



HAL
open science

A Scoring System to Determine Patients' Risk of Colectomy Within 1 Year After Hospital Admission for Acute Severe Ulcerative Colitis Short title: Predictors of colectomy in patients with ASUC

Guillaume Le Baut, Julien Kirchgesner, Aurélien Amiot, Jérémie H Lefevre, Najim Chafai, Cécilia Landman, Isabelle Nion, Anne Bourrier, Charlotte Delattre, Chloé Martineau, et al.

► To cite this version:

Guillaume Le Baut, Julien Kirchgesner, Aurélien Amiot, Jérémie H Lefevre, Najim Chafai, et al.. A Scoring System to Determine Patients' Risk of Colectomy Within 1 Year After Hospital Admission for Acute Severe Ulcerative Colitis Short title: Predictors of colectomy in patients with ASUC. *Clinical Gastroenterology and Hepatology*, 2021, 19 (8), pp.1602-1610.e1. 10.1016/j.cgh.2019.12.036 . hal-03390913

HAL Id: hal-03390913

<https://hal.sorbonne-universite.fr/hal-03390913v1>

Submitted on 21 Oct 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

A Scoring System to Determine Patients' Risk of Colectomy Within 1 Year After Hospital Admission for Acute Severe Ulcerative Colitis

Short title: Predictors of colectomy in patients with ASUC

G Le Baut¹, J Kirchgesner^{2,3}, A Amiot^{4,5}, JH Lefevre⁶, N Chafai⁶, C Landman², I Nion², A Bourrier², C Delattre², C Martineau², H Sokol^{2,7}, P Seksik^{2,7}, Y Nguyen^{8,9}, Y Marion¹⁰, G Lebreton¹⁰, F Carbonnel¹¹, S Viennot¹, L Beaugerie^{2,3}, for the Saint Antoine IBD network

(1) University Hospital of Caen, Department of gastroenterology, F-14000, Caen, France

(2) Sorbonne Université, Department of gastroenterology, AP-HP, Hôpital Saint Antoine, F-75012, Paris, France

(3) Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, Paris, France

(4) Department of Gastroenterology, Henri Mondor Hospital, APHP, Paris Est-Créteil (UPEC) Val de Marne University, Creteil, France

(5) EA 7375 (EC2M3 research team), Paris Est-Créteil (UPEC) Val de Marne University, Creteil, France

(6) Sorbonne Université, Department of Digestive Surgery, AP-HP, Hôpital Saint Antoine, F-75012, Paris, France

(7) Sorbonne Universités, École Normale Supérieure, CNRS, INSERM, APHP Laboratoire des Biomolécules (LBM), Paris, France.

(8) Beaujon Hospital, Department of internal medicine, F-92110, Clichy, France

(9) Paris-Sud Université, INSERM U1018, Centre de Recherche en épidémiologie et santé des populations (CESP), F-94800, Villejuif, France

(10) University Hospital of Caen, Department of surgery, F-14000, Caen, France

(11) Department of Gastroenterology, Bicetre University Hospital, APHP, Université Paris Sud, le Kremlin Bicêtre, Paris, France

Financial support: None.

Abbreviations used in this paper: ulcerative colitis: UC; ASUC: Acute severe ulcerative colitis; tumor necrosis factor blockers: anti-TNFs; Inflammatory bowel disease: IBD; C-reactive protein: CRP; Clostridioides difficile infection: CDI; inflammatory bowel disease unclassified: IBDU; Cytomegalovirus: CMV; interquartile ranges: IQR; 95% confident interval: 95%CI; WCC: white cell count

Corresponding authors:

Guillaume Le baut, University Hospital of Caen, Department of gastroenterology, F-14000, Caen; 02 31 06 45 43; 06 27 87 15 99; email: lebaut.guillaume@gmail.com

Julien Kirchgesner, Sorbonne Université, Department of gastroenterology, AP-HP, Hôpital Saint Antoine, F-75012, Paris; +33 (0)1 49 28 31 72 - Fax: +33 (0)1 49 28 31 88; e-mail: julien.kirchgesner@gmx.com

Conflicts of interest: The authors disclose the following:

G. Le Baut, J Kirchgesner, N Chafai, I Nion, A Bourrier, C Delattre, C Martineau, Y Nguyen, Y Marion, G Lebreton: none

A Amiot: from Abbvie, Hospira, Takeda, Gilead, Tillotts, Janssen and Biocodex as well as lecture fees and travel accommodations from Abbvie, Janssen, Biocodex, Hospira, Tillotts, Ferring, Takeda and MSD. This author has also received advisory board fees from Gilead, Takeda and Abbvie. These COI are not related with the present work.

J H. Lefevre: fees from Takeda (2018); SafeHeal (2018-2019) and Consultant; Biomup (2018) travel; Ethicon (2018). These COI are not related with the present work.

C Landman: fees from Abbvie, Hospira-Pfizer, Janssen-Cilag and Ferring, travel support from Abbvie, Hospira-Pfizer, Takeda, Janssen-Cilag and Mayoly Spindler and research support from Biocodex. These COI are not related with the present work.

H Sokol: Fees from Enterom, Astellas, Roche, Merck, Maat et Danone. These COI are not related with the present work.

P Seksik: Fees from Takeda, Abbvie, Merck-MSD, Astellas, Janssen, Biocodex, and grants from Biocodex. These COI are not related with the present work.

F Carbonnel: Fees from Abbvie, Amgen, Astra, BMS, Enterome, Ferring, Janssen, Medtronic, Merck, MSD, Pfizer, Pharmacosmos, Pileje, Roche and Takeda. These COI are not related with the present work.

S Viennot: Fees from Abbvie, Takeda, MSD, Janssen, Astrella, Ferring. These COI are not related with the present work.

L Beaugerie: Fees from Abbott, Abbvie, MSD, Ferring Pharmaceuticals. These COI are not related with the present work.

Word count: 3030

Guarantor of the article: G Le Baut

Author contributions: G.LB: study concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript and statistical analysis. J.K: study concept and design, analysis and interpretation of data, drafting of manuscript and statistical analysis. A.A: acquisition of data and critical revision of manuscript for important intellectual content. JH.L, N.C, C.L, I.N, A.B, C.D, C.M, P.M, H.S, P.S, Y.M, G.L, S.V, F.C: critical revision of manuscript for important intellectual content. Y.N: critical revision of manuscript for important intellectual content and statistical analysis. L.B.: study concept and design, analysis and interpretation of data, critical revision of manuscript for important intellectual content, and study supervision. All authors have approved the final draft submitted.

Members of the Saint Antoine IBD Network: ARRIVE Lionel, BEAUGERIE Laurent, BOURRIER Anne, CAMUS Marine, CHAFAI Najim, CHAPUT Ulriikka, MARTINEAU Chloé, CHOLLEY MONNIER Laurence, DEBOVE Clotilde, DRAY Xavier, Fléjou Jean-François, LE GALL Guillaume, HOYEAU Nadia, KIRCHGESNER Julien, LANDMAN Cecilia, LEFEVRE Jérémie H., MARTEAU Philippe, NION-LARMURIER Isabelle, OZENNE Violaine, PARC Yann, SEKSIK Philippe, SOKOL Harry, SVRCEK Magali, TIRET Emmanuel.

Abstract

Background & Aims: There is consensus on the criteria used to define acute severe ulcerative colitis (ASUC) and on patient management, but it has been a challenge to identify patients at risk for colectomy based on data collected at hospital admission. We aimed to develop a system to determine patients' risk of colectomy within 1 y of hospital admission for ASUC based on clinical, biomarker, and endoscopy data.

Methods: We performed a retrospective analysis of consecutive patients with ASUC treated with corticosteroids, ciclosporin, or tumor necrosis factor (TNF) antagonists and admitted to 2 hospitals in France from 2002 through 2017. Patients were followed until colectomy or loss of follow up. A total of 270 patients with ASUC were included in the final analysis, with a median follow-up time of 30 months (derivation cohort). Independent risk factors identified by Cox multivariate analysis were used to develop a system to identify patients at risk for colectomy 1 y after ASUC. We developed a scoring system based on these 4 factors (1 point for each item) identify high-risk (score 3 or 4) vs low-risk (score 0) patients. We validated this system using data from an independent cohort of 185 patients with ASUC treated from 2006 through 2017 at 2 centers in France.

Results: In the derivation cohort, the cumulative risk of colectomy was 12.3% (95% CI, 8.6–16.8). Based on multivariate analysis, previous treatment with TNF antagonists or thiopurines (hazard ratio [HR], 3.86; 95% CI, 1.82–8.18), Clostridioides difficile infection (HR, 3.73; 95% CI, 1.11–12.55), serum level of C-reactive protein above 30 mg/L (HR, 3.06; 95% CI, 1.11–8.43), and serum level of albumin below 30 g/L (HR, 2.67; 95% CI, 1.20–5.92) were associated with increased risk of colectomy. In the derivation cohort, the cumulative risks of colectomy within 1 y in patients with scores of 0, 1, 2, 3, or 4 were 0.0%, 9.4% (95% CI, 4.3%–16.7%), 10.6% (95% CI, 5.6%–17.4%), 51.2% (95% CI, 26.6%–71.3%), and 100%. Negative predictive values ranged from 87% (95% CI, 82%–91%) to 92% (95% CI, 88%–95.0%). Findings from the validation cohort were consistent with findings from the derivation cohort.

Conclusion: We developed a scoring system to identify patients at low-risk vs high-risk for colectomy within 1 y of hospitalization for ASUC, based on previous treatment with TNF antagonists or thiopurines, C difficile infection, and serum levels of CRP and albumin. The system was validated in an external cohort.

Key words: Ulcerative colitis, acute severe colitis, colectomy, predictors

WHAT YOU NEED TO KNOW

Background: It has been a challenge to identify patients with acute severe ulcerative colitis (ASUC) at risk for colectomy within the next year based on data collected at hospital admission.

Findings: We identified 4 factors associated with increased risk of colectomy within 1 y after hospital admission (previous treatment with tumor necrosis factor antagonists or thiopurines, Clostridioides difficile infection, increased serum level of C-reactive protein, decreased serum level of albumin). We used this information to develop a scoring system that identified patients at high-risk vs low-risk for colectomy, and validated it in an external cohort.

Implications for patient care: This scoring system can be used to identify patients at low risk of colectomy at 1 year (score 0) who can make an early transition to oral therapy and be discharged from the hospital, and patients at high-risk (scores of 3 or 4) who should be carefully monitored.

Introduction

Acute severe ulcerative colitis (ASUC) affects approximately 25% of patients with ulcerative colitis (UC) ¹. This complication is well defined by Truelove and Witts criteria as well as the therapeutic management after hospital admission ². Medical treatment notably intravenous corticosteroids, ciclosporin, and tumor necrosis factor blockers (anti-TNFs) have changed the prognosis of ASUC. However, colectomy is still required in a substantial subgroup of patients. Predictors of colectomy are needed in clinical practice, since morbidity, mortality and costs increase with the duration of hospitalization before colectomy ³⁻⁵. Several predictive scores of colectomy in patients with ASUC have been already described ⁶, and include clinical and/or biological parameters, notably albumin or C-reactive protein (CRP) level. Although they are strongly associated with the response to corticosteroids ⁷, several points limit their use in clinical practice. They were established before the era of biologics and are generally calculated on day 3 after admission. Moreover, some critical items, such as the presence of *Clostridioides difficile* infection (CDI) are not included ^{8,9}. Nevertheless, none was created to foresee patients with a low risk of colectomy to allow decreased monitoring. Two recent studies have identified CRP / albumin ratio as a good predictor of colectomy over the medium to long term ^{10,11}. One recent review concludes that new scoring systems are required to predict response to treatment and colectomy ⁶. The aims of our study were to identify predictive factors, among clinical, biological, endoscopic, and radiological criteria and to perform a new score assessing the probability of colectomy during the first year after ASUC.

Methods

Patients

A derivation cohort was created by reviewing medical files of consecutive patients with UC, defined by European consensus criteria ², or inflammatory bowel disease unclassified (IBDU) (whose diagnosis remained unclassified at the end of follow-up), hospitalized in emergency for IBD flare between 2002 and 2017 at Saint–Antoine Hospital, Paris and between 2008 and 2017 at Caen University hospital, and treated with intravenous corticosteroids, ciclosporin, or anti-TNFs. In case of

recurrence of ASUC during follow-up, only the first episode was considered. Patients with Crohn's disease at the time of hospital admission or during follow-up, and patients without information on albumin and CRP levels at admission were excluded. Date of cohort entry was the date of hospital admission for ASUC. Patients were followed until April 31th, 2018, or at last news including loss to follow-up, colectomy or death, whichever occurred first. Secondly, an independent cohort including all consecutive patients with an ASUC treated between 2006 and 2017 from two French centers, Kremlin Bicetre hospital and Henri Mondor hospital, was built for external validation. Inclusion criteria were similar between the two cohorts and data were independently collected in each cohort.

Therapeutic management

Patient hospitalized for ASUC were treated according to standard guidelines¹². In case of absence of response after 3 to 5 days of corticosteroids, options for colectomy, ciclosporin or anti-TNFs as a salvage medical therapy were considered. *Cytomegalovirus* (CMV) infection was confirmed by presence of inclusion body in histopathological examination and testing for CDI was systematic at admission in our centers.

Data collection

Variables were collected at Saint Antoine hospital from the SUVIMIC registry (a prospective clinical database of all patients with IBD evaluated by Saint-Antoine Hospital digestive disease medical staff), endoscopic and medical records, and collected at Caen University hospital from medical records.

The following variables were collected at cohort entry: age, gender, IBD type (UC or IBDU), comorbidities according to the Charlson's index¹³, previous appendectomy, date of IBD diagnosis, disease extent defined by Montreal classification², and previous treatment exposure, including thiopurines and anti-TNFs. Clinical variables, such as Truelove and Witts criteria¹⁴ or Clinical activity index¹⁵, the number of stools, extra-intestinal manifestations, date of the onset of symptoms and the used of oral corticosteroids before admission were analyzed. We recorded biological data (hemoglobin, albumin, C-reactive protein, white cells count, and platelet count) and microbiological data (CDI and histological signs of CMV

infection), that were obtained during the first full day following admission. Radiological (disease extent) and endoscopic (Mayo endoscopic score, mucosal damage) variables were collected from original reports at the start of hospitalization. Then, treatment exposures during hospitalization were assessed: drug classes (aminosalicylates, corticosteroids, thiopurines, ciclosporin and anti-TNFs), date of introduction and withdrawal, and therapy at hospital discharge, including colectomy. During follow-up, occurrences of treatment modifications for IBD, hospitalizations, and colectomy were assessed. In the validation cohort, collected data were: age, previous treatment exposure, including thiopurines and anti-TNFs, albumin and C-reactive protein levels, CDI, occurrence of colectomy, and date of last visit.

Outcomes

The primary outcome was the occurrence of colectomy within one year after hospital admission. The secondary outcomes included response to corticosteroids, need for rescue therapy and occurrence of colectomy, and were assessed at hospital discharge and end of follow-up.

Statistical analyses

Continuous data are presented as medians and interquartile ranges (IQR) and were compared with a Wilcoxon–Mann–Whitney test. Categorical variables were summarized as frequencies with percentages and compared with a Chi-square or Fisher’s test. Cumulative risk of colectomy was assessed in the whole cohort. Cox regression was used to assess the relationship between clinical, biological and endoscopic variables with the risk of colectomy within one year. Variables with a P values below than 0.10 at univariate analysis were included in multivariate analysis. Sensitivity analysis was performed by excluding patients with IBDU.

According to the coefficient estimates in the multivariate Cox regression analysis, we built a prognostic score. To assess the quality of the prognostic score, patients were classified as having a low, intermediate or high probability of colectomy. Percentages (95% confident interval [95%CI]) of colectomy depending on the calculated score were estimated from 1000 bootstrapped samples of 270 patients (uniform selection with replacement) ¹⁶. In the validation cohort, cumulative risk of colectomy at one year was assessed according to the developed score. P values <0.05 were

considered statistically significant. The study was approved by the Saint-Antoine Hospital ethics committee for the both centers (N°2014-A01788-39). Statistical analyses were performed using SAS (version 9.4, Inc, Cary, NC, USA) and R (version 3.4.2, R Foundation for Statistical Computing, Vienna, Austria).

Results

Derivation cohort

Baseline characteristics

In the derivation cohort, 421 patients with UC or IBDU were hospitalized and screened. Of these, 270 patients were included in the analysis (Figure 1). Baseline characteristics are presented in Table 1. Thirty percent (81/270) of the patients were previously exposed to thiopurines. Among the 34 patients exposed to anti-TNFs before cohort entry, 7 had discontinued anti-TNFs before admission index, due to severe skin side effects (1), allergic reactions (2), serious infections (1), primary failure (1), remission (1), and nonadherence (1). Among patients with no missing data to assess the clinical activity index (Lichtiger index) and Truelove and Witts criteria (n=215, 80% of the total cohort), 83.2% had a clinical activity index above 10 and 75.2% had an ASUC defined by Truelove and Witts criteria. CRP level above 30mg/L, and albumin level below 30g/L were observed in 64.8% (175/270) and 44.4% (120/270) of patients, respectively. Endoscopy was performed in 241 patients (89.2%) and an abdominal CT scan in 70 patients (25.9%) (Supplementary table 1).

Therapeutic Management

Before admission index, 121 patients (45%) were treated with oral corticosteroids. Among them, 71 had no response to corticosteroids and 40 had a recurrence of symptoms during the decrease of corticosteroids. The first line treatment after hospital admission was intravenous corticosteroids in 94.1% (n=254) of patients, infliximab in 3.7% (n=10), ciclosporin in 1.5% (n=4), and adalimumab in 0.7% (2 patients, who failed to response to oral corticosteroids and infliximab during the last year prior to admission). Thirty-nine percent of patient treated with corticosteroids (n=98) needed a 2nd line therapy. Among non-responders to the first line (38%, 102 patients, in any treatment group), 7%, 65%, 25%, and 3% were treated with colectomy, infliximab, ciclosporin, or other treatments (adalimumab or

golimumab), respectively. The rate of response to infliximab and ciclosporin was 91% and 85%, respectively. Only 4 patients had a third medical line of treatment. Colectomy was performed in 4.8% (n=13) of patients during the hospitalization after a median duration of 15 days (IQR: 8–19). No patients died during hospitalization.

Long term follow-up

Median time of follow-up was 30 months (IQR: 7–66). One patient died during the follow-up related to a cholangiocarcinoma. Forty-three percent of patients (n=83) were hospitalized for flare during the first year following ASUC. The cumulative risk of colectomy according to the time since the index hospitalization is shown in the figure 2. Colectomy was performed in 30 (12.3%), 43 (20.1%) and 47 (33.3%) at 1, 5, and 10 years after the index hospitalization, respectively. Among patients with missing data at admission about Lichtiger Index and Truelove and Witts criteria, no difference was observed on the rate of colectomy at one year (9% versus 11,6% in patients with available data, $p=0.77$).

Predictors of colectomy at one year

By univariate analysis, patients with colectomy at one year were significantly older at diagnosis of IBD (Table 2). Previous treatment with thiopurines or anti-TNFs were associated with an increased risk of colectomy (Table 2). Considering previous treatment with thiopurines or anti-TNFs, hazard ratio was 2.4 (95%CI 1.19–5.00, $p=0.01$). Among patients with no missing data, clinical activity index was not associated with an increased risk of colectomy (HR: 1.07, 95%CI 0.93–1.22, $p=0.36$). Regarding biological parameters, presence of *CDI*, CRP level above 30 mg/L and serum albumin level below 30 g/L measured during the first day following admission were predictors (Table 2). By multivariate analysis, four criteria were significantly associated with an increased risk of colectomy within one year after admission: previous treatment with anti-TNFs or thiopurines (HR: 3.86; 95%CI, 1.82–8.18), presence of *CDI* (HR: 3.73; 95%CI, 1.11–12.55), CRP level above 30 mg/L (HR: 3.06; 95%CI, 1.11–8.43), and albumin level below 30 g/L (HR: 2.67; 95%CI, 1.20–5.92). Results were consistent after exclusion of patients with IBDU. Results were consistent across centers.

We developed a prognostic score based on these four predictors. Since the β -coefficients of the Cox multivariate regression analysis varied around 1.19 between 0.98 and 1.35, the same weight for all variables was chosen to simplify: 1 point for each item, from 0 to 4. Forty-one patients (15.2%) had no criteria, 91 patients (33.7%) had one criteria, 113 (41.8%) patients had 2 criteria, 24 patients (8.9%) had 3 criteria and one patient (0.4%) had 4 criteria. The cumulative risk of colectomy within one year in patients with a score of 0, 1, 2, 3 and 4 items at admission was respectively 0.0%, 9.4% (95%CI 4.3–16.7), 10.6% (95%CI 5.6–17.4), 51.2% (95%CI 26.6–71.3), and 100% (Figure 3 and 4). Colectomy was performed during hospitalization in the patient with 4 criteria. Characteristics of the score are presented in table 3. The negative predictive value varied between 87% (95%CI 82–91) and 92% (95%CI 88–95). The positive predictive value (PPV) increased gradually according to the score 1, 2, 3, 4 (respectively 9%, 10%, 42% and 100%). As estimated with the 95%CI from the bootstrap method, the percentage of patient with a low (score=0; n=41 (IQR: 30–53)), intermediate (score=1 or 2; n=204 (IQR: 192–217)) and high score (score=3 or 4; n=25 (IQR: 16–34)) was respectively 0.0 (0.0–0.0), 9.9 (5.7–14.2) and 53.3 (30.7–74.9).

Validation cohort

In the validation cohort, 185 patients were included (100 and 85 from Kremlin Bicetre hospital and Henri Mondor hospital, respectively), with a median age at admission of 38.0 (IQR: 25-51) and 35.6% (66/185) were previously exposed to anti-TNFs or thiopurines. Median CRP and albumin levels were respectively 48.5mg/L (IQR: 20.2-117.0) and 29.9g/L (IQR: 25.0-35.0). CRP above 30mg/L, albumin below 30g/L and CDI were observed in 65.9% (122/185), 49.7% (92/185) and 5.4% (10/185) of patients, respectively. Seven patients were lost to follow-up before one year. The cumulative risk of colectomy within one year was 21.6% (95%CI:15.9-27.9). In this cohort, cumulative probability of colectomy according to the score 0, 1, 2, 3, 4 at admission were respectively 6.2% (95%CI:0.4-25.5) (1/17), 8.4% (95%CI:3.4-16.4) (6/71), 29.4% (95%CI:19.3-40.3) (21/74), 50% (95%CI:26.3-69.8) (10/21), and 50% (95%CI:0.0-96.0) (1/2) (Figure 4 and Supplementary data 2), which is consistent with findings from the derivation cohort among patients with a score of 0 (low-risk profile) and score 3-4 (high-risk profile). The patient with a score of 0 and who underwent colectomy during hospitalization was 68 years old and had, besides

no response to intravenous CS, a known low grade colonic dysplasia and a latent *Mycobacterium tuberculosis* infection.

Discussion

Among data on hospital admission of 270 unselected patients with ASUC, 4 predictors of colectomy within one year have been identified: previous treatment with anti-TNFs or thiopurines, presence of *CDI*, CRP level above 30 mg/L and albumin level below 30 g/L. We combined the variables into a score, which is highly predictive of having a colectomy or not within one year after admission. Results were consistent in the validation cohort for low- and high-risk profile patients.

Our population is similar to others studies, notably regarding clinical and biological characteristics ¹⁷⁻¹⁹. The rate of *CDI* (4.3%) is homogenous with recent studies ²⁰. Corticosteroid therapy for ASUC was the cornerstone of first-line treatment in our study (94.0%) as previous studies ²¹, and the overall response rate to corticosteroids in our cohort (61%) was similar with the literature ²². Despite no difference was reported regarding efficacy and short-term safety between infliximab and ciclosporin in the two randomized controlled trials ^{19,24}, a higher proportion of patient were treated with infliximab (65%) compared to ciclosporin (25%) in our study. This may be related to the substantial proportion of patients previously exposed to thiopurines and thus not eligible for ciclosporin, and also related to physician preferences, as reported in previous studies ^{12,23}. We observed a high response to infliximab (91%) and ciclosporin (85%), compared to a meta-analysis of non-randomized studies (respectively, 74.8% and 55.4%) ²³. However, these rates of response are similar to the CySIF study, which observe at day 7 86% of response to ciclosporin and 84% to infliximab ²⁴. Since the response rate of the second line therapy was higher, the percentage of colectomy during hospitalization (4.8%) was lower compared to that of literature, which is usually ranging from 11% to 25% ^{18,25,26}. After one year of follow-up, probability of colectomy (12.3%) was nevertheless close to recent studies (12%) ¹⁸.

Four criteria at admission were associated with colectomy within one year after ASUC in multivariate analysis. First, previous exposure to anti-TNFs or thiopurines was predictive of colectomy. Two studies have already reported a strong association between colectomy and previous exposure to immunosuppressants ^{25,27}. None

reported an association with anti-TNFs, which may be related to the period of inclusion. Second, *CDI* is a well-known predictor, especially for the long term risk (OR: 2.96; 95% CI: 1.19–7.34) but not for the short term risk^{8,9}. Third, a level of albumin below 30 g/L was already included in previous scores^{10,28}. Lastly, CRP level, which is also a marker of inflammation, was associated with colectomy in historical cohorts^{29,30}.

From these 4 items, a predictive score of colectomy has been developed. Firstly, an internal validation was performed with bootstrapping technique. Secondly, a validation cohort was built to assess external validation. Results were consistent in the validation cohort for low- and high-risk profile patients. When no criterion is present, the risk of colectomy at one year is minimal (0% to 6%), allowing an early transition to oral therapy and discharge from hospital. When one or two criteria are identified, 10 to 30% of patients will be operated within one year. Among patients with a score of 2, discrepancies were observed between derivation and validation cohorts was observed about the score 2 (10.6% (95%CI: 5.6-17.4) versus 29.4% (95%CI: 19.3-40.3)). A potential residual confounding cannot be excluded, but this difference may be also related to the physician preference. Indeed, patients with this score range are at intermediate risk, among whom physicians preference may have the highest impact on colectomy occurrence in this area of uncertainty. Further studies are required to assess the impact of referent physician preference on the decision of colectomy. Among patients with a score greater than three, the risk is higher and colectomy may be discussed earlier, decreasing the morbi–mortality of surgery. PPV is similar with those observed in an English cohort published by Lynch *et al.*⁷.

The score developed in this study has several strengths: it is easy to use because only four items are included, with one point for each, improving the reproducibility between physicians and could be widely used. Since it is assessed at the first day of hospitalization, it can help physicians early in the therapeutic management. Previous treatments with anti-TNFs or thiopurines and *CDI* have been included for the first time in a predictive score of colectomy after ASUC.

Some limitations need to be discussed. Radiological and endoscopic criteria were too often lacking to be included in the analysis. Xie *et al.* have shown a higher

performance of the UCEIS to predict colectomy after a median follow - up of 73 months than the mayo endoscopic score ³¹. The number of Truelove and Witts criteria and the clinical activity index were not available for all patients. The later was nevertheless not predictive of colectomy in several studies ^{32,33} and *Lindgren et al.* had also included patients with moderately severe flare according to Truelove and Witts criteria ²⁹. Fecal calprotectin seems to have a predictive value in ASUC, but it was not routinely measured in our centers ^{6,34}. Moreover, we focused on colectomy after ASUC, but, nowadays, it would be interesting to have predictors of others issues such as mucosal healing, or success of specific biologics or small molecules ³⁵. Further studies are required to identify these predictors.

To conclude, in this exploratory cohort of consecutive patients with ASUC, four independent predictors of colectomy within one year were identified: previous treatment with anti-TNFs or thiopurines, presence of *CDI*, CRP level above 30 mg/L, and albumin level below 30 g/L. A score combining these predictors is highly predictive of the occurrence and risk magnitude of colectomy within one year after admission and a replicative cohort confirmed these results.

REFERENCES

1. Cesarini M, Collins GS, Rönnblom A, et al. Predicting the Individual Risk of Acute Severe Colitis at Diagnosis. *Journal of Crohn's and Colitis* September 2016;jjw159.
2. Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis. *Journal of Crohn's and Colitis* 2012;6:965-990.
3. Kaplan GG, McCarthy EP, Ayanian JZ, et al. Impact of Hospital Volume on Postoperative Morbidity and Mortality Following a Colectomy for Ulcerative Colitis. *Gastroenterology* 2008;134:680-687.e1.
4. Leeds IL, Truta B, Parian AM, et al. Early Surgical Intervention for Acute Ulcerative Colitis Is Associated with Improved Postoperative Outcomes. *Journal of Gastrointestinal Surgery* 2017;21:1675-1682.
5. Saha SK, Panwar R, Kumar A, et al. Early colectomy in steroid-refractory acute severe ulcerative colitis improves operative outcome. *International Journal of Colorectal Disease* 2018;33:79-82.
6. Venthram NT, Kalla R, Kennedy NA, et al. Predicting outcomes in acute severe ulcerative colitis. *Expert Review of Gastroenterology & Hepatology* 2015;9:405-415.
7. Lynch RW, Churchhouse AMD, Protheroe A, et al. Predicting outcome in acute severe ulcerative colitis: comparison of the Travis and Ho scores using UK IBD audit data. *Alimentary Pharmacology & Therapeutics* 2016;43:1132-1141.
8. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with *Clostridium difficile* in patients with inflammatory bowel disease. *Gut* 2008;57:205-210.
9. Law CCY, Tariq R, Khanna S, et al. Systematic review with meta-analysis: the impact of *Clostridium difficile* infection on the short- and long-term risks of colectomy in inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics* 2017;45:1011-1020.
10. Gibson DJ, Hartery K, Doherty J, et al. CRP/Albumin Ratio: An Early Predictor of Steroid Responsiveness in Acute Severe Ulcerative Colitis. *Journal of Clinical Gastroenterology* 2018; 52(6):e48-e52.
11. Choy MC, Seah D, Gorelik A, et al. Predicting response after infliximab salvage in acute severe ulcerative colitis. *J Gastroenterol Hepatol* 2018;33:1347-1352.

12. Harbord M, Eliakim R, Bettenworth D, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *Journal of Crohn's and Colitis* 2017;11:769-784.
13. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-383.
14. Truelove SC, Witts LJ. Cortisone in ulcerative colitis. *British medical journal* 1955;2:1041.
15. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in Severe Ulcerative Colitis Refractory to Steroid Therapy. *New England Journal of Medicine* 1994;330:1841-1845.
16. Efron B, Tibshirani R. *An Introduction to the Bootstrap*. Vol New York: Chapman & Hall, 1990.
17. Parian A, Limketkai B, Koh J, et al. Appendectomy does not decrease the risk of future colectomy in UC: results from a large cohort and meta-analysis. *Gut* 2017;66:1390-1397.
18. Jain S, Kedia S, Sethi T, et al. Predictors of long-term outcomes in patients with acute severe colitis: A northern Indian cohort study: Acute severe colitis: Long-term outcome. *Journal of Gastroenterology and Hepatology* 2018;33:615-622.
19. Williams JG, Alam MF, Alrubaiy L, et al. Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. *The Lancet Gastroenterology & Hepatology* 2016;1:15–24.
20. Regnault H, Bourrier A, Lalande V, et al. Prevalence and risk factors of *Clostridium difficile* infection in patients hospitalized for flare of inflammatory bowel disease: A retrospective assessment. *Digestive and Liver Disease* 2014;46:1086-1092.
21. Lynch RW, Lowe D, Protheroe A, et al. Outcomes of rescue therapy in acute severe ulcerative colitis: data from the United Kingdom inflammatory bowel disease audit. *Alimentary Pharmacology & Therapeutics* 2013;38:935-945.
22. Turner D, Walsh CM, Steinhart AH, et al. Response to Corticosteroids in Severe Ulcerative Colitis: A Systematic Review of the Literature and a Meta-Regression. *Clinical Gastroenterology and Hepatology* 2007;5:103-110.
23. Narula N, Marshall JK, Colombel J-F, et al. Systematic Review and Meta-Analysis: Infliximab or Cyclosporine as Rescue Therapy in Patients With Severe Ulcerative Colitis Refractory to Steroids. *The American Journal of Gastroenterology* 2016;111:477-491.

24. Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. *The Lancet* 2012;380:1909–1915.
25. Deiana S, Bagnoli S, Manetti N, et al. Outcome of acute severe ulcerative colitis in patients previously exposed to immunosuppressive therapy. *Digestive and Liver Disease* 2016;48:1432-1437.
26. Mokhele NN, Thomson SR, Watermeyer GA. Predictors of emergency colectomy in patients admitted with acute severe ulcerative colitis. *S Afr J Surg* 2017;55:20-26.
27. Patrick D, Doecke J, Irwin J, et al. The effect of pre-admission immunosuppression on colectomy rates in acute severe ulcerative colitis. *Therapeutic Advances in Gastroenterology* 2018;11:175628481880978.
28. Ho GT, Mowat C, Goddard CJR, et al. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Alimentary Pharmacology and Therapeutics* 2004;19:1079-1087.
29. Lindgren SC, Flood LM, Kilander AF, et al. Early predictors of glucocorticosteroid treatment failure in severe and moderately severe attacks of ulcerative colitis. *Eur J Gastroenterol Hepatol* 1998;10:831-835.
30. Travis SP, Farrant JM, Ricketts C, et al. Predicting outcome in severe ulcerative colitis. *Gut* 1996;38:905-910.
31. Xie T, Zhang T, Ding C, et al. Ulcerative Colitis Endoscopic Index of Severity (UCEIS) versus Mayo Endoscopic Score (MES) in guiding the need for colectomy in patients with acute severe colitis. *Gastroenterology Report* 2018;6:38-44.
32. Kohn A, Daperno M, Armuzzi A, et al. Infliximab in severe ulcerative colitis: short-term results of different infusion regimens and long-term follow-up: INFLIXIMAB IN SEVERE REFRACTORY ULCERATIVE COLITIS. *Alimentary Pharmacology & Therapeutics* 2007;26:747-756.
33. Monterubbianesi R, Aratari A, Armuzzi A, et al. Infliximab three-dose induction regimen in severe corticosteroid-refractory ulcerative colitis: Early and late outcome and predictors of colectomy. *Journal of Crohn's and Colitis* 2014;8:852-858.
34. Xie T, Zhao C, Ding C, et al. Fecal calprotectin as an alternative to ulcerative colitis endoscopic index of severity to predict the response to corticosteroids of acute severe ulcerative colitis: A prospective observational study. *Digestive and Liver Disease* 2017;49:984-990.

35. Motobayashi M, Matsuoka K, Takenaka K, et al. Predictors of mucosal healing during induction therapy in patients with acute moderate-to-severe ulcerative colitis. *Journal of Gastroenterology and Hepatology* 2019;34(6):1004-1010.

Table 1: Characteristic at admission (Derivation cohort)

Characteristic	N total=270
Demographic parameters	
Male	134 (49.6)
Age at admission, year	32.0 (24.0–47.0)
At least one item in Charlson’s score	41 (15.2)
Duration of disease, year	2.0 (0.0–7.0)
ASUC within 6 months after diagnosis	80 (29.6)
Disease	
Ulcerative colitis	260 (96.3)
IBDU	10 (3.7)
Extension of disease	
Extensive colitis	162 (60)
Left sided colitis	101 (37.4)
Proctitis	7 (2.6)
Previously exposed to anti-TNFs or thiopurines (past and current users)	88 (32.6)
Clinical parameters	
Number of stools per day	10.0 (7.0–15.0)
Lichtiger index*	12.0 (10.0–14.0)
Extra-intestinal manifestation	31 (11.9)
Biological parameters	
CRP, mg/L	53.0 (18.6–110)
Albumin, g/L	30.7 (26.3–35.5)
Hemoglobin, g/dL	11.6 (10.1–13.2)
WCC (x 10 ⁹ per L)	9.9 (7.56–13.0)
Platelet (x 10 ⁹ per L)	388 (305 - 479)
CMV colitis	5 (5.8)
CDI, n (%)	10 (4.3)

Results are expressed as median (interquartile range) for continuous variables and as N (%) for categorical variables.

* Among 215 patients with no missing data to assess the clinical activity index (Lichtiger index)

ASUC: Acute severe ulcerative colitis; IBDU: Inflammatory bowel disease unclassified; CRP: C-reactive protein; WCC: white cell count; CMV: cytomegalovirus; CDI: *Clostridioides difficile* infection

Table 2: Clinical and biochemical variables of 270 patients admitted with ASUC (Derivation cohort)

	Colectomy at one year (n=30)	No colectomy at one year (n=240)	Hazard ratio (95%CI)	p
Clinical variables				
Male	16 (53.3)	118 (49.2)	0.86 (0.42–1.76)	0.68
Charlson's index	0 (0–1)	0 (0–0)	1.18 (0.93–1.52)	0.18
Previous appendectomy	3 (10)	9 (3.8)	2.70 (0.82–8.89)	0.10
Age at diagnosis (years)	37.0 (25.0–47.0)	26.0 (21.0–40.0)	1.03 (1.01–1.05)	<0.01
Age at admission above 50 (years)	10 (33.3)	49 (20.4)	1.90 (0.89–4.06)	0.10
Disease duration (years)	2 (0.0–7.0)	2 (0.0–7.0)	0.99 (0.94–1.04)	0.75
ASUC onset within 6 months after diagnosis	4 (13.3)	76 (31.7)	0.35 (0.12–0.99)	0.048
Extensive colitis (E3) (vs E2 + E1)	23 (77)	139 (58)	2.21 (0.9–5.2)	0.07
Medication before admission:				
Thiopurines	14 (46.7)	67 (27.9)	2.09 (1.02–4.27)	0.04
Anti-TNFs	9 (30)	34 (12.6)	3.17 (1.45–6.93)	<0.01
Time of flare-up before admission	33.0 (20.0–75.0)	31.0 (16.0–56.0)	1.00 (0.99–1.00)	0.55
Oral steroids before admission to treat flare-up	17 (56.7)	104 (43.5)	1.57 (0.76–3.23)	0.22
Number of stools	10.0 (7.0–15.0)	10.0 (6.0–15.0)	1.03 (0.99–1.08)	0.15
Extra-intestinal manifestation	2 (6.9)	29 (12.5)	0.54 (0.13–2.28)	0.40
Biochemical variables				
CRP above 30 mg/L	25 (83.3)	150 (62.5)	2.84 (1.09–7.43)	0.03
Albumin below 30 g/L	20 (66.7)	100 (41.7)	2.60 (1.22–5.56)	<0.01
Hemoglobin (g/dL) *	10.8 (9.80–12.2)	11.8 (10.2–13.3)	0.88 (0.75–1.03)	0.12
WCC (x 10 ⁹ per L) **	9.32 (7.1–13.0)	9.9 (7.6–13.0)	1.00 (1.0–1.0)	0.44
Platelet (x 10 ⁹ per L) ***	395 (328–495)	388 (299–479)	1.00 (0.99–1.00)	0.52
Presence of <i>C. difficile</i> infection	3 (13.0)	7 (3.4)	3.83 (1.16–12.62)	0.03
CMV colitis	2 (18.2)	3 (4.0)	4.32 (0.93–20.07)	0.06

ASUC: Acute severe ulcerative colitis; WCC: white cell count; CRP: C-reactive protein; CMV: Cytomegalovirus; Risk corresponding to an increase of one unit (*), 1000 WCC/mm³ (**) and 10 000 platelet (***)

Table 3: Characteristics of score one year after admission for ASUC from derivation cohort

	Negative predictive value (NPV) (%) (95%CI)	Positive predictive value (PPV) (%) (95%CI)	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)
Score=0	87 (82–91)	-	-	83 (78–87)
Score=1	88 (82–92)	9 (4–17)	27 (12–46)	65 (59–71)
Score=2	88 (82–93)	10 (5–17)	37 (20–56)	58 (51–64)
Score=3	92 (88–95)	42 (22–63)	33 (17–53)	94 (90–97)
Score=4	89 (85–93)	100 (3–100)	3 (0–17)	100 (98–100)

Figures and caption:

Figure 1: Flow chart of study (Derivation cohort)

IBD: Inflammatory bowel disease; CRP: C-reactive protein

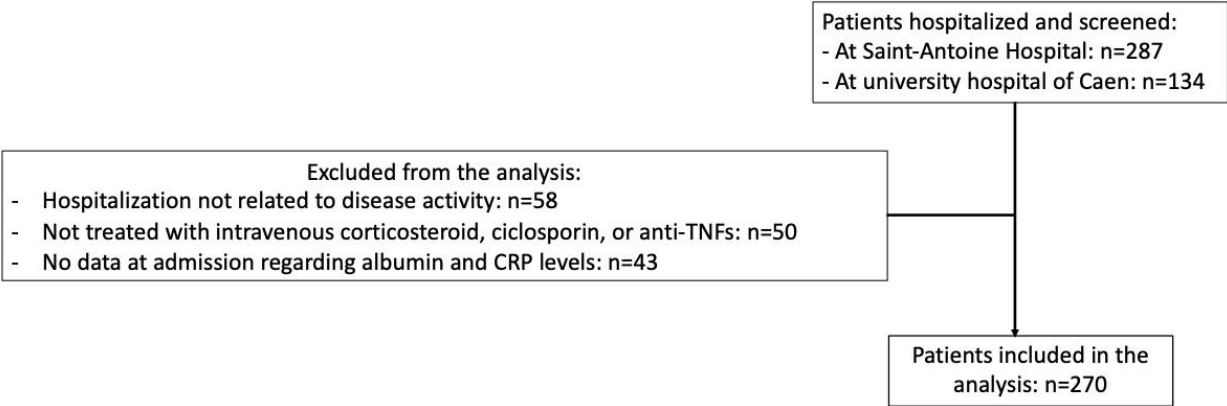


Figure 2: Rate of colectomy according to the time since admission for ASUC (Derivation cohort)

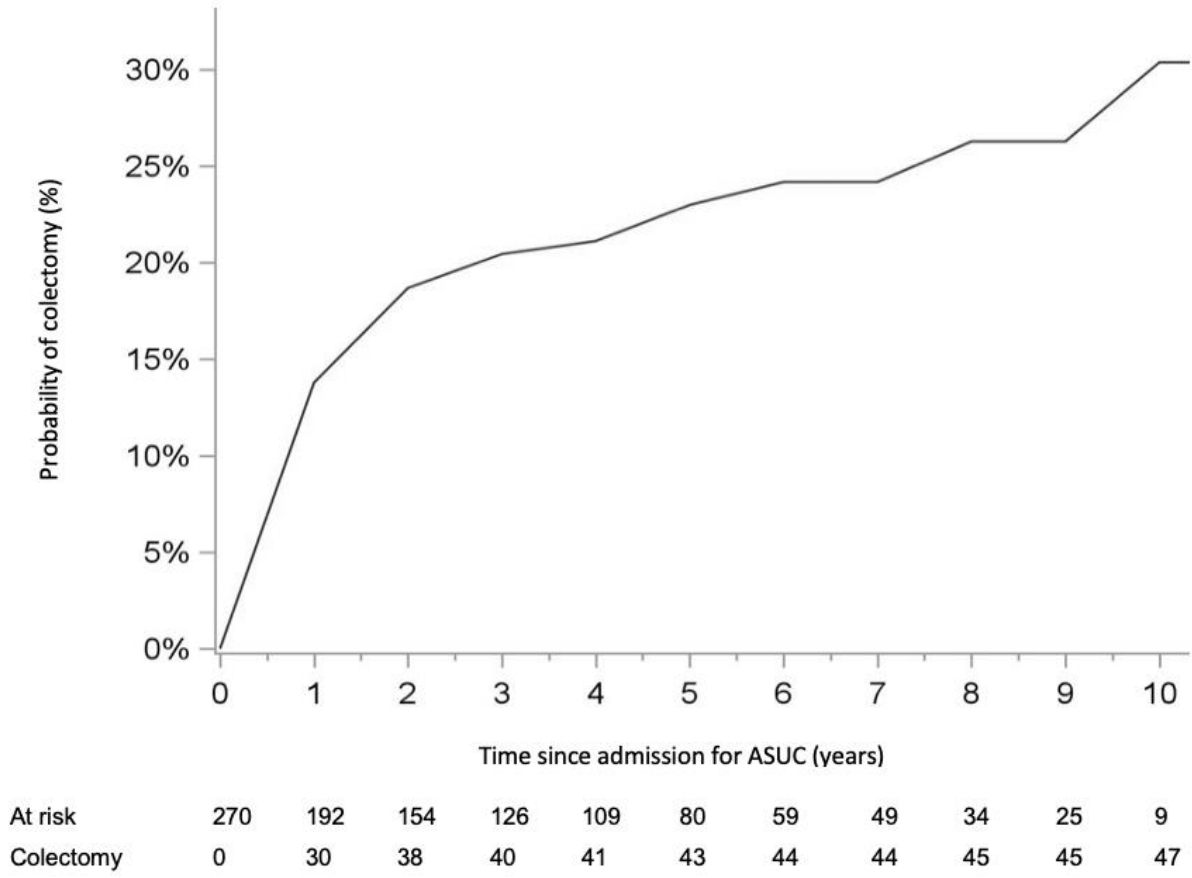
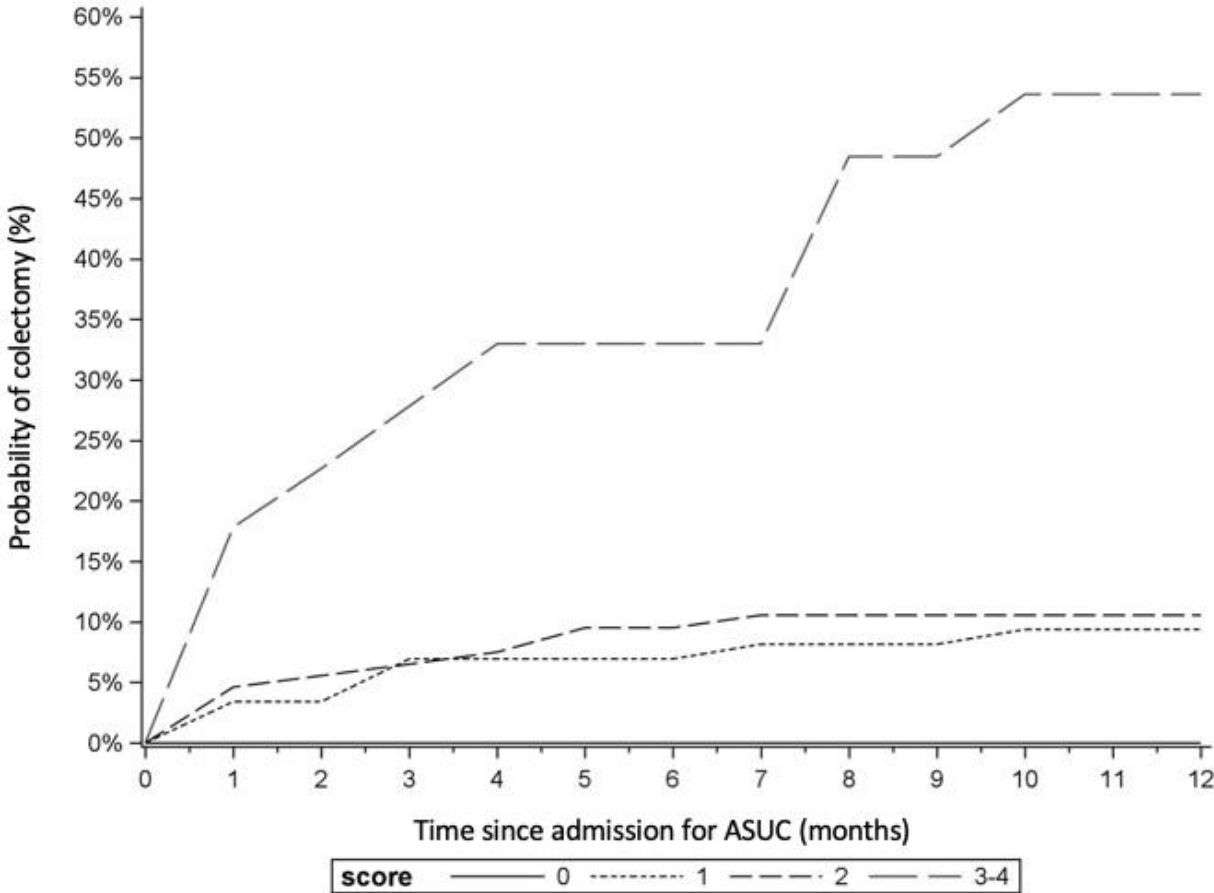
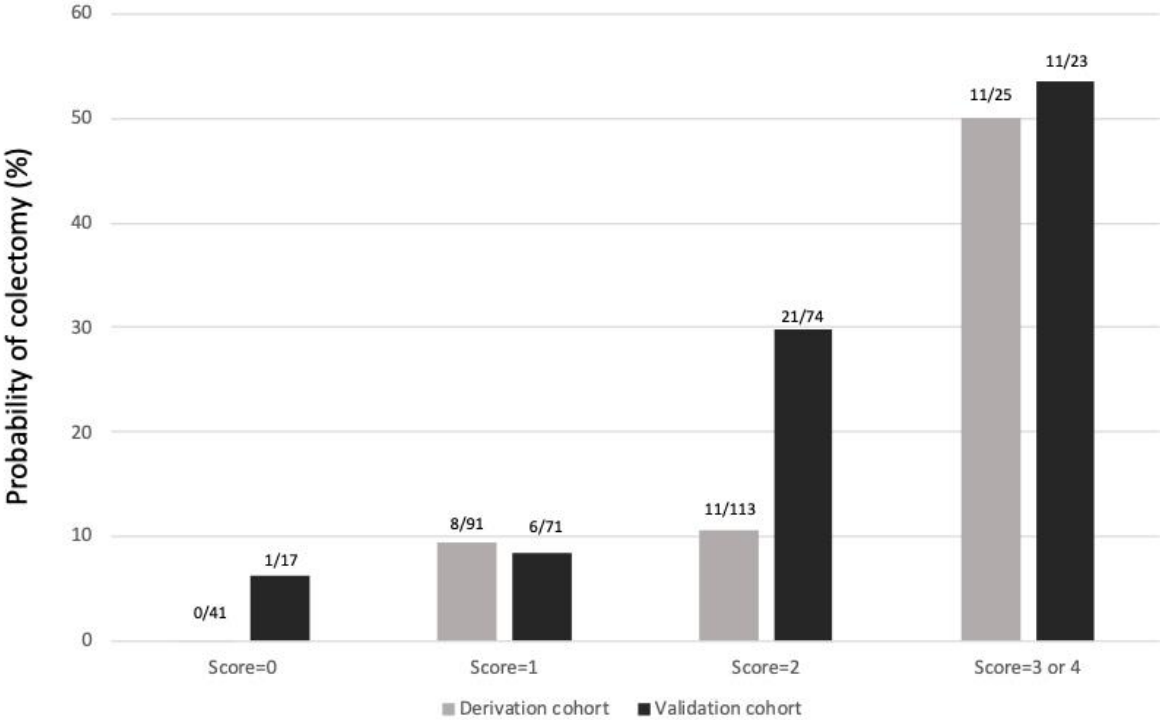


Figure 3: Cumulative probability of colectomy according to the time since admission for ASUC (Derivation cohort)



Score=0	41	34	34	34	33	33	31	31	30	30	30	30	30
Score=1	91	82	82	78	78	78	77	75	75	75	74	74	74
Score=2	113	101	100	97	93	90	89	86	86	83	82	81	81
Score=3 - 4	25	17	16	14	13	13	13	13	10	10	9	9	0

Figure 4: Risk of colectomy within one year after an ASUC according to the predictive score in the derivation and validation cohorts.



Derivation cohort	0.0	9.4 (4.3–16.7)	10.6 (5.6–17.4)	51.2 (26.6–71.3)
Validation cohort	6.2 (0.4-25.5)	8.4 (3.4-16.4)	29.4 (19.3-40.3)	50.0 (27.4-69.0)
	% (95%CI)			

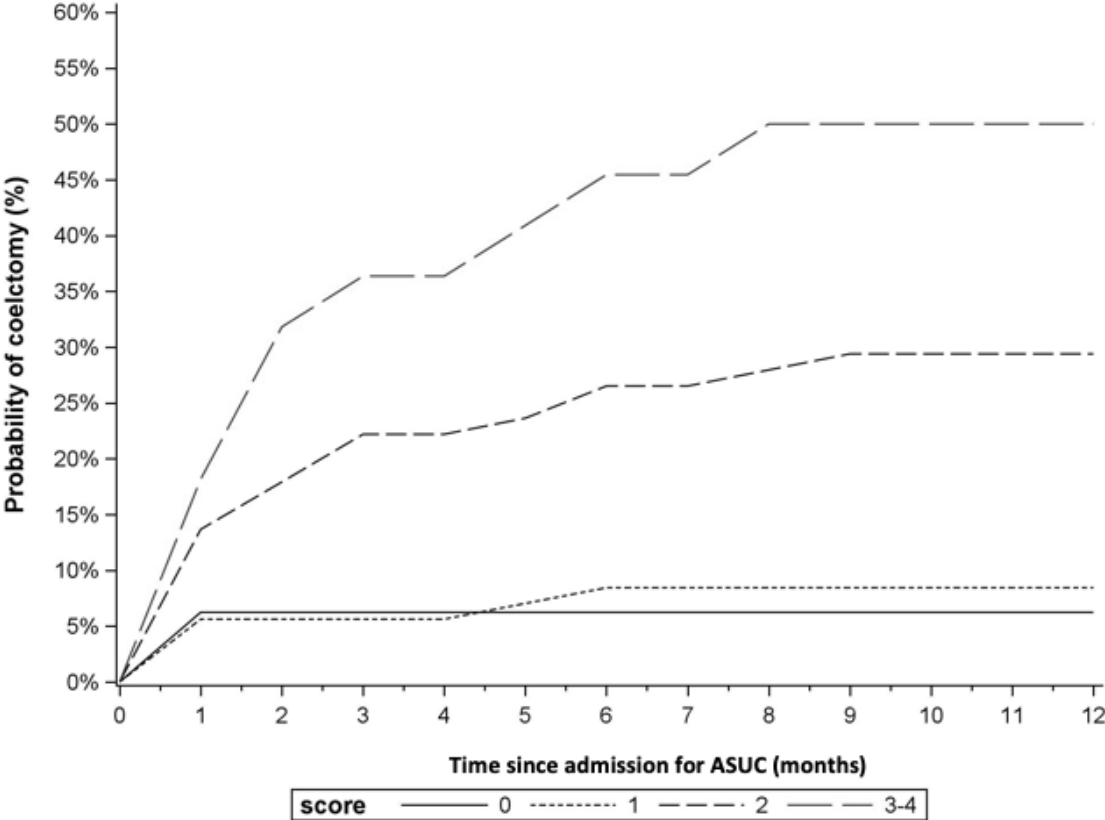
Supplementary data 1: Endoscopic and radiological criteria at admission

	Colectomy at one year (n=30) N (%) or median (IQR)	No colectomy at one year (n=240) N (%) or median (IQR)
Endoscopic criteria*		
Mayo endoscopic score:		
Mayo 1	4.0 (1)	13.0 (27)
Mayo 2	20.0 (5)	21.7 (45)
Mayo 3	76.0 (19)	65.2 (135)
Mucosal damage:		
None	4.3 (1)	7.3 (13)
Erosions	13.0 (3)	20.8 (37)
Superficial ulcer	34.8 (8)	40.4 (72)
Deep ulcer	47.8 (11)	31.5 (56)
Radiological criteria**		
Disease extent on CT-scan:		
Left-sided	8.3 (1)	35.1 (20)
Pancolitis	91.7 (11)	64.9 (37)

* Among 241 patients with no missing data about endoscopic criteria

** Among 70 patients with no missing data about radiological criteria

Supplementary data 2: Cumulative probability of colectomy according to the time since admission for ASUC and to the score in the validation cohort



score	0	1	2	3-4
Score=0	17	15	15	15
Score=1	71	67	67	67
Score=2	74	61	58	54
Score=3 - 4	23	18	15	14