



ORIGINAL ARTICLE

Preoperative hypoalbuminemia is associated with an increased risk for intra-abdominal septic complications after primary anastomosis for Crohn's disease

Xuanhui Liu^{†,1,2}, Xianrui Wu^{†,1,2}, Chi Zhou^{†,1,2}, Tuo Hu^{1,2}, Jia Ke^{1,2}, Yufeng Chen^{1,2}, Xiaosheng He^{1,2}, Xiaobin Zheng^{1,2}, Xiaowen He^{1,2}, Jiancong Hu^{1,2}, Min Zhi³, Xiang Gao³, Pinjin Hu³, Xiaojian Wu^{1,2}, Ping Lan^{*,1,2}

¹Department of Colorectal Surgery, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China, ²Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China and ³Department of Gastroenterology, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

*Corresponding author. The Sixth Affiliated Hospital, Sun Yat-sen University, 26 Yuancun Erheng Road, Guangzhou, Guangdong 510655, China. Tel: +86-020-38254009; Fax: +86-20-38254166; Email: lanping@mail.sysu.edu.cn

[†]These authors contributed equally to this study.

Abstract

Objective: The aim of this study was to evaluate the impact of preoperative hypoalbuminemia on the development of intra-abdominal septic complications (IASCs) after primary anastomosis for patients with Crohn's disease (CD).

Methods: All CD patients undergoing bowel resection with a primary anastomosis during the study period from 2007 to 2015 were enrolled. The association of preoperative hypoalbuminemia (<30 g/L) with the risk for IASCs were assessed using both univariate and multivariate analyses.

Results: A total of 124 eligible patients were included, 117 (94.4%) of whom had available preoperative albumin level. Preoperative hypoalbuminemia occurred in 13 (11.7%) patients. The duration from diagnosis to surgery was longer for patients with preoperative hypoalbuminemia than those without ($p = 0.012$). Patients with preoperative hypoalbuminemia were more likely to have a history of preoperative use of 5-aminosalicylic acid ($p = 0.013$) and have an intraoperative finding of small bowel obstruction ($p = 0.015$). Of all patients, 24 (19.4%) developed postoperative IASCs. Univariate analysis showed that patients with preoperative hypoalbuminemia had an increased risk for IASCs ($p = 0.012$). Multivariate analysis confirmed the association between preoperative hypoalbuminemia and IASCs (odds ratio 4.67, 95% confidence interval: 1.28–17.04, $p = 0.02$). Similar findings were also obtained when preoperative albumin level was analysed as a continuous variable ($p = 0.019$).

Conclusions: Preoperative hypoalbuminemia is a significant predictor for the development of postoperative IASCs in CD patients after bowel resection with a primary anastomosis. Favorable preoperative nutrition status might lessen the risk for IASCs.

Key words: Crohn's disease; hypoalbuminemia; intra-abdominal septic complications; risk factor

Submitted: 19 September 2016; Revised: 11 December 2016; Accepted: 21 December 2016

© The Author(s) 2017. Published by Oxford University Press and Sixth Affiliated Hospital of Sun Yat-Sen University.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Introduction

Crohn's disease (CD) is a chronic inflammatory gastrointestinal (GI) disorder of unclear etiology. Despite increased use of immunosuppressant and anti-tumor necrosis factor (TNF) treatments, approximately 70% of the CD patients will eventually require surgery [1,2]. In patients with CD, postoperative complications, such as wound infection and intra-abdominal septic complications (IASCs), have been reported to occur more frequently than those with other disorders—a phenomena partly due to the inflammatory nature of CD and malnutrition [3]. Malnutrition is a common substantial problem of CD [4], which is considered to be an end product of complex pathophysiological processes, including decreased food intake due to postprandial pain, diarrhea, anorexia, malabsorption, previous gut resection or bypass, drug side effects and active inflammation [5–7].

IASCs not only significantly elongate hospitalization time, but also increase the postoperative relapse rate and decrease patients' quality of life [8]. Since postoperative IASCs are often difficult to be treated, it is of great importance to evaluate the associated predictors to monitor patients who are at risk [3,8–10]. Several studies have reported possible risk factors, including preoperative corticosteroid therapy, an abscess or fistula at the time of laparotomy, poor nutritional status, low albumin levels, advanced age, operating time, immune-modulating medications, hand-sewn anastomosis and so on [2,8,9,11–15].

Serum albumin is an objective marker of nutritional status and index reflecting inflammation and immune status, while it is also plays an important role in wound healing and collagen synthesis [16–19]. The serum albumin measurement is convenient and inexpensive [20], which makes it a potential candidate for practical predictive index. Although several studies have indicated the possible correlation between albumin level and the risk for IASCs, data from Asian population is scarce and controversial [11,21,22]. Therefore, we designed this study, aiming to evaluate the impact of preoperative hypoalbuminemia on the development of IASCs after primary anastomosis for CD.

Patients and methods

Patients

All CD patients undergoing bowel resection with a primary anastomosis at the Sixth Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) from 2007 to October 2015 were included in this study. Demographics, clinicopathological variables and outcomes were all prospectively recorded. Both paper charts and electronic medical records were carefully reviewed when necessary. This study was approved by the Institutional Review Board (IRB) of The Sixth Affiliated Hospital of Sun Yat-sen University.

Inclusion and exclusion criteria

In order to be included in the study, patients needed to meet all the following inclusion criteria: (i) CD patients; (ii) underwent bowel resection with a primary anastomosis at our institution; (iii) had a minimal follow-up period of 30 days following bowel resection. The exclusion criteria were patients who: (i) underwent bowel resection for other underlying diseases; (ii) underwent stoma creation without bowel resection (iii) were lost in follow-up.

Patient groups

Patient's serum albumin level recorded in this study was the last routine test within 1 week before surgery.

Hypoalbuminemia was defined as serum albumin level <30 g/L [9,10]. Based on whether the patients had preoperative hypoalbuminemia, the cohort was divided into two groups: patients with hypoalbuminemia (the study group) and those without (the control group).

Definition and variables

Demographic and clinicopathological variables were defined as follows: 'Duration from diagnosis to surgery'—the time interval from the date of CD diagnosis to the date of operation; 'Current smoking'—consumption of more than seven cigarettes per week for at least 6 months prior to operation; 'Ex-smoking'—cessation of smoking 6 months prior to the operation; 'Location of CD'—L1, terminal ileum; L2, colon; L3, ileocolon; L4, upper gastrointestinal tract; 'Upper gastrointestinal involvement'—the disease occurs in the upper gastrointestinal tract as well; 'Perianal disease'—inflammation at or near the anus, including tags, fissures, fistulae, abscesses or stenosis; 'Disease behavior'—B1, no structuring, no penetrating; B2, structuring; B3, penetrating; Extra-intestinal manifestations (EIM)—including the presence of arthralgia or arthropathy, pyoderma, gangrenosum, erythema nodosum, primary sclerosing cholangitis (PSC), CD-related ocular lesions, thromboembolic events; autoimmune disorders—type 1 diabetes, adult-onset asthma, rheumatoid arthritis, autoimmune thyroid diseases (including Grave's disease and Hashimoto's thyroiditis), psoriasis, systemic lupus erythematosus, autoimmune hemolytic anemia, vitiligo, celiac disease, pernicious anemia, idiopathic thrombocytopenic purpura and multiple sclerosis; 'Significant comorbidities'—congestive heart failure, coronary bypass surgery, chronic obstructive pulmonary diseases, renal stone of insufficiency, non-gastrointestinal cancer, stroke and liver failure; 'Preoperative use of medicines'—the use of any dose of biologics (including infliximab, adalimumab or certolizumab pegol), immunosuppressant, steroids, 5-aminosalicylic acid (5-ASA) or antibiotics within 1 month before the operation; 'Elevated erythrocyte sedimentation rate'—erythrocyte sedimentation rate more than 20 mm/h; 'Elevated C-reactive protein (CRP)'—more than 10 mg/L (dry chemical method) or 3 mg/L (hypersensitive method); 'Low hemoglobin'—hemoglobin less than 120 g/L in blood routine test; 'Elevated white blood cell'—white blood cells more than $10 \times 10^9/L$ in blood routine test; 'Low lymphocytes'—lymphocytes less than $0.8 \times 10^9/L$ in blood routine test; 'Elevated platelet'—platelet more than $300 \times 10^9/L$ in blood routine test.

Outcome measurement

The primary outcome was occurrence of IASCs, which was defined as anastomotic leaks and/or intra-abdominal abscesses, within 1 month after operation. The diagnosis of IASCs was made based on relaparotomy findings, the presence of infected or fecal material in the percutaneous drainage and/or abdominal images.

Statistical analysis

Descriptive statistics were computed for all variables. These included means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous factors and frequencies for categorical factors. Comparisons of the distribution of clinicopathological characteristics between the patients with or without preoperative hypoalbuminemia were made by using the two-tail t-test (or Wilcoxon rank sum test as alternative) for continuous variables and chi-square test (or the Fisher exact

test as alternative) for categorical variables. Both univariate and multivariate analyses of risk factors associated with the IASCs were constructed using the logistic regression analysis. All statistical analyses were performed with the SPSS software (version 16; SPSS, Chicago, IL). *P*-value less than 0.05 was considered statistically significant.

Results

Patient demographics

A total of 124 eligible patients were studied, 117 (94.4%) of whom had available preoperative albumin level. Ninety-eight patients (79.0%) were males. The mean ages at the time of diagnosis of CD and at surgery were 31.6 ± 11.9 years and 33.8 ± 12.1 years, respectively, with a median duration from diagnosis to surgery of 0.5 (0.1–2.2) years. Preoperative body mass index (BMI) was 18.0 ± 2.9 kg/m² (Table 1). Based on Montreal Classification by disease location, 28 (22.6%) patients had L1 (ileal) disease or L2 (colonic) disease, and 94 (75.8%) had L3 (ileocolic) disease. Upper gastrointestinal involvement was identified in 5 patients (4.0%) and 33 (26.6%) patients had perianal disease. With respect to disease behavior, 52 patients (41.9%) had B1 (non-stricturing and non-penetrating) disease or B2 (stricturing) disease and 70 (56.5%) patients had B3 (penetrating) disease. Thirty-eight (30.6%) patients had a history of bowel resection and 22 (17.7%) patients had significant comorbidity (Table 1). The indications for surgical treatment in CD patients were: fibrostenotic segment ($n = 51$, 41.1%), fistula ($n = 66$, 53.2%), perforation ($n = 4$, 3.2%), abscess ($n = 1$, 0.8%), dysplasia or cancer ($n = 1$, 0.8%) and others ($n = 1$, 0.8%).

According to the preoperative albumin level, 13 (11.7%) patients were grouped as cases and the remaining 104 (88.9%) were controls. Six patients (46.2%) with preoperative hypoalbuminemia versus 16 patients (15.4%) without preoperative hypoalbuminemia experienced postoperative IASCs ($p = 0.016$). The duration from diagnosis to surgery was longer for patients with preoperative hypoalbuminemia than those without [1.2 (0–5.0) vs 0.5 (0–2.0), $p = 0.012$]. Patients with preoperative hypoalbuminemia were more likely to have a history of preoperative use of 5-ASA [7 (53.8%) vs 21 (20.2%), $p = 0.013$] and have an intraoperative finding of small bowel obstruction [10 (76.9%) vs 43 (41.3%), $p = 0.015$] (Table 1).

Risk factors associated with postoperative IASCs

Univariate analysis showed that postoperative IASCs were significantly associated with preoperative hypoalbuminemia ($p = 0.012$), intraoperative finding of fistula ($p = 0.026$), preoperative use of anti-TNF biologics ($p = 0.036$) and duration from diagnosis to surgery ($p = 0.029$) (Table 2). No other clinical factor was associated with an increased risk of postoperative IASCs, including patient age, gender, BMI, smoking history, history of any drug allergy, history of bowel resection, significant comorbidities, history of diagnosis of ulcerative colitis (UC) or indeterminate colitis (IC), extra-intestinal manifestation, location of CD, upper GI involvement, perianal disease, disease behavior, preoperative use of immunosuppressant, steroids, 5-ASA or antibiotics, elevated erythrocyte sedimentation rate, low hemoglobin, elevated white blood cell, chronic fistula as the indication for surgery, laparoscopic surgery, type of anastomosis, number of anastomosis and stoma creation.

The factors detected in univariate analysis that associated with the development of postoperative IASCs were then

included into a multivariate analysis model, and only preoperative hypoalbuminemia was found to be an independent risk factor for IASCs [odds ratio (OR) 4.67, 95% confidence interval (CI): 1.28–17.04, $p = 0.02$]. The impact of preoperative hypoalbuminemia was shown to have similar results when preoperative albumin level was analysed as a continuous variable (OR 0.89, 95% CI: 0.82–0.98, $p = 0.019$) (Table 3).

Discussion

CD is a chronic inflammatory gastrointestinal disorder. Approximately 70% of the CD patients will undergo operations [1,2] and have markedly high rates of postoperative IASCs, probably because of the inflammatory nature and decreased nutritional status [3,22–24]. In the current study, 24 (19.4%) patients experienced IASCs—a frequency that is consistent with the reported rates ranging from 5% to 20% [1,8,9]. In this series of 124 CD patients receiving a primary anastomosis, a significant association between preoperative hypoalbuminemia and postoperative IASCs was revealed in the univariate analysis. Furthermore, this finding was also confirmed in the multivariate analysis after adjusting for other potential confounding factors.

Hypoalbuminemia is the result of the combined effects of inflammation and malnutrition [16]. Several studies have demonstrated the association between hypoalbuminemia and surgical outcomes. In the study of a total of 54 215 major non-cardiac surgery cases from the National VA Surgical Risk Study, albumin level is found out as a good predictor of surgical outcomes, especially the mortality and morbidity for surgery, sepsis and major infections [25]. The result of a meta-analysis including 90 cohort studies and 9 prospective controlled studies also shows that hypoalbuminemia was an independent risk factor for poor outcome in the acutely diseases [26]. In patients with CD, similar findings have also been reported [9,10,27]. Yamamoto et al retrospectively analyses 343 patients underwent intestinal anastomosis operations and found that an albumin level less than 30 g/L was an independent risk factor for IASCs [9]. However, there are also several studies failed to find out the significant correlation between albumin level and the happening of IASCs [11,21,22]. Therefore, the relationship between albumin level and postoperative IASCs remains controversial and data from Chinese patients with CD are limited. We designed this retrospective study to evaluate this association and found that serum albumin level was an independent predictor for the development of postoperative IASCs.

Albumin, produced by the liver, is an acute phase protein with a half-life of approximately 20 days, subject to alteration by cytokines and proinflammatory mediators in patients with CD [28]. Recent studies have pointed out that the serum albumin measurement is a simple and convenient method for the assessment of the nutritional and immune status in inflammatory bowel disease (IBD) patients [16–19]. According to the previous studies, albumin levels were likely to be normal in the quiescent phase of the disease [29] and significantly lower levels in patients with active disease compared to those in remission [30,31]. In our study, we found that a much higher proportion of CD patients with hypoalbuminemia had a preoperative use of 5-ASA within a month before operation and had an intraoperative finding of small bowel obstruction. Besides, it has been reported that the duration of the disease was relevant as a determinant of the severity of malnutrition in IBD, which is usually longer in CD [32]. In our study, the median duration from diagnosis to surgery was actually consistent with

Table 1. Patient characteristics

Characteristics	All cases (n= 124)	Patients with available albumin level (n=117)	Patients without hypoalbuminemia (n=104)	Patients with hypoalbuminemia (n=13)	p-value
Age at CD diagnosis, years	31.6±11.9	31.6±12.1	31.9±12.4	28.9±9.5	0.4
Age at surgery, years	33.8±12.1	33.7±12.1	33.9±12.5	31.5±9.2	0.49
Duration from diagnosis to surgery, years	0.5 (0.1–2.2)	0.5 (0–2.1)	0.5 (0–2.0)	1.2 (0–5.0)	0.012
Male gender	98	92	80 (76.9%)	12 (92.3%)	0.29
Body mass index, kg/m ²	18.0±2.9	17.8±2.9	18.0±2.9	16.3±2.6	0.078
Ex or current smoker	4	4	2 (1.9%)	2 (15.4%)	0.06
History of any drug allergy	22	22	20 (19.2%)	2 (15.4%)	1.0
History of bowel resection	38	35	30 (28.8%)	5 (38.5%)	0.53
Significant comorbidity	22	21	17 (16.3%)	4 (30.8%)	0.25
History of diagnosis of UC or IC	3	3	2 (1.9%)	1 (7.7%)	0.3
Extra-intestinal manifestations	7	7	6 (5.8%)	1 (7.7%)	0.57
Location of CD					0.27 ^a
L1	26	25	23 (22.5%)	2 (15.4%)	
L2	2	2	1 (1.0%)	1 (7.7%)	
L3	94	88	78 (76.5%)	10 (76.9%)	
Upper gastrointestinal involvement	5	4	4 (3.9%)	0 (0%)	1.0
Perianal disease	33	28	24 (23.1%)	4 (30.8%)	0.51
Disease behavior					0.52 ^b
B1	2	2	2 (2.0%)	0 (0%)	
B2	50	48	41 (40.2%)	7 (53.8%)	
B3	70	65	59 (57.8%)	6 (46.2%)	
Preoperative use of biologics	8	7	7 (4.8%)	2 (15.4%)	0.17
Preoperative use of steroids	14	14	13 (12.5%)	1 (7.7%)	1.0
Preoperative use of 5-ASA	29	28	21 (20.2%)	7 (53.8%)	0.013
Preoperative use of antibiotics	14	14	14 (13.5%)	0 (0%)	0.36
Elevated erythrocyte sedimentation rate	65	62	55 (77.5%)	7 (63.6%)	0.45
Low hemoglobin	89	85	73 (70.2%)	12 (92.3%)	0.11
Elevated white blood cell	18	15	15 (14.4%)	0 (0%)	0.21
Elevated platelet	46	42	37 (35.6%)	5 (38.5%)	1.0
Chronic fistula as the indication for surgery, n (%)	66	62	56 (53.8%)	6 (46.2%)	0.6
Emergency surgery	2	2	2 (1.9%)	0 (0%)	1.0
Laparoscopic surgery	27	25	23 (22.1%)	2 (15.4%)	0.73
Type of anastomosis					1.0
Hand-sewn	26	22	20 (20.6%)	2 (18.2%)	
Stapled	89	86	77 (79.4%)	9 (81.8%)	
Number of anastomosis					0.64
1	109	104	93 (89.4%)	11 (84.6%)	
≥2	15	13	11 (10.6%)	2 (15.4%)	
Stoma creation	16	16	15 (14.4%)	1 (7.7%)	1.0
Intraoperative finding of fistula	67	63	56 (53.8%)	7 (53.8%)	1.0
Intraoperative finding of abscess	33	32	31 (29.8%)	1 (7.7%)	0.11
Intraoperative finding of perforation	4	3	3 (2.9%)	0 (0%)	1.0
Intraoperative finding of phlegmon	35	34	33 (31.7%)	1 (7.7%)	0.11
Intraoperative finding of small bowel obstruction	56	53	43 (41.3%)	10 (76.9%)	0.015
Intraoperative finding of fibrostenosis	78	74	63 (60.6%)	11 (84.6%)	0.13
Postoperative intra-abdominal septic complications	24	22	16 (15.4%)	6 (46.2%)	0.016

^aL3 vs L1/L2.

^bB3 vs B1/B2. Data presented as mean ± standard deviation, medians (interquartile ranges) or cases (%). CD, Crohn's disease; UC, ulcerative colitis; IC, indeterminate colitis; 5-ASA, 5-aminosalicylic acid.

other studies based on the Chinese mainland [33]. We also found that the CD patients with hypoalbuminemia tended to have a longer duration from diagnosis to surgery, in accordance with the previous study.

Serum albumin is an important material for wound healing and collagen synthesis at the anastomosis site, while hypoproteinemia can give rise to tissue edema and collagen synthesis disorders, resulting in the high risk of an anastomotic leakage [34,35]. The serum albumin also has an effect on immune response [36,37]. A study by Slotwinski *et al.* demonstrates that

critically ill patients treated in the intensive care unit (ICU) had significant disturbances in the expression of genes associated with innate antimicrobial immunity, depending on nutritional status, and may have a significant impact on the clinical outcomes [36]. A study retrospectively analysed 324 patients with IBD and found that the presence of low serum albumin were shared common risk factors for a low serum IgG or IgM level [37]. All the studies aforementioned indicate that serum albumin plays a vital role in tissue repair and immune response. Hypoalbuminemia may reflect the malnutrition and the

Table 2. Univariate analysis of risk factors associated with intra-abdominal septic complications

Characteristics	Odds ratio	95% confidence interval	p-value
Age at CD diagnosis, every 1-year increase	0.99	0.95–1.03	0.69
Age at surgery, every 1-year increase	1.003	0.97–1.04	0.88
Duration from diagnosis to surgery, every 1-year increase	1.14	1.01–1.28	0.029
Gender (male vs female)	7.67	0.98–59.71	0.052
Body mass index, every 1-kg/m ² increase	0.99	0.83–1.18	0.94
Smoking (active or ex vs never)	4.46	0.60–33.37	0.15
History of any drug allergy (yes vs no)	1.29	0.42–3.92	0.66
History of bowel resection (yes vs no)	1.84	0.73–4.62	0.2
Significant comorbidities (yes vs no)	0.91	0.28–2.99	0.88
History of diagnosis of UC or IC (yes vs no)	2.13	0.19–24.52	0.54
Extra-intestinal manifestation (yes vs no)	1.73	0.31–9.49	0.53
Location of CD (L3 vs L1/L2)	3.74	0.82–17.06	0.089
Upper gastrointestinal involvement (yes vs no)	1.08	0.12–10.14	0.95
Perianal disease (yes vs. no)	0.33	0.092–1.20	0.093
Disease behavior (B3 vs B1/B2)	2.65	0.97–7.25	0.057
Preoperative use of biologics (yes vs no)	4.80	1.11–20.82	0.036
Preoperative use of immunosuppressants (yes vs no)	0.75	0.23–2.44	0.64
Preoperative use of steroids (yes vs no)	0.67	0.14–3.20	0.61
Preoperative use of 5-ASA (yes vs no)	2.40	0.92–6.27	0.074
Preoperative use of antibiotics (yes vs no)	0.67	0.14–3.20	0.61
Elevated erythrocyte sedimentation rate (yes vs no)	1.00	0.29–3.50	1.0
Low hemoglobin (yes vs no)	2.25	0.71–7.12	0.17
Elevated white blood cell (yes vs no)	1.23	0.37–4.13	0.74
Elevated platelet (yes vs no)	0.82	0.32–2.09	0.67
Chronic fistula as the indication for surgery (yes vs no)	2.53	0.96–6.63	0.059
Laparoscopic surgery (yes vs no)	0.27	0.06–1.24	0.093
Type of anastomosis (stapled vs hand-sewn)	0.60	0.21–1.65	0.32
Number of anastomosis (≥ 2 vs 1)	2.37	0.73–7.72	0.15
Stoma creation (yes vs no)	0.56	0.12–2.64	0.46
Intraoperative finding of fistula (yes vs no)	3.12	1.14–8.52	0.026
Intraoperative finding of abscess (yes vs no)	0.33	0.092–1.20	0.093
Intraoperative finding of perforation (yes vs no)	1.41	0.14–14.14	0.77
Intraoperative finding of phlegmon (yes vs no)	0.45	0.14–1.41	0.17
Intraoperative finding of small bowel obstruction (yes vs no)	0.84	0.34–2.07	0.7
Intraoperative finding of fibrostenosis (yes vs no)	0.64	0.26–1.57	0.33
Preoperative hypoalbuminemia (yes vs no)	4.71	1.40–15.87	0.012
Albumin level, every 1-g/L increase	0.91	0.83–0.99	0.03

CD, Crohn's disease; UC, ulcerative colitis; IC, indeterminate colitis; 5-ASA, 5-aminosalicylic acid.

Table 3. Multivariate analysis of the risk factors associated with intra-abdominal septic complications

Characteristics	Odds ratio	95% confidence interval	p-value
Albumin level as a categorical variable			
Duration from diagnosis to surgery, every 1-year increase	1.09	0.96–1.24	0.18
Preoperative use of biologics (yes vs no)	1.71	0.28–10.43	0.56
Intraoperative finding of fistula (yes vs no)	2.48	0.83–7.42	0.1
Preoperative hypoalbuminemia (yes vs no)	4.67	1.28–17.04	0.02
Albumin level as a continuous variable			
Duration from diagnosis to surgery, every 1-year increase	1.12	0.98–1.28	0.11
Preoperative use of biologics (yes vs no)	1.82	0.32–10.39	0.5
Intraoperative finding of fistula (yes vs no)	2.61	0.87–7.81	0.087
Albumin level, every 1-g/L increase	0.89	0.82–0.98	0.019

disorder of the immune system, and therefore have a major impact on postoperative outcomes.

Since hypoalbuminemia is the reflection of malnutrition and immunity dysfunction and malnutrition is relevant with higher rate of postoperative complication, the nutritional management is an issue worthy of attention, especially in CD patients. Several publications have pointed out that nutritional

management is of great importance to the successful clinical management of patients with gastrointestinal disease [38,39]. In a study published before, patients with preoperative enteral nutrition for 3 months had a significantly higher serum albumin level and lower CRP at operation, and suffered a lower risk of IASCs [40]. Another study also showed that no IASCs occurred in patients who received preoperative nutrition support,

whereas 27.7% of the matched patients suffered complications [41]. All of these results indicate the importance of nutrition management in reducing the incidence of postoperative complications. However, simply albumin replacement therapy with exogenous human albumin solution did not decrease the rates of death or major complications, probably as the underlying etiology of hypoalbuminemia is not solved and exogenous albumin is rapidly degraded [20,42], so an integrated management of nutritional support to improve the serum albumin level and nutritional and physiological stabilization of patients is necessary.

The findings of the current study have several limitations. Firstly, the surgeon's assessment of the state of inflammatory tissue at the time of surgery is subjective and difficult to quantify. Secondly, the situation of operation cannot be completely recorded and quantified. However, the information used in the study was the same unit by the same group of physicians, used similar guidelines and made decisions collectively, which would strengthen the consistency of our findings.

In summary, preoperative hypoalbuminemia is a significant predictor for the development of postoperative IASCs in CD patients after bowel resection with a primary anastomosis. Therefore, preoperative nutrition correction is of great importance in the clinical practice.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 81400603), Guangdong Natural Science Foundation (No. 2015A030310190) and the Science and Technology Planning Project of Guangdong Province (No. 2015B020229001). X.H.L., X.R.W. and C.Z. contributed to study concept and design, acquisition, analysis, interpretation of data and drafting of the manuscript. T.H., J.K., Y.F.C., X.S.H., X.B.Z., X.W.H. and J.C.H. contributed to data collections and manuscript review. M.Z., X.G., P.J.H., X.J.W. and P.L. contributed to study concept and design, analysis and interpretation of data and critical revision of the manuscript for important intellectual content. X.J.W. and P.L. supervised the study. All authors read and approved the final manuscript.

Conflict of interest statement: none declared.

References

- Bernell O, Lapidus A, Hellers G. Risk factors for surgery and recurrence in 907 patients with primary ileocaecal Crohn's disease. *Br J Surg* 2000;**87**:1697–1701.
- Nandivada P, Poylin V, Nagle D. Advances in the surgical management of inflammatory bowel disease. *Curr Opin Gastroenterol* 2012;**28**:47–51.
- Iesalnieks I, Kilger A, Glass H et al. Intraabdominal septic complications following bowel resection for Crohn's disease: detrimental influence on long-term outcome. *Int J Colorectal Dis* 2008;**23**:1167–74.
- Mijač DD, Janković GL, Jorga J et al. Nutritional status in patients with active inflammatory bowel disease: prevalence of malnutrition and methods for routine nutritional assessment. *Eur J Intern Med* 2010;**21**:315–19.
- Grimble GK. Why are dietary nucleotides essential nutrients? *Br J Nutr* 1996;**76**:475–8.
- Goh J, O'Morain C. Nutrition and adult inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;**17**:307–20.
- Jeejeebhoy KN. Clinical nutrition: 6. Management of nutritional problems of patients with Crohn's disease. *CMAJ* 2002;**166**:913–18.
- Alves A, Panis Y, Bouhnik Y et al. Risk factors for intra-abdominal septic complications after a first ileocecal resection for Crohn's disease: a multivariate analysis in 161 consecutive patients. *Dis Colon Rectum* 2007;**50**:331–6.
- Yamamoto T, Allan RN, Keighley MR. Risk factors for intra-abdominal sepsis after surgery in Crohn's disease. *Dis Colon Rectum* 2000;**43**:1141–5.
- Yang SS, Yu CS, Yoon YS et al. Risk factors for complications after bowel surgery in Korean patients with Crohn's disease. *J Korean Surg Soc* 2012;**83**:141–8.
- Shental O, Tulchinsky H, Greenberg R et al. Positive histological inflammatory margins are associated with increased risk for intra-abdominal septic complications in patients undergoing ileocolic resection for Crohn's disease. *Dis Colon Rectum* 2012;**55**:1125–30.
- El-Hussuna A, Andersen J, Bisgaard T et al. Biologic treatment or immunomodulation is not associated with postoperative anastomotic complications in abdominal surgery for Crohn's disease. *Scand J Gastroenterol* 2012;**47**:662–8.
- Tzivanakis A, Singh JC, Guy RJ et al. Influence of risk factors on the safety of ileocolic anastomosis in Crohn's disease surgery. *Dis Colon Rectum* 2012;**55**:558–62.
- Myrelid P, Olaison G, Sjordahl R et al. Thiopurine therapy is associated with postoperative intra-abdominal septic complications in abdominal surgery for Crohn's disease. *Dis Colon Rectum* 2009;**52**:1387–94.
- Kanazawa A, Yamana T, Okamoto K et al. Risk factors for postoperative intra-abdominal septic complications after bowel resection in patients with Crohn's disease. *Dis Colon Rectum* 2012;**55**:957–62.
- Don BR, Kaysen G. Serum albumin: Relationship to inflammation and nutrition. *Semin Dial* 2004;**17**:432–7.
- Sacks GS, Dearman K, Replogle WH et al. Use of subjective global assessment to identify nutrition-associated complications and death in geriatric long-term care facility residents. *J Am Coll Nutr* 2000;**19**:570–7.
- Kuller LH, Eichner JE, Orchard TJ et al. The relation between serum albumin levels and risk of coronary heart disease in the Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 1991;**134**:1266–77.
- Afinogenova Y, Tapper EB. The efficacy and safety profile of albumin administration for patients with cirrhosis at high risk of hepatorenal syndrome is dose dependent. *Gastroenterol Rep (Oxf)* 2015;**3**:216–21.
- Gibbs J, Cull W, Henderson W et al. Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. *Arch Surg* 1999;**134**:36–42.
- Joksimović V, Karagozov A, Jota G et al. Risk factors for early postoperative complications after surgery for Crohn's disease. *Acta Facultatis Medicinae Naissensis* 2014;**31**:147–54.
- Post S, Betzler M, von Ditfurth B et al. Risks of intestinal anastomoses in Crohn's disease. *Ann Surg* 1991;**213**:37–42.
- Colombel JF, Loftus EV, Tremaine WJ et al. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. *Am J Gastroenterol* 2004;**99**:878–83.
- Subramanian V, Pollok R, Kang JY et al. Systematic review of postoperative complications in patients with inflammatory bowel disease treated with immunomodulators. *Br J Surg* 2006;**93**:793–9.

25. Gibbs J, Cull W, Henderson W et al. Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. *Arch Surg* 1999;134:36–42.
26. Vincent JL, Dubois MJ, Navickis R et al. Hypoalbuminemia in acute illness: is there a rationale for intervention. *Ann Surg* 2003;237:319–34.
27. Huang W, Tang Y, Nong L et al. Risk factors for postoperative intra-abdominal septic complications after surgery in Crohn's disease: a meta-analysis of observational studies. *J Crohn Colitis* 2015;9:293–301.
28. Nisar PJ, Appau KA, Remzi FH et al. Preoperative hypoalbuminemia is associated with adverse outcomes after ileoanal pouch surgery. *Inflamm Bowel Dis* 2012;18:1034–41.
29. Capristo E, Addolorato G, Mingrone G et al. Effect of disease localization on the anthropometric and metabolic features of Crohn's disease. *Am J Gastroenterol* 1998;93:2411–19.
30. Benjamin J, Makharia GK, Kalaivani M et al. Nutritional status of patients with Crohn's disease. *Indian J Gastroenterol* 2008;27:195–200.
31. Vagianos K, Bector S, McConnell J et al. Nutrition assessment of patients with inflammatory bowel disease. *JPEN J Parenter Enteral Nutr* 2007;31:311–19.
32. Cabré E, Gassull MA. Nutrition in inflammatory bowel disease: impact on disease and therapy. *Curr Opin Gastroenterol* 2001;17:342–9.
33. Gao X, Yang RP, Chen MH et al. Risk factors for surgery and postoperative recurrence: analysis of a south China cohort with Crohn's disease. *Scand J Gastroenterol* 2012;47:1181–91.
34. Runstrom B, Hallbook O, Nystrom PO et al. Outcome of 132 consecutive reconstructive operations for intestinal fistula: staged operation without primary anastomosis improved outcome in retrospective analysis. *Scand J Surg* 2013;102:152–7.
35. Ward M, Danzi M, Lewin M et al. The effects of subclinical malnutrition and refeeding on the healing of experimental colonic anastomoses. *Br J Surg* 1982;69:308–10.
36. Slotwinski R, Sarnecka A, Dabrowska A et al. Innate immunity gene expression changes in critically ill patients with sepsis and disease-related malnutrition. *Cent Eur J Immunol* 2015;40:311–24.
37. Rai T, Wu X, Shen B. Frequency and risk factors of low immunoglobulin levels in patients with inflammatory bowel disease. *Gastroenterol Rep (Oxf)* 2015;3:115–21.
38. Sullivan DH, Bopp MM, Roberson PK. Protein-energy undernutrition and life-threatening complications among the hospitalized elderly. *J Gen Intern Med* 2002;17:923–32.
39. Wernerman J. Guidelines for nutritional support in intensive care unit patients: a critical analysis. *Curr Opin Clin Nutr Metab Care* 2005;8:171–5.
40. Li G, Ren J, Wang G et al. Preoperative exclusive enteral nutrition reduces the postoperative septic complications of fistulizing Crohn's disease. *Eur J Clin Nutr* 2014;68:441–6.
41. Jacobson S. Early postoperative complications in patients with Crohn's disease given and not given preoperative total parenteral nutrition. *Scand J Gastroenterol* 2012;47:170–7.
42. Pulimood TB, Park GR. Debate: Albumin administration should be avoided in the critically ill. *Crit Care* 2000;4:151–5.