ORIGINAL ARTICLE

INTESTINAL RESEARCH

pISSN 1598-9100 • eISSN 2288-1956
https://doi.org/10.5217/ir.2020.00146
Intest Res 2022;20(1):101-113

Biomarker dynamics during infliximab salvage for acute severe ulcerative colitis: C-reactive protein (CRP)-lymphocyte ratio and CRP-albumin ratio are useful in predicting colectomy

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Background/Aims: The residual risk of colectomy after infliximab salvage in steroid-refractory acute severe ulcerative colitis (ASUC) is required to inform the need for subsequent maintenance biologic therapy. The aim of this study was to determine the dynamic response of common serum biomarkers to infliximab salvage and assess their utility in predicting subsequent colectomy. **Methods:** A retrospective single-center cohort study was conducted on all patients who received infliximab salvage for steroid-refractory ASUC between January 1, 2010, and July 31, 2019. Biomarkers were assessed on admission and days 1 and 3 post infliximab, and included C-reactive protein (CRP)-albumin-ratio (CAR), CRP-lymphocyte-ratio (CLR), platelet-lymphocyte-ratio (PLR) and neutrophil-lymphocyte-ratio (NLR). **Results:** Of 94 patients (median age, 35 years; 67% of male), 20% required colectomy at 12 months. Biomarkers on day 3 post-infliximab best differentiated nonresponders, who had higher CRP, lower albumin and lower lymphocyte count (each $P<0.05$). Day 3 predictive performance (area under the curve) for 12-month colectomy was best for CAR (0.871) and CLR (0.874), which were similar to Lindgren (0.829; $P>0.05$) but superior to Mayo (0.726), partial Mayo (0.719), PLR (0.719), Ho index (0.714), NLR (0.675), Travis score (0.657) and endoscopic Mayo (0.609) (each $P<0.05$). A day 3 CAR cutoff of 0.47 mg/g had 79% sensitivity, 80% specificity, 94% negative predictive value (NPV) to predict colectomy; while a day 3 CLR cutoff of 6.0 mg/10^9 had 84% sensitivity, 84% specificity, 96% NPV. **Conclusions:** CAR and CLR measured on day 3 post infliximab salvage for steroid-refractory ASUC represent simple and routinely performed biomarkers that appear to be strong predictors of colectomy. Prospective studies are required to confirm the utility of these predictive scores. **(Intest Res 2022;20:101-113)**

Key Words: Inflammatory bowel disease; Precision medicine; Kinetics

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that is characterized by frequent flares, hospitalizations, surgery and psychological morbidity.[1,2] Acute severe ulcerative colitis (ASUC) is a severe exacerbation of UC that warrants intravenous corticosteroids and may require emergency colectomy.[3] Corticosteroid failure necessitates salvage therapy with infliximab or ciclosporin which have demonstrated good short term efficacy.[4-7] However longer term prognosis after medical salvage remains guarded, where up to 50% of patients still proceed to colectomy in the absence of maintenance biologic therapy.[8-10] Conversely, a proportion of patients may have an initial period of significant symptoms, but develop only mild symptoms or even remission in the subsequent 10 years of

Received November 9, 2020. **Revised** January 4, 2021.
Accepted January 22, 2021.
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their disease course.[11]

To date, the ability to distinguish individuals who require maintenance infliximab following salvage therapy from those who could be continued on conventional therapy, such as immunomodulators, has not been established. The ability to accurately predict response to infliximab salvage and the subsequent risk of colectomy is crucial in order to decide the most appropriate maintenance therapy, which is an important concept in modern precision medicine.[12,13] Moreover, the optimal timing and dosing regimen of infliximab salvage is subject to ongoing research,[14] therefore a predictive score for infliximab failure early in the presentation might facilitate timely decisions for potential dose escalation, additional line medical salvage, or early colectomy.[15,16]

Biomarkers are increasingly recognized to play a crucial role in precision medicine, and useful biomarkers to aid in clinical prediction are needed.[17,18] We hypothesize that an improved understanding of the dynamics of biomarkers during infliximab salvage is crucial to identify candidate predictors of response, as well as to determine ideal cutoffs, which may change over time. The C-reactive protein (CRP)-albumin ratio (CAR) after infliximab salvage has been identified as a potential predictor of colectomy,[15] yet the optimal timing of measurements and the utility of serial measurements require further evaluation. Recently, novel biomarkers such as the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have been shown to predict mucosal healing in UC after infliximab[19,20] but their utility in ASUC has not been studied. Additionally, the CRP-lymphocyte ratio (CLR) has been studied in other clinical settings, but not in UC.[21]

The primary aim of this study was to evaluate and compare the dynamic response of serum biomarkers in responders compared with nonresponders to infliximab salvage during steroid-refractory ASUC, and to determine their utility in predicting the need for colectomy at 12 months following the initial presentation. The secondary aim was to determine the utility of these biomarkers in predicting early colectomy by 1 month.

METHODS

1. Study Design

This was a retrospective cohort study conducted at a tertiary health network comprising 3 acute hospitals in Australia. All patients who presented with steroid-refractory ASUC who received infliximab salvage between January 1, 2010 and July 31, 2019 were followed up for 12 months to determine rates and timing of colectomy. The dynamics and predictive performance for colectomy of common biomarkers during ASUC were assessed. The study was approved by the Eastern Health Office of Research and Ethics (approval No. QA20-107), where the requirement for written informed consent was waived due to the observational nature of the study.

2. Patient Selection

The hospital pharmacy database provided automatic records for all infliximab prescriptions dispensed to patients admitted to the gastroenterology unit during the study period. Electronic medical records were manually reviewed to determine the indication for infliximab and check for selection criteria. Inclusion criteria were age ≥18 years, hospitalized with steroid-refractory ASUC (defined as 6 or more bloody stools with any of: temperature >37.8°C, pulse >90 beats/min, CRP >30 mg/L, erythrocyte sedimentation rate >30 mm/hr or hemoglobin <10.5 g/dL on day 3 of intravenous hydrocortisone 100 mg [4 times a day] as per Truelove and Witt's criteria[4]); received salvage infliximab (1–3 doses at 5–10 mg/kg per dose). Patients were excluded if they were on maintenance biologic therapy at baseline, or if they received sequential salvage therapy with cyclosporine then infliximab.

3. Data Collection

Hospital electronic medical records were reviewed to collect data. Endoscopy was performed in all patients during hospitalization prior to salvage therapy. Subsequent maintenance therapy and colectomy rates up to 12 months post ASUC were recorded. Serum biomarkers (CRP, albumin, neutrophils, lymphocytes, and platelets) were uniformly collected on admission (prior to intravenous corticosteroids) and on days 1 and 3 post salvage. Comparator scores included Ho (Edinburgh index[22]), Travis (Oxford index[23]), Lindgren (Sweden index[24]) and Mayo-related scores, which were each calculated on day 1 and 3 post salvage (Supplementary Table 1). Endoscopy was performed in all patients on or shortly after admission, prior to infliximab. Partial Mayo scores were calculated retrospectively by the study investigators with the physician global assessment being based on interpretation of the inpatient notes completed at the time of hospitalization. Complete Mayo score used the partial Mayo calculated on days 1 and 3 with the endoscopic subscore calculated on index endoscopy and the Mayo subscore was documented at the time of the procedure by the endoscopist. Colonic dilatation was recorded based on abdomi-

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nal X-ray on day 1 and day 3 post infliximab salvage. Stool *Clostridioides difficile* toxin A assay (enzyme-linked immunosorbent assay) was performed in all patients. Fecal calprotectin was not analyzed given they were not routinely performed at our centers during ASUC events.

4. Statistical Analysis

Nonparametric continuous variables were expressed as medians with interquartile range (IQR). The association of biomarkers and their ratios with colectomy over time were assessed in 2 ways: comparison of distributions using the Mann-Whitney *U* (rank-sum) test and Spearman rank correlation rho for nonparametric data.

The utility of biomarker ratios in predicting colectomy as a binary outcome variable was assessed using receiver operating characteristic analysis and by calculating the area under the curve (AUC). Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were assessed at different cutoff values. The optimal cutoff was chosen as the maximum Youden statistic (defined as sensitivity+specificity–1). Logistic regression analysis was used to estimate odds ratios (OR) and confidence intervals (CIs) for colectomy. In the multivariable logistic regression models, biomarker ratios were controlled for all variables significantly associated with colectomy on univariable analysis. For the primary aim of analyzing 12-month colectomy, 2 multivariable models were developed: (1) using the entire cohort; (2) using the sub-cohort of patients who avoided colectomy at index admission, and additionally adjusting for cumulative infliximab dose received as well as type of maintenance therapy. For the secondary aim, a third multivariable model was developed using 1-month colectomy as the outcome.

Complete clinical data (stool count, partial Mayo score and colonic dilatation) was available for 100% of patients on day 1 post infliximab salvage. For 8 patients (9%) who were discharged prior to day 3 due to clinical improvement post salvage, single imputation using last-observation-carried-forward was used for clinical data. For missing biomarker data on day 1 (1% for CRP and full blood count; 4% for albumin) and day 3 post salvage (11% for CRP and full blood count; 14% for albumin), multiple imputation was used to estimate their distributions. For this analysis, missing data were assumed to be missing at random and estimated assuming the multivariate normal distribution (after log transformation of CRP and lymphocyte count to correct skewness). The imputation procedure was repeated 10 times to generate the final distribution.

As sensitivity analysis, predictive performance was evaluated when using only patients with complete data for the re-

Table 1. Baseline Characteristics of Patients Who Received Salvage Infliximab for Steroid-Refractory ASUC

Characteristics	Value (n = 94)
Age (yr)	35 (26–53)
Male sex	63 (67)
Disease duration (yr)	1 (0–5)
Baseline disease extent	
E1 (proctitis)	8 (8)
E2 (left sided)	42 (45)
E3 (extensive)	44 (47)
Smoking history	
Nonsmoker	72 (76)
Ex-smoker	11 (12)
Current smoker	11 (12)
Charlson comorbidity index	
0	64 (68)
1	11 (12)
2	7 (7)
≥ 3	12 (13)
Baseline medications	
Azathioprine ± allopurinol	21 (22)
Mercaptopurine ± allopurinol	5 (5)
Methotrexate	3 (3)
Aminosalicylates	57 (61)
Corticosteroids	30 (32)
Previous treatments	
Biologics	6 (6)
Abdominal surgery[a]	2 (2)
Mayo endoscopic score during ASUC	
Mild	4 (4)
Moderate	36 (38)
Severe	54 (58)
Disease extent during ASUC[b]	
E1 (proctitis)	5 (5)
≥ E2 (left sided or extensive)	89 (95)

Values are presented as median (interquartile range) or number (%).
[a]Abdominal surgeries included: right hemicolectomy for cecal volvulus 8 months prior to acute severe ulcerative colitis (ASUC) in 1 patient; anterior resection for sigmoid diverticulitis with subsequent anastomotic restoration 2 years prior in another patient. Both patients were subsequently diagnosed with extensive (E3) ulcerative colitis, before presenting with ASUC.
[b]Endoscopy most commonly performed only up to level of sigmoid colon due to perforation risk.

spective biomarker ratio. Due to the long study period, a second sensitivity analysis was conducted by assessing predictive performance in patients who entered the study on or after 2016, and in patients who entered the study prior to 2016. Additional post-hoc exploratory analyses included assessing the predictive utility of the difference and ratio of CAR and CLR from day 1 to day 3 post salvage.

All analysis was performed in Stata/IC 14 (StataCorp, College Station, TX, USA). A two-sided $P<0.05$ was used to indicate statistical significance.

RESULTS

1. Patient Characteristics

A total of 94 steroid-refractory ASUC patients who received infliximab salvage were included (Table 1). A flowchart of the patient identification process is shown in Supplementary Fig. 1. Median age was 35 years (IQR, 26–53 years) and 63 patients (67%) were male. Median disease duration was 1 year (IQR, 0–5 years). The majority of patients had either left sided (45%) or extensive colitis (47%) prior to ASUC. Six percent had prior exposure to infliximab and 2% had prior intestinal surgery. Initial dose of infliximab received was 5 mg/kg in 85% and 10 mg/kg in 15% of patients.

2. Outcomes

Of 94 patients, 19 (20%) required colectomy by 12 months (10 proceeded to colectomy during index admission). Univariable predictors of 12-month colectomy included older age (OR, 1.03 per year; 95% CI, 1.00–1.06; $P=0.035$), shorter disease duration ≤3 years (OR, 5.4; 95% CI, 1.2–24.9; $P=0.032$) and baseline steroid requirement (OR, 4.1; 95% CI, 1.4–11.6; $P=0.009$). There was no significant association with baseline aminosalicylate or immunomodulator requirement, current/previous smoking, prior intestinal surgery, prior infliximab exposure, initial infliximab dose received (10 mg/kg vs. 5 mg/kg) or sex (Supplementary Table 2). Although not statistically significant, there was a numerically higher rate of colectomy in patients with E2 (8/42, 19%) and E3 extent (11/44, 25%) compared to patients with E1 extent (0/8, 0%), with corresponding ORs of 5.4 (95% CI, 0.3–108.6) for E2 versus E1, and 8.0 (95% CI, 0.4–159.7) for E3 versus E1.

When considering only the patients who avoided index colectomy (defined as colectomy during index admission; n=84), greater cumulative infliximab dose was protective for 12-month colectomy (OR, 0.3 per 5 mg/kg; $P=0.010$), where the median cumulative dose received was 15 mg/kg (IQR, 10–15; range, 5–30). In this sub-cohort, 50% were maintained with immunomodulator monotherapy, 35% were maintained with infliximab and immunomodulator combination therapy and 15% were maintained with aminosalicylates only. The 12-month colectomy rate in patients who avoided index colectomy was 31% in patients on aminosalicylates only, 10% in patients on immunomodulator monotherapy and 3% in patients on dual therapy. Compared to patients maintained on aminosalicylates alone, the corresponding ORs for avoiding colectomy were 4.2

Table 2. Spearman Rank Correlations ρ between Biomarkers and Stool Count on Admission, Day 1 and Day 3 Post Salvage, with Colectomy within 12 Months

Biomarkers	Timing	ρ	*P*-value
CRP (mg/L)	Admission (n=94)	0.153	0.140
	Day 1 (n=93)	0.408	<0.001
	Day 3 (n=84)	0.480	<0.001
Albumin (g/L)	Admission (n=94)	−0.232	0.025
	Day 1 (n=90)	−0.317	0.002
	Day 3 (n=81)	−0.368	0.001
Lymphocytes (10^9/L)	Admission (n=94)	−0.196	0.060
	Day 1 (n=93)	−0.178	0.090
	Day 3 (n=84)	−0.361	0.001
Neutrophils (10^9/L)	Admission (n=94)	−0.060	0.570
	Day 1 (n=93)	−0.124	0.240
	Day 3 (n=84)	−0.210	0.060
Platelets (10^9/L)	Admission (n=94)	0.046	0.660
	Day 1 (n=93)	−0.054	0.610
	Day 3 (n=84)	−0.051	0.640
Stool count	Day 1 (n=94)	0.099	0.340
	Day 3 (n=94)	0.270	0.009
CRP-albumin ratio (mg/g)	Admission (n=94)	0.183	0.080
	Day 1 (n=90)	0.437	<0.001
	Day3 (n=81)	0.516	<0.001
CRP-lymphocyte ratio (mg/10^9)	Admission (n=94)	0.229	0.026
	Day 1 (n=93)	0.396	<0.001
	Day3 (n=84)	0.518	<0.001
Neutrophil-lymphocyte ratio	Admission (n=94)	0.100	0.340
	Day 1 (n=93)	−0.027	0.790
	Day3 (n=84)	0.253	0.020
Platelet-lymphocyte ratio	Admission (n=94)	0.242	0.019
	Day 1 (n=93)	0.148	0.160
	Day3 (n=84)	0.325	0.003

CRP, C-reactive protein.

https://doi.org/10.5217/ir.2020.00146 • Intest Res 2022;20(1):101-113

(P=0.07) in the immunomodulator group and 12.4 (P=0.033) in the combination therapy group.

3. Biomarker Dynamics during ASUC

1) C-Reactive Protein

Correlations with colectomy at 12 months are given in Table 2, while differences in biomarker levels are given in Fig. 1 and Supplementary Table 3. There was no significant difference in CRP at baseline between patients who required or avoided colectomy (median 65 mg/L vs. 46 mg/L, P=0.14). CRP fell over time in both groups, but the rate of decline was greatest in patients who avoided colectomy. From baseline to day 1, CRP fell by a median of 43% in the colectomy group compared to 80% in the non-colectomy group (P=0.004). From day 1 to day 3, CRP fell by a median of 16% and 51% respectively (P=0.024). This resulted in higher CRPs in the colectomy group on both day 1 (median 32 mg/L vs. 11 mg/L, P<0.001) and day 3 (median 27 mg/L vs. 5 mg/L, P<0.001) post salvage therapy. The corresponding rank correlations between CRP and 12-month colectomy were moderate on day 1 (ρ=0.408, P<0.001) and day 3 (ρ=0.480, P<0.001).

2) Albumin

Baseline albumin was lower in patients requiring 12-month colectomy (27 g/L vs. 32 g/L, P=0.025). In all patients, albumin fell from baseline to day 1 post salvage, but did not significantly change from day 1 to day 3. The change was similar in both groups from baseline to day 1 (median reduction 14% vs. 12%, P=0.56) and day 1 to day 3 (median 0% vs. 0%, P=0.96). Concordantly, albumin remained lower in patients who required colectomy on day 1 (median 21 g/L vs. 27 g/L, P=0.003) and day 3 (median 23 g/L vs. 28 g/L, P<0.001) compared to patients who avoided colectomy. The corresponding negative rank correlations between albumin and 12-month colectomy were weak at baseline (ρ=–0.232, P=0.025) and weak-to-moderate on days 1 (ρ=–0.317, P=0.002) and 3 (ρ=–0.369, P<0.001).

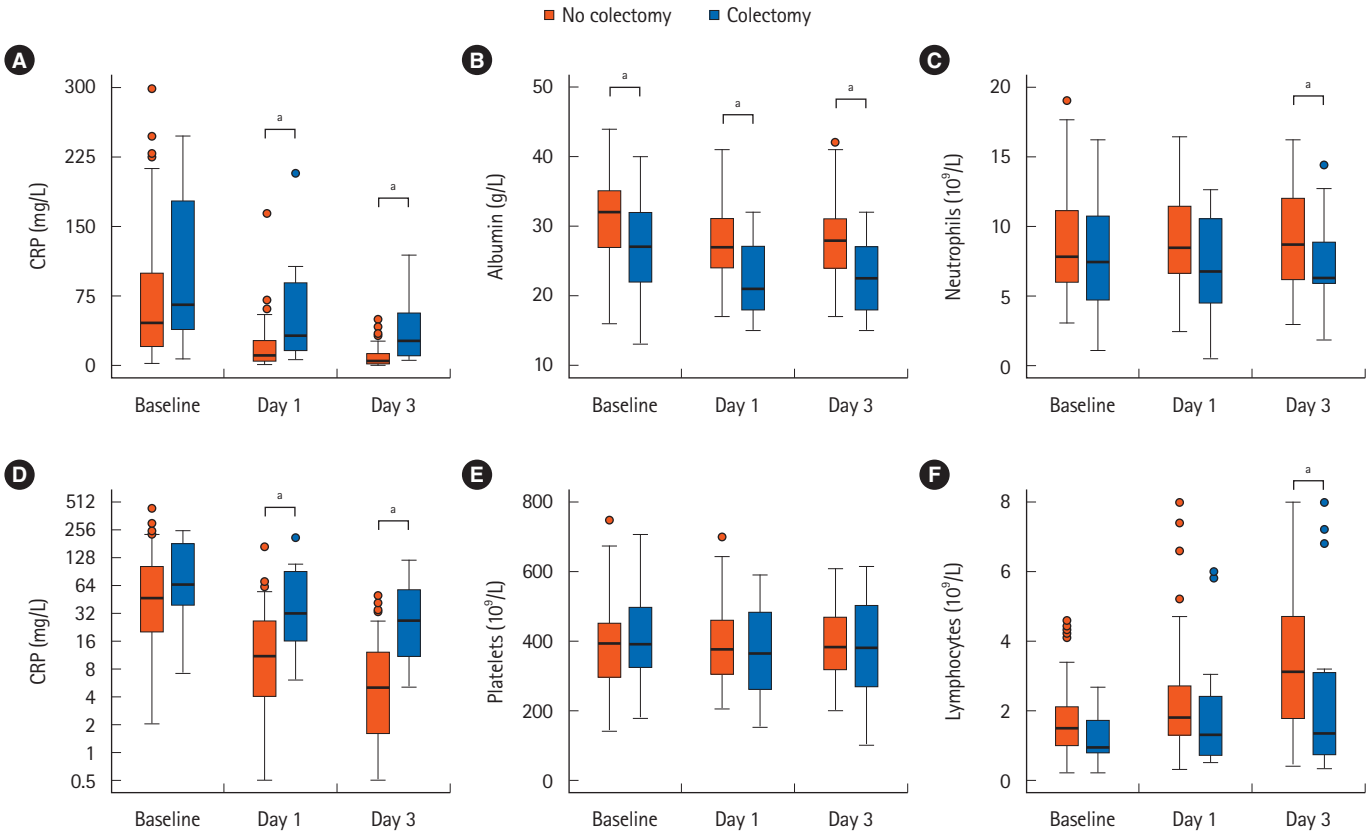

Fig. 1. Distribution (median, IQR, range) of biomarkers at baseline, day 1 post infliximab salvage and day 3 post infliximab salvage. (A) CRP; (B) albumin; (C) neutrophil count; (D) CRP on a logarithmic scale; (E) platelet count; (F) lymphocyte count. Values given for patients who avoided colectomy (■) or proceeded to colectomy (■) by 12 months. [a]Significant differences. IQR, interquartile range; CRP, C-reactive protein.

3) Lymphocyte Count

There was a numerically lower lymphocyte count on admission in patients requiring 12-month colectomy, however this did not reach statistical significance (median vs. 1.0×10^9/L vs. 1.5×10^9/L, $P=0.06$). Lymphocyte count did not substantially change over time in patients who required 12-month colectomy (median 1.0, 1.3, and 1.3×10^9/L on admission, day 1, and day 3 respectively, each comparison $P>0.05$), while in patients who avoided 12-month colectomy, lymphocyte count increased at each time point (median 1.5×10^9/L at baseline to 1.8×10^9/L on day 1, $P=0.045$ and up to 2.8×10^9/L on day 3 post salvage, $P<0.001$). From baseline, the corresponding percentage increases by day 3 were 17% for 12-month colectomy patients and 96% for non-colectomy patients. This resulted in a significantly lower lymphocyte count on day 3 in patients who required 12-month colectomy compared to patients who avoided colectomy (median vs. 1.3×10^9/L vs. 2.8×10^9/L, $P=0.001$). The corresponding rank correlation of day 3 lymphocyte count was weak-to-moderate with 12-month colectomy ($\rho=-0.361$, $P<0.001$).

4) Neutrophil and Platelet Count

Both neutrophil count and platelet count were similar between patients requiring and avoiding 12-month colectomy at all time points and did not significantly change between time points. There were no significant correlations with colectomy at any time point.

5) Biomarker Ratios

Each biomarker ratio decreased over time (Fig. 2, Supplementary Table 4). From day 1 to day 3 post infliximab salvage, CAR decreased from a median of 0.52 mg/g (IQR, 0.23–1.29) to 0.30 mg/g (IQR, 0.09–0.68) ($P=0.004$); CLR decreased from a median of 9.09 mg/10^9 (IQR, 3.00–20.77) to 2.75 mg/10^9 (IQR, 0.98–10.00) ($P<0.001$); PLR decreased from a median of 225.2 (IQR, 140.0–335.4) to 147.0 (IQR, 103.2–254.0) ($P=0.004$) and NLR decreased from a median of 5.05 (IQR, 2.72–7.57) to 3.15 (IQR, 1.99–5.38) ($P=0.004$).

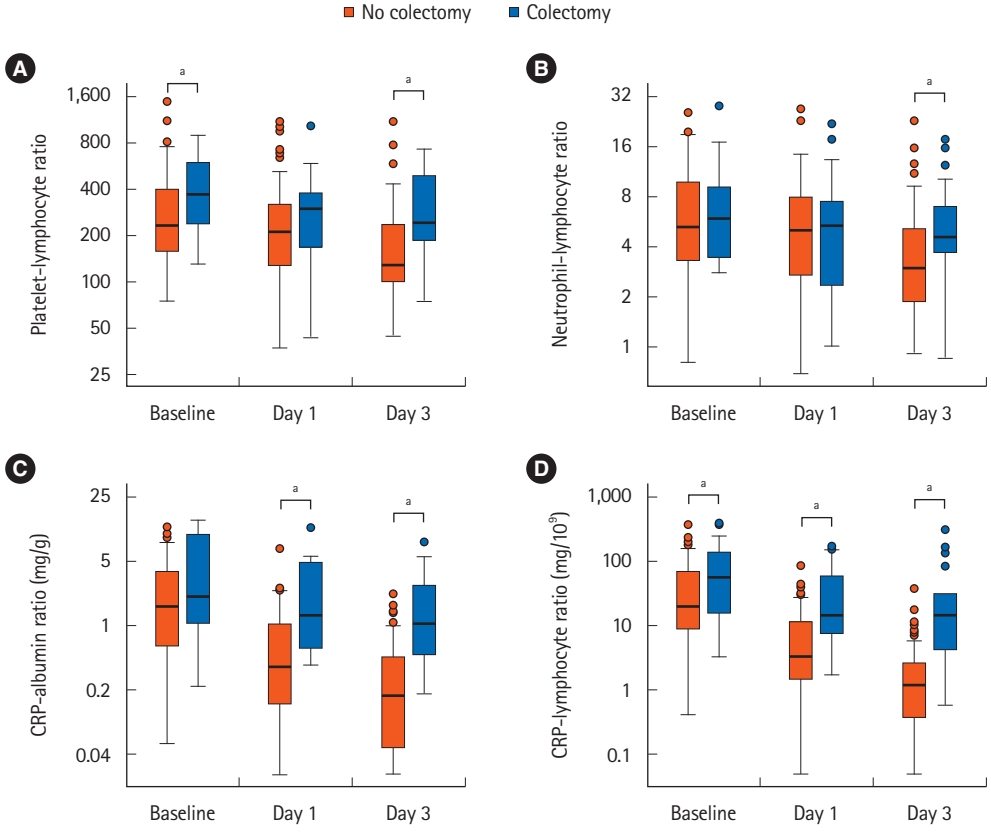

Fig. 2. Distribution (median, IQR, range) of predictive scores calculated at baseline (on admission), day 1 post infliximab salvage and day 3 post infliximab salvage. (A) Platelet-lymphocyte ratio; (B) neutrophil-lymphocyte ratio; (C) CRP-albumin ratio; and (D) CRP-lymphocyte ratio. Values are given for patients who avoided colectomy (■) or proceeded to colectomy (■) by 12 months. Each graph is displayed using a logarithmic Y-axis. [a]Significant differences. IQR, interquartile range; CRP, C-reactive protein.

https://doi.org/10.5217/ir.2020.00146 • Intest Res 2022;20(1):101-113

4. Utility of Biomarker Ratios in Predicting Colectomy

1) Correlations

Overall, correlations with 12-month colectomy were strongest on day 3 post salvage for all biomarkers (Table 2). On day 3, both CAR and CLR had a moderately positive rank correlation with colectomy ($\rho = 0.516$ and $\rho = 0.518$ respectively, each $P < 0.001$). PLR had a weak-to-moderate correlation with colectomy ($\rho = 0.325$, $P = 0.003$) while NLR had a weak correlation ($\rho = 0.253$, $P = 0.020$). There was no significant correlation with CAR at baseline with colectomy ($\rho = 0.183$, $P = 0.08$) and a weak correlation with CLR at baseline and colectomy ($\rho = 0.229$, $P = 0.026$).

2) Predictive Performance

Day 3 CAR and CLR demonstrated the highest predictive performance (AUC) for 12-month colectomy (0.871, 0.874 respectively) (Table 3). Day 3 CAR and CLR were superior to day 3 NLR and PLR, which both had fair predictive performance (0.672, 0.707 respectively, each $P < 0.05$). Predictive properties at various thresholds are given in Supplementary Table 5. When considering the sub-cohort of patients who avoided index colectomy, day 3 CAR and CLR maintained high AUC for 12-month colectomy (0.810 and 0.818 respectively), while day 3 NLR and PLR maintained low-fair AUCs (0.653 vs. 0.642 respectively).

3) Optimal Cutoff Values

To predict 12-month colectomy, the optimal cutoff by Youden index for CAR on day 3 was 0.47 mg/g (sensitivity 79%, specificity 80%, PPV 50%, NPV 94%), while the optimal cutoff for CLR on day 3 was 6.0 mg/10^9 (sensitivity 84%, specificity 84%, PPV 57%, NPV 96%). When applied to the sub-cohort of patients who avoided index colectomy, the predictive properties for 12-month colectomy of day 3 CAR >0.47 mg/g were: sensitivity 67%, specificity 80%, PPV 29%, NPV 95%, while the properties of day 3 CLR >6.0 mg/10^9 were: sensitivity 78%, specificity 84%, PPV 37%, NPV 97%. Kaplan-Meier survival estimates after stratifying by CAR >0.47 mg/g and CLR >6.0 mg/10^9 are shown in Fig. 3, where the difference in survival curves were significant using either biomarker ratio (both $P < 0.001$ by log-rank test).

CAR >0.47 mg/g occurred in 32% of patients and was independently associated with 12-month colectomy (unadjusted OR 15.0, $P < 0.001$; adjusted OR 13.6, $P = 0.002$), while CLR >6.0 mg/10^9 occurred in 30% of patients and was also independently associated with 12-month colectomy (unadjusted OR 28.0, $P < 0.001$; adjusted OR 20.9, $P < 0.001$) (Supplementary Table 2). Amongst the patients who avoided index colectomy (Supplementary Table 6), CAR >0.47 mg/g predicted 12-month colectomy on unadjusted analysis (OR, 8.0; $P = 0.006$), but did not reach significance after multivariable adjustment (OR, 4.7; $P = 0.12$). However, CLR >6.0 mg/10^9 predicted 12-month colectomy on unadjusted (OR, 18.4; $P = 0.001$) and multivariable analysis (OR, 6.8; $P = 0.032$). Using day 3 CLR,

Table 3. Predictive Performance for Colectomy by 12 Months Given as AUC with Confidence Intervals

Predictor	All patients (n = 94)		Patients who avoided index colectomy (n = 84)	
	AUC	95% CI	AUC	95% CI
CRP-albumin ratio (mg/g)				
Day 1	0.805	0.706–0.904	0.736	0.596–0.875
Day 3	0.871	0.787–0.955	0.810	0.673–0.946
CRP-lymphocyte ratio (mg/10^9)				
Day 1	0.785	0.675–0.894	0.742	0.579–0.905
Day 3	0.874	0.776–0.972	0.818	0.656–0.980
Neutrophil-lymphocyte ratio				
Day 1	0.483	0.329–0.637	0.497	0.320–0.674
Day 3	0.675	0.538–0.813	0.653	0.473–0.834
Platelet-lymphocyte ratio				
Day 1	0.606	0.460–0.753	0.630	0.419–0.840
Day 3	0.719	0.584–0.855	0.641	0.449–0.834
Partial Mayo score				
Day 1	0.614	0.468–0.760	0.601	0.428–0.775
Day 3	0.719	0.588–0.850	0.589	0.369–0.809
Mayo endoscopic subscore				
Admission	0.609	0.460–0.722	0.523	0.349–0.697
Mayo score				
Day 1	0.638	0.497–0.780	0.603	0.420–0.785
Day 3	0.726	0.599–0.853	0.594	0.386–0.802
Ho (Edinburgh) index				
Day 1	0.707	0.589–0.825	0.621	0.461–0.780
Day 3	0.714	0.578–0.850	0.542	0.326–0.759
Lindgren (Sweden) score				
Day 1	0.697	0.544–0.849	0.655	0.460–0.850
Day 3	0.829	0.721–0.937	0.752	0.568–0.936
Travis (Oxford) index				
Day 1	0.683	0.560–0.806	0.587	0.418–0.755
Day 3	0.657	0.534–0.780	0.587	0.418–0.755

Distribution of missing data was estimated using multiple imputations.
AUC, area under the receiver operator characteristic curve; CI, confidence interval; CRP, C-reactive protein.

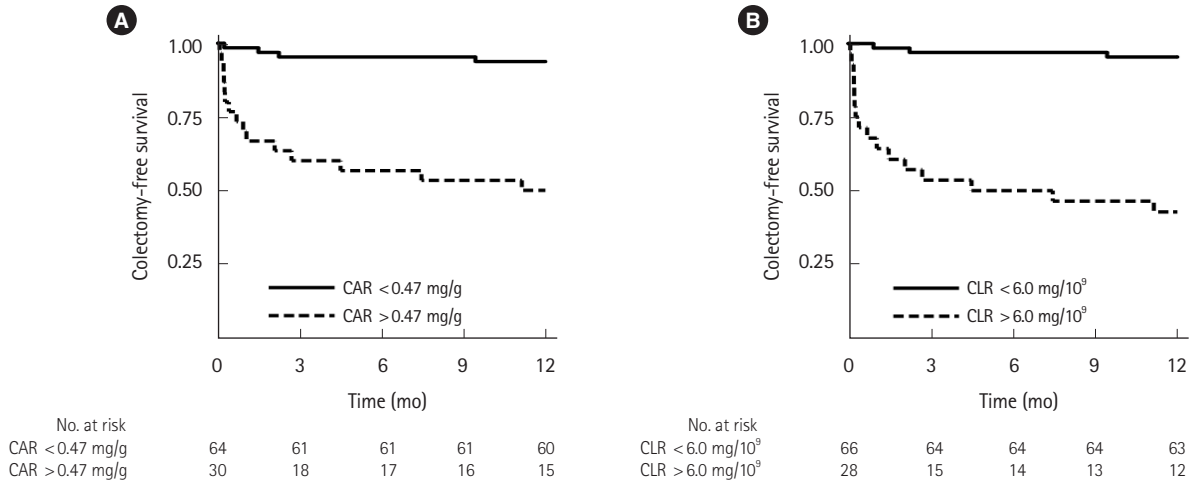

Fig. 3. Kaplan-Meier estimates for colectomy-free survival for patients who received salvage infliximab for steroid-refractory acute severe ulcerative colitis. Kaplan-Meier curves according to risk group stratified by: (A) day 3 CAR at 0.47 mg/g; (B) day 3 CLR at 6.0 mg/10^9. CRP, C-reactive protein; CAR, CRP-albumin ratio; CLR, CRP-lymphocyte ratio.

high risk compared to low-risk patients who avoided index colectomy had an increased residual 12-month colectomy risk regardless of whether they were maintained on a biologic (n=29, 20% vs. 0%, P=0.026) or not (n=55, 44% vs. 3%, P=0.001). Using day 3 CAR, high risk compared to low-risk patients who avoided index colectomy had an increased residual 12-month colectomy risk regardless of whether they were maintained on a biologic (n=29, 25% vs. 0%, P=0.011) or not (n=55, 29% vs. 8%, P=0.036).

When considering 1-month colectomy, day 3 CAR >0.47 mg/g had 90% sensitivity, 75% specificity, 30% PPV and 98% NPV, while day 3 CLR >6.0 mg/10^9 had 90% sensitivity, 77% specificity, 32% PPV 32% and 98% NPV. Both CAR >0.47 mg/g colectomy (unadjusted OR 27.0, P=0.002; adjusted OR 22.0, P=0.022) and CLR >6.0 mg/10^9 (unadjusted OR 30.8, P=0.002; adjusted OR 15.9, P=0.012) were independently associated with 1-month colectomy (Supplementary Table 7).

4) Sensitivity Analysis

CAR and CLR performed similarly in predicting colectomy in patients with complete data (Supplementary Table 8). CAR performed similarly in patients who entered the study after or before 2016 for both 12- and 1-month colectomy. However, CLR appeared to perform better for both 12- and 1-month colectomy in patients who entered the study on or after 2016 (n=49; AUC 0.936, 0.989 respectively) compared to before 2016 (n=45; AUC 0.834, 0.850 respectively).

The indices also performed similar in predicting colectomy after excluding 8 patients with mild endoscopic disease and/or E1 proctitis during ASUC. CAR predicted 12- and 1-month colectomy with AUC 0.872, 0.905 respectively, while CLR had AUC 0.878 and 0.907 respectively.

We further explored the utility of the rate of decline of CAR and CLR in predicting outcomes. The predictive performances of the absolute differences in CAR (AUC, 0.566) and CLR (AUC, 0.611) from day 1 to day 3 were only fair. The predictive performance of the ratios of day 3 and day 1 values for CAR (AUC, 0.677) and CLR (AUC, 0.700) were moderate.

5) Comparison with Existing Scores

Overall, scores performed better when calculated on day 3 (Table 3). To predict 12-month colectomy (AUC), CLR (0.874) and CAR (0.871) had numerically higher but statistically non-significant predictive performance compared to the Lindgren score (0.829) (each P>0.05). However, CAR and CLR were significantly better than day 3 Mayo (0.726), partial Mayo (0.719), PLR (0.719), Ho index (0.714), NLR (0.675), Travis score (0.657) and admission endoscopic Mayo subscore (0.609) (each P<0.05). To predict 12-month colectomy amongst patients who avoided index colectomy, the respective day 3 predictive performances were: CLR (0.818), CAR (0.810), Lindgren (0.752), NLR (0.653), PLR (0.642), Mayo score (0.594), partial Mayo score (0.590), Travis index (0.587), Ho index (0.542), and admission endoscopic Mayo subscore (0.523).

To predict colectomy by 1 month (AUC), CAR (0.908) and CLR (0.907) performed best, with numerically higher but not statistically significantly different AUCs compared to Lindgren (0.884), Ho (0.860), Mayo (0.831), and partial Mayo scores

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(0.821) (each $P>0.05$). However, CAR and CLR were significantly better than day 3 PLR (0.785), Travis score (0.711), NLR (0.684) and admission Mayo endoscopic subscore (0.685) (each $P<0.05$).

The previously established Lindgren cutoff of 8.0[12,25] classified 21% of patients as high risk and had 58% sensitivity, 88% specificity, 55% PPV, 89% NPV for 12-month colectomy, and 70% sensitivity, 85% specificity, 35% PPV, 96% NPV for 1-month colectomy. Using a less stringent cutoff of 6.7, which classified 30% of patients as high risk (the distribution that corresponds to the optimal cutoffs identified for CAR and CLR), the Lindgren score had 63% sensitivity, 79% specificity, 43% PPV, 89% NPV for 12-month colectomy, and 70% sensitivity, 70% specificity, 25% PPV and 95% NPV for 1-month colectomy.

DISCUSSION

Biomarkers have the potential to predict outcomes and tailor therapeutic options to the individual, which are core components of modern IBD management algorithms and precision medicine.[17,26] Our study has highlighted the difference in biomarker dynamics between patients who required and avoided colectomy and demonstrated the potential utility of CAR and CLR early in the treatment course (day 3 post salvage) in predicting infliximab failure. With the expansion of efficacious treatments such as newer biologic therapies and small molecule inhibitors,[27-30] the ability to predict disease trajectory in ASUC should inform treatment choice—for example, a patient who is likely to require longer term colectomy despite infliximab salvage may warrant more proactive optimization of maintenance therapy with a biologic agent (a top-down approach), while patients with a lower risk of colectomy may only require conventional therapy.[31-33] Although the ability to continue biologic therapy in all patients may appear attractive, a careful risk-benefit assessment should be made given such a strategy introduces an additional risk of infections and may not be cost-effective.[34,35] Our study further stresses the importance of discovering an optimal management algorithm after ASUC, as the risk of colectomy in our study appeared to be dependent on the type of maintenance therapy received.

This study has demonstrated that the utility of biomarker ratios is predicated by the early dynamics of the constituent biomarkers after infliximab salvage. CRP falls in most patients following infliximab, but the fall is attenuated in patients who proceed to colectomy. Even if such patients avoid an early colectomy, there is still a higher likelihood of longer-term colectomy, so clinicians need to remain vigilant in such patients and have a low threshold to continue aggressive medical therapy. Lymphocyte count rises in most patients shortly after salvage therapy yet appears to remain static in patients who fail infliximab. The association between elevated CRP and both steroid and infliximab failure has been demonstrated previously and is expected.[15,23] An association between lymphocyte count is much less understood, although our results support a recent study which showed that lymphocytosis occurs after anti-tumor necrosis factor (anti-TNF) therapy and may be associated with treatment response.[36] In other disease entities, anti-TNF therapy purportedly impairs marginalization of lymphocytes to the site of inflammation as part of its mechanism of action, thereby causing a transient increase in circulating lymphocytes.[37] Although subject to replication in other IBD cohorts, the lack of a transient lymphocytosis after infliximab may thus suggest ongoing lymphocyte marginalization to the inflamed gut and hence portend infliximab failure.

As expected, serum albumin remained lower across all time points in patients who failed infliximab. The association with hypoalbuminemia and infliximab failure has been attributed to increased colonic infliximab clearance with the former.[38,39] Indeed, a higher baseline clearance and lower serum concentrations of infliximab have been shown to predict treatment failure and colectomy.[16,40] A suppressed albumin is also reflective of the systemic inflammatory burden and is a known poor prognostic marker in multiple disease entities. Surprisingly, although a higher platelet count has been associated with steroid failure in ASUC,[23] there was no association with infliximab failure in our study. Although we have shown that platelet count and neutrophil count were not useful as acute phase reactants, their suppression later in the treatment course might be useful to indicate a response to therapy and predict mucosal healing.[19]

These data emphasize that the timing of biomarker measurement is crucial. Not only did biomarkers perform better when calculated on day 3 than on day 1, biomarkers and their ratios were shown to change over time, so cutoffs derived from optimizing sensitivity and specificity will change depending on which day the tests are performed. A previous study that showed an optimal CAR cutoff for 0.37 unfortunately did not specify the timing of the measurements.[15] The optimal cutoffs identified in our cohort were CAR >0.47 mg/g and CLR >6.0 mg/10^9, which both applied to just under a third of patients in this study. Using either of the ratios, the probability of requiring colectomy by 12 months in patients identified as high risk was 50%–

57% (or 29%–37% in those who avoided index colectomy), and in over two-thirds of patients identified as low risk, the probability of requiring colectomy was only 4%–6% (or 3%–5% correspondingly). CLR seemed to provide the best risk stratification: using day 3 CLR, low-risk patients not on biologic maintenance only had a 3% probability of requiring colectomy, compared to high-risk patients on biologic maintenance (20%) and high-risk patients not on biologic (44%). CLR therefore had substantial utility in identifying patients likely to fail infliximab, independent of other variables associated with colectomy such as age, baseline steroid requirement and type of maintenance therapy used following ASUC as shown by our multiple regression analysis.

In addition to guiding the choice of maintenance therapy, predictive scores may also guide optimal salvage therapy in ASUC, which remains an area of ongoing research. Observational studies have suggested a possible improved outcome with accelerated infliximab dosing,[41] although this remains contentious and has yet to be confirmed in a randomized trial.[14,42] The use of a predictive score calculation on day 3 post infliximab salvage may therefore be useful in deciding whether the patient is likely to respond to therapy, require further (potentially intensified) medical therapy or require surgical intervention. The ability to quantify the risk of having a poor response can also better facilitate shared decision making between patients and clinicians.[43] However, before these scores can be applied in clinical care, prospective controlled validation is required, specifically by demonstrating an improved outcome with the incorporation of biomarker-guided decision making in ASUC management algorithms.

This study has also validated and compared existing indices in predicting colectomy during index admission for ASUC after infliximab salvage. The Lindgren score and Ho index were originally derived to predict steroid failure, while the Mayo-related scores reflect general disease severity, but it is unsurprising that they also predict short term outcomes after infliximab given they incorporate clinical findings and reflect the immediate clinical response. However, it is notable that, with the exception of the Lindgren score, objective biomarkers such as CAR and CLR are superior in predicting longer term infliximab failure. Additionally, the CAR and CLR were superior to the initial endoscopic Mayo subscore and subsequent Mayo scores, which are normally considered important indicators of disease severity.[44] The objectivity, and therefore reliability of biomarkers makes them a more appealing candidate as predictive scores. Yet the continued relatively strong performance of the Lindgren score and the correlation between stool count and colectomy suggests the inclusion of clinical markers in prediction scores may still be useful.

The predominant limitation of this study is the retrospective design and therefore it is subject to information bias due to misclassification. A small proportion of data were missing however the risk of bias was mitigated by the use of multiple imputation for biomarker data. Also, though most patients received standard infliximab dosing (5 mg/kg at weeks 0, 2, and 6), this was not consistent and was at the discretion of the treating clinician. The strong association with CRP and early colectomy is confounded by auto-correlation, where the early CRP trend is used as part of the subjective decision-making process by surgeons for index colectomy. However, early CRP is not used for decisions regarding later colectomy (the focus of this study) beyond index admission at our institution. Additionally, a small proportion of patients had mild disease on endoscopy which may suggest an alternative cause may have been contributing to their ongoing symptoms. Fecal calprotectin was not routinely performed at our centers and therefore could not be analyzed. Endoscopy was performed on admission prior to infliximab and not routinely following salvage treatment, therefore we could not investigate the utility of endoscopic findings immediately post infliximab. The lack of long term clinical, biomarker and endoscopic outcome data represents a limitation to this study, where ideally these alternate endpoints would be studied in addition to 12-month colectomy. Further, biomarker calculations later during the disease course (such as at week 6 post infliximab) may provide additional predictive value, however these were not uniformly tested in all patients and therefore could not be analyzed in this study. The study may not have been powered to identify additional independent predictors of colectomy in multivariable analyses, however this was not a primary focus. The study was performed at a single health service which may limit its external validity. Further, this study was observational and therefore the utility of the predictive scores evaluated is only speculative, and confirmatory controlled studies are required to prove their usefulness in ASUC management algorithms.

In conclusion, in this large series of patients presenting with steroid-refractory ASUC, simple and routinely performed biochemistry in the biomarker ratios CAR and CLR calculated on day 3 post infliximab salvage show significant promise in predicting infliximab failure and need for longer term colectomy by 12 months. Thus, biomarkers have the potential to aid in decision making for the optimal maintenance strategy after

infliximab salvage. These biomarkers are advantageous because they are simple to calculate, widely available, objective and exhibit dynamics that align well with current mechanistic understandings of anti-TNF therapy and the rapidly changing nature of ASUC. Furthermore, CAR and CLR had superior predictive performance for 12-month colectomy compared with the Mayo score, partial Mayo score, Ho index and Travis score, while the Lindgren score performed similarly. Prospective controlled studies are required to confirm the utility of incorporating predictive scores in current ASUC management algorithms.

ADDITIONAL INFORMATION

Funding Source

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

Vasudevan A has received financial support to attend educational meetings from Ferring. van Langenberg DR has served as a speaker and/or received travel support from Takeda, Ferring and Shire. He has consultancy agreements with Abbvie, Janssen and Pfizer. He received research funding grants for investigator-driven studies from Ferring, Shire and AbbVie. For the remaining authors, there are no relevant conflicts of interest to declare.

Author Contribution

Conceptualization: Con D, van Langenberg DR, Vasudevan A. Formal analysis: Con D. Investigation: Con D, Andrew B, Nicolaides S. Writing - original draft: Con D. Writing - review & editing: Con D, Nicolaides S, van Langenberg DR, Vasudevan A. Approval of final manuscript: all authors.

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See "Biomarker dynamics during infliximab salvage for acute severe ulcerative colitis: C-reactive protein (CRP)-lymphocyte ratio and CRP-albumin ratio are useful in predicting colectomy" on page 101-113.

Supplementary Table 1. Definitions Used for Existing Severity Scores in ASUC

Score	Definition
Mayo score	Sum of the following criteria (nominal): ▪ Daily stool count: 1–2 more than usual (1), 3–4 more than usual (2), ≥ 5 more than usual (3) ▪ Blood: streaks (1), majority blood (2), only blood (3) ▪ Physician global assessment: mild (1), moderate (2), severe (3) ▪ Endoscopic Mayo[a]: mild (1), moderate (2), severe (3)
Partial Mayo score	Sum of the following criteria (nominal): ▪ Daily stool count: 1–2 more than usual (1), 3–4 more than usual (2), ≥ 5 more than usual (3) ▪ Blood: streaks (1), majority blood (2), only blood (3) ▪ Physician global assessment: mild (1), moderate (2), severe (3)
Lindgren/Sweden index	Continuous score defined as sum of: ▪ Daily stool count+0.14 × CRP (mg/L)
Ho/Edinburgh index	Sum of the following criteria (nominal): ▪ Daily stool count: 4–6 (1), 7–9 (2), ≥ 10 (4). ▪ Colonic dilatation: presence (4) ▪ Albumin: < 30 g/L (1)
Travis/Oxford index	High risk if meeting one of the below criteria (dichotomous): ▪ > 8 stools per day or ▪ 3–8 stools per day with CRP > 45 mg/L

Existing Severity Scores were calculated on day 1 and day 3 post infliximab salvage.
[a]Endoscopy performed during intravenous steroid administration prior to infliximab salvage.
ASUC, acute severe ulcerative colitis; CRP, C-reactive protein.

https://doi.org/10.5217/ir.2020.00146 • Intest Res 2022;20(1):101-113

Supplementary Table 2. Estimated Odds Ratio and Confidence Intervals for 12-Month Colectomy (n = 94) on Univariable Analysis as well as 2 Multivariable Models Separately Including Day 3 CAR and CLR Respectively

Predictor	Univariable		Multivariable including CAR		Multivariable including CLR	
	OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age	1.03 (1.00–1.06)	0.035	1.05 (1.01–1.09)	0.025	1.03 (0.99–1.07)	0.110
Male sex	0.8 (0.3–2.3)	0.690	0.8 (0.2–3.5)	0.780	0.5 (0.1–2.4)	0.360
Baseline IM	1.4 (0.5–4.0)	0.530	4.1 (0.6–29.0)	0.160	2.1 (0.3–16.1)	0.480
Baseline steroids	4.1 (1.4–11.6)	0.009	1.6 (0.4–7.3)	0.520	2.4 (0.4–13.1)	0.310
Prior IFX	0.30 (0.01–5.10)	0.390	0.80 (0.00–87.50)	0.940	1.00 (0.00–126.90)	0.990
Prior surgery	0.8 (0.0–16.4)	0.860	0.3 (0.0–510.0)	0.760	0.6 (0.0–426.9)	0.880
Disease duration ≤ 3 yr	5.4 (1.2–24.9)	0.032	3.1 (0.5–17.6)	0.200	2.6 (0.4–17.0)	0.320
Baseline ASA	1.5 (0.5–4.5)	0.440	1.8 (0.4–7.3)	0.440	1.9 (0.4–8.0)	0.410
Current/ex-smoker	0.8 (0.2–2.9)	0.790	0.4 (0.1–2.1)	0.280	0.5 (0.1–2.9)	0.420
Initial IFX dose (10 vs. 5 mg/kg)	0.6 (0.1–3.0)	0.550	1.0 (0.2–5.8)	0.990	1.2 (0.2–8.5)	0.850
CAR > 0.47 mg/g	15.0 (4.3–51.8)	0.001	13.6 (2.6–70.3)	0.002	-	-
CLR > 6.0 mg/10^9	28.0 (7.1–111.2)	0.001	-	-	20.9 (4.2–103.2)	0.001
Disease extent						
E1	1.0	-	1.0	-	1.0	-
E2	4.2 (0.2–80.0)	0.340	2.4 (0.1–65.8)	0.600	2.4 (0.1–74.6)	0.610
E3	5.8 (0.3–109.3)	0.240	4.1 (0.2–104.0)	0.390	6.3 (0.2–198.0)	0.290

Missing CAR and CLR data were estimated using multiple imputation.
OR, odds ratio; CI, confidence interval; CAR, C-reactive protein (CRP)-albumin ratio; CLR, CRP-lymphocyte rate; IM, immunomodulator; IFX, infliximab; ASA, aminosalicylate.

Supplementary Table 3. Biomarker Values in Patients Who Proceeded to Colectomy Compared to Patients Who Avoided Colectomy by 12 Months, Taken at Baseline, Day 1 Post Infliximab Salvage and Day 3 Post Infliximab Salvage

Biomarker	Colectomy	No colectomy	*P*-value
Baseline (admission)			
CRP, mg/L (n = 94)	65 (39–177)	46 (20–100)	0.140
Albumin, g/L (n = 94)	27 (22–32)	32 (27–35)	0.025
Neutrophils, 10^9/L (n = 94)	7.4 (4.7–10.7)	7.9 (6.0–11.3)	0.560
Lymphocytes, 10^9/L (n = 94)	1.0 (0.8–1.7)	1.5 (1.0–2.1)	0.060
Platelets, 10^9/L (n = 94)	392 (324–496)	392 (298–449)	0.660
Day 1 post infliximab			
CRP, mg/L (n = 93)	32 (16–89)	11 (4–26)	< 0.001
Albumin, g/L (n = 91)	21 (18–27)	27 (24–31)	0.003
Neutrophils, 10^9/L (n = 93)	7.0 (4.5–11.4)	8.5 (6.6–11.4)	0.240
Lymphocytes, 10^9/L (n = 93)	1.3 (0.7–2.4)	1.8 (1.3–2.7)	0.090
Platelets, 10^9/L (n = 93)	362 (259–481)	376 (306–459)	0.600
Day 3 post infliximab			
CRP, mg/L (n = 84)	27 (11–56)	5 (2–12)	< 0.001
Albumin, g/L (n = 81)	23 (18–27)	28 (24–31)	< 0.001
Neutrophils, 10^9/L (n = 84)	6.3 (5.9–8.8)	8.7 (6.2–12.0)	0.060
Lymphocytes, 10^9/L (n = 84)	1.3 (0.7–2.0)	2.8 (1.8–4.2)	0.001
Platelets, 10^9/L (n = 84)	380 (271–500)	382 (318–466)	0.640

Values are presented as median (interquartile range).
CRP, C-reactive protein.

https://doi.org/10.5217/ir.2020.00146 • Intest Res 2022;20(1):101-113

Supplementary Table 4. Biomarker Ratios in Patients Who Proceeded to Colectomy Compared to Patients Who Avoided Colectomy by 12 Months, Calculated at Baseline (on Admission), Day 1 Post Infliximab Salvage and Day 3 Post Infliximab Salvage

Biomarker ratios	Colectomy	No colectomy	*P*-value
Admission			
CAR, mg/g (n = 94)	2.04 (1.05–9.50)	1.52 (0.61–3.58)	0.060
CLR, mg/10^9 (n = 94)	68.3 (21.4–159.7)	26.0 (12.9–82.6)	0.023
NLR (n = 94)	5.88 (3.43–9.07)	5.15 (3.25–9.70)	0.300
PLR (n = 94)	367.8 (235.3–586.6)	232.2 (154.8–398.0)	0.020
Day 1 post infliximab			
CAR, mg/g (n = 91)	1.29 (0.57–4.80)	0.38 (0.16–0.96)	< 0.001
CLR, mg/10^9 (n = 93)	19.4 (10.8–72.0)	5.8 (2.5–16.1)	< 0.001
NLR (n = 93)	5.33 (2.33–7.50)	4.85 (2.72–7.87)	0.850
PLR (n = 93)	295.5 (167.9–373.6)	216.7 (127.0–316.4)	0.190
Day 3 post infliximab			
CAR, mg/g (n = 81)	1.05 (0.48–2.70)	0.18 (0.05–0.43)	< 0.001
CLR, mg/10^9 (n = 84)	19.7 (6.5–40.0)	2.1 (0.7–4.0)	< 0.001
NLR (n = 84)	4.57 (3.65–6.95)	2.93 (1.80–4.90)	0.018
PLR (n = 84)	239.6 (186.0–485.4)	127.1 (99.6–233.3)	0.004

Values are presented as median (interquartile range).
CAR, C-reactive protein (CRP)-albumin ratio; CLR, CRP-lymphocyte rate; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio.
Spearman rank correlation ρ between biomarkers and need for colectomy are given.

Supplementary Table 5. Diagnostic Properties of CAR and CLR on Day 3 Post Salvage, Using Outcomes of 12-Month Colectomy and 1-Month Colectomy

Cutoff	Predicting colectomy by 12 months				Predicting colectomy by 1 month				Proportion classified as low risk (%)
	Sens.	Spec.	PPV	NPV	Sens.	Spec.	PPV	NPV	
CAR (mg/g)									
≥ 0.14	1.00	0.44	0.31	1.00	1.00	0.39	0.16	1.00	35
≥ 0.28	0.90	0.59	0.35	0.96	1.00	0.55	0.21	1.00	50
≥ 0.47[a]	0.79	0.80	0.50	0.94	0.90	0.75	0.30	0.98	68
≥ 1.1	0.53	0.93	0.67	0.89	0.70	0.91	0.47	0.96	85
≥ 1.7	0.42	0.99	0.89	0.87	0.50	0.95	0.56	0.94	90
CLR (mg/10^9)									
≥ 1.5	0.95	0.41	0.29	0.97	1.00	0.38	0.16	1.00	35
≥ 2.6	0.84	0.60	0.35	0.94	0.90	0.56	0.20	0.98	50
≥ 6.0[a]	0.84	0.84	0.57	0.96	0.90	0.77	0.32	0.98	70
≥ 16	0.63	0.96	0.80	0.91	0.80	0.92	0.53	0.97	85
≥ 24	0.42	0.99	0.89	0.87	0.50	0.95	0.56	0.94	90

[a]Optimal cutoff defined as maximum Youden's statistic.
CAR, C-reactive protein (CRP)-albumin ratio; CLR, CRP-lymphocyte rate; Sens., sensitivity; Spec., specificity; PPV, positive predictive value; NPV, negative predictive value.

https://doi.org/10.5217/ir.2020.00146 • Intest Res 2022;20(1):101-113

Supplementary Table 6. Estimated Odds Ratio and Confidence Intervals for 12-Month Colectomy in Patients Who Avoided Index Colectomy (n = 84), on Univariable Analysis as well as 2 Multivariable Models Separately Including Day 3 CAR and CLR Respectively

Predictor	Univariable		Multivariable including CAR		Multivariable including CLR	
	OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age	1.00 (0.96–1.05)	0.850	1.02 (0.97–1.07)	0.450	1.01 (0.96–1.06)	0.650
Male sex	0.6 (0.1–2.4)	0.460	0.6 (0.1–3.2)	0.580	0.6 (0.1–3.1)	0.580
Baseline IM	1.9 (0.5–7.9)	0.360	4.5 (0.3–64.2)	0.270	2.6 (0.3–25.4)	0.410
Baseline steroids	3.7 (0.9–15.2)	0.070	1.0 (0.1–7.6)	0.970	1.2 (0.2–8.9)	0.850
Prior IFX	0.6 (0.0–10.8)	0.700	0.9 (0.0–34.4)	0.940	0.8 (0.0–28.8)	0.920
Prior surgery	1.5 (0.1–34.7)	0.780	0.7 (0.0–30.4)	0.870	1.0 (0.0–44.3)	0.990
Disease duration ≤ 3 yr	5.0 (0.6–42.4)	0.140	6.1 (0.4–83.9)	0.170	3.9 (0.3–43.3)	0.270
Baseline ASA	2.5 (0.5–12.7)	0.280	2.4 (0.3–16.6)	0.390	2.8 (0.4–22.5)	0.320
Current/ex-smoker	0.9 (0.2–4.8)	0.910	0.6 (0.1–4.4)	0.590	0.7 (0.1–4.7)	0.740
Total induction IFX dose (per 5 mg/kg)	0.3 (0.1–0.7)	0.010	0.7 (0.3–2.0)	0.560	0.9 (0.4–2.3)	0.850
CAR > 0.47 mg/g	8.0 (1.8–35.7)	0.006	4.7 (0.7–33.1)	0.120	-	-
CLR > 6.0 mg/10^9	18.4 (3.4–99.4)	0.001	-	-	6.8 (1.2–39.4)	0.032
Disease extent						
E1	1.0	-	1.0	-	1.0	-
E2	2.7 (0.1–53.9)	0.510	7.1 (0.1–975.1)	0.440	3.7 (0.1–239.3)	0.530
E3	2.3 (0.1–46.7)	0.590	5.9 (0.0–842.5)	0.480	3.8 (0.1–233.0)	0.530
Maintenance therapy						
Biologic+IM	1.0	-	1.0	-	1.0	-
IM	2.9 (0.3–27.8)	0.350	1.3 (0.2–10.1)	0.790	1.4 (0.2–10.3)	0.740
ASA only	12.4 (1.2–126.0)	0.033	5.9 (0.6–61.5)	0.140	5.9 (0.7–49.2)	0.100

Missing CAR and CLR data were estimated using multiple imputation.
OR, odds ratio; CI, confidence interval; CAR, C-reactive protein (CRP)-albumin ratio; CLR, CRP-lymphocyte rate; IM, immunomodulator; IFX, infliximab; ASA, aminosalicylate.

Supplementary Table 7. Estimated Odds Ratio and Confidence Intervals for 1-Month Colectomy (n = 94) on Univariable Analysis as well as 2 Multivariable Models Separately Including Day 3 CAR and CLR Respectively

Predictor	Univariable		Multivariable including CAR		Multivariable including CLR	
	OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age	1.05 (1.01–1.09)	0.007	1.07 (1.01–1.13)	0.014	1.05 (1.01–1.10)	0.021
Male sex	1.2 (0.3–4.9)	0.830	1.0 (0.1–6.4)	0.970	0.4 (0.1–3.0)	0.380
Baseline IM	1.0 (0.2–4.0)	0.950	2.2 (0.2–25.1)	0.520	1.9 (0.2–20.1)	0.580
Baseline steroids	3.8 (1.0–14.5)	0.060	0.9 (0.1–7.6)	0.890	1.3 (0.2–10.2)	0.770
Prior IFX	0.6 (0.0–11.0)	0.710	3.3 (0.0–554.5)	0.650	2.3 (0.0–642.9)	0.770
Prior surgery	1.6 (0.1–35.0)	0.780	0.4 (0.0–955.0)	0.810	0.8 (0.0–1,914.8)	0.940
Disease duration ≤ 3 yr	0.2 (0.0–2.1)	0.200	1.4 (0.1–13.5)	0.790	2.0 (0.2–25.0)	0.590
Baseline ASA	1.0 (0.3–3.7)	0.970	1.4 (0.2–9.7)	0.720	1.0 (0.2–6.1)	0.970
Current/ex-smoker	0.8 (0.2–4.1)	0.790	0.4 (0.1–3.3)	0.420	0.5 (0.0–4.3)	0.500
Initial IFX dose (10 vs. 5 mg/kg)	1.5 (0.3–7.9)	0.630	2.9 (0.4–19.8)	0.280	4.2 (0.5–37.5)	0.190
CAR > 0.47 mg/g	27.0 (3.2–225.9)	0.002	22.0 (1.6–309.9)	0.022	-	-
CLR > 6.0 mg/10^9	30.8 (3.7–258.6)	0.002	-	-	15.9 (1.8–139.2)	0.012
Disease extent						
E1	1.0	-	1.0	-	1.0	-
E2	1.5 (0.1–31.9)	0.790	0.4 (0.0–16.3)	0.610	0.6 (0.0–51.2)	0.840
E3	3.4 (0.2–65.5)	0.420	1.3 (0.0–45.3)	0.900	3.2 (0.0–214.7)	0.580

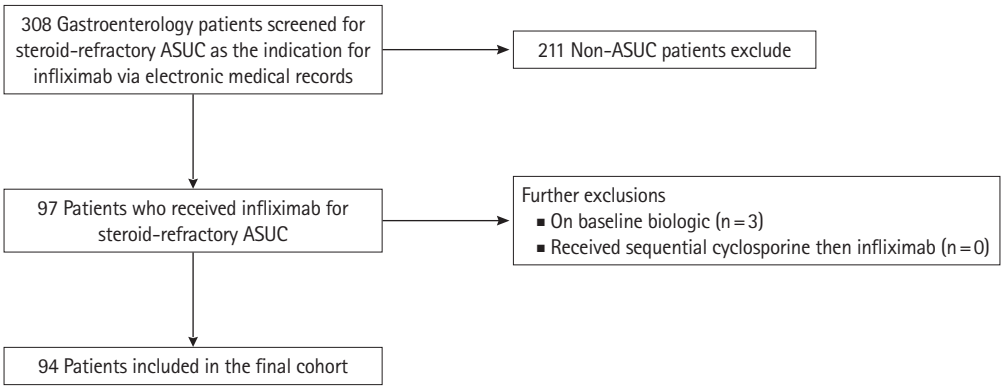
Missing CAR and CLR data were estimated using multiple imputation.
OR, odds ratio; CI, confidence interval; CAR, C-reactive protein (CRP)-albumin ratio; CLR, CRP-lymphocyte rate; IM, immunomodulator; IFX, infliximab; ASA, aminosalicylate.

https://doi.org/10.5217/ir.2020.00146 • Intest Res 2022;20(1):101-113

Supplementary Table 8. Predictive Performance for Colectomy by 12 Months and by 1 Month Given as AUC with Confidence Intervals, Using Complete Data Only

Biomarker ratios	Colectomy by 12 months		Colectomy by 1 month	
	AUC	95% CI	AUC	95% CI
Admission				
CAR, mg/g (n = 94)	0.640	0.500–0.781	0.756	0.592–0.920
CLR, mg/10^9 (n = 94)	0.669	0.536–0.802	0.767	0.624–0.909
NLR (n = 94)	0.578	0.439–0.716	0.560	0.361–0.758
PLR (n = 94)	0.673	0.536–0.809	0.754	0.595–0.913
Day 1 post infliximab				
CAR, mg/g (n = 91)	0.814	0.717–0.911	0.854	0.734–0.975
CLR, mg/10^9 (n = 93)	0.780	0.670–0.890	0.795	0.654–0.937
NLR (n = 93)	0.486	0.334–0.638	0.469	0.231–0.706
PLR (n = 93)	0.598	0.453–0.743	0.564	0.374–0.753
Day 3 post infliximab				
CAR, mg/g (n = 81)	0.867	0.780–0.955	0.914	0.826–1.000
CLR, mg/10^9 (n = 84)	0.865	0.762–0.968	0.909	0.794–1.000
NLR (n = 84)	0.682	0.539–0.826	0.693	0.501–0.885
PLR (n = 84)	0.724	0.585–0.862	0.779	0.611–0.947

AUC, area under the receiver operator characteristic curve; CI, confidence interval; CAR, C-reactive protein (CRP)-albumin ratio; CLR, CRP-lymphocyte rate; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio.



Supplementary Fig. 1. Flowchart of participant identification process. ASUC, acute severe ulcerative colitis.