

# Preoperative Biological Therapy and Postoperative Outcomes Following Ileocolic Resection for Crohn's Disease

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**ABSTRACT** **Background:** Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract. Biological therapy has transformed disease management; however, its association with postoperative outcomes remains debated.

**Objectives:** To evaluate the association between preoperative biological therapy and postoperative outcomes following ileocolic resection for Crohn's disease, and to identify additional factors associated with postoperative complications.

**Methods:** We conducted a single-center retrospective observational study of Crohn's disease patients who underwent ileocolic resection between 2021 and 2023. Patients were stratified according to preoperative exposure to biological therapy.

**Results:** Of 208 screened patients, 150 met inclusion criteria. Postoperative complications were more common in patients receiving biological therapy compared with controls (56% vs. 36.4%,  $P = 0.017$ ), which was primarily driven by minor complications (48% vs. 30%,  $P = 0.022$ ). Rates of major complications and length of hospital stay did not differ between the groups. Patients who developed major complications had significantly lower preoperative serum albumin levels (3.08 vs. 3.7 g/dl,  $P = 0.021$ ).

**Conclusions:** Preoperative biological therapy was associated with a higher rate of postoperative complications, predominantly minor in severity. Low preoperative serum albumin was associated with major postoperative complications, highlighting the importance of preoperative nutritional assessment and optimization.

*IMAJ 2026; 28: 289–294*

**KEY WORDS:** biological therapy, Crohn's disease, ileocolic resection, postoperative complications, serum albumin

incidence peak in later life. Historically, Crohn's disease has been described as particularly prevalent among Jewish populations, a finding that remains relevant in contemporary Israeli cohorts [1,2]. Although Crohn's disease may affect any part of the gastrointestinal tract, the terminal ileum is most frequently involved, accounting for approximately 40% of cases. Additional patterns include ileocolonic or proximal small bowel disease (30%), isolated colonic involvement (25%), and, less commonly, upper gastrointestinal disease affecting the stomach or duodenum (approximately 5%) [3].

The introduction of biological therapy has revolutionized the medical management of Crohn's disease, significantly reducing inflammatory burden, steroid dependence, and disease-related complications. Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) plays a central role in the pathogenesis and persistence of intestinal inflammation, providing the rationale for monoclonal antibody-based therapies [4,5]. Despite these advances, a substantial proportion of patients still require surgical intervention, with up to 50% undergoing bowel resection within 10 years of diagnosis [6]. The impact of preoperative biological therapy on postoperative outcomes remains controversial. Concerns persist regarding potential immunosuppression and impaired wound healing, particularly in the context of bowel anastomosis. Several studies have reported increased rates of postoperative complications, including infectious morbidity, wound complications, and anastomotic leak, among patients receiving preoperative biological agents [7]. In contrast, other reports have demonstrated no adverse effect on surgical outcomes and, in some cases, a reduction in postoperative complications, possibly reflecting improved disease control at the time of surgery [8].

Given the expanding use of biological therapies and ongoing uncertainty regarding their perioperative safe-

Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract characterized by periods of relapse and remission and may involve any segment from the mouth to the anus. Crohn's disease most commonly presents in young adulthood, with a second

ty, further data from contemporary surgical cohorts are needed. The aim of the present study was to evaluate the association between preoperative biological therapy and postoperative outcomes following ileocolic resection for Crohn's disease, and to identify additional factors associated with postoperative complications.

## PATIENTS AND METHODS

This retrospective cohort study included all consecutive patients with Crohn's disease who underwent elective ileocolic resection Shaare Zedek Medical Center, a large academic referral center, between January 2021 and December 2023. The study was approved by the institutional review board, and all data were obtained from a prospectively maintained database.

### CLINICAL VARIABLES AND OUTCOMES

Demographic, clinical, and perioperative variables were collected, including age, sex, body mass index (BMI), smoking status, American Society of Anesthesiologists (ASA) classification, Montreal classification [9], surgical indication, and preoperative serum albumin levels.

Preoperative biological therapy was defined as exposure to a biologic agent within 6 weeks prior to surgery, approximating one dosing cycle for commonly used agents and capturing recent immunomodulatory effects.

All ileocolic anastomoses were performed using a standardized stapled side-to-side extracorporeal technique, applied uniformly across the cohort to ensure technical consistency. The primary outcome was the occurrence of postoperative complications, classified according to the Clavien-Dindo system [10]. Complications were grouped as minor (Grades I–II) or major (Grades III–IV). Secondary outcomes included length of hospital stay and readmission due to postoperative complications.

### STATISTICAL ANALYSIS

Continuous variables were expressed as means with range or median with range, as appropriate. Categorical variables were presented as frequencies and percentages. Associations between categorical variables were assessed using the chi-square test or Fisher's exact test, as appropriate. Comparisons of continuous variables between two independent groups were performed using the two-sample *t*-test for normally distributed data or the Mann–Whitney U test for non-normally distributed data. All statistical tests were two-tailed, and a *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 29 (SPSS, IBM Corp, Armonk, NY, USA).

## RESULTS

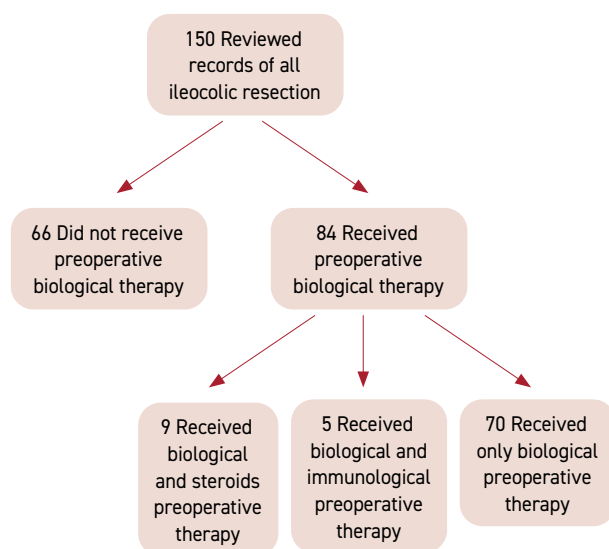
The final study cohort consisted of 150 patients, 84 (56%) received preoperative biological therapy and 66 (44%) did not. Baseline demographic and clinical characteristics were comparable between the two groups, including age, sex, BMI, smoking status, American Society of Anesthesiologists (ASA) score, surgical indication, and Montreal classification [9] [Table 1].

Among patients receiving biological therapy, 47 were treated with infliximab, 17 with risankizumab, 15 with adalimumab, 4 with vedolizumab, and 1 with certolizumab.

Laparoscopic ileocolic resection was performed in 139 patients (92.7%). Conversion to open surgery was required in only 4 cases (2.7%) due to dense adhesions and severe inflammatory changes.

Additional procedures were frequently required at the index operation: fistula takedown was performed in 59 patients (39.3%) and intra-abdominal abscesses were identified and drained intraoperatively in 31 patients (20.6%).

Figure 1. Flow diagram of study group selection



**Table 1.** Patient demographics and perioperative data

	Biologic therapy group, n=84	Control group, n=66	P-value
Sex (male/female), n (%)	50 (59.5)/34 (40.5)	37 (56)/29 (44)	0.67
Age in years, median (range)	28 (9–66)	30.5 (11–82)	0.32
ASA class, median (range)	2 (1–3)	2 (1–4)	0.24
Smoking, n (%)	14 (17)	13 (19)	0.5
BMI, n (%)	21.5 (4.73)	22.4 (5.56)	0.38
Surgical approach, n (%): laparoscopic/open/laparoscopic to open	80 (95)/4 (5)/0 (0)	59 (89)/3 (5)/4 (6)	0.165
<b>Indication for surgery, n (%)</b>			
Stricture	52 (62)	40 (45)	0.19
Fistula and/or abscess	32 (38)	26 (54)	
Preoperative albumin	3.67 (0.71)	3.62 (0.76)	0.68
Montreal classification (n, %)	0	0	
<b>Age at diagnosis, in years</b>			
A1 (≤ 16)	29 (34)	17 (26)	0.47
A2 (17–40)	46 (55)	39 (59)	
A3 (> 40)	9 (11)	10 (15)	
<b>Behavior</b>			
B2: stricturing	48 (57)	39 (59)	0.224
B3: Penetrating	5 (6)	7 (11)	
Both stricturing and penetrating (B2+B3)	31 (37)	20 (30)	
<b>Location</b>			
L1: ileal	1 (1)	2 (3)	0.5
L3: ileocolic	82 (98)	64 (97)	
L3 + L4: ileocolic + upper gastrointestinal	1 (1)	0 (0)	

ASA = American Society of Anesthesiologists, BMI = body mass index

**POSTOPERATIVE OUTCOMES**

The overall postoperative complication rate was 47.3% (71 patients). Major complications (Clavien–Dindo grade ≥ III) occurred in 11 patients (7.3%). The mean length of hospital stay was 7 days (range 3–34 days). Six patients (4%) required readmission due to postoperative complications. All were managed conservatively without the need for reoperation.

Patients receiving preoperative biological therapy experienced a significantly higher rate of overall postoperative complications compared with the control group (56.0% vs. 36.4%, *P* = 0.017). This difference was primarily driven by an increased rate of minor complications (48.0% vs. 30.0%, *P* = 0.022). When assessed individually, no minor complication demonstrated a statistically significant difference between the groups.

Rates of major complications did not differ significantly between groups, nor was there a difference in length of hospital stay [Table 2].

No significant association was observed between smoking status and postoperative complication rates (45.0% in smokers vs. 59.3% in non-smokers, *P* = 0.185). Similarly, surgical indication was not associated with overall postoperative complication rates.

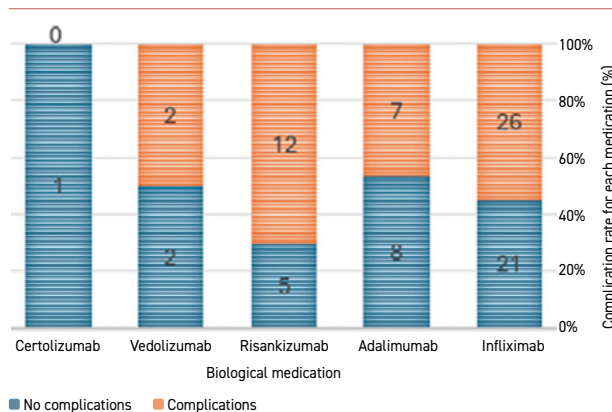
**SUBGROUP AND RISK FACTOR ANALYSIS**

Postoperative complication rates did not differ significantly according to the type of biological agent used (55.3%, 46.7%, 70.6%, and 50.0%, respectively; *P* = 0.510), as shown in Figure 2.

In our cohort, only 9 of 84 patients (10.7%) in the biologic therapy group received corticosteroids prior to

**Table 2.** Length of stay and complication rates among the two groups

	Biologic therapy group, n=84 (56%)	Control group, n=66 (44%)	P-value
Length of stay (days)	6.5 ± 3	5.8 ± 2.7	0.134
Overall complications	47 ± 56	24 ± 36	0.017
<b>Minor complications (Grade I-II)</b>	<b>40 (48%)</b>	<b>20 (30%)</b>	<b>0.022</b>
Noninfectious diarrhea	5 (6%)	2 (3%)	0.347
Acute kidney injury	5 (6%)	2 (3%)	0.347
Surgical site infection	3 (4%)	1 (1%)	0.536
Ileus requiring total parenteral nutrition	27 (32%)	15 (23%)	0.196
<b>Major complications (Grade III-IV)</b>	<b>7 (8%)</b>	<b>4 (6%)</b>	<b>0.587</b>
Anastomotic leak	2 (2%)	1 (1%)	0.644
Reoperation	2 (2%)	1 (1%)	0.644
Readmission	2 (2%)	2 (3%)	1
Thrombosis	1 (1%)	0 (0%)	1

**Figure 2.** Association between biological medications and postoperative complication rates

surgery, whereas none of the patients in the control group were treated with steroids. In these patients, steroid therapy had been gradually discontinued at least 6 weeks prior to surgery. Complication rates among steroid-exposed patients (3/9, 33.3%) were not significantly different from biologic-treated patients without steroid exposure (44/75, 58.7%;  $P = 0.21$ ) or from the remainder of the cohort (46.3%;  $P = 0.44$ )

When complications were stratified by severity, stricture as an indication for surgery was associated with a higher proportion of minor complications compared with major complications (87.7% vs. 12.3%,  $P = 0.044$ ). Patients who developed major postoperative complications had significantly lower preoperative serum albumin levels compared with those without major complications (3.08 g/dl vs. 3.70 g/dl,  $P = 0.021$ ).

## DISCUSSION

In our study, we found that preoperative exposure to biological therapy was associated with an increased rate of postoperative complications following ileocolic resection for Crohn's disease. Notably, this association was primarily attributable to minor complications. The incidence of major complications, duration of hospitalization, and the requirement for reoperation did not show significant differences. In addition, lower preoperative serum albumin levels were significantly associated with the occurrence of major postoperative complications.

The relationship between biological therapy and postoperative outcomes in Crohn's disease remains controversial. Concerns regarding perioperative immunosuppression, impaired wound healing, and infectious complications have led to ongoing debate regarding the safety of biological agents in the surgical setting. Several studies have reported increased postoperative morbidity, including abdominal sepsis and anastomotic complications, among patients treated with preoperative biologics [8].

Conversely, other investigations have demonstrated no adverse effect on surgical outcomes and in some cases a protective effect, potentially reflecting improved disease control at the time of surgery [7].

Prospective data from the PUCINI trial, which included nearly 1000 patients across multiple centers, demonstrated no association between detectable anti-TNF- $\alpha$  levels and postoperative infectious complications [11]. However, subsequent meta-analyses have sug-

gested a modest increase in postoperative complication rates associated with preoperative anti-TNF therapy [12]. These seemingly conflicting findings underscore the complexity of isolating the independent effects of biological therapy from disease severity, inflammatory burden, and patient-related factors.

In the present study, no significant differences in postoperative outcomes were observed between different classes of biological agents. Although this finding is reassuring, it should be interpreted with caution given the limited sample size, which resulted in a lack of statistical power to detect agent-specific effects. Notably, newer biological therapies such as ustekinumab and vedolizumab have not been consistently associated with increased postoperative morbidity in previous analyses [13,14]. This finding supports the notion that the observed increase in minor complications may reflect factors beyond the pharmacologic mechanism alone. Nutritional and inflammatory status are increasingly recognized as critical determinants of postoperative outcomes in patients with inflammatory bowel disease. Several studies have demonstrated that preoperative optimization, including nutritional support, is associated with improved surgical outcomes [15,16]. Serum albumin is a well-established predictor of postoperative morbidity and mortality [17], and in Crohn's disease it may serve as a surrogate marker of both nutritional depletion and systemic inflammation [18].

Hypoalbuminemia in Crohn's disease is often multifactorial, resulting not only from malnutrition but also from inflammation-mediated reductions in hepatic protein synthesis, increased vascular permeability, and cytokine-driven metabolic alterations [19]. Our findings that lower preoperative serum albumin levels were significantly associated with major postoperative complications reinforce the importance of careful preoperative assessment and supports efforts toward nutritional and metabolic optimization prior to surgery.

The interaction between biological therapy, inflammatory control, and postoperative recovery is complex. While biological agents effectively reduce disease activity and systemic inflammation, inflammation also plays a critical role in tissue repair and wound healing. The balance between achieving adequate disease control before surgery and allowing for optimal postoperative recovery remains an unresolved clinical challenge. Determining the optimal timing of surgery in relation to biological exposure still warrants further investigation.

**LIMITATIONS**

This study is limited by its retrospective design and single-center nature, which limits causal inference and generalizability. The sample size was insufficient to evaluate outcomes according to individual biological agents, and drug levels were not available, which prevented accurate assessment of residual biologic activity. In addition, although disease behavior and extent were systematically classified according to the Montreal classification and were comparable between groups, residual confounding from unmeasured markers of disease activity could not be excluded. Due to the limited number of major events, multivariable modeling was not feasible; thus, the observed association should not be interpreted as causal. In addition, the assessment of nutritional status was limited to BMI and serum albumin. Given the small number of steroid-exposed patients and the ≥ 6-week washout period (a time frame generally considered sufficient to reduce steroid-related postoperative risk), inclusion of steroid exposure in our analysis would risk unstable estimates and therefore was not included. Despite these limitations, the study reflects a contemporary surgical cohort and provides clinically relevant data from real-world practice.

**CONCLUSIONS**

Preoperative biological therapy was associated with a higher rate of postoperative complications following ileocolic resection for Crohn's disease, predominantly of minor severity, without an increase in major complications or length of hospital stay. These findings highlight the need for individualized perioperative decision-making and further prospective studies to better define the optimal integration of biological therapy and surgical intervention in Crohn's disease.

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### Capsule

## 2'-O-Methyl-guanosine RNA fragments antagonize TLR7 and TLR8 to limit autoimmunity

**Alharbi** and co-authors demonstrated that RNA fragments containing 2'-O-methyl-guanosine act as endogenous antagonists of the innate immune receptors TLR7 and TLR8. These receptors typically detect viral RNA but are also implicated in autoimmune activation. The modified RNA fragments inhibited TLR-mediated signaling, reducing inflammatory cytokine production and dampening immune

activation. In vivo, administration of these fragments attenuated autoimmune pathology in experimental models. The findings uncover a natural regulatory mechanism that constrains excessive innate immune activation and suggest a novel therapeutic strategy for autoimmune diseases.

*Nat Immunol* 2026; 27: 762  
Eitan Israeli

### Capsule

## NK cell dysfunction and interferon gamma production underlie autoinflammation in mevalonate kinase deficiency

Prenylopathies such as mevalonate kinase deficiency (MKD) are an emerging family of monogenic autoinflammatory diseases with an underlying defect in isoprenoid lipid synthesis and protein prenylation. The mechanisms linking defective protein prenylation to systemic inflammation remain unclear. **Munoz** and colleagues revealed that mice and humans with MKD had significant decreases in the frequency of mature natural killer (NK) cells, impaired trafficking of cytolytic granules, reduced cytotoxic activity, and increased production of the cytokine interferon  $\gamma$  (IFN- $\gamma$ ). Mice with MKD failed to clear murine cytomegalovirus (MCMV) infections and

had elevated serum IFN- $\gamma$  and inflammatory pathology, likely the result of decreased and dysregulated cytotoxic cells. The authors describe the beneficial effect of cytokine signaling blockade with a Janus kinase (JAK) inhibitor in an infant with severe MKD. Together, these findings reveal a fundamental role for dysregulated cytotoxic cells and IFN- $\gamma$  production in MKD and likely other prenylopathies. Importantly, this work provides a rationale for the use of JAK inhibitors in the treatment of MKD.

*Immunity* 2026: S1074-7613 (26) 00138-X  
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