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Post-inflammatory polyps burden as a prognostic marker of disease-outcome in patients with inflammatory bowel disease

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Abstract

Introduction and Aim: Post-inflammatory polyps (PIPs) are considered as indicators of previous episodes of severe inflammation and mucosal ulceration. Inflammatory bowel disease (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC), exhibit a perpetuating, relapsing, and remitting pattern and PIPs is a frequent sequela of chronicity. The aim of this study was to determine whether a high PIPs burden is associated with a more severe disease course in patients with IBD.

Methods: This was a multinational, multicentre, retrospective study. IBD patients previously diagnosed with PIPs were retrieved from the endoscopic database of each centre. PIPs burden was evaluated and associated with demographic and clinical data as well as factors indicating a more unfavorable disease course.

Results: A total of 504 IBD patients with PIPs were recruited (male: 61.9%). The mean age at IBD diagnosis was 36.9 (± 16.8) years. Most patients (74.8%) were diagnosed with UC. A high PIPs burden was present in 53.4% of patients. On multivariable Cox regression analysis, high PIPs burden was independently associated with treatment escalation (HR 1.35, 95% CI 1.04-1.75; *P*=0.024), hospitalization (HR 1.90; 95% CI 1.24 – 2.90; P=0.003), need for surgery (HR 2.28; 95% CI 1.17-4.44, P=0.02) and younger age at diagnosis (HR 0.99, 95% CI 0.98–0,99; p=0.003).

Conclusion: PIPs burden was associated with a more severe outcome. Future prospective studies should focus on the characterisation of PIPs burden as to further risk stratify this patient cohort.

Keywords: Post-Inflammatory polyps, pseudo polyps, colorectal cancer, Inflammatory bowel disease, Crohn`s disease, Ulcerative colitis

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Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article.

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Introduction

Post-inflammatory polyps (PIPs) are polypoid structures, projecting above the surface of the mucosa without malignant potential.[1] They arise following repeated cycles of mucosal inflammation, ulceration and healing, as suggested by the alternative terms "inflammatory polyps" or "pseudopolyps". Colonic PIPs are commonly encountered in patients with inflammatory bowel disease (IBD), with their prevalence in ulcerative colitis (UC) reportedly being twice that seen in colonic Crohn's disease (CD).[2]

PIPs in IBD have been associated with more severe inflammation, higher colectomy rates and a greater need for biologic therapy.[3,4] A recent meta-analysis evaluated the risk of colorectal cancer (CRC) in IBD patients with and without PIPs. IBD patients with PIPs were at an increased risk of CRC as compared to those without (Odds Ratio [OR] 2.01; 95% confidence interval [CI] 1.43–2.83).[5] However, large studies within the meta-analysis revealed a higher risk of colectomy and hospitalisation but not CRC. [3,4]

Dysplasia and CRC are possible complications of IBD and increase both morbidity and mortality associated with IBD. There are several risk factors for CRC such as disease duration, extent and activity, family history of CRC and primary sclerosing cholangitis. Based on these criteria patients are classified into low, intermediate or high risk to develop cancer. Accordingly, patients may undergo more frequent surveillance colonoscopies as the presence of PIPs immediately classify them into the intermediate risk category.[6,7] Patients may have very few and small and/or multiple, and/or large PIPs. However, current guidelines do not distinguish between these differences in morphological characteristics of PIPs in terms of risk of complications secondary to IBD.

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The concept of the 'therapeutic window of opportunity' highlights the importance of identifying poor prognostic signs and avoiding under-treatment, thereby achieving deep remission early in the disease course to maximize therapeutic benefit. [8]

The primary aim of this study was to determine whether a high colonic PIPs burden is associated with a more severe disease course in patients with IBD, as indicated by the need for treatment escalation, administration of biologic agents and an increased rate of IBD-related hospitalization and surgery.

Methods

Study design and population

We performed a retrospective, multinational, multicentre cohort study. Patients with a confirmed diagnosis of IBD based on established clinical, endoscopic and imaging criteria were recruited from 9 European centres and 1 centre in Israel. Eligible patients were identified through an electronic search in the endoscopy database of each centre.

Clinical records were reviewed, and the following baseline characteristics were extracted: date of birth, gender, age at diagnosis of IBD, IBD type, phenotype according to Montreal classification, smoking status and IBD-related medication use both at initial diagnosis of IBD and at the time of identification of PIPs. The most recent outpatient consultation or inpatient evaluation before the deadline of data collection was set as the date of last follow-up. The date of the most recent endoscopic procedure was also captured.

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In CD, disease activity was defined according to the Crohn`s disease activity index (CDAI) score and the Simple endoscopic score for Crohn`s disease (SES-CD. In UC, the Mayo scores were used to determine disease activity.

Outcomes of interest

The endoscopic procedure at which PIPs were initially detected was defined as the index colonoscopy and the following data were collected: date of procedure, indication for colonoscopy (either surveillance or to investigate clinical symptoms) and the presence or absence of mucosal healing. Data on the characteristics of the PIPs was then collected from the endoscopy reports.

PIPs were classified as following:

1. Number of PIPs: Patients were classified as having "numerous" PIPs if more than 10 were identified or if the endoscopy report had descriptors such as "many", "numerous", "diffuse" or "fields". These descriptors have been described in previous studies on PIPs. Patients with 10 or fewer PIPs, and in the absence of such descriptors were classified as having "few".[3,4]
2. Size of PIPs: PIPs larger than 1.5cm in size were classified as "large" PIPs. The rest were classified as "small".
3. PIPs burden: Patients were classified as having a high burden if they had numerous and/or large PIPs. Patients with small and few PIPs were classified as having a low PIPs burden.

With regards to our primary outcome, data was extracted on treatment escalation (this was defined as initiation of an immunomodulator and/or a biological agent for patients who were

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naïve to these treatments prior to colonoscopy), introduction of biological agents and the need for IBD-related hospitalization or surgery, following the identification of PIPs. IBD-related hospitalization and surgery were defined as the need for admission to hospital for a true IBD-related cause which was not related to treatment modifications or diagnostic procedures or to undergo surgery due to active disease or complications resulting from IBD, respectively.

Data was anonymized by each centre and then transferred to the study co-ordinators (P.E, J.S. and A.V.B.). Informed consent for data process for scientific analyses had already been obtained in each participating centre following local regulatory procedures. Endoscopy and histology reports were not shared between centres and only information strictly needed for the purpose of the present study was extracted and transferred.

Statistical analyses

Descriptive statistics were used for baseline characteristics, with categorical variables described using frequencies and percentages, while continuous variables were described using means and standard deviations if normally distributed. The baseline characteristics of patients with low PIPs burden were compared to those with high PIPs burden using the independent t-test and the Chi-square test as appropriate.

In order to determine the effect of PIPs burden on the cumulative incidence of the outcomes of interest time-to-event methods were employed. Kaplan-Meier curves were drawn to compare the cumulative probabilities of the outcomes of interest according to PIPs burden and IBD subtype. Log-rank analyses were performed to test for significance. Time-to-event

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was defined as the time from PIPs diagnosis to primary outcome or censoring. Patients were censored at last follow-up.

Univariate and multivariate Cox regression analyses were then carried out to explore the independent associations of different variables with the outcomes of interest. The variables included in the model were age at diagnosis, gender, IBD type, smoking and PIPs burden. Statistical significance was set as a P value <0.05. All statistical analyses were carried out using SPSS software version 28 (IBM, Chicago, IL, USA)

Results

Baseline characteristics of the study population

A total of 504 IBD patients with colonic PIPs were recruited from the 10 participating centres: 61.9% were male and the mean age at IBD diagnosis was 36.9 (± 16.8) years.

The majority of patients (74.8%) were diagnosed with UC, 23.6% with CD and 1% were classified as having IBD-U. Smokers accounted for 19% of the total study cohort. Table 1 demonstrates the clinical characteristics of this patient cohort. The index colonoscopy was conducted for surveillance in 49% of patients while the rest had ongoing clinical symptoms and 38.1% of patients exhibited mucosal healing. PIPs were evaluated, classified and confirmed histologically in 75.6% of cases, while for the rest a 'resect and discard' approach was followed. Medication exposure at the time of index colonoscopy is summarised in Table 2.

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Numerous PIPs were found in 51.0% (n=257) and large PIPs were present in 12.5% (n=63) of patients with 9.9% exhibiting both findings. Based on the definitions of PIPs burden, 53.4% had a high PIPs burden.

The two groups were similar in terms of gender, age at diagnosis of IBD and IBD type. A higher proportion of patients with a high PIPs burden were smokers (31% vs 15.4%; P<0.001). While the phenotype of CD was similar among the two groups, patients with UC and a high PIPs burden had more extensive disease (75.1%) compared to patients with a low PIPs burden (58.0%, P=0.002). Patients with a low PIPs burden had a significantly longer follow-up period from IBD diagnosis (mean follow-up 183±126 months) compared to patients with high PIPs burden (151±117 months; P=0.003). The two groups were comparable regarding exposure to different IBD-related medication, and rates of appendicectomies and ileocolonic resections prior to PIPs detection.

Outcomes according to PIPs burden

Treatment escalation

Approximately half of the patients (48.2%; n=243) required treatment escalation after PIPs were first detected. The majority of patients (79.3%; n=191) had endoscopically active disease at the time of PIPs detection although in 32.5% of them the indication for the index colonoscopy was disease surveillance.

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CD patients with a high PIPs burden required more frequently treatment escalation (55.3%, n=142) than those in the low PIPs burden group (44.1%, n=100, pooled log rank *P*=0.022) Such a difference was not observed in UC patients (Fig 1).

On multivariable Cox regression analysis, high PIPs burden was independently associated with treatment escalation (Hazard Ratio [HR] 1.35, 95% CI 1.04-1.75; *P*=0.024) and younger age at diagnosis of IBD (HR 0.99, 95% CI 0.98–0.99; p=0.003) (Table 3).

Administration of a biological agent

Following the identification of PIPs, 152 patients (30.1%) required the introduction of a biological agent. Of these, 56.6% were started on infliximab, 17.8% adalimumab, 19.1% vedolizumab , 3.3% golimumab and 2% ustekinumab .

The introduction of biological therapy was more frequent in patients with a high PIPs burden (35.6%; n=88) when compared to patients with a low PIPs burden (27.5%; n=61). Whilst on pooled analysis this did not reach statistical significance (log-rank p=0.86), subgroup analysis showed that the difference was again significant in CD patients but not in UC (Fig 2). On Cox regression analysis, no association was observed between the PIPs burden and the introduction of a biological agent (Table 3).

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IBD-related hospitalization

Following detection of PIPs, 28.4% (n=143) of patients required an IBD-related hospitalization. The main reason for hospitalization was active disease (82.9%, n=121). Patients with a high PIPs burden demonstrated a significantly higher probability of requiring hospitalization than those with a low PIPs burden (35.7%; n= 95 vs 20.4%; n=47, log-rank *P*=<0.001) and the difference was significant in both UC and CD patients (Fig 3). The mean time to IBD-related hospitalization after PIPs detection was 400 months (95% CI 360-438) in the high PIPs burden group, this being 719 months (95% CI 671-767) in the low PIPs burden group. In a multivariable Cox regression analysis, high PIPs burden (HR 1.90; 95% CI 1.24–2.90; P=0.003) and smoking (HR 1.72 95% CI 1.13-2.61; p=0.01) were independently associated with hospitalization (Table 3).

IBD-related surgery

A total of 43 patients required IBD-related surgical intervention following the detection of PIPs. The indications for surgery were disease refractory to conservative treatment (65.1%), colonic CRC (16.3%), colonic non-malignant strictures (7%), fistulizing CD (7%) and colonic dysplasia (4.6%). There was no significant difference in the PIPs burden in those requiring colectomy for dysplasia or malignancy (high PIPs burden: 55.6%)

The probability of requiring surgery was significantly increased in the high PIPs burden group (11.5% vs 5.1%, OR 2.3; 95% CI 1.2 – 4.4, log-rank *P*=0.009) (Fig 4). Whilst this difference was noted in both UC and CD patients it only reached statistical significance in the

former (Fig 4). On Cox regression analysis, male gender (HR 2.11; 95% CI 1.04-4.27, P=0.04) and high PIPs burden (HR 2.28; 95% CI 1.17-4.44, P=0.02) were independently associated with surgery (Table 3).

Discussion

PIPs are considered non-malignant, neoplastic lesions originating from the mucosa after repeated periods of inflammation and ulceration associated with excessive healing processes. In this multicentre retrospective cohort study of 504 IBD patients with PIPs, those with a high PIPs burden had a more complex IBD outcome.

Politis et al identified that PIPs presence in UC patients was a risk factor for treatment escalation and need for biological agents or surgery when compared to patients without PIPs.[1] The need for surgery was also confirmed in two other retrospective studies, where PIPs were associated with higher colectomy rates but were not associated with the development of CRC. [3,4] **Patients with many PIPs were more likely to have extensive disease and more severe inflammation.**[3,4] We aimed to investigate if PIPs burden and not merely PIPs presence is associated with a worse disease outcome.

Patients with a high PIPs burden, as defined based on number and/or size of polyps, required more frequent treatment escalation, hospitalization or IBD-related surgery than their low PIPs burden counterparts. In our UC cohort, patients with a high PIPs burden had **significantly more extensive disease, and higher colectomy and hospitalisation rates. This is in accordance with the existent literature.** [1,3,4] **However, patients with a high PIPs burden were not more likely to use immunosuppressant treatment. A possible reason could be a**

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high rate of corticosteroids usage in our UC cohort and an overall reluctance to start immunosuppressive treatment with the hope that remission could be achieved on corticosteroids.

The existing data on CD and PIPs relates mostly to the risk of CRC. Current literature does establish an association between PIPs and CRC in CD patients. [3,4,5] Our analysis on PIPs burden demonstrated an increased need for the introduction of both immunomodulator and biological treatment in CD patients rather than in UC patients. Unlike in UC, we could not document any difference in the phenotype between CD patients with a high and low PIPs burden. The limited role of 5-ASA treatment in CD may have led to an earlier introduction of immunomodulator and biological treatment.

Early age of IBD diagnosis was not associated with PIPs burden. Patients with a high PIPs burden were more frequently smoking, although only one fifth of the total cohort declared smokers. Smoking has also been associated with a more severe and refractory to treatment disease course serving as an additional risk factor for disabling outcomes.

Our study has certain advantages. We did not restrict our cohort to a single type of IBD but we included also patients with CD as PIPs are formed irrespective of IBD subtype, and will therefore reflect disease severity in UC as well as in CD.Moreover, to our knowledge, this is the largest cohort of IBD patients reporting on the association of PIPs with disease outcome

We recruited patients from 10 different centres from several countries thus reporting on a more representative patient population with a relatively long follow-up, which permitted the investigation of infrequent events like hospitalization and surgery. Finally, we sought for the

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first time to investigate the burden and not only the presence of PIPs as a prognostic marker for a more debilitating disease evolution.

There are also limitations in our study. First, the retrospective design cannot exclude unmeasured confounding variables and recall bias. Second, a quarter of the polyps detected was not verified with histology and were characterized as PIPs based on endoscopy report. A previous study demonstrated minimal misclassification of PIPs based on endoscopic assessment.[9] Third, characterization of PIPs burden was not standardized. Considering the retrospective nature of the study it was not possible to assess precisely corticosteroid usage. Another limitation both for this study and daily clinical practice is the routine use of formal scoring system for PIPs. Thus, a perception of a higher PIPs burden may lead to a perception of more severe disease and thus initiation of any immunosuppressant treatment. However, in our cohort, increase usage of immunosuppressant treatment after PIPs detection was only significant in CD patients and not UC patients.

If one had to hypothesise that the risk of dysplasia and CRC is related to the degree of inflammation and mucosal damage, then patients with a high PIPs burden may be at an increased risk of such outcomes when compared to those with a low PIPs burden. Based on the results of this study we could suggest that PIPs burden is a more accurate surrogate of severity of inflammation in IBD than the net presence of PIPs without further characterization. Thus, classifying all patients with PIPs in the intermediate risk surveillance category independently of the burden may be incorrect. The number, location and size should perhaps be taken into account for risk stratification. Furthermore, detailed description of PIPs and identification of patient groups with a higher risk can serve as a marker for more intense

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endoscopic follow up in the assessment for disease activity as to prevent structural bowel damage through timely introduction of the appropriate therapy,[10] a concept that would be in keeping with the current strategies of personalised treatment.[11-13]

Conclusion

In this retrospective, multicentre study, PIPs burden was independently associated with a younger age at diagnosis, treatment escalation in CD patients and IBD-related hospitalization and surgery. Prospective studies should focus on adequate characterisation of PIPs burden as to further risk stratify this patient cohort.

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Table 1: **Baseline characteristics**

Characteristic	**High PIPs burden**	**Low PIPs burden**	***P* value**
Males	63.9%	59.6%	0.31
Mean age at diagnosis (±SD)	37.9 (±17.4)	35.6 (±16.0)	0.13
Smokers	31.0%	15.4%	<0.001
IBD type			0.54
CD	25.6%	21.4%	
UC	72.5%	78.6%	
IBD-U	1.9%	0%	
UC extent			
E1	1.0%	3.3%	0.002
E2	23.8%	38.7%	
E3	75.2%	58.0%	
CD classification			
L2	35.8%	36.7%	0.67
L3	64.2%	63.3%	
L4	7.4%	14.6%	0.21
B1 B2 B3	66.2% 11.8% 22.1%	61.2% 22.4% 16.3%	0.27
Mean follow-up after IBD diagnosis (±SD)	150 months (±114.7)	180.8 months (±115.8)	0.003
Mean follow up after PIPs detection	53.4 months	47.2 months	0.05
Treatment exposure			
Aminosalicylates	62.8%	55.3%	0.1
Immunomodulators	28.0%	21.6%	0.11
Biologic agents	19.9%	17.8%	0.56
Combination therapies	9.2%	6.3%	0.25
Appendectomy	12.6%	7.1%	0.06

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CD patients UC patients	19.1% 9.9%	12.8% 5.3%	0.37 0.14
Ileocolonic resection	1.5%	1.7%	0.85

SD: Standard Deviation; UC: Ulcerative colitis; CD: Crohn`s disease; IBD-U: Inflammatory bowel disease-unclassified ; E1 - ulcerative proctitis ; E2 - Left-sided colitis UC ; E3 pancolitis ; L2 – colon; L3 – ileocolonic ; L4 : Upper GI ; B1- non stricturing, non-penetrating; B2 – Stricturing ; B3 – penetrating ; PIP – post-inflammatory polyps

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Table 2. Medication use at time of identification of PIPs

	Total cohort n (%)	**UC n (%)**	**CD n (%)**	**IBD-U n (%)ˇ**
5-ASA	284 (56.3)	234 (62.1)	45 (37.8)	40
IMM	120 (23.8)	76 (20.2)	41(34.4)	0
Biologic agents	91 (18.1)	61 (16.2)	28 (23.5)	0
Combination therapies*	38 (7.5)	25 (6.6)	12 (10.1)	0

*Combination treatment includes patients who were receiving both a biologic agent and an immunosuppressant

ˇ The rest of the patients were not having medications at the time of the study

IMM: Immunossupressants ; 5-ASA: 5-aminosalicylates

UC: Ulcerative colitis; CD: Crohn`s disease; IBD-U: Inflammatory bowel disease-unclassified

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Table 3: Multivariable analysis

	Treatment Escalation	**Introduction of a biologic agent**	**IBD-related hospitalization**	**IBD-related surgery**
Variable	HR (95% CI) p value	HR (95% CI) p value	HR (95% CI) p value	HR (95% CI) p value
Gender (male)	1.27 (0.92-1.74) p=0.14	1.13 (0.75-1.69) p=0.57	1.42 (0.92-2.21) p=0.12	2.11 (1.04–4.27) p=0.04
IBD type (CD)	1.25 (0.90-1.73) p=0.19	1.65 (1.11-2.45) p=0.014	1.33 (0.87–2.03) p=0.18	0.83 (0.32–2.15) p=0.69
Smoking	1.0 (0.71-1.41) p=0.99	1.52 (1.01-2.28) p=0.04	1.72 (1.13–2.61) p=0.01	1.01 (0.41–2.49) p=0.98
PIPs burden (high)	1.35 (1.04-1.75) p=0.024	1.3 (0.88-1.92) p=0.20	1.90 (1.24–2.90) p=0.003	2.28 (1.17–4.44) p=0.02
Age of IBD diagnosis (years)	0.99 (0.98-0.995) p=0.003	0.98 (0.97-0.99) p=0.004	0.99 (0.98–1.01) p=0.26	1.00 (0.98–1.03) p=0.89

PIP: post-inflammatory polyps; HR: Hazard Ratio; CI: Confidence Intervals; CD: Crohn`s Disease

IBD – Inflammatory Bowel disease ; CD: Crohn`s disease;

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Figures

Figure 1

Figure 1A UC Treatment Escalation

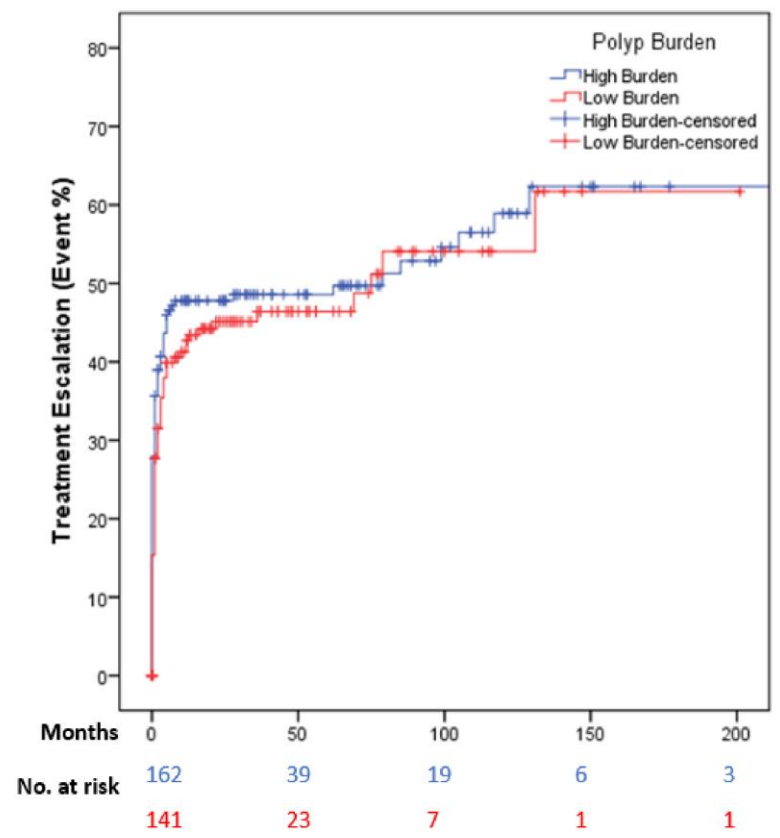

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Figure 1B: CD Treatment Escalation

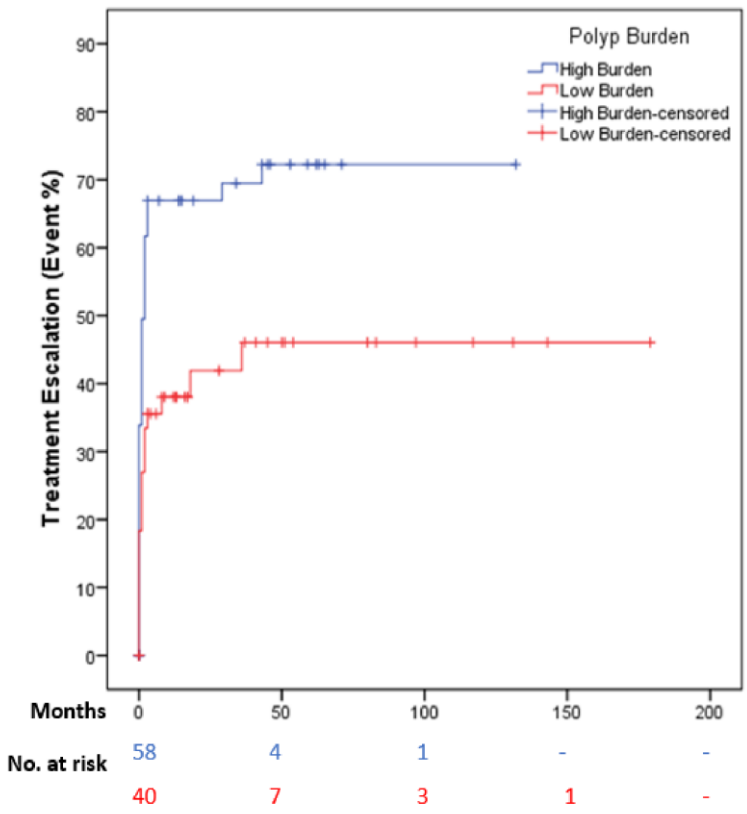

Fig 1. Kaplan-Meier curve of cumulative incidence for treatment escalation in UC (1a) and CD (1b) patients. Pairwise comparison of treatment escalation proportion in high PIP burden vs low PIP burden was statistically significant in CD (p=0.004) but not in UC (p=0.347).

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Figures

Figure 2

Figure 2A UC Biological Drug

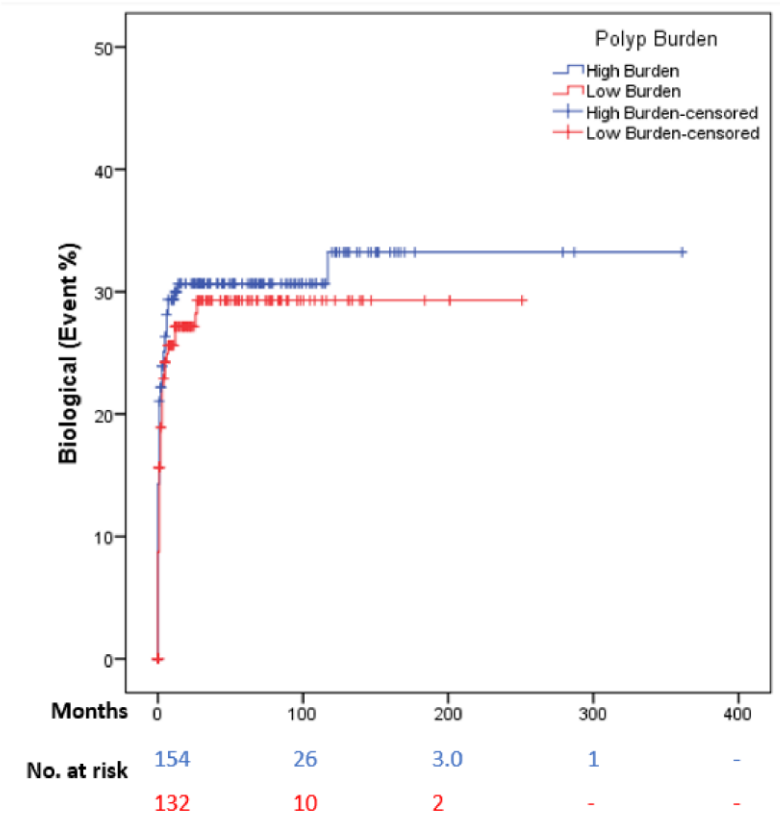

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Figure 2B: CD Biological Drug

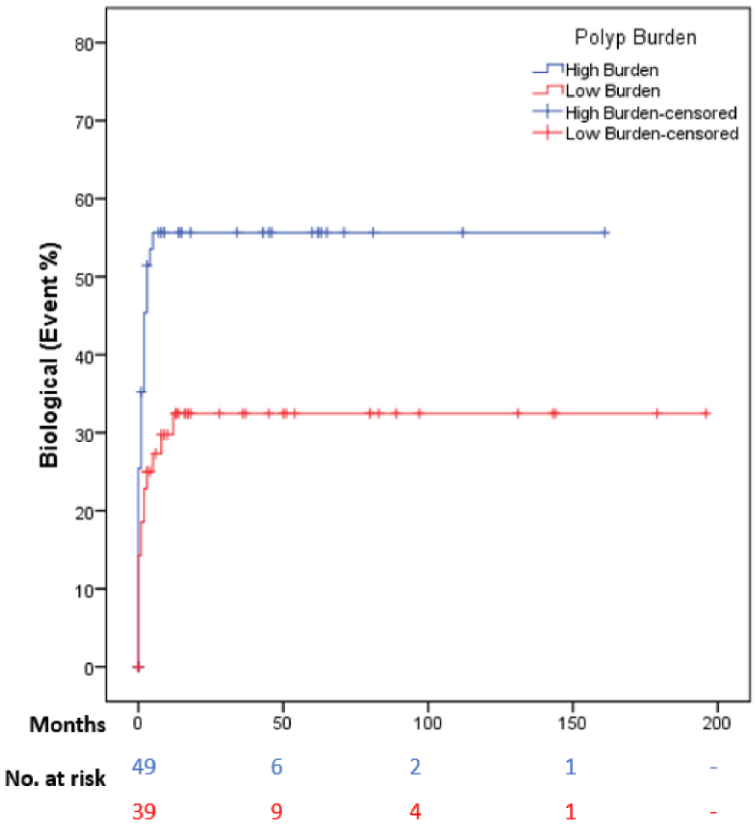

Fig 2. Kaplan-Meier curve of cumulative incidence for introduction of biological agent in UC (2a) and CD (2b) patients. Proportion of biological agent introduction in high PIP burden vs low PIP burden was statistically significant in CD (p=0.014) but not in UC (p=0.531).

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Figures

Figure 3

Figure 3A UC Hospitalisation

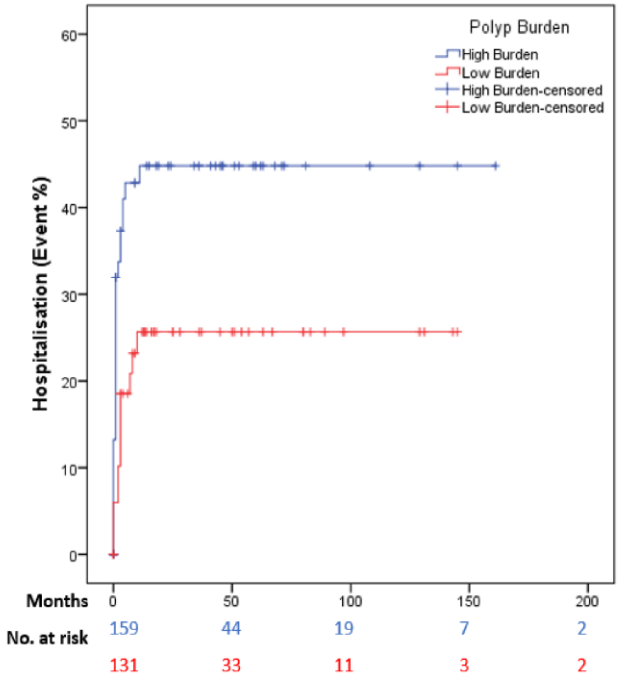

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Figure 3B: CD Hospitalisation

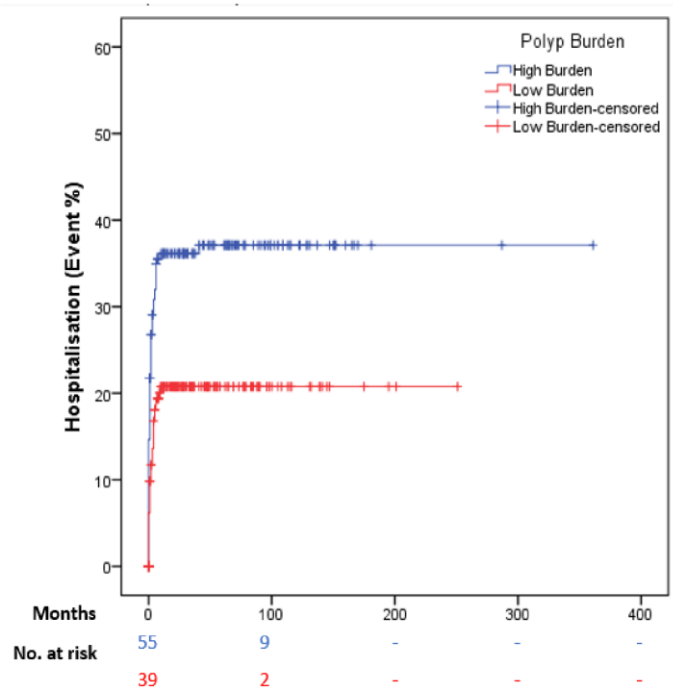

Fig 3. Kaplan-Meier curve of cumulative incidence for hospitalisation in UC (3a) and CD (3b) patients. Pairwise comparison of time to hospitalisation in high vs low PIP burden was statistically significant in both UC and CD patients (p=0.001 and p=0.024 respectively).

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Figures

Figure 4

Figure 4A UC Surgery

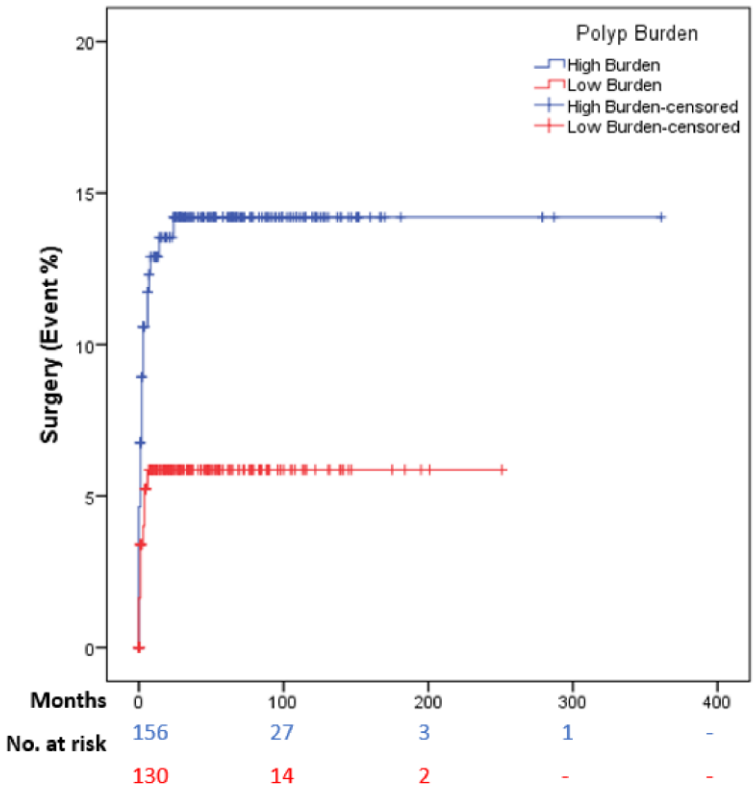

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Figure 4B: CD Surgery

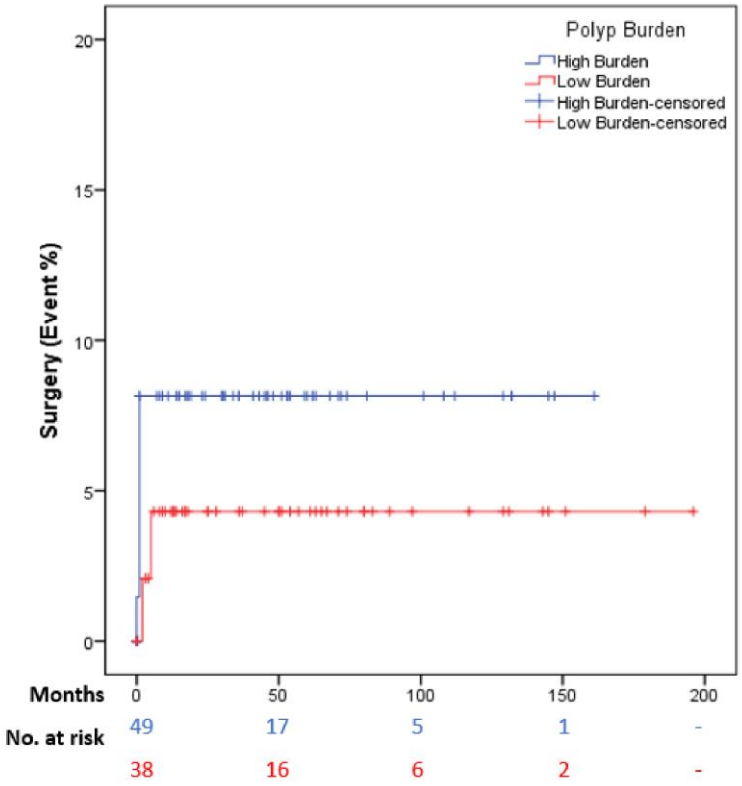

Fig 4. Kaplan-Meier curve of cumulative incidence for surgery in UC (4a) and CD (4b) patients. Pairwise comparison of time to surgery in high vs low PIP burden showed differences in both UC (p=0.012) and CD (p=0.379) but was only statistically significant in the former.