UPPER GASTROINTESTINAL TRACT INVOLVEMENT IN CROHN`S DISEASE: FREQUENCY, RISK FACTORS AND DISEASE COURSE

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ABSTRACT

BACKGROUND: The frequency of upper gastrointestinal (GI) tract involvement in Crohn`s disease (CD) has been reported with a large variation. Risk factors and disease course of patients with upper GI tract involvement remain largely elusive.

METHODS: Data on CD patients in the Swiss Inflammatory Bowel Disease Cohort were analyzed. Patients with upper GI tract involvement were compared to controls. Logistic regression models for prediction of upper GI tract involvement and Cox proportional hazard models for occurrence of complications were computed.

RESULTS: We included 1638 CD patients, of whom 107 (6.5%) presented with upper GI tract involvement at the time of diagnosis and 214 (13.1%) at any time. Prevalence of such involvement at diagnosis increased over time (5.1% for 1955-1995 vs. 11.3% for 2009-2016). In a multivariate logistic regression model, male sex and diagnosis between 2009-2016 (vs. before 1995) were independent

predictors for presence of upper GI tract involvement at CD diagnosis (OR 1.600, p=0.021 and OR 2.686, p<0.001), while adult age was a negative predictor (OR 0.388, p=0.001). Patients with upper GI tract involvement showed a disease course similar to control patients (HR for any complications 0.887 [95% CI 0.409-1.920]), and a trend towards occurrence of fewer intestinal fistulas (log-rank test p=0.054).

CONCLUSIONS: Prevalence of upper GI tract involvement has been increasing over the past decades. Male sex and young age at diagnosis were identified as the main predictive factors for such involvement at CD diagnosis. Involvement of upper GI tract did not result in a worse outcome.

Key words: *Inflammatory bowel disease; natural history; upper gastrointestinal tract; Crohn's disease; esophagus; stomach; duodenum; jejunum.*

INTRODUCTION

Crohn's disease (CD) is a chronic disorder of the gastrointestinal (GI) tract that leads to development of bowel damage and impaired gut function.[1,2] Although CD most frequently affects the ileocecum, it may involve any portion of the GI tract, from the oral cavity to the anus. Upper GI tract involvement refers to the affection of esophagus, stomach, duodenum and jejunum, which may occur either isolated (Montreal Classification L4) or together with other CD locations (L1-3).[3] Typical CD-related endoscopic lesions of the esophagus consist of aphthae, erosions and ulcers (not related to gastro-esophageal reflux disease).[4-8] For gastroduodenal CD, endoscopic findings include apthae, longitudinal/irregular erosions, ulcers, and bamboo-like appearances.[9-12]

The frequency of endoscopic lesions in the upper GI tract has been reported with a large variation. Early studies documented a low prevalence between 0.5-4% of CD patients.[13-15] However, more recently reported rates have been much higher ranging from 30 to 75%.[16,17] Horjus and colleagues systematically assessed newly diagnosed CD patients and observed endoscopic lesions in the upper GI tract in 60 out of 108 examined patients (55%).[18] These discrepancies regarding prevalence rates of upper GI tract lesions are probably related to i) non-uniform definitions of CD-related lesions, ii) the use of different diagnostic modalities (radiologic exams in early studies vs. endoscopies in later investigations), iii) differences in the examined patient populations (newly diagnosed patients versus treated patients), and iv) differences regarding the frequency of upper endoscopy as an initial diagnostic procedure. Current ECCO guidelines recommend – irrespective of the findings at ileo-colonoscopy – further investigations (including upper endoscopy) to assess location and extent of any CD in the upper GI tract.[1] In clinical practice – however – such investigation for mapping disease extent is not regularly performed at CD diagnosis except for symptoms that are suggestive for upper GI tract involvement.[19] This is mostly attributed to the fact, that the evidence level for this particular ECCO recommendation is weak (evidence level 5, expert opinion) and the grade of recommendation is low (D).[20]

Previous studies on upper GI tract involvement have been limited by the small number of patients or by a cross-sectional study design.[21-23] As of yet, the frequency of upper GI tract involvement, its risk factors and its impact on future disease course have not been systematically assessed in a large, nation-wide IBD cohort from a cross-sectional and longitudinal perspective. It remains further unknown whether the increasing use of upper endoscopies and anti-TNF treatment have changed the landscape and outcome of upper GI tract involvement. Given this current lack of knowledge, we launched this study using data from the nation-wide Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) to answer the following questions: 1) *What is the prevalence of upper GI tract involvement in the SIBDCS?* 2) *What are associated risk factors that predict such*

involvement? And 3) *Is involvement of the upper GI tract associated with a complicated disease outcome?*

METHODS

Study design

In this large, observational study, we retrospectively analyzed prospectively obtained data from the SIBDCS. The SIBDCS started enrolment of IBD patients in 2006 and includes patients from all regions across Switzerland. All patients were diagnosed with IBD according to international guidelines. The SIBDCS is funded by the Swiss National Science Foundation and has been approved by the local ethics committee of each participating center (institutional review board approval No. EK-1316, approved on February 5, 2007). All patients had provided written informed consent prior to inclusion into the SIBDCS.

Study population and data collection

Inclusion criteria for the SIBDCS have been published elsewhere.[24] A thorough clinical and laboratory assessment is performed at the time of inclusion into the study. Patients enrolled in the SIBDCS attend follow-up visits at least once a year. Detailed questionnaires are completed by the patients and the responsible physicians at enrolment and at each follow-up visit. These questionnaires capture clinical, socioeconomic and psychosocial data. These data are collected and validated by the data center of the SIBDCS, which follows rigorous rules to ensure data quality. For the purpose of this study, the following inclusion criteria were applied: i) diagnosis of CD, ii) enrolment into the SIBDCS between 2006 and 2016, and iii) detailed documentation of disease location at the time of diagnosis and during follow-up. The questionnaire used in the SIBDCS assesses current disease location as follows (see **Supplementary Figure 1**): esophagus/stomach (segment A), duodenum/jejunum (segment B), ileum (segment C), cecum (segment D), ascending colon (segment E), transverse colon (segment F), descending colon (segment G), sigmoid (segment H), rectum (segment I), and anus (segment J). In addition, disease location is classified into i) upper gastrointestinal tract, ii) ileal disease only, iii) ileo-colonic disease, and iv) colonic disease only. The SIBDCS questionnaire further assesses disease location at CD diagnosis using the Montreal classification (see definitions). Diagnostic modalities for assessment of disease location are reported and consist of: i) radiological studies, ii) endoscopic studies, and iii) surgery. In case of diagnosis before 2006, data on upper GI tract involvement was retrospectively assessed. For the purpose of this study, patients were excluded if no initial assessment of disease location was available.

Outcome measures and definitions

The following outcome parameters were assessed as possible predictors for the presence of upper GI tract involvement at diagnosis and at any time during the follow-up: gender (females vs. male), age at diagnosis (≤16years vs. >16 years), length of diagnostic delay (continuous variable), smoking at CD diagnosis (yes vs. no), current smoking (yes vs. no), positive family history for CD (at least one first-degree relative with CD; yes vs. no), presence of extra-intestinal manifestations during disease course (yes vs. no), disease duration (continuous variable), and perianal fistulizing disease (yes vs. no).

In order to assess whether or not upper GI tract involvement affects disease outcome, the following surrogate markers for a complicated disease course were assessed: presence of bowel strictures, presence of intestinal and perianal fistulas, and need for CD-related intestinal surgery. Patients presenting with at least one of these complications or undergoing at least one type of CD-related intestinal surgery were summarized as having "any complication". Intestinal surgery was defined as any of the following intervention: surgery for fistula or abscess, ileal resection, ileo-cecal resection, small bowel resection other than terminal ileum, right or left colectomy, colectomy, proctocolectomy, ileostomy, and colostomy.

Disease location was classified according to the Montreal classification.[3] For CD, L1 denotes disease in the terminal ileum, L2 denotes disease in the colon, L3 denotes ileocolonic disease, and L4 denotes disease in the upper gastrointestinal tract. For the purposes of this study, upper GI tract involvement was defined as follows: i) involvement of esophagus or stomach, or ii) involvement of duodenum or jejunum (**Supplementary Figure 1**), based on available diagnostic modalities (endoscopy, radiology, or surgery). Disease duration was defined as the time between CD diagnosis and the beginning of the last available follow-up period. Current age was defined as age at the beginning of the last available follow-up period, while current smoking status referred to the smoking status at the beginning of the last available follow-up period. Diagnostic delay was defined as the time interval from onset of CD-related symptoms, until CD diagnosis was established.[25]

Statistical analysis

All statistical analyses were performed with the statistical package program STATA (version 13.1, College Station, Texas, USA). Data distribution was analyzed using Normal-QQ-Plots. Quantitative data are presented as either mean ± standard deviation (SD) in case of normal distribution or median and interquartile range (IQR) (for non-normally distributed data). Categorical data are summarized as the percentage of the group total. Differences in distributions of quantitative data were assessed by the Student's *t*-test (for normally distributed data) and by the Wilcoxon rank-sum test in case of non-

normally distributed data. Comparison between categorical data was performed using the chi-square test or the exact Fisher's test in case of small sample size (n<10). Stepwise logistic regression modeling was performed in order to evaluate the association between potential risk factors and upper GI tract involvement (=dependent variable). In a first step, the potential risk factors were tested separately (in a univariate model). In a second step, all risk factors with a p-value <0.1 in the univariate analysis were entered together into the multivariate logistic regression model. Kaplan-Meier estimates were used to compute the cumulative incidence of complications stratified by upper GI tract involvement (yes vs. no). The log-rank test was used to detect overall statistical difference in estimates. Cox proportional hazard analysis was used to examine the association of upper GI tract involvement with occurrence of complications. Patients were censored at the time, when first complication occurred, or December 31, 2016. For the purpose of this study, a p-value of <0.05 was considered statistically significant.

RESULTS

Patient demographics

Of the 1840 CD patients enrolled in the SIBDCS at the time of analysis, we included a total of 1638 CD patients. 202 patients were excluded due to unknown disease location. Median age at diagnosis was 26 years (IQR 20-37) with a median diagnostic delay of 5 months (IQR 1-24), 46.8% were males. Median follow-up of these patients (enrolment to last visit) was 5 years (IQR 2-8 years, range 0-11 years). Patient demographic and disease characteristics are shown in **Supplementary Table 1**. The following diagnostic modalities were used to diagnose upper GI tract involvement at CD diagnosis

and during follow-up: 1) radiology 2.8 and 7.5%, 2) endoscopy 97.2% and 90%, and 3) surgery 0 and 2.5%.

Upper gastrointestinal tract involvement at CD diagnosis

We identified 107 patients with upper GI tract involvement at the time of CD diagnosis corresponding to 6.5% of the studied CD cohort. Compared to controls with CD without upper GI tract involvement, these patients were more often males (57.9 vs. 46.1%, p=0.017), younger at diagnosis (median 24 vs. 27 years, p=0.027) and showed a trend towards a longer diagnostic delay (median 7 vs. 5 years, p=0.058). For details see **Table 1**. Frequency of upper GI tract involvement at the time of CD diagnosis was increasing over time. While such involvement was seen in 5.1% of the patients diagnosed between 1955 and 1995, the prevalence of upper GI tract involvement was 11.3% for patients diagnosed between 2009 and 2016 (p=0.001, **Figure 1)**. Most of the patients did not show exclusive upper GI tract involvement as first manifestation of CD. They rather presented with ileocecal CD (56.1%) followed by ileal (16.8%) and colonic CD (14.0%). Frequency of ileal (16.8 vs. 27.6%, p=0.015) and colonic CD (14.0 vs. 22.9%, p=0.034) was lower compared to control patients.

Upper gastrointestinal tract involvement at any time

In a total of 214 patients, upper GI tract involvement was identified at any time of the follow-up (13.1%). Patients with upper GI tract involvement at any time were more often males (57.0 vs. 45.3, p=0.001) and were younger at diagnosis (median 25 vs. 27 years, p=0.011). They more often suffered from Erythema nodosum (11.7 vs. 6.7%, p=0.009) and aphthous ulcers (20.1 vs. 12.2%, p=0.002), and were more likely to be treated with anti-TNF (72.9 vs. 60.5%, p=0.001), but less likely with 5-ASA (48.6 vs. 58.5%, p=0.006) compared to CD controls (**Table 2)**. Compared to controls, patients with upper GI tract involvement were less likely to have colonic CD, both at CD diagnosis (16.4 vs. 23.2%, p=0.025) and at latest follow-up (18.1 vs. 35.7%, p<0.001, **Figure 2)**.

Predictive factors associated with upper gastrointestinal tract involvement

In a multivariate logistic regression model, male sex and diagnosis between 2009 and 2016 (compared to a diagnosis before 1995) were identified as independent predictive factors for the presence of upper GI tract involvement at the time of CD diagnosis (OR 1.600, p=0.021, and OR 2.686, p<0.001), while adult age at diagnosis (>16 years) was a negative predictor (OR 0.388, p=0.001, **Table 3**). Male sex (OR 1.779, p<0.001), presence of Erythema nodosum (OR 1.793, p=0.019), apthous ulcers (OR 1.838, p=0.002), and anti-TNF treatment (OR 1.534, p=0.010) were associated with the presence of upper GI tract involvement at any time, while longer disease duration and adult age at diagnosis (>16 years) were negative predictors (OR 0.981 per year,

p=0.016, and OR 0.585, p=0.014, **Table 4)**.

Impact of upper gastrointestinal tract involvement on CD complications and intestinal surgery

To investigate the impact of upper GI tract involvement on disease course, we analyzed the follow-up of all patients with upper GI tract involvement at the time of CD diagnosis and compared them to controls without such involvement. During a median follow-up of 5 years (IQR 2-8 years), we identified 1049 cases with occurrence of complications (=composite of intestinal stenosis, perianal fistula, intestinal fistula, any fistula, intestinal resection surgery, and surgery for abscess or fistula): 60 cases were detected in the group of patients with upper GI tract involvement at the time of CD diagnosis (56.1%), while 989 cases were observed in the control group (64.6%). Follow-up time of patients with upper GI tract involvement was comparable to that of patients without such involvement (median 4 years, IQR 2-8 years vs. 5 years, IQR 2-8 years, n.s.). Kaplan Meier curves for complication-free survival are depicted in **Figure 3**. There was no significant difference detected between patients with upper GI tract involvement versus patients without such involvement (median time until any complications 6.17 (95% CI 5.67-7.41) vs. 6.42 years (95% CI 5.00-13.01), logrank test p=0.341). Kaplan Meier analysis for internal-fistula free survival showed a trend towards significance with a better outcome in patients with upper GI involvement at the time of CD diagnosis (logrank test p=0.054), other examined complications did not show any differences between the two groups (**Figure 3** and **Supplementary Figure 2**). Hazard ratios for development of complications are summarized in **Table 5**. Again, no significant differences were seen between patients with upper GI tract involvement compared to controls. Subgroup analyses stratified by demographics and risk factors for occurrence of complications did not show any significant effect modification (**Supplementary Table 2**). To further dissect specific locations of L4 phenotype, patients with involvement of esophagus/stomach (Segment A, Supplementary Figure 1) and patients with involvement of duodenum/jejunum (Segment B) were analyzed separately and compared to non-L4 patients with regards to development of future complications. Since data on Segment A vs. B involvement was available from first follow-up visit on only, first follow-up visit was considered baseline evaluation to compute Kaplan Meier curves. No differences were seen between Segment A and B involvement compared to non-L4 involvement in terms of development of stenosis, development of fistula and occurrence of any complications (Supplementary Figure 3). Patients with esophageal/stomach involvement showed even a trend towards less complications and fistula development. However, patients with duodenal/jejunal involvement were more likely to undergo intestinal resection in the follow-up compared to non-L4 patients.

DISCUSSION

Although CD most often affects the ileocecum, CD may actually involve any part of the GI tract. Frequency of upper GI tract involvement has been reported with a large variation. Up to date and in the era of increasing use of upper endoscopies and early-TNF treatment, prevalence rates in a large, nation-wide IBD cohort are unknown, and possible risk factors for and the impact of upper GI involvement on future disease course remain largely elusive. We therefore investigated in a large cohort of CD patients 1) the frequency of upper GI tract involvement at diagnosis and at any time during follow-up; 2) predictive factors associated with the presence of such involvement; and 3) the disease outcome in patients with upper GI tract involvement compared to controls.

Upper GI tract involvement was observed in 6.5% of the patients at the time of CD diagnosis and in 13.1% of the patients at any time during the follow-up. Of note, these rates were increasing over time with 5.1% of the patients showing upper GI involvement at CD diagnosis before 1995, while 11.3% of the patients that were diagnosed between 2009 and 2016 had such involvement. The rates reported in our study are considerably lower than those of recent articles including a comprehensive analysis of the NIDDK IBD Genetics Consortium database (16.4%).[23] They rather mirror prevalence rates of earlier studies. [13-15] This is most probably due to the fact that upper endoscopy is not regularly performed at the time of CD diagnosis, if symptoms are not suggestive for upper GI tract involvement. However, increasing rates over the past few decades with the highest frequency within the past few years go in line with the ECCO guidelines, which actually recommend – although with very low evidence – such an approach.[1] It has yet to be determined whether the difference between rates at diagnosis vs. at any time during the follow-up is due to progressing disease or due to the increasing use of upper endoscopy over time.

Male sex, young age at diagnosis (≤16 years), and a diagnosis after 2009 (compared to before 1995) were the only factors associated with the presence of upper GI tract involvement at CD diagnosis. This is in accordance with a previous publication by Lazarev and colleagues who demonstrated a higher rate of male patients suffering from L4 compared to non-L4 disease (53 vs. 47%, p=0.02).[23] Our multivariate logistic regression model makes this data more robust. The identification of the time point of diagnosis as a predictive factor may be largely attributed to the increasing use of upper endoscopy over time regardless of initial symptoms as suggested by the current ECCO guidelines.[1] Of note, no other predictive factors were identified in this logistic regression analysis. Neither BMI, family history, smoking status nor diagnostic delay was able to predict upper GI tract involvement *at the time of CD diagnosis*. However, anti-TNF treatment, and presence of Erythema nodosum and oral ulcers were positively associated with upper GI tract involvement *at any time*, while disease duration was negatively associated. The effect of anti-TNF treatment has to be interpreted cautiously; it is actually more likely, that patients with upper GI tract involvement have a higher chance of being treated with biologics given previous data suggesting higher complication rates in these patients, although the latter was not confirmed in our study. The retrospective nature of the analysis does not make it possible to disentangle this relationship.

Disease course of patients with upper GI tract involvement at the time of CD diagnosis does not appear to be significantly different from that of control CD patients. Moreover, patients with upper GI tract involvement seem to show an even better outcome regarding development of intestinal fistulas, which was particularly observed in patients with esophageal/stomach involvement. Even a subgroup analysis for patients with duodenal/jejunal involvement revealed an outcome

similar to that of non-upper GI tract patients, except for higher rates of intestinal resection. This contrasts previous findings, which suggested higher rates of complications in L4 patients. It has been previously shown that L4 phenotype is associated with structuring disease and abdominal surgery (compared to non-L4 CD).[23] There are two possible explanations for our results: 1) upper GI tract involvement is indeed no risk factor for a complicated disease outcome. This is supported by a Cox regression model stratified by demographics and multiple risk factors without any significant modifying effect on disease outcome in patients with upper GI tract involvement. 2) Increased detection of patients with upper GI tract involvement at the time of diagnosis due to increased use of upper endoscopy over time may have resulted in over-diagnosis of such involvement considering even minor and particularly asymptomatic involvement as significant. Therefore, its potentially negative effect on disease course may have been vanished. Either or our data question the current guidelines, which recommend – based on expert opinion only – upper endoscopy regardless of symptoms.[1] One might argue that increased use of anti-TNF in patients with upper GI tract involvement has resulted in a favourable outcome. However, even after correcting for anti-TNF treatment, outcome of patients with vs. without such involvement appears to be the same. In patients never treated with anti-TNF, there was even a trend towards a better outcome with upper GI tract involvement at the time of CD diagnosis. Prospective trials are needed in order to investigate, whether or not upper endoscopy and early identification of upper GI tract involvement has its value.

Our study has several strengths and limitations. We analyzed a large number of patients (>1600) in a nation-wide IBD cohort. Stringent inclusion and exclusion criteria, close follow-up, and standardized enrolment and follow-up questionnaires completed by both patients and physicians minimized the drawback of a retrospective data analysis. In addition, disease location is reported in detail in the Swiss IBD cohort, both at enrolment and during follow-up. In most of the patients (>90%), disease location was assessed by endoscopy, although the SIBDCS questionnaire did not capture the number of upper vs. lower endoscopies for assessment of disease location. A median follow-up of 5 years makes the outcome analysis of patients with upper GI tract involvement at the time of CD diagnosis vs. controls more reliable. However, there might be a possible selection bias given the fact that the SIBDCS is not population based. Patients with more severe course (recruited at tertiary referral centers) might be overrepresented. Thus, our findings cannot be applied one to one to a general IBD population. It cannot be ruled out that some non-specific endoscopic changes due to NSAR intake or H. pylori infection were misinterpreted as CD manifestations, therefore the frequency of upper GI tract involvement might have been overestimated. Due to the nature of our study and the reliance on retrospective questionnaires, independent verification of physician`s findings was not feasible. Given the fact that these data are not independent, it was not possible to determine direction of the association between anti-TNF treatment and upper GI tract involvement. A clear

limitation is that our questionnaire does not distinguish between duodenal and jejunal disease. Therefore, a separate analysis for jejunal upper GI tract involvement vs. non-jejunal upper GI tract involvement was not feasible, although jejunal disease has been previously identified as a risk factor for CD complications.[23] Very lately, both L4 jejunal and L4 proximal ileal disease were associated with higher rates of intestinal resection.[26] At least, we were able to perform subgroup analysis for esophageal/stomach and duodenal/jejunal involvement. While the latter group was more likely to undergo intestinal resection in the follow-up, there were otherwise no differences in terms of development of future complications in both groups compared to non-L4 patients. We defined severe disease course as development of complications in the follow-up only, which is a rather hard outcome. There might be differences between non-L4 and L4 regarding softer outcomes such as seen for Erythema nodosum, which was associated with upper GI tract involvement in the follow-up. However, we did not include extraintestinal manifestations in our definition of severe disease.

In conclusion, upper GI tract involvement is frequently observed and prevalence has been increasing over the past decades, most probably due to an increasing use of screening upper endoscopies. Male sex and young age ≤16 years were identified as the main predictive factors for upper GI tract involvement at the time of CD diagnosis. Even after correcting for anti-TNF treatment, patients with upper GI tract involvement at CD diagnosis did not show a worse outcome compared to controls. This questions the current recommendation for screening by upper endoscopy at the time of CD diagnosis regardless of symptoms. Prospective trials are needed evaluating the value of such early upper endoscopy.

WHAT IS KNOWN?

- Frequency of upper gastrointestinal (GI) tract involvement in Crohn`s disease (CD) has been reported with a large variation.
- Risk factors and disease course of patients with upper GI tract involvement remain elusive.
- Current guidelines recommend screening for upper GI tract involvement at the time of CD diagnosis regardless of symptoms, although evidence level is low.

WHAT IS NEW?

- Upper GI tract involvement was observed in 6.5% of patients at the time of CD diagnosis and in 13.1% of patients at any time during the follow-up.
- Frequency of upper GI tract involvement at diagnosis was increasing over time with the highest rates between 2009 and 2016.
- Male sex, young age ≤16 years and a diagnosis between 2009 and 2016 were identified as predictive factors for upper GI tract involvement at the time of CD diagnosis.
- Patients with upper GI tract involvement did not show a worse outcome compared to controls, questioning the role of upper endoscopy at CD diagnosis in all patients regardless of symptoms.

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CONFLICT OF INTERESTS

The authors declare that no conflict of interests exists.

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TABLES AND FIGURES

Table 1: Patient demographic and disease characteristics of CD patients with upper GI tract involvement at diagnosis versus control CD patients without such involvement of the proximal GI tract.

Table 2: Patient demographic and disease characteristics of CD patients with upper GI tract involvement at any time versus control CD patients without such involvement of the proximal GI tract.

Table 3: Univariate and multivariate logistic regression model for prediction of upper GI tract involvement at the time of CD diagnosis.

Table 4: Univariate and multivariate logistic regression model for prediction of upper GI tract involvement at any time.

Table 5: Hazard ratios for development of complications in patients with upper GI tract involvement at the time of CD diagnosis compared to controls.

Figure 1: Frequency of upper GI tract involvement at diagnosis according to the year of CD diagnosis.

Figure 2: Disease location other than upper GI tract at CD diagnosis and at latest follow-up in patients with upper GI tract involvement (at any time) versus CD controls.

Figure 3: Kaplan Meier analysis for occurrence of stenosis (A), internal fistula (B), resection surgery (C), and any complications (D).

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TABLES

Table 1

	No Upper GI involvement at diagnosis	Upper GI involvement at diagnosis	p-value
Number of patients	1531	107	
Sex			
Male	705 (46.1)	62 (57.9)	
Female	826 (53.9)	45 (42.1)	0.017
Age at diagnosis [years]	27, 20-37	24, 18-35	
(median, IQR, range)	1-81	11-74	0.027
Age at diagnosis			
16 or less	143 (9.4)	19 (17.8)	
More than 16	1387 (90.7)	88 (82.2)	0.005
Year of diagnosis			
1955-1995	431 (28.2)	23 (21.5)	
1996-2003	380 (24.8)	17 (15.9)	
2004-2008	396 (25.9)	26 (24.3)	
2009-2016	323 (21.1)	41 (38.3)	<0.001
Diagnostic delay [months]	5, 1-23	7, 2-32	
(median, IQR, range)	0-404	0-531	0.058
BMI [kg/m^2]	24, 21-27	23, 21-26	
(median, IQR, range)	13-49	15-46	0.383
Other disease location at diagnosis			
L1	423 (27.6)	18 (16.8)	
L2	350 (22.9)	15 (14.0)	
L3	758 (49.5)	60 (56.1)	0.019
No other location	-	14 (13.1)	
Smoking status at diagnosis			
Non-Smoker	755 (51.3)	54 (52.9)	
Smoker	718 (48.7)	48 (47.1)	0.742
NSAID intake at CD onset			
No	1000 (82.6)	76 (84.4)	
Yes	210 (17.4)	14 (15.6)	0.663
Family history of IBD			
No	1166 (84.6)	84 (87.5)	
Yes	212 (15.4)	12 (12.5)	0.447

Table 1: Patient demographic and disease characteristics of CD patients with upper GI tract involvement at diagnosis versus control CD patients without such involvement of the proximal GI tract.

Table 2

	No Upper GI involvement at any time during disease history	Upper GI involvement any time during disease history	p-value
Number of patients	1424	214	
Sex			
Male	645 (45.3)	122 (57.0)	
Female	779 (54.7)	92 (43.0)	0.001
Age at diagnosis [years]	27, 20-37	25, 19-34	
(median, IQR, range)	1-81	5-74	0.011
Age at diagnosis			
16 or less	129 (9.1)	33 (15.4)	
More than 16	1294 (90.9)	181 (84.6)	0.004
Year of diagnosis			
1955-1995	406 (28.5)	48 (22.4)	
1996-2003	354 (24.9)	43 (20.1)	
2004-2008	361 (25.4)	61 (28.5)	
2009-2016	302 (21.2)	62 (29.0)	0.019
Diagnostic delay [months]	5, 123	6, 1-24	
(median, IQR, range)	0-404	0-530	0.501
Age [years]	44, 33-56	37, 29-51	
(median, IQR, range)	16-94	17-81	<0.001
Disease duration [years]	12, 7-21	10, 6-19	
(median, IQR, range)	0-57	0-52	0.009
BMI [kg/m^2]	24, 21-27	23, 21-26	
(median, IQR, range)	13-49	15-46	0.232
Other disease location at diagnosis			
L1	393 (27.6)	48 (22.4)	
L2	330 (23.2)	35 (16.4)	
L3	701 (49.2)	117 (54.5)	0.042
No other location	-	14 (6.5)	
Other disease location at latest follow-up			
L1	416 (33.5)	63 (30.7)	
L2	443 (35.7)	37 (18.1)	
L3	382 (30.8)	64 (31.2)	0.003
No other location	-	41 (20.)	
Smoking status at diagnosis			
Non-Smoker	703 (51.2)	106 (52.5)	
Smoker	670 (48.8)	96 (47.5)	0.735
Smoking status at latest follow-up			
Non-smoker	964 (68.2)	146 (68.2)	
Smoker	449 (31.8)	68 (31.8)	1.000
NSAID intake at CD onset			
No	932 (82.8)	144 (82.3)	
Yes	193 (17.2)	31 (17.7)	0.856
Family history of IBD			
No	1092 (85.1)	158 (83.2)	
Yes	192 (14.9)	32 (16.8)	0.498
Disease behavior			
B1	743 (52.2)	109 (50.9)	

B2 B3	452 (31.7) 229 (16.1)	72 (33.7) 33 (15.4)	0.854
Perianal disease			
No Yes	913 (64.1) 511 (35.9)	139 (65.0) 75 (35.0)	 0.812
Surgical history			
Intestinal resection	574 (40.3)	91 (42.5)	0.539
Fistula/Abscess surgery	345 (24.2)	54 (25.2)	0.749
Any surgery	716 (50.3)	110 (51.4)	0.760
EIM history			
No Yes	646 (45.4) 778 (54.6)	85 (39.7) 129 (60.3)	 0.121
Arthritis/Arthralgia	676 (47.5)	109 (50.9)	0.344
Uveitis/Iritis	150 (10.5)	18 (8.4)	0.340
Pyoderma gangrenosum	22 (1.5)	2 (0.9)	0.760
Erythema nodosum	95 (6.7)	25 (11.7)	0.009
Aphtous/oral ulcers	174 (12.2)	43 (20.1)	0.002
Ankylosing spondylitis	108 (7.6)	11 (5.1)	0.199
PSC	8 (0.6)	1 (0.5)	1.000
Medication history			
5-ASA	833 (58.5)	104 (48.6)	0.006
Antibiotics	234 (16.4)	45 (21.0)	0.095
Steroids	1225 (86.0)	194 (90.7)	0.064
Immunomodulators	1153 (81.0)	178 (83.2)	0.440
Anti-TNF agents	862 (60.5)	156 (72.9)	0.001
Calcineurin inhibitors	24 (1.7)	4 (1.9)	0.778

Table 2: Patient demographic and disease characteristics of CD patients with upper GI tract involvement at any time versus control CD patients without such involvement of the proximal GI tract.

Table 3

Outcome: Upper GI involvement at diagnosis	Univariate		Multivariate	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Sex				
Male (ref)	1.000 (-)		1.000 (-)	
Female	0.619 (0.417-0.921)	0.018	0.625 (0.418-0.932)	0.021
Age at diagnosis				
16 or less	1.000 (-)		1.000 (-)	
More than 16	0.478 (0.283-0.807)	0.006	0.388 (0.225-0.668)	0.001
Age at diagnosis [per year]	0.988 (0.972 – 1.003)	0.113		
Year of diagnosis				
1955-1995 (ref)	1.000 (-)		1.000 (-)	
1996-2003	0.838 (0.441-1.593)	0.590	0.830 (0.435-1.582)	0.571
2004-2008	1.230 (0.691-2.192)	0.482	1.270 (0.710-2.274)	0.421
2009-2016	2.379 (1.399-4.044)	0.001	2.686 (1.559-4.625)	<0.001
Initial location				
No ileal involvement (ref)	1.000 (-)			
Ileal involvement	0.797 (0.512-1.241)	0.315		
BMI [kg/m^2]				
< 30	1.000 (-)			
≥ 30	0.925 (0.485-1.762)	0.812		
Family history of IBD				
No (ref)	1.000 (-)			
Yes	0.786 (0.422-1.464)	0.448		
Smoking status at diagnosis				
Non-smoker (ref)	1.000 (-)			
Smoker	0.935 (0.625-1.397)	0.742		
Diagnostic delay [per month]	1.003 (0.999-1.006)	0.128		

Table 3: Univariate and multivariate logistic regression model for prediction of upper GI tract involvement at the time of CD diagnosis.

Table 4

Outcome: Upper GI involvement at any time	Univariate		Multivariate	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Sex				
Male (ref)	1.000 (-)		1.000 (-)	
Female	0.624 (0.467-0.834)	0.001	0.562 (0.415-0.761)	<0.001
Age at diagnosis				
16 or less	1.000 (-)		1.000 (-)	
More than 16	0.547 (0.362-0.826)	0.004	0.585 (0.382-0.897)	0.014
Initial location				
No ileal involvement (ref)	1.000 (-)			
Ileal involvement	1.016 (0.722-1.430)	0.929		
BMI				
< 30	1.000 (-)			
≥ 30	0.733 (0.440-1.222)	0.234		
Disease duration [per year]	0.984 (0.970-0.999)	0.037	0.981 (0.966-0.996)	0.016
Family history of IBD				
No (ref)	1.000 (-)			
Yes	1.152 (0.765-1.735)	0.499		
Smoking status at diagnosis				
Non-smoker (ref)	1.000 (-)			
Smoker	0.950 (0.707-1.277)	0.735		
Appendectomy history				
No (ref)	1.000 (-)		1.000 (-)	
Yes	0.617 (0.350-1.090)	0.096	0.648 (0.364-1.152)	0.139
EIM history				
No (ref)	1.000 (-)			
Yes	1.260 (0.940-1.689)	0.122		
EIM history				
Arthritis/Arthralgia	1.149 (0.862-1.531)	0.345		
Uveitis/Iritis	0.780 (0.468-1.301)	0.341		
Pyoderma gangrenosum	0.601 (0.140-2.575)	0.493		
Erythema nodosum	1.850 (1.161-2.949)	0.010	1.793 (1.100-2.982)	0.019
Aphtous/Oral ulcers	1.806 (1.248-2.615)	0.002	1.838 (1.249-2.705)	0.002
Ankylosing spondylitis	0.660 (0.649-1.249)	0.202		
PSC	0.831 (0.103-6.677)	0.862		
CD-related surgery				
No (ref)	1.000 (-)			
Yes	1.046 (0.785-1.394)	0.760		
Behaviour				
B1 (ref)	1.000 (-)			
B2	1.085 (0.789-1.495)	0.614		
B3	0.982 (0.648-1.490)	0.933		
Perianal disease				
No (ref)	1.000 (-)			
Yes	0.964 (0.713-1.303)	0.812		
Immunomodulator				
No (ref)	1.000 (-)			
Yes	1.162 (0.793-1.702)	0.441		
Anti-TNF				

No (ref) Yes	1.000 (-) 1.754 (1.274-2.414)	0.001	1.000 (-) 1.534 (1.106-2.127)	0.010

Table 4: Univariate and multivariate logistic regression model for prediction of upper GI tract involvement at any time.

Table 5

	HR (95% CI)	p-value
Stenosis	1.063 (0.445 – 2.540)	p=0.758
Perianal Fistula	0.988 (0.399 – 2.448)	p=0.955
Intestinal Fistula	0.418 (0.064 – 3.046)	p=0.369
Any Fistula	0.783 (0.325 – 1.892)	p=0.228
Resection Surgery	0.945 (0.427 – 2.090)	p=0.730
Fistula/Abscess Surgery	0.902 (0.323 – 2.517)	p=0.708
Any Complication	0.887 (0.409 – 1.920)	p=0.438

Table 5: Hazard ratios for development of complications in patients with upper GI tract involvement at the time of CD diagnosis compared to controls.