


Incidence of and Risk Factors for Free Bowel Perforation in Patients with Crohn's Disease

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Abstract

Background Incidence of and risk factors for intestinal free perforation (FP) in patients with Crohn's disease (CD) are not established.

Aim To establish rate of and risk factors for FP in a large cohort of CD patients.

Methods Medical records of CD patients who visited Asan Medical Center from June 1989 to December 2012 were reviewed. After matching the FP patients to controls (1:4) by gender, year, and age at CD diagnosis, and disease location, their clinical characteristics were compared using conditional logistic regression analysis.

Results Among 2043 patients who were included in our study cohort, 44 patients (2.15%) developed FP over a median follow-up period of 79.8 months (interquartile range 37.3–124.6), with an incidence of 3.18 per 1000 person-years [95% confidence interval (CI) 2.37–4.28]. All 44 patients underwent emergency surgery, and eight

patients underwent reoperation within 12 months (8/44, 18.2%). Multivariable-adjusted analysis revealed that anti-TNF therapy [odds ratio (OR), 3.73; 95% CI 1.19–11.69; $p = 0.024$] was associated with an increased risk of FP.

Conclusions The incidence of FP in a large cohort of Korean CD patients was 2.15%, which was similar to that in Western reports. Anti-TNF therapy could be risk factors for FP.

Keywords Crohn's disease · Intestinal perforation · Anti-TNF · Stricture

Introduction

Free perforation (FP) of the bowel is a rare but serious, potentially life-threatening emergency in patients with Crohn's disease (CD). Spontaneous FP into the peritoneal cavity is a dramatic event that is fortunately rare but necessitates urgent surgical intervention [1]. According to Western studies, 1–3% of CD patients experience FP as an initial presentation or after being diagnosed with CD [2–5]. Interestingly, the incidence of FP in Japan has been reported to be as high as 9.4%, which is significantly higher than in the Western reports [6, 7]. A recent study of 1346 Korean patients with CD has reported a frequency of FP to be 6.5% [8]. However, because this complication is not frequent, reports on the incidence of FP in CD are scarce. A relatively large-scale study of 1476 patients was published by Greenstein et al. [4] and by Doh et al. [8], while only a small study of 233 patients has been published in Japan [7]. Recently, anti-tumor necrosis factor (TNF) agent has been suggested as a risk factor for FPs in CD patients, and a nonsignificant majority of patients who experienced perforation received corticosteroids [6]. However, only 13

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cases of FP were examined, which limits the power of the study [6]. Although corticosteroids may predispose patients to FP, their relationship with the development of FP has been controversial [9–11]. Therefore, although anti-TNF agents and corticosteroids could be risk factors for FP in patients with CD, more studies are needed.

In this study, we investigated the incidence of, clinical features of, and risk factors for free bowel perforation in Korean CD patients who were managed in a large tertiary referral center that specializes in inflammatory bowel diseases (IBDs).

Patients and Methods

Patients

A total of 2314 consecutive CD patients were managed at the Asan Medical Center, a tertiary university hospital in Seoul, South Korea, between June 1989 and December 2012. Of these patients, 2043 were enrolled in the present study, and 271 patients were excluded. Of these, 253 patients had been referred only for a second opinion without continued follow-up, and 18 had IBD unclassified. The CD diagnosis was based on conventional clinical, radiologic, endoscopic, and histopathological criteria [12–14]. FP due to CD was defined as a spontaneous perforation of the small or large bowel, with free flowing intestinal contents into the general peritoneal cavity [7], excluding sealed perforations or ruptured abscesses [1].

Study Design

We used a retrospective cohort study design to analyze the incidence of FP in our cohort of CD patients. To analyze the risk factors for FP, we also employed a case–control study using a matched control group selected from our CD cohort (CD patients who did not experience FP) that was four times as large as the FP patient group. Clinical information for the study subjects was acquired from the previously described IBD registry of the Asan Medical Center [15]. The case and control groups were matched by gender, age at diagnosis of CD (± 4 years), the year at diagnosis of CD (± 6 years), and disease location. For matching purposes, only controls with follow-up durations longer than those of their matched cases were selected to compare medication use during the same length of time. The use of corticosteroids and anti-TNF agents within the previous 3 months [6] and thiopurines within the previous 6 months prior to FP for cases was investigated. For the controls, the medication uses within the same duration of follow-up time as their matching cases were investigated. The corticosteroid doses were defined as follows: (1) low dose (oral prednisone < 20 mg/day or

> 20 mg/day for < 2 months), (2) moderate dose (intravenous or oral prednisone ≥ 20 mg/day for > 2 months), and (3) high dose (intravenous or oral prednisone ≥ 40 mg/day) [16]. For the referred patients, if the clinical information provided was insufficient, the referring physicians were contacted to obtain more detailed patient histories. The design and conduct of this study align with the STROBE statement [17].

Statistical Analysis

Continuous variables are presented as the medians with interquartile ranges (IQRs). Logistic regression model or cumulative logit model with generalized estimating equation was used to compare the clinical characteristics among case–control matched dataset; $p < 0.05$ was considered to be significant. The variables of interest included the disease duration since the initial diagnosis of CD, age, gender, smoking, past medication history (e.g., corticosteroids, thiopurines, and anti-TNF agents), history of perianal fistula, and disease location and behavior, according to the Montreal classification [18]. For disease location/behavior and perianal fistula, the last determined phenotypes before perforation for the cases and at the corresponding follow-up time point for the controls were used. Upper gastrointestinal involvement and perianal disease modifiers were not added when categorizing the disease locations and behaviors, respectively. To analyze the risk factors for FP, a multivariable-adjusted analysis was performed using conditional logistic regression with forward selection. For multivariable analysis, the variables with $p < 0.050$ on bivariate analysis were entered into the model. Correlation between the variables and free bowel perforation was expressed as an odds ratio (OR), with a 95% confidence interval (CI). A Kaplan–Meier curve was plotted to show the cumulative rate of FP during the follow-up after the initial diagnosis of CD. Stata ver. 12.1 (StataCorp, College Station, TX, USA) was used for statistical analysis.

Ethical Considerations

This study was approved by the Institutional Review Board of the Asan Medical Center (IRB No. 2013-0606).

Results

Demographic Characteristics

Among the 2043 CD patients who were included for analysis, there were 1462 males (71.6%) (Table 1). The median age at the time of CD diagnosis was 23 years

Table 1 Baseline demographic characteristics of the Crohn's disease patients with and without subsequent free bowel perforation

Variables	Total (<i>n</i> = 2043)	Cases (<i>n</i> = 44)	Matched controls (<i>n</i> = 176)	<i>p</i> value ^a
Male gender	1462 (71.6%)	34 (77.3%)	136 (77.3%)	NA
Age at diagnosis of CD, years, median (IQR)	23 (19–30)	29.7 (21.1–34.3)	29.0 (20.7–33.7)	NA
Smoking status at diagnosis				0.052
Current smoker	541 (26.5%)	11 (25.0%)	89 (50.6%)	
Ex-smoker	123 (6.0%)	4 (9.1%)	10 (5.7%)	
Never smoked	1338 (65.5%)	29 (65.9%)	70 (39.8%)	
Not documented	41 (2.0%)		7 (4.0%)	
Follow-up duration, months, median (IQR) ^b	75.3 (32.7–117.6)	35.8 (12.3–84.6)	35.8 (12.3–84.6)	NA
Disease location ^c				NA
L1 (terminal ileum)	482 (23.6%)	17 (38.6%)	69 (39.2%)	
L2 (colon)	152 (7.4%)	1 (2.3%)	4 (2.3%)	
L3 (ileocolon)	1390 (68.0%)	25 (56.8%)	103 (58.5%)	
Not documented	19 (0.9%)	1 (2.3%)		
Disease behavior ^c				0.179
B1 (non-stricturing, non-penetrating)	1591 (77.9%)	18 (40.9%)	91 (51.7%)	
B2 (stricturing)	206 (10.1%)	15 (34.1%)	37 (21.0%)	
B3 (penetrating)	246 (12.0%)	11 (25.0%)	48 (27.3%)	
Perianal fistula ^c	882 (43.2%)	24 (54.6%)	97 (55.1%)	0.749
History of medication				
Corticosteroids ^d				0.286
None		38 (86.4%)	160 (90.9%)	
Low dose		2 (4.6%)	10 (5.7%)	
Moderate dose		1 (2.3%)	1 (0.6%)	
High dose		3 (6.8%)	5 (2.8%)	
Thiopurines ^e		12 (27.3%)	70 (39.8%)	0.080
Anti-TNF agents ^{d,f}		7 (15.9%)	9 (5.1%)	0.017
Management during post-biologic era (from January 2000) ^g		41 (93.2%)	171 (97.2%)	0.329

IQR interquartile range, NA not applicable, TNF tumor necrosis factor

^a Cases versus matched controls

^b Time until free perforation for the cases

^c Disease location/behavior and perianal fistula at the time of diagnosis of Crohn's disease for the 2043 patients; the last determined disease location/behavior and perianal fistula before perforation for the cases and at the corresponding follow-up time point for the controls

^d During the previous 3 months prior to free perforation (cases) or corresponding follow-up time (controls)

^e During the previous 6 months prior to the free perforation (cases) or corresponding follow-up time (controls)

^f Infliximab was the only anti-TNF agent administered to the cases and controls

^g Management during post-biologic era before perforation event for cases, and management during post-biologic era before corresponding last follow-up date for controls

(IQR 19–30). At the time of diagnosis, the disease behaviors were non-stricturing, non-penetrating (NSNP) in 1591 patients (77.9%), stricturing in 206 patients (10.1%), and penetrating in 246 patients (12.0%). The disease locations were as follows: ileum in 482 patients (23.6%), colon in 152 patients (7.4%), and ileocolon in 1390 patients (68.0%). The median follow-up time from CD diagnosis to FP or last contact was 75.3 months (IQR 32.7–117.6).

Incidence of FP

Among the 2043 study subjects, forty-four (2.15%) experienced free bowel perforation during the follow-up (*n* = 41) or as an initial presentation of CD (*n* = 3). Among 44 patients with FP, there were 34 males (77.3%), and the median age at CD diagnosis was 29.6 years (IQR 20.9–34.3) (Table 1). Free air in the abdominal cavity was radiologically detected in all 44 patients. There were 26 FP

patients (59.0%) who were diagnosed by computed tomography (CT) only, nine patients (20.5%) by X-ray only, and nine patients (20.5%) by both X-ray and CT. In nine FP patients who were diagnosed by X-ray only, CT could not be checked before the surgery due to emergent conditions. The last known disease behavior before FP among cases was NSNP in 18 (40.9%), stricturing in 15 (34.1%), and penetrating in 11 (25.0%) patients. The median time to perforation was 35.8 months after the CD diagnosis (IQR 12.3–84.6). The incidence of FP was 3.18 per 1000 person-years [95% confidence interval (CI) 2.37–4.28]. The cumulative FP rates at 1, 3, 5, 10, and 20 years since the initial diagnosis of CD was 0.5, 1.2, 1.7, 3.0, and 6.2%, respectively. The cumulative probability of perforation is shown in Fig. 1.

Surgical Findings of 44 CD Patients with FP

In most cases (39/44 [88.6%]), the perforation was solitary. Among the 39 patients with solitary FP, 34 patients had ileal perforations, four had jejunal perforations, and one had a colonic perforation. Five patients had multiple perforations (11.4%, patients A–E). The patients primarily had small bowel perforations (43/44, 97.7%); there were ileal perforations in 36 patients (81.8%), jejunal in 4 (9.1%) patients, and a colonic perforation in one patient (2.3%), and two patients (4.5%) had both ileal and colonic perforations. In one patient with small bowel perforation (2.3%), the exact anatomic site could not be abstracted from the surgical record (patient E). Among 39 patients with solitary perforation, 27 were managed with small bowel resection and anastomosis, seven with ileocecectomy, two with right hemicolectomy, two with primary repair, and one with

temporary colostomy followed by total proctocolectomy with end ileostomy. Among the five patients with multiple perforations, patient A underwent distal ileal resection; patients B and C underwent terminal ileal resection with right hemicolectomy; patient D underwent ileocecectomy; and patient E underwent primary repair with ileostomy. Overall, temporary ostomies were created in 15 of 44 patients (34.1%). Concomitant stricture near the perforation site could be identified in 28 patients (28/43 [65.1%], and the presence of stricture was not documented in one patient).

Postoperative Outcomes of Patients with FP

The short-term postoperative outcomes of 44 patients who experienced FP were evaluated postoperatively at 3 and 12 months. Four patients (9.1%) underwent a second operation within 3 months of the initial operation. Between 3 and 12 months after the initial operation, another four patients (9.1%) underwent a second operation. The indications for reoperation within 12 months of the initial operation are summarized in Table 2.

Risk Factors for FP

In the unadjusted analysis of the matched FP cases and controls (Table 3, $n = 220$), anti-TNF use was significantly associated with FP [OR 3.77 (95% CI 1.24–11.46)]. In the multivariable-adjusted analysis, anti-TNF agent use (OR 3.73; 95% CI 1.19–11.69, $p = 0.024$) remained to be a significant factor that was associated with FP. Out of 44 cases of FP, 41 cases (91.1%) developed in the post-biologic era (after Jan 2000), and seven (15.9%) had been treated with infliximab before FP (Table 4). The median number of previous infliximab infusions was 5 (IQR 3–8). All patients had shown clinical responses to infliximab before developing FP.

Discussion

In this study, we report the incidence of free intestinal perforation among a well-defined large cohort of CD patients. Stricturing behavior and anti-TNF therapy could be possible risk factors for FP.

Forty-four (2.15%) of our patients experienced FP during a median follow-up period of 35.8 months. The incidence in our study is more similar to that in Western reports [3, 5] rather than the Japanese report by Ikeuchi et al. [7] or the Korean multicenter study by Doh et al. [8]. In our study, to determine whether the perforation was truly free, the occurrence of FP was confirmed by two gastroenterology researchers. Only the cases showing

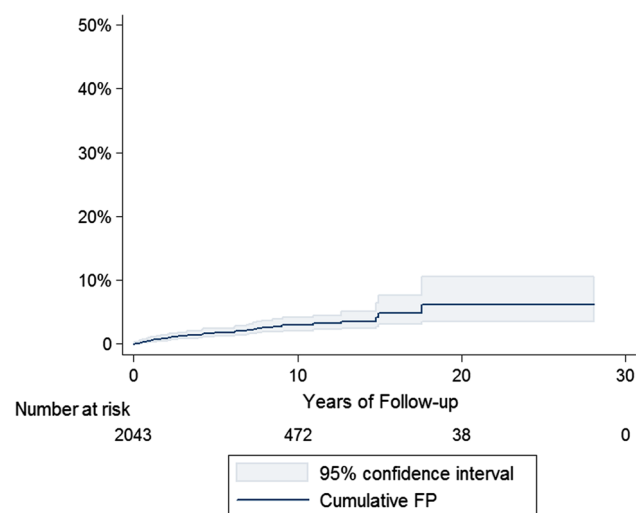


Fig. 1 A Kaplan–Meier curve showing the cumulative rate of free bowel perforation during the CD patients' follow-up period ($n = 2043$). CD Crohn's disease, FP free perforation

Table 2 Postoperative outcomes of 44 patients with free bowel perforation

Outcomes	Time since free perforation	
	<3 months	3–12 months
Second operation	4 (9.1%)	4 (9.1%)
Cause of second operation		
Anastomotic leakage	3	
Intestinal perforation, newly identified	1	1
Intestinal stricture, newly identified		1
Intra-abdominal abscess, newly developed		1
Medical refractoriness		1

Table 3 Unadjusted and multivariable-adjusted odds ratios of various factors for free bowel perforation among the patients with free perforation and their matched controls ($n = 220$)

Variables	<i>n</i>	Unadjusted		Multivariable-adjusted ^a	
		OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Perianal fistula	121	0.98 (0.50–1.92)	0.945		
Disease behavior					
Non-stricturing, non-penetrating	129	1.00 (reference)		1.00 (reference)	
Stricturing	40	2.03 (0.93–4.42)	0.076	1.98 (0.89–4.43)	0.094
Penetrating	51	1.16 (0.50–2.71)	0.730	1.09 (0.46–2.61)	0.845
Corticosteroid therapy ^b					
None	198				
Low dose	12	0.84 (0.18–3.95)	0.821		
Moderate–high dose	10	3.76 (0.79–17.96)	0.096		
Thiopurine therapy ^c	82	0.54 (0.26–1.16)	0.114		
Anti-TNF agent therapy ^b	16	3.77 (1.24–11.46)	0.019	3.73 (1.19–11.69)	0.024
Management during post-biologic era (from January 2000) ^d	212	0.27 (0.04–1.78)	0.173		

CD Crohn's disease, CI confidence interval, OR odds ratio, TNF tumor necrosis factor

^a Adjusted for the factors listed in the multivariable analysis

^b During the previous 3 months prior to free perforation (cases) or corresponding follow-up time (controls)

^c During the previous 6 months prior to free perforation (cases) or corresponding follow-up time (controls)

^d Management during post-biologic era before perforation event for cases, and management during post-biologic era before corresponding last follow-up date for controls

radiological free air and/or demonstration of free flow of intestinal contents during surgery were included. The Japanese study [7] was a review of Japanese literature together with data from a single hospital; therefore, the incidence of FP could have been overestimated by including perienteric abscess or localized perforation, as is the case with the Korean study [8].

To create comparable case and control groups, control patients were matched by gender, age of and year of CD diagnosis, and disease location. To assign similar treatment periods and similar propensities to be exposed to certain medications for both the controls and their matched cases, we only investigated the medication use among the controls during the same period as their matched cases. For

instance, if a case experienced FP 18 months after the initial diagnosis, the use of corticosteroids and anti-TNF agents during a period of 15–18 months and the use of thiopurines during a period of 12–18 months after the initial diagnosis of CD were investigated for both the cases and controls. For the cases and controls to have a similar propensity to receive certain medication, such as anti-TNF agents, we also matched them by the year at the time of diagnosis of CD.

One important finding of our study is the association between anti-TNF use and FP. In a case–control study matched for equal disease severity among cases and controls, Eshuis et al. reported that the occurrence of FP was higher in the CD patients who underwent anti-TNF

Table 4 Characteristics of patients who were on infliximab treatment and experienced free bowel perforation

No.	Gender	Age at FP	Disease duration at FP (months)	Disease location ^a	Disease behavior ^b	Indication for infliximab	No. of infliximab infusions before FP	Days after the final infliximab infusion	Clinical response to infliximab ^c	Site of perforation	No. of perforating sites	Operation
1	Male	43	27	Ileocolon	Penetrating	Inflammatory	12	53	Improved	Ileum	1	ICR
2	Female	25	101	Ileum	Stricturing	Inflammatory	10	26	Improved	Ileum	1	Small bowel R&A
3	Male	44	131	Colon	Inflammatory	Complex perianal fistula	8	51	Improved	Sigmoid colon	1	TPC with end ileostomy
4	Male	25	84	Ileocolon	Penetrating	Inflammatory	3	53	Improved	Ileum	1	ICR
5	Male	15	8	Ileocolon	Stricturing	Inflammatory	1	15	Improved	Ileum	1	Small bowel R&A
6	Female	33	44	Ileum	Stricturing	Inflammatory	2	Unknown	Improved	Ileum	1	Small bowel R&A
7	Male	47	151	Ileocolon	Inflammatory	Inflammatory	5	19	Improved	Ileum	1	Small bowel R&A

FP free perforation, ICR ileocecal resection, R&A resection and anastomosis, TPC total proctocolectomy

^a The last determined Montreal location prior to the initiation of infliximab

^b The last determined Montreal behavior prior to initiation of infliximab

^c The clinical response to infliximab before free bowel perforation

treatment [6]. Three hypotheses may explain the mechanism of perforation in CD: obstruction with proximal bowel distension, ischemia through inflammation, and abscess with secondary perforation [5]. Nasr et al. [19] proposed that FP occurs in a setting of acute or fulminant disease in which a channel rapidly forms between the mucosa and serosa but is not protected by adherent omentum or bowel. A possible reason for increased FP with anti-TNF might be decreased inflammatory responses due to TNF blockage and failure to seal off the imminent perforation [6]. In our study, all patients who had been exposed to anti-TNF agents showed good clinical responses before developing FP; therefore, the reduced inflammatory response by blocking TNF around the imminently perforating sites, not the disease activity itself, may be responsible for FP. However, since this study was not designed to prove causality of various risk factors for FP, cautious interpretation of our study results is warranted; use of anti-TNF may also merely reflect severe disease activity, rather than actual cause of FP.

In the final evaluation before FP, stricturing disease behavior was observed in 34.1% (15/44) of FP patients. However, there were 28/43 (65.1%) cases where intestinal strictures were identified during surgery. Undetected intestinal strictures, caused either by prolonged time gap between the final disease evaluation before FP and the event of FP, or limited sensitivity of diagnostic tools, could have led to the discrepancy between Montreal classification of stricturing behavior and the presence of strictures on surgical fields [20]. Also, because anatomic strictures without prestenotic dilatation or obstructive signs/symptoms are not classified into Montreal stricturing behaviors, the discrepancy between Montreal behavior before surgery and surgical findings might have been caused [21].

In our patients, there was a preponderance of perforations of the ileum. Among 25 patients with ileocolonic disease who experienced FP, ileal perforation was predominant (23 cases, 92%), and there were only two cases (8%) of colonic perforation. Although we cannot exactly explain the reason for this predominance of ileal perforation, high proportion of small bowel perforation was also observed in previous reports by Greenstein et al. (77/99, 77.8%) [4], Eshuis et al. (9/13, 69.2%) [6], Ikeuchi et al. (109/126, 86.5%) [7], and Werbin et al. (12/13, 92.3%) [22].

Our study had several limitations. First, the research was conducted in a single referral center, and referral bias could be present. However, because CD is still a rare disease in Korea, more than 70% of CD patients are initially diagnosed at university hospitals [14], which may decrease the possibility of referral bias. Conversely, well established and maintained IBD registry as a study source in our study is a strong point, reducing the risk of incorrect data

collection which is commonly occurred in multicenter retrospective design. Second, because this study was retrospective in nature, some important potential confounders, such as the presence and location of strictures in relation to the perforated site, could not be reviewed in detail. Finally, there may have been other unmeasured predisposing risk factors for FP, such as immune function, genetics, vascular changes, nutrition, or the microbiome. While we did not have detailed data for these factors, future studies should include these issues in the analysis. Despite these limitations, this study is the largest to date, to the best of our knowledge, and it may help to establish risk factors for FP among CD patients.

In conclusion, the incidence of FP among a large cohort of Korean CD patients was 2.15%. Anti-TNF therapy could be a risk factor for FP. Further population-based studies are required to further define the risk factors for this potentially life-threatening condition.

Compliance with ethical standards

Conflict of interest and Funding sources Suk-Kyun Yang received a research grant from Janssen Korea Ltd., but this grant is not related to the current study topic. The remaining authors have no competing interests.

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