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Does Hospitalization Predict the Disease Course in Ulcerative Colitis? Prevalence and Predictors of Hospitalization and Re-Hospitalization in Ulcerative Colitis in a Population-based Inception Cohort (2000-2012)

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ABSTRACT

Background & Aims: Limited data are available on the hospitalization rates in population-based studies. Since this is a very important outcome measure, the aim of this study was to analyze prospectively if early hospitalization is associated with the later disease course as well as to determine the prevalence and predictors of hospitalization and re-hospitalization in the population-based ulcerative colitis (UC) inception cohort in the Veszprem province database between 2000 and 2012.

Methods: Data of 347 incident UC patients diagnosed between January 1, 2000 and December 31, 2010 were analyzed (M/F: 200/147, median age at diagnosis: 36, IQR: 26-50 years, follow-up duration: 7, IQR 4-10 years). Both in- and outpatient records were collected and comprehensively reviewed.

Results: Probabilities of first UC-related hospitalization were 28.6%, 53.7% and 66.2% and of first re-hospitalization were 23.7%, 55.8% and 74.6% after 1-, 5- and 10- years of follow-up, respectively. Main UC-related causes for first hospitalization were diagnostic procedures (26.7%), disease activity (22.4%) or UC-related surgery (4.8%), but a significant percentage was unrelated to IBD (44.8%). In Kaplan-Meier and Cox-regression analysis disease extent at diagnosis (HR extensive: 1.79, p=0.02) or at last follow-up (HR: 1.56, p=0.001), need for steroids (HR: 1.98, p<0.001), azathioprine (HR: 1.55, p=0.038) and anti-TNF (HR: 2.28, p<0.001) were associated with the risk of UC-related hospitalization. Early hospitalization was not associated with a specific disease phenotype or outcome; however, 46.2% of all colectomies were performed in the year of diagnosis.

Conclusion: Hospitalization and re-hospitalization rates were relatively high in this population-based UC cohort. Early hospitalization was not predictive for the later disease course.

Key words: ulcerative colitis – population-based – hospitalization – disease course – predictors.

Abbreviations: AZA: azathioprine; EIM: extraintestinal manifestation; IBD: inflammatory bowel disease; TNF: tumor necrosis factor; UC: ulcerative colitis.

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic, progressive diseases. Ulcerative colitis (UC) has a variable course; the majority of patients experience multiple relapses repetitively, while some patients experience chronic continuous symptoms, eventually developing complications with multiple possible outcomes from necessitating hospitalization or surgery. The majority of UC patients are managed on an outpatient basis [1]; yet the number of patients requiring colectomy is continually increasing. In addition, medical and/or surgical hospitalization events contribute significantly to the economic burden of the disease [2]. In UC, hospitalization usually reflects disease severity and lack of response to medical therapy, and is associated with the need for colectomy and mortality. In the Oxford cohort, the need for hospitalization for acute severe colitis was the most important predictor for colectomy [3].

Limited data are available on hospitalization and/or re-hospitalization rates in UC in population-based cohorts.

The majority of the studies assessed the need for colectomy in UC [4]. Most studies investigating surgical requirements in UC were published before the biologics era and the shift in medical therapeutic strategy to early aggressive combined immunosuppression. In one of the earliest studies from Denmark, 235 out of 1,161 patients underwent colectomy during the 25-year follow-up study period (1962-1987). The colectomy rate was 9% in the year of the diagnosis and 3% in the following 4 years and thereafter 1% per year. The cumulative colectomy rate was 24%, 30% and 32% after 10, 15, 25 years after diagnosis [1]. In contrast, in a relatively recent publication from the IBSEN group, a lower colectomy rate (7.5%) during the first 5 years of follow-up in patients diagnosed between1990-1993 was reported and the cumulative colectomy rate was 9.8% during the 10-year follow-up in the same cohort [5]. Of note, 71% of the colectomies were performed in the first 2 years after the diagnosis [6]. Already these studies highlight the importance of surgery-related hospitalization requirements in the early disease course in UC.

There were only few data published on hospitalization rates in UC. In a population-based study from Canada the age adjusted hospitalization rate in UC was 12.6-13.3 per 100,000 per year between 1994 and 2001, during a 7-year follow-up. In addition, 33.7% of the patients required at least one readmission. The average length was 11 days and about 55% of all hospitalizations were surgery-related [7].

In a study from the Olmsted County, the cumulative probability of first hospitalization was 29.4% at 5 years, 38.7% at 10 years, 49.2% at 20 years, in the 369 patients diagnosed between 1970 and 2004. Early need for corticosteroids and early need for hospitalization were independent predictors of hospitalization. The cumulative probability of first hospitalization increased with successive decades of diagnosis. In addition, the cumulative probability of colectomy in the same cohort was 13.1% at 5 years, 18.9% at 10 years and 25.4% at 20 years [8]. Interestingly, increasing hospitalization rates were reported in the United States from 1990 to 2003 in both IBD in the National Hospital Discharge Survey [9], with 8.2 to 12.4 per 100,000 people for UC and in the Nationwide Inpatient Sample (increasing from 56,911 in 1998 to 86,611 in 2007) [10].

The aim of the present study was to prospectively analyze the prevalence and predictors of hospitalizations and re-hospitalizations in a population-based inception cohort from Veszprem province in the early years of the biological era, in patients diagnosed between January 1, 2000 and December 31, 2010, with follow-up until December 31, 2012. Our additional aim was to investigate whether an early need for hospitalization was associated with negative disease outcomes or treatment strategy.

METHODS

Patients

Three hundred forty-seven incident UC patients (M/F: 200/147, median age at diagnosis: 36 years; IQR, interquartile range 26-50 years, median follow-up: 7 years; IQR 4-10 years) diagnosed between January 1, 2000 and December 31, 2010 were included in this study. Both in- and outpatient records were collected from the Veszprem province database and comprehensively reviewed.

A more detailed description of our data collection method, case ascertainment, geographical and socioeconomic background of the province, and the Veszprem Province IBD Group was published in our previous epidemiological studies [11, 12].

Methods

Ulcerative colitis diagnosis was based on the Lennard-Jones Criteria [13]. The disease phenotype (age at onset, duration, disease extent) was determined according to the Montreal Classification [14]. Medical records, including data regarding the presence of major extraintestinal manifestations (EIM), previous frequency of flare-ups (frequent flare-up: >1 clinical relapse/year) [15], previous surgical procedures (colectomy or perianal procedures), the presence of familial IBD, smoking habits, and perianal involvement, were determined by a thorough review of the patients' medical charts, which had been collected in a uniform format. Medical therapy (steroid, immunosuppressive, or biological therapy) was registered. Biological therapy was first approved (infliximab) in 1998, while adalimumab was registered in 2008. In addition, due to the regulations of the National Health Fund, the patients were monitored by an IBD specialist at a specialized gastroenterology center every 6 months resulting in a close patient-specialist relationship [16].

All-cause and IBD-related hospitalization events (including medical-surgical complications) were registered throughout the disease course. Clinical, laboratory data, drug use, hospitalizations – including surgeries – were captured prospectively in all patients from the time of the diagnosis. In referral patients, disease phenotype, course, and hospitalization events were captured retrospectively at the time of the referral visit and prospectively thereafter.

Definitions: Major surgical events were defined as colectomy, while minor surgeries were defined as perianal fistula drainage, fistulectomy and abscess drainage. IBD-related hospitalizations included medical or surgical hospitalizations related to disease flare (symptom aggravation necessitating a change in the medical therapy, requiring hospitalization or surgery). Other events and patients hospitalized solely for diagnostic purposes (end not due to severe clinical activity) were excluded from the prediction analysis when we assessed the predictive potential of the importance of early hospitalizations. Disease extension change was defined as a change from proctitis (E1 - involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction) to either left sided colitis (E2 - involvement limited to a proportion of the colorectum distal to the splenic flexure) or pancolitis (E3 - involvement extends proximal to the splenic flexure) or from E2 to E3 during the follow-up.

Ethical consideration

The central coordination and database management was completed at the 1st Department of Internal Medicine, Semmelweis University (by P.L.L.). The study was approved by the Semmelweis University Regional and Institutional

Committee of Science and Research Ethics, and by the Csolnoky F. Province Hospital Institutional Committee of Science and Research Ethics (2004/193 and 2009/1207). An informed consent was obtained from all patients.

Statistical analyis

Variables were tested for normality by Shapiro Wilk's W-test. The χ2-test and χ2-test with Yates correction or Fischer exact test were used to assess the association between categorical variables. The Kaplan-Meier curves were plotted and Cox regression analysis was used for time-dependent univariate and multivariate analysis. Variables with a $p < 0.2$ in univariate analysis were included in multivariate testing. Results for continuous variables are expressed as median (interquartile range, IQR) unless otherwise stated. For statistical analysis, SPSS® 20.0 (SPSS Inc., Chicago, IL) was used. A p-value < 0.05 was considered significant.

RESULTS

Patient phenotype, previous disease course and exposure to medications

The clinical characteristics of the 347 patients are summarized in Table I. Almost half of the patients had left sided colitis (44.3%), while the proportions of proctitis (27.8%) and pancolitis (27.8%) were equal. During the median 7-year follow-up, the change in disease extension was 11%. Total drug exposures were recorded: 17% and 7.5% of patients required azathioprine (AZA) or anti-TNFs, while 38.8% of patients received at least one course of systemic steroids at last follow-up.

T**able I**. Disease characteristics of the inception patients with ulcerative colitis

Male/Female	200/147
Age at presentation (years)	36, IQR:26-50
Duration (years)	7, IQR: 4-10
Familial IBD	65 (18.7%)
Location at diagnosis	
1 = proctitis	97 (27.8%)
2 = left sided colitis	154 (44.3%)
3 = pancolitis	96 (27.8%)
Change in disease extension	38 (10.9%)
Arthritis	52 (14.9%)
Steroid use	135 (38.8%)
Azathioprine use	59 (17.0%)
Biological use	26 (7.5%)
Smoking habits at diagnosis	
no	223 (64.3%)
ex	81 (23.3%)
yes	43 (12.4%)

Probabilities of first all-cause and UC-related hospitalization and re-hospitalization

The probability of first all-cause hospitalization in UC was 28.6%, 53.7%, 66.2% after 1-year, 5 and 10-years, and the probabilities of first all-cause re-hospitalization 23.7%, 55.8%, 74.6% after 1-year, 5 and 10-years in a Kaplan-Meier analysis (Fig. 1). In addition, the probability of first UC-related hospitalization (medical, surgical hospitalizations or disease complications) was 8.6%, 19.3%, 34.3% after 1-year, 5 and 10-years (Fig. 2).

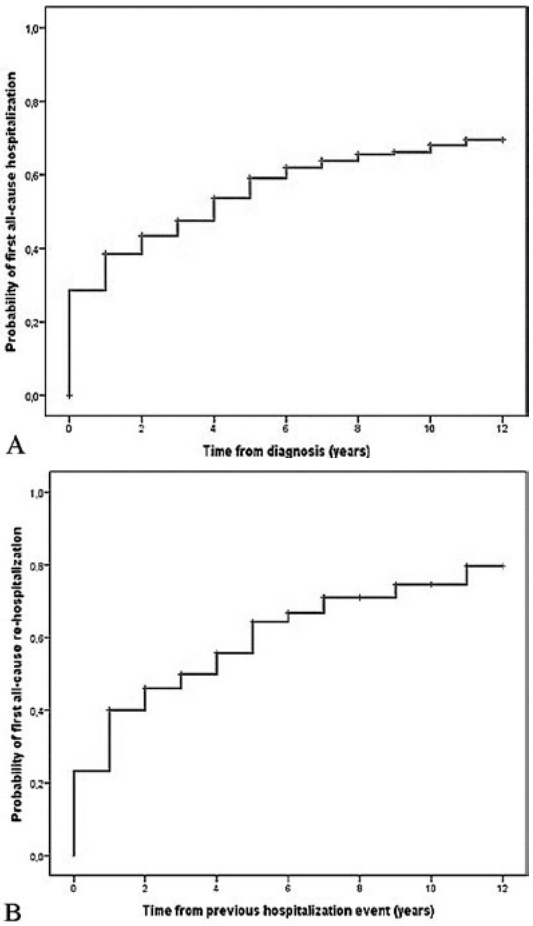

Fig. 1. Probability of first all-cause hospitalization (A) and re-hospitalization (B) in UC

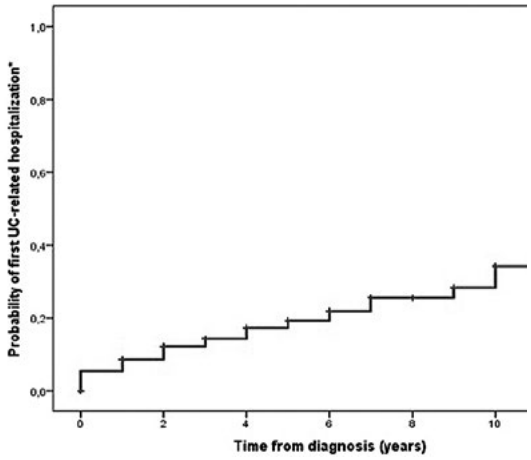

Fig. 2. Probability of first UC-related hospitalization medical, surgical hospitalizations or disease complications.

Indications for hospitalization

The main reasons for hospitalization in the first year were: diagnostic procedures (26.7%), medical activity (22.4%),

surgery (4.8%), UC-related complications (infections/sepsis, 1.4%) and in a high percentage UC-unrelated causes (44.8%). Of note, 46.2% of all colectomies were performed during the first year after diagnosis (Fig. 3) equalling 6% of all patients.

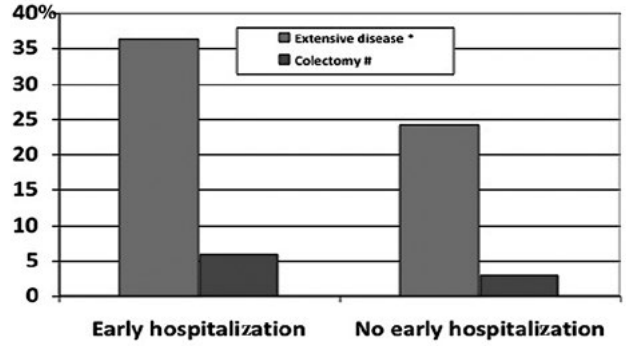

Fig. 3. Association between early hospitalizations and disease extent and risk for colectomy

Predictors for all-caused first hospitalization

Extensive disease at the diagnosis (p =0.02, HR: 1.79, 95% CI: 1.05-1.73) or during follow-up (p <0.001, HR: 1.56, 95% CI: 1.20-2.03), need for steroids (p <0.001, HR: 1.98, 95% CI: 1.37-2.85), need for AZA (p=0.038, HR: 1.55, 95% CI: 1.02-2.33) and need for anti-TNFs (p <0.001, HR: 2.28, 95% CI: 1.39-3.72) were the predictive factors for the first all-cause hospitalization in univariate Cox-analysis. In a multivariate Cox-analysis the female gender (p=0.004, HR: 1.50, 95% CI: 1.14-1.98) and the need for anti-TNFs (p =0.01, HR: 1.97, 95% CI: 1.18-3.29) were predictive factors for first all-cause first hospitalization.

Predictors for UC-related first hospitalization

The predictor factors for the first UC-related hospitalization were extensive disease at diagnosis and disease extent during follow-up, need for steroids, need for AZA and biologics in univariate Cox analysis (see Table IIA). In multivariate Cox analysis female gender, extensive disease, need for steroids and need for anti-TNFs were predictive for first UC-related hospitalization (see Table IIB).

Is early hospitalization requirement associated with disease phenotype and outcomes?

Patients requiring a hospitalization within the 1st year after the diagnosis were not significantly different with regards to gender, smoking, and later disease outcomes including need for steroid, need for AZA, need for anti-TNFs or colectomy rates (data not shown), but early hospitalization rates were higher in patients with extensive colitis (p=0.02, Fig. 3) and 46.2% of all-colectomies were performed in the 1st year after the diagnosis.

DISCUSSION

This is the first report on long-term hospitalization rates from a population-based cohort from Eastern Europe in the biological era. Interestingly, hospitalization and re-hospitalization rates were relatively high in this population-based, inception UC cohort. A significant proportion of patients were hospitalized first for diagnostic procedure or UC-unrelated causes. The UC- related hospitalization rate was the highest in the year of the diagnosis.

Table II. Predictive factors for UC-related hospitalization in univariate (A) and multivariate (B) Cox -regression analysis in UC

A			
Predictive factors for first UC-related hospitalization	P value	HR	95%CI
Female gender	0.06	1.62	0.97-2.70
Disease extent at diagnosis	0.08	1.35	0.96-1.91
Extensive vs. proctitis	0.003	5.89	1.84-18.8
Disease extent at last follow-up	<0.001	2.15	1.45-3.17
Steroid use	<0.001	3.41	1.98-5.89
Azathioprine use	<0.001	2.55	1.51-4.30
Need for anti TNF	<0.001	3.50	1.89-6.49

B			
Predictive factors for first UC-related hospitalization	P value	HR	95%CI
Female gender	0.02	1.85	1.10-3.10
Extensive vs. proctitis	0.04	3.47	1.02-11.8
Need for steroid	0.025	2.16	1.10-4.22
Need for azathioprine	0.88	-	-
Need for anti TNF	0.036	2.27	1.06-4.87

Relatively few data are available on hospitalization rates from population-based cohorts and most of them were made before the concomitant medication paradigm shift in patient management. Somewhat lower 10-year cumulative hospitalization rates were reported in the EC-IBD study [17]. The cumulative risk of hospitalization was 52.7% within ten years since diagnosis, with considerable geographical differences. In concordance with the present study, the highest hospitalization rates were within the first year of diagnosis and the hospitalization rates decreased after the first year. In addition, cumulative hospitalization rates were 29.4% and 38.7% at 5 and 10-years, while re-hospitalization risk was 51.1% at 5 years copled with a cumulative colectomy rate of 13.1% in the relatively recent population-based study from the Olmsted County [7]. Interestingly, the cumulative probability of first hospitalization increased with successive decades since diagnosis with 5-year cumulative hospitalization rates of 21.4% in those diagnosed in 1970 to 1979, while 28.6% in the 1980 to 1989, 28.6% in the 1990 to 1999, and 44.2% in the 2000 to 2004 subset. In parallel, highlighting the importance of disease severity as a major driver of hospitalizations, the cumulative probability of colectomy from the time of diagnosis was 13.1% at 5 years, 18.9% at 10 years and 25.4% at 20 years. Male gender, diagnosis in the 1990s and diagnosis in 2000 to 2004 were significantly associated with a colectomy risk. In a long-term population based study from the Manitoba Database during the 25 years follow up, from 3,752 UC-patients, 367 underwent colectomy. The 5-, 10- and 20-year risk of requiring colectomy was 7.5%, 10.4%, and 14.8%. Importantly, male sex, and diagnosis by hospitalization were predictive factors for the early colectomy

(90 days from the diagnosis) [18]. Of note, a similar trend was identified in the present study, with almost 50% of colectomies performed in the 1st year after the diagnosis. However, early all-cause or UC-related hospitalization requirement was not predictive for the subsequent disease course. Of note, UC-related hospitalization and colectomy rates were somewhat lower in the present study.

In addition, stable hospitalization rates were reported from other studies from North America in UC from referral centers [19] with cumulative UC-related hospitalization rates up to 40-45%. At a global scale, the total number of hospitalizations for UC in the United States increased by 52% from 1998 to 2004-2007 as reported from the Nationwide Inpatient Sample [9] with an annual increase of 3% coupled with stable colectomy rates of 1.2 colectomies per 100,000 UC patients [20]. Interestingly, a large variance among hospitalization rates (from 0.7 to 4.7 discharges per 10,000 for UC) has been reported in 9 European countries in 1994 and 2007 [21]. Furthermore, UC hospitalization was characterized by a small peak in younger patients followed by a large peak in older patients. Finally, overall low early hospitalization rates were reported in the very recent population-based EpiCom study in patients diagnosed in 2010 [22].

The indication for hospitalization may be dependent also on additional factors other than disease severity, including health insurance reimbursement policies and ethnic differences. For example, data from Kaiser Permanente Northern California (a health maintenance organization) reported a decline in hospitalization rates and UC-related surgery by 29% and 50% between 1998 and 2005 [23]. The reasons for this rapid change are not clear. Of note, major surgery represents 10-50% of all UC-related hospitalization events and 18-25% of the patients with UC require hospitalization for severe colitis [3].

Few studies have investigated possible predictors for hospitalization requirements in UC. In a population-based study from Olmstead county [7], the factors associated with first hospitalization included extensive UC and early need for steroids. In concordance, female gender, extensive disease, disease extent at last follow-up, need for steroids, AZA and anti-TNFs were identified as the pivotal predictive factors for UC-related hospitalization in the present study.

Of note, lower hospitalization and surgery rates were reported for moderate to severe UC patients treated with anti-TNFs in clinical trials [24-26] and in cohort studies. Similarly, a meta-analysis [27] reported that infliximab reduced short-term hospitalization risk in IBD. The risk reduction was comparable in UC and CD and between randomized clinical trials (OR: 0.51) and case-control studies (OR: 0.29). Total exposure of anti-TNFs was low in the present trial, limited to patients with severe disease, and it was associated with the need for hospitalization. Other predictors for first UC-related hospitalizations identified in the present study included disease extent, need for steroids or immunosuppressives, also identifying a subgroup of patients with higher disease severity. This is also in line with what was reported in referral setting, where requiring infliximab therapy (OR 3.12) and need for medical hospitalization in UC (OR 5.37) were independent predictors of colectomy [17]. In contrast, the need for early hospitalization was not predictive for the later disease course. However, almost half of the colectomies were performed during the 1st-year after the diagnosis.

The authors are aware of the possible limitations of the study. The indication for hospitalization is partly subjective and may be affected by factors other than disease severity, such as reimbursement policies, ethnical differences or hospital setting. Worth noting is that the reimbursement policy and IBD specialists remained largely unchanged during the observational period. The strength of the study is its population-based design, which enabled study of the full spectrum of the disease, allowing the generalizability of our results to other population-based settings and real-life IBD cohorts. Finally, an advantage of the present study was that we aimed to study hospitalization trends in an era when the anti-TNFs have become increasingly available for UC. Thus, we could investigate hospitalization trends and indications of hospitalizations in the biological era. Interestingly, only a relatively small proportion of the UC cohort was exposed to anti-TNFs (7.5%). Nonetheless, our study provides an up-to-date view on the patterns and reasons for hospitalization in patients with ulcerative colitis. In addition, our data can contribute to the more accurate planning of health care access requirements of UC patients during the first 5-10 years of their disease.

CONCLUSION

The hospitalization and re-hospitalization rates were still relatively high in this population-based cohort; more than one-third of UC patients required disease-related hospitalizations within one year after the diagnosis in the biological era. Disease extent at diagnosis, need for steroids and anti-TNF were associated with the risk of UC-related hospitalization. In addition, almost half of the colectomies were performed in the first year of the disease.

Conflicts of interest: none.

Authors' contribution: P.A.G., L.L.: study design, data collection, supervising the collection and validation of patients, database construction, and manuscript preparation. I.S., M.B., T.P.: data collection and manuscript preparation. M.D.M., B.D.L., Z.V., Z.K., L.S.K.: database construction, data validation, data analysis and manuscript preparation. P.L.L.: study design, data collection, supervising the collection and validation of patients, database construction, the statistical analysis, and manuscript preparation. All authors have approved the final draft submitted.

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