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Clinical Significance of Prognostic Nutrition Index in Patients with Crohn's Disease after Primary Bowel Resection

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Purpose: Although advancements in medical treatments have been made, approximately half of patients with intestinal Crohn's disease (CD) require intestinal resections during their lifetime. It is well-known that the nutritional status of CD patients can impact postoperative morbidity. The objective of this study was to evaluate the clinical significance of prognostic nutritional index (PNI) in patients with intestinal CD who underwent primary bowel resection.

Materials and Methods: We retrospectively investigated patients who were diagnosed with CD and underwent intestinal surgery at Severance Hospital between January 2005 and October 2018. The patients were divided into two groups: PNI ≤40 (n=150) and PNI >40 (n=77). We assessed the clinical significance of PNI in terms of the incidence of postoperative infectious complications (PICs) and the postoperative recurrence of CD.

Results: The low PNI group had significantly higher rates of infectious complications (32.0% vs. 10.4%, p=0.001) compared to the high PNI group. Multivariable analysis identified low PNI (≤40) and longer operation time (>180 min) as independent risk factors associated with PICs [odds ratio (OR)=2.754, 95% confidence interval (CI)=1.140–6.649, p=0.024; OR=2.986, 95% CI=1.451–6.143, p=0.003]. PICs were significantly associated with surgical recurrence (hazard ratio=2.217, 95% CI=1.064–4.617, p=0.034).

Conclusion: Preoperative PNI could serve as a predictive factor for PICs in CD patients who undergo intestinal resection. Additionally, PICs are significantly associated with a higher risk of surgical recurrence in CD.

Key Words: Crohn's disease, intestinal Crohn's disease, surgery, nutrition, prognostic nutritional index

INTRODUCTION

Crohn's disease (CD) is a chronic, idiopathic, immune-mediated inflammatory disease that can occur in any segment of the digestive tract.[1] The prevalence rate of CD in Korea was 11.24 cases per 105 persons from 1986 to 2005, which was lower than that in Western countries.[2] However, the number of patients with CD has been rapidly increasing in recent years, and CD has risen as an important clinical disease in Korea. Moreover as the incidence of CD has increased, the annual number of surgeries in patients with CD has also increased.[3]

Although advancements in medical treatments, such as immunomodulators and anti-tumor necrosis factor (anti-TNF) agents, have changed the treatment strategy for CD, approxi-

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mately 50% of patients with CD require CD-related surgery during their entire lifetime due to failure of medical therapy.[4,5] Thus, surgery is still an important treatment option for refractory and complicated CD. Moreover, the incidence of postoperative complications, especially infectious complications, is higher in CD patients who undergo intestinal resection at a rate of 10%–37% compared to in those with other intestinal diseases. This is due to the internal disease characteristics and, at least in part, since patients with CD are often malnourished.[6,7]

Several retrospective studies have attempted to identify the risk factors for morbidity after CD-related surgery, and have reported that poor preoperative nutritional status or complicated forms of CD were associated with an increased risk of postoperative morbidity.[8-11] In hopes of decreasing postoperative complications, nutritional optimization using enteral nutrition or total parenteral nutrition have been tried for many years before surgery.[12] A previous study reported that the occurrence of postoperative intra-abdominal septic complications was associated with an increased risk of recurrence in patients with CD.[13] Therefore, it is important to estimate the risk of surgical complications in CD patients.

Many studies have shown that the prognostic nutritional index (PNI), which is calculated by serum albumin (ALB) concentration and total lymphocyte count in the peripheral blood, can be used to predict the risk of postoperative complications and prognosis in patients with gastrointestinal and hepatopancreatobiliary cancers.[14-16] However, the clinical significance of PNI in predicting postoperative outcomes, including long-term prognosis in CD, remains unknown.

This study analyzed a large cohort of patients with CD in our hospital to investigate the role of PNI in postoperative CD in Korea. The aim of the current study was to evaluate the clinical significance and prognostic value of the PNI in patients undergoing bowel resection for CD.

MATERIALS AND METHODS

Patients

In total, 303 patients underwent intestinal resection for CD at our institute during the study period; among them, 227 CD patients who underwent their first intestinal surgical resection between January 2005 and October 2018 at Yonsei University College of Medicine, Seoul, Korea were eligible for the analysis and were retrospectively reviewed. The diagnosis of CD was pathologically confirmed both before and after surgery. The exclusion criteria were as follows: patients who only underwent surgery for simple appendicitis, stoma closure, strictureplasty, reoperation for postoperative complications, and a history of concurrent or prior malignancies. The study protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (approval number: 4-2022-0367), in accordance with the Declaration of Helsinki.

Data collection and definitions

All baseline characteristics, perioperative data, and laboratory data were retrospectively collected from electronic medical records. The baseline characteristics included age, sex, body mass index, comorbidity, smoking history, and disease phenotype (Montreal classification).[17] For preoperative medications, antibiotic therapy was defined as preoperative antibiotic usage within 1 week before surgery; immunomodulator therapy (thiopurines or methotrexate), 5-aminosalicylic acid use, steroid use, and biologic therapy (infliximab, adalimumab, vedolizumab, or ustekinumab) were defined as use within 4 weeks before surgery. Intraoperative data collected included operation time, intraoperative blood loss, anastomosis method (stapled or hand-sewn), and surgical approach (open or laparoscopy). Laboratory data included hemoglobin levels, ALB levels, C-reactive protein levels, and lymphocyte counts. Within 2 days before the operation, peripheral blood samples were collected. In case of emergency operation, blood sampling was done at the same day with the operation. If there were more than one result, we selected the nearest one to the surgery. The PNI was calculated from the serum ALB level and total peripheral lymphocyte count (TLC), using the following formula: PNI=10×ALB (g/dL)+0.005 TLC (per mL). The cutoff value for the PNI was 40, based on the study by Onodera, et al.[18]

We investigated the clinical significance of PNI in terms of the incidence of postoperative infectious complications (PICs), including wound infections, abdominal abscesses, enterocutaneous fistula, and anastomotic leakage. Other infectious complications, such as urinary tract infections, pneumonia, or catheter-related bloodstream infections, were excluded. This study also evaluated the correlation between PNI and the postoperative recurrence of CD. Surgical recurrence was defined as repeated intestinal resections due to CD, with the exception of surgery-related complications and stoma closure. Clinical recurrence was defined as the recurrence of CD-related symptoms confirmed by objective signs of radiologic or endoscopic findings.[19]

Treatment of CD

The extent of CD was assessed based on intraoperative findings, radiological imaging using abdominal and pelvic computed tomography (CT), CT enterography, magnetic resonance imaging (MRI) enterography, and colonoscopy. After primary intestinal resection, reassessment was performed using CT enterography, MRI enterography, and/or colonoscopy after 6 to 12 months. The strategy of medical treatment for CD was based on a "step-up or accelerated approaches," in which more potent therapies were added if patients became refractory to first-line or less toxic agents according the Korean CD treatment guidelines.[20,21] The indication for surgery was discussed by a multidisciplinary team consisting of gastroenterologists, surgeons, and radiologists. Before surgery, we attempted to taper or discontinue immunomodulators, anti-TNF agents, or steroids

during perioperative period. If the patient was assessed as having poor nutritional condition at the time of determining surgery, nutritional support was performed for 1 to 2 weeks before surgery—with total parenteral method most frequently. Determining the surgical method was largely dependent on the surgeon's judgment. If laparoscopic approach was considered as feasible, laparoscopic surgery was attempted.

Statistical analysis

The mean±SD or median (range) was used to represent continuous data, while categorical data were presented as numbers (%). Continuous variables were analyzed using the Student's t-test or Mann-Whitney U test, depending on the normality of the data distribution, and categorical variables were analyzed using the Pearson's χ^2 test or Fisher's exact test, as appropriate. Risk factors with a p value<0.10 in the univariable analysis were included in the multivariable analyses. Logistic regression with a backward stepwise selection was used to select risk factors for the multivariable model. The cumulative incidence of recurrence was evaluated as "1-(recurrence free survival probability)" using Kaplan–Meier estimator survival analysis, and log-rank analysis was conducted to verify the significance of differences. Multivariable analysis with Cox proportional hazards models was performed to identify independent associated factors. All analyses were performed using the SPSS v25.0 software (IBM Corp., Armonk, NY, USA). Statistical significance was set at p<0.05.

RESULTS

Patients characteristics

Patient characteristics are summarized in Table 1. Data from 227 patients with CD were analyzed. The mean follow-up time was 71.4 months (range, 1–181 months), the mean age at surgery was 31.0±11.5 years, and the majority (77.1%) of patients were diagnosed with CD between the ages of 17 and 40 years. According to the Montreal classification, 105 (46.3%) patients presented with disease in the ileocolon region (L3), 98 (43.2%) in the terminal ileum (L1), and 19 (8.4%) in the colon region (L2). Among 227 patients, 131 (57.7%) had penetrating disease (B3), 73 (32.2%) had stricturing disease (B2), and 23 (10.1%) had inflammatory disease (B1). A total of 104 (45.8%) patients suffered perianal disease. Preoperatively, 60 (26.4%) patients had a medical history of anti-TNF therapy, 186 (81.9%) with 5-ASA, 47 (20.7%) with steroids, 110 (48.5%) with immunomodulators, and 48 (21.1%) with antibiotics. One hundred fifty (66.1%) patients were in the low PNI group (≤40) and 77 (33.9%) patients were in the high PNI group (>40). Body mass index, ASA score (1, 2 vs. 3, 4), behavior (Montreal classification), CD activity index, ALB level, hemoglobin level, and C-reactive protein level were significantly different between patients with low and high PNI, as shown in Table 1.

Operative data and postoperative complications

The surgical characteristics and postoperative outcomes of the 227 patients are shown in Table 2. A total of 47 (20.7%) patients underwent emergency surgery for generalized peritonitis or severe obstruction. The low PNI group had a higher rate of emergency surgery compared to the high PNI group (26.7% vs. 9.1%, p=0.003). Laparoscopic surgery was performed in 137 (60.4%) patients. The high PNI group had higher laparoscopic surgery rate compared to the low PNI group (70.1% vs. 55.3%, p=0.044). The mean operation time (186.4±90.3 vs. 195.7±95.0, p=0.030), blood loss >300 mL (33.1% vs. 15.5%, p=0.011), and postoperative hospital stay (13.8±12.6 vs. 8.5±4.1, p<0.001) were significantly different between the two groups, respectively. The overall postoperative complication (54.0% vs. 36.3%, p=0.017) and infectious complication rates (32.0% vs. 10.4%, p=0.001) were significantly higher in the low PNI group than in the high PNI group. The incidence of complications for each type is shown in Fig. 1. The common complications were postoperative ileus (22.5%) and wound infection (16.3%). The incidence of anastomosis leakage and entero-cutaneous fistula were both 4.0%. In the high PNI group, none of the patients experienced anastomosis leakage and only one patient suffered entero-cutaneous fistula. A difference between the low and high PNI groups was observed in wound infection (p=0.007) and intra-abdominal abscess (p=0.046).

Factors associated with PICs

Univariable and multivariable analyses were performed to identify risk factors for PICs in patients with CD. The results are presented in Table 3. Colonic involvement (p=0.010), penetrating behavior (p<0.001), ASA score >2 (p=0.004), emergency operation (p=0.006), laparoscopic approach (p<0.001), C-reactive protein>level>100 (p=0.008), PNI ≤40 (p<0.001), operation time >180 min (p<0.001), and blood loss >300 mL (p=0.001) were all found to be significantly associated with PICs in univariable analysis. Multivariable analysis identified low PNI (≤40) and longer operation time (>180 min) as independent risk factors associated with PICs [odds ratio (OR)=2.754, 95% confidence interval (CI)=1.140–6.649, p=0.024; OR=2.986, 95% CI=1.451–6.143, p=0.003). The laparoscopic approach [hazard ratio (HR)=0.256, 95% CI=0.126–0.523, p<0.001] was a protective factor against PICs. Meanwhile, none of the preoperative medical treatments were associated with the occurrence of PICs (Supplementary Table 1, only online). In addition, the results of the analysis on other variables are presented in Supplementary Table 1 (only online).

Postoperative recurrence of CD

The 1-, 5-, and 10-year clinical recurrence rates of CD after the first intestinal resection were 14.9% (95% CI=14.6%–15.2%), 55.7% (95% CI=54.8%–56.6%), and 78.3% (95% CI=75.3%–81.3%), respectively (Fig. 2A). To determine the independent factors associated with clinical recurrence, variables including

baseline characteristics, preoperative medications, and perioperative characteristics were analyzed (Table 4 and Fig. 2A-C). There was no significant difference in the clinical recurrence of CD between the low- and high-PNI groups (p=0.094) (Fig. 2B).

A total of 30 (13.2%) patients underwent repeated intestinal resection for CD recurrence during the follow-up period, leading to an estimated mean surgical recurrence time of 148.2±5.2 months. The 1-, 5-, and 10-year cumulative incidence of surgi-

Table 1. Patient Demographics and Disease Characteristics

Variables	All (n=227)	PNI ≤40 (n=150)	PNI >40 (n=77)	*p* value
Sex				0.438
Male	150 (66.1)	96 (64.0)	54 (70.1)	
Female	77 (33.9)	54 (36.0)	23 (29.9)	
Body mass index, kg/m^2	18.6±3.5	19.6±3.7	18.0±3.3	0.002
Hypertension	15 (6.6)	9 (6.0)	6 (7.8)	0.816
Diabetes mellitus	10 (4.4)	7 (4.7)	3 (3.9)	0.542
ASA score				0.037
1–2	192 (84.6)	121 (80.7)	71 (92.2)	
3–4	35 (15.4)	29 (19.3)	6 (7.8)	
Age at diagnosis, yr	25.3±11.1	25.6±11.0	24.9±11.2	0.636
Age at operation, yr	31.0±11.5	31.5±11.6	30.1±11.3	0.411
Age at diagnosis, yr				0.756
A1 (≤16)	32 (14.1)	23 (15.3)	9 (11.7)	
A2 (17–40)	175 (77.1)	114 (76.0)	61 (79.2)	
A3 (≥41)	20 (8.8)	13 (8.7)	7 (9.1)	
Location				0.138
L1 (ileal)	98 (43.2)	58 (38.7)	40 (51.9)	
L2 (colonic)	19 (8.4)	16 (10.7)	3 (3.9)	
L3 (ileocolonic)	105 (46.3)	73 (48.7)	32 (41.6)	
L4 (isolated upper disease)	5 (2.2)	3 (2.0)	2 (2.6)	
Behavior				<0.001
B1	23 (10.1)	15 (10.0)	8 (10.4)	
B2	73 (32.2)	33 (22.0)	40 (51.9)	
B3	131 (57.7)	102 (68.0)	29 (37.7)	
Perianal disease	104 (45.8)	72 (48.0)	32 (41.6)	0.434
Crohn's disease activity index				0.006
0–150	12 (5.3)	4 (2.7)	8 (10.4)	
151–219	35 (15.4)	22 (14.7)	13 (16.9)	
≥220	101 (44.5)	77 (51.3)	24 (31.2)	
Missing	79 (34.8)	47 (31.3)	32 (41.6)	
Smoking history (current smoker+ex-smoker)	44 (17.1)	32 (21.3)	12 (15.6)	0.390
Familial history	6 (2.6)	4 (2.7)	2 (2.6)	0.851
Preoperative medical treatment				
Anti-TNF therapy	60 (26.4)	39 (26.0)	21 (27.3)	0.963
5-ASA	186 (81.9)	122 (81.3)	64 (83.1)	0.882
Steroid	47 (20.7)	34 (22.7)	13 (16.9)	0.398
Immunomodulator	110 (48.5)	68 (45.3)	42 (54.5)	0.240
Antibiotics	48 (21.1)	40 (26.7)	8 (10.4)	0.008
Preoperative nutrition				
Enteral nutrition	2 (0.9)	2 (1.3)	0 (0.0)	0.789
Parenteral nutrition	15 (6.6)	15 (10.0)	0 (0.0)	0.010
Albumin, g/dL	3.3±0.7	3.0±0.5	4.0±0.4	<0.001
Prognostic nutrition index	38.5±8.0	34.0±5.3	47.2±4.3	<0.001
Hemoglobin	11.4±2.1	10.8±2.0	12.4±1.8	<0.001
C reactive protein, mg/dL	48.5±74.0	64.8±82.4	13.7±30.4	<0.001

PNI, prognostic nutritional index; ASA, American Society of Anesthesiologists; Anti-TNF, anti-tumor necrosis factor; 5-ASA, aminosalicylates.
Data are presented as mean±standard deviation or n (%).

cal recurrence were 3.2% (95% CI=3.0%–3.4%), 11.3% (95% CI=10.9%–11.7%), and 24.0% (95% CI=22.0%–26.0%), respectively (Fig. 2D). Table 4 shows the univariable and multivariable analyses of the predictive factors for surgical recurrence in patients with CD. PICs were significantly associated with surgical recurrence (HR=2.217, 95% CI=1.064–4.617, p=0.034) (Fig. 2F). Regarding the effects of each drug used as a preoperative medical treatment, the risk was reduced with only pre-

Table 2. Perioperative Characteristics of the Study Participants

Variables	All (n=227)	PNI ≤40 (n=150)	PNI >40 (n=77)	*p* value
Emergency surgery	47 (20.7)	40 (26.7)	7 (9.1)	0.003
Surgical approach				0.044
Laparoscopic	137 (60.4)	83 (55.3)	54 (70.1)	
Open	90 (39.6)	67 (44.7)	23 (29.9)	
Operation name				
Ileocecectomy	81 (35.7)	56 (37.3)	25 (32.5)	
Right hemicolectomy	43 (18.9)	30 (20.0)	13 (16.9)	
Small bowel resection and anastomosis	88 (38.8)	51 (34.0)	37 (48.1)	
Total or subtotal colectomy	10 (4.4)	8 (5.3)	2 (2.6)	
Others	5 (2.2)	5 (3.3)	0 (0.0)	
Number of anastomosis sites				0.592
1	209 (92.1)	137 (91.3)	72 (93.5)	
2 or more	11 (4.8)	7 (4.7)	4 (5.2)	
Permanent ostomy	7 (3.1)	6 (4.0)	1 (1.3)	
Type of anastomosis				0.448
Hand-sewn	118 (52.0)	81 (54.0)	37 (48.1)	
Stapled	98 (43.2)	61 (40.7)	37 (48.1)	
Both	4 (1.8)	2 (1.3)	2 (2.6)	
Permanent ostomy	7 (3.1)	6 (4.0)	1 (1.3)	
Operation time, min	186.4±90.3	195.7±95.0	168.3±77.9	0.030
Operation time >180 min	103 (45.4)	73 (48.7)	30 (39.0)	0.211
Blood loss >300 mL	58 (27.2)	47 (33.1)	11 (15.5)	0.011
Postoperative hospital stay, day	12.0±10.8	13.8±12.6	8.5±4.1	<0.001
Postoperative complication	109 (48.0)	81 (54.0)	28 (36.4)	0.017
Postoperative infectious complication	56 (24.7)	48 (32.0)	8 (10.4)	0.001

PNI, prognostic nutritional index.
Data are presented as mean±standard deviation or n (%).

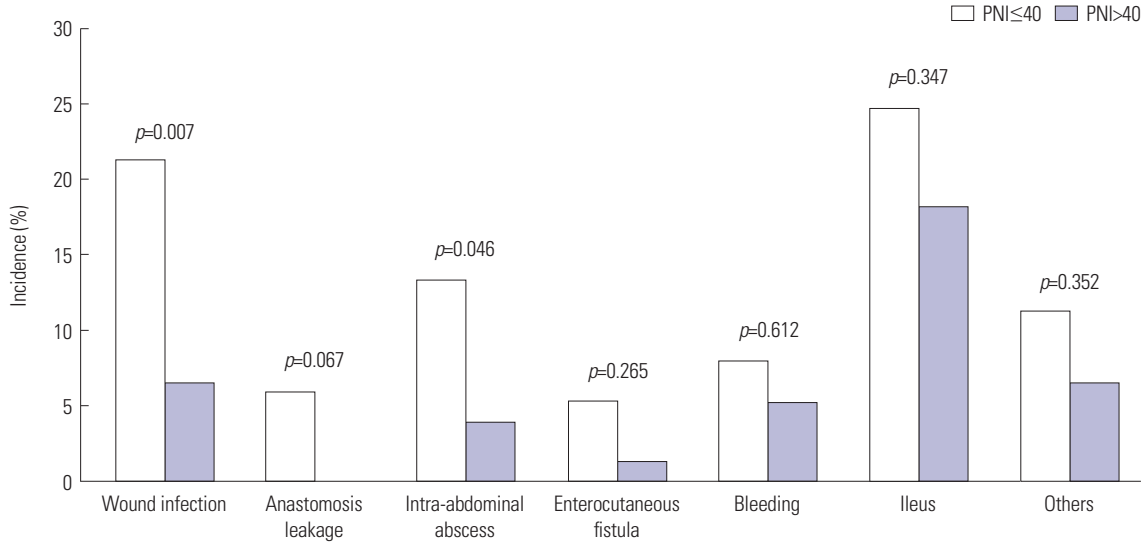

Fig. 1. Comparison of each complication between patients with low (≤40) and high PNI (>40). Urinary retention, urinary tract infection, pleural effusion, catheter-related infection, and pneumonia were classified as "Others". PNI, prognostic nutritional index.

Table 3. Univariable and Multivariable Analyses of Factors Associated with Postoperative Infectious Complications

	Univariable			Multivariable		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Colonic involvement (L2 and L3)	0.431	0.223–0.820	0.010			
Penetrating behavior (B3)	0.283	0.140–0.572	<0.001			
ASA score >2	3.110	1.444–6.696	0.004			
Anti-TNF	1.819	0.949–3.490	0.072			
Emergency operation	2.623	1.321–5.206	0.006			
Open laparotomy (vs. laparoscopic approach)	4.336	2.284–8.232	<0.001	3.906	1.912–7.937	<0.001
Hemoglobin ≤12.5 g/dL	0.489	0.235–1.016	0.055			
C-reactive protein >100 mg/dL	3.144	1.391–7.109	0.008			
Prognostic nutrition index ≤40	0.246	0.110–0.553	<0.001	2.754	1.140–6.649	0.024
Operation time >180 min	3.443	1.815–6.530	<0.001	2.986	1.451–6.143	0.003
Blood loss >300 mL	3.022	1.579–5.783	0.001			

CI, cofidence interval; ASA, American Society of Anesthesiologists; Anti-TNF, anti-tumor necrosis factor.

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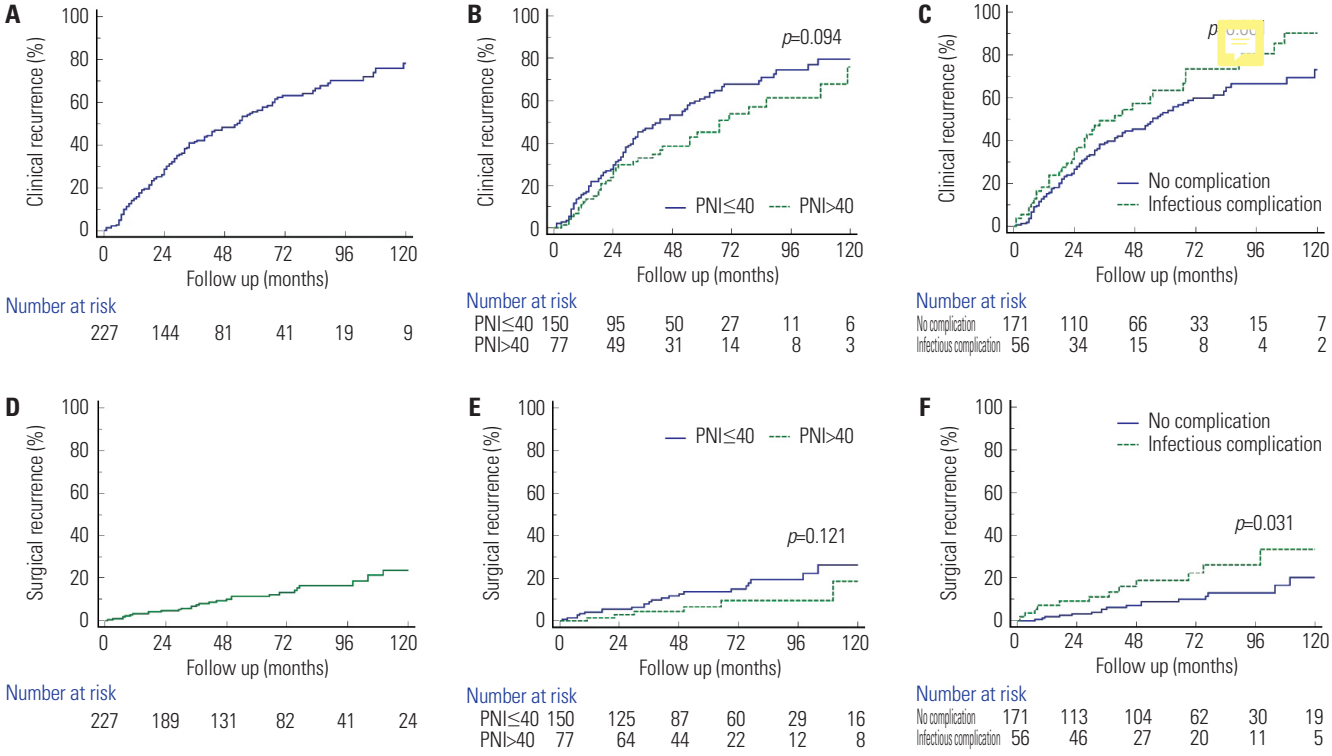

Fig. 2. Postoperative recurrence of patients who underwent intestinal resection for Crohn's disease. Cumulative rate of clinical recurrence (A) in all patients (B) according to PNI (C) and according to the occurrence of postoperative infectious complication. Cumulative rate of surgical recurrence (D) in total patients (E) according to PNI (F) and according to the occurrence of postoperative infectious complications. PNI, prognostic nutritional index.

operative immunomodulator use (HR=0.271, 95% CI=0.111–0.664, *p*=0.002). A history of other medications before intestinal resection was not associated with postoperative recurrence of CD. Moreover, low PNI (≤40) was found to not be a significant factor for surgical recurrence (*p*=0.121) (Fig. 2E). Additionally, analysis information on other variables are described in Supplementary Table 2 (only online).

DISCUSSION

Over the past few decades, the incidence and prevalence of CD in Korea have consistently increased. Furthermore, it is common for CD patients to require intestinal resection at some point in their lifetime. Accordingly, it has become increasingly important to efficiently predict the short- and long-term prognosis after surgery. Several studies have attempted to identify the preoperative nutritional status associated with short-term complications; however, to the best of our knowledge, most

Table 4. Univariable and Multivariable Analyses of Factors Associated with Surgical and Clinical Postoperative Recurrence-Free Survival

	Univariable			Multivariable		
	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Clinical recurrence-free survival						
Perianal lesion	1.473	1.043–2.080	0.028	1.397	0.987–1.976	0.059
Prognostic nutrition index ≤40	0.725	0.495–1.061	0.098			
Infectious complication	1.431	0.980–2.090	0.064	1.407	0.962–2.057	0.078
Surgical recurrence-free survival						
Immunomodulator	0.273	0.111–0.668	0.005	0.271	0.111–0.664	0.004
Open laparotomy (vs. laparoscopic approach)	2.084	0.982–4.425	0.056			
Infectious complication	2.188	1.052–4.547	0.036	2.217	1.064–4.617	0.034

CI, cofidence interval.

have not focused on long-term prognosis. In the current study, we evaluated the short- and long-term clinical significance of the PNI in patients with CD who underwent initial intestinal resection. Our results showed that preoperative PNI, surgical approach (open laparotomy or laparoscopic), and operation time (>180 min or not) were significant prognostic factors for the development of PICs. We also found that preoperative immunomodulator use and PICs were significantly associated with postoperative surgical CD recurrence as protective and risk factors, respectively.

The PNI was originally established as a surgical risk indicator in patients undergoing gastrointestinal surgery.[15,18] The PNI has further been reported to be useful in predicting the prognosis of patients undergoing surgery for cancer.[14-16] Although the prognostic significance of PNI has been reported in several types of cancer, its use in long-term outcomes for patients with CD has not been examined. The PNI value, determined by serum ALB concentration and total lymphocyte count, was used to evaluate the immunological and nutritional aspects of patients undergoing surgery. The concentration of serum ALB is closely associated with nutritional status and other factors, including infection, inflammatory response, and fluid retention status.[22] Several studies have attempted to identify the predictive value of preoperative nutritional status for postoperative complications in patients with CD by assessing ALB, BMI, and sarcopenia.[9,23-25] The TLC count indicates the immunological status of the patient. Decreased lymphocyte counts can be caused by poor cellular immune function.[26] Recently, Gil-Borras, et al.[27] found that peripheral B1a lymphocyte deficiency in patients with CD was related to postoperative complications. To date, there have been very few previous studies of small cohorts showing that PNI is a predictor of postoperative complications in CD patients.[8,10] In this study, investigated both short-term and long-term postoperative outcomes according to PNI in a relatively larger patient group. Although the PNI did not appear to be significantly associated with clinical and surgical recurrence of CD in our study population, it was nevertheless a significant risk factor for PICs. Patients with CD often show mild-to-severe malnutrition due to reduced oral intake, absorption disorders, and systemic inflammation. Therefore, preoperative nutritional optimization is often recommended. A recent meta-analysis demonstrated that preoperative nutritional supplementation, including enteral and total parenteral nutrition, reduced postoperative complications in patients with CD.[12] Although the appropriate parameters for determining which patients require aggressive preoperative nutritional supplementation are still ambiguous, we expect that PNI could play a role in this.

Our results also showed that open laparotomy and long operation time (>180 min) were significant risk factors for PICs in the multivariable analysis. In our study population, 60.4% of patients underwent laparoscopic surgery. Previous studies have found that laparoscopic surgery appears to reduce the risk of perioperative complications compared to open surgery.[28,29] In addition, a recent meta-analysis demonstrated reduced perioperative complications in patients undergoing laparoscopic resection versus open resection in CD patients.[30] Laparoscopic surgery is associated with reduced postoperative pain and a lower incidence of disease in the ileus. In other words, early diet and ambulation are possible after surgery. Furthermore, this may promote recovery and prevent further complications. Similarly, prolonged operative time is considered to increase the risk of postoperative complications. This may take longer for patients with more complex diseases. Therefore, it is expected that the morbidity rate will increase in patients with more complex and severe CD, which is associated with an increased risk of anastomotic leakage after colorectal surgery.[31,32] A recent study demonstrated that an operation time >180 min increased the risk of intra-abdominal septic morbidity in a retrospective series of 550 patients undergoing surgery for CD.[33] During the study, postoperative complication closely related to anastomosis (anastomosis leakage and entero-cutaneous fistula) occurred very rarely in the high PNI group. Although there was no statistical significance, the nutritional status before surgery predicted as the PNI value could have affected anastomosis healing. Therefore, more defensive surgical strategy (avoidance of primary anastomosis) should be discussed with the patient with low PNI value. Some studies have raised concerns that anti-TNF treatment during the perioperative period would increase the risk of surgical complica-

tions.[8,34] Furthermore, a recent prospective study showed that preoperative anti-TNF therapy increased the risk of morbidity after surgery for ileocolonic CD, regardless of disease severity.[28] In the present analysis, patients treated with anti-TNF medication before surgery showed a trend towards a higher rate of infectious complications, but this difference did not reach a statistically significant level.

In terms of medical treatments, 54.5% of patients used immunomodulators and 27.3% of patients used anti-TNF medications before their first intestinal resection surgery. A similar trend was observed in a previous study.[35] During the study period, anti-TNF agents were strictly regulated under the national insurance, but were allowed in cases of CD unresponsive to more than two drugs, or moderate CD with contraindication to corticosteroids or immunomodulators. In our study, preoperative immunomodulator use significantly decreased the risk of postoperative surgical CD recurrence. Owing to the lack of data on postoperative medical treatment, it is difficult to determine the prophylactic effectiveness of each medication directly. Nevertheless, this can be interpreted by the regulated use of anti-TNF because of the national insurance policy and exposure to anti-TNF prior to intestinal resection. Anti-TNF is considered the most effective medication for preventing preoperative recurrence, although the use of thiopurines has also been reported.[19,35-37] In addition, it was suggested that anti-TNF therapy is more effective at preventing postoperative CD recurrence in patients who did not experience anti-TNF preoperatively.[36] In the present study, the above analysis was possible since patients who were treated with an immunomodulator before surgery were highly likely to be naïve to anti-TNF therapy. Moreover, they could be allowed to receive prophylactic anti-TNF therapy, satisfying the condition since they showed a poor response to thiopurines, resulting in surgical intervention.

In contrast, multivariable analysis demonstrated that PICs were significant risk factors for surgical recurrence. As mentioned above, medical treatment after surgery is important for preventing recurrence. According to the ECCO guidelines, prophylactic treatment is recommended after ileocolonic intestinal resection in patients with at least one risk factor for recurrence.[19] If infectious complications occur, the necessary management might take considerable time, delaying the necessary medical prophylaxis. This delay is likely to adversely affect the prognosis of CD patients, especially if they have a risk factor for recurrence. Recent studies have indicated that vedolizumab is associated with lower rates of perioperative complications than anti-TNF.[38] In our analysis, a low PNI (≤40) before intestinal resection was an independent risk factor for PICs. When considering medical treatment in patients with poor nutrition during the perioperative period, vedolizumab may be a better option.

This study had several limitations. First, it was designed as a retrospective observational study and included patients from a single center. The perioperative treatment and surgical option could not be randomly controlled. Second, this study population included approximately 20% of patients who underwent emergency surgery. This could have affected the analysis since their preoperative nutritional status would be worse compared to elective patients. Third, we excluded the variables of postoperative medical treatments from the analysis due to a lack of data. Also, there were some missing data in the CDAI. This limited the analysis of postoperative recurrence and related factors. Further prospective clinical trials are required to confirm the results of our study. Nevertheless, this study included a relatively large cohort of patients with near-complete follow-up, reflecting the clinical importance of the Asian population.

In conclusion, the present study indicated that the preoperative PNI could predict PICs in patients who underwent intestinal resection for CD. Additionally, PICs were significantly associated with a higher risk of surgical recurrence of CD. Therefore, preoperative nutritional optimization should be applied for patients with low PNI values to reduce the risk of postoperative complications; and if such efforts do not result in complications, repeated surgery may be prevented.

AUTHOR CONTRIBUTIONS

Conceptualization: Min Soo Cho. Data curation: Hyeon Woo Bae. Formal analysis: Hyeon Woo Bae and Seung Yoon Yang. Funding acquisition: Min Soo Cho. Investigation: Hyeon Woo Bae. Methodology: Min Soo Cho and Yoon Dae Han. Project administration: Min Soo Cho and Jae Hee Cheon. Resources: Hyuk Hur, Kang Young Lee, and Byung Soh Min. Software: Hyeon Woo Bae. Supervision: Hyuk Hur, Kang Young Lee, Joseph C. Carmichael, and Byung Soh Min. Validation: Yong Joon Lee and Min Young Park. Visualization: Hyeon Woo Bae. Writing—original draft: Hyeon Woo Bae. Writing—review & editing: Min Soo Cho and Jae Hee Cheon. Approval of final manuscript: all authors.

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Supplementary Table 1. Univariable and Multivariable Analyses of Factors Associated with Postoperative Infectious Complications

	Univariable			Multivariable		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Female	1.232	0.657–2.309	0.515			
Age	0.995	0.968–1.022	0.687			
Hypertension	0.750	0.204–2.760	0.665			
Diabetes mellitus	2.115	0.575–7.785	0.260			
CDAI	1.001	0.996–1.005	0.745			
Early onset (A1)	0.647	0.250–1.672	0.404			
Colonic involvement (L2 and L3)	0.431	0.223–0.820	0.010			
Penetrating behavior (B3)	0.283	0.140–0.572	<0.001			
ASA score >2	3.110	1.444–6.696	0.004			
Perianal lesion	1.137	0.621–2.081	0.678			
Smoking history	1.185	0.562–2.496	0.656			
Preoperative medical treatment						
Anti-TNF	1.819	0.949–3.490	0.072			
5-ASA	0.832	0.370–1.870	0.656			
Steroid	1.060	0.506–2.218	0.878			
Immunomodulator	0.816	0.445–1.496	0.511			
Antibiotics	0.761	0.351–1.648	0.488			
Preoperative nutrition	1.746	0.614–4.959	0.296			
Emergency operation	2.623	1.321–5.206	0.006			
Open laparotomy (vs. laparoscopic approach)	4.336	2.284–8.232	<0.001	3.906	1.912–7.937	<0.001
Stapled anastomosis			0.165			
Body mass index ≤18.5 kg/m^2	0.957	0.516–1.773	0.888			
Hemoglobin ≤12.5 g/dL	0.489	0.235–1.016	0.055			
C-reactive protein >100 mg/dL	3.144	1.391–7.109	0.008			
Prognostic nutrition index ≤40	0.246	0.110–0.553	<0.001	2.754	1.140–6.649	0.024
Operation time >180 min	3.443	1.815–6.530	<0.001	2.986	1.451–6.143	0.003
Blood loss >300 mL	3.022	1.579–5.783	0.001			

CI, confidence interval; CDAI, Crohn's disease activity index; ASA, American Society of Anesthesiologists; Anti-TNF, anti-tumor necrosis factor; 5-ASA, aminosalicylates.

Supplementary Table 2. Univariable and Multivariable Analyses of Factors Associated with Surgical and Clinical Postoperative Recurrence-Free Survival

	Univariate			Multivariate		
	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Clinical recurrence-free survival						
Female	1.159	0.810–1.656	0.420			
Age	0.992	0.976–1.007	0.297			
Hypertension	0.830	0.387–1.778	0.632			
Diabetes mellitus	1.260	0.572–2.806	0.564			
CDAI	1.001	0.998–1.003	0.715			
Early onset (A1)	1.292	0.807–2.069	0.286			
Colonic involvement (L2 and L3)	0.917	0.649–1.294	0.621			
Penetrating behavior (B3)	0.964	0.678–1.372	0.839			
ASA score >2	1.218	0.739–2.006	0.439			
Perianal lesion	1.473	1.043–2.080	0.028	1.397	0.987–1.976	0.059
Smoking history	1.191	0.763–1.858	0.443			
Preoperative medical treatment						
Anti-TNF	1.102	0.733–1.658	0.641			
5-ASA	1.156	0.735–1.818	0.531			
Steroid	1.013	0.675–1.519	0.952			
Immunomodulator	0.999	0.708–1.410	0.997			
Antibiotics	0.964	0.637–1.459	0.861			
Preoperative nutrition	0.672	0.308–1.482	0.320			
Emergency operation	0.987	0.645–1.509	0.951			
Open laparotomy (vs. laparoscopic approach)	0.911	0.641–1.295	0.631			
Stapled anastomosis	1.053	0.746–1.488	0.768			
Body mass index ≤18.5 kg/m^2	1.001	0.703–1.426	0.996			
Hemoglobin ≤12.5 g/dL	0.890	0.704–1.313	0.558			
C-reactive protein >100 mg/dL	1.019	0.594–1.749	0.946			
Prognostic nutrition index ≤40	0.725	0.495–1.061	0.098			
Operation time >180 min	0.971	0.686–1.374	0.867			
Blood loss >300 mL	1.046	0.703–1.551	0.829			
Infectious complication	1.431	0.980–2.090	0.064	1.407	0.962–2.057	0.078
Surgical recurrence-free survival						
Female	1.475	0.716–3.039	0.293			
Age	0.986	0.952–1.021	0.415			
Hypertension	0.572	0.078–4.205	0.583			
Diabetes mellitus	1.047	0.141–7.755	0.964			
CDAI	1.000	0.994–1.006	0.950			
Early onset (A1)	1.405	0.573–3.443	0.458			
Colonic involvement (L2 and L3)	1.516	0.736–3.122	0.259			
Penetrating behavior (B3)	0.741	0.346–1.586	0.440			
ASA score >2	0.829	0.250–2.750	0.760			
Perianal lesion	1.809	0.870–3.764	0.113			
Smoking history	1.109	0.421–2.923	0.835			
Preoperative medical treatment						
Anti-TNF	0.554	0.192–1.600	0.275			
5-ASA	0.829	0.286–2.400	0.729			
Steroid	1.719	0.814–3.629	0.156			
Immunomodulator	0.273	0.111–0.668	0.005	0.271	0.111–0.664	0.004
Antibiotics	1.756	0.820–3.758	0.147			
Preoperative nutrition	2.314	0.784–4.061	0.108			
Emergency operation	0.989	0.404–2.420	0.981			
Open laparotomy (vs. laparoscopic approach)	2.084	0.982–4.425	0.056			
Stapled anastomosis	0.933	0.453–1.921	0.850			
Body mass index ≤18.5 kg/m^2	0.975	0.464–2.051	0.947			
Hemoglobin ≤12.5 g/dL	0.659	0.269–1.616	0.362			
C-reactive protein >100 mg/dL	1.520	0.579–3.989	0.395			
Prognostic nutrition index ≤40	0.500	0.204–1.224	0.129			
Operation time >180 min	1.002	0.487–2.062	0.999			
Blood loss >300 mL	1.060	0.471–2.386	0.888			
Infectious complication	2.188	1.052–4.547	0.036	2.217	1.064–4.617	0.034

CI, confidence interval; CDAI, Crohn's disease activity index; ASA, American Society of Anesthesiologists; anti-TNF, Anti-tumor necrosis factor; 5-ASA, aminosalicylates.