Journal of Crohn's and Colitis, 2019, 1–9
doi:10.1093/ecco-jcc/jjz065
Advance Access publication April 10, 2019
Original Article

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Systematic Analysis of the Impact of Diagnostic Delay on Bowel Damage in Paediatric Versus Adult Onset Crohn's Disease

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Abstract

Background and Aims: Length of diagnostic delay is associated with bowel strictures and intestinal surgery in adult patients with Crohn's disease [CD]. Here we assessed whether diagnostic delay similarly impacts on the natural history of paediatric CD patients.

Methods: Data from the Swiss IBD Cohort Study were analysed. Frequency of CD-related complications [bowel stenosis, perianal fistula, internal fistula, any fistula, resection surgery, fistula/abscess surgery, any complication] at diagnosis and in the long term [up to 30 years after CD diagnosis] was compared between paediatric patients [diagnosed <18 years] and adult patients [diagnosed ≥18 years] using multivariate Cox proportional hazard regression modelling.

Results: From 2006 to 2016, 387 paediatric and 1163 adult CD patients were included. Median [interquartile range: IQR] diagnostic delay was 3 [1–9] for the paediatric and 6 [1–24] months for the adult group, respectively. Adult onset CD patients presented at diagnosis more frequently with bowel stenosis [$p < 0.001$] and bowel surgery [$p < 0.001$] compared with paediatric CD patients. In the long term, length of diagnostic delay was significantly associated with bowel stenosis [$p = 0.001$], internal fistula [$p = 0.038$], and any complication [$p = 0.024$] in the adult onset CD population. No significant association between length of diagnostic delay and CD-related outcomes in the long term was observed in the paediatric population.

Conclusions: Adult CD patients have longer diagnostic delay compared with paediatric CD patients and present at diagnosis more often with bowel stenosis and surgery. Length of diagnostic delay was found to be predictive for CD-related complications only in the adult but not in the paediatric CD population.

Key Words: Crohn's disease; bowel damage; natural history

1. Introduction

We have recently shown that median diagnostic delay [time from IBD-related symptoms to diagnosis] in adult Crohn's disease [CD] patients in the Swiss IBD cohort was 9 months, and that 25% of CD patients had a diagnostic delay >2 years.[1] Age <40 years at diagnosis and ileal disease were identified as significant independent risk factors for long diagnostic delay. In a subsequent study we showed that in a cohort of adult CD patients, length of diagnostic delay was directly correlated with bowel strictures and the risk to undergo CD-related surgery.[2]

Approximately 25% of all IBD patients are diagnosed during childhood or adolescence.[3] We found that median diagnostic delay was 4 months in a paediatric cohort of Swiss CD patients.[4] As paediatric CD patients have a long lifetime with the disease, it would be of particular importance to know whether length of diagnostic delay in this population is associated with development of bowel damage in a similar way to what has been shown in adults.

Given the lack of data regarding this question we aimed to evaluate whether diagnostic delay impacts similarly on the natural history of paediatric Crohn's disease patients compared with adults.

2. Methods

2.1. Study design

The Swiss IBD Cohort Study [SIBDCS] has been including IBD patients from all regions of Switzerland starting in 2006. The SIBDCS is a national prospective cohort study on IBD patients, and provides up-to-date information regarding different aspects of IBD in Switzerland for the Swiss and international scientific community, public health authorities, and medical staff.[5] Ethics approval was obtained for the study protocol by the ethics committee of the cantons or regions in which patients were included, as well as individual consent of patient and parents. Patients are included in the cohort once diagnosis of Crohn disease [CD], ulcerative colitis [UC], or IBD unclassified [IBDU] has been established for at least 4 months.[5]

2.2. Methods

The collected data were recorded using a Microsoft Access database [Access 2000, Microsoft Switzerland, Wallisellen, Switzerland] at the data centre of the SIBDCS and the Swiss Paediatric IBD Cohort Study [SPIBDCS], which is located at the Institute of Social and Preventive Medicine at the University of Lausanne. For this manuscript, the analysis was based on the validated data obtained from IBD patients enrolled into the SIBDCS and SPIBDCS between May 2006 and April 2016. Data were extracted from physician questionnaires at enrolment and annual follow-up using demographic variables [age, date of birth, age at diagnosis, date of diagnosis, date of first symptoms, date of visit, and gender] and medical items [initial disease location, latest disease location, current therapy, extraintestinal manifestations, non-steroidal anti-inflammatory drug [NSAID] intake, complications, fistula, anal fissure, abscess, stenosis, surgery including intestinal surgery, surgery for fistula and abscesses and other abdominal surgery, past therapies including response, and reason for discontinuation].

Diagnostic delay was defined as the time interval between the first appearance of IBD-related symptoms until IBD diagnosis was made. Diagnostic delay was reported in months. A stratification was performed into an interval between the appearance of the first IBD-related symptoms and the first physician visit, and the interval from first physician visit [due to IBD-related complaints] until IBD diagnosis was established. The term 'short diagnostic delay' was used to describe diagnostic delays laying from in the first to the third quartile, and the term 'long diagnostic delay' describes a delay lying in the fourth quartile. The impact of the length of diagnostic delay on CD-related complications was analysed according to quartiles.

2.3. Patients

A total of 1550 patients were analysed, among whom 387 patients were diagnosed with CD in the paediatric age group [<18 years] and 1163 in the adult age group [≥18 years], respectively. Patients were prospectively included if IBD diagnosis had been established in 2006 or later, whereas a retrospective inclusion of patients diagnosed with IBD in 2005 and earlier was also possible. At the time of inclusion, patients underwent a thorough clinical and laboratory assessment. Clinical, socioeconomic, and psychosocial data were collected. The treating physician completed physician-reported outcomes, and patients completed patient-reported outcomes such as questionnaires on quality of life. Disease location was recorded according to the Montréal classification in adults and Paris classification in children.[6,7] Yearly patient-reported questionnaires about quality of life, social impairment, health resources consumption, and symptoms, and yearly physician follow-up questionnaires about treatments and complications, were collected.

2.4. Statistical analysis

Data were retrieved from the database of the SIBDCS at the Institute of Social and Preventive Medicine at the University of Lausanne, Switzerland. All statistical analyses were performed by the cohort statistician [NF] using the statistical program Stata [version 14.2, College Station, TX, USA]. Quantitative data distribution was analysed using Normal-QQ-Plots. Results of quantitative data are presented either as median plus interquartile ranges [for data with non-Gaussian distribution] or mean ± standard deviation [SD] and range [for normally distributed data]. Categorical data were summarised as the percentage of the group total. For quantitative data, differences in distribution between two groups were evaluated using either the Wilcoxon/Mann-Whitney rank test [for data with non-Gaussian distribution] or the Student's t test [for normally distributed data]. For categorical outcomes, differences in observed frequencies

between groups were compared using the chi square test, or using the exact Fisher's test for groups with a small number of observations [n <20]. Time-to-event data were analysed using the Kaplan-Meier estimator, using the Turnbull method to deal with left- and interval-censored data. Cumulative curves and number at risk were reported. The log-rank test was used to assess differences in cumulative curves between two or more groups. For the present study, a p-value <0.05 was considered as statistically significant. A Bonferroni correction was performed in case of multiple testing. The impact of the length of diagnostic delay in both paediatric and adult CD patients was assessed on the following outcomes: stenosis, perianal fistula, internal fistula, any fistula, resection surgery, fistula/abscess surgery, and any complication. For this purpose, we performed multivariate Cox proportional hazard regressions including the following variables: 1] diagnostic delay, stratified into four quartiles; 2] age at CD diagnosis [paediatric versus adult]; and 3] ileal disease location at diagnosis. In addition, we included an interaction term between diagnostic delay and age at CD diagnosis in order to assess if the effect of diagnostic delay is different between adult and paediatric CD patients.

3. Results

3.1. Baseline characteristics

A total of 1550 CD patients were analysed, of whom 387 [25%] were diagnosed in the paediatric age group [<18 years] and 1163 [75%] patients were diagnosed as adults [≥18 years]. The demographic characteristics are shown in Table 1. Median disease duration at the latest follow-up in the paediatric onset group was 8 years, compared with 11 years in the adult onset group [p <0.001]. The percentage of patients with long diagnostic delay, defined as delay >75th percentile, was not different between the paediatric and the adult cohorts. Disease location at latest follow-up showed more frequently ileocolonic disease in the paediatric cohort when compared with the adult population [42.9% vs 30.6%, p <0.001].

A systematic analysis of diagnostic delay in the paediatric and the adult CD cohorts is shown in Table 2 and in Figure 1. Median diagnostic delay was 3 months in the paediatric group compared with 6 months in the adult cohort [p <0.001]. The median time interval between first IBD-related symptoms and first physician visit was equal to the time interval between first physician visit and IBD

Table 1. Baseline characteristics.

CD patients	Paediatric diagnosis [<18 years old]	Adult diagnosis [≥18 years old]	p-value
Number of patients	387	1163	-
Gender			
Male	207 [53.5]	546 [47.0]	
Female	180 [46.5]	617 [53.0]	0.026
Age at diagnosis	14.1, 11.6–16.1	28.7, 22.6–38.7	
[median, IQR, range]	0.5–18.0	18.0–81.4	<0.001
Age at enrolment	17.7, 14.1–23.5	39.5, 29.3–52.1	
[median, IQR, range]	1.3–63.8	18.2–87.6	<0.001
Disease duration at enrolment [years]	2.9, 1.0–8.9	5.5, 1.4–13.7	
[median, IQR, range]	0.1–48.6	0.0–44.9	<0.001
Age at latest follow-up	21.3, 17.0–29.5	44.7, 33.8–57.6	
[median, IQR, range]	1.3–69.2	18.8–93.9	<0.001
Disease duration at latest follow-up [years]	8.0, 4.1–14.7	11.0, 6.1–19.2	
[median, IQR, range]	0.3–51.6	0.1–46.6	<0.001
Diagnostic delay [months]	3, 1–9	6, 1–24	
[median, IQR, range]	0–116	0–531	<0.001
Diagnostic delay categorisation			
Short delay [≤75th percentile]	300 [77.5]	885 [76.1]	
Long delay [>75th percentile]	87 [22.5]	278 [23.9]	0.574
Disease location at diagnosis			
L1 [ileal]	59 [15.3]	300 [25.8]	
L2 [colonic]	55 [14.2]	245 [21.1]	
L3 [ileocolonic]	236 [61.0]	508 [43.7]	
L4 [upper GI only]	5 [1.3]	13 [1.1]	
Unknown/unclear	32 [8.3]	97 [8.3]	<0.001
Disease location at enrolment			
L1 [ileal]	72 [18.6]	352 [30.3]	
L2 [colonic]	91 [23.5]	352 [30.3]	
L3 [ileocolonic]	208 [53.8]	414 [35.6]	
L4 [upper GI only]	4 [1.0]	15 [1.3]	
Unknown/unclear	12 [3.1]	30 [2.6]	<0.001
Disease location at latest follow-up	88 [22.7]	375 [32.2]	
L1 [ileal]	120 [31.0]	386 [33.2]	
L2 [colonic]	166 [42.9]	356 [30.6]	
L3 [ileocolonic]	8 [2.1]	29 [2.5]	
L4 [upper GI only]	5 [1.3]	17 [1.5]	<0.001
Unknown/unclear			

CD, Crohn's disease; GI, gastrointestinal; IQR, interquartile range.

Table 2. Analysis of overall length of diagnostic delay as well as stratification into the two intervals that determine the overall length.

Intervals of diagnostic delay	Paediatric CD diagnosis [< 18 years old] [*n* = 387]	Adult CD diagnosis [≥18 years old] [*n* = 1163]	*p*-value
Time between first symptoms and IBD diagnosis [months] [median, IQR, range]	3, 1–9, 0–116	6, 1–24, 0–531	<0.001
Time between first symptoms and physician visit [months] [median, IQR, range]	1, 1–4, 0–36	2, 1–6, 0–360	0.006
Time between physician visit and IBD diagnosis [months] [median, IQR, range]	1, 1–7, 0–95	2, 1–17, 0–395	0.001

IBD, inflammatory bowel disease; IQR, interquartile range.

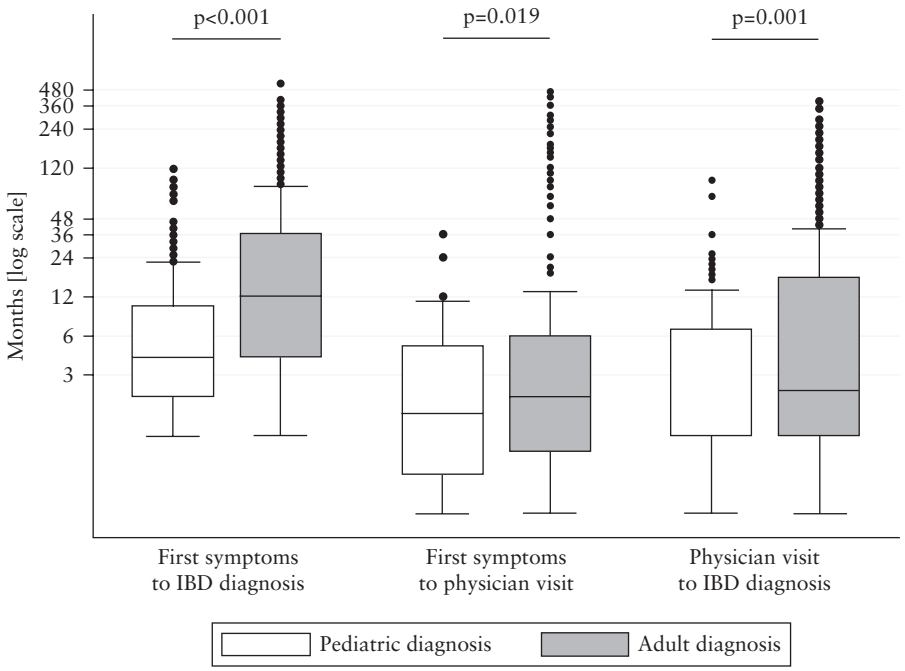

Figure 1. Diagnostic delay [in months] comparing Crohn's disease [CD] patients with adult onset diagnosis versus patients with paediatric onset diagnosis. Results are presented by means of box plots. The horizontal line in the box represents the median, whereas the box contains the 25th to the 75th percentile of all values.

diagnosis [1 month in the paediatric cohort and 2 months in the adult cohort].

The prevalence of extraintestinal manifestations [EIM] in both paediatric and adult onset CD patients is shown in Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online. EIM were more frequently diagnosed in adult onset CD patients when compared with paediatric onset CD patients [58% vs 48.1%, p <0.001]. Oral ulcers was the only EIM that was diagnosed more frequently in paediatric onset CD patients compared with adult onset CD patients [18.1% vs 13.6%, p = 0.030]. Arthritis/arthralgia, uveitis/iritis, and ankylosing spondylitis/sacroileitis were all more frequently diagnosed in adult onset CD patients when compared with paediatric onset CD patients [50.5% vs 32%, p <0.001; 13.9% vs 6.2%, p <0.001; 8.9% vs 2.8%, p <0.001, respectively].

The medical therapies ever applied are shown in Table 3. No differences were observed with respect to oral 5-aminosalicylates [5-ASA], topical 5-ASA, any 5-ASA, any steroids, calcineurin inhibitors, and vedolizumab when comparing paediatric onset CD patients with adult onset CD patients. There was a trend for more frequent use of systemic steroids in paediatric onset CD patients compared with adult onset CD patients [77.8% vs 72.7%, p = 0.050]. Topical steroids were used more frequently in adult onset CD patients compared with paediatric onset CD patients [50.2% vs 38.8%, p <0.001], whereas azathioprine/mercaptopurine, methotrexate, and TNF antagonists were more frequently applied in paediatric onset CD patients compared with adult onset CD patients [88.6% vs 76.8%, p <0.001; 27.6% vs 22.2%, p = 0.028; and 74.4% vs 61.7%, p <0.001, respectively].

3.2. Frequency of complications at CD diagnosis according to length of diagnostic delay

We analysed the prevalence of different complications at CD diagnosis according to the length of diagnostic delay. We anticipated that patients with longer diagnostic delay would have an increased frequency of the different complications at diagnosis when compared with patients with short diagnostic delay.

Table 3. IBD therapies ever applied, stratified according to paediatric or adult diagnosis.

Drugs ever applied	Paediatric CD diagnosis [<18 years old] [*n* = 387]	Adult CD diagnosis [≥18 years old] [*n* = 1163]	*p*-value
Oral 5ASA	209 [54.0%]	629 [54.1%]	0.978
Topical 5ASA	43 [11.1%]	120 [10.3%]	0.660
Any 5ASA	219 [56.6%]	664 [57.1%]	0.862
Systemic steroids	301 [77.8%]	846 [72.7%]	0.050
Topical steroids	150 [38.8%]	584 [50.2%]	<0.001
Any steroids	338 [87.3%]	1010 [86.8%]	0.803
Azathioprine/mercaptopurine	343 [88.6%]	893 [76.8%]	<0.001
Methotrexate	107 [27.6%]	258 [22.2%]	0.028
Calcineurin inhibitors	5 [11.2%]	18 [1.5%]	0.719
Anti-TNF [IFX, ADA, CZP, GOL]	288 [74.4%]	717 [61.7%]	<0.001
Vedolizumab	30 [7.8%]	82 [7.1%]	0.644

CD, Crohn's disease; IBD, inflammatory bowel disease; ADA, adalimumab; CZP, certolizumab pegol; IFX, infliximab; GOL, golimumab; 5ASA, 5-aminosalicylates.

Table 4. Rate of complications at diagnosis [% and 95% confidence interval].

	Short delay adult	Long delay adult	Short delay paediatric	Long delay paediatric	*p*-value short adult vs long adult delay	*p*-value short paediatric vs long paediatric delay	*p*-value paediatric vs adult
Stenosis	15.8 [13.4–18.2]	22.7 [17.6–27.4]	9.8 [6.3–13.1]	0.0 [-]	0.008	0.002	<0.001
Perianal fistula	9.8 [7.8–11.7]	14.8 [10.5–18.9]	10.1 [6.7–13.5]	8.9 [2.7–14.7]	0.020	0.741	0.508
Internal fistula	4.2 [2.8–5.5]	8.0 [4.8–11.1]	5.2 [2.6–7.6]	0.0 [-]	0.012	0.030	0.382
Any fistula	14.2 [11.8–16.4]	22.5 [17.5–27.3]	15.8 [10.7–18.7]	12.2 [5.0–18.8]	0.001	0.408	0.576
Resection surgery	10.1 [8.1–12.0]	14.0 [9.9–18.0]	4.3 [2.0–6.6]	4.6 [0.1–8.9]	0.070	0.904	<0.001
Fistula surgery	4.9 [3.4–6.3]	11.2 [7.4–14.8]	8.3 [5.2–11.4]	4.7 [0.1–9.0]	<0.001	0.261	0.453
Any complication	22.8 [20.0–25.5]	33.2 [27.4–38.5]	21.5 [16.7–26.0]	16.5 [8.3–23.9]	0.001	0.308	0.051

3.3. Paediatric onset CD diagnosis

We found a significantly higher rate of stenosis [p = 0.002] and internal fistulas [p = 0.030] in children with short diagnostic delay when compared with the paediatric group with long diagnostic delay [Table 4]. The rates of perianal fistulas, any fistula, resection surgery, fistula surgery, and any complication were not different between the two paediatric groups.

3.4. Adult onset CD diagnosis

We documented a significantly higher rate of any complication [p = 0.001], stenosis [p = 0.008], perianal fistula [p = 0.020], internal fistulas [p = 0.012], any fistula [p = 0.001], resection surgery [p = 0.070], and fistula surgery [p < 0.001] at CD diagnosis in the adult onset population with long diagnostic delay compared with the adult onset CD group characterised by a short diagnostic delay.

When comparing the rate of complications between the paediatric onset CD group and the adult onset CD group, we found that, compared with the paediatric onset CD group, adult onset CD patients had significantly more frequently bowel stenosis [p <0.001] and resection surgery [p <0.001] at CD diagnosis [Table 4]. There was a trend for any complications to be more prevalent at CD diagnosis in the group with adult onset CD [p = 0.051].

3.5. Comparison of complication rate in the long term between the paediatric and adult onset CD groups according to the length of diagnostic delay

We evaluated the occurrence of different complications in the long term in the paediatric onset CD cohort compared with the adult CD onset group using Cox proportional hazard models [Supplementary Table 2, available as Supplementary data at *ECCO-JCC* online]. We found that the effect of diagnostic delay was less harmful in the paediatric onset CD group compared with the adult onset group for the outcomes bowel stenosis, internal fistula, intestinal resection, fistula/abscess surgery, and any complication [as shown by hazard ratios <1 when using the interaction term between diagnostic delay and age at CD diagnosis, results in Supplementary Table 2 shown for outcomes bowel stenosis, intestinal resection, and any complication]. The p-values for the corresponding Kaplan-Meier curves are shown in Table 5. In the long term, length of diagnostic delay was significantly associated with bowel stenosis [p = 0.001], internal fistula [p = 0.038], and any complication [p = 0.024] in the adult onset CD population. No significant association between length of diagnostic delay and CD-related outcomes in the long term was observed in the paediatric population. The Kaplan-Meier curves for the outcomes 'bowel stenosis', 'resection surgery' and 'any complication' are shown in Figures 2–4.

4. Discussion

This is the first study to compare the impact of diagnostic delay in patients with paediatric versus adult onset CD. Our study carries several messages that are clinically relevant. First, diagnostic delay was shorter in paediatric when compared with adult onset CD patients. Second, adult patients were more frequently diagnosed with bowel stenosis and bowel surgery when compared with paediatric patients. And last, length of diagnostic delay was found to be predictive for CD-related complications [stenosis, internal fistula, any complication] only in the adult but not in the paediatric cohort.

Diagnostic delay was significantly shorter in the paediatric onset CD group when compared with the adult onset CD group [median 6 vs 3 months, p <0.001]. The same observation was also made when stratifying into the time interval from symptom onset to physician visit [median 1 vs 2 months, p = 0.006] and the time interval from physician visit to CD diagnosis [median 1 vs 2 months, p = 0.001]. Length of diagnostic delay in CD patients varies among different countries and seems strongly influenced by the characteristics of the health care system. Our Swiss data on diagnostic delay in adult onset CD patients are in accordance with data from an adult CD population [n = 497] in France, who had a median diagnostic delay of 5 months [IQR 2–13 months].[8] These aforementioned data compare also well with a Romanian adult cohort of 478 CD patients in whom median diagnostic delay was 5 months.[9] Median diagnostic delay in a Korean cohort of 1047 adult CD patients was 16.0 ± 33.1 months.[10] On the other hand, diagnostic delay in Swiss paediatric onset CD patients is shorter when compared with a paediatric Canadian cohort [n = 111] of CD patients in whom a diagnostic delay of 6.8 months [IQR 2.9–12.5 months] was found.[11] Several factors may play a role in this different length of diagnostic delay in the paediatric compared with the adult onset CD group. One reason might be that in adult onset CD patients, the presence of symptoms compatible with irritable bowel syndrome [IBS] may mask the onset of CD.[1] Furthermore, whereas adult patients tend to wait for symptoms to improve and/or self-medicate before consulting a physician, parents usually are worried about their children's health and seek for medical attention earlier. In addition, children with CD often present with growth retardation, which represents an alarm sign to paediatricians and pushes them to seek for underlying causes.[12,13]

Table 5. *p*-values of the log-rank tests regarding the different outcomes, stratified according to adult and paediatric CD onset.

Outcome	*p*-value log-rank among adult CD	*p*-value log-rank among paediatric CD
Stenosis	0.001	0.732
Perianal fistula	0.567	0.672
Internal fistula	0.038	0.626
Any fistula	0.591	0.814
Resection surgery	0.084	0.950
Fistula/abscess surgery	0.744	0.147
Any complication	0.024	0.954

CD, Crohn's disease.

Several groups have meanwhile shown that long diagnostic delay, mostly defined as delay in the upper quartile, is associated with an increased risk for bowel damage and/or CD-related surgery. The first study published in 2013 found that in a cohort of 905 adult CD patients, length of diagnostic delay was associated with the risk of bowel stenosis and the risk to undergo CD-related surgery.[2] These initial findings were corroborated by a French cohort of 497 adult CD patients who showed that diagnostic delay >13 months was associated with increased risk of early surgery.[8] A recent publication in an adult cohort of 110 patients from the USA found that a long diagnostic delay increased the risk for bowel strictures.[14] In a Chinese cohort of 343 CD patients, long diagnostic delay was significantly associated with an increased rate of intestinal surgery.[15] Risk factors identified for diagnostic delay were age >40 years at diagnosis, basic education level, and no family history of CD.

Given the fact that adult onset CD patients were characterised by a longer diagnostic delay compared with the paediatric onset CD patients, we were not astonished to see that at CD diagnosis the group with adult onset CD had significantly more frequently bowel stenosis [p <0.001] and had to undergo more frequently CD-related surgery [p <0.001]. In addition, bowel damage and CD-related surgery were significantly more frequent at the time of diagnosis in adult onset CD patients with long diagnostic delay when compared with adult onset CD patients with short diagnostic delay. Our observation that paediatric onset CD patients with short diagnostic delay had significantly more frequently stenosis and internal fistulas at diagnosis, when compared with paediatric onset CD patients with long diagnostic delay, seems counter-intuitive at first sight. However, we explain this observation by the fact that CD onset patients with short

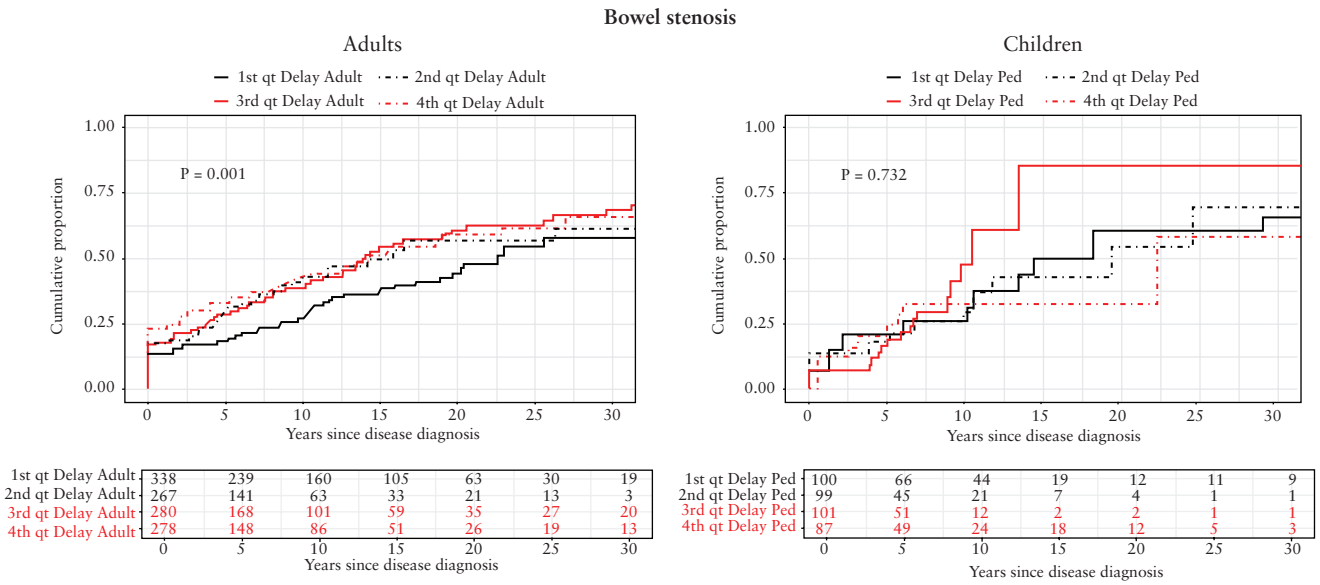

Figure 2. Kaplan-Meier graphs for the outcome 'bowel stenosis' in adult versus paediatric CD patients. Length of diagnostic delay was significantly associated with bowel stenosis in adults [p = 0.001] but not in children [p = 0.732]. CD, Crohn's disease.

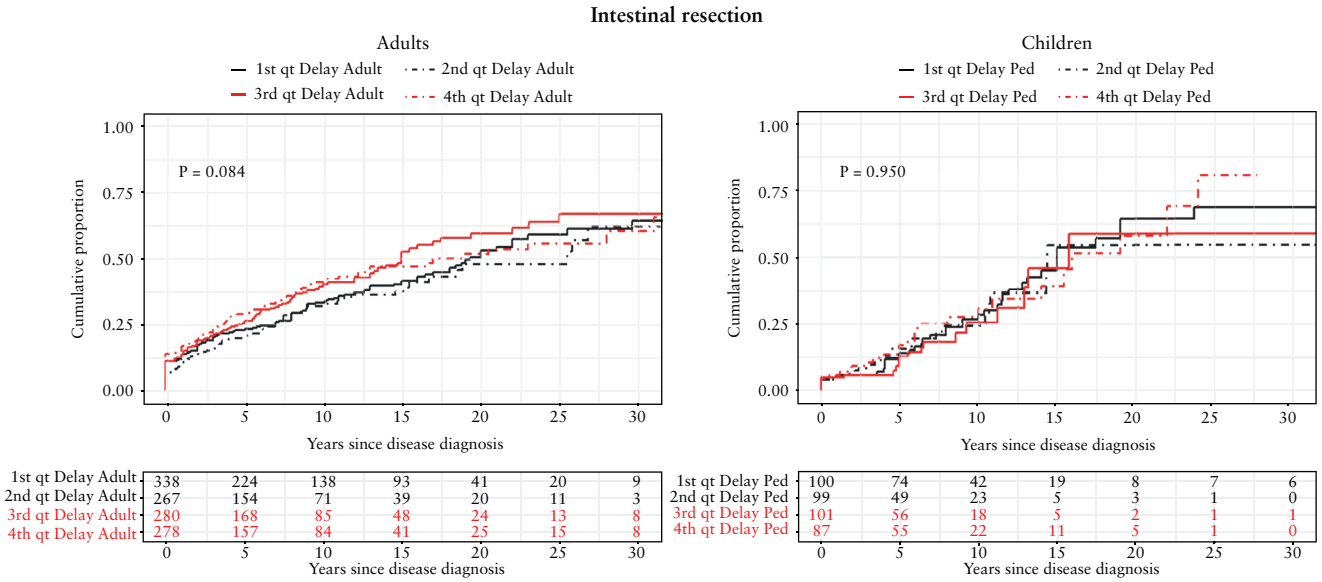

Figure 3. Kaplan-Meier graphs for the outcome 'intestinal resection' in the adult versus paediatric CD patients. No significant relationship was observed between length of diagnostic delay and intestinal resection in children, whereas an association [$p = 0.084$] between length of diagnostic delay and intestinal resection was observed in adults. CD, Crohn's disease.

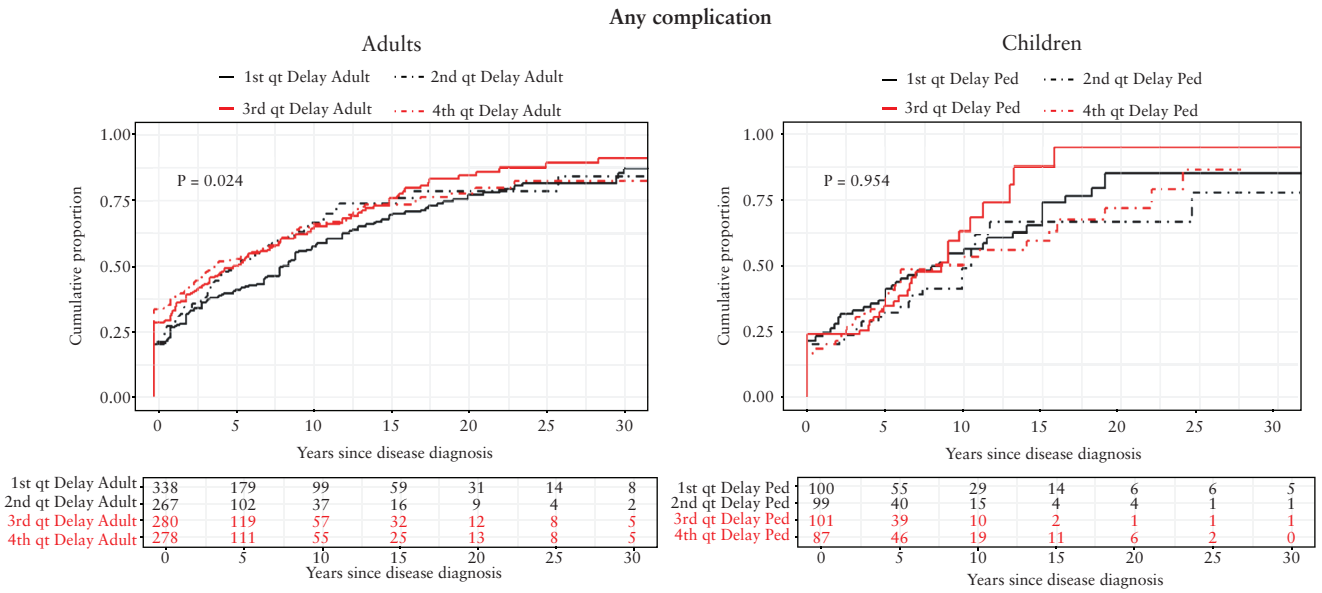

Figure 4. Kaplan-Meier graphs for the outcome 'any complication' in adult versus paediatric CD patients. Length of diagnostic delay was significantly associated with any complication in adults [$p = 0.024$] but not in children [$p = 0.954$]. CD, Crohn's disease.

diagnostic delay represented a patient cohort with aggressive disease behaviour that drove a rapid diagnostic evaluation. We consistently found in the adult onset CD cohort that complications were more frequent at CD diagnosis in the group with long diagnostic delay compared with patients with short diagnostic delay. This observation corresponds well with data from some of the above-mentioned studies that showed that length of diagnostic delay increases the risk of bowel damage.[2,8,12] We observed a strong trend [$p = 0.051$] for bowel damage at CD diagnosis to be observed more frequently in the adult onset CD population when compared with the paediatric onset CD group. It is important to remember that diagnostic delay in the adult onset CD group was significantly longer when compared with the paediatric onset CD group; as such, bowel damage is to be expected to appear more frequently in the group with long diagnostic delay.[1,4] One might suspect that paediatric CD presents at diagnosis with a more benign phenotype when compared with the adult onset CD population, which could explain the higher complication rate in the adult onset CD group at diagnosis. However, our baseline findings do not support this hypothesis. Significantly more patients in the paediatric onset CD cohort had ileocolonic disease at enrolment and at latest follow-up when compared with the adult onset CD population. Our findings in the paediatric cohort compare well with

the findings from the French paediatric cohort described by Vernier-Massouille, in which ileocolonic location was the most frequent disease manifestation.[18]

In the long term, length of diagnostic delay was associated with bowel damage only in the adult onset but not the paediatric onset CD group. Several factors might explain this observation. First of all, diagnostic delay is longer in the adult onset CD population compared with the paediatric onset CD group. Early CD treatment with immunomodulators and/or biologics has been shown to reduce long-term complications.[16–18] As such, it seems relevant to achieve disease control during the 'window of opportunity'. Paediatric onset CD patients, who are characterised by a shorter diagnostic delay when compared with adult onset CD patients, would therefore profit more from early intensified treatment compared with adult onset CD patients. Indeed, Vernier-Massouille *et al*. examined a cohort of 404 paediatric CD patients, and they found that azathioprine was introduced earlier in the course of the disease in patients not undergoing surgery than in patients undergoing surgery.[19] Furthermore, adult patients may smoke cigarettes, which has been shown in multiple studies to promote bowel damage and CD-related surgery.[20] In a recent study from the Swiss IBD cohort, Biedermann *et al.* found that 39.6% of CD patients were current smokers.[21]

Additionally, CD children may present with growth retardation which is perceived as an alarm sign by parents and caregivers and drives rapid diagnostic work-up.[10,11,22] In order to counteract growth retardation, paediatric gastroenterologists might use early aggressive therapy with either immunomodulators and/or biologic therapies. Of note, despite a significantly shorter disease duration at latest follow-up in the paediatric onset CD cohort compared with the adult onset CD cohort [median 8 years vs 11 years, p <0.001], immunomodulators and biologic therapies were used significantly more often in the paediatric onset CD cohort when compared with the adult onset CD cohort. This finding speaks in favour of paediatric onset CD patients receiving rapid step-up to gain disease control. This attitude is well supported by several studies which showed that use of immunomodulators and/or biologic therapies can be associated with a decrease of bowel damage and associated surgery.[23–25] The rate of CD patients needing surgery at 5 years after CD diagnosis was about 25% in the paediatric and in the adult onset CD cohort. Our data are in accordance with the study of Vernier-Massouille *et al.* who showed that in their cohort of paediatric CD patients the cumulative risk of surgery was 34% at 5 years.[19] A recent publication from an international multicentre cohort on 1442 paediatric CD patients revealed that the 5-year risk of bowel surgery did not change from 2002 through 2014 and that it remained between 13% and 14%. Most of the surgeries occurred within 3 years from diagnosis.[26] The only predictor of surgery was disease behaviour at diagnosis. The authors found that early use of biologics slowed disease progression from an inflammatory to a stricturing or fistulising phenotype; however, this effect became only evident after 5 years of disease.[26]

Our study has several strengths and some limitations as well. We present the first data in a national cohort study evaluating the impact of diagnostic delay on bowel damage in CD patients with paediatric versus adult onset. As a limitation, we have to acknowledge that the data presented herein are not population-based, as 80% of participants are included by gastroenterologists working in hospital. As such, our findings may not apply to the entire IBD population in Switzerland.

In summary, we found that adult CD patients have longer diagnostic delay compared with paediatric CD patients and present at diagnosis more often with bowel stenosis and intestinal surgery. Length of diagnostic delay was found to be predictive for CD-related complications [bowel stenosis, internal fistula, any complication] only in the adult but not in the paediatric CD population.

Funding

This work was supported by grants from the Swiss National Science Foundation [33CS30_177523/1 to GR]. This is an investigator-initiated study; pharmaceutical companies played no role in study design, acquisition, analysis, interpretation, or presentation of the data.

Conflict of Interest

The authors report no conflict of interest

Acknowledgements

The authors thank all members of the SIBDCS who were involved in the acquisition of data: Claudia Anderegg; Peter Bauerfeind; Christoph Beglinger; Stefan Begré; Dominique Belli; José Bengoa; Luc Biedermann; Janek Binek; Mirjam Blattmann; Stephan Boehm; Jan Borovicka; Christian Braegger; Patrick Bühr; Emmanuel Burri; Sophie Buyse; Matthias Cremer; Dominique Criblez; Philippe de Saussure; Lukas Degen; Joakim Delarive; Christopher Dörig; Barbara Dora; Tobias Ehmann; Ali El Wafa; Mara Egger; Matthias Engelmann; Markus Fliegner; Nicolas Fournier; Pascal Frei; Remus Frei; Michael Fried; Florian Froehlich; Raoul Furlano; Suzanne Gallot-Lavallée; Martin Geyer; Marc Girardin; Beat Gysi; Horst Haack; Johannes Haarer; Beat Helbling; Peter Hengstler; Denise Herzog; Cyrill Hess; Klaas Heyland; Thomas Hinterleitner; Philippe Hiroz; Claudia Hirschi; Petr Hruz; Pascal Juillerat; Christoph Knoblauch; Henrik Köhler; Rebekka Koller; Claudia Krieger; Markus Landolt; Frank Lehmann; Valérie McLin; Philippe Maerten; Christine Manser; Urs Marbet; Michael Manz; George Marx; Rémy Meier; Christa Meyenberger; Jonathan Meyer; Pierre Michetti; Benjamin Misselwitz; Patrick Mosler; Christian Mottet; Christoph Müller; Pascal Müller; Beat Müllhaupt; Claudia Münger; Andreas Nagy; Cristina Nichita; Natacha Noël; Andreas Nydegger; Carl Oneta; Franziska Piccoli; Julia Pilz; Gaëlle Pittet; Valérie Pittet; Ronald Rentsch; Sophie Restellini, Jean-Pierre Richterich; Jocelyn Roduit; Daniela Rogler; Gerhard Rogler; Jean-Benoît Rossel; Markus Sagmeister; Bernhard Sauter; Mikael Sawatzki; Michael Scharl; Sylvie Scharl; Nora Schaub; Martin Schelling; Susanne Schibli; Hugo Schlauri; Daniela Schmid; Sybille Schmid; Jean-François Schnegg; Alain Schoepfer; Christiane Sokollik; Frank Seibold; Gian-Marco Semadeni; Mariam Seirafi; David Semela; Arne Senning; Marc Sidler; Johannes Spalinger; Holger Spangenberger; Philippe Stadler; Volker Stenz; Michael Steuerwald; Alex Straumann; Michael Sulz; Alexandra Suter; Michela Tempia-Caliera; Joël Thorens; Sarah Tiedemann; Stephan Vavricka; Francesco Viani; Roland Von Känel; Alain Vonlaufen; Dominique Vouillamoz; Rachel Vulliamy; Helene Werner; Paul Wiesel; Reiner Wiest; Tina Wylie; Jonas Zeitz; Dorothee Zimmermann.

Author Contributions

All authors have made substantial contributions to all the following: [1] the concept and design of the study, or acquisition of data, or analysis and interpretation of data; [2] drafting the article or revising it critically for important intellectual content; [3] final approval of the version to be submitted. AS, JS, NF,

ES, and AN initiated and designed the study. AS, SS, JS, SV, NA, GR, CB, and AN collected data. NF, AS, ES, and AN performed the statistical analysis. All authors contributed to data interpretation and manuscript writing and had full access to all data in the study. All authors read and approved the final manuscript.

Supplementary Data

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

References

1. 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.
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. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of paediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis* 2011;**17**:423–39.
4. Schoepfer AM, Vavricka S, Safroneeva E, *et al.* Systematic evaluation of diagnostic delay in paediatric inflammatory bowel disease. *J Paediatr Gastroenterol Nutr* 2017;**64**:245–7.
5. 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.
6. 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.
7. Levine A, Griffiths A, Markowitz J, *et al.* Paediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011;**17**:1314–21.
8. Nahon S, Lahmek P, Paupard T, *et al.* Diagnostic delay is associated with a greater risk of early surgery in a French cohort of Crohn's disease patients. *Dig Dis Sci* 2016;**61**:3278–84.
9. Zaharie R, Tantau A, Zaharie F, *et al.*; IBDPROSPECT Study Group. Diagnostic delay in Romanian patients with inflammatory bowel disease: risk factors and impact on the disease course and need for surgery. *J Crohns Colitis* 2016;**10**:306–14.
10. Moon CM, Jung SA, Kim SE, *et al.*; CONNECT study group. Clinical factors and disease course related to diagnostic delay in Korean Crohn's disease patients: results from the CONNECT study. *PLoS One* 2015;**10**:e0144390.
11. Ricciuto A, Fish JR, Tomalty DE, *et al.* Diagnostic delay in Canadian children with inflammatory bowel disease is more common in Crohn's disease and associated with decreased height. *Arch Dis Child* 2018;**103**:319–26.
12. Vasseur F, Gower-Rousseau C, Vernier-Massouille G, *et al.* Nutritional status and growth in paediatric Crohn's disease: a population-based study. *Am J Gastroenterol* 2010;**105**:1893–900.
13. Valentini L, Schaper L, Buning C, *et al.* Malnutrition and impaired muscle strength in patients with Crohn's disease and ulcerative colitis in remission. *Nutrition* 2008;**24**:694–702.
14. Nguyen VQ, Jiang D, Hoffman SN, *et al.* Impact of diagnostic delay and associated factors on clinical outcomes in a U.S. Inflammatory Bowel Disease Cohort. *Inflamm Bowel Dis* 2017;**23**:1825–31.
15. Li Y, Ren J, Wang G, *et al.* Diagnostic delay in Crohn's disease is associated with increased rate of abdominal surgery: a retrospective study in Chinese patients. *Dig Liver Dis* 2015;**47**:544–8.
16. Safroneeva E, Vavricka SR, Fournier N, *et al.*; Swiss IBD Cohort Study Group. Impact of the early use of immunomodulators or TNF antagonists on bowel damage and surgery in Crohn's disease. *Aliment Pharmacol Ther* 2015;**42**:977–89.
17. Ma C, Beilman CL, Huang VW, *et al.* Anti-TNF therapy within 2 years of Crohn's disease diagnosis improves patient outcomes: a retrospective cohort study. *Inflamm Bowel Dis* 2016;**22**:870–9.
18. Kariyawasam VC, Selinger CP, Katelaris PH, *et al.* Early use of thiopurines or methotrexate reduces major abdominal and perianal surgery in Crohn's disease. *Inflamm Bowel Dis* 2014;**20**:1382–90.
19. Vernier-Massouille G, Balde M, Salleron J, *et al.* Natural history of paediatric Crohn's disease: a population-based cohort study. *Gastroenterology* 2008;**135**:1106–13.
20. To N, Gracie DJ, Ford AC. Systematic review with meta-analysis: the adverse effects of tobacco smoking on the natural history of Crohn's disease. *Aliment Pharmacol Ther* 2016;**43**:549–61.
21. Biedermann L, Fournier N, Misselwitz B, *et al.*; Swiss Inflammatory Bowel Disease Cohort Study Group. High rates of smoking especially in female Crohn's disease patients and low use of supportive measures to achieve smoking cessation—data from the Swiss IBD Cohort Study. *J Crohns Colitis* 2015;**9**:819–29.
22. Walters TD, Griffiths AM. Mechanisms of growth impairment in paediatric Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2009;**6**:513–23.
23. Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology* 2010;**139**:1147–55.
24. Wolters FL, Russel MG, Stockbrügger RW. Systematic review: has disease outcome in Crohn's disease changed during the last four decades? *Aliment Pharmacol Ther* 2004;**20**:483–96.
25. Feagan BG, Panaccione R, Sandborn WJ, *et al.* Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology* 2008;**135**:1493–9.
26. Kerur B, Machan JT, Shapiro JM, *et al.* Biologics delay progression of Crohn's disease, but not early surgery, in children. *Clin Gastroenterol Hepatol* 2018;**16**:1467–73.