



# Risk factors for early postoperative complications in patients with Crohn's disease after colorectal surgery other than ileocecal resection or right hemicolectomy

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## Abstract

**Purpose** To evaluate risk factors for early postoperative complications in patients with Crohn's disease (CD) after extensive colorectal resection excluding mere ileocecal resection or right hemicolectomy at a university center.

**Methods** A retrospective analysis of the prospectively maintained database for surgical patients with CD at our institution was performed. All consecutive patients operated between December 2009 and December 2017 were included.

**Results** In total, 126 patients were eligible for this study. Most common types of operations performed were subtotal colectomy or proctocolectomy (37.3%) and resections of the rectum (34.1%) or the sigmoid colon (14.3%). Major postoperative complications occurred in 29 patients (23.0%). The rate of local septic complications (anastomotic leak, postoperative abscess) was 11.1%. In univariate analysis, low preoperative albumin, elevated preoperative C-reactive protein (CRP), and emergency surgery were factors associated with major postoperative complications. When multivariable analysis was performed, low preoperative albumin was the only independent risk factor for the occurrence of major postoperative complications ( $p = 0.0033$ ; OR 0.899). The cut-off value for albumin was 32.6 g/L.

**Conclusions** In this large cohort of consecutive patients undergoing surgery of the colorectum in CD, the rate of major postoperative complications was considerably higher compared to our recently published data from patients with ileocecal resection or right hemicolectomy. Preoperative albumin is the only independent risk factor for the occurrence of major postoperative complications. Preoperative albumin levels  $> 32.6$  g/L significantly reduce the risk for postoperative complications.

**Keywords** Crohn's disease · Postoperative complications · Left hemicolectomy · Colectomy · Rectal surgery · Anastomotic leak

## Introduction

Despite the advances in drug therapy in the era of biologic agents, the majority of patients with Crohn's disease (CD) still require surgery during the course of their disease [1, 2]. In a large US register-based cohort study including 443,950

patients with CD, about one fifth of the patients ( $n = 91,013$ ) needed bowel surgery within an observation period of 10 years. Among patients who underwent bowel resection, 50% had small bowel disease, 20% large bowel disease, and the remaining 30% had both [3]. Thus, around half of the patients with CD requiring bowel resection undergo colonic or colorectal resection. Several studies have shown that bowel resection in patients with CD has a different risk profile compared to bowel surgery in non-inflammatory bowel disease (IBD) patient cohorts. Particularly, higher rates of intraabdominal septic complications, such as enteric fistula and intraabdominal abscess, have been described [4, 5].

Recently, we published data of 305 consecutive patients with CD who underwent either ileocecal resection or right hemicolectomy. High-grade complications (Clavien–Dindo grade  $\geq$  III [6]) were observed in 9.5% of the patients (29/305). In multivariate analysis, independent risk factors for

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major complications were bowel perforation, elevated preoperative leucocyte count, and preoperative hypoalbuminemia [7]. Previous studies have shown that in CD, colonic resections have higher complication rates compared to small bowel or ileocecal resections. Moghadamyeghaneh, for example, found significantly higher mortality (adjusted odds ratio (AOR) 2.42, 95% confidence interval (CI) 1.91–3.07,  $p < 0.01$ ) and overall morbidity (AOR 2.42, 95% CI 1.91–3.07,  $p < 0.01$ ) rates for patients with colonic CD compared to patients with small bowel CD after bowel surgery [3].

Since the evidence—especially based on prospectively collected data—regarding the outcomes of surgery for large bowel CD and potential risk factors for postoperative complications is still scarce, the present study was designed to (1) examine surgical morbidity after colorectal resections other than ileocecal resection or right hemicolectomy for benign indications in patients with histologically proven CD, (2) to determine risk factors for high-grade morbidity, defined as Clavien–Dindo  $\geq$  grade III [6], and (3) to compare the results with those of right-sided and ileocecal resections.

## Patients and methods

### Ethics approval

Ethics board approval was obtained from the Medical Ethics Commission II of the Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany (2018-840R-MA). The study was performed according to the Declaration of Helsinki.

### Patients

A retrospective analysis of the prospectively maintained database for patients with CD at our institution was performed. Medical records of 736 patients with CD who underwent abdominal surgery between December 2009 and December 2017 were examined, and those with surgical procedures of the colon and rectum excluding isolated ileocecal resection or right hemicolectomy alone were identified. Patients receiving isolated small-bowel resections and patients with malignant disease were excluded. We included elective and emergency procedures. Preoperative patient data and intraoperative findings were recorded and evaluated with respect to early postoperative complications (Clavien–Dindo classification of surgical complications [6]).

### Statistical analysis

The mean and standard deviation were calculated for quantitative variables. The median, together with the range or interquartile range (IQR), are presented for skewed or ordinal scaled parameters. Qualitative variables were quoted as

absolute and relative frequencies. Student's  $t$  test was used for comparing approximately normally distributed quantitative variables. The Mann–Whitney  $U$  test was used for variables that were not normally distributed. For qualitative variables, an  $X^2$  test or Fisher's exact test was used, as appropriate. All statistical tests for the comparison of two groups were two-tailed. In general, a test result was considered statistically significant if  $p < 0.05$ .

For the binary outcome “occurrence of major postoperative complications”, a univariable logistic regression analysis combined with a receiver operating characteristic (ROC) analysis has been performed aiming to determine an optimal cut-off value for albumin that separates patients with major complications from patients without major complications. Furthermore, a multiple logistic regression analysis was done. Odds ratios are presented together with their 95% confidence intervals. In the multiple analyses, the “selection = forward” option was used and a significance level of  $\alpha = 0.10$  chosen to detect several parameters that might influence the outcome. Prior to multiple analyses, binary comparison was used to investigate whether each factor was associated with the outcome to check for possible confounders. All analyses were performed using the SAS statistical analysis software (release 9.4; Cary, NC, USA).

## Results

### Patients' characteristics

Patient's characteristics are shown in Table 1. Between December 2009 and December 2017, a total of 736 patients underwent abdominal surgery for CD at our institution. Of these, 20 patients were excluded because of malignancy. Surgical procedures of the colon or rectum other than isolated ileocecal resection or right hemicolectomy alone were performed in 126 patients (17.1%) which were all included in this study. There were 43 males (34.1%) and 83 females (65.9%). The mean age at surgery was  $40.7 \pm 15.4$  years. Median length of hospital stay was 10 days (IQR 7–16.3 days).

### Preoperative medications

Forty-two patients (38.9%) were taking oral corticosteroids at the time of surgery. For elective procedures, preoperative dosages of oral corticosteroids were reduced to equivalents of 10 mg/day prednisolone or less until surgery depending on disease activity, which was achieved in all but 4 elective cases. Classic immunosuppressive medications such as azathioprine or 5-aminosalicylic-acid (5-ASA) were taken by 31 patients (28.2%). Thirty-four patients (28.2%) received preoperative treatment with biologicals. Biologicals used were anti-TNF-

**Table 1** Patients' characteristics

Patients' characteristics			
Male	<i>n</i> (%)	43	34.1
Female		83	65.9
Age at surgery (years)	Mean (SD)	40.7	± 15.4
Duration of disease (years)	Median (range)	16.2	0–48.5
ASA classification	<i>n</i> (%)		
I		4	3.6
II		81	72.3
III		24	21.4
IV		3	2.7
V		0	0.0
Preoperative medications	<i>n</i> (%)		
Corticosteroids		42	38.9
Immunosuppressants		31	28.2
Biologicals		34	31.8
Infliximab		7	6.5
Adalimumab		17	15.9
Vedolizumab		7	6.5
Ustekinumab		3	2.8
Unknown		19	17.8
Biological data at surgery			
Albumin (34–50 g/L)	Median (IQR)	33.35	28.6–37.3
Creatinine (0.66–1.09 mg/dL)		0.86	0.65–1.00
CRP (0–5 mg/L)		18.45	4.73–47.65
INR (0.9–1.15)		0.99	0.96–1.06
Leucocytes (4.2–10.2/mm <sup>3</sup> )	Mean (SD)	9.62	± 4.17
Thrombocytes (165–387/mm <sup>3</sup> )		347.6	± 131.6

ASA American Society of Anesthesiologists

agents (infliximab or adalimumab) or integrin- and interleukin-antagonists (vedolizumab or ustekinumab). Biological treatment was paused at least 3 to 4 weeks prior to surgery for all elective procedures.

## Surgical procedures

Indications for surgery were stricture(s) and penetrating complications of CD. All non-emergency procedures were performed by colorectal surgeons specialized in IBD. All emergency procedures were performed by senior surgeons with longstanding experience in colorectal surgery. Data on the different types of surgery are listed in Table 2. In the majority of cases, subtotal colectomy or proctocolectomy were performed (37.3%), followed by rectal resections (34.1%), and resections of the (recto-)sigmoid (14.3%). Resection of the left or transverse colon was performed in 7.1% and 3.2% of cases, respectively.

Data on surgery is listed in Table 3. The vast majority of cases were non-emergency procedures (95.2%). More than

**Table 2** Type of resection performed

Performed resection	<i>n</i>	%
Transverse colonic resection	4	3.2
Left hemicolectomy	9	7.1
(Recto-)sigmoid resection	18	14.3
Anterior (rectal) resection	14	11.1
Low anterior (rectal) resection	13	10.3
Abdomino-perineal resection	16	12.7
(Sub-)total colectomy or proctocolectomy	47	37.3
Other	5	4.0

half of the patients (56.4%) had undergone previous intestinal resection for CD. The majority of procedures were performed with an open surgical approach. The conversion rate of laparoscopically intended operations was 26.6%. Intraoperative abscesses were found and drained in 19.8% of patients. Preoperative image-guided percutaneous abscess drainage was performed in 4.0% of cases. Indication for preoperative image-guided percutaneous abscess drainage was accessible and clinically relevant macro-abscess formations (> 2 cm). Smaller inter-enteric abscesses were drained intraoperatively. Nearly half of the patients presented with fistulating disease at the time of surgery (49.2%). The rate of intestinal stoma formation was 55.6%. Of the 70 patients with stoma formation, 18 patients received protective ileostomies,

**Table 3** Additional data on surgery

Data on surgery	<i>n</i>	%
Emergency procedures	6	4.8
Previous intestinal resection	71	56.4
Intraoperative abscess	25	19.8
Preoperative abscess drainage	5	4.0
Fistulating disease	62	49.2
Surgical approach		
Laparoscopy	47	37.3
Laparotomy	79	62.7
Conversion	17	26.6 <sup>2</sup>
Additional procedures		
Ileocecal resection	11	8.7
Small bowel surgery	10	7.9
Big bowel surgery	5	4.0
Strictureplasty	5	4.0
Ileoanal pouch	4	3.2
Appendectomy	2	1.6
Cholecystectomy	5	4.0
Stoma creation	70	55.6

<sup>2</sup> Of laparoscopically intended procedures

2 patients received a colonic resection enterostomy, and 50 patients received end ileostomies or colostomies. In 76 patients, (60.3%) at least one anastomosis was created.

### Postoperative complications

Surgical complications graded according to the Clavien–Dindo classification are shown in Table 4. Major complications (Clavien–Dindo grade  $\geq$  III) were observed in 29 patients (23.0%); 97 patients (77.0%) had minor (31.7%) or no (45.2%) postoperative complications. Two patients (1.6%) with grade IIIa complications underwent interventional image-guided drainage of postoperative intraabdominal abscesses. Revisional surgery was necessary in 27 cases (21.4%). Reasons were anastomotic leakage ( $n=8$ ), postoperative abscess ( $n=6$ ), bowel obstruction ( $n=3$ ), bowel perforation ( $n=2$ ), lesions of the ureter or urinary bladder ( $n=2$ ), postoperative bleeding ( $n=1$ ), bowel ischemia ( $n=1$ ), acute cholecystitis ( $n=1$ ), and general septic condition/peritonitis ( $n=2$ ). The rate of local septic complications (anastomotic leak, postoperative abscess) was 11.1% ( $n=14$ ).

The only grade V complication occurred in a multimorbid patient who presented with free bowel perforation and died postoperatively in prolonged sepsis.

### Factors associated with the occurrence of postoperative complications

In univariate analysis, low levels of preoperative albumin, elevated preoperative C-reactive protein (CRP), and emergency surgery were factors significantly associated with the occurrence of major postoperative complications. All other evaluated parameters were not significantly associated with major complications (Table 5). In

**Table 4** Postoperative complications

Clavien–Dindo complications	<i>n</i>	%
None	57	45.2
I	13	10.3
II	27	21.4
III a	2	1.6
III b	21	16.7
IV a	2	1.6
IV b	3	2.4
V	1	0.8
Minor or no complications (< III)	97	77.0
Major complications ( $\geq$ III)	29	23.0

**Table 5** Factors associated with the occurrence of postoperative major complications

Postoperative major complications in univariate analysis	
Variable	<i>p</i> value
Emergency procedure	0.0024*
Albumin	0.0016*
CRP	0.0350*
ASA-score	0.0640
Age	0.5581
Gender	0.6589
Duration of disease	0.2752
Fistulating disease	0.6740
Intraoperative abscess	0.5962
Preoperative abscess drainage	0.3247
Type of surgery (laparotomy vs. laparoscopy)	0.5143
Conversion	0.5375
Previous intestinal resection	0.6705
Additional ileocecal resection	1.0000
Additional small bowel surgery	1.0000
Additional colorectal surgery	1.0000
Additional strictureplasty	1.0000
Number of anastomoses	0.3141
Appendectomy	0.4088
Cholecystectomy	0.5886
Ileoanal pouch	1.0000
Stoma creation	0.2876
Classical immunosuppressants	0.2284
Steroids	0.2648
Biologicals	0.3343
Creatinine	0.9008
Leucocytes	0.0821
Thrombocytes	0.7853
INR (international normalized ratio)	0.0671
Postoperative major complications in multivariable analysis	
Variable	OR 95% CI
Albumin	0.899; 0.838–0.965

multiple logistic regression analysis, low preoperative albumin was the only independent risk factor for major postoperative complications ( $p=0.0033$ ; OR 0.899).

### Subgroup analysis for non-emergency procedures

To exclude a possible bias caused by an inhomogeneous study population, emergency procedures ( $n=6$ , 4.8%) were excluded, and the subgroup of non-emergency patients was analyzed. In this subgroup analysis, low preoperative albumin was the only risk factor for the occurrence of major postoperative complications in univariate ( $p=0.0083$ ) and multiple analysis ( $p=0.0166$ ; OR 0.910; 95%-CI 0.842–0.983).

## Albumin cut-off level with respect to surgical complications

A logistic regression model was used to determine the optimal cut-off value for preoperative albumin levels with regard to the occurrence of postoperative complications. When sensitivity and specificity were considered as equally important, the optimal cut-off value for albumin was 32.6 g/L (sensitivity 74.1%, specificity 63.7%, Youden's index 0.38). The corresponding ROC curve is shown in Fig. 1.

## Discussion

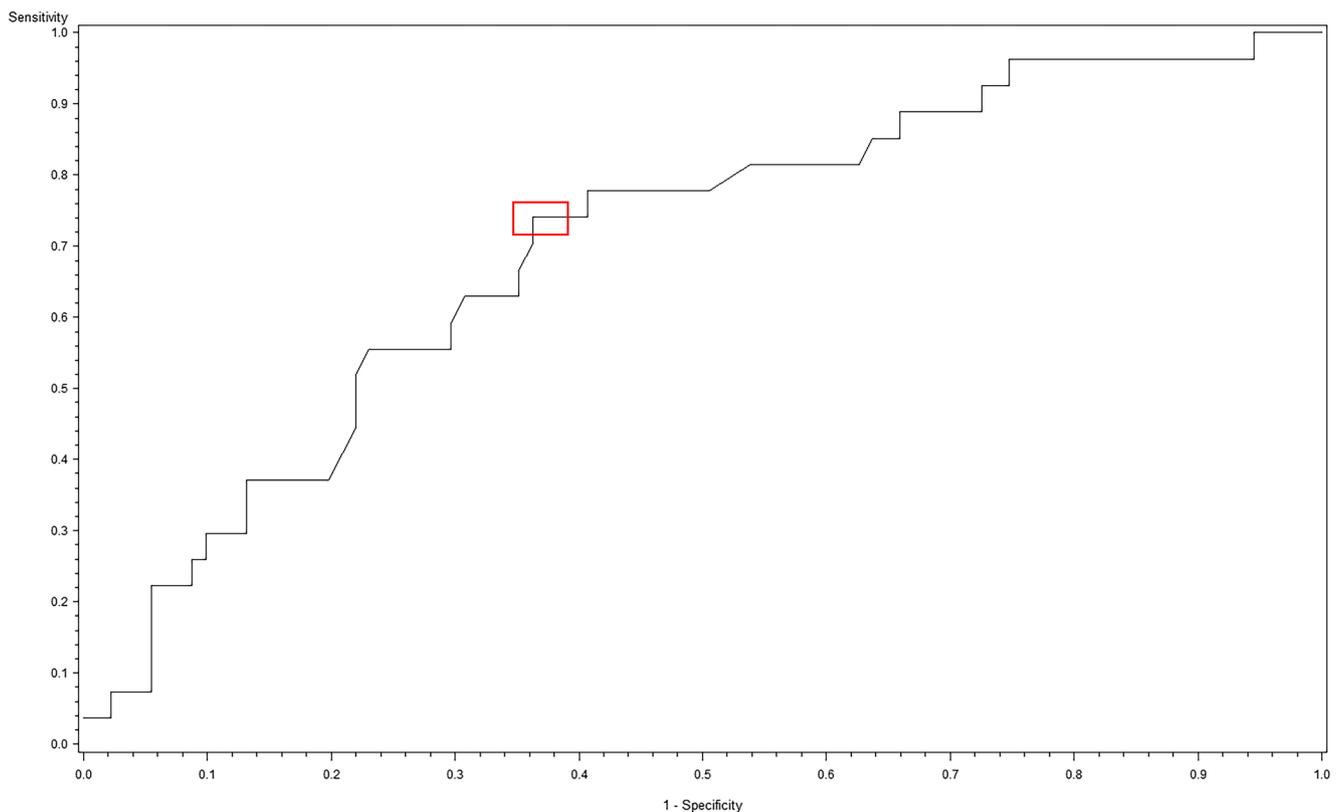
The present study reports the surgical outcomes of 126 consecutive patients who underwent colorectal resections other than ileocecal resection or right hemicolectomy for CD and benign indications at a tertiary referral center between December 2009 and December 2017. Potential risk factors for postoperative morbidity were examined. Almost every fourth patient experienced a major complication (Clavien–Dindo grade  $\geq$  III), mainly in the form of anastomotic leakage, intraabdominal abscess, and bowel perforation or obstruction. Such relatively high morbidity rates are in line with the literature: Yamamoto et al. recently reported rates of overall morbidity, intraabdominal septic complications, and anastomotic

leakage of 24%, 12%, and 8% after ileocolonic resection for CD at seven IBD referral centers in Japan, Brazil, and Italy [8].

Our findings demonstrate that preoperative hypoalbuminemia (cut-off value 32.6 g/L) is potentially the clinically most relevant and the only independent risk factor for postoperative high-grade morbidity after colorectal resections other than ileocecal resection or left hemicolectomy for CD. Other factors significantly associated with the occurrence of major complications in the univariate analysis were elevated CRP levels and emergency surgery. In order to exclude confounding by emergency versus elective indication, we conducted a subgroup analysis which included only non-emergency cases. However, hypoalbuminemia still remained the only independent risk factor for high-grade morbidity.

It is well known that albumin levels have a major impact on postoperative complications after gastrointestinal surgery [9]. As Moghadamyeghaneh et al. showed, even mild hypoalbuminemia ( $30 \leq$  serum albumin  $< 35$  g/L) is a significant risk factor for postoperative complications after colorectal resections [10]. This is in concordance with the findings of the present study, which identified a preoperative serum albumin level of 32.6 g/L as the clinically relevant cut-off level.

Moreover, there is solid evidence that, especially in the context of IBD surgery, hypoalbuminemia plays an important role both as a risk factor and predictor of surgical



**Fig. 1** ROC curve for determination of an optimal albumin cut-off: 32.6 g/L when a sensitivity of 74.1% and a specificity of 63.7% are chosen

complications [4, 5, 7, 8, 11, 12]. Huang et al. conducted a systematic review of observational studies investigating risk factors for postoperative intraabdominal septic complications after CD surgery. The statistical meta-analysis including 15 studies, 3807 patients, and 4189 operations, respectively, identified preoperative hypoalbuminemia (OR 1.93, 95% CI 1.36–2.75), preoperative steroids use (OR 1.99, 95% CI 1.54–2.57), preoperative abscess (OR 1.94, 95% CI 1.26–3.0), and a history of previous surgery (OR 1.50, 95% CI 1.15–1.97) as risk factors for postoperative intraabdominal septic complications. Use of biologics or immunomodulation as well as anastomosis methods (handsewn versus stapled) were not associated with a higher risk for postoperative intraabdominal septic complications [4].

Similar findings were reported by Yamamoto et al. who investigated risk factors for intraabdominal septic complications, defined as anastomotic leakage, intraabdominal abscess, or enterocutaneous fistula, after surgery for CD. The patient cohort consisted of 343 patients who underwent 1008 intestinal anastomoses during 566 operations. Intraabdominal septic complications were observed after 13% (76/566) of the operations and were significantly associated with preoperative hypoalbuminemia (< 30 g/l), preoperative steroids use, and presence of abscess or fistula at the time of surgery. The more of these independent risk factors were present at the time of surgery, the higher was the rate of intraabdominal septic complications: 50% (8/16 operations) in patients with all four risk factors, 29% (10/35 operations) in patients with three risk factors, 14% (14/98 operations) in patients with two risk factors, 16% (33/209 operations) in patients with one risk factor, and only 5% (11/208 operations) in patients with none of these risk factors ( $p < 0.0001$ ) [5].

This is consistent with the results of a recently published analysis of the surgical outcomes after ileocecal and right-sided colon resections for CD using data from our prospectively maintained institutional database [7]. Interestingly, hypoalbuminemia is not only the most relevant risk factor for high-grade morbidity in both study cohorts, but also the cut-off value of the preoperative serum albumin level was identical in both cohorts (32.5 vs. 32.6 g/L).

Comparing our own institutional results after right-sided and left-sided colon resections, it should be noticed that morbidity, in particular intraabdominal septic complications, was higher after resections including left-sided and rectal resections [7]: whereas high-grade morbidity occurred in only 9.5% (29/305) of the patients after ileocecal or right-sided colonic resection, the rate of high-grade complications was 23% (29/126) after procedures including left-sided resections. As a result, revisional surgery was necessary in 21.4% (27/126) of the latter patients in comparison with only 7.5% (23/305) after ileocecal or right-sided resection.

Though there is some evidence that, in CD patients, large bowel resections have a more unfavorable risk profile than

small bowel resections [3], it is still unknown whether there is a relevant difference between mere right-sided colonic resections and colonic resection including the right side and the rectum regarding the risk to develop postoperative complications. This special aspect should be subject of further, ideally prospective, studies.

Identifying risk factors for postoperative mortality and morbidity, i.e., in the form of intraabdominal septic complications, is the first step in order to prevent them. Defining strategies for prevention of major morbidity is of paramount importance. Intraabdominal septic complications after bowel resection are significantly associated with increased risks of surgical recurrence and reoperation and may therefore have a detrimental influence on the short- and long-term outcome after bowel resection for CD. As Iesalnieks demonstrated, patients suffering intraabdominal septic complications have statistically significantly higher 1-, 2-, 5-, and 10-year surgical recurrence rates (25%, 29%, 50%, and 57%) than patients without such complications (4%, 7%, 19%, and 38%,  $p = 0.0003$ ) [13]. Similarly, Kanazawa et al. who conducted a retrospective chart review of 550 patients undergoing 728 intestinal anastomoses during 633 operations for CD demonstrated a significantly increased 1-year reoperation rate for patients with intraabdominal septic complications compared to patients without intraabdominal septic complications (41.2% vs. 2.3%,  $p < 0.0001$ ) [14].

In this context and based on our data, preoperative serum albumin may help to reliably identify patients at increased risk for perioperative complications. Albumin levels, on the one hand, could therefore have an effect on the individual treatment plan and the extent of surgery (e.g., stoma construction) of a specific patient. On the other hand, in case of hypoalbuminemia indicating malnutrition, an effort to improve the patient's nutritional status prior to surgery may be undertaken, e.g., additional enteral nutrition and even parenteral nutrition in order to potentially prevent perioperative complications. The importance of preoperative nutritional screening, including serum albumin measurement and preoperative optimization, is underlined by the findings of a recently published systematic review: Zangenberg et al. reviewed the available evidence on perioperative optimization in patients with IBD undergoing gastrointestinal surgery. Based on the identified evidence, the authors recommend, among other measures, nutritional risk screening in order to identify and correct malnutrition prior to surgery [15].

However, if a patient's nutritional status fails to improve despite adequate measures, a more defensive surgical strategy (i.e., avoidance of primary anastomoses) should be discussed with the patient or, if possible, surgery may be delayed until malnutrition is corrected, in order to prevent postoperative morbidity [16].

There are some limitations to the present study, mainly due to its single-center, observational design: the small sample size

compared to register-based studies, the risk of bias inherent in its non-randomized design, and the potential confounding regarding the effect of hypoalbuminemia by unknown factors not adjusted for in our multivariable analysis. Since hypoalbuminemia is not only a surrogate of malnutrition, but also a marker of inflammation and stress as induced by surgery, particularly in an emergency context, confounding of the results by the degree of urgency of surgery (emergency versus elective procedures) cannot not be ruled out. To minimize the risk of confounding, we additionally performed a subgroup analysis which only included non-emergency cases.

The preoperative administration of immunosuppressive medication had no significant effect on the occurrence of postoperative major complications in our cohort. Other studies demonstrated an increased perioperative risk for patients under immunosuppressive medication at the time of surgery, especially for high doses of corticosteroids [4, 17].

In the treatment concept at our institution, these drugs are reduced (corticosteroids) or paused completely 3 to 4 weeks (biologics) prior to elective procedures in patients with CD. Therefore, our results must be assessed with caution in this respect and cannot be compared with other studies.

In conclusion, preoperative hypoalbuminemia, defined as a serum albumin level of  $\leq 32.6$  g/L, was the only independent risk factor for postoperative high-grade morbidity (Clavien–Dindo grade  $\geq$  III) after colorectal resections including left-sided colon and rectal resection for CD. The knowledge of the major impact of hypoalbuminemia on the surgical outcome should guide surgeons when discussing alternative treatment options and surgical strategies with their patients. Hypoalbuminemic patients should be considered as high-risk patients who need multimodal and individually tailored preoperative optimization prior to surgery. If the patient's nutritional status fails to improve despite nutritional support or if surgery cannot be delayed, a more defensive surgical strategy (e.g., formation of a stoma instead of an anastomosis) should be considered.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

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