
Risk Stratification and Outcomes of Management in Egyptian Patients with Fistulizing Crohn's Disease

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Abstract

Background: Crohn's disease (CD) is a chronic, relapsing inflammatory condition of uncertain origin that can affect any segment of the gastrointestinal tract in a transmural pattern, often resulting in complications such as fistulae or perforation. Although its prevalence appears to be rising in Egypt, precise epidemiological figures are lacking. The present study was designed to identify risk factors associated with fistulizing CD and to examine treatment outcomes in affected Egyptian patients.

Methods: The present retrospective–prospective cohort study comprised 90 Egyptian individuals with Crohn's disease, divided into a fistulizing group (n = 45) and a non-fistulizing group (n = 45). The clinical features, risk factors, and treatment outcomes were evaluated. The

clinical, radiographic, and colonoscopic examinations were also performed and assessed before and after treatment.

Results: Male sex and smoking were more prevalent but not significant among cases with fistulizing CD. Enteroenteric fistulas were the most common subtype, while infliximab therapy and surgical intervention were the most frequent treatment strategies. The use of non-steroidal anti-inflammatory drugs (NSAIDs) was significantly higher in the fistula group. Both groups showed significant improvement following treatment, as indicated by the simplified endoscopic activity score for Crohn's disease (SES-CD) and the Crohn's Disease Activity Index (CDAI), with the fistula group demonstrating a more substantial response.

In conclusion, this study identifies NSAID use as a significant risk factor for the development of fistulizing Crohn's disease. It reinforces the clinical utility of CDAI scores in evaluating disease activity and monitoring treatment outcomes.

Keywords: *Crohn's disease, fistulizing Crohn's disease, Outcomes of Management, CDAI scores, Colonoscopy, Endoscopic Score for Crohn's Disease, Risk factors, NSAID, Infliximab, Adalimumab.*

INTRODUCTION

Crohn's disease (CD) is most prevalent in industrialized regions [1]. A recent review reported annual incidence rates of 20.2 per 100,000 in North America, 12.7 per 100,000 in Europe, and 5.0 per 100,000 across the Middle East and Asia [2]. Its pathogenesis is linked to dysregulated immune responses, where an imbalance between pro-inflammatory and anti-inflammatory cytokines in the intestinal mucosa drives the onset and progression of inflammatory bowel disease (IBD) [3].

The evaluation of suspected CD cases should involve colonoscopy with ileal assessment and biopsy, followed by complementary imaging studies. Gross endoscopic

findings suggestive of CD should be supplemented with histological examination of mucosal biopsies to determine disease extent and severity [4].

Treatment decisions are influenced by multiple factors, including patient age, individual risk factors, disease site and severity, previous response to therapy, and the presence of complications [5]. Sepsis must be controlled before initiating immunomodulators or systemic steroids, and patients should be adequately informed of potential adverse effects [6].

Biologic agents, such as infliximab, adalimumab, and certolizumab pegol, target tumor necrosis factor- α (TNF- α), a key mediator in the pathogenesis of IBD. Additionally, ustekinumab and vedolizumab have demonstrated efficacy in inducing remission in patients refractory to anti-TNF therapy, with ustekinumab exhibiting superior outcomes [7, 8].

Surgical intervention remains necessary for patients with pre-neoplastic or neoplastic lesions, obstructive stenosis, suppurative complications, fistulizing disease, or medically refractory CD [9].

Fistulizing CD is more likely in cases with early age at onset, long disease duration, ileocolonic distribution, and penetrating or perianal manifestations. Smoking and genetic predisposition may further accelerate progression, while isolated ileal disease appears less prone to fistula formation. Current biomarkers exhibit limited predictive value, underscoring the need for improved risk stratification to guide timely interventions [10].

This study aimed to assess the risk factors for the development of fistulizing Crohn's disease and evaluate the outcomes of management strategies among Egyptian patients.

PATIENTS AND METHODS:

Study Design and Population

This retrospective–prospective cohort study was conducted on 90 Egyptian patients diagnosed with CD, recruited from the outpatient clinics and inpatient wards of the gastroenterology and hepatology departments at Ain Shams and Al Kasr Al-Ainy University hospitals. Participants were categorized into two groups: the fistula group included 45 patients diagnosed with CD who presented with any fistula (internal or external), and the non-fistula group included 45 patients diagnosed with CD who had no history of fistula formation, regardless of the severity of the disease.

Sample size was calculated using MedCalc (v22.009) with a 95% confidence level, 80% power, and hospitalization rates from Fan et al. (2022): 50% in non-fistulizing and 80% in fistulizing Crohn’s disease [11]. The required sample was 80, increased by 10% to 90 to account for dropout. Participants were evenly assigned to either the fistula or non-fistula groups (1:1).

Ethical Considerations

The study was conducted in accordance with ethical guidelines and was approved by the Faculty of Medicine, Ain Shams University Research Ethics Committee (Approval No: FMASU MS 771/2022). All participants provided written informed consent before enrollment. Each patient was assigned a unique number and recorded on the master sheet to ensure data confidentiality and compliance with ethical standards.

Inclusion and Exclusion Criteria

Adult patients with CD, with available clinical, radiographic, and endoscopic data, and a willingness to participate in the study and provide informed consent, were included.

The included cases were recruited from December 2022 to June 2023, and all were monitored for one year to assess treatment outcomes, recurrences, and relapses.

Pregnant women, patients who refused to participate in the trial, critically ill patients, patients with any mental health problems, patients with gastrointestinal malignancies, or active tuberculosis, and patients with the human immunodeficiency virus (HIV) were all excluded from the study.

Data Collection and Clinical Assessment

All subjects underwent a complete medical history and clinical assessment. The collected data includes the following:

- **Demographic and Clinical Characteristics:** Age at disease onset, sex, socioeconomic status, smoking history, family history of CD, disease duration, and comorbidities (e.g., diabetes mellitus, hypertension, obesity).
- **Long-term NSAID consumption** is defined as the use of any NSAID an average of 3 times per week for more than 3 months [12]. In this study, we defined NSAID intake as being more than once per week for at least three months.
- **Extraintestinal Manifestations:** Joint, skin, ocular, hematologic, and hepatobiliary involvement.
- **Laboratory Investigations:** Measurement of inflammatory markers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin (FCP).

Disease Management and Outcome Assessment

The management plan was selected based on recommendations from a multidisciplinary team, case characteristics, and the availability and affordability of treatment options. The management approaches included surgical intervention, biologic therapy

(infliximab, adalimumab, and ustekinumab), and conventional therapy (corticosteroids and immunomodulatory).

The severity of CD and treatment response were assessed using multiple modalities:

- **Clinical Assessment:** The Crohn's Disease Activity Index (CDAI) was used to evaluate disease severity, calculated via the MdCalc application. The CDAI is a composite score derived from eight variables recorded over seven days: the number of liquid or soft stools, the severity of abdominal pain, general well-being, the presence of complications, the use of antidiarrheal medications, the presence of an abdominal mass, hematocrit, and body weight. Scores <150 indicate remission, 150–219 mild activity, 220–450 moderate activity, and >450 severe disease activity.

- **Radiological Assessment:** Computed tomography enterography (CTE) and magnetic resonance enterography (MRE) were performed before and after treatment to monitor disease progression.

- **Endoscopic Assessment:** Disease activity was evaluated using the Simplified Endoscopic Score for Crohn's Disease (SES-CD). The SES-CD assesses four endoscopic variables in five ileocolonic segments (ileum, right colon, transverse colon, left colon, and rectum): size of ulcers, ulcerated surface, affected surface, and presence/type of narrowing. Each variable is graded on a scale of 0 to 3, resulting in a total score ranging from 0 to 56. A score of 0–2 indicates inactive disease, 3–6 mild, 7–15 moderate, and ≥ 16 severe disease activity [13].

- **Histopathological Assessment:** The Nancy Histological Index was used to assess histological disease activity [14].

Study Design and Statistical Analysis

The study incorporated both retrospective and prospective analyses:

- Retrospective analysis: Investigated associations between clinical, demographic, and biochemical parameters and the presence of fistulizing disease.
- Prospective analysis: Evaluated treatment outcomes over a one-year follow-up period, considering the impact of significant risk factors on disease progression and management efficacy.

The SPSS statistical analysis application (IBM Inc., Chicago, IL, USA) was used to examine, code, and analyze the data. The standard deviation, mean, and median were used to express the numerical variables. Frequencies had been used to characterize categorical parameters. Fisher's, McNemar, Mann-Whitney, Wilcoxon, and chi-square tests, as well as independent t-tests, were used. A P-value ≤ 0.05 was considered statistically significant. For within-group comparisons of SES-CD before and after treatment, the Friedman test was applied because SES-CD is ordinal and assessed across multiple intestinal segments. The P value was determined using the signed-rank test and the marginal homogeneity test. The logistic regression for independent risk factors for fistulizing CD was evaluated using the regression coefficient (binary logistic regression) with stratified analysis.

RESULTS

Patient Demographics and Baseline Characteristics

This study included 90 cases diagnosed with CD, with a mean age of 33.69 ± 12.34 years. The study consisted of 35 females (38.9%) and 55 males (61.1%).

In the fistula group (n =45), the most frequently observed fistula type was enteroenteric fistula in 16 patients (35.5%), followed by perineal fistula in 12 patients (26.7%) and enterocutaneous fistula in 8 patients (17.8%). Less commonly observed were enterovesical fistulas in 2 patients (4.44%), combined enteroenteric-enterocutaneous fistulas in 4 patients

(8.88%), enteroenteric-enterovesical fistulas in 2 patients (4.44%), and entero-vesical-enterocutaneous fistulas in 1 patient (2.22%). Regarding the management plan, surgical intervention was performed in 31.1% (n = 14) of patients, of whom seven were biologic-naïve and 7 had prior biologic therapy. Infliximab therapy was administered to 53.3% (n = 24) of patients, including five who were newly initiated on treatment and 19 who had previously received infliximab. Adalimumab therapy was used in 11.1% (n = 5) of patients. Ustekinumab therapy was prescribed for 2.2% (n = 1) of patients. Conventional treatment (immunomodulators and corticosteroids) was administered to 2.2% (n = 1) of patients who were bio-naïve. According to the Montreal classification, concerning the age of disease onset, there were 5 cases classified as A1, 36 cases as A2, and 4 cases as A3. About the location of lesions, there were 6 cases with L1, 7 cases with L2 (4 of which had anorectal lesions), and 32 cases with L3 (4 of which also had anorectal lesions). Regarding the behavior, all cases in this group were classified as B3, with two exhibiting stricturing lesions.

Regarding the non-fistula group (n = 45), the management strategy is presented as follows: 31.1% of patients (n = 14) received infliximab, comprising two who were newly starting therapy and 12 who were already undergoing treatment. Twenty % of patients (n = 9) were administered adalimumab, comprising one patient who was newly starting therapy and eight patients who were already on biological treatment. 13.33% of patients (n = 6) were given ustekinumab (all of whom were already on biological therapy), and 35.55% of patients (n = 16) received conventional treatment (bio-naïve). According to the Montreal classification, based on the age of disease onset, 8 cases were classified as A1, 33 as A2, and four as A3. Concerning lesion distribution, 9 cases were categorized as L1, six as L2 (including one with anorectal involvement), and 30 as L3 (with 7 cases exhibiting anorectal involvement).

Regarding disease behavior, 41 cases were classified as B1, while four were categorized as B2; one of them presented with stricturing lesions.

Table 1. Sociodemographic characteristics, comorbidities among the study groups, and Logistic regression for independent risk factors of fistulizing Crohn's disease.

Variables		Fistula group (Total=45)	Non-Fistula group (Total=45)		p-value	
Age (years)	Mean±SD	33.9±11.8	33.5±13.1		^0.893	
	Range	17.0–66.0	15.0–75.0			
Sex	Male	29 (64.4%)	26 (57.8%)		#0.517	
	Female	16 (35.6%)	19 (42.2%)			
Socioeconomic class	Low	14 (31.1%)	8 (17.8%)		#0.283	
	Average	19 (42.2%)	20 (44.4%)			
	High	12 (26.7%)	17 (37.8%)			
Smoking		17 (37.8%)	12 (26.7%)		#0.259	
Family history of IBD		5 (11.1%)	3 (6.7%)		§0.714	
Comorbidities		8 (17.8%)	6 (13.3%)		#0.561	
Hypertension		6 (13.3%)	4 (8.9%)		#0.502	
Diabetes mellitus		2 (4.5%)	1 (2.3%)		§0.999	
Rheumatoid arthritis		0 (0.0%)	1 (2.3%)		§0.494	
NSAID		18 (40 %)	7 (15.6%)		#0.008*	
		For arthritis	Not for arthritis	For arthritis	Not for arthritis	#0.748
		9 (20%)	9 (20%)	4 (8.9%)	3 (6.7%)	
Age of onset (years)	Mean±SD	26.8±10.6	26.8±13.0		^0.986	
	Range	13.0–64.0	9.0–71.0			
Duration of illness (years)	Mean±SD	7.1±4.8	6.6±3.9		^0.647	
	Range	2.0–22.0	2.0–21.0			
Extra-intestinal manifestations(arthritis)	total	19 (42.2%)	12 (26.6%)		#0.120	
	types	peripheral	axial	peripheral	axial	#0.546
		16(35.6%)	3(6.6%)	11(24.4%)	1(2.2%)	
Factors	β	SE	p-value		Odds ratio (95% CI)	
NSAID	1.39	0.54	0.010		4.03 (1.40–11.61)	
Constant	-0.35	0.26	0.168		0.70	

Data are presented as n (%) unless mentioned otherwise. NA: Not ^Independent t-test. # Chi-square test. §Fisher's Exact test.

*Significant. β: Regression coefficient. SE: Standard error. CI: confidence interval.

Our study indicated that several factors, including male sex, smoking, lower socioeconomic status, family history of disease, presence of comorbidities (particularly

hypertension and diabetes mellitus), age at disease onset, duration of illness, extra-intestinal manifestations, and NSAID use, were more frequently observed in the fistula group. However, among these variables, only NSAID use demonstrated a statistically significant association, being notably higher in the fistula group ($p=0.008$). Furthermore, logistic regression analysis identified NSAID use as an independent risk factor significantly contributing to the development of fistulas. Regarding extra-intestinal manifestations, 19 patients in the fistula group had arthritis, and one of them had pyoderma gangrenosum (16 with peripheral arthritis and 3 with axial arthritis). In the non-fistula group, 12 patients had arthritis, and two of them had pyoderma gangrenosum (11 with peripheral arthritis and 1 with axial arthritis). No other extraintestinal manifestations were observed in either group **Tab 1**.

The impact of NSAID use on treatment outcomes, as assessed through imaging studies (MRE and CTE) conducted before and after treatment, demonstrated that patients who did not use NSAIDs achieved the most favorable therapeutic responses. This association was statistically significant in both study groups, with a p -value of <0.001 **Tab 2**.

Tab 2. Relationship between the NSAID intake and the outcome of the treatment plan regarding the imaging study.

Number (Total=90)		NSAIDs				Chi-Square	
		Yes		No		X ²	P-value
		N	%	N	%		
Imaging Outcome	Remission	12	48.00	58	89.23	17.759	<0.001*
	Incomplete Remission	13	52.00	7	10.77		
		NSAIDs				Chi-Square	
		Yes		No		X ²	P-value
		N	%	N	%		
Fistula group (Total=45)	Remission	7	38.89	22	81.48	8.551	0.003*
	Incomplete Remission	11	61.11	5	18.52		
Non-Fistula group (Total=45)	Remission	5	71.43	36	94.74	3.965	0.046*
	Incomplete Remission	2	28.57	2	5.26		

Imaging outcome according to MRI or CT scan. *Significant.

The analysis of SES-CD scores before treatment revealed a statistically significant difference in disease severity between the studied groups, with higher median values observed in the fistula group. Following treatment, both groups exhibited notable improvement; however, the fistula group demonstrated a more pronounced response, as all patients with

severe disease activity improved to either mild or moderate levels of disease activity. In contrast, in the non-fistula group, two patients achieved complete remission, while one out of the total 16 patients remained in the severe disease category **Tab 3**.

Tab 3. Comparison regarding simplified endoscopic score for Crohn's disease (SES-CD) before and after treatment among the study groups.

	Fistula group N (45)	Non-Fistula group N (45)	Total N (90)	TEST
SES-CD Grade before treatment	Mild N (3) 6.7% Mod N (17) 37.8% Severe N (25) 55.6%	N (7) 15.6% N (22) 48.9% N (16) 35.6%	N (10) 11.1% N (39) 43.3% N (41) 45.6%	X*= 4.21 P=0.12
SES-CD Grade after treatment	Remission N (0) Mild N (17) 37 % Mod N (28) 62 % Severe N (0)	N (2) 4.4% N (29) 68.4 % N (13) 28.9% N (1) 2.2%	N (2) 2.2% N (46) 51.1% N (41) 45.6% N (1) 1.1%	
Test	X#=2.27 P=0.13	X#=0.88 P=0.3	X#=2.79 P=0.09	
SES-CD Before treatment				
Median (25%-75%)	19 (10.5- 21)	13 (7-19)	14 (10- 20.25)	U [§] =681 P=0.007
Min - Max	3 - 31	3 - 36	3- 36	
SES-CD After treatment				
Median (25%-75%)	7 (6- 9)	6 (3 -8.5)	6 (4- 9)	U [§] =664 P= 0.004
Min - Max	3- 15	0 -21	0 - 21	
Test	Z [^] = -5.5 P<0.001	Z [^] = -5.7 P<0.001	Z [^] = -7.9 P<0.001	

*PERSON CHI SQUAR, # FRIEDMAN TEST, § Mann-Whitney, ^ Wilcoxon Signed Ranks Test

Pathology findings, along with CDAI score, ESR, CRP, and fecal calprotectin (FCP), demonstrated significant improvement following treatment in both study groups **Tab 4**.

Tab 4. Comparison regarding pathology, CDAI score, and laboratory tests (ESR, CRP, and FCP) before and after treatment among the study groups.

Time		Fistula group (Total=45)	Non-fistula group (Total=45)	p-value (groups)
Pathology findings	Mild	7 (15.6%)	14 (31.1%)	#0.066
	Moderate	20 (44.4%)	22 (48.9%)	
	Severe	18 (40.0%)	9 (20.0%)	
	Normal	2 (4.4%)	7 (15.6%)	§0.045*
	Mild	27 (60.0%)	31 (68.9%)	
	Moderate	16 (35.6%)	7 (15.6%)	
□p-value (times)		<0.001*	<0.001*	
CDAI score	Before	Mean±SD Range	349.1±69.7 180.0–480.0	0.001*
	After	Mean±SD	213.9±54.3	
			185.3±71.0	

		Range	63.0–360.0	100.0–550.0	0.035*
		□p-value (times)	<0.001*	<0.001*	
ESR (ml/hr)	Before	Mean±SD	51.6±24.5	46.1±27.1	0.316
		Range	10.0–120.0	13.0–130.0	
	After	Mean±SD	19.7±8.2	16.9±8.0	0.114
		Range	9.0–46.0	8.0–60.0	
	#p-value (times)		<0.001*	<0.001*	
	CRP (mg/dL)	Before	Mean±SD	31.7±27.8	26.1±32.7
Range			1.0–139.0	1.0–190.0	
After		Mean±SD	10.1±7.8	8.3±5.0	0.190
		Range	1.0–47.0	1.0–21.0	
#p-value (times)		<0.001*	<0.001*		
Fecal Calprotectin (µg/mg)		Before	Median (IQR)	804 (535- 1105)	600 (422.5 – 899.5)
	Range		26.0–2100.0	19.0–2683.0	P=0.03*
	After	Median (IQR)	599 (362.5- 875)	350 (254 – 520)	U\$=643.5
		Range	42.0–1332.0	20.0–1200.0	P=0.003*
			Z^= -3.5	Z^= -4.4	
	#p-value (times)		P<0.001*	P<0.001*	

Data presented as n (%). # Chi-square test. §Fisher's Exact test. □Marginal homogeneity test. *Significant. \$ Mann-Whitney. ^ Wilcoxon Signed Ranks Test.

The comparison of treatment responses in the fistula group revealed significant improvements in CDAI score, ESR, and CRP in the surgery, infliximab, and adalimumab groups. Additionally, improvements in pathology and FCP were statistically significant in the infliximab and surgery groups, whereas no significant changes were observed in the adalimumab group Tab 5.

Table 5. Comparison between management plans of patients in the fistula group regarding colonoscopic pathology findings, CDAI score, and Labs (ESR, CRP, and FCP) before and after treatment

Time			Surgery (Total=14)	Infliximab (Total=24)	Adalimumab (Total=5)	p-value (groups)
colonoscopic pathology (SES-CD)	Before	Mild	3 (21.4%)	3 (12.5%)	1 (20.0%)	§0.968
		Moderate	6 (42.9%)	11 (45.8%)	2 (40.0%)	
		Severe	5 (35.7%)	10 (41.7%)	2 (40.0%)	
	After	Normal	0 (0.0%)	2 (8.3%)	0 (0.0%)	§0.313
		Mild	8 (57.1%)	17 (70.8%)	2 (40.0%)	

	Moderate	6 (42.9%)	5 (20.8%)	3 (60.0%)	
	□p-value (times)	0.025*	<0.001*	0.257	
CDAI score	Before	375.7±78.1	334.2±66.9	346.0±62.7	0.225
	After	194.5±64.1	222.2±38.7	192.0±49.2	0.186
	□p-value (times)	<0.001*	<0.001*	<0.001*	
ESR (ml/hr)	Before	51.7±28.7	47.7±20.6	75.6±14.9	0.059
	After	16.2±8.4	21.3±8.2	22.0±5.7	0.147
	□p-value (times)	<0.001*	<0.001*	0.003*	
CRP (mg/dL)	Before	29.7±27.7	27.3±21.0	59.8±44.4	0.052
	After	7.8±6.1	10.3±5.3	16.6±17.1	0.097
	□p-value (times)	0.004*	<0.001*	0.025*	
Fecal Calprotectin (µg/mg)	Before Median (IQR)	875(445-1200)	779.5(641-985)	660(550-1400)	0.959
	After Median (IQR)	379(250-850)	649.5(436.5-885)	630(521-900)	0.254
	#p-value (times)	0.030*	0.007*	0.225	

Data presented as n (%). §Fisher's Exact test. □Marginal homogeneity test. #Wilcoxon Signed Ranks Test.

In the fistula group, 40.9% of patients were NSAID users, whereas 15.6% of patients in the non-fistula group used NSAIDs **Fig. 1**.

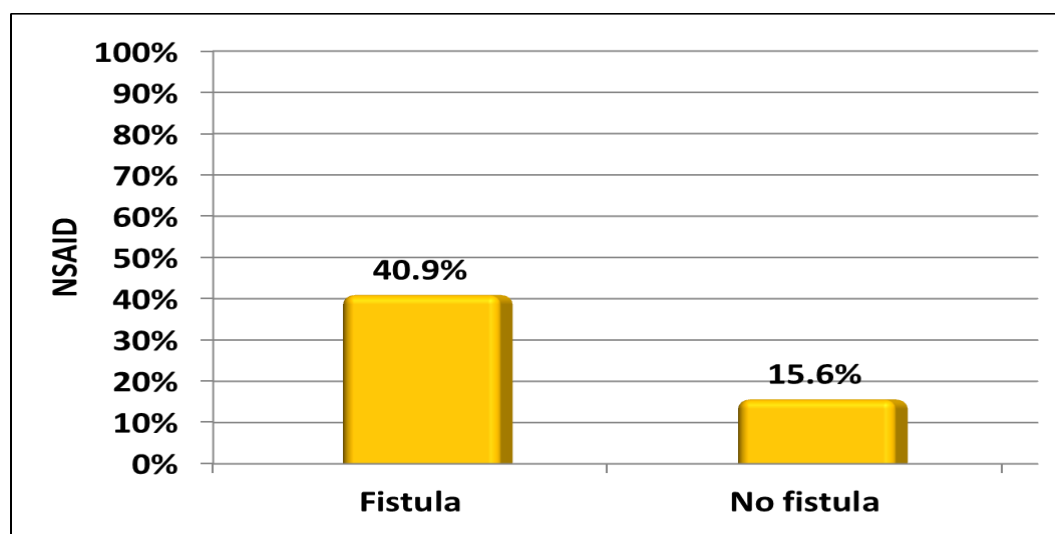


Fig 1. NSAID intake among the study groups.

Almost all patients in the fistula group experienced fistula closure, as confirmed by cross-imaging studies, with only one patient exhibiting a persistent fistula. This patient was receiving conventional treatment, including immunomodulators and corticosteroids Fig. 2.

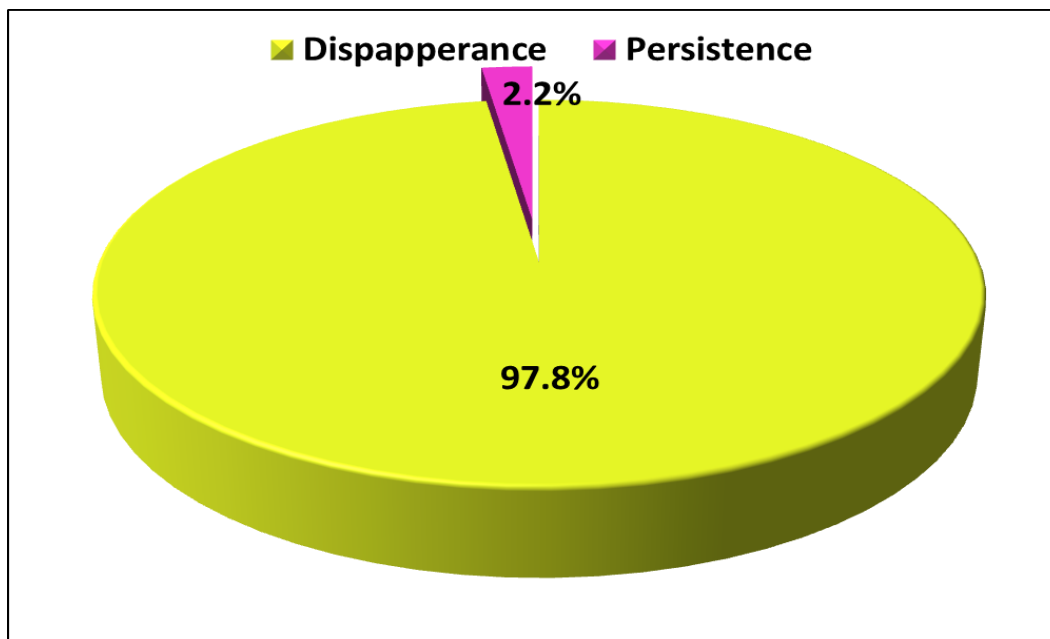


Fig 2. Fistula's outcome after treatment among patients of fistula group.

DISCUSSION

Identifying clinical predictors of fistula formation in CD is vital for effective management. Although prior studies have examined serologic, clinical, and genetic factors, their predictive value remains limited. Improved understanding of these markers could enhance risk stratification and enable earlier, targeted therapy [15]. Unfortunately, this study lacked genetic and serologic markers. An extended follow-up period was recommended.

In our study, although male patients were more frequently observed in the fistula group, the difference between groups was not statistically significant. Similarly, age differences did not reach statistical significance. This aligns partly with Zeitz et al., who, using SIBDCS data from 1,600 patients, linked male sex and younger age at diagnosis to higher risks of perianal and non-perianal fistulae [10]. Similarly, Cosnes et al. found that Crohn's disease diagnosed

before age 40 increased the likelihood of penetrating complications and a more severe disease course [16].

In this study, smoking was more common in the fistula group, but it was not statistically significant. This supports Braithwaite et al.'s review, which found smoking was not a strong predictor of fistulae [17]. However, Patel et al. (2016) linked smoking to poor disease control, supporting cessation in Crohn's management [18].

A significant finding in this study was the strong association between NSAID use and the development of fistulizing Crohn's disease ($p=0.008$). Logistic regression analysis confirmed that NSAID intake was an independent risk factor for fistula formation, increasing the likelihood by approximately fourfold ($OR=4.03$). Our study further demonstrated that NSAID users had poorer treatment outcomes, as assessed by imaging studies (MRE and CTE), compared to non-NSAID users ($p<0.001$). These results underscore the importance of minimizing NSAID use in patients with CD to prevent disease progression and improve therapeutic efficacy.

NSAIDs are widely prescribed for arthritis management; however, they are known to aggravate intestinal inflammation in individuals with Crohn's disease (CD). This association suggests a possible link between arthritis, NSAID use, and the development of fistulizing CD. In the fistula group, 9 out of 18 patients who reported NSAID use were taking them for arthritis treatment. Similarly, in the non-fistula group, 4 out of 7 NSAID users used them for arthritis management.

In two individuals with CD and ileo-colonic conditions, Rofecoxib (12.5 mg/day) was discontinued after 1 and 3 days, respectively, due to bleeding from a perianal fistula, as reported in a prospective, open-label study by Reinisch et al. This emphasizes the possible hazards

associated with using Cox-2 selective NSAIDs (Rofecoxib) and additional NSAIDs among people with CD [19].

Consistent with our findings, Long et al. demonstrated that frequent NSAID intake (≥ 5 times per month) was linked to a higher risk of Crohn's disease relapse. In their cohort of 791 patients in remission, 247 (43.2%) reported NSAID use, and those with regular exposure showed a significantly greater likelihood of active disease at six months (23% vs. 15%, $p = 0.04$; adjusted RR = 1.65, 95% CI = 1.12–2.44). These results suggest that habitual NSAID consumption may contribute to disease reactivation. [20].

In this study, arthritis was observed in 19 patients (42.2%) in the non-fistula group, comprising 16 with peripheral arthritis and 3 with axial arthritis. In the non-fistula group, 12 patients (26.6%) had arthritis, with 11 cases of peripheral arthritis and 1 case of axial arthritis. Although the difference between the two groups is not statistically significant—either in the overall prevalence of arthritis or in its specific subtypes—the higher occurrence of arthritis in the fistula group aligns with previous studies suggesting that arthritis is a marker of more aggressive disease phenotypes, such as fistulizing and stricturing forms.

Vavricka et al. conducted a prospective cohort study on patients with inflammatory bowel disease (IBD) from an adult clinic in Switzerland. The study included 950 patients, of whom 580 (61%) had CD, with a mean age of 41 years. Among those with CD, 249 patients (43%) exhibited extraintestinal manifestations, with arthritis being the most prevalent (33%), followed by aphthous stomatitis (10%), uveitis (6%), erythema nodosum (6%), ankylosing spondylitis (6%), psoriasis (2%), pyoderma gangrenosum (2%), and primary sclerosing cholangitis (1%). Multiple logistic regression analysis identified active disease (OR = 1.95, 95% CI = 1.17–3.23, $P = 0.01$) and a family history of IBD (OR = 1.77, 95% CI = 1.07–2.92, $P = 0.025$) as significant predictors of persistent extraintestinal manifestations in CD [21].

Palm et al. evaluated peripheral arthritis six years after IBD diagnosis in a cohort of 654 patients, of whom 521 underwent rheumatologic assessment. Only 0.8% had arthritis at follow-up, although 12% reported prior symptoms, indicating that while peripheral arthritis may occur early in IBD, its long-term prevalence is low. [22].

In our study, no statistically significant differences were observed between the two groups concerning the SES-CD before treatment. However, both groups demonstrated significant improvement following management, with the fistula group showing a more pronounced response to treatment. These findings suggest that the SES-CD is primarily reflective of luminal disease activity rather than a reliable marker for fistula development. Moreover, despite the increased disease burden, cases with fistulizing CD are capable of achieving substantial clinical improvement with appropriate therapeutic interventions.

Additionally, we observed that in the fistula group, the most frequent site of involvement was the entero-enteric fistula (48.9%), with infliximab being the most commonly employed treatment. Surgical intervention was carried out in 31.1% of cases. Among the surgical treatments, three patients with perianal fistulas underwent fistulotomy with Ligation of the Intersphincteric Tract (LIFT). In comparison, the remaining 11 patients received various fistulotomy procedures (all surgeries were performed before the commencement of the study). Throughout the one-year follow-up period, all patients experienced significant clinical improvement with their respective treatment strategies. However, one patient who received only conventional therapy showed limited improvement and continued to experience fistulizing disease. This particular patient was unable to access biological therapy due to unavailability and delays in state-sponsored treatment provision.

In 2019, Schwartz et al. conducted a systematic review to assess the prevalence of fistulizing CD (FCD) in the United States. The study encompassed 76,600 cases of CD and

15,700 new incident cases of FCD in 2017. The distribution of fistula types among patients was as follows: 52,000 with perianal fistulas, 7,400 with recto-vaginal fistulas, 2,300 with entero-cutaneous fistulas, and 14,100 with internal fistulas. These findings indicate that 11.7% of individuals with Crohn's disease in the U.S. have FCD at any given time, with 8.1% presenting with perianal fistulas, 1.1% with recto-vaginal fistulas, 0.3% with entero-cutaneous fistulas, and 2.2% with internal fistulas [23].

In our study, CDAI scores before and after treatment were substantially greater in the fistula group than the non-fistula group (p -value = 0.001, p -value = 0.035, respectively). CDAI scores significantly improved after treatment compared to those before treatment in each study group, with a p -value < 0.001 for each group. Additionally, our study revealed no substantial statistical variation among different management plans in the fistula group regarding the CDAI score, neither before nor after treatment.

Hanauer et al. conducted a randomized controlled trial in 2002, involving 573 patients with a CDAI of ≥ 220 who received a 5 mg/kg infusion of infliximab at baseline. The response was assessed at week 2, after which patients were randomized to receive either a placebo, continued 5 mg/kg infusions, or escalation to 10 mg/kg. Remission was defined as CDAI < 150 at week 30. Overall, 58% of patients improved after the initial infusion. By week 30, remission occurred in 21% of the placebo group, 39% of those maintained on 5 mg/kg, and 45% of those escalated to 10 mg/kg, with differences reaching statistical significance ($P < 0.001$) [24].

In this study, no statistically significant differences were observed among the various management strategies in the fistula group with respect to fistula characteristics. Additionally, all patients in the management plans demonstrated clinical improvement and fistula closure within the one-year follow-up period, except one patient who had a persistent fistula despite receiving conventional treatment. No significant differences were found regarding the clinical

and fistula outcomes across the different management options. Furthermore, improvements in the SES-CD and histological activity were achieved with infliximab and surgery, but not with adalimumab.

Similar to our results, Zhu et al. published a retrospective study in 2021. Utilizing clinical and MRI studies, the authors examined the effectiveness of infliximab on the rehabilitation of perianal FCD (PFCD) as observed throughout follow-up. The data they collected were intended to discover predictors of reaching profound radiologic remission. The use of infliximab for perianal fistulas was associated with significant rates of healing, which rose as the duration of therapy was extended [25].

In 2017, Yarur et al. conducted a study on 117 individuals with PFCD who received infliximab for a minimum of 24 weeks. The results showed that individuals with clinically healed fistulas had greater levels of infliximab in their blood than those with active fistulas (15.8 vs. 4.4 $\mu\text{g/mL}$, $P < 0.001$). The authors concluded that, to cure perianal fistulas completely, infliximab levels above 10 $\mu\text{g/mL}$ may be required. These findings clearly indicate that, to handle PFCD optimally with infliximab, serum levels of the medication must be targeted at significantly higher levels throughout both the induction and maintenance stages of therapy. [26].

The first trial to assess the effectiveness of adalimumab (ADA) in treating FCD was the CHARM study, conducted in 2007. 117 (15.2%) of the 778 CD individuals whose maintenance treatment was evaluated by Colombel et al. had perianal or enterocutaneous fistulas that were draining. Thirty percent of the individuals receiving ADA experienced fistula repair, in contrast to thirteen percent receiving a placebo [at week 26 ($p\text{-value} = 0.043$) and week 56 (ADA 33% vs. placebo 13%, $p\text{-value} = 0.016$)] [27].

In this study, fecal calprotectin levels remained significantly higher after treatment in the fistula group compared to the non-fistula group ($p = 0.003$). Additionally, ESR, CRP, and FCP showed significant improvement in both groups following treatment, as compared to their baseline levels ($p < 0.001$ for each). In the fistula group, laboratory markers improved significantly with infliximab therapy and surgical intervention. However, fecal calprotectin levels did not exhibit a statistically significant reduction in cases treated with adalimumab.

A 2016 meta-analysis by Zhuge et al. found that fecal calprotectin has limited reliability in assessing CD activity. The pooled sensitivity was approximately 0.75, with specificity ranging from 0.47 to 0.78. For CD recurrence, the sensitivity was approximately 0.74, and the specificity ranged from 0.56 to 0.71. Due to significant pooled asymmetry and variability in study quality, the diagnostic accuracy of fecal calprotectin may be overestimated [28].

In a retrospective analysis, Li et al. found that a higher level of ESR, combined with a lower eosinophil count, may more precisely identify CD patients who are at risk of developing a fistula [29].

Despite these valuable insights, several limitations must be considered. This study was conducted on an Egyptian patient population, which may limit the generalizability of the findings. Additionally, financial and administrative barriers to biologic therapy access may have influenced treatment selection and outcomes. Given the challenges associated with biological therapies, we recommend a further and future cost-effectiveness analysis of different treatment strategies, particularly for healthcare systems in resource-limited settings. Additionally, the small sample sizes resulted from the exclusion of critically ill patients and some patients' refusal to participate in the study. The genetic and serologic markers were not available. Future studies should consider incorporating genetic markers (e.g., NOD2

mutations) and serologic markers (e.g., ASCA, ANCA) to better predict disease behavior and therapeutic responses. An extended follow-up period was recommended.

CONCLUSION:

This study highlights NSAID use as a significant risk factor for the development of fistulizing Crohn's disease, reinforcing its detrimental impact on disease progression and treatment outcomes. The findings also underscore the utility of CDAI and SES-CD in assessing disease severity and monitoring therapeutic response. Furthermore, the study demonstrates that biologic therapy, particularly infliximab, and surgical intervention are the most effective treatment strategies for managing fistulizing Crohn's disease. While adalimumab contributed to clinical improvement, infliximab and surgery yielded superior outcomes, particularly in terms of fistula closure and reduction in inflammatory markers.

Abbreviations

CD: Crohn's Disease, CDAI: Crohn's Disease Activity Index, ECCO: European Crohn's and Colitis Organization, IL: Interleukin, IFN: Interferon, TNF: Tumor Necrosis Factor, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, TPMT: Thiopurine S-methyltransferase, TB: Tuberculosis, IBD: Inflammatory Bowel Disease, FCP: Fecal Calprotectin, IFX: Infliximab, ADA: Adalimumab, FCD: Fistulizing Crohn's disease, ACG: American College of Gastroenterology, SES-CD: Simplified Endoscopic Score for Crohn's Disease.

Footnotes.

Ahmed Agrodey (lecturer in the internal medicine, gastroenterology, and hepatology unit), Mohamed Emara (Professor in the gastroenterology, and hepatology and infectious diseases department), and Amany Mohamed (Biostatistician and Professor of Family Medicine) were peer reviewers.

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Ethics approval

Ethics approval and consent to participate

This study was approved by the Faculty of Medicine, Ain Shams University Research Ethical Committee, No. FMASU MS 771/2022. Each patient was provided with a written informed consent form for the analysis of anonymized data.

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

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Authors' contributions:

Yehia A M collected and followed up on the patients and carried out the requested investigations. Elfors M A, Awad E A, Saleh S AB, Hamdy K, El Essawy H A, Shehab H, Badary H A, and Farrag A A shared in following up the patients and analysis of the collected data. All authors read and approved the final manuscript.

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