RESEARCH

Predictors of surgical intervention in patients with inflammatory bowel disease (two-center study)

Khaled Hamdy Abd El Megeed¹, Shereen Abou Bakr Saleh¹, Ahmed Elkattary Mohamed² and Christina Alphonse Anwar^{1*}

Abstract

Background: Sixty percent of Crohn's disease (CD) patients require intestinal resection, and 20% of ulcerative colitis (UC) patients undergo proctocolectomy for medically refractory disease. Scarcity of literature about predictors for surgical intervention in inflammatory bowel disease (IBD) encouraged the conduction of this study to assess risk factors for surgical intervention in IBD patients.

Results: This cohort study included 80 Egyptian inflammatory bowel disease patients recruited from two medical centers. Patients were classified into two groups, 40 patients each, according to their need for surgical intervention to control inflammatory bowel disease. The two groups were compared regarding age of onset, type and location of disease, smoking, extraintestinal manifestations, perianal disease, granuloma, severity scores, stool calprotectin, complete blood count, erythrocyte sedimentation rate, C-reactive protein, and serum albumin at diagnosis for Crohn's disease patients.

Twelve ulcerative colitis and 28 Crohn's disease patients required surgical intervention in the form of total colectomy (30%), fistulectomy (32.5%), resection anastomosis (17.5%) or abscess drainage (20%). Perianal disease, smoking, and disease severity scores showed high significant differences (P value < 0.001); disease type and presence of granuloma showed statistically significant difference (P value < 0.05) between both groups. But, patient age at onset, location of the disease or extraintestinal manifestation had no statistical significance (P value > 0.5). Surgical interventions were more likely to be needed in patients with higher stool calprotectin level, C-reactive protein, erythrocyte sedimentation rate, and lower serum albumin for Crohn's disease patients (P value < 0.001 for each).

Conclusion: Smoking, perianal disease, higher severity scores, stool calprotectin, C-reactive protein, and erythrocyte sedimentation rate levels are predictors of surgical treatment.

Keywords: Inflammatory bowel disease, Surgical, Ulcerative colitis, Crohn's disease

Background

Severe bleeding in up to 10% of UC patients, fistulae, peritonitis, abscess, intestinal obstruction in Crohn's disease patients as well as intestinal perforation and toxic megacolon are indications of surgery in IBD patients.

¹Internal Medicine Department, Hepatology and Gastroenterology Unit, Full list of author information is available at the end of the article

Toxic megacolon should be suspected in IBD patients presenting with abdominal distension and diarrhea, clinical signs of systemic toxicity combined with radiographic evidence of colonic dilatation (diameter > 6 cm) are diagnostic. Toxic megacolon can be treated early using intravenous glulcocorticoids. Yet if there was no response within 3 days in the form of less toxic patient, decreased fluid and transfusion requirements, resolution of abdominal and colonic dilatation with improvement of abnormal laboratory findings, and then the patient

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* Correspondence: Christina.alfons@yahoo.com; Christinalfons7@gmail.com Faculty of Medicine, Ain Shams University, Cairo, Egypt





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should receive either infliximab or cyclosporine as second-line therapy for further 3 days. If there was no improvement thereafter or if the patient was already on biological therapy, then subtotal colectomy with end-ileostomy should be held without delay [1].

Fistulae may develop between the diseased bowel and adjacent tissues, as enteroenteric, enterovesicular, enterogenital or enterocutaneous fistulae in the perianal area which may form subcutaneous abscesses. Immunomodulators, biologic agents, antibiotics and total parenteral nutrition with bowel rest can be used to treat fistulizing disease. Yet if the disease is refractory, intestinal diversion surgeries should be used [2]. In case of abscess formation, antibiotics with percutaneous drainage for abscesses > 2 cm in diameter with optimization of Crohn's therapy are usually required, yet there may be recurrence of the abscess, so surgical resection of the diseased bowel is frequently needed [2].

Partial or complete intestinal obstruction may result from stricture formation due to severe disease of the small intestinal lumen, with ulceration and transmural inflammation. A stricture becomes symptomatic with superimposed inflammation and spasm. Accordingly, the resulting obstruction can be relieved with bowel rest and parenteral glucocorticoids, yet urgent surgery should be done in case of acute deterioration. Fibrotic strictures causing recurrent obstructive episodes should be resected with elective surgery [2].

In spite of the agreement that need for surgical intervention is reducing with the introduction of biologics, yet up to 60–80% of CD patients still require an intestinal resection and 20% of UC patients undergo proctocolectomy for medically refractory disease [3].

Some previous reports mentioned high relapse rate, need for hospital admission, extraintestinal manifestations, development of penetrating disease, multiple admissions for flares, early age at diagnosis, smoking, extensive ulceration of the mucosa, high titers of serum antibodies and mutations of the NOD2 gene as predictors for the need for surgical intervention for IBD patients [4].

Scarcity of published literature regarding the predictors for surgical intervention for IBD encouraged the conduction of the present study in order to assess risk factors for surgical intervention in Egyptian IBD patients in two different centers.

Methods

A comparative study included 80 inflammatory bowel disease patients selected from two centers in Egypt.

Through this study, data of IBD patients in both centers in the period between May 2017 and November 2019 were analyzed. After exclusion of patients with other comorbidities and those with incomplete medical follow-up reports, included patients were selected and divided into two equal groups according to their need for any surgical intervention (group 1 was counted from records first then group 2 was selected to match number and current age of group 1).

- Group 1: Included patients who needed surgical intervention (40 patients)
- Group 2: Included patients controlled on medical treatment (40 patients)

The two groups of patients had been studied regarding the following items: age at disease onset, sex, type of disease (CD or UC), location of the disease, presence or absence of extraintestinal manifestations, presence or absence of perianal disease, presence or absence of granuloma in tissue biopsy, smoking, Crohn's disease activity index (CDAI) [5] for patients with CD, Mayo score for patients with ulcerative colitis [6], laboratory data including stool calprotectin level, complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum albumin at disease diagnosis for CD patients.

Data were collected, tabulated and analyzed using mean, standard deviation, Chi-square, and analysis of variance (ANOVA) tests by SPSS V17. For ANOVA test significance: P value > 0.05 is non-significant, \leq 0.05 is significant, and < 0.01 is highly significant.

Results

This study included 80 IBD patients with ages ranging between 34 and 65 years; 40 of them were males; 29 patients were smokers. The mean age at the onset of the disease was 25.81 ± 6.8 years. Colon only was affected in 50% of the patients, and 33.75%of the patients had both colonic and small intestinal affection. Extraintestinal manifestations—in the form of uveitis, arthritis, and arthralgia—were present in 61.3% of the cases and 37.5% of the cases had perianal disease and 27.5% had granulomas on histopathological reports. Mean CDAI score was $298.45 \pm$ 83.3 for CD, and mean Mayo score was 8.65 ± 1.9 for ulcerative colitis patients.

The 40 patients enrolled in the surgical group were found to be 12 patients (30%) with UC and 28 patients (70%) with CD; those patients had either total colectomy (12patients [30%]), fistulectomy (13 patients [32.5%]), resection anastomosis (7 patients [17.5%]), or abdominal abscess drainage (8 patients [20%]).

Perianal disease and smoking were more prevalent among the surgical group; CDAI score for CD patients and Mayo score for UC patients were also higher among surgical group (P value < 0.001), Crohn's disease and granuloma formation were more common among surgical group (P value < 0.05). On the contrary, neither of patient age at the onset of the disease, location of the disease, or extraintestinal manifestation had any statistical significance (P value > 0.5) on comparing both patient groups (Table 1).

Surgical patients were more likely to have statistically significant higher stool calprotectin level (P value < 0.001), CRP (P value < 0.001), ESR (P value < 0.001), and lower serum albumin at onset of the disease for CD patients (P value < 0.001), yet there was no significant differences concerning CBC parameters between the two study groups (Table 2).

Cutoff values, sensitivity, and specificity of significant scores and laboratory parameters are attached in Table 3.

Discussion

Multiple effective therapeutic options exist for the treatment of IBD, yet a proportion of patients either fail to respond or lose response to therapy [7]. Those require an intestinal resection or proctocolectomy for medically refractory disease [3].

 Table 1
 Comparison between both groups as regard smoking and disease characteristics

Variable	Group 1	Group 2	P value
Age at onset in years—Mean \pm SD	26.5 ± 7.8	25.12 ± 5.6	0.372
Type, No. (%)			
UC	12 (30%)	28 (70%)	0.02
CD	28 (70%)	12 (30%)	
Location, No. (%)			
Colon	12 (30%)	28 (70%)	0.11
Small Intestine	8 (20%)	5 (12.5%)	
Both	20 (50%)	7 (17.5%)	
Perianal disease, No. (%)			
Yes	24 (60%)	6 (15%)	< 0.001
No	16 (40%)	34 (85%)	
Granuloma, No. (%)			
Yes	16 (40%)	6 (15%)	0.012
No	24 (60%)	34 (85%)	
Smoking, No. (%)			
Yes	23 (57.5%)	6 (15%)	< 0.001
No	17 (42.5%)	34 (85%)	
CDAI for CD $(n = 40)$			
Mean ± SD	360 ± 64.5	236.9 ± 45.6	< 0.001
Mayo score for UC ($n = 40$)			
Mean ± SD (≤ 12)	9.85 ± 0.93	7.45 ± 1.9	< 0.001

SD standard deviation

Characterization of patients with high probability of undergoing surgical intervention for IBD is mandatory, yet identifying predictors for surgical intervention is still lagging.

Therefore, this comparative double-center study was conducted on 80 Egyptian IBD patients, in order to assess risk factors for surgical intervention in patients with IBD.

As regard the onset of the disease, the mean age was 25.81 ± 6.8 years old. This agrees with De Barros et al. [8] on analyzing the epidemiological profile of 40 patients with IBD under biologic therapy through a retrospective observational clinical study, the mean age at onset was around 25 years old.

In the present study, the most common location of the disease was colon; Lehtinen et al. [9] *as well* demonstrated that the colon was the most commonly affected site. Additionally, *Aziz et al.* [10], while determining different clinical presentations of IBD in a 5-year retrospective study, the colon was the most commonly affected site.

Results indicated no statistically significant difference between surgical and medical patients in terms of age at onset of the disease (P value = 0.37). In consistence with our findings, Lee et al. [11] stated that surgery rates were not significantly associated with age at onset in Korean UC patients, another study from a larger North American registry demonstrated that the age of onset of UC was not related to the rate of surgical intervention [12] as well.

In the present study, we found that smoking, being statistically significantly higher among group 1 (P < 0.001), is a predictor of surgical treatment. This matches with Karczewski et al. [13], *who* investigated the effect of tobacco use on the clinical course of IBD.

Extraintestinal manifestations were present in 61.3% of the cases which is close to de Barros et al. [8] study, were extraintestinal manifestations were present in 70% patients. In our study, although more in CD patients, there was no statistically significant difference between surgical and medical patients in terms of extraintestinal manifestations (P = 0.25), this was against a retrospective analysis of endoscopic balloon dilatation of intestinal strictures in CD reporting that the presence of extraintestinal manifestations and extensive preoperative disease were more likely to require further dilatation or surgery following an index dilatation [14]. This may be attributed to different ethnic groups between study populations.

Statistically significant differences were found between surgical and medical patients in terms of type of IBD; CD patients were more than UC patients in group 1 (P= 0.02); surgical patients were more likely to have perianal disease (P < 0.01) and granulomas (P < 0.012). In

Variable	Group 1 Mean ±SD	Group 2 Mean ±SD	P value
Stool Calprotectin level (μg/g)	543.35 ± 210.1	342.12 ± 229.2	< 0.001
CRP level (mg/dl)	67.57 ± 14.1	33.35 ± 10.6	< 0.001
Albumin level at time of diagnosis (g/dl) for CD	3.10 ± 0.42	4.62 ± 0.39	< 0.001
ESR(mm/h)	59.95 ± 5.1	30.75 ± 4.1	< 0.001
Hemoglobin (g/dL)	10.14 ± 0.59	9.87 ± 0.63	0.058
Hematocrit %	35.9 ± 2.9	36.32 ± 2.9	0.52
White blood cells (× 1000 cell/mm ³)	12.25 ± 0.9	14.3 ± 1.4	0.41
Platelet count (× 1000 cell/mm ³)	519.2 ± 54.3	498.42±44.3	0.064

Table 2 Comparison between both groups as regard laboratory data

SD standard deviation

concordance with our findings, *Nasir et al.* [15] documented that perianal disease and the NOD2 genotype were the only independent factors associated with the need for surgery. Agar et al. [16] revealed that presence of complicated disease at diagnosis (intestinal stenosis, fistula) were independent predictive risk factors for subsequent surgery in CD.

In the present study, there were statistically significantly higher CDAI for CD (P value<0.001) and Mayo score for UC (P value < 0.001) among group 1. CDAI score > 287 and Mayo score > 8.5 achieved high sensitivity and specificity for the detection of surgical treatment. Similarly, Agar et al. [16] reported that CDAI > 250 was independent predictive risk factors for subsequent surgery in CD.

In the present study, the mean CRP level was $50.46 \pm 21.2 \text{ (mg/dl)}$; while the mean ESR and WBC count were $45.35 \pm 15.4 \text{ mm/h}$ and $13.28 \pm 10.9 \times 1000 \text{ cell/mm}^3$ respectively indicating high expression of those biomarkers. In agreement with our findings, Alper et al. [17], correlating ESR and CRP with diagnosis of IBD and with clinical, endoscopic, histological, and radiographic disease activity during follow-up showed that patients with IBD had significantly higher ESR and leucocytic count, this was also agreed on by Solem et al. [18].

Analysis showed that there were statistically significant differences between surgical and medical patients in terms of CRP (P value < 0.001), and ESR (P value <

Table 3 Cutoff values of different scores and inflammatory

 markers in prediction of surgical intervention in IBD patients

Variables	Surgical TTT			
	Cutoffs	Sensitivity	Specificity	value
CDAI for CD	> 287	90%	85%	0.01
Mayo score for UC	> 8.5	90%	70%	0.01
Stool calprotectin level (µg/g)	> 341.5	92.5%	78.5%	0.01
CRP (mg/dl)	>44	99%	87.5%	0.01
ESR (mm/h)	>55	92.5%	100%	0.01

0.001) being higher in group 1. CRP level is a predictor of surgical treatment at a level of > 44 mg/dL with high sensitivity (99%) and specificity (87.5%). A prospective study from Oxford evaluated 49 severe UC patients, those with an increased CRP (> 45 mg/L) predicted with 85% certainty the need for colectomy [19]. Henriksen et al. [20] investigated the predictive value of CRP levels for disease outcome, in patients with UC and extensive colitis, CRP levels above 23 mg/l at diagnosis predicted an increased risk of surgery. A significant association between CRP levels at diagnosis and risk of surgery in patients with CD, CRP > 53 mg/l was associated with increased risk [20].

In this study, stool Calprotectin level is a predictor of surgical treatment at a level of > 341.5 μ g/g with high sensitivity 92.5% and specificity 78.5%. This is in line with Kennedy et al. [21] on reporting that increased level of fecal calprotectin at the first visit was associated with subsequent progression of CD and need for surgery. Calprotectin concentration in UC patients correlated with worse outcome including need for surgery [22]. Theede et al. [23] showed that in UC, baseline stool calprotectin of more than 321 μ g/g predicted worse outcome including need for surgery.

Study's limitations

Sample size of this cohort was relatively small which may affect the generalization of findings, the study was a retrospective analysis of prospectively collected data which did not allow any further study of suspected additive parameters as genetic studies. Moreover, long-term outcomes and postoperative follow-up were not studied in this study.

Conclusion

Smoking, Crohn's disease, perianal disease, granuloma formation, higher severity scores, higher stool calprotectin level, higher C-reactive protein, and higher erythrocyte sedimentation rate were associated with higher risk of surgical intervention. Smoking, perianal disease, CDAI, Mayo score, stool calprotectin level, C-reactive protein level, and erythrocyte sedimentation rate can be considered as predictors of surgical treatment as they were highly significant in patients who needed surgical intervention.

Abbreviations

CBC: Complete blood count; CD: Crohn's disease; CDAI: Crohn's disease activity index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; WBC: White blood cell count

Acknowledgements

Authors are thankful to the IBD groups at both involved centers for their help in supplying data.

Authors' contributions

KH did the final approval of the version to be published; SA designed the work; AK carried data collection, data analysis, and interpretation; and CA did drafting of the article. The authors have read and approved the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participation

This study had been performed in accordance with the ethical standards. Approval of Ain Shams University, Faculty of Medicine, Research Ethics Committee (REC FWA 000017858) was obtained in July 2019 before starting the study, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Consent of publication

A consent was taken from participants after the study steps were explained and before starting the study.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Internal Medicine Department, Hepatology and Gastroenterology Unit, Faculty of Medicine, Ain Shams University, Cairo, Egypt. ²Quabbary General Hospital, Alexandria, Egypt.

Received: 8 March 2021 Accepted: 6 May 2021 Published online: 08 July 2021

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