

Original Article

# Natural Disease Course of Ulcerative Colitis During the First Five Years of Follow-up in a European Population-based Inception Cohort—An Epi-IBD Study

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## Abstract

**Background and Aims:** Few population-based cohort studies have assessed the disease course of ulcerative colitis [UC] in the era of biological therapy and widespread use of immunomodulators. The aim of this study was to assess the 5-year outcome and disease course of patients with UC in the Epi-IBD cohort.

**Methods:** In a prospective, population-based inception cohort of unselected patients with UC, patients were followed up from the time of their diagnosis, which included the collection of their clinical data, demographics, disease activity, medical therapy, and rates of surgery, cancers, and deaths. Associations between outcomes and multiple covariates were analysed by Cox regression analysis.

**Results:** A total of 717 patients were included in the study. During follow-up, 43 [6%] patients underwent a colectomy and 163 [23%] patients were hospitalised. Of patients with limited colitis [distal to the left flexure], 90 [21%] progressed to extensive colitis. In addition, 92 [27%] patients with extensive colitis experienced a regression in disease extent, which was associated with a reduced risk of hospitalisation (hazard ratio [HR]: 0.5 95% CI: 0.3–0.8). Overall, patients were treated similarly in both geographical regions; 80 [11%] patients needed biological therapy and 210 [29%] patients received immunomodulators. Treatment with immunomodulators was found to reduce the risk of hospitalisation [HR: 0.5 95% CI: 0.3–0.8].

**Conclusions:** Although patients in this population-based cohort were treated more aggressively with immunomodulators and biological therapy than in cohorts from the previous two decades, their disease outcomes, including colectomy rates, were no different. However, treatment with immunomodulators was found to reduce the risk of hospitalisation.

**Key Words:** Ulcerative colitis; surgery; hospitalisation; prognosis; treatment; biologics

## 1. Introduction

Ulcerative colitis [UC] belongs to the group of inflammatory bowel diseases [IBD] and is a chronic, progressive disorder of unknown aetiology. Both its clinical presentation and its course vary between patients and can range from mostly quiescent to chronic, refractory disease in need of surgery, sometimes being complicated by cancer or contributing to cause of death.<sup>1</sup> Recent treatment strategies for UC have been using immunomodulators and biological agents both earlier in the disease course and more frequently. The introduction of mucosal healing as an important treatment goal is likewise a recent development.<sup>2</sup>

The beneficial impact of biological therapy on the disease course of UC is partly supported by data from randomised controlled trials<sup>3</sup> and epidemiological studies,<sup>4,5</sup> whereas the impact of

immunomodulators remains uncertain. To date, there have been few population-based cohort studies from this era of widespread use of immunomodulators and biological therapy, and hence little is known about the present real-life disease outcomes of UC patients. To assess the impact of treatment strategies on disease outcome, prospective, population-based cohorts of unselected patients representing the broad spectrum of the disease are necessary in order to build the most accurate picture of effectiveness and practice regarding medication and surgery in the community setting.

The Epi-IBD [formerly EpiCom] study uses a prospective, population-based inception cohort of unselected IBD patients for investigating the occurrence, disease course, and prognosis of these diseases in Europe.<sup>6,7</sup> The aim of the present study was to: [1] evaluate the disease course of UC and the impact of treatment choices on

it during the first 5 years following diagnosis, and [2] assess a possible west-east gradient in treatment strategies and disease outcomes within this cohort.

## 2. Methods

### 2.1. Study population and design

The Epi-IBD cohort is a prospective, population-based inception cohort of IBD patients diagnosed in 2010 in 22 European countries and Israel.<sup>8</sup> Participating centres were required to have a well-defined primary catchment area with up-to-date population data, including age and sex distribution. They were also required to have an established network of gastroenterologists, colorectal surgeons, and general practitioners [GPs] within the uptake area to be contacted twice during the inclusion period, to ensure complete coverage and recruitment of patients. Case ascertainment methods, diagnostic criteria, inclusion period, and patient data were all standardised.

Two centres [France, Malta] joined the study group after the start of the inclusion period, both of them having included incident patients in prospective, inception cohorts in 2010 in parallel. Five centres from the original cohort were unable to perform follow-up for technical or logistical reasons. Consequently, 29 centres from eight Eastern, and 13 Western, European countries, including Israel, participated in the study [see Supplementary File, available as Supplementary data at *ECCO-JCC* online]. The study population consisted of 1289 IBD patients, 488 with Crohn's disease [CD], 717 with UC, and 84 with IBD unclassified [IBDU], all recruited within well-described geographical areas covering a total background population of 9.7 million people [2.6 million in Eastern, and 7.1 million in Western, Europe].

### 2.2. Classifications and definitions

All incident patients diagnosed with IBD according to the *Copenhagen Diagnostic Criteria*<sup>9–11</sup> between 1 January and 31 December 2010, aged 15 years or older and living in the predefined catchment areas at the time of diagnosis, were prospectively included. The date of inclusion was the date of their diagnosis. A small number of patients had their diagnosis changed during follow-up, and those patients were reclassified as having the newly diagnosed disease from the time of the original diagnosis.

Disease extent for UC was defined according to the *Montreal Classification*.<sup>12</sup> Disease extension was defined as a proximal progression from the initial extent at diagnosis, as determined by endoscopy. In cases where no investigative procedures were performed before surgery owing to acute symptoms, macroscopic description of the surgical specimen was used to describe the disease extent. Regression in extent was assessed by comparing the most recent endoscopic examination with the worst disease extent found previously. Hospitalisations were defined as either admission for UC-related surgery [surgical hospitalisations] or other UC-related complaints [medical hospitalisations]. Elective admissions, e.g. for endoscopy procedures or drug administration, were excluded from consideration.

Treatment was grouped into five levels of ascending therapeutic potency: 5-aminosalicylates [5-ASA] [oral and/or topical 5-ASA treatment ± topical steroids], glucocorticosteroids [GCS] [oral steroids ± 5-ASA or topical steroids], immunomodulators [azathioprine, 6-mercaptopurine, cyclosporine, or methotrexate ± steroids], biologics [infliximab or adalimumab, in combination with any of the above], and surgery [colectomy]. Immunomodulators were combined in one category because 95% of patients treated with

immunomodulators received thiopurines. An early need for immunomodulators or biological therapy was defined as the initiation of these drugs within 6 months of diagnosis. An early need for GCS was defined as patients starting on 40 mg or more of it within 30 days of their diagnosis.

The disease activity of UC was measured using the *Simple Clinical Colitis Activity Index* [SCCAI].<sup>13</sup> A SCCAI score of ≤2 was defined as remission, 3–5 as mild, 6–11 as moderate, and ≥12 as severe disease activity.<sup>14</sup> Causes of death and cancers were categorised according to the Tenth<sup>b</sup> revision of the *International Classification of Diseases*.<sup>15</sup> Endoscopic activity was determined using the Mayo endoscopic subscore<sup>16</sup> and mucosal healing was defined as a subscore ≤1.

### 2.3. Data collection and validity

Incident patients were followed prospectively from their diagnosis for 5 years, or until the date of their emigration or death. Data regarding demographics, disease activity, medical therapy including dose, date of initiation and date of cessation, surgery, hospitalisation, disease classification, cancers and deaths were collected and entered prospectively in the web-based Epi-IBD database.<sup>17</sup> A follow-up period of 5 years, with a 3-month margin on either side, was chosen for assessing the outcome of the cohort. Measures to ensure data validity have been thoroughly described elsewhere<sup>6</sup>; in short, there were built-in control and validation tests, locked diagnostic criteria in the database, manual data standardisation, and random audits of case ascertainment and data quality.

### 2.4. Statistical analysis

Statistical analyses were performed using SAS software version 9.4 [SAS Institute Inc., Cary, NC, USA]. Continuous variables are expressed as the median [interquartile range; IQR] unless otherwise stated. Groups were compared using a chi-square test or Fisher's exact test, where appropriate. Differences regarding time to events were compared using the Wilcoxon two-sample test. A *p*-value of <0.05 was considered statistically significant.

Possible associations between primary endpoints [progression in disease extent, regression in disease extent, surgery, hospitalisation, or biological treatment] and multiple covariates were analysed by stepwise Cox regression analysis using the proportional hazards assumption, and associations were visualised by Kaplan–Meier plots in order to test these assumptions. As the aim was to describe the disease course following diagnosis, only events occurring after the date of diagnosis were included in the Cox regression analysis.

The following covariates were included in the statistical models: age at diagnosis [continuous variable], sex, geographical region [Western vs Eastern Europe], disease extent at diagnosis, smoking status [never, currently, former], diagnostic delay [continuous variable], need for early corticosteroids, treatment with immunomodulators, treatment with biologics, and regression in extent. The reported hazard ratios [HR] are all adjusted. The use of immunomodulators and biologics were included in the regression model as time-dependent variables and with an initial lag time of 3 months for immunomodulators and 2 months for biologics, so that only treatments before an event and lasting longer than the lag time would count as active treatment. We also included age and diagnostic delay as categorical variables, as well as smoking as a binary variable [current vs former/never smoker], with no impact on the results.

We demonstrated the prevalence of treatment types using two prevalence plots. In the first variant, each patient was classified, on any given day since their diagnosis, as being in one of the treatment steps according to the treatment[s] received on that specific

day. In the case of combination therapy, the patient was counted for all treatment steps given. In the second variant [shown in the Supplementary File, available as Supplementary data at ECCO-JCC online], in the case of the patient receiving combination treatment, the level assigned was that of the most potent treatment. In both plots, patients undergoing surgery were considered as remaining in this treatment step for 1 year.

2.5. Ethical considerations

The study was approved by the local ethical committees and according to local regulations.

3. Results

Initially, 701 patients aged 15 years or older were diagnosed with UC. During follow-up, 20 patients initially diagnosed with IBDU, and six diagnosed with CD, had their diagnosis changed to UC after a median of 6 months [IQR 3–12]. Furthermore, 10 patients initially diagnosed with UC had their diagnosis changed to CD and were excluded. As such, the cohort consisted of 717 UC patients, of whom 591 [82%] were diagnosed in Western, and 126 [18%] in Eastern, European centres. These patients were followed for a median of 63 months [IQR: 44–63]. Patients’ sociodemographic characteristics [Table 1] did not differ significantly between the two geographical regions, except in that more Eastern European patients had extra-intestinal manifestations at diagnosis.

Data regarding disease activity during follow-up were available for analysis from 626 [87%] patients. The proportion of patients in clinical remission rose from 27% during the first year of disease to 71% in the fifth year of follow-up [Figure 1].

3.1. Disease extent

Information about disease extent at diagnosis was not available in the case of nine [1%] patients, who were excluded from this part of the analysis. At the time of diagnosis, 435 [61%] patients had limited UC [E1, proctitis or E2, left-sided colitis], and during follow-up 90

[21%] patients experienced a progression in extent, among whom 67 [15%] patients progressed to E3 [extensive colitis] [Figure 2]. The median time to progression was 25 months [IQR: 12–28] for E1 to E2, 17 months [IQR: 8–38] for progression from E1 to E3, and 12 months [IQR: 7–22] for progression from E2 to E3. No statistically significant geographical differences were found in terms of the proportion of patients experiencing these progressions in disease nor length of time in which these progressions occurred. Predictors associated with progression in extent are shown in Table 2.

Of patients diagnosed with extensive colitis, 69 [25%] regressed to either proctitis [*n* = 23, 33%] or left-sided colitis [*n* = 46, 67%] after a median of 41 months [IQR: 17–50] after diagnosis. Of those patients [*n* = 67] who progressed to extensive colitis during follow-up, 23 [34%] later regressed to proctitis [*n* = 3, 13%] or left-sided colitis [*n* = 20, 87%] after a median of 27 months [IQR: 9–46] since they first progressed [Figure 2]. Overall, of patients with extensive colitis either at diagnosis or during follow-up, 92 [27%] regressed to a more limited disease extent.

We found no predictor for regression in extent among patients diagnosed with extensive colitis [Table 2]. For this subgroup we also analysed predictors of surgery and hospitalisation, including whether they regressed in disease extent or not. The results of this analysis are shown in Table 3; regression in extent was associated with a lower risk for all outcomes.

3.2. Medical treatment

The cumulative 5-year exposures to medical treatments are shown in Figure 3, and the median duration of treatment is shown in Table 1. Overall, the use of treatments was similar between Eastern and Western Europe. However, significantly more patients in Western Europe [7%] than in Eastern Europe [0%] received no treatment during follow-up [*p* < 0.01]. The distribution of patients between the defined treatment steps at any given time during follow-up is shown in Figure 4, and the pattern of changes between treatment steps is shown in Supplementary Figure 1, available as Supplementary data at ECCO-JCC online.

Table 1. Characteristics of incident ulcerative colitis patients from the Epi-IBD cohort.

	All patients		Western Europe [ <i>n</i> = 591, 82%]		Eastern Europe [ <i>n</i> = 126, 18%]	
Male, <i>n</i> [%]	397 [55%]		329 [56%]		68 [54%]	
Age at diagnosis, years, [IQR]	37 [27–55]		38 [27–56]		35 [26–51]	
Median time to diagnosis, months, [IQR]	3 [1–6]		3 [1–6]		2 [1–6]	
Extra-intestinal manifestations at diagnosis, <i>n</i> [%]	66 [9%]		48 [8%]		18 [14%]	
Smoking status at diagnosis, <i>n</i> [%]						
Never smoker	368 [58%]		292 [57%]		76 [61%]	
Current smoker	54 [9%]		44 [9%]		10 [8%]	
Former smoker	213 [33%]		174 [34%]		39 [31%]	
Disease extent at diagnosis, <i>n</i> [%]						
E1: proctitis	144 [20%]		118 [20%]		26 [21%]	
E2: left-sided	291 [41%]		233 [40%]		58 [46%]	
E3: extensive colitis	273 [39%]		231 [40%]		42 [33%]	
Cumulative frequency and duration of medical treatment						
	<i>n</i> [%]	Months, median [IQR]	<i>n</i> [%]	Months, median [IQR]	<i>n</i> [%]	Months, median [IQR]
5-aminosalicylate	535 [91%]	49 [19–62]	126 [100%]	45 [24–63]	661 [92%]	49 [20–62]
Prednisolone	305 [52%]	4 [1–3]	56 [44%]	3 [2–6]	361 [50%]	4 [2–6]
Immunomodulators	176 [30%]	29 [8–49]	34 [27%]	25 [9–48]	210 [29%]	28 [8–49]
Biological therapy	70 [12%]	14 [5–28]	10 [8%]	19 [10–32]	80 [11%]	14 [6–29]

IQR, interquartile range.

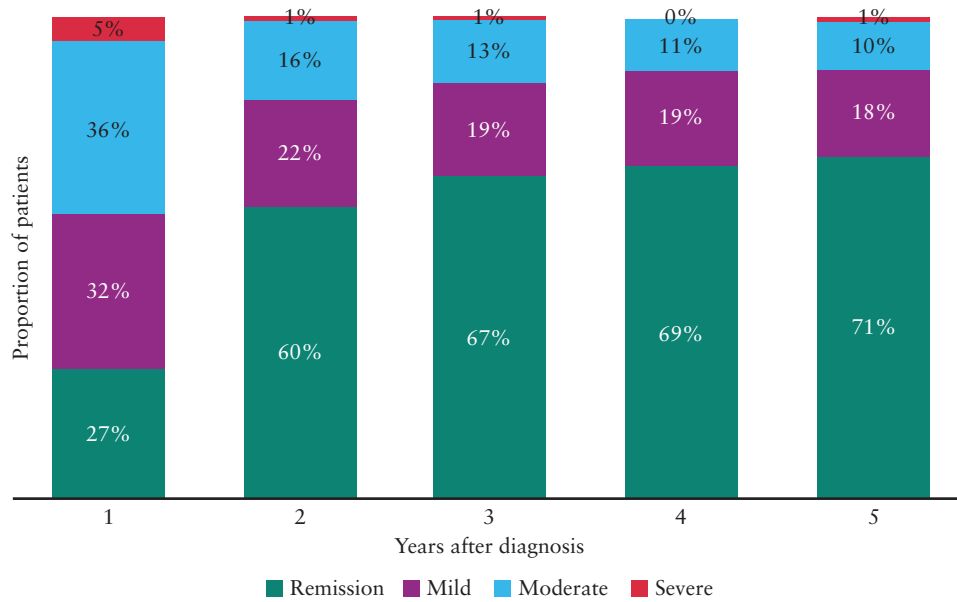


Figure 1. Distribution of disease activity in ulcerative colitis patients during 5 years of follow-up.

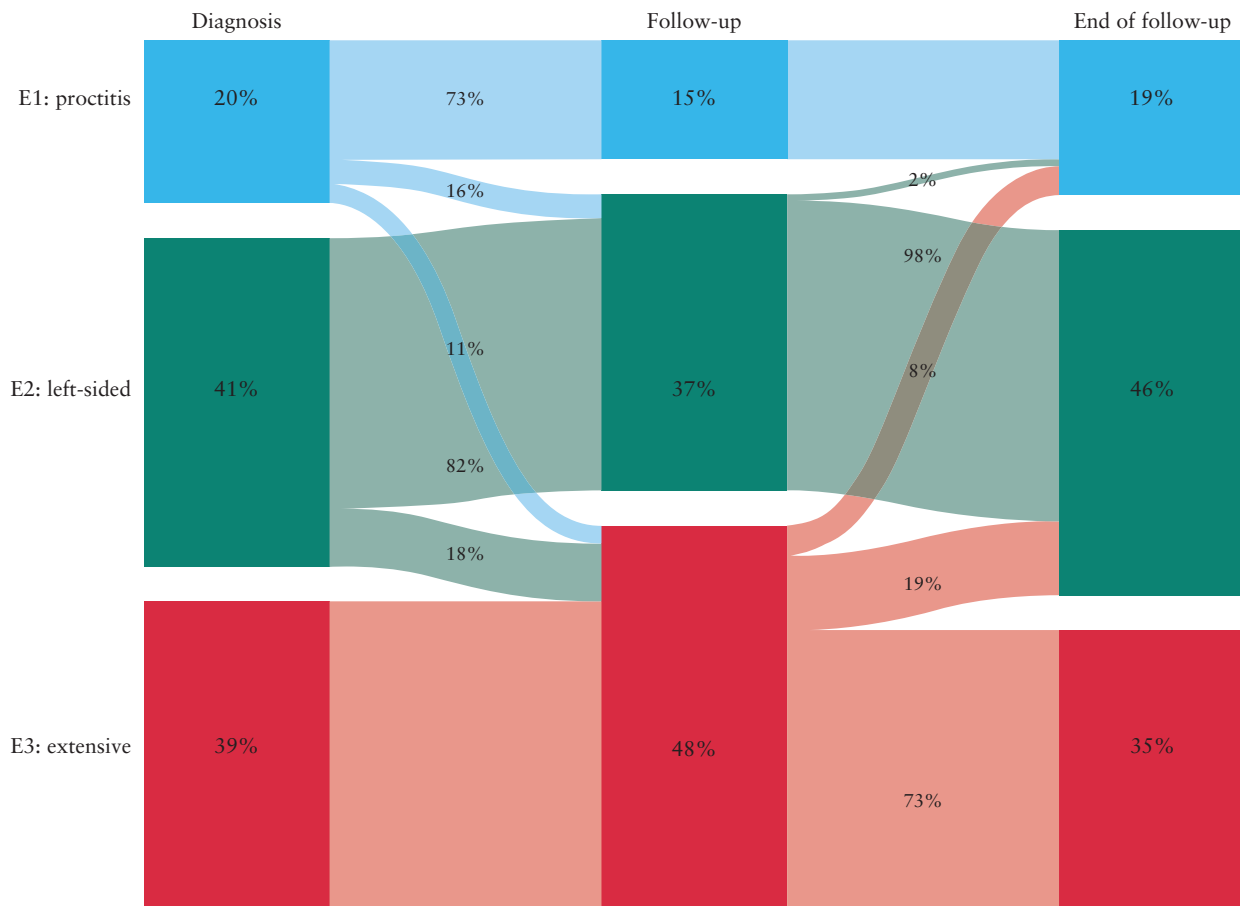


Figure 2. Disease extent and changes in extent in ulcerative colitis patients during 5 years of follow-up in a European population-based inception cohort. The figure shows disease extent at diagnosis, the greatest extent during follow-up, and the extent at the end of follow-up.

During follow-up, 99 [14%] patients received systemic GCS for a cumulative period longer than 6 months, and 47 [7%] patients received this treatment for more than 6 consecutive months, with

no geographical difference observed in either case. Of those receiving GCS for more than 6 consecutive months, most patients had E3 [ $n = 24, 51\%$ ], 15 [32%] had E2, and eight [17%] had E1.

**Table 2.** Factors associated with progression in disease extent, hospitalisation, and surgery in ulcerative colitis patients in the Epi-IBD-cohort.

	Progression in extent [n = 435]	Regression in extent [n = 273]	Hospitalisation, all [n = 717]	Hospitalisation, only medical [n = 717]	Surgery [n = 717]
Age at diagnosis [per year]	0.98 [0.96–0.99]*	1.00 [0.99–1.02]	0.98 [0.97–0.99]*	0.98 [0.97–0.99]*	0.99 [0.97–1.01]
Sex					
Female	0.9 [0.6–1.5]	0.7 [0.4–1.3]	1.3 [0.9–1.7]	1.3 [0.9–1.8]	1.2 [0.7–2.4]
Male	reference	reference	reference	reference	reference
Diagnostic delay [per day]	1.0 [1.0–1.0]	1.0 [0.9–1.0]	1.0 [1.0–1.0]	1.0 [1.0–1.0]	1.0 [1.0–1.0]
Geographical region					
Eastern Europe	0.6 [0.3–1.2]	0.9 [0.4–1.8]	0.6 [0.4–0.9]*	0.6 [0.4–0.97]*	0.3 [0.1–1.1]
Western Europe	reference	reference	reference	reference	reference
Smoking status at diagnosis					
Currently	1.1 [0.5–2.8]	0.7 [0.3–2.1]	0.7 [0.4–1.4]	0.7 [0.4–1.4]	0.3 [0.1–2.4]
Former	1.2 [0.7–2.1]	1.1 [0.6–1.9]	1.1 [0.7–1.5]	1.1 [0.8–1.7]	1.3 [0.7–2.7]
Never	reference	reference	reference	reference	reference
Disease extent	-	-			
E3: extensive colitis			1.4 [1.4–4.1]*	2.2 [1.3–3.8]*	3.5 [1.01–12.3]*
E2: left-sided colitis			1.5 [0.9–2.6]	1.4 [0.8–2.3]	2.3 [0.7–8.1]
E1: proctitis			reference	reference	reference
Extra-intestinal manifestations at diagnosis	1.3 [0.6–2.8]	0.6 [0.3–1.4]	1.4 [0.9–2.2]	1.4 [0.9–1.0]	1.3 [0.5–3.1]
Use of immunomodulators	0.6 [0.3–1.1]	0.7 [0.4–1.3]	0.5 [0.3–0.8]*	0.5 [0.3–0.8]*	1.3 [0.7–2.7]
Use of biologicals	0.7 [0.2–2.2]	1.5 [0.8–2.8]	0.8 [0.3–1.7]	0.6 [0.1–1.4]	1.4 [0.6–3.2]
Need for early corticosteroids	1.1 [0.6–2.2]	1.4 [0.8–2.3]	1.7 [1.2–2.4]*	1.8 [1.3–2.6]*	0.9 [0.5–1.9]

\*p < 0.05\*

**Table 3.** Factors associated with hospitalisation and surgery in 273 ulcerative colitis patients with extensive colitis in the Epi-IBD-cohort

	Hospitalisation, all	Hospitalisation, only medical	Surgery
Age at diagnosis [per year]	0.98 [0.97–0.99]*	0.98 [0.96–0.99]*	0.99 [0.96–1.02]
Sex			
Female	1.0 [0.7–1.6]	1.2 [0.8–1.9]	1.0 [0.4–2.5]
Male	reference	reference	reference
Diagnostic delay [per day]	1.0 [1.0–1.0]	1.0 [1.0–1.0]	1.0 [1.0–1.0]
Geographical region			
Eastern Europe	0.8 [0.4–1.5]	0.8 [0.4–1.5]	0.7 [0.2–2.6]
Western Europe	reference	reference	reference
Smoking status at diagnosis			
Currently	0.9 [0.4–2.2]	1.1 [0.5–2.5]	0.5 [0.1–4.2]
Former	1.2 [0.7–1.9]	1.3 [0.8–2.3]	1.2 [0.5–3.0]
Never	reference	reference	reference
Extra-intestinal manifestations at diagnosis	1.4 [0.8–2.6]	1.4 [0.7–2.5]	1.8 [0.6–5.0]
Use of immunomodulators	0.5 [0.2–0.9]*	0.5 [0.3–0.9]*	0.7 [0.3–2.0]
Use of biologicals	1.0 [0.4–2.6]	0.8 [0.3–2.3]	1.8 [0.6–5.5]
Need for early corticosteroids	1.8 [1.2–2.8]*	1.8 [1.2–2.9]*	2.0 [0.8–4.8]
Regression to proctitis or left-sided colitis			
Yes	0.1 [0.01–0.4]*	0.1 [0.01–0.5]*	0.4 [0.1–1.4]
No	reference	reference	reference

\*P < 0.05.

Furthermore, 18 [38%] of those patients went on to receive immunomodulators as their highest treatment step (Western Europe: 17 [44%]; Eastern Europe: 1 [13%]), 13 [28%] were treated with biologics (Western Europe: 9 [23%]; Eastern Europe: 4 [50%]), and seven [15%] had a subsequent colectomy (Western Europe: 7 [18%]; Eastern Europe: 0 [0%]).

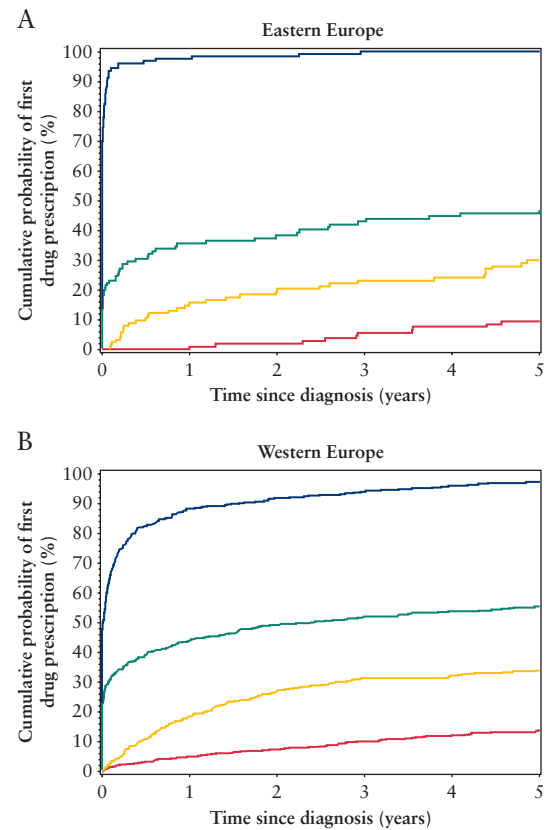
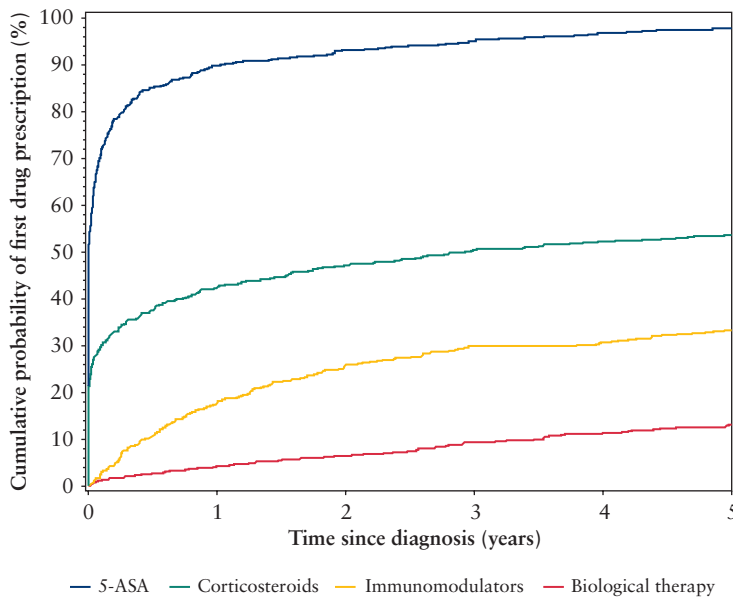
A total of 80 [11%] UC patients were treated with biologics during follow-up (Western Europe: 70 [12%]; Eastern Europe: 10 [8%]; p > 0.05). Most patients received infliximab as the initial type of biological treatment [infliximab: n = 72, 90%; adalimumab: n = 7, 9%; golimumab: n = 1, 1%]. Of the Western European patients, three

[4%] patients had E1, 28 [40%] had E2, and 39 [56%] had E3, whereas in Eastern Europe, two [20%] patients had E1, three [30%] had E2, and five [50%] had E3. The data for treatment given before biological therapy are shown in [Supplementary Table 1, available as Supplementary data at ECCO-JCC online.](#)

### 3.3. Hospitalisation

A total of 163 [23%] patients were hospitalised at least once because of UC. The majority of those [n = 151, 93%] hospitalisations were for UC-related reasons [medical hospitalisation], and the others were due to surgery [n = 12, 7%]. More patients in Western Europe





**Figure 3.** Cumulative 5-year exposures for medical treatment of patients with ulcerative colitis in a European inception cohort for the entire cohort, as well as in A) Eastern Europe and B) Western Europe. 5-ASA, 5-aminosalicylates

[ $n = 142$ , 24%] were hospitalised than in Eastern Europe [ $n = 21$ , 17%;  $p < 0.05$ ] [Figure 5a]. The median time to first hospitalisation was 10 months [IQR: 3–23] and the median number of hospitalisations per patient was one [IQR: 1–2], a figure similar in both Western and Eastern Europe. Data regarding treatment preceding hospitalisation are shown in Supplementary Table 1.

When looking only at medical hospitalisations, 153 [22%] patients were hospitalised at least once after a median of 10 months [IQR: 3–22] until first hospitalisation, with no geographical differences. In Western Europe, 133 [23%] patients were hospitalised as compared with 29 [16%] patients in Eastern Europe [ $p = 0.06$ ] [Figure 5a]. The median number of medical hospitalisations per patient was one [IQR: 1–1], which was similar in Western and Eastern Europe. In Western Europe, one [1%] patient underwent surgery as their highest treatment step before hospitalisation, six [5%] patients received biologics, 20 [15%] patients received immunomodulators, and 70 [53%] received GCS. In Eastern Europe, five [25%] patients received immunomodulators, seven [35%] received GCS, and no patients received biologics or underwent surgery. Predictors associated with medical hospitalisation are shown in Table 2.

### 3.4. Surgery

A total of 43 [6%] UC patients underwent a colectomy during follow-up, of which the majority of operations took place within the first 2 years after diagnosis [ $n = 29$ , 67%] and significantly more came from Western [ $n = 40$ , 7%] than from Eastern [ $n = 3$ , 2%;  $p < 0.05$ ] Europe [Figure 5b]. At 11 months [IQR: 4–31], the median time to colectomy did not differ between regions. Among Western European patients, three [8%] had E1, 16 [40%] had E2,

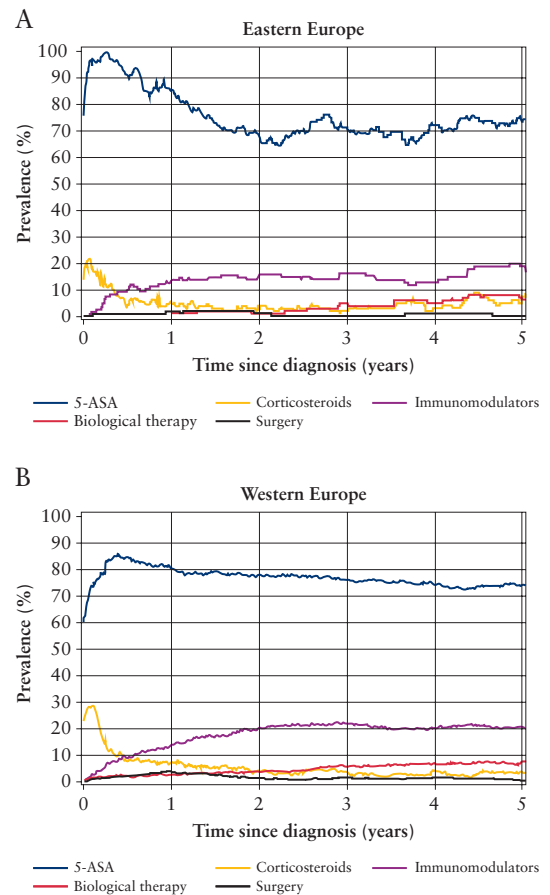
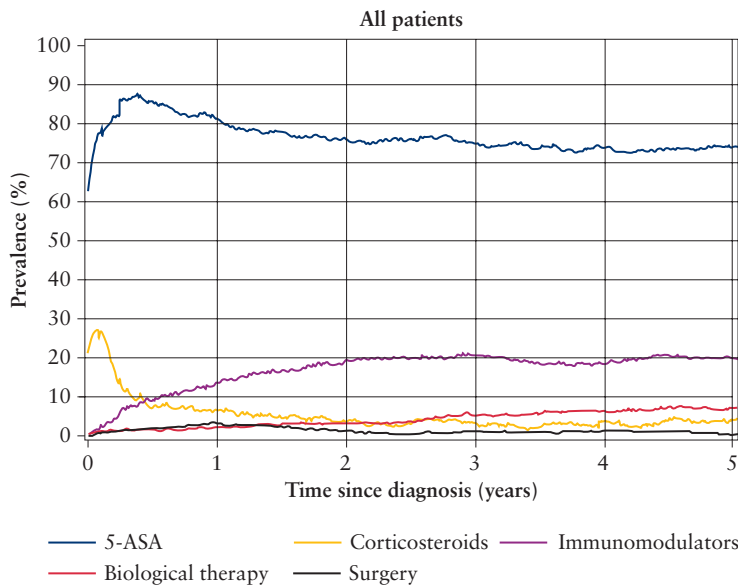
and 21 [53%] had E3, whereas all Eastern European patients had E3. Predictors associated with surgery are shown in Table 2. The difference in colectomy rates between regions was significant in the univariate analysis, but this was not the case in the multivariate Cox regression model [East vs West HR: 0.3 95% CI: 0.1–1.1]. Data regarding the highest treatment step reached before surgery are shown in Supplementary Table 1. Of those 43 patients, 24 [56%] subsequently received a pouch during the follow-up period.

Mayo endoscopic subscores were available for 635 [89%] patients during the first year following their diagnosis. Of those patients, 255 [40%] achieved mucosal healing. Other than those undergoing colectomy during the first year [ $n = 23$ ], patients who did not experience mucosal healing during the first year had a non-significantly increased risk of colectomy in subsequent years [HR: 2.3 95% CI: 0.8–6.2] [Supplementary Figure 2, available as Supplementary data at ECCO-JCC online]. Other covariates, including biological therapy, were not found to influence the risk of colectomy in a statistically significant way, either.

### 3.5. Cancer and death

A total of 14 [2%] patients were diagnosed with 15 cancers a median of 34 months after their diagnosis [IQR: 11–48]. Colorectal cancer occurred in two patients; all others were extra-intestinal cancers [one stomach, three breast, one urinary tract, three lung, three skin, one brain, one cancer in the female genital organs].

During follow-up, eight [1%] patients died a median of 35 months [IQR: 22–44] after their diagnosis. One patient died because of respiratory complications following colectomy, whereas the remaining patients died of non-UC-related causes.



**Figure 4.** The time-varying distribution of ulcerative colitis patients receiving different levels of treatment on any given day during follow-up for the entire cohort, as well as in A) Eastern Europe and B) Western Europe. Patients receiving combination therapy will appear in each of the respective curves, thus the curves will not add up to 100%. 5-ASA, 5-aminosalicylates

#### 4. Discussion

We have presented the real-life disease course and treatment strategies of UC in the era of biological therapy and widespread use of immunomodulators. Although patients were treated earlier and more aggressively with immunomodulators and biological therapy as compared with population-based cohorts from the previous two decades, disease outcomes, including the frequency of colectomy and rates of disease progression, did not differ substantially. Treatment strategies did differ between Eastern and Western Europe in that patients were treated earlier, but not more frequently, with immunomodulators and biological therapy and more patients went untreated in Western Europe; nonetheless, disease outcomes were similar. Finally, we found that immunomodulators reduced the risk of hospitalisation and the risk of progression, but the latter did not appear to be statistically significant.

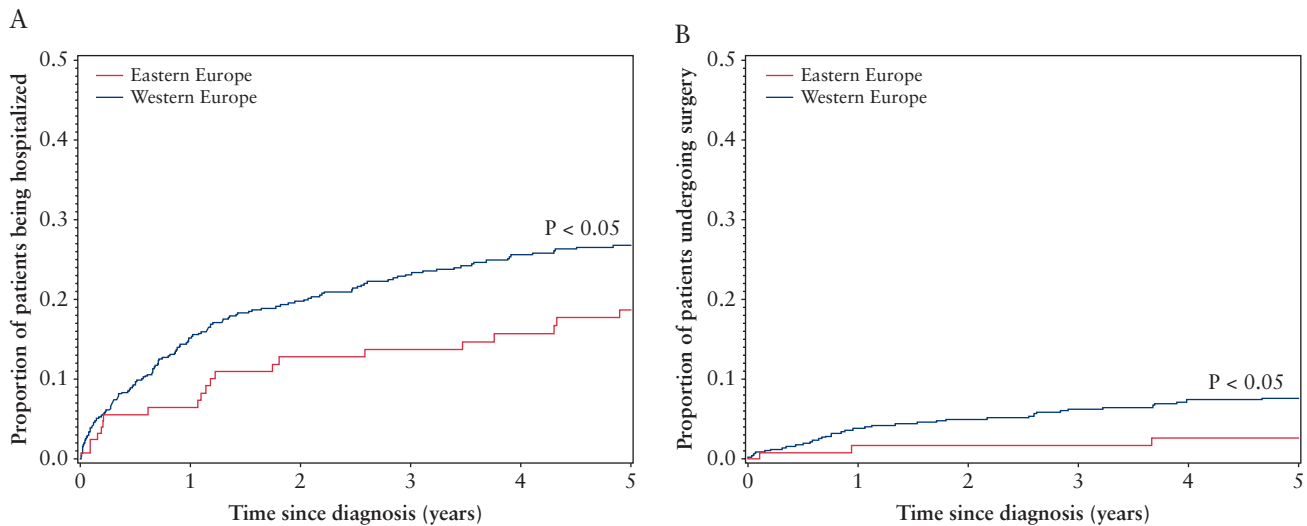
Whether colectomy rates have decreased as a result of recent changes in UC management remains uncertain. In the present cohort, 6% of patients had a colectomy after 5 years, a figure similar both in concurrent cohorts<sup>5,18–20</sup> and in older cohorts from the 1990s.<sup>21,22</sup> Time-trend studies have associated increasing and earlier use of immunomodulators and biological therapy with reduced rates of colectomy.<sup>4,23</sup> However, several recent population-based cohort studies have found that colectomy rates were already decreasing before the advent of biological therapy and have remained stable during the past two decades.<sup>5,18,24</sup> A meta-analysis of population-based cohort

studies also found that colectomy rates 5 years after diagnosis had not decreased over time.<sup>25</sup> Similar to the European Collaborative Study Group of Inflammatory Bowel Disease [EC-IBD] cohort, the majority of patients underwent colectomy during the first 2 years of follow-up,<sup>22</sup> suggesting severe disease activity in those patients. However, after 5 years of follow-up, indications were of colectomy change from fulminant or refractory colitis to, among others, corticosteroid-dependent or chronically active disease. It remains to be proven that current treatment strategies for maintenance therapy can influence the disease course in the long term.

Data about immunomodulators such as azathioprine and their use as disease modifiers in UC are limited, and current clinical practice around azathioprine treatment of UC is based on minimal and controversial evidence.<sup>26</sup> Whereas biological therapy was not associated with the risk of either surgery or hospitalisation, immunomodulators—as was the case in our findings regarding CD<sup>7</sup>—significantly reduced the risk of hospitalisation. Hence, further studies are needed in order to determine their efficacy for treating UC. It is worth mentioning that treatment with immunomodulators was included as a time-dependent variable in the analysis with a 3-month lag time, and that the association was also found to be significant in the subanalysis of patients with extensive colitis.

In our study, significantly fewer patients in Eastern Europe underwent a colectomy than in Western Europe, yet the figures reported in a previous study in Hungary<sup>24</sup> were comparable and





**Figure 5.** Cumulative probability for hospitalisation [A] and surgery [B] during the first 5 years of disease in a European population-based cohort of ulcerative colitis patients.

patient characteristics did not differ between the regions.<sup>27</sup> However, in our multivariate analysis taking also patient and disease characteristics into consideration, geographical region was not significantly associated with the risk of surgery. In the EC-IBD cohort, regional differences in colectomy rates were noted as well, and these cannot be explained by differences in disease course alone.<sup>22</sup> Regional factors such as attitudes towards surgery, availability of treatments, and prevalence of bacterial superinfections might have contributed to these differences.

The extent to which the colon is involved in UC can change over time, having a significant impact on treatment choices, disease severity, and prognosis.<sup>28–30</sup> We found that one in five patients with proctitis or left-sided colitis progressed to extensive colitis, in accordance with a recent systematic review of 41 studies<sup>31</sup> as well as other recent population-based studies.<sup>5,32</sup> Our data therefore indicate that the rate of progression has not changed during the past decade. The data also indicate that the use of biological therapy and immunomodulators does not appear to have statistically reduced the risk of disease progression. Furthermore, of patients in our cohort diagnosed with, or who progressed to, extensive colitis, approximately 30% regressed during follow-up. A recent study from the Swiss IBD cohort found that 16% of patients experienced a regression of extent; however, this difference could be due to differences in study design as this was not a population-based study. Only two Scandinavian population-based cohorts, from 1962 to 1987<sup>33</sup> and 1991 to 1993,<sup>34</sup> have assessed the rates of regression of extent and, to our knowledge, ours is the first population-based cohort study to do so since the introduction of biological therapy. We have also demonstrated that patients diagnosed with extensive colitis, and who experienced a regression in extent due to medical therapy, had a significantly lower risk of hospitalisation but the reduced risk for undergoing a colectomy did not reach statistical significance.

Finally, we have examined treatment choices, as well as changes in treatments over time, in a cohort representative of the whole UC population. The use of biological therapy in UC increased during follow-up but was used in less than 10% of patients on any given day. These figures are similar to those found in other recent cohorts,<sup>35–37</sup> although patients were started on immunomodulators earlier in the present study. In contrast to CD,<sup>7</sup> treatment with biologicals did not

differ between regions, although the treatment duration was longer in Eastern European patients as were the treatments used before initiation of biological therapy. However, and as discussed previously, these differences did not result in different surgery, hospitalisation, or disease progression rates. Choices regarding investigations and medical and surgical treatments, as well as their availability, are closely linked to extra-medical considerations and therefore the differences observed between Western and Eastern Europe might have been caused by considerable variations between national health care systems. A proportion of patients [7%] were treated with corticosteroids for more than 6 months and a similar proportion did not receive any medical treatment at all during follow-up. Whereas this contradicts recent guidelines,<sup>38</sup> these decisions might be influenced by patient or physician preference or patient non-compliance.

Strengths of the present study include the prospective inclusion and follow-up of incident IBD patients diagnosed within well-defined geographical areas. Diagnostic criteria, case ascertainment methods, and the recorded data were all standardised. Several measures previously described<sup>8</sup> ensured that all centres contributed good quality, valid data to this study. The patients were unselected and represent the whole spectrum of disease severity; therefore, the choices of treatment in this cohort are the result of community effectiveness rather than the requirements of a randomised controlled trial, and they all occurred in a real-life clinical setting.

Limitations of this study include its observational design and the heterogeneity of the participating centres in terms of the health care systems of which they are a part. In addition, the distribution of participating centres is skewed, as the Eastern European centres are in mostly low-incident areas<sup>1</sup> and hence a majority of patients in this study originate in Western Europe. However, and as in previous findings,<sup>7,39</sup> the patient populations from Western and Eastern Europe were similar in terms of socioeconomic characteristics, disease classification, diagnostic procedures used, and length of diagnostic delay.<sup>8</sup> Therefore, we have no reason to believe that the region of origin influenced the disease course. However, the absence of geographical differences in treatment outcomes as well as differences in outcomes compared with previous cohorts might not reflect true non-differences but be caused by, for example, lack of power or confounding by indication.

In conclusion, we have found that in this prospective, population-based cohort of unselected UC patients, patients were treated earlier and more aggressively with immunomodulators and biological therapy than were cohorts from the beginning of the biological era. However, 5-year surgery, hospitalisation, and disease progression rates are similar to cohorts from 20 years ago. The use of immunomodulators appeared to improve the disease course of UC in terms of the risk of hospitalisation, but we could not demonstrate a comparable benefit in the use of biological therapy.

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## Conflict of Interest

JB: consulting fees from Celgene, Janssen-Cilag, AbbVie A/S, and Ferring; lecture fees from Abbvie A/S, Pfizer, MSD, and Takeda Pharma A/S; unrestricted grant support from Takeda Pharma A/S. VA: consultancy for Janssen and MSD. R Salupere: consulting fees and/or lecture fees from AbbVie, MSD, Takeda, Janssen-Cilag, R D'Inca: consulting fees from Abbvie, Biocure; and lecture fees from Takeda and Mundipharma. MF: speaker/lecture fees from Abbvie, Ferring, MSD, Takeda, Boehringer, and Hospira. CG-R: lecture fees from Takeda, MSD, Ferring, and Tillots. CE: lecture fees from Takeda. JH: research grants from Janssen, MSD, and Takeda, and lecture and/or consultancy fees from Abbvie, Cellgene, Ferring, Hospira, Janssen, Medivir, MSD, Pfizer, Vifor Pharma, Takeda, and Tillots Pharma. EL: lecture or consultancy fees from MSD, Abbvie, and Ferring Pharmaceuticals. DD: lecture or consultancy fees from AbbVie, Takeda and Janssen. NA: lecture fees from MSD and Jansen. VH: personal fees, non-financial support, and other from MSD, AbbVie, Ferring, Faes Farma, Shire, Falk Pharma, Tillots, Otsuka, Hospira Biologicals, Takeda, Jansen, and Kernpharma Biologics. SC-C: lecture fees from Takeda, MSD, Abbvie. PO: lecture or consultancy fees from Janssen, Takeda, Tillots. LK: lecture fee from Abbvie. LDC: non-financial support from MSD, Abbvie, Ferring, Faes Farma, Shire, Falk Pharma, Tillots, Pfizer, Jansen, and Kernpharma Biologics outside the submitted work. FM: fee for presenting from AbbVie, Ferring, Falk, Hospira, PharmaKern, MSD, Schering, Lab. Vitoria, Vifor, OmPharma. SS: research grants from Takeda, Abbvie, Tillots pharma, Ferring, and speaker fees and advisory board fees from Takeda, Jaansen, AbbVie, MSD, Ferring, Pharmacocosmos, and Tillots. PLL: speaker and/or advisory board member for AbbVie, EGIS, Falk Pharma GmbH, Ferring, Genetech, Jansen, Kyowa Hakko Kirin Pharma, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka Pharma, Pharmacocosmos, Pfizer, Roche, Shire, and Takeda, and has received unrestricted research grant from AbbVie, MSD, and Pfizer. All other authors report no competing interests.

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## Author Contributions

All authors participated in the study design and data acquisition, have critically reviewed the draft manuscript for content, and approved the final version

for publication. JB had full access to the data in the study and takes full responsibility for its veracity and statistical analysis. JB and PM analysed and interpreted the data. JB drafted the manuscript.

## Supplementary Data

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

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