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**Original Article**

# Post-inflammatory Polyp Burden as a Prognostic Marker of Disease-outcome in Patients with Inflammatory Bowel Disease

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## Abstract

**Background and Aims:** 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 are a frequent sequela of chronicity. The aim of this study was to determine whether a high PIP 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. PIP burden was evaluated and associated with demographic and clinical data as well as factors indicating a more unfavourable 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 PIP burden was present in 53.4% of patients. On multivariable Cox regression analysis, a high PIP burden was independently associated with treatment escalation (hazard ratio [HR] 1.35, 95% confidence interval [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:** PIP burden was associated with a more severe outcome. Future prospective studies should focus on the characterization of PIP burden as to further risk stratify this patient cohort.

**Key Words:** Post-inflammatory polyps, pseudo polyps, colorectal cancer, inflammatory bowel disease, Crohn's disease, ulcerative colitis

## 1. 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 hospitalization but not CRC.[3,4]

Dysplasia and CRC are possible complications of IBD and increase both the 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 of developing cancer. Accordingly, patients may undergo more frequent surveillance colonoscopies as the presence of PIPs immediately classify them within 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.

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 PIP 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.

## 2. Methods

### 2.1 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 nine European centres and one 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 the 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.

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.

### 2.2 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 were then collected from the endoscopy reports.

PIPs were classified as follows:

1. Number of PIPs: patients were classified as having 'numerous' PIPs if more than ten 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 ten or fewer PIPs, and in the absence of such descriptors, were classified as having 'few'.[3,4]
2. Size of PIPs: PIPs larger than 1.5 cm in size were classified as 'large' PIPs. The rest were classified as 'small'.
3. PIP 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 PIP burden.

With regard to our primary outcome, data were extracted on treatment escalation [this was defined as initiation of an immunomodulator and/or a biological agent for patients who were 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 were anonymized by each centre and then transferred to the study co-ordinators [P.E, J.S. and A.V.B.]. Informed consent for data processing 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.

### 2.3 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 PIP burden were compared to those with high PIP burden using the independent *t*-test and the Chi-square test as appropriate.

To determine the effect of PIP 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 PIP burden and IBD subtype. Log-rank analyses were performed to test for significance. Time-to-event was defined as the time from PIP 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 PIP burden. Statistical significance was set as $p < 0.05$. All statistical analyses were carried out using SPSS software version 28 [IBM].

## 3. Results

### 3.1 Baseline characteristics of the study population

A total of 504 IBD patients with colonic PIPs were recruited from the ten 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-unclassified [IBD-U]. Smokers accounted for 19% of the total study cohort. Table 1 gives the clinical characteristics of this patient cohort. 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 summarized in Table 2.

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 PIP burden, 53.4% had a high PIP 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 PIP 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 PIP burden had more extensive disease [75.1%] compared to patients with a low PIP burden [58.0%, $p = 0.002$]. Patients with a low PIP burden had a significantly longer follow-up period from IBD diagnosis [mean follow-up 183 ± 126 months] compared to patients with a high PIP burden [151 ± 117 months; $p = 0.003$]. The two groups were comparable regarding exposure to different IBD-related medication, and regarding rates of appendicectomies and ileocolonic resections prior to PIP detection.

### 3.2 Outcomes according to PIP burden

#### *3.2.1 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 PIP detection although in 32.5%

**Table 1.** Baseline characteristics

| Characteristic | High PIP burden | Low PIP burden | *p*-value |
|---|---|---|---|
| Males, % | 63.9 | 59.6 | 0.31 |
| Mean age at diagnosis [±SD], years | 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 | 66.2 | 61.2 | 0.27 |
| B2 | 11.8 | 22.4 | |
| B3 | 22.1 | 16.3 | |
| Mean follow-up after IBD diagnosis [±SD], months | 150 [±114.7] | 180.8 [±115.8] | 0.003 |
| Mean follow-up after PIP detection, months | 53.4 | 47.2 | 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 |
| CD patients | 19.1 | 12.8 | 0.37 |
| UC patients | 9.9 | 5.3 | 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.

**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[a] | 38 [7.5] | 25 [6.6] | 12 [10.1] | 0 |

[a]Combination treatment includes patients who were receiving both a biologic agent and an immunosuppressant. The remaining 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.

of them the indication for the index colonoscopy was disease surveillance.

CD patients with a high PIP burden more frequently required treatment escalation [55.3%, *n* = 142] than those in the low PIP burden group [44.1%, *n* = 100, pooled log rank *p* = 0.022] Such a difference was not observed in UC patients [Figure 1].

On multivariable Cox regression analysis, a high PIP 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].

### 3.2.2 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 PIP burden [35.6%; *n* = 88] when compared to patients with a low PIP 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 patients [Figure 2]. On Cox regression analysis, no association was observed between PIP burden and the introduction of a biological agent [Table 3].

### 3.2.3 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 PIP burden demonstrated a significantly higher probability of requiring hospitalization than those with a low PIP 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 [Figure 3]. The mean time to IBD-related hospitalization after PIP detection was 400 months [95% CI 360–438] in the high PIP burden group, this being 719 months [95% CI 671–767] in the low PIP burden group. In a multivariable Cox regression analysis, a high PIP 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].

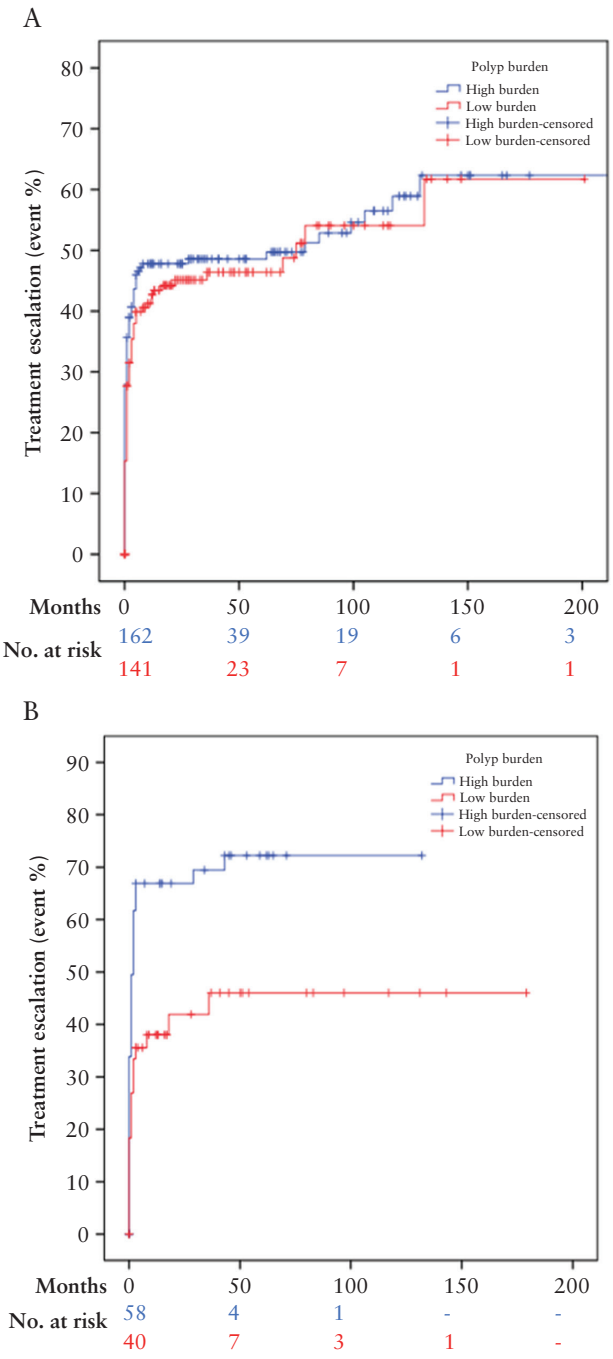


**Figure 1.** Kaplan–Meier curve of cumulative incidence for treatment escalation in UC [A] and CD [B] patients. Pairwise comparison of treatment escalation proportion in high PIP burden vs low PIP burden was statistically significant in CD [*p* = 0.004] but not in UC [*p* = 0.347].

### 3.2.4 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 PIP burden in those requiring colectomy for dysplasia or malignancy [high PIP burden: 55.6%].

The probability of requiring surgery was significantly increased in the high PIP burden group [11.5% vs 5.1%, OR

**Table 3.** Multivariable analysis

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

PIP: post-inflammatory polyps; HR: hazard ratio; CI: confidence intervals; CD: Crohn's disease; IBD: inflammatory bowel disease.

2.3; 95% CI 1.2–4.4, log-rank $p = 0.009$] [Figure 4]. Whilst this difference was noted in both UC and CD patients, it only reached statistical significance in the former [Figure 4]. On Cox regression analysis, male gender [HR 2.11; 95% CI 1.04–4.27, $p = 0.04$] and high PIP burden [HR 2.28; 95% CI 1.17–4.44, $p = 0.02$] were independently associated with surgery [Table 3].

## 4 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 PIP burden had a more complex IBD outcome.

Politis *et al*. identified that PIP 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 PIP burden and not merely presence of PIPs is associated with a worse disease outcome.

Patients with a high PIP burden, as defined based on the number and/or size of polyps, required more frequent treatment escalation, hospitalization or IBD-related surgery than their low PIP burden counterparts. In our UC cohort, patients with a high PIP burden had significantly more extensive disease, and higher colectomy and hospitalization rates. This is in accordance with the existent literature.[1,3,4] However, patients with a high PIP burden were not more likely to use immunosuppressant treatment. A possible reason could be a high rate of corticosteroid 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 relate mostly to the risk of CRC. The current literature does establish an association between PIPs and CRC in CD patients.[3–5] Our analysis on PIP 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 PIP burden. The limited role of 5-aminosalicylic acid [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 PIP burden. Patients with a high PIP burden were more frequently smokers, although only one fifth of the total cohort declared as 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 ten 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 such as hospitalization and surgery. Finally, we sought for the 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 were not verified with histology and were characterized as PIPs based on endoscopy reports. A previous study demonstrated minimal misclassifications of PIPs based on endoscopic assessment.[9] Third, characterization of PIP burden was not standardized. Considering the retrospective nature of the study it was not possible to assess corticosteroid usage precisely. Another limitation both for this study and daily clinical practice is the routine use of a formal scoring system for PIPs. Thus, a perception of a higher PIP 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 PIP detection was only significant in CD patients and not UC patients.

If one had to hypothesize that the risk of dysplasia and CRC is related to the degree of inflammation and mucosal

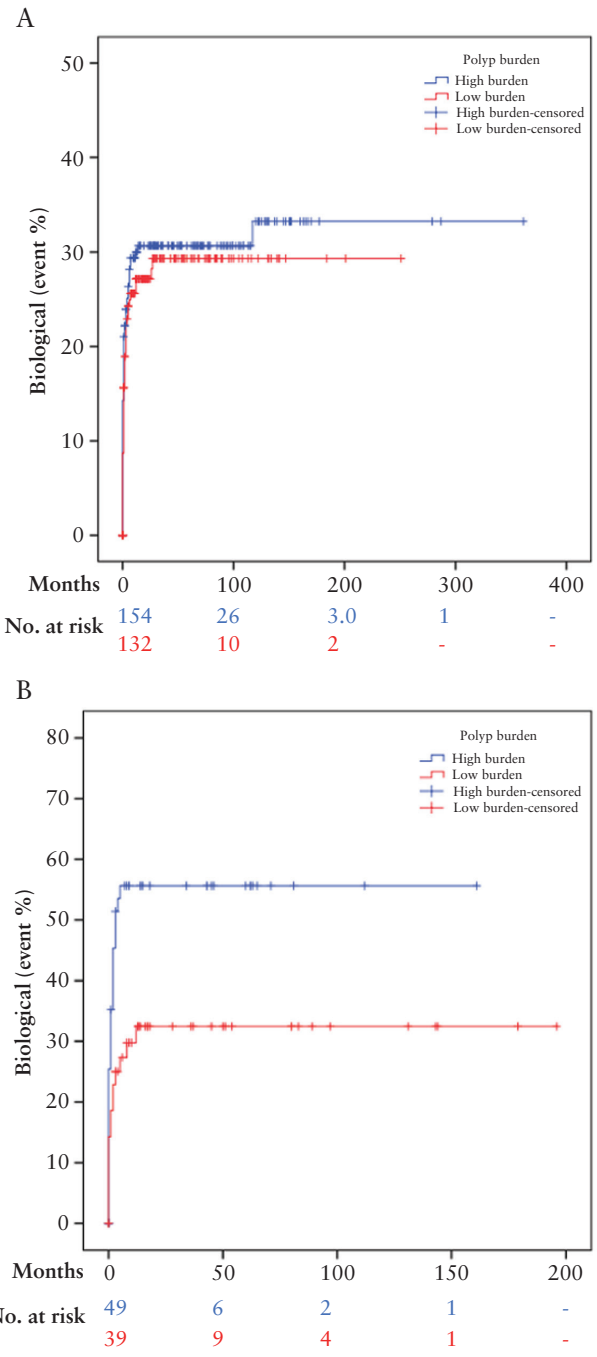


**Figure 2.** Kaplan–Meier curve of cumulative incidence for introduction of a biological agent in UC [A] and CD [B] patients. Proportion of biological agent introduction in high PIP burden vs low PIP burden was statistically significant in CD [$p = 0.014$] but not in UC [$p = 0.531$].

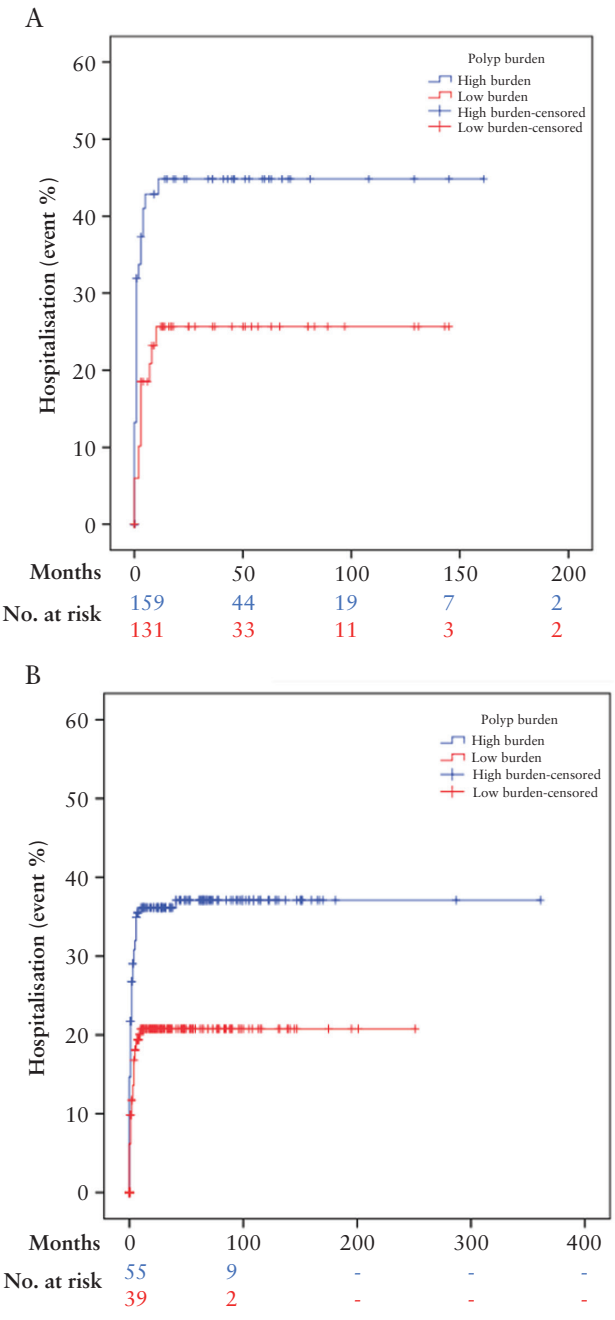


**Figure 3.** Kaplan–Meier curve of cumulative incidence for hospitalization in UC [A] and CD [B] patients. Pairwise comparison of time to hospitalization in high vs low PIP burden was statistically significant in both UC and CD patients [$p = 0.001$ and $p = 0.024$ respectively].

damage, then patients with a high PIP burden may be at an increased risk of such outcomes when compared to those with a low PIP burden. Based on the results of this study, we suggest that PIP 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 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 endoscopic follow-up in the assessment for disease activity 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 personalized treatment.[11–13]

## 5. Conclusion

In this retrospective, multicentre study, PIP 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

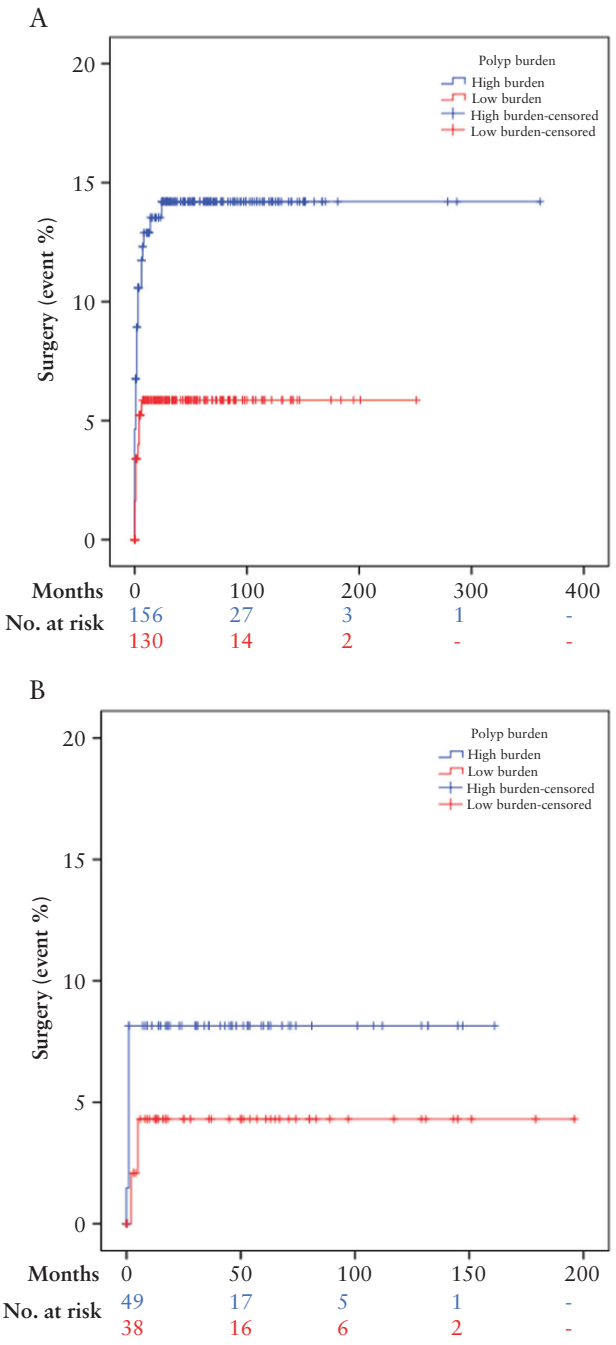


**Figure 4.** Kaplan–Meier curve of cumulative incidence for surgery in UC [A] and CD [B] patients. Pairwise comparison of time to surgery in high vs low PIP burden showed differences in both UC [$p = 0.012$] and CD [$p = 0.379$] but was only statistically significant in the former.

adequate characterization of PIP burden as to further risk stratify this patient cohort.

## Funding

None.

## Conflict of Interest

EP—Lecture fee from Janssen. SJ, VBA, RT, AMA, FF, DB, TA, FM, TE, MGJ, PF, RS, GHA, FF, SY, LZ, Michalopoulos G, TJ, CL—none. MG—speaker fee for Takeda, Pfeizer, Jannsen, MSD, Abbvie, Ferring. SS—research grants from Takeda, AbbVie, Warner Chilcott, Biogen, Janssen, Ferring, MSD, Biohit and Cellgene, serves on the advisory boards of Takeda, AbbVie, Merck, Ferring, Pharmacocosmos, Warner Chilcott, Janssen, Falk Pharma, Biohit, TriGenix, Cellgene and Tillots Pharma, and has received speakers fees from Abbvie, Tillotts, Warner Chilcott, Janssen, Amgen, and Falk Pharma. CD—as per previous JCC COI. Yanai H—Consulting fees Abbvie, Ferring, Janssen, Neopharm Ltd., Pfizer, Takeda; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events Abbvie, Janssen, Pfizer, Takeda, Neopharm Ltd.; Participation on a Data Safety Monitoring Board or Advisory Board Abbvie, Neopharm Ltd., Pfizer, Takeda. KP—Scientific advisory board fees: ProciseDx Inc and Scipher Medicine Corporation; consultant: Prometheus Laboratories Inc. and Lecture/speaker fees from Mitsubishi Tanabe Pharma, Physicians Education Resource LLC and Grifols. Karmiris K has served as speaker, consultant, and advisory member for Abbvie, Amgen, Enorasis, Ferring, Galenica, Genesis, Janssen, MSD, Pfizer, Takeda and Vianex. Katsanos K as per JCC COI.

## Author Contributions

EP—Data analysis, co-ordinator between centres, drafting of manuscript. SJ—drafting of manuscript, statistical analysis. VBA—drafting of manuscript, co-ordination of data collection from all centres. MT, RT, AMA, FF, DB, TA, FM, TE, MGJ, PF, RS, MG, GHA, SS, FF, CD, SY, LZ, YH. Michalopoulos G—data collection from own centre, data analysis, reviewing of manuscript. TJ—data collection from own centre; CL—statistical analysis; KP reviewing and writing of paper, review of statistics. KarmirisK—design of the study, acquisition of data, analysis and interpretation of data, review of manuscript. Katsanos K—the conception and design of the study, acquisition of data, interpretation of data, review of manuscript.

## Data Availability

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

## Supplementary Data

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

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