Fecal calprotectin predicts complete mucosal healing in patients with ulcerative colitis: Systematic review and meta-analysis

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Abstract. Complete mucosal healing (MH) is a significant therapeutic goal for ulcerative colitis (UC). Fecal calprotectin (FC) is a promising biomarker for the assessment of the endoscopy activity of UC. However, the accuracy of FC for predicting complete MH in patients with UC has yet to be clearly demonstrated. The present study aimed to evaluate the accuracy of FC in predicting complete MH in patients with UC. A systematic search was made of the databases from 1992 to October, 2020 that evaluated MH in UC. The methodological quality of each study was assessed according to the quality assessment of diagnostic accuracy studies checklist. Colonoscopy is considered the gold standard for the assessment of mucosal inflammation. The data were pooled using a summary receiver operating characteristic curve model. The diagnostic odds ratio, sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were summarized by the random-effects model. A total of 7 publications comprising 820 patients with UC were included in the meta-analysis. The pooled sensitivity and specificity values for predicting complete MH in the patients with UC 0.77 (95% CI, 0.72-0.82) and 0.80 (95% CI, 0.77-0.83), respectively. The fecal calprotectin level had a high rule-in value (PLR, 3.76; 95% CI, 3.07-4.60) and a moderate rule-out value (NLR, 0.30; 95% CI, 0.24-0.37) for predicting complete MH in patients with UC. The results of the ROC curve analysis (area under the curve, 0.85; standard error of the mean, 0.02) and diagnostic odds ratio (13.06; 95% CI, 9.04-18.88) also revealed discrimination for predicting complete MH in patients with UC. On the whole, the present study found that FC is a reliable non-invasive biomarker for predicting complete MH in patients with UC.

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Abbreviations: FC, fecal calprotectin; MH, mucosal healing; MES, Mayo endoscopic subscore; UC, ulcerative colitis

Key words: inflammatory bowel disease, ulcerative colitis, fecal calprotectin, complete mucosal healing, meta-analysis

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by episodes of exacerbation and periods remission (1). In this context, the evaluation of disease severity is of importance for selecting the suitable treatment. Therapeutic goals that focus on clinical remission have failed to modify the natural course of UC (2). Therefore, the therapeutic goal of UC has evolved beyond the control of symptoms towards the tight control of intestinal inflammation (3). Over the past years, mucosal healing (MH) has emerged as a major therapeutic goal for patients with UC, as MH is associated with better outcomes for patients with inflammatory bowel disease. Patients who achieve MH have been shown to have a lower rate of relapse and a reduced risk of colectomy and hospitalization (4-6). However, the definition of MH in patients with UC has yet to be formally established. An international organization of inflammatory bowel disease task defines MH as the absence of friability, blood, erosions, or ulcers in the colonic mucosa (7). Since the study by Colombel *et al* (8), MH has been defined as a Mayo endoscopy subscore (MES, 0/1), regardless of histological findings. However, this definition of MH is associated with mild friability and erythema in the colonic mucosa (9). Erythema and mild friability indicate an inflammatory condition in the colonic mucosa. Moreover, some studies have demonstrated that the relapse rate of patients who achieved complete MH (MES=0) was lower than that of patients who achieved MH (MES, 1) (10,11). It is a desired therapeutic endpoint for patients with UC to achieve complete MH rather than MH. Colonoscopy is considered the

gold standard for the assessment of mucosal inflammation, which is reliable and accurate (12). However, it is an invasive, expensive and time-consuming procedure. In this regard, a reliable, noninvasive biomarker to predict complete MH is of utmost importance. Fecal markers for the status of intestinal mucosa have been evaluated in some studies and have been shown to correlate well with endoscopic activity (13,14). The common fecal markers include fecal calprotectin (FC) and fecal immunochemical test (FIT). FIT is a surrogate marker for detecting stool hemoglobin derived from blood loss in mucosal ulceration. In addition, the predictive utility of FIT has been evaluated in some studies (15-18). FC, which has been found in the cytosol of macrophages and neutrophils, is a calcium and zinc binding protein of the S-100 protein family. It is noteworthy that FC is resistant to degradation and stable. The amount of FC is proportional to the amount of neutrophil migration into the gut lumen and can be used as a sensitive biomarker of intestinal inflammation (19).

Although the utility of FC in UC has been evaluated in some studies, the accuracy of FC for predicting complete MH have yet to be clearly demonstrated (18,20-25), at least to the best of our knowledge. The aim of the present study was to evaluate the overall diagnostic accuracy of FC for predicting complete MH in patients with UC.

Materials and methods

Literature search. The PRISMA guidelines for systematic reviews were strictly followed. A systematic search was performed of the databases, including PubMed and EMBASE for relevant studies from 1992 to October, 2020 that evaluated MH in UC by FC. Both medical subject heading (MeSH) terms and free words were used. Suitable search terms were used as follows: 'inflammatory bowel disease' OR 'IBD' OR 'Crohn's enteritis' OR 'Crohn's disease' OR 'ulcerative colitis' OR 'colitis' OR 'enteritis' AND 'fecal calprotectin' OR 'calprotectin'. The language was limited to English. Reviews and references of related literature were searched manually.

Study selection. Articles were first screened by 2 independent reviewers (W.P. and Z.C.) based on the title and abstract. The full text of an eligible study was then assessed independently. Disagreements were resolved by discussion. Studies were eligible if they met the following inclusion criteria: i) All the patients included had an established diagnosis of UC according to endoscopic and histologic assessments; ii) the study evaluated FC for predicting complete MH in patients with UC; iii) endoscopic activity was evaluated by the MES; iv) colonoscopy was considered the gold standard for the assessment of mucosal inflammation; and v) the studies contained appropriate data to calculate true-positive, false-positive, true-negative and false-negative results.

Data extraction and quality assessment. The 2 investigators, J.J. and Z.C., extracted the relevant data independently. The data extracted from the articles included the authors, country, the publication year, age, patient characteristics, the criteria and the FC features (method and cut-off). The true-positive, false-positive, false-negative and true-negative values were calculated for each included study.

The methodological quality of the included articles was assessed by 2 authors (Z.C. and L.L.) independently using the quality assessment of diagnostic accuracy studies (QUADAS-2) tool (26). The QUADAS-2 tool comprises 4 domains: Patient selection, reference standard, index test, and flow and timing. Each domain is assessed in terms of the risk of bias. This tool consisted of 14 predefined validated questions as described in Table I. Disagreements were resolved by discussion with the senior reviewer (J.J.).

Data synthesis and statistical analysis. Standard methods were used in the current meta-analysis, as recommended in the 'Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy' (https://methods.cochrane.org/sdt/handbook-dta-reviews). Sensitivity, specificity, the positive likelihood ratio (PLR), the negative likelihood ratio (NLR) and the diagnostic odds ratio (DOR), were calculated for each study, respectively. For the data analysis, summary receiver operating characteristic (SROC) curves and average operating points were estimated with each commonly applied cut-off value. An SROC curve with 95% confidence region and 95% prediction region was performed to examine the interaction between sensitivity and specificity. DOR and the area under the SROC curve were calculated to evaluate the diagnostic performance of FC for complete mucosal healing in patients with UC. Area under the curve of 0.5 indicates a completely uninformative test and 1 a perfect test. Pooled sensitivity, specificity and their 95% confidence intervals (CIs) were calculated using a random-effects model at each threshold. The heterogeneity was evaluated by a Chi-squared test or Q-statistic and Higgins I-squared statistic (I^2). A P-value <0.1 was considered statistically significant heterogeneity for the Chi-squared or Q-statistics. The percentage of I^2 represented the degree of heterogeneity. I^2 percentages of 25, 50 and 75% indicated a low, moderate and high degree of heterogeneity, respectively. Potential sources of heterogeneity investigated were age, sample size, race and study type. Heterogeneity was evaluated by including all potential covariates into a regression model. Publication bias was assessed using Deeks' test. P<0.05 was considered to indicate statistically significant publication bias. Statistical analysis was performed on META-DISC (version 1.4 for Windows), REVIEW MANAGER (version 5.3) and STATA (version 15).

Results

Study characteristics. As shown in Fig. 1, 6,499 publications are available after the initial search. After reading the titles and abstracts and reviewing the full texts, 7 publications, including 820 patients with UC were included in the analysis. The clinical characteristics of the included studies are listed in Table II. All studies enrolled patients diagnosed with UC. In total, 3 of the studies were conducted in Europe [1 study in Spain (22), 1 study in Denmark (23) and 1 study in Norway (20)]. In addition, 3 of the studies were conducted in Asia [1 study in Korea (25) and 2 in Japan (18,21)]. Furthermore, 1 study was conducted in the USA (24). In the USA or Europe, FC is widely used in monitoring the disease activity and MH in UC. The gold standard of the included studies was based on

Table I. QUADAS Results for assessment of included studies

Author/(Refs.), year	Quality assessment using the QUADAS tool													
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14
Hiraoka *et al* (21), 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Takashima *et al* (18), 2015	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Mak *et al* (24), 2018	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Lobatón *et al* (22), 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kristensen *et al* (20), 2015	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Theede *et al* (23), 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Unclear	Yes	Yes	Yes
Ryu *et al* (25), 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	Unclear	Yes	Yes	Yes

Item 1, representative spectrum of patients; item 2, selection criteria; item 3, reference standard reliable; item 4, time interval between FC test and reference standard (defined as ≤3 days); item 5, whole or random sample received verification; item 6, same reference standard; item 7, reference standard independent of the index test; item 8, clear description of the index test; item 9,: clear description of the reference standard; item 10, interpretation of FC test blinded from reference; item 11, interpretation of reference blinded from FC test; item 12, clinical data same as practice; item 13, uninterruptable test results reported; item 14, withdrawals explained (studies without withdraws also treated as a 'yes').

Table II. Characteristics of the included studies.

Author/(Refs.), year	Country	Mean age (years)	Design	Criteria	No. of patients	Cut-off (μg/g)	TP	FP	FN	TN	SEN	SPE	PPV	NPV
Theede *et al* (23), 2015	Denmark	36.6	Cross-sectional	MES=0	120	192	24	11	8	77	0.75	0.88	0.71	0.90
Ryu *et al* (25), 2019	Korea	47.2	Retrospectively	MES=0	174	170	40	31	11	92	0.78	0.75	0.56	0.89
Takashima *et al* (18), 2015	Japan	35.5	Prospectively	MES=0	105	200	34	17	10	44	0.77	0.72	0.67	0.81
Mak *et al* (24), 2018	USA	29.3	Prospectively	MES=0	61	200	4	11	1	45	0.75	0.80	0.22	0.98
Lobatón *et al* (22), 2013	Spain	47	Prospectively	MES=0	146	160	24	17	12	93	0.67	0.85	0.59	0.89
Hiraoka *et al* (21), 2018	Japan	44	No statement	MES=0	152	224	62	16	16	58	0.79	0.78	0.79	0.78
Kristensen *et al* (20), 2015	Norway	35.5	Prospectively	MES=0	62	96	16	7	2	37	0.91	0.83	0.93	0.79

MES, Mayo endoscopic subscore; PPV, positive predictive value; NPV, negative predictive value; SEN, sensitivity; SPE, specificity; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

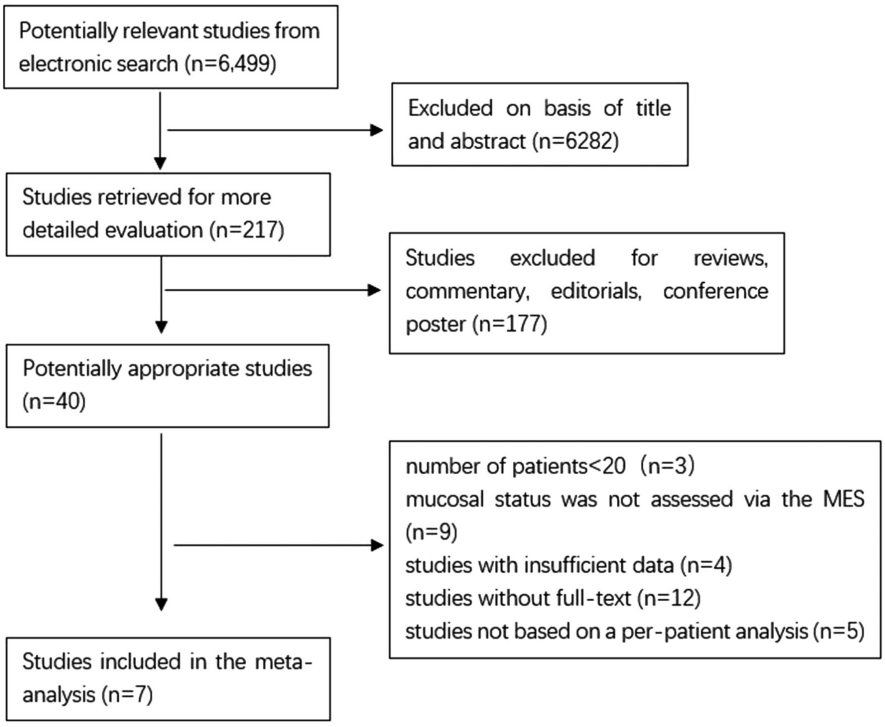

Figure 1. Flow diagram of articles retrieved and inclusion progress through the stage of meta-analysis.

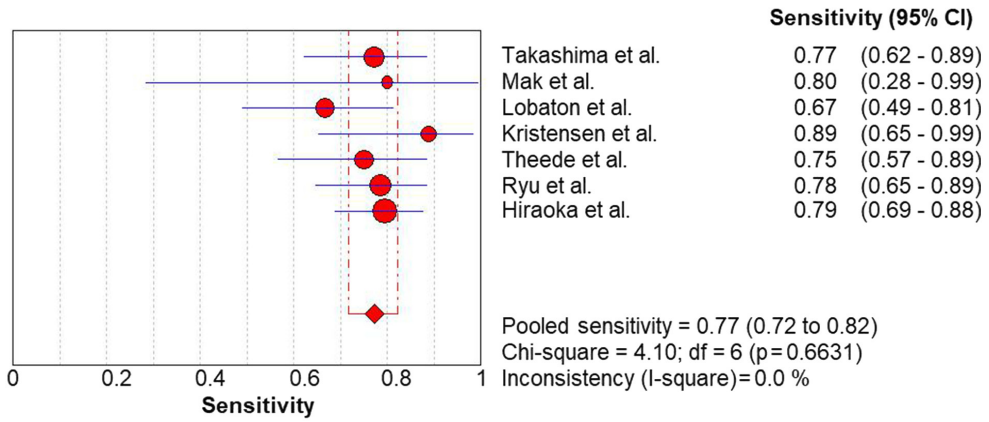

Figure 2. Forest plot of the sensitivity for predicting complete mucosal healing in ulcerative colitis by fecal calprotectin. CI, confidence interval.

endoscopy. The MES was used to assess the mucosal status of patients with UC. Complete MH was defined as a MES of 0.

Methodological quality assessment. The methodological quality was assessed by 2 authors independently, using the QUADAS-2 tool. All trials included in the present study were of good quality, and the results are presented in Table I. The scores of the included studies were over 10 rated with a 'yes', indicating that the included studies were of high quality. The weakness of the majority of studies was the FC test lacking blinding from the reference standard. The gold standard for evaluating complete MH was based on endoscopy in all studies. All studies were deemed to have a representative spectrum of patients. The clinical characteristics of the included studies are listed in Table II. There was no evidence of commercial funding in the included studies.

Diagnostic accuracy meta-analysis. The pooled sensitivity (Fig. 2) and specificity (Fig. 3) values for predicting complete MH in UC were 0.77 (95% CI, 0.72-0.82) and 0.80 (95% CI, 0.77-0.83), respectively. The FC level had a high rule-in value (PLR, 3.76; 95% CI, 3.07-4.60) (Fig. 4) and a moderate rule-out value (NLR, 0.30; 95% CI, 0.24-0.37) (Fig. 5) for predicting complete MH in UC. The results of the ROC curve analysis (area under the curve, 0.85; standard error of the mean, 0.02) (Fig. 6) and DOR (13.06; 95% CI, 9.04-18.88) (Fig. 7) also revealed high discrimination for predicting complete MH in UC.

Heterogeneity and meta-regression. Results of the meta-regression examining the effect of various parameters on study outcomes are shown in Fig. 8. Among the parameters included in the meta-regression, study type and race appeared

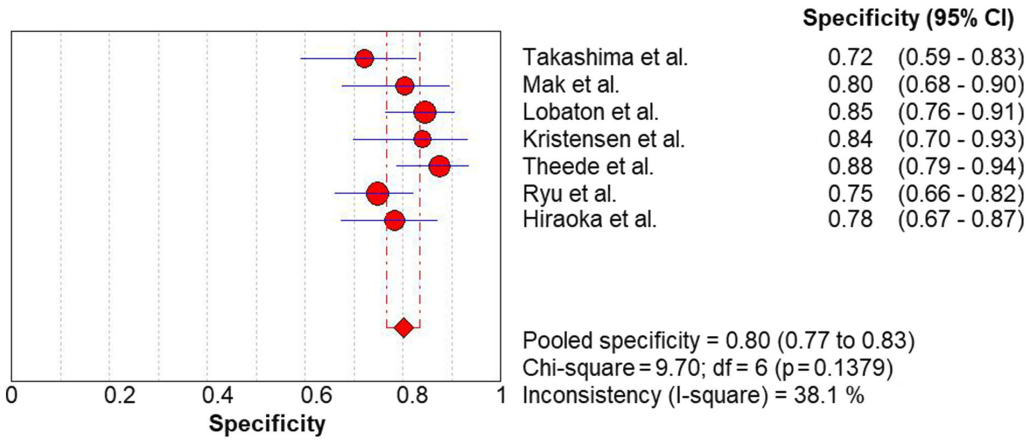

Figure 3. Forest plot of the specificity for predicting complete mucosal healing in ulcerative colitis by fecal calprotectin. CI, confidence interval.

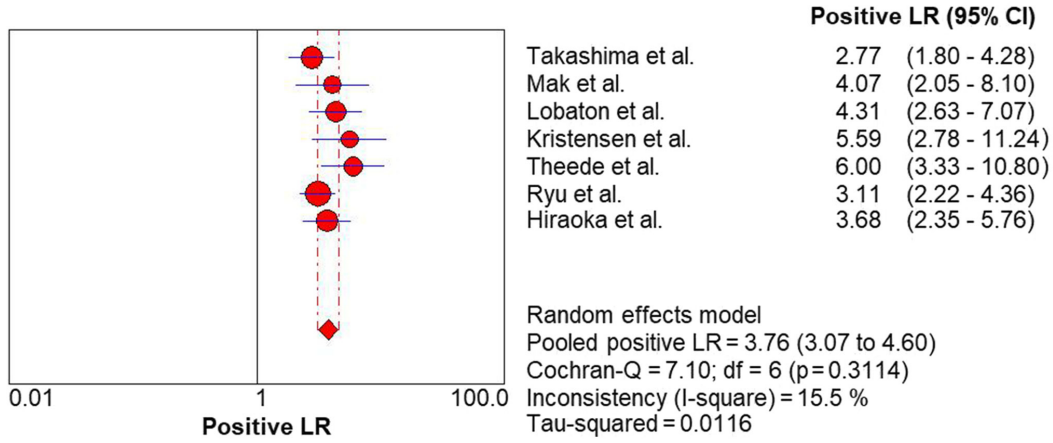

Figure 4. Forest plot of the positive likelihood ratio for predicting complete mucosal healing in ulcerative colitis by fecal calprotectin. CI, confidence interval.

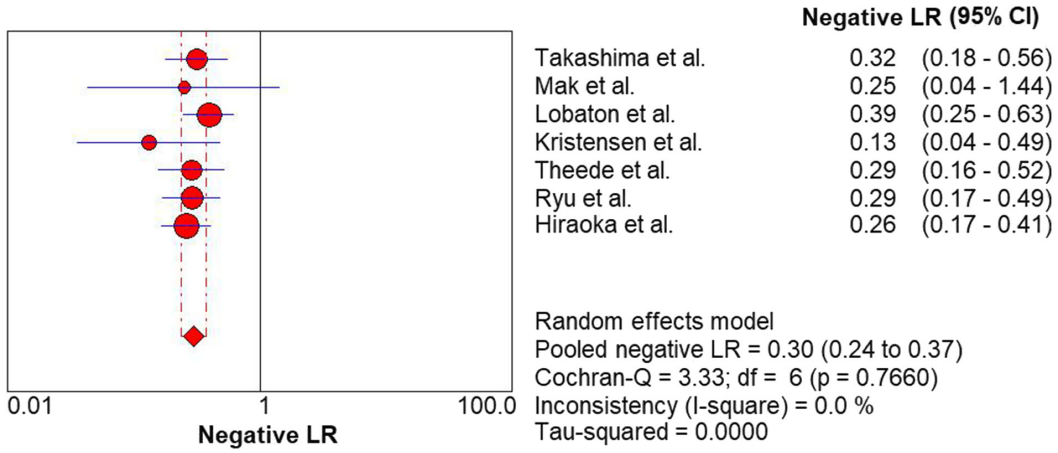

Figure 5. Forest plot of the negative likelihood ratio for predicting complete mucosal healing in ulcerative colitis by fecal calprotectin. CI, confidence interval.

to contribute significantly to heterogeneity in FC studies (P<0.05).

Publication bias. A funnel plot for the analysis of publication bias was performed to compare the yield of FC levels for assessing complete MH in UC. The Deeks' test revealed no evidence of publication bias (P=0.30) (Fig. 9).

Discussion

Over the past years, MH has emerged as a major therapeutic endpoint for patients with UC. Patients who achieve MH have been shown to have a lower rate of relapse and a reduced risk of colectomy and hospitalization (4-6). Several scoring systems are used for evaluating endoscopic activity of UC,

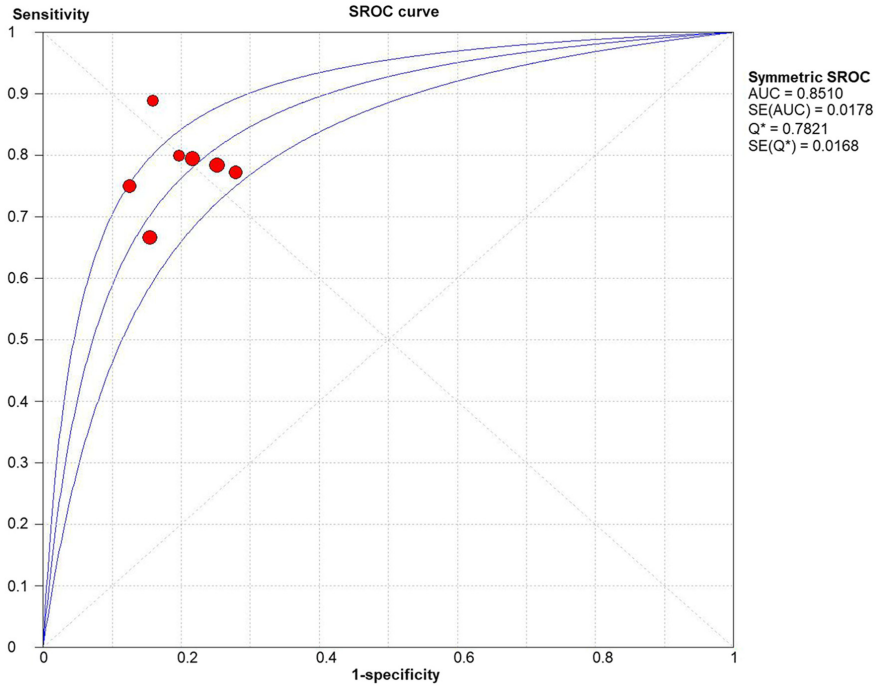

Figure 6. SROC curve for predicting complete mucosal healing in ulcerative colitis by fecal calprotectin. SROC, summary receiver operating characteristic.

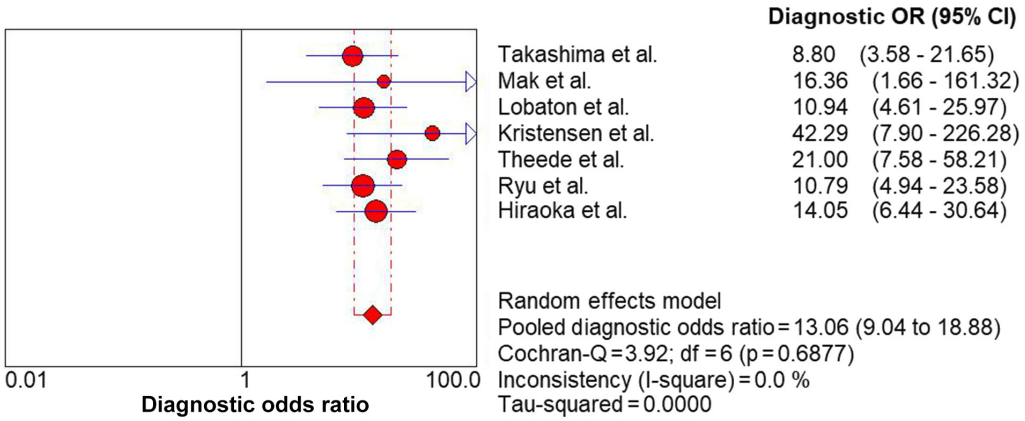

Figure 7. Forest plot of the diagnostic odds ratio for predicting complete mucosal healing in ulcerative colitis by fecal calprotectin. AUC, area under the curve; CI, confidence interval.

among which MES is the most common one. MES is easy to use, and has a demonstrated prognostic value. According to MES, MH is often defined as a MES of 0/1, which includes mild friability and erythema (9). Erythema and mild friability indicate an inflammatory condition in the colonic mucosa. Moreover, some studies have shown that the relapse rate of patients who achieved complete MH was lower than that of patients who achieved MH. Complete MH should be a desired therapeutic goal for patients with UC to improve long-term outcomes (10,11). Colonoscopy is considered the gold standard for assessment of mucosal status. It is an invasive and costly procedure. Therefore, the identification of a reliable, non-invasive marker to predict MH is crucial. The common fecal markers in UC include FIT and FC. A recent meta-analysis revealed that the sensitivity and specificity of the FIT result for predicting MH in UC were 0.77 and 0.81, respectively (27). FIT measures the amount of blood from the damaged bowel mucosa, and it is used for colorectal cancer screening. The level of FIT is also increased in colorectal cancer (28). Therefore, FIT is only used to evaluate IBD mucosal status, rather than distinguishing between UC and other diseases. FC is a neutrophil-derived protein of the S-100 protein family. The amount of FC is proportional to the amount of neutrophil migration into the gut lumen and can be used as a sensitive biomarker of intestinal inflammation. The level of FC is related to endoscopic severity (29), the prediction of relapse (30) and the prediction of mucosal healing. An early meta-analysis (31) comprising 1,471 patients with IBD [UC, 744; Crohn's disease (CD), 727] evaluated the accuracy of FC for differentiating between patients with active IBD and those in remission. FC exhibited an AUROC value of 0.89 in distinguishing between active and inactive IBD, being slightly higher for UC than for CD. The pooled sensitivity and specificity values were 0.80 and 0.82, respectively.

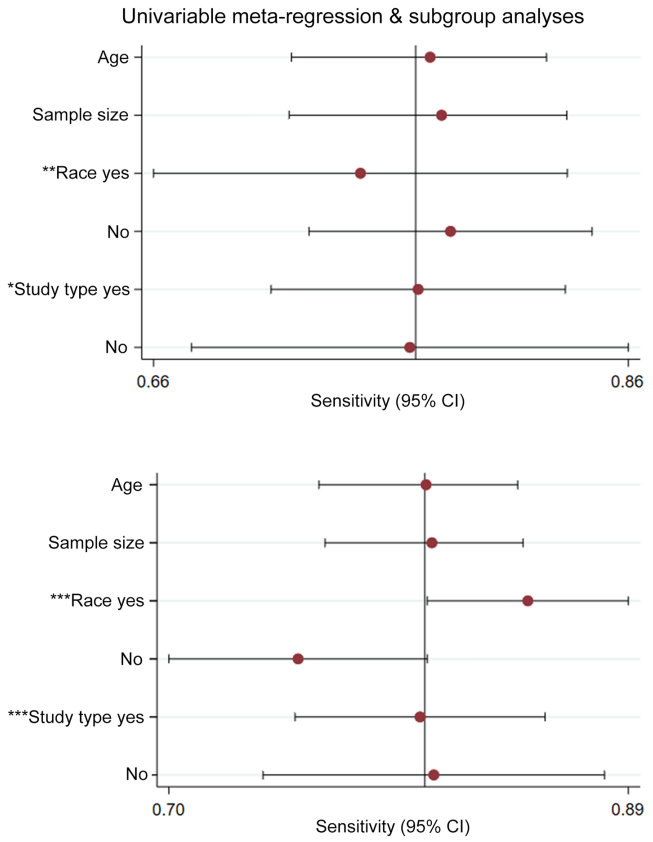

Figure 8. Meta-regression and subgroup analysis for sources of heterogeneity. CI, confidence interval. Race yes/no, other/mongoloid; study type yes/no, prospective study/other. *P<0.05, **P<0.01, ***P<0.001.

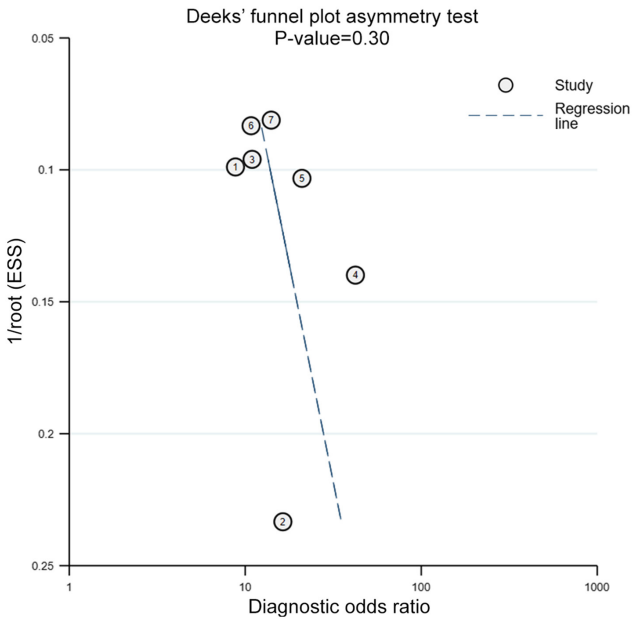

Figure 9. Deeks' funnel plot for evaluating publication bias.

A later meta-analysis (32) comprising 2,102 patients with IBD (UC, 1,069; CD, 1,033) compared 3 biomarkers (CRP, FC and fecal lactoferrin) with endoscopic activity as the gold standard. FC exhibited the highest combined values of pooled sensitivity and specificity (0.88 and 0.73, respectively). Although the usefulness of FC has been examined in some studies and meta-analyses in the past, the accuracy of FC for predicting complete MH (MES, 0) has yet to be clearly demonstrated, at least to the best of our knowledge. The aim of the present study was to evaluate the overall diagnostic accuracy of FC for predicting complete MH (MES, 0) in patients with UC. In the present study, through a systematic review and an appropriately performed meta-analysis, FC had a high sensitivity (0.77; 95% CI, 0.72-0.82) and a high specificity (0.80; 95% CI, 0.77-0.83) for predicting complete MH in UC. The estimated DOR for the FC in predicting complete MH of UC was 13.06 in the present study. This indicates that for the FC, the odds for positivity among subjects with complete MH of patients with UC is 13.06-fold higher than the odds for positivity among subjects without complete MH in patients with UC. In the present study, the pooled PLR and NLR were 3.76 and 0.30, respectively, suggesting that patients with UC with complete MH are 3-fold more likely to have lower FC levels. If the FC level is above the cut-off value, the probability of non-complete MH is 30%.

The concentration of FC is usually measured by quantitative enzyme-linked immunosorbent assay (ELISA). On the one hand, ELISA is reliable and most frequently used. On the other hand, ELISA has disadvantages, such as requiring a well-equipped laboratory, being a costly and time-consuming process (19). Currently, a new quantitative-point-of-care test (QPOCT) has been developed. The QPOCT is simple, and able to provide an exact number as ELISA (33). Some studies have explored its ability to predict endoscopic activity in patients with UC. Lee *et al* found that a cut-off value of 150.5 μg/g for the QPOCT had a sensitivity of 85.7% and a specificity of 100% for the prediction of endoscopic remission (19). Lobatón *et al* demonstrated that the Spearman's correlation coefficient rank between QPOCT and ELISA was 0.911 (P<0.001) (33). The good correlation between ELISA and the QPOCT allows the use of FC more easily in clinical practice. Recently, a new home test known as IBDOC has been validated. Weber *et al* demonstrated that the performance of the home testing system was comparable to laboratory-based ELISA method (34). Wei *et al* validated that the use of IBDOC to detect FC was feasible. The IBDOC consists of a stool extraction device called CALEX Value and an immunochromatographic rapid test (35). The test is simple and the results rapidly available to the physician. The educational level of patients with UC may be an obstacle. If the tool is implemented for the home monitoring of patients, thorough instruction and guidance are necessary.

The standardized measurement method and cut-off value of FC test have not been established. The included studies have used different assay kits, and the cut-off values used for prediction have varied among these studies (18,20-25). Thus, a standard measurement method of FC is warranted. Further large-scale studies are required to determine the optimal cut-off value of FC for predicting complete MH.

Through excluding studies that did not apply an endoscopy index as a reference standard, the present meta-analysis avoided the risk of partial verification bias. However, the present study has several limitations. Firstly, due to the limitation of the implementation conditions of FC assay, the majority of the included studies were conducted in tertiary centers. The majority of studies only recruited the patients with regular surveillance.

More multicenter large sample trials and strict patient access systems are required to precisely investigate the diagnostic accuracy of the FC for predicting complete MH in patients with UC. Secondly, the standardized measurement method and cut-off value of FC test have not been established, the non-uniform measurement methods may be the reason for the heterogeneous data. Thirdly, the majority of the corresponding authors could not be reached for further information of the clinical characteristics of the patients, restricting us from carrying out more analysis to investigate the source of heterogeneity.

In conclusion, the present study demonstrated that FC is a reliable non-invasive biomarker for predicting complete MH in patients with UC. Further designed studies are required to confirm such benefits and to find the best strategy of FC for predicting complete MH in patients with UC.

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Availability of data and materials

All data included in the present meta-analysis have been previously published and referenced.

Authors' contributions

WP, JJ, ZC, LL and CY carried out the literature search, selection, validity assessment, data abstraction and data analysis. WP, JJ and ZC wrote the manuscript and incorporated the comments from other authors and the peer reviewers. ZC, CY, LL, XG, WP and JJ conceived the study and contributed to data abstraction and analysis. All authors reviewed and approved the final draft of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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