

Association of Perianal Fistulas with Clinical Features and Prognosis of Crohn's Disease in Korea: Results from the CONNECT Study

Jaeyoung Chun¹, Jong Pil Im¹, Ji Won Kim², Kook Lae Lee², Chang Hwan Choi³, Hyunsoo Kim⁴, Jae Hee Cheon⁵, Byoung Duk Ye⁶, Young-Ho Kim⁷, You Sun Kim⁸, Yoon Tae Jeon⁹, Dong Soo Han¹⁰, Won Ho Kim⁵, and Joo Sung Kim¹

¹Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, ²Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, ³Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, ⁴Department of Internal Medicine, Chonnam National University Medical School, Gwangju, ⁵Department of Internal Medicine, Yonsei University College of Medicine, ⁶Department of Internal Medicine, University of Ulsan College of Medicine, ⁷Department of Internal Medicine, Sungkyunkwan University School of Medicine, ⁸Department of Internal Medicine, Inje University College of Medicine, ⁹Department of Internal Medicine, Korea University College of Medicine, Seoul, and ¹⁰Department of Internal Medicine, Hanyang University College of Medicine, Guri, Korea

Background/Aims: The disease course and factors associated with poor prognosis in Korean patients with Crohn's disease (CD) have not been fully determined. The aim of this study was to explore potential associations between the clinical characteristics and long-term outcomes of CD and perianal fistulas in a Korean population. **Methods:** The retrospective Crohn's Disease Clinical Network and Cohort (CONNECT) study enrolled patients diagnosed with CD between July 1982 and December 2008 from 32 hospitals. Those followed for <12 months were excluded. Clinical outcomes were CD-related surgery and complications, including nonperianal fistulas, strictures, and intra-abdominal abscesses. **Results:** The mean follow-up period was 8.77 years (range, 1.0 to 25.8 years). A total of 1,193 CD patients were enrolled, of whom 465 (39.0%) experienced perianal fistulas. Perianal fistulizing CD was significantly associated with younger age, male gender, CD diagnosed at primary care clinics, and ileocolonic involvement. Both nonperianal fistulas ($p=0.034$) and intra-abdominal abscesses ($p=0.020$) were significantly more common in CD patients with perianal fistulas than in those without perianal fistulas. The rates of complicated strictures and CD-related surgery were similar between the groups. Independently associated factors of nonperianal fistulas were perianal fistulas ($p=0.015$), female gender ($p=0.048$), CD diagnosed at referral hospital ($p=0.003$), and upper gastrointestinal (UGI) involvement ($p=0.001$). Furthermore, perianal fistulas ($p=0.048$) and

UGI involvement ($p=0.012$) were independently associated with the risk of intra-abdominal abscesses. **Conclusions:** Perianal fistulas predicted the development of nonperianal fistulas and intra-abdominal abscesses in Korean CD patients. Therefore, patients with perianal fistulizing CD should be carefully monitored for complicated fistulas or abscesses. (**Gut Liver 2018;12:544-554**)

Key Words: Anal fistula; Crohn disease; Prognosis

INTRODUCTION

Crohn's disease (CD) is a chronic and relapsing inflammatory disorder characterized by transmural inflammation that occurs in the gastrointestinal tract.^{1,2} It has been recognized as an immune-mediated disease that can result in impaired quality of life and serious complications including fibrotic strictures, intestinal fistulas, and intra-abdominal abscesses.^{3,4} Although the pathogenesis of CD remains unclear, accumulating evidence suggests that complex interactions between genetic and environmental factors are closely related to the development and perpetuation of intestinal inflammation.⁵⁻⁷

Recently, the incidence and prevalence of CD have been increasing in East Asia.^{1,8} This could be due to environmental changes such as Westernization of diet and lifestyle.⁹ However, the genetic susceptibilities and epidemiological characteristics of CD in East Asians are thought to differ from those in Cau-

Correspondence to: Ji Won Kim

Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Korea

Tel: +82-2-870-2221, Fax: +82-2-870-3863, E-mail: kjwjor@snu.ac.kr

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Jaeyoung Chun and Jong Pil Im contributed equally to this work as first authors.

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casians. For example, nucleotide-binding oligomerization domain protein 2/caspase recruitment domain protein 15 (*NOD2/CARD15*) mutations, which are common genetic variants for susceptibility to CD in Caucasians,^{10,11} are reported to have no association with CD in Korean,¹² Japanese,¹³ and Chinese populations.¹⁴ Furthermore, East Asian CD patients have ileocolonic involvement more often than Caucasians.^{15,16} Because of the differences between East Asians and Caucasians in both genotypes and phenotypes of CD, it is important to define the specific clinical characteristics of Korean CD patients in order to select appropriate treatment strategies. However, the disease course and factors associated with poor prognosis for CD in Koreans have not been fully determined.

Perianal fistula is detected in up to 90% of CD patients with rectal involvement.¹⁷ Compared to Western countries, the prevalence of perianal complication is likely to be higher in East Asia, ranging from 30.3% to 58.8%.¹⁷ Perianal lesions present with a spectrum of clinical severity from asymptomatic to severe diseases requiring repeated surgical interventions with medical treatment including antibiotics and tumor necrosis factor (TNF)- α antagonists in patients with CD.¹⁸ In addition, perianal complications generally denote an aggressive and disabling phenotype of CD.¹⁹ However, the relationships between the presence of perianal fistula and the development of CD-related complications including nonperianal fistulas, strictures, or intra-abdominal abscesses remain unclear, particularly in East Asians. Thus, the aim of this study was to assess the clinical characteristics and long-term outcomes of CD in terms of potential associations with perianal fistulas in a Korean population.

MATERIALS AND METHODS

1. Study population

The Crohn's Disease Clinical Network and Cohort (CONNECT) study included patients diagnosed with CD between July 1982 and December 2008 from 32 hospitals in Korea.²⁰⁻²⁴ The aims of this retrospective multicenter cohort study were as follows: (1) to determine epidemiological and clinical characteristics by establishing a registered database of CD patients; (2) to establish a genetic research management system for CD patients; (3) to establish a network of patients and of doctors who specialize in the management of CD in the form of a private nonprofit organization; and (4) to develop Korean-specific diagnostic and therapeutic guidelines for CD.²⁰ All subjects were diagnosed and treated by inflammatory bowel disease (IBD) specialists who were members of the Korean Association for the Study of Intestinal Diseases. CD was diagnosed on the basis of clinical, radiological, endoscopic, and pathological criteria.^{15,25} Patients who were diagnosed with indeterminate colitis, intestinal tuberculosis, or intestinal Behçet's disease were excluded from this cohort. Patients with a follow-up period of <12 months or incomplete medical records were also excluded. This study was

approved by the institutional review boards at the participating medical centers.

2. Study protocol

The medical records of all subjects were reviewed at each participating hospital until May 2014. We evaluated demographic data and clinical characteristics including age at diagnosis, gender, family history of IBD, hospital where patients were diagnosed with CD, exposure to antituberculosis medication, disease location, history of perianal fistulas, medical therapy for CD, and disease-related complications (i.e., nonperianal fistulas, strictures, and intra-abdominal abscess formation) during follow-up of the cohort. Age at diagnosis and disease location were classified according to the revised Montreal classification.²⁶ Briefly, age at diagnosis (A1, ≤ 16 years; A2, 17–40 years; and A3, >40 years) and location criteria (L1, small bowel; L2, colon; L3, small bowel and colon; and L4, upper gastrointestinal [UGI] tract) were noted. With respect to perianal fistulas, the diagnosis was based on physical examination and endoscopic and/or radiological findings.²⁷ The detection time of perianal fistulas was also collected.

Clinical outcomes were CD-related surgery and complications including nonperianal fistulas, strictures, and intra-abdominal abscesses. Nonperianal fistulas (Montreal classification B3) were defined as the development of enteroenteric, enterovesical, or enterocutaneous fistulas.^{26,28} Strictures (Montreal classification B2) were defined as the occurrence of constant luminal narrowing demonstrated by radiological, endoscopic, and/or pathological findings.^{26,28} The detection of strictures required obstructive signs/symptoms or prestenotic dilatation. Intra-abdominal abscesses were defined as extraintestinal fluid collection located in the peritoneal cavity, abdominal wall, or subphrenic region.²⁹ Abscess formation located in the anal region was excluded. CD-related surgery was defined as intestinal resection for medical refractoriness and/or complications of CD except perianal lesions. Time to the first occurrence of each outcome from diagnosis of CD was calculated in months.

3. Statistical analysis

Statistical analysis was performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Pearson chi-square test, Fisher exact test, and Student t-test were used, as appropriate, to calculate the statistical significance of the demographic and clinical variables, according to the presence and detection time of perianal fistulas. Rates of clinical outcomes including nonperianal fistulas, strictures, intra-abdominal abscesses and surgery were calculated with actuarial life tables. The Kaplan-Meier method was used to estimate the cumulative probability of clinical outcomes. Log-rank test was performed to determine the significance of perianal fistulas with respect to difference for each clinical outcome. Multivariable analysis with Cox proportional hazards models was performed to identify independent

associated factors for nonperianal fistulas and intra-abdominal abscesses. A p -value <0.05 was considered statistically significant.

RESULTS

1. Baseline demographic and clinical characteristics

We reviewed the medical records of 1,382 patients who were diagnosed with CD between July 1982 and December 2008 in this cohort. All subjects were ethnically Korean. We excluded 189 of these patients (13.7%) due to a follow-up duration of <12 months (75 patients) or incomplete medical records (114 patients). A total of 1,193 CD patients were finally enrolled in the study (Fig. 1).

The study population comprised 840 men (70.4%). The mean age at diagnosis of CD was 26.9 ± 11.9 years (range, 0 to 77 years). The mean follow-up period was 8.77 years (range, 1.0 to 25.8 years). At the discretion of the physicians, 280 patients (23.5%) received antituberculosis medication to differentiate intestinal tuberculosis from CD or because of a first impression of intestinal tuberculosis. Thirty patients (2.5%) had a family history of IBD. With regard to disease location, 733 patients (61.4%) had ileocolonic involvement at the time of diagnosis of CD. Concomitant UGI disease was detected in 281 patients (23.6%).

A total of 465 CD patients (39.0%) experienced perianal fistulas. Among them, perianal fistulas were detected before and after diagnosis of CD in 318 (68.4%) and 147 patients (31.6%), respectively. Among the 147 patients with perianal fistulas which were detected after diagnosis of CD, perianal fistulas were diagnosed after the occurrence of CD-related surgery and complications including nonperianal fistulas, strictures, and intra-abdominal abscesses in 15 (10.2%) and 11 patients (7.5%), respectively. Perianal fistulas were significantly associated with younger age at diagnosis ($p < 0.001$), male gender ($p = 0.043$), diagnosis of CD at primary care clinics ($p < 0.001$), and ileocolonic

involvement ($p < 0.001$) (Table 1). Patients with perianal fistulas after diagnosis of CD showed a female predominance ($p < 0.001$) and a higher proportion of CD diagnosed at referral hospital ($p = 0.012$) compared to those with perianal fistulas before diagnosis of CD (Supplementary Table 1).

2. Treatment and clinical outcomes of CD according to the presence of perianal fistulas

During the follow-up period, 748 patients (62.7%) received systemic corticosteroids for the treatment of CD. Azathioprine and 6-mercaptopurine were administered to 880 patients (73.8%), and TNF- α antagonists including infliximab and adalimumab were prescribed to 336 patients (28.2%). Rates of administration of 5-aminosalicylic acid (5-ASA), antibiotics, systemic corticosteroids, azathioprine/6-mercaptopurine, and TNF- α antagonist (infliximab) for the treatment of CD were significantly higher in patients with perianal fistulas than in those without perianal fistulas (Table 2). Moreover, patients who experienced perianal fistulas after diagnosis of CD showed significantly higher rates of antibiotics, topical corticosteroids, methotrexate, and TNF- α antagonist treatment compared to those with perianal fistulas before diagnosis of CD (Supplementary Table 2).

Nonperianal fistulas were found in 192 patients (16.1%) during the follow-up period. The median time to complicated nonperianal fistulas was 20 months (range, 0 to 202 months) from diagnosis of CD. Cumulative rates of nonperianal fistulas at 5, 10, and 15 years were 11.1%, 19.5%, and 22.3%, respectively (Fig. 2A). Stricture complications occurred in 338 patients (28.3%), and the median time to complicated strictures was 10 months (range, 0 to 273 months) from diagnosis of CD. Cumulative rates of complicated strictures at 5, 10, and 15 years were 21.2%, 32.1%, and 38.4%, respectively (Fig. 2B). Intra-abdominal abscesses were detected in 163 patients (13.7%), and the median time to intra-abdominal abscess formation was 21

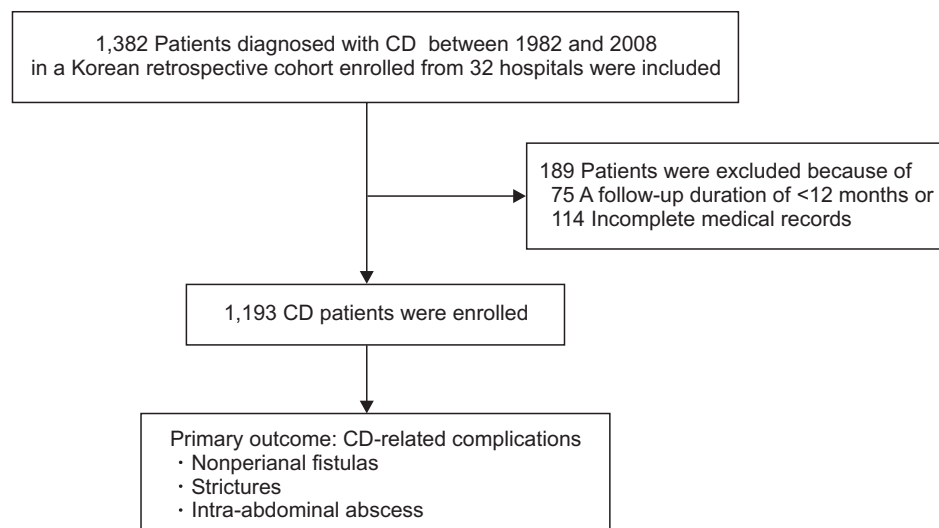


Fig. 1. Flowchart for patient selection. CD, Crohn's disease.

Table 1. Baseline Characteristics

Characteristics	Without perianal fistulas	With perianal fistulas	p-value
No. of patients	728 (61.0)	465 (39.0)	-
Age at diagnosis, yr	29.0±13.3	23.6±8.4	<0.001
Age at diagnosis (Montreal classification)*			<0.001
≤16 yr (A1)	76 (10.4)	69 (14.8)	
17–40 yr (A2)	521 (71.6)	377 (81.1)	
≥41 yr (A3)	131 (18.0)	19 (4.1)	
Male sex	497 (68.3)	343 (73.8)	0.043
Hospital where patients were diagnosed with CD			<0.001
Primary care clinic	111 (15.4)	131 (28.3)	
Referral hospital	602 (83.7)	332 (71.7)	
Overseas	6 (0.8)	0	
Anti-tuberculosis medication	171 (23.7)	109 (23.6)	0.985
Family history of IBD	16 (2.3)	14 (3.1)	0.382
Location of disease (Montreal classification)*			<0.001
Ileum (L1)	203 (27.9)	73 (15.7)	
Colon (L2)	107 (14.7)	68 (14.6)	
Ileocolon (L3)	409 (56.2)	324 (69.7)	
Concomitant UGI disease (L4)	185 (25.4)	96 (20.6)	0.058

Data are presented as number (%) or mean±SD.

CD, Crohn's disease; IBD, inflammatory bowel disease; UGI, upper gastrointestinal.

*Age at diagnosis and disease location was determined according to the revised Montreal classification.

Table 2. Perianal Fistulas and Treatment for Crohn's Disease

	Without perianal fistulas (n=728)	With perianal fistulas (n=465)	p-value
5-ASA	691 (97.3)	451 (99.1)	0.031
Antibiotics	364 (52.4)	327 (72.7)	<0.001
Topical corticosteroids	99 (13.8)	63 (13.9)	0.980
Systemic corticosteroids	436 (60.3)	312 (68.1)	0.007
Azathioprine/6-mercaptopurine	502 (69.0)	378 (81.3)	<0.001
Methotrexate	12 (1.7)	9 (1.9)	0.713
TNF- α antagonist	179 (24.6)	157 (33.8)	0.001
Infliximab	155 (21.3)	145 (31.2)	<0.001
Adalimumab	48 (6.6)	28 (6.0)	0.693

Data are presented as number (%).

5-ASA, 5-aminosalicylic acid; TNF- α , tumor necrosis factor- α .

months (range, 0 to 218 months) from diagnosis of CD. Cumulative rates of intra-abdominal abscess at 5, 10, and 15 years were 10.0%, 14.7%, and 20.2%, respectively (Fig. 2C). During the follow-up, 324 patients (27.2%) with CD underwent surgery for refractory disease and/or complications. The median time to

surgery was 4 months (range, 0 to 193 months) from diagnosis of CD. Cumulative rates of surgery at 5, 10, and 15 years were 21.7%, 30.3%, and 38.5%, respectively (Fig. 2D).

The clinical outcomes of CD according to the presence of perianal fistulas are shown in Table 3 and Fig. 3. Complicated nonperianal fistulas were significantly more common in patients with perianal fistulizing CD (18.9%) than in those without perianal fistulizing CD (14.3%) ($p=0.034$). Cumulative rates of nonperianal fistulas in patients with versus without perianal fistulizing CD were 12.7% versus 10.0%, 21.9% versus 17.8%, and 30.0% versus 23.9% at 5, 10, and 20 years, respectively (Fig. 3A). Furthermore, intra-abdominal abscess was detected more frequently in CD patients with perianal fistulas (16.6%) compared to those who had not experienced perianal fistulas (11.8%) ($p=0.020$). Cumulative rates of intra-abdominal abscess in patients with versus without perianal fistulizing CD were 11.2% versus 9.3%, 17.8% versus 12.4%, and 29.3% versus 21.8% at 5, 10, and 20 years, respectively (Fig. 3B). However, no significant difference was found in complicated strictures between CD patients with (30.1%) and without perianal fistulas (27.2%) ($p=0.564$). Cumulative rates of complicated strictures in patients with versus without perianal fistulizing CD were 22.3% versus 20.5%, 32.6% versus 31.8%, and 44.2% versus 49.8% at 5, 10, and 20 years, respectively (Fig. 3C). There was no significant difference in surgical rates between the two groups ($p=0.202$).

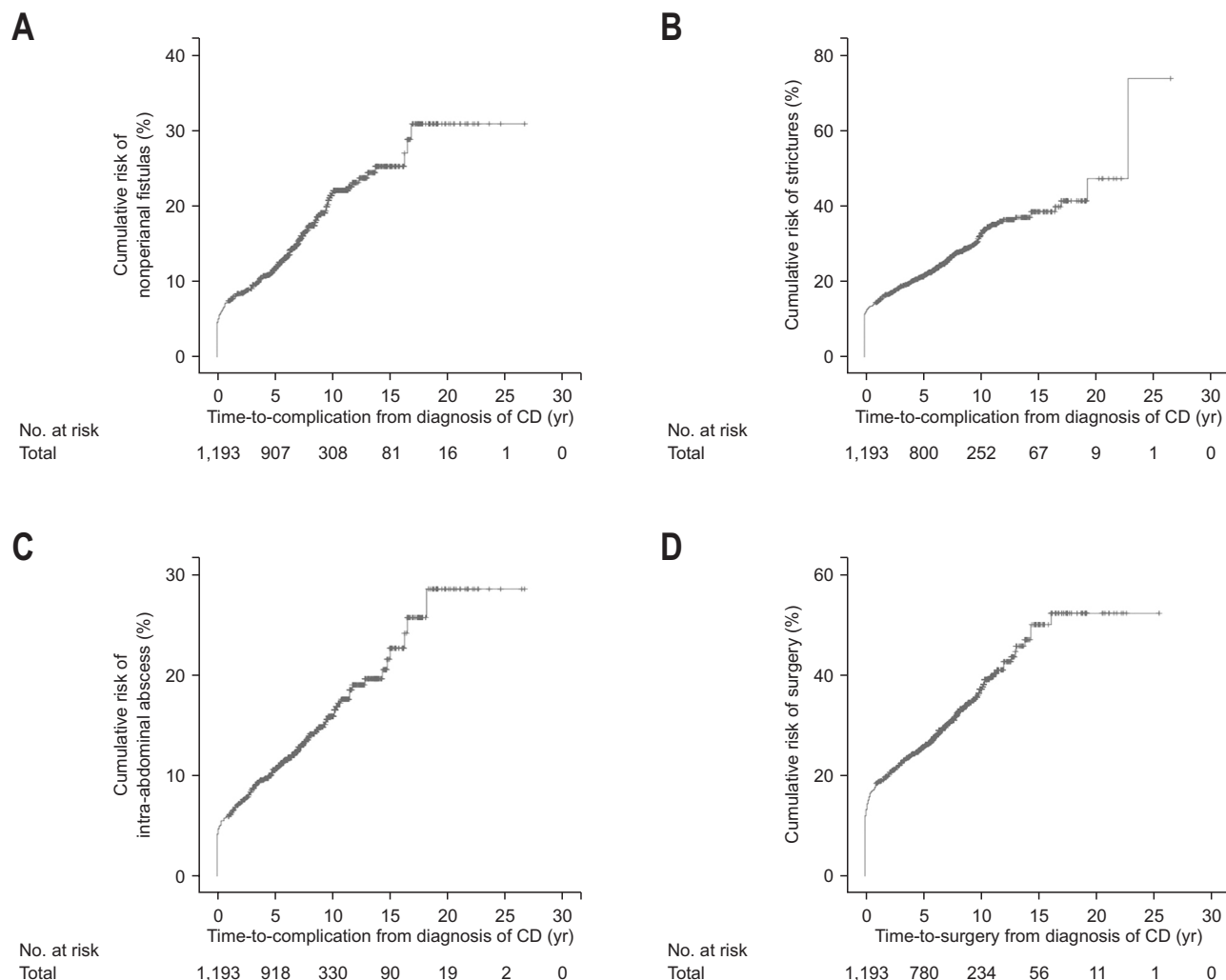


Fig. 2. Kaplan-Meier curves for clinical outcomes of Crohn's disease (CD). (A) Cumulative risks of complicated nonperianal fistulas, (B) intra-abdominal abscess formation, (C) complicated strictures, and (D) CD-related surgery.

Table 3. Perianal Fistulas and Clinical Outcomes of Crohn's Disease

	Without perianal fistulas (n=728)	With perianal fistulas (n=465)	p-value
CD-related complications			
Nonperianal fistulas	104 (14.3)	88 (18.9)	0.034
Strictures	198 (27.2)	140 (30.1)	0.564
Intra-abdominal abscess	86 (11.8)	77 (16.6)	0.020
CD-related surgery	202 (27.7)	122 (26.2)	0.202

Data are presented as number (%).
CD, Crohn's disease.

Cumulative rates of surgery in patients with versus without perianal fistulizing CD were 20.7% versus 22.5%, 29.1% versus 30.9%, and 36.1% versus 40.5% at 5, 10, and 15 years, respectively (Fig. 3D).

In terms of detection time of perianal fistulas, patients with

perianal fistulas after diagnosis of CD underwent surgery related to CD more frequently, compared to those with perianal fistulas before diagnosis of CD ($p=0.050$). However, no significant differences in CD-related complications between the two groups were found (Supplementary Table 3 and Supplementary Fig. 1).

3. Associated factors of nonperianal fistulas and intra-abdominal abscesses

Univariable analysis revealed that associated factors of complicated nonperianal fistulas were female gender ($p=0.046$), ileocolonic involvement ($p=0.011$), concomitant UGI involvement ($p=0.001$), and perianal fistulas ($p=0.034$). Multivariable analysis indicated that independent associated factors of nonperianal fistulas were perianal fistulas (adjusted hazard ratio [HR], 1.430; 95% confidence interval [CI], 1.072 to 1.908; $p=0.015$), female gender (adjusted HR, 1.341; 95% CI, 1.003 to 1.793; $p=0.048$), diagnosis of CD at a referral hospital (adjusted HR, 1.852; 95% CI, 1.227 to 2.796; $p=0.003$), and concomitant UGI involvement (adjusted HR, 1.655; 95% CI, 1.222 to 2.241, $p=0.001$) (Table 4).

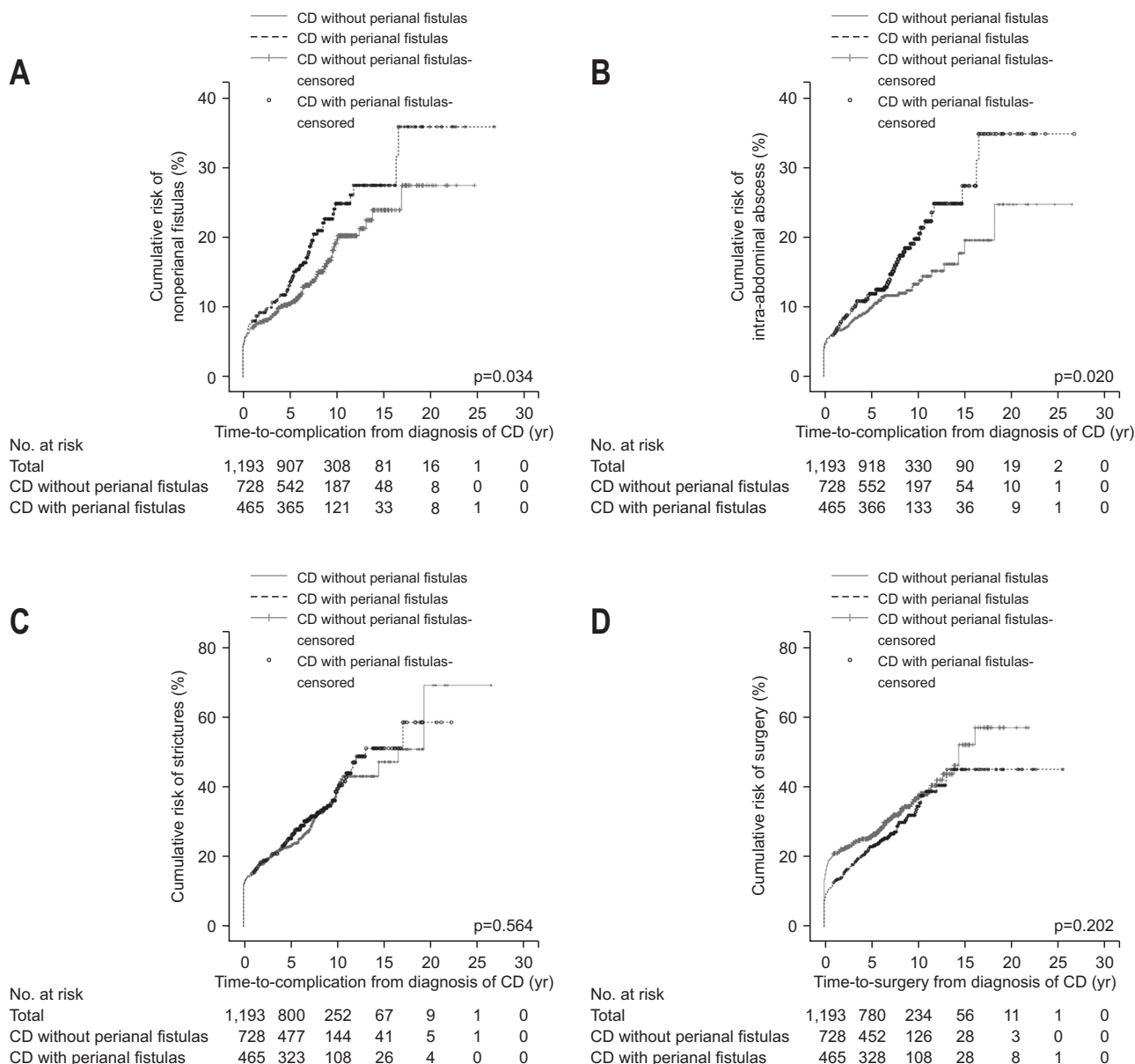


Fig. 3. Kaplan-Meier curves for clinical outcomes of Crohn's disease (CD) according to the presence of perianal fistula. (A) Cumulative risks of complicated nonperianal fistulas, (B) intra-abdominal abscess formation, (C) complicated strictures, and (D) CD-related surgery.

Univariable analysis revealed that associated factors of intra-abdominal abscess formation were 17 to 40 years of age (Montreal classification A2, $p=0.020$), concomitant UGI involvement ($p=0.028$), and perianal fistulas ($p=0.020$). Multivariable analysis showed that perianal fistulas (adjusted HR, 1.292; 95% CI, 1.005 to 1.748, $p=0.048$) and concomitant UGI involvement (adjusted HR, 1.510; 95% CI, 1.094 to 2.082; $p=0.012$) were independently associated with the risk of intra-abdominal abscesses. (Table 5).

DISCUSSION

In this large multicenter cohort study, patients with perianal

fistulizing CD were more likely to have experienced complications of nonperianal fistulas and intra-abdominal abscesses, but not strictures, than those without perianal fistulizing CD. To the best of our knowledge, this study was the first to investigate the relationships between perianal fistulizing CD and these disease-related complications in an Asian population. Our results are comparable with those of a population-based cohort study from Canada in which CD patients with perianal fistulas were at a 5-fold increased risk of nonperianal fistulas compared to those who had not had perianal fistulas.³⁰ In a multicenter study in the United States and Europe, there was also a significant association between perianal disease and intestinal fistulas, espe-

Table 4. Predictors of Nonperianal Fistula in the Study Population

Variable	Univariate analysis (log-rank test)		Multivariate analysis (Cox proportional hazard models)		
	%	p-value	Adjusted HR	95% CI	p-value
Age at diagnosis (Montreal classification)*		0.271	-	-	-
≤16 yr (A1)	17.2				
17-40 yr (A2)	16.8				
≥41 yr (A3)	10.7				
Sex		0.046			
Male	14.4		1 (reference)		
Female	20.1		1.341	1.003-1.793	0.048
Hospital where patients were diagnosed with CD		0.068			
Primary care clinic	11.2		1 (reference)		
Referral hospital	17.3		1.852	1.227-2.796	0.003
Overseas	16.7		4.393	0.214-19.027	0.489
Anti-tuberculosis medication		0.927	-	-	-
No	15.7				
Yes	17.1				
Family history of IBD		0.169	-	-	-
No	16.4				
Yes	6.7				
Location of disease (Montreal classification)*		0.011			
Ileum (L1)	14.1		1 (reference)		
Colon (L2)	8.6		0.627	0.353-1.113	0.111
Ileocolon (L3)	18.7		1.263	0.887-1.798	0.195
Concomitant UGI disease (L4)		0.001			
No	14.0		1 (reference)		
Yes	22.7		1.655	1.222-2.241	0.001
Perianal fistula		0.034			
No	14.3		1 (reference)		
Yes	18.9		1.430	1.072-1.908	0.015

HR, hazard ratio; CI, confidence interval; CD, Crohn's disease; IBD, inflammatory bowel disease; UGI, upper gastrointestinal.

*Age at diagnosis and disease location was determined according to the revised Montreal classification.

cially in CD patients with colonic disease.³¹ These findings suggest that perianal fistulas are highly associated with nonperianal fistulas in CD patients regardless of ethnicity, although perianal and nonperianal fistulas might represent distinct phenotypes with different behaviors.³⁰ In addition, perianal fistulizing CD was associated with the development of intra-abdominal abscess in the disease course, a finding that is consistent with the significant relationship between perianal and nonperianal fistulas found in this study.

We also found that the presence of perianal fistulas was an independent associated factor of the complications including nonperianal fistula and intra-abdominal abscess. To date, a few cohort studies have reported independent associated factors for CD-related complications including nonperianal fistulas, strictures, and intra-abdominal abscesses in Western countries. In a

single-center cohort study in France, anoperineal disease was a significant risk factor for fistulizing complications.³² By contrast, a population-based cohort study in the United States³³ showed that perianal disease at diagnosis of CD was not an independent risk factor for developing either stricturing or penetrating complications. However, this study did not investigate whether perianal disease could predict nonperianal fistulas alone in the study population. Considering the relationship between perianal and nonperianal fistulas reported by previous studies,^{30,31} the presence of perianal fistulas may be a good clinical indicator of complicated nonperianal fistulas and/or intra-abdominal abscesses in CD patients.

Some previous reports have demonstrated that perianal fistulizing CD is a risk factor for poor clinical outcome. In a multicenter randomized controlled trial of patients with active

Table 5. Predictors of Intra-abdominal Abscess in the Study Population

Variable	Univariate analysis (log-rank test)		Multivariate analysis (Cox proportional hazard models)		
	%	p-value	Adjusted HR	95% CI	p-value
Age at diagnosis (Montreal classification)*		0.020			
≤16 yr (A1)	9.0		1 (reference)		
17-40 yr (A2)	15.4		1.816	0.989-3.643	0.076
≥41 yr (A3)	8.0		1.153	0.544-2.444	0.710
Sex		0.338	-	-	-
Male	14.0				
Female	12.7				
Hospital where patients were diagnosed with CD		0.236	-	-	-
Primary care clinic	10.7				
Referral hospital	14.0				
Overseas	33.3				
Anti-tuberculosis medication		0.807	-	-	-
No	13.4				
Yes	14.3				
Family history of IBD		0.097	-	-	--
No	13.9				
Yes	3.3				
Location of disease (Montreal classification)*		0.099	-	-	-
Ileum (L1)	12.7				
Colon (L2)	8.6				
Ileocolon (L3)	15.1				
Concomitant UGI disease (L4)		0.028			
No	12.4		1 (reference)		
Yes	17.8		1.510	1.094-2.082	0.012
Perianal Fistula		0.020			
No	11.8		1 (reference)		
Yes	16.6		1.292	1.005-1.748	0.048

HR, hazard ratio; CI, confidence interval; CD, Crohn's disease; IBD, inflammatory bowel disease; UGI, upper gastrointestinal.

*Age at diagnosis and disease location was determined according to the revised Montreal classification.

CD, perianal disease increased the risk of resistance to corticosteroids.³⁴ Beaugerie *et al.*³⁵ showed that perianal disease at initial presentation of CD was associated with disabling clinical course related to corticosteroid dependence, hospitalization, and surgical intestinal resection for disease flares. In a retrospective study, patients with perianal fistulizing CD had a 1.7-fold increased risk of surgery compared to those who had not had perianal fistulizing CD.³⁶ Moreover, a recent study reported that patients with perianal CD had a higher risk of reoperation after primary bowel resection related to CD compared to those without perianal CD.³⁷ However, in this observational cohort study, presentation of perianal fistulas in CD was not associated with the risk of CD-related surgery. CD patients who required surgery for free perforation experienced less intra-abdominal abscess, perianal and intestinal fistulas, but were significantly associated

with bowel strictures in a retrospective study of results from the CONNECT.²⁴ Taken together, it remains unclear whether perianal fistulas are the indicator of bowel resection in patients with CD. However, patients with perianal fistulizing CD also required more frequent corticosteroids, immunomodulators, and TNF- α antagonists for the treatment of CD than those without perianal fistulizing CD, suggesting that perianal fistulizing CD is likely to be a severe relapsing disease during follow-up. Therefore, patients with perianal fistulizing CD should be carefully monitored for the development of disabling complications including nonperianal fistulas and intra-abdominal abscesses. In addition, early treatment with TNF- α antagonists can be considered to prevent complications and reduce surgical requirements in patients with perianal fistulizing CD, as well as those in Western countries.³⁸

In terms of detection time of perianal fistulas, patients with perianal fistulas after CD diagnosis required intestinal resection for medical refractoriness and/or complications of CD except perianal lesions more frequently, compared to presentation of perianal fistulas before diagnosis of CD regardless of CD-related complications. In this study, the patients who experienced perianal fistulas following diagnosis of CD also required more intensive medical treatment including antibiotics, methotrexate and TNF- α antagonist for treatment of active CD than those with perianal fistulas before diagnosis of CD. It remains unclear how the detection time of perianal fistulas affects the clinical course of disease in CD, but the presentation of perianal fistulas after diagnosis of CD might be an indicator of disease activity and aggressive clinical course.

The cumulative frequency of perianal fistulizing CD at referral centers has been reported to range from 13% to 38% in Western countries.³⁹ In the present multicenter cohort study, the prevalence of perianal fistulas in Korean patients with CD was 39% at referral hospitals. A previous hospital-based study at a tertiary care center in Korea showed that the prevalence of perianal fistulas was 46.8%.⁴⁰ Thus, perianal fistulas may occur more frequently in Korean patients with CD than in patients with CD from Western countries. However, the high prevalence of perianal fistulas found by previous studies in Korea might have been due to referrals to tertiary care centers, because the presence of perianal fistulas requires a multidisciplinary approach for management of CD. This level of care is available at tertiary care centers rather than primary care clinics. Further population-based studies are needed to determine whether Korean patients with CD show a higher prevalence of perianal fistulas compared to Caucasians.

In this study, perianal fistulas were significantly more common in CD patients of younger age, male gender, and ileocolonic involvement and in those who were diagnosed at primary care clinics. Patients who are younger when first diagnosed with CD appear to be at the greatest risk of perianal fistulas.¹⁹ In previous reports, age <40 years at diagnosis was a risk factor for fistulizing disease including perianal fistulas.^{30,32}

Some previous studies have reported that male patients with CD are more likely to have perianal fistulas compared to female patients with CD,^{41,42} however, there was no significant gender difference with respect to the presence of perianal fistulas in a population-based study.⁴³ Male gender might be a possible risk factor for perianal fistulizing CD in spite of the conflicting results reported thus far. With respect to the location of disease, earlier studies in Western countries have reported that patients with isolated ileal CD are at the lowest risk of perianal fistulas.¹⁹ The negative association between perianal fistulas and isolated ileal disease was also found in the present study. However, perianal fistulas occurred most often in patients with ileocolonic disease in our cohort, in contrast to previous studies in Western countries, which reported that CD patients with active rectal dis-

ease are most likely to develop perianal fistulas.¹⁹ In accordance with the results of previous studies,^{40,44} the Korean population in this study was more likely to have ileocolonic CD compared to Caucasians, especially in those with perianal fistulas. Interestingly, both male predominance and more ileocolonic involvement is the epidemiologic characteristics of Korean CD patients compared to Western countries.⁴⁵ It may be associated with the high prevalence of perianal fistulas in Korean.

The frequency of perianal fistulas was relatively high in patients who were diagnosed with CD at primary care clinics compared to those diagnosed at referral hospitals. The reasons for this observation remain unclear, but possible explanations include both the large proportion (68%) of perianal fistulas that were detected before diagnosis of CD and the high degree of suspicion of CD among primary care physicians managing young patients who present with perianal fistulas in Korea. Some of the patients who present with perianal fistulas might prefer primary care clinics specialized for coloproctology in which surgeons work, although the information on the specialty of primary care clinics was not available in this study.

We also observed that concomitant UGI involvement was an independent associated factor for both complicated nonperianal fistulas and/or intra-abdominal abscesses in patients with CD. In accordance with our results, Tang *et al.*³⁰ reported that fistulizing CD including perianal fistulas was associated with a predisposition to UGI disease in Canadian patients. Moreover, UGI involvement was significantly associated with the time to first major abdominal surgery in a population-based cohort study from the United States.⁴⁶ These findings suggest that UGI involvement is also a marker for poor clinical outcomes, especially penetrating complications, in patients with CD regardless of ethnicity.

This multicenter cohort study has several limitations. First, further information regarding the characteristics of perianal fistulas including type, activity, treatment, and outcomes of lesion was not available because of its retrospective nature. Second, a variety of confounding factors including smoking, clinical disease activity, and biological markers such as C-reactive protein⁴⁷ could not be controlled for due to a lack of medical records. Finally, this was a hospital-based cohort study that included patients from 32 referral hospitals. Thus, it may be biased toward more severe disease compared to population-based studies and may overestimate disease-related complications in a Korean population.

In conclusion, the presence of perianal fistulas was associated with the development of nonperianal fistulas and intra-abdominal abscesses in Korean patients with CD. Therefore, patients with perianal fistulizing CD should be carefully monitored for complicated nonperianal fistulas and intra-abdominal abscesses.

CONFLICTS OF INTEREST

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

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