ROLE OF FECAL CALPROTECTIN IN DIFFERENTIATION OF INFLAMMATORY BOWEL DISEASES IN PATIENTS COMPLAINING OF ABDOMINAL SYMPTOMS AND REFERRED FOR COLONOSCOPY

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ABSTRACT

Background

The difficulty in differentiating functional gastrointestinal disorders and inflammatory bowel diseases in patients presenting with abdominal symptoms direct us to the use of fecal inflammatory biomarkers that are specific to intestinal inflammation.

Objectives

To assess the benefits of fecal calprotectin (FC) in patients presenting with lower abdominal symptoms. Also, correlating the FC and CRP titer with abdominal pain severity.

Patients and Methods

It is a prospective cross-sectional study in Kurdistan Center for Gastroenterology and Hepatology (KCGH), Sulaimaniyah city, Northern Iraq. A total of 174 patients with IBS according to Rome IV criteria, who visited KCGH, met the inclusion criteria. FC titer measured before colonoscopy appointment, abdominal pain severity scored according to visual scale, and colonoscopy performed by specialized gastroenterologists.

Results

The FC level was below 50ug/g for 91.3% of patients with normal endoscopy; all of the IBD cases had FC level above 100ug/g. Seven of the eight patients with non-inflamed polyp or diverticuli had an FC level of less than 50ug/g. Moreover, in this study, the CRP level is also significantly higher among IBD cases than in patients with normal colonoscopy.

Conclusion

FC titer is a useful measure before the decision for colonoscopy especially in cases not having alarm symptoms and other comorbidities. FC and CRP level is associated with the severity of abdominal pain.

Keywords: *Inflammatory bowel disease; Fecal calprotectin; Colonoscopy, Sulaimaniyah.*

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INTRODUCTION

About 8% to 10% of the newly presented cases to the primary care complain of Gastrointestinal symptoms[1] Common gastrointestinal symptoms like abdominal pain, bloating and chronic diarrhea have a diverse differential diagnosis from organic causes, like inflammatory bowel disease (IBD), colorectal cancer, celiac disease, food intolerance, to functional causes like irritable bowel syndrome (IBS)[2]. Irritable bowel syndrome is the most commonly diagnosed gastrointestinal disorder that affects approximately 11% of the population worldwide. In Asia, the prevalence of IBS is around 10-20 % [3].

General practitioners and even specialists face difficulty in the differentiation between functional gastrointestinal disorders and IBD. While individuals having functional gastrointestinal disorder can be managed in primary care centers, in contrast to those with organic gastrointestinal diseases like IBD should be managed in the specialized centre often with colonoscopy and imaging [4] but most cases with functional gastrointestinal diseases are unnecessarily referred for colonoscopy [5].

Irritable bowel syndrome is a multifactorial functional disease as opposed to inflammatory organic diseases like IBD [6]. Calprotectin is a zinc-binding protein in granulocytes with roles against microbes and inflammation through competitive inhibition of zinc-dependent enzymes, biostatic activity against microbes, apoptosis induction in malignant cells, and regulation of the inflammatory process [7]. The FC is a promising non-invasive technique to distinguish between inflammatory and functional disorders [8]. FC is also a promising method to assess mucosal healing during patient monitoring [9]. The detection of FC confirms the presence of low-grade inflammation in IBS. Nevertheless, the British Society of Gastroenterology consensus guideline considers values less than 50 µg/g as a normal FC level[10]. Some studies unanimously concluded that an FC level less than 50ug/g has a very high negative predictive value for IBD [10-14].

Although, Fecal calprotectin help in the differentiation of those with IBS from IBD but FC is not recommended in patients suspecting of colorectal cancer or having red-flag features with abdominal symptoms [15]. FC has adequate sensitivity and specificity to identify patients most likely to have organic bowel disease, therefore permitting the effective usage of colonoscopy resources[16]. However, FC measurement alone is not enough to rule out neoplastic gastrointestinal disease in patients over 50 due to the high risk of neoplasia in this age group [17].

Therefore, this study aims to assess the benefit of FC titer in the differentiation of functional gastrointestinal diseases from inflammatory or organic diseases and correlate the FC titer with the abdominal pain severity.

MATERIALS AND METHODS

This prospective cross-sectional study was conducted in Kurdistan Center for Gastroenterology and Hepatology (KCGH) in Sulaimaniyah City from January 2017 to December 2018. Consecutive patients having IBS-like symptoms (but no red flag signs) and referred for colonoscopy were assessed for eligibility criteria following history taking, detailed physical examination and thorough investigations. Rome IV criteria for the assessment of patient clinical condition used and only those who match the criteria were chosen.

Rome IV IBS Diagnostic Criteria

1. Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months and associated with two or more of the following:

a. Related to defecation.
b. Associated with a change in frequency of stool.
c. Associated with a change in stool form.

2. Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis. [18]. Depending on the disturbance in stool consistency, IBS has been classified as constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), mixed bowel habits (IBS-M); and unclassified (IBS-U) [19]. For the current study, only IBD-D or IBS-M were included, so all patients had abdominal pain, diarrhea with or without alternating constipation.

Of a total of 2000 cases, 177 met inclusion criteria and were enrolled in the study. These patients were fully informed about the objective of the study and written informed consents obtained from all of them before enrolment. FC measured in Sixty-five volunteers having no gastrointestinal symptoms were selected as healthy controls for comparison. Approval of the College of Medicine Ethical committee, University of Sulaimani was obtained.

Inclusion and Exclusion criteria

Any patients above 18 years of age with diarrhea-predominant (IBS-D) and alternating bowel habit

(IBS-M), were enrolled in the study.

Patients who had one of the following were excluded from the study; red flags including unexplained rectal bleeding, fever, weight loss, anemia, nocturnal diarrhea that prevents sleep, the onset of symptoms after 50 years of age, and had the first-degree relative with IBD or early colon cancer. Also, patients on non-steroidal anti-inflammatory drugs (NSAID) or proton pump inhibitors (PPI), as well as pregnant or lactating ladies, were excluded. Moreover, patients with tumors, hepatic and/or renal insufficiency, congestive heart failure, bleeding tendency, major gastrointestinal procedures, recent respiratory or urinary tract infection, or inflammatory bowel disease (IBD). Also, patients having abnormal findings on investigations like abnormal thyroid function test, those with positive tissue transglutaminase antibody test, parasitic infestation on general stool examination, abnormal abdominal ultrasound findings.

Detailed questionnaires were obtained from all patients, including questions about sociodemographic data, medical, surgical, drug and family history, detailed symptoms and duration of symptoms.

Height and weight were measured. Body mass index (BMI) of all the patients were calculated, accordingly, patients were classified as having a normal body weight if their value was ranged between 18.5 - 24.9, overweight if 25 -29.9, and obese if ≥30.

Patients were classified according to their age into four different age groups <30y, 30-40, 41-50, >50. Pain score was calculated for all patients using the visual numeric rating scale [20], The patients were asked to choose the number that best describes their pain severity from 1-10 on the pain scale.

Fecal sample for measuring FC titer was obtained from each patient before preparation for colonoscopy. Each patient was given a plastic container for sampling. Fecal calprotectin titer measured using the commercially available enzyme-linked immunosorbent assay test (ELISA, Euroimmun, Germany).

Based on calprotectin manufacturers and NICE recommendations, the pre-specified calprotectin cut-offs were: calprotectin ≥100 µg/g = positive, calprotectin 50-99 µg/g = intermediate and calprotectin <50 µg/g = negative [21].

Statistical analysis

The statistical analysis performed by the SPSS program, version 21 (IBM SPSS Statistical Package for the Social Sciences). The data presented in tabular forms showing the frequency and relative frequency distribution of different variables among both groups of patients (positive and negative groups). The normality test was performed on all variables, the data that are not normally distributed were log-transformed and the skewness was corrected. Chi-square tests were used to compare the categorical data between these two groups of patients concerning different variables.

For comparing the mean of certain variables as age and BMI between groups the statistical significance of the difference in mean between two groups were assessed using an independent sample t-test. P-values of 0.05 were used as a cut off point for the significance of statistical tests. The correlation between variable was assessed using Spearman's correlation.

RESULTS

From 2000 cases referred for colonoscopy in the 18 months of conducting the study, 177 cases met the inclusion criteria, with ages ranging from 24 -67 years, 94 females (53.1%) and 83 males (46.9%). Socio-demographic characteristics of the studied population, colonoscopy and histology results were demonstrated in Table 1. Control cases were 65 cases (male/female ratio 31/34) with mean age 42.63 ± 8.61yrs, (Range 22-59 yrs.) without abdominal symptoms.

Of the 177 cases, 161 cases had normal colonoscopy and histopathology; eight cases were diagnosed as IBD (6 UC, 2 CD), three cases of diverticuli & 5 polyps without inflammation on histological examination.

There is no significant difference regarding gender and BMI, except those having polyp and diverticuli were significantly older than all other groups ($p<0.05$). IBD cases were younger than all the other groups but statistically not significant except for those having polyp or diverticuli.

Mean FC level was significantly different between those with normal endoscopy and both IBD and controls but not those with polyp and diverticuli. The mean FC level in the healthy control cases was highly significantly lower than all other groups except those with polyp and diverticuli ($p= 0.074$). Table 2 and Figure 1A. Both CRP and WBC were significantly higher in those with IBD than those with normal endoscopy and

healthy controls, Table 2, Figure 1 B, C. while there was a non-significant difference between healthy control and normal endoscopy group (p=0.06 CRP, p= 0.904 WBC) and those with polyp and diverticuli (p= 0.403 CRP, p=0.934 WBC). Table 2, Figure 2. There is a non-significant difference between the diagnostic classifications in the presence of bloating and heartburn (p-value = 0.169 and 0.178 respectively).

Patients are classified according to FC level to four groups: < 50 µg/gm, 50-100 µg/gm, 100-200 µg/gm and ≥200 µg/gm. All cases of IBD have an FC level of more than 100 (Table 3). All except one case of the control cases have an FC level of less than 50µg/gm.

Abdominal pain severity according to the visual score described by the patient was classified as mild (1-3), moderate (4-6) and severe (7-10). Most cases had moderate abdominal severity. There was no significant association between the severity of abdominal pain and age and gender (Figure 2).

In all the 177 cases involved, there was a significant weak association between the abdominal pain severity described by patients and the level of FC and CRP levels (Figure 3 A, B). Whereas WBC and BMI do not show significant association (r=0.063, p= 0.406 and r= -0.087, p= 0.247 respectively).

Table1. Socio-demographic and clinical parameters of the study participants.

Parameter		Frequency No. (%)
Gender	Male	83 (46.9)
	Female	94 (53.1)
Residency	Urban	163 (92.1)
	Rural	14 (7.9)
Education level	Illiterate and Primary school	44 (24.9)
	Secondary school	75 (42.4)
	University and Post-graduate	58 (32.8)
Marital state	Single	25 (14.1)
	Married	149 (84.2)
	Divorced	3 (1.7)
BMI group	Normal	61 (34.5)
	Overweight	67 (37.9)
	Obese	49 (27.7)
Diagnosis	Normal colonoscopy and histopathology	161 (91.0)
	Ulcerative colitis	6 (3.4)
	Crohn's disease	2 (1.1)
	Diverticuli	3 (1.7)
	Polyp	5 (2.8)

Parameter	Mean ± SD
Age (years)	42.4 ± 9.6
BMI kg/m2	27.2 ± 5
Duration of symptoms (months)	38.130 ± 35.5
FC level µg/gm	33.3 ± 42
CRP level mg/L	3.8 ± 4
WBC count /mm3	4478.8 ±2252.6

Table 2. Comparison of Clinical and laboratory parameters in the diagnostic classification and control cases.

Parameter		Cases with normal endoscopy and biopsy (161)	P^a value	Control cases (65)	Cases of IBD (8)	P^b value	Polyp and Diverticuli (8)	P^c value
Age		42.12±9.45	0.982	42.63±8.61	39.25±11.27	0.828	52±8	0.018
Gender	**Male**	76(47%)		31(48%)	3(37.5%)		4(50%)	0.95
	Female	85(53%)		34 (52%)	5(62.5%)		4(50%)	
BMI kg/m2		27.27±5.54	0.999	27.16±4.14	25.69±2.02	0.823	27.27±2.5	1
Mean FC µg/gm		24±17.3	<0.001	14±9.9	210±23	<0.001	29±20	0.888
Mean CRP (mg/L)		2.9728±1.27031	0.061	2.26±2.48	21.5±5.58	<0.001	3.38±1.2	0.934
Mean WBC/mm³		4104.3±1189.6	0.904	4250.3±1119	13775±5254	<0.001	4575±901.9	0.809

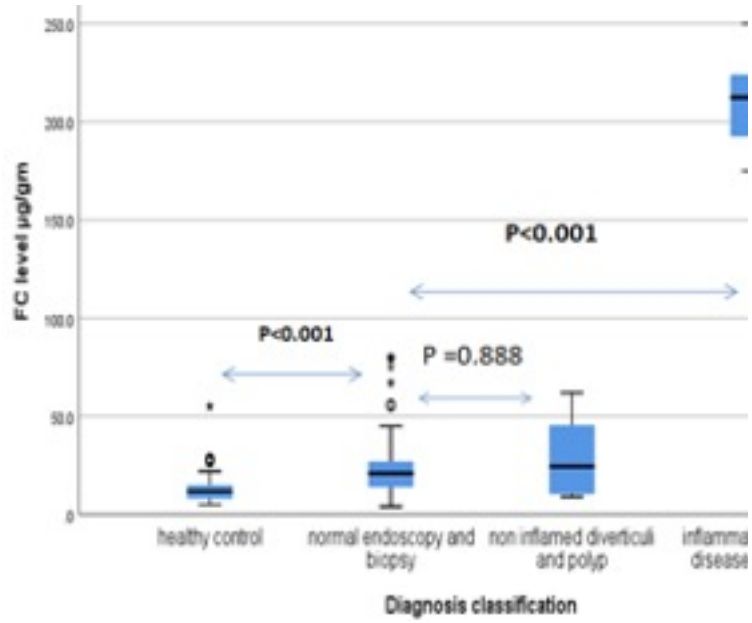
Pa p-value between cases with normal endoscopy and biopsy and control

Pb p-value between Cases with normal endoscopy and biopsy and IBD

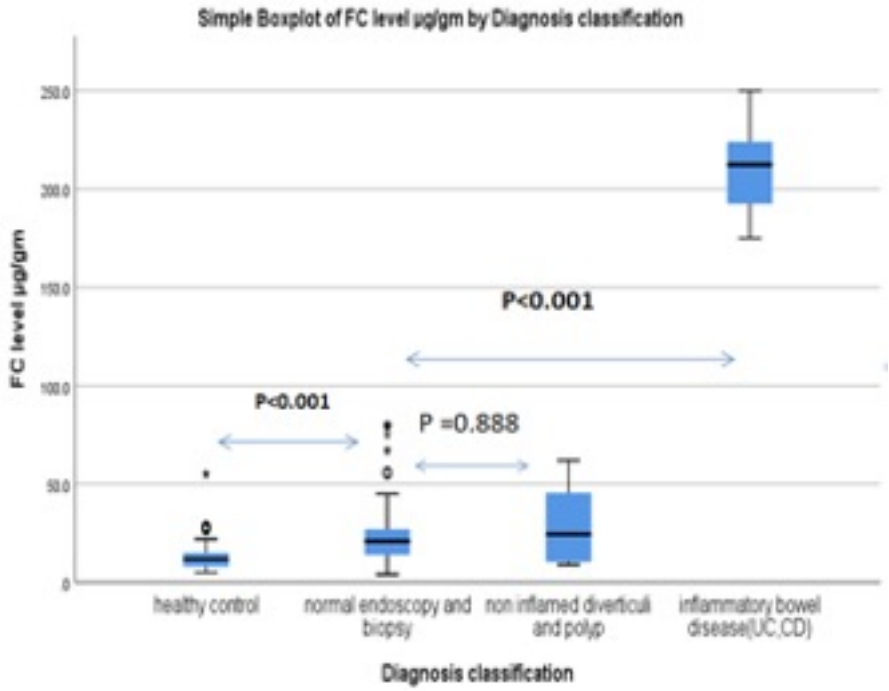
Pc p-value between Cases with normal endoscopy and biopsy and cases with polyp and diverticuli

IBD, inflammatory bowel disease; CRP, C-reactive protein.

A. Fecal calprotectin



B. C- reactive protein



C. WBC count

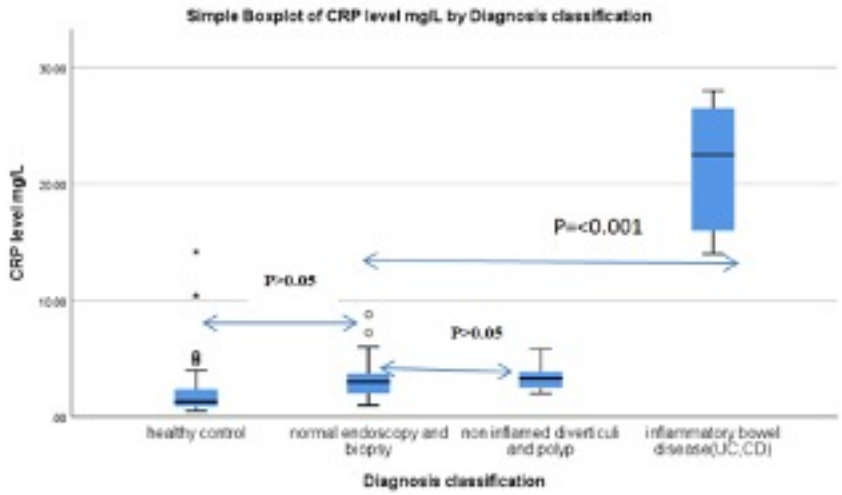


Figure 1 Mean FC level (A), CRP level (B) and WBC count (C) in the different diagnostic groups and control cases.

Table 3. Frequency of low, medium, high and very high fecal calprotectin levels in different diagnostic groups.

FC groups µg/gm	Normal endoscopy and biopsy	Inflammatory bowel disease (UC, CD)	Non-inflamed polyp or diverticuli	Total	P-value
< 50 µg/gm	147	0	7	154	<0.001
50-100 µg/gm	14	0	1	15	<0.001
100-200 µg/gm	0	3	0	3	0.001
>200 µg/gm	0	5	0	5	0.001
Total	161	8	8	177	

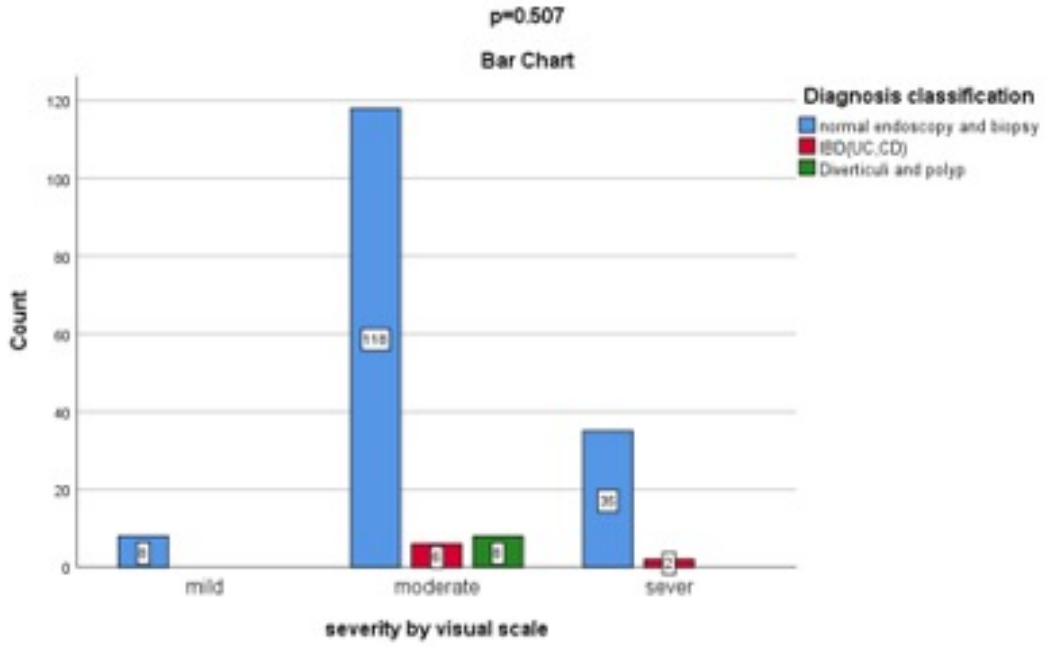
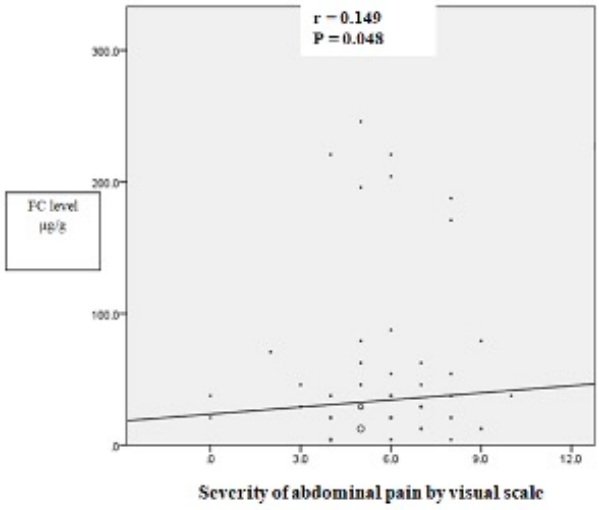


Figure 2. Frequency of (mild, moderate and severe) abdominal pain severity in different diagnostic classifications.

A. FC and abdominal pain severity



B. CRP level and abdominal pain severity

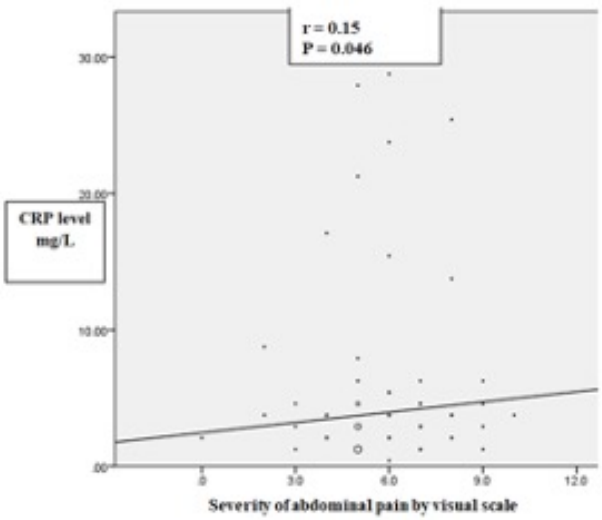


Figure 3. Correlation of abdominal pain severity with FC (A) and CRP (B) levels.

DISCUSSION

The current study evaluates the use of FC and CRP level to differentiate IBS from inflammatory and organic bowel diseases. The mean FC level was significantly associated with the presence of IBD, The FC level was less than 50µg/g for 91.3% of patients with normal endoscopy; all of the IBD cases had FC level above100 µg/g. In the current study, seven of the eight patients with polyp or diverticuli had an FC level of less than 50µg/g. the raised FC level in the cases of polyp might be due to neutrophil shedding from the polyp as inflammation is higher in the polyp than in the adjacent mucosa [22].

This finding strengthens the outcomes of previous studies conducted in other setups on IBS and IBD differentiation based on FC [23-25]. the recommended cutoff level in literature for the diagnosis of IBD is an FC threshold of 50µg/g, although this might face problem due to the use of different methods for measurement [26].

Several similar studies concluded that the FC level <50 µg/g can distinguish non-organic gastrointestinal conditions with high sensitivity among patients with gastrointestinal symptoms [12-14, 23]. Similarly, a study from Taiwan also showed a significant increase in the FC level in IBD compared with IBS [11]. A recent meta-analysis has recommended FC measurement as a useful screening test to rule out IBD with a 66.7% reduction in the need for colonoscopy [27].

In this study FC level of more than 100 µ g/g were

significantly associated with IBD, a finding parallel to other studies that dictate a better diagnosis using 100 µ g/g FC[23]. Moreover, the significant association of IBD with an FC level of >200 µ g/g in this study might indicate the presence of active IBD in these cases [28].

A metanalysis on the role of FC level in IBD [29] documented better accuracy in IBD diagnosis using 100 instead of 50 µg/g, however other researchers concluded 50 µg/g as the best cutoff value in deciding invasive colonoscopy, although few false-negative results might be present below that level most of the patient do not have IBD [30], recently a cutoff level of 40 µg/g is suggested by Menees et al. to have less false-negative results [23].

The use of FC in the differentiation of IBS and IBD was also considered to be very useful economically due to the high negative predictive value of the test [14]. This indicates that preventing the patient from invasive colonoscopy can be achieved with a negative FC level.

A meta-analysis by Freeman and colleagues [31], failed to predict the sensitivity and specificity of FC testing in primary care due to inconclusive evidence supporting it. Another study conducted by Conroy et al. [32], stated low sensitivity and specificity of FC for the diagnosis of IBD in primary care in comparison to the secondary care settings. The Canadian Association of Gastroenterology also does not support the routine use of FC to rule out inflammatory disorders [33], considering the low risk of IBD in IBS cases and that levels between 50 - 250 µg/g are inconclusive.

The current study showed that serum CRP level was also significantly higher among IBD cases than patients with normal endoscopy similar to several other studies that associated abnormal CRP levels with IBD [34, 35]. The high CRP level in IBD cases might be either due to the concomitant presence of a low grade of systemic inflammation or another extra-intestinal cause for the inflammation [36], also might reflect systemic inflammation in severely active cases of IBD [37, 38], while in mild mucosal inflammation FC is more sensitive. It is worth mentioning that IBS inflammation can never even approximates to the degree and level of IBD inflammation [37, 39].

Both FC and CRP were significantly higher among IBD cases, although some study better correlates FC than CRP with the diagnosis [28, 40]. Despite the shown importance of CRP in the differentiation of IBD from non-inflammatory conditions by studies in children and adults [36, 41], but CRP considered of limited value in the diagnosis of IBD by some researchers, as many IBD patients found to have CRP level within the normal range at the time of diagnosis [34].

The peak age for IBD regarded as 15-30 years [42], and in our study IBD cases were younger (39.25±11.27y), Those having IBD were significantly younger than those with polyp and diverticuli ($p = 0.032$), constant with the idea that IBD is the disease of young people with less prevalence above 60 years [43]. While those having polyp or diverticuli were significantly older than other groups, parallel to what is observed by other researchers [44] and with the already known association of increased prevalence of diverticular diseases with age [45].

In this study, the abdominal pain severity had a significant weak association with both FC and CRP titers. These results are in agreement with studies showing the association of FC with the severity of abdominal pain and mucosal healing [16, 46, 47]. This asserts the role of FC in patient monitoring.

A significant correlation between four-day FC levels was documented by Tibble et al [48], and low variability detected between three-day levels of FC in CD cases by a recent study [49], which is an excuse for the single fecal sample used for analysis in this study.

In conclusions, all of the IBD cases have FC level above 100µg/g. The majority of patients with normal endoscopic findings have FC level below 50µg/g. The severity of abdominal pain increases with FC titer and CRP. Last but not the least, we recommend further studies on the role of FC on patient monitoring in the study area.

Strength and Limitations

The current study is the first of its kind in Kurdistan, Iraq. This study has the following strengths: strict inclusion criteria not to alter the reliability of FC detection and blinding of the laboratory professionals about the clinical sign and symptoms of the patients to avoid possible bias. There are two important limitations. First, although 2000 patients were screened, only 177 patients fulfilled the inclusion criteria. Therefore, the small sample size decreases the reliability of the current findings. Second, only eight of the patients had IBD. This will compromise the significance of the comparison between the IBS and IBD in the current study.

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