Risk Factors for the Development of Fistulae and Stenoses in Crohn Disease Patients in the Swiss Inflammatory Bowel Disease Cohort

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Keywords

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Abstract

Background: Fistulae and stenoses represent frequent and severe complications in patients with Crohn disease (CD). Our study aimed to identify risk factors for fistula and stenosis formation in CD patients. **Summary:** We retrieved data of 1,600 CD patients from the nationwide Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). The risk for fistulae and stenoses in relation to gender, age at diagnosis, smoking status at diagnosis, and ileal involvement at diagnosis were analyzed. In the multivariate analysis, female gender showed a lower risk for developing perianal and any fistula (risk ratio [RR] 0.721, 95% confidence interval [CI] 0.582–0.893, $p = 0.003$ and RR 0.717, 95% CI 0.580–0.888, $p = 0.002$, respectively), and older age at diagnosis showed a lower risk for developing perianal fistula (RR 0.661, 95% CI 0.439–0.995, $p = 0.047$). Furthermore, ileal involvement was associated

with a lower risk for perianal fistula (RR 0.713, 95% CI 0.561–0.906, $p = 0.006$), a lower risk for any fistula (RR 0.709, 95% CI 0.558–0.901, $p = 0.005$), and a higher risk for stenosis (RR 2.170, 95% CI 1.728–2.725, $p < 0.001$). **Key Messages:** In the nationwide SIBDCS, younger age at diagnosis and male gender were risk factors for developing perianal and nonperianal fistulae. Additionally, ileal involvement was revealed to be a potent risk factor (RR 2.170) for developing a stenosis.

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Introduction

Environmental, genetic, and immunological factors as well as the intestinal microbiota have been considered as the major etiological factors in the pathogenesis of inflammatory bowel disease (IBD) [1]. Evidence suggests that the development of IBD is the result of an inappro-

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priate and ongoing activation of the mucosal immune system driven by the presence of intestinal microbiota in the genetically susceptible host [2].

Though most IBD patients initially present with an inflammatory pathology, due to a longstanding and chronically relapsing disease severe complications, such as stenoses or fistulae, may occur. With respect to Crohn disease (CD), about 70% of patients suffer from fistula or stenosis and resulting intestinal obstruction during their disease course. At least 60% require surgery at least once within 20 years following their initial diagnosis [3]. However, even surgery often does not provide a definite solution as severe inflammation, fistulae, and restenosis frequently re-occur [4, 5]. To date, the impact of early treatment of CD with immunomodulators and/or tumor necrosis factor (TNF) antagonists on bowel damage/complications is not fully known. In the past years, there has been increasing evidence that treating patients more aggressively earlier in the disease course, the so-called “top-down” treatment strategy, may prevent the development of IBD-related complications [6–8]. Moreover, recent studies proposed that an early diagnosis of IBD or an early treatment with TNF antagonists was associated with a reduced risk for developing complications of IBD [9, 10].

CD-associated fistulae, mainly perianal fistulae, represent a frequent complication in CD, affecting between 17 and 50% of the patients [5]. At diagnosis up to one-third of the patients have evidence of a stricturing or penetrating intestinal complication, and half of all patients experience an intestinal complication within 20 years after diagnosis [11]. So far, fistulae in CD patients are medically treated with antibiotics, immunosuppressants, and/or anti-TNF antibodies. However, the therapeutic outcome is often insufficient to achieve fistula closure, and surgical treatment is frequently required [12]. In a recently published single-center retrospective cohort study in Japan, it was shown that stenoses and fistulae increased with time, with stenoses or fistulae appearing in about half of the patients after 5 years [13]. Furthermore, the cumulative rate of initial surgery also increased with time with the majority of patients having undergone surgery at 10 years after diagnosis. When upper gastrointestinal disease or complicated small intestinal lesions were seen at the time of diagnosis, the cumulative rate of initial surgery was significantly higher [13]. Interestingly, a complete and long-standing fistula closure was not consistently observed with treatment with any of the routinely used CD medications [14–19].

Patients affected by fistulae often have an impaired quality of life, as these can be painful and may impair psychosocial and sexual function; external fistulae can show significant discharge. Furthermore, the risk for infections is considerable, since fistulae are often the basis for the formation of abscesses because of insufficient drainage of the fistula tract. All these factors also negatively influence the social life and partnership of fistula patients [20, 21]. Besides intestinal and perianal fistulae, the development of strictures is another frequent and severe health issue with clinical features of a sub-ileus or ileus that requires endoscopic or surgical management, including segmental resection, in CD patients [5].

To date, little is known about the pathophysiology as well as the risk factors for the development of CD-associated fistulae. We recently demonstrated a key role for epithelial-to-mesenchymal transition in fistula pathogenesis [22–27]. Previous studies have demonstrated that the extent of disease at diagnosis is associated with the development of fistulae [5]. In contrast, patients with ileitis alone and patients after laparotomy in combination with resection of the bowel have a reduced risk [28].

A further problem that affects both CD and ulcerative colitis patients is intestinal fibrosis and the resulting intestinal stenosis. A key problem with respect to inflammation-associated intestinal fibrosis is the fact that anti-inflammatory strategies, such as anti-TNF antibodies or immunosuppressants, are not effective in resolving already existing fibrosis and that no specific antifibrotic medical therapy currently exists [29]. But recent evidence indicates that most stenotic lesions in CD have a mixed component (fibrosis plus inflammation), and a differentiation can be important for the therapeutic management. A recent study by Rimola et al. [30] indicated that MRI can discriminate different degrees of coexisting fibrosis and inflammation in CD bowel lesions.

From a clinical point of view, therefore, it is essential to identify patient characteristics predicting the development of fistulae and/or stenoses in CD. In the past, tools to predict CD behavior, including clinical, serologic, and genetic markers, have been assessed, albeit with limited success [31]. An increase in knowledge would help to stratify patients according to their risk profile for developing a complicated disease course and to initiate the appropriate treatment strategy early. To further address this aim, here, we evaluated the well-characterized patient collective of the Swiss IBD Cohort Study (SIBDCS). Our analysis included 1,600 CD patients, thus providing a robust basis for the analysis of risk factors that are associated with the occurrence of fistulae and stenoses.

Methods

Study Design

Patient data were entirely obtained from the register of the nationwide SIBDCS, in which patients with IBD from all regions of Switzerland have prospectively been included since 2006 [32]. The cohort study is supported by the Swiss National Science Foundation and was approved by the local ethical committees (institutional review board approval No. EK-1316, approved on February 5, 2007, by the Cantonal Ethics Committee of the Canton Zurich, Switzerland). The cohort goals and methodology are described elsewhere [32]. We included all of the 1,600 CD patients that were enrolled in the study at the time of data acquisition.

On the one hand, we aimed to identify predictive factors for the development of fistulae and stenoses/strictures in CD. We took 4 covariates into account that do not change over time and are known from the start: gender, age at diagnosis, smoking status at diagnosis, and ileal involvement at diagnosis. We analyzed 4 different kinds of outcomes: perianal fistula, other type of fistula (i.e., nonperianal fistula), any fistula, and stenosis.

On the other hand, we analyzed factors associated with fistulae and stenoses/strictures at the time of occurrence. For this purpose, clinical phenotypes were classified regarding disease location, which was categorized into 1 of 4 groups according to the Montreal classification and was analyzed separately for initial location and current location: ileal disease with or without disease limitation to the cecum (L1), a disease limited to the colon (L2), an ileal disease with disease of the colon beyond the cecum (L3), and additively disease of the upper gastrointestinal tract (L4). We also assessed the history of intestinal surgery. Patients with fistulae were classified into 4 groups: perianal fistula, other type of fistula (i.e., nonperianal fistula), multiple fistulae, and any type of fistula. Perianal fistula and other type of fistula were distinct categories, whereas multiple fistulae and any type of fistula were overlapping with perianal fistula and other type of fistula. Stenoses/strictures were analyzed as any intestinal stenosis. Gender, age at diagnosis, and a smoking history were also taken into account. We further obtained data on therapy with 5-aminosalicylate (5-ASA), antibiotics, steroids, immunosuppressants (azathioprine/6-mercaptopurine), calcineurin inhibitors, and anti-TNF drugs (infliximab, adalimumab, and certolizumab) at enrollment or according to the term “ever treated with.”

Statistical Analysis

Clinical data were retrieved from the data center of the SIBDCS at the University of Lausanne. These data and additional data obtained from a review of the patients' files were entered into a database (Access 2000; Microsoft Switzerland Ltd Liab. Co., Wallisellen, Switzerland). The Statistical Package for the Social Sciences (SPSS, version 21, Chicago, IL, USA) was used for the statistical analysis.

Regarding the risk for developing fistulae and stenoses, for the covariates that do not change over time and are known from the start (gender, age at diagnosis, smoking status at diagnosis, and ileal involvement at diagnosis) a Cox proportional hazards analysis and a multivariate logistic regression model were calculated including all the covariates in the model at the same time. A risk ratio (RR) <1 means that the risk for complications is diminished, while a RR >1 means that the risk is increased in that particular group.

Table 1. SIBDCS patient characteristics

Gender	
Male	762 (47.6)
Female	838 (52.4)
Age at diagnosis, years	
Median	26
IQR	20–37
Range	1–81
Age, years	
Median	39
IQR	28–52
Range	16–88
Initial CD location	
L1 (ileal)	368 (23.0)
L2 (colonic)	329 (20.6)
L3 (ileocolonic)	719 (44.9)
L4 (upper GI tract only)	13 (0.8)
Other/unknown/unclear	171 (10.7)
Current CD location (at enrollment)	
L1 (ileal)	464 (29.0)
L2 (colonic)	492 (30.8)
L3 (ileocolonic)	572 (35.8)
L4 (upper GI tract only)	16 (1.0)
Other/unknown/unclear	56 (3.5)
Smoking status at diagnosis	
Nonsmoker	754 (47.1)
Smoker	836 (52.3)
Unknown	10 (0.6)
Smoking status at enrollment	
Nonsmoker	955 (59.7)
Smoker	635 (39.7)
Unknown	10 (0.6)
Medication history (“ever treated with”)	
5-ASA	888 (55.5)
Antibiotics	604 (37.8)
Steroids	1,303 (81.4)
Immunosuppressants	1,232 (77.0)
Anti-TNF agents	687 (42.9)
Calcineurin inhibitors	19 (1.2)
Current medication (at enrollment)	
5-ASA	290 (18.1)
Antibiotics	68 (4.3)
Steroids	469 (29.3)
Immunosuppressants	792 (49.5)
Anti-TNF agents	519 (32.4)
Calcineurin inhibitors	3 (0.2)
Intestinal resection surgery history	
None	1,031 (64.4)
Yes	569 (35.6)
Outcomes	
Perianal fistula	213 (13.3)
Nonperianal fistula	321 (20.1)
Multiple fistulae	105 (6.6)
Any type of fistula	482 (30.1)
Any stenosis	537 (33.6)

Values are *n* (%) unless otherwise indicated. SIBDCS, Swiss Inflammatory Bowel Disease Cohort Study; IQR, interquartile range; CD, Crohn disease; GI, gastrointestinal; 5-ASA, 5-aminosalicylate; TNF, tumor necrosis factor.

Table 2. Risk factors for perianal, nonperianal, and other fistulae as well as stenoses in the univariate and multivariate analyses

	Univariate analysis			Multivariate analysis		
	risk ratio	95% CI	<i>p</i> value	risk ratio	95% CI	<i>p</i> value
<i>Outcome: perianal fistulae</i>						
Gender						
Male	1.000 (ref)	–	–	1.000 (ref)	–	–
Female	0.727	0.596–0.886	0.002	0.721	0.582–0.893	0.003
Age at diagnosis						
≤17 years	1.000 (ref)	–	–	1.000 (ref)	–	–
18–40 years	1.032	0.786–1.354	0.822	0.951	0.703–1.288	0.747
>40 years	0.740	0.506–1.082	0.121	0.661	0.439–0.995	0.047
Smoker at diagnosis						
No	1.000 (ref)	–	–	1.000 (ref)	–	–
Yes	1.027	0.842–1.253	0.793	1.062	0.849–1.330	0.597
Ileal involvement at diagnosis						
No	1.000 (ref)	–	–	1.000 (ref)	–	–
Yes	0.740	0.586–0.934	0.011	0.713	0.561–0.906	0.006
<i>Outcome: nonperianal fistulae</i>						
Gender						
Male	1.000 (ref)	–	–	1.000 (ref)	–	–
Female	1.273	0.988–1.640	0.062	1.399	1.065–1.837	0.016
Age at diagnosis						
≤17 years	1.000 (ref)	–	–	1.000 (ref)	–	–
18–40 years	0.899	0.703–1.288	0.747	0.836	0.580–1.203	0.335
>40 years	0.723	0.439–0.995	0.047	0.612	0.369–1.017	0.058
Smoker at diagnosis						
No	1.000 (ref)	–	–	1.000 (ref)	–	–
Yes	1.257	0.973–1.624	0.080	1.151	0.867–1.527	0.331
Ileal involvement at diagnosis						
No	1.000 (ref)	–	–	1.000 (ref)	–	–
Yes	1.123	0.817–1.543	0.474	1.098	0.790–1.526	0.577
<i>Outcome: any fistula</i>						
Gender						
Male	1.000 (ref)	–	–	1.000 (ref)	–	–
Female	0.837	0.706–0.994	0.042	0.717	0.580–0.888	0.002
Age at diagnosis						
≤17 years	1.000 (ref)	–	–	1.000 (ref)	–	–
18–40 years	1.029	0.784–1.351	0.837	0.951	0.702–1.289	0.746
>40 years	0.722	0.494–1.056	0.093	0.663	0.439–1.002	0.051
Smoker at diagnosis						
No	1.000 (ref)	–	–	1.000 (ref)	–	–
Yes	1.106	0.930–1.316	0.254	1.063	0.850–1.330	0.594
Ileal involvement at diagnosis						
No	1.000 (ref)	–	–	1.000 (ref)	–	–
Yes	0.895	0.727–1.101	0.295	0.709	0.558–0.901	0.005

Table 2 (continued)

	Univariate analysis			Multivariate analysis		
	risk ratio	95% CI	<i>p</i> value	risk ratio	95% CI	<i>p</i> value
<i>Outcome: stenoses</i>						
Gender						
Male	1.000 (ref)	–	–	1.000 (ref)	–	–
Female	0.912	0.782–1.063	0.238	0.918	0.784–1.075	0.289
Age at diagnosis						
≤17 years	1.000 (ref)	–	–	1.000 (ref)	–	–
18–40 years	0.977	0.793–1.203	0.827	1.022	0.813–1.284	0.855
>40 years	1.170	0.903–1.517	0.235	1.112	0.841–1.470	0.456
Smoker at diagnosis						
No	1.000 (ref)	–	–	1.000 (ref)	–	–
Yes	1.141	0.980–1.328	0.089	0.992	0.841–1.170	0.922
Ileal involvement at diagnosis						
No	1.000 (ref)	–	–	1.000 (ref)	–	–
Yes	2.153	1.723–2.691	<0.001	2.170	1.728–2.725	<0.001
CI, confidence interval; ref, reference.						

Crude differences about the development of fistulae and stenoses in relation to smoking status, disease location, age at diagnosis, medications, and history of intestinal resection surgery were assessed using the Pearson χ^2 test or the Fisher exact test (Fisher exact test used if strata comprised a sample size ≤ 5). A multivariate logistic regression model was calculated including only factors that were significant in the univariate analysis to identify risk factors for fistulae or stenoses.

Results

Patients' Characteristics

In total, we included 1,600 CD patients for the retrospective analysis of pre-enrollment data. The detailed characteristics are summarized in Table 1.

Univariate Analysis Identifies Male Gender and Younger Age at Diagnosis as Risk Factors for the Development of Fistulae

In the univariate analysis, female gender was associated with a lower risk for developing perianal fistulae (RR 0.727, 95% confidence interval [CI] 0.596–0.886, $p = 0.002$) and any fistula (RR 0.837, 95% CI 0.706–0.994, $p = 0.042$), while there was a nonstatistically significant trend towards a higher risk for developing nonperianal fistulae (RR 1.273, 95% CI 0.988–1.640, $p = 0.062$) (Table 2). While age at diagnosis had no influence on the develop-

ment of perianal fistulae, older age at diagnosis (>40 years) compared to age at diagnosis of <18 years was associated with a lower risk for developing nonperianal fistulae (RR 0.723, 95% CI 0.439–0.995, $p = 0.047$) and with a trend towards a lower risk for any fistula (RR 0.722, 95% CI 0.494–1.056, $p = 0.093$). Regarding smoking status at diagnosis, there was a trend towards a development of nonperianal fistulae in smokers (RR 1.257, 95% CI 0.973–1.624, $p = 0.080$) (Table 2). Ileal involvement at diagnosis was associated with a lower risk for developing perianal fistulae (RR 0.740, 95% CI 0.586–0.934, $p = 0.011$) with no statistical difference for developing nonperianal or any fistula (Table 2).

Multivariate Analysis Confirms Male Gender and Younger Age at Diagnosis as Risk Factors for the Development of Fistulae

In the multivariate analysis, female gender was associated with a lower risk for developing perianal fistulae (RR 0.721, 95% CI 0.582–0.893, $p = 0.003$) and any fistula (RR 0.717, 95% CI 0.580–0.888, $p = 0.002$) and with a higher risk for developing nonperianal fistulae (RR 1.399, 95% CI 1.065–1.837, $p = 0.016$) (Table 2), which is in line with the data from the univariate analysis. While age at diagnosis had no influence on the development of perianal fistulae in the univariate analysis, in the multivariate analysis older age at diagnosis (>40 years) compared to an age of diagno-

sis <18 years was associated with a lower risk for developing perianal fistulae (RR 0.661, 95% CI 0.439–0.995, $p = 0.047$) and with a trend towards a lower risk for nonperianal (RR 0.612, 95% CI 0.369–1.017, $p = 0.058$) and any fistula (RR 0.663, 95% CI 0.439–1.002, $p = 0.051$) (Table 2).

While there was a trend towards the development of nonperianal fistula in smokers at diagnosis, there was no statistical difference for developing perianal, nonperianal, and any fistula in the multivariate analysis. Ileal involvement at diagnosis was associated with a lower risk for developing perianal fistula (RR 0.713, 95% CI 0.561–0.906, $p = 0.006$), as in the univariate analysis, and any fistula (RR 0.709, 95% CI 0.558–0.901, $p = 0.005$) with no risk for the development of nonperianal fistula (RR 1.098, 95% CI 0.790–1.526, $p = 0.577$) (Table 2).

Univariate Analysis Identifies Smoking and Ileal Involvement at Diagnosis as Risk Factors for the Development of Stenoses

In the univariate analysis, there was no significant difference in the risk for developing stenoses when comparing gender and age at diagnosis (≤ 17 , 18–40, and >40 years). On the other hand, smoking at diagnosis was associated with a trend towards a higher risk for developing stenoses (RR 1.141, 95% CI 0.980–1.328, $p = 0.089$). Ileal involvement at diagnosis was associated with a significant risk for developing stenoses (RR 2.153, 95% CI 1.723–2.691, $p < 0.001$) (Table 2).

Multivariate Analysis Identifies Ileal Involvement at Diagnosis as a Risk Factor for the Development of Stenoses

In the multivariate analysis, there was no significant difference in the risk for developing stenoses when comparing gender, age at diagnosis (≤ 17 , 18–40, and >40 years), and smoking. On the other hand, as in the univariate analysis, ileal involvement at diagnosis was associated with a highly significant risk for developing stenoses (RR 2.170, 95% CI 1.728–2.725, $p < 0.001$) (Table 2).

Markers of Severe Disease Course Are Associated with the Occurrence of Fistulae and Stenoses/Strictures in CD at the Time of Occurrence

Factors Associated with the Occurrence of Fistulae in CD

In the univariate analysis, female gender was associated with perianal fistulae (see online suppl. material, www.karger.com/doi/10.1159/000458144). Younger age at diagnosis of CD as well as at the time of enrollment was associated with perianal and multiple fistulae. Compared

to ileal disease at the time of initial diagnosis, ileocolonic or colonic CD manifestation was associated with the occurrence of fistulae. During follow-up, colonic CD was associated with a higher likelihood of perianal as well as any fistula. Smoking at the time of initial diagnosis was associated with perianal fistulae. On the other hand, smoking was not significantly associated with nonperianal fistulae. The current smoking status did not significantly affect the incidence of fistulae at all. 5-ASA use was associated with a lower incidence of nonperianal fistulae.

In the multivariate analysis, a history of antibiotics, immunosuppressants, and anti-TNF agents was associated with the occurrence of perianal, nonperianal, and any fistula, while treatment with steroids was not. Use of antibiotics, anti-TNF antibodies, and calcineurin inhibitors at any time was also associated with the development of multiple fistulae. Both a stenosis and a history of intestinal resection were associated with formation of perianal fistula, nonperianal fistula, multiple fistulae, and fistula of any type. In contrast, anemia was not associated with an increased occurrence of fistulae. Multivariate analysis identified male gender, smoking, colonic involvement of CD, stenosis, and use of, or ever having been treated with, antibiotics as well as anti-TNF agents to be associated with perianal fistulae (see online suppl. material). Disease duration, colonic CD, a history of intestinal resection, stenosis, and treatment with antibiotics and/or anti-TNF agents were independently associated with the occurrence of nonperianal fistulae, while a history of 5-ASA use was inversely associated with the occurrence of nonperianal fistulae (see online suppl. material). The detected associations for multiple fistulae were quite similar. Disease duration, an initial colonic or ileocolonic CD location, use of antibiotics and/or anti-TNF agents at any time, current treatment with antibiotics, and an intestinal resection surgery history were independently associated with occurrence of multiple fistulae (see online suppl. material). Independent factors associated with any fistula were initial colonic or ileocolonic CD, treatment with antibiotics and/or anti-TNF agents at any time, current treatment with antibiotics, intestinal resection surgery history, and stenosis in the disease history. Female gender was identified as an independent factor that lowered the risk for developing any fistula (see online suppl. material).

Factors Associated with the Occurrence of Stenoses/Strictures in CD

In the univariate analysis, gender, age, and disease duration were not associated with stenosis. Colonic involvement in CD had an inverse association with stenosis com-

pared to ileal disease as the reference. Smoking at any time was slightly associated with the development of stenosis. Treatment with antibiotics, steroids, or immunomodulators at any time was associated with the occurrence of stenosis. Anemia, a history of intestinal resection, and fistulae of any type were also associated with the onset of stenosis in CD patients (see online suppl. material). Multivariate analysis identified disease duration, fistulae, a history of intestinal resection, anemia, and treatment with antibiotics and steroids in the past to be independently associated with stenosis, while colonic CD was inversely associated with stenosis (see online suppl. material). Only statistically significant results are mentioned in the multivariate analysis.

Discussion

Using data from 1,600 SIDBCS patients, we showed that younger age at diagnosis and male gender are associated with a higher risk for developing perianal and non-perianal fistulae. Furthermore, ileal involvement was revealed to be a potent risk factor for developing stenoses.

Also, when assessing factors that are associated with current fistulae and stenoses, younger age at diagnosis as well as at enrollment, an ileocolonic, colonic, or upper gastrointestinal manifestation, and a history (but not current use) of antibiotic, immunosuppressant, or anti-TNF antibody treatment were associated with both fistulae and stenoses. This supports the hypothesis that markers of a severe disease course in IBD can indicate the development of fistulae and stenoses.

Cosnes et al. [33, 34] demonstrated that in the evolution of the disease the initial location of the lesions was the main determinant of the time and type of the complication in CD. Our study revealed that ileal involvement at diagnosis was a potent risk factor for developing stenosis. Furthermore, in our additional analysis of factors that were associated with the occurrence of fistulae, ileocolonic, colonic, or upper gastrointestinal manifestations of CD were associated with fistula formation.

When assessing the role of age in the development of fistulae and stenoses, younger age at diagnosis was a risk factor for developing perianal fistula. In contrast, surprisingly, a young age at diagnosis was no risk factor for the development of stenosis. This supports the hypothesis that fistulae and stenoses might be due to different pathogenic mechanisms. In the additional analysis of associated factors, younger age at diagnosis as well as at the time of enrollment was associated with current perianal and

multiple fistulae. These data are also supported by Cosnes et al. [33], who showed that the development of a penetrating complication was predicted by being younger than 40 years at diagnosis, and in younger patients, the clinical course of CD seems to be more complicated [35].

We also assessed the role of smoking in the development of fistulae and stenoses in CD. To date, the evidence strongly suggests that smoking adversely affects outcome of CD [36]. In a meta-analysis by Reese et al. [37] of 16 observational studies of 2,962 CD patients, it was demonstrated that patients with CD who smoked had a 2.5-fold increased risk for surgical recurrence and a 2-fold risk for clinical recurrence compared to nonsmokers. In our study, smoking revealed a trend towards a higher risk for developing nonperianal fistula and stenosis.

However, in the additional analysis of the association of smoking with the development of fistulae and stenoses, current smoking status, compared to smoking at the initial diagnosis, was not associated with the occurrence of fistulae at all. A limitation which might have influenced our results is that we do not have information on the number of cigarettes smoked per day and on the duration of current smoking, even though in the literature it was shown that also light smoking has significant adverse effects on the outcome in CD patients [38].

In a meta-analysis of 3 large double-blind randomized studies on the treatment of active CD it was found that Pentasa 4 g/day is superior to placebo in reducing the CD Activity Index (CDAI), but the clinical significance of the magnitude of this difference was not clear [39]. Also, in the current treatment guidelines, the use of 5-ASA formulations for active ileal or colonic CD is not supported [40]. In our complete analysis of associated factors, 5-ASA use was associated with a lower occurrence rate of current fistulae. This is most likely due to the fact that only patients with mild CD activity are treated with 5-ASA. This is in contrast to the fact that immunosuppressant or anti-TNF antibody treatment was associated with both fistulae and stenoses, since in particular anti-TNF antibodies are regularly used in severe CD. This might be a plausible explanation of the association of the use of immunosuppressants and anti-TNF antibodies, which are treatments that are used for a more severe disease course, with the onset of fistula, which is an indicator of a severe disease course. This is also underlined by data in the past years demonstrating that IBD-related complications may be prevented by an earlier, more aggressive treatment with immunomodulators and/or anti-TNF antibodies [6, 7]. In population-based cohort studies assessing the impact of immunomodulators on the natural his-

tory of IBD, it could be shown that an increased exposure to thiopurines reduced the likelihood of surgery [41, 42]. But there are also conflicting results regarding this topic; in a recent population-based cohort study on 413 IBD patients, overall, one-third of newly diagnosed IBD patients in the cohort experienced an IBD-related complication in the first few years after diagnosis (one-fifth had extraintestinal manifestations, 13% had fistulae or abscesses, and 14% required surgery). The study did not demonstrate a beneficial effect of starting anti-TNF agents early compared to starting anti-TNF agents late with respect to the occurrence of disease complications, mucosal healing, and surgery [43].

Our study has strengths but also limitations. A clear strength is that we present data from a large nation-wide IBD population in which the risk factors for the development of CD-associated fistulae and stenoses were assessed. The particular value is that the data were prospectively gathered over a period of about 7 years. Further, due to the fact that the data were obtained from a nation-wide registry, our data not only reflect the findings of tertiary referral centers but rather those of a general population, including IBD patients from smaller hospitals or private practices. Of note, in Switzerland, there are about 12,000 IBD patients, which amounts to about 0.2% of the Swiss population, and about 3,000 of them have already been included in the SIBDCS. A limitation of our study is that we, in particular with respect to the analysis of stenosis data, could not discriminate in our analysis between patients who suffered from inflammatory stenosis and those who suffered from fibrotic stenosis.

In summary, using a nationwide patient cohort of CD patients, we have demonstrated that age ≤ 40 years at diagnosis and male gender were associated with a higher risk for developing perianal and nonperianal fistulae and that ileal involvement was revealed to be a potent risk factor for developing stenoses. Furthermore, the development of CD-associated fistulae and stenoses is associated with markers of a severe disease course, such as younger age at diagnosis, a history of intestinal resection, and upper gastrointestinal manifestations. These findings support the current knowledge and suggest a specific awareness of the presence of these complications in these patients.

Appendix

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Statement of Ethics

The cohort study was approved by the local ethical committees (institutional review board approval No. EK-1316, approved on February 5, 2007, by the Cantonal Ethics Committee of the Canton Zurich, Switzerland).

Disclosure Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

J.Z. and C.L. wrote the manuscript and interpreted the data. N.F. performed the statistical analysis. All other authors were involved in data acquisition and data interpretation. M.S. conceived the study design and supervised the project. All authors wrote, corrected, and approved the final draft of the manuscript.

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