


ORIGINAL ARTICLE

Left-sided colitis and extensive colitis have similar colectomy rates after index episode of acute severe colitis: A long-term follow-up study

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Introduction

Ulcerative colitis (UC) is characterized by relapses and remission, and severe exacerbation (acute severe colitis, ASC) requires hospitalization and time-bound management. ASC episodes complicate 25% of UC during their disease course.¹ Occurrence of ASC redefines the natural history of UC as these patients, if they survive surgery at the index episode, are at a greater risk of adverse outcomes, including colectomy, repeat episodes of ASC, and steroid dependence.^{1,2} Identification of factors determining the long-term outcome after ASC would improve management decisions and prognostication in

Abstract

Background and Aim: The extent of disease of ulcerative colitis (UC) has been found to be a predictor of acute severe colitis (ASC), but it is unclear whether the extent of disease at the index episode of ASC is a predictor of long-term outcome.

Methods: Hospitalized patients satisfying Truelove and Witts' criteria under follow-up at a single center from January 2003 to December 2016 were included. The extent of disease at index ASC was classified according to the Montreal classification as left-sided or extensive colitis. Extent was used to predict the long-term risk of colectomy or steroid dependence following an index episode of ASC.

Results: Of 2076 patients with ulcerative colitis, 241 (12%) had an index episode of ASC. In total, 34 (14%) patients underwent a colectomy at index admission and 53 (26%) over a median follow-up of 48(1–172) months. Left-sided colitis and extensive colitis did not differ in the rate of colectomy at index admission (12% vs 15%, $P = 0.4$) and colectomy in follow-up (31% vs 23%, $P = 0.17$). Readmission due to ASC was also similar between the two groups (28% vs 32%, $P = 0.6$).

Conclusion: Extent of disease at index ASC does not predict colectomy at admission and over the long term.

these patients. As per the current literature, the most important factor predicting long-term outcome in ASC is 7-day response to intravenous steroids.^{2,3} The extent of disease as classified by the Montreal classification⁴ has been a risk factor for many long-term outcomes in UC, including colectomy,⁵ development of CRC,⁶ and increased incidence of ASC.^{7,8} However, the effect of the extent of disease on the long-term outcomes of ASC has not been studied systematically, with some studies finding extensive disease as a predictor of colectomy,⁹ whereas others did not,^{2,7,10} with median follow-up ranging from 18 to 122 months. The difference in outcome, if any, would be important in view of the management of acute episodes of

severe colitis and patient counseling. Thus, our objective was to determine if extensive colitis had a different clinical course than left-sided colitis after an index episode of ASC.

Methods

Study population. Patients with ASC who satisfied Truelove and Witts' criteria¹¹ and who were first hospitalized and then followed up at the Inflammatory Bowel Disease (IBD) Clinic at the All India Institute of Medical Sciences (AIIMS), New Delhi, India, from January 2003 until March 2016 were included.

Study design. We conducted a retrospective analysis of a prospectively maintained database at the IBD Clinic, AIIMS, New Delhi. Patient files contain all dated information concerning the disease and distribution, including history, medical examination, test results, and follow-up symptom assessment. A team of physicians maintains the files, and internal audit has shown that the parameters used for assessment are consistent between physicians. The following information was extracted from the database: age at ASC, gender, extraintestinal manifestations (EIMs), disease duration before index admission, extent of disease at index colonoscopy, smoking status at admission, prior steroid or immunomodulator use, steroid use during first year of diagnosis, duration of intravenous (IV) steroids on the index admission, use of rescue therapy, presence of toxic megacolon, or colectomy at index admission. Patients were followed up from date of index admission to death, colectomy, or study end-point of May 2017, whichever occurred earlier. The parameters considered during follow-up included steroid dependence on follow-up, immunomodulator use (including thiopurines, cyclosporine, methotrexate, or anti-tumor necrosis factor [TNF]- α agent), rehospitalization, relapse, and colectomy.

Patients admitted for ASC were managed according to standard guidelines.^{12,13} Patients were admitted and treated with intravenous hydrocortisone (300–400 mg/day) for 5–7 days. Antibiotics were administered, as well as blood transfusions as and when required. If the patient was unresponsive to 5–7 days of first-line medical therapy, the options of colectomy or cyclosporine rescue medical therapy were advised, with infliximab as a further option for patients since 2011. Patients responding to first-line medical therapy were discharged on 40 mg/day oral prednisolone with a taper period of 3–4 months. Biologicals were used in a small minority because of prohibitive costs.

The Institutional Review Board of AIIMS approved this study protocol (IRB number: IESC/T-277).

Definitions

Acute severe colitis. Based on Truelove and Witts' criteria, ASC was defined as six or more stools with blood and one or more of following: hemoglobin < 10.5 g/dL, erythrocyte sedimentation rate (ESR) > 30 mm/h, fever >37.8°C, or tachycardia > 90/min.^{11,13}

Response at day 7. Using the criteria defined by Travis *et al.*² response to IV steroids at day 7 of therapy was divided into complete responder (CR), defined as ≤ 3 stools/day without blood, and nonresponder (NR), defined as patients undergoing

colectomy during index admission. Those patients having >3 stools/day or blood in stool at day 7 and who avoid colectomy at index admission were followed up as an incomplete responder (IR).

Steroid use during first year. This was defined as systemic steroid use in the first year, including index ASC if occurring within first year of diagnosis of UC.

Extent of disease. Extent of disease was defined as the maximum endoscopic extent at the most recent colonoscopy according to the Montreal classification.⁴ In patients with first presentation of disease as ASC, extent was determined from the surgical specimen if they underwent colectomy or from first available full-length colonoscopy after discharge.

Steroid dependent. Steroid dependence was defined as either the inability to reduce the steroid dose below the equivalent of prednisolone 10 mg/day within 3 months after discharge or the occurrence of a relapse within 3 months of stopping steroids.¹⁴

Rehospitalization. Rehospitalization was defined as hospitalization for a repeat episode of ASC. Hospitalizations for diagnostic workup or conditions unrelated to UC were excluded.

Disease relapse. Relapse was defined as simple clinical colitis index ≥ 5 .¹⁵

Statistical analysis. Continuous variables were expressed as the mean \pm SD or as median and range in the case of a non-normal distribution. Categorical variables were summarized as frequencies with percentages. Quantitative variables at admission were compared using Student's *t* test or the Mann–Whitney test and qualitative variables using the chi-square test. Comparison of the means of continuous variables for two groups was based on analysis of variance or the nonparametric Kruskal–Wallis test, where indicated. *P* values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS software (IBM SPSS statistics 24; IBM, New Orchard Road, Armonk, NY, USA).

Results

In total, 2076 patients with UC were treated at AIIMS between January 2003 and December 2016. Of these patients, 241 (11.6%) experienced an index episode of ASC and were hospitalized, 34 patients underwent colectomy at this admission, and 207 patients who avoided colectomy were followed up for a median duration of 48 (1–172) months. Twenty patients were lost to follow-up (Fig. 1). The mean age at index ASC was 35 ± 12 years, 52% were male, 13% had an index admission for ASC as the initial presentation of UC, 32% had EIMs, 64% had at least one course of prior steroid use, and 20% had prior immunomodulator use (Table 1). The median duration of hospital stay was 10 (3–90) days.

Comparison between patients who had left-sided and extensive colitis at index hospitalization. Of 241 patients, 84 (35%) had left-sided colitis at index

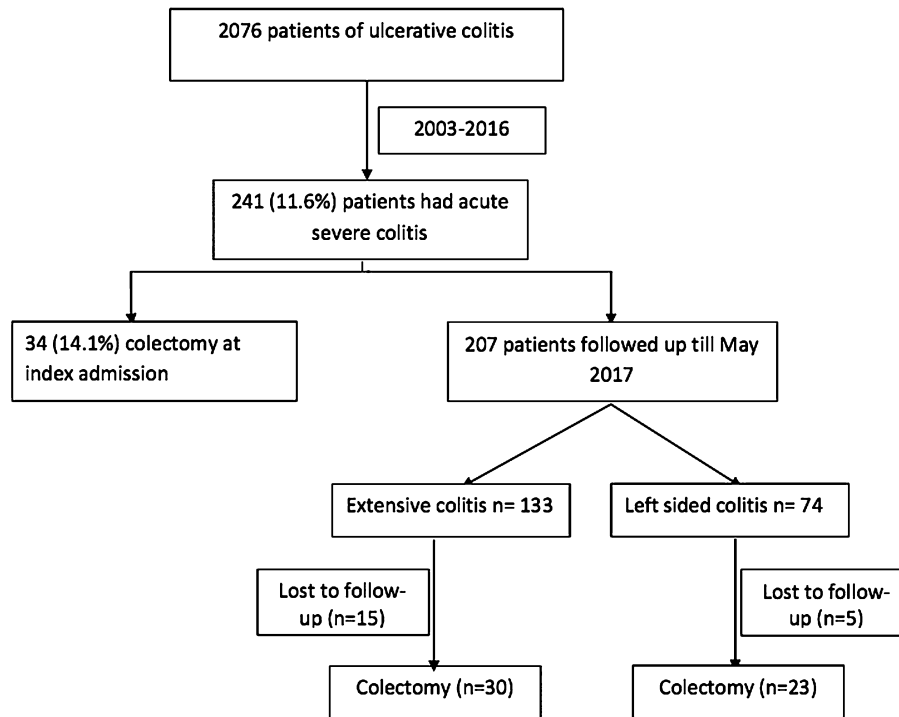


Figure 1 Flow chart: study population.

hospitalization. There were no differences between the two groups in terms of age at ASC, gender, median duration of disease before index episode, frequency of index presentation, smoking status at admission, prior steroid or immunomodulator

use, presence of EIMs, prior immunomodulator treatment, response to intravenous steroid, and use of rescue therapy or colectomy. There were no deaths during index hospitalization (Table 1). Of the 34 patients who underwent colectomy at index

Table 1 Characteristics of patients with left-sided colitis *versus* extensive colitis at index admission for ASC

	Total (n = 241)	Left-sided colitis (n = 84)	Extensive colitis (n = 157)	P value
Age at ASC (years)	35.5 ± 12.3	34.6 ± 11.8	35.9 ± 12.4	0.4
Male	125 (52)	42 (50)	83 (53)	0.7
Duration of UC at time of admission (months)	24 (0–240)	24 (0–228)	24 (0–240)	0.3
Index presentation [†]	30 (12.5)	7 (8.3)	23 (14.6)	0.15
Presence of EIMs	78 (32.4)	22 (26.2)	56 (35.7)	0.13
Smoking	17 (7)	5 (5.9)	12 (7.6)	
Prior immunomodulator treatment	48 (19.9)	17 (20.2)	31 (19.7)	0.9
Prior steroid use	155 (64.3)	54 (64.3)	17 (64.3)	0.9
Response at day 7				0.8
Complete responder	94 (39)	34 (40.5)	60 (38.2)	
Partial responder	113 (47)	40 (47.6)	73 (46.5)	
Nonresponder	34 (14.1)	10 (11.9)	24 (15.3)	
Toxic megacolon	5 (2.1)	0	5 (3.2)	0.09
Rescue therapy				0.9
Cyclosporine	11 (4.6)	4 (4.8)	7 (4.5)	
Infliximab	4 (1.7)	1 (1.2)	3 (1.9)	
Steroid use during first year of diagnosis	151 (62.7)	48 (57.1)	103 (65.6)	0.19
Colectomy	34 (14.1)	10 (11.9)	24 (15.3)	0.4
Duration of intravenous steroids	5 (3–11)	5 (3–10)	5 (3–11)	0.3

[†]Index presentation, defined as index admission for ASC being the initial presentation of UC.

Values as mean ± SD, median (range), or n (%) as appropriate.

ASC, acute severe colitis; EIMs; extraintestinal manifestations; UC, ulcerative colitis.

Table 2 Long-term outcomes in patients who avoided colectomy during index admission for ASC according to extent at index ASC

	Total (n = 207)	Left-sided colitis (n = 74)	Extensive colitis (n = 133)	P value
Steroid dependence	84 (40.6)	31 (42)	53(40)	0.7
Immunomodulator use	157 (76)	55 (74.3)	102 (76.7)	0.7
Readmission due to ASC	63 (30.4)	21 (28.4)	42 (31.6)	0.6
Time to first readmission due to ASC (months)	16 (1–155)	21 (2–63)	15.5 (1–155)	0.6
Number of relapses/year	0.8 (0–3)	0.6 (0–3)	0.8 (0–3)	0.8
Time of surgery from index hospitalization (months)	21 (1–157)	25 (3–84)	16 (1–157)	0.5
Maximum duration of remission (months)	23 (0–137)	19 (2–137)	24 (0–113)	0.8
Colectomy	53 (25.6)	23 (31.1)	30 (22.6)	0.17
Duration of follow-up	48 (1–172)	51.5 (3–169)	40 (1–172)	0.6
Mortality	8 (3.3)	2 (2.4)	6 (3.8)	0.5

Mean follow-up 48 (1–172) months. Values as mean \pm SD, median (range), or n (%) as appropriate. ASC, acute severe colitis.

admission, the colectomy rates were similar for left-sided colitis and extensive colitis (10 [11.9%] vs 24 [15.3%]).

Long-term outcome according to extent of disease at index hospitalization. Of 241 patients, 207 avoided colectomy during index admission and were followed up. Long-term outcomes were analyzed according to the extent of UC at admission (Table 2). Among 207 patients, 74 had left-sided colitis and 133 had pancolitis.

Steroid dependence and immunomodulator use. Steroid dependence at any time during follow-up was observed in 84 of 207 (41%) patients (Table 2). The rate of steroid dependence and immunomodulator use did not differ between the two groups. Among immunomodulators, thiopurines were most commonly used 129 of 207 (62%), and anti-TNF- α agent and cyclosporine were used by 13 patients each. Methotrexate was used in two patients only.

Colectomy. Fifty-three (25.6%) patients underwent colectomy after discharge following the index admission over a median follow-up of 48 months (Table 2). Colectomy rate did not differ among patients with left-sided versus extensive colitis (31% vs 22%, $P = ns$). The two groups also did not differ in the time to colectomy from index hospitalization. A survival analysis did not reveal any significant difference in colectomy rates between left-sided colitis and extensive colitis, with HR (95% confidence interval) 1.3 (0.79–2.3) and $P = 0.26$ (Fig. 2).

Recurrent ASC, relapses, and re-hospitalization. Of 207 patients, 63 (30%) had repeat episodes of ASC (Table 2). Readmission due to repeat ASC was not different between left-sided colitis and extensive colitis. The two groups also did not differ in number of relapses/year and duration of remission.

Mortality. Among 207 patients, we observed eight deaths in follow-up; one death was due to exacerbation of UC. One patient had concomitant chronic kidney disease and died due to acute chronic kidney disease, two had decompensated cirrhosis (hepatitis C and Non-alcoholic steatohepatitis related), one expired due to colon cancer, one had acute myocardial infarction, and two had malnutrition with secondary infection. There was no difference in mortality rate between the two groups.

Discussion

The long-term course of UC is influenced by two distinct disease-related processes: the extent of disease and disease severity at presentation. The Montreal classification⁴ for extent of disease and severity of UC was proposed in 2006 with the same intent to predict the response to medical therapy, along with the natural history in terms of rates of medication usage, hospitalization, colectomy, or risk of colorectal cancer. Since then, many prospective studies have evaluated the effect of the extent of disease on long-term outcomes of UC, with some reporting poor long-term outcomes with extensive colitis. Extensive colitis had a higher risk of colectomy in the next 10 years in the inflammatory bowel disease South-Eastern Norway (ISBEN) cohort,⁵ and

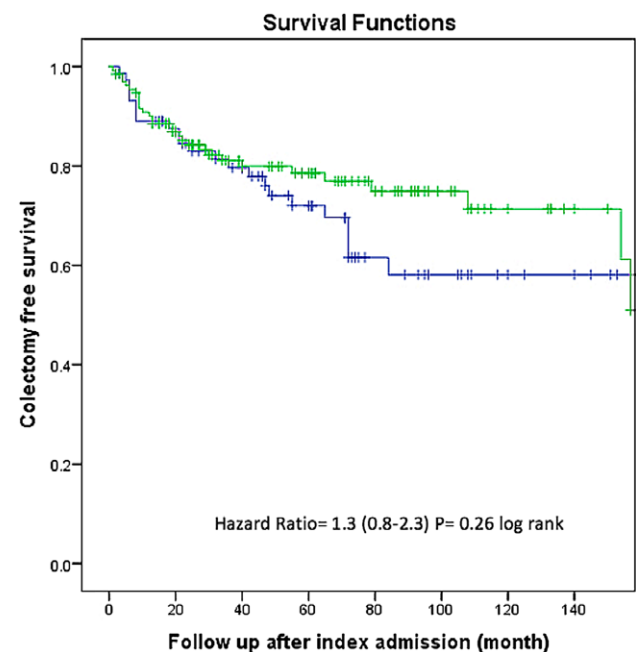


Figure 2 Kaplan–Meir survival analysis showing high colectomy rates in patients with acute severe colitis according to the extent of disease. —, Left-sided colitis; —, extensive colitis; —, censored; —, censored.

it also predicted the development of ASC over the next 3 years.⁸ The effect of disease severity on long-term outcome was also reported in the IBSEN cohort, with the 2-year cumulative colectomy rate among patients diagnosed with extensive colitis being 3% in the group with an ESR <30 mm/h compared with 21% in the group with elevated ESRs ≥30 mm/h. The poor long-term outcomes of patients with ASC are another example of the effect of disease severity on long-term disease course. However, the combined effect of both the extent of disease and disease severity on long-term outcomes in UC remains unknown, and the present study has tried to address this issue.

We found that in one of the largest cohort of patients with ASC, there was no effect of the extent of disease on long-term outcomes, and the rates of colectomy, steroid dependence, and immunomodulator use was similar between patients with left-sided and extensive colitis. The colectomy-free survival rate obtained using Kaplan–Meir analysis, despite a trend extensive colitis, also not differ significantly between left-sided and extensive colitis. The extent of disease did not have any effect on short-term outcomes as well, and the rates of rescue therapy and colectomy at index admission were similar between left-sided and extensive colitis. This indicates that it is the quantum of inflammation that decides the long-term outcome in a patient with severe colitis, and the effect of the extent of disease, if any, is nullified by this inflammation. ASC is the extreme end of the spectrum of disease severity in UC and occurs when this inflammation spills beyond the intestine and manifests in the form of elevated ESR, fever, tachycardia, and anemia, and these features form the part of Truelove and Witt's criteria¹¹ for diagnosis of ASC. In this severe subgroup of UC as well, the extent of severity can predict short-term outcomes as shown in the landmark paper, which led to the development of Oxford criteria,¹⁶ and by us in a recent study,¹⁷ in which fecal calprotectin could predict short-term outcomes in ASC. Regarding long-term outcomes in ASC, the only factor that is consistent across all studies is the response to intravenous steroids at day 7,^{2,3} and this in turn depends on the severity of ASC at index admission. Therefore, among the patients with ASC, long-term outcome is likely to be affected by disease severity rather than the extent of disease.

These findings contrast those of Molnár *et al.*⁹ but are consistent with other long-term studies.^{2,7,10} The reason for these findings could be that the individual inflammatory state not only depends on the extent but the intensity of inflammation, which in turn is influenced by genetic factors and gut microbiome.¹⁸ This is particularly relevant in clinical settings where it can help the physician plan rescue therapy/colectomy in steroid NRs and manage the expectations of the patient.

Treatment options for UC have changed over time, and biological agents can provide better immunosuppression; thus, cases enrolled in recent years might have been exposed to treatment that is more effective and are therefore less likely to experience a colectomy. However, this would have affected both our arms. We used cyclosporine/infliximab in only 28 of 207 (14%) patients due to prohibitive costs, with similar use in left-sided and extensive colitis (10/74 vs 18/133, $P = ns$). In addition, in the long-term follow-up of the CYSIF trial,¹⁹ 39 of 115 (34%) patients treated with cyclosporine/infliximab underwent a colectomy within a median follow-up of 5 years, which is similar to our results.

Nevertheless, our study has limitations, which include the retrospective nature of the study and that it reflects practice in a tertiary center, which may influence the generalizability of results. The sample size of cohort, although large, was a convenience sample, and this could have prevented further comprehensive multivariate analyses, such as adjustment for medication dosage and quantification of risk factors, from being underpowered for these interpretations. The extent of disease can vary over time, and it is possible that our patients' extents of disease could have changed over follow-up, but this should not influence our inferences as we aimed to predict long-term outcomes at index ASC.

To conclude, left-sided colitis and extensive colitis at index ASC have similar colectomy rates at index episode and on long-term follow-up. This knowledge can influence decision making at the time of index ASC.

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