

The albumin to globulin ratio is associated with mucosal healing in Japanese patients with ulcerative colitis: A cross-sectional study

Sen Yagi

Saiseikai Matsuyama Hospital

Shinya Furukawa (✉ shinya.furukawa@gmail.com)

Ehime University

Kana Shiraishi

Ehime University

Masakazu Hanayama

Ehime University

Kazuhiro Tange

Ehime University

Yu Hashimoto

Ehime University

Shogo Kitahata

Ehime University

Kenichirou Mori

Ehime Prefectural Central Hospital

Tomoyuki Ninomiya

Ehime Prefectural Central Hospital

Seiyuu Suzuki

Sumitomo Besshi Hospital

Naozumi Shibata

Ehime prefectoral Niihama Hospital

Hidehiro Murakami

Saiseikai Matsuyama Hospital

Katsuhisa Ohashi

Ohashi Clinic

Makoto Yano

Yano Clinic

Aki Hasebe

Shikoku Cancer Center

Hideomi Tomida

Ehime University

Yasunori Yamamoto

Ehime University

Eiji Takeshita

Ehime University

Yoshio Ikeda

Ehime University

Yoichi Hiasa

Ehime University

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Abstract

Background

Ulcerative colitis (UC) is a chronic inflammatory disease. Mucosal healing (MH) is inversely associated with clinical outcome. The albumin to globulin ratio (AGR) is known as chronic inflammation marker. While some evidence regarding an association between AGR and some chronic diseases has been reported, no evidence regarding association between AGR and UC exists. The aim of this study to evaluated the association between AGR and MH among Japanese patients with UC.

Methods

The study subjects consisted of 273 Japanese patients with UC. AGR was divided into quartiles on the basis of the distribution of all study subjects. One endoscopic specialist was responsible for evaluating MH, which was defined as a Mayo endoscopic subscore of 0 or 0–1. Age, sex, steroid use, body mass index, age at onset of UC, and anti-TNF α preparation were selected *a priori* as potential confounding factors.

Results

The mean age was 51.2 years, and the percentage of male patients was 59.0%. The percentage of MH was 26.4%. High AGR ($1.483 < \text{AGR} \leq 1.643$) and very high AGR (> 1.643) was significantly positively associated with MH (OR 2.21 [95% CI: 1.12–4.47], p for trend = 0.001) after adjustment for confounding factors. No association between AGR and partial MH was found. The independent positive association between AGR and MH was found in only low C-reactive protein group.

Conclusion

Among Japanese patients with UC, AGR was significantly positively associated with MH, was significantly positively associated with MH especially in the low C-reactive protein group.

Background

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by a disease course involving relapses and remissions [1]. Mucosal healing (MH) is inversely associated with clinical relapse, rates of hospitalization and surgery, and incidence of colorectal cancer [2–7]. Thus, MH has been indicated as the therapeutic goal for UC.

The prospective studies have shown that strict control based on monitoring of inflammatory biomarkers and maintenance of MH [8]. The concept of the treat-to-target in UC had accepted to improve the

prognosis. The implications of MH had led to improved endoscopic and clinical outcomes. Colonoscopy findings are essential for assessing MH and Fecal calprotectin (FC) is most reliable marker for MH. However, repeated endoscopy and stool examination are extremely burdensome for patients. repeated fecal examinations may be distressing for women, the young, or patients without symptoms. More serum markers for MH that can be measured repeatedly, easily, and rapidly is needed for achieve the concept of the treat-to-target among ulcerative colitis.

Albumin and globulin are the two major components of serum proteins. The albumin to globulin ratio (AGR), calculated as serum albumin/ (total protein – albumin), has been used one of marker for chronic inflammation. AGR has been reported to be a prognostic marker in patients with cancers [9–15], chronic heart failure [16], stroke [17], and sarcoidosis [18]. However, no evidence regarding association between AGR and clinical outcomes among patients with UC exists. Thus, we aimed to evaluate the association between AGR and MH among Japanese patients with UC.

Materials And Methods

Study population

The study subjects consisted of 387 Japanese patients with UC at the Department of Gastroenterology and Metabolism at the Ehime University Graduate School of Medicine, and at several affiliated hospitals in Ehime prefecture (The Ehime Clinical Network for Alimentary Diseases study group). All patients were diagnosed with UC according to endoscopic, radiological, histological, and clinical criteria. After 114 patients were excluded due to incomplete data, the final analysis sample in this study consisted of 273 patients assessed for endoscopy examination, medication, serum albumin, and serum globulin. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). This protocol was approved by the Institutional Review Board of the Ehime University Graduate School of Medicine (1505011). Well trained staff obtained written informed consent from all patients enrolled.

Measurements

Information on endoscopic findings, age at onset of UC, use of drugs for UC, C-reactive protein (CRP), AGR was collected using medical records and self-. Serum albumin, globulin and CRP were determined from routine blood levels obtained from patient files at the time the patients were included in the study. Blood samples were taken the morning after overnight fasting. Blood examination was collected when a colonoscopy is reserved or when the colonoscopy examination is performed. There could be a time difference of about two months. Height was measured to the nearest millimeter using a stadiometer with the patients standing completely erect. Weight was measured in light clothing. BMI was calculated as weight in kilograms divided by square height in meters.

Definition of mucosal healing

We evaluated mucosal status by total colonoscopy. The Mayo endoscopic score (MES) consists of the following four categories [19]: 0, normal or inactive disease; 1, mild disease with erythema, decreased

vascular patterns, and mild friability; 2, moderate disease with marked erythema, absence of vascular patterns, friability, and erosions; 3, severe disease with spontaneous bleeding and ulceration. MH and partial MH were defined as category 0 and 0–1, respectively, in this study. One endoscopic specialist was responsible for evaluating MES and MH, and was blinded to AGR.

Statistical analysis

AGR was divided into quartiles on the basis of the distribution of all study subjects. AGR level was classified into four categories: 1) low AGR, < 1.281 (reference); 2) moderate AGR, 1.281–1.483; 3) high AGR, 1.483–1.643; and 4) very high AGR, > 1.643. Estimations of crude odds ratios (ORs) and their 95% confidence intervals (CIs) for MH and partial MH in relation to AGR were performed using logistic regression analysis. Multiple logistic regression analyses were used to adjust for potential confounding factors. Age, sex, steroid use, BMI, onset age, and anti-TNF α preparation were selected *a priori* as potential confounding factors. A receiver operating characteristic (ROC) curve was generated, and the area under the curve was calculated to indicate the utility of the AGR for mucosal healing. We used Youden Index to calculate the cut off value of platelet. Statistical analyses mainly were performed using SAS software package version 9.4 (SAS Institute Inc., Cary, NC, USA). ROC curve, cut off value of AGR, sensitivity and specificity were analyzed using JMP 14.2 (SAS Institute Inc., Cary, NC, USA). All probability values for statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the characteristics of the 273 study participants. The mean age was 51.2 years, and the percentage of male patients was 59.0%. Use of 5-aminoasalicylates, prednisolone, and TNF- α monoclonal antibody preparations were reported at 90.8%, 21.3%, and 5.9%, respectively. The percentage of MH was 26.4%, and the mean AGR was 1.461 ± 0.291 . In this cohort, median CRP was 0.099 mg/dl. The ROC curve of AGR for identifying the mucosal healing had an area under curve of 0.613 (Fig. 1)

Table 1
Clinical characteristics of 273 study participant

Variable	n (%)
Age, years, mean ± SD	51.2 ± 16.2
Male (%)	161 (59.0)
Disease extent (pancolitis/left-sided/proctitis/others)	114/74/78/7
Age at onset of UC, age, mean ± SD	42.4 ± 16.3
BMI, mean ± SD	22.69 ± 4.60
Medication	
5-aminosalicylates (%)	248 (90.8)
Prednisolone (%)	58 (21.3)
TNF- α monoclonal antibody (%)	16 (5.9)
Clinical remission, (%)	157 (57.5)
Mayo endoscopic subscore, mean ± SD	1.18 ± 0.91
Mucosal healing (Mayo endoscopic subscore < 1) (%)	72 (26.4)
Partial mucosal healing (Mayo endoscopic subscore ≤ 1) (%)	172 (63.0)
AGR, mean ± SD	1.461 ± 0.291
CRP mg/dl, median ± IQR	0.099 ± 0.23
BMI, body mass index; SD, standard deviation; TNF, tumor necrosis factor; AGR, albumin globulin ratio; CRP, C-reactive protein; IQR, inter-quartile range	

Table 2 shows crude and adjusted ORs and 95% CIs for MH and partial MH in relation to AGR. Very high AGR was positively associated with MH and partial MH (MH: crude OR 3.52 [95% CI: 1.53–8.69] and partial MH: crude OR 2.07 [95% CI: 1.02–4.25]). High AGR was positively associated with MH but not partial MH (crude OR 3.52 [95% CI: 1.53–8.69]). After adjustment for age, sex, steroid use, body mass index, age at onset of UC, and anti-TNF α preparation, very high AGR and high AGR were significantly positively associated with MH, respectively (adjusted OR 5.57 [95% CI: 2.12–15.80] and adjusted OR 4.22 [95% CI: 1.65–11.63], p for trend = 0.001). The positive association between AGR and partial MH disappeared after adjustment for these confounding factors.

Table 2
Crude and adjusted odds ratios and 95% confidence intervals for MH and partial MH relation to AGR

Variable	Prevalence (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
MH			
AGR ≤ 1.281	9/67 (13.4)	1.00	1.00
1.281 < AGR ≤ 1.483	16/70 (22.9)	1.91 (0.79–4.85)	2.40 (0.93–6.53)
1.483 < AGR ≤ 1.643	23/68 (33.8)	3.29 (1.43–8.16)	4.22 (1.65–11.63)
1.643 < AGR	24/68 (35.3)	3.52 (1.53–8.69)	5.57 (2.12–15.80)
<i>P</i> for trend			0.001
Partial MH			
AGR ≤ 1.281	36/67 (53.7)	1.00	1.00
1.281 < AGR ≤ 1.483	41/70 (58.6)	1.22 (0.62–2.40)	1.09 (0.52–2.28)
1.483 < AGR ≤ 1.643	47/68 (69.1)	1.93 (0.96–3.93)	1.59 (0.72–3.54)
1.643 < AGR	48/68 (70.6)	2.07 (1.02–4.25)	1.84 (0.82–4.19)
<i>P</i> for trend			0.096
Adjusted for age, sex, use of prednisolone, BMI, onset age, and use of TNF- α . OR, odds ratio; CI, confidence interval; MH, mucosal healing; AGR, albumin to globulin ratio			

The association between AGR and MH after CRP stratification was shown in Table 3. In low CRP group (≤ 0.1 mg/dL), AGR was significantly positively associated with MH but not partial MH (very high: adjusted OR 4.48[95%CI: 1.09–22.19], *p* for trend = 0.014). In high CRP group (CRP > 0.1 mg/dL), no association between AGR and MH found.

Table 3

Crude and adjusted odds ratios and 95% confidence intervals for mucosal healing in relation to AGR after CRP stratification

Variable	Prevalence (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
CRP ≤ 0.1 mg/dL (n = 158)			
MH (MES 0)			
AGR ≤ 1.281	4/19 (21.1)	1.00	1.00
1.281 < AGR ≤ 1.483	10/44 (22.7)	1.10 (0.31–4.53)	1.59 (0.39–7.55)
1.483 < AGR ≤ 1.643	16/41 (39.0)	2.40 (0.72–9.59)	3.54 (0.87–17.08)
1.643 < AGR	20/54 (37.0)	2.21 (0.69–8.56)	4.48 (1.09–22.19)
<i>p</i> for trend			0.014
Partial MH (MES 0–1)			
AGR ≤ 1.281	15/19 (79.0)	1.00	1.00
1.281 < AGR ≤ 1.483	27/44 (61.4)	0.42 (0.11–1.40)	0.41 (0.10–1.49)
1.483 < AGR ≤ 1.643	31/41 (75.6)	0.83 (0.20–2.94)	0.67 (0.14–2.71)
1.643 < AGR	39/54 (72.2)	0.69 (0.18–2.28)	0.60 (0.13–2.34)
<i>p</i> for trend			1.00
CRP > 0.1 mg/dL (n = 115)			
MH (MES 0)			
AGR ≤ 1.281	5/48 (10.4)	1.00	1.00
1.281 < AGR ≤ 1.483	6/26 (23.1)	2.58 (0.70–9.94)	2.34 (0.58–9.73)
1.483 < AGR ≤ 1.643	7/27 (25.9)	3.01 (0.86–11.31)	3.28 (0.81–14.75)
1.643 < AGR	4/14 (28.6)	3.44 (0.74–15.46)	3.35 (0.63–18.30)
<i>p</i> for trend			0.09
Partial MH (MES 0–1)			

Adjusted for age, sex, use of prednisolone, BMI, onset age, and use of TNF- α .

OR, odds ratio; CI, confidence interval; AGR, albumin to globulin ratio; CRP, C-reactive protein

Variable	Prevalence (%)	Crude OR	Adjusted OR
		(95% CI)	(95% CI)
AGR ≤ 1.281	21/48 (43.8)	1.00	1.00
1.281 < AGR ≤ 1.483	14/26 (53.9)	1.50 (0.58–3.97)	1.04 (0.35–3.07)
1.483 < AGR ≤ 1.643	16/27 (59.3)	1.87 (0.73–4.97)	1.47 (0.48–4.60)
1.643 < AGR	9/14 (64.3)	2.31 (0.69–8.51)	1.93 (0.46–9.08)
<i>p</i> for trend			0.33
Adjusted for age, sex, use of prednisolone, BMI, onset age, and use of TNF-a.			
OR, odds ratio; CI, confidence interval; AGR, albumin to globulin ratio; CRP, C-reactive protein			

Discussion

In the present study, AGR was independently positively associated with MH among 273 Japanese patients with UC, and ours is the first such study to show a significant positive association between AGR and MH among patients with UC. AGR is independently positively associated with MH but not partial MH among patients with only low CRP UC.

Albumin and globulin are the two major components of serum proteins, and their levels correlate with systemic inflammation [11–13]. Albumin maintains osmotic pressure and functions [20]. Low serum albumin is associated with not only nutritional status but also chronic inflammation [13, 21]. Low serum albumin could weaken the human immune system, thus increasing susceptibility to infection and resulting in cytokine-induced suppression [22, 23]. On the other hand, globulin consists of all types of proinflammatory proteins. A high level of globulin indicated a systematic inflammatory response [24]. Serum globulin level is thought to reflect the degree of continuous systemic inflammation. AGR is less sensitive and less susceptible to measurement variability such as dehydration or fluid retention since it is a ratio rather than an absolute value [9].

AGR has been reported to be a prognostic marker in patients with colorectal [8], lung [10], and breast cancers [11]. Furthermore, AGR is an independent predictor of mortality in patients with chronic heart failure [16]. AGR is significantly inversely associated with cardiovascular diseases and incidence of stroke [17, 25]. Additionally, an inverse association between AGR and the clinical activity was reported among patients with sarcoidosis [18]. The findings in the present study consistent with these findings regarding the AGR and clinical outcomes.

Colonoscopy findings are essential for assessing mucosal status in patients with UC and determining treatment strategies. FC is useful and reliable marker for MH. However, repeated endoscopy is extremely burdensome for patients. Similarly, repeated fecal examinations may be distressing for the young, women, or patients without symptoms. Additionally, colonoscopy and FC might be not suitable for

assessment for early response for medication. AGR is simple, rapid, relatively non-invasive, repeatable, and can be measured at all medical institutions. AGR monitoring might be useful to assessment disease activity, treatment response, and prognosis especially among UC patients with low CRP level. However, further research is needed for assessment AGR as a biomarker for diseases activity among patients with UC.

The underlying mechanism linking AGR and MH remains unclear, but there are several biologically plausible options. Serum albumin is known to decrease during inflammation [26]. In fact, in 43 patients with UC, CRP was significantly inversely associated with serum albumin [27]. Because of intestinal tract inflammation, protein loss from the gut and malnutrition may influence serum albumin levels [28]. AGR was associated with plasma TNF- α levels in community-dwelling Japanese elderly women [29]. Levels of α_1 globulins (α_1 -antitrypsin, thyroid-binding globulin, and transtertin) and α_2 globulins (ceruloplasmin, α_2 -macroglobulin, and haptoglobin) are also increased in acute inflammation [30]. Intestinal tract inflammation might elevate AGR with protein loss and elevated TNF- α .

This study has several limitations. First, this was a cross-sectional analysis; therefore, we cannot conclude that there is a causal association between AGR and MH. Second, in this cohort, the sample size was small. Third, the exclusion rate was high. Fourth, we could not estimate the dietary intake of protein. Fifth, most of the patients have been receiving treatment for UC. The long duration of medication might therefore affect AGR value. Finally, the current study patients might be an unrepresentative sample of Japanese patients with UC. The use of medication in Japanese study based on claims data were similar to those in the present study [31]. However, since this cohort consist of Japanese patients, the findings in the present study might not be generalized to other cohorts.

Conclusions

Among Japanese patients with UC, AGR may be independently positively associated with MH was significantly positively associated with MH especially in the low C-reactive protein group.

Abbreviations

AGR: albumin to globulin ratio; MH: mucosal healing; UC: ulcerative colitis; FC: Fecal calprotectin; TNF: tumor necrosis factor; IBD: inflammatory bowel disease; CRP: C-reactive protein; MES: Mayo endoscopic subscore; ROC: receiver operating characteristic

Declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of the Ehime University Graduate School of Medicine (1505011). Well-trained staff obtained written informed consent from all patients enrolled.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

Not applicable.

Competing interests

Not applicable

Authors' contribution

Conception and design: SY, FS, ET, YI, YH; Material preparation and data collection: SY, SF, KS, MH, KT, SK, KM, TN, SS, NS, HM, KO, MY, AH, HT, YY, ET, YI; Data analysis: SF; Interpretation of data: SY, SF, ET, YI, and YH; The first draft of the manuscript was written by SY and SF; Supervision: YH. All authors read and approved the final manuscript.

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Figures

Figure 1

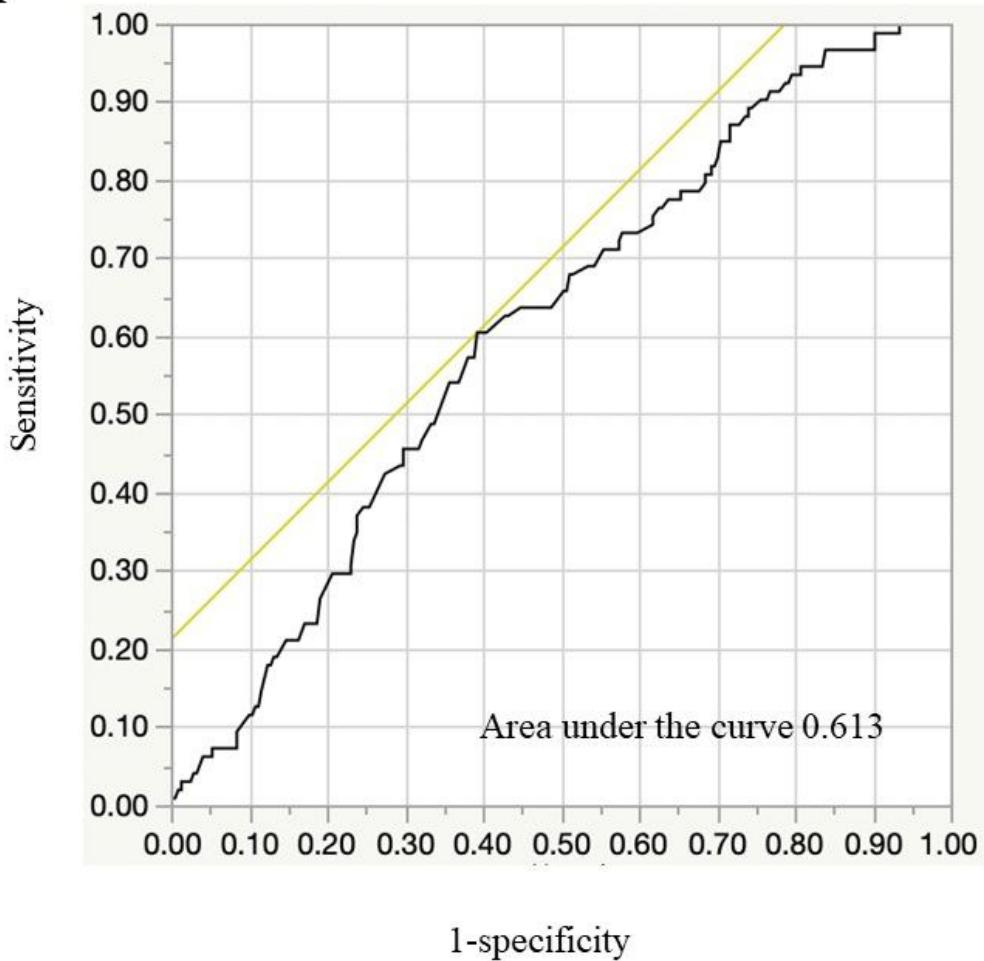


Figure 1

Receiver operating characteristic curve of AGR for identifying the mucosal healing based on Mayo endoscopic subscore 0. The receiver operating characteristic (ROC) curve AGR for identifying the mucosal healing had an area under curve of 0.613. When cut off value of AGR was determined as 1.52, the sensitivity and specificity were 60.6% and 62.1%, respectively. We used Youden Index to calculate the cut off value of AGR