

Preoperative Corticosteroid Usage and Hypoalbuminemia Increase Occurrence of Short-term Postoperative Complications in Chinese Patients with Ulcerative Colitis

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Abstract

Background: Clarifying the risk factors for postoperative complications and taking measures to minimize these complications will improve the outcomes in patients with ulcerative colitis (UC). This study aimed to systemically explore the risk factors for short-term postoperative complications in Chinese UC patients undergoing ileocolorectal surgery.

Methods: Forty-nine UC patients undergoing proctocolectomy or ileostomy were retrospectively enrolled. Univariate and multivariate logistic regression analyses were conducted to reveal the risk factors among the clinical, laboratory, and surgical variables as well as preoperative medications.

Results: Twenty-two (44.9%) patients who suffered from at least one short-term postoperative event had more severe hypoalbuminemia ($P = 0.007$) and an increased prevalence of preoperative corticosteroid usage (prednisone more than 20 mg daily or equivalent) for more than 6 weeks (59.1% vs. 25.9%, $P = 0.023$) compared with patients without short-term postoperative complications. Based on the multivariate logistic regression analysis, the odds ratio (95% confidence interval) values of these two risk factors were 1.756 (0.889–3.470, $P = 0.105$) and 3.233 (0.916–11.406, $P = 0.068$), respectively. In 32 severe UC patients, prolonged preoperative hospital stay worsened the short-term postoperative outcomes.

Conclusions: Preoperative corticosteroids usage and hypoalbuminemia worsened the short-term outcomes following ileocolorectal surgery in Chinese UC patients.

Key words: Corticosteroids; Hypoalbuminemia; Postoperative Complication; Ulcerative Colitis

INTRODUCTION

Ulcerative colitis (UC) is a chronic nonspecific inflammatory disease involving the colon and rectum. Although the incidence of UC is still lower in Asia compared with Western countries, the number of overall UC patients is increasing very quickly in Asia, including China.^[1-3] Most UC patients have a well-controlled disease and good quality of life under certain medical therapies, especially with the recent advances in immunosuppressants and biologics. However, proctocolectomy is still an important and underutilized therapy in the 7–34% UC patients who have life-threatening complications, severe refractory disease, or colitis associated neoplasm or

cancer.^[4-6] Proctocolectomy is a curable treatment that has been frequently practiced in high-volume medical centers. The occurrence of short- and long-term postoperative complications influences patient outcome following proctocolectomy.

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Clarifying the risk factors for the postoperative complications and taking measures to minimize these complications will improve the outcomes following surgery in UC patients. Many studies from Western countries indicated that poor nutrition status, preoperative moderate-to-high doses of corticosteroids, old age, more comorbidities, prolonged preoperative hospital stay, and emergent surgery are risk factors for complications following colectomy in UC patients.^[7-9] Recently, some studies also found that *Clostridium difficile* infection and cytomegalovirus (CMV) reactivation are closely correlated with postoperative outcomes in UC patients.^[10-12]

It is well-established that there are many differences between the clinical manifestations and incidence of operation in UC patients as well as the medical therapy options and healthcare systems in the West versus East. The incidence of proctocolectomy is only 3.0–7.0% in UC patients in Asian countries, which is lower than that in Western countries.^[3,13-15] Furthermore, there are limited studies from the Asian countries that focused on the risk factors for postoperative complications; they showed that preoperative corticosteroids, old age, emergent and delayed surgery worsened the outcomes following colectomy.^[16-19]

To the best of our knowledge, no relevant study has systemically involved demographic, clinical, and laboratory variables as well as preoperative medications and other variables in Chinese UC patients undergoing ileocolorectal surgery. Therefore, we conducted this retrospective study to explore the risk factors for short-term postoperative complications following ileocolorectal surgery in Chinese UC patients, which may lend insight into the development of a better healthcare system for UC patients in the Asian countries.

METHODS

Patients' data

Forty-nine UC patients were retrospectively enrolled in this study who were hospitalized and underwent proctocolectomy and/or ileostomy in Peking Union Medical College Hospital (PUMCH) from January 2005 to December 2013. All patients were diagnosed according to the Lennard-Jones criteria.^[20] Our study was approved by the Ethical Committee of PUMCH.

Data were obtained from our UC database and chart review. Demographics, clinical manifestations, laboratory tests, medication prior to surgery, surgery type and technique, and short-term postoperative complications were collected. For patients who underwent more than two ileocolorectal surgeries, data from the primary surgery were used for the statistical analysis.

Demographic information included gender, age at onset, age at operation, living circumstance, and preoperative hospital length of stay. Disease distribution was classified into E1, E2, and E3 based on the Montreal classification.^[21] Disease activity was defined according to the modified Truelove-Witts index. Comorbidities included cardiovascular

disease, neurological disease, rheumatologic disease, and hematologic disease.

Laboratory tests, such as the white blood cell (WBC) count, hemoglobin, C-reaction protein (CRP), high sensitivity CRP, and serum albumin level, were performed within 1 week prior to surgery. Hypoalbuminemia was defined as mild ($30 \text{ g/L} \leq \text{serum albumin} < 35 \text{ g/L}$), moderate ($20 \text{ g/L} \leq \text{serum albumin} < 30 \text{ g/L}$), and severe ($\text{serum albumin} < 20 \text{ g/L}$). Other tests involving perinuclear antineutrophil cytoplasmic antibody (p-ANCA), *Clostridium difficile* toxin A/B, serum CMV antigen pp65, IgM, and DNA were performed within 2–3 weeks prior to surgery.

The usage of preoperative medications, such as 5-aminosalicylates, azathioprine (AZA), cyclosporine A and infliximab, within 1 month prior to surgery was recorded. Preoperative corticosteroid (prednisone more than 20 mg daily or equivalent) usage for more than 6 weeks was recorded.

Elective surgery was performed in patients who were generally less sick but required an operation due to a lack of response to outpatient medical therapies or for the management of colonic dysplasia or cancer.^[7] Other surgeries were categorized as emergency surgery. The surgery technique was classified as laparoscopic and open, and the surgery type was classified as proctocolectomy plus ileostomy or ileostomy alone.

Short-term postoperative complications were defined as complications within 30 days following surgery, which were defined based on the predefined ICD-9 codes for postoperative complications in inflammatory bowel disease.^[5,22] These complications included systemic and local complications, such as cardiac and respiratory complications, ileus, hematoma, and wound disruption.

According to the occurrence of short-term postoperative complications, UC patients were categorized into one group with complications and another group without complications.

Statistical analysis

The continuous variables were presented as mean \pm standard deviation (SD). Differences in the quantitative data between the two groups were statistically examined through univariate analysis, using the independent *t*-test and Chi-square test for continuous and categorical variables, respectively. *P* values were two-tailed, and the significance level was set at $P < 0.05$. For multivariate logistic regression analysis, risk factors with $P < 0.05$ were entered to select for independent risk factors and to calculate their odds ratio (OR, 95% confidence interval [CI]). Statistical analyses were performed using SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

Distribution of short-term postoperative complications in ulcerative colitis patients

Twenty-eight short-term postoperative events occurred in 22 patients (44.9%), who were categorized into the

group with complications. The distributions of short-term postoperative events were as follows: ileus (6 cases, 12.2%), gastrointestinal hemorrhage (2 cases, 4.1%), cardiac complications (2 cases, 4.1%), neurological complications (2 cases, 4.1%), pneumonia (2 cases, 4.1%), abscess (2 cases, 4.1%), stoma prolapse (2 cases, 4.1%), and disruption, infection or nonhealing of wound (10 cases, 20.4%). No mortality occurred within 30 days following surgery.

Risk factors for short-term postoperative complications in all ulcerative colitis patients

Based on univariate analysis, the group with complications had an increased prevalence of taking corticosteroids (prednisone more than 20 mg daily or equivalent) for more than 6 weeks prior to surgery (59.1% vs. 25.9%, $P = 0.023$) and more significant hypoalbuminemia ($P = 0.007$) compared with the group without complications. Moderate hypoalbuminemia occurred in 63.5% patients with complications and only 25.9% patients without complications. Between two groups, there was no significant difference in age at onset, age at operation, disease activity, disease distribution, surgery timing, surgery technique, WBC count, the incidence of positive p-ANCA, CMV reactivation, and the prevalence of taking AZA or cyclosporine A prior to surgery [Table 1].

Based on multivariate logistic regression analysis, the usage of corticosteroid (prednisone more than 20 mg daily or equivalent) for more than 6 weeks and hypoalbuminemia prior to surgery increased the risk of postoperative complications with *OR* (95% *CI*) values of 3.233 (0.916–11.406) and 1.756 (0.889–3.470), respectively, although no independent risk factor was revealed [Table 1].

Risk factors for short-term postoperative complications in severe ulcerative colitis patients

Sixteen patients (50.0%) with severe UC had at least one short-term postoperative event. Based on univariate analysis, the group with complications had an increased prevalence of taking corticosteroids (prednisone more than 20 mg daily or equivalent) for more than 6 weeks prior to surgery (75.0% vs. 25.0%, $P = 0.012$), more significant hypoalbuminemia ($P = 0.035$) and a prolonged preoperative hospital stay (31.2 days vs. 13.6 days, $P = 0.026$) compared with the group without complications. These three risk factors worsened the short-term postoperative outcomes with *OR* (95% *CI*) values of 1.918 (0.671–5.487), 5.274 (0.797–34.901), and 1.023 (0.968–1.081), respectively, although these difference did not reach statistical significance based on multiple logistic regression analysis [Table 2].

DISCUSSION

Following the medical advances in immunosuppressants and biologics, the incidence of colectomy significantly decreased in UC patients from Western countries.^[6,23] However, 16% of UC patients still had to undergo colectomy at 10 years after their diagnosis.^[24] Of the patients with severe colitis, 20.1% of UC patients required proctocolectomy and/or

ileostomy during their hospitalization in PUMCH from 2005 to 2012 (not published). The risk factors for short-term postoperative complications were well-established in Western UC patients,^[7-9] but not in the Asian UC patients.^[16-19] In this retrospective study, we found that 44.9% UC patients suffered from short-term postoperative complications. The usage of corticosteroid (prednisone more than 20 mg daily or equivalent) for more than 6 weeks and hypoalbuminemia prior to surgery were two risk factors in all UC patients undergoing ileocolorectal surgery. Beyond these two factors, a prolonged preoperative hospital stay also worsened the postoperative outcomes in severe UC patients.

The occurrence of postoperative complications was found in 27–53% of UC patients. Gastrointestinal and wound-associated complications and systemic or local infection were common short-term complications after colectomy.^[7,25] Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the current gold standard used for the surgical treatment of UC refractory to medical management. One study from China enrolled 95 UC patients who underwent IPAA; the early postoperative complications (17.0%) were as follows: intestinal obstruction 3.2%, abdominal/pelvic infection 7.4%, anastomotic leakage 3.2%, anastomotic bleeding 2.1%, and anastomotic fistula 1.1%.^[19] Our results were consistent with the previous studies.

Patient nutrition status is another risk factor for postoperative complications. Low body mass index (BMI) and hypoalbuminemia are two major indicators of poor nutrition status and are shown to be associated with reoperation and postoperative infections in UC patients undergoing proctocolectomy.^[26] Our study also revealed that hypoalbuminemia but not low BMI prior to surgery increased the risk for postoperative complications. As such, optimization to improve the nutrition status of UC patients might favor better postoperative outcomes.

The predictive value of p-ANCA for the complications after colectomy in UC patients has not been well-established. Some studies focused on its predictive value for long-term complications (pouchitis and mortality), but not for short-term complications. One study found that high level of p-ANCA was associated with higher occurrence of chronic pouchitis after IPAA.^[27] However, there was no correlation between p-ANCA and pouchitis in another study.^[28] Our study found that p-ANCA was not associated with short-term postoperative complications.

For the risk factors related to preoperative medications, it is well-established that use of preoperative corticosteroid increases short-term complications, particularly systemic and local infections, following colectomy in UC patients.^[8] In a Belgian cohort study, a moderate-to-high dose of corticosteroid (≥ 20 mg methylprednisolone for ≥ 2 months) prior to the primary colectomy was an independent risk factor for postoperative infectious complications with an *OR* (95% *CI*) value of 5.19 (1.72–15.66, $P = 0.003$).^[29] Another study involved 7235 UC patients who underwent major abdominal surgery in the

Table 1: Risk factors for short-term postoperative complications in patients with ulcerative colitis

Items	Total patients (N = 49)	Patients with short-term postoperative complications (n = 22)	Patients without short-term postoperative complications (n = 27)	Univariate analysis		Multivariate analysis	
				Statistical values	P	OR (95% CI)	P
Male, n (%)	29 (59.2)	11 (50.0)	18 (66.7)	1.394*	0.260		
Age at onset (years), mean ± SD	37.7 ± 15.1	37.8 ± 14.4	37.6 ± 15.9	-0.050†	0.961		
Age at surgery (years), mean ± SD	44.9 ± 15.6	44.4 ± 15.0	45.4 ± 16.3	0.231†	0.832		
Preoperative hospital stay (days), mean ± SD	22.2 ± 16.9	26.8 ± 19.6	18.4 ± 13.6	-1.761†	0.085		
Smoking status, n (%)				0.366*	1.000		
Never smoking	35 (71.4)	16 (72.7)	19 (70.4)				
Ex-smoker‡	8 (16.3)	3 (13.6)	5 (18.3)				
Current smoking	6 (12.2)	3 (13.6)	3 (11.1)				
Living place, n (%)				0.146*	0.768		
Rural	17 (34.7)	15 (68.2)	17 (63.0)				
Urban	32 (65.3)	7 (31.8)	10 (37.0)				
Distribution of disease, n (%)				0.880*	0.436		
E2	7 (14.3)	2 (9.1)	5 (18.5)				
E3	42 (85.7)	20 (90.9)	22 (81.5)				
Activity of disease, n (%)				1.538*	0.816		
Remission	1 (2.0)	0 (0.0)	1 (3.7)				
Mild	5 (10.2)	2 (9.1)	3 (11.1)				
Moderate	11 (22.4)	4 (18.2)	7 (25.9)				
Severe	32 (65.3)	16 (72.7)	16 (59.3)				
WBC (×10 ⁹ /L), mean ± SD	7.4 ± 4.0	7.2 ± 3.7	7.5 ± 4.3	0.209†	0.836		
Hemoglobin (g/L), mean ± SD	93.0 ± 25.2	89.1 ± 25.7	96.1 ± 24.8	0.944†	0.350		
Serum albumin, n (%)				10.775*	0.007	1.756 (0.889–3.470)	0.105
≥35 g/L	14 (28.6)	5 (22.7)	9 (33.3)				
30–34 g/L	11 (22.4)	1 (4.5)	10 (37.0)				
20–29 g/L	21 (42.9)	14 (63.6)	7 (25.9)				
<20 g/L	3 (6.1)	2 (9.1)	1 (3.7)				
CRP or hs-CRP, n (%)				0.122*	1.000		
Normal values	14 (28.6)	6 (27.3)	8 (29.6)				
1–3 times of upper normal limit	11 (22.4)	5 (22.7)	6 (22.2)				
>3 times of upper normal limit	24 (49.0)	11 (50.0)	13 (48.1)				
BMI (kg/m ²), mean ± SD	20.0 ± 3.0	19.5 ± 3.0	20.5 ± 3.0	1.027†	0.311		
<i>Clostridium difficile</i> toxin A/B, n (%)				1.118*	0.481		
Positive	1 (3.7)	1 (7.7)	0 (0.0)				
Negative	26 (96.3)	12 (92.3)	14 (100.0)				
Missing	22	9	13				
p-ANCA, n (%)				0.500*	0.724		
Positive	16 (50.0)	9 (56.3)	7 (43.8)				
Negative	16 (50.0)	7 (43.8)	9 (56.3)				
Missing	17	6	11				
CMV pp65, CMV-IgM, or DNA, n (%)				2.184*	0.228		
Positive	9 (32.1)	6 (46.2)	3 (20.0)				
Negative	19 (67.9)	7 (53.8)	12 (80.0)				
Missing	21	9	12				
Preoperative 5-aminosalicylates, n (%)				0.002*	1.000		
Yes	38 (77.6)	17 (77.3)	21 (77.8)				
No	11 (22.4)	5 (22.7)	6 (22.2)				
Preoperative steroid for >6 weeks, n (%)§				5.520*	0.023	3.233 (0.916–11.406)	0.068
Yes	20 (40.8)	13 (59.1)	7 (25.9)				
No	29 (59.2)	9 (40.9)	20 (74.1)				
Preoperative AZA, n (%)				0.122*	0.478		
Yes	10 (20.4)	3 (13.6)	7 (25.9)				
No	39 (79.6)	19 (86.4)	20 (74.1)				

Contd...

Table 1: Contd...

Items	Total patients (N = 49)	Patients with short-term postoperative complications (n = 22)	Patients without short-term postoperative complications (n = 27)	Univariate analysis		Multivariate analysis	
				Statistical values	P	OR (95% CI)	P
Preoperative cyclosporine A, n (%)				0.167*	0.747		
Yes	12 (24.5)	6 (27.3)	6 (22.2)				
No	37 (75.5)	16 (72.7)	21 (77.8)				
Comorbidity, n (%)				2.375*	0.339		
0	18 (36.7)	8 (36.4)	10 (37.0)				
1–2	28 (57.1)	14 (63.6)	14 (51.9)				
>2	3 (6.1)	0 (0.0)	3 (11.1)				
Surgery timing, n (%)				0.526*	0.549		
Emergency	33 (67.3)	16 (72.7)	17 (63.0)				
Elective	16 (32.7)	6 (27.3)	10 (37.0)				
Surgery technique, n (%)				0.011*	1.000		
Laparoscopic	13 (26.5)	6 (27.3)	7 (25.9)				
Open	36 (73.5)	16 (72.7)	20 (74.1)				
Surgery type, n (%)				2.227*	0.158		
Proctocolectomy and ileostomy	28 (57.1)	10 (45.5)	18 (66.7)				
Ileostomy	21 (42.9)	12 (54.5)	9 (33.3)				
Dysplasia or cancer, n (%)				4.314*	0.117		
Yes	4 (14.3)	0 (0.0)	4 (22.2)				
No	24 (85.7)	10 (100.0)	14 (77.8)				

*Chi-square values; †t values. ‡Ex-smoker is defined as a patient who has given up smoking for more than 6 months before admission; §Prednisone >20 mg daily or equivalent for more than 6 weeks prior to surgery; ||The histopathology results in patients with colectomy. AZA: Azathioprine; BMI: Body mass index; CMV: Cytomegalovirus; p-ANCA: Perinuclear antineutrophil cytoplasmic antibody; OR: Odds ratio; CI: Confidence interval; WBC: White blood cell; hs-CRP: High-sensitivity C-reactive protein; CRP: C-reactive protein.

Table 2: Risk factors for short-term postoperative complications in patients with severe ulcerative colitis

Risk factors	Total severe patients (N = 32)	Patients with short-term postoperative complications (n = 16)	Patient without short-term postoperative complications (n = 16)	Univariate analysis		Multivariate analysis	
				Statistical values	P	OR (95% CI)	P
Preoperative hospital stay (days), mean ± SD	24.0 ± 18.7	31.2 ± 20.6	13.6 ± 16.8	-2.342*	0.026	1.023 (0.968–1.081)	0.424
Serum albumin, n (%)				7.713†	0.035	1.918 (0.671–5.487)	0.224
≥35 g/L	5 (15.6)	2 (12.5)	3 (18.8)				
30–34 g/L	8 (25.0)	1 (6.3)	7 (43.8)				
20–29 g/L	17 (53.1)	12 (75.0)	5 (31.3)				
<20 g/L	2 (6.3)	1 (6.3)	1 (6.3)				
Preoperative steroid for >6 weeks, n (%) [‡]				8.000†	0.012	5.274 (0.797–34.901)	0.085
Yes	16 (50.0)	12 (75.0)	4 (25.0)				
No	16 (50.0)	4 (25.0)	12 (75.0)				

*t values; †Chi-square values; ‡Prednisone >20 mg daily or equivalent for >6 weeks prior to surgery. OR: Odds ratio; CI: Confidence interval; SD: Standard deviation.

American College of Surgeon's National Surgical Quality Improvement Program and found that the use of preoperative steroid was associated with postoperative complication with an OR (95% CI) of 1.44 (1.28–1.61).^[30] In our study, we also found that corticosteroid (prednisone more than 20 mg daily or equivalent) use for more than 6 weeks prior to surgery increased the risk of short-term postoperative complications. These studies suggested that weaning or tapering of corticosteroids

might help to improve the postoperative outcomes, especially infectious complications. However, high-dose corticosteroids intravenously are still the recommended the first-line medication for severe UC, which makes it impossible to quickly taper corticosteroids. Furthermore, it is well-known that a prolonged preoperative hospital stay worsens the postoperative outcomes in severe UC.^[8,31,32] In a retrospective study, 71 patients with severe colitis underwent emergent

colectomy. The preoperative hospital length of stay (median: 15 days vs. 6 days, $P = 0.032$) was longer in the group with postoperative complications.^[9] Our study also indicated a correlation between a prolonged preoperative hospital stay and the increased incidence of postoperative complications. The European Crohn's and Colitis Organization consensus suggests that earlier assessment of the nonresponders to corticosteroids at approximately the 3rd day and medical salvage therapy at approximately the 7th day in all severe UC patients will help to avoid the incidence of postoperative complications.^[8] Severe UC patients might benefit if colorectal surgeons and gastroenterologists collaborate earlier in the care process to optimize patient medications and make decisions regarding the timing of the operation to avoid an unexpected prolonged preoperative hospital stay.

For other preoperative medications, such as AZA, cyclosporine A, and biologics, there is no powerful evidence showing a correlation between the above medications and postoperative complications,^[31,33] which is also in accordance with our study.

As mentioned above, emergent colectomy has worse postoperative outcomes compared with elective colectomy in UC patients.^[7,18,34] In our study, we did not find a difference in the incidence of postoperative complications between elective and emergency surgeries, due to the following reasons: (1) 21 (42.9%) patients received ileostomy without colectomy as the primary surgery in our study. Among the above patients, 20 (95.2%) patients underwent emergency surgery with severe colitis. Chinese patients' willingness to receive surgery and surgeons' concern about decreasing the risk of complications following emergency colectomy in severe UC patients might contribute to the high incidence of ileostomy without colectomy. (2) The sample size of this study was insufficient to reveal a significant difference. It is still unestablished whether emergency ileostomy without colectomy has better postoperative outcomes compared with emergency ileostomy with colectomy, although there was no significant difference in the incidence of short-term postoperative complications between ileostomy with colectomy and ileostomy without colectomy in the severe UC patients in our study.

As a retrospective study from a single tertiary medical center, there were some limitations. First, some important information was not available, e.g., *Clostridium difficile* toxin A/B, CMV antigen, IgM, or DNA, which makes it impossible to accurately reveal the correlation between the opportunistic infections and postoperative complications. Second, it was very difficult to further analyze the correlation between the subtype of complications and preoperative corticosteroids or hypoalbuminemia based on the small sample of our study. Third, there is no independent risk factor with significant value based on the multivariate logistic analysis. One reason is that prolonged hospital stay may lead to low albumin due to acute disease process, which might be a confounding factor and hence no difference in multivariate analysis. Finally, long-term complications involving pouchitis, pelvic dysfunction, and re-operation are also very important for the

evaluation of postoperative outcomes but were not involved in our study. In the future, a prospective multicenter study could be conducted among Asian countries to reveal the characteristic risk factors for postoperative complications.

In conclusion, a moderate-to-high dose of corticosteroid for more than 6 weeks and hypoalbuminemia prior to surgery are two risk factors for short-term postoperative complications in UC patients. A prolonged hospital stay will worsen the postoperative outcomes in severe UC. Appropriately weaning or tapering the corticosteroid, improving nutrition status and optimizing the collaboration between surgeons and gastroenterologists might lend more insight into the development of treatments with better postoperative outcomes in UC patients.

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Conflicts of interest

There are no conflicts of interest.

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