Risk factors associated with progression to intestinal complications of Crohn disease

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Abstract

Background: Crohn disease is a chronic bowel disease that causes serious complications. Prevalence of Crohn disease is increasing. Studies have shown that the behavior of the disease is not stable and severe complications secondary to behavior change over time have been shown. In this study, we aimed to evaluate the prognostic risk factors associated with phenotypic change in Crohn disease in a Turkish patient cohort.

Methods: Patients followed up from March 1986 to August 2011 were evaluated for demographic and clinical characteristics to determine possible risk factors and initial clinical phenotype of the disease based on the Montreal classification. The cumulative probabilities of developing stricturing or penetrating intestinal complications were estimated using the Kaplan-Meier analysis. Univariate and multivariate Cox-proportional hazard models were used to assess associations between baseline clinical characteristics and intestinal complications.

Results: Three hundred and thirty patients (mean age, 30.6 ± 11.1 years; 148 female) were included in the study. Mean follow-up duration was 7.4 ± 5.3 years (range: 1.0–25.0 years). At baseline 273 patients had inflammatory-type disease, 57 patients experienced stricturing/penetrating intestinal complications before or at the time of diagnosis. The cumulative probability of developing complicated disease was 37.4% at 5 years, 54.3% at 10 years, 78.8% at 25 years. Independent predictors associated with progression to intestinal complications were current smoking, perianal disease, extra-intestinal manifestations, and location of disease.

Conclusions: Location of disease is the most powerful indicator for the development of stenosis and penetrating complications in inflammatory-type disease. Patients with ileal involvement should be considered for more aggressive immunosuppressive therapy.

Keywords: Disease behavior; Surgery; Location; Perianal disease; Smoking

Introduction

Crohn disease (CD) is a multifactorial disease caused by the combination of genetic susceptibility and pathogenic contributions of several environmental and host risk factors.[1] The disease has a very heterogeneous clinical presentation and course. During the course of CD nearly two-thirds of patients develop complications.[2] Main complications associated with CD include development of inflammatory or fibrotic strictures and the development of intra-abdominal or perianal fistulae and abscesses. According to published data acquired from real-life cohorts in population and referral-based studies, it is very common to experience a change in behavior and development of stricturing/penetrating complications over the course of the disease while having a relatively stable disease location.[3-5] Unfortunately, widespread use of immunomodulators or biologics has not changed the natural course of the disease dramatically and most patients with CD require surgery in the long term due to the development of complications.[6,7] Therefore, it is very important to predict patients with a higher risk of progression to intestinal complications, and initiate an early aggressive combination treatment with biologic agents plus immunomodulators which have the potential of changing natural course by achieving early mucosal healing.[8]

Studies that evaluated the natural course and prognosis of the disease used different definitions of severity as time to first surgery, disabling disease, complicated disease, relapsing disease or change in disease behavior/phenotype. Because of this variety in definition and differences in

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cohorts each study found different combination of risk factors that determined the prognosis of CD including but not limited to, young age at diagnosis,[9,10] ileal,[9] or ileocolonic involvement,[3,11] perianal disease,[4,5] rectal involvement, upper gastrointestinal involvement,[10] stricturing/penetrating disease phenotype, initial need for corticosteroids,[12] smoking habit,[5] elevated C-reactive protein,[13] anti-*Saccharomyces cerevisiae* antibodies (ASCA) positivity,[9] and genetic factors.[14] In the present study, we aimed to investigate prognostic risk factors associated with phenotypic change of CD, which is a more standardized definition as a prognostic end-point, in Turkish patients with CD.

Methods

Ethical approval

To conduct this study, ethical approval was obtained from the Ethics Committee of Istanbul University, Faculty of Medicine (No. 2011/831-577). All the applied procedures were complied with the ethical standards of Human Testing Committee of our institution and the *Helsinki Declaration*. Written informed consent forms were received from all participants who were examined by a gastroenterologist.

Study design

Patients with a diagnosis of CD who were followed up in the Department of Gastroenterohepatology, Istanbul Faculty of Medicine, Istanbul University between March 1986 and August 2011, were included in this retrospective, single-center cohort study. For all patients who were diagnosed with CD, the inclusion criteria for the study were having positive results of the tissue samples taken in endoscopy in histopathological examination. Selection criteria for inclusion in the study were (1) a definitive diagnosis of CD, (2) a follow-up duration of at least 1 year after diagnosis, and (3) absence of any malignancy at diagnosis. Patients with a diagnosis of indeterminate colitis were excluded from the study.

Definitions and classification of the disease

Demographic characteristics (age of diagnosis, gender) and presence of CD in family of the patients who were included in the study were documented. Age of diagnosis, location and type of the disease, and presence of perianal disease were determined according to the Montreal Classification.[15] Type of the disease was defined in three categories as inflammatory, stricturing and penetrating according to presence of intestinal complications such as stricture, fistula, and/or abscess formation.[16] Development of a perianal fistula or abscess was defined as a modifier of disease in accordance with the Montreal Classification.[15] Smoking was defined as consuming seven or more cigarettes per week. All patients with a history of smoking underwent counseling for smoking cessation. The presence of extra-intestinal manifestations (EIMs) in patients with CD was determined. EIMs including musculoskeletal, mucocutaneous, ocular, hepatobiliary, and miscellaneous manifestations were assessed separately.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 (IBM SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation (SD) or median (range) while categorical variables were expressed as frequencies (%). Differences between categorical variables were evaluated using the Pearson Chi-square or Fisher exact test when necessary. The cumulative probabilities of developing intestinal complications during the follow-up were calculated using the Kaplan-Meier method and log-rank test. Cox proportional hazard model was used to assess univariate and multivariate analysis. The results are reported as hazard ratios (HR) with 95% confidence intervals (CIs). A two-tailed P value <0.05 was considered statistically significant.

Results

Baseline patient characteristics

Three hundred and thirty patients with CD (mean age, 30.6 ± 11.1 years; 148 female) were under follow-up between March 1986 to August 2011 for a total of 2408 person-years, with a mean follow-up duration of 7.4 ± 5.3 years (range: 1.0–25.0 years). The number of patients according to age at diagnosis, disease location, and behavior are summarized in Table 1.

Phenotype change and the cumulative risk of developing intestinal complications

In 330 patients, 181 (54.8%) patients experienced a stricturing or penetrating intestinal complication either at diagnosis or during the follow-up. Fifty-seven patients (17.3%) had complications before or at the time of diagnosis. In the remaining 124 patients who experienced intestinal complications, 48 and 76 patients developed stricturing and penetrating complications within the follow-up, respectively. The cumulative incidence of either stricturing or penetrating intestinal complication in 330 patients was 17.3% (95% CI: 13.6–21.8) at diagnosis, 27.0% (95% CI: 22.5–32.1) at 1 year, 35.0% (95% CI: 30.0–40.0) at 2 years, 48.2% (95% CI: 42.7–54.1) at 5 years, 62.2% (95% CI: 55.3–69.1) at 10 years, 78.1% (95% CI: 68.9–86.0) at 20 years, and 82.4% (95% CI: 71.0–91.3) at 25 years [Figure 1A]. Estimated median time to occurrence of any complication was 72.0 months (95% CI: 52.1–91.8). The cumulative risk of stricturing disease was found to be 4.5% (95% CI: 2.8–7.4) at diagnosis, 8.5% (95% CI: 5.9–12.1) at 1 year, 17.7% (95% CI: 13.7–22.6) at 5 years, 22.3% (95% CI: 17.3–28.5) at 10 years, 33.3% (95% CI: 21.9–48.4) at 20 years, and 44.4% (95% CI: 25.3–69.3) at 25 years [Figure 1B]. The cumulative probability of developing a penetrating complication was 12.7% (95% CI: 9.6–16.8) at diagnosis, 18.5% (95% CI: 14.7–23.1) at 1 year, 31.1% (95% CI: 26.2–36.6) at 5 years, 40.7% (95% CI: 34.4–47.6) at 10 years, 49.8% at 15 years, 52.3% (95% CI: 43.0–62.2) at 20 and 25 years [Figure 1C].

The cumulative risk of change in disease behavior was evaluated among 273 patients with inflammatory disease at diagnosis, after excluding patients who already had any

Table 1: Baseline demographic and clinical characteristics of patient with Crohn disease.

Characteristics	Overall	B1	B2	B3
Patients, *n* (%)	330 (100.0)	273 (82.7)	15 (4.5)	42 (12.7)
Gender, *n* (%)				
Female	148 (44.8)	125 (45.8)	5 (33.3)	18 (42.9)
Male	182 (55.2)	148 (54.2)	10 (66.7)	24 (57.1)
Age of diagnosis, *n* (%)				
A1	19 (5.8)	17 (6.2)	1 (6.7)	1 (2.4)
A2	246 (74.5)	200 (73.3)	11 (73.3)	35 (83.3)
A3	65 (19.7)	56 (20.5)	3 (20.0)	6 (14.3)
Involvement location, *n* (%)				
L1	120 (36.4)	91 (33.3)	7 (46.7)	22 (52.4)
L2	42 (12.7)	40 (14.7)	0	2 (4.8)
L3	156 (47.3)	131 (48.0)	8 (53.3)	17 (40.5)
L4	2 (0.6)	2 (0.7)	0	0
L1 + L4	8 (2.4)	7 (2.6)	0	1 (2.4)
L2 + L4	1 (0.3)	1 (0.4)	0	0
L3 + L4	1 (0.3)	1 (0.4)	0	0
Perianal disease, *n* (%)				
Yes	43 (13.0)	37 (13.6)	2 (13.3)	4 (9.5)
No	287 (87.0)	236 (86.4)	13 (86.7)	38 (90.5)
Smoking history, *n* (%)				
No	164 (49.7)	138 (50.6)	8 (53.3)	18 (42.9)
Current Smokers	126 (38.2)	103 (37.7)	4 (26.7)	19 (45.2)
Former Smokers	40 (12.1)	32 (11.7)	3 (20.0)	5 (11.9)
Family history, *n* (%)				
Yes	21 (6.4)	15 (5.5)	0	6 (14.3)
No	309 (93.6)	258 (94.5)	15 (100.0)	36 (85.7)
Extra-intestinal manifestation, *n* (%)				
Yes	161 (49.0)	141 (52.0)	4 (27.0)	16 (38.0)
No	169 (51.0)	132 (48.0)	11 (73.0)	26 (62.0)

B1: Inflammatory disease; B2: Stricturing disease; B3: Penetrating disease; A1: 16 years old and younger; A2: 17 to 40 years; A3: 41 years old and older; L1: Terminal ileum; L2: Colon; L3: Ileocolonic; L4: Upper gastrointestinal tract.

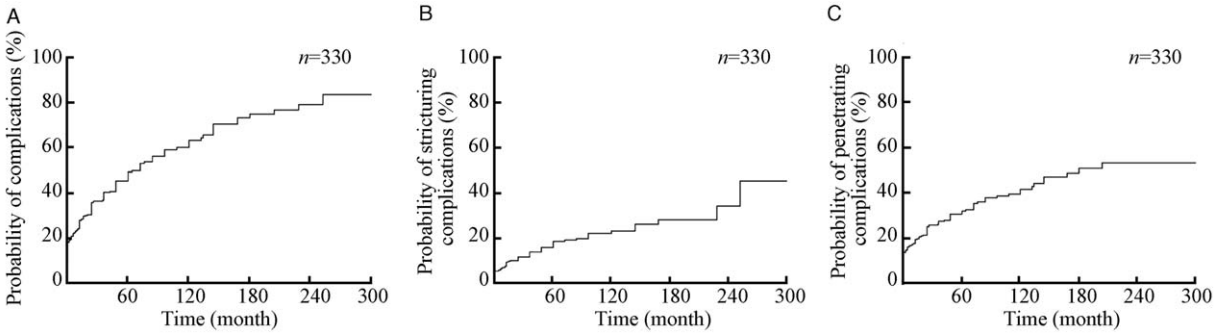

Figure 1: Cumulative risk of developing intestinal complications with Crohn disease. (A) Total (stricturing or penetrating) complications; (B) stricturing complications; (C) penetrating complications.

complication at baseline or before the diagnosis. The cumulative probability of developing penetrating or stricturing disease was 11.7% (95% CI: 8.4–16.2) at 1 year, 37.4% (95% CI: 31.6–44.0) at 5 years, 54.3% (95% CI: 46.4–62.5) at 10 years, 73.5% (95% CI: 62.7–83.2) at 20 years, and 78.8% (95% CI: 65.4–89.6) at 25 years [Figure 2A]. Estimated median time to occurrence of any complication was 108 months (95% CI: 75–141). Forty-eight (17.6%) patients developed a penetrating complication and 76 (27.8%) patients developed stricturing disease within the follow-up. The cumulative probability of developing stricturing disease was 4.8% (95% CI: 2.8–8.1) at 1 year, 15.5% (95% CI: 11.4–20.8) at 5 years, 20.9% (95% CI: 15.5–27.8) at 10 years, 32.5% (95% CI: 20.9–48.4) at 20 years, and 43.8% (95% CI: 24.5–69.2) years at 25 years [Figure 2B]. The cumulative probability of experiencing penetrating complications was shown to be 7.0% (95% CI: 4.5–10.7) at 1 year, 22.1% (95% CI:

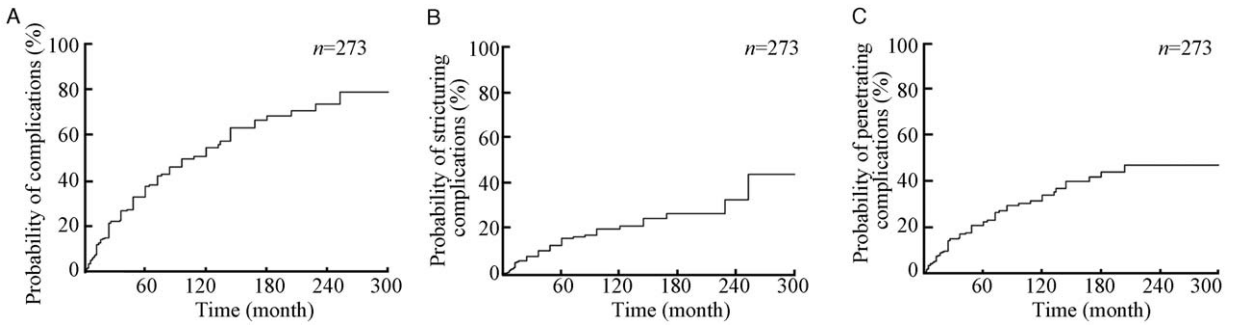

Figure 2: The cumulative risk of intestinal complications with inflammatory-type Crohn disease. (A) Stricturing or penetrating complications; (B) stricturing complications; (C) penetrating complications.

17.3–27.8) at 5 years, 33.7% (95% CI: 26.9–41.7) at 10 years, 46.7% (95% CI: 36.6–58.0) at 20 and 25 years [Figure 2C].

Factors associated with progression to penetrating or stricturing complications

The association between time to development of an intestinal complication and baseline risk factors were evaluated in 273 patients with the inflammatory disease using univariate and multivariate Cox regression analyses. In univariate Cox regression analyses, male gender (HR: 1.44, 95% CI: 1.00–2.07, $P = 0.048$), current smoking status (HR: 1.87, 95% CI: 1.28–2.74, $P = 0.001$), and EIMs (HR: 0.61, 95% CI: 0.43–0.87, $P = 0.007$) were significantly associated with occurrence of intestinal complications. When colonic involvement was taken as reference, location of disease (ileocolonic [HR: 2.29, 95% CI: 1.14–4.62, $P = 0.020$], ileum [HR: 2.89, 95% CI: 1.41–5.90, $P = 0.004$], upper gastrointestinal [HR: 6.49, 95% CI: 2.48–17.0, $P < 0.001$]) found to be significant predictors of developing intestinal complications. Age of diagnosis, family history, being a former smoker, and baseline perianal disease did not predict intestinal complications in univariate Cox regression analyses [Table 2]. However, perianal disease included as a time-varying risk factor was associated with subsequent development of intestinal complication (HR: 1.72, 95% CI: 1.19–2.50, $P = 0.004$). Involvement of colon (HR: 0.63, 95% CI: 0.44–0.89, $P = 0.010$), especially isolated colonic involvement (HR: 0.38, 95% CI: 0.19–0.75, $P = 0.006$), was found to be protective against intestinal complications. The association between risk factors and development of intestinal complications were examined using a multivariate Cox proportional hazard model including gender, smoking status, EIMs, perianal disease, and location of disease as possible risk factors. Current smoking (HR: 1.73, 95% CI: 1.16–2.58, $P = 0.008$), perianal disease (HR: 1.58, 95% CI: 1.08–2.32, $P = 0.019$), EIMs (HR: 0.65, 95%CI: 0.45–0.95, $P = 0.025$), and disease location at diagnosis were found to be independent predictors of intestinal complications. Patients with ileocolonic (HR: 2.06, 95% CI: 1.02–4.19, $P = 0.045$), ileal (HR: 3.03, 95% CI: 1.47–6.24, $P = 0.003$), and upper gastrointestinal (GI) disease (HR: 5.69, 95% CI: 2.15–15.07, $P < 0.001$) had a significantly increased risk to develop a complication relative to those with colonic disease [Table 3 and Figure 3].

Mortality

Thirty-one patients included in the study died. The cause of mortality was evaluated as three separate groups: related to disease, probably due to disease and unrelated to disease. The deaths of 11 patients were related to disease (eight patients had sepsis after intestinal surgery, one patient had malnutrition due to amyloidosis, two patients had colorectal cancer). The death of three patients was probably due to disease (one patient with renal insufficiency and sepsis, one with pulmonary embolism, one with complications due to liver cirrhosis). Seventeen patients died due to unrelated to disease reasons (five patients from non-gastrointestinal system malignancy, including lung, trachea, cholangiocarcinoma, ovary and servix, two from cerebrovascular events, nine from cardiovascular diseases, and one from accident). When the relationship between mortality and disease type was evaluated; 20 patients, including eight related to disease, three probably due to disease and nine unrelated to disease, were in the inflammatory group. Five patients were in the stenosis group, two of them related to disease and three of them are unrelated to disease. Six patients were in the penetrating group, one of them was related to disease and five of them were unrelated to disease.

Discussion

In our study, younger age was associated with ileal involvement, and location of the disease was almost stable throughout the follow-up, which was also supported by previous studies. However, there are conflicting results in the literature regarding the relationship between age at diagnosis and prognosis of CD. It has been suggested that patients younger than 40 at diagnosis are more likely to develop early intestinal complications.[10] Several studies found this association only for penetrating disease,[2-4] and several others did not find any relationship.[3,5,17] Our results suggested that younger age at diagnosis is a factor related to the location of disease instead of having a direct influence over the disease course.

There are studies that examined behavior change as a primary endpoint in CD patients with inflammatory-type phenotype in different population settings. For the first time, Louis *et al* retrospectively evaluated behavior change in 297 patients with CD using Vienna classification. At diagnosis 219 (73.7%) patients had inflammatory disease,

Table 2: Univariate Cox regression analyses of baseline risk factors for developing intestinal complications in patients with baseline inflammatory-type disease, *n* (%).

Baseline risk factors	Patients ($n=273$)	Events ($n=124$)	Hazard ratio	95% CI	*P*
Age					
16 years old or younger	17 (6.2)	10 (8.1)	1.000	Reference	
17–40 years old	200 (73.3)	95 (76.6)	0.850	0.440–1.640	0.640
41 years old and older	56 (20.5)	19 (15.3)	0.570	0.260–1.230	0.150
Gender					
Female	125 (45.8)	52 (41.9)	1.000	Reference	
Male	148 (54.2)	72 (58.1)	1.440	1.000–2.070	**0.048**
Smoking status					
Non-smoker	138 (50.6)	48 (38.7)	1.000	Reference	
Former smoker	32 (11.7)	16 (12.9)	1.650	0.940–2.910	0.083
Current smoker	103 (37.7)	60 (48.4)	1.870	1.280–2.740	**0.001**
Extra-intestinal manifestation					
No	112 (41.0)	68 (55.0)	1.000	Reference	
Yes	161 (59.0)	56 (45.0)	0.610	0.430–0.870	**0.007**
Perianal disease*					
No	236 (86.4)	106 (85.5)	1.000	Reference	
Yes	37 (13.6)	18 (14.5)	1.120	0.680–1.840	0.660
Perianal disease†					
No	184 (69.2)	77 (62.1)	1.000	Reference	
Yes	89 (30.8)	47 (37.9)	1.720	1.190–2.500	**0.004**
Location of disease					
Colon	40 (14.7)	9 (7.3)	1.000	Reference	
Ileocolonic	131 (48.0)	61 (49.2)	2.290	1.140–4.620	**0.020**
Ileum	91 (33.3)	46 (37.0)	2.890	1.410–5.900	**0.004**
Upper gastrointestinal	11 (4.0)	8 (6.5)	6.490	2.480–17.000	**<0.001**

*Patients with perianal disease at baseline. †Including patients who develop perianal disease during the follow-up (time-dependent variable). CI: Confidence interval.

Table 3: Multivariate Cox proportional hazard model to identify factors independently associated with developing intestinal complications in patients with baseline inflammatory-type disease ($n=273$).

					95% CI for Exp (*B*)	
Parameters	***B***	**SE**	***P***	**HR**	**Lower**	**Upper**
Gender	0.028	0.199	0.890	1.030	0.700	1.520
Smoking status						
Non-smoker (reference)						
Former smoker	0.394	0.305	0.200	1.480	0.820	2.700
Current smoker	0.546	0.205	**0.008**	**1.730**	1.160	2.580
Extra-intestinal manifestations	–0.424	0.190	**0.025**	0.650	0.450	0.950
Perianal disease*						
No (reference)						
Yes	0.459	0.195	**0.019**	**1.580**	1.080	2.320
Location of disease						
Colon (reference)						
Ileocolonic	0.724	0.361	**0.045**	**2.060**	1.020	4.190
Ileum	1.109	0.368	**0.003**	**3.030**	1.470	6.240
Upper gastrointestinal	1.738	0.497	**<0.001**	**5.690**	2.150	15.070

*Time-dependent variable. CI: Confidence interval; HR: Hazard ratio (expB); SE: Standard error.

which substantially decreased during the follow-up up to 25 years.[3] It showed that disease behavior was not a stable indicator to determine the phenotype of CD. Location of disease was found to be the sole factor associated with this changing disease phenotype. Specifically, this association was found to be between small bowel disease with stricturing and colonic disease with penetrating phenotype. In a subsequent study, Cosnes *et al*[2] investigated risk factors associated with time to development of stricturing or penetrating complications in a large cohort of patients from France. Vienna classification was used to determine disease behavior in this cohort including 2002 patients, and the investigators reported that an estimated 88% of patients evolved to have a complicated

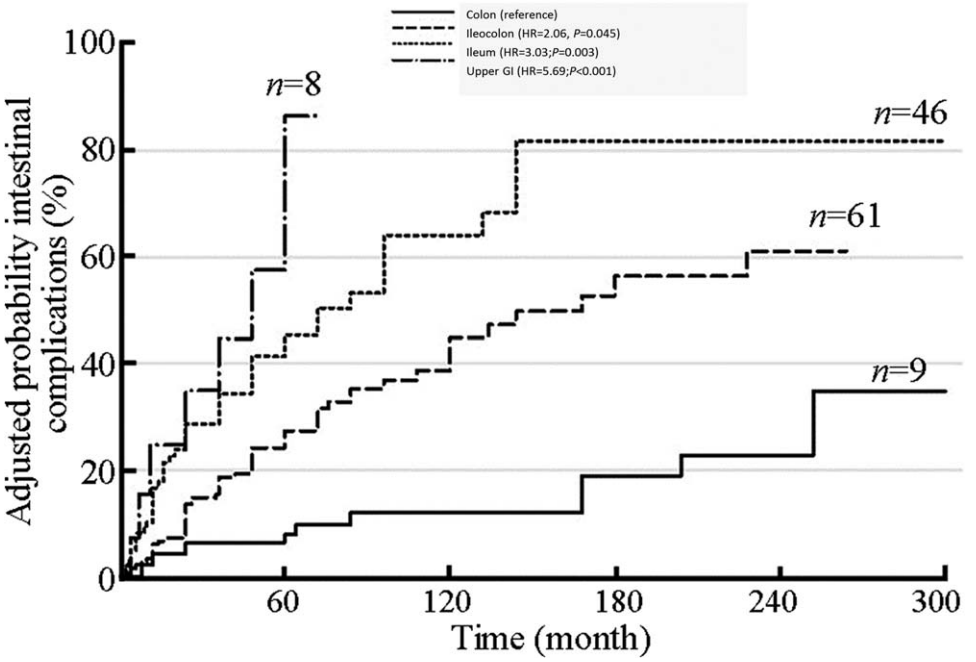

Figure 3: Probability of intestinal complications according to the baseline location of Crohn disease.

disease in 20 years follow-up. They found that the most important factor for determining disease behavior was again the location of the disease. Small bowel and anoperineal involvement at diagnosis were indicators of time to stricturing and/or penetrating complication, whereas upper GI and colonic disease had an opposite effect. In the present study, colonic disease had a protective effect against intestinal complications, yet patients with upper GI disease demonstrated the highest risk of developing a complicated disease course.

Genetic and environmental determinants of disease phenotype had become a matter of interest since the recognition of susceptibility genes for CD. In a report by Louis *et al*,[18] the evolution of disease behavior and its association with NOD2/CARD15 and ASCA status was investigated in their cohort of 163 patients with inflammatory-type CD. After 5 years of follow-up, 18 (11%) and 35 (21.5%) patients developed a stricturing and penetrating phenotype, respectively. The development of stricturing or penetrating behavior at 5 years was independently associated with disease location, number of flares, and smoking habit of patients, but not by *NOD2/CARD15* or ASCA status. In a later study, Smith *et al*[9] examined 231 patients with CD (70% had B1 disease) to evaluate the relationship of clinical features, ASCA and NOD2/CARD15 status with evolution of disease behavior over 20-year follow-up. They demonstrated that ileal disease, ASCA positivity, and age at diagnosis were independent variables associated with progression.[19,20]

Aldhous *et al*[21] reported that stricturing disease and progression to surgery was higher in patients with upper GI or ileal involvement. The risk of intestinal penetrating disease was higher in patients with upper GI and ileocolonic disease than in patients with either ileal or colonic disease. Interestingly, smoking was associated with the location of disease, but not with intestinal complications. In ex-smokers or non-smokers, the authors reported a higher frequency of colonic disease, which has been demonstrated to be a protective feature against intestinal complications. Since the location of disease is a powerful indicator of behavior change, it could have suppressed the effect of smoking status due to a multicollinearity effect in the regression model. This might have led to a type II error regarding the influence of smoking on behavior change in the study by Aldhous *et al*[21] Also Zheng *et al*[22] reported that; smoking to be a potential risk factor for the development of anal abscess and anal fistula diseases in population without inflammatory bowel disease. In our study, location of disease was evenly distributed among patients with different smoking habits, and current smoking was found to be independently associated with intestinal complications.

In a population-based study from New Zealand using the Montreal classification, 404 patients with inflammatory disease behavior were evaluated for behavior change during a 10-year follow-up.[4] Perianal disease was the only independent predictor for behavior change with a HR of 1.62 (95% CI: 1.28–2.05), which was a novel observation at that time. In contrast to other studies, disease location influenced subsequent disease behavior only at univariate analysis. A recent study by Thia *et al* also confirmed once again the relationship between disease location and risk of intestinal complications using the Montreal classification.[17] Perianal disease was found to be associated with subsequent complications at a borderline significance ($P = 0.051$). Interestingly, they found a cumulative risk of 43.9% (95% CI: 32.5–53.4) for developing intestinal complications at 30 years in patients with non-stricturing non-penetrating disease, which was

much lower than the estimated risk of 78.8% (95% CI, 65.4–89.6) in our study. This discrepancy between estimated risks can be readily explained by the referral-based setting of our study and fewer isolated colonic disease found in our cohort (12.7% *vs*. 32%).

There are some limitations in our study. First, genetic and serologic testing was not available in our study, which would be helpful in predicting disease progression and complications. There are other limitations to our study including the retrospective single-center design and evolution of diagnostic and therapeutic tools for CD during the study period. The referral-based setting in our study may overestimate the risk of intestinal complications compared to a population-based study; nonetheless, this improves the sensitivity of the analysis to determine significant risk factors.

In conclusions, overall cumulative evidence inarguably shows that location of the disease is the most stable and powerful indicator for development of intestinal complications. Although results may differ among studies due to different settings, populations and methods of analyses, perianal disease, and smoking status should be taken into account while assessing the prognosis of CD. Smoking cessation has an utmost importance to change the course of the disease. A previously unidentified association between EIMs and disease behavior was an interesting finding in the present study that shows EIMs can predict a luminal disease course. Further studies are needed to confirm and evaluate the association between EIMs and inflammatory disease course. Those patients with a higher risk of developing intestinal complications, should be regularly and carefully evaluated for mucosal remission and have to be considered for a more aggressive immunosuppressive therapy.

Conflicts interest

None.

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