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CUMULATIVE INCIDENCE AND RISK FACTORS FOR HOSPITALIZATION AND SURGERY IN A POPULATION-BASED COHORT OF ULCERATIVE COLITIS

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Abstract

Background and Aims—We sought to identify clinical and demographic features influencing hospitalization and colectomy in a population-based inception cohort of ulcerative colitis.

Methods—Between 1970 and 2004, a total of 369 patients (58.5% males) from Olmsted County, Minnesota were followed from diagnosis for 5,401 person-years. The cumulative probability of hospitalization and colectomy were estimated using the Kaplan-Meier method. Cox proportional hazards regression was used to identify factors associated with hospitalization and colectomy.

Results—The cumulative probability of first hospitalization was 29.4% at 5 years (95% confidence interval [CI], 24.5%–34.1%), 38.7% at 10 years (33.1%–43.8%), 49.2% at 20 years (42.7%–55.2%) and 52.3% at 30 years (45.1%–59.7%). The incidence rate of hospitalizations decreased over the last four decades, although cumulative probability of first hospitalization increased with successive decades of diagnosis. Early need for corticosteroids (hazard ratio [HR], 1.8; 95% CI, 1.1–2.7) and early need for hospitalization (HR, 1.5; 1.02–2.4) were independent predictors of hospitalization after 90 days of illness. The cumulative probability of colectomy from time of diagnosis was 13.1% at 5 years (95% CI, 9.4%–16.6%), 18.9% at 10 years (14.4%–23.2%), and 25.4% at 20 years (19.8%–30.8%). Male gender (HR, 2.1; 95% CI, 1.3–3.5), diagnosis in the 1990s (HR, 2.0; 1.01–4.0) and diagnosis in 2000–2004 (HR, 3.7; 1.7–8.2) were significantly associated with colectomy risk.

Conclusion—Colectomy rates were comparable to reports from northern Europe. The numbers of hospitalizations show a decreasing trend. Male gender and being diagnosed in the 2000–04 period predicted colectomy while extensive colitis predicted future hospitalizations.

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Keywords

Ulcerative colitis; colectomy; ileal pouch-anal anastomosis; hospitalizations; corticosteroids

INTRODUCTION

Ulcerative colitis is a chronic inflammatory bowel condition with unclear etiology and no medical cure. This disease accounts for significant morbidity and healthcare resource utilization. In Olmsted County, Minnesota, the prevalence of ulcerative colitis increased by 21% between 2001 and 2005, and the age- and sex- adjusted prevalence on January 1, 2005 was 273 cases per 100,000 persons.^{1, 2} Extrapolating this prevalence to the estimated 2009 U.S. population of 307 million would suggest that over 800,000 Americans have ulcerative colitis.³

The natural course of ulcerative colitis is that of exacerbation interspersed with periods of remission. Hospitalizations account for a large part of the costs involved in the care of ulcerative colitis.^{4–10} The Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality estimated the aggregate in-hospital costs of enteritis and ulcerative colitis in the year 2004 to be \$821 million.¹¹ Data on temporal trends in hospitalization for ulcerative colitis are conflicting. There was a 48% increase in hospital stays for regional enteritis and ulcerative colitis in the United States between 1994 and 2004.¹¹ This trend could be explained by increasing prevalence and surgical interventions for inflammatory bowel disease (IBD). Hospitalization data could be a predictor of aggressive disease--in a recent study, patients with ulcerative colitis who required medical hospitalization were five times more likely to require colectomy, even after adjusting for other factors.¹² However, there has been considerable variability in hospitalization rates across North America. Stable rates of hospitalizations over a 7-year period (1994–2001) were reported from Canada,¹³ while in a multilevel study conducted among 3.2 million members of Kaiser Permanente, Northern California, hospitalization rates for ulcerative colitis had declined by 29% between 1998 and 2005.¹⁴

Many patients with ulcerative colitis will need surgery during the course of their disease. Population-based studies from Stockholm and Copenhagen have reported 10-year cumulative colectomy rates of 28% and 24%, respectively.^{15, 16} Two studies from Europe and one from Canada recently reported 10-year cumulative colectomy rates of approximately 10%, considerably lower than previously reported.^{17–19} The nature of surgery in patients with ulcerative colitis has also evolved over the last 4 decades, with 2- or 3-stage total proctocolectomy (TPC) with ileal pouch-anal anastomosis (IPAA) more commonly replacing single-stage TPC with Brooke ileostomy.²⁰ This change in practice might result in increasing hospitalization rates.^{21, 22}

Identification of early predictors of colectomy in ulcerative colitis would be potentially useful in attempting to medically influence these colectomy rates. As mentioned previously, medical hospitalization may be a “red flag” for subsequent colectomy.¹² Several population-based studies from Europe had reported the presence of extensive colitis at diagnosis to be a risk factor for colectomy.^{16, 18, 23}

Longitudinal analysis of hospitalization and colectomy in a population-based inception cohort of ulcerative colitis would help to study changes in the nature of the disease and evolving trends in the treatment of this chronic condition. In the current study, the inception cohort of Olmsted County residents diagnosed with ulcerative colitis between 1970 and 2004 were studied to describe the cumulative incidence of and risk factors for hospitalizations and colectomies.

METHODS

Study Setting and Patients

Olmsted County, situated in southeastern Minnesota, had a population of 124,277 inhabitants in the 2000 U.S. Census. The majority of people reside in Rochester, the urban center of an otherwise mostly rural county. In the 2000 census, 89% of residents were non-Hispanic white, and a substantial portion were of northern European heritage. Although 25% of county residents are employed in health care services (versus 8% nationwide), and the level of education is consequently higher (30% of adults have completed college versus 21% nationwide), the residents of Olmsted County are otherwise socioeconomically similar to the U.S. white population.²⁴

Since medical care is practically self-contained within Olmsted County and provided by Mayo Medical Center, Olmsted Medical Center, and their affiliated clinics and hospitals, it is possible to trace all IBD patients in the common medical record linkage system known as the Rochester Epidemiology Project.²⁴ Diagnoses are generated from all hospitalizations, outpatient episodes of care, emergency room visits, and endoscopic and surgical procedures. In previous studies, we have identified all Olmsted County residents who were diagnosed with ulcerative colitis between 1940 and 2004.^{1, 25, 26} A subset of this cohort, those diagnosed with ulcerative colitis between 1970 and 2004, served as the study group. This group was followed through their medical records from date of ulcerative colitis diagnosis until date of death, last follow-up, or date of last medical record abstraction (approximately 2006).

The present study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. As per Minnesota state law, we did not include patients who had withdrawn authorization to review their medical records for research purposes.

Study Variables

The medical records of the study group patients were abstracted for relevant demographic and clinical characteristics, including date of ulcerative colitis diagnosis, age at diagnosis, gender, dates of hospitalization for an ulcerative colitis-related reason, and dates and types of ulcerative colitis-related surgeries. Extensive colitis was defined as diffuse disease with involvement proximal to the splenic flexure of the colon, left-sided colitis was defined as diffuse disease with involvement distal to the splenic flexure but proximal to the rectum, and proctitis was defined as disease limited to the rectum. Surgical hospitalizations were defined as hospitalizations which included an ulcerative colitis-related surgery, and medical hospitalizations were defined as all other ulcerative colitis-related hospitalizations.

Colectomies were classified into four categories: 1) TPC with IPAA; 2) subtotal colectomy (SC) with ileostomy and Hartmann pouch; 3) TPC with Brooke ileostomy; and 4) partial colectomy (PC)/miscellaneous procedures.

The following variables were assessed within the first 90 days of diagnosis: maximal extent of ulcerative colitis, early requirement (within 90 days) for corticosteroids for treatment of ulcerative colitis, and early need (within 90 days) for hospitalization for an ulcerative colitis-related condition.

Statistical Analysis

Descriptive statistics such as percentage, median, range and interquartile range (IQR, 25th percentile to 75th percentile) were utilized depending on the scale of specific variables (i.e., discrete or continuous). The primary endpoints of interest in this study were ulcerative colitis related hospitalizations and ulcerative colitis-related surgeries. The cumulative probabilities of first hospitalization for ulcerative colitis and of colectomy were estimated using the Kaplan-Meier product-limit method. For the hospitalization endpoint, patients were followed from time of colitis diagnosis until first hospitalization or last follow-up. If the patient was hospitalized at diagnosis, patients were followed from the date of initial hospitalization discharge until the next hospitalization or the last follow-up date. For the colectomy endpoint, patients were followed from time of diagnosis until colectomy or last follow-up.

The associations of demographic and clinical risk factors with time to initial hospitalization or time to colectomy were assessed using Cox proportional hazards regression modeling. Results were expressed as hazard ratios (HR) with 95% CI. Since clinical features measured within the first 90 days of diagnosis (e.g., early maximal extent, early need for steroids or hospitalization) were utilized, only events which occurred after the first 90 days after diagnosis were included in the proportional hazards analysis. After univariate Cox modeling, a multiple variable model was constructed using forward, backward, and stepwise selection of factors.

Since hospitalization could occur multiple times in the same patient, hospitalization rates were summarized using crude incidence rates and expressed as events per 1,000 patient-years of follow-up.

In secondary analyses, the cumulative probability of first hospitalization, and separately, colectomy, were stratified by clinical variables of interest such as age, gender, calendar period of diagnosis (1970–79, 1980–89, 1990–99, 2000–04), use of corticosteroids within 90 days of UC diagnosis, and hospitalization within 90 days of UC diagnosis, and the univariate associations of these clinical variables with the Kaplan-Meier-estimated cumulative probability were assessed using the log-rank test.

RESULTS

Study Population

A total of 369 Olmsted County residents were diagnosed with ulcerative colitis between 1970 and 2004. Two hundred sixteen patients (58%) were males, and the median age at ulcerative colitis diagnosis was 35.7 years (range, 1.2 – 86.9) (Table 1). The other baseline characteristics of the study patients are as shown in Table 1.

The study group was followed through their medical records for a total of 5,401 person-years. The median follow-up per patient was 13.9 years (range, 1 month to 36.3 years). An ulcerative colitis-related hospitalization occurred within the first 90 days in 70 patients (19%), and early use of corticosteroids was required in 69 patients (19%). Eight patients (2%) underwent initial surgery within 90 days of UC diagnosis.

Hospitalizations: Crude Incidence and Length of Stay

One hundred seventy-three patients (47%) required at least one ulcerative colitis-related hospitalization, including 18 patients who were hospitalized at time of diagnosis and not hospitalized thereafter, and 10 who were hospitalized post-diagnosis within 90 days and not hospitalized thereafter. In total, there were 518 ulcerative colitis-related hospitalizations within this cohort. Overall, the median number of hospitalizations per patient was 0 (range, 0 to 33), but among those hospitalized at least once, the median number of subsequent hospitalizations was 2 (range, 1 to 33). Eighty-three patients required a total of 174 hospitalizations that included a bowel surgery, while 150 patients required a total of 344 medical hospitalizations.

The crude rate of any ulcerative colitis-related hospitalization over the entire study period was 96 per 1,000 patient-years, decreasing from 134 per 1,000 patient-years in 1970–79 to 88 per 1,000 patient-years in the time period from 2000 onwards (Figure 1). Surgical hospitalizations occurred at a crude incidence rate of 32 per 1,000 patient-years overall, decreasing from a rate of 41 per 1,000 patient-years in 1970–79 to 30 per 1,000 patient-years in the time period from 2000 onwards. Medical hospitalizations occurred at a crude incidence rate of 64 per 1,000 patient-years, decreasing from a rate of 93 per 1,000 in the 1970s to 58 per 1,000 in 2000 onwards.

The median length of stay (LOS) for all hospitalizations was 6 days (IQR, 4 to 10 days). The median LOS for surgical hospitalizations was 9 days (IQR, 6 to 14 days), and the median LOS for medical hospitalizations was 5 days (IQR, 3 to 8 days).

Cumulative Probability of First Hospitalization

The cumulative probability of ulcerative colitis-related hospitalization was 29.4% at 5 years (95% CI, 24.5%–34.1%), 38.7% at 10 years (95% CI, 33.1%–43.8%), 49.2% at 20 years (95% CI, 42.7%–55.2%), and 52.3% at 30 years (95% CI, 45.1%–59.7%) (Figure 2A). The cumulative incidence of hospitalization at 5 years from diagnosis was 21.4% in those diagnosed in 1970–79 (95% CI, 11.8%–30.0%), 28.6% in the 1980–89 subset (95% CI, 18.9%–37.2%), 28.6% in those diagnosed in 1990–99 (95% CI, 19.8%–36.5%), and 44.2%

in the 2000–04 subset (95% CI, 28.1%–57.4%) ($p = 0.14$, log-rank test) (Figure 2B). Initial extent was significantly associated with the risk of hospitalization ($p = 0.016$, log-rank test). The five-year cumulative risk of hospitalization in patients whose initial extent was proctitis only was 15.3% (95% CI, 8.1%–22.0%), compared to 29.9% at 5 years (95% CI, 21.5%–37.4%) in those with initial left-sided disease and 41.9% in patients with extensive colitis (95% CI, 31.9%–50.7%) (Figure 2C). Use of corticosteroids within the first 90 days after diagnosis was significantly associated with risk of hospitalization ($p < 0.001$, log-rank test). The cumulative incidence of hospitalization at 5 years was 48.7% among patients who required corticosteroids within the first 90 days of diagnosis (95% CI, 34.6%–59.8%) versus 19.5% (95% CI, 14.7%–24.0%) among those who did not (Figure 2D). Hospitalization within the first 90 days after diagnosis was significantly associated with risk of hospitalization ($p < 0.001$, log-rank test). The cumulative risk of hospitalization at 5 years was 43.8% among patients who required hospitalization within the first 90 days of diagnosis (95% CI, 30.3%–54.6%) versus 20.4% among those who did not require early hospitalization (95% CI, 15.5%–25.0%) (Figure 2E).

Risk Factors for Hospitalization

Cox proportional hazards regression was used to assess the association between baseline variables and time to first hospitalization (Table 2). A patient with extensive ulcerative colitis noted within the first 90 days of diagnosis had an approximately 60% increased risk of hospitalization (HR, 1.6; 95% CI, 1.1–2.3). Other significant predictors of hospitalization after the first 90 days of illness included early need for corticosteroids (HR, 2.1; 95% CI, 1.4–3.1) and early need for hospitalization (HR, 1.9; 95% CI, 1.3–2.8). Gender, age at diagnosis, and decade of diagnosis were not significantly associated with time to first hospitalization.

The final multiple variable model included corticosteroid use in the first 90 days after diagnosis (HR, 1.8; 95% CI, 1.1–2.7) and need for hospitalization within the first 90 days after diagnosis (1.5; 95% CI, 1.02–2.4). The interaction between early corticosteroid use and early hospitalization was not significant ($p = 0.51$).

Rehospitalization

Of the 173 patients who required at least one medical or surgical hospitalization, 96 were rehospitalized for an ulcerative colitis-related reason at least once during their disease course. The cumulative risk of rehospitalization was 51.1% (95% CI, 42.7% – 58.4%) at 5 years, 58.8% (95% CI, 49.8% – 66.2%) at 10 years, and 64.6% (95% CI, 54.5% – 73.7%) at 20 years from initial hospitalization.

Colectomy Indications and Subtypes

Seventy-six patients underwent colectomy. Indications for colectomy included medically refractory disease in 49 (64.5%), fulminant colitis in 16 (21.1%), colorectal dysplasia or cancer in 8 (10.5%), and other indications in 3 (3.9%) (diverticulitis with abscess, cecal ischemia due to pseudo-obstruction, and rectal lymphoma). The indication for colectomy appeared to change over time. Of the 19 colectomies performed before January 1, 1990, 17 were for medically refractory disease (89.4%), 1 was for fulminant colitis (5.3%), and 1 was

for colorectal dysplasia (5.3%). On the other hand, of the 57 surgeries performed after January 1, 1990, 32 were for medically refractory disease (56.1%), 15 were for fulminant colitis (26.3%), 7 were for colorectal dysplasia or cancer (12.3%), and 3 were for other indications (5.3%). The colectomy subtypes were TPC-IPAA in 41 (54%), TPC-ileostomy in 25 (33%), SC-ileostomy in 9 (12%), and PC/miscellaneous in 1 (1%). Twenty-six patients had undergone testing for *Clostridium difficile* toxin within 30 days of colectomy, and these tests were all negative. One patient was noted to have cytomegalovirus infection (positive immunohistochemical stains for CMV).

Cumulative Incidence of Colectomy

The cumulative probability of colectomy was 3.8% at 1 year (95% CI, 1.8%–5.8%), 13.1% at 5 years (95% CI, 9.4%–16.6%), 18.9% at 10 years (95% CI, 14.4%–23.2%), and 25.4% at 20 years from diagnosis (95% CI, 19.8%–30.8%) (Figure 3A). There was a significant association between decade of diagnosis and the risk of colectomy ($p = 0.005$, log-rank test) (Figure 3B). The 5-year risk of colectomy among those diagnosed between 1970 and 1979 was 6.5% (95% CI, 0.8%–11.9%), compared to 5-year risks of 11.8% in the 1980–89 subset (95% CI, 5.0%–18.1%), 13.1% among those diagnosed between 1990 and 1999 (95% CI, 6.7%–19.0%), and 24.2% in the 2000–04 subset (95% CI, 11.5%–36.9%). Male gender was significantly associated with an increased risk of colectomy ($p = 0.004$, log-rank test) (Figure 3C). The 5-year cumulative probability of colectomy was 6.1% among women (95% CI, 2.1%–10.0%) versus 18.1% among men (95% CI, 12.6%–23.4%), while the 10-year probabilities were 10.6% (95% CI, 5.1% – 15.9%) and 24.8% (95% CI, 18.3% – 31.1%), respectively. There were no significant differences in cumulative incidence of colectomy between patients with non-extensive and extensive disease within the first 90 days of diagnosis ($p = 0.16$, log-rank) or between those diagnosed < 40 years of age and ≥ 40 years ($p = 0.79$). The 5-year cumulative probability of colectomy was 11.7% (95% CI, 7.4% – 15.7%) in patients with non-extensive disease within first 90 days and 15.7% (95% CI, 8.5% – 22.6%) in those with early extensive disease. Among patients diagnosed under the age of 40 years, the 5-year cumulative incidence of colectomy was 12.4% (95% CI, 7.7% – 16.8%) compared to 14.1% (95% CI, 8.1% – 19.7%) in those 40 years or older at diagnosis.

Risk Factors for Colectomy

The associations between a variety of baseline demographic and clinical factors and time to colectomy were assessed by Cox proportional hazards regression (Table 2). Males with ulcerative colitis were twice as likely as females to require colectomy (HR, 2.1; 95% CI, 1.3 – 3.4). Patients diagnosed in the 1990s, relative to those diagnosed in the 1970s, were approximately twice as likely to require colectomy (HR, 2.1; 95% CI, 1.04 – 4.1), while those diagnosed in 2000–04 were nearly four times more likely (HR, 3.8; 95% CI, 1.7 – 8.4). Patients who required corticosteroids in the first 90 days after diagnosis were 70% more likely to require colectomy (HR, 1.7), but this was not quite statistically significant (95% CI, 0.9 – 3.0). Age at diagnosis, initial disease extent, and early need for hospitalization were not significantly associated with time to colectomy.

The final multiple variable model of time to colectomy included male gender (HR, 2.1; 95% CI, 1.3 – 3.5), diagnosis in the 1980s relative to the 1970s (HR, 1.2; 95% CI, 0.6 – 2.4),

diagnosis in the 1990s (HR, 2.0; 95% CI, 1.01 – 4.0), and diagnosis in 2000–04 (HR, 3.7; 95% CI, 1.7 – 8.2).

DISCUSSION

In this population-based study, approximately one half of the ulcerative colitis inception cohort required at least one colitis-related hospitalization during their disease course. Almost a quarter (22%) of these admissions included a bowel surgery. The crude incidence of both medical and surgical hospitalizations decreased during the study period. Duration of hospitalization for both medical and surgical causes was comparable to previous reports in the literature.²⁷ The cumulative probability of first hospitalization increased steadily with time and reached more than 50% after 30 years of disease. The cumulative incidence of colectomy also increased, with 25.2% needing colectomy after 20 years. Surprisingly, those diagnosed during the last five years of the study period carried the highest risk of hospital admission and colectomy. Male gender and the decade of diagnosis were independent predictors of colectomy.

One of the major strengths of this study was the availability of complete medical records for all potential cases of ulcerative colitis. Olmsted County, Minnesota only represents a small region of the United States, but ascertainment of cases with consistent diagnostic criteria approached 100%, which allowed for analysis of temporal trends in hospitalizations and surgeries. We also had longitudinal data on these patients, with median follow-up per patient of 13.9 years. Regression modeling allowed us to assess the association between decade of diagnosis and time to hospitalization or colectomy. This study therefore provides true population-based information on the changes in colitis-related hospitalizations and colectomies. Prior to the approval of infliximab by the Food & Drug Administration for ulcerative colitis in 2005, clinicians in the county prescribed very little or no off-label infliximab for ulcerative colitis, and follow-up for most patients in the study ended in 2006, so almost all of the observational time in this study was in the pre-biologic era; therefore, the data from this study could represent a benchmark against which subsequent studies in the biologic era are measured.

Age at diagnosis of ulcerative colitis (median of 35 years) was generally comparable with previous reports from Canada and Copenhagen.^{13, 28} In the US, hospitalizations for IBD may be increasing,^{27, 29} with older ulcerative colitis patients having a significant increase in hospital admissions compared to younger sufferers.^{27, 30} It was estimated that ulcerative colitis accounted for between 500,000 and 700,000 ambulatory care visits and between 35,000 and 80,000 hospitalizations in the United States in 2004.¹⁰ We did not find any association between risk of first hospitalization and age at diagnosis. These studies had analyzed the time trends of ulcerative colitis and Crohn's disease using annual data from the US National Hospital Discharge Survey (NHDS). While this gives useful information on the burden of disease within the United States health care system, they do not essentially reflect the hospitalization rates among a population of patients with ulcerative colitis. We found a decreasing trend in the crude incidence of medical and surgical hospitalization within our ulcerative colitis cohort. This decrease is unlikely to be due to more potent medical therapy, since biological therapy for ulcerative colitis was not approved till 2005. With increasing

age of the US population, there has a burgeoning interest in defining the cost and resource utilization in patients with IBD. There was a 8.6% annual increase in the total hospital charges for UC from \$592 million to \$945 million between 1998 and 2004.²⁹ Hospitalization accounts for the vast majority of resource utilization in ulcerative colitis. It is therefore more likely to reflect time trends in the attitude of physicians geared towards outpatient management of ulcerative colitis in a cost saving measure.

Despite the trend of decreasing crude incidence of hospitalization, our analysis also found an increase in the cumulative incidence to first hospitalization, with an estimated cumulative probability of 50% in 30 years' time. Compared to earlier subsets (1970–79 and 1980–89), patients diagnosed in the 2000–2004 period had a higher chance of being hospitalized. It is probably of relevance that between 1998 and 2004, the incidence of *Clostridium difficile*-associated disease (CDAD) among hospitalized patients with UC in the United States had tripled, and the vast majority of these infections were acquired before hospitalization.³¹ Although we have not directly studied the prevalence of *Clostridium difficile* in our UC cohort, we hypothesize that the substantial increase in hospitalization may partly have been contributed by the increasing incidence of this organism in IBD. While there are no data to directly support the hypothesis of increasing disease severity accounting for these increased hospitalizations, application of the Montreal classification to Olmsted County patients with UC showed an increasing trend for left-sided and extensive involvement of the colon in recent years.³²

We found first hospitalization to be a predictor for future admissions, with a cumulative rehospitalization risk of over 60% at 10 years from the initial event. This ability to predict future inpatient care would lend itself to treatment manipulations at an early stage to prevent rehospitalizations. There is probably a high degree of colinearity between the need for repeated hospitalizations and disease activity. This information can be used to stratify patients into groups that may benefit from more aggressive medical therapy. Identification and appropriate management of these high-risk patients may have implications in healthcare resource savings in the long term.

Our 10-year cumulative incidence of colectomy of 18.6% is far higher than recent reports from the European multicenter population-based cohort.¹⁸ The overall colectomy rate in this recent European cohort was 8.7%, which increased to 20% for patients having extensive colitis at diagnosis. Solberg et al reported a similar cumulative colectomy rate of 9.8% after 10 years of disease in a cohort of patients from southeastern Norway (IBSEN).¹⁷ Targownik and colleagues estimated that the 10-year cumulative colectomy rate in Manitoba between 1987 and 2008 was 10.4%.¹⁹ These stand in contrast to population-based studies from Stockholm²³ and Copenhagen¹⁶, published more a decade ago, showing 10-year colectomy rates of 28% and 24%, respectively. Geographic variations in the natural course of IBD have been reported both from United States and Europe with higher hospitalizations and colectomy rates in the Northern states.^{18, 33} Our 10-year colectomy rates are comparable to results recently reported from the northern countries in Europe (Copenhagen).^{18, 28} There are no recent population-based data on colectomy rates in ulcerative colitis from United States. A multilevel study among members of Kaiser Permanente, Northern California, reported a decline in colitis-related surgery by 50%.¹⁴

Similar to our hospitalization results, we found that those diagnosed in 2000–2004 were four times more likely to require colectomy. Whether the increasing colectomy risk reflects increasing severity of the disease, with patients diagnosed in the recent years showing increased propensity to progress with time, from proctitis or left-sided colitis to extensive disease, is unclear. This trend of increasing incidence of extensive disease was noted in a recent study from Olmsted County, Minnesota.³² A study of proximal extension of colitis in this cohort found that among those with an initial diagnosis of proctitis or left-side colitis, the cumulative incidence of progression to extensive colitis was 44% at 5 years;³⁴ however, year of colitis diagnosis was not significantly associated with risk of progression. In the present study, the disease extent was only assessed at the time of diagnosis, and we did not detect an association between disease extent and time to colectomy. In the IBSEN study, patients who progressed from limited to extensive disease showed a trend towards increased 10-year colectomy rates (28% for extensive versus 19% for left-sided and proctitis).¹⁷ The prevalence of patients with fulminant colitis as the indication for colectomy increased from approximately 5% before 1990 to over 25% after 1990, and the reason for this remains unexplained. As discussed previously, the increased incidence of CDAD in patients with IBD might account for the higher colectomy rates in the recent subset of patients. A recent report from New York demonstrated significantly increased colectomy rates in *C. difficile*-positive ulcerative colitis patients compared to those who were *C. difficile*-negative.³⁵ On the other hand, none of the patients in our cohort who underwent colectomy tested positive for CDAD in the month preceding colectomy. Male patients were twice as likely to undergo surgery, and this was an independent predictor of time to colectomy. Other similar studies have not seen such a difference in surgical risk with gender.^{17, 18} The reason for this increased risk is not entirely obvious, but some studies of ulcerative colitis suggest that the incidence of UC in males continues to rise with a corresponding decrease in females^{2, 25} and therefore could have a contributory role in increased colectomy risk seen in male gender.

Our study has potential limitations. First of all, the geographic region studied is small and thereby the sample size was relatively small. Secondly, the results of our study may not be generalizable to the rest of United States because of racial and ethnic differences. Only 11% of the Olmsted County population was non-white as of 2000, and the vast majority of the white population was of northern European descent. Additionally, a higher-than-expected percentage of the population is employed in the healthcare field. Finally, as this was a retrospective, observational study of a population-based cohort served by a referral center with expertise in the management of IBD, it is not clear that the variables associated with hospitalization and surgery in our cohort would be generalizable to other cohorts of UC patients, due to differences in treatment policies across space and time.

In conclusion, in this population-based inception cohort, medical and surgical hospitalization was predicted by the extent of the disease and need for early hospitalization. Rehospitalizations were common in patients who at least had one admission. The 10-year colectomy rate was comparable to some but not all reports from Northern Europe. Patients diagnosed after 1990 and males were significantly more likely to undergo colectomy. Confirmatory studies of factors associated with hospitalization and colectomy in ulcerative colitis may enable us to better identify high-risk patients.

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REFERENCES

- Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940–2000. *Inflamm Bowel Dis*. 2007; 13:254–261. [PubMed: 17206702]
- Ingle SB, Loftus EV Jr, Tremaine WJ, et al. Increasing incidence and prevalence of inflammatory bowel disease in Olmsted County, Minnesota, 2001 – 2004. *Gastroenterology*. 2007; 132:A19–A20.
- Loftus EV Jr, Friedman HS, Delgado DJ, et al. Colectomy subtypes, follow-up surgical procedures, postsurgical complications, and medical charges among ulcerative colitis patients with private health insurance in the United States. *Inflamm Bowel Dis*. 2009; 15:566–575. [PubMed: 19143006]
- Hay JW, Hay AR. Inflammatory bowel disease: costs-of-illness. *J Clin Gastroenterol*. 1992; 14:309–317. [PubMed: 1607607]
- Blomqvist P, Ekbom A. Inflammatory bowel diseases: health care and costs in Sweden in 1994. *Scand J Gastroenterol*. 1997; 32:1134–1139. [PubMed: 9399395]
- Bassi A, Dodd S, Williamson P, et al. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. *Gut*. 2004; 53:1471–1478. [PubMed: 15361497]
- Odes S, Vardi H, Friger M, et al. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. *Gastroenterology*. 2006; 131:719–728. [PubMed: 16952541]
- Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology*. 2008; 135:1907–1913. [PubMed: 18854185]
- Everhart, JE. Burden of digestive diseases in the United States. Chapter 19: Inflammatory bowel disease ed., editor. Washington D.C.: US Government Printing Office; 2008. NIH publication no. 09-6443.
- Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part II: lower gastrointestinal diseases. *Gastroenterology*. 2009; 136:741–754. [PubMed: 19166855]
- Milenkovic, M.; Russo, CA.; Elixhauser, A. Hospital Stays for Gastrointestinal diseases. HCUP Statistical Brief #12 ed., editor. Rockville, MD: Agency for Healthcare Research and Quality; 2004.
- Ananthakrishnan AN, Issa M, Beaulieu DB, et al. History of medical hospitalization predicts future need for colectomy in patients with ulcerative colitis. *Inflamm Bowel Dis*. 2009; 15:176–181. [PubMed: 18680197]
- Bernstein CN, Nabalamba A. Hospitalization, surgery, and readmission rates of IBD in Canada: a population-based study. *Am J Gastroenterol*. 2006; 101:110–118. [PubMed: 16405542]
- Herrinton LJ, Liu L, Fireman B, et al. Time trends in therapies and outcomes for adult inflammatory bowel disease, Northern California, 1998–2005. *Gastroenterology*. 2009; 137:502–511. [PubMed: 19445944]
- Leijonmarck CE, Lofberg R, Ost A, et al. Long-term results of ileorectal anastomosis in ulcerative colitis in Stockholm County. *Dis Colon Rectum*. 1990; 33:195–200. [PubMed: 2311462]
- Langholz E, Munkholm P, Davidsen M, et al. Colorectal cancer risk and mortality in patients with ulcerative colitis. *Gastroenterology*. 1992; 103:1444–1451. [PubMed: 1358741]
- Solberg IC, Lygren I, Jahnsen J, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). *Scand J Gastroenterol*. 2009; 44:431–440. [PubMed: 19101844]

18. Hoie O, Wolters FL, Riis L, et al. Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years. *Gastroenterology*. 2007; 132:507–515. [PubMed: 17258717]
19. Targownik LE, Singh H, Nugent Z, et al. The epidemiology of colectomy in ulcerative colitis: results from a population-based cohort. *Am J Gastroenterol*. 2012; 107:1228–1235. [PubMed: 22613902]
20. Leijonmarck CE. Surgical treatment of ulcerative colitis in Stockholm county. *Acta Chir Scand Suppl*. 1990; 554:1–56. [PubMed: 1970209]
21. Ozturk E, Kiran RP, Remzi F, et al. Early readmission after ileoanal pouch surgery. *Dis Colon Rectum*. 2009; 52:1848–1853. [PubMed: 19966631]
22. Datta I, Buie WD, Maclean AR, et al. Hospital readmission rates after ileal pouch-anal anastomosis. *Dis Colon Rectum*. 2009; 52:55–58. [PubMed: 19273956]
23. Leijonmarck CE, Persson PG, Hellers G. Factors affecting colectomy rate in ulcerative colitis: an epidemiologic study. *Gut*. 1990; 31:329–333. [PubMed: 2323599]
24. Melton LJ 3rd, et al. History of the Rochester Epidemiology Project. *Mayo Clin Proc*. 1996; 71:266–274. [PubMed: 8594285]
25. Loftus EV Jr, Silverstein MD, Sandborn WJ, et al. Ulcerative colitis in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. *Gut*. 2000; 46:336–343. [PubMed: 10673294]
26. Sedlack RE, Nobrega FT, Kurland LT, et al. Inflammatory colon disease in Rochester, Minnesota, 1935–1964. *Gastroenterology*. 1972; 62:935–941. [PubMed: 5029078]
27. Bewtra M, Su C, Lewis JD. Trends in hospitalization rates for inflammatory bowel disease in the United States. *Clin Gastroenterol Hepatol*. 2007; 5:597–601. [PubMed: 17382602]
28. Jess T, Riis L, Vind I, et al. Changes in clinical characteristics, course, and prognosis of inflammatory bowel disease during the last 5 decades: a population-based study from Copenhagen, Denmark. *Inflamm Bowel Dis*. 2007; 13:481–489. [PubMed: 17206705]
29. Nguyen GC, Tuskey A, Dassopoulos T, et al. Rising hospitalization rates for inflammatory bowel disease in the United States between 1998 and 2004. *Inflamm Bowel Dis*. 2007; 13:1529–1535. [PubMed: 17828784]
30. Sonnenberg A. Hospitalization for inflammatory bowel disease in the United States between 1970 and 2004. *J Clin Gastroenterol*. 2009; 43:297–300. [PubMed: 18936713]
31. Rodemann JF, Dubberke ER, Reske KA, et al. Incidence of *Clostridium difficile* infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2007; 5:339–344. [PubMed: 17368233]
32. Helou EF, Loftus EV, Tremaine WJ, et al. Phenotypic classification of Crohn's disease and ulcerative colitis in Olmsted County Minnesota: assessment of temporal changes. *Gastroenterology*. 2006; 130:A-654.
33. Sonnenberg A, McCarty DJ, Jacobsen SJ. Geographic variation of inflammatory bowel disease within the United States. *Gastroenterology*. 1991; 100:143–149. [PubMed: 1983816]
34. Tremaine WJ, Timmons LJ, Harmsen WS, et al. Proximal extension of left-sided ulcerative colitis: A population-based study. *Gastroenterology*. 2008; 134:A5.
35. Jodorkovsky D, Young Y, Abreu MT. Clinical outcomes of patients with ulcerative colitis and co-existing *Clostridium difficile* infection. *Dig Dis Sci*. 2009

FIGURE 1.

Unadjusted incidence rates of any ulcerative colitis-related hospitalization, surgical hospitalization, and medical hospitalization among 369 patients with ulcerative colitis from Olmsted County, Minnesota, 1970–2004, stratified by calendar period of observation.

A

B

C

D

E

FIGURE 2.

Cumulative incidence of first ulcerative colitis-related hospitalization among 369 patients with ulcerative colitis from Olmsted County, Minnesota, 1970–2004. A. Overall cumulative incidence. B. Cumulative incidence stratified by decade of diagnosis. C. Cumulative incidence stratified by disease extent measured within first 90 days of diagnosis. D. Cumulative incidence stratified by requirement for corticosteroids within the first 90 days. E. Cumulative incidence stratified by requirement for hospitalization within the first 90 days.

FIGURE 3.

Cumulative incidence of colectomy among 369 ulcerative colitis patients from Olmsted County, Minnesota, 1970–2004. A. Overall cumulative incidence. B. Cumulative incidence stratified by calendar period of diagnosis. C. Cumulative incidence stratified by gender.

TABLE 1

Baseline characteristics of 369 patients from Olmsted County with ulcerative colitis, 1970–2004.

Patient Characteristics	Number	Percent
Gender		
Female	153	42%
Male	216	58%
Age at UC diagnosis		
< 40 years	218	59%
40 years	151	41%
Diagnosis period		
1970–79	80	22%
1980–89	96	26%
1990–99	117	32%
2000–04	76	20%
Extent (first 90 days):		
Not available	6	2%
Proctitis	108	29%
Left-sided	138	37%
Extensive	117	32%
Early Hospitalization:		
No	296	81%
Yes	70	19%
Early Corticosteroid Use:		
No	300	81%
Yes	69	19%

TABLE 2

Assessment of association between baseline demographic and clinical features with time to first hospitalization and time to colectomy using bivariate Cox proportional hazards regression modeling.

Characteristic	Time to first hospitalization			Time to colectomy		
	Hazard Ratio	95% CI	P-value *	Hazard Ratio	95% CI	P-value *
Gender:						
Female	1.0	Reference		1.0	Reference	
Male	1.1	0.8 – 1.6	0.19	2.1	1.3 – 3.4	0.004
Age at diagnosis:						
< 40 years	1.0	Reference		1.0	Reference	
40 years	1.1	0.8 – 1.6	0.55	0.9	0.6 – 1.5	0.79
Diagnosis period:						
1970–79	1.0	Reference	0.31	1.0	Reference	0.007
1980–89	1.0	0.6 – 1.6		1.4	0.7 – 2.7	
1990–99	1.3	0.8 – 2.1		2.1	1.04 – 4.1	
2000–04	1.5	0.9 – 2.8		3.8	1.7 – 8.4	
Extent [†] :						
Not extensive	1.0	Reference		1.0	Reference	
Extensive	1.6	1.1 – 2.3	0.009	1.4	0.9 – 2.3	0.16
Early [‡] Hospitalization:						
No	1.0	Reference		1.0	Reference	
Yes	1.9	1.3 – 2.8	<0.001	1.4	0.8 – 2.6	0.24
Early [‡] Corticosteroids:						
No	1.0	Reference		1.0	Reference	
Yes	2.1	1.4 – 3.1	<0.001	1.7	0.9 – 3.0	0.08

* Log-rank test.

[†] Maximal extent within first 90 days of diagnosis.

[‡] Early defined as within 90 days of diagnosis.