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Accuracy of Fecal Calprotectin in Detecting Small Bowel Crohn's Disease: A Meta-Analysis and Systematic Review

Manjusha Das[1], Muhammad Asghar[1], Daniel K. Martin[1], and Srinivas R. Puli[1]*

Division of Gastroenterology and Hepatology, University of Illinois College of Medicine, Peoria, Illinois, USA

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*Corresponding author: Manjusha Das, Department of Gastroenterology, 5105 North Glen Park Place, 61614 Peoria, Illinois, Tel: (309) 308-5900; E-mail: Manjusha.das@osfhealthcare.org

Abstract

Background: *Identifying active small bowel Crohn's Disease (CD) is often challenging due to various reasons. The location of Crohn's disease and often the disease process itself make direct visualization difficult. Fecal calprotectin (FCP) is a well-established marker of mucosal inflammation. Several studies have confirmed FCP's utility in colonic inflammation; however, the diagnostic accuracy in active small bowel inflammation had yet to be established. The aim of the present study is to update the previous meta-analysis of FCP and its diagnostic accuracy in detecting active small bowel Crohn's disease.*

Methods: *Study Selection Criteria: A comprehensive search was performed using PubMed/OVID studies. Studies from 2010 until 2018 addressing patients with suspected or known CD and evaluated with noninvasive testing with FCP and confirming disease with video capsule endoscopy or imaging were included. Studies in which a 2 × 2 table with true positives, false negatives, false positives and true negative values could be constructed were included.*

Statistical Method: *Meta-analysis for the diagnostic accuracy of fecal calprotectin in diagnosing active small bowel CD was performed by calculating pooled estimates of sensitivity, specificity, likelihood rations, and diagnostic odds ratios. Pooling was conducted by both fixed and random effects models.*

Results: *Data was extracted from 17 studies which met the inclusion criteria. In CD patients, pooled sensitivity of fecal calprotectin was 76.50% (95% CI: 73.00 – 79.00) in diagnosing small bowel Crohn's disease. Fecal calprotectin had a pooled specificity of 71.10% (95% CI: 68.00 – 73.00) for detecting active small bowel Crohn's disease. The diagnostic odds ratio, of having active small bowel disease with elevated FCP was 12.28 (95% CI: 6.55 – 23.01). The positive likelihood ratio of FCP was 3.09 (95% CI: 2.16 – 4.41), and the negative likelihood ratio was 0.30 (95% CI: 0.21 – 0.43).*

Conclusion: *Fecal calprotectin has moderate diagnostic accuracy for detecting active small bowel CD. Our results suggest a fecal calprotectin of at least 50 µg/g has moderate sensitivity and specificity in detecting active small bowel disease.*

Keywords: Meta-analysis; Systematic review; Small bowel Crohn's disease; Fecal calprotectin; Crohn's disease activity index

Introduction

Isolated small bowel Crohn's disease (SBCD) occurs in approximately 30% of Crohn's patients [1]. Crohn's disease, specifically SBCD, usually progresses to forming fistulas, stenosis or strictures of the intestine. Identifying active lesions in the small bowel is often challenging due to the location, with difficulty endoscopically visualizing the area. Active disease has been defined in most clinical trials using the Clinical Disease Activity Index (CDAI). CDAI was developed in the 1970's as a tool to assess response to therapy. It consists of 8 variables, 2 of which are subjective and related to the disease. The total score ranges from 0 to over 600. A CDAI >220 is the cut off value to indicate active disease. Severe disease is defined as symptoms despite intensive treatment with a CDAI >450. Measuring response to treatment is often quantified by a decrease in the CDAI score by 100 points from baseline. Relapsing disease is often difficult to determine as it requires repeat imaging or endoscopies [2].

Since introducing video capsule endoscopy (VCE) into clinical practice in the early 2000s, it has allowed for excellent visualization of the small bowel mucosa [3]. The use of VCE has become very important in cases where the diagnosis is equivocal. Compared with computed tomography enterography or magnetic resonance enterography, capsule endoscopy has been shown to be superior to other modalities for diagnosing small bowel CD [4]. The advantages of VCE include avoiding radiation exposure, pain, and sedation. The procedure is also relatively simple to perform.

European Society clinical guidelines recommend capsule endoscopy as first line investigation for suspected small bowel CD without obstructive symptoms after a negative ileoscopy [5]. Although VCE is non-invasive and has low complication rates, the procedure is time consuming and costly. There is also a risk of capsule retention in approximately 13% of patients, especially in those with SBCD [6].

Calprotectin is a neutrophilic cytosolic calcium and zinc-binding protein. It is the main product of neutrophil degranulation and is excreted through the stool [1]. As calprotectin is poorly degraded during passage through the intestinal tract, it remains intact and stable in refrigeration [7]. Therefore, standard enzyme-linked immunosorbent assay is able to detect the protein in stool specimens.

Fecal calprotectin (FC) has been previously shown to correlate with endoscopic disease activity in IBD better than classic serum markers [8]. Studies previously have identified fecal calprotectin as a surrogate marker for gastrointestinal inflammation. However, it was not disease specific [9]. Recent studies have identified fecal calprotectin at high concentrations are able to distinguish IBD from IBS [7]. It is an inexpensive test, and well established as a marker of colonic inflammation, and could be used as a predictor of disease relapse, and as an indicator of endoscopic healing [8].

FC and its association with colonic inflammation is well established compared with small bowel findings [1,2]. The aim of this meta-analysis was to assess from previous studies the sensitivity and specificity of elevated fecal calprotectin in detecting active SBCD.

This meta-analysis and systematic review was written in accordance with the QUOROM (Quality of Reporting of Meta-analyses) statement [10]. As this manuscript looks at diagnostic accuracy of a test, the study design conformed to the guidelines of STARD (Standards for Reporting of Diagnostic Accuracy) initiative [11].

Materials and Methods

Study selection criteria: Only English-language, fully published articles were included in the preliminary search. Studies which evaluated active small bowel inflammation for detection of SBCD by capsule endoscopy were selected or comparison with other modalities such as MRE, CTE, or ileoscopy. Additional inclusion criteria needed was to have further evaluation with fecal calprotectin in correlation with small bowel evaluation. Small bowel CD was classified by various scoring systems including the Lewis scoring system and clinical disease activity scoring with the Harvey Bradshaw index. Only studies in which a 2 × 2 table with true and false positive and negative values could be extracted were included.

Data collection and extraction: A comprehensive literature search was performed using PubMed, Ovid journals, and Medline databases. The search terms used with fecal calprotectin, non-invasive testing for small bowel Crohn's Disease, small bowel Crohn's Disease, small bowel capsule endoscopy, sensitivity, specificity, positive predictive value and negative predictive value. 2 × 2 tables were created with data extracted from each study. Two authors (MD and MA) independently searched and pulled the data into individual 2 × 2 tables.

Any differences were resolved and agreed upon by the authors.

Statistical methods: Meta-analysis and systematic review for the accuracy of fecal calprotectin in diagnosing active small bowel CD was performed by calculating pooled estimates of sensitivity, specificity, likelihood ratios, and diagnostic odds ratios. Pooling was done with both Mantel-Haenszel Method (fixed effects model) and DerSimonian Laird Method (random effects model). F Distribution Method was used for calculating the confidence intervals. Point estimates in each study in relation to the summary pooled estimate was shown using Forrest plots. The width of the point estimates was assigned to the weight of that specific study in the Forrest plots. The heterogeneity of likelihood ratios and diagnostic odds ratios were tested using Cochran's Q test based upon inverse variance weights. Summary receiver operating characteristic (SROC) curves also tested the heterogeneity among the studies included. SROC curves were used to calculate the area under the curve (AUC). The effect of publication and selection bias on the summary estimates was tested by Egger and Begg-Mazumdar bias indicators.

Results

A total of 27 articles were identified on initial search; 17 studies (N=1505) which met inclusion criteria were included in the analysis [3-5,7,9,12-23]. Table 1 shows the search results and the characteristics for studies included in this meta-analysis. All the 17 studies included were published as full-text articles in peer reviewed journals. The pooled estimates were estimates calculated by the fixed effect model.

Table 1: Table showing characteristics of studies included in this analysis.

S No	Author	Year of Publication	Type of Enrollment	Confirmatory test
1	Koulaouzidis et al	2010	Retrospective	Video
2	Jensen et al	2011	Prospective	Ileocolonoscopy/Video
3	Sipponen et al	2012	Prospective	Video
4	Olsen et al	2014	Retrospective	Video
5	Kopylov et al	2014	Retrospective	Video
6	Kopylov et al	2015	Prospective	Video
7	Egea-Valenzuela et al	2016	Retrospective	Video
8	Hale et al	2016	Prospective	Video
9	Bar-Gil Shitrit et al	2016	Prospective	Video
10	Lei Ye et al	2017	Retrospective	MRE/small bowel endoscopy
11	Aggarwal et al	2017	Prospective	Video
12	Tsunetaka et al	2017	Prospective	Balloon enteroscopy
13	Yousuf et al	2017	Prospective	Video
14	Kawashima et al	2017	Prospective	Balloon enteroscopy
15	Chen et al	2017	Prospective	Video
16	Chao et al	2017	Retrospective	Video
17	Iwamoto et al	2018	Cross sectional observational	Balloon enteroscopy

Accuracy of Fecal Calprotectin to diagnose SBCD: Pooled sensitivity of FC in diagnosing SBCD was 76.5% (95% CI: 73.0 – 79.7). FC had a pooled specificity of 71.1% (95 CI: 68.2 - 73.9). Figure 1 shows the sensitivity and Figure 2 shows specificity of FC to diagnose small bowel Crohn's disease. The positive likelihood ratio of FC was 30.9 (95% CI: 21.66 – 44.18) and the negative likelihood ratio was 30.9 (95% CI: 21.9 – 43.6). Figure 3 shows diagnostic odds ratio, the odds of having active small bowel Crohn's disease compared to no small bowel disease was 12.28 (95% CI: 6.55 – 23.01). All the pooled estimates calculated by fixed and random effect models were similar. SROC curves showed an area under the curve of 0.86. Figure 4 shows

the SROC curves for FC to diagnose SBCD. The p value for I2 for all the pooled accuracy estimates was greater than 0.0.

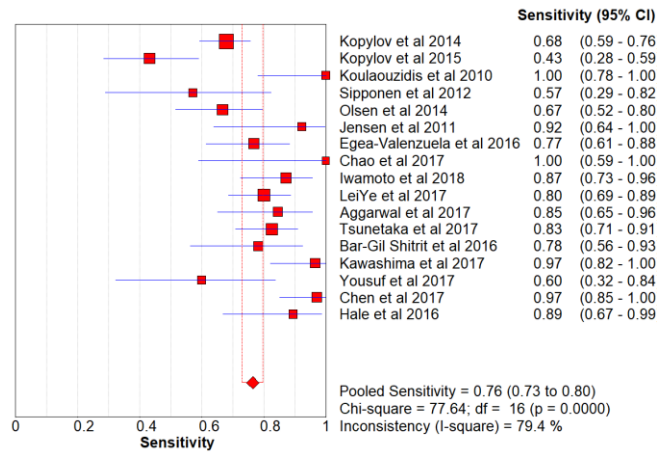

Figure 1: Figure shows sensitivity.

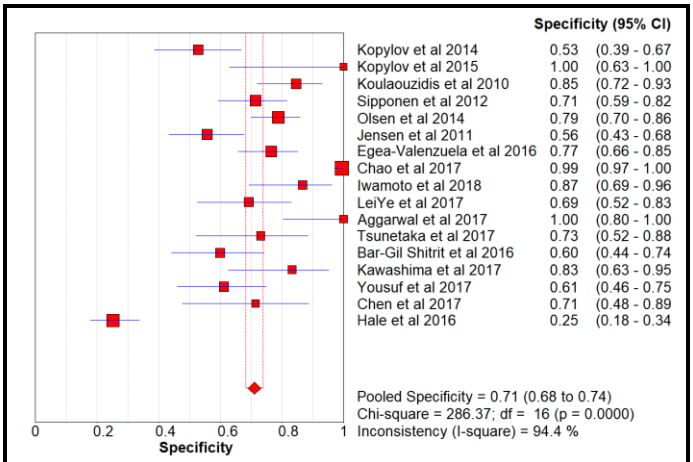

Figure 2: Figure shows specificity.

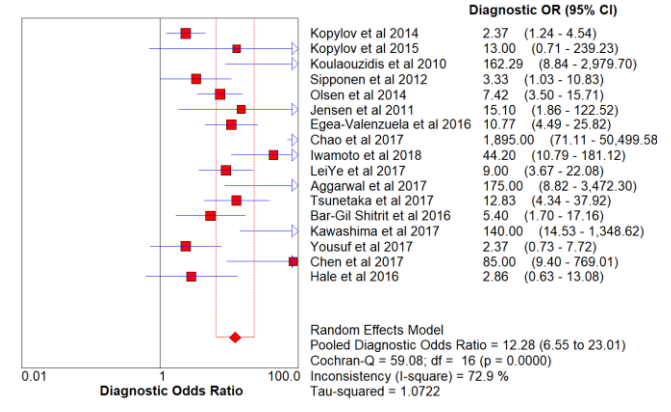

Figure 3: Diagnostic Odds Ratio.

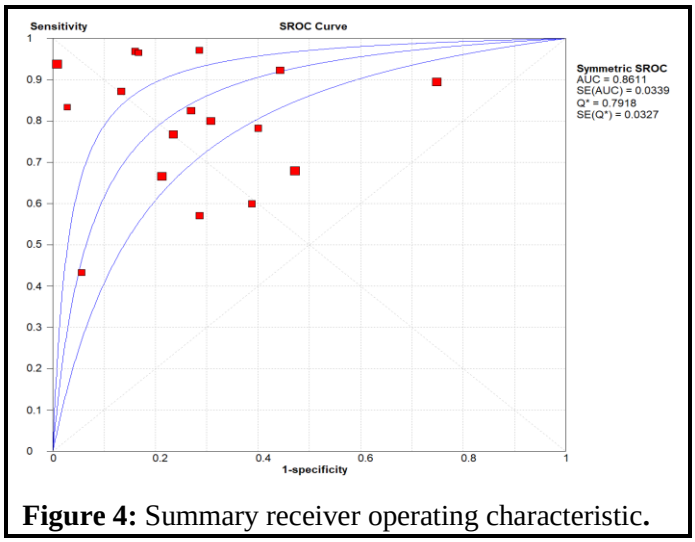

Figure 4: Summary receiver operating characteristic.

Abdominal pain and diarrhea: Data was simultaneously collected on patients who presented with complaints of abdominal pain or diarrhea as initial presenting symptom. Pooled proportion using DerSimonian-Laird for diarrhea was 0.48 (95% CI 0.27 to 0.71) and using fixed effects it was 0.39. Proportion analysis on abdominal pain as the initial complaint resulted in a value of 0.55 with random effects model and 0.48 with fixed effects model. Bias indicators used with Begg-Mazumdar, Egger, and Harbord.

Bias Estimates: The publication bias calculated by Begg-Mazumdar bias indicator gave a Kendall's tau b value of 0.33, p = 0.46. Egger bias indicator gave a value of 8.40 (95% CI = -4.94 to 21.76, p = 0.15). Harbord bias gave a value of 9.34 (92.5% CI -3.43 to 22.13 p= 0.15).

Discussion

The presence of active intestinal inflammation in patients with known CD would change medical management. Patients with active intestinal inflammation would justify further diagnostic workup or intensifying treatment regimens. In Crohn's patients specifically, mucosal healing would be a goal or treatment target for practitioners. Therefore, answering this question with an easy to perform, inexpensive test would be of significant value in clinical practice.

Our results suggest that elevated fecal calprotectin (>50 µg/g) is a moderately sensitive and specific test to detect active small bowel inflammation. FC offers a simple noninvasive and cheaper tool for identifying patients with active small bowel inflammation. The pooled sensitivity of fecal calprotectin from the meta-analysis

and review was 76% and specificity was 71% for active small bowel CD correlated with capsule endoscopy.

The sensitivity is similar to Hale et al, however the specificity is significantly higher at a FC cut off of 50 ug/g [5]. Diagnostic odds ratio (OR) is the odds of having a positive test indicating that the patient truly has small bowel CD when compared to patients who do not have the disease. The pooled diagnostic OR 12.28 meaning a patient who has an elevated fecal calprotectin > 50 µg/g has a 12 times higher chance of having active small bowel CD.

Limitations of this study include heterogeneity and is a common difficulty to over-come in meta-analyses. The heterogeneity of the studies was determined by drawing SROC curves and finding the AUC. The AUC was calculated as 0.8611. The other limitation of this study was the cutoff value for FC was limited to 50 µg/g. Other studies [1,5,21,22] had noted higher sensitivities and NPV with higher FC cutoff value. Hale et al noted higher sensitivity and specificity at lower cut off value suggesting it may be more useful as a screening tool however this study proves its usefulness in specificity as well at a cut off of only 50 ug/g.

Conclusion

Fecal calprotectin has moderate diagnostic accuracy for detecting active small bowel CD. Our results suggest a fecal calprotectin of at least 50 µg/g has moderate sensitivity and specificity. Compared with video capsule endoscopy or abdominal imaging, fecal calprotectin is a non-invasive and an inexpensive diagnostic test. It should be considered in patients with small bowel Crohn's disease as well as a marker for continued surveillance of active disease and can yield significant clinical value.

Conflict of Interest

None declared.

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