Crohn's & Colitis 360, XXXX, **4**, 1–8
https://doi.org/10.1093/crocol/otac047
Advance access publication 28 November 2022
Observations and Research

Inflammatory Response in Patients With Crohn's Disease Compared With Ulcerative Colitis: Secondary Results of a Prospective Pilot Study

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Background: The aim of this study was to compare the inflammatory response (IR) to surgery between patients with Crohn's disease (CD) and patients with ulcerative colitis (UC).

Methods: This study is a secondary analysis of data collected in a previous study by the authors. We included all adult patients who underwent elective surgery for CD and UC. The primary outcome variable was the difference in postoperative IR as measured by interleukin 6 (IL-6), interleukin 10 (IL-10), C-reactive protein (CRP), and the count of white blood cells (WBCs) in peripheral blood. Two-way repeated-measures analysis of variance with a mixed effect (disease type as the between-patient factor, and time as the within patient factor).

Results: We included 46 patients in this pilot study. Median age was 42.5 years (IQR 30.5–42.2), 25/46 were females (54.3%). Patients with CD had a more marked IR to surgery compared with those with UC as shown by significant differences in levels of IL-6, IL-10, and CRP. Patients with CD were more often treated with postoperative epidural analgesia 17 (53.1%) versus 1 (7.1%), $P = .009$. Patients with colonic CD had a more intense IR to surgery than patients with UC after the same surgical resection. This significant trend continued when patients who underwent small bowel resection compared with those with colectomy. The changes in inflammatory markers and WBC counts from baseline to peak value were also higher in patients with CD indicating a more severe IR. However, there was a similar response in patients undergoing laparoscopic compared with open approaches

Conclusions: The postoperative IR was greater in patients with CD than those with UC. This is important to tackle in preoperative optimization as well as postoperative recovery protocols.

Lay Summary

This study showed that patients with Crohn's disease react with more inflammation to surgery than patients with ulcerative colitis. This finding indicates that Crohn's patients may need more preparation before surgery, and more monitoring after it.

Key Words: Crohn's disease, ulcerative colitis, surgery, inflammatory response, inflammatory bowel disease

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract that is broadly categorized as either Crohn's disease (CD) or ulcerative colitis (UC). Worldwide, it affects almost 7 million individuals.[1] Clinical manifestations peak in the second to fourth decades of life, with significant detriment to patients' quality of life.[2]

Surgery is indicated for patients with IBD in medically resistant cases, those with intolerable side effects of medication, or those who suffer complications of disease such as toxic megacolon and perforation in UC or strictures and intra-abdominal abscesses in CD.[3] Surgery might also be indicated in patients with UC in case of sever dysplasia. The lifetime risk for surgery is approximately 70% in patients with CD and 15% in UC.[4]

The surgical stress response or the systemic inflammatory response is the physiologic response of the body to injury incurred during an operation. During a surgery, there is rapid sympathetic activation and consequently increased of pituitary hormones. This results in increased cortisol, and significant increases in proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-10 (IL-10).

An increased postoperative length of stay at hospital in patients with IBD, compared with non-IBD-related colorectal surgery has been shown in an international cohort study based on European Society of Colo-Proctology (ESCP) audit 2015.[5] Possible explanations of prolonged length of stay at the hospital could be the preoperative treatment with biologics or immune-modulator agents[5–7] postoperative

Received for publication: September 6, 2022. Editorial Decision: November 21, 2022

inflammatory response (IR) or disease severity. As CD and UC have 2 different genetic backgrounds[8] and postoperative recovery might be different, the question is whether these 2 diseases have different postoperative IR?

The aim of this study is to compare the IR to surgery between patients with CD and patients with UC.

Methodology

This study is a secondary analysis of data collected in a previous study by the authors,[9] where the methods and sample size calculations are also explained.

We included all adult patients who underwent elective surgery for IBD. We excluded patients with preoperative sepsis, acute intestinal obstruction, those operated in an acute setting (within 48 hours of admission) and patients who had loop ileostomy take down without laparotomy or laparoscopy.

The primary outcome variable was the difference in postoperative IR in patients with CD compared with those with UC.

To minimize type 1 error, 4 markers, found to be most representative of the postoperative IR were selected for this secondary analysis[9,10] and included—interleukin 6 (IL-6), interleukin 10 (IL-10), C-reactive protein (CRP), and the count of white blood cells (WBCs) in peripheral blood. These were chosen based on previous literature[9,10] that showed significant change of these markers with inflammation.

All patients underwent either intestinal resection (laparoscopic or laparotomy approach) or stoma closure with laparotomy. All the operations took place between 08:00 AM and 04.00 PM to avoid circadian rhythm as a confounder. General anesthesia was administered according to the standard practices of the participating hospitals' anesthesia departments. All patients received a single prophylactic preoperative antibiotic at the induction of anesthesia, the type and dose determined by the local standard of preoperative care. Peripheral blood samples were taken before induction of anesthesia, and 6, 24, and 48 hours after surgical incision. All surgeries were done as elective operations. Major indication for surgery in both groups was nonresponse to medical treatment. Patients with UC were evaluated at the time of admission for colectomy or rectal resection.

Statistical Analysis

Categorical data are presented as frequencies and parentages. Normally distributed variables are reported as mean (SD) and nonnormally distributed variables as median (IQR). χ^2 test was used to compare categorical variables. Continuous variables were compared using independent samples *t*-test or Mann–Whitney *U*-test, depending on the data distribution. The changes in postoperative IR markers were taken from the difference between the 6-hour measurements and the preoperative measurements of IL-6, IL-10, and the difference between the 48-hour measurement and the preoperative measurements for CRP.

Two-way repeated-measures analysis of variance (ANOVA) with a mixed effect (IBD type as the between-patient factor, and time as the within patient factor) was performed to compare the postoperative IR markers IL-6, IL-10, CRP, and WBC. These markers were set a priori. Outliers were excluded and *Q*–*Q* plots stratified by time and disease status were interrogated to determine the need for log-transformation (which was applied with a continuity correction of +1 to IL-6, IL-10, and CRP but not WBC). Post hoc testing was performed via 1-way ANOVAs, and *P* values were calculated with a Bonferroni correction. A *P* value of <.05 was deemed statistically significant.

A subgroup analysis was performed of patients that had colectomies only. Further descriptive analysis of the postoperative IR associated with the location of IBD was performed by comparing small intestinal disease with large intestinal disease.

Results

We included 46 patients in this pilot study. Detailed demographics data are shown in Table 1. Median age was 42.5 years (IQR 30.5–42.2). There were 25 females (54.3%) in the cohort. Median body mass index was (23.5, IQR 6.3). Patients with UC were more likely to be older (P = .028), with higher body mass index (P = .003). No statistically significant differences were noticed in preoperative hemoglobin, albumin, nutritional support, or preoperative medications between the 2 groups. More patients with UC received a single dexamethasone dose upon induction of anesthesia compared with patients with CD. Anti-TNF used were: adalimumab, infliximab, and golimumab.

All patients with UC had elective laparoscopic surgery, while patients with CD had a mixture of laparoscopic, converted and open access to abdominal cavity (P = .005). This difference is reflected in postoperative epidural analgesia where only 7% of patients with UC received and 53% of patients with CD (P = .009). Patients with CD were more often treated with postoperative epidural analgesia 17 (53.1%) versus 1 (7.1%), P = .009.

IR to Surgery

Patients with CD had a more marked IR to surgery compared with those with UC as shown by significant differences in IL-6, IL-10, and CRP (Table 2, Figures 1A, 2A, and 3A).

To investigate the behavior of colonic CD, we included patients with CD who underwent colectomy and compared the level of cytokines, CRP, and WBC counts to the values seen in patients with UC (Figures 1B, 2B, and 3B). The comparison showed that patients with CD had a more intense IR to surgery than patients with UC after the same surgical resection as demonstrated by elevated IL-6 at 24 (P = .02) and 48 (P = .03) hours postoperatively, and elevated CRP (P = .04) 48 hours. There were no significant differences in IL-10 or WBC between the 2 groups.

We then investigated the effect of organ-specific surgical intervention on the postoperative IR by comparing colon and small bowel resections in CD and UC. Patients who had colectomies (which usually requires more surgical dissection) did not have greater surgical stress responses compared with small bowel resections. The results showed that patients with CD who had small bowel resections had actually a greater increase in IR markers IL-6, IL-10, and CRP (P < .001) as shown in Figures 1C, 2C, and 3C.

We also compared the change in concentration of IR markers and WBC counts between CD and UC. The concept of change is explained above in the statistical section.

Table 1. Demographic characteristics of 46 patients with Crohn's disease and ulcerative colitis operated electively in 3 tertiary centers.

		Crohn's disease N = 32	Ulcerative colitis N = 14	Total	P
Age (years)	Median (IQR)	40.5 (28–48.2)	53.5 (34.0–60.2)	42.5 (30.5–52.8)	.039
Gender	Female	16 (50.0)	9 (64.3)	25 (54.3)	.566
	Male	16 (50.0)	5 (35.7)	21 (45.7)	
BMI	Median (IQR)	22.5 (21.0–24.9)	27.5 (24.5–29.9)	23.5 (21.0–27.0)	.003
Smoking status	Non or ex-smoker	24 (75.0)	12 (85.7)	36 (78.3)	
	Smoker	8 (25.0)	2 (14.3)	10 (21.7)	
Steroid treatment	No	21 (65.6)	9 (64.3)	30 (65.2)	1
	Yes	11 (34.4)	5 (35.7)	16 (34.8)	
Immunotherapy	Yes	12 (37.5)	3 (21.4)	15 (32.6)	.467
	No	20 (62.5)	11 (78.6)	31 (67.4)	
Anti-TNF-α treatment	Yes	13 (40.6)	5 (35.7)	18 (39.1)	1.000
	No	19 (59.4)	9 (64.3)	28 (60.9)	
NSAID	No	31 (96.9)	14 (100.0)	45 (97.8)	1
	Yes	1 (3.1)	0 (0.0)	1 (2.2)	
Anticoagulants	No	32 (100.0)	13 (92.9)	45 (97.8)	.667
	Acetylsalicylate		1 (7.1)	1 (2.2)	
Preoperative albumin ($g\ L^{-1}$)	Median (IQR)	36.5 (33.8–40.2)	36.5 (34.0–39.0)	36.5 (34.0–39.0)	.811
Preoperative hemoglobin ($mmol\ L^{-1}$)	Median (IQR)	8.1 (7.5–8.6)	7.5 (6.8–8.6)	8.1 (7.3–8.6)	.357
Nutritional risk score[a]	Mild nutritional risk	6 (18.8)	4 (28.6)	10 (21.7)	.378
	Moderate nutritional risk	4 (12.5)	1 (7.1)	5 (10.9)	
	No nutritional risk	17 (53.1)	9 (64.3)	26 (56.5)	
	Sever nutritional risk	5 (15.6)		5 (10.9)	
Preoperative parenteral nutrition	No	28 (87.5)	12 (85.7)	40 (87.0)	1
	Yes	4 (12.5)	2 (14.3)	6 (13.0)	
Preoperative steroid stress dose	No	28 (87.5)	13 (92.9)	41 (89.1)	.982
	Yes	4 (12.5)	1 (7.1)	5 (10.9)	
Dexamethasone dose[c]	Dexamethasone 8 mg administration at the induction of anesthesia	5 (15.6)	6 (42.9)	11 (23.9)	.007
	No dexamethasone administration at the induction of anesthesia	27 (84.4)	6 (42.9)	33 (71.7)	
	Dexamethasone 4 mg administration at the induction of anesthesia		2 (14.3)	2 (4.3)	
Preoperative epidural	No	21 (65.6)	13 (92.9)	34 (73.9)	.116
	Yes	11 (34.4)	1 (7.1)	12 (26.1)	
Surgical approach	Laparoscopic	16 (50.0)	14 (100.0)	30 (65.2)	.005
	Laparoscopic converted to open	5 (15.6)		5 (10.9)	
	Open	11 (34.4)		11 (23.9)	
Resection	Colectomy[b] and/or rectal	5 (15.6)	14 (100.0)	19 (41.3)	<.001
	SM and IC	21 (65.6)		21 (45.7)	
	Stoma closure	6 (18.8)		6 (13.0)	
Postoperative epidural	No	15 (46.9)	13 (92.9)	28 (60.9)	.009
	Yes	17 (53.1)	1 (7.1)	18 (39.1)	
Postoperative NSAIDs	No	32 (100.0)	12 (85.7)	44 (95.7)	.161
	Yes	(0.0)	2 (14.3)	2 (4.3)	
Postoperative parenteral nutrition	No	28 (87.5)	12 (85.7)	40 (87.0)	1
	Yes	4 (12.5)	2 (14.3)	6 (13.0)	

Abbreviations: BMI, body mass index; CD, Crohn's disease; TNF-α, tumor necrosis factor-alpha; UC, ulcerative colitis; NSAID, Non-steroidal anti-ionflammatory drugs; SM, Small bowel resection; IC, Ileo-colic resection.
[a]Nutrition Risk Screening score 2002 (NRS-2002) developed by KONDRUP et al 2003 and recommended by ESPEN (https://espen.info/documents/screening.pdf).
[b]Patients with CD had segmental or subtotal colectomies while those with UC had total/subtotal colectomies only.
[c]The guidelines in the participating hospitals classified colectomies as major procedures that must be preoperatively managed with single dose of dexamethasone at the induction of anesthesia.

Table 2. Postoperative inflammatory response in patients with Crohn's disease compared with patients with ulcerative colitis.

		Crohn's disease[a] $N = 32$	Ulcerative colitis[a] $N = 14$	*P* value
IL-6 (pg mL^{-1})	Preoperative	2.6 (1.3–7.4)	2.2 (1.4–6.6)	.633
	6 h postoperative	147.3 (33.6–478.0)	34.7 (16.8–96.8)	.027
	24 h postoperative	83.5 (17.6–291.0)	15.2 (7.4–45.8)	.016
	48 h postoperative	30.0 (20.1–151.3)	8.2 (5.7–19.4)	.005
IL-10 (pg mL^{-1})	Preoperative	0.3 (0.2–0.5)	0.4 (0.1–1.5)	.943
	6 h postoperative	1.7 (1.0–4.4)	1.9 (0.4–7.9)	.86
	24 h postoperative	1.2 (0.4–3.0)	0.5 (0.2–2.0)	.066
	48 h postoperative	0.9 (0.5–1.3)	0.5 (0.1–0.8)	.033
CRP (mg L^{-1})	Preoperative	8.1 (3.6–21.7)	5.7 (4.0–12.7)	.574
	6 h postoperative	11.0 (4.8–20.6)	5.9 (3.9–12.5)	.256
	24 h postoperative	122.6 (84.8–148.4)	63.5 (30.2–112.2)	.004
	48 h postoperative	174.6 (82.0–236.8)	62.5 (44.2–98.2)	.002
WBC (10^9 L^{-1})	Preoperative	6.3 (5.2–8.4)	8.9 (7.6–12.9)	.06
	6 h postoperative	12.9 (11.3–15.8)	14.0 (12.6–21.8)	.2
	24 h postoperative	12.5 (9.3–13.9)	13.5 (11.9–14.5)	.308
	48 h postoperative	10.7 (7.3–13.4)	11.7 (10.2–13.5)	.316

Abbreviations: CRP, C-reactive protein; IL-6, interleukin-6; IL-10, interleukin-10; WBC, white blood cell.
[a]Median (IQR) of the concentrations.

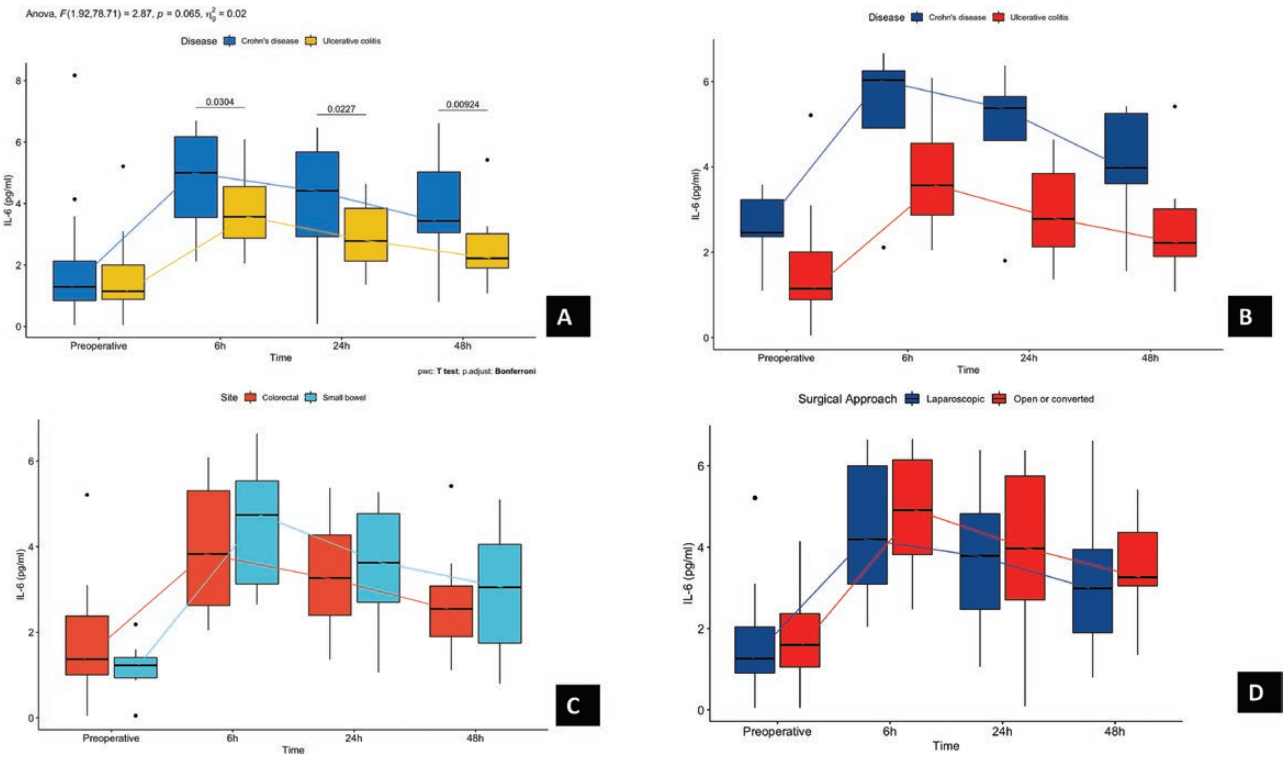

Figure 1. Postoperative inflammatory response as measured by IL-6. A comparison between Crohn's disease and ulcerative colitis. A, The whole cohort (46 patients). B, Patients who had colectomy only (19 patients). C, Patients who had intestinal resection compared with those who had colectomy (39 patients). D, Patients who had laparoscopic compared with open or converted resections (40 patients). Abbreviation: IL-6, interleukin-6.

The results are shown in Table 3. The changes in inflammatory markers and WBC counts between CD and UC patients showed a significantly higher baseline-to-peak change in CD than in UC indicating that a more severe IR is generated in CD (Table 3).

There was a similar response in patients undergoing laparoscopic compared with open approaches (Figures 1D, 2D, 3D, and 4D).

The results of postoperative outcomes including complications, length of postoperative stay at hospital, and

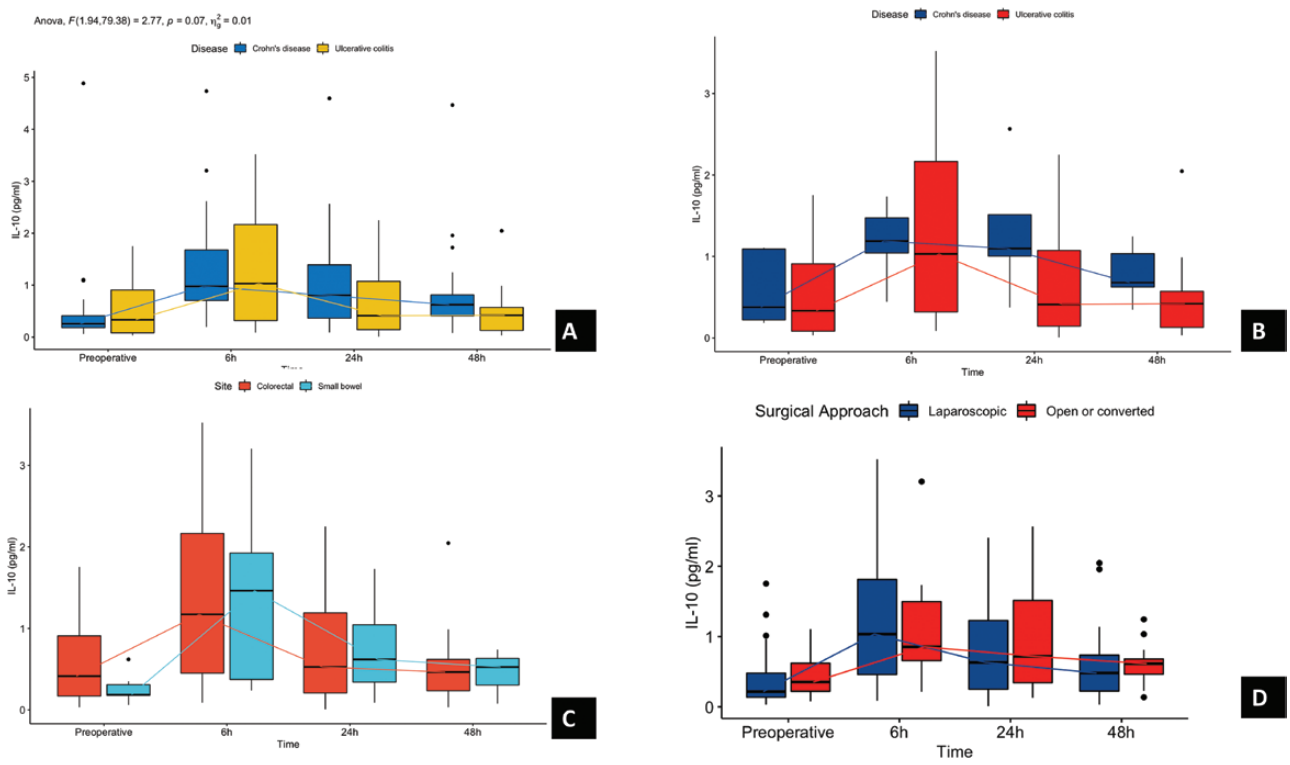

Figure 2. Postoperative inflammatory response as measured by IL-10. A comparison between Crohn's disease and ulcerative colitis. A, The whole cohort (46 patients). B, Patients who had colectomy only (19 patients). C, Patients who had intestinal resection compared with those who had colectomy (39 patients). D, Patients who had laparoscopic compared with open or converted resections (40 patients). Abbreviation: IL-10, interleukin-10.

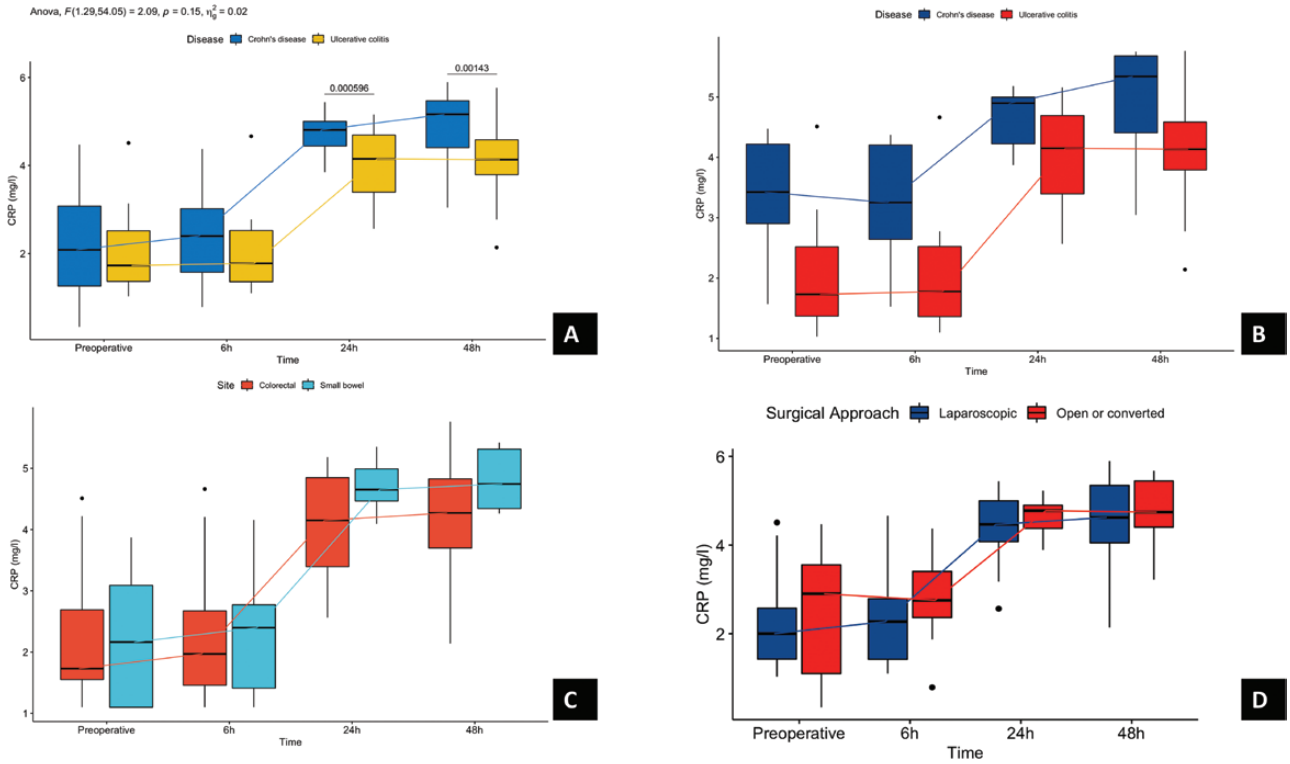

Figure 3. Postoperative inflammatory response as measured by CRP levels. A comparison between Crohn's disease and ulcerative colitis. A, The whole cohort (46 patients). B, Patients who had colectomy only (19 patients). C, Patients who had intestinal resection compared with those who had colectomy (39 patients). D, Patients who had laparoscopic compared with open or converted resections (40 patients). Abbreviation: CRP, C-reactive protein.

Table 3. Change in postoperative inflammatory response in patients with Crohn's disease compared with patients with ulcerative colitis showing the change in inflammatory markers from baseline to peak.

		Crohn's disease	Ulcerative colitis	*P*
Delta IL-6	Median (IQR)	123.4 (20.7–453.1)	25.2 (15.1–81.4)	.047
Delta IL-10	Median (IQR)	1.0 (0.2–3.1)	0.8 (0.1–5.8)	.821
Delta CRP	Median (IQR)	152.6 (77.0–222.0)	55.0 (40.1–81.1)	.002
Delta WBC	Median (IQR)	6.5 (3.5–8.1)	5.7 (4.8–6.2)	.826

Abbreviations: CRP, C-reactive protein; IL-6, interleukin-6; IL-10, interleukin-10; WBC, white blood cell.
[a]Median (IQR) of the concentrations.

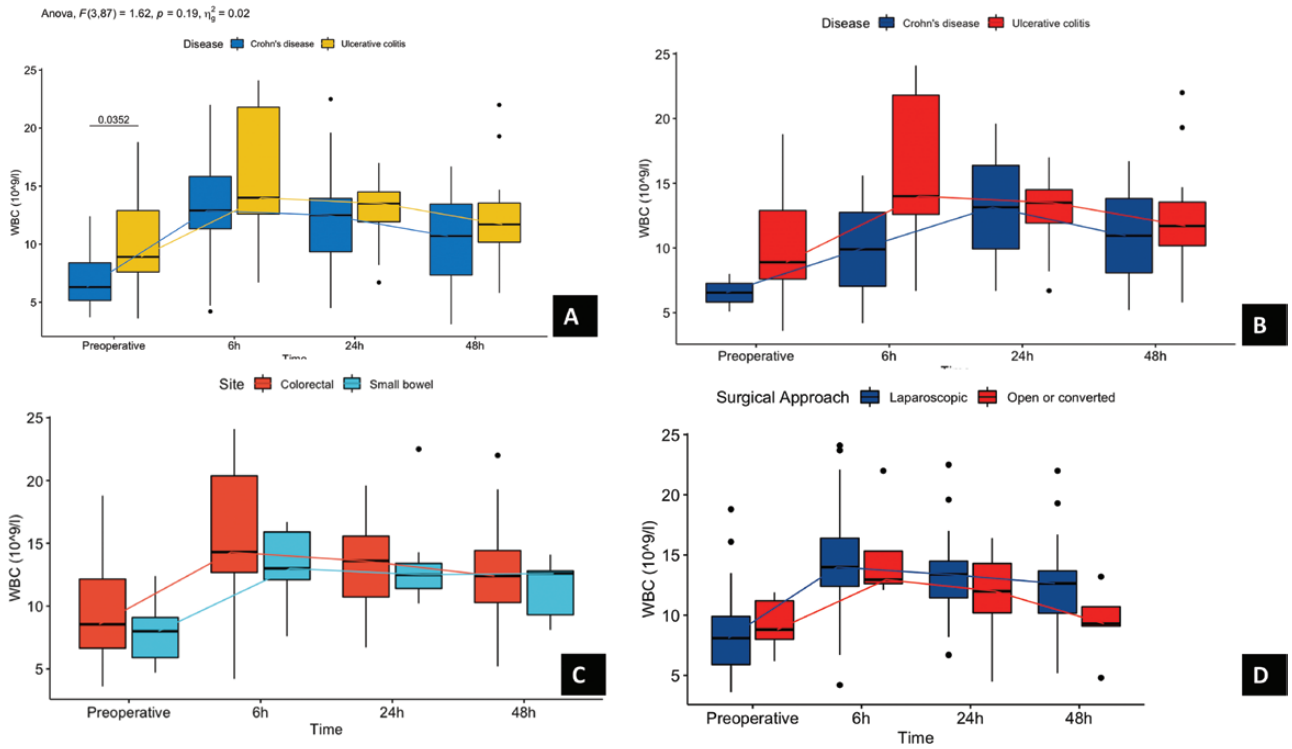

Figure 4. Postoperative inflammatory response as measured by WBC count. A comparison between Crohn's disease and ulcerative colitis. A, The whole cohort (46 patients). B, Patients who had colectomy only (19 patients). C, Patients who had intestinal resection compared with those who had colectomy (39 patients). D, Patients who had laparoscopic compared with open or converted resections (40 patients). Abbreviation: WBC, white blood cell.

Table 4. Complication and postoperative outcomes in patients with Crohn's disease compared with patients with ulcerative colitis.

Complication	Crohn's disease *N* (%) *N* = 32	Ulcerative colitis *N* (%) *N* = 14	Total *N* (%)	*P*
Overall complications	10 (31.2)	3 (21.4)	13 (28.3)	.745
Abscess	1 (3.1)	1 (7.1)	2 (4.3)	1
Surgical site infection	5 (15.6)	2 (14.3)	7 (15.2)	1
Intra-abdominal septic complications (IASC)	2 (6.2)	1 (7.1)	3 (6.5)	1
30-Day readmission	7 (21.9)	4 (28.6)	11 (23.9)	.909

readmission were presented in the main paper based on this project.[9] In Table 4, a brief comparison is presented. No significant difference in blood loss or postoperative length of stay at hospital between patients with CD and those with UC. The Harvey–Bradshaw index was higher than median in 12/32 patients with CD (37.5%).

Discussion

Our pilot study showed that postoperative IR is greater in CD than UC. The IR in CD seems to be more significant regardless of the type of surgical resection (small bowel resection vs colectomy) or surgical access to abdominal cavity (laparoscopic or open access).

Patients with CD appear to develop a greater IR postoperatively compared with those without IBD, probably reflecting the proinflammatory nature of the disease itself.[7] Because of this, patients with CD may have higher risk of postoperative complications or may react differently to the same procedure compared with those without IBD. Corresponding data on UC are lacking.[7]

It has been suggested that IBD may be due to an inappropriate IR to the intestinal bacterial flora in genetically susceptible individuals. Many susceptibility genes in IBD are also found in other immune-mediated diseases, indicating overlaps in pathogenic pathways.[11] IBD patients have therefore higher prevalence of autoimmune diseases such as celiac disease, primary sclerosing cholangitis, insulin-dependent diabetes mellitus, psoriasis, Sjögren syndrome, and systemic lupus erythematosus.[12]

The key difference between the 2 subtypes of IBD is the relative dominance of proinflammatory cytokines in CD, compared with UC.[11] This may be due to selective activation of type 1 T-helper lymphocyte (TH1) and TH17-related cytokines.[13] IL-23p19, IL-27p28, and EBI3 transcription are strongly upregulated in CD. The stimulatory effects of these cytokines on naive T cells in addition to synergistic action with IL-12 trigger interferon-γ production potentially contributing to the perpetuation of the inflammatory process in patients with CD. In UC, however, the cytokines produced by Th2 cells—mutual antagonists to Th1 produced cytokines—dominate, resulting in a different immune response for the same degree of inflammation.[14] These genetic differences potentially explain the findings in our study in addition to disease severity, preoperative treatment with biologics, immunomodulator, and steroids. The transmural infection might play a role in the inflammatory reactions seen in CD compared with UC but the data cannot provide a definitive answer.

The elevated inflammatory profile in patients with CD has been shown to contribute to delayed recovery and longer hospital stays. In a prospective audit conducted by the ESCP, it was demonstrated that even if patients with CD were younger, had had fewer comorbidities, were operated on by experienced surgeons, or underwent less radical resection compared with patients with colon cancer,[5] they had longer postoperative stay after the same surgical procedure compared with patients with colon cancer.[5]

Another interesting finding was the lack of difference between the IRs in open abdominal surgery versus laparoscopic abdominal surgery. However, we acknowledge that this might be caused by small sample size. Lack of information about disease phenotype in patients with CD, endoscopic score in both diseases and dysplasia in patients with UC was limitations that must be addressed in future research.

While our pilot study has limited sample size, 1 strength of our study is the depth of data, with each patient's IR markers comprehensively characterized. These data may guide future comparisons of surgical stress responses in patients with UC and CD, and inform subsequent power calculations. Patients with CD may need more preoperative support to improve their postoperative recovery compared with UC. Preoperative optimization may consist of nutrition, antibiotics, drainage of intra-abdominal abscess, and psychological support; however, the impact of such interventions should be thoroughly investigated in randomized trials. Our results will hopefully raise awareness of the differential postoperative IR profiles of patients with CD as the disease process can be devastating.[15]

To use these results as pivotal point to actionable clinical risk stratification, we need to increase the sample size probably using augmented data techniques.

Conclusion

The postoperative IR was greater in patients with CD than those with UC. The IR in CD was similar in both laparoscopic and open approaches.

What Does This Paper Add to the Literature?

This pilot study showed that postoperative inflammatory response is greater in CD than UC regardless of the type of surgical resection (small bowel resection vs colectomy) or surgical access to abdominal cavity (laparoscopic or open access). The elevated inflammatory profile in patients with CD needs to be addressed in the preoperative optimization and postoperative recovery setups.

Funding

The financial support received from different funds was essential to conduct the expensive blood investigations, pay the salaries of the staff who interviewed the patients, collected blood samples, registered and analyzed data. Special thanks to:

1. Research fund: The region of Zealand-Denmark
2. Research fund: Slagelse Hospital-Denmark
3. Aage og Johanne Louise Hansens Fond
4. Research fund: The region of north Jutland-Denmark
5. Crohn & Colitis organization research fund
6. King Christian the 10th fund

Authors' Contributions

The conception of the study: A.E.-H.. Data collection: A.E.-H. and N.Q. Statistical analysis: A.E.-H. and C.V. All the authors contributing to writing the article and proof readings of the manuscript. OpenSourceResearch collaboration is an international independent organization with special focus on implementing information technologies and artificial intelligence in clinical research. More about the organization and its projects can be found on its website: OSRC.network.

Conflicts of Interest

None declared.

Data Availability

Due to ethical concerns, supporting data cannot be made openly available. Further information about the data and conditions for access are available upon request.

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