CLINICAL RESEARCH

The prognostic nutritional index for postoperative infectious complication in patients with ulcerative colitis undergoing proctectomy with ileal pouch-anal anastomosis following subtotal colectomy

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Abstract:

Objectives: Restorative proctocolectomy and ileal pouch-anal anastomosis is frequently performed in patients with ulcerative colitis and factors suspected of increasing the risk of postoperative infectious complications. Using a three-stage approach may result in improvement in overall outcomes, because this leads to improvement in nutritional status and reduction of immunosuppressive doses. However, the influence of preoperative nutritional status on postoperative infectious complications after this procedure has not been examined. The aim of this study was to clarify the potential associations between nutritional status and postoperative infectious complications in patients with ulcerative colitis undergoing proctectomy with ileal pouch-anal anastomosis. Methods: The records of 110 patients who had undergone proctectomy with ileal pouch-anal anastomosis from January 2000 to March 2018 in Mie University and met the eligibility criteria were reviewed and possible associations between postoperative infectious complications and clinical factors were assessed. Results: Of the remaining 110 patients, 18 (16.4%) had developed postoperative infectious complications. Multivariate analysis revealed that operative bleeding ≥270 g and prognostic nutritional index <47 were significant predictors of postoperative infectious complications (P = 0.033, 0.0076, respectively). Various variables associated with immunosuppressives before ileal pouch-anal anastomosis were not associated with postoperative infectious complications. Conclusions: Our findings suggest that immunosuppressives have no association with postoperative infectious complications, whereas a poor prognostic nutritional index may be a significant predictor of postoperative infectious complications in patients with ulcerative colitis undergoing proctectomy with ileal pouch-anal anastomosis.

Keywords:

ulcerative colitis, ileal pouch-anal anastomosis, three-stage approach, prognostic nutritional index, postoperative infectious complications

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Introduction

Although restorative proctocolectomy and ileal pouch-anal anastomosis (IPAA) is recognized as a standard surgical procedure for patients with ulcerative colitis (UC)[1], it is generally believed that such patients are at higher risk of septic complications with benign colonic neoplasms[2-4]. Surgery for UC is frequently performed in patients with factors suspected of increasing the risk of postoperative infectious complications (PICs), such as concomitant active inflammation, impaired nutritional status, and chronic therapy with immunosuppressives[4,5].

Surgical site infection (SSI) is the most frequent nosocomial infection in surgical patients, and it has been reported to increase medical costs and prolong hospital stay[6]. Patients undergoing colorectal surgery for UC are at a high risk of deep incision and organ/space SSI, which remains a major source of morbidity[3]. Thus, an understanding of the factors predictive of SSI may assist in formulating a surgical plan and could be useful markers for avoiding compromised quality of life after pouch surgery.

A three-stage approach is generally adopted in patients with severe active disease, poor nutritional status, long-term or high doses of steroid therapy, or in whom the diagnosis is unclear[7]. It is believed that using a three-stage approach improves overall outcomes because it allows time for nutritional status to improve and doses of immunosuppressives to be reduced before IPAA, making this procedure safer[7]. However, to the best of our knowledge, the influence of preoperative nutritional status on PICs in patients undergoing proctectomy with IPAA (PC-IPAA) following subtotal colectomy has not been examined.

Some recent studies have demonstrated that nutritional and immunological status can be useful in identifying strategies for preventing postoperative complications or improving overall survival[8,9]. A prognostic nutritional index (PNI), which can be calculated from the serum albumin concentration and peripheral blood lymphocyte count[10], has been proposed for assessing perioperative nutritional status, risk of postoperative complications, and survival outcome in patients with malignant disease.

Therefore, the aim of this study was to clarify the potential associations between PNI and PICs in patients with UC undergoing PC-IPAA.

Materials and Methods

Patients

This retrospective review of relevant data from the surgical UC database of Mie University study was performed to evaluate the clinical characteristics of PICs in patients with UC who had undergone restorative proctectomy and IPAA (PC-IPAA). Of the 350 patients who had undergone IPAA for diagnosis of UC from January 2000 to March 2018 at this center, the records of 110 patients who met the following eligibility criteria were reviewed. All study patients had undergone subtotal colectomy with ileostomy as the first stage of a three-stage restorative proctectomy and IPAA, with diverting ileostomy being the second stage and ileostomy closure being the third stage. Of these 110 patients, 82 underwent the first stage at Mie University hospital. We usually perform subcutaneous placement of rectosigmoid stump to prevent pelvic sepsis. The management of (colo)rectal stump at other hospitals at first operation is typi-

cally based on the surgeon's preferences. We introduced laparoscopic PC-IPAA in 2013. The surgical approach was chosen based on a combination of the patient's and surgeon's preferences. Patients who had undergone one-or two-stage procedures and those for whom white blood cell fraction data were unavailable were excluded.

This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board. All patients provided their informed consent to their personal data being used for research purposes.

The standard second stage of the three-stage approach comprised a restorative proctectomy with hand sewn or stapled IPAA using a two-limbed J-shaped ileal pouch and creation of ileostomy. PC-IPAA was performed over 3 months after the first stage. Ileostomies were created in all patients. Intra-abdominal drainage tubes were passed through a stab incision separate from the wound and the skin was closed using stainless steel staples or subcuticular sutures.

All patients received standard postoperative care. A second-generation cephalosporin was administered prophylactically, 30 min before the incision, repeated 3 hourly during the surgery, and stopped within 48 h of the surgery in all patients. All patients had their wounds irrigated with saline water before closure of the skin.

Diagnosis of PICs

The patients were assessed for PICs, including SSI and remote infection (RI), by the surgeon or attending physician. PICs were defined as infections that occurred within the first 30 postoperative days and met the definition of the Centers for Disease Control and Prevention[11]. RI, such as respiratory infection, bacteremia/septicemia, and urinary tract infection, were defined as distant site infections and recorded during the same period.

Definitions of assessed variables

The following possible predictive factors for PICs were evaluated: sex, age at surgery, disease duration, American Society of Anesthesiologists (ASA) score, body mass index (BMI), rectosigmoid stump at first stage, procedure for creating anastomosis, laparoscopic surgery, perioperative blood transfusion, operative time, operative blood loss, cumulative dosage of prednisolone before IPAA, dosage of prednisolone per day immediately before IPAA, history of immunomodulator use, history of anti-TNF-α antibody use, albumin, white blood cell count, hemoglobin, C-reactive protein (CRP), neutrophil count, lymphocyte count, and PNI. Cumulative dosage of prednisolone since the initial diagnosis was calculated based on previous prednisolone dosage. Blood samples were collected preoperatively for complete blood cell count and blood chemistry. The PNI was calculated according to the following formula: 10 × albumin concentra-

tion (g/dL) + 0.005 × total lymphocyte count (per mm^3) as reported by Onodera et al[10]. Cut-off values for disease duration, BMI, operative time, operative blood loss, cumulative dosage of prednisolone before colectomy, daily dosage of prednisolone immediately before colectomy, albumin, CRP, white blood cell count, hemoglobin, neutrophil count, and lymphocyte count were determined by receiver-operating-characteristic analysis for occurrence of PICs.

Stratification of PNI was informed on the basis of the best predictive values for PICs, which were calculated using the most sensitive and specific values based on peak and cut-off points as determined by analysis of receiver operating characteristic (ROC) curves.

Statistical analysis

Statistical analysis was performed as follows. Odds ratios and 95% confidence intervals were calculated for all variables. Quantitative data are presented as mean ± standard deviation and were compared using the Mann-Whitney U test. Univariate analysis was used to examine the relationships between PICs and the variables studied. All variables associated with PICs with Wald P value of <0.02 on univariate analysis were subsequently examined by multivariate logistic regression analysis. The JMP software suite (SAS Institute, Cary, NC, USA) was used to perform all analyses. A P value of <0.05 was considered statistically significant.

Results

Incidence of PICs, SSI, and RI

Six of the 116 original study patients who lacked white blood cell fraction data were excluded. Relevant clinical characteristics of the remaining 110 patients are shown in Table 1. There were 40 women and 70 men, with a mean age of 39 ± 17 years. The mean BMI and PNI were 21.1 ± 3.9 and 48.7 ± 5.9, respectively.

Eighteen patients (16.4%) with PICs were identified, comprising 15 with incisional SSI, 2 with organ/space SSI, and 1 with RI (pneumonia).

Predictors of PICs

ROC analysis was performed to evaluate the ability of the PNI to predict PICs. The optimal cut-off values for PNI and AUC were determined as 47 and 0.66, respectively, which correspond to a sensitivity and specificity of 67% and 72%, respectively (Figure 1).

The results of univariate analysis for predictive factors potentially associated with PICs in patients with and without PICs are presented in Table 1. As shown, the development of PICs was found to be significantly associated with disease duration ≥16 years (OR, 0.11; 95% CI, 0.017-0.72; P = 0.021), operative bleeding ≥270 g (OR, 0.23; 95% CI,

0.070-0.75; P = 0.015), albumin <4.1 g/dL (OR, 2.97; 95% CI, 1.02-8.62; P = 0.045), and PNI <47 (OR, 5.08; 95% CI, 1.72-14.94; P = 0.0032). Measures of immunosuppressives before IPAA, including cumulative dose of prednisolone before IPAA ≥10 g, dose of prednisolone per day before IPAA ≥5 mg, history of immunomodulator use, and history of anti-TNF-α antibody were not associated with PICs after PC-IPAA.

The statistically significant potential predictors with P < 0.02, namely operative bleeding ≥270 g, and PNI <47, were subsequently subjected to multivariate analysis, which revealed that operative bleeding ≥270 g (OR, 3.79; 95% CI, 1.12-12.85; P = 0.033) and PNI <47 (OR, 4.52; 95% CI, 1.49-13.67; P = 0.0076) are significant predictors of PICs (Table 2).

Discussion

In this study, we found that low PNI and operative blood loss are independent predictors of PICs in patients with UC undergoing PC-IPAA. To the best of our knowledge, this is the first study to demonstrate an association between PNI and PICs in patients with UC.

The PNI described by Onodera et al[10], which is calculated from albumin concentration and total lymphocyte count, was initially designed to assess the nutritional status of patients undergoing surgery for gastrointestinal malignancy. Zhao et al[8] performed a meta-analysis of 23 studies with a total of 7,384 patients to determine the predictive potential of PNI in patients with digestive system cancers. They found that a low PNI is significantly associated with shorter overall survival; however, only three studies demonstrated a significant association between low PNI and high risk of postoperative complications. Although the PNI reportedly has cancer-related prognostic significance for several types of cancer, its value in predicting short-term postoperative outcomes has not been fully examined.

Chono et al[12] reported that, in patients undergoing IPAA with ileostomy for UC, an ASA score ≥3, prednisolone dosage immediately before surgery >14 mg/day, and PNI <35.5 were predictors of pouch-related complications. However, in our study, PNI and operative blood loss were independent predictors of PICs, whereas administration of anti-inflammatory drugs such as steroids, immunomodulatory agents, and anti-TNF-α agents, had no significant association with PICs. In the study by Chono et al. on patients undergoing IPAA with ileostomy, 12.4% of them had ASA scores ≥3 and 16.2% were undergoing urgent/emergency surgery, whereas in our study, no patients underwent urgent/emergency surgery and few patients had ASA scores ≥3. In addition, their study cohort included more patients with a high risk of postoperative complications than did ours. In a previous study reported by Miki et al[13], we found an inde-

Table 1. Results of Univariate Analysis for Predictive Factors Potentially Associated with Postoperative Infectious Complications.

Perioperative Factors	Total n = 110	PIC (-) n = 92	PIC (+) n = 18	P value	Odds Ratio (95% CI)
Gender					
Female	40	31	9	0.19	1.97 (0.71-5.46)
Male	70	61	9		
Age at surgery (years)	39 ± 17	41 ± 17	32 ± 18	0.056	
<18	12	9	3	0.40	1.84 (0.45-7.61)
≥18	98	83	15		
<65	101	84	17	0.66	1.62 (0.19-13.80)
≥65	9	8	1		
Disease duration (years)	4.8 ± 5.7	4.5 ± 5.0	6.4 ± 8.5	0.53	
<16	105	90	15	0.021	0.11 (0.017-0.72)
≥16	5	2	3		
ASA score					
<3	106	89	17	0.64	1.75 (0.17-17.79)
≥3	4	3	1		
Body mass index (kg/m^2)	21.1 ± 3.9	21.3 ± 4.0	20.0 ± 3.5	0.11	
<18.0	27	20	7	0.130	2.44 (0.79-6.67)
≥18.0	83	72	11		
Procedure of anastomosis					
Hand sewn	104	87	17	0.98	0.98 (0.11-8.90)
Staple	6	5	1		
Rectosigmoid stump at first stage					
Intraperitoneal	22	3	19	0.70	0.77 (0.20-2.93)
Subcutaneous	88	15	73		
Laparoscopic surgery					
Yes	28	27	1	0.064	0.14 (0.018-1.12)
No	82	65	17		
Perioperative blood transfusion					
Yes	7	5	2	0.38	2.17 (0.39-12.20)
No	103	87	16		
Operative time (min)	351 ± 115	354 ± 115	335 ± 119	0.35	
<265	84	73	11	0.10	2.44 (0.84-7.15)
≥265	26	19	7		
Operative blood loss (g)	384 ± 366	363 ± 368	493 ± 345	0.031	
<270	55	41	14	0.015	0.23 (0.070-0.75)
≥270	55	51	4		
Cumulative dose of prednisolone (g)	8.9 ± 13.3	7.3 ± 9.0	17.5 ± 25.0	0.36	
<10	86	74	12	0.20	0.49 (0.16-1.47)
≥10	24	18	6		
Dose of prednisolone per day (mg)	2.1 ± 4.2	1.8 ± 3.9	3.6 ± 5.5	0.14	
<5	89	77	12	0.10	0.39 (0.13-1.20)
≥5	21	15	6		
History of immunomodulator use					
Yes	39	34	5	0.46	0.66 (0.22-2.00)
No	71	58	13		
History of anti-TNFa antibody use					
Yes	19	18	1	0.18	0.24 (0.030-1.94)
No	91	74	17		
Alb (g/dL)	4.0 ± 0.5	4.1 ± 0.39	3.8 ± 0.69	0.022	
<4.1	49	37	12	0.045	2.97 (1.02-8.62)
≥4.1	61	55	6		

Table 1. Results of Univariate Analysis for Predictive Factors Potentially Associated with Postoperative Infectious Complications. (continued)

Perioperative Factors	Total n = 110	PIC (-) n = 92	PIC (+) n = 18	P value	Odds Ratio (95% CI)
WBC (/μL)	6600 ± 2400	6550 ± 1970	711 ± 3840	0.90	
<8000	87	75	12	0.16	2.21 (0.73-6.71)
≥8000	23	17	6		
Hb (g/dL)	12.5 ± 1.7	12.7 ± 1.6	11.5 ± 1.9	0.010	
<12.8	58	45	13	0.078	2.72 (0.90-8.24)
≥12.8	52	47	5		
CRP (mg/dL)	0.45 ± 1.34	0.43 ± 1.38	0.52 ± 1.12	0.22	
<0.15	62	55	7	0.11	0.43 (0.15-1.21)
≥0.15	48	37	11		
Neutrophil (/μL)	4170 ± 2140	4130 ± 1820	440 ± 3400	0.28	
<9000	107	91	16	0.053	0.088 (0.0075-1.03)
≥9000	3	1	2		
Lymphocyte (/μL)	1650 ± 720	1670 ± 740	1540 ± 630	0.35	
<1660	58	46	12	0.20	2.00 (0.69-5.78)
≥1660	52	46	6		
PNI	48.7 ± 5.9	49.3 ± 5.2	45.5 ± 8.1	0.034	
<47	38	26	12	0.0032	5.08 (1.72-14.95)
≥47	72	66	6		
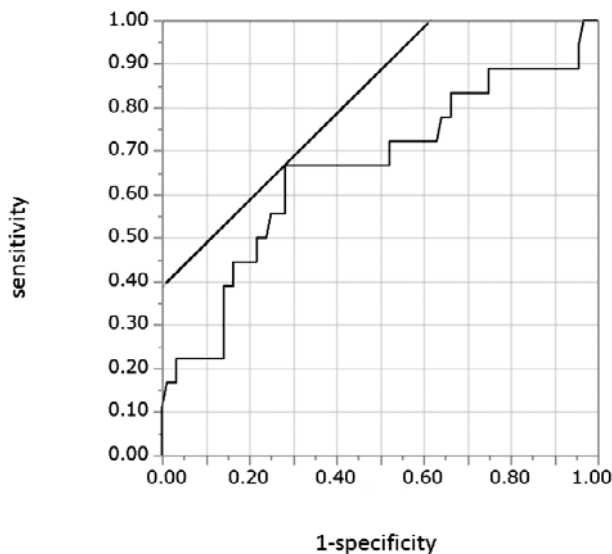
Figure 1. Receiver operating characteristic curve (ROC) analysis was performed to evaluate the ability of PNI to predict PICs. The optimal cut-off values for PNI and AUC were determined as 47 and 0.66, respectively, corresponding to a sensitivity and specificity of 67% and 72%, respectively.

pendent association between the cumulative dose of prednisolone and development of PICs in patients undergoing restorative proctocolectomy and IPAA.

Prednisolone dosage before surgery was found to be an independent predictor of postoperative complications in two published studies, but not in this study. This discrepancy

Table 2. Multivariate Analysis for Predictive Factors Potentially Associated with Postoperative Infectious Complications.

Perioperative Factors	P value	Odds Ratio (95% CI)
Operative blood loss ≥ 270 g	0.033	3.79 (1.12-12.85)
PNI < 47	0.0076	4.52 (1.49-13.67)

may be attributable to immunosuppressives having little influence on short-term outcomes after PC-IPAA because of the long interval between the first and second stage, or to the reduction of immunosuppressive dosages. Nutritional status before PC-IPAA, which is usually performed when the patient's condition is stable, is likely to have a greater influence on short-term outcomes, especially PICs, than anti-inflammatory drug intake.

The mechanism for the independent correlation between PNI and postoperative outcomes in patients undergoing surgery for digestive diseases is not clear.

Serum albumin concentration is regarded as a good index not only of malnutrition but also of inflammation, chronic disease, and fluid status in a wide variety of patient groups[14-17]. The other component of the PNI, total lymphocyte count, is considered a useful indicator of systemic inflammatory status[10]. Several studies have reported that increased systemic inflammation and poor nutrition are also risk factors for SSIs after gastrointestinal surgery[18-20]. The preoperative PNI, which reflects both nutritional and inflammatory statuses, can thus be used to predict the development

of PICs in patients with UC undergoing three-stage IPAA.

We also found that operative blood loss is an independent predictor of PICs. A study reported by Uchino et al.[21] showed that operative blood loss is an independent predictor of organ/space SSI in patients with UC. Others have also shown that operative blood loss, which is one of the factors related to surgical stress, is an independent predictor of postoperative complications in patients with other digestive diseases[22-24].

The limitations of this study include its retrospective, single-center design, the small sample size, and potential selection bias.

In conclusion, our findings suggest that immunosuppressives have no association with the development of PICs and that a low PNI is a significant predictor of PICs after PC-IPAA. PNI may be a simple and useful tool for assessing the risk of PICs in patients undergoing PC-IPAA for UC. Physicians should pay particular attention to perioperative nutritional care in patients with UC undergoing PC-IPAA who have a low PNI. Pre-PC-IPAA PNI may be a useful indicator of the optimal timing for the second operation in regard to the incidence of PICs.

Conflicts of Interest
There are no conflicts of interest.

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