

**Predictors of long-term outcomes in patients with acute severe colitis: A Northern Indian cohort study**

**Short title: Acute severe colitis: Predictors of long-term outcome**

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## **Abstract:**

**Background and Aim:** Knowledge of long-term outcomes following an index episode of acute severe colitis (ASC) can help informed decision-making at a time of acute exacerbation especially when colectomy is an option. We aimed to identify long-term outcomes and their predictors after a first episode of ASC in a large North Indian cohort.

**Methods:** Hospitalized patients satisfying Truelove and Witts' criteria under follow-up at a single centre from January 2003–December 2013 were included. Patients avoiding colectomy at index admission were categorized as complete ( $\leq 3$  non bloody stool per day) or incomplete responders (CR, IR), based upon response to corticosteroids at day 7. Random Forest based machine learning models were constructed to predict the long term risk of colectomy or steroid dependence following an index episode of ASC.

**Results:** Of 1731 patients with ulcerative colitis, 179(10%) had an index episode of ASC. Nineteen(11%) patients underwent colectomy at index admission and 42(26%) over a median follow-up of 56(1-159) months. Hazard ratio for colectomy for IR was 3.6(1.7-7.5,  $p=0.001$ ) compared to CR. Modeling based on four variables: response at day 7 of hospitalization, steroid use during first year of diagnosis, longer disease duration prior to ASC and number of extra-intestinal manifestations, was able to predict colectomy with an accuracy of 77%.

**Conclusions:** Disease behavior of ASC in India is similar to the West, with a third undergoing colectomy at 10 years. Clinical features, especially response at day 7 hospitalization for index ASC, can predict both colectomy and steroid dependence with reasonable accuracy.

**Key words:** colectomy; acute severe colitis; prediction

## **Introduction**

Ulcerative colitis (UC) is characterized by periods of remission and relapse, with the cumulative risk of hospital admission with acute severe colitis (ASC) being 25%.<sup>1</sup> Around a third of patients with ASC present at diagnosis.<sup>1,2</sup> Corticosteroids remain first line therapy for ASC and in 2007, a systematic review of 1991 patients reported a overall response rate of 67%, colectomy rate of 29% and mortality of 1% that had not changed since the 1970s<sup>3</sup>.

Predictors of short term response to IV steroids have been proposed<sup>4</sup>, with CRP and stool frequency response at day 3 being widely adopted<sup>5,6</sup>. However the long-term outcome in different geographic regions after IV steroids has been little explored, with only 6 studies reporting to date<sup>1,7-11</sup>. Colectomy rates across these studies vary from 30-64% with a median follow-up from 4.4 years to more than 10 years. Predictors of long-term response have not been well defined. In South and East Asia, the disease burden of UC is rising, but there is only one study from South Korea reporting outcomes in patients with UC<sup>7</sup>. It is unclear whether the disease course of UC in Asians is similar to or milder than Caucasians. The present study was therefore undertaken to evaluate long-term outcomes after IV steroids in a cohort of patients with ASC from a South Asian region and to develop predictive models for long-term colectomy and steroid dependence based on machine learning after an episode of ASC.

## **Methods**

### **Study population**

Patients with ASC satisfying Truelove and Witts' criteria<sup>12</sup> who first were hospitalized and then followed-up at the IBD clinic at All India Institute of Medical Sciences(AIIMS), New Delhi, India from 2003 till 2013 were included.

### **Study Design**

We did 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

parameters used for assessment are consistent between physicians. The following information was extracted from the database: age at ASC, sex, presence and number of extra-intestinal manifestations (EIMs) at or prior to index ASC, 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 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 April 2016 whichever occurred earlier. The parameters considered in follow-up included: steroid dependence on follow-up, immunomodulator use (including thiopurines, ciclosporin, methotrexate, or antiTNF $\alpha$  agent), rehospitalization, and relapse.

Patient admitted for ASC were managed according to standard guidelines.<sup>6,13</sup> Patients were admitted and treated with intravenous hydrocortisone (300-400 mg/d) for 5-7 days, whilst continuing 5ASA therapy. CMV infection was confirmed by presence of inclusion body in histopathological examination and treated if present, testing for *C difficile* toxin was done routinely after 2009. Antibiotics were given and blood transfusions as and when required. If unresponsive to 5-7 days of first line medical therapy, options for colectomy or ciclosporin 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 40mg/day oral prednisolone with a taper period of 3 to 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:** ASC based on Truelove and Witts' criteria defined as 6 or more stools with blood and one or more of following: hemoglobin <10.5 g/dl, erythrocyte sedimentation rate >30 mm/hr, fever >37.8°C, or tachycardia >90/minute.<sup>12,14</sup>

**Response at day 7:** Using the criteria defined by Travis et al<sup>5</sup> response to IV steroids at day 7 of therapy was divided into complete responder (CR) defined as  $\leq 3$  stools/day without blood, non responder (NR) was defined as patients undergoing colectomy during index admission.

Patients having >3 stools/day or blood in stool at day 7, and those who avoided colectomy at index admission were followed up as incomplete responder (IR).

**Steroid use during 1<sup>st</sup> year:** This was defined as systemic steroid use in first year, including index ASC if occurring within 1<sup>st</sup> year of diagnosis of UC.

**Disease extent:** Extent of disease was defined as the maximum endoscopic extent at most recent colonoscopy according to Montreal classification<sup>15</sup>. In patients with their 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 which was defined as either the inability to reduce the steroid dose below the equivalent of prednisolone 10 mg/d within 3 months after discharge or the occurrence of a relapse within 3 months of stopping steroids.<sup>14</sup>

**Rehospitalization:** 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  $\geq 5$ .<sup>16</sup>

### 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 Mann-Whitney test and qualitative variables by 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. The cumulative probability of colectomy after discharge from index hospitalization was calculated using the Kaplan-Meier method and compared between complete and incomplete responder using the log-rank test. P values <0.05 were considered statistically significant. Statistical analyses were performed using Stata software 11.2 (College Station, Texas, USA).

### Machine learning models

Machine learning is a predictive analytical tool that automates analytical model building. Using algorithms that iteratively learn from data, machine learning allows computers to find hidden insights without being explicitly programmed where to look. Supervised Machine

Learning algorithms were applied upon the data available at index admission to identify early predictive markers and predictive accuracies of long-term colectomy and steroid dependence following index episode of ASC. Machine learning analysis was conducted in a reproducible manner using in-house developed codes in the R Programming Language for Statistical Computing<sup>17</sup>. Only the variables available at time of index episode of ASC (such as demographic, clinical, hematological features) were considered. Further selection of statistically significant predictors was implemented using the Boruta algorithm in R<sup>18,19</sup>. Variables with a large number of missing values were discarded and the remaining missing data were imputed by the median/mode of the respective variable. Training set (67%) and test set (33%) were created by random sampling of the original data. Supervised learning random forest, a classification approach using majority vote from an ensemble of decision trees was trained on and optimized for predicting outcomes. Standard model performance measures were evaluated on the testing set.

## Results

A total of 1731 patients with UC were treated at AIIMS between January 2003 and December 2013. Of these, 179 patients (10%) experienced index episode of ASC and were hospitalized, 19 patients underwent colectomy at index admission and 160 patients who avoided colectomy were followed up for a median duration of 56(1-159) months. 19 patients were lost to follow-up (Figure 1).

### Baseline clinical and demographic characteristics

The mean age at index ASC was 35±12 years, 53% were male, 12% had index presentation of UC as ASC, 65% had E3 disease, 32% had EIMs, 63% had at least one course of prior steroid use and 18% had prior immunomodulator use (Table 1). We had data for stool test for *C difficile* in 113/179 patients (63.2%) and *C difficile* positivity was found in 2/113 patients (1.76%). CMV inclusion bodies were seen in 5 patients (2.8%). The median duration of hospital stay was 10(3–90) days.

### Comparison between patients who had colectomy and those who avoided colectomy at index hospitalization

Nineteen of 179 patients (11%) underwent colectomy at index hospitalization. More patients who required colectomy at index hospitalization received prior steroid courses (90% vs. 59%,  $p=0.01$ ) and steroids in first year of diagnosis of UC (89% vs. 60%  $p=0.01$ ) than patients who avoided colectomy. Patients who underwent colectomy had a longer median duration of

hospital stay than those who avoided it (18 vs. 9 days,  $p=0.001$ ). There were no differences between the two groups in terms of age at ASC, sex, median duration of disease before index episode, smoking status at admission, presence of EIMs, extent of disease at admission, or prior immunomodulator treatment. There were no deaths during index hospitalization (Table 1).

### **Long-term outcome according to response at day 7**

One hundred and sixty out of 179 patients avoided colectomy during index admission and were followed up. Long-term outcomes were analyzed according to response on day 7 of admission (Table 2). Among 160 patients, 74 were complete responders (CR) and 86 were incomplete responders (IR). There was no difference between CR and IR in rates of CMV and *C difficile* infection at index admission.

#### *Steroid dependence and immunomodulator use (Table 2)*

Steroid dependence at any time during follow-up was observed in 66/160(41%) patients. The rate of steroid dependence (20% vs. 72%,  $p=0.001$ ) and immunomodulator use (62% vs. 91%,  $p=0.001$ ) was significantly lower in CR as compared to IR. Among immunomodulators, thiopurines were most commonly used and though not statistically significant, their use was lower in CR (61% vs. 71%,  $p=ns$ ). Anti TNF $\alpha$  agent and ciclosporin were used by 9 and 8 patients respectively. Methotrexate was used in one patient only.

#### *Colectomy (Table 2)*

Forty two (26%) patients underwent colectomy after discharge following the index admission over a median follow-up of 56 months. Colectomy rate was significantly lower in CR as compared to IR (12% vs. 38%  $p=0.001$ ). The cumulative probability of colectomy at 10 years was 32% and was significantly lower in CR as compared to IR (19% vs. 43%,  $p=0.001$ ; HR: 3.6(1.7-7.5)) (Figure 2 and Table 4).

### **Recurrent ASC, relapses and re-hospitalization (Table 2)**

Fifty six out of 160(35%) patients had repeat episodes of ASC. Re-admission due to repeat ASC was significantly less in CR as compared to IR (24% vs. 44%,  $p=0.01$ ). CR also had significantly lower median number of relapses/year (0.3 vs. 1.5,  $p=0.001$ ) and longer duration of remission than IR (39 vs. 15 months,  $p=0.001$ ). The cumulative probability of repeat ASC was 46% at 10 years and was significantly lower in CR as compared to IR (29% vs. 59%,  $p=0.01$ ; HR 2.1(1.2-3.8)) (Figure 2 and Table 4). There was no difference in mortality rate between the two groups.



### **Comparison between patients who had colectomy compared to those who avoided colectomy on long-term follow-up**

EIMs were present in 54 (34%) patients who avoided colectomy at index ASC.. Most common EIM was peripheral arthralgia (n=30) followed by central arthralgia (n=20), aphthous ulcer (n=9), deep venous thrombosis (n=8), ankylosing spondylitis (n=6), pyoderma gangrenosum (n=3) and erythema nodosum (n=2). The frequency of EIMs was significantly higher in patients who underwent colectomy at follow-up (55% vs. 26%,  $p=0.001$ ) than those who avoided it. Patients who underwent colectomy also had significantly higher rate of use of immunomodulators (91% vs. 73%,  $p=0.01$ ), re-hospitalization due to recurrent ASC prior to colectomy (55% vs. 28%,  $p=0.001$ ), median number of relapses/year (2(0.2-5) vs. 0.5(0-3),  $p=0.001$ ) than those who avoided it. However there was no difference in age at index ASC, sex, extent of disease at time of ASC, smoking, thiopurines, ciclosporin or antiTNF $\alpha$  use between the two groups (Table 3). 41% of those individual who had a repeat episode of ASC had colectomy as compared to 18% of those who did not ( $p=0.002$ ).

On multivariable analysis by cox regression method, number of EIMs present and response to IV steroid at day 7 of index hospitalization independently predicted colectomy in follow-up (supplementary appendix).

On multivariable analysis by logistic regression only response to IV steroid at day 7 of index hospitalization and steroid use prior to index ASC predicted steroid dependence in follow-up (supplementary appendix).

### **Mortality**

Among 160 patients we observed 4 deaths in follow-up; no death was due to exacerbation of UC. 1 patient had concomitant chronic kidney disease died due to acute on chronic kidney disease, 1 had hepatitis C related cirrhosis, 1 expired due to colon cancer and 1 had malnutrition with secondary infection.

### **Predictive models**

Boruta analysis identified 4 variables: steroid use during 1<sup>st</sup> year of diagnosis, longer duration of disease prior to ASC, number of EIMs present and response to IV steroid at day 7 of index hospitalization to predict colectomy in follow-up (Figure 3). Using these we were able to predict the likelihood of colectomy with a sensitivity of 75%, specificity of 80% and positive predictive value (PPV) of 85%, negative predictive value (NPV) of 67% and accuracy of 77% in testing set. The sensitivity, NPV and accuracy of the model decreased significantly when the number of variables was decreased.

Using 2 variables: response to IV steroid at day 7 of index hospitalization and steroid use prior to index ASC (Figure 3), we were able to predict the likelihood of steroid dependence during follow-up with sensitivity of 69%, specificity of 80%, PPV of 85%, NPV of 62% and accuracy of 75% in the testing set.

## **Discussion**

The present study highlights the long-term outcome of acute severe colitis in a large cohort with a median follow-up of 5 years. Of 1731 patients with UC, 179(10%) developed ASC with 247 episodes, which included 179 index and 68 repeat episodes. 19(11%) patients underwent colectomy at the index episode.. During follow-up, another 42 patients underwent colectomy giving an overall colectomy rate of 34%. Response at day 7 of index hospitalization was significantly associated with steroid dependence, repeat episode(s) of ASC, more relapses per year, shorter maximum period of remission and higher colectomy rates on long-term follow-up. Based on a machine learning algorithm, predictive factors for long-term colectomy as well as steroid-dependent disease were derived.

The study has direct relevance to global practice, because it shows the long-term outcomes in a region which has traditionally considered being a low incidence area for inflammatory bowel disease. The study shows that the disease course in patients with UC in Asia may not be as mild as suggested in a study from Korea<sup>7</sup>. Our study is also important because it confirms the long-term prognostic value of therapeutic response on day 7 following hospitalization for ASC. This is the first study from Asia which shows that day 7 response can be a risk-predictor of long-term colectomy, steroid-dependence and an overall aggressive disease course. An another study from India involving 50 patients showed only short term predictors of steroid failure<sup>20</sup>. The study from Oxford<sup>8</sup> which pioneered the concept of the long-term prognostic value of day 7 response was based on a small cohort of 32 patients. Our long-term data from a much larger cohort from India establishes the applicability of that finding. It is particularly relevant for developing countries in South Asia where such simple, clinical prognostic markers can help the physician plan long-term therapy and manage the expectations of the patient. Strength of this study is that it was performed in a region where access to biological therapy is limited. Consequently it defines a reference point for the long-

term outcomes of treatment with steroids and traditional immunosuppressive therapy after an episode of ASC. Only 9 patients received rescue therapy with biologicals.

The rate of ASC during UC disease course (10%) is similar to a Korean study (8%)<sup>7</sup> but lower than that of West (15–25%)<sup>1,2</sup>. Colectomy rate at index admission (11%) was lower than that reported in the meta-analysis by Turner et al<sup>3</sup> (older Western data, 27%) but matched other Asian data: 15% in another Indian study<sup>20</sup>, 16% in a study from Korea<sup>7</sup> and recent Western data<sup>1</sup>. The long term colectomy rate of 34% in the present study was lower than that reported by two earlier studies from Sweden (64%)<sup>9</sup> and Oxford (61%)<sup>8</sup>, but comparable to more recent studies from Oxford (40%)<sup>1</sup>, Hungary (25%)<sup>10</sup> Northern California (32%)<sup>11</sup> and South Korea (29%)<sup>7</sup>. These differences could be explained by absence of immunomodulator use in the Swedish cohort and differences in duration of follow-up. Compared to other studies, only 15% of our patients received rescue therapy during index admission or follow-up. This was due to cost concerns and limited availability of these drugs in health care insurance programs. The cumulative probability of colectomy at 1, 5 and 10 years was 12%, 23% and 32% respectively, which was higher than the Korean study<sup>7</sup>. Univariate analysis identified the presence of response at day 7, steroid use during first year of diagnosis, EIMs, and steroid treatment before admission (although not statistically significant) as predictors of future colectomy. Response at day 7 was the most important predictor of long-term colectomy, with IR having a three-fold higher (HR=3.6, 95% CI 1.7-7.5 p=0.001) colectomy rate than CR. IR had a rapid progression to colectomy, with 19% IR undergoing colectomy within a year, compared to just 4% of CR. Studies from Oxford<sup>8</sup>, Hungary<sup>10</sup> and Korea have also demonstrated the long-term prognostic value of day 7 response on index hospitalization. Presumably the relationship to EIMs reflects the systemic nature of UC in these patients, which is conceivably less responsive to therapy. This may be relevant to newer agents offering gut-specific immunosuppression, but interestingly, azathioprine use did not reduce the risk of colectomy after ASC.

A third of patients who avoided colectomy at index admission had at least one repeat episode of ASC. This is similar to data from Dinesen et al (36%)<sup>1</sup> and Lee et al (40%)<sup>7</sup>, indicating that the risk of recurrent ASC is similar in West and Asia. As with the risk of colectomy, the risk of recurrent ASC could be predicted by the response at day 7, with IR having twice the risk of CR (HR: 2.1 95% CI 1.2-3.8 p= 0.01). A repeat episode of ASC in the present study doubled the chance of colectomy in the next 5 years, similar to recent Oxford experience (1).

We developed a predictive model based on significant variables that predicted these outcomes, using a machine-learning approach for variable selection, the Boruta algorithm. Boruta is a Random Forest based wrapper algorithm for feature selection. The advantages of using this algorithm are capability to handle mixed categorical and continuous data, robustness to noise and outliers in the data and capability to account for nonlinear dependencies in the data. Using the Boruta selected variables; we rigorously tuned the Random Forest algorithm to avoid over fitting and to test stability over multiple randomized datasets. The model achieved prediction of long-term colectomy with a balanced accuracy of 77 % employing 4 variables: response at day 7, number of EIMs, steroid use during the first year of disease and longer disease duration at time of ASC. Only 2 variables (response at day 7 and steroid therapy before ASC), could predict steroid-dependence during follow-up with a balanced accuracy of 75% and PPV of 85%.

Our study is limited by its retrospective design, and that it reflects practice in a tertiary centre, which may influence generalizability of results. The results need to be globally practiced and external validation of the predictive model over different geographical regions is appropriate.

The relevant clinical messages are that 10% of our patients with UC develop ASC and that 10% of these patients undergo colectomy during the index episode. Response on day 7 of hospitalization for ASC is the major determinant of the long-term outcome. Steroid dependence and colectomy can be predicted by clinical criteria with reasonable accuracy on day 7 of admission with ASC, which can inform decision making.

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**Table 1** Characteristics of patients who underwent colectomy vs. who avoided colectomy at index admission for ASC

	Total (n=179)	No colectomy (n=160)	Colectomy at admission (n=19)	p value
Age at ASC (years)	35.4± 11.8	35.3 ± 11.8	35.5 ±12.1	ns
Male	94 (52.5)	82 (51.3)	12(53.2)	ns
Duration of UC at time of admission (months)	18(0-240)	19.5(0-240)	13(2-144)	ns
Index presentation	21 (11.7)	19(11.8)	2(10.5)	ns
Extent †				ns
E1 (Proctitis)	4 (2.3)	4 (2.6)	0	
E2 (Distal colitis)	57 (32.4)	53 (33.7)	4 (21.1)	
E3 (Extensive colitis)	115 (65.4)	100 (63.7)	15 (78.9)	
Presence of EIMs	58 (32.4)	54(33.8)	4(21.1)	ns
Smoking	12 (6.7)	11(6.9)	1 (5.3)	ns
Prior immunomodulator treatment	32 (17.9)	30(18.8)	2 (10.5)	ns
Prior steroid use	112 (62.6)	95 (59.4)	17 (89.5)	0.01
Response at day 7				0.001
Complete responder	74 (41.4)	74 (46.3)	0	
Partial responder	86 (48)	86 (53.7)	0	
Non responder	19 (10.6)		19 (100)	

Toxic megacolon	2 (1.1)	0	2 (10.5)	0.01
Rescue therapy				ns
Ciclosporin	6 (3.3)	6 (3.8)	0	
Infliximab	3 (1.7)	3 (1.9)	0	
Steroid use during 1 <sup>st</sup> year of diagnosis	113 (63.1)	96 (60)	17(89.5)	0.01
Duration of hospital stay (day)	10(3-90)	8.5(3-33)	18(13-90)	0.001

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

†Extent not available in 3 patients.

ASC: acute severe colitis, UC: ulcerative colitis, EIMs: extra intestinal manifestations



**Table 2:** Long term outcomes in patients who avoided colectomy during index admission for ASC according to response at day 7 (follow-up 56 (1-159) months)

	Complete responder (n= 74)	Incomplete responder (n=86)	OR(95% CI)	p value
Steroid dependence	11(19.6)	55(72.4)	10.7(4.7-24.6)	0.001
Immunomodulator use	46(62.2)	78(90.7)	5.9(2.5-14.2)	0.001
Readmission due to ASC	18(24.3)	38(44.1)	2.5(1.3-4.9)	0.01
Number of relapses/year	0.3(0-3)	1.46(0-5)		0.001
Time of surgery from index hospitalization (month)	19(4-108)	13(1-154)		0.79
Maximum duration of remission (month)	39(1-124)	14.5(0-105)		0.001
Colectomy	9 (12.2)	33 (38.4)	4.5(1.9-10.2)	0.001
Mortality	1(1.4)	3(3.5)	2.6(0.2-25)	0.62

Values as mean± standard deviation, median (range) or n(%) as appropriate. OR odds ratio, CI confidence interval, ASC: acute severe colitis

**Table 3:** Characteristics of patients who underwent colectomy on follow-up versus those who did not undergo colectomy (n= 160)

	No colectomy (n=118)	Colectomy at follow-up (n=42)	p value
Age at ASC (year)	36.2±12.2	32.8±10.8	ns
Male	61(51.7)	21 (50)	ns
Index presentation	5(11.9)	14(11.8)	ns
Duration of UC at time of admission (months)	17.5(0-240)	25(0-228)	ns
Extent †			ns
E1 (Proctitis)	4 (3.5)	0	
E2 (Distal colitis)	38 (33)	15 (35.7)	
E3 (Extensive colitis)	73 (63.5)	27 (64.3)	
Number of EIMs			0.001
0	87 (73.7)	19 (45.2)	
1	18 (15.3)	17 (40.5)	
2 or more	13 (11)	6 (14.3)	
Smoking	7(5.9)	4(9.5)	ns
Response at day 7			0.001
Complete responder	65 (55.1)	9 (21.4)	
Incomplete responder	53 (44.9)	33 (78.6)	
Prior steroid use to 1 <sup>st</sup> ASC	65(55.1)	30(71.4)	ns (0.07)
	No colectomy	Colectomy at follow-up (n=42)	p value

(n=118)			
Drug therapy during follow-up			
Azathioprine	75(63.6)	31(73.1)	ns
Ciclosporin	5(4.2)	3(7.1)	ns
Methotrexate	0	1 (2.3)	ns
Infliximab	6(5.1)	3(7.1)	ns
Use of any immunomodulator on follow-up	86(72.8)	38(90.5)	0.01
Steroid use during 1 <sup>st</sup> year of diagnosis	66(55.9)	30(71.4)	ns (0.07)
Steroid dependence during follow-up	31(32.9)	35(92.1)	0.001
Readmission due to ASC	33(27.9)	23(54.8)	0.001
Median duration of longest period of steroid free remission (months)	36(2-124)	5(0-72)	0.001
Number of relapses/year	0.5(0-3)	2(0.18-5)	0.001

Values as mean  $\pm$  standard deviation, median (range) or n (%) as appropriate

UC: ulcerative colitis, ASC: acute severe colitis, EIMs: extra intestinal manifestations

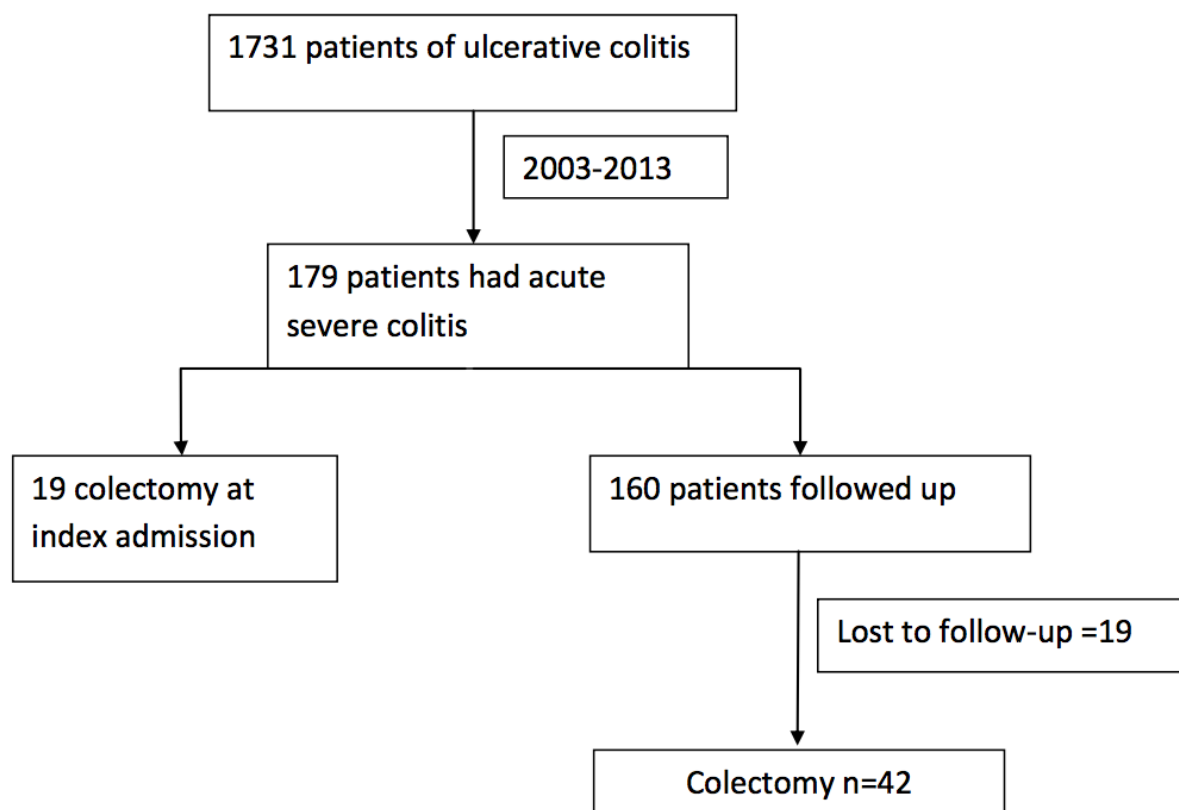
† Extent not available in 3 patients.

**Table 4:** Cumulative probability of colectomy and repeat ASC in follow-up

	Total N= 160 %(95% CI)	Complete responder N= 74 %(95% CI)	Incomplete responder N= 86 %(95% CI)	p value
Cumulative probability of colectomy				0.001
1 yr	11.9(7.8-17.1)	4.1 (1.3-12.1)	18.6 (11.8-28.6)	
5 yr	22.8(16.9-30.3)	9.9 (4.9-19.8)	33.5 (24.4-44.8)	
10 yr	32.2(23.6-42.8)	19.7 (9.2-39.7)	43.1 (31.8-56.3)	
Cumulative probability of repeat ASC:				0.01
1 yr	13.3(9.4-20.4)	5.5 (2.1-14)	21.2(13.9-31.6)	
5 yr	37.8(30.7-46.8)	28.7(19-41.9)	45.8(34.9-58.3)	
10 yr	46(34.9-58.6)	28.7 (19.41.9)	58.8(43.2-75.2)	

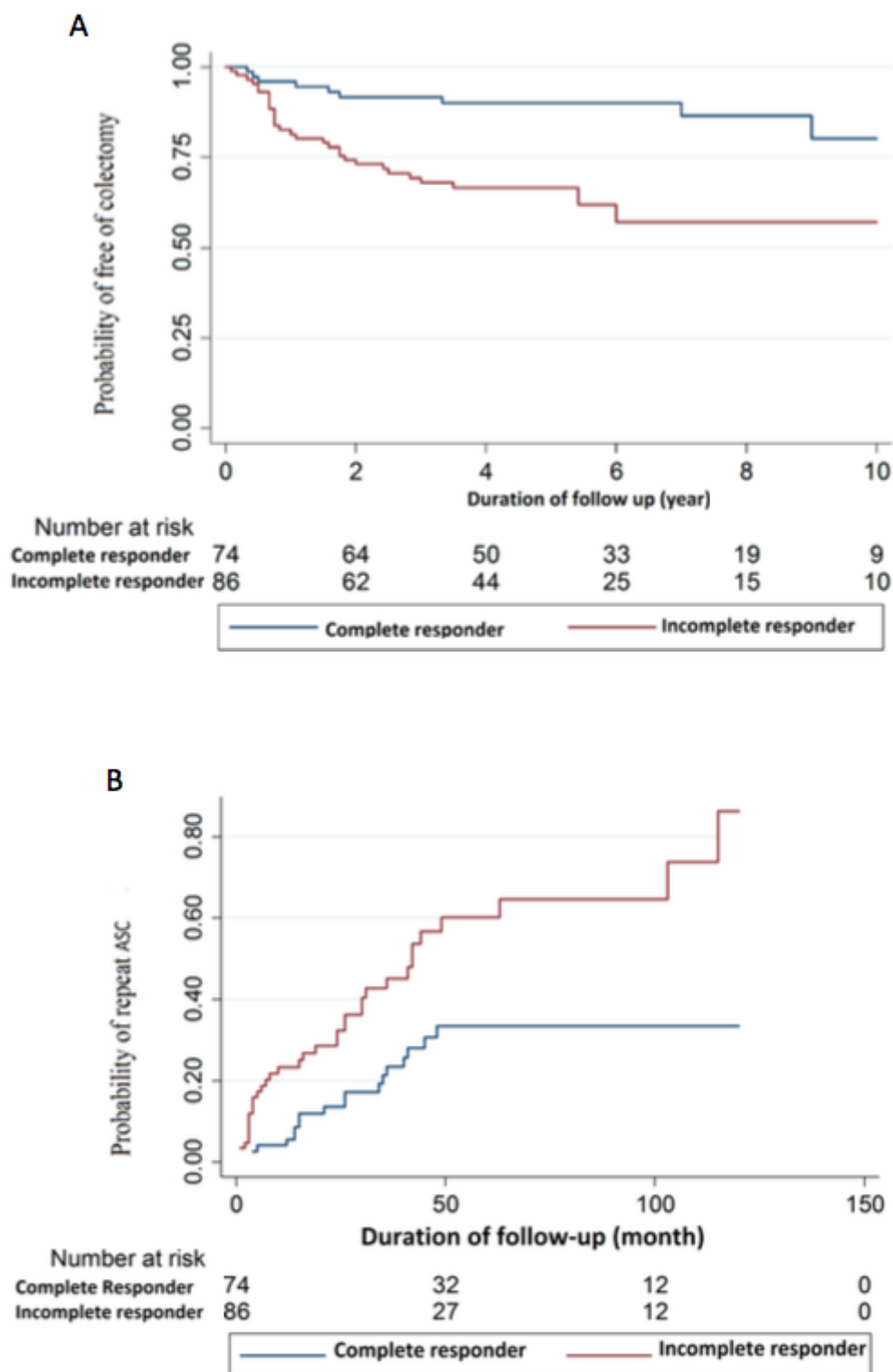
ASC: acute severe colitis, CI confidence interval

Figure 1:



**Figure 1:** Flow chart: Study population

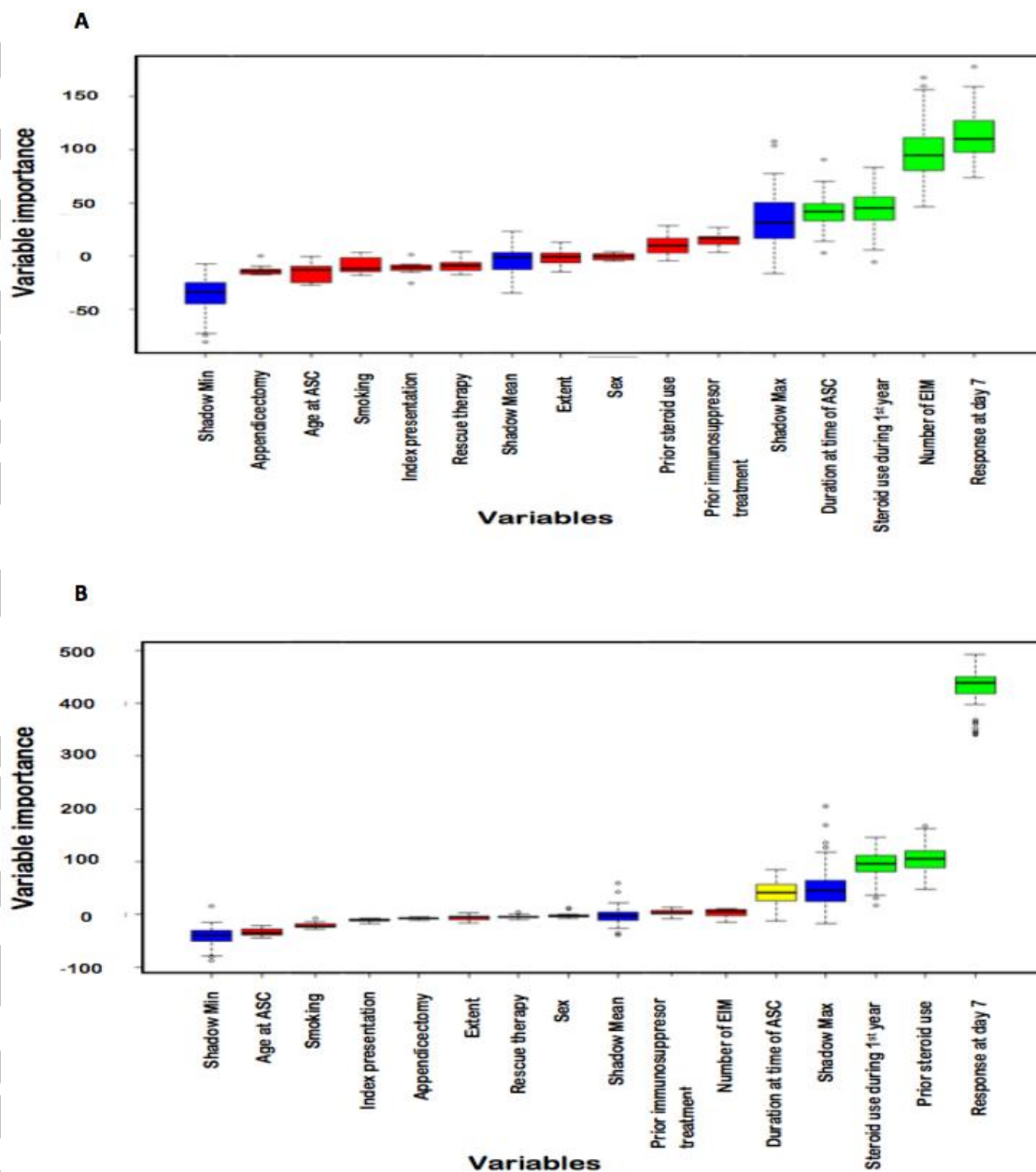
Figure 2:



**Figure 2:** Long-term outcome for those who avoid colectomy at index admission: (A) cumulative probability of colectomy among complete responders (CR, blue line) and incomplete responders (IR, red line) on day 7 of intravenous steroid therapy (Hazard ratio

3.6(1.7-7.5)  $p=0.001$ ; according to the log-rank test); and (B) cumulative probability of rehospitalization due to repeat ASC in CR (blue line) and IR (red line) (Hazard ratio 2.1(1.2-3.8)  $p=0.01$ ; according to the log-rank test). ASC: acute severe colitis

Figure 3:



**Figure 3:** A) Multivariate feature selection for prediction of colectomy in follow-up using the Boruta algorithm. B) Multivariate feature selection for prediction of steroid dependence in follow-up using the Boruta algorithm.

The box-plots represent the distribution of variable importances after adjusting for the interactions among the variables. The X axis denotes variables and the minimal set of selected features (green) are the ones whose medians lie above the maximal possible median importance in the shadow data (blue). ASC: acute severe colitis, EIM: Extraintestinal manifestation