Journal of Crohn's and Colitis, 2018, 1399–1409
doi:10.1093/ecco-jcc/jjy121
Advance Access publication August 25, 2018
Original Article

Original Article

Upper Gastrointestinal Tract Involvement in Crohn's Disease: Frequency, Risk Factors, and Disease Course

Thomas Greuter,[a,*] Alberto Piller,[a,*] Nicolas Fournier,[b] Ekaterina Safroneeva,[c] Alex Straumann,[a] Luc Biedermann,[a] Sébastien Godat,[d] Andreas Nydegger,[e] Michael Scharl,[a] Gerhard Rogler,[a] Stephan R. Vavricka,[a,§] Alain M. Schoepfer[d,§]; on behalf of the Swiss IBD Cohort Study Group

[a]Department of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland [b]Insitute of Social and Preventive Medicine, University Hospital Lausanne – CHUV, Lausanne, Switzerland [c]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland [d]Division of Gastroenterology and Hepatology, University Hospital Lausanne – CHUV, Lausanne, Switzerland [e]Division of Pediatrics, University Hospital Lausanne – CHUV, Lausanne, Switzerland

Corresponding author: Alain M. Schoepfer, MD, Division of Gastroenterology and Hepatology, Centre hospitalier universitaire Vaudois/CHUV and University of Lausanne, Rue du Bugnon 44, 1011 Lausanne, Switzerland. Tel.: +41 21 314 2394; fax: +41 21 314 4718; email: alain.schoepfer@chuv.ch

*These authors contributed equally.

[§]These authors share last authorship.

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 analysed. Patients with upper GI tract involvement were compared with 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 1955–95 versus 11.3% for 2009–16]. In a multivariate logistic regression model, male sex and diagnosis between 2009 and 2016 [versus before 1995] were independent predictors for presence of upper GI tract involvement at CD diagnosis (odds ratio [OR] 1.600, $p = 0.021$ and OR 2.686, $p < 0.001$, respectively), whereas 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 (hazard ratio [HR] for any complications 0.887, (95% confidence interval [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; oesophagus; stomach; duodenum; jejunum

1. 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 ileocaecum, it may involve any portion of the GI tract, from the oral cavity to the anus. Upper GI tract involvement refers to affection of oesophagus, stomach, duodenum, and jejunum, which may occur either isolated [Montreal Classification L4] or together with other CD locations [L-13].[3] Typical CD-related endoscopic lesions of the oesophagus consist of aphthae, erosions, and ulcers [not related to gastro-oesophageal 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 of 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 [radiological examinations in early studies versus 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, nationwide IBD cohort from a cross-sectional and longitudinal perspective. It remains further unknown whether the increasing use of upper endoscopies and anti-tumour necrosis factor [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 nationwide 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? 3] Is involvement of the upper GI tract associated with a complicated disease outcome?

2. Methods

2.1. Study design

In this large, observational study, we retrospectively analysed 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 centre [institutional review board approval No. EK-1316, approved on February 5, 2007]. All patients had provided written informed consent before inclusion into the SIBDCS.

2.2. 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 centre 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, available as Supplementary data at *ECCO-JCC* online]: oesophagus/stomach [segment A], duodenum/jejunum [segment B], ileum [segment C], caecum [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 in the Introduction section]. 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.

2.3. 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 versus male], age at diagnosis [≤ 16 years versus > 16 years], length of diagnostic delay [continuous variable], smoking at CD diagnosis [yes versus no], current smoking [yes versus no], positive family history for CD [at least one first-degree relative with CD; yes versus no], presence of extra-intestinal manifestations during disease course [yes versus no], disease duration [continuous variable], and perianal fistulising disease [yes versus 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 summarised as having 'any complication'. Intestinal surgery was defined as any of the following interventions: surgery

for fistula or abscess, ileal resection, ileo-caecal 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 oesophagus 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 latest available follow-up period. Current age was defined as age at the beginning of the latest available follow-up period, and current smoking status referred to the smoking status at the beginning of the latest available follow-up period. Diagnostic delay was defined as the time interval from onset of CD-related symptoms to established CD diagnosis.[25]

2.4. Statistical analysis

All statistical analyses were performed with the statistical package program STATA [version 13.1, College Station, TX, USA]. Data distribution was analysed 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 summarised as the percentage of the group total. Differences in distributions of quantitative data were assessed by 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 Fisher's exact test in case of small sample size [$n < 10$]. Stepwise logistic regression modelling 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 versus 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 on December 31, 2016. For the purpose of this study, a p-value of < 0.05 was considered statistically significant.

3. Results

3.1. 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 latest visit] was 5 years [IQR 2–8 years, range 0–11 years]. Patient demographic and disease characteristics are shown in Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online. The following diagnostic modalities were used to diagnose upper GI tract involvement at CD diagnosis and during follow-up, respectively: 1] radiology 2.8% and 7.5%; 2] endoscopy 97.2% and 90%; and 3] surgery 0 and 2.5%.

3.2. 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 with controls with CD without upper GI tract involvement, these patients were more often males [57.9% versus 46.1%, $p = 0.017$], younger at diagnosis [median 24 versus 27 years, $p = 0.027$], and showed a trend towards a longer diagnostic delay [median 7 versus 5 years, $p = 0.058$]; for details see Table 1. Frequency of upper GI tract involvement at the time of CD diagnosis increased over time. Whereas 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 ileocaecal CD [56.1%] followed by ileal [16.8%] and colonic CD [14.0%]. Respective frequency of ileal [16.8% versus 27.6%, $p = 0.015$] and colonic CD [14.0% versus 22.9%, $p = 0.034$] was lower compared with control patients.

3.3. Upper gastrointestinal tract involvement at any time

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

3.4. Predictive factors associated with upper gastrointestinal tract involvement

In a multivariate logistic regression model, male sex and diagnosis between 2009 and 2016 [compared with a diagnosis before 1995] were identified as independent predictive factors for the presence of upper GI tract involvement at the time of CD diagnosis (odds ratio [OR] 1.600, $p = 0.021$, and OR 2.686, $p < 0.001$), whereas 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, whereas 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, $p = 0.014$, respectively Table 4].

3.5. 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 analysed the follow-up of all patients with upper GI tract involvement at the time of CD diagnosis and compared them with controls without such involvement. During a median follow-up of

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.

	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	0.027
[median, IQR, range]	1–81	11–74	
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	0.058
[median, IQR, range]	0–404	0–531	
BMI [kg/m^2]	24, 21–27	23, 21–26	0.383
[median, IQR, range]	13–49	15–46	
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

CD, Crohn's disease; GI, gastrointestinal; IQR, interquartile range; BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug; IBD, inflammatory bowel disease.

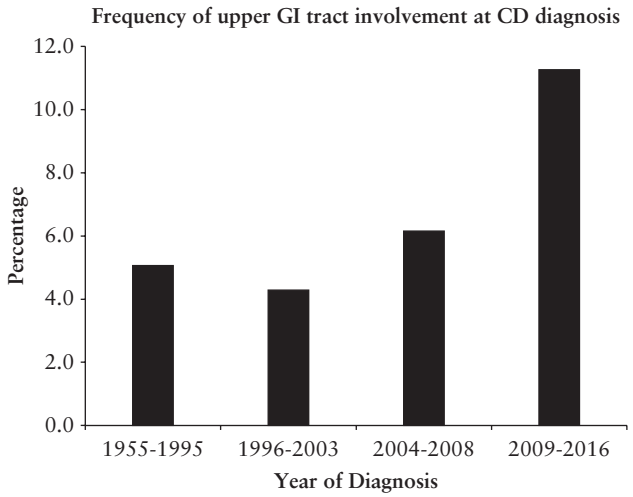

Figure 1. Frequency of upper GI tract involvement at diagnosis according to the year of CD diagnosis. GI, gastrointestinal; CD, Crohn's disease.

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%], and 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 versus 5 years, IQR 2–8 years, not significant]. 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] versus 6.42 [95% CI 5.00–13.01] years, log-rank 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 [log-rank test $p = 0.054$]; other examined complications did not show any differences between the two groups [Figure 3, and Supplementary Figure 2, available as Supplementary data at *ECCO-JCC* online]. Hazard ratios for development of complications are summarised in Table 5. Again, no significant differences were seen between patients with upper GI tract involvement compared with controls. Subgroup analyses stratified by demographics and risk factors for occurrence of complications did not show any significant effect modification [Supplementary Table 2, available as Supplementary data at *ECCO-JCC* online].

To further dissect specific locations of L4 phenotype, patients with involvement of aesophagus/stomach [Segment A, Supplementary

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

	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	0.011
[median, IQR, range]	1-81	5–74	
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	0.501
[median, IQR, range]	0–404	0–530	
Age [years]	44, 33–56	37, 29–51	<0.001
[median, IQR, range]	16–94	17–81	
Disease duration [years]	12, 7–21	10, 6–19	0.009
[median, IQR, range]	0–57	0–52	
BMI [kg/m^2]	24, 21–27	23, 21–26	0.232
[median, IQR, range]	13–49	15–46	
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 behaviour			
B1	743 [52.2]	109 [50.9]	
B2	452 [31.7]	72 [33.7]	
B3	229 [16.1]	33 [15.4]	0.854
Perianal disease			
No	913 [64.1]	139 [65.0]	
Yes	511 [35.9]	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	646 [45.4]	85 [39.7]	
Yes	778 [54.6]	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

Table 2. Continued

	No upper GI involvement at any time during disease history	Upper GI involvement any time during disease history	*p*-Value
Erythema nodosum	95 [6.7]	25 [11.7]	0.009
Aphthous/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

CD, Crohn's disease; GI, gastrointestinal; IQR, interquartile range; BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug; IBD, inflammatory bowel disease; EIM, extra-intestinal manifestation; PSC, primary sclerosing cholangitis; 5-ASA, 5-aminosalicylic acid; TNF, tumour necrosis factor.

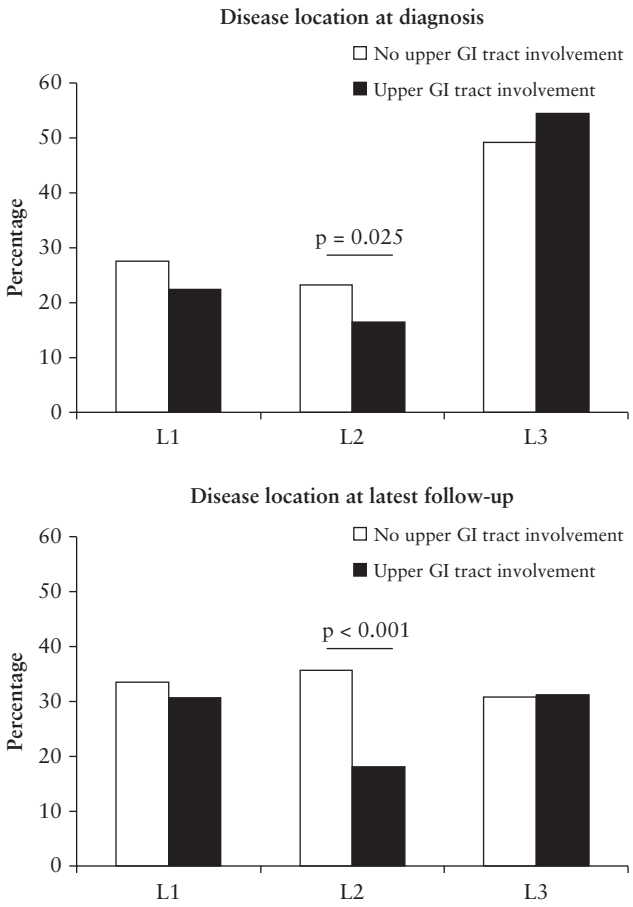

Figure 2. Disease location other than upper GI tract at CD diagnosis and at latest follow-up in patients with upper GI tract involvement [at any time] versus CD controls. GI, gastrointestinal; CD, Crohn's disease.

Figure 1] and patients with involvement of duodenum/jejunum [Segment B] were analysed separately and compared with non-L4 patients with regards to development of future complications. Since data on Segment A versus Segment B involvement were 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 with non-L4 involvement in terms of development of stenosis, development of fistula, and occurrence of any complications [Supplementary Figure 3, available as Supplementary data at *ECCO-JCC* online]. Patients with oesophageal/stomach involvement even showed 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 with non-L4 patients.

4. Discussion

Although CD most often affects the ileocaecum, CD may actually involve any part of the GI tract. Frequency of upper GI tract involvement has been reported with a large variation. To date and in the era of increasing use of upper endoscopies and early TNF treatment, prevalence rates in a large, nationwide 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 with 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, whereas 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 [rate of 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 versus at any time during the follow-up is due to progressing disease or due to the increasing use of upper endoscopy over time.

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

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		

GI, gastrointestinal; CD, Crohn's disease; OR, odds ratio; CI, confidence interval; ref, reference value; BMI, body mass index; IBD, inflammatory bowel disease.

Male sex, young age at diagnosis [≤ 16 years], and a diagnosis after 2009 [compared with 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 with non-L4 disease [53% versus 47%, $p = 0.02$].[23] Our multivariate logistic regression model makes thede 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 body mass index [BMI], family history, smoking status, oror 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, whereas 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 were 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 oesophageal/stomach involvement. However, 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 with previous findings, which suggested higher rates of complications in L4 patients. It has been previously shown that the L4 phenotype is associated with stricturing disease and abdominal surgery [compared with non-L4 CD].[23] There are two possible explanations for our results. First, 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. Second, 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 vanished. Either of 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 versus 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 analysed a large number of patients [> 1600] in a nationwide IBD cohort.

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

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
Aphthous/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]	1.000 [-]		1.000 [-]	
Yes	1.754 [1.274–2.414]	0.001	1.534 [1.106–2.127]	0.010

GI, gastrointestinal; CD, Crohn's disease; OR, odds ratio; CI, confidence interval; ref, reference value; BMI, body mass index; IBD, inflammatory bowel disease; EIM, extra-intestinal manifestation; PSC, primary sclerosing cholangitis; TNF, tumour necrosis factor.

Stringent inclusion and exclusion criteria, close follow-up, and standardised enrolment and follow-up questionnaires completed by both patients and physicians minimised the drawbacks 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 versus 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, versus 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 centres] might be over-represented. 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 non-steroidal

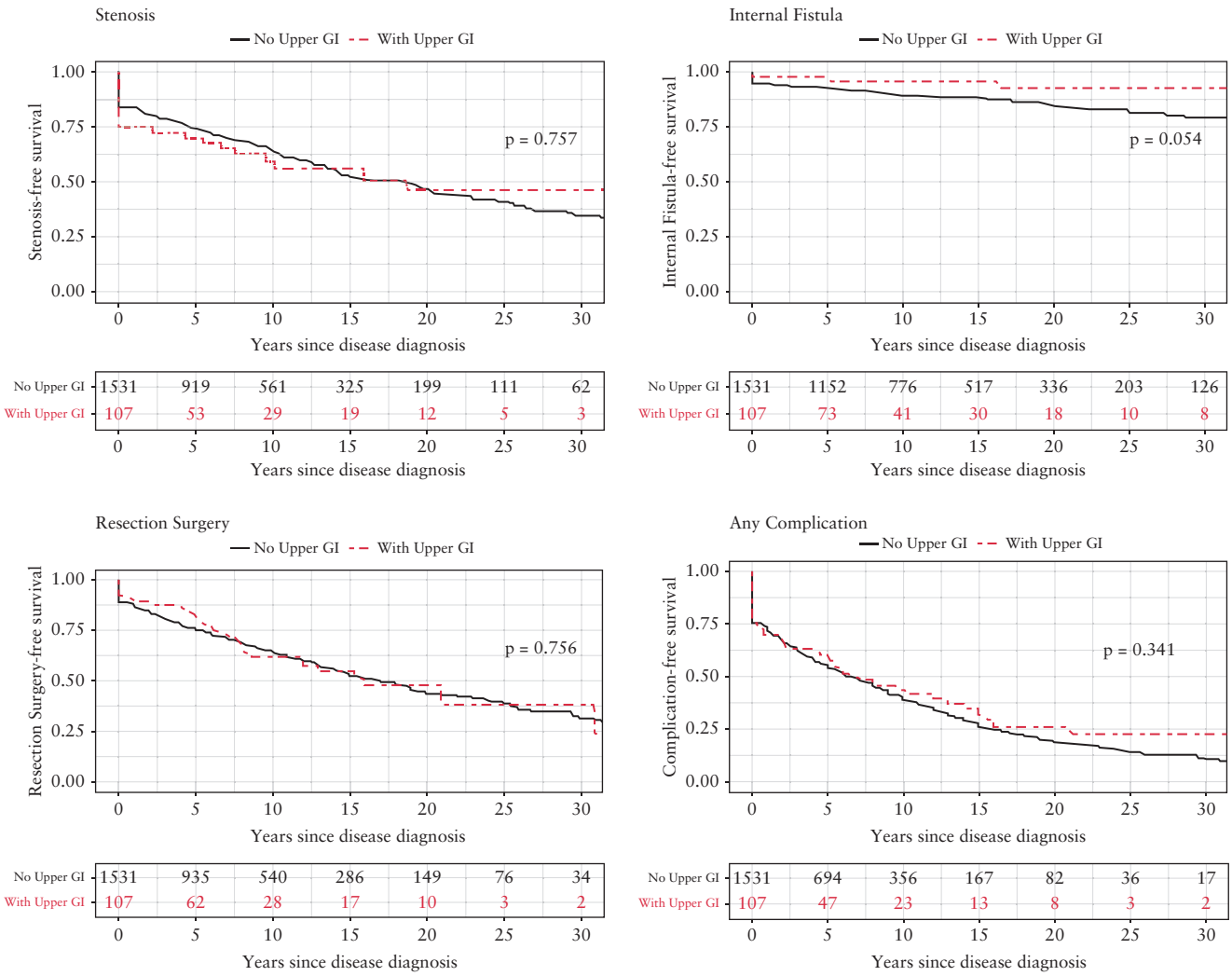

Figure 3. KaplanMeier analysis for occurrence of stenosis [A], internal fistula [B], resection surgery [C], and any complications [D].

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

	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]	$p = 0.438$

GI, gastrointestinal; CD, Crohn's disease; HR, hazard ratio; CI, confidence interval.

anti-infammatory drugs intake or *Helicobacter 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 versus 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 have been associated with higher rates of intestinal resection.[26] At least we were able to perform subgroup analysis for oesophageal/stomach and duodenal/jejunal involvement. The latter group was more likely to undergo intestinal resection in the follow-up, but there were otherwise no differences in terms of development of future complications in either group compared with 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 recent 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 with controls. This questions the current recommendation for screening by upper endoscopy at the time of CD diagnosis, regardless of symptoms. Prospective trials are needed to evaluate the value of such early upper endoscopy.

4.1. 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.

4.2. 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 with controls, questioning the role of upper endoscopy at CD diagnosis in all patients regardless of symptoms.

Funding

This work was supported by research grants from the Swiss National Science Foundation to AMS [grant No. 32003B_160115/1], to GR [grant No. 310030-120312], to SRV [grant No. 320000-114009/3 and 32473B_135694/1], to TG [grant No. P2ZHP3_168561] and to the Swiss IBD Cohort [grant no. 33CS30_148422].

Conflict of Interest

The authors declare that no conflict of interests exists.

Acknowledgements

The authors would like to thank all patients and members of the Swiss IBD cohort study.

Members of the SIBDCS study group include: Karim Abdelrahman, Gentiana Ademi, Patrick Aepli, Amman Thomas, Claudia Anderegg, Anca-Teodora Antonino, Eva Archanioti, Eviano Arrigoni, Diana Bakker de Jong, Bruno Balsiger, Polat Bastürk, Peter Bauerfeind, Andrea Becocci, Dominique Belli, José M. Bengoa, Luc Biedermann, Janek Binek, Mirjam Blattmann, Stephan Boehm, Tujana Boldanova, Jan Borovicka, Christian P. Braegger, Stephan Brand, Lukas Brügger, Simon Brunner, Patrick Bühr, Bernard Burnand, Sabine Burk, Emanuel Burri, Sophie Buyse, Dahlia-Thao Cao, Ove Carstens, Dominique H. Criblez, Sophie Cunningham, Fabrizia D'Angelo, Philippe de Saussure, Lukas Degen, Joakim Delarive, Christopher Doerig, Barbara Dora, Susan Drerup, Mara Egger, Ali El-Wafa, Matthias Engelmann, Jessica Ezri, Christian Felley, Markus Fliegner, Nicolas Fournier, Montserrat Fraga, Yannick Franc, Pascal Frei, Remus Frei, Michael Fried, Florian Froehlich, Raoul Ivano Furlano, Luca Garzoni, Martin Geyer, Laurent Girard, Marc Girardin, Delphine Golay, Ignaz Good, Ulrike Graf Bigler, Beat Gysi, Johannes Haarer, Marcel Halama, Janine Haldemann, Pius Heer, Benjamin Heimgartner, Beat Helbling, Peter Hengstler, Denise Herzog, Cyrill Hess, Roxane Hessler, Klaas Heyland, Thomas Hinterleitner, Claudia Hirschi, Petr Hruz, Pascal Juillerat, Carolina Khalid-de Bakker, Stephan Kayser, Céline Keller, [Christina Knellwolf [-Grieger]], Christoph Knoblauch, Henrik Köhler, Rebekka Koller, Claudia Krieger[-Grübel], Patrizia Künzler, Rachel Kusche, Frank Serge Lehmann, Andrew Macpherson, Michel H. Maillard, Michael Manz, Astrid Marot, Rémy Meier, Christa Meyenberger, Pamela Meyer, Pierre Michetti, Benjamin Misselwitz, Patrick Mosler, Christian Mottet, Christoph Müller, Beat Müllhaupt, Leilla Musso, Michaela Neagu, Cristina Nichita, Jan Niess, Andreas Nydegger, Nicole Obialo, Diana Ollo, Cassandra Oropesa, Ulrich Peter, Daniel Peternac, Laetitia Marie Petit, Valérie Pittet, Daniel Pohl, Marc Porzner, Claudia Preissler, Nadia Raschle, Ronald Rentsch, Alexandre Restellini, Sophie Restellini, Jean-Pierre Richterich, Frederic Ris, Branislav Risti, Marc Alain Ritz, Gerhard Rogler, Nina Röhrich, Jean-Benoît Rossel, Vanessa Rueger, Monica Rusticeanu, Markus Sagmeister, Gaby Saner, Bernhard Sauter, Mikael Sawatzki, Michael Scharl, Martin Schelling, Susanne Schibli, Hugo Schlauri, Dominique Schluckebier, Daniela Schmid, Sybille Schmid [-Uebelhart], Jean-François Schnegg, Alain Schoepfer, Vivianne Seematter, Frank Seibold, Mariam Seirafi, Gian-Marco Semadeni, Arne Senning, Christiane Sokollik, Joachim Sommer, Johannes Spalinger, Holger Spangenberger, Philippe Stadler, Peter Staub, Dominic Staudenmann, Volker Stenz, Michael Steuerwald, Alex Straumann, Bruno Strebel, Andreas Stulz, Michael Sulz, Aurora Tatu, Michela Tempia-Caliera, Joël Thorens, Kaspar Truninger, Radu Tutuian, Patrick Urfer, Stephan Vavricka, Francesco Viani, Jürg Vögtlin, Roland Von Känel, Dominique Vouillamoz, Rachel Vulliamy, Paul Wiesel, Reiner Wiest, Stefanie Wöhrle, Samuel Zamora, Silvan Zander, Tina Wylie, Jonas Zeitz, Dorothee Zimmermann.

Author Contributions

Study concept and design: TG, AP, SRV, and AMS; acquisition and analysis of data: TG, NF and AMS; interpretation of data: TG, AP, ES, AS, LB, SG, AN, MS, GR, SRV, and AMS; drafting of manuscript: TG and AMS; critical revision of the manuscript for important intellectual content: ES, AS, LB, SG, AN, MS, GR, and SRV; supervision: TG, SRV, and AMS.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Gomollón F, Dignass A, Annese V, *et al.*; ECCO. Third European evidence-based consensus on the diagnosis and management of Crohn's disease 2016. Part 1: diagnosis and medical management. *J Crohns Colitis* 2017;**11**:3–25.
2. Schoepfer AM, Dehlavi MA, Fournier N, *et al.*; IBD Cohort Study Group. Diagnostic delay in Crohn's disease is associated with a complicated disease course and increased operation rate. *Am J Gastroenterol* 2013;**108**:1744–53; quiz 1754.
3. Silverberg MS, Satsangi J, Ahmad T, *et al.* Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;**19[Suppl A]**:5A–36A.
4. Dancygier H, Frick B. Crohn's disease of the upper gastrointestinal tract. *Endoscopy* 1992;**24**:555–8.
5. Decker GA, Loftus EV Jr, Pasha TM, Tremaine WJ, Sandborn WJ. Crohn's disease of the esophagus: clinical features and outcomes. *Inflamm Bowel Dis* 2001;**7**:113–9.
6. Gore RM, Ghahremani GG. Crohn's disease of the upper gastrointestinal tract. *Crit Rev Diagn Imaging* 1986;**25**:305–31.

7. Ghahremani GG, Gore RM, Breuer RI, Larson RH. Esophageal manifestations of Crohn's disease. *Gastrointest Radiol* 1982;**7**:199–203.
8. Heller T, James SP, Drachenberg C, Hernandez C, Darwin PE. Treatment of severe esophageal Crohn's disease with infliximab. *Inflamm Bowel Dis* 1999;**5**:279–82.
9. van Hogezand RA, Witte AM, Veenendaal RA, Wagtmans MJ, Lamers CB. Proximal Crohn's disease: review of the clinicopathologic features and therapy. *Inflamm Bowel Dis* 2001;**7**:328–37.
10. Sakuraba A, Iwao Y, Matsuoka K, *et al.* Endoscopic and pathologic changes of the upper gastrointestinal tract in Crohn's disease. *Biomed Res Int* 2014;**2014**:610767.
11. Yokota K, Saito Y, Einami K, *et al.* A bamboo joint-like appearance of the gastric body and cardia: possible association with Crohn's disease. *Gastrointest Endosc* 1997;**46**:268–72.
12. Tseng TC, Chang YT, Wong JM. Education and imaging. Gastrointestinal: gastric Crohn's disease. *J Gastroenterol Hepatol* 2007;**22**:1690.
13. Fielding JF, Toye DK, Beton DC, Cooke WT. Crohn's disease of the stomach and duodenum. *Gut* 1970;**11**:1001–6.
14. Jones GW Jr, Dooley MR, Schoenfield LJ. Regional enteritis with involvement of the duodenum. *Gastroenterology* 1966;**51**:1018–22.
15. Rutgeerts P, Onette E, Vantrappen G, Geboes K, Broeckaert L, Talloen L. Crohn's disease of the stomach and duodenum: a clinical study with emphasis on the value of endoscopy and endoscopic biopsies. *Endoscopy* 1980;**12**:288–94.
16. Kuriyama M, Kato J, Morimoto N, Fujimoto T, Okada H, Yamamoto K. Specific gastroduodenoscopic findings in Crohn's disease: comparison with findings in patients with ulcerative colitis and gastroesophageal reflux disease. *Dig Liver Dis* 2008;**40**:468–75.
17. Sawczenko A, Sandhu BK. Presenting features of inflammatory bowel disease in Great Britain and Ireland. *Arch Dis Child* 2003;**88**:995–1000.
18. Horjus Talabur Horje CS, Meijer J, Rovers L, van Lochem EG, Groenen MJ, Wahab PJ. Prevalence of upper gastrointestinal lesions at primary diagnosis in adults with inflammatory bowel disease. *Inflamm Bowel Dis* 2016;**22**:1896–901.
19. Annunziata ML, Caviglia R, Papparella LG, Cicala M. Upper gastrointestinal involvement of Crohn's disease: a prospective study on the role of upper endoscopy in the diagnostic work-up. *Dig Dis Sci* 2012;**57**:1618–23.
20. Goldet G, Howick J. Understanding GRADE: an introduction. *J Evid Based Med* 2013;**6**:50–4.
21. Wolters FL, Russel MG, Sijbrandij J, *et al.* Phenotype at diagnosis predicts recurrence rates in Crohn's disease. *Gut* 2006;**55**:1124–30.
22. Romberg-Camps MJ, Dagnelie PC, Kester AD, *et al.* Influence of phenotype at diagnosis and of other potential prognostic factors on the course of inflammatory bowel disease. *Am J Gastroenterol* 2009;**104**:371–83.
23. Lazarev M, Huang C, Bitton A, *et al.* Relationship between proximal Crohn's disease location and disease behavior and surgery: a cross-sectional study of the IBD Genetics Consortium. *Am J Gastroenterol* 2013;**108**:106–12.
24. Pittet V, Juillerat P, Mottet C, *et al.*; Swiss IBD Cohort Study Group. Cohort Profile: The Swiss Inflammatory Bowel Disease Cohort Study [SIBDCS]. *Int J Epidemiol* 2009;**38**:922–31.
25. Vavricka SR, Spigaglia SM, Rogler G, *et al.*; Swiss IBD Cohort Study Group. Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. *Inflamm Bowel Dis* 2012;**18**:496–505.
26. Mao R, Tang RH, Qiu Y, *et al.* Different clinical outcomes in Crohn's disease patients with esophagogastroduodenal, jejunal, and proximal ileal disease involvement: is L4 truly a single phenotype? *Therap Adv Gastroenterol* 2018;**11**:1756284818777938.