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Risk factors for the development of fistulae and stenoses in Crohn's disease patients in the Swiss IBD Cohort

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Short title: Risk factors for development of Crohn's fistulae and stenoses

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Key words: Inflammatory bowel disease, IBD, Crohn's disease, fistula, stenosis

ABSTRACT

Background: Fistulae and stenoses represent frequent and severe complications in patients with Crohn's disease (CD). Our study aimed to identify risk factors for fistulae and stenosis formation in CD patients.

Summary: We retrieved data of 1'600 CD patients from the nationwide Swiss IBD cohort study (SIBDCS). The risk of 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 (RR 0.721, 95% 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 stenoses (RR 2.170, 95% CI 1.728-2.725, p<0.001).

Key Messages: In the nationwide Swiss IBD cohort younger age at diagnosis and male gender were risk factors developing perianal and non-perianal fistulae. Additionally, ileal involvement revealed to be a potent risk factor (RR 2.170) to develop a stenoses.

INTRODUCTION

Environmental, genetic and immunological factors as well as the intestinal microbiota have been considered as the major etiological factors in inflammatory bowel disease (IBD) pathogenesis [1]. Evidence suggests that the development of IBD is a result from an inappropriate and ongoing activation of the mucosal immune system driven by the presence of intestinal microbiota in the genetically susceptible host [2].

Though most of IBD patients initially present with an inflammatory pathology, due to longstanding and chronically relapsing disease, severe complications, such as stenosis or fistulae occur. With respect to Crohn's 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 on the bowel damage/complications of early treatment of CD with immunomodulators (IM) and/or TNF-antagonists 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, in recent studies proposed that an early diagnosis of IBD or an early treatment with TNF-antagonists was associated with reduced risk of developing complications of IBD[9, 10].

CD-associated fistulae, mainly perianal fistulae, represent a frequent complication in CD affecting between 17 and 50 % of 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 experienced an intestinal complication within 20 years after diagnosis[11]. So far, fistulae in CD patients are medically treated with antibiotics, immune-suppressants and/or anti-tumor necrosis factor (TNF)-antibodies. However, 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 stenosis and fistula increased with time, with stenosis or fistula 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 by treatment with any of the routinely used CD medications [14-19].

Patients affected with fistulae often have an impaired quality of life, as these can be painful, may impair psychosocial and sexual function and external fistulas 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 peri-anal 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, ileitis alone and patients after laparotomy in combination with resection of the bowel feature a reduced risk [28].

A further problem that affects both, CD as well as UC 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 anti-fibrotic 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. indicated that MRI can discriminate different degrees of coexisting fibrosis and inflammation in CD bowel lesions [30].

From a clinical point of view, therefore, it is essential to identify patient characteristics predicting the development of fistulae and/or stenosis in CD. In the past tools have been assessed to predict CD behavior, including clinical, serologic and genetic markers with albeit limited success [31]. An increase in knowledge would

help to stratify patients according to their risk profile for developing complicated disease course and to early initiate the appropriate treatment strategy. 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 stenosis.

METHODS

Study Design

Patient data were entirely obtained from the register of 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 approved by the local ethical committees (IRB approval number: EK-1316, approved on 05.02.2007 by the Cantonal Ethics Committee of the Canton Zürich, Switzerland). The cohort goals and methodology are described elsewhere[32].

We included all of the 1600 CD patients that were enrolled in the study at 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 into account four co-variates 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 four different kind of outcomes: perianal fistula, other type of fistula (non-perianal), 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 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 history of intestinal surgery. Patients with fistulae were classified into four groups: perianal fistula, other type fistula (i.e. non-perianal fistula), multiple fistulae and any type fistula. Perianal fistula and other type fistula were distinct categories whereas multiple fistulae and any type fistula were overlapping with perianal fistula and other type 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, 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 Swiss IBD Cohort Study 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 (version 21; SPSS, Chicago, IL) was used for the statistical analysis.

Regarding the risk of developing fistula and stenosis, for the co-variates 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 multivariate logistic regression model was calculated including all the co-variates in the model at the same time. A RR<1 means that the risk of complication is diminished, while a RR >1 means that the risk is increased in the particular group.

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

RESULTS

Patient's 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.

Table 1: SIBDCS patient characteristics

Univariate analysis identifies male gender and younger at diagnosis as risk factors for the development of fistulae

In the univariate analysis female gender was associated with a lower risk of developing perianal fistulae (RR 0.727, 95% 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 non-statistical significant trend towards a higher risk for developing non-perianal fistulae (RR 1.273, 95% CI 0.988-1.640, p=0.062) (Table 2). While age at diagnosis had no influence on the development of perianal fistulae, older age at diagnosis (>40 years) compared to age at diagnosis of <18 years was associated with a lower risk of developing non-perianal fistulae (RR 0.723, 95% CI 0.439-0.995, P=0.047) and a trend towards a lower risk for any fistulae (RR 0.722, 95% CI 0.494-1.056, p=0.093). Regarding smoking status at diagnosis there was a trend towards development of non-perianal fistulae (RR 1.257, 95% CI 0.973-1.624, p=0.080) (Table 2). Ileal involvement at diagnosis was associated with a lower risk to develop perianal fistulae (RR 0.740, 95% CI 0.586-0.934, P=0.011) with no statistical difference for developing non-perianal or any fistulae (Table 2).

Table 2: Risk factors for perianal, non-perianal, other fistulae and stenoses in the uni- and multivariate analysis. Results are stated as Risk Ratio (RR); 95% confidence interval; p-value (Pval).

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 of 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 a higher risk of developing non-perianal 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 diagnosis <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 a trend towards a lower risk for non-perianal (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 development of non-perianal fistula regarding smoking status at diagnosis, there was no statistical difference for developing perianal, non-perianal and any fistulae in the multivariate analysis. Ileal involvement at diagnosis was associated with a lower risk of 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 non-perianal fistula (RR 1.098, 95% CI 0.790-1.526, p=0.577) (Table 2).

Univariate analysis identifies smoking status and ileal involvement at diagnosis as a 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 years, 18-40 years and >40 years). On the other hand, smoking status at diagnosis was associated with a trend towards a higher risk for developing stenosis (RR 1.141, 95%

CI 0.980-1.328, p=0.089). Ileal involvement at diagnosis was associated with a significant risk to develop 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 years, 18-40 years 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 to develop 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 Supplementary Material). 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, ileo-colonic or colonic CD manifestation was associated with the occurrence of fistula. During follow-up, colonic CD was associated with a higher likelihood of perianal as well as any fistulae. A smoking status at the time of initial diagnosis was associated with perianal fistulae. On the other hand, smoking was not significantly associated non-perianal fistulae. The current smoking status did not significantly affect the incidence of fistulae at all. 5-ASA use was associated with a lowered incidence of non-perianal fistulae.

In the multivariate analysis a history of antibiotics, immunosuppressants and anti-TNF agents was associated with the occurrence of perianal, non-perianal and any fistula type, while treatment with steroids was not. Ever use of antibiotics, anti-TNF antibodies and calcineurin inhibitors was also associated with the development of multiple fistula. Both, a stenosis and a history of intestinal resection were

associated with formation of perianal fistula, non-perianal fistula, multiple fistula and fistula of any type. In contrast anemia was not associated with an increased occurrence of fistula. Multivariate analysis identified male gender, smoking, colonic involvement of CD, stenosis, and use of, respectively ever been treated with, antibiotics as well as of anti-TNF agents to be associated with perianal fistulae (see Supplementary Material). Disease duration, colonic CD, a history of intestinal resection, stenosis and treatment with antibiotics and/or anti-TNF agents independently were associated with the occurrence of non-perianal fistulae while a history of 5-ASA use was inversely associated (see Supplementary Material). The detected associations for multiple fistulae were quite similar. Disease duration, an initial colonic or ileo-colonic CD location, an ever-occurred treatment with antibiotics and/or anti-TNF, current treatment with antibiotics and an intestinal resection surgery history were independently associated with multiple fistula occurrence (see Supplementary Material). Independent factors associated with any fistula were initial colonic or ileo-colonic CD, a treatment with antibiotics and/or anti-TNF, a currently treatment with antibiotics, an intestinal resection surgery history and stenosis in disease history. Female gender was identified as an independent factor that lowered the risk to develop any fistula (see Supplementary 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 of CD had an inverse association with stenosis compared to ileal disease as the reference. Smoking in 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 Supplementary Material). Multivariate analysis identified disease duration, fistulae, a history of intestinal resection, anemia, treatment with antibiotics and steroids in the past to be independently associated with stenosis, while colonic CD was inversely associated (see Supplementary 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 of developing perianal and non-perianal fistulae. Furthermore, ileal involvement revealed to be a potent risk factor to develop stenoses.

Also, when assessing factors that are associated with current fistulae and stenoses, younger age at diagnosis as well as at enrollment, an ileo-colonic, colonic or upper GI 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 stenosis.

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

When assessing the role of the age in the development of fistula and stenosis, 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 stenosis 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. This data is also supported by Cosnes et al, 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[33, 35].

We also assessed the role of smoking for the development of fistula and stenosis in CD. To date, the evidence strongly suggests that smoking adversely affects outcome of CD[36]. In a meta-analysis by Reese et al of 16 observational studies of 2,962 CD patients it could be shown that patients with CD who smoke have a 2.5-fold increased risk of surgical recurrence and a twofold risk of clinical recurrence compared to non-smokers[37]. In our study smoking revealed a trend towards a higher risk to develop non-perianal fistula and stenosis.

However, in the additional analysis of the association of smoking and the development of fistula and stenosis, current smoking status, compared to smoking at initial diagnosis, was not associated with the occurrence of fistula at all. A limitation which might have influenced our results is, that we do not have information of the amount of cigarettes per day and the duration of the current smoking status, even though in the literature it was be 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 in the treatment of active Crohn's disease it could be shown that Pentasa 4 g/day is superior to placebo in reducing the CDAI in CD, 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 completive analysis of associated factors 5-ASA use was associated with a lowered 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 stenosis, since in particular anti-TNF antibodies are regularly used in severe CD. This might be a plausible explanation for the association between the use of immunosuppressants and anti-TNF antibodies, which are treatments that are used for a more severe disease course, and the onset of fistula, which is an indicator of a severe disease course. This is also underlined by data in the past years that IBD related complications may be prevented by an earlier, more aggressive, treatment with IM and/or anti-TNF antibodies[6, 7]. In population based cohorts accessing the impact of IM on the natural history 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 with 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 EIMs, 13% had fistulas or abscesses and 14% required surgery). The study did not demonstrate a beneficial effect of starting anti-TNF early compared to starting anti-TNF 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 the data from a large nation-wide IBD population in which the risk factors for the development of CD-associated fistulae and stenosis are assessed. The particular value is that the data have been prospectively gathered over a period of about seven years. Further, due to the fact that the data have been obtained from a nationwide registry, our data not only reflect the findings of tertiary referral centers, but rather those from a general population including also IBD patients from smaller hospitals or private practice. Of note, in Switzerland there are about 12'000 IBD patients counting for about 0.2 % of the Swiss population and about 3'000 of those 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 which patients suffered from inflammatory and 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 of developing perianal and non-perianal fistulae and that ileal involvement revealed to be a potent risk factor to develop stenoses. Furthermore, the development of CD-associated fistulae and stenosis is associated with markers of a severe disease course, such as younger age at diagnosis, history of intestinal resection and upper GI manifestation. These findings support the current knowledge and suggest a specific awareness for the presence of these complications in these patients.

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	N (%)
Gender	
Male	762 (47.6)
Female	838 (52.4)
Age at diagnosis [years]	
Median, IQR, range	26, 20-37, 1-81
Age [years]	
Median, IQR, range	39, 28-52, 16-88
Initial CD location	
L1 (ileal)	368 (23.0)
L2 (colonic)	329 (20.6)
L3 (ileo-colonic)	719 (44.9)
L4 (Upper GI 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 (ileo-colonic)	572 (35.8)
L4 (Upper GI only)	16 (1.0)
Other/unknown/unclear	56 (3.5)
Smoking status at diagnosis	
Non-smoker	754 (47.1)
Smoker	836 (52.3)
Unknown	10 (0.6)
Smoking status at enrollment	
Non-smoker	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	1303 (81.4)
Immunosuppressants	1232 (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	1031 (64.4)
Yes	569 (35.6)
Outcomes	
Perianal fistula	213 (13.3)
Non-perianal fistula,	321 (20.1)
Multiple fistulae	105 (6.6)
Any type fistula	482 (30.1)
Any stenosis	537 (33.6)

Table 1: SIBDCS patient characteristics

Outcome: Perianal fistulae	**Univariate analysis**			**Multivariate analysis**		
	Risk Ratio	95% CI	Pval	Risk Ratio	95% CI	Pval
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	1.000 (ref)	-	-	1.000 (ref)	-	-
18-40	1.032	0.786-1.354	0.822	0.951	0.703-1.288	0.747
> 40	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 ileal involv.	1.000 (ref)	-	-	1.000 (ref)	-	-
Ileal involved	0.740	0.586-0.934	0.011	0.713	0.561-0.906	0.006
Outcome: non-perianal fistulae	**Univariate analysis**			**Multivariate analysis**		
	Risk Ratio	95% CI	Pval	Risk Ratio	95% CI	Pval
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	1.000 (ref)	-	-	1.000 (ref)	-	-
18-40	0.899	0.703-1.288	0.747	0.836	0.580-1.203	0.335
> 40	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 ileal involv.	1.000 (ref)	-	-	1.000 (ref)	-	-
Ileal involved	1.123	0.817-1.543	0.474	1.098	0.790-1.526	0.577
Outcome: Any fistula	**Univariate analysis**			**Multivariate analysis**		

	Risk Ratio	95% CI	Pval	Risk Ratio	95% CI	Pval
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	1.000 (ref)	-	-	1.000 (ref)	-	-
18-40	1.029	0.784-1.351	0.837	0.951	0.702-1.289	0.746
> 40	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 ileal involv.	1.000 (ref)	-	-	1.000 (ref)	-	-
Ileal involved	0.895	0.727-1.101	0.295	0.709	0.558-0.901	0.005
Outcome: Stenoses	**Univariate analysis**			**Multivariate analysis**		
	Risk Ratio	95% CI	Pval	Risk Ratio	95% CI	Pval
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	1.000 (ref)	-	-	1.000 (ref)	-	-
18-40	0.977	0.793-1.203	0.827	1.022	0.813-1.284	0.855
> 40	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 ileal involv.	1.000 (ref)	-	-	1.000 (ref)	-	-
Ileal involved	2.153	1.723-2.691	< 0.001	2.170	1.728-2.725	< 0.001

Table 2: Risk factors for perianal, non-perianal, other fistulae and stenoses in the uni- and multivariate analysis. Results are stated as Risk Ratio (RR); 95% confidence interval; p-value (Pval).