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Use of Laboratory Markers in Addition to Symptoms for Diagnosis of Inflammatory Bowel Disease in Children
A Meta-analysis of Individual Patient Data

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IMPORTANCE Blood markers and fecal calprotectin are used in the diagnostic workup for inflammatory bowel disease (IBD) in pediatric patients. Any added diagnostic value of these laboratory markers remains unclear.

OBJECTIVE To determine whether adding laboratory markers to evaluation of signs and symptoms improves accuracy when diagnosing pediatric IBD.

DATA SOURCES A literature search of MEDLINE and EMBASE from inception through September 26, 2016. Studies were identified using indexing terms and free-text words related to child, target condition IBD, and diagnostic accuracy.

STUDY SELECTION Two reviewers independently selected studies evaluating the diagnostic accuracy of more than 1 blood marker or fecal calprotectin for IBD, confirmed by endoscopy and histopathology or clinical follow-up, in pediatric patients with chronic gastrointestinal symptoms. Studies that included healthy controls and/or patients with known IBD were excluded.

DATA EXTRACTION AND SYNTHESIS Individual patient data from each eligible study were requested from the authors. In addition, 2 reviewers independently assessed quality with Quality Assessment of Diagnostic Accuracy Studies–2.

MEAN OUTCOMES AND MEASURES Laboratory markers were added as a single test to a basic prediction model based on symptoms. Outcome measures were improvement of discrimination by adding markers as a single test and improvement of risk classification of pediatric patients by adding the best marker.

RESULTS Of the 16 eligible studies, authors of 8 studies (n = 1120 patients) provided their data sets. All blood markers and fecal calprotectin individually significantly improved the discrimination between pediatric patients with and those without IBD, when added to evaluation of symptoms. The best marker—fecal calprotectin—improved the area under the curve of symptoms by 0.26 (95% CI, 0.21-0.31). The second best marker—erythrocyte sedimentation rate—improved the area under the curve of symptoms by 0.16 (95% CI, 0.11-0.21). When fecal calprotectin was added to the model, the proportion of patients without IBD correctly classified as low risk of IBD increased from 33% to 91%. The proportion of patients with IBD incorrectly classified as low risk of IBD decreased from 16% to 9%. The proportion of the total number of patients assigned to the intermediate-risk category decreased from 55% to 6%.

CONCLUSIONS AND RELEVANCE In a hospital setting, fecal calprotectin added the most diagnostic value to symptoms compared with blood markers. Adding fecal calprotectin to the diagnostic workup of pediatric patients with symptoms suggestive of IBD considerably decreased the number of patients in the group in whom challenges in clinical decision making are most prevalent.

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Supplemental content

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It is a diagnostic challenge to differentiate between inflammatory bowel disease (IBD) and functional gastrointestinal disorders, such as irritable bowel syndrome, in pediatric patients. Unnecessary invasive diagnostic testing and endoscopy need to be balanced against the risk of missing or delaying a diagnosis of IBD. The diagnostic workup of children and adolescents with gastrointestinal symptoms starts with history and physical examination. Endoscopy is needed to make a definitive diagnosis of IBD, but this is an invasive and unpleasant procedure, especially in pediatric patients.[1] The key question, therefore, is whether commonly used blood markers or fecal calprotectin improve the accuracy of the diagnostic workup beyond the findings of history and physical examination to select children for endoscopy.[2] Information on whether the tests add value would help the clinician in choosing tests that are most appropriate and correctly interpreting the results.

A recent meta-analysis provided an overview of the accuracy of signs, symptoms, tests, and test combinations for diagnosing IBD in pediatric patients presenting with symptoms suggestive for IBD in whom a pediatrician could consider endoscopy.[3] This meta-analysis was based only on published data, and it was therefore not possible to determine any added value of tests beyond signs and symptoms. Moreover, the various combinations of test results were often evaluated in a single study; thus, limited information was available on how robust these results were.

High-quality evidence to determine any added value of tests to symptoms can be achieved by using individual patient data (IPD) from all relevant studies. In the IPD meta-analysis, we determined the added diagnostic value of commonly used blood markers and fecal calprotectin on top of symptoms for diagnosing IBD in symptomatic children and adolescents.

Key Points

Question Is there added diagnostic value of blood markers and fecal calprotectin beyond signs and symptoms for inflammatory bowel disease in symptomatic pediatric patients?

Findings In an individual patient data meta-analysis including 1120 pediatric patients, fecal calprotectin added the most diagnostic value to symptoms compared with blood markers. Addition of fecal calprotectin to the diagnostic workup of pediatric patients with symptoms suggestive of inflammatory bowel disease considerably decreased the number of patients in the intermediate risk of inflammatory bowel disease group, in which challenges in clinical decision making are most prevalent.

Meaning Fecal calprotectin should be recommended for the triage of pediatric patients with symptoms suggestive of inflammatory bowel disease.

Methods

Search Strategy

We searched MEDLINE and EMBASE from inception until September 26, 2016, to identify diagnostic studies that evaluated more than 1 laboratory test for IBD in pediatric patients with symptoms suggestive of IBD. We updated the literature search used in a recently published meta-analysis[3] that incorporated indexing terms and free-text words related to child, target condition IBD, and diagnostic accuracy (eMethods in the Supplement). In addition, we hand searched references of full-text articles, reviews, and guidelines on pediatric IBD.[1,4-8] No language restrictions were applied.

Selection Criteria

Two independent reviewers (G.A.H. and Y.L.L.) identified and selected eligible studies. All studies examining the diagnostic accuracy of more than 1 laboratory test (blood markers or fecal calprotectin) for a diagnosis of IBD were eligible for inclusion. Inflammatory bowel disease had to be confirmed or rejected by histopathologic analysis of biopsies retrieved at endoscopic examination or rejected by the absence of symptoms at clinical follow-up. We included studies that evaluated children or adolescents (from birth to 18 years) with gastrointestinal symptoms suggestive of IBD. We excluded studies that included healthy controls and/or patients with known IBD.

IPD Data Set, Data Extraction, and Quality Assessment

We contacted the corresponding authors of eligible studies and invited them to share their data sets. In case of nonresponse, we sent 2 reminder emails. If we had no response after the third email, the study was excluded from analysis. From the published reports, 2 reviewers (G.A.H. and Y.L.L.) independently abstracted information on country, study design, setting, and age. In addition, the following IPD from each included study were requested: final diagnosis (IBD/no IBD), levels of laboratory tests (blood markers [C-reactive protein, erythrocyte sedimentation rate, platelet count, albumin, and hemoglobin] and fecal calprotectin), and, if available, information on the presence of symptoms (abdominal pain, diarrhea, rectal bleeding, and weight loss). These IPD were compared with the published results. Discrepancies were discussed with the authors and corrected.

Two reviewers (G.A.H. and Y.L.L.) independently assessed the risk of bias and concerns for applicability, using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) instrument.[9] The study of Holtman et al[10] was assessed by 2 other reviewers who had not participated in this study (P.H. and D.C.W.). The QUADAS-2 instrument consists of 4 domains: patient selection, index test, reference standard, and flow and timing. Disagreements between reviewers were resolved by consensus or, if necessary, by a third reviewer (M.Y.B.).

Statistical Analysis

We used a 2-step approach in this IPD meta-analysis to determine the discriminative ability of single laboratory markers and any added value to symptoms. In the first step, the results were calculated in each of the studies. In the second step, the results were meta-analyzed.

Discrimination of Markers

In the first step, we determined the discriminative ability of single laboratory markers by calculating the area under the receiver-operating characteristic curve (AUC) with 95% CIs for each data set. In the second step, we calculated the pooled AUC with 95% CIs, using the random-effects generic inverse variance model.[11]

Added Value of Markers

First, we developed a common basic model of symptoms considered predictive for IBD (dichotomous dependent variable), using logistic regression analysis in each data set. The symptoms were abdominal pain, diarrhea, and rectal bleeding. Other signs and symptoms (eg, involuntary weight loss, perianal lesions, and growth failure) were not included in the basic model, because these were not available for all studies. To estimate the added predictive value of single laboratory markers, we added these factors as continuous variables to the basic symptoms model. The difference in AUC (Δ AUC) with 95% CI between the basic model and the different extended models with a single laboratory marker was calculated for each data set, using the method of DeLong.[12,13] In the second step, a pooled estimate and 95% CI of the Δ AUC was calculated by the generic inverse variance method, using random-effects models.[11] Moreover, a forest plot was constructed to visualize the AUC and Δ AUC of each data set and the heterogeneity between data sets.

Improvement in Diagnostic Risk Classification

To provide more insight in how the pediatric patients were classified by using the basic model and the shift in classification after adding the overall best marker, we constructed a reclassification table. The predicted probability of IBD in all pediatric patients was calculated in each data set for both models. We defined 2 threshold probabilities, 1 below which a pediatrician decides not to perform endoscopy (probability <35%) and 1 above which a pediatrician decides to perform endoscopy (probability >60%). Therefore, 3 risk groups were created: low risk (predicted probabilities <35%), intermediate risk (predicted probabilities 35%-60%), and high risk (predicted probabilities >60%) of IBD. The 2 threshold probabilities were used to calculate 2 × 2 tables for the basic model and basic model with the best marker in each data set. The sensitivities and specificities in each data set were pooled with bivariate random-effects models.[14] These pooled sensitivities and specificities and the median prevalence of IBD were used to construct a reclassification table of 100 hypothetical pediatric patients with 3 relevant risk groups of IBD.

Missing Data

If a specific marker was not evaluated in a single study (systematically missing data), this data set was not included when calculating a pooled estimate of that marker. If 1 or more of the 3 key symptoms was not evaluated in a study, this study was not included in the evaluation of the added value of the various markers. In case of sporadic missing data, we used multiple imputations (fully condition specification, predictive mean matching, 20 iterations, and 5 data sets), with the following variables as predictors: all symptoms (if present), all laboratory markers, and diagnosis.[15,16] We used the Rubin rule to calculate the pooled AUC.[17]

Statistical analyses were performed with IBM SPSS, version 20.0.0 (IBM Corp), STATA/SE, version 13 (StataCorp), and SAS, version 9.2 (SAS institute). Findings were considered significant at $P < .05$.

Results

Selection of Studies

Of the 2974 unique studies identified from the literature search, 16 diagnostic studies were eligible (eFigure in the Supplement). The IPD were not obtained from 8 studies (n = 1719 patients) because 3 authors did not respond to emails,[18-20] the data were no longer available,[21-24] or the author declined to share data.[25] The median prevalence of IBD in the 7 excluded cohort studies was 45% (range, 19%-67%).[18-24] One excluded study used a case-control design in symptomatic pediatric patients.[25] Five of the 8 excluded studies reported on symptoms and blood markers,[20,21,23-25] 2 reported on blood markers only,[18,22] and 1 study discussed blood markers and fecal calprotectin.[19] Two excluded studies were performed in Europe[18,19] and 6 studies were conducted in North America.[20-25] The test characteristics of the laboratory markers of the available and excluded studies were comparable,[3] except for 1 excluded study that showed to be an outlier for C-reactive protein and platelet count.[22]

Characteristics and Quality of Included Studies

We were able to obtain the IPD from 8 studies with a total of 1120 pediatric patients, 560 of whom had IBD. Study and patient characteristics are given in **Table 1** and **Table 2**. The median prevalence of IBD in the 5 cohort studies was 43% (range, 19%-62%).[10,26,29,30,32] Five of the 8 included studies were performed in European countries,[10,26,27,29,32] 2 in Australia,[28,30] and 1 in North America.[31] All studies were performed in referred children or adolescents (hospital setting); 3 used a case-control design in symptomatic pediatric patients.[27,28,31] Quality assessment of all included studies identified risk of bias in 1 or more domain. We had applicability concerns for patient selection in 1 study.[10] eTable 1 in the Supplement presents the full QUADAS-2, and eTable 2 in the Supplement presents the systematically missing and sporadically missing values; the sporadically missing values were imputed.

Discrimination of Markers

The AUC of the markers, except for platelets and hemoglobin, were heterogeneous across studies (eTable 3 in the Supplement). The pooled AUC of erythrocyte sedimentation rate (8 studies), albumin (5 studies), C-reactive protein (8 studies), platelets (6 studies), hemoglobin (5 studies), and fecal calprotectin (6 studies) were 0.84 (95% CI, 0.82-0.87), 0.82 (95% CI, 0.73-0.90), 0.79 (95% CI, 0.73-0.85), 0.79 (95% CI, 0.75-0.83), 0.76 (95% CI, 0.71-0.80), and 0.95 (95% CI, 0.93-0.98), respectively (**Figure 1**).

Table 1. Study Characteristics of 8 Included Studies Providing Individual Patient Data

Characteristic	Source							
	Fagerberg et al,[26] 2005	Henderson et al,[27] 2012	Holtman et al,[10] 2016	Leach et al,[28] 2007	Perminow et al,[29] 2009	Sidler et al,[30] 2008	Tsampalieros et al,[31] 2011	Van de Vijver et al,[32] 2012
Country	Sweden	Scotland	The Netherlands	Australia	Norway	Australia	Canada	The Netherlands
Design	Prospective cohort	Case-control	Prospective cohort	Nested case-control	Prospective cohort	Prospective cohort	Case-control	Prospective cohort
Setting[a]	Referred children, high risk	Referred children, high risk	Referred children, moderate risk	Referred children, high risk	Referred children, moderate/high risk	Referred children, high risk	Referred children, high risk	Referred children, moderate/high risk

[a] Referred moderate risk: children referred by their primary care physician (either primary care physician or pediatrician) to a pediatrician or pediatric gastroenterologist for diagnostic workup; referred high risk: children referred by a pediatrician to a pediatric gastroenterologist and endoscopy.

Added Value of Markers

In 2 studies, the basic model could not be fitted, because 1 or more of the key symptoms was systematically missing (eTable 2 in the Supplement).[27,28] The AUC of the basic model ranged from 0.65 to 0.77, and the pooled AUC of the basic model was 0.70 (95% CI, 0.65-0.75). The Δ AUCs were fairly homogeneous across studies (eTable 4 in the Supplement). Pooled Δ AUC values for addition of blood test markers to the basic model of symptoms were 0.16 (95% CI, 0.11-0.21) for erythrocyte sedimentation rate (5 studies), 0.13 (95% CI, 0.08-0.19) for platelets (4 studies), 0.13 (95% CI, 0.08-0.19) for hemoglobin (4 studies), 0.13 (95% CI, 0.05-0.21) for albumin (3 studies), and 0.08 (95% CI, 0.04-0.11) for C-reactive protein (5 studies) (**Figure 2**). The improvement in AUC when adding fecal calprotectin to the basic model ranged from 0.21 to 0.29 and was statistically significant in all data sets ($P < .05$). The pooled Δ AUC of fecal calprotectin was 0.26 (95% CI, 0.21-0.31).

Improvement in Diagnostic Risk Classification

The reclassification table of 100 hypothetical pediatric patients with IBD prevalence of 43% illustrates that adding the best marker (fecal calprotectin) to the basic model of symptoms leads to a decrease in the intermediate-risk group from 55 to 6 pediatric patients (**Table 3**).

The proportion of pediatric patients without IBD correctly classified as low risk of IBD increased from 33% to 91% and patients with IBD incorrectly classified as low risk of IBD decreased from 16% to 9%. The proportion of IBD cases in the low-risk group decreased (from 27% to 7%) and increased in the high-risk group (from 74% to 95%) when fecal calprotectin was added to symptoms in the workup.

Discussion

This IPD meta-analysis, including 1120 referred pediatric patients with symptoms suggestive of IBD, demonstrated that all laboratory markers (erythrocyte sedimentation rate, C-reactive protein, platelets, hemoglobin, albumin, and fecal calprotectin) as a single test improved the discrimination between patients with and those without IBD when added to a model with symptoms alone. The addition of fecal calprotectin to symptoms improved the AUC more than any of the individual blood markers. Moreover, fecal calprotectin added to symptoms improved the diagnostic risk classification by decreasing the number of pediatric patients in the intermediate-risk group from 55% to 6%. The pediatric patients were more often correctly classified in the low- and high-risk groups after adding fecal calprotectin to the diagnostic process.

The basic model in different data sets performed poorly to fairly (AUC varied between 0.65 and 0.77). We have to consider that the performance of discrimination of the basic model might have been better when more signs and symptoms would have been included in the model. This was not possible, since the included studies did often not record involuntary weight loss, growth failure, perianal lesions, family history of IBD, or extraintestinal symptoms. We found that, in referred symptomatic pediatric patients, all laboratory markers added significant discriminative value to symptoms alone and hence are potentially of value in the triage for endoscopy. Clinical relevance, however, depends on treatment thresholds and the trade-off between the utility of a missed (or delayed) diagnosis of IBD and an unnecessary endoscopy under full anesthesia. Guidelines suggest performing blood tests in pediatric patients with symptoms suggestive for IBD.[1,8] Because blood markers, such as hemoglobin and albumin, also may have consequences for treatment choices, this recommendation should not be abandoned. However, for the triage of pediatric patients for endoscopy, fecal calprotectin showed the highest discriminative performance and should be recommended for this purpose, especially since a normal fecal calprotectin value (<50 μg/g) makes the diagnosis of IBD unlikely.[4,6] Blood test results within the reference ranges do not rule out an IBD diagnosis.[3,33]

The results of this study are applicable to clinicians who evaluate referred pediatric patients for symptoms suggestive of IBD. One disadvantage to the routine use of fecal calprotectin in clinical practice might be the difficulty in obtaining stool from adolescents. None of the studies was performed in nonreferred pediatric patients in primary care. The results in referred pediatric patients are not generalizable to primary care, because differences in patient spectrum and disease severity can affect the pretest probability and added value of markers. In only 1 study, 24 of 90 patients were initially assessed in primary care and referred to specialist care for further diagnostic workup.[10] More studies in primary care are needed to determine the added value of markers in this setting.

Comparison With Literature

To our knowledge, this is the first meta-analysis using IPD to investigate the added value of commonly used laboratory

Table 2. Patient Characteristics of 8 Included Studies Providing Individual Patient Data

	Source															
	Fagerberg et al,[26] 2005		Henderson et al,[27] 2012		Holtman et al,[10] 2016		Leach et al,[28] 2007		Perminow et al,[29] 2009		Sidler et al,[30] 2008		Tsampalieros et al,[31a] 2011		Van de Vijver et al,[32b] 2012	
Characteristic	IBD	No IBD	IBD	No IBD	IBD	No IBD	IBD	No IBD	IBD	No IBD	IBD	No IBD	IBD	No IBD	IBD	No IBD
No. of patients	20	16	91	99	17	72	39	33	62	38	31	30	258	197	42	75
Age range, y	6-17	6-17	3-18	1-16	8-17	4-17	5-14	5-12	2-18	1-18	2-16	2-16	1-17	2-17	6-18	6-18
Symptoms, No./No. (%)[c]																
Abdominal pain	15/19 (79)	13/15 (87)	Missing data	Missing data	15 (88)	42 (58)	Missing data	Missing data	50 (81)	32 (84)	17 (55)	21 (70)	123/156 (79)	Missing data	29 (69)	67 (89)
Diarrhea	18 (90)	11/14 (79)	Missing data	Missing data	16 (94)	45 (63)	Missing data	Missing data	42 (68)	19 (50)	18 (58)	7 (23)	Missing data	Missing data	8 (19)	2 (3)
Rectal bleeding	16 (80)	9 (56)	Missing data	Missing data	8 (47)	18 (25)	Missing data	Missing data	32 (52)	10/37 (27)	9 (29)	5 (17)	90/156 (58)	Missing data	26 (62)	32 (43)
Weight loss	10/16 (63)	7/12 (58)	Missing data	Missing data	12 (71)	11 (15)	Missing data	Missing data	Missing data	Missing data	9 (29)	10 (33)	Missing data	Missing data	23 (55)	35 (47)
Blood markers, median (IQR)																
CRP, mg/L	6.9 (7-10)	6.9 (7-7)	11 (3-35)	1 (1-3)	12 (3-22)	1 (0.3-3)	11 (1-43)	1 (1-2)	7.5 (6-28)	7 (5-7)	8 (3-48)	1 (1-1.5)	15.4 (4.4-45.5)	0 (0-2.5)	16 (5-34)	5 (5-5)
ESR, mm/h	12 (5-27)	4 (2-8)	30 (17-50)	6 (2-11)	25 (10-32)	6 (4-10)	28 (14-40)	3 (2-7)	22 (9-34)	5 (3-11)	27 (14-43)	5 (4-7)	34 (20-48)	12 (6.5-18.5)	26 (17-51)	7.5 (4-17)
Platelets, $\times 10^3/\mu L$	369 (314-450)	295 (273-300)	415 (327-505)	306 (239-343)	409 (257-448)	292 (251-332)	414 (331-534)	301 (246-341)	369 (300-427)	268 (223-325)	444 (323-529)	296 (254-340)	459 (347-562)	Missing data	Missing data	Missing data
Hb, g/dL	11.8 (10.6-12.8)	13.4 (12.6-14.8)	11.5 (10.0-12.3)	12.9 (12.0-13.5)	11.8 (11.3-12.9)	13.1 (12.9-14.5)	Missing data	Missing data	11.5 (10-13)	12.6 (12-13)	Missing data	Missing data	11.4 (10.3-12.4)	Missing data	11.3 (9.7-12.9	12.9 (12.9-12.9)
Albumin, g/dL	3.6 (3.3-4.0)	4.4 (4.0-4.6)	3.8 (3.4-4.1)	4.6 (4.3-4.7)	Missing data	Missing data	3.3 (2.9-3.8)	4.0 (3.9-4.1)	3.8 (3.3-4.2)	4.1 (3.7-4.3)	3.3 (2.7-3.5)	4.0 (3.8-4.2)	3.6 (3.2-4.1)	Missing data	Missing data	Missing data
Fecal marker, median (IQR)																
FCal, µg/g	389 (219-713)	17.5 (8-28)	1265 (714-2035)	65 (20-235)	711 (470-824)	20 (20-30)	Missing data	Missing data	1183 (359-2000)	33 (14-113)	1265 (575-2517)	31 (20-67)	Missing data	Missing data	1408 (1067-1800)	40 (40-100)

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FCal, fecal calprotectin; Hb, hemoglobin; IBD, inflammatory bowel disease; IQR, interquartile range.

SI conversion factors: To convert albumin to grams per liter, multiply by 10; CRP to nanomoles per liter, multiply by 9.524; ESR to millimeters per hour, multiply by 1; Hb to grams per liter, multiply by 10; and platelets to $\times 10^9$/L, multiply by 1.

[a] Abdominal pain and rectal bleeding were recorded only for Crohn disease (n = 156).

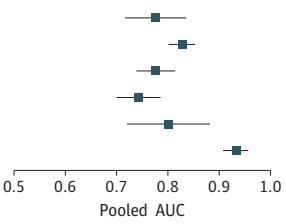
[b] Abdominal pain included abdominal pain and diarrhea.

[c] No./No. indicates number of patients with symptom per sample when denominator differs from total.

markers for diagnosing IBD. However, another IPD meta-analysis concerning fecal calprotectin in referred pediatric patients with suspected IBD developed an individual risk prediction rule for IBD.[7] The prediction rule was based on fecal calprotectin value and the age of the child. The AUC of the prediction model was 0.92 (95% CI, 0.89-0.94). In daily practice, signs and symptoms are used before testing with blood markers or fecal calprotectin. Therefore, it is important to ascertain the incremental value of signs and symptoms alongside laboratory testing. In the present IPD meta-analysis, we evaluated the most commonly used laboratory markers and provided insight into which tests are appropriate for triage for endoscopy.

Figure 1. Pooled Area Under the Curve (AUC)

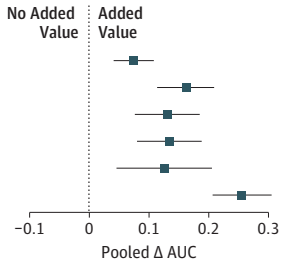
Laboratory Test	Studies, No.	Pooled AUC (95% CI)
CRP	8	0.79 (0.73-0.85)
ESR	8	0.84 (0.82-0.87)
Platelets	6	0.79 (0.75-0.83)
Hb	5	0.76 (0.71-0.80)
Albumin	5	0.82 (0.73-0.90)
FCal	6	0.95 (0.93-0.98)



CRP indicates C-reactive protein; ESR, erythrocyte sedimentation rate; FCal, fecal calprotectin; and Hb, hemoglobin.

Figure 2. Pooled Improvement in Area Under the Curve (AUC) When Adding Markers to the Basic Model

Laboratory Test	Studies, No.	Pooled Δ AUC (95% CI)
CRP	5	0.08 (0.04-0.11)
ESR	5	0.16 (0.11-0.21)
Platelets	4	0.13 (0.08-0.19)
Hb	4	0.13 (0.08-0.19)
Albumin	3	0.13 (0.05-0.21)
FCal	5	0.26 (0.21-0.31)



A Δ AUC value greater than 0 implies an added discriminative value of the laboratory test, and a value of 0 or less implies no added discriminative value. CRP indicates C-reactive protein; ESR, erythrocyte sedimentation rate; FCal, fecal calprotectin; and Hb, hemoglobin.

Degraeuwe et al[7] found in their IPD meta-analysis that the AUC of testing with fecal calprotectin was 0.94 (95% CI, 0.92-0.95). In the present IPD meta-analysis, the AUC of fecal calprotectin was comparable, even though we included different studies. Four studies included in the earlier IPD were not analyzed in the present IPD, because 2 included only fecal calprotectin testing,[34,35] 1 study included pediatric patients with known IBD,[36] and the authors of 1 study did not respond to our efforts to contact them.[19] In our IPD meta-analysis, we included 2 additional studies,[10,29] 1 of which was published after the earlier IPD.[10]

Strengths and Limitations

Of the 16 eligible studies, we were able to obtain data sets from 8 studies. Therefore, there might be selection bias. Because the test characteristics of the laboratory markers of the available and excluded studies were comparable, we expect that the excluded studies will not have a large effect on the results.

The median and AUC of some laboratory tests varied considerably between the included studies. These heterogeneous results might be explained by the different assays that were used for the laboratory tests. Moreover, the AUC may vary due to different designs (cohort or case-control) and the number and choice of the reference standards (endoscopy or follow-up). However, the Δ AUCs were more homogeneous than the AUCs. We chose a 2-step approach, because this is a transparent method that takes into account the hierarchical nature of the data, which means that patients and procedures from 1 study are more consistent and similar to each other than across different studies.

Due to the absence of the registration of symptoms in 3 data sets,[27,28,31] it was not possible to determine the added value of the markers in these data sets. We did not ask the authors to retrospectively review the symptoms in the medical records, since this would make the information less reliable. In addition, only 3 of the 8 studies evaluated all included laboratory markers, causing a varied number of studies per marker. Another limitation is that the number of patients in the included studies was small. Too many predictors for a low number of patients in the

Table 3. Improved Diagnostic Risk Classification After Adding Fecal Calprotectin to Symptoms in a Hypothetical Cohort of 100 Children With IBD Prevalence of 43%[a]

	Observed IBD, %		
Predicted Risk of IBD	Yes	No	Total, %
Basic Model			
Low, <35%	7	19	26
Intermediate, 35%-60%	22	33	55
High, >60%	14	5	19
Total risk group	43	57	100
Basic Model Plus Fecal Calprotectin			
Low, <35%	4	52	56
Intermediate, 35%-60%	3	3	6
High, >60%	36	2	38
Total risk group	43	57	100

Abbreviation: IBD, inflammatory bowel disease.

[a] The numbers are based on the median prevalence of IBD of 43% across cohort studies and pooled sensitivities and specificities of the basic and the basic plus fecal calprotectin model at low and high predicted probabilities of IBD. The pooled sensitivities for the basic and basic plus fecal calprotectin model at low predicted probabilities were 0.84 and 0.91, respectively, and the pooled specificities were 0.33 and 0.92, respectively. At high predicted probabilities, the respective pooled sensitivities were 0.33 and 0.84, and pooled specificities were 0.92 and 0.96.

studies may cause perfect discrimination. The AUC of fecal calprotectin was very high, which might be an overestimation. Due to the high AUC of symptoms and fecal calprotectin, there is a small chance that blood markers could have had added value. However, the number of pediatric patients in the included studies of this IPD meta-analysis was too small to determine the added value of blood markers to symptoms and fecal calprotectin. We did not correct for overoptimism, because we did not develop a single clinical prediction rule and the Δ AUC is less sensitive for overoptimism since both the basic model and the extended model are not corrected. A methodologic study is needed to provide more insight in the overoptimism of the Δ AUC. A large study with more patients with and without IBD is needed to develop a prediction model for IBD based on patient characteristics, single signs and symptoms, blood markers, and fecal calprotectin. Moreover, age would be important to incorporate in the prediction rule, because age influences the probability of IBD and the fecal calprotectin values.

Since the AUC is an overall measure of discrimination and gives no insight to clinical interpretation, we provided a reclassification table of the best marker as an illustration of the potential impact of adding a marker to the basic model. We assume that, when referred patients are classified into the low-risk group (probability <35%), the pediatrician decides not to perform an endoscopy, while patients in the high-risk group (probability >60%) are considered likely to have IBD and require an endoscopy to determine the diagnosis. The choice of thresholds and the resulting risk groups may be debated, because the thresholds could be variable among, for example, clinicians and regions. Other thresholds to define the 3 risk groups could change the reclassifications. However, 35% and 60% are reasonable thresholds in specialist care, because studies show that pediatric patients with a probability for IBD of approximately 35% are referred to the pediatric gastroenterologist and pediatric patients with a probability of approximately 60% received an endoscopy.[32,37] For the clinician, the intermediate-risk group is the most challenging, because uncertainty about appropriate management is highest. Nevertheless, uncertainty about diagnosis remains in all risk categories, and children and parents should be informed about this.

Conclusions

In referred pediatric patients, fecal calprotectin added the most diagnostic value to symptoms compared with commonly used blood markers. Addition of fecal calprotectin to the diagnostic workup of referred pediatric patients with symptoms suggestive of IBD considerably decreased the number of pediatric patients in the intermediate-risk for IBD group.

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