# Chronic Pouchitis and Crohn's Disease of the Pouch after Ileal Pouch-Anal Anastomosis: Incidence and Risk Factors

Clément Bresteau, Aurelien Amiot, Julien Kirchgesner, Nicola De'Angelis, Jeremie H. Lefevre, Yoram Bouhnik, Yves Panis, Laurent Beaugerie, Matthieu Allez, Antoine Brouquet, et al.

Version of Record: https://www.sciencedirect.com/science/article/pii/S1590865821001432
Manuscript_88abb0ca6bb56db5bdbd87b28d1beccb

# Chronic pouchitis and Crohn's disease of the pouch after ileal pouch-anal anastomosis: incidence and risk factors

**Short title: Chronic inflammation of the pouch**

**Authors:** Clément Bresteau[1], Aurélien Amiot MD-PhD[2], Julien Kirchgesner MD[3], Nicola de'Angelis MD-PhD[2], Jérémie H. Lefevre MD-PhD[3], Yoram Bouhnik MD-PhD[4], Yves Panis MD-PhD[4], Laurent Beaugerie MD-PhD[3], Matthieu Allez MD-PhD[5], Antoine Brouquet MD-PhD[1], Franck Carbonnel MD-PhD[1], Antoine Meyer MD[1]

[1]Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, Université Paris Saclay, Le Kremlin Bicêtre, France.

[2]Assitance-Publique-Hôpitaux de Paris, Hôpitaux Universitaires Henri Mondor, EA7375, Universite Paris Est Creteil, Créteil, France

[3]Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Antoine, Sorbonne Université, Paris, France

[4] Assistance Publique-Hôpitaux de Paris, Hôpital Beaujon, Université de Paris, Clichy, France

[5] Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Louis, Université de Paris, Paris, France

**Corresponding author**:

Professor Franck CARBONNEL

Department of Gastroenterology. CHU Bicêtre

78, rue du Général Leclerc, 94270 Kremlin Bicêtre, France

Tel.: +33 145213722

Fax: +33 145212042

E-mail: fcarbonnel7@gmail.com

**Contributors:**

Guarantor of article: FC

Conception and design of the study: CB, AM and FC

Generation, collection, assembly, analysis and/or interpretation of data: CB, AA, JK, NA, JHL, YB, YP, LB, MA, AB, FC, AM

Drafting or revision of the manuscript: CB, FC, AM

Approval of the final version of the manuscript: CB, AA, JK, NA, JHL, YB, YP, LB, MA, AB, FC, AM

**Word count:** 3030 words

**Competing interests:**

CB, JK, NA, YP and AM declare no competing interest. AA received honoraria from Abbvie, Hospira, Takeda, Gilead, Biocodex, Janssen, Tillotts, Ferring, Pfizer and MSD. JHL received honoraria from Takeda. YB received honoraria from Abbvie, Biogaran, Boehringer Ingelheim, Celgene, Ferring, Gilead, Hospira, Janssen, Mayoly-Spindler, MSD, Norgine, Pfizer, Roche, Samsung Bioepis, Sandoz, Sanofi, Shire, Takeda, UCB. LB received honoraria from Janssen, Pfizer, Allergan, AbbVie, Janssen, MSD, Ferring Pharmaceuticals, Mayoly-Spindler, Takeda and Tillotts, and research support from

Abbott, Ferring Pharmaceuticals, Hospira-Pfizer, Janssen, MSD, Takeda and Tillotts. MA received honoraria from Abbvie, MSD, Janssen, Takeda, Pfizer, Novartis, Ferring, Tillotts, Celgene and Genentech/Roche. AB received speaker fees from Takeda, Merck-Serono, Abbvie, Roche, Amgen and Janssen-Cilag and invitation to scientific meeting from Biom'up, Roche, Win'up surgical system and Intuitive surgical. FC received honoraria from Amgen, Arena, BMS, Celltrion, Enterome, Ferring, Janssen, Medtronic, Pfizer, Pharmacosmos, Roche, Takeda and Tillotts as well as lecture fees from Abbvie, Astra, Biogen, BMS, Ferring, Janssen, MSD, Pfizer, Pileje, Takeda and Tillotts.

**Funding:** None

**Data availability statement :** the data underlying this article will be shared on reasonable request to the corresponding author.

**ORCID:**

- Clément Bresteau: 0000-0003-3506-1519
- Aurélien Amiot: 0000-0001-6676-1222
- Jérémie H. Lefevre: 0000-0001-7601-7464
- Antoine Meyer: 0000-0003-1156-9289
- Franck Carbonnel: 0000-0002-4779-5168

**Abstract**

**Background:** Restorative proctocolectomy with ileal-pouch anal-anastomosis (IPAA) is the operation of choice for patients with ulcerative colitis (UC) or with inflammatory bowel diseases unclassified (IBDU).

**Aims:** to assess the incidence and risk factors of chronic pouchitis (CP) and Crohn's disease of the pouch (CDP) in patients with UC or IBDU.

**Methods:** We conducted a retrospective study. We included consecutive patients who underwent IPAA between 2011 and 2019. The main outcome was the occurrence of CP or CDP. We looked for risk factors with multivariable and a least absolute shrinkage and selection operator (LASSO) Cox models.

**Results:** 247 patients were included. The 5-year cumulative incidence of CP or CDP was 35.3% (95%CI: 26.2-43.2). In multivariable analysis, diagnosis of IBDU, age less than 35 years at surgery and extra-intestinal manifestations other than articular and primary sclerosing cholangitis were associated with higher incidence. The LASSO analysis identified these three prognostic factors and articular manifestations. In patients with two or more prognostic factors, 5-year cumulative incidence, was 65.2% (95%CI: 41.8-79.2).

**Conclusions:** Five years after IPAA, approximately one-third of patients had either CP or CDP. Risk factors were IBDU, an age less than 35 years at surgery, articular manifestations and other extra-intestinal manifestations.

**Keywords :** Ulcerative colitis, colectomy, ileal-pouch-anal anastomosis, pouchitis, Crohn's disease

# Introduction

## Background

Ulcerative colitis (UC) affects approximately two million people in Europe (1). Ten years after the diagnosis, 15 % of patients with UC undergo surgery (2). Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the operation of choice in patients with UC or inflammatory bowel diseases unclassified (IBDU) (3) who had failed medical treatment or who have colon dysplasia or cancer.

Overall, IPAA is associated with a good functional outcome (4). However, some patients develop chronic inflammation of the pouch, i.e., chronic pouchitis (CP) or Crohn's disease of the pouch (CDP). In CP, the inflammation is limited to the pouch and there are no granulomas, whereas in CDP, there is inflammation of the afferent limb or proximal small bowel, fistulizing disease or granulomas. CP and CDP lead to symptoms (diarrhoea, rectal bleeding, abdominal cramps, fever) and negatively affect quality of life (5,6). Patients with CP or CDP may require immunosuppressants and/or biologics (7,8) and are at risk for pouch failure, defined as the need for an end ileostomy or a new IPAA (9,10). The proportion of patients who develop chronic inflammation of the pouch is highly variable among studies: from 11.5 to 31.3% for CP (11–13) and from 3.1% to 21.3% for CDP (14). Some studies have found high incidence rates of CP or CDP (15,16); this raises the question of endoscopic pouch monitoring, as well as prevention and treatment of chronic inflammation before irreversible damage of the pouch occurs.

### Objectives

The aim of the present study was to appraise the incidence of CP and CDP after IPAA in patients with UC or IBDU, to assess their risk factors and to delineate subgroups of patients at high risk of chronic inflammation of the pouch.

## Methods

### Patients

We conducted a retrospective study in five French tertiary inflammatory bowel disease centers of the Paris area. All consecutive patients older than 15 years of age with UC or IBDU who underwent IPAA (J-Pouch) between January 1, 2011 and December 31, 2019, were included. All surgical procedures were performed by experienced colorectal surgeons. Patients were excluded for the following reasons: Crohn's disease diagnosed before proctocolectomy or based on the histology of the proctocolectomy specimen, familial adenomatous polyposis, ileostomy not removed after IPAA, and follow-up of less than 2 months after ileostomy closure. Patients were followed-up by gastroenterologists and surgeons until December 31, 2019. As recommended by the ECCO guidelines, endoscopy of the pouch was not systematic. It was performed in cases of primary sclerosing cholangitis, atrophic pouch mucosa, presence of dysplasia in the original colectomy specimen or symptoms suggestive of pouchitis (17).

### Variables

The primary outcome was a diagnosis of chronic inflammation of the pouch defined as the first event between CDP and CP. Secondary outcomes included CDP, CP and acute pouchitis. CDP was defined as endoscopic inflammation of the pouch associated with inflammation and ulceration of afferent limb or proximal small bowel, and/or strictures of

the afferent limb or proximal small bowel, and/or the presence of intestinal or anal fistula or granulomas (14). CP was defined as a modified Pouchitis Disease Activity Index (mPDAI) ≥ 5 with symptoms lasting at least 4 weeks, not responding to a 2-week course of antibiotics and not meeting the criteria for CDP (18). Acute pouchitis was defined as mPDAI ≥ 5 lasting less than 4 weeks. mPDAI includes clinical items (stool frequency, rectal bleeding, faecal urgency or abdominal cramps, fever) and endoscopic items (edema, friable and granular mucosa, loss of vascular pattern, mucous exudate and ulcerations)(18). This score is presented in supplementary table 1; mPDAI (which does not include histology) has been compared to PDAI and appears to be similarly sensitive and specific as PDAI (19).

We also assed the rates of proctocolectomy complications and pouch failure. Pouch failure was defined as the need for permanent ileostomy or a new IPAA (20). Post-operative complications were defined as abscesses, fistula, peritonitis, stenosis and obstruction.

## Data sources

Patients' demographic, clinical and endoscopic characteristics were collected from medical records at the time of surgery. These included: age, gender, smoking habits, weight, body mass index, history of medical treatment for UC or IBDU, disease duration, history of appendectomy, extent of disease according to Montreal classification and indication for surgery (fulminant colitis, active disease despite the medical treatment or dysplasia/cancer). The diagnosis of UC or IBDU was that reported by the physician in charge of the patient before surgery. It was made on the basis of history, imaging data, endoscopic appearance and histopathology of perendoscopic biopsies. Immunosuppressants consisted in thiopurines or methotrexate. Biologics included adalimumab, infliximab, golimumab, certolizumab, vedolizumab, ustekinumab or tofacitinib. Although tofacitinib is not a biologics, its indication is similar as that of biologics and is therefore included in this

category. Surgical characteristics were also collected: proctocolectomy performed either as a 1- or 2- or 3-staged procedure, time from ileal pouch-anal anastomosis to restoration of intestinal continuity and mechanical or manual anastomosis.

Disease activity at the time of colectomy, was assessed by C-reactive protein, haemoglobin, albumin, endoscopic Mayo score, deep ulcerations and reflux ileitis at the latest endoscopic evaluation before surgery. Extra-intestinal manifestations included articular manifestations, primary sclerosing cholangitis and other extra-intestinal manifestations (involving the eyes, skin and lungs). Additionally, we identified patients with auto-immune diseases associated with IBD (thyroiditis, thrombocytopenia, hepatitis, pancreatitis, vasculitis, systemic lupus erythematosus, sarcoidosis, celiac disease).

## Statistical methods

Categorical variables were described as number and percentage; quantitative variables were described as median (IQR: interquartile range). Quantitative variables were transformed into binary variables according to the median value. The proportion of missing values was specified.

We performed a survival analysis for each outcome: primary outcome, CDP, CP and acute pouchitis. Follow-up started at the time of restoration of ileostomy closure, after IPAA and ended either at an event or loss to follow-up or study end (December 31, 2019). We estimated survival rates by the Kaplan-Meier method and calculated its confidence interval by the Greewood method.

Then, we searched risk factors associated with the outcomes. All candidate factors with a p-value <0.20 by a Cox univariate analysis were included in a multivariable Cox regression model to identify the factors independently associated with the outcomes. Backward elimination was performed to achieve the final multivariable model with the

hazard ratios (HR) and 95% confidence intervals (CI). The proportional hazards assumption were checked using graphical diagnoses, based on the scaled Schoenfeld residuals. No imputation was computed for missing data; we performed a complete cases analysis.

Because of the small number of events per prognostic factors, and to obtain an optimal model with as few factors as possible we performed a sensitivity analysis with a least absolute shrinkage and selection operator (LASSO) Cox model using the glmnet package in R (21,22). In this analysis, all candidate risk factors were included. The LASSO method allows variable selection by shrinking down to zero coefficient weights for variables non-related to the outcome based on the value of lambda, so that only the strongest predictors remain in the model. We identified the optimal lambda penalty under 10-fold cross-validation by maximizing the cross-validation partial-likelihood, *i.e.* to find the smallest error. For this sensitivity analysis, since the LASSO Cox model does not allow missing values, assuming the missing at random hypothesis, we imputed missing values by their mode/median.

All tests were two-sided, and p-value <0.05 was considered statistically significant. All statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria) version 3.6.0(23).

This protocol was approved by the local ethics committee and the national data protection commission (CNIL), according to MR-004 reference methodology (n°2217502). This study complied with the STROBE guidelines for observational studies. No commercial entity had any role in the study. All authors had access to the study data, reviewed and approved the final manuscript. The study received no funding.

# Results

## Study population

We screened 401 patients who had an IPAA between January 2011 and December 2019. The following patients were not included: 110 patients had Crohn's disease or familial adenomatous polyposis, three patients had an ileostomy left in place after IPAA and 41 had a follow-up of less than 2 months. Thus, 247 patients were included (Supplementary figure 1).

Demographic and baseline patients' characteristics are shown in the table 1. Two hundred and ten (85.0%) patients had a diagnosis of UC and 37 (15.0%) had IBDU. Seventy-three (29.6%) patients were operated for a fulminant colitis, 95 (38.5%) for an active refractory disease and 79 (32.0%) for dysplasia or cancer. In all patients, the pathological specimens of proctocolectomy were consistent with UC or indeterminate colitis. The median age at surgery was 42.0 years (IQR: 30.8-56.3), the median disease duration was 8.0 years (IQR: 3.3-14.6). One hundred and seventy-six patients (74.6%) had been exposed to immunosuppressant and 170 (68.8%) to at least one biologic. Among the 67 (27.1%) patients with extra-intestinal manifestations, 35 (14.2%) had articular manifestations and 34 (13.8%) were diagnosed with primary sclerosing cholangitis. The median follow-up was 3.1 years (IQR: 1.1-5.7).

## Primary outcome

Sixty patients developed either CP or CDP after a median time of 2.1 (IQR: 1.0-3.6) years. Two and five years after surgery, 15.6% (95%CI: 10.2-20.7) and 35.3% (95%CI: 26.2-43.2) of patients had either CP or CDP, respectively (figure 1). In univariate analysis, the diagnosis of IBDU (HR 3.61; 95%CI: 2.03-6.43), age of less than 35 years at surgery (HR 2.45;

95%CI: 1.46-4.09), articular manifestations (HR 1.91; 95%CI: 1.06-3.44), and other extra-intestinal manifestations (HR 5.09; 95%CI: 2.49-10.41) were associated with CDP or CP (Supplementary table 1). In multivariable analysis, diagnosis of IBDU (HR 3.18; 95%CI: 1.77-5.70; p<0.001), age of less than 35 years at surgery (HR 2.03; 95%CI: 1.20-3.43; p=0.008) and extra-intestinal manifestations other than articular and primary sclerosing cholangitis (HR 4.37; 95%CI: 2.12-9.02; p<0.001) were associated with either CP or CDP (table 2). The LASSO sensitivity analysis identified these three prognostic factors but also found articular manifestations as a minor prognostic factor (LASSO-derived Multivariate Hazard Ratio: 1.05) (table 3). The event-free survival with these prognostic factors are shown in figure 2.

One hundred and eighteen (47.8%) patients had none, 96 patients (38.9%) had one and 33 (13.4%) had two or more of the four factors associated with either CP or CDP (IBDU, age of less than 35 years at surgery, articular manifestations and other extra-intestinal manifestations). In patients with none and two or more prognostic factors, the rate of CP or CDP, two years after surgery were 7.1% (95%CI: 1.4-12.4) and 35.2% (95%CI: 15.9-50.1) respectively. Five years after surgery, these rates were 18.6% (95%CI: 7.1-28.6) and 65.2% (95%CI: 41.8-79.2) respectively.

## Crohn disease of the pouch

After IPAA, 28 patients developed CDP with a median time of 1.9 (IQR: 1.0-3.0) years. The incidence was 7.9% (95%CI: 3.9-11.8) 2 years after surgery and 18.3% (95%CI: 11.0-25.0), five years after surgery (figure 1). On these 28 patients with CDP, two had an initial diagnosis of chronic pouchitis, but subsequently developed a small bowel disease.

In multivariable analysis, IBDU (HR 2.68; 95%CI: 1.18-6.09; p=0.02), articular manifestations (HR 3.00; 95%CI: 1.39-6.49; p=0.005), and other extra-intestinal manifestations (HR 3.48; 95%CI: 1.18-10.26; p=0.02) were associated with an increased risk

of CDP (table 2). The LASSO method identified the same factors and two additional factors: primary sclerosing cholangitis (LASSO-derived Multivariate Hazard Ratio: 0.66) and an age of less than 35 years (LASSO-derived Multivariate Hazard Ratio: 1.24) (supplementary figure 2). The other prognostic factors identified with the LASSO method had only a minimal effect on CDP incidence (LASSO-derived Multivariate Hazard Ratio <1.2) (Table 3).

## Chronic pouchitis

After IPAA, 34 patients developed CP with a median time of 2.4 (IQR: 0.9-4.3) years. Two and five years after surgery, 7.6% (95%CI: 3.8-11.3) and 19.5% (95%CI: 12.2-26.2) of patients had a CP, respectively (figure 1).

In multivariable analysis, IBDU (HR 2.74; 95%CI: 1.24-6.07; p=0.01), primary sclerosing cholangitis (HR 2.89; 95%CI: 1.30-6.41; p=0.009), other extra-intestinal manifestations (HR 3.44; 95%CI: 1.25-9.51; p=0.02) and an age of less than 35 years at surgery (HR 2.62; 95%CI: 1.28-5.35; p=0.008) were associated with CP (table 2). The LASSO method confirmed these results but found that IBDU, primary sclerosing cholangitis and other extra-intestinal manifestations had a predominant role, as shown in table 3 (supplementary figure 3).

## Acute pouchitis

After IPAA, 88 patients developed at least one episode of acute pouchitis with a median time of 1.0 (IQR: 0.5-2.3) years. The incidence was 30.4% (95%CI: 23.6-36.6), two years after surgery and 48.4% (95%CI: 39.2-56.1), five years after surgery (Figure 1). In multivariable analysis, articular manifestations (HR 1.80; 95%CI: 1.03-3.16; p=0.04), primary sclerosing cholangitis (HR 1.83; 95%CI: 1.05-3.18; p=0.03), pancolitis (HR 2.55; 95%CI: 1.21-5.35; p=0.01) and an age of less than 35 years (HR 1.67; 95%CI: 1.05-2.65; p=0.03) were

associated with an increased risk of acute pouchitis (Table 2). The same factors were found with the LASSO method. The LASSO-derived multivariate Hazard Ratios are shown in Table 3.

Among the 88 patients with acute pouchitis, 34 patients developed a CP (38.6%) with a median time of 6.9 (IQR: 3.2-20.4) months after the first episode of acute pouchitis. Patients who had an acute pouchitis in the first year following IPAA had a similar risk of CP as compared to those whose acute pouchitis appeared later in the course.

### Complications of surgery and pouch failure

Surgical complications occurred in 81 (32.8%) patients including 25 (10.1%) fistula, 16 (6.5%) abscess without fistula, 9 (3.6%) peritonitis, 16 (6.5%) symptomatic stenosis and 12 intestinal obstructions (4.9%) without stenosis (Supplementary table 3).

Seventeen patients (6.9%) had a pouch failure: five patients (2.0%) needed a permanent ileostomy and 12 patients (4.9%) required removal of the pouch with a new IPAA. The median time from IPAA to pouch failure was 2.6 (IQR: 1.2-3.8) years. Pouch failure was due to CP in three patients (17.6%), to CDP in 4 patients (23.5%) and to postoperative complications in 10 patients (58.8%) (Supplementary table 3).

## Discussion

In this study of 247 patients with UC or IBDU who underwent IPAA, we found that approximately one-third of the patients had either CDP or CP after 5 years. Predictive factors were IBDU, an age of less than 35 years at surgery, articular manifestations and other extra-intestinal manifestations. Approximately two-third of patients with at least two of these factors had CP or CDP, compared to 18.6% of those with none of them. The two statistical approaches, ie, multivariable analysis and LASSO gave similar results.

The observed rates of 18.3% of CDP and 19.5% of CP at 5 years, lie within the highest range of recently published studies (15,16). Several risk factors of CDP have been reported previously: current smoking (24), family history of Crohn's disease (25). We found that age, IBDU and extraintestinal manifestations (excluding primary sclerosing cholangitis) were positively associated with CDP while the reverse was true for primary sclerosing cholangitis. Numerous risk factors associated with CP such as primary sclerosing cholangitis (26,27) and extraintestinal manifestations (28,29) have already been reported. We reproduce these findings and found that young age and IBDU were additional factors of CP. Although already reported, a young age has not been found in all studies (30,31). In the study by Kayal et al. published in 2020 (15) the incidence of CP and CDP were 15.5% and 11.9% respectively; IBDU was the only risk factor for CP. In this study, endoscopic examinations of the pouch were performed systematically, even in asymptomatic patients. By contrast, in the present paper, pouch endoscopy was performed in patients with symptoms.

There is some consistency in the fact that risk factors of chronic inflammation of the pouch such as young age and extraintestinal manifestations are also prognostic factors of UC (32–34). This might suggest that the forces that drive UC activity persist after colectomy. Yet, and unexpectedly, patients who had received several lines of biologics were not at higher risk of chronic inflammation of the pouch.

Although most risk factors are shared by CDP and CP, there are slight differences between them. Articular manifestations and BMI are exclusively associated with CDP; primary sclerosing cholangitis is negatively associated with CDP(35) and positively associated with CP. Genetic and serological differences between CDP and CP have previously been reported (16,36). Taken together, these results suggest that CP and CDP are two entities among a continuum of chronic inflammation of the pouch.

We identified a subgroup of patients at high risk of chronic inflammation of the pouch. These patients had two or more prognostic factors among the following: IBDU, an age of less than 35 years at surgery, articular manifestations and other extra-intestinal manifestations. In these patients, the risk of chronic inflammation of the pouch reached 65.2% after 5 years of follow-up. In view of the high rates of chronic inflammation of the pouch, preventive strategies to limit pouch damage could be proposed. By analogy with prevention of postoperative recurrence of Crohn's disease after ileocaecal resection (37), serial, scheduled endoscopies of the pouch could be recommended to identify early inflammation of the pouch (38) and treat patient pre-emptively. High-risk patients might also benefit from postoperative medical therapy. Further prospective studies are needed to evaluate such strategies.

Our study has some limitations. First, it was a retrospective study. However, the rate of missing data was low, except for biological data; ASCA, pANCA and NOD2insC allele were missing in our study whereas they are known prognostic factors (16,36,39). Second, 41 patients with a follow-up of less than two months were excluded. Most of these patients were followed in a local hospital after they had been operated in one of the centers of this study. Third, CDP share similarities with CP (40). Some patients with recent CP might have been misdiagnosed despite our definitions and the extensive workup, including magnetic resonance imaging and capsule endoscopy, to evaluate small bowel and perianal disease.

Our study has also several strengths. First, this was a multicenter study including 247 consecutive patients with a median follow-up of 3.1 years. Second, we used a clear definition of CDP and CP in symptomatic patients where CP was identified with mPDAI, a validated score (19). Third, we performed a LASSO sensitivity to confirm the results of the multivariable model.

In conclusion, our study shows than CP and CDP are common complications after IPAA. The main prognostic factors are IBDU, an age of less than 35 years at surgery, articular manifestations and other extra-intestinal manifestations.

**Acknowledgments:** None

## References

1. Burisch J, Jess T, Martinato M, Lakatos PL. The burden of inflammatory bowel disease in Europe. Journal of Crohn's and Colitis. 2013 May;7(4):322–37.

2. Frolkis AD, Dykeman J, Negrón ME, Debruyn J, Jette N, Fiest KM, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. Gastroenterology. 2013 Nov;145(5):996–1006.

3. Fumery M, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. Clin Gastroenterol Hepatol. 2018;16(3):343-356.e3.

4. Hahnloser D, Pemberton JH, Wolff BG, Larson DR, Crownhart BS, Dozois RR. Results at up to 20 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. Br J Surg. 2007 Mar;94(3):333–40.

5. Turina M, Pennington CJ, Kimberling J, Stromberg AJ, Petras RE, Galandiuk S. Chronic pouchitis after ileal pouch-anal anastomosis for ulcerative colitis: effect on quality of life. J Gastrointest Surg. 2006 Apr;10(4):600–6.

6. Shen B, Fazio VW, Remzi FH, Delaney CP, Bennett AE, Achkar J-P, et al. Comprehensive evaluation of inflammatory and noninflammatory sequelae of ileal pouch-anal anastomoses. Am J Gastroenterol. 2005 Jan;100(1):93–101.

7. Ferrante M, D'Haens G, Dewit O, Baert F, Holvoet J, Geboes K, et al. Efficacy of infliximab in refractory pouchitis and Crohn's disease-related complications of the pouch: a Belgian case series. Inflamm Bowel Dis. 2010 Feb;16(2):243–9.

8. Colombel J-F, Ricart E, Loftus EV, Tremaine WJ, Young-Fadok T, Dozois EJ, et al. Management of Crohn's disease of the ileoanal pouch with infliximab. Am J Gastroenterol. 2003 Oct;98(10):2239–44.

9. Shen B, Yu C, Lian L, Remzi FH, Kiran RP, Fazio VW, et al. Prediction of late-onset pouch failure in patients with restorative proctocolectomy with a nomogram. J Crohns Colitis. 2012 Mar;6(2):198–206.

10. Shen B, Remzi FH, Brzezinski A, Lopez R, Bennett AE, Lavery IC, et al. Risk factors for pouch failure in patients with different phenotypes of Crohn's disease of the pouch. Inflamm Bowel Dis. 2008 Jul;14(7):942–8.

11. Lian L, Fazio VW, Lavery IC, Hammel J, Remzi FH, Shen B. Evaluation of association between precolectomy thrombocytosis and the occurrence of inflammatory pouch disorders. Dis Colon Rectum. 2009 Nov;52(11):1912–8.

12. Hashavia E, Dotan I, Rabau M, Klausner JM, Halpern Z, Tulchinsky H. Risk factors for chronic pouchitis after ileal pouch-anal anastomosis: a prospective cohort study. Colorectal Dis. 2012 Nov;14(11):1365–71.

13. Fazio VW, Kiran RP, Remzi FH, Coffey JC, Heneghan HM, Kirat HT, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. Ann Surg. 2013 Apr;257(4):679–85.

14. Barnes EL, Kochar B, Jessup HR, Herfarth HH. The Incidence and Definition of Crohn's Disease of the Pouch: A Systematic Review and Meta-analysis. Inflamm Bowel Dis. 2019 20;25(9):1474–80.

15. Kayal M, Plietz M, Rizvi A, Radcliffe M, Riggs A, Yzet C, et al. Inflammatory Pouch Conditions Are Common After Ileal Pouch Anal Anastomosis in Ulcerative Colitis Patients. Inflamm Bowel Dis. 2020 Jun 18;26(7):1079–86.

16. Tyler AD, Milgrom R, Stempak JM, Xu W, Brumell JH, Muise AM, et al. The NOD2insC polymorphism is associated with worse outcome following ileal pouch-anal anastomosis for ulcerative colitis. Gut. 2013 Oct;62(10):1433–9.

17. Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. Journal of Crohn's and Colitis. 2017 Jun 1;11(6):649–70.

18. Shen B, Achkar JP, Lashner BA, Ormsby AH, Remzi FH, Bevins CL, et al. Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. Gastroenterology. 2001 Aug;121(2):261–7.

19. Shen B, Achkar J-P, Connor JT, Ormsby AH, Remzi FH, Bevins CL, et al. Modified pouchitis disease activity index: a simplified approach to the diagnosis of pouchitis. Dis Colon Rectum. 2003 Jun;46(6):748–53.

20. Mark-Christensen A, Erichsen R, Brandsborg S, Pachler FR, Nørager CB, Johansen N, et al. Pouch failures following ileal pouch-anal anastomosis for ulcerative colitis. Colorectal Dis. 2018;20(1):44–52.

21. Tibshirani R. The lasso method for variable selection in the Cox model. Stat Med. 1997 Feb 28;16(4):385–95.

22. Tibshirani R. Regression shrinkage and selection via the lasso: a retrospective: Regression Shrinkage and Selection via the Lasso. Journal of the Royal Statistical Society: Series B (Statistical Methodology). 2011 Jun;73(3):273–82.

23. R Core Team. R: A Language and Environment for Statistical Computing. Vienna: R Foundation for Statistical Computing. 2016;https://www.R-project.org.

24. Shen B, Fazio VW, Remzi FH, Brzezinski A, Bennett AE, Lopez R, et al. Risk factors for diseases of ileal pouch-anal anastomosis after restorative proctocolectomy for ulcerative colitis. Clin Gastroenterol Hepatol. 2006 Jan;4(1):81–9; quiz 2–3.

25. Shen B, Remzi FH, Hammel JP, Lashner BA, Bevins CL, Lavery IC, et al. Family history of Crohn's disease is associated with an increased risk for Crohn's disease of the pouch. Inflamm Bowel Dis. 2009 Feb;15(2):163–70.

26. Abdelrazeq AS, Kandiyil N, Botterill ID, Lund JN, Reynolds JR, Holdsworth PJ, et al. Predictors for acute and chronic pouchitis following restorative proctocolectomy for ulcerative colitis. Colorectal Dis. 2008 Oct;10(8):805–13.

27. Wu X-R, Ashburn J, Remzi FH, Li Y, Fass H, Shen B. Male Gender Is Associated with a High Risk for Chronic Antibiotic-Refractory Pouchitis and Ileal Pouch Anastomotic Sinus. J Gastrointest Surg. 2016 Mar;20(3):631–9.

28. Achkar J-P, Al-Haddad M, Lashner B, Remzi FH, Brzezinski A, Shen B, et al. Differentiating risk factors for acute and chronic pouchitis. Clin Gastroenterol Hepatol. 2005 Jan;3(1):60–6.

29. Hata K, Ishii H, Anzai H, Ishihara S, Nozawa H, Kawai K, et al. Preoperative Extraintestinal Manifestations Associated with Chronic Pouchitis in Japanese Patients with Ulcerative Colitis After Ileal Pouch-anal Anastomosis: A Retrospective Study. Inflamm Bowel Dis. 2017;23(6):1019–24.

30. Ferrante M, Declerck S, Coopmans T, De Hertogh G, Van Assche G, Penninckx F, et al. Development of pouchitis following ileal pouch-anal anastomosis (IPAA) for ulcerative colitis: A role for serological markers and microbial pattern recognition receptor genes. J Crohns Colitis. 2008 Jun;2(2):142–51.

31. Weaver KN, Kochar B, Hansen JJ, Isaacs KL, Jain A, Sheikh SZ, et al. Chronic Antibiotic Dependent Pouchitis Is Associated With Older Age at the Time of Ileal Pouch Anal Anastomosis (J-pouch) Surgery. Crohns Colitis 360. 2019 Oct;1(3):otz029.

32. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, Tilloy E, Brazier F, Merle V, et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. Am J Gastroenterol. 2009 Aug;104(8):2080–8.

33. Solberg IC, Lygren I, Jahnsen J, Aadland E, Høie O, Cvancarova M, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scand J Gastroenterol. 2009;44(4):431–40.

34. Reinisch W, Reinink AR, Higgins PDR. Factors Associated With Poor Outcomes in Adults With Newly Diagnosed Ulcerative Colitis. Clinical Gastroenterology and Hepatology. 2015 Apr;13(4):635–42.

35. Wu X, Mukewar S, Kiran RP, Hammel JP, Remzi FH, Shen B. The presence of primary sclerosing cholangitis is protective for ileal pouch from Crohn's disease. Inflamm Bowel Dis. 2013 Jun;19(7):1483–9.

36. Tyler AD, Milgrom R, Xu W, Stempak JM, Steinhart AH, McLeod RS, et al. Antimicrobial antibodies are associated with a Crohn's disease-like phenotype after ileal pouch-anal anastomosis. Clin Gastroenterol Hepatol. 2012 May;10(5):507-512.e1.

37. Marteau P, Laharie D, Colombel J-F, Martin L, Coevoet H, Allez M, et al. Interobserver Variation Study of the Rutgeerts Score to Assess Endoscopic Recurrence after Surgery for Crohn's Disease. J Crohns Colitis. 2016 Sep;10(9):1001–5.

38. Kayal M, Plietz M, Radcliffe M, Rizvi A, Yzet C, Tixier E, et al. Endoscopic activity in asymptomatic patients with an ileal pouch is associated with an increased risk of pouchitis. Aliment Pharmacol Ther. 2019;50(11–12):1189–94.

39. Fleshner PR, Vasiliauskas EA, Kam LY, Fleshner NE, Gaiennie J, Abreu-Martin MT, et al. High level perinuclear antineutrophil cytoplasmic antibody (pANCA) in ulcerative colitis patients before colectomy predicts the development of chronic pouchitis after ileal pouch-anal anastomosis. Gut. 2001 Nov;49(5):671–7.

40. Ståhlberg D, Gullberg K, Liljeqvist L, Hellers G, Löfberg R. Pouchitis following pelvic pouch operation for ulcerative colitis. Incidence, cumulative risk, and risk factors. Dis Colon Rectum. 1996 Sep;39(9):1012–8.

**Figure 1: Event-free survival**

**Figure 2: Crohn's disease of the pouch and chronic pouchitis free survival by risk factors**

**Figure 1: Event-free survival**

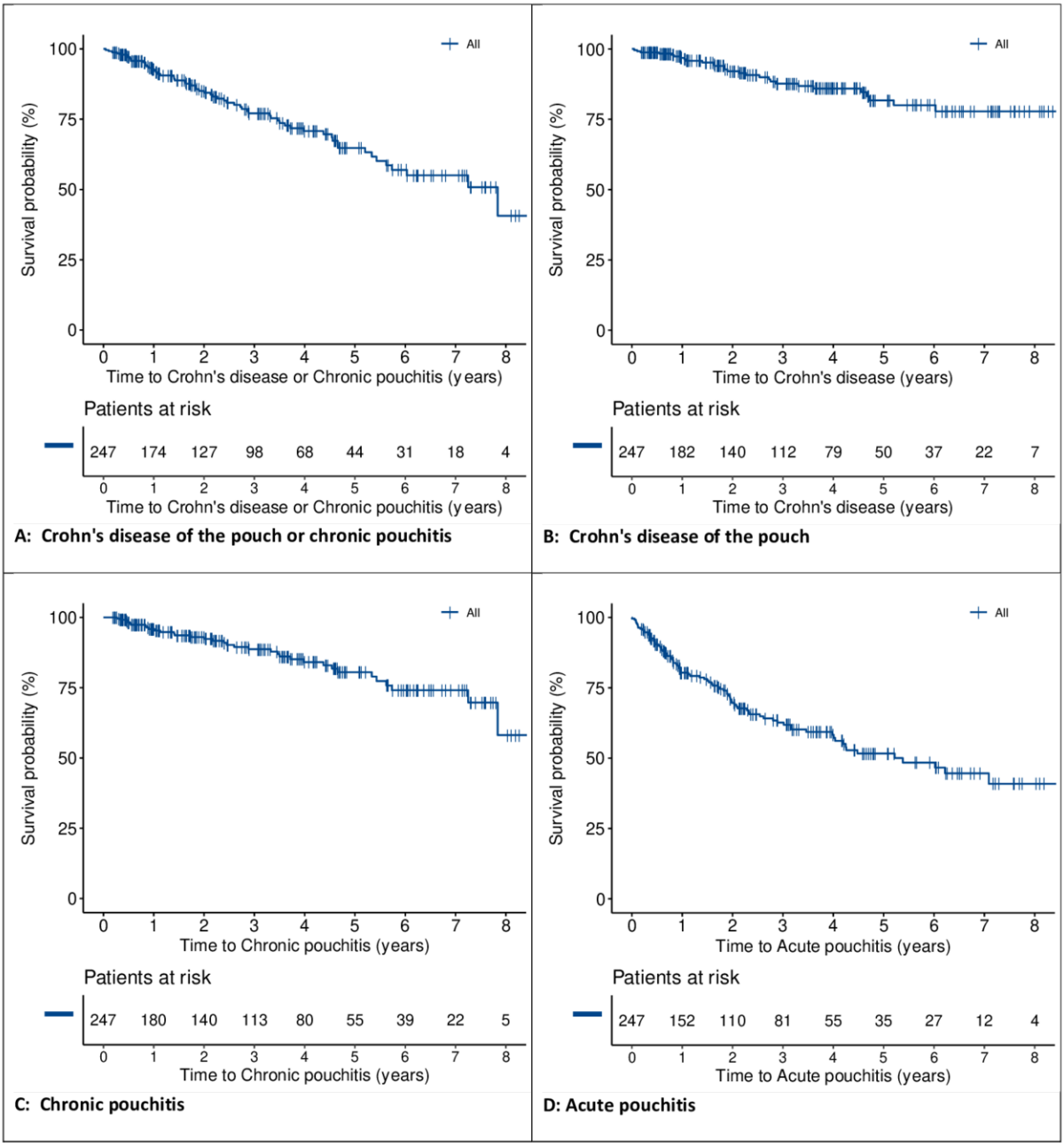
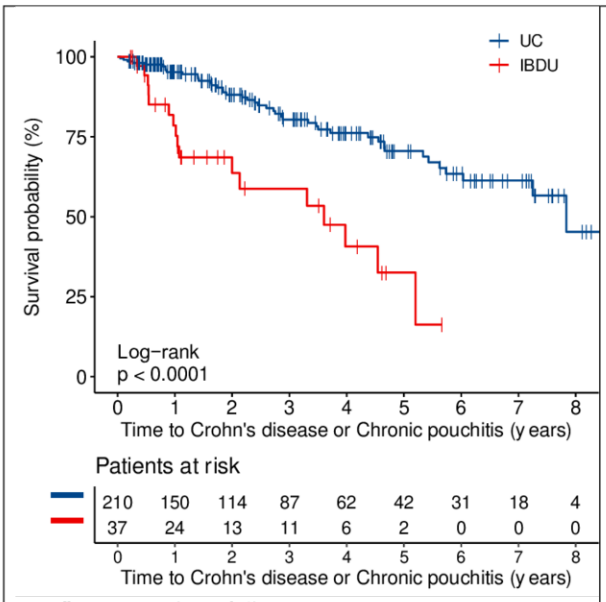
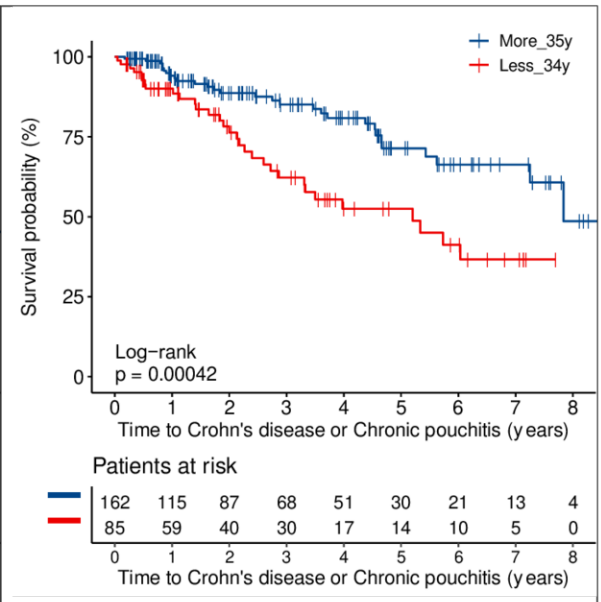


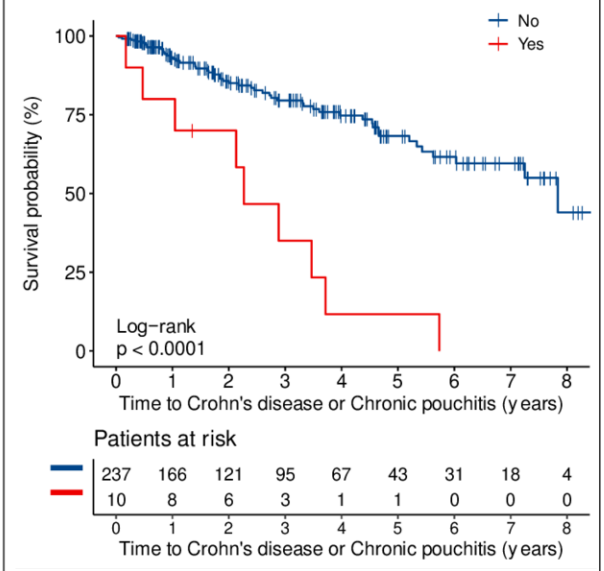
**Figure 2: Crohn's disease of the pouch and chronic pouchitis free survival by risk factors**



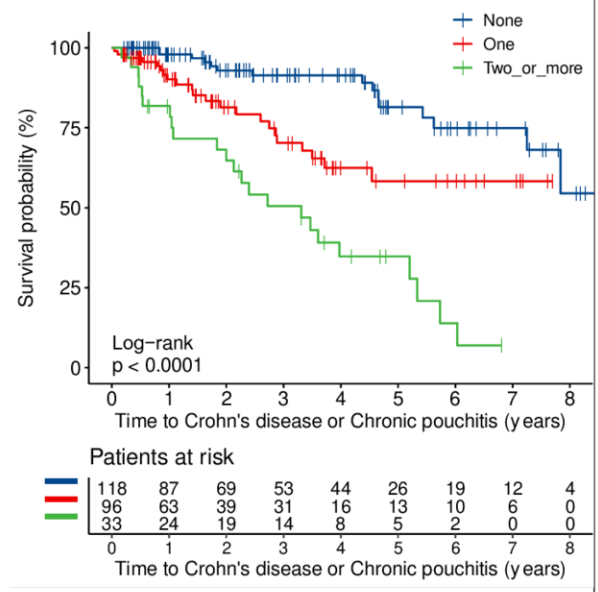

**A: Inflammatory bowel disease type**




**B: Age**




**C: Other extra-intestinal manifestations**




**D: 1 point for each prognostic factor: IBDU, age at surgery <35years, articular manifestations and other extra-intestinal manifestations**

**Table 1. Demographic and baseline patient characteristics**

| | Total | Missing (%) |
|---|---|---|
| **N** | 247 | |
| **Female gender, N (%)** | 107 (43.3) | 0.0 |
| **Age (years)†** | 42.4 [30.8 - 56.3] | 0.0 |
| **Body mass index†** | 22.0 [20.0 - 25.0] | 8.1 |
| **Appendectomy, N (%)** | 19 (7.7) | 0.0 |
| **Smoking, N (%)** | | 0.0 |
| Never smoker | 193 (78.1) | |
| Former smoker | 42 (17.0) | |
| Active smoker | 12 (4.9) | |
| **Inflammatory bowel disease, N (%)** | | 0.0 |
| Unclassified | 37 (15.0) | |
| Ulcerative colitis | 210 (85.0) | |
| **Cause of surgery, N (%)** | | 0.0 |
| Dysplasia or cancer | 79 (32.0) | |
| Fulminant colitis | 73 (29.6) | |
| Active refractory disease | 95 (38.5) | |
| **Time from UC diagnosis to ileal pouch-anal anastomosis (years)†** | 8.0 [3.3 - 14.6] | 0.4 |
| **Time from ileal pouch-anal anastomosis to restoration of intestinal continuity (days)†** | 62.0 [46.0 - 78.0] | 0.0 |
| **Mechanical anastomosis, N (%)** | 169 (69.3) | 1.2 |
| **Stages of proctocolectomy** | | 0.0 |
| 1 | 19 (7.7) | |
| 2 | 123 (49.8) | |
| 3 | 105 (42.5) | |
| **Family History of Crohn's Disease, N (%)** | 12 (4.9) | 0.0 |
| **Extra-intestinal manifestations, N (%)** | 67 (27.1) | 0.0 |
| Articular manifestations | 35 (14.2) | |
| Primary sclerosing cholangitis | 34 (13.8) | |
| Other extra-intestinal manifestations‡ | 10 (4.0) | |
| **Autoimmune disease, N (%) §** | 19 (7.7) | 0.0 |
| **UC extent, N (%)** | | 2.4 |
| E1 | 3 (1.2) | |
| E2 | 48 (19.9) | |
| E3 | 190 (78.8) | |
| **Corticosteroids 3 months before surgery, N (%)** | 61 (25.5) | 3.2 |
| **History of immunosuppressant use, N (%)** | 176 (74.6) | 4.5 |
| **History of biologics use, N (%)** | | 0.0 |
| 0 | 77 (31.2) | |
| 1 | 73 (29.6) | |
| 2 | 69 (27.9) | |
| 3 or more | 28 (11.3) | |
| **Corticosteroids at surgery, N (%)** | 90 (37.7) | 3.2 |
| **Immunosuppressant at surgery, N (%)** | 94 (39.3) | 3.2 |
| **Biologics at surgery, N (%)** | 131 (54.8) | 3.2 |
| **C-reactive protein (mg/L)†** | 16.0 [5.0 - 60.0] | 34.0 |
| **Platelets (G/L)†** | 343.0 [257.0 - 439.0] | 23.5 |
| **Hemoglobin (g/dL)†** | 11.9 [10.3 - 13.7] | 21.5 |
| **Endoscopic Mayo score†** | 2.0 [2.0 - 3.0] | 14.2 |
| **Ulceration at endoscopy, N (%)** | 141 (65.6) | 13.0 |
| **Deep ulceration at endoscopy, N (%)** | 36 (16.7) | 13.0 |
| **Reflux ileitis, N (%)** | 10 (4.7) | 13.8 |
| **Year of inclusion, N (%)** | | 0.0 |
| 2011 – 2013 | 91 (36.8) | |
| 2014 – 2016 | 77 (31.2) | |
| 2017 – 2019 | 79 (32.0) | |

*† Quantitative variable. Median [interquartile range]. ‡ Include inflammatory aphthosis, cutaneous, bronchial, ophthalmologic, pyoderma gangrenosum. § Include autoimmune thyroiditis, thrombocytopenia, hepatitis, pancreatitis, celiac disease, lupus, vasculitis. UC: Ulcerative colitis.*

**Table 2. Prognostic factors with multivariable Cox model**

| | **Crohn's disease or chronic pouchitis** | **Crohn's disease** | **Chronic pouchitis** | **Acute pouchitis** |
|---|---|---|---|---|
| | aHR (95%CI) | aHR (95%CI) | aHR (95%CI) | aHR (95%CI) |
| **Age < 35 years** | **2.03 [1.20 - 3.43]** | 1.72 [0.80 - 3.69] | **2.62 [1.28 - 5.35]** | **1.67 [1.05 - 2.65]** |
| **Inflammatory bowel disease: unclassified** | **3.18 [1.77 - 5.70]** | **2.68 [1.18 - 6.09]** | **2.74 [1.24 - 6.07]** | |
| **Family History of Crohn's Disease** | | | 2.88 [0.82 - 10.17] | |
| **Articular manifestations** | | **3.00 [1.39 - 6.49]** | | **1.80 [1.03 - 3.16]** |
| **Primary sclerosing cholangitis** | | 0.19 [0.03 - 1.41] | **2.89 [1.30 - 6.41]** | **1.83 [1.05 - 3.18]** |
| **Other extra-intestinal manifestations** | **4.37 [2.12 - 9.02]** | **3.48 [1.18 - 10.26]** | **3.44 [1.25 - 9.51]** | |
| **UC extent: E3** | | | | **2.55 [1.21 - 5.35]** |
| **History of immunosuppressant use** | | | 0.47 [0.21 - 1.04] | |
| **Reflux ileitis** | | | | 2.17 [0.92 - 5.11] |

*aHR: adjusted hazard ratio; CI: confidence interval; UC: ulcerative colitis*

**Table 3. LASSO-derived multivariate models of prognostic factors**

| | **Crohn's disease or chronic pouchitis** LASSO-derived Multivariate HR | **Crohn's disease** LASSO-derived Multivariate HR | **Chronic pouchitis** LASSO-derived Multivariate HR | **Acute pouchitis** LASSO-derived Multivariate HR |
|---|---|---|---|---|
| **Age < 35 years** | **1.48** | **1.24** | **1.43** | **1.21** |
| **Body mass index > median** | | **1.07** | | |
| **Inflammatory bowel disease: unclassified** | **2.27** | **1.91** | **1.58** | |
| **Time from UC diagnosis to ileal pouch-anal anastomosis > median** | | **1.10** | | |
| **Articular manifestations** | **1.05** | **2.23** | **0.97** | |
| **Primary sclerosing cholangitis** | | **0.66** | **1.50** | **1.25** |
| **Other extra-intestinal manifestations** | **3.31** | **2.58** | **2.25** | |
| **Autoimmune disease** | | | **1.07** | |
| **UC extent: E3** | | | | **1.22** |
| **Immunosuppressant at surgery** | | **1.15** | **0.88** | |

*LASSO: Least absolute shrinkage and selection operator; UC: ulcerative colitis; HR: Hazard Ratio*