Original Article

Diagnostic Accuracy of Fecal Calprotectin for the Detection of Small Bowel Crohn's Disease through Capsule Endoscopy: An Updated Meta-Analysis and Systematic Review

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See editorial on page 637.

Background/Aims: The diagnosis of small bowel Crohn's disease with negative ileocolonoscopic findings has been challenging. Fecal calprotectin (FC) has been used to detect colonic inflammation, but its efficacy for detecting small bowel inflammation is less established. We performed an updated meta-analysis to evaluate the diagnostic accuracy of FC to detect active small bowel inflammation observed during capsule endoscopy.

Methods: We conducted a systematic literature search for studies that evaluated the correlation between small bowel inflammation and FC in patients with suspected/established Crohn's disease. We calculated the pooled sensitivity, specificity, and diagnostic odds ratios (DORs) and constructed hierarchical summary receiver operating characteristic curves for FC cutoffs of 50, 100, and 200 μg/g.

Results: Fourteen studies were eligible for the final analysis. The DORs of all FC cutoffs were significant. The highest DOR was observed at 100 μg/g (sensitivity, 0.73; specificity, 0.73; and DOR, 7.89) and was suggested as the optimal diagnostic cutoff. If we analyzed only studies that included patients with suspected Crohn's disease, the DOR was 8.96. If we analyzed only studies that included patients with a Lewis score ≥135 as a diagnostic criterion for active disease, the DOR was 10.90.

Conclusions: FC has significant diagnostic accuracy for detecting small bowel inflammation, and an FC cutoff of 100 μg/g can be used as a tool to screen for small bowel Crohn's disease. **(Gut Liver 2021;15:732-741)**

Key Words: Biomarker; Capsule endoscopy; Fecal calprotectin; Small bowel Crohn's disease

INTRODUCTION

Crohn's disease is a chronic inflammatory disorder that is usually accompanied by anemia, bloody stool, and weight loss.[1] The presence of these symptoms is necessary to differentiate Crohn's disease from irritable bowel syndrome, with which Crohn's disease shares other symptoms such as abdominal pain, diarrhea, and bloating. It is difficult to differentiate Crohn's disease from irritable bowel syndrome in the absence of alarm symptoms. The small bowel is the most frequently involved site for Crohn's disease in both Asian (72.8% to 91.7%)[2-4] and Western populations (41% to 60.2%).[5-10] Ileocolonoscopy with biopsy is the gold standard to differentiate Crohn's disease from irritable bowel syndrome, but diagnosis can be challenging if ileocolonic manifestations are absent.[11] Therefore, biomarkers to detect small bowel inflammation are being widely investigated.

Fecal calprotectin (FC) is a 36-kDa protein secreted from stimulated neutrophils,[12] and it can be used to distinguish inflammatory bowel disease from functional gastrointestinal disorders such as irritable bowel syndrome.[13,14] In a meta-analysis of eight studies, a FC level of ≤40 μg/g excluded the likelihood that a patient had inflammatory bowel disease.[15]

Although FC can identify patients with small bowel inflammation, gastroduodenoscopy, colonoscopy, or small bowel capsule endoscopy are needed to correlate the diagnosis.[16] The predictive value of FC is well established in patients with colonic involvement of Crohn's disease,[17] and the addition of small bowel capsule endoscopy has been confirmed in several studies using inflammatory indices such as a Lewis score.[16,18-25] Recent prospective studies have suggested that FC can be used as a screening tool before patients undergo capsule endoscopy;[26-30] however, these studies have been limited by sample size and statistical power. Therefore, we conducted an updated meta-analysis to provide pooled diagnostic accuracy and a cutoff value of FC for the diagnosis of small bowel Crohn's disease.

MATERIALS AND METHODS

1. Literature searching strategy

A comprehensive literature search was performed on June 8, 2020, using PubMed, Embase, and the Cochrane Central Register of Controlled Trials in the Cochrane Library. This was a systematic review conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[31] We conducted a broad search using the terms "fecal calprotectin" and "capsule endoscopy" to capture as many number of citations as possible. Two authors (E.S.J. and H.J.J.) independently reviewed the titles and abstracts of all articles from the initial search and then reviewed the full text of articles of the most interest.

An independent evaluator (J.H.K.) resolved any disagreements.

2. Selection criteria

We included studies that met the following criteria: (1) the focus was FC and small bowel capsule endoscopy; (2) the design included randomized-controlled trials, open-label prospective studies, observational studies, or case-control studies; (3) the patients were undergoing evaluation for suspected Crohn's disease or reassessment of Crohn's disease activity;[32,33] (4) there were 35 or more cases; and (5) full-text publications in English. We excluded studies that evaluated suspected small bowel malignancy or obscure gastrointestinal bleeding.

3. Methodological quality assessment

To evaluate the methodological quality of the included studies, the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was used. Review Manager 5.4.0 (The Cochrane Collaboration, London, UK) was used to generate the summary figure of QUADAS-2 results.

4. Data extraction, primary outcome, and additional analyses

For each study, the number of true positive, false positive, false negative, and true negative results were extracted for FC level cutoffs of 50, 100, and 200 µg/g as available in each study.

The primary outcome of this study was diagnostic accuracy of FC to identify small bowel Crohn's disease or
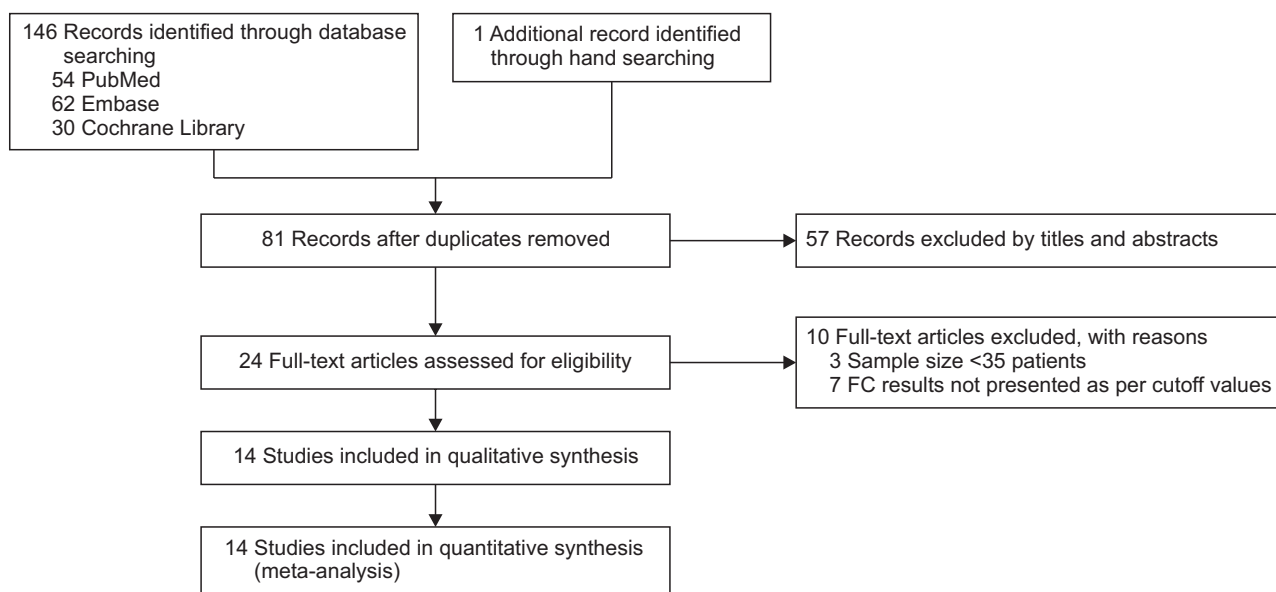
Fig. 1. Study flow diagram.
FC, fecal calprotectin.

Table 1. Summary of Data from the Included Studies

Author (year)	Study design	Indication	No. of patients	Negative ileo-colonoscopy	CE model	Diagnostic standard	Diagnostic criteria for CD	Country	Risk of bias
Koulaouzidis et al. (2011)[16]	Retrospective	Suspected CD	67	Yes	Pillcam Mirocam	Clinical	Clinical	UK	Low
Jensen et al. (2011)[20]	Prospective	Suspected CD	83	Yes	Pillcam	Clinical	Clinical	Denmark	Low
Sipponen et al. (2012)[25]	Prospective	Suspected CD (n=77) CD reassessment (n=7)	84	Yes	Pillcam Mirocam	CE	More than three ulcers on CE	Finland	Low
Kopylov et al. (Jan 2015)[21]	Retrospective	CD reassessment	106	NA	Pillcam Mirocam Olympus	CE	LS ≥135 for active disease	Canada, Sweden, UK	Low
Olsen et al. (2015)[24]	Retrospective	Suspected CD	50	Yes	Pillcam	CE	Characteristic CE findings	Norway	Low
Egea Valenzuela et al. (2015)[19]	Retrospective	Suspected CD	68	Yes	Not specified	CE	Characteristic CE findings	Spain	Unclear
Kopylov et al. (Sep 2015)[22]	Prospective	CD reassessment	52	NA	Pillcam	CE	LS ≥135 for active disease	Israel	Low
Egea-Valenzuela et al. (2016)[18]	Retrospective	Suspected CD	124	Yes	Pillcam	CE	Characteristic CE findings	Spain	Low
Hale et al. (2016)[28]	Prospective	Suspected CD	146	Yes	Pillcam Mirocam	CE	More than three ulcers on CE	UK	Low
Bar-Gil Shitrit et al. (2017)[27]	Prospective	Suspected CD	68	Yes	Pillcam	CE	More than three ulcers on CE	Israel	Unclear
Aggarwal et al. (2017)[26]	Prospective	CD reassessment	43	Yes	Olympus	CE	LS ≥135 for active disease	Australia	Low
Kopylov et al. (2018)[29]	Prospective	Suspected CD	64	Yes	Pillcam	CE	LS ≥135 for active disease	Canada	Low
Yousuf et al. (2018)[30]	Prospective	Suspected CD CD reassessment	64	NA	Pillcam	CE	LS ≥135 for active disease	Ireland	Low
Monteiro et al. (2018)[23]	Retrospective	Suspected CD	75	Yes	Pillcam	CE	LS ≥135 for active disease	Portugal	Low

CD, Crohn's disease; CE, capsule endoscopy; LS, Lewis score; NA, not applicable.

to find active inflammation of the small intestine in established Crohn's disease. The diagnosis of small bowel Crohn's disease was made by the criteria used in the original studies.

We also assessed the effects of the following covariates on the results: (1) study design (prospective vs retrospective); (2) study indication (suspected Crohn's disease vs Crohn's disease reassessment); (3) exclusion of patients with abnormal ileocolonoscopy; (4) definition of Crohn's disease (clinical vs capsule endoscopy); (5) diagnostic criteria for Crohn's disease (Lewis score ≥135); and (6) bias assessment.

5. Statistical analysis

We calculated sensitivity, specificity, and diagnostic odds ratio (DOR), using only direct test comparisons. To quantify heterogeneity, the I^2 statistic was used. A value of more than 50% was used as a threshold for high heterogeneity. Because of high heterogeneity, the DerSimonian-Laird random-effects model was applied.

A bivariate model was used to assess the relationship between pooled sensitivity and false-positive rates.[34] The model's parameter estimates were used to acquire hierar-

chical summary receiver operating characteristic (HSROC) with 95% confidence intervals (CI) and a 95% prediction region, defining the sensitivity and false-positive rate values within which we may expect the results of a future study results to lie. An estimated area under the curve (AUC) was used to measure test accuracy. Analyses were carried out using the meta[35] and mada[36] packages in R version 4.0.2 and Review Manager 5.4.0.
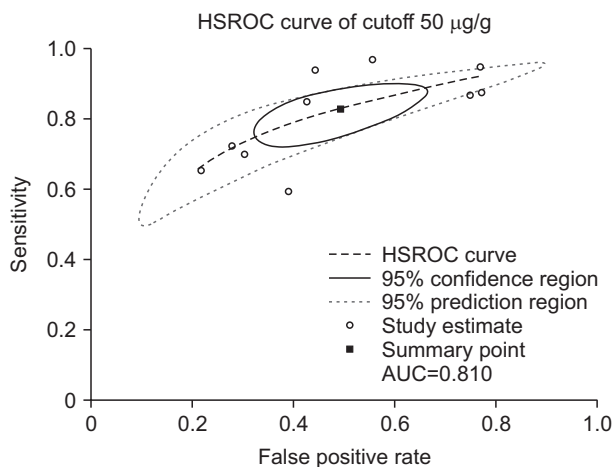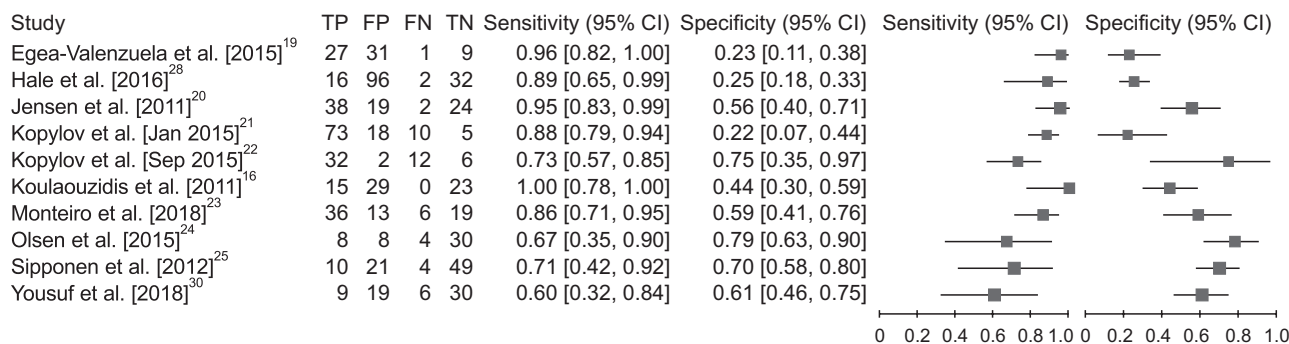
RESULTS

1. Study selection

We identified 147 studies through the database search and manual searches. After removing 61 duplicates, the titles and abstracts of 81 articles were screened. A further 57 articles were removed, and we then reviewed the full text of 24 studies. Ten of these were removed, and 14 studies were finally included in the systematic review (Fig. 1).[16,18-30]

2. Study characteristics

There were eight prospective studies[20,22,25-30] and six retrospective studies[16,18,19,21,23,24] (Table 1). Three studies

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Egea-Valenzuela et al. [2015][19]	27	31	1	9	0.96 [0.82, 1.00]	0.23 [0.11, 0.38]
Hale et al. [2016][28]	16	96	2	32	0.89 [0.65, 0.99]	0.25 [0.18, 0.33]
Jensen et al. [2011][20]	38	19	2	24	0.95 [0.83, 0.99]	0.56 [0.40, 0.71]
Kopylov et al. [Jan 2015][21]	73	18	10	5	0.88 [0.79, 0.94]	0.22 [0.07, 0.44]
Kopylov et al. [Sep 2015][22]	32	2	12	6	0.73 [0.57, 0.85]	0.75 [0.35, 0.97]
Koulaouzidis et al. [2011][16]	15	29	0	23	1.00 [0.78, 1.00]	0.44 [0.30, 0.59]
Monteiro et al. [2018][23]	36	13	6	19	0.86 [0.71, 0.95]	0.59 [0.41, 0.76]
Olsen et al. [2015][24]	8	8	4	30	0.67 [0.35, 0.90]	0.79 [0.63, 0.90]
Sipponen et al. [2012][25]	10	21	4	49	0.71 [0.42, 0.92]	0.70 [0.58, 0.80]
Yousuf et al. [2018][30]	9	19	6	30	0.60 [0.32, 0.84]	0.61 [0.46, 0.75]

Fig. 2. Forest plot and HSROC curve showing the diagnostic accuracy of a fecal calprotectin cutoff of 50 μg/g for detecting small bowel Crohn's disease. TP, true positive; FP, false positive; FN, false negative; TN, true negative; CI, confidence interval; HSROC, hierarchical summary receiver operating characteristic; AUC, area under the curve.

included patients evaluated for reassessment of Crohn's disease;[21,22,26] nine studies included patients with suspected Crohn's diseases;[16,18-20,23,24,27-29] and two studies included both patient groups.[25,30] Most studies included patients with negative ileocolonoscopies,[16,18-20,23-29] although three studies were not applicable due to lack of information.[21,22,30] Two studies used clinical diagnosis,[16,20] but 12 studies used capsule endoscopy-based diagnosis.[18,19,21-30] Twelve studies had a low risk of bias[16,18,20-26,28-30] although the bias risks of two studies were unclear.[19,27]

3. Diagnostic accuracy of the 50 μg/g FC level

We assessed 10 studies with a total of 794 patients to evaluate the diagnostic accuracy of FC with a cutoff value of 50 μg/g (Fig. 2). This cutoff had a sensitivity of 83% (95%

CI, 74% to 90%); specificity of 50% (95% CI, 36% to 64%); and DOR of 5.52 (95% CI, 3.31 to 9.19) (Table 2). The partial AUC of the HSROC was 0.81 (Fig. 2).

4. Diagnostic accuracy of the 100 μg/g FC level

We assessed 12 studies with 961 patients to evaluate the diagnostic accuracy of FC with a cutoff value of 100 μg/g (Fig. 3). At this level, FC had a sensitivity of 73% (95% CI, 66% to 78%); specificity of 73% (95% CI, 62% to 81%); and DOR of 7.89 (95% CI, 4.32 to 14.44) (Table 2). The partial AUC of the HSROC was 0.72 (Fig. 3).
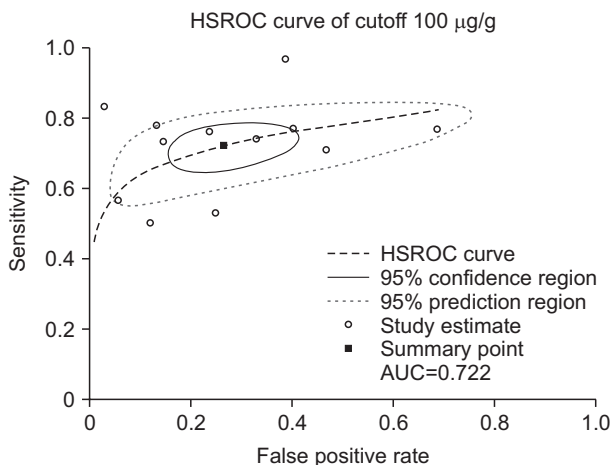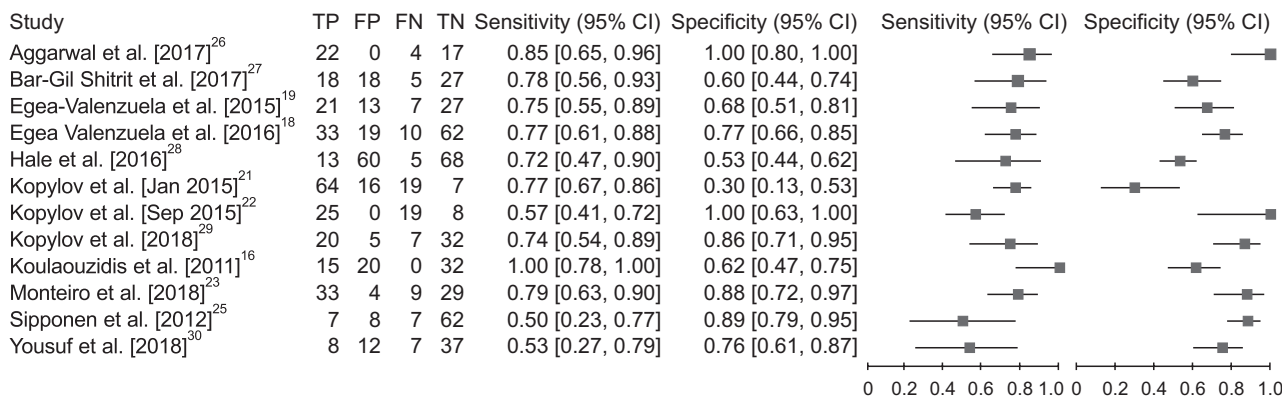
5. Diagnostic accuracy of the 200 μg/g FC level

We assessed seven studies with 594 patients to evaluate the diagnostic accuracy of FC with a cutoff value of 200

Table 2. Diagnostic Accuracy of FC for the Detection of Small Bowel Crohn's Disease through Capsule Endoscopy

FC cutoff	No. of studies	No. of patients	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	AUC	Partial AUC
50 μg/g	10	794	0.831 (0.740–0.895)	0.502 (0.359–0.644)	5.517 (3.313–9.186)	0.774	0.810
100 μg/g	12	961	0.725 (0.657–0.784)	0.728 (0.622–0.814)	7.894 (4.315–14.440)	0.763	0.722
200 μg/g	7	594	0.495 (0.361–0.629)	0.882 (0.738–0.952)	7.205 (2.681–19.366)	0.670	0.579

FC, fecal calprotectin; CI, confidence interval; DOR, diagnostic odds ratio; AUC, area under the curve.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Aggarwal et al. [2017][26]	22	0	4	17	0.85 [0.65, 0.96]	1.00 [0.80, 1.00]
Bar-Gil Shitrit et al. [2017][27]	18	18	5	27	0.78 [0.56, 0.93]	0.60 [0.44, 0.74]
Egea-Valenzuela et al. [2015][19]	21	13	7	27	0.75 [0.55, 0.89]	0.68 [0.51, 0.81]
Egea Valenzuela et al. [2016][18]	33	19	10	62	0.77 [0.61, 0.88]	0.77 [0.66, 0.85]
Hale et al. [2016][28]	13	60	5	68	0.72 [0.47, 0.90]	0.53 [0.44, 0.62]
Kopylov et al. [Jan 2015][21]	64	16	19	7	0.77 [0.67, 0.86]	0.30 [0.13, 0.53]
Kopylov et al. [Sep 2015][22]	25	0	19	8	0.57 [0.41, 0.72]	1.00 [0.63, 1.00]
Kopylov et al. [2018][29]	20	5	7	32	0.74 [0.54, 0.89]	0.86 [0.71, 0.95]
Koulaouzidis et al. [2011][16]	15	20	0	32	1.00 [0.78, 1.00]	0.62 [0.47, 0.75]
Monteiro et al. [2018][23]	33	4	9	29	0.79 [0.63, 0.90]	0.88 [0.72, 0.97]
Sipponen et al. [2012][25]	7	8	7	62	0.50 [0.23, 0.77]	0.89 [0.79, 0.95]
Yousuf et al. [2018][30]	8	12	7	37	0.53 [0.27, 0.79]	0.76 [0.61, 0.87]

Fig. 3. Forest plot and HSROC curve showing the diagnostic accuracy of a fecal calprotectin cutoff of 100 μg/g for detecting small bowel Crohn's disease. TP, true positive; FP, false positive; FN, false negative; TN, true negative; CI, confidence interval; HSROC, hierarchical summary receiver operating characteristic; AUC, area under the curve.

µg/g (Fig. 4). At this level, FC had a sensitivity of 50% (95% CI, 36% to 63%); specificity of 88% (95% CI, 74% to 95%); and DOR of 7.21 (95% CI, 2.68 to19.37) (Table 2). The partial AUC of the HSROC was 0.58 (Fig. 4).

6. Subgroup analyses

Although partial AUC with a 50 µg/g cutoff was the highest, the specificity at this level was relatively low. The difference between the partial AUC of cutoff levels of 100 µg/g and 50 µg/g was not large; moreover, the specificity and DOR was relatively high at 100 µg/g. Therefore, 100 µg/g was considered an optimal cutoff value. Subsequent subgroup analyses were only performed at the 100 µg/g level.

In the subgroup analyses, results remained statistically significant except in the studies that reassessed Crohn's disease (Table 3). The prospective studies had a sensitivity of 0.68 and specificity of 0.73 (DOR of 7.52). The retrospective studies had a sensitivity of 0.78 and specificity of 0.67 (DOR of 8.41). The studies for patients with suspected Crohn's disease had a sensitivity of 0.75 and specificity of 0.74 (DOR of 8.96). The studies that included only patients with normal ileocolonoscopies had a sensitivity of 0.76 and specificity of 0.75 (DOR of 10.07). The studies for patients with active disease that used a Lewis score of 135 or higher as a diagnostic criterion had a sensitivity of 0.72 and specificity of 0.81 (DOR of 10.90).

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hale et al. [2016][28]	9	30	9	98	0.50 [0.26, 0.74]	0.77 [0.68, 0.84]
Kopylov et al. [Jan 2015][21]	53	13	30	10	0.64 [0.53, 0.74]	0.43 [0.23, 0.66]
Kopylov et al. [Sep 2015][22]	14	0	30	8	0.32 [0.19, 0.48]	1.00 [0.63, 1.00]
Koulaouzidis et al. [2011][16]	10	3	5	49	0.67 [0.38, 0.88]	0.94 [0.84, 0.99]
Monteiro et al. [2018][23]	26	2	16	31	0.62 [0.46, 0.76]	0.94 [0.80, 0.99]
Sipponen et al. [2012][25]	2	1	12	69	0.14 [0.02, 0.43]	0.99 [0.92, 1.00]
Yousuf et al. [2018][30]	7	5	8	44	0.47 [0.21, 0.73]	0.90 [0.78, 0.97]
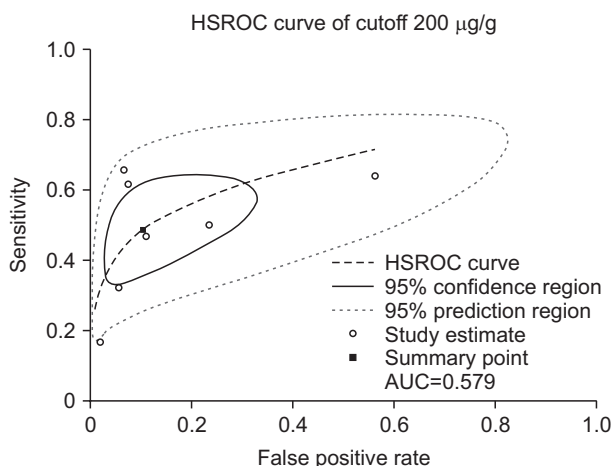
Fig. 4. Forest plot and HSROC curve showing the diagnostic accuracy of a fecal calprotectin cutoff of 200 µg/g for detecting small bowel Crohn's disease. TP, true positive; FP, false positive; FN, false negative; TN, true negative; CI, confidence interval; HSROC, hierarchical summary receiver operating characteristic; AUC, area under the curve.

Table 3. Diagnostic Accuracy of Fecal Calprotectin for the Detection of Small Bowel Crohn's Disease through Capsule Endoscopy by Subgroup Analyses

Subgroup	No. of studies	No. of patients	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)
Prospective	7	521	0.675 (0.568–0.767)	0.728 (0.622–0.814)	7.518 (3.574–15.814)
Retrospective	5	440	0.776 (0.713–0.828)	0.667 (0.497–0.803)	8.406 (2.831–24.958)
Suspected CD	8	696	0.746 (0.678–0.805)	0.735 (0.624–0.823)	8.961 (5.260–15.266)
CD reassessment	3	201	0.730 (0.552–0.855)	0.836 (0.173–0.992)	13.941 (0.657–259.924)
Negative ileocolonoscopy	9	739	0.757 (0.692–0.811)	0.750 (0.639–0.835)	10.065 (5.589–18.125)
CE	11	894	0.719 (0.654–0.776)	0.743 (0.625–0.833)	7.375 (4.015–13.546)
LS ≥135 for active disease	6	404	0.718 (0.616–0.802)	0.806 (0.579–0.926)	10.898 (3.024–39.276)
Low risk of bias	10	825	0.718 (0.629–0.788)	0.754 (0.625–0.849)	8.955 (4.181–19.180)

CI, confidence interval; DOR, diagnostic odds ratio; CD, Crohn's disease; CE, capsule endoscopy; LS, Lewis score.

7. Bias assessment of included studies

The QUADAS-2 assessment is summarized in Fig. 5. The included studies were of good quality and had a low risk of bias.

DISCUSSION

Our study demonstrated a strong correlation between FC levels and active inflammation in the small bowel as diagnosed by small bowel capsule endoscopy. The diagnosis of small bowel Crohn's disease with a normal ileocolonoscopy is challenging. To address this issue, cross-sectional imaging techniques such as computed tomographic enterography or magnetic resonance enterography are used, although these techniques have less sensitivity for detecting subtle mucosal inflammation in the small bowel.[37-39] Small bowel capsule endoscopy is a preferred method for detecting small bowel inflammation, but it is not readily available, is expensive, and presents a risk of small bowel obstruction;[40] therefore, biomarkers such as FC have become an inexpensive and simple screening tool.

FC is a useful surrogate marker to detect bowel inflammation and to diagnose and monitor patients with inflammatory bowel diseases.[22,41-45] Mosli et al.[42] reported that endoscopic activity in symptomatic patients with inflammatory bowel diseases could be detected by FC with a pooled sensitivity of 0.88 (95% CI, 0.84 to 0.90) and specificity of 0.73 (95% CI, 0.66 to 0.79). Another recent meta-analysis showed that an FC cutoff of 150 μg/g could be used to detect a postoperative endoscopic recurrence of Crohn's disease (pooled sensitivity was 0.70 [95% CI, 0.59 to 0.81], specificity 0.69 [95% CI, 0.61 to 0.77], and DOR 0.92 [95% CI, 2.61 to 12.17]).[46]

Researchers disagree on whether FC can accurately detect intestinal inflammation in both the small and large bowels. Some studies report that FC can detect Crohn's disease throughout the intestinal tract,[20,47] but others have suggested a lower degree of accuracy for diagnosis in the small intestine.[19,48] The preferred FC cutoff value to detect small bowel inflammation is also unresolved. A recent meta-analysis of seven studies with 463 patients suggested that an FC level of 50 μg/g could detect small bowel Crohn's disease.[49] However, this study was limited because it only included a small number of studies and only three prospective studies.

Our pooled data indicate that an FC cutoff of 100 μg/g is associated with optimal diagnostic accuracy for active small bowel inflammation. When we compared three FC cutoff levels, a higher level was generally associated with decreasing sensitivity and increasing specificity (Fig. 6). Although the sensitivity of the 50 μg/g cutoff was the highest among the three cutoffs, the specificity was relatively low (0.50). A cutoff of 100 μg/g had relatively high sensitivity and specificity among the three measurements. Moreover, the DOR for a 100 μg/g cutoff was higher than the 50 μg/g cutoff. Therefore, we suggest that an FC cutoff of 100 μg/g has the most advantageous screening value for small bowel inflammation.

Our meta-analysis study has some limitations. We included retrospective studies along with prospective studies because of the low number of available studies. If we looked at only the eight prospective studies that were
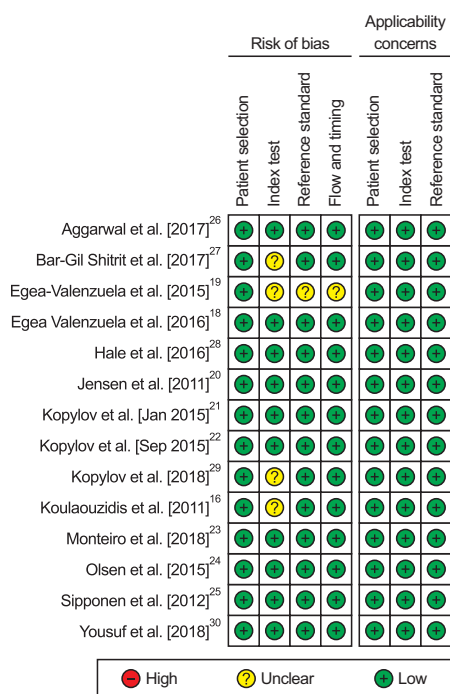
Fig. 5. Quality Assessment of Diagnostic Accuracy Studies-2 for evaluating methodology quality.
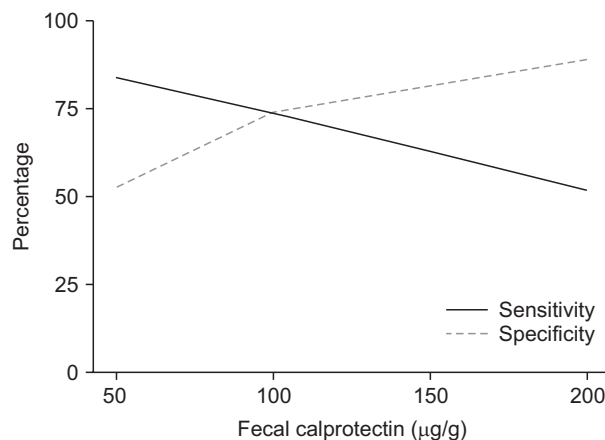
Fig. 6. Graph of sensitivities and specificities from three fecal calprotectin cutoffs (50, 100, and 200 μg/g).

included, the DOR was still significant. Furthermore, an indication of capsule endoscopy and diagnostic criteria of Crohn's disease on small bowel capsule endoscopy were not identical. Our subgroup analyses showed that an FC cutoff of 100 µg/g had significant accuracy in diagnosing suspected Crohn's disease but was not significant for reassessing Crohn's disease; however, we only had three studies that reassessed Crohn's disease, and the DOR was affected by the results of one study. The findings would have been significant if more studies were included. In another subgroup analysis, FC with a cutoff of 100 µg/g was significant in the studies using a Lewis score of 135 or higher as diagnostic criteria for active disease.

Despite these limitations, and to the best of our knowledge, our meta-analysis study on the diagnostic accuracy of FC for small bowel inflammation includes the largest number of studies correlating FC and small bowel inflammation on capsule endoscopy.

In conclusion, an FC cutoff of 100 µg/g had the highest diagnostic accuracy and could be used as a screening tool to detect small bowel Crohn's disease.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception and design of the study: E.S.J., H.J.J. Data collection: E.S.J., J.H.K., H.J.J. Statistical analysis: E.S.J., H.S.K., H.J.J. Interpretation of data: E.S.J., S.P.L., S.H.K., H.S.K. Writing of the draft manuscript: E.S.J. Approval of the final version of the manuscript: H.S.K., H.J.J. Supervision: H.S.K., H.J.J.

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