Colonic Diverticulosis: Level of Fecal Calprotectin as Predictor of Disease Severity

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Background and study aim: Colonic diverticulosis is a common condition characterized by small pouches (diverticula) in the colon. These pouches can become inflamed or infected, leading to a condition called diverticulitis, or complicated by bleeding and perforation. Data about the utility of fecal calprotectin (FC) in managing colonic diverticular disease (DD) in the Egyptian literature is lacking. Fecal calprotectin (FC) is a protein used as a sensitive marker of colonic inflammation. The current study aims to evaluate the FC levels in different degrees of colonic diverticular disease. **Patients and Methods:** Three hundred sixty patients, 215 females and 145 males visiting the outpatient clinic of the participating centers were recruited. Patients were endoscope due to various indications All patients were exposed to full history taking, laboratory tests, abdominal CT scan with contrast, and colonoscopy with biopsies together ELISA based FC assay.

Results: In the current study most patients were females, with a mean age of 46.61±11.57 years. The mean FC level was 92,36+48,6 µg/g. Fecal calprotectin values were classified as mild, moderate, and marked elevations. The FC had a significant association with the severity of diverticulosis (P 0,00). FC positively correlates with other parameters used to assess the disease activity including CRP, ESR, and NIS classification. **Conclusion:** Based on the current study FC is potentially a reliable marker for assessing the disease severity in non-complicated diverticular diseases.

INTRODUCTION

Diverticulosis was considered an anatomic variant; however, it is now considered a routine finding among elderly patients. Its prevalence has risen from 5% to more than 50% in the last century among this sub-group of patients [1].

Recent observations suggest that diverticular disease (DD) could be considered a chronic inflammatory bowel disease (IBD). Mesalamine, a 5-ASA anti-inflammatory drug widely used in the treatment of IBD, has been recently found remarkably effective in treating both symptomatic uncomplicated and reducing the recurrence of symptomatic DD. The inflammatory background of DD has been confirmed histologically; cellular inflammatory infiltrate in DD was higher than in healthy controls and correlated with different degrees of DD [2].

Fecal calprotectin (FC) is a cytoplasmic antimicrobial compound prominent in granulocytes, monocytes, and macrophages. It accounts for approximately 60% of the total cytosolic protein. It is released from cells during cell activation or death, and it is stable in feces for several days after excretion [3].

This was found to be a sensitive marker of activity in Crohn's disease (CD) and to be correlated well with endoscopic and histological activity in ulcerative colitis (UC) [4]. This inflammatory marker is considered a stronger predictor of relapse in UC than in CD [5].

Increased levels of FC may also be found in patients harboring colonic polyps [6] but not in celiac disease [7]. There is growing evidence that slightly increasing FC levels were seen in DD than in healthy controls, but information about a specific

correlation between levels of FC and clinical degree of colonic DD is scarce, especially in our locality [7]. The current study aimed to evaluate the role of FC in differentiating different phenotypes of colonic DD and assess its relation to activity scores used to diagnose DD.

METHODS

Study type: Cross-sectional.

Study settings: This study was conducted simultaneously in Karel Sheikh University Hospitals, Kafr El Sheikh, Egypt, Zagazig University Hospitals, Zagazig, Egypt and Dar Alsalem Hospital, AL Khobar Saudi Arabia, AL Yousif Hospital, Al Khobar Saudi Arabia, in the period from to December 2023 to June 2024.

Patients: This study enrolled 360 consecutive patients who had undergone a total colonoscopy; affected by different stages and degrees (asymptomatic, symptomatic) of colonic DD, and in whom DD was diagnosed for the first time. The indications for total colonoscopy in the current study were not limited to colon cancer screening, unexplained abdominal pain (either long-lasting or recurrent); suspected DD either asymptomatic, symptomatic without diverticulitis, or acute uncomplicated diverticulitis (those are patients who had abdominal pain with or without increased inflammatory markers including ESR, WBCs, CRP) after exclusion of complications by the relevant imaging modality following the modified Hinchy classification [8].

Exclusion criteria: The following patients were excluded from the study: Patients with any colonic polyps or colorectal (CRC) cancer, previous personal or family history of CRC, IBD even if associated with diverticulosis, colon resection, IBS (through Rome IV criteria), prior use of non-steroidal anti-inflammatory drugs or COX inhibitors within one month before being enrolled in the study, and patients with confirmed complicated DD were also ruled out.

Workup: In addition to colonoscopy and FC assay patients were thoroughly evaluated by history and clinical examination. Investigations comprised routine stool analysis, fecal calprotectin, ESR, CRP, and blood cell counts (CBC) along with other investigations such as e.g., electrolytes, thyroid, liver, and renal functions. Serologic assays for suspected celiac disease (e.g., anti-transglutaminase IgA and IgG), …etc, were done whenever indicated to rule out associated pathology that can cause an increase in fecal calprotectin or assess complicated DD.

Colonoscopy: All patients underwent pan-colonoscopy following the standard bowel preparation using the neutral oral polyethylene glycol solution (Moviprep, Norgine Limited, UK) to be taken in the evening before the procedure with a clear liquid diet for 2 days before colonoscopy to secure optimal bowel cleansing. The procedure was done under the standards of care with sedation under anaesthesiologist observation. A standard six mucosal snips were obtained from the sigmoid colon for histological examination. In DD, biopsies were taken from the mucosa intervening in the diverticula [9].

Histological assessment: Hematoxylin and eosin staining was used to stain the mucosal snips taken during colonoscopy, with a focus on the lymphocytic and neutrophil cellular infiltrate, which was assessed in the whole depth of the mucosa as semi-quantitatively mild, moderate, and severe [9,10].

Fecal calprotectin assessment

In all patients, we assessed quantitively FC before performing a colonoscopy to avoid any colonoscopy-related elevations of this marker [11]. The collected stool samples were stored at 2–8°C according to the manufacturer's instructions. FC assay was quantitatively measured utilizing the two-site (sandwich) ELISA technique with two selected antibodies that bind to different epitopes of human calprotectin.

Number, Inflammation and Site (NIS) Classification

We proposed this classification as a predictor for disease severity. This comprises three items: namely number of diverticula, inflammatory condition of the colon, and site of diverticulum to be a simple indicator of disease severity with FC. The items of the score are described as follows: Number (N) of the diverticula described by CT or colonoscopy; less than 3 diverticulum - given score 1, from 3-6 diverticulum -given score 2, while more than 6 – given score 3. Inflammation (I) of the colon mucosa by colonoscopy and biopsy; erythema of mucosal wall with edema - given score 1, wall erosion - given score 2, If all criteria are present -given score 3. Site (S) of the diverticulum left colon or

sigmoid -given score 1, right colon -given score 2, whole colon -given score 3.

According to NIS

If the score is less than 3 - this is mild DD

if score (4-6) This is -moderate DD

If score (7-9)-severe DD

Follow-up

After the assessment and grading of DD, only symptomatic DD patients were medically treated. Patients with asymptomatic diverticulosis did not receive any drugs and were scheduled for regular visits with dietary and lifestyle modifications. Patients suffering from acute uncomplicated diverticulitis and patients suffering from symptomatic uncomplicated DD were treated according to the guidelines [12].

Statistics

The data were entered and analyzed using SPSS version 22. The means of FC in the different stages of DD underwent statistical evaluation. Statistical evaluation was done using the Wilcoxon test with Yate's correction for small numbers and Mann–Whitney two samples U test, as appropriate. The correlation between FC values and inflammatory markers and NIS score. A statistically significant difference was considered positive when $p < 0.05$.

RESULTS

Patient characteristics

The study included three hundred sixty patients, 215 (59.7%) were females and 145 were males with a mean age of 46.61±11.57 years. The inflammatory markers (CRP, ESR, total white blood cells, and FC) are shown in Table 1. The mean Fecal calprotectin level among patients of DD in the current study was 92.36±48.6 µg/g.

According to the FC level, the patients were divided into 3 groups as mild (≤100 µg/g), moderate (>100-<150 µg/g), and marked (≥150 µg/g) elevations. In the current study, mild cases represent the majority (71.9%). The characteristics of the three groups are shown in Table 2 without significant differences among the three groups.

Disease Severity

The disease severity in the current study was evaluated by many parameters. First, the colonoscopy features (Table 3) with a comment on site, number, and the associated signs of inflammation. The majority of cases were associated with sigmoid colon affection (71.1%), while the number assessment showed 71.7% of patients had ≤ 3 diverticula, whereas morphologically the majority had Erythema, edema (64.4%).

We proposed the NIS score as a marker of DD disease activity. This NIS score in the current study varied between 3 and 9 with a median of 4 which means that most of the cases in the current study were of moderate activity.

Faecal Calprotectin and Disease Severity

The primary aim of the current study was to evaluate how valuable is FC in the prediction of DD activity. Consequently, FC was assessed versus other parameters used to assess the disease severity. There was a significant relation between FC and NIS score especially cases with marked FC elevation (Table 4). Regression analysis showed that FC had a positive correlation with NIS score and CRP level while there were no significant correlations with ESR and total WBC count (Table 5).

Diagnostic accuracy of Faecal Calprotectin in assessing Disease Activity/Severity

As shown in Table 5, the FC was used as a prognostic marker to assess the severity of DD in comparison to the acute phase reactants. For severe DD, FC at a cutoff >175 had a sensitivity of 85.0% and a specificity of 92.5%. While FC with cutoff >162 <175 can predict moderate DD with a sensitivity of 83.3% and specificity of 96.0%. Furthermore, FC with cutoff >65 had a sensitivity of 97.0%and specificity of 82.8%. These figure looks promising when compared with commonly used markers ESR and CRP where these have a sensitivity of 75.0% and 83.5%, and specificity of 92.0% and 78% respectively.

Table (1). Baseline characteristics of the studied patients

Age (years)	**Mean± SD**	**46.61±11.57**	
	Median (Range)	**48.0 (15-80)**	
		N	%
Sex	Female	215	59.7
	Male	145	40.3
	Total	360	100.0

	CRP	**ESR**
Mean± SD	10.22±5.8	31.05±14.37
Median (Range)	9.0 (2-37)	28.0 (3-90)

		Fecal calprotectin (µg/g)	
Mean± SD		92.36±48.6	
Median (Range)		70.0 (23-350)	
		N	%
Fecal calprotectin	**Mild**	259	71.9
	Moderate	40	11.1
	Marked	61	16.9
	Total	360	100.0

Table (2). Comparison between different levels of fecal calprotectin.

			Mild	**Moderate**	**Marked**	**P**
Age (years)			47.13±11.59	44.12±13.61	46.04±9.89	0.286
WBC (x10^3)			8.73±2.58	7.90±2.41	8.64±1.87	0.478
Platelet count (x10^3)			227.31±51.6	244.12±61.5	223.37±54.84	0.129
HB level (gm/dl)			11.85±1.97	12.13±1.75	11.62±2.64	0.063
CRP			9.95±3.25	9.92±3.25	11.54±3.62	0.152
ESR			31.31±11.36	28.50±9.25	31.62±10.63	0.48
Sex	**Female**	**N**	160	21	34	
		%	61.8%	52.5%	55.7%	0.42
	Male	**N**	99	19	27	
		%	38.2%	47.5%	44.3%	
Total		**N**	259	40	61	
		%	100.0%	100.0%	100.0%	

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Table (3). Colonoscopy/Histology parameters

		NUMBER	
Mean± SD		4.48±2.27	
Median (Range)		4.0 (3-9)	
		N	%
Number score*	1.00	258	71.7
	2.00	17	4.7
	3.00	85	23.6
	Total	360	100.0

		N	%
Inflammation	**All**	59	16.4
	Erosions	69	19.1
	Erythema, edema	232	64.4
	Total	360	100.0

		N	%
Site	**Left**	37	10.2
	Pan	67	18.6
	Sigmoid	256	71.1
	Total	360	100.0

score 1; less than 3 diverticula, score 2; 4-6 diverticula, score ; 3 more than 6 diverticula

Table (4). Relation between fecal calprotectin and NIS

	Mild	**Moderate**	**Marked**	**F**	**P**
NIS	3.23±0.66	6.12±1.45	8.70±1.03	1094.58	0.00**

Table (5). Correlation between Fecal calprotectin and other parameters

		Fecal calprotectin
ESR	R	0.051
	P	0.336
CRP	R	0.178**
	P	0.001
WBC	R	0.013
	P	0.812
NIS	R	0.862**
	P	0.000

Table (6). Diagnostic accuracy of FC in assessing disease activity

For Severe Disease						
ROC Area	**Cutoff**	**P**	**95% Confidence Interval**		**Sensitivity**	**Specificity**
			Lower Bound	Upper Bound		
0.916	>175	0.00**	0.879	0.952	85.0%	92.5%
For Moderate Disease						
Area	**Cutoff**	**P**	**95% Confidence Interval**		**Sensitivity**	**Specificity**
			Lower Bound	Upper Bound		
0.953	>162 <175	0.00**	0.926	0.981	83.3%	96.0%
For Mild Disease						
Area	**Cutoff**	**P**	**95% Confidence Interval**		**Sensitivity**	**Specificity**
			Lower Bound	Upper Bound		
0.91	>65	0.00**	0.84	0.97	97.0%	82.8%

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DISCUSSION

Fecal calprotectin has been established as a biological marker of gastrointestinal diseases and hence can be used to differentiate between organic and functional bowel disorders [13]. Furthermore, FC level has been an adjective tool reflecting the severity of inflammatory colonic diseases.

In the current study, the mean age of included patients with DD was 46.61 +11.57 years (15- 80 years), while females were the majority; 59.7%. These data are consistent with the data in the literature where DD is common with advancing age [14,15], although we reported DD in younger age groups. The data shown in the literature showed increasing reports of DD in younger age groups [16], in Egypt the median age for DD was 55 years [17], while in Saudi Arabia it was 53 years [18]**,** in Taiwan the prevalence among young age group < 39 years was 4.9% in young adults undergoing colonoscopy [19]**.** The prevalence of DD in Egypt is variable, one large cohort study reported a rate of 2%, among patients residing in the Nile Delta [17].

In the current study, most of the cases (71.1%) had DD limited to the sigmoid region, although pan-colonic affection was reported among 18.6% of cases, results that run in agreement with the literature [20].

In the current study, the mean level of FC was 92.36±48.6 and cases were classified as mild, moderate, and marked although most of our patients (71.9%) had mild elevations. This was consistent with earlier studies, Nakov et al., reported an FC level of 115 in symptomatic DD [21].

In the current study, a great proportion of patients had endoscopic features consistent with active inflammation represented as erythema and edema by histopathology (64.4%), while 19.1% had erosions alone and 16.4% of patients had both inflammation and erosions. Nakov et al. reported that all symptomatic cases with diverticulitis had histologic evidence of inflammation with > 5 lymphocyte infiltration in one field on histologic examination of the colonoscopy specimens [21].

In our study we proposed NIS classification to detect the degree of disease severity where N represents several diverticula, I represents inflammation with histopathology and S represents the site of diverticulum. To the best of our knowledge, this is the first time to combine DD number, site together with inflammation grade in one score to evaluate such cases and we found that NIS distribution was **4.48±2.27**, the use of this score would help both clinicians as well as endoscopists to evaluate the severity of patients with DD. Many scores either clinical, laboratory, or radiological have been proposed, however NIS is unique in combining endoscopic and histopathologic criteria.

In the current study, FC showed a correlation with markers of DD disease severity (NIS score), and acute phase reactants which makes it a reliable marker for monitoring the severity of DD. FC at cut-off 175 can predict severe DD with a sensitivity of 85% and specificity of 92% (ROC area 0.912), while for moderate DD a level between 162 and 175 had a sensitivity of 83.3% And specificity of 96% (ROC 0.95), furthermore, FC > 65 had a sensitivity of 97% and specificity of 82.2 % in diagnosis of DD making is more reliable than CRP and ESR. FC has been studied as a diagnostic as well as a prognostic marker for DD in many earlier studies and it was found valuable. Tursi et al. found that FC may be useful in detecting colonic inflammation in DD and in distinguishing symptomatic DV from IBS, as well as in assessing response to therapy in DD [9] a result that was re-emphasized by Nakov et al. [21], although in a smaller cohort of patients. It should be mentioned also that in patients with a normal colonoscopy, a simultaneously measured increased FC level was not associated with an increased risk for significant GI disease during a follow-up period of 3 years as recently reported by Hovstadius et al. [22].

The current study had its own limitations that are not limited to the small number of patients recruited, lack of long-term follow-up, and lack of patients with complicated disease to evaluate the role of FC among patients with complicated DD. Lack of validation of NIS scoring system as a reliable prognostic index for DD. Hopefully, we run a larger study covering all these limitations shortly.

CONCLUSION

In conclusion, based on the current study Fecal calprotectin is potentially a reliable marker for assessing the disease severity in non-complicated diverticular disease.

Ethical approval:

The study was carried out according to sound clinical practice. This study was approved by the Institutional Review Board of AL Yousif Hospital, Al Khobar, Saudi Arabia (AYH-IRB# 10/12/23) and each subject gave written informed consent to participate in the study.

Conflict of Interest Statement: None.

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Author Contributions: Salam R., Ahmed M, El Hendawy R., and Emara M. developed the concept of the study. Salam R., Ahmed M, and El Hendawy R. searched the literature. Salam R., Ahmed M, El Hendawy R., and Emara M. analyzed the evidence. All authors participated in the management plan. Salam R., Ahmed M, and Emara M. drafted the manuscript. All authors revised and approved the manuscript.

HIGHLIGHTS

- Fecal calprotectin is a reliable non-invasive predictor of disease activity among patients with non-complicated diverticular disease.
- NIS classification is a probably useful marker for assessment of disease activity in diverticular disease

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