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Original Article

Incidence, Risk Factors, and Outcomes of Chronic Antibiotic-Refractory Pouchitis in Korean Patients with Ulcerative Colitis

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Background/Aims: The study investigated the incidence, risk factors, and clinical outcomes of chronic antibiotic-refractory pouchitis (CARP) in Korean patients with ulcerative colitis (UC).

Methods: This single-center retrospective study included patients with UC who underwent total proctocolectomy with ileal pouch-anal anastomosis at the Asan Medical Center in Korea between January 1987 and December 2022. The primary outcomes were endoscopic remission and pouch failure. The Cox's proportional hazard model was used to identify the risk factors for CARP.

Results: The clinical data of 232 patients were analyzed. The most common cause of surgery was steroid refractoriness (50.9%), followed by dysplasia/colorectal cancer (26.7%). Among 74 patients (31.9%) with chronic pouchitis (CP), 31 (13.4%) had CARP, and 43 (18.5%) had chronic antibiotic-dependent pouchitis (CADP). The most frequent endoscopic phenotype was focal inflammation of the pouch (CP, 47.3%; CARP, 35.5%; CADP, 55.8%). Patients with CARP were less likely to use concomitant probiotics than patients with CADP (29.0% vs 72.1%, p<0.01). The endoscopic remission rate of CP, CARP, and CADP was 14.9%, 9.7%, and 18.6%, respectively. The pouch failure rate associated with CP, CARP, and CADP was 13.5%, 16.1%, and 11.6%, respectively. Current smoking status (adjusted hazard ratio [aHR], 2.96; 95% confidence interval [CI], 1.27 to 6.90; p=0.01) and previous use of biologics/small molecules (aHR, 2.40; 95% CI, 1.05 to 5.53; p=0.04) were significantly associated with CARP development.

Conclusions: UC patients who were current smokers and previously used biologics/small molecules had a higher risk of developing CARP. Concomitant use of probiotics was less likely to be associated with CARP development. **(Gut Liver, 2025;19:388-397)**

Key Words: Ulcerative colitis; Pouchitis; Proctocolectomy, Restorative; Korea

INTRODUCTION

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is a standard surgical procedure for medically refractory ulcerative colitis (UC), which occurs in about 10% to 30% of total UC patients in long-term follow-up.[1,2] Unfortunately, up to 80% of patients who undergo IPAA remain at risk of developing inflammation of the pouch, termed pouchitis.[3,4] Pouchitis has variable clinical presentations, from asymptomatic disease to increased stool frequency, abdominal pain, fecal urgency, and incontinence.[5] Pouchitis can be classified into acute or chronic pouchitis (CP) with a cutoff of 4 weeks of persistent symptoms despite standard antibiotic therapy and about 5% to 19% of patients with acute pouchitis develop CP.[6-8] Moreover, CP can be divided into antibiotic-dependent or antibiotic-refractory types on the basis of responses to standard antibiotic treatment. For chronic antibiotic-refractory pouchitis (CARP), which has no favorable response to antibiotic therapy, clinicians have used anti-inflammatory therapies such as 5-aminosalicylic acid (5-ASA), steroids, immunomodulators, or biologic/small molecules.[9,10]

Even though the remarkable development of many biologics and small molecule agents for patients with UC has reduced the rate of proctocolectomy with IPAA, the incidence rate of pouchitis within the first 2 years after IPAA has increased by 15% over 22 years in Western countries.[11-13] Moreover, in the United States, patients with pouchitis spent more than USD 21,617 during the second year after IPAA than patients without pouchitis.[14] Therefore, in order to reduce the significant clinical and economic burden of pouchitis, many studies have investigated optimal treatments for pouchitis, especially CARP, using biologics or small molecules.[15-18] However, data and reports on CARP are still lacking in Asian populations. Therefore, we conducted this study to investigate the incidence, risk factors, and clinical outcomes of CARP in Korean patients with UC.

MATERIALS AND METHODS

1. Study design and population

We conducted a retrospective cohort study of patients diagnosed with UC and who underwent total proctocolectomy with IPAA at the Asan Medical Center in South Korea from January 1987 to December 2022. CP, chronic antibiotic-dependent pouchitis (CADP), and CARP were defined according to the consensus guidelines from the International Ileal Pouch Consortium. CP refers to pouchitis with persistent symptoms despite 4 weeks of conventional antibiotic therapy. CADP refers to pouchitis with symptomatic or endoscopic response to conventional antibiotic treatment but with more than four recurrences in a year requiring persistent antibiotics. CARP refers to pouchitis without any response to conventional antibiotic treatment and needing prolonged (>4 weeks) 5-ASA, steroids, immunomodulators, or biologics/small molecules.[19] The exclusion criteria were as follows: (1) patients younger 18 years of age; (2) patients who had IPAA for other conditions except for UC; (3) patients diagnosed with Crohn's disease before surgery or based on the histology of a colectomy specimen; (4) patients using anti-inflammatory therapy due to other diseases such as pyoderma, ankylosing spondylitis, or rheumatoid arthritis rather than pouchitis; or (5) patients who had insufficient medical records.

2. Variables

Demographic, clinical, and endoscopic variables were collected from the medical records of patients at the time of diagnosis of UC, at the time of surgery, and at the time of diagnosis of pouchitis. The data included age, sex, body mass index, smoking habits, indication for IPAA (steroid refractory/acute fulminant colitis, steroid dependent, dysplasia/colorectal cancer, obstruction, perforation, toxic megacolon, or massive hemorrhage), stage of surgery, anastomosis type, previous usage of 5-ASA, systemic corticosteroids, immunosuppressants, and biologics/small molecules at least once for the treatment of UC, Mayo score, partial Mayo score, disease extent of UC according to Montreal classification, extraintestinal manifestations (primary sclerosing cholangitis, arthralgia, pyoderma gangrenosum, erythema nodosum and others), preoperative *Clostridioides difficile* infection and cytomegalovirus infection, endoscopic phenotype of pouchitis according to Chicago classification, treatment of pouchitis, and laboratory values (white blood cells, hemoglobin, serum albumin, C-reactive protein, erythrocyte sedimentation rate, and others).[20,21]

3. Outcomes

Treatment outcomes of pouchitis vary among reported studies, ranging from improvement of symptoms to endoscopic or histological responses.[22] Unfortunately, due to the retrospective design of our study, a unified clinical symptom assessment was difficult. Therefore, we decided that pouch failure and endoscopic remission of CARP would be the primary outcomes. Pouch failure was defined as a requirement of diverting loop ileostomy with or without pouch excision for any reasons until the last follow-up date.[19] Endoscopic remission was defined as a sustained complete mucosal healing state of pouchitis without any edema, granularity, friability, loss of vascular pattern, mucus exudates, or ulceration on the pouch, which were the components of the endoscopic criteria in Pouchitis Disease Activity Index, for at least 1 year.[23] Secondary outcomes included incidence, therapeutic strategy, and risk factors of CARP. In addition, we also calculated the incidence of *de novo* Crohn's disease, which was defined as a change in diagnosis from UC to Crohn's disease after pouch creation with the presence of inflammation, fibrostenosis, and/or fistulas beyond the pouch body, afferent limb, small bowel, and perianal area.[24]

4. Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences version 29.0 (IBM Corp., Armonk, NY, USA). Categorical variables were described as numbers and percentages, and continuous variables were described as means with standard deviations or medians with interquartile range (IQR). The Student t-test or Mann-Whitney U-test for continuous variables and the chi-square or Fisher exact tests for categorical variables were used to evaluate risk factors of CARP in the CP popu-

lation. We also performed a multivariable Cox proportional hazard model with backward elimination to identify risk factors for CARP in the IPAA population, entering variables with p-values <0.1 in the Cox univariate analysis. The Kaplan-Meier analysis was used to evaluate the cumulative risk of CP, CADP, and CARP development. All tests were two-tailed, and p-values <0.05 were considered statistically significant.

5. Ethics statement

This study was approved by the Institutional Review Board of the Asan Medical Center (approval number: 2023-0759). Informed consent from patients was waived due to the retrospective setting.

RESULTS

1. Patient characteristics

A total of 251 patients with UC undergoing IPAA at our institution were included and 232 patients were finally analyzed in this study, excluding six patients who were under 18 years of age and 13 patients who had no visit after IPAA (Fig. 1). Demographic data and baseline characteristics of patients at the time of surgery are reported in Table 1. We compared the baseline characteristics between patients with CP and those without. Patients who developed CP had an earlier diagnosis of UC (median age, 33.5 years vs 38.0 years, p=0.01) and earlier surgical treatment for UC (median age, 39.0 years vs 46.0 years, p=0.01) compared with patients without CP. However, the time from UC diagnosis to surgery was not statistically different (median age, 4.0 years, p=0.81). The CP group had lower rate of dysplasia/colorectal cancer for surgery (14.9% vs 32.3%, p=0.01), higher rate of previous use of systemic corticosteroids (93.2% vs 82.3%, p=0.03), and higher rate of extraintestinal manifestation of arthralgia (5.4% vs 0.6%, p=0.05) compared with patients without CP. Moreover, the CP group had more current smokers (20.3% vs 10.1%, p=0.04) and fewer past smokers (17.6% vs 29.7%, p=0.01) compared with the non-CP group. However, both groups had a similar sex ratio, body mass index, stages and anastomosis type in surgery, previous use of biologics/small molecules, immunosuppressants, and 5-ASA, Mayo score, disease extent, preoperative cytomegalovirus infection, and baseline laboratory values (Table 1).

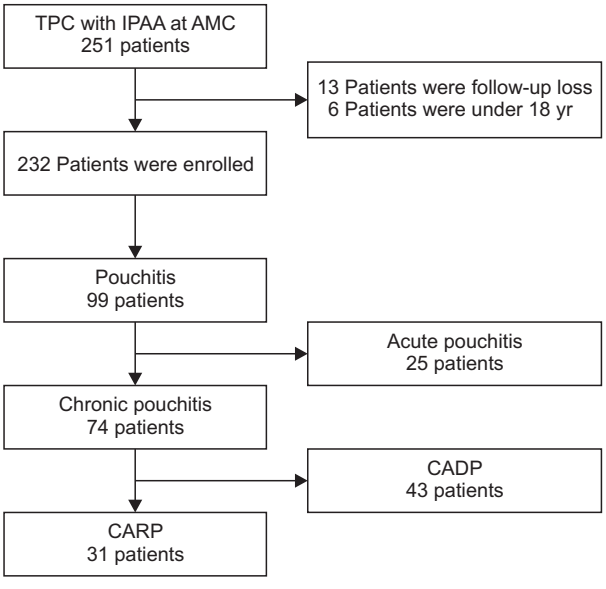

Fig. 1. Patient flow diagram. TPC, total proctocolectomy; IPAA, ileal pouch-anal anastomosis; AMC, Asan Medical Center; CADP, chronic antibiotic-dependent pouchitis; CARP, chronic antibiotic-refractory pouchitis.

2. Clinical outcomes and incidence of CP

Clinical data and outcomes of CP, CADP, and CARP are shown in Table 2. Among 232 patients, 74 (31.9%) developed CP with a median time of 48 months (IQR, 23.5 to 100.0 months), 43 (18.5%) developed CADP with a median time of 40 months (IQR, 24.5 to 75.5 months), and 31 (13.4%) developed CARP with a median time of 61 months (IQR, 24.0 to 106.0 months). All patients with CP were classified into CADP or CARP groups. Focal inflammation of the pouch was the most common endoscopic phenotype according to the Chicago classification in all groups (CP, n=35, 47.3%; CARP, n=11, 35.5%; CADP, n=24, 55.8%). Due to the chronicity of the disease, multiple antibiotics were used for CADP treatment. The most frequently used antibiotics for CADP were ciprofloxacin (n=36, 83.7%), followed by metronidazole (n=22, 51.2%). Other antibiotics such as moxifloxacin, meropenem, and imipenem were used in patients with severe pouch complications (n=5, 11.6%). In contrast to CADP treatment, 5-ASAs, systemic corticosteroids, immunomodulators, and biologics/small molecules were prescribed to 25 (80.6%), 16 (51.6%), 11 (35.5%), and nine (29.0%) patients with CARP, respectively. Among nine patients with biologics/small molecules, eight patients (25.8%) received tumor necrosis factor-α antagonists and one patient (3.2%) received ustekinumab.

For the primary outcomes, after a median follow-up of 99.0 months (IQR, 44.8 to 164.5 months), of 74 patients with CP, 10 (13.5%) had pouch failure and 11 (14.9%) achieved endoscopic remission. Among 31 patients with CARP, five (16.1%) had pouch failure and three (9.7%) had endoscopic remission after a median follow-up of 55.0 months (IQR, 21.0 to 99.0 months). Among 43 pa-

Table 1. Baseline Patient Characteristics

Characteristic	Total (n=232)	Chronic pouchitis (n=74)	Without chronic pouchitis (n=158)	p-value
Age at diagnosis of UC, yr	37.0 (27.0–46.0)	33.5 (23.8–41.3)	38.0 (28.8–47.0)	0.01
Age at surgery, yr	44.0 (32.3–54.0)	39.0 (29.8–49.3)	46.0 (35.8–56.0)	0.01
Time from UC diagnosis to surgery, yr	4.0 (1.0–11.0)	4.0 (2.0–10.3)	4.0 (1.0–12.0)	0.81
Male sex	133 (57.3)	40 (54.1)	93 (58.9)	0.49
Body mass index, kg/m^2	20.7 (18.3–23.0)	20.4 (17.8–22.4)	20.8 (18.7–23.1)	0.10
Smoking				
Current	31 (13.4)	15 (20.3)	16 (10.1)	0.04
Past	60 (25.9)	13 (17.6)	47 (29.7)	0.01
Non-smoker	141 (60.8)	46 (62.2)	95 (60.1)	0.10
Surgery indication				
Steroid refractory/acute fulminant colitis	118 (50.9)	44 (59.5)	74 (46.8)	0.15
Steroid dependent	30 (12.9)	13 (17.6)	17 (10.8)	0.54
Dysplasia/colorectal cancer	62 (26.7)	11 (14.9)	51 (32.3)	0.01
Obstruction	4 (1.7)	2 (2.7)	2 (1.3)	0.61
Perforation	10 (4.3)	3 (4.1)	7 (4.4)	0.65
Toxic megacolon	5 (2.2)	1 (1.4)	4 (2.5)	0.45
Massive hemorrhage	3 (1.3)	0	3 (1.9)	-
Stages of surgery				
1	11 (4.7)	5 (6.8)	6 (3.8)	0.40
2	206 (88.8)	66 (89.2)	140 (88.6)	0.36
3	15 (6.5)	3 (4.1)	12 (7.6)	0.17
Anastomosis type				0.91
Stapled	184 (79.3)	59 (79.7)	125 (79.1)	
Hand sewn	48 (20.7)	15 (20.3)	33 (20.9)	
Previous use of biologics/small molecules	55 (23.7)	16 (21.6)	39 (24.7)	0.81
TNF-α inhibitor	50 (21.6)	14 (18.9)	36 (22.8)	0.41
Vedolizumab	8 (3.4)	4 (5.4)	4 (2.5)	0.50
Tofacitinib	4 (1.7)	2 (2.7)	2 (1.3)	1.00
Previous use of immunosuppressants	92 (39.7)	30 (40.5)	62 (39.2)	0.85
Previous use of systemic corticosteroids	199 (85.8)	69 (93.2)	130 (82.3)	0.03
Previous use of 5-ASAs	194 (83.6)	63 (85.1)	131 (82.9)	0.36
Oral	187 (80.6)	59 (79.7)	128 (81.0)	0.75
Topical (suppository)	80 (34.5)	34 (45.9)	46 (29.1)	0.16
Mayo score	8.0 (3.0–10.3)	8.0 (6.0–10.0)	8.0 (2.0–11.0)	0.15
Partial Mayo score	6.0 (2.0–8.0)	5.5 (4.0–7.0)	6.0 (1.5–8.0)	0.23
Disease extent by Montreal classification				
Proctitis (E1)	2 (0.8)	0	2 (1.3)	-
Left-sided colitis (E2)	22 (9.5)	6 (8.1)	16 (10.1)	0.61
Extensive colitis (E3)	208 (89.7)	68 (91.9)	140 (88.6)	0.88
Extraintestinal manifestations	19 (8.2)	10 (13.5)	9 (5.7)	0.20
Primary sclerosing cholangitis	8 (3.4)	5 (6.8)	3 (1.9)	0.07
Arthralgia	5 (2.2)	4 (5.4)	1 (0.6)	0.05
Pyoderma gangrenosum	2 (0.8)	0	2 (1.3)	-
Erythema nodosum	2 (0.8)	1 (1.4)	1 (0.6)	0.56
Others	2 (0.8)	0	2 (1.3)	-
Preoperative *Clostridioides difficile* infection	5 (2.2)	0	5 (3.2)	-
Preoperative CMV infection	45 (19.4)	12 (16.2)	33 (20.9)	0.40
Baseline laboratory values				
White blood cells, /mm^3	8,500 (5,900–11,500)	9,350 (6,325–11,950)	8,150 (5,700–13,500)	0.06
Hemoglobin, g/dL	11.0 (9.7–12.9)	11.6 (9.8–13.0)	11.0 (9.6–12.8)	0.64
Serum albumin, g/dL	3.1 (2.4–3.6)	3.0 (2.3–3.6)	3.1 (2.4–3.7)	0.29
ESR, mm/hr	36.0 (17.3–54.0)	30.0 (14.5–52.0)	43.0 (24.0–59.0)	0.12
Serum CRP, mg/dL	2.0 (0.5–5.6)	2.4 (0.6–6.7)	1.8 (0.4–5.2)	0.94

Data are presented as median (interquartile range) or number (%).

UC, ulcerative colitis; TNF, tumor necrosis factor; 5-ASA, 5-aminosalicylic acid; CMV, cytomegalovirus; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Table 2. Characteristics of Chronic Pouchitis

Characteristic	Chronic pouchitis (n=74)	CARP (n=31)	CADP (n=43)	p-value
Duration of follow-up, mo	99 (44.8–164.5)	55 (21.0–99.0)	121 (74.5–179.0)	
Age at diagnosis of chronic pouchitis, yr	47 (35.5–56.5)	46 (36.0–52.5)	47 (33.5–58.0)	0.89
Male sex	40 (54.1)	19 (61.3)	21 (48.8)	0.29
Time from IPAA to chronic pouchitis, mo	48 (23.5–100.0)	61 (24.0–106.0)	40 (24.5–75.5)	0.07
Chicago classification				0.25
Afferent limb involvement	9 (12.2)	6 (19.4)	3 (7.0)	
Diffuse inflammation	17 (23.0)	8 (25.8)	9 (20.9)	
Focal inflammation	35 (47.3)	11 (35.5)	24 (55.8)	
Cuffitis	13 (17.6)	6 (19.4)	7 (16.3)	
Concomitant use of probiotics	40 (54.1)	9 (29.0)	31 (72.1)	<0.01*
Treatment				
Metronidazole			22 (51.2)	
Ciprofloxacin			36 (83.7)	
Other antibiotics (moxifloxacin, meropenem, imipenem)			5 (11.6)	
5-ASAs		25 (80.6)	3 (7.0)	
Systemic corticosteroids		16 (51.6)	4 (9.3)	
Immunomodulators		11 (35.5)		
Biologics/small molecules		9 (29.0)		
Pouch failure	10 (13.5)	5 (16.1)	5 (11.6)	0.73
Endoscopic remission	11 (14.9)	3 (9.7)	8 (18.6)	0.34
De novo Crohn's disease	5 (6.8)	5 (16.1)	-	

Data are presented as median (interquartile range) or number (%).
CARP, chronic antibiotic-refractory pouchitis; CADP, chronic antibiotic-dependent pouchitis; IPAA, ileal pouch-anal anastomosis; 5-ASA, 5-aminosalicylic acid.
*Odds ratio (95% confidence interval)=0.16 (0.06–0.44).

tients with CADP, five (11.6%) had pouch failure and eight (18.6%) had endoscopic remission after a median follow-up of 121.0 months (IQR, 74.5 to 179.0 months). However, five patients (2.2%) were finally diagnosed with *de novo* Crohn's disease after a median follow-up of 31.0 months (IQR, 29.0 to 51.0 months) and all five patients were from the CARP group.

Based on the Kaplan-Meier analysis, the cumulative incidence of CP was 4.8% (95% confidence interval [CI], 2.0% to 7.6%) at 1 year, 8.1% (95% CI, 4.4% to 11.6%) at 2 years, 21.3% (95% CI, 15.4% to 26.9%) at 5 years, and 35.0% (95% CI, 27.0% to 42.1%) at 10 years from the time of IPAA (Fig. 2A). The cumulative incidence of CARP was 2.2% (95% CI, 0.3% to 4.1%), 3.2% (95% CI, 0.8% to 5.4%), 8.0% (95% CI, 3.9% to 11.8%), and 16.4% (95% CI, 9.7% to 22.6%) at 1, 2, 5, and 10 years after IPAA, respectively (Fig. 2B), whereas 2.7% (95% CI, 0.5% to 4.8%), 5.1% (95% CI, 2.1% to 8.0%), 14.5% (95% CI, 9.4% to 19.4%), and 22.3% (95% CI, 15.2% to 28.7%) were the cumulative incidences of CADP at 1, 2, 5, and 10 years after IPAA, respectively (Fig. 2C).

3. Risk factors of CARP

Patients developing CARP were less likely to use concomitant probiotics compared with the CADP group (29.0% vs 72.1%, p<0.01) (Table 2). We defined the concomitant use of probiotics as prescribing probiotics with a standard antibiotic therapy for pouchitis treatment until the end of the study date. The most common probiotics used in our study were mixed bacteria cultures of *Lactobacillus rhamnosus*/*Lactobacillus helveticus*. However, endoscopic phenotypes according to the Chicago classification showed no significant difference between the CARP and CADP groups (p=0.25).

In a multivariable analysis of 232 patients with IPAA, current smoking status (adjusted hazard ratio, 2.96; 95% CI, 1.27 to 6.90; p=0.01) and previous usage of biologics/small molecules (adjusted hazard ratio, 2.40; 95% CI, 1.05 to 5.53; p=0.04) were significantly associated with CARP development (Table 3). Among 55 patients with previous usage of biologic/small molecules, 34 (61.8%) had surgery for steroid refractoriness, six (10.9%) had steroid dependency, 13 (23.6%) had dysplasia/colorectal cancer, and two (3.6%) had perforation, respectively. Age at UC diagnosis and previous usage of immunomodulators were associated with developing CARP on univariate analysis, but after multivariable analysis, this was not statistically significant.

DISCUSSION

To the best of our knowledge, this is the largest study

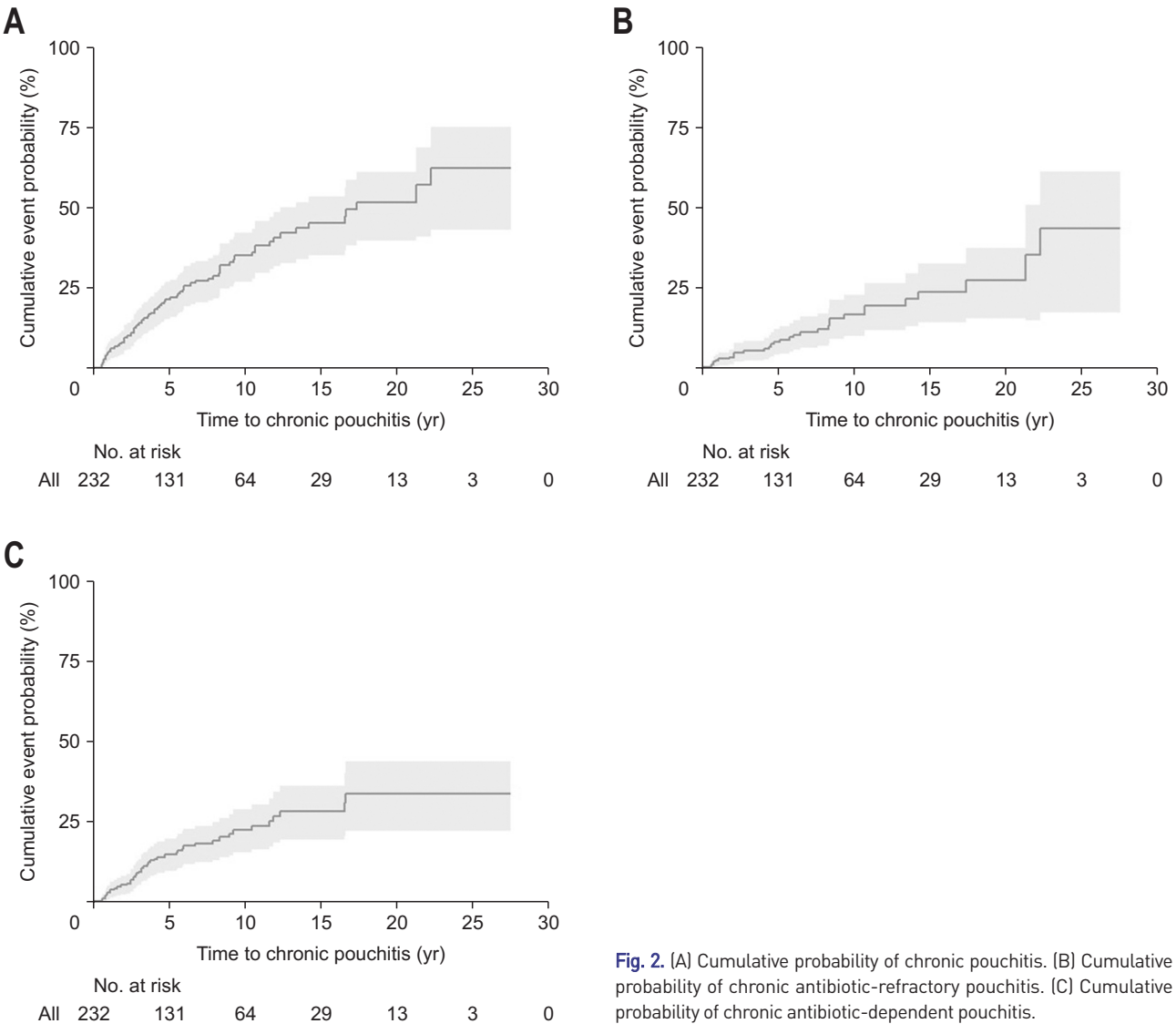

Fig. 2. (A) Cumulative probability of chronic pouchitis. (B) Cumulative probability of chronic antibiotic-refractory pouchitis. (C) Cumulative probability of chronic antibiotic-dependent pouchitis.

describing the incidence, risk factors, and clinical outcomes of CARP in Korean patients with UC. In our study population, the overall incidence rate of CARP was 13.4%, which is in line with previous studies.[25] The pouch failure rate for CARP was 16.1% and the endoscopic remission rate was 9.7% during a median follow-up of 4.6 years. Compared with the pooled pouch failure rate in IPAA (7.7% to 10.3%, a median follow-up of 5 to 10 years) and pouch failure rate in CADP (17.9%, a median follow-up of 6 years) in other studies, the pouch failure rate of our study seems much higher considering the short-term follow-up time.[22,26] This result suggests that CARP is a debilitating condition that can worsen a patient's quality of life in a short period. Moreover, our study showed a lower endoscopic remission rate compared with a previous study of vedolizumab treatment in CARP (13% to 15%) because various advanced therapies other than vedolizumab were included in our study population (25.8% with tumor necrosis factor-α antagonists; 3.2% with ustekinumab).[27] Therefore, further studies with a larger population comparing endoscopic outcomes of each treatment strategy in CARP are needed to develop an optimized therapy for CARP.

To the best of our knowledge, this is the first study to report the cumulative probability of CARP using Kaplan-Meier analysis. There are numerous prior reports about the cumulative incidence of CP and the 5-year cumulative incidence of CP in our study (21.3%) lies within the highest range of recent studies.[28,29] However, there is little published data on CARP. We calculated the cumulative incidence of CARP was 8.0% and 16.4% at 5 and 10 years after IPAA, which demonstrates the alarming risk and high prevalence of CARP over time.

Our study also provided new information showing that the previous usage of biologics/small molecules is a risk

Table 3. Factors Associated with Chronic Antibiotic-Refractory Pouchitis

Factor	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	aHR (95% CI)	p-value
Female sex	0.72 (0.35–1.49)	0.38		
Age at UC diagnosis	0.97 (0.95–1.00)	0.09	0.97 (0.94–1.00)	0.10
Body mass index	0.93 (0.83–1.03)	0.16		
Smoking				
Non-smoker	Reference	0.01		
Current	3.27 (1.43–7.49)	0.01	2.96 (1.27–6.90)	0.01
Past	0.77 (0.25–2.31)	0.64	0.82 (0.25–2.63)	0.73
Family history of IBD	0.56 (0.20–1.61)	0.28		
Stage of surgery				
1	Reference	0.86		
2	0.83 (0.24–2.84)	0.76		
3	0.53 (0.05–5.15)	0.58		
Anastomosis type				
Staple				
Hand sewn	0.75 (0.30–1.83)	0.52		
Previous use of biologics/small molecules	2.52 (1.09–5.81)	0.03	2.40 (1.05–5.53)	0.04
Previous use of systemic steroids	1.60 (0.38–6.78)	0.52		
Previous use of immunomodulators	2.12 (1.00–4.48)	0.04	1.52 (0.65–3.53)	0.34
Previous use of 5-ASA	Reference	0.33		
Oral	0.97 (0.35–2.73)	0.95		
Topical	0.82 (0.10–7.04)	0.85		
Both	1.94 (0.67–5.62)	0.22		
Mayo score	1.02 (0.91–1.13)	0.76		
Partial Mayo score	1.01 (0.88–1.17)	0.88		
Disease extent by Montreal classification				
Proctitis (E1) and left-sided colitis (E2)	Reference			
Extensive colitis (E3)	1.78 (0.40–7.99)	0.45		
EIM	Reference	0.22		
PSC	1.94 (0.46–8.20)	0.37		
Arthralgia	6.81 (1.55–29.98)	0.11		
Preoperative CMV infection	1.14 (0.43–3.03)	0.79		

HR, hazard ratio; CI, confidence interval; aHR, adjusted HR; UC, ulcerative colitis; IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylic acid; EIM, extraintestinal manifestations; PSC, primary sclerosing cholangitis; CMV, cytomegalovirus.

factor for CARP development in South Korea. Although several previous studies have evaluated IPAA-related complications in Korean patients, those studies were mostly conducted when a variety of biologics/small molecules were not introduced to the South Korean market.[30-32] However, our study was conducted in the recent biologic era and over a long-term study period, which enabled the enrollment of a high proportion of patients (23.7%) with previous use of biologics/small molecules. Therefore, gastroenterologists and surgeons in Korea should to be more aware of the risk of developing CARP after total colectomy with IPAA for patients who previously treated with biologics/small molecules.

Many previous studies have reported several contributing factors to pouchitis development.[33] Smoking is a well-known protective factor for UC; therefore, the relationship between smoking status and pouchitis development is of interest. Shen *et al.*[34] reported that never-smokers had a significantly higher rate of pouchitis development after IPAA. However, a recent retrospective study and meta-analysis reported that active smoking status does not seem to prevent the development of pouchitis.[35,36] Our results, which revealed current smoking status was a risk factor for CARP development, reinforced these results. Unlike many other previous studies, our study failed to show a significant association between extraintestinal manifestations including primary sclerosing cholangitis and CARP development. This may be due to the low prevalence rates of primary sclerosing cholangitis among Asian inflammatory bowel disease patients and a relatively small number of patients with extraintestinal manifestations in our population (8.2%) compared with other studies (18.0% to 27.1%).[28,37,38]

In addition, our study suggests that the concomitant use of probiotics reduced the risk of CARP development among CP patients. Microbial dysbiosis is known to be one of the major mechanisms for developing pouchitis and

the benefit of probiotics for the treatment of pouchitis was previously demonstrated.[39-41] However, the recent American Gastroenterological Association guidelines make no recommendation for using probiotics as a treatment for pouchitis due to the lack of evidence. Instead, American Gastroenterological Association recommends using prophylactic probiotics to prevent recurrent pouchitis in patients with CADP.[42] A recent study exploring the species and functions of the microbiome in the pouch proved that dysbiosis of the normal pouch already resembles the microbial signature of Crohn's disease, rather than that of UC, and the similarities with Crohn's disease seem to be more evident in patients with pouchitis.[43] These data emphasize the clinical burden of dysbiosis in pouchitis and some recent studies have tried to overcome this microbial burden with fecal microbiota transplantation.[44,45] Even though the precise impact of probiotics on dysbiosis is still controversial, our results reinforce the importance of managing dysbiosis in CP. However, because of the small CP population sample size in our study, we were unable to draw a meaningful conclusion in a multivariable analysis. Therefore, a further large-scale study with multivariable analysis among the CP population is needed to confirm our results.

We acknowledge that our study had several limitations. First, we conducted a retrospective single-center study, which might lead to potential referral or selection bias. Even though our medical center is the largest inflammatory bowel disease center in South Korea, a high proportion of patients in our center often have diseases that are difficult to manage. This might not reflect general situations in community gastroenterology practices. Moreover, due to the retrospective design of our study, it was hard to obtain a detailed description of the risk factors including medical history of taking nonsteroidal anti-inflammatory drugs, presence of anti-neutrophil cytoplasmic antibodies, and results of surgical biopsy. Therefore, a further large-scale study with a prospective design is essential to determine more detailed risk factors related to CARP development. Second, our study contained a relatively small sample size of CARP patients, which might lead to type II errors in statistical analyses. Moreover, due to the small number of patients in each treatment group with CARP, comparing the efficacy of each therapy was difficult. Third, to compare CADP and CARP, we included *de novo* Crohn's disease in the CP population. Even though CARP shares many similarities with *de novo* Crohn's disease, Crohn's disease is a different disease entity from UC. Therefore, further studies separating *de novo* Crohn's disease from CARP are needed to draw robust conclusions.

In conclusion, this study highlights the clinical characteristics and risk factors of CARP after total proctocolectomy with IPAA in Korean patients affected by UC. These results indicate the severity of CARP as well as current smoking status and previous exposure to biologics/small molecules as a risk factor and concomitant use of probiotics as a protective factor for developing CARP. Further multi-center studies with a larger population are needed to develop more appropriate preventive and therapeutic strategies for CARP.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: J.E.B., S.H.P. Data acquisition: J.E.B., J.B.P., J.H.B. Data analysis and interpretation: J.E.B., S.H.P. Drafting of the manuscript: J.E.B., S.H.P. Critical revision of the manuscript for important intellectual content: J.E.B., M.H.K., S.W.H., S.W.H., J.Y.L., Y.S.Y., D.H.Y., B.D.Y., J.S.B., S.J.M., C.S.Y., S.K.Y., S.H.P. Statistical analysis: J.E.B. Obtained funding; Administrative, technical, or material support; Study supervision: S.H.P. Final approval of the version to be submitted: all authors.

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