

Long-term outcomes of acute severe ulcerative colitis in the rescue therapy era: A multicentre cohort study

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Abstract

Background: The long-term course of ulcerative colitis after a severe attack is poorly understood. Second-line rescue therapy with cyclosporine or infliximab is effective for reducing short-term colectomy but the impact in the long-term is controversial.

Objective: The purpose of this study was to evaluate the long-term course of acute severe ulcerative colitis patients who avoid early colectomy either because of response to steroids or rescue therapy.

Methods: This was a multicentre retrospective cohort study of adult patients with acute severe ulcerative colitis admitted to Italian inflammatory bowel disease referral centres from 2005–2017. All patients received intravenous steroids, and those who did not respond received either rescue therapy or colectomy. For patients who avoided early colectomy (within three months from the index attack), we recorded the date of colectomy, last follow-up visit or death. The primary end-point was long-term colectomy rate in patients avoiding early colectomy.

Results: From the included 372 patients with acute severe ulcerative colitis, 337 (90.6%) avoided early colectomy. From those, 60.5% were responsive to steroids and 39.5% to the rescue therapy. Median follow-up was 44 months (interquartile range, 21–85). Colectomy-free survival probability was 93.5%, 81.5% and 79.4% at one, three and five years, respectively. Colectomy risk was higher among rescue therapy users than in steroid-responders (log-rank test, $p = 0.02$). At multivariate analysis response to steroids was independently associated with a lower risk of long-term colectomy (adjusted odds ratio = 0.5; 95% confidence interval, 0.2–0.8), while previous exposure to anti-tumour necrosis factor alpha agents was associated with an increased risk (adjusted odds ratio = 3.0; 95% confidence interval, 1.5–5.7). Approximately 50% of patients required additional therapy or new hospitalization within five years due to a recurrent flare. Death occurred in three patients (0.9%).

Conclusions: Patients with acute severe ulcerative colitis avoiding early colectomy are at risk of long-term colectomy, especially if previously exposed to anti-tumour necrosis factor alpha agents or if rescue therapy during the acute attack was required because of steroid refractoriness.

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Key Summary

- In ulcerative colitis patients experiencing a severe attack, the risk of long-term colectomy is relevant even in patients who initially respond to medical therapy.
- This risk is significantly higher in patients who need rescue therapy compared to those who respond to intravenous steroids.
- A significant proportion of patients who avoid early colectomy will require additional therapy and new hospitalizations during follow-up.
- Previous exposure to anti-tumour necrosis factor alpha (anti-TNF α) agents and need of rescue therapy for steroid refractoriness are independently associated with the risk of long-term colectomy.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disorder of the large intestine characterised by a relapsing course. Approximately 15% to 25% of UC patients experience an acute severe attack during their disease course.^{1,2} Although acute severe ulcerative colitis (ASUC) is a potentially life-threatening condition, its mortality rate has dropped dramatically over the past decades to approximately 1%.^{3–5} This improved outcome is attributed to the introduction of intensive intravenous treatment (IIVT) with steroids and a policy of early surgery for non-responders. However, despite the use of steroids, at least 30% of patients fail to respond and, until recently, were candidates for colectomy. According to a 2007 systematic review of cohort studies and controlled trials,⁶ the short-term colectomy rate was approximately 30%; this rate was stable across three decades, from the 1970s until the turn of the 20th century. Furthermore, a population-based study found that the need for emergent or urgent colectomy did not change from 1997 to 2009, despite a decrease in elective colectomy for UC.⁷

Even if surgery is considered curative for UC, patients' quality of life after restorative proctocolectomy may be poorer than that of patients who respond to medical therapy and avoid surgery.⁸ Therefore, rescue attempts have been made to avoid surgery in patients with ASUC not responding to intravenous steroids, while maintaining mortality at a low rate.^{9,10} Both cyclosporine and infliximab reduce the need for short-term colectomy, with comparable efficacies.^{11–13} Nevertheless, the impact of these rescue therapies on the long-term colectomy rate is controversial.

Long-term colectomy rates after rescue therapy with cyclosporine or infliximab vary across studies because of different study designs, patient populations and time points for defining long-term colectomy.^{14–20} Still, some UC patients successfully treated with rescue therapy for an acute, steroid-refractory attack require colectomy in subsequent years for persistent disease activity or a recurrent attack. According to a recent systematic review of 78 studies,²¹ colectomy rates 12 months after cyclosporine rescue therapy ranged from 17–68% and those after infliximab ranged from 3.8–43%. Moreover, the three-year colectomy rate was 57–62% following cyclosporine and 27–50% following infliximab.

To clarify the effectiveness of rescue therapy and to contribute to our understanding of the long-term need for colectomy, this multicentre retrospective study evaluated the long-term outcomes of a large group of ASUC patients who escaped early colectomy. In addition, it identified predictive factors for long-term colectomy and examined time trends in the use of rescue therapy across Italy.

Patients and methods

This observational retrospective cohort study considered adult UC patients admitted to Italian inflammatory bowel disease (IBD) referral centres for an acute severe attack between January 2005–December 2017. The study protocol (protocol number 2158/CE Lazio1) was approved by the institutional review board (Comitato Etico Lazio 1) of the coordinating centre (IBD Unit, San Filippo Neri Hospital, Rome) and by the institutional review boards of all

participating centres. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. No informed consent was required because of the retrospective nature of the study.

The diagnosis of UC had been established according to criteria of the European Crohn's and Colitis Organization.²² Severity had been defined according to Truelove and Witts' criteria,²³ as modified by Chapman et al.,²⁴ namely six or more bloody stools per day with at least one of the following: fever (mean evening temperature $\geq 37.5^{\circ}\text{C}$ or $\geq 37.8^{\circ}\text{C}$ for at least two days), tachycardia (mean pulse rate >90 per min), anaemia (decrease in haemoglobin levels $\geq 75\%$), and erythrocyte sedimentation rate (ESR) >30 mm/h. All patients >18 years of age were included; patients with missing or inconsistent data and patients with a follow-up shorter than three months were excluded.

An online database was used to collect data from participating centres. These data included patients' clinical and demographic characteristics recorded at admission, namely sex, age, smoking habit, disease duration, disease extent, previous treatment with corticosteroids, immunomodulators or anti-tumour necrosis factor alpha (anti-TNF α), and type of attack (first or recurrent). Collected data from laboratory exams included ESR, haemoglobin and C-reactive protein (CRP) levels. Information from diagnostic examinations included abdominal radiographs, obtained according to clinical judgment, and results of flexible sigmoidoscopy, performed to assess endoscopic severity. Severe endoscopic activity had been defined by the presence of ulcerations or spontaneous bleeding according to the Mayo endoscopic subscore.²⁵ Rectal biopsies to rule out cytomegalovirus (CMV) infection had been performed according to clinical judgment.

All patients had received IIVT with 0.75–1 mg/kg day methylprednisolone or equivalent, as recommended.²⁶ Response to steroid IIVT was defined as the patient being discharged from the hospital without initiation of further induction treatment for active UC, either medical or surgical. Patients who responded to IIVT (called 'steroid responders') were discharged and received maintenance treatment according to clinical judgment. Lack of response ('steroid refractoriness') was defined as no substantial improvement within 3–5 days of IIVT.²⁶ Steroid-refractory patients received either rescue therapy (cyclosporine or infliximab) or early colectomy, according to clinical judgment. Response to rescue therapy was defined as being discharged from hospital without colectomy. Response or refractoriness to IIVT or rescue therapy were

considered according to the clinical judgment of attending physician.

Patients who failed to respond to rescue therapy had a colectomy: the decision to perform early colectomy in each patient was made according to local clinical-surgical judgment. Early colectomy was defined as surgery performed within three months of hospital admission. For patients escaping early colectomy, because of a response to either steroids or rescue therapy, we recorded the date of long-term colectomy, last follow-up visit or death.

The primary end-point of the study was the long-term colectomy rate in patients escaping early colectomy. The secondary end-points were: (a) rate of repeat hospitalizations for recurrent flares; (b) rate of additional drug therapies (i.e. need for a new steroid course, introduction of immunomodulators or anti-TNF α agents, infliximab intensification or switch to a second biologic agent) due to disease flare, treatment intolerance or complications; (c) identification of predictive factors of long-term colectomy; and (d) time trends in rescue therapy use.

Statistical analysis

The intention-to-treat (ITT) population included all patients who avoided early colectomy because of a response to steroids or rescue therapy. Differences in continuous variables between responders to steroids and rescue therapy were tested for significance using Student's *t* or Mann-Whitney U test as appropriate, whereas the significance of associations of patient groups with categorical variables was examined with chi-square or Fisher's exact test. A $p < 0.05$ indicated significance.

The Kaplan–Meier survival method was used to estimate the probability of a course without major events (i.e. long-term colectomy, repeat hospitalization or additional drug therapies) after the acute attack. The log-rank test was used to assess possible associations of survival trends with patient group.

To look for predictive factors of long-term colectomy, univariate analysis with log-rank test was used considering the following covariates: sex, age, smoking habit, disease duration, disease extent, previous treatment with corticosteroids, immunomodulators or anti-TNF α , haemoglobin and CRP levels, type of attack (first or recurrent), endoscopic activity, initial response to steroids or rescue therapy, and maintenance treatment after the acute attack. Stepwise Cox regression was performed with all variables that had $p \leq 0.10$ at univariate analysis. Odds ratios (ORs) were calculated with 95% confidence intervals (CIs).

To identify time trends in the use of rescue therapy and short-term colectomy, patients were divided into

four groups according to the year in which their acute attack occurred: 2005–2007, 2008–2010, 2011–2013 and 2014–2017. For each period, the proportion of patients who responded to steroids, required rescue therapy or underwent early colectomy was calculated. Significant variations over time were examined with chi-square test for trend. Statistical analyses were performed using IBM SPSS version 25 and StatsDirect statistical software.

Results

From January 2005–December 2017, a total of 390 UC patients with an acute severe attack were hospitalised and treated in 14 Italian IBD referral centres (Figure 1). Eighteen patients were excluded because of missing data ($n=10$) or follow-up less than three months ($n=8$). Therefore, 372 patients were included in the study. Of these, 204 (54.8%) responded to first-line steroid IIVT while 168 (45.2%) did not. Among the steroid-refractory patients, 22 had urgent or emergent colectomy because of rapid deterioration or complications and 146 received second-line rescue therapy with infliximab ($n=121$), cyclosporine ($n=23$) or both

($n=2$). Thirteen patients receiving rescue therapy underwent colectomy after a median of two months (interquartile range (IQR) 0.7–2.8) because of no response or early clinical deterioration after an initial partial response. Therefore, in the total population, 35 patients (9.4%) had early colectomy while 337 patients avoided early colectomy because of a response to steroids ($n=204$) or rescue therapy ($n=133$).

The 337 patients who escaped early colectomy formed the ITT population for this study (Table 1). The patients had a median age of 38 years (IQR, 25–50). There was a slight preponderance of men (58.2%), and 61.1% were never or former smokers. Their median disease duration was 2.6 years (IQR, 0.25–9). A majority of patients had extensive colitis (75.7%), and most (274, 81.3%) had severe endoscopic activity (Mayo endoscopic subscore, 3) at baseline; 63.5% had received at least one steroid course in the past, and 30.5% had received immunomodulators or anti-TNF α agents but no patient was receiving anti-TNF α at the time of the enrolment. Median follow-up after discharge was 44 months (IQR, 21–85). Maintenance treatment after the hospital discharge included aminosalicylates, immunomodulators or scheduled infliximab

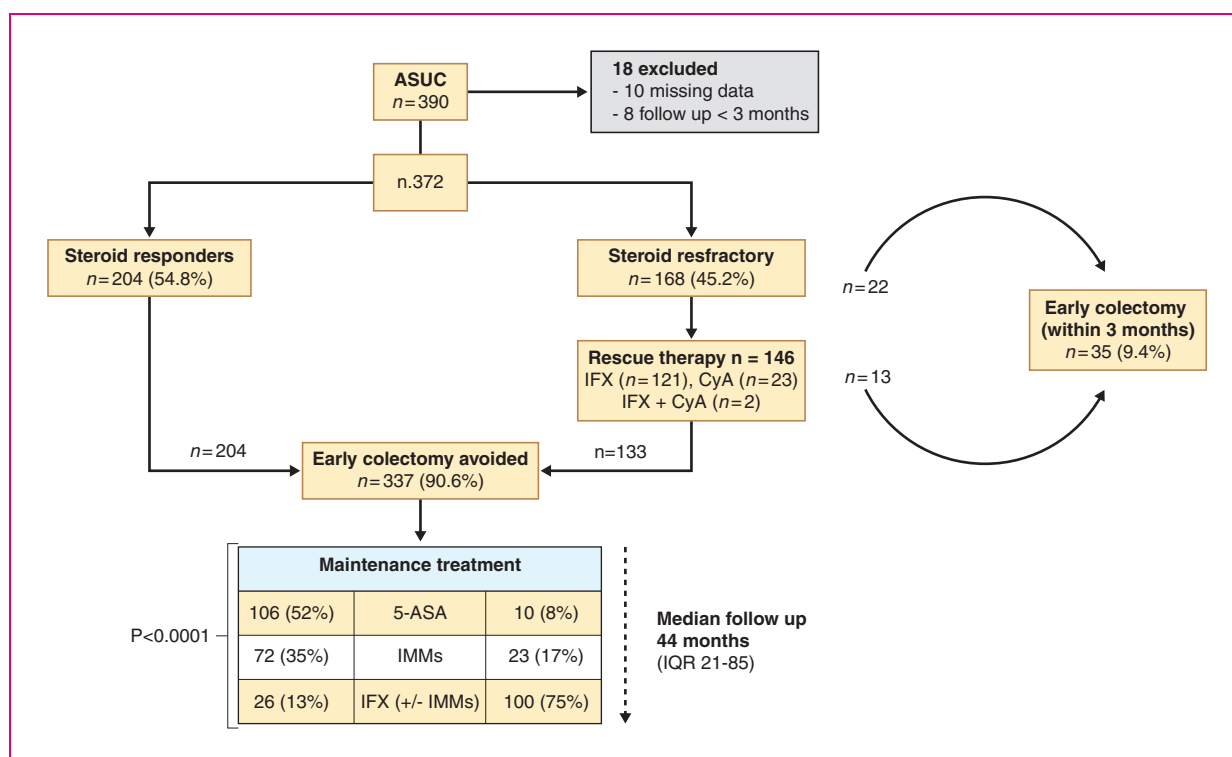


Figure 1. Flow chart showing the short-term outcomes of 390 patients with acute severe ulcerative colitis (ASUC). Maintenance treatment in patients avoiding early colectomy refers the maximum level of treatment prescribed. Patients in the 5-aminosalicylic acid (5-ASA) group received aminosalicylate monotherapy. Patients in the immunomodulators (IMMs) group received thiopurines for at least three months irrespective of co-medication with aminosalicylates. Patients in the infliximab (IFX) group received at least one maintenance dose irrespective of combo therapy with AZA. AZA: Azathioprine; CyA: cyclosporine A; IIVT: intensive intravenous treatment with steroids; IQR: interquartile range.

Table 1. Demographic and clinical characteristics of patients at baseline.

			Overall (n=337)	Steroid responders (n=204)	Rescue therapy responders (n=133)	p Value
Gender	M	n (%)	196 (58)	123 (60)	73 (55)	0.32
	F		141 (42)	81 (40)	60 (45)	
Age	years	Median (IQR range)	38 (25–50)	38 (27–53)	38 (26–48)	0.38
Disease duration	years	Median (IQR range)	2.6 (0.25–9)	2.6 (0–9)	3.2 (0.7–10)	0.21
Occurrence of severe attack	First attack	n (%)	269 (79.8)	166 (81.4)	103 (77.4)	0.38
	Recurrent attack		68 (20.2)	38 (18.6)	30 (22.6)	
Disease extension	Left-sided	n (%)	82 (24.3)	50 (24.5)	33 (24.1)	0.98
	Extensive		255 (75.7)	154 (75.5)	101 (75.9)	
Endoscopic severity	Mayo 3	n (%)	274 (81.3)	163 (79.9)	111 (83.5)	0.55
	Mayo 2		42 (12.5)	27 (13.2)	15 (11.3)	
	Missing data		21 (6.2)	14 (6.9)	7 (5.2)	
Haemoglobin	g/dl	Median (IQR)	10.3 (9–11.8)	10.4 (9–11.9)	10.4 (9–11)	0.83
CRP	g/dl	Median (IQR)	30 (15–55.2)	30 (15–56.6)	30 (15–57.1)	0.17
Smoking habits	No/former smoker	n (%)	206 (61.1)	122 (59.8)	84 (63.1)	0.29
	Active smoker		60 (17.8)	31 (15.1)	29 (21.8)	
	Missing data		71 (21.1)	51 (25.1)	20 (15.1)	
Previous medications	Corticosteroids	n (%)	214 (63.5)	116 (56.8)	98 (73.7)	<0.001
	IMMs		69 (20.5)	38 (18)	30 (22.5)	
	Anti-TNF		34 (10)	22 (10.7)	12 (9)	
Maintenance treatment after the acute attack	Aminosalicylates	n (%)	116 (34.4)	106 (52.0)	10 (8.0)	0.001
	IMMs		95 (28.1)	72 (35.0)	23 (17.0)	
	IFX±IMMs		126 (37.3)	26 (13.0)	100 (75.0)	

Anti-TNF: anti-tumour necrosis factor; CRP: C reactive protein; IFX: infliximab; IMMs: immunomodulators; IQR: interquartile range.

(with or without immunomodulators), according to clinical judgment (Figure 1). Among steroid responders, 52% were maintained with aminosalicylates alone. Conversely, 75% of patients receiving rescue therapy were maintained with scheduled infliximab (median, 8 infusions; IQR, 4–14).

Three deaths (0.9%) occurred during follow-up at a median of 46 months (range, 21–83 months) after the severe attack. An 80-year-old man died from comorbidities unrelated to UC. An 86-year-old man with severe chronic obstructive pulmonary disease and cardiovascular comorbidity died from respiratory failure after pneumonia during a repeat hospitalization for a recurrent severe UC flare. The third patient was a 24-year-old man who died from cholangiocarcinoma, which had been diagnosed several years after the acute attack. These three patients were initially steroid responders and maintained with aminosalicylates.

Long-term colectomy rate

Overall, 66 patients (19.6%) required colectomy during follow-up after a median of 27.4 months (IQR, 9–61.2). All surgeries in the long-term were performed because of disease activity. Thirty-nine of 66 (59%) colectomies occurred in the first 24 months and 85% within five

years of the acute attack. The probability of a course free from colectomy, in the ITT population, was 93.5%, 87.4%, 81.5% and 79.4% at one, two, three and five years, respectively (Figure 2(a)). The probability of colectomy was significantly higher in patients who received rescue therapy with infliximab or cyclosporine than in steroid responders (log-rank test, $p=0.02$) (Figure 2(b)). The long-term colectomy rate was similar among patients who received infliximab or cyclosporine (23.8% and 27.2%, respectively, $p=0.9$).

Need for new hospitalization and additional therapy

Overall, 116 of 337 patients (34.4%) required hospitalization for a recurrent flare. Sixty-eight percent of these repeat hospitalizations occurred in the first two years after the acute attack. The probability of a hospitalization-free clinical course within five years of the acute attack was 89.1%, 80.2%, 63.8% and 45.9% at one, two, three and five years, respectively. The probability of repeat hospitalization was similar for steroid responders and steroid-refractory patients who responded to rescue therapy (Figure 3(a)).

Escalation of therapy during follow-up, because of a disease flare, treatment intolerance or complications,

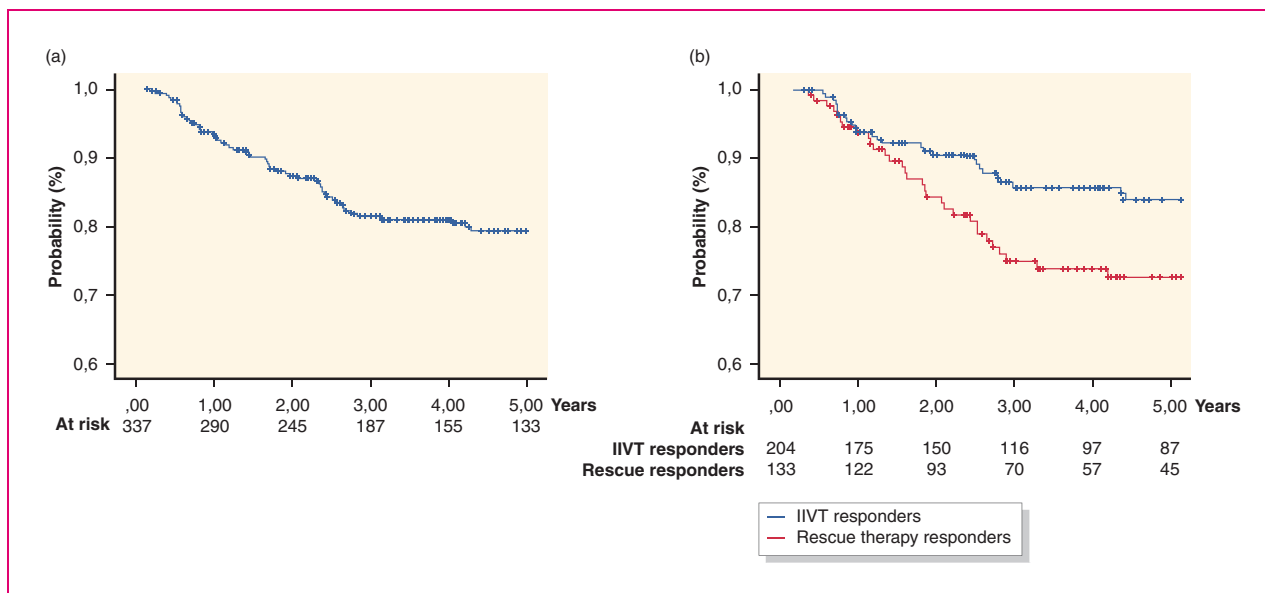


Figure 2. Kaplan–Meier analyses of survival free from long-term colectomy in acute severe ulcerative colitis (ASUC) patients who avoided early colectomy. (a) All 337 patients; (b) subgroups of patients according to the type of therapy. IIVT: intensive intravenous treatment with steroids.

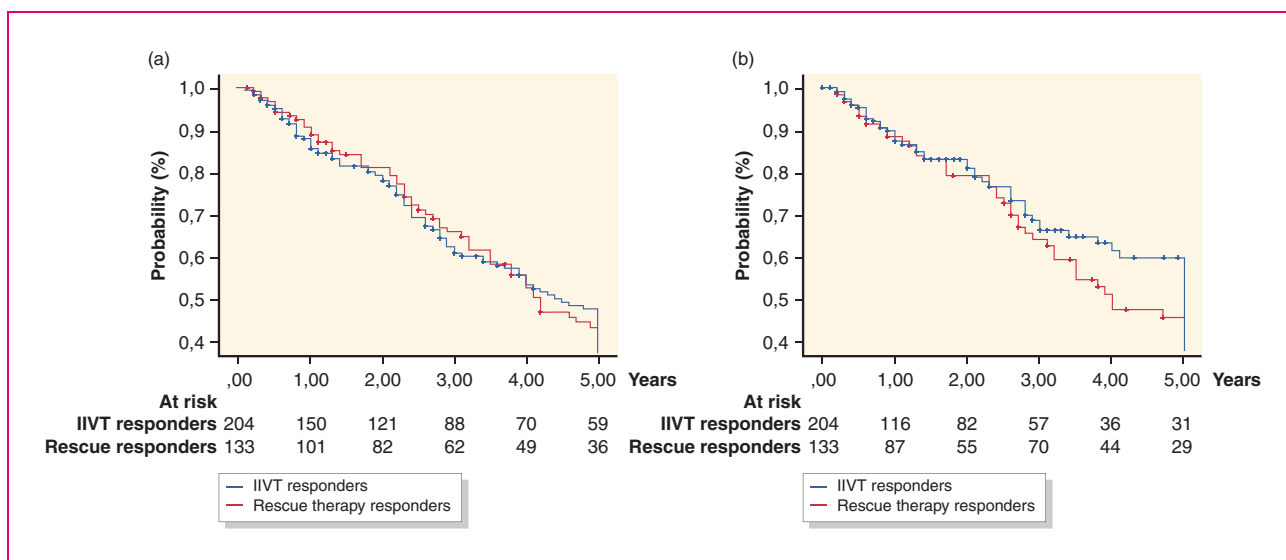


Figure 3. (a) Kaplan–Meier analyses of survival free from new hospitalization in 337 acute severe ulcerative colitis (ASUC) patients who avoided early colectomy, by treatment group. (b) Kaplan–Meier analyses of survival free from additional drug therapy due to a disease flare, treatment intolerance or complications in 337 ASUC patients who avoided early colectomy, by treatment group. IIVT: intensive intravenous treatment with steroids.

was needed in 199 patients (59%). Most therapeutic adjustments occurred within the first two years (68%). The probability of a course without additional drug therapy within five years of the acute attack was 89.3%, 81.4%, 66.7% and 53.2% at one, two, three and five years, respectively, with similar results for the two groups (Figure 3(b)). However, compared to rescue therapy responders, more steroid responders received

additional steroid courses (50.4% vs 36.8%; $p < 0.001$) and a new biologic treatment (40.1% vs 27%; $p < 0.001$).

Predictors of long-term colectomy

Univariate analysis and stepwise Cox regression were done to identify baseline clinical characteristics or treatment variables that predicted the long-term outcomes (Table 2). At univariate analysis, previous

Table 2. Predictors of long-term colectomy. Univariate analysis and stepwise Cox regression model. Only variables with a p -value ≤ 0.10 at univariate analysis were included in the stepwise Cox regression model.

Variable	Univariate analysis (log rank test)	Stepwise Cox regression model (OR, 95% CI)
Gender: female vs male	$p = 0.67$	
Age: >40 years vs <40 years)	$p = 0.16$	1.70 (0.90–2.95) $p = 0.06$
Disease duration <12 months vs >12 months	$p = 0.60$	
Smoking habits: yes vs no/former	$p = 0.47$	
Endoscopy: Mayo 2 vs Mayo 3	$p = 0.15$	0.48 (0.23–0.97) $p < 0.05$
Disease extension: left sided vs extensive	$p = 0.95$	
Response achievement: IIVT vs rescue	$p = 0.02$	0.50 (0.29–0.85) $p = 0.01$
Maintenance: 5-ASA vs IMM/anti-TNF α	$p = 0.13$	1.23 (0.61–2.47) $p = 0.56$
Haemoglobin: >10 g/dl vs <10 g/dl	$p = 0.26$	
CRP: <5-fold increase vs >5-fold increase	$p = 0.89$	
First attack vs recurrent	$p = 0.68$	
Previous steroid exposure: yes vs no	$p = 0.006$	1.18 (0.62–2.23) $p = 0.61$
Previous anti-TNF α exposure: yes vs no	$p = 0.002$	3.01 (1.57–5.77) $p = 0.001$
Previous IMM exposure: yes vs no	$p = 0.58$	

anti-TNF α : anti-tumour necrosis factor alpha; CI: confidence interval; CRP: C reactive protein; IIVT: intensive intravenous treatment; IMM: immunomodulators; OR: odds ratio.

exposures to corticosteroids and anti-TNF α agents were significantly associated with the risk of long-term colectomy (log-rank test, $p = 0.006$ and $p = 0.002$, respectively). A steroid response was associated with a lower risk of long-term colectomy than was rescue therapy (log-rank test, $p = 0.02$).

Six variables with $p \leq 0.10$ at univariate analysis were included in the stepwise Cox regression model: age, previous corticosteroid exposure, previous anti-TNF α agent exposure, endoscopic severity, treatment response (steroids vs. rescue therapy), and maintenance therapy. This analysis showed that a previous exposure to anti-TNF α agents was independently associated with the risk of long-term colectomy (OR = 3.0; 95% CI, 1.5–5.7). Conversely, steroid responsiveness was significantly associated with a lower risk of colectomy in the long-term (OR = 0.5; 95% CI, 0.2–0.8). Patients with mild to moderate endoscopic activity at index colonoscopy (Mayo endoscopic subscore 2) had a lower risk of colectomy than patients with severe endoscopic activity (Mayo endoscopic subscore = 3) (OR = 0.4; 95% CI, 0.2–0.9). None of the other variables considered was associated with the risk of colectomy in the long term.

Time trend in rescue therapy use

To explore the time trend in rescue therapy usage, we divided the entire study population into four groups according to year of their acute attack (Figure 4). This analysis showed that rescue therapy was used in only 26.6% of patients hospitalised in the years 2005–2007, but this proportion increased over time, reaching 40.9% in 2011–2013 and 40.0% in 2014–

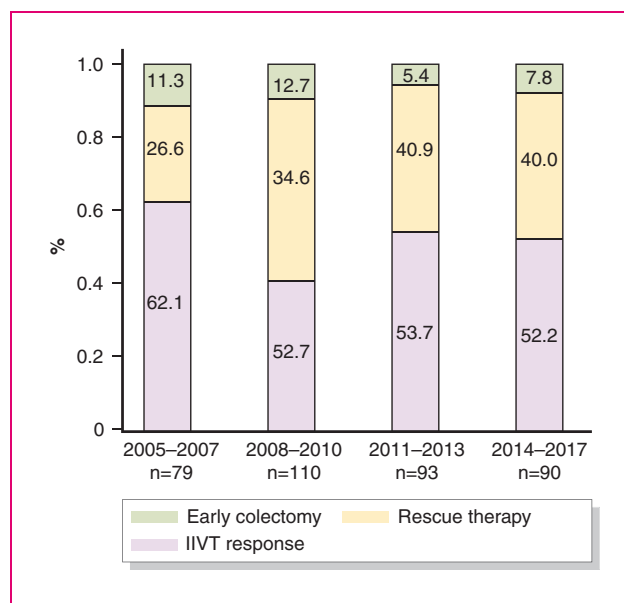


Figure 4. Time trend in rescue therapy utilization and short-term colectomy rate. Rescue therapy usage increased over time (p for linear trend = 0.04) while short-term colectomy rate showed a slight but not significant decrease over time (p for linear trend = 0.2). IIVT: intensive intravenous treatment with steroids.

2017 ($p = 0.04$ for linear trend). Instead, the short-term colectomy rate showed a slight but not significant decrease over time ($p = 0.2$ for linear trend). In all four time periods, more patients received infliximab rescue therapy than cyclosporine, and the proportion of patients receiving infliximab significantly increased

with time: 61.9%, 84.2%, 81.5%, 91.6% in the years 2005–2007, 2008–2010, 2011–2013 and 2014–2017 respectively ($p=0.01$ for linear trend).

Discussion

This retrospective study reports real-life data from a large cohort of patients with ASUC since 2005, when infliximab was approved in Italy for the management of UC. Over 90% of 372 patients included in the study responded to medical therapy and avoided colectomy within the first three months of admission. However, the clinical course in the following years was unfavourable: additional treatment, as well as repeat hospitalization because of a recurrent severe flare were required in approximately 40% and 50% of patients at three and five years, respectively. This clinical course was similar in patients who escaped early colectomy because of a response to steroids or rescue therapy.

The 9.4% rate of early colectomy here is significantly lower than that reported in early studies.^{6,27–30} However a reduction in the early colectomy rate for refractory ASUC has been observed recently: a United Kingdom inflammatory bowel disease audit reported short-term colectomy rates of 19% and 17% in 2008 and 2010, respectively,³¹ and a colectomy rate as low as 6.5% was obtained in a recent Spanish study.³² Several factors can explain the decreasing early colectomy rate in ASUC: overall improved UC management, early recognition of prognostic factors, careful monitoring and early assessment of non-response to steroids. Early and more frequent use of rescue therapies can also account for the reduction of colectomy, but this issue is controversial. In a Canadian retrospective cohort study, the rate of colectomy for medically refractory UC declined substantially since 2005, paralleling the increased use of anti-TNF α therapy.³³ In our series, approximately 40% of patients received rescue therapy with infliximab or cyclosporine for lack of a steroid response; this figure is similar to that in other recent studies.^{31,32}

The use of rescue therapy significantly increased from 2005 to 2017 in our study, but we did not observe a significant reduction of short-term colectomy rate in the same period. The choice of second-line rescue therapy (infliximab or cyclosporine) was made by the attending physician, with infliximab being chosen in more than 80% of cases. This finding indicates that Italian gastroenterologists manage rescue strategies differently from their colleagues in other countries where the proportions of patients receiving infliximab and cyclosporine are similar or skewed to cyclosporine.^{31,34} Although randomised controlled trials (RCTs) do not suggest any difference in efficacy and safety between infliximab and cyclosporine as rescue therapies for

steroid-refractory ASUC,^{11,12} observational data suggest a lower risk of long-term colectomy with infliximab compared with cyclosporine.³ This may be one of the reasons why infliximab is preferred over cyclosporine as rescue therapy but the experience of treating physicians and patient preferences, should also be taken into account. A theoretical advantage of infliximab over cyclosporine is that it is an easier treatment regimen with less monitoring and this may explain why many gastroenterologists are more familiar with infliximab than with cyclosporine.

The probability of long-term colectomy was approximately 20% within five years. This figure is less than that reported in historical series prior to the immunosuppressive treatment era²⁷ but is similar to our previous findings.^{17,18} Interestingly, the probability of long-term colectomy was significantly higher in patients who required rescue therapy than in patients who responded to steroid IIVT. At multivariate analysis, receiving rescue therapy and previous exposure to anti-TNF α were independently associated with the risk of long-term colectomy. We speculate that steroid-refractory patients, even when they achieve remission with second-line rescue therapy, have more severe disease than steroid-responsive patients.

Endoscopic severity at index colonoscopy was also associated with the risk of long-term colectomy. Patients with a Mayo endoscopic subscore of 2 at index colonoscopy had a lower risk of colectomy than those with severe endoscopic activity (OR = 0.4; 95% CI, 0.2–0.9). This finding confirms data from our previous study¹⁸ and several other retrospective studies^{29,35,36} in which endoscopic lesion severity, particularly the presence of deep or large ulcers, is associated with the risk of colectomy. On the other hand, in a randomised, placebo-controlled trial by Järnerot et al.,¹⁰ endoscopic lesion severity predicted neither infliximab response nor colectomy. Considering the retrospective design of our study, we cannot exclude that patients with severe endoscopic lesions were more likely to undergo colectomy because clinicians were convinced of their prognostic importance.

Another important observation in the present study is that maintenance treatment after the acute attack did not affect the long-term colectomy rate. Maintenance treatment in patients escaping early colectomy was not randomised but rather prescribed by attending physicians according to their clinical judgment. Overall, 52% of patients who responded to steroid IIVT were maintained on aminosalicylates, 35% on immunomodulators and 13% on infliximab despite steroid responsiveness. Conversely 92% of patients receiving rescue therapy were maintained with infliximab, immunomodulators or both. However, in the long term, up to 50% of patients in the two groups required escalation of

therapy and, as a consequence, the differences in maintenance strategies were reduced. The optimal maintenance treatment after the acute attack is not well established, and the role of early immunosuppression in patients who respond to steroids is controversial.³⁷

The major limitation of this study is its retrospective design. Nonetheless, the large number of patients studied, the length of follow-up and the clinically relevant outcomes considered are its major strengths. Furthermore, these data provide important insight into current Italian practices in the management of ASUC in the rescue therapy era.

In conclusion, our study describes the long-term outcomes of a large cohort of UC patients experiencing an acute severe attack. Use of rescue therapies, mainly infliximab, has significantly increased over time. This trend may have contributed to the drop of early colectomy rate below 10%. However, patients escaping early colectomy present a clinical course characterised by a high probability of needing additional drug therapy, repeat hospitalization and long-term colectomy. Previous exposure to anti-TNF α agents, need for rescue therapy because of intravenous steroid refractoriness, and endoscopic severity are independent predictors of long-term colectomy.

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Declaration of conflicting interests

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Ethics approval

The study protocol was approved by the institutional review board Comitato Etico Lazio 1 of the coordinating centre (IBD Unit, San Filippo Neri Hospital, Rome) protocol number 2158/CE Lazio1 and by the institutional review boards of all participating centres.

Informed consent

No informed consent was required because of the retrospective nature of the study.

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References

1. Edwards FC and Truelove SC. The course and prognosis of ulcerative colitis. Part 1: short-term prognosis. *Gut* 1963; 4: 300–308.
2. Dinesen LC, Walsh AJ, Protic MN, et al. The pattern and outcome of acute severe colitis. *J Crohns Colitis* 2010; 4: 431–437.
3. King D, Rees J, Mytton J, et al. The outcomes of emergency admissions with ulcerative colitis between 2007 and 2017 in England. *J Crohns Colitis* 2020; 14: 764–772.
4. Clemente V, Aratari A, Papi C, et al. Short term colectomy rate and mortality for severe ulcerative colitis in the last 40 years. Has something changed? *Dig Liver Dis* 2016; 48: 371–375.
5. Dong C, Metzger M, Holsbø E, et al. Systematic review with meta-analysis: mortality in acute severe ulcerative colitis. *Aliment Pharmacol Ther* 2020; 51: 8–33.
6. Turner D, Walsh CM, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol* 2007; 5: 103–110.
7. Kaplan GG, Seow CH, Ghosh S, et al. Decreasing colectomy rates for ulcerative colitis: a population-based time trend study. *Am J Gastroenterol* 2012; 107: 1879–1887.
8. Cohen RD, Brodsky AL and Hanauer SB. A comparison of the quality of life in patients with severe ulcerative colitis after total colectomy versus medical treatment

- with intravenous cyclosporin. *Inflamm Bowel Dis* 1999; 5: 1–10.
9. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994; 30: 1841–1845.
 10. Järnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology* 2005; 128: 1805–1811.
 11. Laharie D, Bourreille A, Branche J, et al.; Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. Cyclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. *Lancet* 2012; 380: 1909–1915.
 12. Williams JG, Alam MF, Alrubaiy L, et al. Infliximab versus cyclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. *Lancet Gastroenterol Hepatol* 2016; 1: 15–24.
 13. Narula N, Marshall JK, Colombel JF, et al. Systematic review and meta-analysis: infliximab or cyclosporine as rescue therapy in patients with severe ulcerative colitis refractory to steroids. *Am J Gastroenterol* 2016; 111: 477–491.
 14. Moskovitz DN, Van Assche G, Maenhout B, et al. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2006; 4: 760–765.
 15. Laharie D, Bourreille A, Branche J, et al. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. Long-term outcome of patients with steroid-refractory acute severe UC treated with cyclosporin or infliximab. *Gut* 2018; 67: 237–243.
 16. Sjöberg M, Magnuson A, Björk J, et al. Swedish Organization for the Study of Inflammatory Bowel Disease (SOIBD). Infliximab as rescue therapy in hospitalised patients with steroid-refractory acute ulcerative colitis: a long-term follow-up of 211 Swedish patients. *Aliment Pharmacol Ther* 2013; 38: 377–387.
 17. Aratari A, Papi C, Clemente V, et al. Colectomy rate in acute severe ulcerative colitis in the infliximab era. *Dig Liver Dis* 2008; 40: 821–826.
 18. Monterubbianesi R, Aratari A, Armuzzi A, et al.; Italian Group for the study of Inflammatory Bowel Disease (IG-IBD). Infliximab three-dose induction regimen in severe corticosteroid-refractory ulcerative colitis: early and late outcome and predictors of colectomy. *J Crohns Colitis* 2014; 8: 852–858.
 19. Gustavsson A, Järnerot G, Hertervig E, et al. Clinical trial: colectomy after rescue therapy in ulcerative colitis - 3-year follow-up of the Swedish-Danish controlled infliximab study. *Aliment Pharmacol Ther* 2010; 32: 984–989.
 20. Choy MC, Seah D, Faleck DM, et al. Systematic review and meta-analysis: optimal salvage therapy in acute severe ulcerative colitis. *Inflamm Bowel Dis* 2019; 25: 1169–1186.
 21. Thorne K, Alrubaiy L, Akbari A, et al. Colectomy rates in patients with ulcerative colitis following treatment with infliximab or cyclosporin: a systematic literature review. *Eur J Gastroenterol Hepatol* 2016; 28: 369–382.
 22. Magro F, Gionchetti P, Eliakim R, et al.; European Crohn's and Colitis Organisation (ECCO). Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis* 2017; 11: 649–670.
 23. Truelove SC and Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. *Br Med J* 1955; 2: 1041–1048.
 24. Chapman RW, Selby WS and Jewell DP. Controlled trial of intravenous metronidazole as an adjunct to corticosteroids in acute severe ulcerative colitis. *Gut* 1986; 27: 1210–1212.
 25. Schroeder KW, Tremaine WJ and Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. *N Eng J Med* 1987; 317: 1625–1629.
 26. Gionchetti P, Rizzello F, Annese V, et al.; Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). Use of corticosteroids and immunosuppressive drugs in inflammatory bowel disease: clinical practice guidelines of the Italian Group for the Study of Inflammatory Bowel Disease. *Dig Liver Dis* 2017; 49: 604–617.
 27. Gustavsson A, Halfvarson J, Magnuson A, et al. G. Long-term colectomy rate after intensive intravenous corticosteroid therapy for ulcerative colitis prior to the immunosuppressive treatment era. *Am J Gastroenterol* 2007; 102: 2513–2519.
 28. Travis SP, Farrant JM, Ricketts C, et al. Predicting outcome in severe ulcerative colitis. *Gut* 1996; 38: 905–910.
 29. Carbonnel F, Gargouri D, Lémann M, et al. Predictive factors of outcome of intensive intravenous treatment for attacks of ulcerative colitis. *Aliment Pharmacol Ther* 2000; 14: 273–279.
 30. Allison J, Herrinton LJ, Liu L, et al. Natural history of severe ulcerative colitis in a community-based health plan. *Clin Gastroenterol Hepatol* 2008; 6: 999–1003.
 31. Lynch RW, Lowe D, Protheroe A, et al. Outcomes of rescue therapy in acute severe ulcerative colitis: Data from the United Kingdom inflammatory bowel disease audit. *Aliment Pharmacol Ther* 2013; 38: 935–945.
 32. Llaó J, Naves JE, Ruiz-Cerulla A, et al. Improved outcome of acute severe ulcerative colitis while using early predictors of corticosteroid failure and rescue therapies. *Dig Liver Dis* 2016; 48: 608–612.
 33. Reich KM, Chang HJ, Rezaie A, et al. The incidence rate of colectomy for medically refractory ulcerative colitis has declined in parallel with increasing anti-TNF use: a

- time-trend study. *Aliment Pharmacol Ther* 2014; 40: 629–638.
34. Ordás I, Domènech E, Mañosa M, et al. Long-term efficacy and safety of cyclosporine in a cohort of steroid-refractory acute severe ulcerative colitis patients from the ENEIDA Registry (1989–2013): A nationwide multicenter study. *Am J Gastroenterol* 2017; 112: 1709–1718.
 35. Carbonnel F, Lavergne A, Lemann M, et al. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. *Dig Dis Sci* 1994; 39: 1550–1557.
 36. Cacheux W, Seksik P, Lemann M, et al. Predictive factors of response to cyclosporine in steroid-refractory ulcerative colitis. *Am J Gastroenterol* 2008; 103: 637–642.
 37. Vedamurthy A, Xu L, Luther J, et al. Long-term outcomes of immunosuppression-naïve steroid responders following hospitalization for ulcerative colitis. *Dig Dis Sci* 2018; 63: 2740–2746.