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ORIGINAL ARTICLE

Clinical utility of C-reactive protein-to-albumin ratio in the management of patients with inflammatory bowel disease

Anke L Nguyen,*,† Claudia Brick,* David Liu,* David J Gibson,* Peter R Gibson* and Miles P Sparrow*

*Department of Gastroenterology, Central Clinical School, Monash University and Alfred Health and †Department of Gastroenterology, Monash Health, Melbourne, Victoria, Australia

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Correspondence
Anke L Nguyen, Department of Gastroenterology, Central Clinical School, Monash University and Alfred Health, 99 Commercial Rd, Melbourne, Victoria, 3004, Australia. Email: anke.nguyen@alfred.org.au

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Abstract

Background and Aim: C-reactive protein (CRP)-to-albumin ratio (CAR) is a novel score with prognostic value in inflammatory conditions. This study assessed the performance of CAR as an objective marker of disease activity and prediction of subtherapeutic infliximab trough levels in patients with inflammatory bowel disease (IBD).
Methods: A retrospective study was conducted on three different patient cohorts with IBD: patients who had (i) fecal calprotectin (FC) measurements; (ii) Mayo Endoscopic Scores; and (iii) infliximab trough levels available. The relative performances of CAR, albumin, and CRP were compared in predicting disease activity (based on FC or Mayo Endoscopic Score) and infliximab trough levels.
Results: In both the FC ($n = 289$) and endoscopy ($n = 65$) cohorts, albumin and CAR correlated with objective disease activity. CAR (area under the curve [AUC] 0.70) was only marginally better at detecting active disease, measured by FC, compared to CRP (AUC 0.68). A CAR >0.15 was able to detect Mayo 3 disease (AUC 0.83, sensitivity 81%, specificity 89%). Albumin ($r = 0.38$) and CAR ($r = -0.42$) correlated with infliximab trough levels ($n = 204$). The optimal CAR for detecting subtherapeutic infliximab trough levels was >0.08 (AUC 0.70, sensitivity 66%, specificity 64%). Both albumin and CAR were independent predictors of subtherapeutic infliximab trough levels but correlated poorly with infliximab trough levels longitudinally in the same patient.
Conclusion: CAR was only a modest discriminator of subtherapeutic infliximab levels and offers little more than CRP in detecting active disease. CAR has potential to detect severe Mayo 3 disease and could be calculated in patients admitted with suspected acute severe ulcerative colitis.

Introduction

A primary goal in the management of inflammatory bowel disease (IBD) is prevention of symptomatic clinical relapse. This requires regular monitoring of intestinal inflammation and assessing adequacy of therapy. Intestinal inflammation can be monitored directly, by colonoscopy, or indirectly, by quantifying inflammation with fecal calprotectin (FC) measurements.[1–3] Adequacy of therapy can be assessed by measuring drug metabolites or drug trough levels in serum blood samples.[4,5] Unfortunately, all these methods are costly, and monitoring with common serum biomarkers, such as C-reactive protein (CRP) and albumin, is more convenient and cost-effective for patients.

CRP is routinely used as a surrogate measure of intestinal inflammation and as a prognostic measure of nonresponse to medical therapy and colectomy in patients with IBD.[6–8] CRP can, however, also be elevated in extra-intestinal inflammatory diseases, may be within normal limits even with active inflammatory disease, and is affected by genetic variation.[9] Serum albumin is inversely associated with clinical and endoscopic disease activity[1,10,11] and predicts colectomy in patients with ulcerative colitis (UC).[12,13] Furthermore, serum albumin has been associated with infliximab trough levels and used as a covariate in dashboard-driven models targeting specific infliximab trough levels, emphasizing its role in infliximab pharmacokinetics and therapy monitoring.[14,15] Despite this, the role of albumin in disease monitoring is not clearly delineated in patients with IBD.

In other inflammatory diseases, combining CRP and albumin as a CRP-to-albumin ratio (CAR) has improved the performance of either used alone; for example, CAR was a superior predictor of 90-day mortality compared with albumin or CRP in patients with sepsis.[16–18] Its application in patients with IBD is limited to its ability to predict symptomatic disease and mucosal healing in Crohn's disease[1,10,19] and its prognostic value in patients with acute severe UC.[20,21] Its relationship to objective inflammatory disease and in the detection of subtherapeutic infliximab levels has not been reported.

Hence, the current study aimed to determine the utility of measuring CAR and its performance compared with albumin alone in the prediction of objective disease activity and in identifying patients with subtherapeutic infliximab trough levels.

Methods

Patient selection. A single-center retrospective study was conducted on three separate patient cohorts with IBD. Patient demographics including age, sex, disease duration, and Montreal classification were documented.

- *FC cohort*: All patients with IBD who had FC values documented between May 2012 and May 2020 were included. The Buhlmann EK-Cal ELISA, Schönenbuch, Switzerland, was used to quantify FC at this institution. A FC ≥150 μg/g was considered active disease.[22] Patients were only included if CRP and albumin were available within 1 month of the disease activity assessment.
- *Endoscopy cohort with UC*: All patients with UC who underwent endoscopy between June 2012 and February 2018 were included. Endoscopic disease severity was determined by the 4-point Mayo Endoscopic Score,[23] as reported routinely by endoscopists. A Mayo score ≥1 was considered active disease and 3 considered severe disease. Patients were only included if CRP and albumin were available within 1 month of the disease activity assessment.
- *Infliximab cohort*: All patients with IBD treated with maintenance intravenous infliximab (defined as ≥14 weeks' therapy) between November 2012 and April 2020 were included. Patients were included if their infliximab therapy was at a dose of 5–10 mg/kg given 4–12 weekly and with infliximab trough levels tested within 1 week of other laboratory values, including CRP and albumin. Infliximab levels were measured reactively at the clinician's discretion, rather than as routine practice. Measurement of infliximab concentrations was performed using various commercial ELISA kits, including Matriks Biotek Shikari (Q-INFLIXI, Ankara, Turkey), LISA-tracker IFX assay (Theradiag, Croissy Beaubourg, France), or Promonitor-IFX 1DL kit (Progenika Biopharma, Bizkaia, Spain). Kit results were pooled together, as the same analytical method (ELISA) with the same gold standards (infliximab) was used to create calibration curves. Previous kit comparisons only showed minor differences between the detected infliximab concentrations.[24] FC within 3 months of the trough level was also documented if available. Infliximab trough levels <5 μg/ml were considered subtherapeutic.[25,26]

Statistical analysis. All statistical analyses and graphs were performed with STATA 13 (StataCorp LLC, College Station, Texas, USA) and GraphPad Prism 9 (Dotmatics, Boston, Massachusetts, USA). Continuous variables were presented as medians (interquartile range) and categorical variables as frequency (percentage).

In the FC and infliximab cohorts, all values were divided into quartiles, and in the endoscopy cohort, Mayo Endoscopic Score was divided into four groups (Mayo 0, 1, 2, 3). Albumin and CAR values were compared across quartiles/groups using the Kruskal–Wallis test and pairwise comparisons using Dunn's test. A statistically significant P-value was <0.05. Spearman correlation coefficients were determined for the relationship of albumin, CRP, and CAR with active disease and infliximab trough levels. Receiver-operating-characteristic (ROC) curves were used to determine the area under the curve (AUC) of albumin, CRP, and CAR for detecting active disease measured by FC and Mayo Endoscopic Score and severe disease measured by Mayo Endoscopic Score and subtherapeutic infliximab trough levels. Cutoff values were then calculated using Youden's index. In the FC cohort, a subanalysis was undertaken to generate the same ROC curves for patients with CRP ≥5 mg/l. Univariable logistic regression analysis was used to find independent associations with active disease and subtherapeutic infliximab trough levels in each cohort to calculate odd's ratios (OR). Any significant associations ($P < 0.05$) were then used in a multivariable analysis to define independent associations. Two models (models 1 and 2) were used in the multivariable analysis to avoid multicollinearity of albumin and CRP with CAR.[27]

A longitudinal analysis was undertaken in all three cohorts, where patients had two consecutive infliximab trough levels or disease activity assessments (FC or Mayo Endoscopic Score) available. Additional laboratory markers, albumin and CRP, had to be available within 1 week of the infliximab trough levels and within 1 month of the disease activity assessments. Percentage change in each longitudinal measurement was calculated as (follow-up value) minus (baseline value) divided by (baseline value), multiplied by 100 and then compared with albumin, CRP, and CAR using Spearman correlation coefficients.

Ethical considerations. The study was approved by the Alfred Health Ethics Committee (Local Reference No. 319/20, approved on 3 June 2020).

Results

Analyses using fecal calprotectin as a biomarker of disease activity. Patient demographics of 289 patients

Table 1 Baseline characteristics of patients with inflammatory bowel disease (IBD)

		FC cohort ($n = 289$)	Endoscopy cohort ($n = 65$)	Infliximab cohort ($n = 204$)
Age, years		37 (29–50)	34 (27–47)	36 (30–48)
Sex, male		155 (54%)	37 (57%)	117 (57%)
Smokers, %		22 (8%)	1 (2%)	9 (4%)
Disease duration, years		8 (3–17)	4 (1–10)	9 (4–17)
Immunomodulator	Thiopurines	156 (54%)	25 (38%)	117 (57%)
	Methotrexate	19 (7%)	4 (6%)	28 (14%)
Biologic therapy		200 (69%)	22 (34%)	204 (100%)
Disease type	Crohn's disease	216 (75%)	-	154 (75%)
	Ulcerative colitis	61 (21%)	65 (100%)	41 (20%)
	IBD unclassified	12 (4%)	-	9 (4%)
Crohn's disease				
Age at diagnosis	A1: <17 years	41 (14%)		22 (14%)
	A2: 17–40 years	137 (47%)		110 (71%)
	A3: >40 years	37 (13%)		21 (14%)
Distribution	Ileum (L1)	70 (24%)		43 (28%)
	Colon (L2)	64 (22%)		42 (27%)
	Ileocolonic (L3)	82 (28%)		67 (44%)
Phenotype	Upper gastrointestinal (L4)	2 (1%)		2 (1%)
	Inflammatory (B1)	157 (54%)		89 (58%)
	Fibrostenotic (B2)	46 (16%)		40 (26%)
	Penetrating (B3)	13 (4%)		25 (16%)
	Perianal (p)	75 (26%)		64 (42%)
Ulcerative colitis				
Distribution	Proctitis (E1)	1 (0.3%)	1 (2%)	0
	Left-sided colitis (E2)	29 (10%)	29 (45%)	20 (49%)
	Extensive colitis (E3)	31 (11%)	35 (54%)	21 (51%)

FC, fecal calprotectin.

identified are summarized in Table 1. There were 0 (0–5) days between FC and other laboratory values. The FC was 133 (40–600) µg/g. In 140 (48%) fecal samples, FC values indicated active disease and, in 149 (52%), inactive disease. Serum albumin, CRP, and CAR differed across patients divided into quartiles according to the FC ($P < 0.0001$ for all, Kruskal–Wallis test; Fig. 1). Statistically significant pairwise differences were observed for all quartiles, except Q1 *versus* Q2 and Q3 *versus* Q4 for albumin, CRP, and CAR.

FC levels correlated (all $P < 0.001$) with albumin ($r = -0.27$), CRP ($r = 0.35$) and CAR ($r = 0.35$). On ROC analysis for identifying active disease, the AUC was highest for CAR (0.70) compared to albumin (AUC 0.66) or CRP (AUC 0.68) alone (Fig. 2). The optimal CAR for predicting active disease was >0.17 (sensitivity 45%, specificity 89%), and the optimal albumin concentration was <37 g/l (sensitivity 59%, specificity 68%) (Table 2). On analysis of patients with CRP ≥5 mg/l ($n = 102$), AUC remained highest for CAR (0.71, cutoff 0.25, sensitivity 79%, specificity 68%), compared to CRP (0.70, cutoff 7.5 mg/l, sensitivity 80%, specificity 58%) and albumin (0.65, cutoff 34 g/l, sensitivity 48%, specificity 81%) in identifying patients with active disease.

On multivariable logistic regression analysis (Table 3), independent associations with active disease were albumin (OR 0.92), CRP (OR 1.04), CAR (OR 5.31), and UC compared to Crohn's disease (OR 2.44).

A subset of 216 patients had two consecutive FC levels available, separated by 13 (7–23) months. The percentage change in FC was associated (all $P \leq 0.0001$) with albumin ($r = -0.26$), CRP ($r = 0.28$), and CAR ($r = 0.26$) (Fig. 3).

Analyses using Mayo Endoscopic Score to measure disease activity in patients with ulcerative colitis. Patient demographics of 65 patients with UC are summarized in Table 1. Of all endoscopies, 31 (48%) were colonoscopies and 34 (52%) flexible sigmoidoscopies, 34 (52%) were performed as outpatient and 31 (48%) as inpatient procedures. Inactive disease was found in 14% (Mayo 0: $n = 9$) and active disease was found in 86% (Mayo 1: $n = 12$, Mayo 2: $n = 28$, Mayo 3: $n = 16$). There were 0 (0–3) days between endoscopy and other laboratory values.

With disease activity defined by Mayo Endoscopic Scores 0–3, there were differences detected across all groups for albumin ($P = 0.003$, Kruskal–Wallis test), CRP ($P = 0.027$) and CAR ($P = 0.015$; Fig. 1). There was a downward trend of median albumin concentration with increasing Mayo scores, with differences between Mayo 0 (35 g/l) and Mayo 3 (26 g/l, $P = 0.012$), and between Mayo 1 (36.5 g/l) and Mayo 3 disease ($P = 0.014$). CRP and CAR increased with increasing Mayo scores, where Mayo 0 differed from Mayo 3 disease for both CRP (3 mg/l *vs* 15 mg/l, $P = 0.019$) and CAR (0.09 *vs* 0.63, $P = 0.013$).

Mayo Endoscopic Score demonstrated significant correlations with albumin ($r = -0.46$, $P < 0.0001$), CRP ($r = 0.36$, $P = 0.003$), and CAR ($r = 0.40$, $P = 0.001$). On ROC analysis, all markers were associated with active (Mayo 1/2/3) disease, including albumin (AUC 0.73, $P = 0.031$), CRP (AUC 0.73, $P = 0.030$), and CAR (AUC 0.74, $P = 0.024$) (Fig. 2). The optimal values for albumin were < 33 g/l (sensitivity 59%, specificity

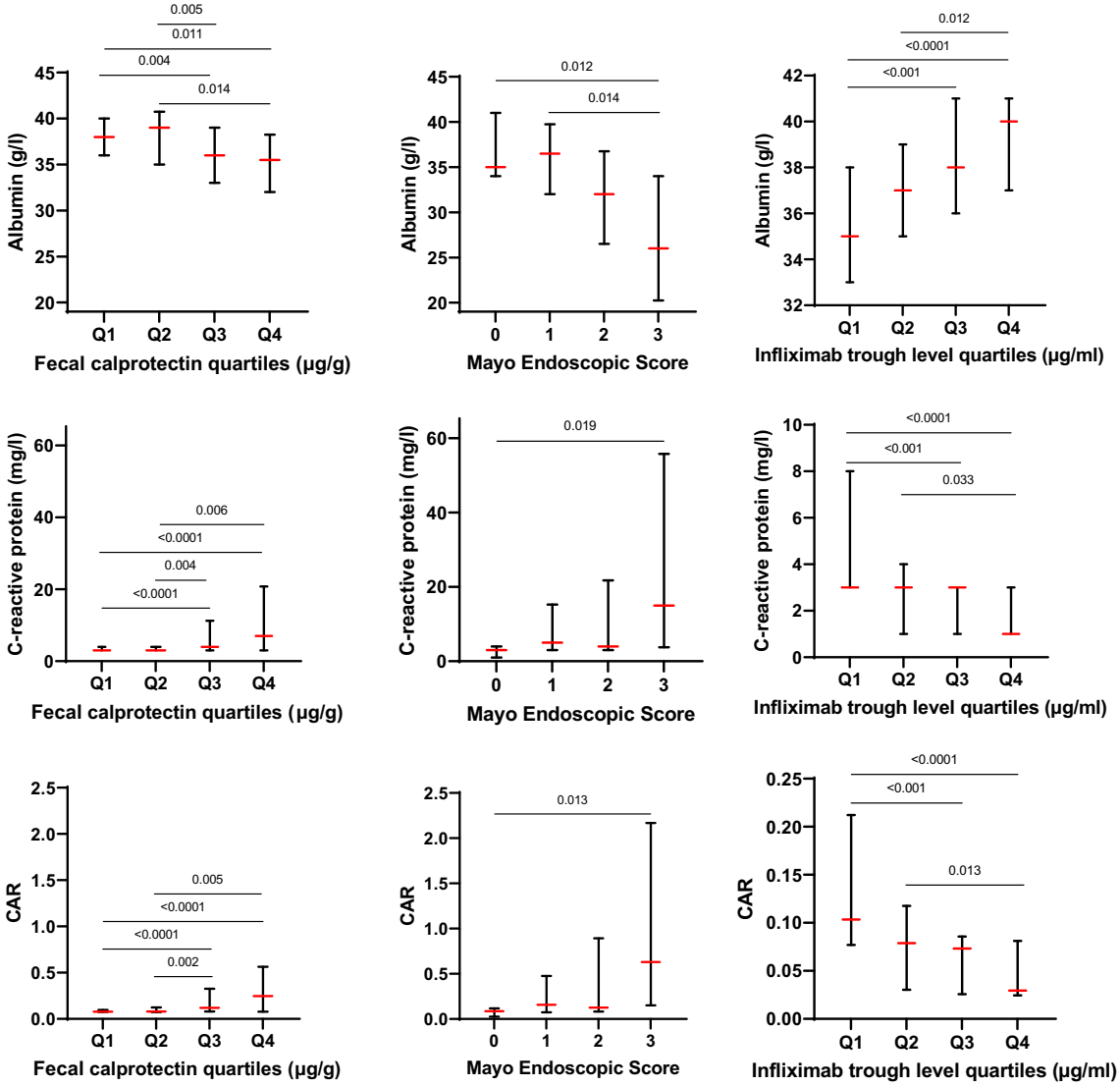

Figure 1 Albumin, C-reactive protein and C-reactive protein-to-albumin ratio (CAR) in different quartiles of fecal calprotectin ($n = 289$, left column); Q1 (7.5–40 µg/g), Q2 (41–133 µg/g), Q3 (135–600 µg/g), and Q4 (609–2375 µg/g), Mayo Endoscopic Score ($n = 65$, middle column) 0–3, and quartiles of infliximab trough levels ($n = 204$, right column); Q1 (0.1–2.3 µg/ml), Q2 (2.4–5 µg/ml), Q3 (5.03–7.46 µg/ml), and Q4 (7.47–32.3 µg/ml). Each bar represents the interquartile range with median in red. *P*-values between groups were calculated with Dunn's test.

89%) and CAR >0.09 (sensitivity 71%, specificity 78%) for predicting active disease (Table 2). When inactive Mayo 0 disease was compared to Mayo 3 disease, CAR was the best predictor of severe disease with a cutoff of 0.15 (AUC 0.83, sensitivity 81%, specificity 89%) compared with albumin or CRP alone. When Mayo 0 disease was compared to Mayo 1 disease, CRP (AUC 0.69) was better at predicting mild active disease than CAR (AUC 0.65).

On multivariable logistic regression analysis, biologic use (OR 0.16) was the only independent association with active (Mayo 1/2/3) endoscopic disease in patients with UC (Table 3). There were no independent associations of any variables with severe (Mayo 3) or mild (Mayo 1) endoscopic disease.

A total of 40 patients had two consecutive endoscopies performed with a median of 15 (5–26) months between the procedures. Comparing change in Mayo Endoscopic Score to other laboratory markers, associations were found for albumin ($r = -0.60$, $P < 0.0001$), CRP ($r = 0.33$, $P = 0.037$), and CAR ($r = 0.41$, $P = 0.009$; Fig. 3).

Analyses using infliximab trough levels. Patient demographics of the 204 patients identified are summarized in Table 1. Concomitant immunomodulators included thiopurines in 57% and methotrexate in 14% of patients. At the time of the infliximab trough levels, the median CRP was 3 (interquartile range [IQR] 1–4) mg/l, albumin was 38 (35–40) g/l and FC was

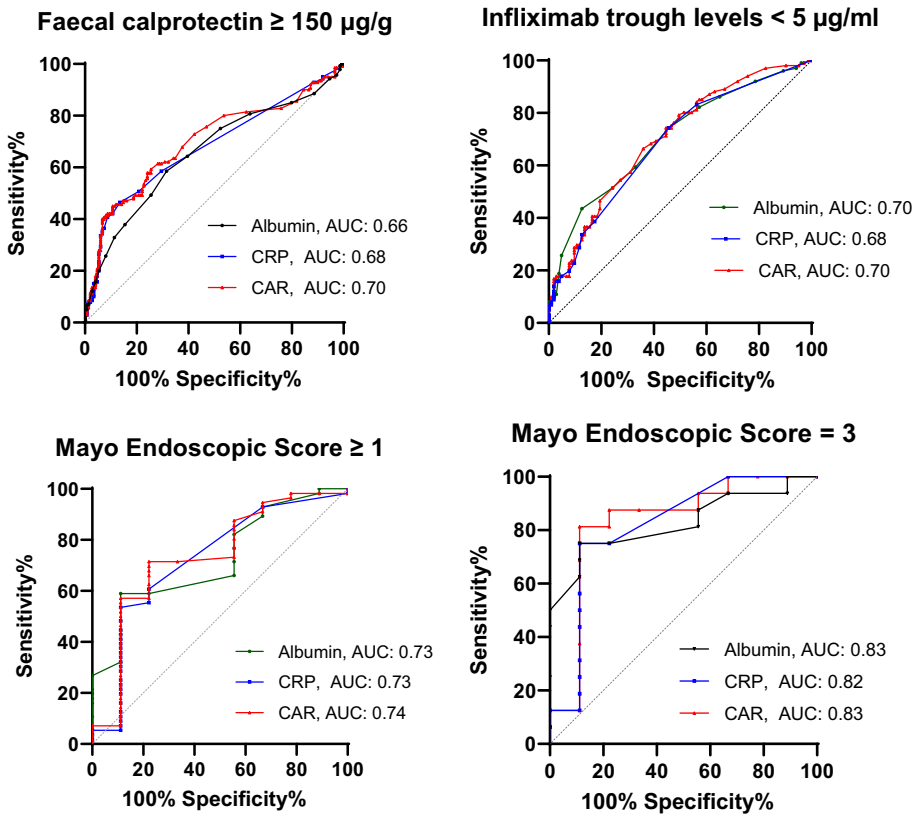

Figure 2 Receiver-operating characteristic curves demonstrating the area under the curve (AUC) for albumin, C-reactive protein (CRP), and CRP-to-albumin ratio (CAR) for active disease defined by fecal calprotectin ≥ 150 µg/g and Mayo Endoscopic Score ≥ 1, severe disease defined by Mayo Endoscopic Score = 3 and for detecting subtherapeutic infliximab trough levels.

138 (30–600) µg/g. Median time on infliximab until the trough level was 2 (1–5) years. There were 101 (50%) subtherapeutic infliximab trough levels. Albumin, CRP, and CAR differed across patients divided into quartiles according to the infliximab levels ($P < 0.0001$ for all; Fig. 1). The median albumin concentration increased with increasing quartiles where the concentration in Q1 (35 g/l) was different from Q3 (38 g/l, $P < 0.001$) and Q4 (40 g/l, $P < 0.0001$). CRP in Q1 (3 mg/l, $P < 0.0001$) and Q2 (3 mg/l, $P = 0.033$) differed significantly from Q4 (1 mg/l). Similarly, CAR was highest in Q1 (0.10) compared to Q3 (0.07, $P < 0.001$) and Q4 (0.03, $P < 0.0001$).

Infliximab trough levels correlated (all $P < 0.0001$) with albumin ($r = 0.38$), CRP ($r = -0.39$), and CAR ($r = -0.42$), but not with FC levels ($r = -0.19$, $P = 0.144$). Figure 2 shows the ROC curves for albumin, CRP, and CAR for subtherapeutic infliximab trough levels. The AUC for subtherapeutic trough levels was highest for CAR (0.70) and albumin (0.70) followed by CRP (0.68), all $P < 0.0001$. FC was not significantly associated with infliximab trough levels (AUC 0.61, $P = 0.141$). In patients with Crohn's disease ($n = 154$), all markers detected subtherapeutic infliximab trough levels, albumin (AUC 0.74), CRP (AUC 0.70), and CAR (AUC 0.72). There were no significant associations seen in patients with UC ($n = 41$). The optimal values to predict a subtherapeutic infliximab trough level in all patients were an albumin of <36 g/l (sensitivity 44%, specificity 87%), CRP of >2.5 mg/l (sensitivity 74%, specificity 54%), or CAR of >0.08 (sensitivity 66%, specificity 64%) for CAR (Table 2).

On multivariable logistic regression analysis (Table 4), independent associations with subtherapeutic infliximab trough levels were found for albumin with an OR of 0.85, CAR (OR 34.03), and years on infliximab (OR 0.88). CRP was not independently associated with subtherapeutic infliximab trough levels.

On analysis of patients receiving infliximab doses of 5 mg per kg every 8 weeks ($n = 125$), albumin was the best predictor of subtherapeutic infliximab trough levels (AUC 0.71), compared with CAR (AUC 0.68) and CRP (AUC 0.65). In this group, albumin (OR 0.81) was the only marker independently associated with subtherapeutic infliximab trough levels on multivariable logistic regression analysis.

A subset of 153 patients had two consecutive infliximab trough levels available. Time between infliximab trough levels was 8 (3–13) months. Comparing percentage change in infliximab trough levels to other laboratory markers, significant associations were found for CAR ($r = -0.20$, $P = 0.014$) and CRP ($r = -0.17$, $P = 0.035$) (Fig. 3). Change in albumin had no association with change in infliximab trough levels.

Table 2 Receiver-operating-characteristic curve analysis and performance characteristics of albumin and C-reactive protein-to-albumin ratio (CAR) in patients with active inflammatory bowel disease, defined by fecal calprotectin ≥150 μg/g, Mayo Endoscopic Score ≥ 1 or = 3 and subtherapeutic infliximab drug levels, defined by <5 μg/ml

	Area under the curve	Cutoff value	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Active disease defined by fecal calprotectin ≥ 150 μg/g						
Albumin (g/l)	0.66	<37	59	68	63	64
C-reactive protein (mg/l)	0.68	>5.5	46	87	77	64
CAR	0.70	>0.17	45	89	79	64
Active disease defined by Mayo Endoscopic Score ≥ 1						
Albumin (g/l)	0.73	<33	59	89	97	26
C-reactive protein (mg/l)	0.73	>5.5	54	89	97	24
CAR	0.74	>0.09	71	78	95	30
Severe disease defined by Mayo Endoscopic Score = 3						
Albumin (g/l)	0.83	<32	75	89	69	91
C-reactive protein (mg/l)	0.82	>5.5	75	89	69	91
CAR	0.83	>0.15	81	89	71	93
Subtherapeutic trough level < 5 μg/ml						
Albumin (g/l)	0.70	<36	44	87	77	61
C-reactive protein (mg/l)	0.68	>2.5	74	54	62	68
CAR	0.70	>0.08	66	64	65	65

Table 3 Multivariable logistic regression analysis to determine associations with active disease defined by fecal calprotectin ≥ 150 μg/g in all inflammatory bowel disease patients and Mayo Endoscopic score ≥ 1 in patients with ulcerative colitis

	Univariable logistic regression			Multivariable logistic regression		
	OR	95% CI	*P*-value	Adjusted OR	95% CI	*P*-value
Fecal calprotectin ≥ 150 μg/g						
Age, years	0.99	0.98–1.01	0.494			
Sex (female *vs* male)	0.88	0.55–1.39	0.572			
Smoking status (yes *vs* no)	0.78	0.32–1.92	0.596			
Disease type (UC *vs* CD)	2.10	1.32–3.34	**0.002**	2.44	1. 49–4.01	**0.000**
Disease duration, years	0.99	0.97–1.02	0.551			
Biologic use (yes *vs* no)	1.01	0.61–1.66	0.977			
Immunomodulator use (yes *vs* no)	1.07	0.67–1.72	0.768			
Albumin level (g/l): model 1	0.87	0.82–0.93	**0.000**	0.92	0.86–0.98	**0.012**
C-reactive protein level (mg/l): model 1	1.06	1.02–1.09	**0.001**	1.04	1.01–1.07	**0.014**
CAR: model 2[†]	6.64	2.30–19.12	**0.000**	5.31	1.83–15.39	**0.002**
Platelets ($\times 10^9$/l)	1.00	1.00–1.01	**0.002**	1.00	1.00–1.00	0.319
Hemoglobin (g/l)	0.97	0.96–0.99	**0.002**	0.99	0.97–1.01	0.238
Mayo Endoscopic Score ≥ 1						
Age, years	0.98	0.94–1.03	0.493			
Sex (female *vs* male)	1.61	0.37–7.10	0.527			
Disease duration, years	0.92	0.84–1.00	0.060			
Biologic use (yes *vs* no)	0.11	0.02–0.59	**0.010**	0.16	0.03–0.93	**0.041**
Immunomodulator use (yes *vs* no)	0.37	0.08–1.64	0.191			
Albumin level (g/l)	0.86	0.75–0.99	**0.034**	0.88	0.75–1.03	0.114
C-reactive protein level (mg/l)	1.02	0.98–1.05	0.426			
CAR	1.52	0.58–4.01	0.396			
Platelets ($\times 10^9$/l)	1.00	1.00–1.01	0.249			
Hemoglobin (g/l)	0.96	0.92–1.01	0.089			

[†]C-reactive protein-to-albumin ratio (CAR) is included in another multivariable logistic regression analysis (model 2) to avoid multicollinearity with albumin and C-reactive protein (mean variance inflation factors > 13).

All variables were included as continuous variables except sex, smoking status, disease type, biologic use, and immunomodulator use, which were binary variables.

Bold values indicate significance, $P < 0.05$.

CAR, C-reactive protein-to-albumin ratio; CD, Crohn's disease; CI, confidence interval; OR, odds ratio; UC, ulcerative colitis.

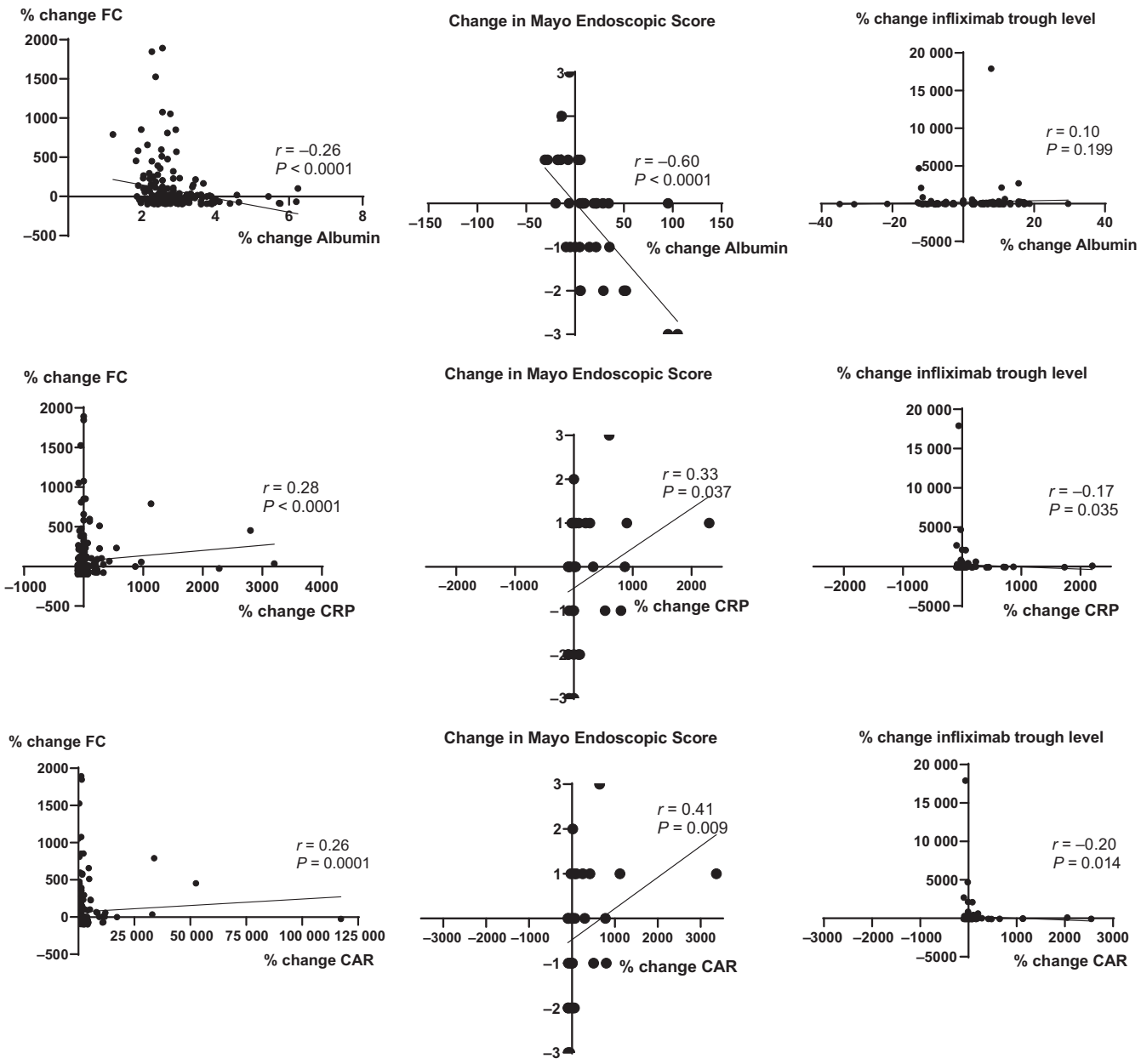

Figure 3 Comparison of % change of albumin, C-reactive protein and C-reactive protein-to-albumin ratio (CAR) with % change in fecal calprotectin (FC) ($n = 216$), change in Mayo Endoscopic Score ($n = 40$), and % change in infliximab trough levels ($n = 153$) using two consecutive time points in patients with inflammatory bowel disease. Spearman correlation coefficients were used for all graphs.

Discussion

Our study examined the role of albumin and CAR as noninvasive biomarkers of disease activity monitoring and infliximab trough levels in IBD. On assessment of intestinal inflammation, increasing disease activity was associated with reduced serum albumin levels and increased CAR. Both markers were independently associated with disease activity measured by FC. In patients receiving maintenance infliximab therapy, both markers correlated with infliximab trough levels and were independently associated with subtherapeutic levels.

We studied the role of albumin and CAR as surrogate markers of objective disease activity. The significant associations found in this study reflect others where albumin correlated with FC ($r = -0.45$ to -0.27),[28,29] and both albumin and CAR ($r = 0.59$) correlated with Mayo Endoscopic Score.[30,31] While CAR has been shown to be superior to its individual components in other studies[30] and predict active disease better than CRP alone,[1,10] our analysis showed only a slightly superior AUC for CAR compared to CRP and albumin. Similar findings were demonstrated in patients with CRP ≥5 mg/l, a group where active disease is suspected.

Table 4 Univariable and multivariable logistic regression analysis to determine associations with subtherapeutic (<5 μg/ml) infliximab trough levels

	Univariable logistic regression			Multivariable logistic regression		
	OR	95% CI	*P*-value	Adjusted OR	95% CI	*P*-value
Age, years	1.02	1.00–1.05	**0.035**	1.01	0.99–1.04	0.373
Sex (female *vs* male)	1.26	0.73–2.21	0.408			
Smoking status (yes *vs* no)	3.76	0.76–18.56	0.104			
Disease type (UC *vs* CD)	1.22	0.61–2.43	0.573			
Disease duration, years	1.00	0.96–1.03	0.782			
Time on infliximab, years	0.85	0.76–0.95	**0.004**	0.88	0.78–0.99	**0.030**
Immunomodulator use (yes *vs* no)	1.45	0.78–2.69	0.243			
Albumin level (g/l): model 1	0.80	0.73–0.88	**0.000**	0.85	0.77–0.95	**0.003**
C-reactive protein level (mg/l): model 1	1.11	1.04–1.20	**0.004**	1.07	1.00–1.14	0.068
CAR: model 2[†]	76.78	4.31–1369.47	**0.003**	34.03	2.18–532.02	**0.012**
Fecal calprotectin (μg/g) (<150 *vs* ≥150)	2.19	0.77–6.23	0.144			
Platelets ($\times 10^9$/l)	1.00	1.00–1.01	0.111			
Hemoglobin (g/l)	0.97	0.95–0.99	**0.011**	0.99	0.97–1.01	0.541

[†]C-reactive protein-to-albumin ratio (CAR) is included in another multivariable logistic regression analysis (model 2) to avoid multicollinearity with albumin and C-reactive protein (mean variance inflation factors > 8).

All variables included as continuous variables except sex, smoking status, disease type, immunomodulator use, and fecal calprotectin, which were binary variables.

Bold values indicate significance, $P < 0.05$.

CAR, C-reactive protein-to-albumin ratio; CD, Crohn's disease; CI, confidence interval; OR, odds ratio; UC, ulcerative colitis.

Albumin had a higher cutoff for detecting active disease in the FC cohort (<37 g/l), compared to the endoscopy cohort (<33 g/l). The two cohorts differed in disease type and acuity, with the FC cohort consisting mostly of patients with Crohn's disease and a median FC within normal range compared to a median Mayo 2 score in the endoscopy cohort, which may account for the different cutoffs. Another study of 601 patients with Crohn's disease showed a similar albumin cutoff of 36.8 g/l.[1] On the other hand, our CAR cutoff values (>0.09–0.17) were all lower than other studies in Crohn's disease (0.43–0.69)[1,10] and UC (0.18–0.6)[1,31] for detecting active disease. Potential explanations may include that other studies used clinical scores to define disease activity, known to have weak correlation with endoscopic inflammation[32] and UC studies included numerous patients with acute severe UC,[1] while our cohorts included routine outpatient procedures and a median FC within normal range. However, similar to other studies, all our cutoffs for active disease had low sensitivity compared to specificity,[1,10] thus limiting the clinical utility of albumin and CAR in disease activity assessment.

In the FC cohort, albumin, CRP, and CAR all independently predicted active disease, while in the endoscopy cohort (noting a smaller sample size), none of the markers were associated with active or severe disease. CAR has previously been shown to be an independent predictor of active disease according to symptomatic activity indices.[1] Longitudinally, albumin, CRP, and CAR all correlated with disease activity scores.

Overall, the findings of this study suggest that albumin and CAR are both able to identify active disease in patients with IBD, although perform equivalently or only marginally better than the already utilized serum marker, CRP. In clinical practice, the greatest potential of CAR may be in detecting severe Mayo 3 disease in UC, where sensitivity and specificity were ≥81% if CAR is >0.15. As both CRP and albumin are readily accessible and inexpensive,[1] CAR could help in quantifying the risk of severe endoscopic disease in inpatients and outpatients, allowing for early stratification of patients requiring urgent endoscopy and timely escalation of medical therapy.

This study also examined the association of albumin and CAR with infliximab trough levels. Infliximab trough levels are measured to help optimize infliximab efficacy in patients with IBD; however, they are costly and not widely available. Albumin and CAR increased and decreased, respectively, with increasing infliximab trough levels. This albumin pattern was also demonstrated in 728 patients with UC after 8 and 52 weeks of infliximab therapy,[4] and a positive correlation was seen between albumin and infliximab trough levels in patients with Crohn's disease (0.379, $P = 0.004$).[5] To our knowledge, no studies have compared CAR to infliximab trough levels.

In our study, albumin and CAR were only marginally superior to CRP for detecting subtherapeutic infliximab trough levels, albeit with suboptimal sensitivity and specificity. These markers were also independent predictors of subtherapeutic infliximab trough levels, while CRP and FC were not. However, on repeated measurement in the same patient, there was no correlation for albumin and poor correlation for CAR with change in infliximab levels. Taken together, this suggests that while albumin and CAR may be suggestive of subtherapeutic infliximab levels and could be a trigger for performing therapeutic drug monitoring in individual patients, they have minimal utility in a monitoring capacity.

We acknowledge limitations in our analysis, including its single-center, retrospective design. Blood testing was performed within 1 month of the disease activity assessment and 1 week of the infliximab trough levels, which may introduce other confounders. In the FC and infliximab cohorts, we used FC as a disease activity marker, which is slightly inferior to endoscopy. In the endoscopy cohort, the Mayo Endoscopic Score was performed by different endoscopists and was not confirmed by a blinded, central reading of endoscopic findings. In the infliximab

cohort, the FC levels were performed within 3 months of the infliximab trough levels, which may be an inaccurate representation of disease activity.

In conclusion, this study demonstrated that albumin and CAR are only modest discriminators of subtherapeutic infliximab levels and should not be used in a monitoring capacity to predict infliximab levels. In measuring objective disease activity in Crohn's disease and UC, albumin and CAR offered little more than CRP alone. In the absence of systemic inflammation, with a normal albumin and CRP, CAR offers very little as a prognostic tool. Ranges in CAR for this cohort of patients are too low, so to use it as a discretionary tool at these levels serves limited purpose. The potential utility of CAR was in detecting Mayo 3 disease in patients with UC. CAR could be a valuable additional serum marker measured in patients admitted with suspected acute severe UC, with the additional benefit of providing prognostic value as demonstrated in previous studies.

Patient consent

Given the retrospective design of the study and the use of anonymized patient data, the requirement for written informed consent was waived.

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Data availability statement. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1 Chen YH, Wang L, Feng SY, Cai WM, Chen XF, Huang ZM. The relationship between C-reactive protein/albumin ratio and disease activity in patients with inflammatory bowel disease. *Gastroenterol. Res. Pract.* 2020; **2020**: 3467419.
2 Mosli MH, Zou G, Garg SK *et al*. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: a systematic review and meta-analysis. *Am. J. Gastroenterol.* 2015; **110**: 802–19; quiz 20.
3 State M, Negreanu L, Voiosu T, Voiosu A, Balanescu P, Mateescu RB. Surrogate markers of mucosal healing in inflammatory bowel disease: a systematic review. *World J. Gastroenterol.* 2021; **27**: 1828–40.
4 Fasanmade AA, Adedokun OJ, Olson A, Strauss R, Davis HM. Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. *Int. J. Clin. Pharmacol. Ther.* 2010; **48**: 297–308.
5 Grinman AB, de Souza M, Bouskela E, Carvalho ATP, de Souza HSP. Clinical and laboratory markers associated with anti-TNF-alpha trough levels and anti-drug antibodies in patients with inflammatory bowel diseases. *Medicine*. 2020; **99**: e19359.
6 Lewis JD. The utility of biomarkers in the diagnosis and therapy of inflammatory bowel disease. *Gastroenterology*. 2011; **140**: 1817–26.e2.
7 Cacheux W, Seksik P, Lemann M *et al*. Predictive factors of response to cyclosporine in steroid-refractory ulcerative colitis. *Am. J. Gastroenterol.* 2008; **103**: 637–42.
8 Monterubbianesi R, Aratari A, Armuzzi A *et al*. Infliximab three-dose induction regimen in severe corticosteroid-refractory ulcerative colitis: early and late outcome and predictors of colectomy. *J. Crohns Colitis*. 2014; **8**: 852–8.
9 Henderson P, Kennedy NA, Van Limbergen JE *et al*. Serum C-reactive protein and CRP genotype in pediatric inflammatory bowel disease: influence on phenotype, natural history, and response to therapy. *Inflamm. Bowel Dis.* 2015; **21**: 596–605.
10 Qin G, Tu J, Liu L *et al*. Serum albumin and C-reactive protein/albumin ratio are useful biomarkers of Crohn's disease activity. *Med. Sci. Monit.* 2016; **22**: 4393–400.
11 Yagi S, Furukawa S, Shiraishi K *et al*. Effect of disease duration on the association between serum albumin and mucosal healing in patients with ulcerative colitis. *BMJ Open Gastroenterol.* 2021; **8**: e000662.
12 Ho GT, Mowat C, Goddard CJ *et al*. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Aliment. Pharmacol. Ther.* 2004; **19**: 1079–87.
13 Lees CW, Heys D, Ho GT *et al*. A retrospective analysis of the efficacy and safety of infliximab as rescue therapy in acute severe ulcerative colitis. *Aliment. Pharmacol. Ther.* 2007; **26**: 411–9.
14 Dubinsky MC, Mendiolaza ML, Phan BL, Moran HR, Tse SS, Mould DR. Dashboard-driven accelerated infliximab induction dosing increases infliximab durability and reduces immunogenicity. *Inflamm. Bowel Dis.* 2022; **28**: 1375–85.
15 Strik AS, Lowenberg M, Mould DR *et al*. Efficacy of dashboard driven dosing of infliximab in inflammatory bowel disease patients; a randomized controlled trial. *Scand. J. Gastroenterol.* 2021; **56**: 145–54.
16 Wu J, Tan W, Chen L, Huang Z, Mai S. Clinicopathologic and prognostic significance of C-reactive protein/albumin ratio in patients with solid tumors: an updated systemic review and meta-analysis. *Oncotarget*. 2018; **9**: 13934–47.
17 Haider Kazmi SJ, Zafar MT, Zia BF *et al*. Role of serum C-reactive protein (CRP)/albumin ratio in predicting the severity of acute pancreatitis: a retrospective cohort. *Ann. Med. Surg.* 2022; **82**: 104715.
18 Kim MH, Ahn JY, Song JE *et al*. The C-reactive protein/albumin ratio as an independent predictor of mortality in patients with severe sepsis or septic shock treated with early goal-directed therapy. *PloS One*. 2015; **10**: e0132109.
19 Zhou FS, Gao N, Sun X *et al*. C-reactive protein/abumin ratio is a useful biomarker for predicting the mucosal healing in the Crohn disease: a retrospective study. *Medicine*. 2021; **100**: e24925.
20 Gibson DJ, Hartery K, Doherty J *et al*. CRP/albumin ratio: an early predictor of steroid responsiveness in acute severe ulcerative colitis. *J. Clin. Gastroenterol.* 2018; **52**: e48–52.
21 Con D, Andrew B, Nicolaides S, van Langenberg DR, Vasudevan A. 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. *Intest. Res.* 2022; **20**: 101–13.
22 Gisbert JP, Bermejo F, Perez-Calle JL *et al*. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. *Inflamm. Bowel Dis.* 2009; **15**: 1190–8.
23 Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N. Engl. J. Med.* 1987; **317**: 1625–9.
24 Ward MG, Rosella O, Rosella G, Martin C, Gibson PR. Comparison of SB2-infliximab with originator-infliximab in the measurement of

serum concentrations: a short communication. *Ther. Drug Monit.* 2021; **43**: 692–5.
25 Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S, American Gastroenterological Association Institute Clinical Guidelines C. American Gastroenterological Association Institute Guideline on therapeutic drug monitoring in inflammatory bowel disease. *Gastroenterology*. 2017; **153**: 827–34.
26 Kang B, Choi SY, Choi YO *et al*. Infliximab trough levels are associated with mucosal healing during maintenance treatment with infliximab in paediatric Crohn's disease. *J. Crohns Colitis*. 2019; **13**: 189–97.
27 Oh TK, Song IA, Lee JH. Clinical usefulness of C-reactive protein to albumin ratio in predicting 30-day mortality in critically ill patients: a retrospective analysis. *Sci. Rep.* 2018; **8**: 14977.
28 Fukunaga S, Kuwaki K, Mitsuyama K *et al*. Detection of calprotectin in inflammatory bowel disease: fecal and serum levels and immunohistochemical localization. *Int. J. Mol. Med.* 2018; **41**: 107–18.
29 Lee SH, Kim MJ, Chang K *et al*. Fecal calprotectin predicts complete mucosal healing and better correlates with the ulcerative colitis endoscopic index of severity than with the Mayo endoscopic subscore in patients with ulcerative colitis. *BMC Gastroenterol.* 2017; **17**: 110.
30 Yagi S, Furukawa S, Shiraishi K *et al*. The albumin to globulin ratio is associated with clinical outcome in Japanese patients with ulcerative colitis. *Ann. Coloproctol.* 2023; **39**: 155–63.
31 Sayar S, Kurbuz K, Kahraman R *et al*. A practical marker to determining acute severe ulcerative colitis: CRP/albumin ratio. *North. Clin. Istanb.* 2020; **7**: 49–55.
32 Francisco Guilherme Cancela EP, Rosa RM, da Cunha PFS, de Souza SCS, de Abreu Ferrari ML. Faecal calprotectin is the biomarker that best distinguishes remission from different degrees of endoscopic activity in Crohn's disease. *BMC Gastroenterol.* 2020; **20**: 35.