



Original Article

# Treatment Steps, Surgery, and Hospitalization Rates During the First Year of Follow-up in Patients with Inflammatory Bowel Diseases from the 2011 ECCO-Epicom Inception Cohort

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**Conference presentation:** 10<sup>th</sup> Congress of ECCO, Barcelona, Spain, 2015

## Abstract

**Background and Aims:** The ECCO-EpiCom study investigates the differences in the incidence and therapeutic management of inflammatory bowel diseases [IBD] between Eastern and Western Europe. The aim of this study was to analyse the differences in the disease phenotype, medical therapy, surgery, and hospitalization rates in the ECCO-EpiCom 2011 inception cohort during the first year after diagnosis.

**Methods:** Nine Western, five Eastern European centres and one Australian centre with 258 Crohn's disease [CD], 380 ulcerative colitis [UC] and 71 IBD unclassified [IBDU] patients [female/male: 326/383; mean age at diagnosis: 40.9 years, SD: 17.3 years] participated. Patients' data were registered and entered in the web-based ECCO-EpiCom database [www.epicom-ecco.eu].

**Results:** In CD, 36 [19%] Western Europe/Australian and 6 [9%] Eastern European patients received biological therapy [ $p = 0.04$ ], but the immunosuppressive [IS] use was equal and high in these regions [Eastern Europe vs Western Europe/Australia: 53% vs 45%;  $p = 0.27$ ]. Surgery was performed in 17 [24%] CD patients in Eastern Europe and 13 [7%] in Western Europe/Australia [ $p < 0.001$ ,  $p\text{LogRank} = 0.001$ ]. Of CD patients from Eastern Europe, 24 [34%] were hospitalized, and 39 [21%] from Western Europe/Australia, [ $p = 0.02$ ,  $p\text{LogRank} = 0.01$ ]. In UC, exposure to biologicals and colectomy rates were low and hospitalization rates did not differ between these regions during the 1-year follow-up period [16% vs 16%;  $p = 0.93$ ].

**Conclusions:** During the first year after diagnosis, surgery and hospitalization rates were significantly higher in CD patients in Eastern Europe compared with Western Europe/Australia, whereas significantly more CD patients were treated with biologicals in the Western Europe/Australian centres.

**Keywords:** Inflammatory bowel diseases; surgery; hospitalization

## 1. Introduction

Inflammatory bowel diseases [IBD], including Crohn's disease [CD] and ulcerative colitis [UC], are chronic, relapsing conditions requiring frequent contact by the patients with healthcare providers.

Hospitalization and surgery rates are important outcome measures and indicators of disease severity in IBD. The management of both CD and UC has changed significantly in the past two decades, with early acceleration of therapeutic steps including introduction of immunosuppressive [IS] and anti-TNF therapy. A recent meta-analysis by Bernstein *et al.* for the International Organization for the Study of Inflammatory Bowel Diseases [IOIBD], analysing the surgery and hospitalization rates in population-based studies from the pre-biological era, reported declining surgery rates and unchanged/declining hospitalization rates, but the impact of the biological therapy on the disease course, including surgical and hospitalization rates, is awaited.<sup>1</sup>

The European Crohn's and Colitis Organisation–Epidemiological Committee [ECCO-EpiCom] study initiated in 2010 investigates the differences in the incidence, disease characteristics, and therapeutic management of IBD between Eastern and Western Europe. The higher incidence rates for IBD found in the Western European centres in the 2010 inception cohort were repeated in the 2011 inception cohort.<sup>2,3,4</sup>

The 1-year follow-up of the 2010 cohort revealed higher use of biological agents in Western Europe compared with Eastern Europe, but surgical and hospitalization rates did not differ between these two geographical regions and they were similar to the results reported in recent population-based studies.<sup>5</sup>

Interestingly, in the 2011 inception cohort, the number of CD patients with complicated disease behaviour [stricturing and/or penetrating  $\pm$  perianal involvement] was more frequent in the Eastern European centres compared with the Western European centres. The disease characteristics were not different between the Western European and Australian CD patients.<sup>3</sup>

In the present study our aim was to compare the disease phenotype, therapeutic strategy, and surgery and hospitalization rates during the first year after diagnosis between the participating Eastern European and Western Europe/Australian centres in the 2011 ECCO-EpiCom inception cohort.

## 2. Materials and Methods

A total of 14 centres—4 centres from Eastern Europe, 9 centres from Western Europe and 1 centre from Australia—participated in the 1-year follow-up of the ECCO-EpiCom 2011 inception cohort.

The methodology of the case ascertainment and data collection of the present cohort was the same as the ECCO-EpiCom 2010 inception cohort.<sup>6</sup>

Newly diagnosed IBD patients between 1 January and 31 December 2011 were included in the 2011 ECCO-EpiCom inception cohort. For participation in the incident cohort, a well-defined up-take area with up-to-date demographics on the background population [age and gender distribution] was required. General practitioners and specialists in the local area were informed about the inception cohort by local investigator meetings or letters, and centres contacted them twice a year regarding patient file information of incident IBD patients. Patients' data regarding disease characteristics, medical therapy, and events such as hospitalizations, surgery, pregnancy, cancer, and death were registered and data were entered by physicians and/or IBD specialist trained nurses into the web-based EpiCom database [www.epicom-ecco.eu] every third month during the first year after diagnosis. The validity of the data was enhanced by built-in control and validation tests, manual data standardisation and random audits of case ascertainment and data quality.<sup>3,7</sup>

For identifying CD, UC, and IBD unclassified [IBDU], the Copenhagen Diagnostic Criteria<sup>8,9</sup> were applied by all participating centres. Location and disease behaviour of CD, as well as the extent of UC, were defined according to the Montreal classification.<sup>10</sup>

Definition of treatment steps: treatment was grouped into five levels stratified by therapeutic potency: 5-aminosalicylates [5-ASA] [oral and/or topical 5-ASA treatment  $\pm$  topical steroids], glucocorticosteroids [GCS] [oral steroids  $\pm$  5-ASA or topical steroids], immunosuppressives [azathioprine, 6-mercaptopurine, cyclosporine or methotrexate  $\pm$  steroids], biologicals [infliximab or adalimumab in combination with any of the above], and surgery [major abdominal surgery due to IBD regardless of medical treatment before surgery].<sup>2,3,5,6</sup>

### 2.1. Statistical considerations

The statistical analyses were performed using SPSS software v. 20.0 [Chicago, IL].

Frequency distributions were performed for categorical data and calculation of means and standard deviations for continuous variables. Differences between groups after 1 year were analysed by chi-square test for categorical data, and also in time-dependent models [Kaplan-Meier analysis and Log-rank test]. A multivariate logistic regression model was used to assess the predictive factors for surgery, hospitalization, and biological therapy; factors with  $p$ -values  $< 0.2$  were included in the logistic regression model; smoking and gender were included arbitrarily, irrespective of the  $p$ -values.

A  $p$ -value of  $< 0.05$  was considered statistically significant.

## 2.2. Ethical statement

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

## 3. Results

Out of the 711 adult patients of the 2011 ECCO-EpiCom inception cohort, 258 [36%] patients with Crohn's disease [CD], 380 [54%] with ulcerative colitis [UC], and 71 [10%] with IBD unclassified [IBDU], were included in the 1-year follow-up. In all, 178 [25%] patients were diagnosed in Eastern, 460 [65%] in Western Europe and 71 [10%] patients in Australia. Patient characteristics are shown in Table 1.

In total, 69 [10%] patients did not have follow-up after diagnosis: 22 [32%] patients were lost to follow-up, 46 [67%] patients did not want to participate, and 1 [1%] patient moved away from the uptake area.

During the first year of follow-up, 12 [2%] patients from Western Europe/Australia and no patients from Eastern Europe changed diagnosis. Out of the 10 IBDU patients, 6 patients changed diagnosis to CD and 4 patients to UC, and 2 UC patients changed diagnosis to CD.

### 3.1. Treatment steps during the first year of follow-up

The probability of highest level of treatment steps reached within 1 year after diagnosis in CD and UC in Eastern and Western Europe/Australia is illustrated in Figures 1 and 2 [in CD  $p = 0.001$ , and in UC  $p = 0.003$  for the maximum treatment steps at 1 year between Eastern Europe and Western Europe/Australia].

In every region, a high number of CD patients received 5-ASA [Eastern Europe: 74% Western Europe/Australia: 56%;  $p = 0.01$ ,  $p$ LogRank = 0.001], which was associated with disease location [L1 ileal] and B1 [non stricturing-non-penetrating] disease behaviour [ $p$ LogRank = 0.001] in the Eastern European CD patients. Respectively, 61% and 67% of the patients from Eastern Europe and Western Europe/Australia received systemic steroids [ $p = 0.45$ ,  $p$ LogRank = 0.875]. Immunosuppressive [IS] therapy was introduced in 53% of the patients in Eastern Europe and 45% of the patients in Western Europe/Australia [ $p = 0.27$ ,  $p$ LogRank = 0.109]. The median time to IS therapy was 36 days [0–363].

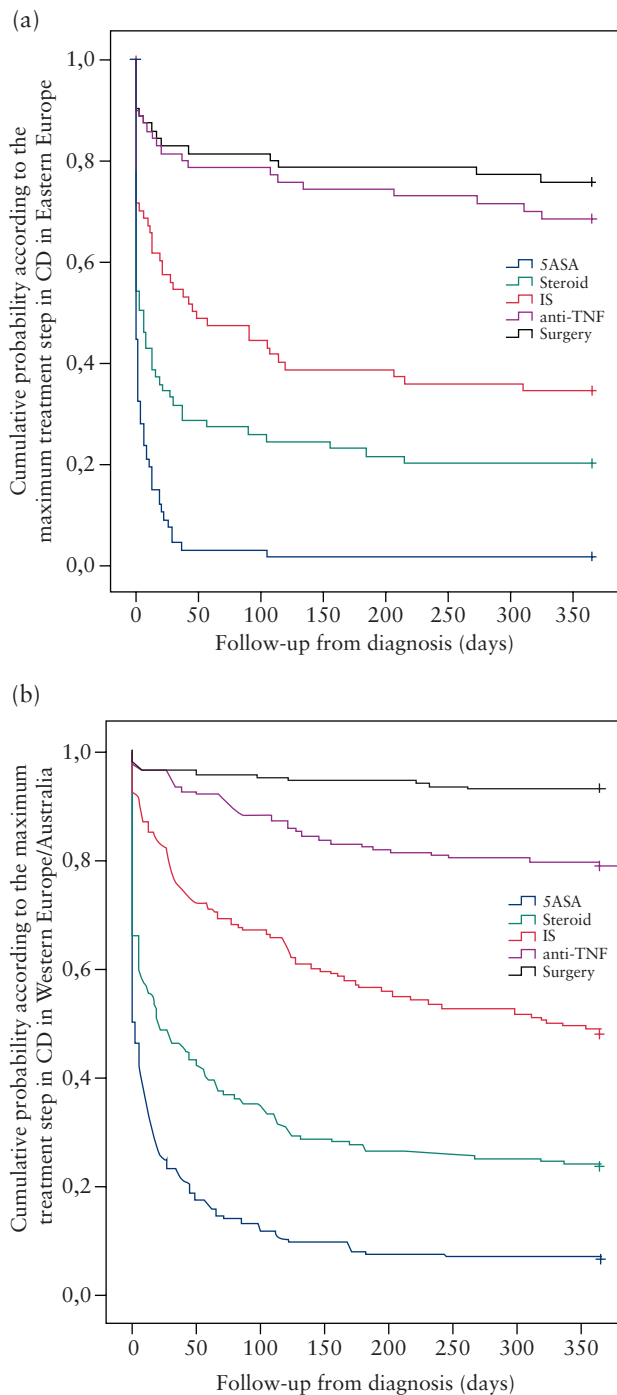
Overall, the need for IS therapy was associated with disease behaviour [B2/B3  $\pm p$ ; Supplementary Figure S1a, available as Supplementary data at JCC online; [ $p$ LogRank  $< 0.001$ ] and L3 [ileocolonic] location [ $p$ LogRank = 0.037].

**Table 1.** Characteristics of patients with inflammatory bowel diseases in the ECCO-EpiCom 2011 inception cohort

	Western Europe/Australia			Eastern Europe		
	CD	UC	IBDU	CD	UC	IBDU
No. of patients [%]*	188 [35]	274 [52]	69 [13]	70 [39]	106 [60]	2 [1]
Males [%]*	106 [56]	152 [56]	41 [59]	33 [47]	50 [47]	1 [50]
Median age at diagnosis, years [range]	36 [17–79]	40 [15–90]	44 [18–89]	35 [16–72]	35 [15–87]	25 [23–27]
Median time to diagnosis, months [range]	4.0 [0–116]	2.4 [0–359]	2.5 [0–92]	3.1 [0.3–65]	2.2 [0–312]	1.4 [1.3–1.5]
Smoking status [%]*						
Never	81 [49]	114 [48]	25 [44]	34 [51]	65 [66]	1 [50]
Current	49 [30]	28 [12]	10 [17]	17 [26]	9 [9]	1 [50]
Former	35 [21]	93 [40]	22 [39]	15 [23]	25 [25]	0 [0]
Disease behaviour [%]*						
B1	122 [65]			34 [49]		
B2	26 [14]			18 [26]		
B3	18 [10]			9 [13]		
B1+p	19 [10]			6 [8]		
B2+p	3 [1]			1 [1]		
B3+p	0 [0]			2 [3]		
Disease location						
L1	54 [29]			28 [40]		
L2	47 [25]			12 [17]		
L3	36 [19]			19 [27]		
L4	11 [6]			1 [1]		
L1+L4	18 [10]			6 [9]		
L2+L4	6 [3]			3 [5]		
L3+L4	16 [8]			1 [1]		
Disease extent [%]						
E1		72 [26]			24 [23]	
E2		105 [38]			49 [47]	
E3		97 [35]			33 [30]	

CD, Crohn's disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified; B1, non-stricturing, non-penetrating; B2, stricturing; B3, penetrating; L1, ileal; L2, colonic; L3, ileocolonic; p, perianal disease, E1, proctitis; E2, left-sided colitis; E3, extensive colitis.

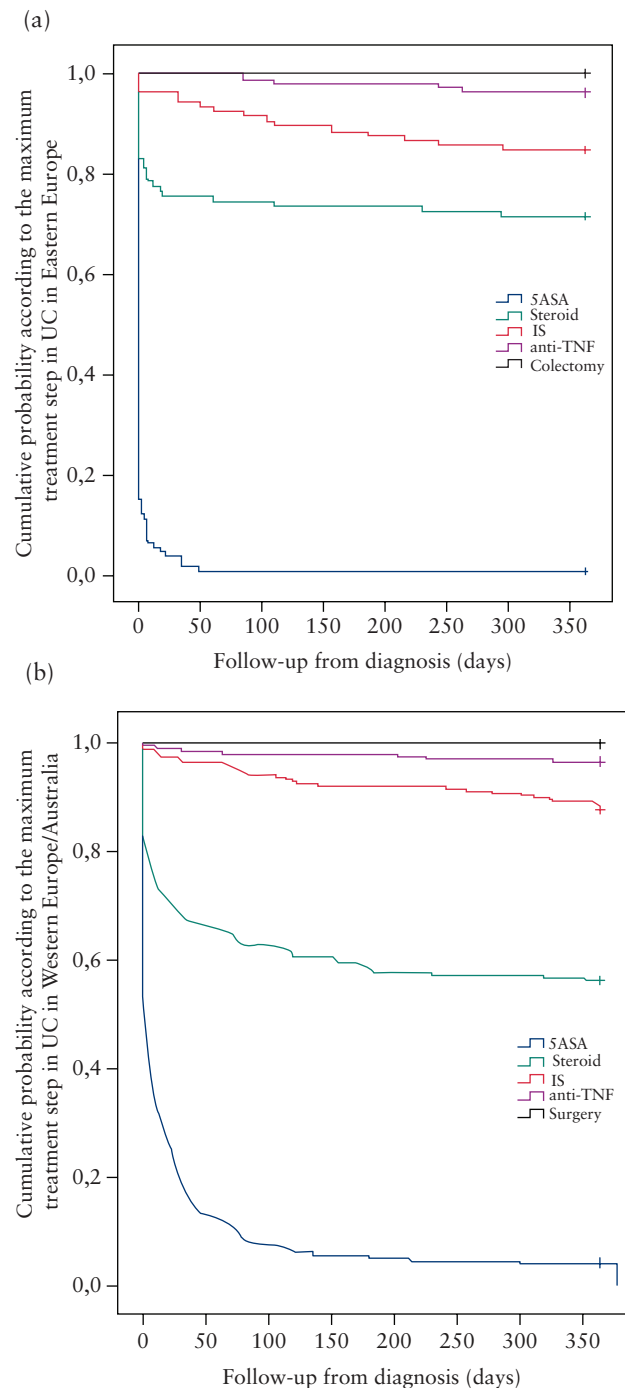
\*  $p < 0.05$ ;  $p$ -values are given for comparison between Eastern Europe and Western Europe/Australia.



**Figure 1.** [a] Cumulative probability of the highest level of treatment steps in patients with Crohn's disease in Eastern Europe. [b] Cumulative probability of the highest level of treatment steps in patients with Crohn's disease in Western Europe/Australia.

In UC, 99% of the patients in Eastern Europe and 95% in Western Europe/Australia were treated with 5-ASA [ $p = 0.06$ ]. Interestingly, the percentage of patients receiving systemic steroids was higher in Western Europe/Australia compared with Eastern Europe [43% vs 26%,  $p = 0.03$ ,  $p\text{LogRank} = 0.01$ ]. IS therapy was used by 13% of the patients in Eastern Europe and 12% in Western Europe/Australia [ $p = 0.76$ ].

Time to 5-ASA, IS or biological therapy was not different between Eastern and Western Europe/Australia. Time to 5-ASA and steroid



**Figure 2.** [a] Cumulative probability of the highest level of treatment steps in patients with ulcerative colitis in Eastern Europe. [b] Cumulative probability of the highest level of treatment steps in patients with ulcerative colitis in Western Europe/Australia.

treatment was dependent on disease extent [ $p\text{LogRank}_{5\text{-ASA}} = 0.007$  and  $p\text{LogRank}_{\text{steroid}} < 0.001$ ].

### 3.2. Biological therapy

In Eastern Europe, 6 [9%] CD patients were treated with biological therapy compared with 36 [19%] CD patients in Western Europe/Australia [ $p = 0.04$ ]. The median time to biological therapy was 122 days [7–365]. In Eastern Europe, all CD patients received

infliximab [IFX], and in Western Europe/Australia 20 [56%]/16 [44%] patients were treated with IFX/adalimumab [ADA]. In both Eastern Europe and Western Europe/Australia, disease behaviour [B3 penetrating] was the driver for biological therapy [ $p$ LogRank = 0.035; Figure S1b, available as Supplementary data at JCC online]. In a multivariate logistic regression model including gender, smoking, disease location, disease behaviour, presence of perianal disease, and geographical region, independent predictors for biological therapy were disease behaviour, presence of perianal disease, and geographical region (disease behaviour:  $p = 0.003$ , odds ratio [OR]: 2.04, 95% confidence interval [CI]: 1.27–3.26; perianal disease:  $p = 0.008$ , OR: 3.52, 95% CI: 1.39–8.94; geographical region:  $p = 0.02$ , OR: 3.21, 95% CI: 1.21–8.5). In UC, 5 [5%] patients from Eastern Europe and 12 [4%] patients from Western Europe/Australia were administered biological therapy [ $p = 0.89$ ]. All Eastern European UC patients received IFX, whereas 10 [83%]/2 [17%] Western European/Australian patients were administered IFX/ADA treatment.

In Western Europe/Australia, 2 [3%] IBDU patients were treated with biological agents.

### 3.3. Hospitalization

In Eastern Europe, 24 [34%] CD patients were hospitalized compared with 39 [21%] patients in Western Europe/Australia [ $p = 0.02$ ,  $p$ LogRank = 0.01; Figure 3]. Patients with ileocolonic localisation  $\pm$  upper gastrointestinal [GI] involvement [L3  $\pm$  L4,  $p$ LogRank<sub>L3</sub> = 0.007,  $p$ LogRank<sub>L3+L4</sub> < 0.001] and complicated disease behaviour [ $p$ LogRank<sub>B1 vs B2/B3</sub> < 0.001,  $p$ LogRank<sub>B2 vs B3</sub> = 0.05; Figure S1c, available as Supplementary data at JCC online] were more frequently hospitalized. Within the first year after diagnosis, 17% of the Eastern European and 21% of the Western European/Australian CD patients were admitted for the second time with complicated disease behaviour as major driver [ $p$ LogRank = 0.008; 69% of these patients had stricturing and/or penetrating disease behaviour].

In UC, 17 [16%] patients from Eastern Europe and 45 [16%] patients from Western Europe/Australia were hospitalized [ $p = 0.93$ ] and of these 12% from Eastern Europe and 13% from Western Europe/Australia required a second hospitalization.

In IBDU, 13 [19%] patients were hospitalized in Western Europe/Australia during the first year after diagnosis, with a second hospitalization rate of 38%.

### 3.4. Surgery

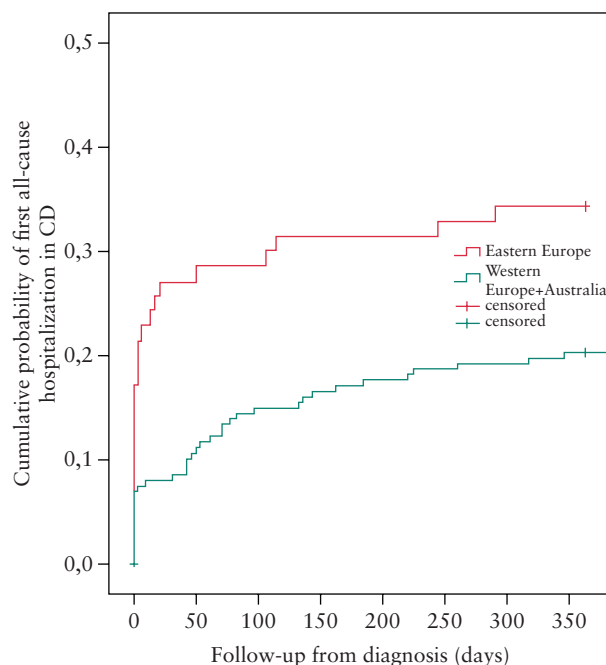
In CD, 17 [24%] patients from Eastern Europe and 13 [7%] patients from Western Europe/Australia underwent surgery within the first year after diagnosis [ $p < 0.001$ ,  $p$ LogRank = 0.001; Figure 4]. In Eastern Europe, the need for surgery was associated to ileal-only location and stricturing behaviour [ $p$ LogRank<sub>Loc</sub> = 0.008,  $p$ LogRank<sub>Beh</sub> < 0.001]. In both regions, disease behaviour was the major driver for surgery [ $p$ LogRank < 0.001; Figure S1d, available as Supplementary data at JCC online.]. One CD patient from Eastern Europe and one from Western Europe/Australia required reoperation within the first year after diagnosis. In Western Europe/Australia, five CD patients received biological therapy before surgery. Out of these patients, three patients had stricturing and two patients had penetrating disease behaviour, and the disease location was ileal in three and colonic in two patients. In Eastern Europe, biological therapy was not introduced before surgical procedure in CD patients. In a multivariate logistic regression model, disease behaviour and geographical region were independent predictors for surgery [Table 2].

In UC, 1 [0.4%] patient from Western Europe/Australia underwent colectomy.

**Table 2.** Logistic regression: predictive factors for surgery in patients with Crohn's disease.

Factor	Coefficient	$p$ -Value	OR	95% CI
Gender	-0.802	0.131	0.45	0.16–1.27
Smoking	0.258	0.355	1.29	0.75–2.23
Disease location	-0.072	0.620	0.93	0.7–1.24
Disease behaviour	2.054	<0.001	7.80	3.97–15.32
Perianal disease	-1.85	0.137	0.16	0.01–1.8
Geographical region	-1.67	0.002	0.19	0.07–0.54

Geographical region: Eastern Europe and Western Europe/Australia; OR, odds ratio; CI, confidence interval.



**Figure 3.** Cumulative probability of first all-cause hospitalization in patients with Crohn's disease in Eastern and Western Europe/Australia,  $p$ LogRank = 0.01.

Two [3%] IBDU patients from Western Europe/Australia had a surgical procedure performed within the follow-up period.

### 3.5. Death

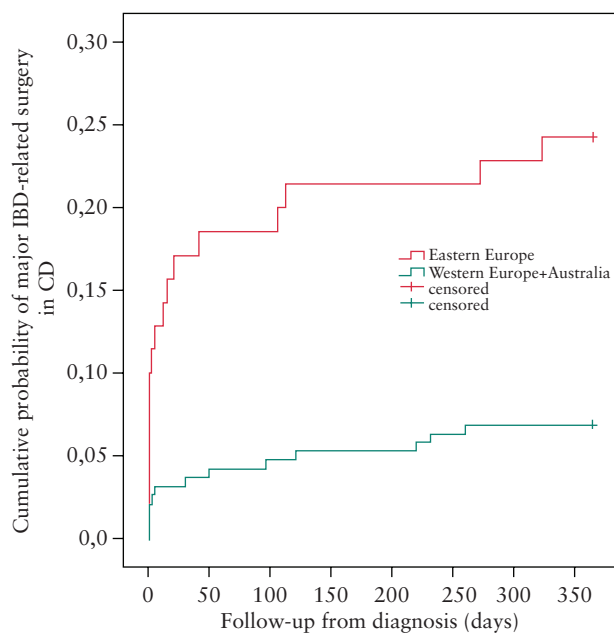
Three [0.4%] patients died during the first year of follow-up; one CD patient with ileal localisation and penetrating disease behaviour from Eastern Europe died due to sepsis after IBD-related major surgery. One CD and one UC patient from Western Europe died from non-IBD-related causes.

### 3.6. Cancer

One gastrointestinal *in situ* carcinoma and three cases of extra-intestinal cancer occurred in four [0.6%] Western European/Australian patients [two CD, one UC, and one IBDU] during the follow-up period with, respectively, dysplastic polyp of the sigmoid colon, cancer of the respiratory and intrathoracic organs, skin cancer, and breast cancer. The UC patient with a dysplastic polyp of the sigmoid colon underwent a surgical resection.

## 4. Discussion

In this pan-European population-based inception cohort of patients with IBD, hospitalization and surgery rates in CD differed



**Figure 4.** Cumulative probability of major IBD-related surgery in patients with Crohn's disease in Eastern and Western Europe/Australia,  $p$ LogRank = 0.001.

significantly between Eastern and Western Europe/Australia and there was a higher use of biologicals in Western Europe/Australia.

Significantly more CD patients from Eastern Europe underwent a surgical procedure within the first year of follow-up compared with Western Europe/Australia [24% vs 7%]. The corresponding rate during the first 3 months after diagnosis was 14% in the Eastern European CD patients, indicating early and inevitable surgeries with more than half of these cases having surgery by 1 year.<sup>3</sup> Interestingly, similar early surgery rates were reported by a retrospective cohort study by Cosnes *et al.* including CD patients diagnosed between 1978 and 2002; 15% of the patients underwent a surgical procedure within the first 3 months following diagnosis, but after the first 3 months, the surgery rate was 3.3–5.7% with no significant change over the 26 years.<sup>11</sup> In contrast, surgery rates found in Western Europe/Australia are similar or somewhat lower compared with the results of recent population-based studies.<sup>5,12,13,14</sup>

As the disease behaviour was the major driver for surgical procedures in both regions, the higher surgery rates observed in Eastern European CD patients can be explained by the differences in the disease phenotype between the Eastern European and Western European/Australian CD patients, with a significantly higher percentage of patients with complicated disease behaviour in Eastern Europe.

Ileal-only localisation and stricturing disease behaviour were associated with the need for surgery in CD patients from the participating Eastern European centres. This may partly represent a treatment decision for limited surgery driven by the clinician rather than the disease phenotype, as highlighted also in the logistic regression model. Of note, significantly more patients with B2 behaviour received biological therapy in Western Europe/Australia compared with Eastern Europe (27.6% vs 5.3% [1 patient],  $p = 0.05$ ) during the first year after the diagnosis. This result corresponds to the findings of the Inflammatory Bowel South-Eastern Norway [IBSEN] population-based cohort study conducted between 1990 and 1994, where terminal ileal localisation, stricturing, and penetrating disease behaviour were independent risk factors for surgery.<sup>15</sup> In the population-based cohort study from Veszprem Province, Hungary, ileal

(hazard ratio [HR]: 2.35, 95% CI: 1.6–3.45) or ileocolonic [HR: 1.79, 95% CI: 1.19–2.68] location and stricturing disease behaviour at diagnosis [HR: 4.33, 95% CI: 2.95–6.36 vs inflammatory disease] were predictors for the first surgical procedure.<sup>16</sup> In the population-based cohort study by Silverstein *et al.*, lifetime clinical course and costs of Crohn's disease were calculated in Olmsted County, MN. Of note, despite high initial costs, well-timed surgeries for limited disease resulted in the longest remission periods during follow-up.<sup>17</sup>

In CD, a significantly higher hospitalization rate was found in the Eastern European centres compared with the Western European centres [34% vs 21%,  $p = 0.02$ ]. In the meta-analysis from Bernstein *et al.*, hospitalization rates in the population-based studies from the pre-biological era were varying between 25–83% ,with the highest rates observed in the first year following the CD diagnosis.<sup>1</sup>

In the present cohort, extensive [ileocolonic] disease location and complicated disease behaviour at diagnosis were associated with the need for hospitalizations. These results are in concordance with the findings of previous population-based inception cohort from Olmsted County, MN, in patients diagnosed from 1970–2004 and followed up until mid-2009<sup>18</sup>, and of the 2010 ECCO-EpiCom cohort.<sup>5</sup> Of note, hospitalization rates and access to biological therapy should be interpreted with caution due to significant differences in local insurance policies and ethnic background across countries.

The higher use of biological therapy in the Western European/Australian centres is in line with the results from the 2010 ECCO-EpiCom cohort.<sup>5</sup> The impact of this more aggressive medical therapeutic approach on long-term disease course and surgery rates needs to be further evaluated.

In conclusion, in this prospective, population-based inception cohort of IBD patients, higher surgery and hospitalization rates were found in CD patients in the Eastern European centres, associated with the higher proportion of stricturing and penetrating disease behaviour in this patient group. More than half of the surgical procedures were performed within the first 3 months after diagnosis. In Eastern Europe, ileal-only location and stricturing disease behaviour were predictors for surgery, which may partly represent a medical decision. Interestingly, there was still a high exposure of 5-ASAs in CD in both regions. In UC, disease extent, surgery and hospitalization rates, and use of biologicals did not differ between Eastern Europe and Western Europe/Australia and surgical rates were reassuringly low.

## Funding

This work was supported by the European Crohn's and Colitis Organisation [ECCO Grant 2014].

## Conflict of Interest

No author reported any potential conflict of interest.

## Acknowledgements

The study was initiated by the EpiCom study group. Z Vegh, J Burisch, P Munkholm, and P Lakatos performed the study design, data capture, and data validation. Z Vegh and P Lakatos performed the statistical analyses. Z Vegh and P Lakatos drafted the manuscript. Z Vegh, J Burisch, N Pedersen, I Kaimaklitois, D Duricova, M Bortlik, S Avnstrøm, K Kofod Vinding, J Olsen, KR Nielsen, KH Katsanos, EV Tsianos, L Lakatos, D Schwartz, S Odes, R D'Incà, M Beltrami, G Kiudelis, L Kupcinskis, A Jucov, S Turcan, LF Barros, F Magro, D Lazar, A Goldis, L de Castro, V Hernandez, O Niewiadomski, S Bell, E Langholz, P Munkholm, and P Lakatos performed the data capture, revised the manuscript, and approved the final version of the manuscript. This work is a part of Z Vegh's PhD thesis. We are grateful to J Williams

[Australia], A Nicolaou [Cyprus], P Weimers [Denmark], R Seerup [Denmark], K Stroggili [Greece], G Demenyi [Hungary], S Kramli [Hungary], M Giannotta [Firenze, Italy], A De Padova [Forli, Italy], L Jonaitis [Lithuania], I Valantiene [Lithuania], A Fernandez [Spain], and L Sanroman [Spain] for their contribution to patient inclusion and entering of data.

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