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RESEARCH ARTICLE

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C-reactive protein/albumin ratio and IL-6 are associated with disease activity in patients with ulcerative colitis

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Abstract

Background: Cytokines are key mediators of the inflammation in ulcerative colitis (UC); there are inconsistent data on cytokines profile in patients with UC. C-reactive protein/albumin ratio (CRP/ALB) has also been found as an inflammatory indicator. However, the role of CRP/ALB in UC remains unclear. We aimed to evaluate the CRP/ALB ratio and cytokines profile in patients with UC. We further explore the association between CRP/ALB and inflammatory markers, such as erythrocyte sedimentation rate (ESR), fecal calprotectin (FC) and cytokines.

Methods: One hundred thirty UC patients and 65 controls were included in the study. Clinical and laboratory findings were retrospectively reviewed; differences in variables between two groups were examined using the Mann–Whitney *U*-test. The association between CRP/ALB, cytokines, and clinical parameters was determined by Spearman's correlation test.

Results: CRP/ALB levels were significantly elevated in active UC patients. The optimal cutoff level of the CRP/ALB was 0.083. The patients with active UC had a median interleukin-6 (IL-6) level of 7.715 pg/ml (interquartile ranges, IQR 3.475–14.63), which was significantly higher than those in remission (2.95 pg/ml, IQR 2.17–5.44) ($p < 0.001$). Positive correlations between CRP/ALB and inflammatory markers were also observed.

Conclusions: Our results suggest that CRP/ALB and IL-6 could be potential biomarkers for assessment of clinical activity in Chinese patients with UC.

KEYWORDS
C-reactive protein/albumin ratio, cytokines profile, disease activity, ulcerative colitis

1 | INTRODUCTION

Ulcerative colitis (UC) is an idiopathic inflammatory disorder affecting the large intestine. The incidence of UC is markedly increasing in China.[1] The clinical symptoms include diarrhea, bloody stool, and abdomen pain. It is characterized by relapsing–remitting intestinal inflammation.[2] The etiology of UC remains unclear. Genetics, environmental factors, impaired immune response, and gut microbiota have been implicated in the initiation and pathogenesis of UC.[3] It has been generally accepted that imbalance between proinflammatory

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and anti-inflammatory cytokines may be a contributing factor in UC.[4]

C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin (FC) are commonly used for the measurement of disease severity.[2,5,6] C-reactive protein/albumin ratio (CRP/ALB) has also been found as an inflammatory indicator. It is simple and cheap. It has a prognostic role in cancer patients, such as pancreatic cancer,[7] colorectal cancer,[8] and small-cell lung cancer.[9] Evidence suggested that CRP/ALB was related to disease activity, such as inflammatory bowel disease (IBD)[10] and acute cholecystitis.[11] However, the potential role of CRP/ALB in UC remains unclear. We evaluate the relationship between CRP/ALB ratio and disease activity and its association with inflammatory parameters, including PLT, ESR, FC, and cytokines.

Cytokines are key mediators of the inflammation. It is reported that interleukin 1 beta (IL-1β), interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-α), and IL-6 play a prominent role in the inflammatory response. Results concerning the cytokines profile in UC were conflicting.[12] Some studies have observed that concentrations of proinflammatory cytokines were markedly elevated in patients with UC.[13] By contrast, several studies did not observe increased level of cytokines.[14,15]

Cytokines level and CRP/ALB reflect the inflammatory status of IBD. We aimed to evaluate the CRP/ALB and cytokines profile in Chinese patients of UC.

2 | MATERIALS AND METHODS

2.1 | Participants

We enrolled 130 UC patients and 65 age and gender-matched controls in our hospital from November 2019 to December 2021. Demographic features, clinical data, laboratory results, and clinical disease activity were retrospectively retrieved from the Electronic Medical Records System of the Jiangsu Province Hospital of Chinese Medicine. We measured the levels of multiple cytokines (IL-1β, IL-2, IL-4, IL-6, IL-10, IL-8, IL-5, IL-17, IFN-α, and TNF-α) in peripheral blood of UC patients. Blood samples were obtained and tested for the cytokine concentrations by multiple microsphere flow immunofluorescence. ALB, CRP, ESR, FC, and platelet counts(PLT) were also detected.

2.2 | Assessment of disease activity

Truelove and Witts' criteria were used to assess disease activity. As is described by previous studies,[16,17] patients with moderate or severe UC were divided into the active disease group, while patients in the mild group were divided into the remission group. The disease extent was classified using the Montreal classification.

2.3 | Cytokine detection

The cytokines detection reagent was provided by Qingdao Raisecare Biotechnology Co., Ltd. (Shandong, China). As is described by previous studies,[18] IL-1β, IL-2, IL-4, IL-6, IL-10, IL-8, IL-5, IL-17, IFN-α, and TNF-α were detected by multiple microsphere flow immunofluorescence according to the manufacturer's instructions. Fluorescence intensity was measured by flow cytometry and cytokine concentrations were calculated according to the protocol of the manufacturer.

2.4 | Statistical analysis

The majority of data do not have a normal distribution. Continuous variables were presented as medians and interquartile range (IQR). Categorical variables were presented as numbers and percentages. Differences in variables between two groups were examined using the Mann–Whitney *U*-test for quantitative variables. Categorical variables were compared using the chi-squared test. Receiver operating characteristics (ROC) curves were conducted to evaluate the optimal cutoff values of IL-6 and CRP/ALB. The correlations between CRP/ALB, IL-6, and inflammatory parameters were evaluated by Spearman's correlation test. p-values <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Clinical characteristics

One hundred thirty UC patients (54% male) with a median age of 43 years and 65 age and gender-matched controls were recruited. The median duration of the disease was 48 months. 81% ($n = 105$), 15% ($n = 20$), 1.5% ($n = 2$), and 6% ($n = 8$) were treated with mesalazine, oral or intravenous steroids, azathioprine, and biologic agents, respectively. The included patients were categorized into two groups: remission group ($n = 52$) and active group ($n = 78$; Table 1). Median ESR, CRP, FC, and platelet counts of active UC patients were significantly higher than those in remission (Table 2).

3.2 | CRP/ALB were increased in UC patients

The median CRP/ALB value was 0.133 (IQR, 0.042–0.29) in UC patients in contrast to 0.038 (IQR, 0.03–0.058) in healthy controls ($p < 0.001$). CRP/ALB levels were significantly increased in active UC patients than inactive cases. The median CRP/ALB in patients with active and inactive UC was 0.24 (IQR, 0.12–0.55) and 0.042 (IQR 0.03–0.07), respectively ($p < 0.001$; Tables 2 and 3).

Receiver operating characteristic analysis was used to evaluate the predictive value of CRP/ALB in identifying patients with active

TABLE 1 Demographic and clinical characteristics of UC patients

Variables	Median (IQR), *n*	%
Age (years)	43 (34–54)	
Gender		
Men	70	54
Women	60	46
Duration of disease(months)	48 (24–96)	
Activity		
Active	78	60
Remission	52	40
Extent of disease		
Proctitis (E1)	24	20
Left sided (E2)	40	23
Pancolitis (E3)	66	57
Treatment (%)		
5-ASA	105	81
Steroids	20	15
Immunosuppressant	2	1.5
Biologics	8	6

Abbreviations: 5-ASA, 5-aminosalicylates; IQR, interquartile range.

TABLE 2 Comparison of parameters in patients during remission and active phase

Variables	Remission	Active	*p*-value
PLT	213 (176–261)	287.5 (200.5–370)	0
ESR	10 (5–20)	28 (14–47.5)	0
CRP	1.86 (1.31–2.94)	8.84 (5.04–19.05)	0
ALB	42.5 (39.95–45.05)	39.8 (37.63–42.05)	0
CRP/ALB	0.042 (0.03–0.07)	0.24 (0.12–0.55)	0
FC	171 (69.9–965)	993 (693–1500)	0
IL-5	2.07 (1.3–3.03)	2.49 (1.525–4.012)	0.331
IFN-a	1.34 (1.03–2.18)	1.71 (1.19–2.22)	0.267
IL-2	1.43 (1.07–1.86)	1.66 (1.24–2.125)	0.106
IL-6	2.95 (2.17–5.44)	7.715 (3.475–14.63)	0
IL-10	1.22 (0.99–1.52)	1.415 (1.13–1.72)	0.102
IL-8	3.61 (1.51–7.195)	4.13 (0.87–12.47)	0.564
IL-17	1.75 (1.32–2.41)	2.375 (1.675–4.23)	0.001
IL-1β	3.495 (0.98–9.47)	3.35 (1.112–11.08)	0.757
TNF-a	2.045 (1.26–6.02)	1.96 (1.022–4.61)	0.275
IL-4	1.46 (1.15–1.7)	1.32 (1.67–1.74)	0.548

Abbreviations: ALB, albumin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; IFN-α, interferon-α; IL, interleukin; PLT, platelet; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis.

UC. The optimal cutoff value of CRP/ALB in distinguishing active UC from remission was 0.083 with a sensitivity of 83.6% and specificity of 76.6% with the area under the curve (AUC) of 0.823 (95% CI 0.744–0.901; Figure 1 and Table 4).

TABLE 3 Comparison of parameters in patients with UC and controls

Variables	Control	UC	*p*-value
CRP	1.66 (1.31–2.65)	5.57 (1.76–12.1)	0
ALB	43 (40.8–45.4)	41.2 (38.25–42.9)	0
CRP/ALB	0.038 (0.03–0.058)	0.133 (0.042–0.29)	0
IL-5	1.78 (1.2–2.55)	2.44 (1.4–3.67)	0.011
IFN-a	1.68 (1.365–2.31)	1.665 (1.132–2.21)	0.132
IL-6	2.86 (1.385–3.81)	4.375 (2.63–11.15)	0
IL-2	1.45 (1.2–1.94)	1.56 (1.198–2.075)	0.406
IL-1β	2.35 (0.46–7.41)	3.445 (1.085–10.01)	0.197
IL-10	1.15 (0.94–1.56)	1.34 (1.04–1.67)	0.069
IL-17	1.53 (1.32–2.06)	2.125(1.515–3.255)	0
IL-8	1.1 (0.225–2.915)	3.72 (1.15–10.16)	0
IL-4	1.4 (1.18–1.825)	1.415 (1.095–1.73)	0.453
TNF-a	1.87 (1.045–2.945)	1.98 (1.137–4.995)	0.323

Abbreviations: ALB, albumin; CRP, C-reactive protein; IL, interleukin; IFN-α, interferon-α; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis.

3.3 | Cytokines profile in patients with UC and control groups

We found that UC patients showed higher IL-5, IL-6, IL-17, and IL-8 levels than controls. The median plasma IL-6 was 4.375 pg/ml (IQR, 2.63–11.15) in patients with UC and 2.86 pg/ml (IQR, 1.385–3.81) in controls ($p < 0.001$). A slight difference in IL-17 concentration was observed in patients with UC (2.125 pg/ml, IQR, 1.5–3.25) and controls (1.53 pg/ml, IQR, 1.32–2.06; $p < 0.001$). IL-8 was elevated in patients with UC (3.72 pg/ml, IQR, 1.15–10.16) compared with healthy subjects (1.1 pg/ml, IQR, 0.225–2.915; $p < 0.001$). IL-5 concentration was slightly increased in patients with UC (2.44 pg/ml, IQR, 1.4–3.67) compared with controls (1.78 pg/ml, IQR, 1.2–2.55; $p = 0.011$; Table 3).

3.4 | IL-6 levels were increased in the patient with active UC

The patients with active UC had a median IL-6 level of 7.715 pg/ml (IQR, 3.48–14.63), which was markedly higher than those in remission (2.95 pg/ml IQR, 2.17–5.44) ($p < 0.001$; Table 2). IL-17 concentration was slightly increased in patients with active UC and those in remission. The median concentration of IL-17 measured in patients with active UC was 2.375 pg/ml (IQR, 1.67–4.23), whereas its concentration in remission was 1.75 pg/ml (IQR, 1.32–2.41; $p = 0.001$; Table 2).

Reactive operating characteristic analysis was used to evaluate the predictive value of IL-6 in identifying patients with active UC. The optimal cutoff value of IL-6 in distinguishing active UC from

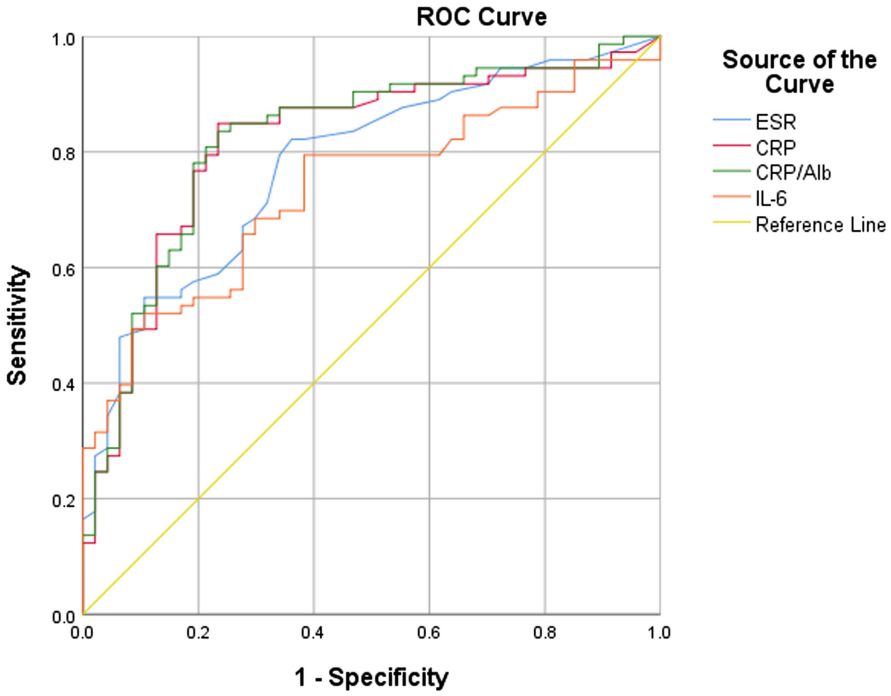

FIGURE 1 Receiver operating characteristic (ROC) curve analysis of inflammatory parameters to differentiate active from inactive UC.

Variables	AUCs	95% CI		Cutoff	Sensitivity	Specificity
ESR	0.78	0.697	0.862	12.5	0.822	0.638
CRP	0.817	0.736	0.897	3.225	0.849	0.766
CRP/ALB	0.823	0.744	0.901	0.083	0.836	0.766
IL-6	0.736	0.648	0.824	7.465	0.521	0.894

TABLE 4 Accuracy of CRP/ALB and inflammatory parameters in differentiating active from inactive UC

Abbreviations: ALB, albumin; AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin.

remission was 7.465 pg/ml with a sensitivity of 52.1% and specificity of 89.4% with an AUC of 0.736 (95% CI 0.648–0.824; Figure 1 and Table 4).

3.5 | Associations between the CRP/ALB, IL-6, and inflammatory parameters

There was a positive correlation between CRP/ALB and IL-6 level ($r = 0.367$, $p < 0.001$). We assessed correlations between IL-6 and laboratory parameters of inflammation such as ESR, PLT, and FC. The IL-6 level was shown to be positively correlated with the platelet count ($r = 0.306$, $p = 0.001$). There was a positive correlation between CRP/ALB and ESR ($r = 0.701$, $p < 0.001$), platelet count ($r = 0.42$, $p < 0.001$), and FC ($r = 0.374$, $p = 0.002$; Table 5).

4 | DISCUSSION

In the present study, we evaluated the cytokines profile and CRP/ALB by retrospectively collecting the clinical and laboratory data of 130 UC patients. We found that CRP/ALB was significantly increased in active UC patients in comparison with those in remission. We also evaluated the cytokines profile in UC patients and found significant elevation in the IL-6 levels among active UC patients compared with the inactive cases and controls. Furthermore, CRP/ALB is correlated with inflammatory parameters, such as IL-6, PLT, ESR, and FC.

C-reactive protein is an acute-phase protein and its production is stimulated by IL-6.[19] Severe UC is commonly marked by increased level of CRP and FC. It has been reported that albumin level was a predictive factor of clinical response in UC patients receiving infliximab.[20] Inflammatory response may promote the degradation of albumin.[21] Albumin concentrations were not only nutritional indexes, but also measurements of systemic inflammation. Khan et al. indicated that low level of albumin at disease diagnosis could predict the clinical course of UC.[22]

Our results are similar to previous studies. In a Chinese cohort study, the median CRP/ALB in patients with active and inactive UC was 0.36 (IQR, 0.1–0.97) and 0.06 (IQR, 0.03–0.1), respectively. They found that the optimal cutoff value for active UC was 0.18.[10] Another study indicated that CRP/ALB ratio was useful to identify Crohn's disease (CD) activity. The ROC curve analysis revealed AUC of CRP/ALB in CD patients was 0.75, with sensitivities of 59.7%, and specificity of 81.6%.[23] Liu et al. included 94 UC

TABLE 5 Spearman's correlation coefficients of CRP/ALB and IL-6 with inflammatory markers in UC patients

	ESR		PLT		FC	
	r	*p*	*r*	*p*	*r*	*p*
CRP/ALB	0.701	0	0.420	0	0.374	0.002
IL-6	0.265	0.003	0.306	0.001	0.189	0.038

Abbreviations: ALB, albumin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; PLT, platelet.

patients and found the optimal cutoff level of CRP/ALB was 0.06 for identifying active disease. The disease activity was classified based on the partial Mayo scores.[24] Sayar et al. retrospectively analyzed 149 UC patients and suggested the cutoff value to determine severe disease for CRP/ALB was 0.6.[25] Recent Japanese study enrolled 273 Japanese UC patients and indicated that CRP/ALB may be closely correlated with moderate-to-severe endoscopic activity.[26]

Our study also found that CRP/ALB is associated with IL-6. IL-6 is a pleiotropic cytokine that plays a prominent role in regulating immune responses and closely correlates with CRP levels. We observed higher concentration of IL-6 in UC than controls, which are consistent with several previous studies. Guimbaud et al. found patients with active UC status displayed higher levels of IL-6.[27] Nishida et al. enrolled 41 patients and found pretreatment IL-6 concentrations were lower in responders (2.01, IQR, 1.14–6.26) in comparison with that in nonresponders (6.67 IQR, 4.07–12.7). They suggested that IL-6 level could be used to evaluate response to infliximab in UC.[28] By contrast, other studies did not find increased concentration of IL-6 in UC patients.[29] A case–control study evaluated the cytokines profile in UC patients. Although a higher level of IL-6 in moderate–severe UC patients was observed (9.54, IQR, 5–16.5), when compared to inactive-mild patients (6.58, IQR, 3.4–14.2), the differences were not statistically significant.[30]

Some proinflammatory cytokines and anti-inflammatory cytokine have been reported as biomarkers of inflammation.[31,32] IL-10 suppresses the secretion of TNF-α and plays a prominent role in regulating immune homeostasis.[33] IL-17 is an important inflammatory cytokine mainly produced from activated T cells and affects the modulation of neutrophil responses.[34,35] Previous study reported that concentrations of cytokines are increased in IBD patients. For example, elevation in levels of IL-1β, TNF-α, IL-17, and IL-8 has been found in IBD patients.[36,37] A case–control study including 67 UC patients indicated IL-8 was closely associated with disease activity.[30] Sahin et al. enrolled 50 CD patients and 40 healthy controls, and they found IL-17 level was not associated with clinical disease activity.[15] Our study found slightly increased IL-17 concentration in patients with active UC compared with those in remission. We did not observe increased concentration of TNF-α in active UC patients. Studied populations, disease extent, medications, and comorbidities may explain the inconsistent results of studies.

There are several limitations in our study. First is the lack of statistical power given the relatively low number of patients. This is a retrospective analysis conducted in a single center. Large number of patients may lead to different results. Second, endoscopic assessment and histopathology data for each patient were not available. We are not able to assess the correlations between CRP/ALB, cytokines profile, and endoscopic disease activity. Another weakness is that potential risk factors affecting the CRP/ALB and cytokines profile were not evaluated, such as medical treatment, disease extent, gender, and comorbidities. Our results should be interpreted with care. Moreover, we measured the concentrations of multiple cytokines only in patients' peripheral blood. Further studies may evaluate the concentrations of cytokines in mucosal samples.

5 | CONCLUSIONS

In conclusion, our study indicated that CRP/ALB and IL-6 were elevated in UC patients and positively associated with inflammatory parameters. This study showed that CRP/ALB and IL-6 were related to disease activity in UC patients. Our results should be validated in prospective studies on large cohorts of UC patients.

AUTHOR CONTRIBUTIONS

HS designed the study. LZ and YJL collected the data. WF and LZX analyzed data and wrote the manuscript. The authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available on request to the corresponding author.

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