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Significant medical and surgical morbidity in perianal Crohn's disease: Results from a territory-wide study

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Short title: Clinical characteristics and outcomes of perianal Crohn's disease

Abbreviations: IBD: inflammatory bowel disease; CD: Crohn's disease; PCD: perianal Crohn's disease, TNF: tumour necrosis factor

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Abstract (Word count: 250)

Background: Presence of perianal fistulas in Crohn's disease (CD) denotes increased disease aggressiveness. We studied epidemiology and clinical outcomes of perianal CD (PCD) using Hong Kong territory-wide IBD Registry (HKIBDR).

Methods: Consecutive patients with PCD were identified from HKIBDR. Disease characteristics, treatments and outcomes were analysed. Risks for medical and surgical therapies were assessed using Kaplan–Meier analysis.

Results: Among 981 patients with CD with 10,530 patient-years follow-up, 283 (28.8%) had perianal involvement, of which 120 (42.4%) were as first presentation. Mean age at diagnosis of PCD was 29.1 years old and 78.8% were male. Median follow-up duration was 106 months (IQR: 65-161 months). Perianal fistula (84.8%) and perianal abscess (52.7%) were the two commonest forms. Male, younger age at diagnosis of CD and penetrating phenotypes were associated with development of PCD in multivariate analysis. Among 242 patients with fistulizing PCD, 70 (29.2%) required ≥ 5 courses of antibiotics and 98 (40.5%) had ≥ 2 surgical procedures. Nine patients required defunctioning surgery and 4 required proctectomy. Eighty-four patients (34.7%) received biologics. Cumulative probabilities for use of biologics were 4.7%, 5.8% and 8.6% at 12 months, 36 months and 96 months while that for surgery were 67.2%, 71.6% and 77.7% at 12 months, 36 months and 96 months respectively. Five mortalities were recorded, including 2 anal cancer, 2 CD-related complications and one case of pneumonia.

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Conclusion: Over 40% CD patients presented with perianal disease at diagnosis. Chinese patients with PCD had poor outcomes, with young age of onset, multiple antibiotic use and repeated surgery.

Keywords: perianal Crohn's disease, epidemiology, clinical outcomes

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Introduction

Perianal Crohn's disease (PCD) affects one-third of patients with Crohn's disease (CD). It represents a distinct, aggressive and disabling phenotype of Crohn's disease. The presence of perianal Crohn's disease at presentation increased number of hospital admissions, increased surgical resections in the subsequent five years and predisposed patients to chronic disabling symptoms.[1]

The epidemiology of PCD is poorly understood. Reported prevalence for PCD varies widely from 10% to 80% in the literature (due to the different definition of "perianal Crohn's disease" used across studies.[2-4] Perianal symptoms can precede intestinal symptoms in Crohn's disease with a varying frequency from 5 to 46% in different series.[5-10] Based on the American Gastrointestinal Association (AGA) technical review 2003 perianal Crohn's disease includes perianal skin lesions (anal skin tags, haemorrhoids), anal canal lesions (anal fissures, anal ulcer, anorectal stricture), perianal abscess and perianal fistula, rectovaginal fistula and cancer.[11]

Studies on the distribution and epidemiology of perianal Crohn's disease in Asian population are lacking. In a population-based study in Asia, we found that around 18% of Asian patients with Crohn's disease had perianal involvement.[12] Perianal disease at presentation was more common in mainland China (33-60%) than other countries in the Asian Pacific region.[13] In the West, the reported cumulative 10-year risk of perianal fistula ranged from 15.8% to 21%.[10,14]

There is a lack of population-based studies on the natural history or long-term outcomes of PCD. PCD is highly prevalent, but how common it is in population-based settings are unclear. Hospital-based data are biased towards more severe phenotype. The aim of this study is to determine the characteristics of perianal Crohn's disease, and evaluate their natural history and clinical outcomes using data from a territory-wide based IBD registry.

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Methods

Materials and subjects

The Hong Kong IBD registry (HKIBDR) is a territory-wide cohort developed in 2013 which aims to investigate the prevalence, disease characteristics, treatment and prognosis of IBD patients in Hong Kong.[16] Thirteen public hospitals in Hong Kong participated in this project. It included 13 Hospital Authority (HA) hospitals across seven clusters in Hong Kong which serves more than 95% of IBD patients in Hong Kong. The Hong Kong Hospital Authority is the sole public healthcare provider for primary, secondary and tertiary health services in Hong Kong, serving a population of around 7.3 million.[17]

All 981 CD patients in the HKIBD registry were identified and included in this study We used the electronic medical records of the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority to collect relevant data. The HA uses the Clinical Management System (CMS), a computerised clinical management system, to record all key clinical information of each individual patient, including demographic data, consultation notes, hospitalisation notes, diagnoses, prescriptions, laboratory results, endoscopic records and procedure information. Patients were followed from the date of diagnosis to the end of data collection (31 December 2016), loss to follow up or death. Demographic data, including age, gender, smoking history, disease phenotypes (according to Montreal Classification), laboratory data including haemoglobin level, C-reactive protein and ESR levels at diagnosis of CD, colonoscopy results, IBD-related medical therapies, including the use of immunosuppressants, 5-aminosalicylates acid, steroid, antibiotics for perianal Crohn's disease and biologics, IBD-related surgeries including incision and drainage of perianal abscess, examination under anaesthesia, seton insertion, fistuolotomy, defunctioning surgery and

proctectomy/ proctocolectomy were retrieved case by case from CMS. Data after the establishment of HKIBDR were prospectively collected, while those before 2013 were retrospectively retrieved from the CMS.

Perianal lesions were classified according to the technical review on perianal Crohn's disease by American Gastroenterology Association (AGA).[11] Perianal fistulas were further classified into simple and complex fistulas. Simple fistula has only single external opening without pain or fluctuation to suggest perianal abscess and is low in position (superficial or low intersphincteric or low transsphincteric origin of the fistula tract) and there is no evidence of anorectal stricture. Complex fistula may have multiple external opening with associated perianal abscess and is high in position (high intersphincteric or high transsphincteric or extrasphincteric or suprasphincteric origin of the fistula tract). Patients were defined as having perianal disease at the same time as the diagnosis of CD if the symptoms occurred within 3 months of CD diagnosis. Perianal disease was diagnosed by clinical examination with examination under anaesthesia (EUA) or MRI images.

Data and Statistical Analysis

All collected clinical information was entered into a custom-built Microsoft Excel database. Univariate and multivariate analyses were performed to examine factors associated with development of PCD. Multivariate analysis by forward stepwise elimination method was performed for factors with p value < 0.10 on univariate analysis. All p values were two-sided and a p value of less than 0.05 was considered statistically significant. Kaplan-Meier analysis was performed in order to calculate the cumulative probabilities of developing PCD, the need for biological therapy and surgical therapy over time. Age was set as a continuous variable in the analysis. Statistical analysis was performed with the use of SPSS version 20(SPSS, Chicago, IL). This study was approved by Ethics committee of each individual hospital who participated.

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RESULTS

Nine hundred and eighty-one patients with Crohn's disease were identified from the Hong Kong IBD registry. Among them, 283 (28.8%) had perianal involvement. The mean age at diagnosis of PCD was 29.1 years old (± 12.7) and 223 (78.8%) were male. Majority were of Chinese ethnicity (98.2%). The median follow-up duration was 106 months (IQR: 65-161 months). The baseline demographics and clinical characteristics of the subjects were shown in **Table 1.** Twelve patients (4.2%) had isolated perianal Crohn's disease without luminal involvement. There was a median of 6.5 months delay between symptom onset and diagnosis of CD (interquartile range: 1.3-25.5 months). The cumulative probabilities of developing PCD were 10.9% at 3 years, 12.7% at 5 years, 16.2% at 10 years, 19.3% at 15 years and 24.8% at 20 years. **(Figure 1)** The prevalence of PCD increased gradually over time, from 8% in 1990 to 28% in 2015.

The types of different perianal lesions according to the AGA definition were presented in **Figure 2.** Perianal fistula was most common (84.8%), followed by perianal abscess (52.7%), anal fissures (6.7%), anal stricture (6.4%) and rectovaginal fistula (4.2%). Majority of the fistulas were classified as complex fistulas (78.4%). Among the 283 PCD patients, 242 of them had fistulising perianal Crohn's disease.

In multivariate analysis, male gender [OR: 2.45; 95% CI 1.75-3.54; p<0.01], younger age at diagnosis of CD [OR 0.97; 95% CI 0.96-0.98; p<0.01] and the presence of penetrating phenotype [OR 3.75; 95% CI 2.34-6.01; p<0.01] were associated with development of PCD. Patients having isolated colonic disease were less likely to develop PCD. [OR: 0.61; 95% CI 0.43-0.85; p<0.01] **(Table 2)**

One hundred and twenty patients (42.4%) presented with perianal involvement at diagnosis of CD. Eighty-five patients (30%) developed perianal symptoms before the diagnosis of CD (median: 2 years; interquartile range: 1-5 years) while in 78 patients (27.6%), perianal disease occurred after diagnosis of CD (median: 4 years; range 1-8.25 years).

Medical therapy

Among the 242 patients with fistulising perianal Crohn's disease, defined as having perianal fistula or rectovaginal fistula, 224 were treated with thiopurines (92.6%) and 84 patients (34.7%) had biological therapy. Seventy patients (29.2%) required 5 or more courses of antibiotics for the treatment of their fistulising PCD. Among the 84 patients who were treated with biological therapy, 67 were on infliximab, 16 were on adalimumab and one was on vedolizumab. Forty-one patients (48.8%) stopped biological therapy after a median of 24 months (IQR 8.5-42.5 months). Twenty-three patients required repeated courses of biological therapy. Eighteen of them switched to another biologic. Cumulative probability for use of biological therapy from PCD diagnosis was 4.7% at 12 months, 5.8% at 36 months and 8.6% at 96 months respectively. **(Figure 3)** The rate of biological therapy used ranged from 13.6% to 66% amongst the 13 hospitals.

Ninety-eight patients (40.5%) had at least two surgical procedures for perianal fistulas, including incision and drainage of perianal abscess, examination under anaesthesia, seton insertion and/ or fistulotomies. The rate of surgical procedures ranged from 0.67 to 3.33 operations per patient amongst the 13 hospitals. Nine patients required defunctioning surgery (3 ileostomy and 6 colostomy) and 4 required proctectomy. Cumulative probability for surgery was 67.2% at 12 months, 71.6% at 36 months and 77.7% at 96 months while that for major surgery (defined as having defunctioning surgery and/or proctectomy) was 4.1% at 1 year, 5.4% at 3 year and 6.8% at 10 year. **(Figure 4)**

Different treatment strategies and clinical outcomes over time

Biological therapy (including infliximab and adalimumab) for Crohn's disease is only available as subsidized item in Hong Kong under stringent criteria after year 2011. Patients with PCD diagnosed in or after year 2011 started biologics at a much earlier time compared to those who were diagnosed with PCD before year 2011 (19.5 months vs. 74 months, $p<0.001$). Total 13 patients required defunctioning surgery or proctectomy for their PCD. All of them were diagnosed before year 2011. None of the patients with PCD diagnosed after year 2011 required major operations (defunctioning surgery/ proctectomy). For the 9 PCD patients requiring defunctioning surgeries, all had defunctioning surgery within 3 years after initial diagnosis of PCD.

Mortality

Five patients succumbed during the review period. Two died of anal carcinoma, two died of CD-related complications (peri-stomal abscess and intestinal obstruction) and one died of pneumonia.

Discussion

In a territory-wide IBD study, we found that the outcome of Chinese patients with PCD is poor. Patients developed PCD at a very young age and many often required multiple courses of antibiotics and surgeries. Over 40% of patients presented with perianal disease at diagnosis of CD.

An early population-based study on the natural history of perianal Crohn's disease among from Stockholm County, Sweden in the years of 1955-1974 showed that the cumulative incidence of perianal fistulas was 23%.[18] Another population-based study in Olmsted, Minnesota 1970 to 1993 demonstrated that the cumulative probabilities of developing perianal fistulas was 21% after 10 years and 26% after 20 years.[10] A recent population based study in Canterbury, New Zealand showed that the cumulative probabilities of development of perianal fistula was 28.3% at 20 years.[2] Our data

are consistent with those from the West in which the cumulative probability of developing PCD were 16.2% at 10 years and 24.8% at 20 years amongst CD patients in Hong Kong. Recent population-based study in Netherlands revealed that there was no significant difference in the risk of developing perianal Crohn's fistula over the last two decades despite the more frequent use of immunomodulators and biologics in the last decade.[14] This underlined the need for further improvement in the treatment strategy in PCD.

Our results showed that the probability of developing fistula was higher than studies from Singapore which revealed that the 10-year and 20-year cumulative probabilities of developing PCD were 7.4% and 11.3% respectively.[15] Singapore is a cosmopolitan country in which 25.7% of its population were non-Chinese.[19] While in Hong Kong, 92% of the population are Chinese.[20] Genetic heterogeneity may explain the difference in cumulative probabilities in the development of PCD in two different Asian countries.

There was a high percentage of PCD patients in our cohort requiring surgery in their disease course. The cumulative probability for surgery was 67.2% at 12 months, 71.6% at 36 months and 77.7% at 96 months. Population-based study in Olmsted, Minnesota revealed that 72% of PCD patients required surgery in the era of 1970-1990.[10] Another earlier study on fistulising Crohn's disease in a specialist bowel hospital in London in 1993-1994 showed that 47% of PCD patients with complex fistula required simple surgery (including drainage, fistulotomy and seton) and 38% of them required complex surgery (including resection, defunctioning stoma and proctectomy). Complex perianal fistulas required a median of 6 operations and 2.6 years to heal.[21] These data were reported before the era of biologics. Recently published data on the natural history of PCD in Danish population revealed that the cumulative risk of undergoing perianal surgery and abdominal surgery at 10 years was 67% and 51% respectively. PCD patients had a significantly higher rate of major surgery, predominantly intestinal resections (HR 3.92, 95% CI 1.86-8.67). [22] Despite the development of

biologics, still large percentage of PCD patients required multiple operations.

One of the possible reasons for the high surgical rates in our PCD patients is because of the low rate of biologics prescription. Only 34.7% patients were given biologics for PCD. Utilisation of biological therapy is low in Hong Kong due to its high cost and lack of insurance coverage.[23] Only 11% of CD patients had received anti-TNF therapy in a University hospital in Hong Kong.[24] Subsidised biological therapy is only available in Hong Kong after year 2011. Another reason is the delay in initiation of biological therapy in PCD patients in our cohort. Only 13.5% of PCD patients were given biological therapy within first year of PCD diagnosis. Biologics (including infliximab and adalimumab) are moderately effective for induction and maintenance of fistula closure and is currently recommended as the first-line drug therapy (with or without concomitant thiopurines) for PCD.[25,26] Further action should be done in promoting the proper and early use of biologics in the management of PCD in Hong Kong.

There was a relatively large percentage of patients having penetrating disease behaviour (B3) at the diagnosis of CD in our study. Almost one-fourth of the patients presented with penetrating disease at diagnosis. Siew et al. previously reported that 17-33% of CD had penetrating behaviour and the rate was highest in East Asia.[12] There was a median of 6.5 months delay between symptom onset and diagnosis of CD (interquartile range: 1.3-25.5 months).

We reported 5 cases of mortality in our study population. There were two cases of anal adenocarcinoma, one case of peri-stomal abscess and one case of CD-related intestinal obstruction. The remaining patient died of pneumonia. The incidence of anal carcinoma in PCD is thought to be rare and is estimated to be around 0.3-0.7%.[27,28] Iesalnieks et al. previously reported 65 cases of anorectal carcinoma associated with perianal fistula in CD patients.[29] Pathogenesis is not fully understood but is thought to be due to chronic inflammation and mucosal regeneration of the long-

standing fistula tract.[30] In our cohort, both patients developed anal adenocarcinoma at 11 years after the diagnosis of PCD. One of them did not receive biological therapy as patient could not afford it financially and was on azathioprine for his PCD. The other patient only received biological therapy 9 years after having perianal Crohn's disease as anti-TNF was only available as a subsidized item in Hong Kong after 2011. The poor outcome in these two patients might be related to the suboptimal control of disease and inflammation that is associated with cancer risk. One patient who was on infliximab developed peristomal abscess after total colectomy with ileostomy performed for complex ileocolonic CD and PCD and failed surgical treatment. Another patient on infliximab developed severe community acquired pneumonia and succumbed. The use of anti-TNF is associated with higher infectious rate and higher rate of post-operative complications in meta-analysis.[31,32] The remaining patient had known stricturing CD with perianal fistula, developed intestinal obstruction and refused operation due to advanced age and finally succumbed.

In contrary to the existing literature, we found that patients having isolated colonic disease were less likely to develop PCD. Possible explanation included the relative short period of follow-up (median follow-up duration: 106 months) and 242 patients in our study cohort (85.5%) were actually treated with thiopurines before the development of PCD, which might have influenced the development of fistulating complications.

One of the strengths of our study is the use of data from large territory-wide data base and included all subjects from the Hong Kong IBD registry. This minimise the bias of a single tertiary hospital. The follow-up period was modest with median follow-up duration of 106 months. This is also the first study to report the Asian epidemiology on perianal Crohn's disease. However, there are several limitations in this study. First, it assumed all perianal lesions developed were related to Crohn's disease. Thirty percent of the cases developed perianal symptoms before the diagnosis of Crohn's disease. This delay may in part relate to delay in diagnosis of CD in the earlier decade even in patients presenting with perianal symptoms. Majority (76%) had recurrent perianal disease after

diagnosis of Crohn's disease was made. Secondly, several information (including smoking history, family history of IBD, the exact number and dates of surgery) may have been inaccurate in some cases or could not be identified from the database. Thirdly, due to limitation of retrospective analysis, if patients have moved from other cities outside Hong Kong to Hong Kong before 2013, their data prior to arrival in Hong Kong will not be available. Lastly, there was lack of evaluation of efficacy of therapy and data on the clinical status of perianal fistulas during the observation time were not available.

In conclusion, the outcome of Chinese patients with PCD is poor. More than 40% had perianal involvement at diagnosis of Crohn's disease. Patients often required multiple courses of antibiotics and surgery for the treatment of PCD. Future studies should focus on identifying risk factors associated with the development of PCD and factors associated with treatment response in PCD so as to derive a tailor-made treatment for individual PCD patient.

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Table 1. Baseline characteristics of patients with perianal Crohn's disease

Male Gender, n (%)	223 (78.8%)
Chinese Ethnicity, n (%)	278 (98.2%)
Mean Age at Diagnosis of CD, Years ± SD	28.6 ± 12.6
Mean Age at Diagnosis of PCD, Years ± SD	29.1 ± 12.7
History of Smoking at Diagnosis	
Current/ Ex-smokers	53 (19.6%)
Proctitis at diagnosis	46 (21%)
Montreal Classification – Location, n (%)*	
L1 – Ileal	52 (18.4%)
L2 – Colonic	104 (36.7%)
L3 – Ileocolonic	127 (44.9%)
L4 – Upper GI involvement	21 (7.4%)
Montreal Classification – Behavior, n (%)	
B1 – Inflammatory	160 (56.5%)
B2 – Stricturing	54 (19.1%)
B3 – Penetrating	69 (24.4%)

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* L4 and L1-L3 are not mutually exclusive

*CD – Crohn's Disease; PCD – Perianal Crohn's Disease

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Table 2. Factors associated with development of perianal Crohn's disease (PCD)

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age at CD diagnosis	**0.97 (0.96-0.98)**	**<0.01**	**0.97 (0.96-0.98)**	**<0.01**
Gender (Male)	**2.32 (1.69-3.19)**	**<0.01**	**2.45 (1.75-3.45)**	**<0.01**
Smoking status at diagnosis of PCD Current/ Ex-smokers vs. non-smokers	0.930 (0.66 -1.31)	0.68		
Disease Location L1 vs. L3	**1.60 (1.14-2.25)**	**0.01**	1.24 (0.84-1.83)	0.28
L2 vs. L3	**0.72 (0.54-0.96)**	**0.02**	**0.61 (0.43-0.85)**	**<0.01**
Disease Behavior B2 vs B1	0.94 (0.69-1.29)	0.71		
B3 vs B1	**3.17 (2.58-5.08)**	**<0.01**	**3.75 (2.34-6.01)**	**<0.01**
Family history of IBD	0.82 (0.35-19.4)	0.66		
Blood tests at CD diagnosis ESR	1.00 (0.99-1.01)	0.62		

CRP	1.00 (0.99-1.00)	0.34		
Hemoglobin level	1.00 (0.96-1.05)	1.00		

Figure 1. Cumulative probabilities of perianal Crohn's disease development in Crohn's disease patients

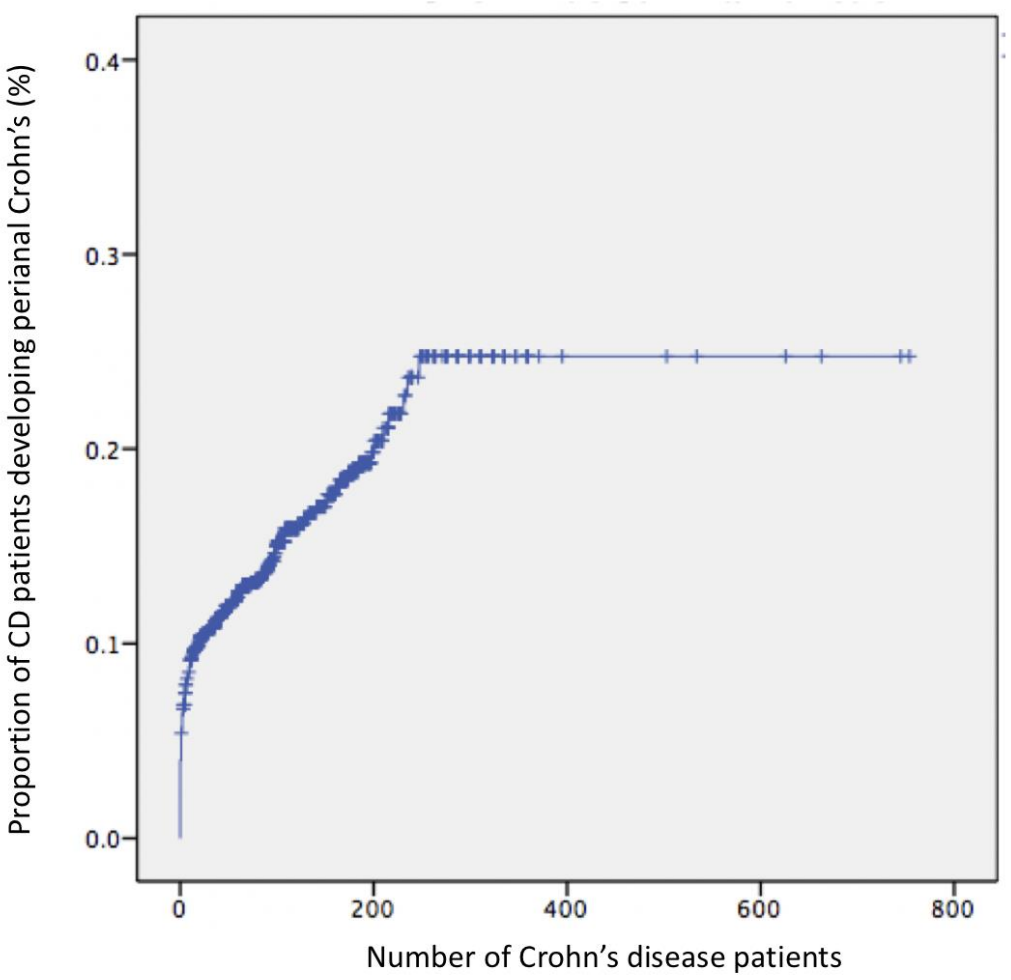

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Figure 2. Types of perianal lesions according to the American Gastroenterology Association (AGA) definitions

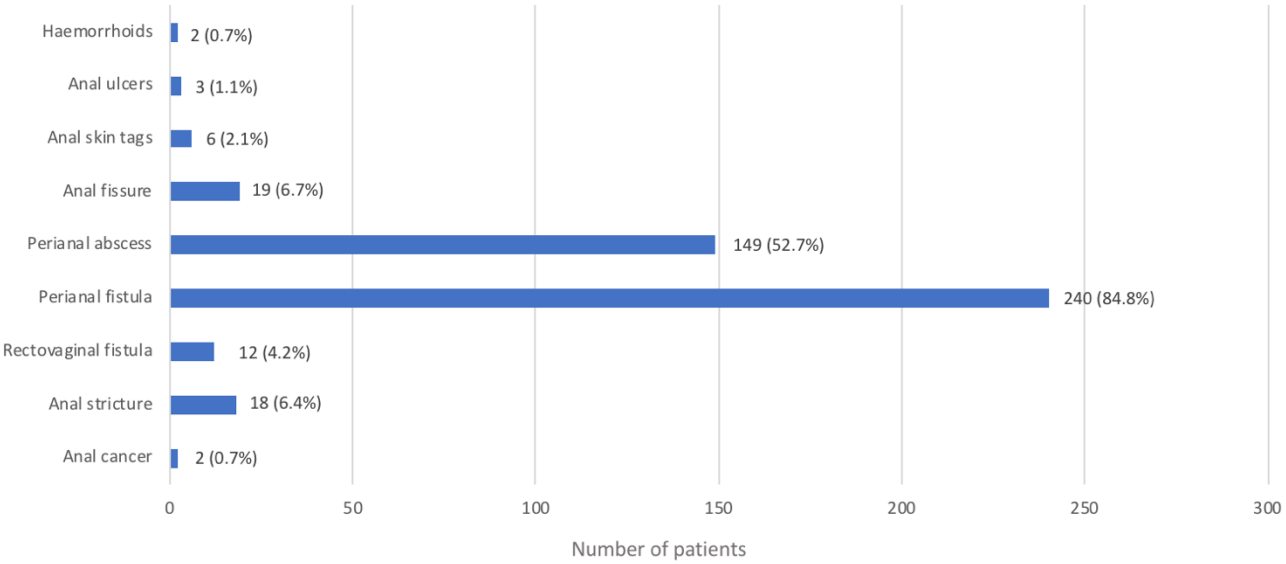

Figure 3. Cumulative probabilities of using biologics in patients with perianal Crohn's disease

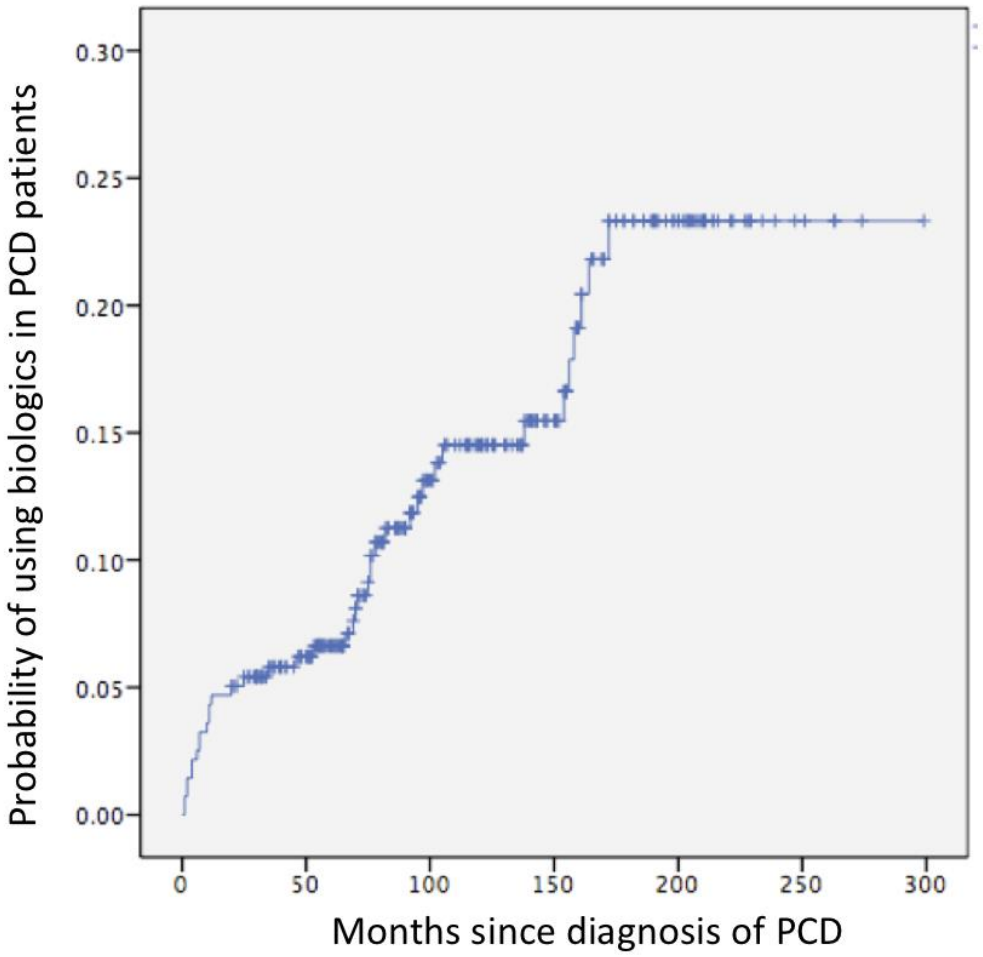

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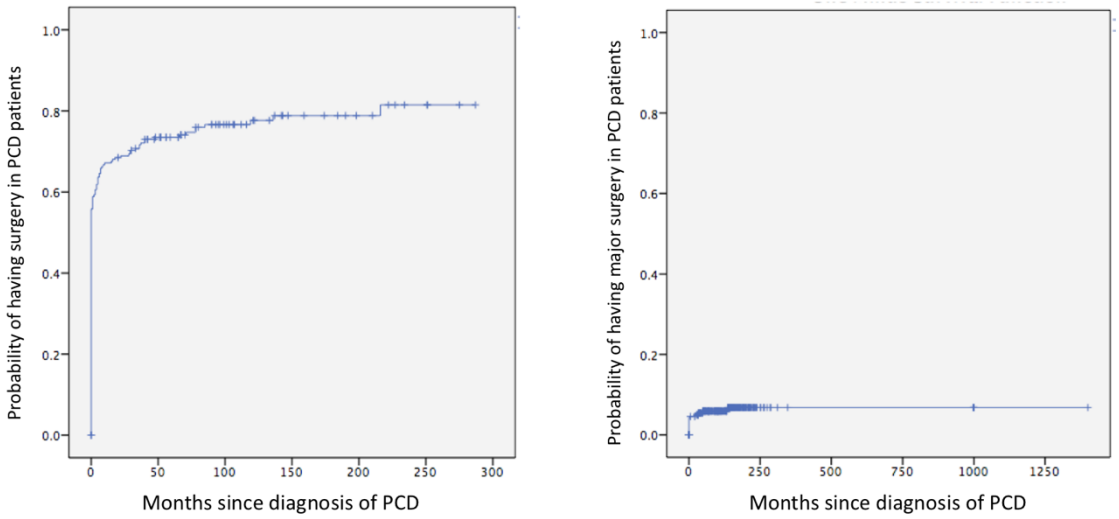
Figure 4. Cumulative probabilities of having surgery (left) and major surgery* (right) in patients with perianal Crohn's disease



**Major surgery is defined as having defunctioning surgery and/ or proctectomy.*