. Our ROC analysis yielded a moderate cut-off value of 1.89 mg/L. Furthermore, our results demonstrated that the decline in CRP values of the UC group after treatment did not exhibit a statistically significant difference when compared to the control group.

Study limitations

Our study has some limitations. First of all, the main limitations of our study are that it was retrospective and single-centered with a small number of patients. In addition, our results could not be supported by a comparative analysis of current biomarkers such as FCal, SAA, and fecal matrix metalloprotease. Again, an endoscopic/histologic comparison of the usability of the four main findings of our study for the proof of remission in mucosal healing could not be made. Since these four parameters are likely to increase/decrease in every inflammatory process and the same inflammatory process is also present in UC patients, the predicted expectation was reflected in our results.

Conclusion

The results of our study suggest that, in cases where children present with gastrointestinal complaints and suspicion of IBD, referral to noninvasive procedures that are easy, inexpensive, and accessible, such as simple blood tests, may be a more appropriate course of action than pursuing a diagnosis with costly, difficult-to-access, invasive procedures. The presence of ESR and CRP elevation, as well as low levels of MCV and albumin, could serve as a triage tool for determining the necessity of histologic diagnosis. Nevertheless, it is our conviction that the findings of this study should be substantiated by the implementation of a more extensive and comprehensive series of studies.

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