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# Clinical course and predictors of total colectomy in ulcerative colitis; a referral center experience from Turkey

COLON

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Original Article

## ABSTRACT

**Background/Aims:** We aimed to describe the clinical course of Ulcerative colitis (UC) and the factors that predict the need for total colectomy in Turkish patients with severe UC receiving regular follow up.

**Materials and Methods:** We analyzed the demographic and clinical characteristics of 612 patients with UC receiving regular follow up between 1994 and 2010 in a tertiary referral center in Ankara.

**Results:** Men accounted for 58% of patients (M:F ratio, 1.4:1), and the mean age at diagnosis was 37.9 years. Of these, 32% had distal colitis and 8.8% had further extension, and 39 patients (6.4%) had chronic active disease. Steroid dependency and steroid resistance rates were 7.5% and 17.2%, respectively. In multivariate analysis, steroid dependency (p=0.04), steroid resistance (p=0.002), further extension (p<0.001), presence of extensive disease (p=0.006), and chronic active disease (p<0.001) were independent predictors of the need for total colectomy. Patients with chronic active disease had lower total colectomy free survival (p<0.001).

**Conclusion:** The predictors of total colectomy were comparable with those previously reported in the literature. However, we identified further extension in disease localization to predict the need for total colectomy.

**Keywords:** Ulcerative colitis, clinical course, total colectomy, Turkish

## INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon and rectum. Although the underlying etiology and exact pathogenesis remain unknown, multiple environmental, genetic, and immunological mechanisms may be involved (1). In its most severe form, UC can require total colectomy and increases the risk of colorectal carcinoma (2,3). While the majority of patients with UC have mild disease and respond well to first or second line therapy, up to one-third of patients may require colectomy. Understanding the prognosis and clinical course of the disease is important when determining the preferred medical and surgical treatment and follow-up strategies among different patient subgroups (4-7).

Although UC occurs worldwide, its incidence is higher in the northern hemisphere and among white populations. Little is known about the differences in the clinical characteristics of UC between high and low-incidence areas or among races (2), and few studies have described the clinical course of patients with UC in recent decades. However, the results to date suggest that there could be some differences between Asian and Western populations in the development and clinical course of UC (8,9).

The clinical course of UC is unclear in Turkish populations. Therefore, we aimed to describe the clinical course of UC and the factors that predict the need for total colectomy in severe UC patients receiving regular follow up over a 16-year period.

## MATERIALS AND METHODS

### Study population

The study included retrospective analysis of medical records of 612 patients with UC who regularly visited the inflammatory bowel disease (IBD) outpatient clinic in a tertiary referral center (Ankara) between 1994 and

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2010. We analyzed age, gender, smoking habits, family history, disease duration, disease localization, clinical course, medical treatment, corticosteroid resistance and dependency, progression and regression of disease localization, total colectomy requirement, and mortality.

### Diagnosis of UC

Confirmed UC had to satisfy the internationally accepted Lennard-Jones criteria for the diagnosis of IBD. The diagnosis is based on appropriate clinical, endoscopic, histopathological, and radiological findings, with careful exclusion of indeterminate colitis, infectious, and other recognized causes of colonic inflammation (10). An accredited gastroenterologist made the final diagnosis.

### Clinical course

The clinical courses of participants were classified into 4 groups according to the UC guidelines published by the European Crohn's and Colitis Organisation (ECCO) in 2008 (11), as follows:

- Chronic Active Disease: Persistent symptoms of active UC without remission;
- Chronic Intermittent, Rare Attacks: <1 relapse per year;
- Chronic Intermittent, Frequent Attacks: >2 relapses per year; and
- Remission: Stool frequency of ≤3/day with no bleeding and normal mucosa at endoscopy following an initial attack.

### Steroid dependency and resistance to steroid

The ECCO definitions of steroid-dependent and steroid-resistant patients (2008) were used (11). Steroid-dependent patients were either unable to reduce steroids to below 10 mg/day of prednisolone (or equivalent) within 3 months of starting them without recurrent active disease, or relapsed within 3 months of stopping steroids. Steroid-resistant patients had active disease despite prednisolone doses of up to 0.75 mg/kg/day over a 4-week period (11).

### Statistical analysis

Statistical analyses were performed using SPSS version 18 (SPSS, Chicago, IL. Descriptive statistics (frequencies, means, and standard deviations) were calculated. Correlation coefficients (r) were used to explore associations between variables: Pearson's r for interval variables, Spearman's r for ordinal variables. Univariate and multivariate logistic regression analyses were performed to determine the association of various factors with the requirement of total colectomy, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Factors with $p<0.2$ in the univariate analyses were included in the multivariate analyses. Kaplan-Meier survival curves for clinical course were used for patients divided into 2 groups (chronic active disease and other types). The decisive event was the requirement of total colectomy.

## RESULTS

### Epidemiologic and demographic characteristics

We analyzed 612 patients; 355 patients (58%) were male, 257 (42%) were female (male: female ratio=1.4:1), and the mean age at diagnosis was 37.9 years (peak incidence among 30-39 year olds). At diagnosis, 70 patients (11.4%) were smokers and 148 (24.2%) were ex-smokers, whereas 41 patients (6.7%) had a positive family history of IBD. The mean disease duration at the end of the study was 9.4 years (range: 1-34). The epidemiologic and demographic characteristics are summarized in Table 1.

**Table 1.** Epidemiologic and demographic characteristics of patients

| | |
|---|---|
| Age (Mean Years±SD) (Min-Max) | 47.3±14.5 (16-91) |
| Age at Diagnosis (Mean Years±SD) (Min-Max) | 37.9±13.9 (10-80) |
| Duration of Disease (Mean Years±SD) (Min-Max) | 9.4±6.5 |
| Gender (Female/Male) (n, %) | 257 (42%)/355 (58%) |
| Family History for IBD (n, %) | 41 (6.7%) |
| Appendectomy in Medical History (n, %) | 33 (5.4%) |
| Tonsillectomy in Medical History (n, %) | 8 (1.3%) |
| **Smoking Habitus** | |
| Non-Smoker (n, %) | 394 (64.4%) |
| Ex-Smoker (n, %) | 148 (24.2%) |
| Smoker (n, %) | 70 (11.4%) |

IBD: inflammatory bowel disease, SD: standard deviation

### Disease localization

By disease localization we identified 196 (32%) with distal localization, 214 (34.9%) with left sided disease, and 202 (33.1%) with extensive disease. Disease progression occurred in 55 cases (8.8%) and regression in 206 cases (33.7%).

### Clinical course

After diagnosis, 17 patients (2.8%) were considered in remission, having not relapsed. The mean duration of remission in this group was 6.1 years. Furthermore, 39 cases (6.4%) were chronically active, 471 (77.0%) had chronic intermittent disease with rare attacks, and 85 (13.8%) had chronic intermittent disease with frequent attacks.

### Medical treatment

Salicylates were used in 99.4% of the patients, and were the only drug used in 55.4%. A total of 162 patients (26.4%) had taken steroids at least once, 45 (7.3%) had been treated with immunosuppressant agents, and 5 (0.7%) with biological agents. Among patients who had taken steroids at least once, 28 (17.2%) were considered steroid-resistant and 12 (7.5%) were considered steroid dependent. The immunosuppressant agent used in our clinical practice was azathioprine.

### Surgical treatment

Total colectomy with ileal pouch anal anastomosis was performed in 61 of 612 patients (9.9%). Indications for surgery were as follows: non-response to medical treatment or drug side effects in 43 (70.5%) cases; emergent complications in 13 (21.3%); and dysplasia and colon cancer in 5 (8.2%). After colectomy, dysplasia was found in 13 patients (2.1%), and colorec-

**Table 2.** Clinical characteristics of patients

| | |
|---|---|
| **Localization of Disease** | |
| Distal (n, %) | 196 (32.0%) |
| Left Sided (n, %) | 214 (34.9%) |
| Extensive (n, %) | 202 (33.1%) |
| Disease Progression (Further Extension in Localization) | 55 (8.8%) |
| **Clinical Course** | |
| No Relapse After Diagnosis (n, %) | 17 (2.8%) |
| Chronic Intermittent Stage (Rare Attacks) (n, %) | 471 (77.0%) |
| Chronic Intermittent Stage (Frequent Attacks) (n, %) | 85 (13.8%) |
| Chronic Active Disease (n, %) | 39 (6.4%) |
| **Medical Treatment (At Least Once)** | |
| Salicylates (n, %) | 608 (99.4%) |
| Steroids (n, %) | 162 (26.4%) |
| 6-MP/AZA (n, %) | 45 (7.3%) |
| Biologic Agents (n, %) | 5 (0.7%) |
| Steroid Dependency (n, %) | 12 (7.5%) |
| Steroid Resistance (n, %) | 28 (17.2%) |
| Total Colectomy (n, %) | 61 (9.9%) |
| **Indications for Total Colectomy** | |
| No response to Medical Treatment/Side Effect of Drug (n, %) | 43 (70.5%) |
| Emergent Complication (n, %) | 13 (21.3%) |
| Dysplasia (n, %) | 5 (8.2%) |
| **Mortality (n, %)** | |
| Underlying Disease | 6 (0.9%) |
| Colorectal cancer | 2 (0.3%) |
| Toxic Megacolon | 1 (0.2%) |

tal cancer in 3 patients. The mortality rate was 0.98% (6/612); 3 died from the underlying disease (0.5%). The clinical characteristics of patients are summarized in Table 2.

On univariate logistic regression analyses, significant associations were observed with steroid dependency (p<0.001), steroid resistance (p<0.001), disease progression (i.e., further extension in disease localization) (p<0.001), extensive disease (p<0.001), chronic active disease (p<0.001), and age at diagnosis (p=0.02). The following remained significant after multivariate logistic regression analysis: steroid dependency (p=0.04), steroid resistance (p=0.002), disease progression (p<0.001), extensive disease (p=0.006), and chronic active disease (p<0.001). Univariate and multivariate adjusted ORs for the factors associated with total colectomy are shown in Table 3.

There were statistically different survival rates between patients with chronic active disease and other clinical courses

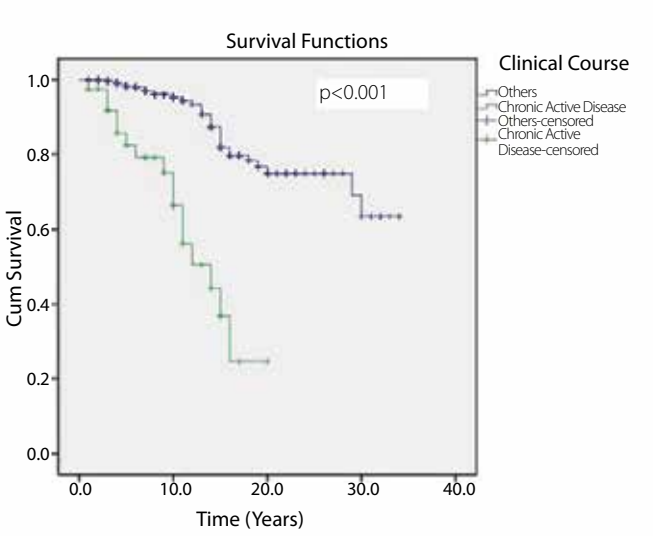


**Figure 1.** Kaplan-Meier Survival Curve for total colectomy free survival comparing patients with chronic active disease and those with milder clinical courses.

using Kaplan-Meier Survival curves for total colectomy free survival (p<0.001) (Figure 1).

## DISCUSSION

Ulcerative colitis is an inflammatory disorder of the colon of unknown etiology that begins in the rectal mucosa and extends proximally to involve other portions of the bowel. It classically has a variable clinical course, including unpredictable relapses and remissions (12-14). Although few studies have analyzed the epidemiologic and demographic features of UC (15,16), we are not aware of any that has reviewed the clinical course of UC in Turkish population. Therefore, we aimed to describe the clinical course of UC and the factors that predict the need for total colectomy in Turkey.

The basic demographic findings in our cohort were comparable to those observed in Western countries. Our data revealed a slight male predominance for UC and a mean age at diagnosis of 37.9 years, which is consistent with other Western and Asian studies. Population-based studies have found that the proportion of Western patients with proctitis ranges from 32% to 59%, while that among Asian patients is 25%-44% (1,17-20). In our study, the proportion of patients with proctitis was 32%. However, just 55 cases (8.8%) demonstrated local extension (disease progression), which is much lower than that reported in studies in Europe and North America. In the Inflammatory Bowel South-Eastern Norway (IBSEN) study for example, progressive extension was observed in 20% of patients over a 10-year follow-up period (21). In other studies, progression has been observed in up to 53%, although study design and duration of follow up varies greatly (22-24).

At 7.3%, the use of immunosuppressives in our cohort was lower than that in Western populations. Indeed, Acosta et al., reported rates of 15% in a Northern Portuguese and Spanish

**Table 3.** Univariate and multivariate logistic regression analyses for association of factors with total colectomy

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| **Factor** | **OR** | **CI 95%** | **p value** | **OR** | **CI 95%** | **p value** |
| Age | 1.7 | -0.002-0.001 | 0.1 | 1.1 | 0.931-1.224 | 0.3 |
| Gender | 2.0 | -0.035-0.227 | 0.1 | 1.1 | 0.625-2.255 | 0.5 |
| Age at Diagnosis | 5.2 | -0.003-0.001 | 0.02 | 0.9 | 0.804-1.055 | 0.2 |
| Duration of Disease | 3.2 | -0.002-0.006 | 0.07 | 0.9 | 0.850-1.132 | 0.7 |
| Family History for IBD | 0.3 | -0.086-0.047 | 0.5 | | | |
| MH for Appendectomy | 1.2 | -0.025-0.093 | 0.2 | | | |
| MH for Tonsillectomy | 0.7 | -0.321-0.123 | 0.3 | | | |
| Presence of Extensive Disease | 12.6 | 0.040-0.139 | <0.001* | 2.3 | 1.260-4.230 | 0.006* |
| Progression in Localization of Disease | 26.4 | 0.131-0.292 | <0.001* | 3.9 | 1.659-8.369 | <0.001* |
| Steroid Dependency | 20.4 | 0.049-0.125 | <0.001* | 4.3 | 1.066-17.579 | 0.04* |
| Steroid Resistance | 21.6 | 0.149-0.368 | <0.001* | 4.7 | 1.749-12.718 | 0.002* |
| Presence of chronic active disease | 20.0 | 0.110-0.283 | <0.001* | 7.9 | 3.542-17.996 | <0.001* |
| Active Cigarette Smoking | 0.2 | -0.120-0.028 | 0.2 | | | |

IBD: inflammatory bowel disease, MH: medical history; OR: odds ratio; CI: confidence interval



cohort (25), while in Canada, the rate was 12% (26). Additionally, only 5 patients (0.7%) were treated with biological agents in our study, and steroid dependency and resistance rates were just 7.5% and 17.2%, respectively. This compares favorably with the steroid dependency rate of 29% reported by Faubion et al., among 185 adults with UC, living in Olmsted County (USA) (27). In a 5-year Scottish hospital-based inception cohort study, the steroid dependency and resistance rates were 17% and 18%, respectively (28).

During a 5-year observation period, 354 (78%) patients in the IBSEN study had at least 1 relapse. Chronic continuous symptoms and chronic relapsing symptoms were experienced by 36 (9%) and 129 (31%) patients, respectively (29). In our study, when patients were classified by their clinical courses using number of relapses, 13.8% patients were classed as chronic intermittent with frequent attacks, and only 6.4% patients had chronic continuous symptoms.

In addition to the number of relapses, the need for surgery is an objective criterion when assessing the clinical course of UC (29), representing a useful end-point measure of disease severity. In the studies from Western countries, surgical operations are reportedly performed in 20%-25% of patients with UC (1,30), and in a population-based study from Stockholm, the cumulative risk of colectomy after 5 years was 20% (95% CI, 18%-22%). Langholtz et al., also reported a cumulative risk of 20% after 5 years in Copenhagen (31,32). Total colectomy was performed in just 61 of our 612 patients (9.9%). Thus, the colectomy rate was much lower than that reported in previous studies in North America and Western Europe.

In patients with UC, lack of response to steroids, chronic continuous symptoms, and persistently elevated inflammatory markers have all been shown to predict colectomy in hospitalized patients (33-35). Although most studies agree that patients with pancolitis are more likely to require colectomy than those with relatively limited disease, there is limited data concerning other factors that predict the need for colectomy in patients with longstanding disease. Evidence for other potential predictive factors, such as malnutrition or an inability to wean steroids, is unclear and limited (36-38). In our study, multiple logistic regression analysis revealed that steroid dependent or resistant disease, disease extension, extensive disease, and chronic active disease were independent predictors of total colectomy in patients with UC. We also demonstrated that patients with chronic continuous symptoms had lower total colectomy free survival rates.

Based on our study, the clinical presentation of UC in our Turkish population appears to be similar to that in developed countries. However, the study is limited by the retrospective nature of the database, and by the relatively mild clinical course, which may have been due to the data being collected from a single referral center with expertise in managing UC. Nevertheless, it should be kept in mind that all tertiary hospitals in Turkey have outpatient clinics to which patients can directly refer themselves. Indeed, the majority of patients with UC are initially diagnosed in these tertiary referral centers. We think that this fact reduces the possibility of selection bias in our study.

In conclusion, total colectomy, steroid-resistant or steroid-dependent disease, chronic continuous symptoms, and disease progression rates were lower than previously reported in Eu-

ropean and North American cohorts, whereas the predictors of total colectomy were comparable. Moreover, we identified disease progression (defined as further extension in disease localization) as a predictor of total colectomy, which has not been described to date.

**Ethics Committee Approval:** N/A

**Informed Consent:** Written informed consent was obtained from patients who participated in this case.

**Peer-review:** Externally peer-reviewed.

**Author contributions:** Concept - Ü.D., İ.H.K.; Design - Ü.D., İ.H.K.; Supervision - Ü.D.; Data Collection&/or Processing - İ.H.K., M.K., Ü.D., B.T., A.Ü.; Analysis&/or Interpretation - İ.H.K., E.Ö.; Literature Search - İ.H.K., E.Ö.; Writing - İ.H.K.; Critical Reviews - Ü.D.

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