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Predicting response after infliximab salvage in acute severe ulcerative colitis

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## TITLE

### Predicting Response after Infliximab Salvage in Acute Severe Ulcerative Colitis

## ABSTRACT

**Objectives:** Acute severe ulcerative colitis (ASUC) is a medical emergency requiring prompt therapeutic intervention. Although Infliximab has been used as salvage therapy for over 15 years, clinical predictors of treatment success are lacking. We performed a retrospective analysis to identify factors that predict colectomy and may guide dose intensification.

**Methods:** 54 hospitalized patients received infliximab for ASUC at 7 Australian centres (April 2014-May 2015). Follow-up was over 12 months. The data was primarily analysed for predictors of colectomy. Accelerated (AI) versus standard (SI) infliximab induction strategies were also compared.

**Results:** Of 54 patients identified, the overall colectomy rate was 15.38% (8/52) at 3 months and 26.92% (14/52) at 12 months. Two patients were lost to followup. There was a numerically higher colectomy rate in those treated with AI compared to SI ( $p=0.3$ ); however those treated with AI had more severe biochemical disease. A CRP/Albumin ratio cut-off of 0.37 post-commencement of infliximab and prior to discharge was a significant predictor of colectomy with an area under receiver operating curve of 0.73. Pretreatment CRP and albumin levels were not predictive of colectomy. A Mayo Endoscopic Score of 2 had a 94% PPV for avoidance of colectomy following infliximab salvage.

**Conclusions:** The baseline Mayo Endoscopic Score and the CRP/Albumin ratio following infliximab salvage are significant predictors of treatment response for

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ASUC and identify patients at high risk of colectomy. Whether this risk can be mitigated using infliximab dose intensification requires prospective evaluation before the CRP/Albumin ratio can be integrated into ASUC management algorithms.

**Keywords:** Ulcerative Colitis; Infliximab; Colectomy.

### **Abbreviations**

AUROC, Area Under the Receiver Operating Curve; AI, Accelerated Induction; ASUC, Acute Severe Ulcerative Colitis; CRP, C-reactive protein; IBD, Inflammatory Bowel Disease; MES, Mayo Endoscopic Score; NPV, Negative Predictive Value; PPV, Positive Predictive Value; Q1, Quartile 1; Q3, Quartile 3; SI, Standard Induction; TNF, Tumour Necrosis Factor; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

### **What does this paper add to the literature?**

Infliximab is effective as salvage therapy for corticosteroid refractory acute severe ulcerative colitis; however assessment of response following the initiation of Infliximab is ill-defined. Here, we demonstrate that the Mayo Endoscopic Score and CRP/Albumin ratio following the commencement of infliximab can predict treatment response and identifies patients at high risk of colectomy.

## INTRODUCTION

Acute Severe Ulcerative Colitis (ASUC) is a potentially life-threatening condition which results in emergency colectomy in up to 30% of patients within three months of presentation.(1) One-third of patients do not respond to first-line corticosteroid therapy.(1) Infliximab and Cyclosporine have demonstrated equivalent efficacy as medical therapies for patients who fail to respond to corticosteroids; however, more than half of patients fail to respond to either drug.(2-4)

The standard induction schedule for infliximab comprising of 3 doses at 5mg/kg given at Week 0, 2 and 6 has been derived from studies of Crohn's disease and Rheumatoid arthritis.(5, 6) However, these diseases differ in their biology and inflammatory disease burden from patients with ASUC.

A retrospective study by Gibson and colleagues found that an accelerated infliximab induction schedule within four weeks reduced early colectomy rates at one month compared to standard induction treatment over six weeks.(7) Such an approach has been supported by recent findings of increased infliximab drug clearance in ASUC and new mechanisms of loss of response due to faecal drug loss;(8, 9) however, identifying which patients are most likely to benefit from an accelerated strategy is unknown.

Previous studies in ASUC have focused on predictors of response to corticosteroid therapy such as the Travis (Oxford) criteria(10) and more recently the use of CRP/Albumin ratio.(11) The Ho index has been applied to predict colectomy prior to treatment with Cyclosporine.(12) There have been few studies which have specifically focused on predictors of response to infliximab salvage therapy in ASUC. We performed this study to identify clinical, endoscopic and biochemical markers of treatment response and failure; and to explore the impact of accelerated infliximab dosing compared with standard dosing in our cohort.



## MATERIALS AND METHODS

### ***Study population***

A retrospective cohort study of 54 consecutive patients admitted to seven Australian tertiary hospitals between April 2014 and May 2015 was undertaken. All patients had steroid refractory ASUC as defined by the Truelove and Witt's(13) and Oxford criteria.(10) All patients had access to three doses of Infliximab 5mg/kg under the Pharmaceutical Benefits Scheme of Australia. The standard Infliximab induction strategy utilized was 5mg/kg at Week 0, 2 and 6 (SI); however, accelerated induction (AI) whereby the second and third doses (both at 5mg/kg) were given ahead of schedule was individually determined at the discretion of the treating clinician based on: (i) a lack of adequate response to the first dose of infliximab; or (ii) an initial response followed by deterioration in symptoms such as stool frequency or rectal bleeding; or (iii) rise in inflammatory markers. Following successful induction, patients naïve to thiopurines were maintained on a combination of mesalazine and a thiopurine, whereas those experienced to thiopurines were maintained on infliximab. This study was approved by the Austin Health Research Ethics Committee, St Vincent's Hospital Research Ethics Committee, Alfred Health Research Ethics Committee, Eastern Health Research Ethics Committee, Melbourne Health Research Ethics Committee, Monash Health Research Ethics Committee and Royal Brisbane and Women's Hospital Ethics Committee.

### ***Statistical considerations***

Descriptive statistics were used to describe the study cohort and results reported as median (Q1-Q3) for continuous data and %(N) for categorical data. Bi-variate analysis was used to evaluate differences between study groups (AI vs SI). Fisher's exact or Chi-square tests were used for categorical data and Wilcoxon Rank-Sum test for continuous data. Continuous data were tested for normality using the Shapiro-Wilk test. Logistic regression and sensitivity analysis (using senspec

command in Stata) were used to determine the optimum CRP/Albumin ratio to predict the risk of colectomy alone and the composite of colectomy and early unplanned readmission for further salvage (within 6 weeks of initial infliximab salvage therapy). Data was analysed using a complete case approach. Comparison between patients who completed the follow-up and those who did not was performed to eliminate selection bias. All analyses were performed using Stata15 (Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC); SPSS Version 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) and  $p < 0.05$  was considered statistically significant.

## RESULTS

### ***Demographics***

Fifty-four patients with ASUC were identified across seven institutions. 2 patients were lost to follow-up at 3 and 12 months. In our cohort, 35.2% (19/54) were female and the median age was 33.2 years (Q1-Q3 27.4-44.7). Twenty percent (11/54) had a new diagnosis of UC and the median disease duration was 2.5 years (Q1-Q3 1.4-6.4). With respect to therapy at time of admission, 44.4% (24/54) were on oral steroids, 64.8% (35/54) were on oral aminosalicylates, 40.7% (22/54) were on a thiopurine and 7.4% (4/54) were on methotrexate. No patients were on Infliximab prior to induction therapy. The median duration of IV steroids prior to initiating infliximab salvage was 4 days (Q1-Q3 3.0-6.0).

### ***Colectomy***

When accounting for the 2 patients who were lost to follow-up the overall colectomy rate was 15.4% (8/52) at 3 months and 26.9% (14/52) at 12 months. The median time to colectomy was 55 days (Q1-Q3 26-131). Two patients underwent an emergency colectomy (within the same admission) after a single dose of infliximab. The remaining 12 patients underwent elective colectomy (following discharge).

## ***Factors associated with colectomy***

Factors associated with colectomy are indicated in Table 1

### *Clinical Factors*

No significant associations were observed between colectomy and age, disease duration or medication use. There was no significant difference in the duration of IV steroids prior to commencing Infliximab between those with colectomy (4.0 days (Q1-Q3 3.0-5.0) versus no colectomy (5.0 days (Q1-Q3 4.0-6.0);  $p=0.43$ ).

### *Endoscopic Factors*

There was a greater proportion of severe endoscopic disease (Mayo 3) in those who underwent colectomy compared to those who did not [90.9% (10/11) vs 51.5% (17/33);  $p=0.03$ ].

### *Biochemical Factors*

Biochemistry was assessed at time of admission, time of induction, day 3 post induction and prior to discharge. Timing of discharge bloods are outlined in Table 2. Neither CRP, Albumin nor the CRP/Albumin ratio were significant predictors of colectomy at admission, induction or day 3. CRP or Albumin prior to discharge were also not significant predictors of colectomy. However, the CRP/Albumin ratio prior to discharge was predictive of future outcome. Those who came to colectomy had a significantly higher CRP/Albumin ratio prior to discharge than those who avoided colectomy at 12 months [0.7 (0.4-1.4) vs 0.3 (0.1-0.7), respectively;  $p=0.02$ ] (Table 1).

### ***Predictors of colectomy***

A Mayo Endoscopic Score (MES) of 2 predicted avoidance of colectomy within 12 months with 48% sensitivity, 91% specificity, a positive predictive value (PPV) of 94% and negative predictive value (NPV) of 37%. A MES of 3 predicted colectomy within 12 months with 91% sensitivity, 48% specificity, a PPV of 37% and NPV of 94%.

A CRP/Albumin ratio of  $>0.37$  at discharge predicted future colectomy with 80% sensitivity, 62% specificity, a 42% PPV and a NPV of 90%; area under receiver operating curve (AUROC) of 0.73 (Figure 1). A cut-off of  $<0.32$  has a 90% sensitivity, 55% specificity, 41% PPV and 94% NPV for avoiding colectomy in the first 12 months.

### ***Accelerated vs Standard Infliximab Strategy***

Of the 54 patients who underwent salvage therapy, 51 patients formed the basis of this analysis as three patients had a single dose of infliximab (two of whom proceeded to colectomy). Seventy-three percent (37/51) underwent Standard induction (SI) and 27.5% (14/51) had Accelerated induction. The comparison between both groups is shown in Table 3. SI was completed over 43.0 days (Q1-Q3 42.0-46.0) vs 25.0 days for AI (Q1-Q3 17.5-32.0);  $p<0.01$ . Patients treated with AI had significantly higher CRP/Albumin ratio at time of induction [2.0 (Q1-Q3 0.6-5.2) vs 0.6 (Q1-Q3 0.2-1.7);  $p=0.02$ ]. Patients with AI had a longer length of stay compared to SI (12.5 days (Q1-Q3 10.8-16.0) vs 8.0 days (Q1-Q3 6.5-10.5);  $p<0.01$ ) and a higher proportion with Mayo 3 severe endoscopic disease activity (84.6% (11/13) vs 56.7% (17/30);  $p=0.10$ ). The median time to colectomy was 104.0 days (Q1-Q3 35.0-231.0) in SI and 46.0 days (Q1-Q3 27.5-170.5) in AI; ( $p=0.53$ ), demonstrated in Figure 2. Although there was no statistically significant difference in colectomy rate between the two induction strategies, there was a numerically higher rate in AI at 3 months (21.4% (3/14) vs 8.6% (3/35);  $p=0.33$ ) and 12 months (35.7% (5/14) vs 20.0% (7/35);  $p=0.29$ ).

## DISCUSSION

Infliximab is an effective therapy in ASUC; however, despite its use in inflammatory bowel disease for over 15 years, the optimal dosing schedule in ASUC is still unknown. Factors determining which patients should be considered for salvage therapy for ASUC following corticosteroid failure are well established. In contrast, predictors of which patients do and do not respond to infliximab therapy following corticosteroid failure in ASUC are poorly understood. This study has demonstrated that accelerated induction was not superior to standard induction in our cohort; that the MES is a useful predictor of colectomy; and the CRP/Albumin ratio following the initiation of infliximab salvage therapy and prior to discharge for ASUC is predictive of colectomy.

A majority of clinicians favour accelerated or intensified Infliximab dose strategies in ASUC (14) with limited evidence to support this practice. Although Gibson and colleagues found an improved colectomy free survival with an accelerated induction schedule, the same was not found by Govani et al,(15) and Al Khoury et al,(16) with a high rate of treatment failure and post colectomy complications in those with accelerated dosing. One reason for this difference was that patients in the latter studies treated with accelerated dosing had biochemically more severe disease. We similarly found a numerically higher colectomy rate in those treated with accelerated induction possibly due to the presence of more severe biochemical and endoscopic disease; however, this lack of statistical difference likely relates to the limitation of our relatively small sample size. In our cohort CRP, Albumin and the CRP/Albumin ratio at admission, induction and Day 3 were not predictive of colectomy contrary to published literature, likely due to the fact that patients with more adverse biochemistry were treated with accelerated dosing which may have relatively improved the expected colectomy rate. Whilst formal costings were not performed in

this study, length of stay is a surrogate marker. Accelerated induction patients had an increased length of stay with no improvement in colectomy free survival, raising the question of the cost effectiveness of more intensive medical therapy.

Emerging evidence suggests that there is a high burden of both circulating and mucosal TNF cytokine in ASUC which acts as a drug 'sink', and highly elevated levels are predictive of anti-TNF failure and colectomy.(17, 18) Infliximab clearance and the development of drug immunogenicity is more rapid in ASUC,(8) which likely relates to faecal drug loss (9) and occurs more commonly in patients with high CRP and low albumin levels.(19) Thus, patient selection is likely to be a key determinant of the optimal dosing schedule for infliximab. It has been proposed that patients with a CRP>50mg/L should receive a 10mg/kg dose of infliximab as this group of patients are likely to have lower drug levels;(19) however, as to whether such an approach can overcome the pharmacokinetic barrier is yet to be proven. Flexible dosing with higher doses or accelerated infusion schedules tied to biochemical responses to treatment have entered clinical practice with limited evidence to support the effectiveness of such strategies (20).

Our data suggest that early post salvage biochemical parameters may more useful in providing practical prognostic information to clinicians and patients when assessing the success of infliximab induction than pre-treatment levels. Day 3 parameters were also not useful predictors, likely due to the influence of early intervention with accelerated dosing. The CRP/Albumin ratio prior to discharge with a cut-off of 0.37 and MES were highly predictive of the hard end-point of long term colectomy-free survival irrespective of whether a standard or accelerated induction strategy was adopted. This finding requires prospective validation as a predictor of colectomy in cohort studies. Whilst the Ulcerative Colitis Endoscopic Index Severity Score (UCEIS) is emerging as a strong predictor of outcome in ASUC (21), the MES is still of important value and was able to stratify those at a low risk of colectomy in our cohort.

Assessment of response to infliximab in ASUC has yet to be clearly defined. There are no defined thresholds to guide what the initial dose of infliximab should be, what the ideal time is to determine clinical or biochemical response, and if and when further salvage doses should be given before primary failure can be judged and medical therapy aborted. Given that the CRP/Albumin ratio prior to discharge identifies patients at high risk of readmission for further salvage and colectomy, it may be clinically beneficial to integrate this biomarker into management algorithms to facilitate objective assessment of response to infliximab salvage, and guide decisions on when to apply dose intensification. We propose that patients who fail to achieve an adequate early improvement in the CRP/Albumin ratio to  $<0.37$  following the commencement of infliximab salvage are high risk, who have poorly responded to initial infliximab treatment and who are in need of close monitoring, consideration of infliximab dose intensification or surgery.

This study has several limitations. Although the timing of discharge bloods is inherently variable, this is a pragmatic parameter that was found to have predictive value. This study may also have benefited from detailed post-induction clinical activity indices such as the Mayo Clinical Score, Lichtiger score or Rachmilewitz index to explore clinical response, however these data were not available to evaluate in this cohort. This study is also retrospective with a relatively small sample size. As such, a valid multivariate analysis could not be performed. Nonetheless this study was an exploratory evaluation which still permitted analysis of predictors of colectomy as the primary end-point of interest. Furthermore, whilst we did not find a statistically significant difference in colectomy rates between accelerated induction and standard induction, both groups had different baseline levels of biochemical inflammatory activity; however our sample size precluded adjustment for these covariates via propensity score weighting or regression analysis. Although this study was multicentric with potential differences in clinical management amongst the sites

and assessment of endoscopic severity, this analysis captured the “real world” outcomes of 54 consecutive patients from seven separate institutions.

In keeping with recent expert consensus guidelines that endorse a treat-to-target strategy as the optimal approach to managing IBD(22) these data emphasize the importance of corroborating clinical improvement following infliximab salvage therapy with objective markers of inflammatory disease. The CRP/Albumin ratio appears to be a promising biomarker to determine response to infliximab therapy and its prognostic value requires prospective evaluation. Whether the risk of colectomy can be mitigated using infliximab dose intensification also warrants further exploration in controlled interventional studies.

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## TABLES

Table 1. Comparison of patients who underwent colectomy vs those who were colectomy free at 12 months

Note: Continuous data reported as median (Q1-Q3) and analysed using Wilcoxon rank-sum test; categorical data reported n(%) and analysed using Fisher's exact test

Median and Q1-Q3	No colectomy N=38	Colectomy N=14	P value
Gender			
Female n(%)	16 (42.1)	3 (21.4)	0.44
Age (years)	32.7 (27.1-42.9)	40.9 (26.9-57.4)	0.21
Disease duration (years)	2.50 (1.4-6.4)	2.48 (0.8-10.7)	0.88
Duration of IV steroids prior to initiating Infliximab (days)	5.0 (4.0-6.0)	4.0 (3.0-5.5)	0.43
Medications on admission n(%)			
-Oral Steroids	18 (47.4)	5 (35.7)	0.54
-Mesalazine	26 (68.4)	8 (57.1)	0.52
-Immunomodulator (Thiopurine or Methotrexate)	17 (44.7)	8 (57.1)	0.54
CRP mg/L			
-admission	38 (19.0-82.0)	54.0 (31.0-170.0)	0.10
-at induction	17.0 (7.5-46.4)	33.0 (10.3-55.0)	0.38
-Day 3 post Infliximab	8.5 (2.8-36.0)	12.3 (10.0-19.0)	0.24
- prior to discharge*	7.00 (2.8-21.7)	17.00 (8.00-30.0)	0.11
Albumin g/L			
-admission	31.0 (27.0-35.0)	31.0 (29.0-34.0)	0.96
-at induction	26.0 (22.0-31.0)	23.0 (20.0-29.0)	0.29
-Day 3 post Infliximab	26.0 (22.5-30.5)	25.5 (22.0-30.5)	0.98
- prior to discharge *	28.0 (24.0-34.0)	27.0 (22.0-29.0)	0.30
CRP/Albumin ratio			
-admission	1.1 (0.5-3.5)	2.0 (0.9-4.3)	0.17
-at induction	0.6 (0.3-1.9)	1.4 (0.6-1.9)	0.45
-Day 3 post Infliximab	0.3 (0.1-1.1)	0.5 (0.4-0.7)	0.17
-prior to discharge*	0.3 (0.1-0.7)	0.7 (0.4-1.4)	0.02
Mayo Endoscopic score			
-2	16/33	1/11	0.03
-3	17/33	10/11	

\*Excluding 2 patients who underwent colectomy prior to discharge and 1 patient who suffered pancreatitis following inpatient use of thiopurine

Tables 2. Timing of discharge bloods  
 Analysis based on 36 patients with available CRP and Albumin levels

Median and Q1-Q3	No colectomy n=26	Colectomy n=10	P value
Time to discharge bloods following last Infliximab dose (days)	3.0 (1.0-5.0)	3.0 (2.0-4.0)	0.80
Number of Infliximab infusions prior to discharge bloods taken n(%)			
-1 infusion	20/26 (76.9)	7/10 (70.0)	0.69
-2 infusions	4/26 (15.4)	3/10 (30.0)	0.37
-3 infusions	2/26 (7.7)	0/10 (0.0)	1.00

Table 3. Comparison of Standard versus Accelerated Induction

Note: Continuous data reported as median (Q1-Q3) and analysed using Wilcoxon rank-sum test; categorical data reported n(%) and analysed using Fisher's exact test

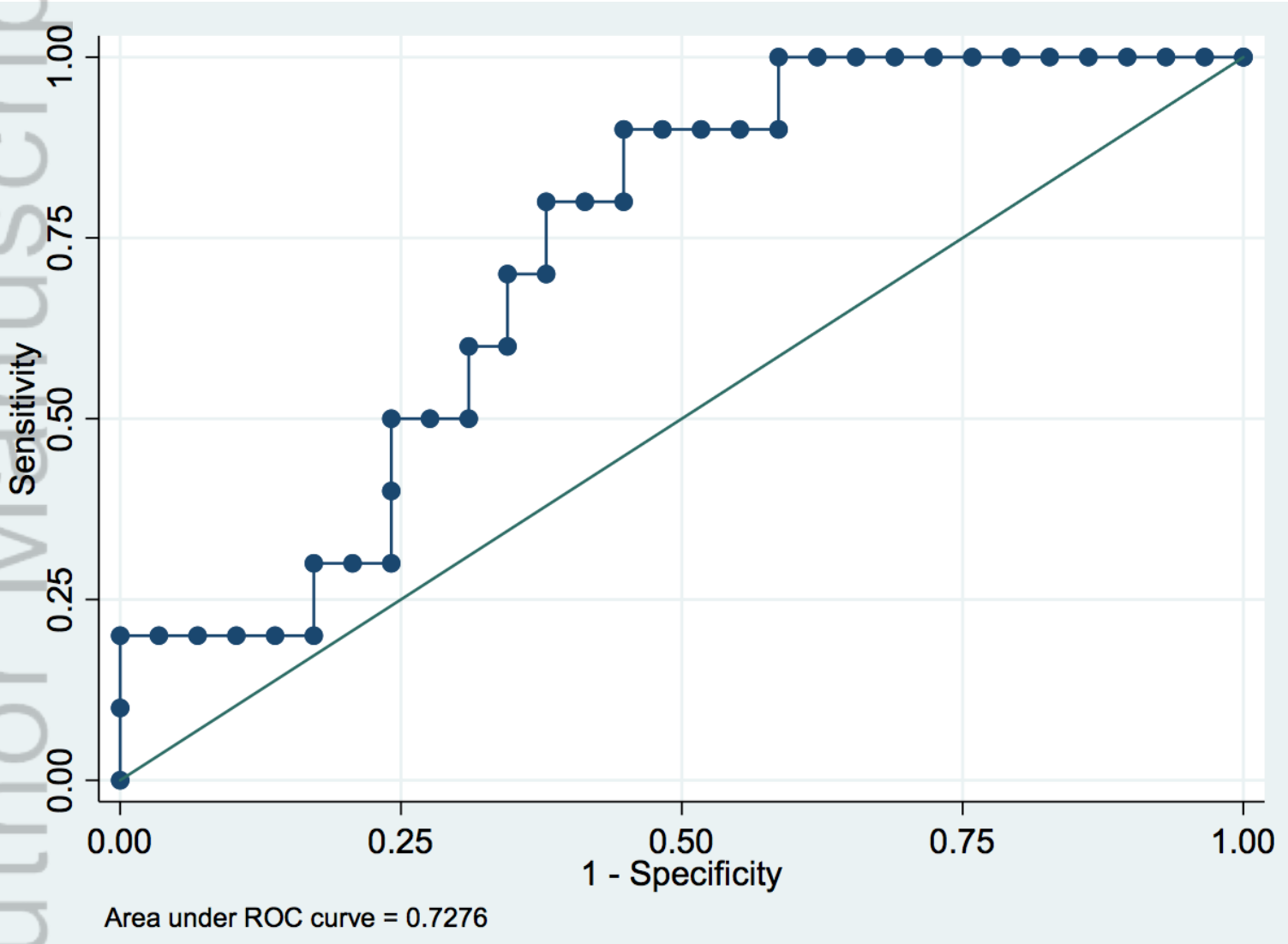
Median and Q1-Q3	Standard induction n=37	Accelerated induction n=14	P value
Gender			
Female, n(%)	14 (37.8)	5 (35.7)	1.00
Age (years)	32.61 (26.7-44.4)	37.33 (26.7-46.6)	0.54
Disease duration (years)	2.50 (1.4-6.4)	2.68 (1.6-7.2)	0.83
Medications on admission, n(%)			
-Oral Steroids	15 (40.5)	7 (50.0)	0.75
-Mesalazine	26 (70.3)	7 (50.0)	0.20
-Immunomodulator	19 (51.4)	5 (35.7)	0.36
Iv steroid duration	5.0 (3.5-6.0)	4.0 (3.0-5.0)	0.28
CRP (mg/L)			
-admission	35.0 (17.5-69.5)	63.0 (20.0-167.5)	0.11
-at induction	17.0 (4.9-42.0)	35.0 (10.3-79.0)	0.15
-Day 3 post Infliximab	6.5 (1.9-15.0)	10.00 (8.1-43.0)	0.15
-prior to discharge	7.5 (2.8-18.5)	17.00 (6.5-40.5)	0.12
Albumin (g/L)			
-admission	31.0 (27.0-35.0)	30.5 (23.0-35.8)	0.63
-at induction	26.0 (22.0-30.8)	23.0 (18.0-30.5)	0.21
-Day 3 post infliximab	25.5 (21.8-30.3)	25.0 (20.3-30.8)	0.66
-prior to discharge	28.0 (26.0-32.0)	26.5 (23.3-34.0)	0.60
CRP Albumin ratio			
-admission	1.0 (0.6-2.7)	2.5 (0.6-5.7)	0.15
-at induction	0.6 (0.2-1.7)	2.0 (0.6-5.2)	0.02
-Day 3 post infliximab	0.3 (0.1-0.6)	0.4 (0.3-1.7)	0.33
-prior to discharge	0.3 (0.1-0.7)	0.5 (0.3-1.3)	0.38
Mayo Endoscopic score n(%)			
-2	13/30 (43.3)	2/13 (15.4)	0.10
-3	17/30 (56.7)	11/13 (84.6)	
Time to induction (days)	5.0 (3.5-6.0)	4.0 (3.0-5.8)	0.45

Time to second dose	14.0 (14.0-16.0)	4.5 (3.0-8.0)	<0.01
Duration of induction (days)	43.0 (42.0-46.0)	25.0 (17.5-32.0)	<0.01
Length of stay (days)	8.0 (6.5-10.5)	12.5 (10.8-16.0)	<0.01
Colectomy rate			
- 3 months	3/35 (8.6)	3/14 (21.4)	0.33
- 12 months	7/35 (20.0)	5/14 (35.7)	0.29
Median time to colectomy (days)	104.0 (35.0-231.0)	46.0 (27.5-170.5)	0.53

### FIGURE LEGENDS

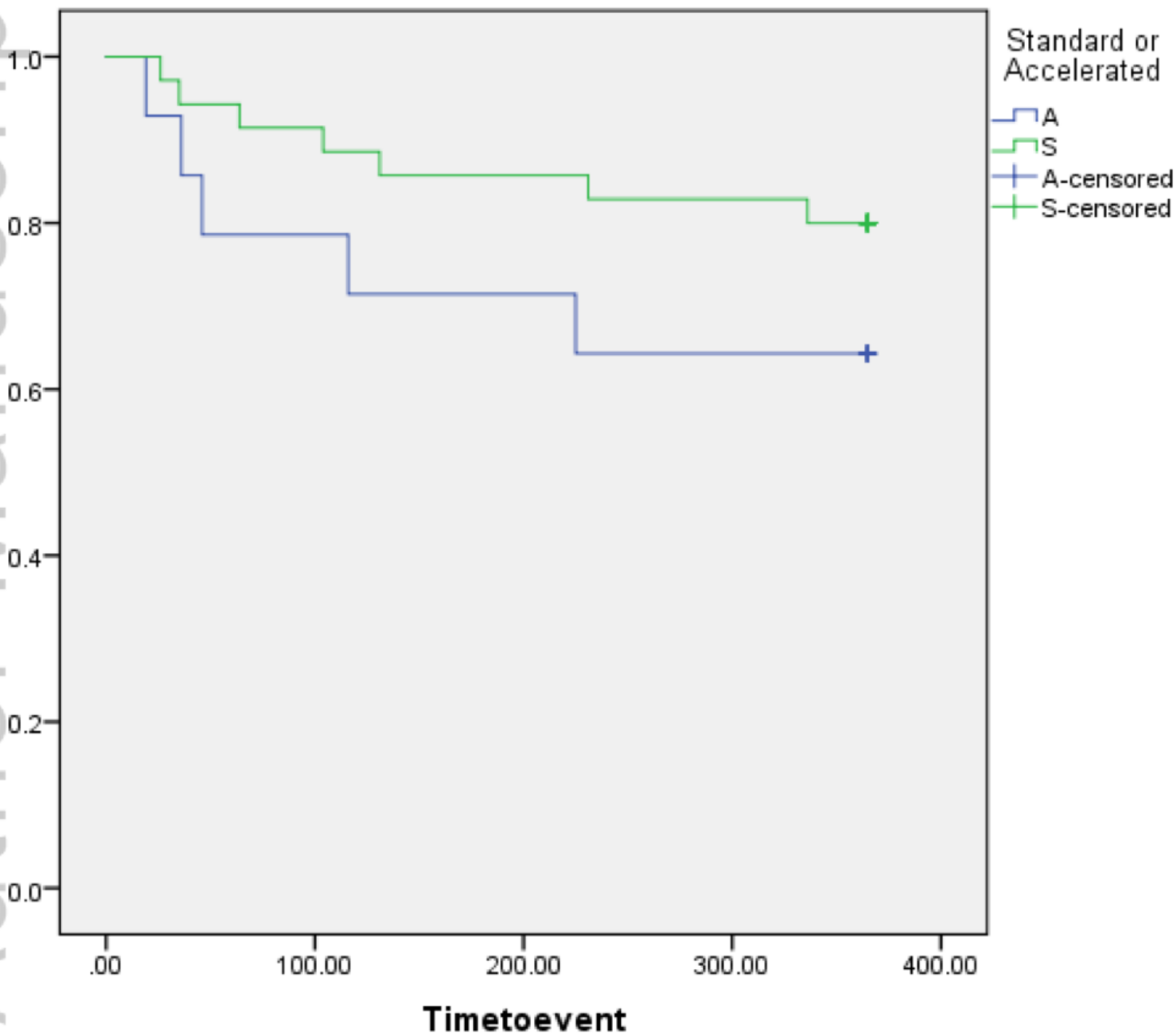
Figure 1. Area under Receiver Operating Curve (ROC) for CRP/Albumin ratio of 0.37 prior to discharge to predict colectomy

Figure 2. Kaplan Meier curve:  
Standard vs Accelerated Induction - Time to Colectomy (p=0.29 at 12 months)



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### Survival Functions



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