

Prealbumin and Retinol-Binding Protein 4: The Promising Inflammatory Biomarkers for Identifying Endoscopic Remission in Crohn's Disease

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Objective: Endoscopic remission is the primary therapeutic target and associated with clinical outcome in Crohn's disease (CD). Non-invasive and accurate biomarkers are important in monitoring endoscopic remission frequently. Our study aimed at investigating the predictive capacity of prealbumin and retinol-binding protein 4 (RBP4) for identifying endoscopic remission.

Methods: From June 2018 to December 2020, 515 endoscopy procedures (332 in the training cohort and 183 in the validation cohort) were enrolled in this multicentre retrospective cohort study. Blood samples were collected for prealbumin or RBP4 testing with 7 days before the endoscopy. A simple Endoscopic Score for CD (SES-CD) was performed to evaluate endoscopic activity and defined endoscopic remission. The area under receiver operating characteristic curve (AUROC), sensitivity, specificity, positive predictive value and negative predictive value were performed to assess the predictive capacity of the biomarkers.

Results: Serum concentration of prealbumin and RBP4 was demonstrated to be higher in patients with endoscopic remission and significantly negatively correlated with SES-CD in the training cohort. The AUROC of prealbumin and specificity of prealbumin and RBP4 were larger than that of C-reactive protein in the training cohort and the validation cohort. The model combining prealbumin and faecal calprotectin had the largest AUROC (0.842 [95% CI: 0.775–0.908]). Furthermore, in both cohorts, prealbumin had a larger AUROC than C-reactive protein for identifying endoscopic remission in patients with anti-tumour necrosis factor therapy.

Conclusion: Prealbumin and RBP4 were promising biomarkers for identifying endoscopic remission, especially in patients with anti-tumour necrosis factor therapy.

Keywords: Crohn's disease, endoscopic remission, prealbumin, retinol-binding protein 4

Introduction

Crohn's disease (CD) is a disabling condition characterized by chronic inflammation all around the gastrointestinal tract with a destructive course.¹ With the development of treat-to-target strategy and advanced therapies, the therapeutic target of CD has been converted from clinical remission to endoscopic remission, which is associated with improved outcome in patients with CD.² However, endoscopy, the optimal approach to assess endoscopic remission, is invasive, costly and lacks the accessibility to popularize under current health care landscapes. Therefore, heterogeneous group of surrogate

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assessing tools, such as serological and faecal biomarkers, are in an acute requirement for monitoring the disease activity.³

Presently, faecal calprotectin (FC) and C-reactive protein (CRP) are two reliable biomarkers in the assessment of endoscopic activity.⁴ FC is a promising biomarker in CD with high accuracy to evaluate the inflammatory process.⁵ Nevertheless, invalided optimal cut-off values and low utilization of FC would limit its ability in clinical practice.⁶ Compared with FC, CRP has been utilized more widely in clinical practice. However, since the serum concentration of CRP is affected by gene polymorphism and lacks clear correlation with mucosal activity, it still requires further research to seek novel serum biomarkers with high predictive capacity and convenience in identifying endoscopic remission.^{7,8}

Prealbumin and retinol-binding protein 4 (RBP4) are traditionally considered as nutritional biomarkers, and they combine together to play an important role in the transportation of vitamin A.⁹ In the past decades, prealbumin and RBP4 were demonstrated to be acute-phase reactants, and their concentration would alter during acute or chronic inflammatory states, such as sepsis, coronary artery disease and rheumatoid arthritis.^{10–12} Furthermore, some pro-inflammatory cytokines including interleukin (IL)-6 and tumour necrosis factor (TNF)- α can affect serum level of prealbumin.^{13,14} The above studies suggested that prealbumin and RBP4 may be potential biomarkers for reflecting inflammation conditions. Our study is aimed at investigating the predictive capacity of prealbumin and RBP4 in distinguishing endoscopic remission from endoscopic activity in CD.

Materials and Methods

Patients and Study Design

Patients undergoing endoscopy procedures at the First Affiliated Hospital of Sun Yat-Sen University from June 2018 to December 2020 or at the Six Affiliated Hospital of Sun Yat-Sen University from June 2020 to December 2020 were recruited in this multicentre retrospective cohort study. Other inclusion criteria included: (1) a confirmed diagnosis of CD based on clinical symptoms, imaging presentations and histological data; (2) available blood samples for prealbumin or RBP4 testing within 7 days before the endoscopy procedures. Patients, who rejected to the recruitment, suffered infection within 3 months before the endoscopy procedure or had a diagnosis of upper gastrointestinal CD were excluded from this study.

Four hundred and thirty-seven samples from the First Affiliated Hospital of Sun Yat-Sen University and 78 samples from the Six Affiliated Hospital of Sun Yat-Sen University were eligible in the study and divided into two independent cohorts. The training cohort included samples obtained from the First Affiliated Hospital of Sun Yat-Sen University between June 2018 and May 2020. The validation cohort recruited samples obtained from the First Affiliated Hospital of Sun Yat-Sen University and the Six Affiliated Hospital of Sun Yat-Sen University between June 2020 and December 2020.

Demographic and Clinical Variables

Demographic and clinical variables, including gender, age at endoscopy procedures, age at diagnosis, disease location, disease behaviour, history of CD-related surgery, body mass index, medication use and endoscopy activity situation, were reported in this study. Age at diagnosis, disease location, and disease behaviour was described following the Montreal Classifications.¹⁵ Medication use referred to more than 3 months continuous use of 5-aminosalicylic acid, thiopurine, thalidomide, corticosteroids or anti-TNF agents.

Biomarker Testing

Blood samples and faecal samples were collected within 7 days before endoscopy procedures. Blood prealbumin concentrations were measured using the latex immune turbidimetry assay with a kit from beckman coulter (CA 92821, USA, OSR6175). The RBP4 concentrations were measured using a latex immune turbidimetry assay with a kit from Labco (Co-Health (Beijing) Laboratories Co., Beijing, China, GG21B2). Serum CRP levels were detected through scattering rate turbidimetry method (Siemens, Marburg, Germany, OQIY21). The FC levels were tested using immunofluorescence chromatography (Guangzhou Forreal Biotechnology Co., Guangzhou, China).

Definition of Endoscopic Remission and Activity

Simple Endoscopic Score for Crohn's Disease (SES-CD) was used to describe the endoscopic activity situation.¹⁶ Two surgeons, blinded to the biomarker testing result, performed SES-CD for all endoscopies in the study, respectively. Endoscopic remission was defined as SES-CD \leq 2. Endoscopic activity was defined as SES-CD \geq 3. Furthermore, endoscopic activity was divided into three

degrees based on SES-CD: mild activity (3–6), moderate activity (7–15) and severe activity (≥ 16).

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of the First Affiliated Hospital of Sun Yat-Sen University [No. IIT-2021-130]. All patients participated in this study had written informed consent.

Statistics Analysis

Continuous and categorical variables were presented as median (interquartile range, IQR) and n (%), respectively. The Mann–Whitney test and χ^2 test were performed to evaluate the difference for continuous and categorical variables, respectively. Spearman's regression was used for correlation analysis. A p -value less than 0.05 was considered to be statistically significant. The receiver operating characteristic (ROC) analysis was performed to calculate the area under ROC curve (AUROC). The cut-off value was determined by the Youden index in the training cohort and acted as a threshold for the biomarkers in the validation cohort. AUROC, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were used to assess the predictive capacity of the biomarkers for identifying endoscopic remission. We performed Pearson's χ^2 test to assess the difference in sensitivity and specificity of the biomarkers for identifying endoscopic remission. Logistic regression analysis was performed to build the model combined with prealbumin and FC. All statistical analysis was performed through R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients Characteristics

From June 2018 to December 2020, 515 endoscopy procedures (332 samples in the training cohort and 183 samples in the validation cohort) were enrolled in this cohort study (Table 1). In the training cohort, 242 (72.9%) patients were male, and the median age at endoscopic procedures was 28.0 years (IQR: 21.9–36.0). According to disease location, 68 (20.5%), 38 (11.4%), 226 (68.1) were ileal, colonic and ileocolonic, respectively. Fifty-nine (17.8%) patients received continuous anti-tumour necrosis factor (TNF) therapy more than 3 months before the endoscopy and 61 (18.4%) of samples were in endoscopic remission. In the validation cohort, only a percentage of patients with history

of CD-related surgery (15.3% vs 22.9%; $p = 0.040$) and prior use of thiopurine (26.2% vs 17.5%; $p = 0.019$) differed significantly from that in the training cohort. Other demographic and clinical characteristics are showed in Table 1.

Relationship Between Biomarkers and Endoscopy Activity in the Training Cohort

First, we performed Mann–Whitney test to investigate the discrepant concentration of potential biomarkers including prealbumin, RBP4, vitamin D, albumin, globulin, CRP and FC, between endoscopic remission and endoscopic activity (Figure 1 and Supplement Table 1). Significantly higher concentration of prealbumin (remission vs activity: 254.0 [IQR 216.2–292.0] mg/l vs 184.0 [IQR 147.0–225.0] mg/L, $p < 0.001$; Figure 1A), RBP4 (remission vs activity: 27.9 [IQR 22.8–32.1] mg/l vs 20.7 [IQR 16.3–25.8] mg/L, $p < 0.001$; Figure 1B), vitamin D ($p = 0.018$; Supplement Table 1) and albumin ($p < 0.001$; Supplement Table 1) was shown in endoscopic remission compared with endoscopic activity, while CRP ($p < 0.001$; Figure 1C), FC ($p < 0.001$; Figure 1D) and globulin ($p < 0.001$; Supplement Table 1) concentrations were significantly lower in patients with endoscopic remission. Furthermore, prealbumin (0.773 [95% CI: 0.705–0.841]), RBP4 (0.728 [95% CI: 0.646–0.809]) and CRP (0.759 [95% CI: 0.692–0.826]) had larger AUROC than other serum biomarkers in distinguishing endoscopic remission from endoscopic activity (Supplement Table 2).

We next assessed the strength of the association between prealbumin, RBP4, CRP and endoscopy activity using Spearman correlation analysis. As shown in Table 2, prealbumin ($r = -0.588$, $p < 0.01$) was strongly correlated with SES-CD and RBP4 ($r = -0.485$, $p < 0.01$) was moderately correlated with SES-CD negatively. In addition to SES-CD, prealbumin ($r = -0.761$, $p < 0.01$) and RBP4 ($r = -0.626$, $p < 0.01$) also had negative correlation with CRP.

Prealbumin and RBP4 Could Identify Endoscopic Remission

In order to assess the predictive capacity of prealbumin and RBP4 for distinguishing endoscopic remission from endoscopic activity, ROC analysis was performed in both training cohort (Table 3) and validation cohort (Table 4). In the training cohort, the result showed that the AUROC of prealbumin (0.773 [95% CI 0.705–0.841]) in identifying endoscopic remission was larger than that of RBP4 (0.728 [95% CI 0.646–0.809]) and CRP (0.759 [95% CI 0.692–0.826]), but

Table 1 Demographic and Clinical Characteristics of Patients in the Study

Characteristics	Training Cohort	Validation Cohort	p value
Endoscopic procedures	332	183	
Gender, male	242 (72.9)	127 (69.4)	0.400
Age at endoscopic procedures, year	28.0 (21.9–36.0)	26.0 (22.0–33.0)	0.264
Age at diagnosis, year			0.603
A1: ≤16	48 (14.5)	22 (12.0)	
A2: 17–40	235 (70.8)	137 (74.9)	
A3: >40	49 (14.7)	24 (13.1)	
CD location			0.268
L1: Ileal	68 (20.5)	30 (16.4)	
L2: Colonic	38 (11.4)	16 (8.7)	
L3: Ileocolonic	226 (68.1)	137 (74.9)	
CD behaviour			0.627
B1: Non-stricturing, non-penetrating	162 (48.8)	95 (51.9)	
B2: Stricturing	108 (32.5)	52 (28.4)	
B3: Penetrating	62 (18.7)	36 (19.7)	
Perianal disease	155 (46.7)	80 (43.7)	0.517
History of CD-related surgery	76 (22.9)	28 (15.3)	0.040
BMI, kg/m ²	18.3 (16.8–20.5)	19.0 (16.9–20.7)	0.304
Medication			
5-aminosalicylic acid	65 (19.6)	32 (17.5)	0.561
Thiopurine	58 (17.5)	48 (26.2)	0.019
Thalidomide	26 (7.8)	7 (3.8)	0.076
Corticosteroids	15 (4.5)	10 (5.5)	0.632
Anti-TNF agents	59 (17.8)	31 (16.9)	0.812
SES-CD	7 (3–16)	7 (4–15)	0.999
Endoscopic remission	61 (18.4)	32 (17.5)	0.965
Endoscopic activity			
Mild activity (SES-CD: 3–6)	93 (28.0)	51 (27.9)	
Moderate activity (SES-CD: 7–15)	93 (28.0)	55 (30.0)	
Severe activity (SES-CD ≥16)	85 (25.6)	45 (24.6)	

Notes: Continuous and categorical variables are presented as median (interquartile range) and n (%), respectively.

Abbreviations: CD, Crohn's disease; BMI, body mass index; Anti-TNF, anti-tumour necrosis factor; SES-CD, simple endoscopic score for Crohn's disease.

smaller than FC's (0.815 [95% CI 0.727–0.904]). The model combining FC and prealbumin had the largest AUROC (0.842 [95% CI: 0.775–0.908]). Moreover, the sensitivity of prealbumin at a cut-off value 215.5 mg/L was 0.770 (95% CI 0.642–0.865) and 0.697 (95% CI 0.638–0.751), respectively. RBP4 at a cut-off value of 24.8 mg/L had a sensitivity of 0.723 (95% CI 0.571–0.839) and a specificity of 0.702 (95% CI 0.639–0.759). We also observed that both prealbumin and RBP4 had higher specificity than CRP (0.587 [95% CI 0.525–0.646]; $p = 0.007$ for prealbumin vs CRP; $p = 0.007$ for RBP4 vs CRP; [Table 3](#)). The sensitivity of FC (0.704 [95% CI 0.497–0.855]) was marginal lower than that of prealbumin and RBP4, but the differences were not significant ($p = 0.505$ for prealbumin vs FC; $p = 0.865$ for RBP4 vs FC) ([Table 3](#)). Although there was lack of head-to-head comparison among prealbumin, RBP4 and FC in the entire training cohort, we performed a ROC

analysis in a smaller cohort (n [total] = 143; n [endoscopic remission] = 22) containing participants with all the data of prealbumin, RBP4 and FC, and found that prealbumin (0.832 [95% CI: 0.764–0.901]) and RBP4 (0.803 [95% CI: 0.726–0.880]) had similar AUROCs with FC (0.816 [95% CI: 0.718–0.915]) ([Supplement Figure 1](#)). Due to the limited sample sizes of endoscopic remission in this cohort, more research was necessary to validate the result.

In the validation cohort, prealbumin also had a larger AUROC (0.817 [95% CI 0.754–0.880]) than that of RBP4 (0.764 [95% CI 0.686–0.842]) and CRP (0.804 [95% CI 0.732–0.876]; [Table 4](#)). At a threshold of 215.5 mg/L, prealbumin had a sensitivity and specificity of 0.875 (95% CI 0.701–0.959) and 0.702 (95% CI 0.621–0.772). The specificity of prealbumin was superior to that of CRP (specificity: 0.556 [95% CI 0.473–0.663]; $p = 0.009$) and

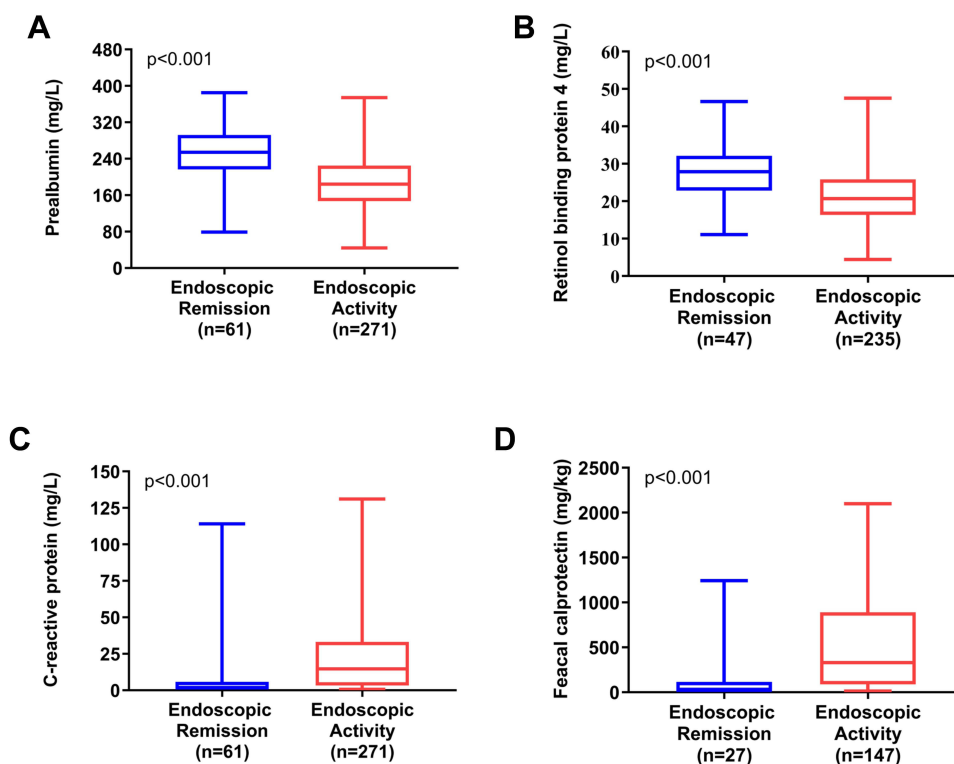


Figure 1 Discrepant concentration of prealbumin (A), retinol-binding protein 4 (B), C-reactive protein (C) and faecal calprotectin (D) between endoscopic remission and endoscopic activity in the training cohort. The box plots present median and interquartile range of the data, and the whiskers show the maximum and minimum values.

the sensitivity of prealbumin is not inferior to that of CRP (sensitivity: 0.844 [95% CI 0.665–0.941]; $p = 0.719$). Furthermore, sensitivity (0.862 [95% CI: 0.674–0.955]) and specificity (0.572 [95% CI: 0.485–0.655]) of RBP4 at a threshold of 24.8 mg/L were similar with that of CRP ($p = 0.522$ for sensitivity; $p = 0.782$ for specificity).

Prealbumin Was Superior to CRP in Patients with Anti-TNF Therapy

To investigate the predictive capacity of prealbumin for identifying endoscopic remission in different CD patients, we developed further subgroup analysis. As the result showed in Figure 2, prealbumin had a larger AUROC for identifying endoscopic remission than CRP in both training cohort (0.808

[95% CI:0.678–0.973] vs 0.716 [95% CI: 0.559–0.873]) and validation cohort (0.807 [95% CI:0.670–0.974] vs 0.753 [95% CI: 0.549–0.958]). Regarding patients with ileal disease, we found that prealbumin had a better predictive capacity than CRP in the validation cohort (0.726 [95% CI:0.589–0.684] vs 0.569 [95% CI: 0.422–0.716]), while both prealbumin and CRP were poor in predicting endoscopic remission in the validation cohort (Supplement Figure 2).

Discussion

Endoscopic remission is now the primary therapeutic target in CD. Although endoscopy is the gold standard in assessing endoscopic activity, it is invasive, costly and unfavourable for CD patients. Therefore, identification of

Table 2 Spearman Correlation Analysis Between Prealbumin, RBP4, CRP and SES-CD in the Training Cohort

	Prealbumin	RBP 4	CRP	SES-CD
Prealbumin	1.000*	0.909*	−0.761*	−0.588*
RBP 4	—	1.000*	−0.626*	−0.485*
CRP	—	—	1.000*	0.615*
SES-CD	—	—	—	1.000*

Note: * $p < 0.01$.

Abbreviations: RBP4, retinol-binding protein 4; CRP, C-reactive protein; SES-CD, simple endoscopic score for Crohn's disease.

Table 3 The Predictive Capacity of Prealbumin, Retinol-Binding Protein 4, CRP and FC for Identifying Endoscopic Remission in the Training Cohort

	AUROC (95% CI)	Cut-Off Value	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Prealbumin (mg/L) [N= 332]	0.773 (0.705–0.841)	215.5	0.770 (0.642–0.865)	0.697 (0.638–0.751)	0.364 (0.283–0.454)	0.931 (0.885–0.963)
RBP 4 (mg/L) [N= 282]	0.728 (0.646–0.809)	24.8	0.723 (0.571–0.839)	0.702 (0.639–0.759)	0.327 (0.240–0.427)	0.927 (0.876–0.959)
CRP (mg/L) [N= 332]	0.759 (0.693–0.826)	8.7	0.820 (0.696–0.902)	0.587 (0.525–0.646)	0.309 (0.240–0.387)	0.935 (0.884–0.966)
FC (mg/kg) [N= 174]	0.815 (0.727–0.904)	54.5	0.704 (0.497–0.855)	0.844 (0.772–0.896)	0.452 (0.302–0.388)	0.939 (0.880–0.972)
FC+ prealbumin [N= 174]	0.842 (0.775–0.908)	0.107	0.963 (0.791–0.998)	0.646 (0.563–0.722)	0.333 (0.233–0.450)	0.990 (0.935–0.999)

Abbreviations: N, number of available participants; RBP4, retinol-binding protein 4; CRP, C-reactive protein; FC, faecal calprotectin; AUROC, the area under ROC curve; PPV, positive predictive value; NPV, negative predictive value.

Table 4 The Predictive Capacity of Prealbumin, Retinol-Binding Protein 4 and CRP and for Identifying Endoscopic Remission in the Validation Cohort

	AUROC (95% CI)	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Prealbumin (mg/L)	0.817 (0.754–0.880)	215.5	0.875 (0.701–0.959)	0.702 (0.621–0.772)	0.384 (0.274–0.505)	0.964 (0.904–0.988)
RBP 4 (mg/L)	0.764 (0.686–0.842)	24.8	0.862 (0.674–0.955)	0.572 (0.485–0.655)	0.298 (0.205–0.409)	0.952 (0.875–0.984)
CRP (mg/L)	0.804 (0.732–0.876)	8.7	0.844 (0.665–0.941)	0.556 (0.473–0.363)	0.287 (0.201–0.391)	0.944 (0.868–0.979)

Abbreviations: RBP4, retinol-binding protein 4; CRP, C-reactive protein; AUROC, the area under ROC curve; PPV, positive predictive value; NPV, negative predictive value.

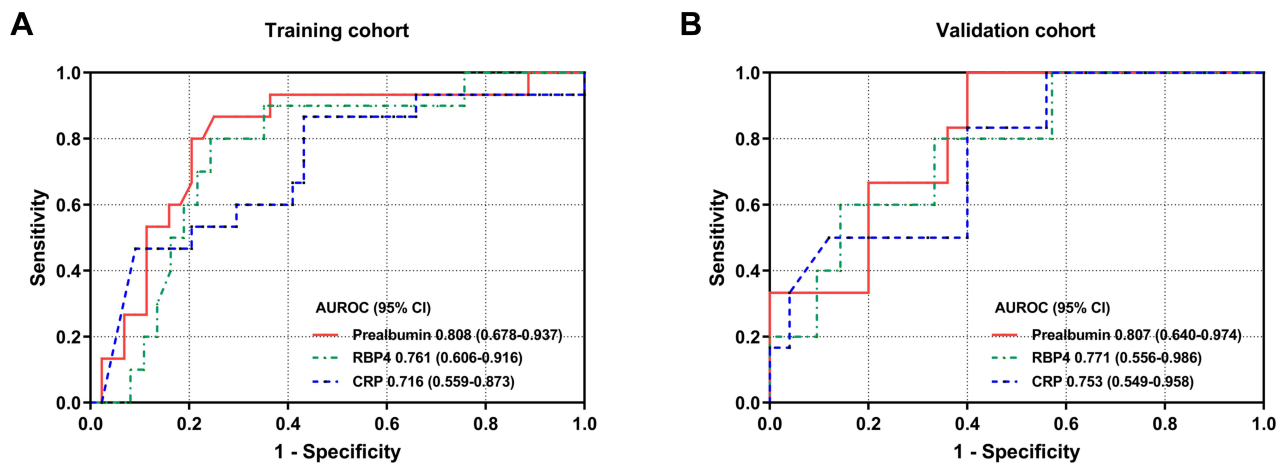


Figure 2 Receiver operating characteristic (ROC) curve of prealbumin, retinol-binding protein 4 (RBP4) and C-reactive protein (CRP) for identifying endoscopic remission in patients with anti-tumour necrosis factor agents use in the training cohort (A) or the validation cohort (B).

non-invasive and widely used biomarkers is important in monitoring endoscopic activity frequently. In this study, we demonstrated that prealbumin as well as RBP4 concentration was significantly higher in endoscopic remission than endoscopic activity and had a negative correlation with SES-CD. Further ROC analysis showed that prealbumin had a larger AUROC in identifying endoscopic remission when compared with CRP, especially in patients with anti-TNF therapy. The results of our study indicated the potential role of prealbumin and RBP4 in monitoring endoscopic remission in patients with CD.

Prealbumin, namely transthyretin, is synthesized in the liver and serves as a transporter of thyroid hormone and vitamin A.¹⁷ In addition to its function of transport, prealbumin also acts as a significant indicator in reflecting nutritional status, or even predicting the effect of nutritional therapy in some diseases, such as CD.¹⁸ For instance, Xu et al illustrated that the change of prealbumin concentration from baseline to the first week of exclusive enteral nutrition treatment could predict the following clinical remission in colonic CD patients.¹⁹ Moreover, previous studies have found that the concentration of prealbumin is associated with the disease activity of inflammatory states such as rheumatoid arthritis and tuberculosis infection.^{20,21} Similar to these studies, we firstly demonstrated that serum prealbumin level was strongly correlated with endoscopic disease severity and had a good capacity in distinguishing endoscopic remission from endoscopic activity. The malnutritional state, as well as the high concentration of IL-6, which could reduce serum prealbumin concentration, in CD patients with endoscopic activity, may explain the findings of our research, while

further basic study needs to be performed to attest to this hypothesis.²²

In this study, we determined the ability of RBP4, another nutritional-inflammatory biomarker, in identifying endoscopic remission. We discovered that RBP4 was similar but slightly inferior to prealbumin in its correlation with CRP and SES-CD and its predictive ability in identifying endoscopic activity. The close relationship between RBP4 and prealbumin seems to explain this result in our study. Previous studies have demonstrated that RBP4 also exhibited an important function in transporting vitamin A and could be combined with prealbumin to compose a retinol circulating complex, which stabilized the structure of prealbumin and prevented RBP4 from filtration through glomerulus.^{18,23} Therefore, the alteration of RBP4 or prealbumin concentration may exert an implication on the other one's concentration. Because prealbumin had a stronger correlation with endoscopic activity than RBP4, we hypothesised that the intestinal inflammation and circulating pro-inflammatory cytokine in CD patients mainly reduced the serum prealbumin concentration, which then affected the serum level of RBP4.

Besides prealbumin and RBP4, other nutritional indicators such as vitamin D, albumin, uric acid-to-creatinine ratio are considered to be associated with the disease or endoscopic activity in CD.²⁴⁻²⁶ Among these indicators, vitamin D is one of the most widely studied biomarkers in CD and is effective in the assessment of disease activity, prediction of clinical outcome and response to biologics therapy.²⁷ Similar to vitamin D, prealbumin and RBP4 are demonstrated to play an important role in the activity

assessment and prognosis prediction of some inflammatory diseases.^{17,28,29} Furthermore, previous study and our study indicated that the predictive capacity of prealbumin and RBP4 was likely superior to vitamin D in identifying endoscopic remission.³⁰ This suggests that prealbumin or RBP4 may be promising biomarkers with broad application in CD, and more research needs to be carried out.

It is important to mention that, in this study, prealbumin was demonstrated to be more accurate in predicting endoscopic remission than CRP, one of the most widely utilized biomarkers in clinical practice. In particular, the AUROC of prealbumin in patients with anti-TNF therapy was obviously superior to that of CRP. Anti-TNF agents are one of the most significant and effective therapy in inducing and maintaining remission in CD. And frequent monitoring of disease or endoscopic activity during anti-TNF therapy was momentous for assessing therapeutic response and selecting optimal approach.³¹ Therefore, based on the result of this study, we suggested the routine utilization of prealbumin in monitoring disease activity during anti-TNF therapy in CD. In addition to the better predictive capacity, prealbumin has an advantage over CRP in identifying endoscopic remission since the serum concentration of prealbumin was not found to be affected by ethnic differences or gene polymorphisms.^{7,17} Thus, we believe prealbumin would become a reliable and universal biomarker for monitoring endoscopic remission and benefit more patients with CD.

There are some limitations in our study. First, this study was a retrospective cohort study, recruiting patients who underwent prealbumin or RBP4 testing within 7 days before endoscopy, which may cause selection bias. Second, we lacked a head-to-head comparison in the entire cohort between prealbumin, RBP4 and FC, which was currently considered the most effective biomarker in disease activity assessment. In order to address this problem to some extent, we performed an ROC analysis on participants that had all data of prealbumin, RBP4 and FC and found similar capacities for these biomarkers to identify endoscopic remission. Nevertheless, only a small number of participants with endoscopic remission were included in this analysis, thus confirming the result necessitated more research with large sample sizes. Moreover, there was only a small cohort of patients with colonic disease in this study, so the predictive capacity of prealbumin and RBP4 in colonic CD patients required further validations.

In conclusion, prealbumin and RBP4 are promising biomarkers for assessing endoscopic activity and identifying endoscopic remission in patients with CD. The application of prealbumin and RBP4 for frequent monitoring of endoscopic activity may be significant for the treat-to-target approaches and benefit CD patients.

Data Availability

The data supporting the result in this study are available from the corresponding author (Shenghong Zhang, China) on request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The Authors declare that there is no conflict of interest.

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