Original Article

# Rate and risk factors of postoperative endoscopic recurrence of moderate- to high-risk Crohn's disease patients - A real-world experience from a Middle Eastern cohort

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## Abstract

**Background:** Crohn's disease (CD) frequently recurs after intestinal resection. Azathioprine (AZA) and biological therapies have shown efficacy in preventing postoperative recurrence (POR). Data on POR from Middle Eastern populations is lacking. This study aimed to evaluate the rate of endoscopic POR in a cohort of CD patients who underwent ileocecal resection (ICR), and to assess the effectiveness of AZA and biological therapies in reducing the risk of disease recurrence.

**Methods:** We performed a retrospective cohort study on 105 CD patients followed at our center, who underwent ileal resection and were at moderate to high risk for POR. Clinical and laboratory data were collected; the primary endpoint was post ICR endoscopic recurrence at 24 months defined by Rutgeerts' score of i2 or more despite treatment.

**Results:** In total, 105 patients with Crohn's disease met our inclusion criteria; 76.2% were in remission and did not have endoscopic POR at 24 months. Further, 41.9% were on biological therapy, and 34.3% were mainly on AZA. Out of the 28.2% who had POR, approximately 15% were on biological therapies. Penetrating phenotype was the only predictive factor for decreasing POR (OR = 0.19, 95% CI: 0.04–0.98, $P = 0.04$) as identified in multiple logistic regression analysis.

**Conclusions:** The use of biological therapies post-surgery was not superior than AZA in reducing the endoscopic POR for mod- high risk CD patients. Only penetrating behavior of the CD was associated with significantly lower risk of endoscopic recurrence. This finding is worth further investigation in more robust study designs and among larger samples of patients.

**Keywords:** Biological therapies, Crohn's disease, ileocecal resection, postoperative recurrence, Rutgeerts score

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## INTRODUCTION

Crohn's disease (CD) is characterized by chronic, relapsing/remitting course. In the natural history of the disease progression, it is common for such patients to encounter complications such as perianal disease, intestinal obstruction due to stricture formation, perforation, and abscess development, all of which may necessitate surgical intervention.[1] Given that fact, approximately 65% of patients with Crohn's disease will require at least one surgery within 10 years of diagnosis.[2] Unfortunately, surgery is not curative most of the time. About 70%–90% of patients will have features of clinical or endoscopic recurrence postoperatively at the anastomosis site or in the neo-terminal ileum, occurring within 3 years following the resection.[3] There are several risk factors that may contribute to recurrence, including smoking, prior intestinal resection, penetrating disease, perianal disease, and extensive bowel disease.[4-7] Therefore, the role of postoperative prevention is essential in reducing the risk of recurrence, either clinically or endoscopically, and preventing a second operation. Furthermore, the early identification of recurrence and introduction of medical therapy aims at controlling the disease trajectory and improving patients' quality of life.[8]

Recently, it was shown that the identification of high-risk patients and the early initiation of therapy along with performing colonoscopies within 12 months postoperatively can guide effective strategies in preventing recurrence.[9] Mucosal healing has been identified as a therapeutic endpoint for medical treatment in Crohn's disease patients;[10] therefore, ileocolonoscopy has become the gold standard for evaluating postoperative recurrence (POR), and is recommended to be performed within 12–18 months after resection.

In Saudi Arabia, data on the value of early medical therapy introduction in preventing or reducing the rate of recurrence postoperatively among Crohn's disease patients are lacking. Furthermore, we aimed to evaluate the rate of endoscopic POR in a cohort of moderate to high risks Crohn's disease patients who underwent ileocecal resection (ICR), to assess the effectiveness of azathioprine and anti-TNF therapies in reducing the risk of disease recurrence and to determine the factors associated with endoscopic recurrence.

## Methods

### Study design, patient population, and outcomes

This was a retrospective chart review of adult patients with Crohn's disease who underwent a surgical intervention (e.g., ileocecal resection or right hemicolectomy with ileal resection) and were followed up for at least 24 months afterwards. The patients were identified through electronic health records of a university-affiliated tertiary hospital in Riyadh, Saudi Arabia. CD patients diagnosed and registered in the Saudi Inflammatory Bowel Disease Information System (IBDIS) were included. Inclusion criteria were CD patients aged 16 years or more who underwent intestinal resection for CD with moderate to high risk of recurrence, defined as at least two of the following criteria: smoker, penetrating or structuring phenotype, and prior surgical ileal resection of 20 cm or more. Demographic, clinical information, and therapies were also collected and included sex, age, type of CD, disease duration, severity (at the time of diagnosis), family history, cigarette smoking, perianal disease, disease behavior, type of medications prior to the surgical resections, number of surgeries, date of the first surgery, type of resection, length of resection, and presence of perforation or granuloma in the surgical specimen.

Laboratory parameters were extracted, including hemoglobin level, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level post-surgical resection. Clinical disease activity of CD patients was assessed using the Harvey–Bradshaw index (HBI).[11] We evaluated the time of endoscopic assessment post-surgical resection and time of resuming or starting biological therapy post-operative to prevent POR.

The primary outcome of this study was disease remission as assessed by Rutgeerts' score (i0–i4), in which a score of i0 and/or i1 is considered a remission. Rutgeerts *et al*.[12] established an endoscopic recurrence scoring system that categorizes patients with endoscopic recurrence post resection. The score ranges from i0 to i4. Patients with a score of i0 (normal appearing neo-terminal ileum with no endoscopic inflammation) and i1 (5 aphthous ulcers in the neoterminal ileum with normal intervening mucosa) have a 20% chance of progression, compared to those with i3 (diffuse aphthous ileitis with diffusely inflamed mucosa) and i4 (diffuse inflammation with large ulcers, nodules, and/or strictures), which has a probability of 70%–80% of progression. The major outcome was endoscopic recurrence of moderate to high risk CD patients within 18–24 months post ICR. The secondary outcome was to assess the efficacy of AZA, biological therapies in preventing endoscopic recurrence.

### Statistical analysis

The minimum sample size was estimated to be 113 patients based on $\alpha = 0.05$, power of 0.80, and an odds ratio (OR) of 2 for postoperative recurrence of Crohn's disease.

Patients' baseline and follow-up characteristics were presented using frequencies, percentages, means, and standard deviations. Different potential predictors of recurrence as defined by Rutgeerts' score ≥i2, such as use of biologics (e.g., adalimumab, infliximab, and ustekinumab) and/or thiopurine (e.g., mercaptopurine and azathioprine), use of biologics post-surgery for biologic-naïve patients, age, gender, family history of IBD, CRP level post-surgery, ESR level post-surgery, smoking status, CD penetrating behavior, duration of illness, type of resection, history of prior resection, bowel perforation, and presence of granulomas were assessed. Simple logistic regressions were conducted to examine the relationship between different patient characteristics and the risk of postoperative recurrence. Additionally, multiple logistic regression was conducted to examine the relationship between the risk of Crohn's disease recurrence and the utilization of biologics (e.g., infliximab, adalimumab, and Ustekinumab) controlling for potential confounders, such as age, sex, family history of IBD, CRP, and ESR levels post-surgery; the presence or absence of a Crohn's disease penetrating behavior; bowel perforation; and ileal or colonic resection as suggested in the literature.[4,6,13] All statistical analyses were conducted using SAS® version 9.4 (SAS institute Inc, Cary, NC, USA).

## Ethical approval

This study was conducted in accordance with the protocol and principles of the Declaration of Helsinki. The study was approved by the Ethical Committee of the Institute for IBD Database registry with IRB project No. E-11-538.

## RESULTS

Of the 105 patients with confirmed CD who were enrolled in this study, 53.33% were males. The enrolled patients had a mean age of 37.0 ± 10.9 years. The mean disease duration was 12.3 ± 4.9 years, and 17 (16.19%) patients had a family history of CD. Approximately 11% of our cohort had a history of prior surgical resection. Disease location was ileal in 62.86% of the patients and ileocolonic in 29.52%, and 7.62% had colonic disease. Of the cohort, 35.24% of patients had stricturing (B2) CD, 26.67% had penetrating disease (B3), 33.3% had inflammatory (B1), and 4.76% had both (B3, B2) phenotypes. In addition, 75 (71%) patients had ileal resection, 30% patients had Rt hemicolectomy with ileal resection. The length of ileal resection was less than 20 cm in 40.95%, while 50.48% of CD patients had a resection between 20 and 70 cm, and approximately 8% had more than 70 cm resection of the ileum. The mean time between CD diagnosis and surgery was 4.6 ± 2.5 years. Non-caseating granulomas and perforations were identified and reported in pathology specimens in 51 (48.57%) and 11 (10.48%) of the patients, respectively. Demographic and clinical features of CD patients are shown in Table 1. Approximately 30% of the patients did not start on any POR prophylaxis within 12 weeks following the first surgical intervention, despite having at least one high risk factor. Seventy-four (70.48%) patients had colonoscopy within 18–24 months post resection; thus, approximately 29% of the patients had ileocolonic examination beyond 2 years post resection. The recurrence rate defined as Rutgeert's score of i2 or more, treatment type post-surgery, and remission on biopsy are listed in Table 2. Approximately 75% of the patients were in endoscopic remission, and 40% were in histological remission at the time of the colonoscopy.

**Table 1: Patients' baseline characteristics**

| Characteristic | Patients (*n*=105) |
|---|---|
| Age, (mean±SD) | 36.99±10.85 |
| Gender, (*n*, %) | |
| Male | 56 (53.33) |
| Female | 49 (46.67) |
| Disease duration in years, (mean±SD) | 12.26±4.87 |
| Family history of Crohn's disease, (*n*, %) | 17 (16.19) |
| Smoking status, (*n*, %) | |
| Smoker | 21 (20.00) |
| Disease location according to Montreal classification, (*n*, %) | |
| Ileal | 66 (62.86) |
| Colonic | 8 (7.62) |
| Ileocolonic | 31 (29.52) |
| Disease behavior (*n*, %) | |
| Non-stricturing, non-penetrating | 35 (33.33) |
| Stricturing | 37 (35.24) |
| Stricturing, and penetrating | 5 (4.76) |
| Penetrating | 28 (26.67) |
| Prior bowel resection, (*n*, %) | 12 (11.43) |
| CRPmg/L, (mean±SD) | 16.80±25.60 |
| ESRmm/hr, (mean±SD) | 33.56±26.85 |
| Type of surgical intervention, (*n*, %) | |
| Ileal resection | 75 (71.43) |
| Right hemicolectomy with ileal resection | 30 (28.57) |
| Presence of granuloma, (*n*, %) | 51 (48.57) |
| length of ileum resected (*n*, %) | |
| <20 cm | 43 (40.95) |
| 20-70 cm | 53 (50.48) |
| >70 cm | 9 (8.57) |
| Presence of perforation, (*n*, %) | 11 (10.48) |
| Post-operative timing of treatment initiation, (*n*, %) | |
| 2-4 weeks | 49 (46.67) |
| 5-12 weeks | 14 (13.33) |
| >12 weeks | 32 (30.48) |
| Not started | 10 (9.52) |
| Type of treatment, (*n*, %) | |
| No treatment | 8 (7.62) |
| Mesalamine | 3 (2.86) |
| (6 mercaptopurine, AZA) | 45 (42.86) |
| Anti-TNF (e.g., adalimumab, infliximab) | 26 (24.76) |
| Mesalamine and AZA | 6 (5.71) |
| AZA and anti-TNF | 17 (16.19) |

AZA; azathioprine, TNF; tumor necrosis factor, CRP; C-reactive protein, ESR: Erythrocyte sedimentation rate

Family history of IBD, high ESR/CRP post-surgery, smoking history, penetrating behavior, and presence of granuloma on pathology specimens or prior surgery were not a significant risk factor for recurrence as shown in Table 3.

### Biological therapies, azathioprine, and POR

Approximately one-third of the study population was not started on any pharmacological prophylaxis within the appropriate time post-surgery (within 12 weeks). Further, 76.2% of the patient population were in remission and did not have endoscopic POR; 41.9% were on biological, and 34.3% were on non-biological therapy, mainly azathioprine. While 23.8% did have POR, approximately 15% of them were on biological therapies as shown in Figure 1. We noted no significant relationship between the use of biological therapies (infliximab, adalimumab) postoperatively and its effect in preventing POR in mod-high risk patients ($P$ = 0.42). Similarly, there was no significant relationship between azathioprine and its effect in preventing POR ($P$ = 0.89). On multiple logistic regression analysis, the use of biological therapies post-surgery was not a predictor for endoscopic remission, as shown in Table 4.

### Risk factors for postoperative Crohn's disease recurrence

Penetrating phenotype was the only predictive factor for decreasing POR (OR = 0.19, 95% CI: 0.04–0.98, $P$ = 0.04) on multiple logistic regression analysis, that controlled for the presence of perforation, type of resection, the postoperative ESR and CRP levels, family history of IBD, gender, age, and the postoperative use of biologics [Figure 2].

**Table 2: Postoperative imaging and lab findings**

| Variable | Participants (*n*=105) |
|---|---|
| Colonoscopy within 18-24 months (*n*,%) | 74 (70.48) |
| CRP level mg/L, (mean±SD) | 8.80±23.36 |
| ESRmm/hr, (mean±SD) | 23.43±18.99 |
| Rutgeerts score, (*n*, %) | |
| i0 | 49 (46.67) |
| i1 | 31 (29.52) |
| i2 | 17 (16.19) |
| i3 | 7 (6.67) |
| i4 | 1 (0.95) |
| Remission on biopsy, (*n*, %) | |
| Yes | 47 (40.87) |
| No | 49 (42.61) |
| Not available | 19 (16.52) |
| Type of treatment, (*n*, %) | |
| No treatment | 7 (6.67) |
| Mesalamine | 3 (2.86) |
| AZA | 30 (28.57) |
| Anti-TNF (e.g., adalimumab, infliximab) | 25 (23.81) |
| Ustekinumab | 2 (1.90) |
| Mesalamine and AZA | 4 (3.81) |
| Mesalamine and anti-TNF | 2 (1.90) |
| AZA and anti-TNF | 30 (28.57) |
| AZA and steroids | 1 (0.95) |
| AZA and anti-TNF | 1 (0.95) |

AZA; azathioprine, TNF; tumor necrosis factor, CRP; C-reactive protein, ESR: Erythrocyte sedimentation rate

## DISCUSSION

This study is the first study to look at the rate of endoscopic POR in a Middle Eastern cohort of CD patients; we found that approximately 75% of the patients on either AZA or biological therapies were in endoscopic remission and 41% were in histological remission at 18–24 months post-resection. The rates of endoscopic recurrence in CD patients post-surgical resection may be as high as 70%–90%, and approximately 50% will require another intestinal surgery at 5 years after the initial resection.[4] The American Gastroenterology Association suggested early pharmacological prophylaxis (8 weeks post resection) over endoscopy-guided pharmacological treatment in CD patients with high risk for recurrence.[14] Hashash and Regueiro proposed two emerging strategies to manage CD postoperatively. One strategy stratifies postoperative treatment based on each patient's risk and treat only those with high risk for recurrence, based on the colonoscopy findings at 6 months from surgery. The second strategy was to start prophylactic treatment for high-risk patients with azathioprine/6-mercaptopurine in combination with an anti-TNF agent post-surgery while using azathioprine/6-mercaptopurine for moderate-risk patients, and those at low risk for recurrence were not given postoperative medications.[15] The endoscopic recurrence rates varied based on the study and medication. Of note, experts suggested that metronidazole, azathioprine, or biological therapies can prevent and/or treat POR in CD.[8,16-19] The efficacy of metronidazole was studied in a retrospective cohort and it was found that endoscopic recurrence (defined by Rutgeert's score ≥ i2) 12 months post ileal resection was significantly lower in the metronidazole group (20%) compared to that in controls (54.3%; $P$ =

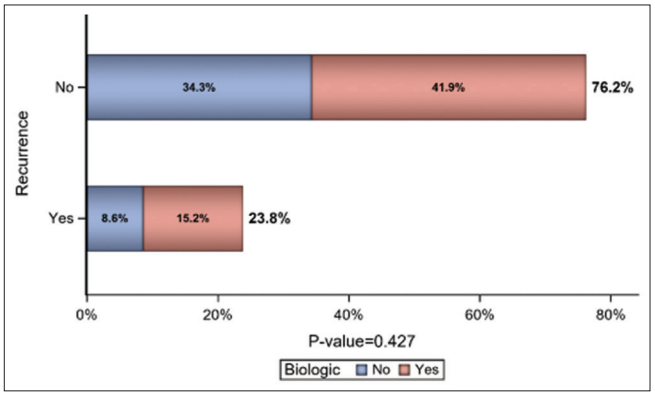


**Figure 1:** The rate of biologics utilization across recurrence status

**Table 3: Univariate odds ratios of potential factors for postoperative recurrence of Crohn's disease**

| Variable | Odds ratio (OR) | 95% Confidence interval (CI) | | *P* |
|---|---|---|---|---|
| | | Lower CI | Upper CI | |
| Biologics Post Surgery | 1.45 | 0.58 | 3.68 | 0.43 |
| Thiopurines Post Surgery | 1.07 | 0.42 | 2.71 | 0.89 |
| Age | 0.97 | 0.92 | 1.01 | 0.15 |
| Gender (Female) | 1.64 | 0.66 | 4.04 | 0.29 |
| Family history of IBD | 2.73 | 0.91 | 8.13 | 0.07 |
| CRP Post Surgery | 1.02 | 0.99 | 1.05 | 0.21 |
| ESR Post Surgery | 1.02 | 1.00 | 1.05 | 0.05 |
| Current smoker | 1.83 | 0.64 | 5.21 | 0.26 |
| Penetrating behavior | 0.41 | 0.11 | 1.51 | 0.19 |
| Duration of Illness | 0.97 | 0.88 | 1.07 | 0.53 |
| Biologic Post Surgery for Biologic-Naïve | 0.71 | 0.21 | 2.33 | 0.57 |
| Limited RT hemicolectomy vs. Ileal resection | 1.24 | 0.47 | 3.28 | 0.66 |
| Ileal vs. Ileocolonic location | 1.60 | 0.53 | 4.85 | 0.22 |
| Perforation | 0.69 | 0.14 | 3.41 | 0.65 |
| Prior resection | 1.08 | 0.27 | 4.33 | 0.92 |
| Granuloma | 0.97 | 0.40 | 2.38 | 0.95 |

0.01).[20] Azathioprine has shown superiority over placebo and mesalazine at preventing POR of CD.[19,21] With regards to the biologicals, infliximab post-surgical resection was superior to placebo at preventing endoscopic and histological recurrence of CD at 1-year postoperatively.[17] Additional similar results were confirmed in other studies.[8,22] The PREVENT trial was the first large, multicenter, placebo-controlled study that evaluated infliximab for prevention of post-surgical CD recurrence after ileocolonic resection, but it was prematurely terminated as it did not meet the primary end point. Clinical recurrence rates were 12.9% and 20.0% for the infliximab and placebo groups, respectively, and these results were not statistically significant ($P = 0.09$). However, in the secondary endpoint, the endoscopic recurrence rates were significantly lower in patients receiving infliximab as compared to those in patients on placebo (22.4 vs. 51.3%; $P < 0.001$).[23] The efficacy of adalimumab in preventing POR was shown in a prospective, single center, open-label study with clinical remission of 56% and endoscopic remission of 60% of the patients.[24] In the POCER study, the 18-month endoscopic recurrence rate in patients who underwent colonoscopy at 6 months was 49% compared with 67% in those who had not had a 6-month colonoscopy. The 6-month POR rate in high-risk patients receiving azathioprine was 45% compared with 21% with adalimumab.[25] Moreover, one study compared the efficacy of infliximab and adalimumab in endoscopic recurrence for CD patients and found that infliximab and adalimumab are equally efficient in POR. The rate of response was comparable between the two groups: 67% in the infliximab group versus 78.3% in the adalimumab group—the same as the rate of re-resection (repeated surgery), 19.1% versus 4.4%, and the rate of endoscopic recurrence, 29% versus 33% at 12 months.[26] In the current study; approximately one-third of our patient population were not on any pharmacological prophylaxis within the appropriate time post-surgery (within 12 weeks). Of the patient population studied, 76.2% did not have endoscopic POR, 41.9% were on biological (infliximab or adalimumab), and 34.3% were on non-biological therapy, mainly azathioprine. Further, while 23.8% did have endoscopic POR, approximately 15% of them were on biological therapies similar to that reported in international literature.[8,23,26] Therefore, it may be reasonable to manage low-risk CD patients conservatively and initiate treatment only if there is endoscopic recurrence at 6 months. However, it might be wise to initiate biologic therapy postoperatively for high-risk CD patients despite the findings of this study of no significant impact of biologics on the rate of postoperative recurrence. This is mainly due to the uncertainty about a potential positive impact of biologic therapy on the rate of recurrence among high-risk CD patients which might have gone undetected in this study due to its design and small size. Better predictors for moderate-high risk populations need to be defined more objectively to guide the therapeutic selection for POR prophylaxis.

Several risk factors have been linked to POR; cigarette smoking is a well-recognized risk factor for POR, and several studies have evaluated the effect of smoking on POR.[27,28] Cottone *et al*.,[7] evaluating several variables as potential risk factors for POR in a study of 182 patients, demonstrated smoking as a predictive factor for endoscopic POR ([OR = 2.2, 95% CI: 1.2–3.8). Moreover, smoking cessation was found to reduce the incidence of surgical recurrence.[29] However, another multicenter observational study failed to recognize smoking as a risk factor for early endoscopic POR,[30] which is similar to our study as we could not demonstrate

**Table 4: Multivariable logistic regression for the relationship between the use of biologics and postoperative recurrence**

| Variable | Odds ratio (OR) | 95% Confidence interval (CI) | | *P* |
|---|---|---|---|---|
| | | Lower CI | Upper CI | |
| Age | 0.96 | 0.91 | 1.01 | 0.11 |
| Gender (Female) | 1.17 | 0.39 | 3.49 | 0.78 |
| Family history of IBD | 2.90 | 0.83 | 10.15 | 0.10 |
| CRP Post Surgery | 1.02 | 0.98 | 1.06 | 0.38 |
| ESR Post Surgery | 1.02 | 1.0 | 1.05 | 0.15 |
| Penetrating behavior | 0.19 | 0.04 | 0.99 | 0.04 |
| Perforation | 1.62 | 0.26 | 10.11 | 0.60 |

smoking as a risk factor for POR. One explanation could be related to the small number of smokers in our cohort. In addition, there is a possibility that smoking is not influential in the course of IBD in Eastern populations as opposed to the Western ones.[31]

Ileal location is another risk factor for POR. Studies have concluded that ileal disease had significantly higher POR rates compared to patients with ileocolonic or colonic disease,[32] whereas a recent population-based Danish cohort could not confirm this correlation,[33] like in our study, where we did not find any correlation between ileal versus ileocolonic location with POR. Penetrating phenotype is associated with early POR, according to many studies.[34,35] A meta-analysis evaluated 13 studies with 3044 patients and concluded that a perforating phenotype was associated with an increased risk of POR (HR: 1.50, 95%CI: 1.16–1.93, $P = 0.002$),[36] while other studies failed to demonstrate any significant differences in penetrating versus non-penetrating behavior.[37,38] We identified that penetrating behavior was associated with a lower risk of postoperative endoscopic recurrence, similar to data from a large prospective national cohort.[34] One explanation is that we usually initiate early pharmacological prophylaxis for patients with penetrating disease postoperatively with biological agents and aim for higher trough levels of biologics compared to other phenotypes. Several surgery-specific risk factors have been explored, but none was significantly linked to recurrence, which includes length of resected bowel, type of anastomosis, and presence of granulomas on pathology specimens,[39,40] and our data had a similar finding. Regarding the impact of family history of IBD and risk of POR, the data are conflicting; some studies have supported this observation,[28,29] whereas others have not.[41] Therefore, we do believe that large-scale and well-designed studies are needed to firmly establish the relation of these risk factors with the risk of endoscopic POR.

There are numerous strengths in this study. One of them is that it is the first study looking at the rate and risk

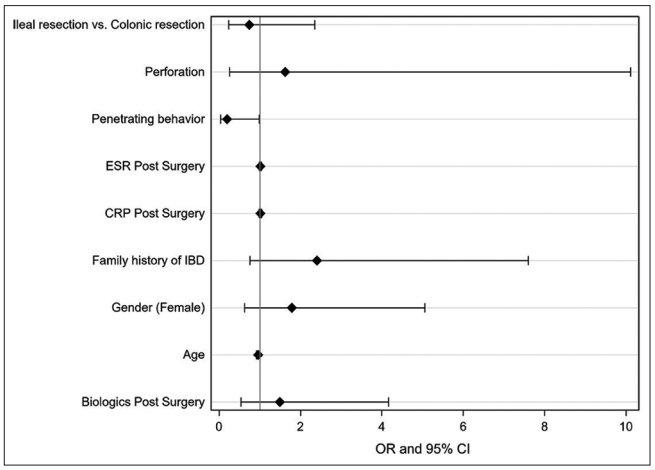


**Figure 2:** Odds ratios of different factors for postoperative recurrence

factors for POR from a Middle Eastern population. We used a robust endpoint, which is endoscopic recurrence, rather than a subjective endpoint, and it is a tertiary center experience that reflects real-life daily practice. However, this study has several limitations, including the small number of patients, retrospective nature, and lack of measurement of antibodies and trough levels of infliximab or adalimumab to all the cases at the time of study, which is an important tool to be integrated in the daily clinical practice for treatment optimization. These limitations should be acknowledged in terms of generalizability as well as the possibility of being underpowered to detect these differences.

## CONCLUSION

The use of biologics does not seem to reduce the post-surgical recurrence rate in comparison to AZA among moderate to high risk Crohn's disease patients. However, this finding should be carefully considered due to the multiple aforementioned limitations of the study, and better predictors for moderate-high risk populations need to be defined more objectively to guide the therapeutic selection for POR prophylaxis. Interestingly, the penetrating behavior of CD was the only variable associated with significantly lower risk of recurrence despite controlling for multiple confounders in the multiple logistic regression model. This is worth further investigation in more robust study designs and among larger samples of patients.

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## Conflicts of interest

There are no conflicts of interest.

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