Title: Infliximab induction regimens in steroid refractory acute severe colitis: a multi-centre retrospective cohort study with propensity score analysis

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Running title: Rescue therapy regimens in ASUC

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Conflicts of interest:

Shaji Sebastian holds research grants from Takeda, AbbVie, Warner Chilcott, Ferring, MSD, Biohit and Celgene, serves on the advisory boards of Takeda, AbbVie, Merck, Ferring, Pharmacocosmos, Warner Chilcott, Janssen, Falk Pharma, Biohit, TriGenix, Cellgene and Tillots Pharma, and has received speaker fees from Abbvie, Jaansen, Merck, Warner Chilcott and Falk Pharma

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Abstract

Background

Accelerated induction regimens of infliximab have been proposed to improve response rates in patients with steroid refractory acute severe colitis.

Aims

We aimed to determine differences in outcome for acute severe ulcerative colitis between accelerated and standard-dose infliximab.

Methods

We collected data on hospitalised patients receiving differing regimens of rescue therapy for steroid refractory Acute Severe Ulcerative Colitis. Our primary outcome was 30-day colectomy rate. Secondary outcomes were colectomy within index admission, 90 days and 12 months. We used propensity score analysis with optimal calliper matching using *a priori* defined high-risk covariates to reduce potential provider selection bias.

Results

We included 131 patients receiving infliximab rescue therapy; 102 patients received standard induction and 29 received accelerated induction. In the unmatched cohort, there was no difference by type of induction in 30-day colectomy rates (18% vs. 20%, p=0.45), colectomy during index admission (13% vs. 20%, p = 0.26) or overall colectomy (20% vs. 24%, p= 0.38).

In the propensity score-matched cohort of 52 patients, 30-day colectomy (57% vs. 27%, p = 0.048) and index admission colectomy (53% vs. 23%,p =0.045) rates were higher in those receiving standard induction compared to accelerated induction but there was no difference in

overall colectomy rates between the 2 groups (57% vs. 31%, p =0.09). There was no significant difference in length of stay or in complication and infection rates.

Conclusion

In a propensity score matched cohort, steroid refractory Acute Severe Ulcerative Colitis patients, short-term, but not long-term, colectomy rates appear to be lower in those receiving accelerated induction regimen.

Key words

Acute severe colitis, Rescue therapy, Accelerated induction, Standard Induction, Colectomy

Abbreviations

ASUC= Acute severe ulcerative colitis

Introduction

Acute severe ulcerative colitis is a medical emergency with up to 30% of patients requiring colectomy during their index admission(1,2) and is associated with a mortality of up to 2.9% in peripheral centres and about 1% in specialist inflammatory bowel disease (IBD) units (3). Acute severe ulcerative colitis is traditionally defined by the Truelove and Witt's criteria (4), which combines frequency of bloody stools (≥6 per day) with at least one marker of systemic toxicity: pulse rate >90 bpm, temperature >37.8 °C, haemoglobin <105 g/L and/or an ESR >30 mm/h. ASUC requiring hospitalization occurs in 10-25% at diagnosis and in 20-30% during the disease course of ulcerative colitis (5,6).

Intravenous corticosteroids remain the cornerstone of first-line therapy for acute severe ulcerative colitis. A meta-analysis of cohort studies and randomized trials, published in 2007, examined response to corticosteroids in acute severe ulcerative colitis. The authors reported a pooled response rate to intravenous steroids of 67%, indicating that up to 40 % of patients fail to respond (7). Over the last decade, in patients failing corticosteroids, rescue therapies including ciclosporin and infliximab (1–3) have been used as an option to avoid colectomy . While there is no difference in response rates between infliximab and cyclosporine (8–10), a majority of clinicians now appear to favour infliximab mainly citing convenience and safety (11).

Despite use of rescue therapies a significant proportion of patients still undergo colectomy(12). The data on rescue therapies indicate that the rates of non-response to infliximab rescue vary from 40-55% (8–10). Reasons for non-response may include patient and disease factors or treatment factors such as timing of rescue and dosing schedules. A key and unanswered question remains the optimal dosing strategy of infliximab in steroid-refractory acute severe ulcerative colitis. Current regimens have extrapolated dosing schedules for management of moderate-to-severe disease in an outpatient clinic setting to the hospitalised in-patient, and use a standard induction regimen of 5 mg/kg intravenously at week 0, 2 and 6. However, there are multiple reasons why acute severe ulcerative colitis may be associated with increased clearance of infliximab. These include hypoalbuminaemia, leakage of infliximab itself into the stool, activation of the reticuloendothelial system and higher circulating TNF levels.(13–15) This enhanced clearance of infliximab may also be associated with worse clinical outcomes.

This has led to the concept of ‘accelerated induction rescue therapy’, where higher dosages or increased frequency of induction dosing have been proposed (15). There are no published randomised controlled trials on the efficacy and safety of accelerated induction. Although

there is increasing use of accelerated induction in clinical practice, the data from the published small cohort studies is conflicting (16–18). Our recent meta-analysis of available cohort studies showed no conclusive evidence for benefit of accelerated induction in reducing colectomy rates in steroid refractory disease (19). However, the majority of existing studies are single centre cohorts with significant limitations including small sample sizes. Furthermore, such studies did not take into account provider bias, which could be an important determinant in selection of the type of rescue therapy (20).

We have now performed a multicentre retrospective cohort study in 11 centres in the United Kingdom to compare the outcomes of using accelerated induction to standard induction regimens for acute severe ulcerative colitis in the real-world setting. We have used propensity score matching method to reduce the impact of provider bias in treatment selection.

Methods

This was a multicentre retrospective cohort study. We included patients with acute severe ulcerative colitis meeting modified Trulove and Witts criteria admitted between May 2016 and May 2018 for intravenous corticosteroids in 11 acute hospitals in UK (6 university teaching hospitals and 5 peripheral secondary care hospitals).

Inclusion and exclusion criteria

We included consecutive hospitalized patients needing intravenous steroids who received at least 3 doses of IV steroids. Physicians completing the case reports assessed them as meeting modified Trulove and Witts criteria. We excluded patients with: a diagnosis of inflammatory bowel disease unclassified, Crohn's colitis, infective colitis; coexistent CMV; admission for elective surgery; and prior therapy with anti-TNF.

Study design

Patients who received infliximab following failure of intravenous rescue therapy were stratified into two groups. The standard induction rescue group comprised of patients who received a dose of infliximab 5 mg/kg at week 0 and no further doses until two weeks after first dose. The accelerated induction group included patients who received at least two doses of 5 mg/kg with a second dose received on or before seven days after the first dose and/or those who received 10 mg/kg for their first dose with a further dose within 2 weeks. We recorded available data on clinical and laboratory data at baseline, at commencement of rescue therapy, 30 days, 90 days, 6 and 12 months.

Our primary outcome measure was colectomy rate at 30 days. Secondary outcome measures were index admission colectomy rates, colectomy rates at 90 days, 6 months and 12 months, the length of hospital admission, and adverse events including post-op complications and mortality.

Statistical analysis

Continuous variables were summarised using mean and standard deviation and compared using Student's t test or the Mann Whitney U test. Categorical variables were expressed as proportions and analysed by Fisher's exact test or Chi-squared test as appropriate.

Propensity score adjusted matching was used to minimise the possibility of provider bias in the choice of rescue treatment. Baseline clinical and demographic variables were matched in a 1:1 fashion to create a matched cohort with baseline variables which are independent of the initial infliximab dose. We ascribed *a priori* determined factors considered to affect choice of rescue therapy including CRP, serum albumin, CRP-albumin ratio, haemoglobin and presence of pancolitis in the propensity score matching. Logistic regression was used to generate bivariate propensity scores using these variables. We used the greedy matching

algorithm with the nearest calliper matching neighbour (random order) within a 0.01 propensity score was selected for the best match in the matched cohort. We confirmed balanced co-variates distribution after matching.

Kaplan-Meier survival curves were plotted for the primary outcome of 30-day colectomy rates in both unmatched and matched cohorts between those receiving standard induction compared to accelerated induction and the rates compared by log-rank statistic.

All tests were two-sided and a p-value of <0.05 was considered significant. We used SPSS Statistics Version 25 (IBM Corp., Armonk, NY, USA) for analysis.

As this was retrospective data collection, in accordance with UK Health Research Authority guidance, no central ethical committee submission was made. Individual institutions sought permissions to conduct a local service evaluation as appropriate.

Results

Study cohort

We included data on 131 patients from 11 centres across UK receiving rescue therapy for steroid refractory acute severe ulcerative colitis, of which 102 received standard induction regime and 29 received accelerated induction regimen. The baseline characteristics are recorded in Table 1. There were differences in blood parameters between the patients receiving standard induction and accelerated induction rescue (Table 2). Patients receiving accelerated regimen were more likely to have higher CRP levels, higher CRP/Albumin ratio and lower albumin levels at day 1 and day 3 and there were no differences between the 2 groups in terms of haemoglobin on day 1 or day 3.

Colectomy rates: entire cohort

The overall colectomy rate among the 131 patients who received rescue therapy was 29%. Table 3 reports the colectomy rates at 30 days, 90 days, 6 month and 12 months in patients receiving rescue therapy. There was no significant difference in overall colectomy rates between in patient receiving standard induction vs accelerated induction group (p=0.996). Table 3 and Figure 1

Colectomy rates: propensity score matched cohort

Using propensity score matching, we included 52 matched patients receiving rescue therapy for comparison. The baseline characteristics and blood markers in the cohort are detailed in Table 4.

In the propensity score matched cohort, there was no difference in overall colectomy rates between standard induction and accelerated induction groups (57% vs. 31%, p = 0.09), but the index admission colectomy (53% vs. 23%, p = 0.045) and 30-day colectomy (57% vs. 27%, p = 0.048) rates were higher in those receiving standard induction. **(Figure 2)**

Duration of hospital stay & Complications

The mean duration of hospital stay in patients treated with standard induction was 4.4 days (SD 1.6) less than patients given accelerated induction rescue therapy (p<0.01) in the unmatched cohort. In the propensity score matched cohort, there was no significant difference in length of stay between standard induction and accelerated induction groups (23.6 ± 4.3 vs. 19.2 ± 7.1 days, p = 0.09). There was no difference in complication rates between the 2 groups (18.6% vs 20.7%, p=0.8) but there was one death in the accelerated induction group. **(Table 5)**

Discussion

Despite the increasing use of infliximab rescue therapy in patients failing intravenous steroids, a significant proportion of acute severe ulcerative colitis patients do not respond adequately to standard induction dosing. Pharmacokinetic data has led to increasing use of intensified or accelerated dosing schedules in rescue therapy for acute severe ulcerative colitis patients. Our large multicentre retrospective study showed no difference in colectomy rates in the overall cohort of patients receiving standard versus accelerated dosing schedules but when provider bias was accounted for in the propensity matched cohort, we found a reduction in short term colectomy rates in patients receiving accelerated induction.

The first study to report the potential benefit of more frequent infliximab infusions in acute severe ulcerative colitis patients was from Gibson et al in Ireland (16), who in their cohort of 50 hospitalised patients with acute severe ulcerative colitis showed a reduction in short term colectomy rates in the 15 patients who received 3 doses of 5mg/kg within 24 days when compared to those receiving standard induction regimen (6.7 % vs 40%, p 0.039). This study also suggested shortened time to colectomy in those receiving standard regime although the long-term colectomy rates were similar. Notably, 38% of these patients had lower endoscopic disease severity (Mayo 2), and the authors did not correct for provider bias in the choice of regimen. Furthermore, the definition of accelerated dosing in this study did not include the need for a further dose seven days after the first dose or increased front loading dose. Subsequent studies examining the use of increased frequency of infliximab at 5 mg/kg (17,18,21,22) and a recent meta-analysis (19) have not confirmed the benefit as reported by Gibson et al. In one study (21), there was an increased risk of colectomy with accelerated induction . Our colectomy rates in the overall unmatched cohort mirrors the results from these studies showing no additional significant benefit in short term colectomy rates with accelerated induction.

Some studies (21,23) have assessed an early aggressive approach aimed at overcoming proposed faecal losses of infliximab using a front-loading higher dose of 10 mg/kg in acute severe ulcerative colitis patients. In our study, only 4 patients received a higher initial dose and hence could not be analysed separately. Results of a randomised controlled trial from Australia (ClinicalTrials.gov Identifier: NCT02770040) comparing various dosing strategies is eagerly awaited.

A number of patient and disease related variables have been suggested as high risk for needing colectomy in patients with acute severe ulcerative colitis (24,25). These indices were developed in the pre-infliximab rescue therapy era and the relevance of this in patients considered for rescue therapy is uncertain. More recently, a number of other patient related factors such as serum albumin, serum albumin-CRP ratio and haemoglobin nadir has been proposed as predictive risk factors for colectomy at index admission (16,26). We have identified CRP-albumin ratio >2 as a predictor for colectomy (unpublished data). However, at present there is no consensus on the consistent identification and risk stratification of patients not only needing rescue therapy but also those who may potentially benefit from different dosing strategies. This lack of consensus inevitably leads to variations in management and dosing regimens (27) as seen in in our study. The blood parameters at first and second doses of rescue therapy indicates lack of improvement or indeed worsening which along with clinical symptom may prompt a second dose as accelerated induction (data on supplementary file 1)

One of the strengths of our study is the attempt to compare the outcomes between the different dosing regimens after accounting for the potential bias of baseline clinical and demographic variables and the potential impact of these in clinicians' choice by using a propensity score matched method. Our model incorporated established disease severity markers such as CRP, serum albumin, CRP albumin ratio and haemoglobin levels at

induction and endoscopic disease severity. This is the first study to report a benefit of accelerated induction regimes when taking into the potential for provider bias based on differing disease severity. Nalagatla et al (23) adjusted for the propensity score in their multivariable model and found no difference in in hospital colectomy rates (OR 0.70, 95% CI 0.16-3.01). However, the overall colectomy rates in both groups in this study (8-9%) was substantially lower than our study (17-21%). This may be related to overall lower disease severity in all parameters in the patients included in this study when compared to our cohort. In a study by Shah et al (21), after adjusting for patient and disease related factors and provider bias in a propensity score matched model no reduction in colectomy rates was found in those receiving higher upfront dosing when compared to standard dosing. This study only included patients from a single centre and differed from ours by including patients with prior infliximab exposure before rescue therapy. Furthermore, in this study and in the study by Nalagatla et al (23), the endoscopic disease severity of patients in the propensity matched cohort was milder (30% having an endoscopic Mayo score of 2) when compared to our study where 97% of the included patients in our matched cohort had severe disease (Mayo 3) at endoscopy. Thus, our results suggest that early identification of patients with high risk features for colectomy may reduce colectomy rates by use of accelerated rescue therapy.

In the unmatched cohort, the duration of hospital stay was significantly shorter in those receiving standard induction. In the matched cohort, on the other hand, there was no difference in length of stay. Our results were similar to that of Shah et al (21), where the median length of stay was identical in those receiving standard induction and accelerated induction in the matched cohort. In that study, in the unmatched cohort there was higher complications in the standard dose group when compared to the high doses group a finding not seen in our unmatched cohort. However similar to our results in that study the overall complication rate including infectious and/or non-infectious complications were not

significantly higher in the high dose group compared to standard dosing group in the propensity matched cohort. Thus, overall accelerated dosing regimens did not seem to increase the risk of complications. There was one death in the accelerated induction group as a result of post-operative rectal stump leak and sepsis resulting in multiorgan failure.

We acknowledge that our study has number of limitations. Due to the retrospective nature of the study, we were unable to collect every variable each day following admission with acute severe ulcerative colitis and were also unable to record the objective assessment of response and remission. We also had no data on serum infliximab levels or biomarkers such as faecal calprotectin in patients receiving rescue therapy. There is increasing focus on the use of therapeutic drug monitoring in IBD patients treated with infliximab and the impact of dose optimisation utilizing drug levels on the outcomes could not be ascertained in this study. There were significant differences in the unmatched cohort of patients and also heterogeneity in dosing regimens and timing indicating variations in practice in the real-world setting. Hence although this was a multicentre study and one of the largest to compare rescue therapy regimes, our attempt to reduce provider variation by propensity score matching led to a relatively small sample size in the matched cohort thus reducing the power of our study for the primary outcome and rate of complications. Furthermore, our model cannot account for variability in management including dose optimisation during the maintenance period which could have affected the outcome. That said, controlling for bias of treatment choice based on disease in a multicentre cohort is a major strength of our study.

Conclusions

In conclusion, we found that in the overall cohort of acute severe ulcerative colitis patients in real world setting receiving rescue therapy infliximab, the initial induction dosing strategy did not change the short term or long-term colectomy rates. In a subgroup of patients with

matched covariates of severity, accelerated induction regimes appears to reduce in-hospital and short-term colectomy rates without any increase in complications. The optimal dosing regimens and risk stratification of patients needing accelerated dosing regimens needs to be evaluated in a prospective study.

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Tables , Figures and Supplementary files

Table 1: Baseline characteristics of the cohort of acute severe colitis patients

Data shown are mean (standard deviation) or n (%) as appropriate

		Steroid with standard rescue therapy (102)	Steroid with accelerated rescue therapy (29)
Age (mean, SD)		39.0 (17.1)	38.6 (17.2)
Gender (n, %)	Male	59 (58%)	22 (76%)
	Female	43 (42%)	7 (24%)
Disease duration in years (mean, SD)		4.0 (5.2)	4.2 (6.0)
Disease location (n, %)	Proctitis (E1)	2 (2%)	0 (0%)
	Left sided colitis (E2)	36 (35%)	4 (14%)
	Extensive Colitis (E3)	64 (63%)	25 (86%)
Presence of Extra-intestinal Manifestations (n, %)	Yes	14 (14%)	7(24%)
	No	88 (86%)	22 (76%)
Presence of comorbidity	Yes	22 (22%)	4 (14%)
	No	80 (78%)	25 (86%)
Thiopurines at admission	Yes	33 (32%)	11 (38%)
	No	69 (678%)	17 (589%)
Steroids at admission	Yes	42 (41%)	10 (35%)
	No	60 (59%)	19 (66%)
Prior Steroids	Yes	68 (67%)	15 (52%)
	No	34 (33%)	14 (48%)
Previous IV steroids	Yes	30 (29%)	7 (24%)
	No	72 (71%)	22 (76%)

Mayo Endoscopic Score:	Not available	5	0
	2	8 (8%)	0(0%)
	3	89 (87%)	29 (100%)
5 ASAs at admission	Yes	77 (75%)	19 (66%)
	No	25 (25%)	10 (34%)
Route of admission (n, %)	Emergency admission	66 (65%)	22 (76%)
	Admission from Outpatient IBD clinics	29 (28%)	6 (21%)
	Others	7 (7%)	1 (3%)

Table 2: Blood Parameters at admission and day 3 – Unmatched cohort

	Standard Induction Group (n=102)	Accelerated induction Group (n=29)	*P*
Haemoglobin Day 1 (Mean± SD)	122±19	116±19	0.11
CRP Day 1 Median (IQR)	56 ±78	101±36	0.001
Serum albumin Day 1 (Mean± SD)	33±6	30±2	0.006
Platelet count Day 1 (Mean± SD)	458±145	577±133	0.21
Monocyte count Day 1 (Mean± SD)	1.2±0.6	1.6±0.6	0.73
CRP/Albumin ratio >2 Day 1 (n, %)	61 (59.8)	24 (82.7)	0.03
Haemoglobin Day 3 (Mean ± SD)	116±17	110±16	0.83
CRP Day 3 (Median± IQR)	75± 91	117± 48	0.001
Serum albumin Day 3 (Mean± SD)	31± 6	27 ±2	0.001
Platelet count Day 3 (Mean± SD)	472±150	615± 134	0.001
CRP/albumin ratio>2 Day 3 (n, %)	49 (48.0)	21 (72.4)	0.01

Table 3: Colectomy rates entire cohort

	Steroid with standard rescue therapy (102)	Steroid with accelerated therapy (29)	*p*
30 days	18 (17.6%)	6 (20.7%)	0.45
90 days	20 (19.6%)	7 (24.1%)	0.38
6 months	26 (25.5%)	8 (27.6%)	0.49
12 months	29 (28.4%)	9 (31.0%)	0.99

Table 4: Characteristics of Propensity score matched cohort (n=52)

	Standard induction N=26	Accelerated induction N=26	*p*-value
Age in years median(range)	31 (17-47)	29 (18-43)	0.93
Gender, n Male Female	 14 12	 11 15	0.34
Disease extent, n Pancolitis Left sided colitis	 23 3	 21 5	0.96
Duration of disease years median (SD)	3.2 (4.1)	2.9 (3.9)	1.00
Prior steroid use, n Yes No	 21 5	 19 7	0.89
Prior Thiopurine Use Yes No	 16 10	 11 15	0.06
Mayo endoscopic scope, (n) Mayo 3 Mayo 2	 24 2	 26 0	0.98
Number of days on IV steroids before Infliximab, Median (range)	4 (2-7)	3 (2-6)	0.91
CRP at rescue, Median (IQR)	116 (39)	124 (41)	0.76
Haemoglobin at rescue Mean (SD)	108 (2)	99 (2)	0.08
Albumin at rescue Mean (SD)	29 (3)	26 (2)	0.64
Platelet count at rescue, mean (SD)	511 (63)	546 (4)	0.07
Haemoglobin nadir <100 g/L at rescue n (%)	18 (69%)	20 (76%)	1.00
CRP/Albumin ratio >2 at rescue n (%)	24 (92%)	25 (96%)	0.99

Table 5: Duration of Hospital stay and complications

		Steroid with standard rescue therapy (102)	Steroid with accelerated therapy (29)
Days of hospital stay unmatched cohort (mean, SD)		14.8 (8.1)	19.2 (5.9)
Days of hospital stay matched cohort (mean, SD)		23.6(4.3)	19.2(7.1)
Complications - infections, post op complications or mortality (n, %) unmatched cohort	Yes	19 (18.6%)	6 (20.7%)
	No	83 (80.4%)	23 (79.3%)

Figure 1. Kaplan Meier plot for colectomy free survival – accelerated induction vs standard induction :Unmatched cohort

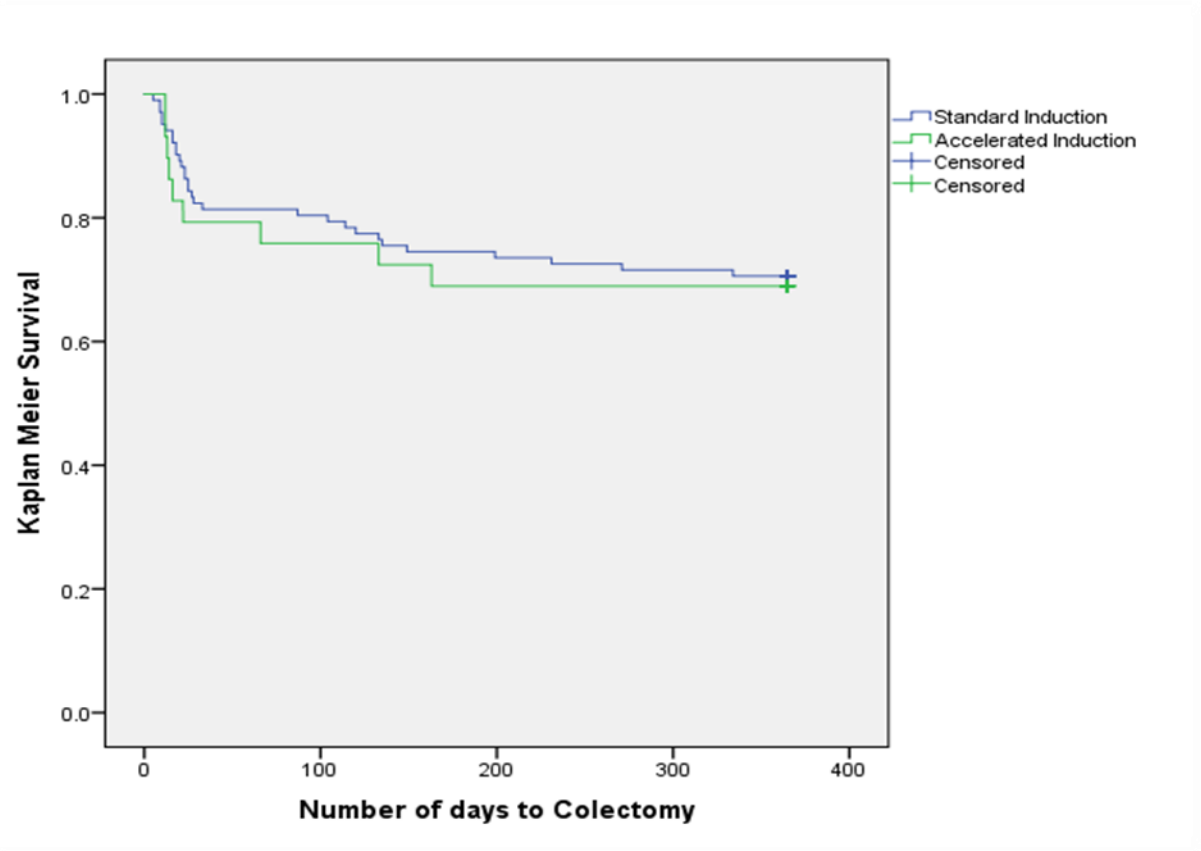
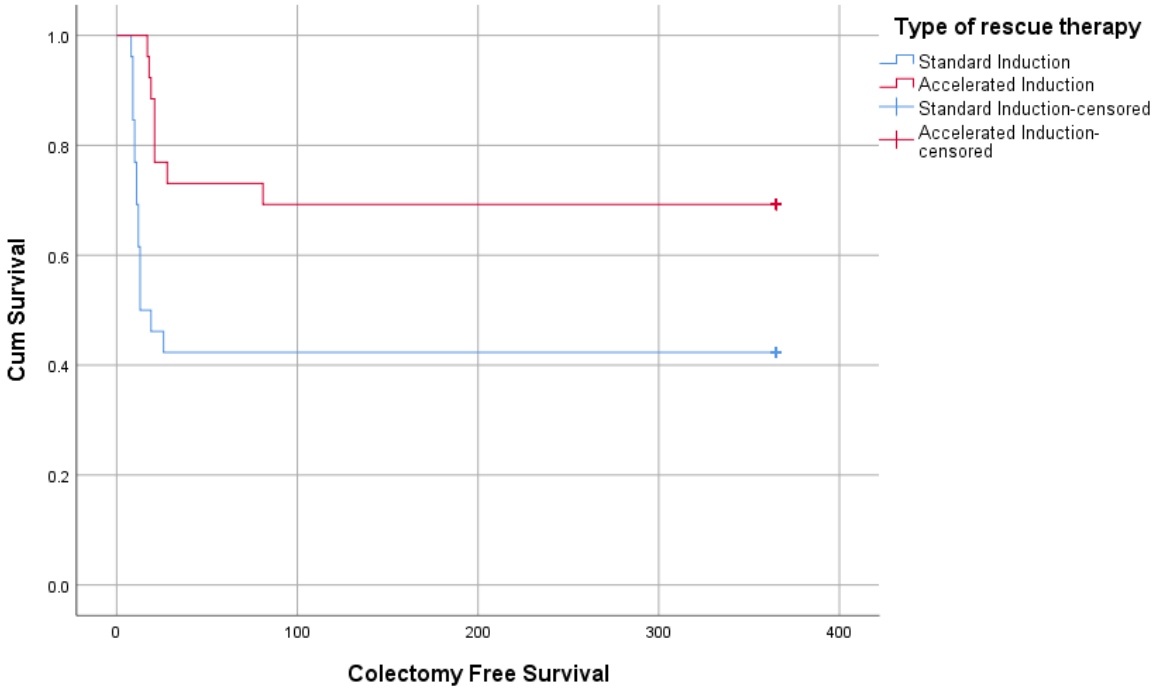


Figure 2: Kaplan Meier plot for colectomy free survival – accelerated induction vs standard induction Matched cohort



Supplementary table 1: Blood parameters at first and second dose rescue in Accelerated induction group (unmatched cohort)

	First dose rescue (29)	Second dose rescue (29)
Haemoglobin	106 (1)	89 (2)
CRP Median (IQR)	105 (43)	147(48)
Serum albumin (Mean± SD)	27 (3)	24 (4)
Platelet count (Mean± SD)	552 (26)	569 (51)
CRP/albumin ratio>2 (n, %)	27 (93%)	28 (97%)

Supplementary table 2: Blood parameters at first and second dose rescue in the accelerated induction group (matched cohort)

	First dose Rescue (26)	Second dose rescue (26)
CRP Median (IQR)	119 (51)	123 (31)
Haemoglobin Mean (SD)	99 (2)	87 (2)
Albumin Mean (SD)	26 (2)	24 (2)
Platelet count at rescue, mean (SD)	546 (44)	563 (63)
CRP/Albumin ratio >2 (%)	25 (96%)	25 (96%)

Appendix 1: ELEVATE-ASUC study Group authors and affiliations

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