

*Review article* ■

# Risk Factors for Early Postoperative Complications after Surgery for Crohn's Disease

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## SUMMARY

The aim of this study was to show the influence of various risk factors on early postoperative complications following surgery for Crohn's disease (CD). In this review, an online internet database was searched, and also systematic review of the literature was performed. Three different studies from different countries were analyzed and compared with the results obtained in our University Clinic of Digestive Surgery - Skopje. The first review shows the influence of positive resection margins in CD on septical complications occurrence in patients undergoing ileocolic resection for CD at the Tel Aviv Medical Centre - Israel. The second review shows the risk factors for complications after bowel surgery in Korean patients with CD using data from the Asan Medical Centre - Seoul, Korea. The third review shows that the delay of surgery is associated with inferior postoperative outcome in patients treated for perforating Crohn's ileitis, and the study was conducted using data from the medical records of patients treated at the Department of Surgery at the University of Regensburg, Germany. Finally, we analyzed the influence of the most common risk factors on early postoperative complications in patients that underwent surgery for Crohn's disease in a five-year period at the University Clinic of Digestive Surgery in Skopje, Macedonia and compared them with the results in the aforementioned articles.

**Key words:** Crohn's disease, risk factors, septic complications

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## INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal tract that can give rise to strictures, inflammatory masses, fistulas, abscesses, hemorrhage and cancer. This disease commonly affects the small bowel, colon, rectum or anus. Less commonly, it affects the stomach, esophagus and mouth. Often, the disease affects multiple areas of the gastrointestinal tract. The cause of CD is not known and there is no curative treatment. Current medical and surgical treatment is effective in controlling the disease, but even with optimal treatment, recurrences and relapses are frequent. The combined approach of optimal medical treatment with timely and strategic surgical intervention offers the most effective management. The goal of surgical treatment similarly to medical treatment is to provide long-lasting symptomatic relief while avoiding excessive morbidity. In that manner treatment of complications and palliation of symptoms while avoiding excessive loss of intestine rather than complete extirpation of the disease should be the aim of surgery. The main surgical options are resection with anastomosis or stoma formation, bypass procedures and more recently various forms of stricturoplasty. Indications for surgical treatment of patients with CD are mainly failure of medical treatment, intestinal obstruction, abscesses and inflammatory masses, perforation, fistulas, hemorrhage, cancer or suspicion of cancer, and in children growth retardation could also be the indication for surgical treatment (1).

Various risk factors specific for the patients with conditions related to the CD can influence the outcome of the surgical treatment especially in the early postoperative period, such as the first 30 days after the operation. Those risk factors can be preoperative conditions like anemia, hypoalbuminemia, duration of symptoms before surgery, site of the disease, poor nutritional status etc., or operative risk factors as indication for surgical treatment and intraoperative finding, type of operation or the condition of resection margins on histologic examination.

The aim of this review was to analyze the influence of those risk factors on surgical outcome in patients undergoing operation for CD in different parts of the world and compare them with the results obtained in our country. Three different studies from different countries were analyzed and compared with the results obtained in our University Clinic of Digestive Surgery - Skopje. The first review shows the influence of positive resection margins in CD on the occurrence of septic complications in patients undergoing ileocolic resection for CD at the Tel Aviv Medical Centre - Israel. The second review shows the risk factors for complications after bowel surgery in Korean patients with CD using data from the Asan Medical Centre - Seoul, Korea. The third review shows that the delay of surgery is associated with inferior postoperative outcome in patients treated for perforating Crohn's ileitis and the study was conducted

from the medical records of patients treated at the Department of Surgery at the University of Regensburg, Germany. Finally, we analyzed the influence of the most common risk factors on early postoperative complications in patients who underwent surgery for CD in a five-year period at the University Clinic of Digestive Surgery in Skopje, Macedonia and compared them with the results in the mentioned articles.

## MATERIAL AND METHODS

The first article, "*Positive histological inflammatory margins are associated with increased risk for intra-abdominal septic complications in patients undergoing ileocolic resection for Crohn's disease*" is a retrospective study conducted upon data extrapolated from computer database of patients with CD who underwent surgical treatment at Tel Aviv Medical Centre - Israel from January 2000 to December 2010. This study includes only patients who underwent ileocolic resection with a primary anastomosis. None of the patients had proximal loop ileostomy. All the data in the study were collected from the patient's medical charts. The data collected related to sex, age, duration of disease before surgical treatment, albumin level, use of steroid therapy (>3 months before surgery), immunomodulating therapy, biological agents treatment, emergency versus elective surgery, surgical approach, type of anastomosis, intraoperative findings, associated procedures performed in addition to the ileocolic resection, status of resection margins as defined by the pathologist and postoperative intra-abdominal septic complications. Intra-abdominal septic complications were defined by the authors as anastomotic leak, intra-abdominal abscess or infected collection and enterocutaneous fistula.

The second reviewed article, "*Risk factors for complications after bowel surgery in Korean patients with Crohn's disease*" is a retrospective study conducted upon data extrapolated from prospectively collected database of patients with CD which describes the incidence and factors predictive of early postoperative complications in Korean patients who underwent surgery for CD at the Asan Medical Centre - Seoul, Korea. The authors retrospectively assessed 350 patients who underwent surgery for primary or recurrent CD at the Asan Medical Centre - Seoul, Korea between January 1991 and May 2010. Patients with surgical interventions such as appendectomy, perineal surgery, closure of loop ileostomy or colostomy and reoperations for postoperative complications were excluded from the study. All of the complications were classified as septic and non-septic. Septic complications cover: wound infections, clinical anastomotic leakage, abdominal abscesses, bowel perforation and enterocutaneous fistulae. In this study, only septic complications occurring in the first 30 days after surgery were included, because late septic complications after 30 days are mainly caused by recurrent CD. Intestinal obstructions, postoperative hemorrhage, pul-

monary edema and effusion, stoma problems, adrenal insufficiency and cerebral infarction were noticed as non-septic complications of CD. Patients were separated in two groups, with and without postoperative complications, and the risk factors are also divided in two groups including preoperative risk factors like age, gender, smoking history, American Society of Anesthesiologists (ASA) score, preoperative treatment with steroids, immunosuppressants or infliximab; history of previous laparotomy, preoperative anemia and hypoalbuminemia, duration of symptoms before surgery, site of disease, and Montreal classification and operative risk factors that include indications for surgery, type of operation and covering stoma.

The third reviewed article "*Perforating Crohn's ileitis: delay of surgery is associated with inferior postoperative outcome*" is a retrospective study conducted upon data extrapolated from 197 patients that had 231 bowel resections for perforating ileitis at the Department of Surgery at the University of Regensburg, Germany in the period from 1992 to 2009. According to the Montreal classification the disease behavior was defined as perforating if intra-abdominal fistula, inflammatory mass and/or abscess were found intraoperatively. The "deterioration period" was calculated from the onset of the clinical exacerbation that was unresponsive to any medical treatment to the time of the surgery. The term intra-abdominal septic complications (IASC) was used for anastomotic leaks, intra-abdominal abscesses, intestinal fistula, leaks from intestinal stumps and leaks of sutured secondary internal fistulas.

Using the structure from the mentioned articles we conducted our own retrospective study using data from the medical charts of the patients with CD who were operated at the University Clinic of Digestive Surgery in Skopje, Republic of Macedonia from January 2008 till September 2013. The indications for surgery with our patients were various forms of penetrating disease, such as enterocutaneous and intra-abdominal fistula or perforation with generalized or localized peritonitis with or without intra-abdominal abscess, stricturing disease with intestinal obstruction, hemorrhage and failure of medical treatment. Patients who were treated conservatively who were operated for their perianal disease only or patients with CD who underwent surgery for closing of their ostomy in that period were excluded from the study. The data that was analyzed included age, sex, total hospital stay, duration of the disease before the operation, previous operations for CD, localization of the disease, preoperative values of the leukocytes, hemoglobin and hematocrit, ASA score, emergency or elective surgery, the indication for operation, the type of operation, duration of the operation, simultaneous interventions on the colon and the condition of the resection margins from the operative specimen as defined by the pathologist. The albumin level below 30 g/dl before the operation is defined as preoperative hypoalbuminemia. The hematocrit level below 0,39 in males and

below 0,36 in females is defined as preoperative anemia and moderate to severe anemia is defined as hematocrit level below 0,30 in both genders. The leukocytes level of above 12000 (leukocytosis) and below 4000 (leukopenia) was taken as a sign of severe inflammatory reaction in the patients and its influence was analyzed on the development of the complications. Early postoperative complications in our patients were divided into abdominal including infection of the laparotomy site, intra-abdominal abscess, dehiscence of the anastomosis and intestinal obstruction, and extra-abdominal including pulmonary edema, basal pneumonia, thromboembolisms and death.

### Statistical analysis

The risk factors for postoperative complications were analyzed by univariate analyses. Descriptive statistics were presented as mean and standard deviation for continuous variables and frequency distributions for categorical variables. The differences between the two groups (with and without complications) for categorical data were examined by  $\chi^2$  and Fisher exact test. The 2-sample t test was used to compare the two groups for continuous variables, such as age at operation, hemoglobin level before surgery, disease duration etc. Statistical significance was defined as P-value  $\geq 0.05$ .

### RESULTS

Shental et al. (3) demonstrated that in the 10-year period, 166 patients underwent ileocolicresection with primary anastomosis. Eighty-five (51%) patients were males and 81 (49%) were females with mean age at operation of  $35.7 \pm 13.79$  years. Emergency operations were done in 15% of the patients, and 25% already had been operated for CD. There were not any postoperative deaths. Twenty-five patients (15%) developed septic complications, 11 (44%) of them underwent repeat surgery and 14 (56%) were treated conservatively. From the 11 patients who underwent simultaneous sigmoidectomy, four of them developed intra-abdominal septic complications. To demonstrate the association between positive inflammatory margins and septic complications which are directly related to the small bowel anastomosis, comparison of the rate of the patients with septic complications between patients with or without positive pathohistological margins was made, after exclusion of the 11 patients who underwent an additional sigmoidectomy. Septic complications in patients with positive inflammatory margins were seen in 60% (vs. 31.2% in patients with negative margins). Risk factors that have been found to be associated with intra-abdominal septic complications also included: duration of the disease longer than 10 years, preoperative steroid treatment of more than three months, emergency surgery and added sigmoidectomy. Only disease duration, added sigmoidectomy and positive histological

margins were found to be independent risk factors for IASC.

The results (4) showed that out of 350 patients (246 males, 104 females; mean age  $29 \pm 9$  years; range, 14 to 74 years), 81 patients (23.1%) experienced postoperative complications of whom 54 patients (66.7%) had septic and 27 patients (33.3%) experienced non-septic complications. Among the patients with septic complications there were 19 patients with wound infection, 17 with intra-abdominal abscess and 13 patients with anastomotic leakage, while other cases were sporadic. Out of the 27 patients with non-septic complications 15 developed intestinal obstruction, 5 hemorrhage and 3 patients developed pulmonary edema, while other cases were sporadic. Thirty patients with major complications, most with septic complications, required relaparotomy. Reoperation rate was significantly higher in patients with septic complication compared with nonseptic complication (48.1% vs. 14.8). The results showed that out of the preoperative risk factors, only moderate to severe anemia and hypoalbuminemia have significant impact on the occurrence of early postoperative complication. Out of the operative risk factors, emergency surgery and covering stoma were the ones that had significant influence on the occurrence of early postoperative complication. Patients with poor nutritional status and anemia were administered parenteral or enteral nutrition before operation, including iron supplementation or blood transfusion to patients with moderate to severe anemia and albumin to patients with hypoalbuminemia. Preoperative anemia was corrected in 70 patients and was not corrected in 38, whereas preoperative hypoalbuminemia was corrected in 40 patients and was not corrected in 64 patients. In comparison with the overall and septic complications of these corrected and non-corrected groups, correction of both preoperative anemia and hypoalbuminemia significantly reduced the incidence of the overall complications, whereas correction of anemia, but not hypoalbuminemia, significantly reduced the rate of septic complications.

Ilesalniks et al. (5) included 197 patients with 231 resections for perforating ileitis in a time period of 17 years from 1992 to 2009. The manifestations of the perforating ileitis were as follows: intra-abdominal abscess, inflammatory mass only, enterocutaneous fistula, enterovesical fistula, enterovaginal fistula and free perforation with generalized peritonitis. The median duration of clinical deterioration which leads to surgical treatment was five months. Patients with preoperative exacerbation that were unresponsive to any medical treatment more than 5 months had a higher incidence of postoperative IASC (31% vs. 13%). Other factors that had significant impact as an independent factors on IASC rate were preoperative weight loss and factors such as the number of strictures in the inflammatory mass, surgery for free perforation, smoking and previous intestinal resection. There was a significant increase in duration of preoperative clinical deterioration, size of the

inflammatory mass, incidence of preoperative weight loss, intake of immunosuppressants and multiple-drug combination, and postoperative morbidity during the last five years of the study.

At the University Clinic of Digestive Surgery - Skopje in a five year period, 41 patients (21 males and 20 females; mean age,  $42.12 \pm 12.08$  years; range, 16 to 72 years) were operated for CD. The disease was localized mainly on the distal small bowel in 33 patients, while in other patients the location was on the large bowel in five patients, on the proximal small bowel in one patient and simultaneously on the large and small bowel in two patients. Eighteen of them were operated for various forms of perforating disease, 15 were operated for obstructing disease, five for failure of the medical therapy and three patients because of intestinal hemorrhage. Emergency operation was performed in 13 patients and the others were elective cases. In most of the patients or in 35 of them, resection of the affected bowel with primary anastomosis was done, two patients were treated with intestinal bypass, three with Hartman's resection and in one patient bitubularenterostomy was done after resection of the affected bowel.

Eleven (26,83%) patients experienced postoperative complications (Table 1). According to our statistical analysis only the perforating form of the disease with P value of 0,036 and preoperative leukocytosis/leukopenia ( $>12000/<4000$ ) with P value of 0,031 were significant in the univariate analysis for the development of the early postoperative complications. All other analyzed factors such as age, gender, smoking history, disease duration before surgery, previous operation for Crohn's disease, ASA score, emergency or elective surgery, the level of hemoglobin before surgery, preoperative hypoalbuminemia, preoperative anemia, preoperative moderate to severe anemia, other indications for surgery, type of the operation, the conditions of the resection margins on the operative specimen, simultaneous intervention on the colon, and the duration of the operation more than three hours had no significant statistical value as shown in Table 2.

**Table 1.** Incidence and type of postoperative complications in patients with Crohn's disease

Type of complication	Patients with complication (n=11)	Total no. of patients (n=41)
Abdominal complications	8 (72.73%)	19.51%
Wound infection	5 (45.45%)	12.20%
Intra-abdominal abscess	1 (9.09%)	2.40%
Anastomotic leakage	2 (18.18%)	4.88%
Intestinal Obstruction	0	0%
Hemorrhage	0	0%
Extra-abdominal complications	4 (36.36%)	9.76%
Basal bronchopneumonia	3 (27.27%)	7.32%
Pulmonary edema	1 (9.09%)	2.40%
Thromboembolisms	0	0%

**Table 2.** Demographic and clinical characteristics of patients with Crohn's disease

Characteristics	Without complications (n=30)	With complications (n=11)	P-value
Mean age (yr)	43,57±11,17	38,18±14,11	0,21
Male gender	14 (46.67%)	7 (63.64%)	0,335
Smoking	12 (40.00%)	2 (18.18%)	0,168
Mean disease duration before surgery (years)	5,00±4,50	3,64±2,58	0,35
First time operated	20 (66,67%)	8 (72,73%)	1
Total hospital stay (days)	10,63±2,85	16,91±5,84	0,00004
ASA score 3	6 (20%)	4 (36,36%)	0,413
Emergency surgery	8 (26,67%)	5 (45,45%)	0,252
<i>Site of disease</i>			
Proximal small bowel	0	1 (9,09%)	
Distal small bowel	27 (90,00%)	7 (63,64%)	
Large bowel	2 (6,67%)	3 (27,27%)	
Small and large bowel	1 (3,33%)	0	
Mean hemoglobin level before surgery	118,87±20,98	107,73±20,09	0,136
Preoperative hypoalbuminemia (<3.0 g/dL)	9 (30,00%)	5 (45,45%)	0,355
Preoperative leukocytosis/leukopenia (>12/<4)	6 (20,00%)	6 (54,55%)	0,031
Preoperative anemia (male h<39%; female h<36%)	13 (43,33%)	7 (63,64%)	0,249
Moderate to severe anemia (hematocrit <30%)	3 (10%)	3 (27,27%)	0,316
<i>Surgery indication</i>			
Perforating disease	10 (33,33%)	8 (72,72%)	0,036
Obstructing disease	13 (43,33%)	2 (18,18%)	
Failure of medical therapy	4 (13,33%)	1 (9,09%)	1
Hemorrhage	3 (10%)	0	0,551
Type of operation (resection)	28 (93,33%)	11 (100%)	0,950
Positive histological margins	7 (23,33%)	5 (45,45%)	0,168
Simultaneous intervention on the colon	6 (20,00%)	2 (18,18%)	1
Operation time, (>3 hours)	11 (36,67%)	7 (63,64%)	0,164

## DISCUSSION

The treatment of CD will end up with surgery in most of the patients. In one study of 907 patients with primary ileocecal CD the resection rates were 66%, 77%, and 83% at 1, 5, and 10 years after the diagnosis (2). The percentage of the early postoperative complications in those patients is higher than with other indications for the same type of operations. There are many studies that report from 8% to 18% of occurrence of the intra-abdominal complications and the overall early postoperative morbidity of nearly 23% in patients operated for CD (3-5). In our own study, the overall rate of early postoperative morbidity is 26.83% and the rate of the abdominal complications is 19.51%, which is very close to the worldwide reported figures. Because of the high rate of the early postoperative complications in many studies, there are attempts to find specific conditions that present as immediate reasons. In the first article, although the accent was placed on the condition of the resection margins on the resected specimen (6, 7) four more risk factors were found to be statistically significant for the occurrence of the intra-abdominal septic complications postoperatively and they were: disease duration over 10 years, preoperative steroid treatment of more than three months, emergency surgery and added sigmoidectomy (3). In the second article, preoperative hypoalbuminemia and preoperative moderate to severe anemia were registered as preoperative risk factors with significant impact on the rate of the overall early postoperative complications and emergency surgery; perioperative transfusion and covering stoma were statistically significant operative risk factors (4). The third article showed the following risk factors as significant for the development of early postoperative complications: number of structures involved in the inflammatory mass, surgery for free perforation and peritonitis, smoking, weight loss, previous intestinal resection and duration of clinical deterioration (5, 8). There are many other studies that proposed various other risk factors as important ones in the development of the high rate of the early postoperative complications after the operation for CD. Yamamoto et al. reported that preoperative low albumin levels, steroid use, and the presence of abscesses or fistulas at the time of laparotomy significantly increased the risk of intra-abdominal septic complications after surgery for CD (9). Alves A. et al. reported that recurrent clinical episode of CD, preoperative steroids use, poor nutritional status, and the presence of abscess at the time of surgery significantly increased the risk of septic abdominal complications after the first ileocecal resection for CD (10). Kanazawa A. et al. concluded that penetrating type of the disease, operation time longer than 180 minutes, and handsewn anastomosis are significant independent risk factors for postoperative intra-abdominal septic complications (11). Tzivanakis A et al. reported that steroid usage and preoperative abscess are associated with higher rates of anastomotic compli-

cations following ileocolic resection for CD (12).

Taken the significant risk factors, various modalities have been proposed to minimize the high morbidity rate after surgery for CD. Preoperatively correction of anemia and hypoalbuminemia is strongly suggested. Enteral and parenteral nutrition should be conducted in severely malnourished patients. If intra-abdominal abscess is found in the preoperative evaluation it is proposed to be drained percutaneously if possible and then wait several weeks for the inflammatory reaction to subside before the operation. Intraoperatively, we should take care not to lose too much blood to avoid intraoperative transfusions. Operating time should be shortened as much as possible. Stapled anastomosis is preferable over the handsewn (13-15) and the consideration should be taken for two-stage operation or creation of diverting proximal ostomy whenever too many risk factors are present in the patient.

From our own research we isolated the perforating form of the disease including localized or free perforation and any form of intra-abdominal and enterocutaneous fistula as significant risk factor for the development of early postoperative complications. We took preoperative leukocytosis/leukopenia as a sign of severe inflammatory reaction in the patients and concluded it to be a significant risk factor. We think that special consideration should be made in cases where there are two factors present.

## CONCLUSION

Based on the data collected for this study, we can conclude that we treat CD according to the worldwide accepted standards regarding the indications for surgery and the types of surgical procedures that we used (although strictireplasty is not a common procedure) (16-21), and our rate of early postoperative complications is not at all any different from that in the other parts of the world. We concluded that there is a strong influence of the two risk factors on the development on the early postoperative morbidity in our CD patients: perforating disease and preoperative leukocytosis/leukopenia. We propose all previously mentioned modalities for lowering the early postoperative morbidity to be used whenever those risk factors are present especially when both of them are present in the same patient. We are certain that if all modalities are conducted we can significantly lower the postoperative morbidity in the CD patients.

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## FAKTORI RIZIKA ZA NASTANAK RANIH POSTOPERATIVNIH KOMPLIKACIJA NAKON HIRURŠKOG TRETMANA KRONOVE BOLESTI

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### Sažetak

Cilj studije bio je da se prikaže uticaj različitih faktora rizika za nastanak ranih postoperativnih komplikacija nakon hirurškog tretmana Kronove bolesti. U ovom preglednom radu prikazani su rezultati pretrage internet baze podataka i urađen je pregled literature. Analizirane su tri studije iz različitih zemalja, a potom su upoređene sa rezultatima dobijenim na Univerzitetskoj klinici za digestivnu hirurgiju u Skoplju. Prva studija ukazuje na uticaj pozitivnih margina resekcije kod Kronove bolesti na razvoj septičnih komplikacija kod bolesnika podvrgnutih ileokoličnoj resekciji u Medicinskom centru u Tel Avivu u Izraelu. Drugi rad prikazuje faktore rizika za razvoj komplikacija nakon hirurških intervencija na crevima kod korejskih bolesnika sa Kronovom bolešću, pri čemu su korišćeni podaci Medicinskog centra ASAN u Seulu, Koreja. Treća studija je pokazala da je odlaganje hirurškog tretmana povezano sa lošim postoperativnim ishodom kod bolesnika sa perforirajućim Kronovim ileitisom. U studiji su korišćeni podaci iz kartona lečenih na Odeljenju za hirurgiju, Univerziteta u Regensburgu, Nemačka. Na kraju smo analizirali uticaj najčešćih faktora rizika za nastanak ranih postoperativnih komplikacija kod bolesnika podvrgnutim hirurškom tretmanu zbog Kronove bolesti u petogodišnjem periodu na Univerzitetskoj klinici za digestivnu hirurgiju u Skoplju, Makedonija i uporedili ih sa rezultatima navedenih studija.

**Ključne reči:** Kronova bolest, faktori rizika, septične komplikacije