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Fecal Calprotectin in Assessing Inflammatory Bowel Disease Endoscopic Activity: a Diagnostic Accuracy Meta-analysis

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ABSTRACT

Background & Aim: Fecal calprotectin (FC) has been suggested as a sensitive biomarker of inflammatory bowel disease (IBD). However, its usefulness in assessing IBD activity needs to be more precisely defined. In this meta-analysis we aimed to determine the diagnostic performance of FC in assessing IBD endoscopic activity in adults.

Methods: We searched the databases Pubmed/Medline and EMBASE, and studies which examined IBD endoscopic activity in association to FC were identified. From each study pooled data and consequently pooled sensitivity, specificity, likelihood ratios (LR), diagnostic odds ratios (DORs) and areas under the curve (AUCs) were calculated, using suitable meta-analysis software. We analyzed extracted data using fixed or random effects models, as appropriate, depending on the presence of significant heterogeneity.

Results: We included 49 sets of data from 25 eligible for meta-analysis studies, with 298 controls and 2,822 IBD patients. Fecal calprotectin in IBD (Crohn's disease, CD and ulcerative colitis, UC) showed a pooled sensitivity of 85%, specificity of 75%, DOR of 16.3 and AUC of 0.88, in diagnosing active disease. The sub-group analysis revealed that FC performed better in UC than in CD (pooled sensitivity 87.3% vs 82.4%, specificity 77.1% vs 72.1% and AUC 0.91 vs 0.84). Examining the optimum FC cut-off levels, the best sensitivity (90.6%) was achieved at 50 μg/g, whereas the best specificity (78.2%) was found at levels >100 μg/g.

Conclusions: This meta-analysis showed that in adults, FC is a reliable laboratory test for assessing endoscopic activity in IBD. Its performance is better in UC than CD.

Key words: Inflammatory bowel disease – Crohn's disease – ulcerative colitis – fecal calprotectin – diagnostic accuracy.

Abbreviations: CD: Crohn's disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FC: fecal calprotectin; IBD: inflammatory bowel diseases; UC: ulcerative colitis.

INTRODUCTION

The diagnosis of inflammatory bowel diseases (IBD), i.e. Crohn's disease (CD) and ulcerative colitis (UC), is achieved by combining clinical, laboratory, endoscopic, histological, and radiological findings, whereas their course is characterized by episodes of exacerbation and periods of remission [1-3]. In this context the evaluation of disease severity is of importance for choosing the suitable treatment. Studies [4–6] have shown that existing bowel symptoms are unspecific and, furthermore, show poor correlation with mucosal inflammation. On the other hand, conventional laboratory tests such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelets, blood leukocyte count, and albumin, although useful in clinical practice, express systemic patient responses instead of intestinal inflammation [7]. In recent years, colonoscopy has been considered as the most accurate diagnostic modality and the "reference test" for quantifying activity in IBD. Various scoring systems have been developed to assess IBD endoscopic severity [8, 9]. However, despite its unequivocal usefulness, colonoscopy has some disadvantages in that it is expensive, uncomfortable, and time-consuming and is also related to some complication risks. Therefore, an accurate, relatively simple and easily available laboratory test reflecting intestinal mucosal inflammation would be beneficial to IBD patients.

Calprotectin is a calcium and zinc binding protein mostly derived from neutrophils and monocytes. It can be detected in body fluids, tissue samples, and stools, and is deemed as a marker of neutrophil activity, since calprotectin represents approximately 60% of the total amount of protein in these cells. Consequently, in IBD, the quantity of FC is proportional to the number of neutrophils, which migrate from the wall of the inflamed bowel to the mucosa [10-12]. It is noteworthy that the concentration of FC is resistant to degradation and stable, thus allowing measurements at a convenient time [13]. For all these reasons, it seems that FC is a promising non-invasive biomarker, compared with other existing conventional laboratory markers, for assessing IBD activity. In this context, although FC usefulness has been examined in various individual studies and meta-analyses in the past [14, 15], our understanding on its exact role remains unsatisfactory and, furthermore, studies have been recently published and are not included in the above meta-analyses. Therefore, the aims of this meta-analysis were first to evaluate the performance of FC in assessing endoscopic activity in IBD adult patients by updating the above mentioned meta-analyses and second, to evaluate the optimum FC cutoff level for diagnosing active disease.

MATERIAL AND METHODS

Selection criteria

PRISMA guidelines for systematic reviews were strictly followed. The inclusion and exclusion criteria of potentially eligible studies for the meta-analysis were defined. Full article studies were included if they met the following criteria: (a) they were written in English language, (b) included only adult IBD patients, (c) included IBD patients with symptomatic active disease, which was confirmed endoscopically and (d) they contained appropriate data to construct 2 by 2 contingency tables, in order to calculate FC sensitivity and specificity and all other diagnostic accuracy parameters. If two papers reported the same data, we selected the more informative study. In order to estimate the quality of the eligible studies, we used the QUADAS-2 evaluation [16].

Study identification and extraction of data

Medical literature searches in English, involving PubMed/MEDLINE and EMBASE databases were performed to identify any relevant publication referring to the role of FC in estimating IBD activity in comparison with reference diagnostic methods such as colonoscopy. Suitable search terms were used as follows: („calprotectin"[All Fields]) AND („faeces"[All Fields] OR „feces"[MeSH Terms] OR „feces"[All Fields]) AND („Crohn disease"[MeSH Terms] OR („Crohn"[All Fields] AND „disease"[All Fields]) OR „Crohn disease"[All Fields] OR („Crohn's"[All Fields] AND „disease"[All Fields]) OR „Crohn's disease"[All Fields]) AND („colitis, ulcerative"[MeSH Terms] OR („colitis"[All Fields] AND „ulcerative"[All Fields]) OR „ulcerative colitis"[All Fields] OR („ulcerative"[All Fields] AND „colitis"[All Fields]). The search was performed till the end of December 2017, whereas no initiation date limit was used. In addition, we screened the articles of the selection process for more appropriate references. Data were extracted independently from each study by two of the authors (T.R. and P.P.) by using a predefined form and disagreements were resolved by discussion with the third investigator (I.K.) and consensus.

Statistical analysis

Fecal calprotectin sensitivity, specificity, positive and negative likelihood ratios (LR), diagnostic odds ratios (DOR) and AUCs, with 95% confidence intervals (CIs) were derived by computing data contained in the analyzed studies. Pooled results were calculated by using the fixed-effects model (Mantel and Haenszel method) [17], unless we found significant heterogeneity, in which case we used the random-effects model (DerSimonian and Laird method) [18]. Forest plots were constructed for visual display of individual and pooled data. In addition, the results of the individual studies were displayed in a receiver operating characteristic (ROC) graph, illustrating the distribution of sensitivities and specificities and furthermore a weighted symmetric summary ROC (sROC) curve was calculated. Consequently, the relevant areas under the curve (AUC) were derived, with accurate tests having an AUC approaching 1 and poor tests having an AUC close to 0.5 [19-21]. The existence of heterogeneity between studies was examined by using the Cochran Q-test and the relevant inconsistency index I squared (I2) was used as a measure for quantifying the degree of heterogeneity [22]. In cases where the Q-test provided a p value of less than 0.1 and if I^2 was more than 50 [23], then heterogeneity was considered to be present. The existence of publication bias was examined by the Deeks' funnel plot, with a superimposed regression line [24]. The analyses were performed by Stata software (version 13.0, College Station, TX) with the MIDAS command.

RESULTS

Descriptive assessment and study characteristics

A flow chart describing the process of study selection is shown in Fig. 1. Out of 683 titles initially generated by the literature searches, 25 prospective cohort studies in adult patients [25-49] containing 49 sets of data were found eligible for meta-analysis. These studies included IBD patients whose symptoms were compatible with active disease and in whom disease activity was confirmed endoscopically. The endoscopic activity was quantitated by using various validated indices of scoring the endoscopic findings. In detail, in CD the Simple Endoscopic Score for Crohn's Disease (SES-CD), Crohn's Disease Endoscopic Index of Severity (CDEIS) and Rutgeert's endoscopy scores were utilized, whereas the Mayo, Schroeder, and Rachmiliewitz scores were utilized in UC. The main characteristics of the 25 meta-analyzed studies are shown in Table I. They contained a total of 2,822 IBD patients and 298 controls. In the IBD group there were 1,464 CD and 1,232 UC patients. One study [45] reported the total number of IBD patients studied without giving separate information on CD and UC groups. The quality assessment of the included studies was relatively good as the majority of included studies fulfilled most of the QUANTAS-2 criteria.

Table I. The main characteristics of studies selected for meta-analysis.

Study, year [Ref.]	Age (yrs)	Country	Type of study	Total number of subjects involved (IBD + Controls)	Number of IBD patients (CD/UC)	Controls	FC Assay	FC Cut-off point (μg/g)
Sipponen T, 2008 [23]	19-70	Finland	Prospective	106	106 (106/0)	NI	ELISA	50, 100, 200
Langhorst J, 2008 [24]	15-70	Germany	Prospective	139	85(42/43)	54 (IBS)	ELISA	48
Vieira A, 2009 [25]	18-80	Brazil	Prospective	78	78 (38/40)	NI	ELISA	200
Schoepfer AM, 2009 [26]	18-74	Switzerland	Prospective	182	134 (0/134)	48 healthy subjects	ELISA	50, 100
Schoepfer AM, 2010 [27]	18-74	Switzerland	Prospective	183	140(140/0)	43 healthy subjects	ELISA	50, 70
Af Bjorkesten CG, 2012 [28]	18–69	Finland	Prospective	126	126(126/0)	NI	ELISA	94, 100
D'Haens G, 2012 [29]	30-64	Netherlands	Prospective	158	126 (87/39)	32 (IBS)	ELISA	250
Onal IK, 2012 [30]	49.7 ±10.7	Turkey	Prospective	80	60(0/60)	20 healthy subjects	ELISA	99.5
Lobaton T, 2013 [31]	32-58	Spain	Prospective	89	89 (89/0)	NI	ELISA	274
Schoepfer AM, 2013 [32]	18-74	Switzerland	Prospective	280	228(0/228)	52 healthy subjects	ELISA	50, 57
Nancey S, 2013 [33]	18-79	France	Prospective	157	133(78/55)	24 healthy subjects	ELISA	250
Yamamoto T, 2013 [34]	32±1.6	Japan	Prospective	20	20 (20/0)	NI	ELISA	140
Lobaton T, 2013 [35]	32-58	Spain	Prospective	146	146 (0/146)	NI	ELISA	280
Mooiweer E, 2014	49 (19-72)	Netherlands	Prospective	157	157 (83/74)	NI	ELISA	140
Naismith GD, 2014	41(15.4)-47.0 (16.0)	United Kingdom	Prospective	92	92 (92/0)	NI	ELISA	240
Boschetti G, 2015	39.3 (18-70)	France	Prospective	86	86 (86/0)	NI	ELISA	100
Falvey JD, 2015	NI	New Zealand	Prospective	97	97 (59/38)	NI	ELISA	125
Goutorbe F, 2015	31 (21-44)	Freance	Prospective	53	53 (53/0)	NI	ELISA	200, 400
Hosseini SV, 2015	42.4 (11.2) F 41.8 (10.8) M	Iran	Prospective	157	157 (0/157)	NI	ELISA	341
Kristensen V, 2015	35.5 (18-72)	Norway	Prospective	62	62 (0/62)	NI	ELISA	61, 96, 110, 259
Kwapisz L, 2015	44.4 ± 16.7	Saudi Arabia	Prospective	126	126	NI	ELISA	100, 200
Buisson A, 2016	36.3 (16.4) CD 42.4 (14.5) UC	France	Prospective	86	86 (54/32)	NI	ELISA	250
Inokuchi T, 2016	32 (25-41)	Japan	Prospective	71	71 (71/0)	NI	ELISA	180
Bodelier, 2017	44 (32-55) CD 50 (40-63) UC	Netherlands	Prospective	228	228 (148/80)	NI	ELISA	250
Chen, 2017	29.5 (18-62) CD 38 (10-70) UC	China	Prospective	161	136 (92 /44)	25 (IBS)	ELISA	250
	Total			**3,120**	**2,822**	**298**		

IBD: Inflammatory bowel disease; FC: Fecal calprotectin; CD: Crohn's disease; UC: Ulcerative colitis; NI: Not Included; ELISA: Enzyme-linked immunosorbent assay; IBS: irritable bowel syndrome.

Diagnostic performance of FC

The pooled data (random-effects analysis) showed that FC had a sensitivity of 85% (95% CI 82–87%) and a specificity of 75% (95% CI 71–79%) for diagnosing active disease. There was significant heterogeneity for both the sensitivity and the specificity results (Q-test = 159.28, d.f. = 48, P=0.00, I^2= 69.87%) and (Q-test=180.50, d.f. =48, P=0.00, I^2=73.41%), respectively. The forest plots of sensitivities and the specificities are presented in Fig. 2. The corresponding ROC plot with sROC is displayed in Fig. 3A, showing an AUC of 0.88 (95% CI 0.85-0.90). Figure 3B depicts the exploration of publication bias (Deek's funnel plot asymmetry test with superimposed regression line). As shown, there was no significant publication bias (p=0.29 for the slope coefficient)]. In addition, Fig. 3C shows the bivariate boxplot

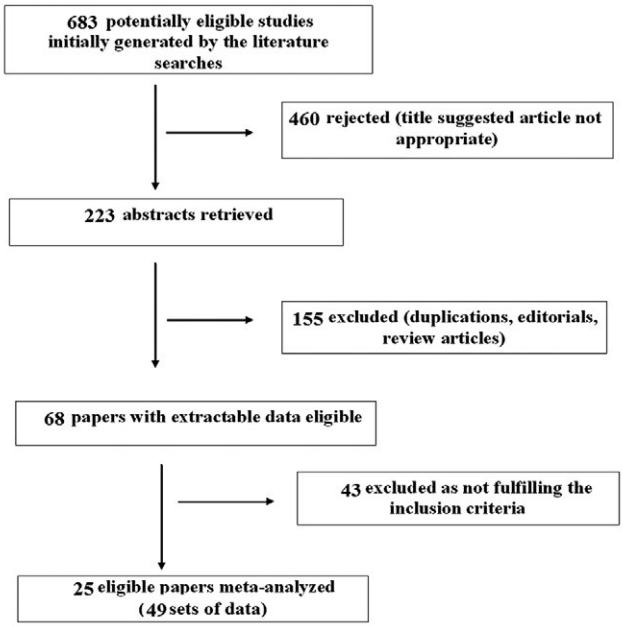

Fig. 1. Flow chart of the studies identified in this meta-analysis.

with most studies clustering within the median distribution and some outliers, suggesting indirectly the magnitude of heterogeneity. The respective likelihood ratio scatter gram is shown in Fig. 3D, providing the summary point of likelihood ratios obtained as functions of mean sensitivity and specificity.

In exploring reasons for the observed significant heterogeneity among studies, further analyses (sensitivity analyses) were conducted, as shown in Supplementary Fig. 1, i.e. the residual-based goodness-of-fit (1A), the bivariate normality (1B), the influence analysis (1C) and the outlier detection (1D). These analyses identified 4 outlier studies that contributed to the significant heterogeneity found. Furthermore, the results of more analyses aiming to identify other factors contributing to significant heterogeneity are depicted in Suppl. Fig. 2C, which shows Forest plots of multiple univariable meta-regression and subgroup analyses for sensitivity and specificity. Suppl. Fig. 2A presents the relevant Fagan's nomogram providing 46% post-test probability of active IBD after an FC-positive result and only a 5% post-test probability after an FC-negative result. Finally, probability modifying plot is shown in Suppl. Fig. 2B with a positive LR=3.46 (95% CI 2.95-4.04) and negative LR= 0.20 (95% CI 0.17-0.24). These results give a 76% (95% CI 73-79%) positive predictive value (PPV) and an 82% (95% CI 79-85%) negative predictive value (NPV).

Subgroup analyses

FC diagnostic accuracy according to different cutoff values

In the 49 sets of meta-analyzed data the cutoff values for testing positive in the FC assay varied between studies,

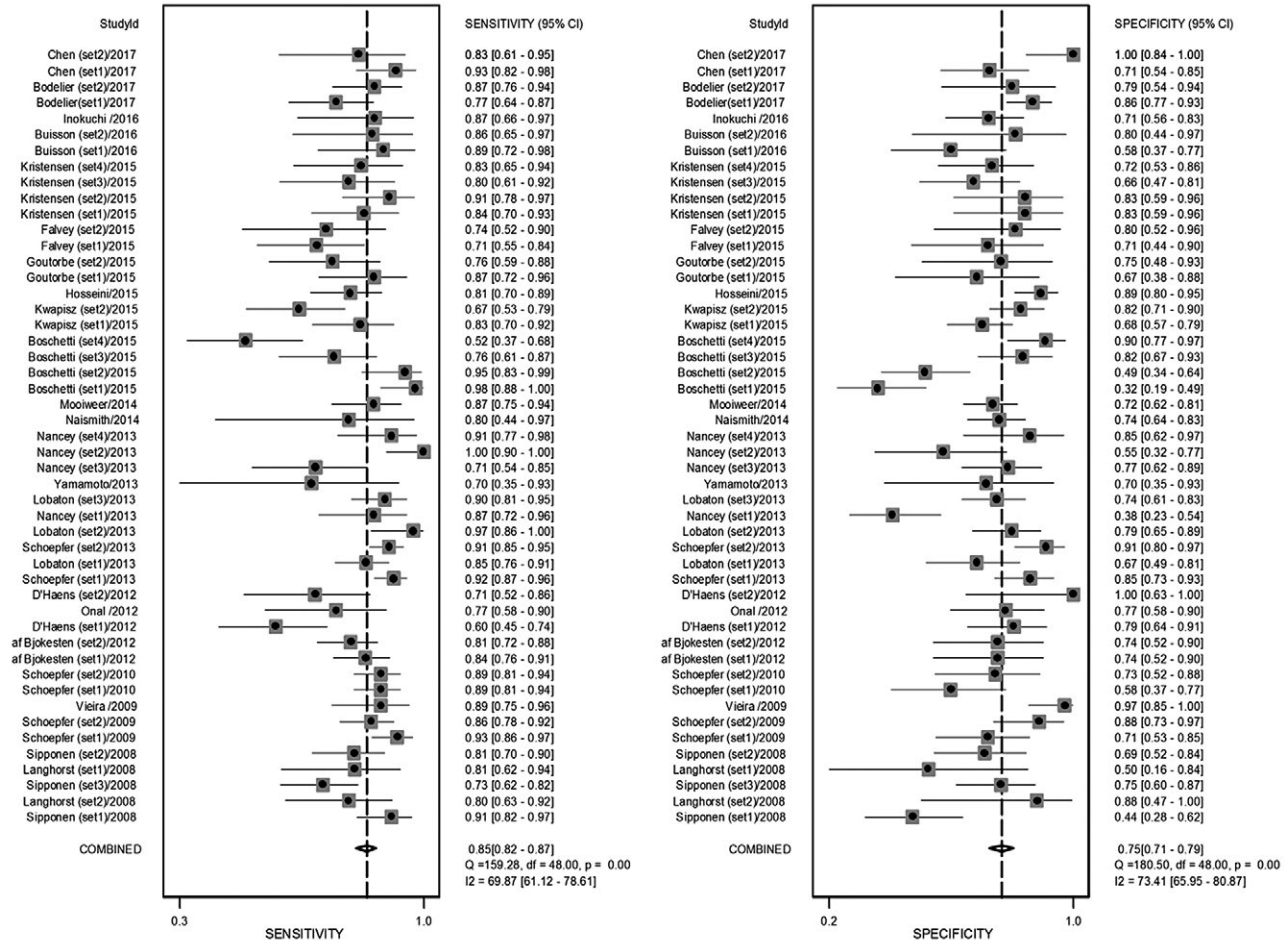

Fig. 2. Forest plot of sensitivities (A) and specificities (B) with corresponding heterogeneity statistics.

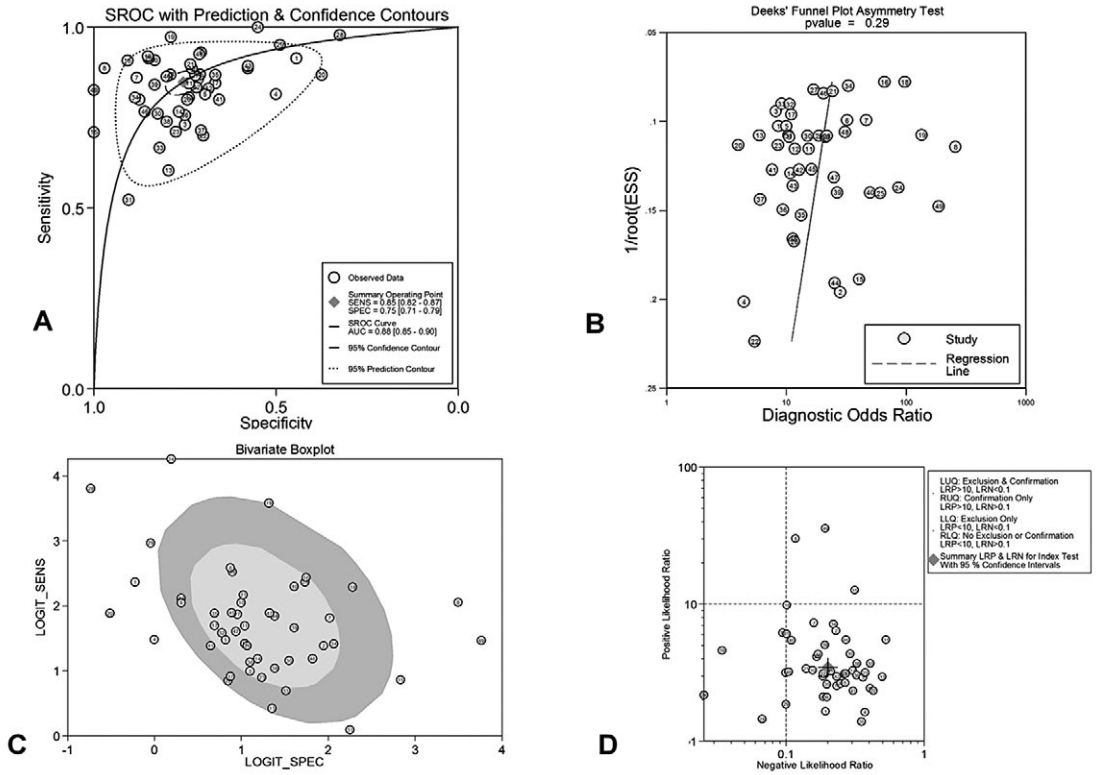

Fig. 3. A. Weighted symmetric summary receiver operating curve (sROC), with 95% confidence intervals and prediction regions around mean operating sensitivity and specificity point. B. Deeks' funnel plot, with superimposed regression line. No evidence of publication bias C. Bivariate box plot with most studies clustering within the median distribution and some outliers suggesting indirectly the existence of heterogeneity D. Likelihood ratio scattergram.

ranging from 48 to 400 μg/g. In order to examine FC accuracy performance at different cutoff values, we carried out subgroup analyses taking into account three cut off levels, i.e. FC up to 50 μg /g (7 studies), FC up to 100 mcg/gr (20 studies) and FC > 100 μg /g (29 studies). Table II summarizes pooled sensitivity and specificity (with 95% CI), pooled PLR and NLR (95% CI), pooled DOR (95% CI) and pooled AUCs for these three cut off levels together with the overall performance for the whole group of 49 sets of data. Thus, for the cut off level of 50 μg/g the relevant pooled results were; sensitivity (95% CI) = 90.6% (87.9-92.9), specificity = 60.7% (53.7-67.4) and AUC 0.91. The respective values for cut off levels up to 100 μg /g and > 100 μg /g were 88.2 % (86.5– 89.8), 67 % (63.3 – 70.6), 0.89 and 80 % (77.7-82.2), 78.2% (75.7-80.6), 0.86, respectively. These pooled results clearly showed that as the cutoff value increases, sensitivity falls and specificity increases.

FC diagnostic accuracy according to disease type

In the 49 sets of data included in the 25 eligible studies, there were 25 sets evaluating FC diagnostic performance in CD and 21 evaluating this performance in UC. Table III summarizes pooled sensitivity and specificity (with 95% CI), pooled PLR and NLR (95% CI), pooled DOR (95% CI) and pooled AUCs for these two diseases separately, together with the overall performance for the whole group of 49 sets of IBD data. For CD, pooled sensitivity, specificity (with 95% CI) and AUC were 82.4% (80.2-84.4), 72.1% (69-75) and 0.84, respectively. For UC these results were 87.3% (85.4– 89.1),

Table II. Fecal calprotectin diagnostic accuracy (random effects model) according to different cutoff values

	Calprotectin 48-400 μg/g All studies (n =49)	Calprotectin up to 50 μg//g (Number of studies = 7)	Calprotectin up to 100 μg /g (Number of studies =20)	Calprotectin > 100 μg /g (Number of studies=29)
Pooled Sensitivity (95% CI)	85% (82-87)	90.6% (87.9-92.9)	88.2 % (86.5– 89.8)	80% (77.7-82.2)
Pooled Specificity (95% CI)	75% (71-79)	60.7% (53.7-67.4)	67 % (63.3 – 70.6)	78.2% (75.7-80.6)
Pooled PLR (95% CI)	3.46 (2.95-4)	2.37 (1.49-3.76)	2.81 (2.15 – 3.69)	3.36 (2.94 - 3. 83)
Pooled NLR (95% CI)	0.2 (0.17-0.24)	0.16 (0.1-0.23)	0.18 (0.14- 0.22)	0.24 (0.21-0. 31)
Pooled DOR (95% CI)	16.3 (12.9-20.5)	18.2(8.53-38.57)	18.4 (12.37 – 27.6)	14.7 (11.28-19.1)
Pooled AUC (95% CI)	0.88	0.91	0.89	0.86

CI: confidence intervals; PLR: Positive Likelihood Ratio; NLR: Negative Likelihood Ratio; DOR: Diagnostic Odds Ratio; AUC: Area Under Curve

Table III. Fecal calprotectin diagnostic accuracy (random effects model) according to underlying disease

	All data sets (n =49)	Crohn's disease (n = 25)	Ulcerative colitis (n=21)
Pooled Sensitivity (95% CI)	85% (82-87)	82.4% (80.2-84.4)	87.3% (85.4– 89.1)
Pooled Specificity (95% CI)	75% (71-79)	72.1% (69-75)	77.1 % (73.7 – 80.3)
Pooled PLR (95% CI)	3.46 (2.95-4.04)	2.86 (2.49-3.45)	3.75 (2.73 – 5.15)
Pooled NLR (95% CI)	0.2 (0.17-0.24)	0.25 (0.21-0.31)	0.18 (0.15- 0.22)
Pooled DOR (95% CI)	16.3 (12.9-20.5)	12.69 (9.92-16.24)	23.22 (15.33 – 35. 1)
Pooled AUC	0.88	0.84	0.91

CI: confidence intervals; PLR: Positive Likelihood Ratio; NLR: Negative Likelihood Ratio; DOR: Diagnostic Odds Ratio; AUC: Area Under Curve

77.1 % (73.7 – 80.3) and 0.91. These results suggest that the FC test performed better in UC than in CD patients. A possible explanation of this finding might be the extent and severity of the colonic lesions in the two disease groups.

DISCUSSION

This meta-analysis updated older meta-analyses [14, 15] using a larger number of included studies. The results showed that FC has a pooled sensitivity of 85%, specificity of 75%, DOR of 16.3 and AUC of 0.88. These data confirmed the results of the former meta-analyses denoting a good level of overall diagnostic accuracy in estimating bowel mucosal inflammation status in IBD. A novelty of this meta-analysis is the sub-group analysis, which revealed that the FC test performed better in UC (pooled sensitivity 87.3 %, specificity 77.1%, AUC 0.91) than CD (pooled sensitivity 82.4%, specificity 72.1%, AUC 0.84). The modest specificity of this test in CD, i.e. 72.1%, is potentially a problem, since the remaining 27.9% are false positive tests and could lead to treating patients with inactive disease. Other studies have stressed this issue in the literature [29, 50-52].

Nowadays, colonoscopy is considered as the most accurate diagnostic modality and the standard method for estimating the inflammatory status of the intestinal mucosa. Consequently, several endoscopic scoring systems have developed to quantify the endoscopic activity in IBD. However, despite its unequivocal usefulness, colonoscopy carries some disadvantages in that it is invasive, time consuming, expensive, and uncomfortable. In addition, colonoscopy could lead to some undesirable events, which might negatively influence the patient's health. Therefore, doctors and patients could both benefit from an accurate and accessible laboratory biomarker reflecting intestinal mucosal inflammation. Conventional biomarkers such as ESR, CRP and blood leukocyte count, although useful and widely used in the clinical management of IBD, express systemic patient responses instead of specifically expressing intestinal inflammation. On the contrary, FC is a surrogate marker for the condition of intestinal mucosa. Therefore, it could be important if this test could perform well in distinguishing active from inactive disease. This would be especially significant in IBD patients under treatment, as it could decisively help the clinician in taking important therapeutic decisions.

In the studies included in this meta-analysis there was variation in the cutoff values for the FC test, ranging from 48 to 400 μg/g. In trying to identify an optimum FC cut-off level, we performed sub-group analyses, i.e. separate meta-analyses of studies at three FC cut off levels, i.e. FC up to 50 μg/g, FC up to 100 μg/g and FC > 100 μg/g. As indicated in Table II, the increase in cutoff value resulted in lower sensitivity and higher specificity. Thus, the best sensitivity of 90% (87.9-92.9) was achieved at the cut-off level of 50 μg/g, whereas the best specificity of 78.2% (75.7-80.6) was achieved for cut-off levels greater than 100 μg/g. Overall, when comparing different cut-off levels, the FC test showed its best performance (sensitivity 90.6%, AUC 0.91) at the cut-off level of 50 μg/g. It seems, therefore, that this cut-off level is optimal for assessing IBD activity and this could be useful in clinical practice. Indeed, apart from our meta-analysis, former meta-analyses [14, 15] have come to a similar conclusion suggesting that in IBD patients with FC <50 μg/g, the likelihood of active disease is very low. On the other hand, this cut-off level has a specificity for active disease of 60.7%, meaning that almost 40% of patients will undergo an unnecessary colonoscopy or treatment escalation by using this cut-off. Especially the upper cut-off level with the higher specificity appropriate for treatment escalation without endoscopy has to be defined by future studies.

The results of our meta-analysis are strengthened by the lack of publication bias. However, the significant heterogeneity found represents a limitation. Similarly, significant heterogeneity was found in a former meta-analysis [15] that included studies with both paediatric and adult patients. We hypothesized that the mixed age groups in their study were responsible for this. However, in our meta-analysis, despite the fact that we included only studies of adult patients the significant heterogeneity still exists. The latter could be the result of the influence of various factors related to lack of standardization concerning design and methodology of the included studies. Thus, factors such as differences in the end point of included studies, spectrum of disease, quality of reporting and different test cut-off points, as detected by the various sensitivity analyses performed, such as the meta-regression analysis, might potentially be confounding factors contributing to overall significant heterogeneity. This could have influenced the interpretation of the results. All the above stress the necessity of standardization in future IBD studies examining the diagnostic accuracy of biomarkers in IBD. However, in our meta-analysis, all limitations mentioned may be compensated by the fact that, in the group of studies evaluated, a relatively large sample size of IBD patients was amenable for analysis.

CONCLUSION

The results of this systematic review and meta-analysis show that FC is a highly sensitive diagnostic tool in estimating endoscopic IBD activity. It appears to have greater accuracy when used in UC in comparison to CD at the cut-off level of 50 μg/g. To overcome some limitations raised by the significant heterogeneity found, large and well-designed prospective studies are required to further evaluate the usefulness of this biomarker in clinical practice.

Conflicts of interest: None to declare.

Authors' contributions: T.R., P.P. and I.E.K. participated in the design of the study. T.R., P.P. and I.E.K. performed the literature search, study retrieval and data collection. T.R. performed the statistical analysis. T.R., P.P., and I.E.K. wrote the paper. All authors read and approved the final manuscript.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://www.jgld.ro/wp/archive/y2018/n3/a15 and http://dx.doi.org/10.15403/jgld.2014.1121.273.pti

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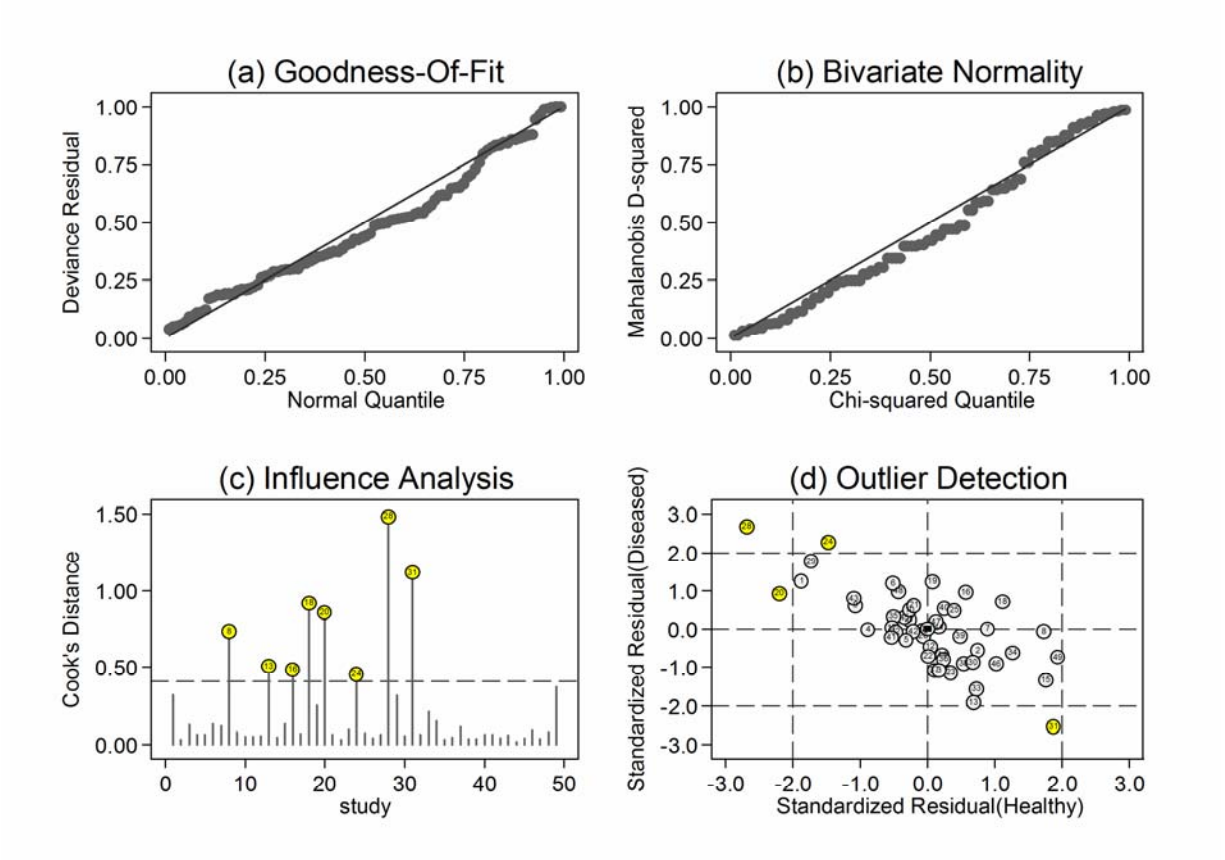
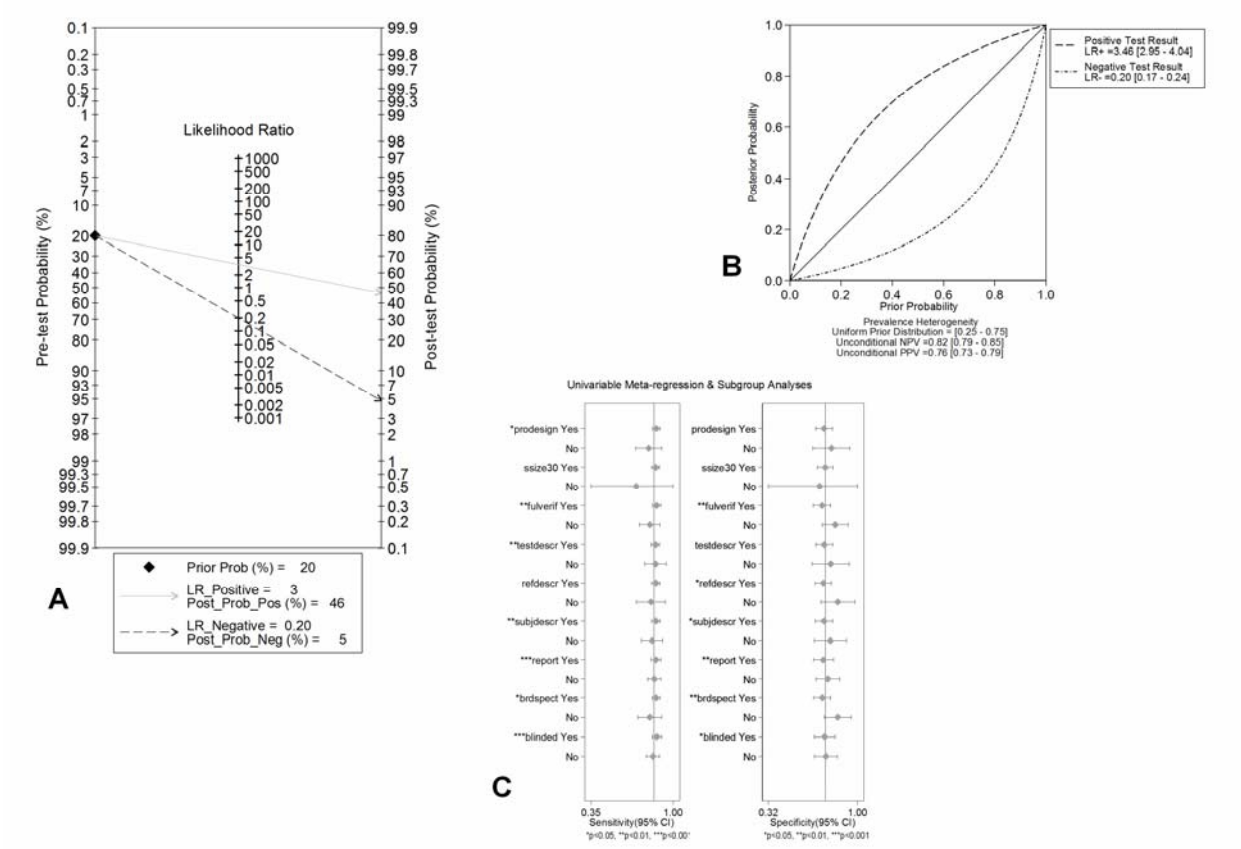


Supplementary Fig. 1. Sensitivity analyses, with graphical depiction of: **A**. residual-based goodness-of-fit, **B.** bivariate normality, **C.** influence analyses, **D.** outlier detection analyses.



Supplementary Fig. 2. **A**. Fagan's nomogram for showing post-test probability of IBD activity after FC-positive result (upper line) and FC-negative result (lower line). **B.** Probability modifying plot **C.** Forest plot of multiple univariable meta-regression and subgroup analyses for detection of sources of heterogeneity in FC.