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## Correlation between Clinical Symptoms and Lab Tests with Endoscopic Severity Indexes in Patients with Inflammatory Bowel Diseases

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### ABSTRACT

#### BACKGROUND

The Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) are two validated endoscopic scoring system to evaluate patients with inflammatory bowel diseases (IBD). We conducted this study to evaluate the correlation between clinical symptoms and lab tests with these indexes in patients with Crohn's disease (CD) and ulcerative colitis (UC).

#### METHODS

In this analytical study, 373 consecutive patients referred to Shahid Mohammadi Hospital with IBD were enrolled. All patients underwent complete ileocolonoscopy, and the endoscopic severity indexes (CDEIS and UCEIS) were calculated, and their relation with clinical symptoms and lab tests was evaluated.

#### RESULTS

Fever observed only in six patients (1.6%). It was associated with significantly higher CDEIS and UCEIS ( $p = 0.02$  and  $p < 0.001$ , respectively). Also, diarrhea was correlated with significantly higher UCEIS ( $p < 0.001$ ). The mean fecal calprotectin was  $647.64 \pm 409.37 \mu\text{g/g}$  in CD and  $567.30 \pm 342.49 \mu\text{g/g}$  in UC patients. Higher calprotectin level was observed in patients with higher CRP level ( $p = 0.001$ ), erythrocyte sedimentation rate (ESR) level, CDEIS, and UCEIS ( $r = 0.438$ ;  $0.473$ ; and  $0.517$ ; respectively, all with  $p < 0.001$ ).

#### CONCLUSION

Our study showed that although fever and diarrhea are associated with higher endoscopic severity scores in patients with IBD, no clinical symptom could reliably predict the endoscopic results, alone. Furthermore, higher fecal calprotectin level is associated with higher ESR and C reactive protein levels, CDEIS, and UCEIS.

#### KEYWORDS:

Inflammatory bowel diseases, Crohn's Disease Endoscopic Index of Severity, Ulcerative Colitis Endoscopic Index of Severity, Fecal calprotectin

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### INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic inflammatory conditions involving the colon and small intestine. Two major types of this disorder include Crohn's disease (CD) and ulcerative colitis (UC).<sup>1,2</sup> Either of them is characterized by an idiopathic, chronic, relapsing, inflammatory



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condition, which is immunologically mediated.<sup>3</sup> Although CD could involve any portion of the gastrointestinal (GI) tract, patients with CD are usually presented with inflammatory changes of the distal small intestine and proximal colon.<sup>4</sup> These inflammatory alterations are accompanying symptoms, including diarrhea (which could turn into bloody diarrhea in case of severe intestinal inflammation), fever, weight loss, and abdominal pain.<sup>5</sup> On the other hand, UC primarily affects the colonic mucosa, especially its distal part. Patients suffering from UC are usually presented with increased stool frequency, abdominal pain, and rectal bleeding with a relapsing-remitting course.<sup>6,7</sup>

Endoscopy is fundamental for diagnosis, evaluation of activity, and management of patients with IBD. It could differentiate between CD and UC and monitor the course of treatment.<sup>8,9</sup> Several different scoring systems have been described over the years for the endoscopic evaluation of the severity of DC and UC.<sup>8</sup> The Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) are two validated endoscopic criteria to assess CD and UC, respectively.<sup>9,10</sup> The former index is a complex scoring system developed by Mary and colleagues, which is not very practical outside of randomized controlled trials, but could be used to monitor endoscopic response to treatment in patients with CD.<sup>11,12</sup> The latter, first reported by Travis and co-workers in 2012, is an easy scoring system, which could be used to predict UC outcome.<sup>13-15</sup>

We conducted this study to evaluate the correlation between clinical symptoms and lab tests with endoscopic severity indexes in patients with IBD.

## MATERIALS AND METHODS

### Study design and setting

This analytical observational study was performed at Shahid Mohammadi Hospital, affiliated to Hormozgan University of Medical Sciences in 2016-2017. It was approved by the ethics board of the University. The research was carried out according to the Helsinki Declaration, and written informed consent was obtained from all participants before enrollment.

### Participants

373 consecutive patients with IBD (either CD or UC) referred to Shahid Mohammadi Hospital were included in this study. The diagnosis of IBD was based on clinical symptoms and previous colonoscopy. The exclusion criteria were: patients' desire as not to participate in the study, incomplete filling of questionnaires, concomitant illnesses such as infection, malignancy, or other GI diseases, pregnancy, regular alcohol or aspirin use, treatment with antibiotics or cytotoxic drugs, and non-steroidal anti-inflammatory drug (NSAID) use for more than twice a week.

### Method

Patients' demographic information, including age, sex, and disease duration was obtained from all patients. The clinical symptoms (e.g. the presence of abdominal pain, fever, diarrhea, rectal bleeding, etc.) at admission time were also reported. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were tested for all patients. CRP was reported as – (CRP = 0), 1 + (CRP level of 0-1 mg/L), 2 + (CRP level of 1-3 mg/L), and 3 + (CRP > 3 mg/L). Fecal calprotectin was also evaluated by a quantitative enzyme immunoassay.

All patients underwent complete ileocolonoscopy by an experienced gastroenterologist and the CDEIS and UCEIS were calculated for CD and UC patients, respectively. For the CDEIS, the presence of mucosal superficial and deep ulcers, the extent of surface involved by the disease and ulceration, and the presence of ulcerated or no ulcerated stenosis were recorded in five segments (i.e. rectum, sigmoid colon and descending colon, transverse colon, cecum and ascending colon, and terminal ileum). The CDEIS ranged from 0 to 44, with a higher score indicating more severe disease.<sup>10</sup> The UCEIS was calculated as a simple sum consisted of the vascular pattern (scored 0–2), bleeding (scored 0–3), and erosions and ulcers (scored 0–3). It ranged from 0 to 8 with zero, meaning normal mucosal appearance and higher scores indicated more severe disease.<sup>9</sup> Detailed calculation of CDEIS and UCEIS is demonstrated in tables 1 and 2, respectively.

### Statistical analysis

Statistical analysis was performed by SPSS software version 23 (SPSS Inc., Chicago, IL, USA). Data were analyzed using descriptive statistical tests, including

**Table 1: Crohn's Disease Endoscopic Index of Severity (CDEIS) calculation**

Score	Rectum	Sigmoid colon and descending colon	Transverse colon	Cecum and ascending colon	Terminal ileum	Total
Deep ulceration (12 present, 0 not)	+	+	+	+	+	= Sum 1
Superficial ulceration (6 present, 0 not)	+	+	+	+	+	= Sum 2
Involved surface (cm)	+	+	+	+	+	= Sum 3
Ulcerated surface (cm)	+	+	+	+	+	= Sum 4
Sum 1 + Sum 2 + Sum 3 + Sum 4						= Sum A
Number of segments fully or partially visualized (1–5)						= n
Sum A/n =						= Sum B
Ulcerated stenosis anywhere (3 present, 0 not)						= Sum C
Non ulcerated stenosis anywhere (3 present, 0 not)						= Sum D
Total Sum B + C + D =						= CDEIS

Reproduced from Mary and Modigliani, Gut. 1989;30(7):983-9. <sup>11</sup>

**Table 2: Ulcerative Colitis Endoscopic Index of Severity (UCEIS) calculation**

Descriptor	Likert scale (anchor point)	Definition
Vascular pattern	Normal (0)	Normal vascular patterns
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of the endoscope or visibly oozing from the mucosa after washing intraluminal blood, or visibly oozing from a hemorrhagic mucosa
Erosion and ulcers	None (0)	Normal mucosa
	Erosions (1)	Tiny (< 5 mm) defects in the mucosa of a white or yellow color with a flat edge
	Superficial ulcer (2)	Larger (> 5 mm) defects in the mucosa, which are discrete fibrin covered ulcers when compared with erosions but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa with slightly raised edge

Reproduced from Travis et al., Gut. 2012 Apr 1; 61(4):535-42 (reference 13) and Gastroenterology 2013 Nov 1; 145(5):987-95. <sup>14</sup>

frequency, percentage, mean and standard deviation, as well as the independent t test. The significant threshold was considered to be less than 0.05.

## RESULTS

Patients' demographics are demonstrated in table 3. Of the 373 patients in this study, 198 were women (53.1%), and 175 were men (46.9%). The mean age of the participants was  $37.29 \pm 12.69$  years, and the mean

duration of IBD after diagnosis was  $30.23 \pm 21.92$  months. 74 patients had CD (19.8%) and 299 patients had UC (80.2%).

As it is shown in table 4, fever was reported in six patients (1.6%) out of the 373 patients, diarrhea in 276 patients (74%), rectal bleeding in 83 patients (22.3%), and abdominal pain in 112 patients (30%). Anal pain and discharge were reported only in patients with CD. Anal pain was reported in 22 (29.7%), and anal discharge was

**Table 3: Participants' demographics**

Characteristic	N	Mean	Std. Deviation
Age, y	373	37.29	12.69
Duration, m	373	30.23	21.92

  

Characteristic	N	Percent
<b>Sex</b>		
Male	175	46.9
Female	198	53.1
<b>Type</b>		
Ulcerative colitis	299	80.2
Crohn's	74	19.8

positive in 15 (20.3%) of the 74 patients with CD.

As it is shown in table 5, higher CRP (27% and 5.4% of patients with 2 + and 3 + CRP level in patients with CD compared with 14% and 1.7% in patients with UC) and ESR levels ( $38.65 \pm 14.56$  mm/hr compared with  $31.56 \pm 8.56$  mm/hr) were associated with CD ( $p = 0.007$  and  $0.001$ , respectively). The mean fecal calprotectin was  $647.64 \pm 409.37$   $\mu\text{g/g}$  in patients with CD and  $567.30 \pm 342.49$   $\mu\text{g/g}$  in patients with UC. We observed no significant difference between the patients with UC and CD regarding the calprotectin levels.

We evaluated the correlation between fecal calprotectin and other measures (table 6). As it is demonstrated, there was no association between calprotectin level and sex, age, and disease duration. Higher calprotectin level was observed in patients with 2 + and 3 + CRP level ( $845.59 \pm 359.26$   $\mu\text{g/g}$  and  $898.33 \pm 252.75$   $\mu\text{g/g}$ , respectively with  $p = 0.001$ ). Also, higher calprotectin level was related to higher ESR level, CDEIS, and UCEIS ( $p < 0.001$ ,  $r = 0.438$ ;  $p < 0.001$ ,  $r = 0.473$ ; and  $p < 0.001$ ,  $r = 0.517$ , respectively)

The mean CDEIS and UCEIS were  $38.65 \pm 14.56$  and  $4.87 \pm 1.34$ , respectively (table 5). In patients with CD, we observed a significantly higher CDEIS only in the presence of fever ( $35.00 \pm 0.00$  compared with  $32.18 \pm 8.65$ , with  $p = 0.02$ ) (table 7). In table 3, the relationship between each symptom of the patients with UC with the score of UCEIS has been investigated. In patients with UC, fever and diarrhea were associated with significantly higher UCEIS ( $7.40 \pm 0.89$  in febrile patients compared with  $4.83 \pm 1.31$ , and  $5.03 \pm 1.35$  if the diarrhea was reported compared with  $4.08 \pm .98$ , both with  $p < 0.001$ ) (table 8).

**Table 4: Clinical symptoms of the participants**

Characteristic	N	Percent
<b>Fever</b>		
Yes	6	1.6
No	367	98.4
<b>Diarrhea</b>		
Yes	276	74
No	97	26
<b>Rectal bleeding</b>		
Yes	83	22.3
No	290	77.7
<b>Abdominal pain</b>		
Yes	112	30
No	261	70
<b>Anal pain</b>		
Yes	22	5.9
No	351	96.1
<b>Anal discharge</b>		
Yes	15	4
No	358	96

## DISCUSSION

Colonoscopy is a time consuming and costly procedure in patients with IBD. Therefore, it is important to find a criterion that can be used to monitor treatment and disorder activity with a relatively low cost while being non-invasive. The aim of this study was to investigate the relationship between clinical symptoms and lab tests with the endoscopic severity score in patients with CD and UC to evaluate whether they could be used as an alternative to predict the endoscopic result in such patients. In patients with CD, the correlation of symptoms such as anal pain and discharge, fever, diarrhea, rectal bleeding, and abdominal pain with CDEIS was evaluated. In patients with UC, the association of clinical symptoms, including diarrhea, fever, abdominal pain, and rectal bleeding with UCEIS was investigated. According to the findings of our study, fever in patients with CD and diarrhea and fever in patients with UC were associated with CDEIS and UCEIS, respectively. As for laboratory tests, higher fecal calprotectin level was correlated with higher ESR, CRP, CDEIS, and UCEIS. Finally, CD was associated with higher CRP and ESR levels compared with UC.

Several studies have described the importance of endoscopic severity indexes in predicting treatment

**Table 5: The Patients' lab test and endoscopic severity indexes**

Measures	All patients	Patients with CD	Patients with UC	P-value
<b>CRP, n (%)</b>				
-	48 (12.9%)	6 (8.1%)	42 (14%)	0.007
1+	254 (68.1%)	44 (59.5%)	210 (70.2%)	
2+	62 (16.6%)	20 (27%)	42 (14%)	
3+	9 (2.4%)	4 (5.4%)	5 (1.7%)	
<b>ESR (mm/hr), mean ± Std. Deviation</b>				
	32.96 ± 10.69	38.65 ± 14.56	31.56 ± 8.56	0.001
<b>Calprotectin (µg/g), mean ± Std. Deviation</b>				
	583.36 ± 357.72	647.64 ± 409.37	567.30 ± 342.49	0.084
<b>Endoscopic severity index [CDEIS in CD patients and UCEIS in UC patients], mean ± Std. Deviation</b>				
		38.65 ± 14.56	4.87 ± 1.34	

CD: Crohn's disease. UC: Ulcerative colitis. CRP: C-reactive protein. ESR: erythrocyte sedimentation rate. CDEIS: Crohn's Disease Endoscopic Index of Severity. UCEIS: Ulcerative Colitis Endoscopic Index of Severity

**Table 6: Calprotectin relation with other measurements**

Measures	Mean	Std. Deviation	p value
<b>CRP</b>			
-	248.33	80.77	0.001
1+	572.46	334.91	
2+	845.59	359.26	
3+	898.33	252.75	
<b>Sex</b>			
Male	368.07	362.00	0.442
Female	596.80	354.30	
<b>Measures</b>	<b>p value</b>	<b>Regression analysis</b>	
Age	0.971	0.971	
Duration	0.708	0.708	
ESR	< .001	< .001	
CDEIS	< .001	< .001	
UCEIS	< .001	< .001	

CRP: C-reactive protein

ESR: erythrocyte sedimentation rate

CDEIS: Crohn's Disease Endoscopic Index of Severity

UCEIS: Ulcerative Colitis Endoscopic Index of Severity

outcomes in patients with IBD. According to Ferrante and colleagues,<sup>10</sup> a 50% decrease from baseline in CDEIS in week 26 after the medical intervention was associated with 50-week sustained clinical remission in patients with CD, with a sensitivity and specificity of 56% and 65%, respectively. Of note, Landi and others<sup>16</sup> suggested that CDEIS had a slight application in clinical practice because of its complex and time-consuming manner. As for UCEIS, Ikeya and co-workers<sup>9</sup> reported that UCEIS

is a superior method to foretell the long-term prognosis of treatment, and it reflects the true clinical outcome after medical intervention due to its ability to distinguish between deep and shallow ulcer in the early stages of the healing process. Corte and colleagues<sup>17</sup> reported that UCEIS > 5 at the admission time was associated with a higher possibility of using rescue therapy or colectomy on the course of treatment. According to this study, the UCEIS of > 7 at admission is a reliable predictor for early

**Table 7:** The relation between clinical symptoms and CDEIS in patients with Crohn's disease

Symptoms	N	Mean CDEIS	Std. Deviation	<i>p</i> value
<b>Fever</b>				
Yes	1	35	0.00	0.020
No	72	32.18	8.65	
<b>Diarrhea</b>				
Yes	27	34.56	9.43	0.127
No	46	31.24	8.49	
<b>Rectal bleeding</b>				
Yes	14	36.36	9.32	0.070
No	59	31.54	8.66	
<b>Abdominal pain</b>				
Yes	53	33.21	9.20	0.251
No	20	30.50	8.07	
<b>Anal pain</b>				
Yes	22	34.05	10.26	0.325
No	51	31.78	8.31	
<b>Anal discharge</b>				
Yes	15	33.67	10.18	0.563
No	58	32.16	8.65	

identification of high-risk patients who would require rescue therapy.

Few studies have described the association between clinical symptoms and endoscopic severity indexes. In the study by Durko and co-workers,<sup>18</sup> CDEIS was correlated with histological findings and not the clinical scales. According to Travis and others,<sup>15</sup> stool frequency and rectal bleeding were associated with the endoscopic severity index in patients with UC with a correlation coefficient of 0.76 and 0.82, respectively.

In the present study, among clinical symptoms, only fever in patients with CD and fever and diarrhea in patients with UC were associated with higher endoscopic severity indexes. The correlation between fever and either endoscopic severity indexes could not be considered a reliable conclusion as we observed fever in a small portion of the participants (one febrile in 74 patients with CD and five in 299 patients with UC) and due to the small febrile population, this finding could not be a reliable conclusion to make a decision on, and it is necessary to be confirmed with further studies with more febrile cases.

As for diarrhea in UC cases, diarrhea and fever associated with positive inflammatory biomarkers could

**Table 8:** The relation between clinical symptoms and UCEIS in patients with ulcerative colitis

Symptoms	N	Mean CDEIS	Std. Deviation	<i>p</i> value
<b>Fever</b>				
Yes	5	7.40	.89	< 0.001
No	294	4.83	1.31	
<b>Diarrhea</b>				
Yes	249	5.03	1.35	< 0.001
No	50	4.08	.98	
<b>Rectal bleeding</b>				
Yes	69	5.17	1.65	0.391
No	230	4.78	1.23	
<b>Abdominal pain</b>				
Yes	58	5.17	1.55	0.372
No	241	4.80	1.28	

be interpreted as a sign of disease activity, but in 30% of patients with inactive IBD, diarrhea alone might be a symptom of irritable bowel syndrome (IBS). On the contrary to our study, several studies have described UCEIS improvement after medical intervention in some cases, despite experiencing sustained rectal bleeding and stool frequency.<sup>9</sup> In a meta-analysis by Narula and colleagues,<sup>19</sup> abnormal stool frequencies was reported despite endoscopic remission. Several reasons have been described to explain the discrepancy between endoscopic severity indexes and elevated stool frequency. Some studies have found abnormal histological findings despite the presence of clinical and endoscopic remission.<sup>20-22</sup> IBS-like symptoms have been observed in some patients with quiescent IBD due to occult inflammation.<sup>23</sup> Other causes are; damage to the enteric nervous system, rectal hypersensitivity as a result of mast cell activation, and alteration of the colon and rectum length and caliber.<sup>24-28</sup>

Based on the above-mentioned issues, we could not mark any of the clinical symptoms as a reliable predictor of endoscopic results.

Some studies have also suggested that factors such as CRP are effective in predicting IBD activity.<sup>29</sup> In the study by Karoui and co-workers,<sup>30</sup> CD activity index score was associated with CRP ( $r = 0.302$ ;  $p = 0.001$ ), and CRP of 19 mg/L seemed to be a reliable marker to diagnose moderate to severe CD with a sensitivity of 76.4% and a specificity of 56.2%. In the review article



by Mosli and co-workers,<sup>31</sup> the pooled data showed a sensitivity and specificity of 0.49 and 0.92, respectively, for CRP regarding the assessment of patients with IBD. In the study by Schoepfer and colleagues,<sup>32</sup> the elevated CRP levels were associated with higher CD severity ( $r = 0.53$ ). In the present study, similar to other studies, inflammatory biomarkers were associated with CD, and more cases with elevated CRP and ESR levels were observed among the patients with CD.

Recently, fecal markers have been studied for assessing intestinal inflammation in patients with IBD with some success. These markers include lactoferrin, polymorphonuclear neutrophil (PMN) elastase, and calprotectin. These three markers could evaluate disease activity in either CD or UC and differentiate IBD and IBS even when there is no disease activity. Either of these markers seems to have superior diagnostic accuracy compared with CRP in patients with IBD. Among these three, fecal calprotectin was also shown to be a useful screening tool for identifying patients suspected of IBD, and it has a better correlation with CDEIS and histopathological findings of inflammation compared with clinical symptoms.<sup>33-38</sup> In the present study, the fecal calprotectin level was associated with endoscopic severity of CD and UC evaluated by CDEIS and UCEIS, respectively. Higher fecal calprotectin was also associated with positive inflammatory biomarkers, i.e. ESR and CRP. These findings are in line with the results of other studies regarding the role of fecal calprotectin in patients with IBD. According to Schoepfer and colleagues,<sup>32</sup> among several markers, fecal calprotectin had the closest association with endoscopic severity in patients with CD (evaluated by Simple Endoscopic Score for Crohn's disease (SES-CD)) with a correlation coefficient of 0.75. Also, it was the only marker with the ability to delineating between inactive and active cases. In the study by Mosli and others,<sup>31</sup> fecal calprotectin showed to be more sensitive than CRP in patients with IBD (0.88 compared with 0.49) and with better specificity in UC than CD (0.79 compared with 0.68). Furthermore, fecal calprotectin has been shown to have a significant association with mucosal healing in patients with IBD, and a cut-off of  $\leq 71 \mu\text{g/g}$  (with a sensitivity of 95.9% and specificity of 52.3%) could be used as a reliable tool for evaluating mucosal healing.<sup>39, 40</sup> It should be noted that a

recent study showed a better diagnostic accuracy for fecal calprotectin in UC compared with CD.<sup>41</sup>

The present study has some limitations. The main limitation was the small sample size, especially for the patients with CD. As it was noted before, several reported symptoms, including fever, were observed in a few cases, which may have affected the results of the study. Also, it was a single-center study. Furthermore, in the present study, disease activity was based on the endoscopic findings, and the histopathological evaluation was not done. Finally, a cut-off point neither for CD nor UC was evaluated. Further multi-center studies with larger sample sizes are recommended in order to achieve more reliable results.

## CONCLUSIONS

Our study showed that although fever and diarrhea are associated with higher endoscopic severity scores in patients with IBD, neither clinical symptoms could reliably predict the endoscopic results, alone. Furthermore, higher fecal calprotectin level is associated with higher ESR and CRP levels, and CDEIS, and UCEIS.

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## ETHICAL APPROVAL

There is nothing to be declared.

## CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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