

# Journal of Gastroenterology and Hepatology Research

Online Submissions: <http://www.ghrnet.org/index./joghr/>  
doi: 10.17554/j.issn.2224-3992.2019.08.816

Journal of GHR 2019 April 21; 8(2): 2858-2863  
ISSN 2224-3992 (print) ISSN 2224-6509 (online)

ORIGINAL ARTICLE

## Is Fecal Calprotectin or Fecal Immunochemical Measurement for Occult Blood a good Marker for Mucosal Healing in Ulcerative Colitis?

Seiji Otsuka, MD, Gou Someya, MD, Hitoshi Asakura, MD, Masahiro Yoshioka, MD, Takuma Kannzaki, MD, Yuuei Hosokawa, MD, Shunsuke Nagata, MD, Atsushi Nakamura, MD, Keiji Okuyama, MD, Osamu Suzuki, MD, Naruaki Matsui, PhD, Yoshiyuki Osamura, MD, Toshio Morizane, MD

Seiji Otsuka, Gou Someya, Masahiro Yoshioka, Takuma Kannzaki, Yuuei Hosokawa, Shunsuke Nagata, Atsushi Nakamura, Keiji Okuyama, Osamu Suzuki, Department of Gastroenterology, Nipponkougann hospital, Kawasaki, Kanagawa, Japan  
Hitoshi Asakura, Department of Gastroenterology at Koukann clinic, Kawasaki, Kanagawa, Japan  
Naruaki Matsui, Yoshiaki Osamura, Department of Pathology, Nipponkougann hospital, Kawasaki, Kanagawa, Japan  
Toshio Morizane, Gastroenterologist and statistician, Japan council-for quality health care, Tokyo, Japan

**Conflict-of-interest statement:** The authors declare that there is no conflict of interest regarding the publication of this paper.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Hitoshi Asakura, MD, Department of gastroenterology at Koukann clinic, 1-2-3, Koukannndori, Kawasaki-ku, Kawasaki, Kanagawa, Japan 210-0852

Email: [asakura-ht@agate.dti.ne.jp](mailto:asakura-ht@agate.dti.ne.jp)

Telephone: +81 44 366 8900

Telephone: +81 44 366 8901

Received: February 8, 2019

Revised: February 20, 2019

Accepted: February 22, 2019

Published online: April 21, 2019

### ABSTRACT

**AIM:** Mucosal healing is an important therapeutic goal for IBD

treatment. This study was performed to evaluate which methods of fecal calprotectin or fecal immunochemical test would be a good biomarker for mucosal healing compared with colonoscopic and/or pathological findings.

**METHODS:** Ulcerative colitis patients in remission, mild and moderate activities took an examination of blood biomarkers and colonoscopy, and their fecal specimens were tested on the day before bowel preparation for colonoscopy.

**RESULTS:** Although blood markers were almost within normal limits, fecal calprotectin and immunochemical test for occult blood were useful biomarkers for judging mucosal healing of ulcerative colitis. Fecal calprotectin and immunochemical test were well correlated with the ulcerative colitis endoscopic index of severity and sum of Mayo subscore at 5 segments of the colonorectum.

**CONCLUSION:** Fecal immunochemical test is useful for estimating mucosal healing as same as fecal calprotectin and low in cost.

**Key words:** Calprotectin; Fecal hemoglobin; Mayo endoscopic subscore; UCEIS; Ulcerative colitis

© 2019 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Otsuka S, Someya G, Asakura H, Yoshioka M, Kannzaki T, Hosokawa Y, Nagata S, Nakamura A, Okuyama K, Suzuki O, Matsui N, Osamura Y, Morizane T. Is Fecal Calprotectin or Fecal Immunochemical Measurement for Occult Blood a good Marker for Mucosal Healing in Ulcerative Colitis. *Journal of Gastroenterology and Hepatology Research* 2019; 8(2): 2858-2863 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2508>

### INTRODUCTION

The main treatment goal for inflammatory bowel disease (IBD) is an induction of inactive disease states, maintenance of clinical remission and prevention of surgery and hospitalization. Mucosal healing has become an important therapeutic goal for the treatment of IBD,

because mucosal healing suggests the possibility to avoid admission to hospital and surgery and to decrease the relapse of disease<sup>[1]</sup>.

Mucosal healing is identified mainly by enterocolonoscopy examinations, but enterocolonoscopy examination is an invasive and expensive procedure and the bowel preparation is needed for it and a burden to patients. Therefore, fecal calprotectin measurement has been recommended to evaluate the disease activity of IBD by ECCO and decreased the need of enterocolonoscopy examination<sup>[2]</sup>. Fecal calprotectin measurement is correlated to the disease activity assessed by colonoscopy<sup>[3]</sup>, but is not necessarily consistent with colonoscopic findings. Therefore, combining clinical activity indices with fecal calprotectin and serum CRP, or erythrocyte sedimentation rate are suggested to have better diagnostic accuracy for intestinal inflammation than fecal calprotectin measurement alone<sup>[4]</sup>.

Recently, fecal immunochemical test for occult blood (hemoglobin) mainly used to detect the colorectal cancer has been applied to assess the mucosal healing of ulcerative colitis (UC)<sup>[5]</sup>. This study was performed to evaluate which method of fecal calprotectin or fecal immunochemical test is useful to estimate mucosal healing assessed by colonoscopic and/or pathological examination.

## MATERIALS AND METHODS

This study was performed in a prospective way and in a single medical center under approval of ethical committee of the hospital. Written informed consent was obtained from each patient.

Twenty-three endoscopic examinations, fecal calprotectin measurements and fecal immunochemical tests for hemoglobin in 19 patients with UC (male 17, female 2) recruited for this study were performed during follow-up treatment at the gastroenterological unit of outpatient Koukann clinic and the Nipponkoukann hospital. The diagnosis of UC was based on clinical, endoscopic, histopathologic and / or radiological criteria. Clinical disease severity for patients of this study was in remission, mild and moderate stages based on the Truelove and Witts criteria excluding the severe patients showing remarkable gross bleeding<sup>[6]</sup>. Four patients had taken the second colonoscopic examination in a year.

Blood biomarkers and mucosal activities were assessed on the day of colonoscopy and fecal specimens were collected on the day before bowel preparation for colonoscopy except three patients whose feces were collected in 5 days after the colonoscopy. Each patient was instructed how to put fecal specimens into a small plastic container at home for the measurement of calprotectin and how to put them into a small plastic container containing a standard volumes of hemoglobin-stabilizing buffer for blood in the feces. Calprotectin in stool samples was measured with an automated fluoroimmunoassay (ThermoFisher scientific, Phadia calprotectin 2 kit, normal range less than 50 µg/g) and hemoglobin in the stool with a quantitative fecal immunochemical test (OC-Hemodia Auto III, Eiken, Japan) for hemoglobin<sup>[8]</sup> respectively. Fecal samples were immediately processed and examined using OC-sensor neo (Eiken Chemical, Ibaragi, Japan) which could accurately measure the fecal hemoglobin concentrations from 50ng/mL to 1,000 ng/mL (normal range less than 100 ng/mL). Blood samples were analyzed routinely for white blood cell counts, serum hemoglobin, albumin and C reactive proteins (CRP), erythrocyte sedimentation rate as the conventional laboratory tests.

Total colonoscopy was performed by 3 experienced endoscopists. All patients had been observed from the anus to the caecum. Endoscopic mucosal activity was assessed by the Mayo endoscopic subscore describing the degree of inflammation on a 4-point scale (0

to 3) for each segment of the rectum, sigmoid, descending, transverse and ascending colon / caecum<sup>[9]</sup>. Total values of Mayo endoscopic subscore (sum Mayo subscore) were calculated for each patient (0 to 15 points). In addition, ulcerative colitis endoscopic index of severity (UCEIS) consisting of three factors of vascular pattern, bleeding and erosions and / or ulcers was used for assessment of endoscopic disease activity and mucosal healing<sup>[10]</sup>. This endoscopic assessment of digital recording video pictures was done by three experienced endoscopists, because assessment of endoscopic features had slight inter-observer variation. We used the mean values for the three endoscopists.

To evaluate the mucosal inflammation, mucosal biopsy specimens were obtained from above-described five segments, and histological inflammatory severity was assessed using grading (normal or mild infiltration of small round cells without neutrophil infiltration: 0, moderate one of small round cells with intraepithelial and mucosal neutrophil infiltration: (1) severe one of small round cells and neutrophils without erosions: (2) and severe one of small round cells and neutrophils with erosions or ulcers: (3)<sup>[11]</sup>. Inflammatory severity grading for histopathology was assessed by two pathologists blindly for endoscopic grading.

### Statistical analysis

Spearman's rank correlation test was performed to determine the correlation coefficients between fecal calprotectin measurement, the fecal immunochemical test for hemoglobin, white blood cell counts, serum hemoglobin, albumin, CRP, and erythrocyte sedimentation rate and the averages of sum Mayo endoscopic subscore, averages of UCESI and the histopathological severity, respectively. All P values were considered statistically significant when < 0.05. To estimate the diagnostic performance of calprotectin and fecal immunochemical test for hemoglobin, receiver operating characteristic (ROC) curve analysis was performed with various cut-off values, and the area under the curve was calculated. An R package pROC was used for this analysis<sup>[12]</sup>.

Sensitivity, specificity, positive predictive value and negative predictive value with 95% confidence intervals, and accuracy for detecting mucosal status were determined based on the data of calprotectin and fecal immunochemical test for occult blood.

Kendall's rank method was employed to assess the coefficients of the concordance of reading the endoscopic pictures among three endoscopists (from 0: no agreement to 1: complete agreement)<sup>[13]</sup>.

## RESULTS

Diseased segments of 19 patients employed for the study were 3 rectum type, 8 left-sided colon type, 7 entire colon type and one right-sided colon type. Clinical course of all patients was remittent-relapse type. Medical treatments were 5-aminosalicylic acid (5-ASA) alone in six patients, 5-ASA and predonisolone in five patients, 5-ASA and azathioprine in four patients, and 5-ASA and anti-TNFα antibody in four patients, respectively. Disease duration was 3 to 30 years with median of 13.7 years.

White blood cell counts, serum hemoglobin, albumin and CRP levels, and erythrocyte sedimentation rate in the peripheral blood of patients studied in this series were almost within normal ranges except three cases in WBC counts, one case in serum hemoglobin levels, one case in albumin levels, three cases in CRP levels and 3 in ESR, respectively. Because these patients studied were in remission stage, mild or moderate in the clinical activities.

To assess the fecal calprotectin and hemoglobin levels for the

mucosal healing, averages of sum Mayo endoscopic subscore (sum Mayo, SM) were divided into three groups; group A:  $0 \leq SM < 1$ , group B:  $1 \leq SM < 5$  without Mayo subscore 2 and/or 3 at any segment, and group C: more than Mayo subscore 2 at any segment. Median (range) of fecal calprotectin and hemoglobin levels were 40.5(5-498) $\mu\text{g/g}$  and 25(0-23) $\text{ng/mL}$  in the group A, 91(21-588)  $\mu\text{g/g}$  and 32(0-228) $\text{ng/mL}$  in the group B, and 621(73-2658)  $\mu\text{g/g}$  and 70(0-1000) $\text{ng/mL}$  in the groupC, respectively. Pairwise comparisons between the groups by Tukey’s multiple comparison method, fecal calprotectin levels were not significantly different among three groups except between the group A and group C ( $p = 0.035$ ) (Figure 1). Fecal hemoglobin levels were not significantly different between pairs among threegrups.

Correlation between fecal calprotectin and hemoglobin levels and averages of sum Mayo subscore, averages of UCEIS and histopathological inflammation index were shown in figures 2 to 5. Fecal calprotectin levels were significantly correlated with averages of sum Mayo endoscopic subscore (Spearman’s rank correlation coefficient: 0.488,  $p < 0.018$ ) and the averages of UCEIS (Spearman’s rank correlation coefficient: 0.627,  $p < 0.0014$ ). At 0.488 and 0.627, R-square or the coefficients of determination was 0.23 and 0.40. Fecal calprotectin levels were not correlated with the histopathological inflammation index (Spearman’s rank correlation coefficient: 0.392,  $p = 0.087$ ). There was no correlation between fecal calprotectin and fecal hemoglobin levels (Spearman’s rank correlation coefficient: 0.319,  $p = 0.137$ ).

Fecal hemoglobin levels were significantly correlated with averages of sum Mayo endoscopic subscore (Spearman’s rank correlation coefficient: 0.644,  $p < 0.001$ ), the averages of UCEIS (Spearman’s rank correlation coefficient: 0.581,  $p < 0.004$ ) and the histopathological inflammation index (Spearman’s rank correlation coefficient: 0.482,  $p < 0.032$ ), respectively. When the mucosal healing is defined as sum Mayo subscore less than 1, the area under the curve by ROC analysis was 0.86 (95%CI: 0.71-1.0) in fecal calprotectin and 0.85 (95%CI: 0.70- 1.0) in fecal hemoglobin. When the mucosal healing is defined as sum Mayo subscore less than 5 without Mayo subscore 2 and /or 3 at any segment, the area under the curve was 0.90 (95%CI: 0.77-1.0) in fecal calprotectin and 0.78 (95%CI: 0.57-0.98) in fecal hemoglobin.

The sensitivity, specificity, positive predictive values, negative predictive and accuracy of fecal calprotectin and fecal hemoglobin results in relation to mucosal healing were shown in table 1. Table 1 shows diagnostic performance of calprotectin and fecal hemoglobin with commonly used cut-off values for these tests, 263  $\mu\text{g/g}$  and 50  $\text{ng/mL}$ . When sum Mayo subscore less than 1 was defined as the mucosal healing, area under the curve by ROC analysis was 0.86 (95%CI: 0.71-1.0) (sensitivity; 87.5, specificity: 53.3, PPV: 50.5, and NPV: 90.0) in fecal calprotectin and 0.85 (95%CI: 0.70-1.0) (sensitivity: 100, specificity: 53.3, PPV: 53.3 and NPV: 100) in fecal hemoglobin, respectively. When sum Mayo subscore of 1 to 5 without Mayo subscore 2 and /or 3 at any segments was defined as the mucosal healing, area under the curve analyzed ROC analysis

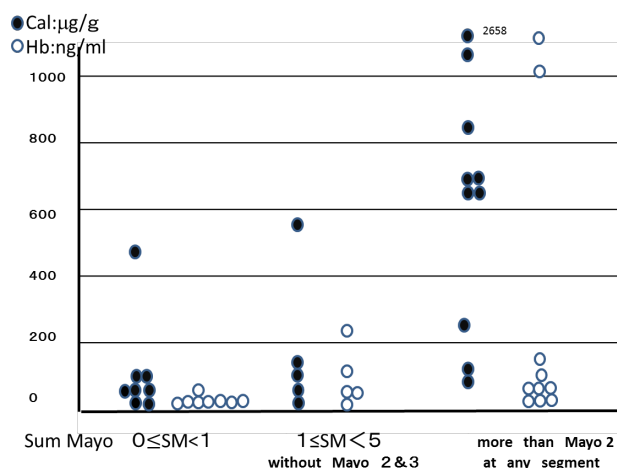


Figure 1 Correlation between fecal calprotectin and hemoglobin levels and averages of sum Mayo endoscopic subscore. SM: sum of Mayo endoscopic subscore.

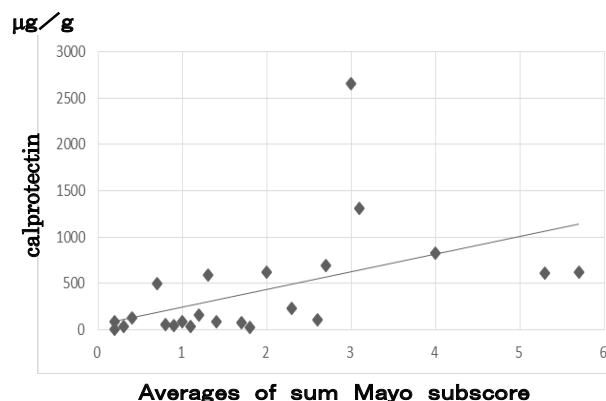


Figure 2 Correlation between fecal calprotectin levels and averages of sum Mayo subscores.

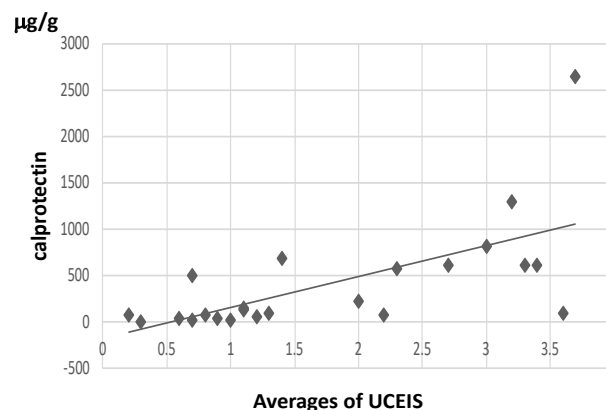


Figure 3 Correlation between fecal calprotectin levels and UCEIS scores.

Table 1 Sensitivity, specificity and accuracy in levels of fecal calprotectin and hemoglobin.

	Sum Mayo $0 \leq \text{sum M} < 1$		Sum Mayo $0 \leq \text{sum M} < 5$ without any 2 and 3	
	Calprotectin $\leq 263$	Fecal hemoglobin $\leq 50$	Calprotectin $\leq 263$	Fecal hemoglobin $\leq 50$
sensitivity	87.50%	100%	90.90%	90.90%
specificity	53.3	53.3	66.6	58.3
PPV	50.5	53.3	71.4	66.6
NPV	90	100	88.8	87.5

was 0.90 (95%CI: 0.77-1.0) (sensitivity; 90.9, specificity: 66.6, PPV: 71.4, and NPV: 88.8) in fecal calprotectin and 0.78 (95% CI: 0.57-0.98) (sensitivity: 90.9, specificity: 58.3, PPV: 66.6 and NPV: 87.5) in fecal hemoglobin, respectively. At cut-off values less than 263  $\mu\text{g/g}$ , the accuracy of fecal calprotectin was 0.73 and at cut-off values less than 50 ng/mL, the accuracy of fecal hemoglobin was 0.65.

Kendall's coefficient of concordance K for assessment of digital video endoscopic pictures evaluated by three endoscopists was 0.70 in the cecum and ascending colon, 0.73 in the transverse colon, 0.94 in the descending colon, 0.62 in the sigmoid colon and 0.65 in the rectum, respectively. All of K values were more than 0.6 and  $p < 0.01$  for all the coefficient (the mean: 0.73).

## DISCUSSION

Calprotectin is an antimicrobial component of neutrophils, monocytes, and macrophages that is stable in feces up to 7 days at room temperature<sup>[14]</sup>. The colonic mucosa of active UC is infiltrated by numerous neutrophils and macrophages with association of lymphocytes and plasma cells, sometimes eosinophils, indicating acute on chronic inflammation. In active UC there was numerous neutrophil infiltration in the colonic mucosa proven by measuring myeloperoxidase levels in the colorectal mucosa that was one of components of neutrophils<sup>[15]</sup>. Patients with active histological inflammation had a significantly higher median level of fecal calprotectin than those without active histological inflammation<sup>[16]</sup>. However, there was the report that fecal calprotectin and Mayo endoscopic subscore were each independent predictors of histological inflammation<sup>[16]</sup>.

Mucosal inflammatory activities were formerly assessed by clinical findings of bowel movements, bloody stools, body temperature, pulse rates and abdominal pain and by blood biomarkers of serum CRP, hemoglobin, erythrocyte sedimentation rate and albumin. Biomarkers of serum CRP, albumin, hemoglobin, and erythrocyte sedimentation rate were almost normal in the cases of remission, and mild stages of ulcerative colitis. The mucosal healing has become the main treatment goal for IBD and could be assessed only by colonoscopy.

Endoscopic disease activity graded by modified Baron index correlated best with fecal calprotectin, followed by the clinical Lichtiger index more than serum CRP, platelets, blood leukocytes, and hemoglobin<sup>[17,18]</sup>. Fecal calprotectin was reported to be the only marker that could discriminate between different grades of endoscopic activity. In ulcerative colitis, a fecal calprotectin  $> 250 \mu\text{g/g}$  indicated active disease (Mayo subscore  $> 0$ ) with a sensitivity of 71.0% and a specificity of 100%<sup>[3]</sup>. Low fecal calprotectin levels correlated well with histological remission (Geboes score  $< 3.1$ ) and mucosal healing<sup>[19]</sup>. In addition, fecal calprotectin measurement can be used to identify patients with increased risk of relapse after 6 and 12 months and to predict histological healing<sup>[20]</sup>. Fecal lactoferrin, polymorphonuclear neutrophil elastase as well as calprotectin are noninvasive markers for the assessment of intestinal inflammation in IBD<sup>[21]</sup>. Fecal calprotectin is better in sensitivity and specificity for the assessment of colonic mucosal activity than serum CRP. Scientific workshop of the ECCO II proposed that biomarkers such as CRP and fecal calprotectin were surrogate markers for mucosal healing<sup>[2]</sup>.

On the other hand, a quantitative fecal immunochemical test (FIT) for measuring hemoglobin in the feces was reported to predict mucosal healing in UC<sup>[22]</sup>. FIT and fecal calprotectin results were significantly correlated with the Mayo endoscopic subscore. The sensitivities of FIT were similar when mucosal healing was defined as Mayo endoscopic subscore 0 or 0 and 1. FIT appeared to be more sensitive than fecal calprotectin for predicating Mayo

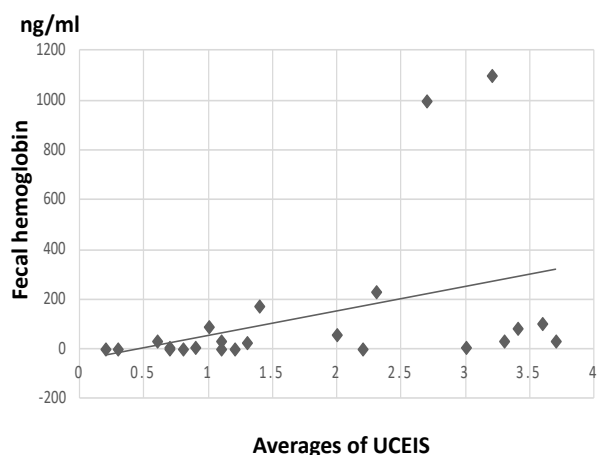


Figure 4 Correlation between fecal hemoglobin levels and UCEIS scores.

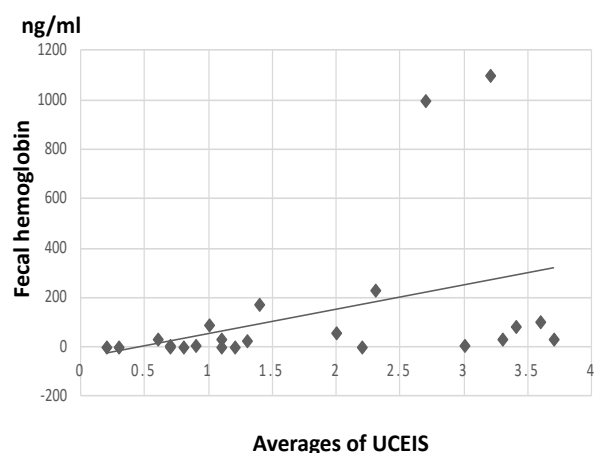


Figure 5 Correlation between fecal hemoglobin levels and histopathological inflammation index.

endoscopic subscore 0 alone. Mooiweer and et al. reported that when they measured fecal hemoglobin and calprotectin for evaluating endoscopic inflammation, combining both tests did not increase the predictive accuracy substantially compared with calprotectin or hemoglobin alone<sup>[23]</sup>.

This study was done to clarify which of fecal calprotectin and / or FIT was better marker for the mucosal healing in UC on the base of averages of sum Mayo endoscopic subscore and UCEIS. Mayo endoscopic subscore 0 is normal mucosa and subscore 1 is composed of erythema, decreased vascular pattern and mild friability. Mayo endoscopic subscore 0 and 1 are thought to be mucosal healing. Score for mucosal healing assessed by UCEIS is now available, but mucosal healing is thought at least to be no bleeding, no erosion and ulcers regardless of mucosal vascular pattern. Abnormal mucosal vascular pattern alone is contained in Mayo endoscopic subscore 1. The area under the curve analyzed by ROC was almost similar fecal calprotectin and hemoglobin in case of sum Mayo subscore less than 1 ( $p = 0.81$ ).

To assess the Youden index based on our data which defines the maximum potential effectiveness of a biomarker, cut-off index of fecal calprotectin levels were settled to be 88.5  $\mu\text{g/g}$  (sensitivity 87%, specificity 86%) and that of fecal hemoglobin levels 16 ng/mL (sensitivity 100%, specificity 80%) in case of sum Mayo subscore less than 1, and 193  $\mu\text{g/g}$  (sensitivity 100%, specificity 83.3%) and 33ng/mL (sensitivity 90.9%, specificity 66.6%) in case of sum Mayo subscore less than 5 without 2 and/ or 3 at any segments, respectively.



Geboes scores good for assessment of histological findings of UC are composed of architectural changes, chronic inflammatory infiltrates, lamina propria neutrophils and eosinophils, neutrophils in epithelium, crypt destruction and erosion or ulceration<sup>[24]</sup>. This study to assess the UC inflammatory severity was made much of chronic and acute inflammatory cell infiltrates in the mucosa and erosions and / or ulceration, because it was thought that calprotectin was derived from the inflammatory infiltrates in the mucosa and much through the erosive mucosa and that fecal hemoglobin are derived from mucosal congestion and erosions and ulcers.

Question whether the mucosal healing in UC is Mayo endoscopic score 0 or score 0 and 1 is very important for IBD clinicians. Arai *et al* reported that the recurrence rate increased gradually as it became more endoscopically severe in patients with clinical remission (5.0% for UCEIS = 0, 22.4% for UCEIS = 1, 27.0% for UCEIS = 2, and 35.7% for UCEIS = 3)<sup>[25]</sup>. Therefore, our study would need prognostic survey of disease relapse, hospitalization and operation rate.

Normal ranges of fecal calprotectin measurements are different among the commercial kits<sup>[7]</sup>; 17 to 128 in Schoepfer's paper, less than 100 in Prell's paper, and less than 250 µg/g<sup>[26]</sup>. It seems to be difficult to determine the normal ranges among the commercial kits. Therefore, the same commercial kits are recommended to assess the follow-up study. The receiver operating characteristic curve (ROC) is used to evaluate a biomarker's ability for classifying disease status.

A limitation of this study is a small sample and its data from single institution. A large -scale multi-center study may be necessary. However, an advantage of this study is that digital endoscopic pictures for each patient were assessed by three experienced endoscopists and mucosal inflammatory severity was histologically assessed by two experienced pathologists. Endoscopic assessment for mucosal inflammatory grades has dispersion among endoscopists<sup>[27]</sup>. To address the inter-observer variability dispersion in the endoscopic assessment will be needed for studies using endoscopy, for examples judging by endoscopic AI. Fecal immunochemical test is a good inflammatory biomarker for estimating mucosal healing in ulcerative colitis and less expensive than fecal calprotectin. Costs of faecal calprotectin and haemoglobin are 25 US dollars (Japanese health insurance) and 3.7, respectively. This is a strong point.

## ACKNOWLEDGEMENT

We thank the cooperation of members of clinical laboratory for the measurement of biomarkers.

**Funding:** This work was supported by the grant of Nipponkoukan hospital.

## REFERENCE

- Neurath MF, Travis SPL. Mucosal healing in inflammatory bowel disease: a systematic review. *Gut* 2012; **61**: 1619-1635. [PMID: 22842618]; [DOI: 10.1136/gutjnl-2012-302830]
- Daperno M, Castiglione F, de Ridder L, Dotan I, Farkkila M, Florholmen J, Fraser G, Fries W, Hebuterne X, Lakatos PL, Panes J, Rimola J, Louis E, Results of the 2nd part scientific workshop of the ECCO (II): Measures and markers of prediction to achieve, detect, and monitor intestinal healing in inflammatory bowel disease. *J Crohns Colitis* 2011; **5**: 484-498. [PMID: 21939926]; [DOI: 10.1016/j.crohns.2011.07.003]
- D'Haens G, Ferrante M, Vermeire S, Baert F, Notman M, Moortgat L, Geens P, Iwens D, Aerden J, Van Assche G, Van Olmen G, Rutgeerts P. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis* 2012; **18**: 2218-2224. [PMID: 22344963]; [DOI: 10.1062/ibd.22917]
- Bodelier AG, Jonkers D, van den Heuvel T, de Boer E, Hameeteman W, Masclee AA, Pierik MJ. High percentage of IBD patients with indefinite fecal calprotectin levels: additional value of a combination score. *Dig Dis Sci* 2017; **62**: 465-472. [PMID: 27933473]; [DOI: 10.1007/s10620-0016-4397-6]
- Nakarai A, Kato J, Hiraoka S, Kuriyama M, Akita M, Hirakawa T, Okada H, Yamamoto K. Evaluation of mucosal healing of ulcerative colitis by a quantitative fecal immunochemical test. *Am J Gastroenterol* 2013; **108**: 83-89. [PMID: 23007005]; [DOI: 10.1038/ajg.2012.315]
- Truelove SC, Witts LJ. Cortisone in ulcerative colitis. *Br Med J* 1955; **2**: 1041-1048. [PMID: 13260656]
- Prell C, Nagel D, Freudenberg F, Schwarzer A, Koletzko S. Comparison of three tests for faecal calprotectin in children and young adults: a retrospective monocentric study. *BMJ Open* 2014; **4**: e004558. [PMID: 24793248]
- Takeshita T, Horiguchi J, Kinoshita T, Kubota Y, Chen PC, Katumata S, Horimukai F, Miyaoka E, Matsumoto T, Saitou T, Ashizawa S. Latex agglutination test for fecal occult blood. *The journal of the Japan society of coloproctology* 1985; **38**: 780-783. (in Japanese with English abstract).
- Lobaton T, Bessissow T, De Hertogh G, Lemmens B, Van Assche G, Vermeire S, Bisschops R, Rutgeerts P, Bitton A, Afif W, Marcus V, Ferrante M. The modified Mayo endoscopic score (MMES): a new index for the assessment of extension and severity of endoscopic activity in ulcerative colitis patients. *J Crohns Colitis* 2015; **9**: 846-852. [PMID:26116558]; [10.1093/ecco-jcc/jjv111]
- Travis SPL, Schnell D, Kizeski P, Abreu MT, Altman DG, Colombel JF, Feagan BG, Hanauer SB, Lemann M, Lichtenstein GR, Marteau P, Reinish W, Sands BE, Yacyszyn BR, Bernhart CA, Mary JY, Sandborn WJ. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the ulcerative colitis endoscopic index of severity (UCEIS). *Gut* 2012; **61**: 535-542. [PMID: 21997563]; [DOI: 10.1136/gutjnl-2011-300486]
- Joseph NE, Weber CR. Pathology of inflammatory bowel disease. In: Baumgart DC, Eds. *Crohn's disease and ulcerative colitis*, 2nd eds. Berlin, Springer, 2017: 245.
- Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez J, Muller M. pROC: an open-source package for R and S to analyze and compare ROC curves. *BMC Bioinformatics*. 2011; **12**: 77. [PMID: 21414208]; [DOI: 16.1186/1471-2105-12-77]
- Kendall MG, Smith B. The problem of m rankings. *Am Mathematic Stat*. 1939; **10**: 275-287.
- Roseth AG, Fagerhol MK, Aadland E, Schjonby H. Assessment of the neutrophil dominating protein calprotectin in feces. A methodologic study. *Scand J Gastroenterol* 1992; **27**: 793-798. [PMID: 1411288]
- Anezaki K, Asakura H, Honma T, Ishizuka K, Funakoshi K, Tsukada Y, Narisawa R. Correlations between interleukin-8, and myeloperoxidase or luminol-dependent chemiluminescence in inflamed mucosa of ulcerative colitis. *Intern Med* 1998; **37**: 253-258. [PMID: 9617859]
- Guardiola J, Lobaton T, Rodriguez-Alonso L, Ruiz-Cerulla A, Arajol C, Loayza C, Sanjuan X, Sanchez E, Rodriguez-Morata F. Fecal level of calprotectin identifies histologic inflammation in patients with ulcerative colitis in clinical and endoscopic remission. *Clin Gastroenterol Hepatol* 2014; **12**: 1865-1870. [PMID: 24993368]; [DOI: 10.1016/j.cjgh.2014.06.020]
- Schoepfer AM, Beglinger C, Straumann A, Safroneeva E, Rometo Y, Armstrong D, Schmidt C, Trummel M, Pittet V, Vavricka ST. Fecal calprotectin more accurately reflects endoscopic activity of ulcerative colitis than the Lichtiger index, C-reactive protein, platelets, hemoglobin, and blood leukocytes. *Inflamm Bowel Dis* 2013; **19**: 332-341. [PMID: 23328771]; [DOI: 10.1097/MIB.06013e3182610066]
- Lichtiger S, Present DH, Kombluth A, Gelernt I, Bauer J, Galler G,

- Michelassi F, Hanauer S. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994; **330**: 1841-1845. [PMID: 8196726]; [DOI: 10.1056/NEJM19940630330260]
19. Zittan E, Kelly OB, Kirsh R, Milgrom R, Burns J, Nguyen GC, Croitoru K, Van Assche G, Silverberg MSD, Steinhart AH. Low fecal calprotectin correlates with histological remission and mucosal healing in ulcerative colitis and colonic Crohn's disease. *Inflamm Bowel Dis* 2016; **22**: 623-630. [PMID: 26829408]
  20. Theede K, Holck S, Ibsen O, Kallemose T, Nordgaard-Lassen I, Nielsen AM. Fecal calprotectin predicts relapse and histological mucosal healing in ulcerative colitis. *Inflamm Bowel Dis* 2016; **22**: 1042 -1048. [PMID: 26911460]; [DOI: 10.1097/MIB0000000000000736]
  21. Langhorst J, Elsenbruch S, Koelzer J, Rueffer A, Michalsen A, Dobos GJ. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elasticase, CRP, and clinical indices. *Am J Gastroenterol* 2008; **103**: 162 -169. [PMID: 17916108]; [DOI: 10.1111/j.1572-02H.2007.01556.x]
  22. Takashima S, Kato J, Hiraoka S, Nakarai A, Takei D, Inokuchi T, Sugihara Y, Takahara M, Harada K, Okada H, Tanaka T, Yamamoto K. Evaluation of mucosal healing in ulcerative colitis by fecal calprotectin vs. fecal immunochemical test. *Am J Gastroenterol* 2015; **110**: 873-880. [PMID: 25823769]; [DOI: 10.1038 /ajg.2015.66]
  23. Mooiweer E, Fidder HH, Siersema PD, Laheij RJ, Oldenburg B. Fecal hemoglobin and calprotectin are equally effective in identifying patients with inflammatory bowel disease with active endoscopic inflammation. *Inflamm Bowel Dis*. 2014; **20**: 307-314. [PMID: 24374878]; [DOI: 10.1097/01MIB0000438428.30800.a6]
  24. Geboes K, Riddell R, Ost A, Jonsfelt B, Persson T, Lofberg R. A 6 Otsuka S et al. Fecal calprotectin, or fecal hemoglobin for mucosal healing in UC reproducible grading scale for histological assessment of inflammation in ulcerative colitis. *Gut* 2000; **47**: 404-409. [PMID: 10940279]; [DOI: PUC1728046]
  25. Arai M, Naganuma M, Sugimoto S, Kiyohara H, Ono K, Mori K, Saigusa K, Nanki K, Mutaguchi M, Mizuno S, Bessho R, Nakazato Y, Hosoe N, Matsuoka K, Inoue N, Ogata H, Iwao Y, Kanai T. The ulcerative colitis endoscopic index of severity is useful to predict medium -to long - term prognosis in ulcerative colitis patients with clinical remission. *J Crohns Colitis* 2016; **10**: 1303-1309. [PMID: 27194529]; [DOI: 10.1093/ecco-jcc/jjw104]
  26. Kristensen V, Roseth A, Ahmad T, Skar V, Moum B. Fecal calprotectin: a reliable predictor of mucosal healing after treatment for active ulcerative colitis. *Gastroenterol Res Pract* 2017; **2017**: 2098293. [PMID: 29225617]; [DOI: 10.1155/2017/2098293]
  27. Samuel S, Bruining DH, Loftus EV Jr, Thia KT, Schroeder KW, Tremaine WJ, Faubion WA, Kane SV, Paradi DS, de Groen PC, Harmsen WS, Zinsmeister AR, Sandborn WJ. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. *Clin Gastroenterol Hepatol* 2013; **11**: 49-54. [PMID: 22902762]; [DOI: 10.1016/j.cgh.2012.08.003]

**Peer Reviewer:** Michael Lim