Diagnostic yield of small-bowel capsule endoscopy in patients with iron-deficiency anemia: a systematic review (CME)

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Background: Iron-deficiency anemia (IDA) is the most common cause of anemia worldwide. Current guidelines recommend the use of small-bowel capsule endoscopy (SBCE) in IDA. Evidence of the validity of SBCE in patients with IDA alone is still limited.

Objective: To assess the diagnostic yield (DY) of SBCE in IDA by pooling data from relevant studies.

Design: Systematic review and meta-analysis. Fixed-effects or random-effects models were used as appropriate.

Setting: Studies that estimated the DY of SCBE in IDA were identified. Two investigators independently conducted the search and data extraction.

Patients: A total of 24 studies enrolling 1960 patients with IDA who underwent SBCE were included.

Main Outcome Measurements: Per-patient DY, with 95% confidence intervals. Subgroup analysis was also performed.

Results: The pooled DY of SBCE in IDA, evaluated by a random-effects model, was 47% (95% CI, 42%-52%), but there was statistically significant heterogeneity among the included studies (inconsistency index [I^2] = 78.8%, $P <$ .0001). The pooled DY of SBCE in studies focused solely on patients with IDA (subset 1, 4 studies) was 66.6% (95% CI, 61.0%-72.3%; I^2 = 44.3%); conversely, that of studies not focusing only on IDA patients (subset 2, 20 studies) was 44% (95% CI, 39%-48%; I^2 = 64.9%). In particular, more vascular (31% vs 22.6%, P = .007), inflammatory (17.8% vs 11.3%, P = .009), and mass/tumor (7.95% vs 2.25%, $P <$ .0001) lesions were detected with SBCE in patients participating in the studies in subset 1.

Limitations: Heterogeneity of studies, retrospective design, and selection bias.

Conclusions: This analysis demonstrates the validity of SBCE in the investigation of patients with IDA and negative findings on a previous diagnostic workup, although certain factors such as heterogeneity and quality of the included studies should be taken into account. (Gastrointest Endosc 2012;76:983-92.)

Abbreviations: CI, confidence interval; DY, diagnostic yield; FOBT, fecal occult blood test; Hb, hemoglobin; I^2, inconsistency index; IDA, iron-deficiency anemia; OGIB, obscure GI bleeding; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; SBCE, small-bowel capsule endoscopy.

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Obscure GI bleeding (OGIB) is defined by visible GI bleeding (eg, melena or hematochezia), iron-deficiency anemia (IDA), or positive results on fecal occult blood tests (FOBTs) in the setting of normal bidirectional endoscopy, ie, upper GI endoscopy and colonoscopy.[1] Furthermore, OGIB is subdivided into occult (ie, IDA and/or positive FOBT results) and overt OGIB. The diagnostic workup of patients with OGIB is often challenging and time-consuming. Nevertheless, the introduction of capsule endoscopy has revolutionized the evaluation of these patients.[2,3] In fact, several studies and meta-analyses showed that small-bowel capsule endoscopy (SBCE) is superior to push enteroscopy and most radiological imaging techniques for diagnosing clinically significant small-bowel pathology in patients with OGIB.[4,5] Therefore, guidelines have been updated to include SBCE as a third step, after negative findings on upper GI endoscopy and colonoscopy, in the diagnostic workup of patients with OGIB.[1,6]

In the setting of occult OGIB, the majority of SBCE studies do not consider patients referred for investigation of positive FOBT results or IDA as separate groups. Moreover, prospective SBCE studies focusing solely on IDA patients are few and likely underpowered. Although results of retrospective studies suggest that the diagnostic yield (DY) of SBCE in the 2 patient subgroups (positive FOBT results and IDA) is similar, evidence of the validity of SBCE in patients with IDA is still limited.

IDA is the most common cause of anemia worldwide, causing significant disease-related morbidity, and has a negative impact on well-being and health outcomes.[7] Furthermore, it represents one of the major indications for referral to gastroenterologists (13% of referrals).[6,7] Even after negative findings on a bidirectional endoscopy, approximately 30% of IDA patients lacking a diagnosis[6]; the majority of those will be eventually referred for SBCE.

With this review, we aimed to evaluate the DY of SBCE in the group of patients who have undergone the procedure because of unexplained IDA. This article was prepared according to previously published guidelines for meta-analyses of observational studies.[8]

Take-home Message

- Pooled data from 1922 patients with iron-deficiency anemia showed small-bowel capsule endoscopy to have a per-patient diagnostic yield (DY) of 48%. Studies with strict inclusion criteria showed a higher DY.
- Clarification of risk factors for sinister small-bowel pathology is needed.

MATERIALS AND METHODS

Data identification and study selection

A thorough and extensive recursive search of PubMed/MEDLINE, EMBASE, Scirus, Biosis, and Scopus databases for human studies, published between January 2001 (the year of the introduction of capsule endoscopy in clinical practice) and November 2011, was performed. To capture as many articles as possible, a broad search strategy was used (using both MeSH and non-MeSH terms, with an "automatic explosion" and "all fields" search where applicable). The following terms were searched first alone and eventually connected either with AND: "capsule endoscopy," "anemia," "bleeding, "hemorrhage," "gastrointestinal bleeding." Furthermore, the reference list of all the selected articles was manually checked for potentially suitable references that were not identified by the initial search. Studies were selected based on title and abstract (where available), by 2 of the authors (A.K. and E.R.). After retrieving the full text of selected papers, both reviewers independently checked whether inclusion criteria were met; in the event of uncertainty, any discrepancies were resolved by discussion and consensus of all of the authors.

For a study to be included in this review, the following predefined inclusion criteria had to be met: written in English language and published as full paper; provided sufficient data for the authors to confirm iron-deficiency either in part or for the entire study cohort; provided either DY or enough data to allow us to calculate the DY of SBCE in IDA patients. Where applicable, we defined DY as the proportion of patients with clinically significant angioectasias (P2 lesions)[9] or other clinically significant SBCE findings (ie, mucosal ulcers, intraluminal bleeding, celiac changes, mass-type lesions). Patients with "suspicious" or "uncertain" SBCE findings (eg, P0 or P1 lesions)[9] were not taken into account in calculation of the DY.

Finally, we excluded those studies in which SBCE was performed in patients with IDA and preexisting clinical conditions that could potentially explain IDA (ie, patients with Crohn's disease, celiac disease, hereditary hemorrhagic telangiectasias, chronic renal failure, and/or cirrhosis).

For the purpose of statistical analysis, any study presenting fewer than 10 cases of IDA was excluded.[10] Duplicate publications were deleted. When 2 or more articles reported results from the same patient cohort, either the more recent or more complete publication was selected.

Data extraction

The 2 authors (A.K. and E.R.) extracted data from each selected study by using a predefined form in Microsoft Excel (Microsoft Corp, Redmond, Wash). From each paper, the 2 reviewers independently abstracted the following: (1) first author name and the year of publication; (2) whether it was a single-center or multicenter study; (3) country where the study was performed; (4) design (prospective or retrospective); (5) whether consecutive patients were included; (6) total number of patients recruited; (7) number of patients with IDA; (8) the DY of SBCE in patients with IDA or the number of IDA patients with clinically significant SBCE findings (as defined by the

study authors) for DY calculation; (9) the category/classification of findings in patients with positive SBCE (if available); (10) the focus of the study, differentiating between SBCE studies enrolling exclusively IDA patients (subset 1, focused on IDA) and studies reporting the DY of SBCE in patients with IDA, but also including patients undergoing SBCE for other indications (subset 2, studies not focused on IDA).

Risk of bias in individual studies

To assess the methodological quality of included studies and detect potential bias, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) was used.[11] The QUADAS tool enables reviewers to evaluate the quality of diagnostic accuracy studies. Because the current work is a systematic review of DY, and not one of diagnostic test accuracy (compared with a reference standard), several of the QUADAS items (items 3-11) cannot be evaluated. The aforementioned QUADAS items were noted as not applicable (N/A).

Risk of bias across studies

To explore the existence of publication or other type of bias, when detected by the inconsistency index (I^2) measuring the proportion of unexplained variation across studies, a funnel plot of standard error by diagnostic yield was produced.

Summary measures

The primary endpoint was the pooled DY of SBCE (per patient) in IDA. Subgroup analysis was performed according to study focus (studies focused on IDA [subset 1] vs studies not focused on IDA [subset 2]). Furthermore, we summarized a detailed account of diagnoses (where presented).

Statistical analysis

Data on the yield of SBCE were extracted, pooled, and analyzed. Pooled results with corresponding 95% CI were derived by using the fixed effects model (Mantel-Haenszel method) unless significant heterogeneity was detected, in which case, a random-effects model (DerSimonian-Laird) was used.

We used the Q statistic of χ^2 test and I^2 to estimate the heterogeneity of individual studies contributing to the pooled estimate. The homogeneity was to evaluate whether the differences across the studies were greater than expected by chance alone. $P < .05$ suggests the presence of heterogeneity beyond what could be expected by chance alone. I^2 describes the percentage of total variation across studies because of heterogeneity rather than chance and was also used as a measure to quantify the amount of heterogeneity. An I^2 of 20% to 50% suggests moderate and an I^2 greater than 50% high heterogeneity. Forest plots were constructed for visual display of individual studies and pooled results.

Publication bias was assessed by using funnel plots (funnel plots were plotted by using the DY vs the standard error ratio). Meta-regression analysis was used to investigate possible sources of heterogeneity related to the type of the study and the focus of the study. Statistical analysis was performed by using the Metan[10] package of STATA version 12.1 (StataCorp, College Station, Tex).

RESULTS

Descriptive assessment and study characteristics

A flow diagram of the process of this systematic review is shown in Figure 1. A total of 1225 titles were initially identified with the aforementioned search strategy. Of those, 1156 were excluded after preliminary review of the titles and/or abstracts, leaving 69 articles for further detailed evaluation. A further 6 articles were identified from reference review. Therefore, the full text of 75 articles was evaluated further; 51 failed to meet the predefined inclusion criteria by reporting only patients with overt OGIB and/or presenting no clear data about IDA and/or not presenting a separate analysis of IDA patients (n = 43), presenting per-capsule instead of per-patient analysis (n = 2), and reporting fewer than 10 cases of patients with IDA (n = 6).

Consequently, a total of 24 studies remained eligible for evaluation.[12-35] A total of 5237 patients were included in these studies; of them, 1960 patients underwent SBCE for investigation of IDA. The main characteristics of the studies eligible for review are shown in Table 1. Five studies were from the United States,[22,24,26-28] 3 studies each were from Italy[12,30,33] and Greece,[17,21,31] 2 studies each from Canada[14,23] France,[15,16] and the Netherlands,[19,29] and 1 study each from Australia,[34] India,[32] Israel,[13] Japan,[35] Norway,[18] Spain,[20] and the United Kingdom.[25] Seven of them were prospective[15,20,21,28,33-35] and 17 were retrospective studies.[12-14,16-19,22-27,29-32] Only 2 were multicenter studies.[12,13] In all but 4 studies (in 3, not reported[18,23,27] and 1 study[31] with EndoCapsule [Olympus, Tokyo, Japan]), SBCE explorations were performed with capsule endoscopes from Given Imaging Ltd (Yoqneam, Israel). Four publications focused exclusively on IDA patients (subset 1),[21,30,33,35] whereas in the remaining 20 articles, patients with IDA represented only a subgroup of a larger patient cohort undergoing SBCE (subset 2).[12-20,22-29,31,32,34]

The QUADAS evaluation of the included studies is shown in Table 2. Nine QUADAS items (items 3-11) were not relevant and thus not assessed. Based on the remaining 5 items (items 1, 2, 12-14), the studies included were of low or moderate quality. Nine studies (39%)[12,13,17,20,21,27,30,33,35] provided data on mean or median pre-SBCE hemoglobin (Hb) levels, 11 (43.5%)[12,13,19-22,27,30,31,33,35] reported data on mean or median patient age. Where median and interquartile range were given instead of mean and standard deviation, ap-

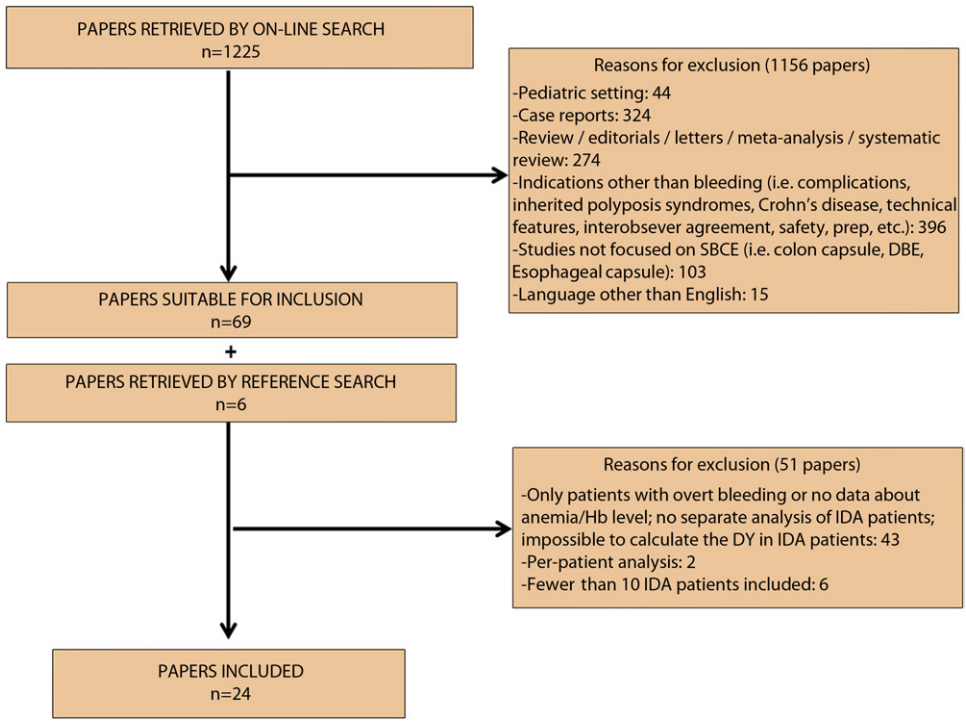

Figure 1. Flow chart of the systematic review and study selection. DBE, double-balloon enteroscopy; DY, diagnostic yield; SBCE, small-bowel capsule endoscopy; Hb, hemoglobin; IDA, iron-deficiency anemia.

proximation was used.[36] Therefore, the pooled random-effects estimate for Hb and age was 9.2 g/dL (95% CI, 8.7 g/dL-9.7 g/dL) and 62.2 years (95% CI, 59.0 years-65.3 years), respectively. Three series (13%)[12,20,22] provided data on pre-SBCE transfusion requirements, but none on the length of clinical history before referring patients for SBCE. Although all studies reported that patients had undergone at least 1 upper and lower GI endoscopy before SBCE, there were no data with regard to the timing of the procedures in relation to SBCE, whereas the exact precapsule diagnostic workup was reported only in 7 studies.[13,16,18,21,30,31,33] Furthermore, most studies included SBCE as the sole diagnostic modality, apart from Apostolopoulos et al[21] and Milano et al[33] (comparison with air-double contrast enteroclysis in all patients), Laine et al[28] (comparison with small-bowel radiography), and De Leusse et al[16] (comparison with push enteroscopy in part of the cohort). None of the included studies reported comparison data of SBCE and device-assisted enteroscopy.

DY of video capsule endoscopy in IDA

There was statistically significant heterogeneity among the 24 included studies (I^2 = 78.8%, $P < .0001$). The pooled DY of SBCE in IDA, evaluated by a random-effects model, was 47% (95% CI, 42%-52%). Using meta-regression techniques,[37] we found no evidence of an effect in the design of the studies ($P = .899$). Subset 1, ie, studies focused on IDA (n = 4/24; 16.6%),[21,30,33,35] included 264 patients (264/1960; 13.47%) patients. In this subset, the pooled DY was 66.6% (95% CI, 61.0%-72.3%), and the I^2 was 44.3% ($P = .145$), indicating that there was only a moderate degree of heterogeneity across the studies (Fig. 2).

Conversely, subset 2 (ie, studies not focused only on IDA [n = 20/24; 83.9%])[12-20,22-29,31,32,34] collectively included 1696 patients (1696/1960; 86.5%); I^2 (64.9%, $P < .0001$) showed high/significant heterogeneity among these studies. Therefore, by using a random-effects model, the pooled diagnostic yield was 44% (95% CI, 39%-48%) (Fig. 2). A plot of the DY versus standard error (Fig. 3) confirms that the studies focused on IDA, and the studies not focused on IDA present a different distribution.[37] Heterogeneity between subsets 1 and 2 ($P < .001$) indicates a difference between the 2 study subsets, although this result should be interpreted with caution because there was a considerable amount of heterogeneity within the studies not purely focused on IDA (subset 2) (Fig. 4).[38,39]

Clear categorization/classification (breakdown) of significant findings from patients with positive SBCE findings was reported in 13 articles,[12-14,21,22,24-28,30,33,35] including a total of 1194 patients with IDA. Of those, 638 (53.4%) had positive findings on SBCE. The DY breakdown revealed that significant angioectasias (vascular P2 lesions) were identified in 293 of 638 (45.9% positive findings), inflammatory lesions in 126 of 638 (19.7% positive findings), and polyp/mass lesions in 42 of 638 (6.6% positive findings on SBCE) (Table 3). Finally, 177 of 638 (27.7%) positive findings (ie, intraluminal bleeding, celiac disease, or other)

TABLE 1. Main characteristics of studies selected for meta-analysis

Authors	Design	Consecutive	Country	No. of centers	Total no. of patients	IDA patients	DY, no. (%)
Pennazio et al, 2004[12]	Retrospective	Yes	Italy	Multicenter	100	43	19 (44.2)
Fireman et al, 2004[13]	Retrospective	Yes	Israel	Multicenter	160	70	37 (52.8)
Enns et al, 2004[14]	Retrospective	Yes	Canada	Single center	209	14	7 (50)
Ben Soussan et al, 2004[15]	Prospective	Yes	France	Single center	35	18	7 (38.8)
De Leusse et al, 2005[16]	Retrospective	Yes	France	Single center	64	20	6 (30)
Kalantzis et al, 2005[17]	Retrospective	Yes	Greece	Single center	193	64	27 (42.2)
Qvigstaad et al, 2006[18]	Retrospective	Yes	Norway	Single center	167	40	11 (27.5)
van Tuyl et al, 2006[19]	Retrospective	Yes	Netherlands	Single center	250	150	49 (32.6)
Estevez et al, 2006[20]	Prospective	Yes	Spain	Single center	100	48	30 (62.5)
Apostolopoulos et al, 2006[21]*	Prospective	Yes	Greece	Single center	51	51	29 (56.9)
Carey et al, 2007[22]	Retrospective	Yes	USA	Single center	260	134	62 (46.3)
Chami et al, 2007[23]	Retrospective	Yes	Canada	Single center	70	12	4 (33.3)
Muhammad et al, 2009[24]	Retrospective	Yes	USA	Single center	652	231	127 (55)
Sidhu et al, 2009[25]	Retrospective	Yes	UK	Single center	427	316	152 (48.1)
Kim et al, 2009[26]	Retrospective	Yes	USA	Single center	193	25	12 (48)
Sheibani et al, 2010[27]	Retrospective	Yes	USA	Single center	82	57	35 (61.4)
Laine et al, 2010[28]	Prospective	Yes	USA	Single center	66	40	13 (32.5)
van Turenhout et al, 2010[29]	Retrospective	Yes	Netherlands	Single center	592	240	106 (44.2)
Riccioni et al, 2010[30]*	Retrospective	*Yes*	Italy	Single center	650	138	91 (65.9)
Katsinelos et al, 2011[31]	Retrospective	Yes	Greece	Single center	63	38	13 (34.2)
Goenka et al, 2011[32]	Retrospective	Yes	India	Single center	505	96	35 (36.5)
Milano et al, 2011[33]*	Prospective	Yes	Italy	Single center	189	45	35 (77.7)
Efthymiou et al, 2011[34]	Prospective	Yes	Australia	Single center	68	40	15 (37.5)
Yamada et al, 2011[35]*	Prospective	Yes	Japan	Single center	91	30	19 (63.3)

DY, Diagnostic yield; *IDA*, iron-deficiency anemia.
*Studies in subset 1 (focusing on IDA patients).

either did not fit in any of the aforementioned categories or no other information was given.

DISCUSSION

IDA remains one of the most common reasons for referral to gastroenterology services.[6,7] National and international guidelines recommend that patients with confirmed IDA should undergo evaluation with bidirectional endoscopy, whereas investigation of the small bowel is generally indicated for recurrent or refractory and/or transfusion-dependent IDA.[1,6] Recent studies established that reduced Hb (<9 g/dL) and ferritin (<50 μg/L) levels are associated with a higher risk of relevant GI pathology.[40,41] Understandably, in this clinical setting, exclusion of underlying GI cancer is paramount. Nevertheless, even after bidirectional endoscopy, approximately 30% of patients remain undiagnosed, and this group represents the most likely candidates for SBCE.[6] Although the value of SBCE has already been proven in patients with OGIB (including several patients with IDA), data specifically regarding the use of SBCE in patients with IDA alone are limited and of variable quality.[42]

For this reason, we decided to undertake a systematic review of all studies published to date to evaluate the DY of SBCE in this subset of patients. Our literature search generated 2 subsets of studies: (1) those specifically designed to evaluate the role of SBCE in patients with IDA

TABLE 2. QUADAS (relevant items) grading of studies selected for meta-analysis

Authors	Item 1*	Item 2†	Items 3-11‡	Item 12§	Item 13‖	Item 14
Pennazio et al, 2004[12]	Yes	Yes	N/A	Yes	Unclear	Yes
Fireman et al, 2004[13]	Yes	Yes	N/A	Yes	No	Unclear
Enns et al, 2004[14]	Yes	Yes	N/A	Yes	Yes	Yes
Ben Soussan et al, 2004[15]	Yes	Yes	N/A	Yes	Yes	Yes
De Leusse et al, 2005[16]	Yes	Yes	N/A	Yes	No	Yes
Kalantzis et al, 2005[17]	Yes	Yes	N/A	Yes	Yes	Unclear
Qvigstaad et al, 2006[18]	Yes	Yes	N/A	Yes	Unclear	Yes
van Tuyl et al, 2006[19]	Yes	Yes	N/A	Yes	Unclear	Unclear
Estevez et al, 2006[20]	Yes	Yes	N/A	Yes	Yes	Yes
Apostolopoulos et al, 2006[21]*	Yes	Yes	N/A	Yes	No	Yes
Carey et al, 2007[22]	Yes	Unclear	N/A	Yes	Yes	Unclear
Chami et al, 2007[23]	Yes	Yes	N/A	Yes	No	Yes
Muhammad et al, 2009[24]	Yes	Yes	N/A	Yes	No	Yes
Sidhu et al, 2009[25]	Yes	Yes	N/A	Yes	No	Unclear
Kim et al, 2009[26]	Yes	Yes	N/A	Yes	Yes	Yes
Sheibani et al, 2010[27]	Yes	Yes	N/A	Yes	Unclear	Yes
Laine et al, 2010[28]	Yes	Yes	N/A	Yes	No	Unclear
van Turenhout et al, 2010[29]	Yes	Yes	N/A	Yes	Unclear	Yes
Riccioni et al, 2010[30]#	Yes	Yes	N/A	Yes	Unclear	Unclear
Katsinelos et al, 2011[31]	Yes	Yes	N/A	Yes	Unclear	Unclear
Goenka et al, 2011[32]	Yes	Yes	N/A	Yes	Yes	Yes
Milano et al, 2011[33]#	Yes	Yes	N/A	Yes	No	Yes
Efthymiou et al, 2011[34]#	Yes	Yes	N/A	Yes	Unclear	Unclear
Yamada et al, 2011[35]#	Yes	Yes	N/A	Yes	Yes	Unclear

QUADAS, Quality Assessment of Diagnostic Accuracy Studies; *N/A*, not applicable.
*Item 1: Was the spectrum of participants representative of the patients who will undergo the procedure in practice?
†Item 2: Were selection criteria clearly described?
‡Item 12: Were the same clinical data available when the procedure results were interpreted as would be available when the procedure is used in clinical practice?
§Item 13: Were interpretable, indeterminate, or intermediate procedure results reported?
‖Item 14: Were withdrawals from the study explained?
#Studies in subset 1 (focusing on IDA patients).

and (2) those that investigated patients with a range of clinical indications including IDA. These 2 subsets have several key differences. The former subset[21,30,33,35] has the methodological advantage of strict inclusion criteria and, although slightly different among studies, a clear definition of IDA (with Hb and ferritin thresholds). Conversely, the latter subset (20 studies, 1658 patients)[12-20,22-29,31,32,34] is more heterogeneous, and the term obscure/occult bleeding was often used as a synonym for chronic IDA. Therefore, although we elected to pool all data to increase the study population size and statistical power, we analyzed separately studies that focused solely on IDA patients to present a more homogeneous data subset.

The pooled SBCE DY for detection of definite small-bowel findings was 46%. By using meta-regression techniques, we found no evidence that study design influenced findings ($P = .899$). Conversely, when studies that presented data exclusively from patients with IDA were pooled together (subset 1), the DY was 66.6% (95% CI, 61.0%-72.3%), whereas pooled data from studies presenting results from larger patient cohorts (subset 2, including subgroups of patients with IDA) undergoing SBCE

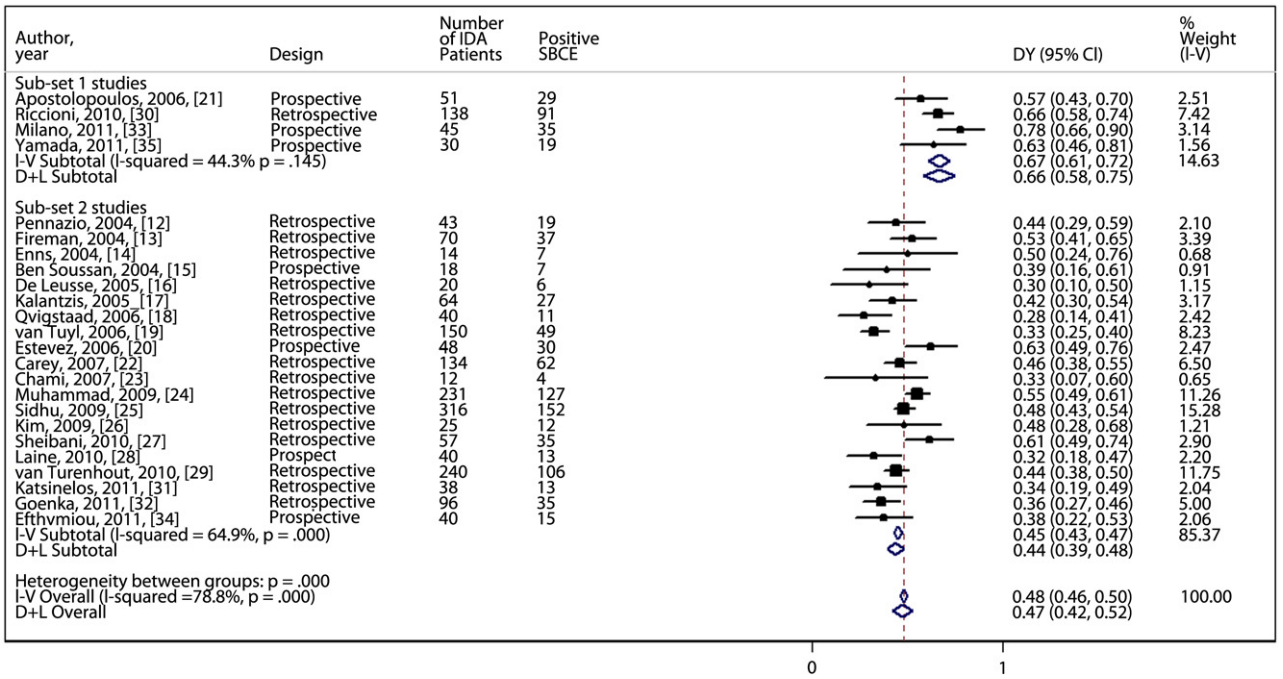

Figure 2. Forest plot of diagnostic yield (DY) given as separate study subsets (subset 1, studies focusing solely on IDA patients in the first part of the figure) and cumulative (at the bottom of the figure). D+L, the random-effects meta-analysis estimate; IDA, iron-deficiency anemia; I-V, fixed effect meta-analysis estimate; SBCE, small-bowel capsule endoscopy.

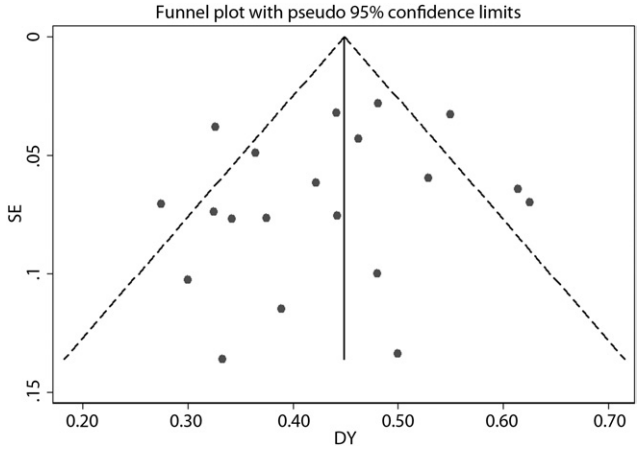

Figure 3. Funnel plot of studies not focused on iron-deficiency anemia (subset 2). There are some studies outside the pseudo 95% confidence limits indicating the presence of heterogeneity and selection bias. There is also asymmetry caused by a lack of small studies with high diagnostic yield (DY). SE, standard error.

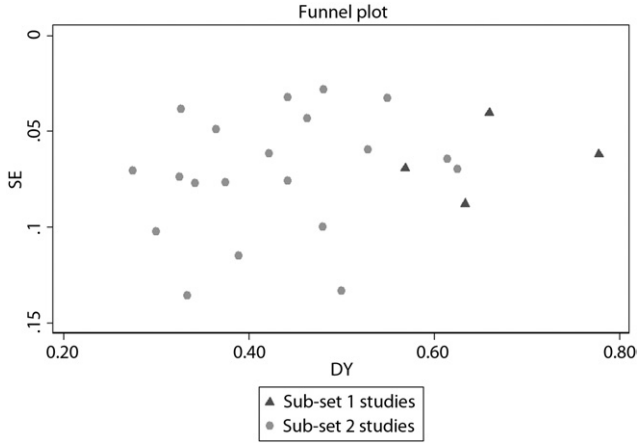

Figure 4. Plot of the diagnostic yield (DY) versus standard error (SE) presented by study subsets (focusing on iron-deficiency anemia [IDA] patients or not). Triangle, studies focusing on IDA; circles, studies not focusing on IDA. It is obvious that subset 1 studies (ie, those focusing exclusively on IDA patients) have a higher DY.

showed a DY of 44% (95% CI, 39%-48%). This may simply reflect a more rigorous patient selection in the former group because 3 of 4 studies focusing solely on IDA patients were prospective with more clearly defined inclusion criteria and evidence of only moderate heterogeneity (I^2 = 44.3%). Furthermore, the possibility of patient selection bias should be considered because studies focused on IDA are more likely to include patients with more severe anemia. Interestingly, these data compare favorably with those obtained in patients undergoing SBCE because of OGIB and represent the spectrum of findings identified by SBCE in patients with IDA. Among the 24 selected studies, only 13[12-14,21,22,24-28,30,33,35] gave a detailed breakdown of definite findings for patients with positive SBCE results. This group of studies collectively included 1194 IDA patients (1194/1960 [60.9%]; I^2 = 73.0%, $P < .0001$) showed high/significant heterogeneity among these studies, albeit less pronounced than in the whole cohort. Therefore, by using a random-effects model, the pooled DY was 54% (95% CI, 49%-60%) (Fig. 5). Common positive findings were siz-

TABLE 3. Breakdown of DY in the studies with details in reported findings

Authors	All patients (with IDA)	DY definitive findings, no. (%)	DY breakdown: Vascular lesions, no. (%)	Inflammatory lesions, no. (%)	Tumor/mass lesions, no. (%)	Other significant or N/S, no. (%)
Pennazio et al, 2004[12]	43	19 (44.2)	4 (9.3)	9 (20.9)	0 (0)	6 (13.9)
Fireman et al, 2004[13]	70	37 (52.8)	18 (25.7)	11 (15.7)	0 (0)	8 (11.4)
Enns et al, 2004[14]	14	7 (50)	2 (14.3)	3 (21.4)	2 (14.3)	0 (0)
Apostolopoulos et al, 2006[21]*	51	29 (56.9)	12 (23.5)	13 (25.5)	4 (7.8)	0 (0)
Carey et al, 2007[22]	134	62 (46.3)	35 (26.1)	16 (11.9)	4 (2.9)	7 (5.2)
Muhammad et al, 2009[24]	231	127 (55)	35 (15.1)	N/R	0 (0)	92 (39.8)
Sidhu et al, 2009[25]	316	152 (48.1)	84 (26.6)	25 (7.9)	10 (3.2)	33 (10.4)
Kim et al, 2009[26]	25	12 (48)	8 (32)	2 (8)	0 (0)	2 (8)
Sheibani et al, 2010[27]	57	35 (61.4)	21 (36.8)	4 (7)	5 (8.7)	5 (8.7)
Laine et al, 2010[28]	40	13 (32.5)	4 (10)	9 (22.5)	0 (0)	0 (0)
Riccioni et al, 2010[30]*	138	91 (65.9)	51 (36.9)	18 (13)	9 (6.5)	13 (9.4)
Milano et al, 2011[33]*	45	35 (77.7)	13 (28.8)	9 (20)	6 (13.3)	7 (15.5)
Yamada et al, 2011[35]*	30	19 (63.3)	6 (20)	7 (23.3)	2 (6.7)	4 (13.3)
Total*	1194	638 (53.4)	293 (24.5)	126 (10.5)	42 (3.5)	177 (14.8)

DY, Diagnostic yield; *IDA*, iron-deficiency anemia; N/R, not reported.
*Studies in subset 1 (focusing on IDA patients).

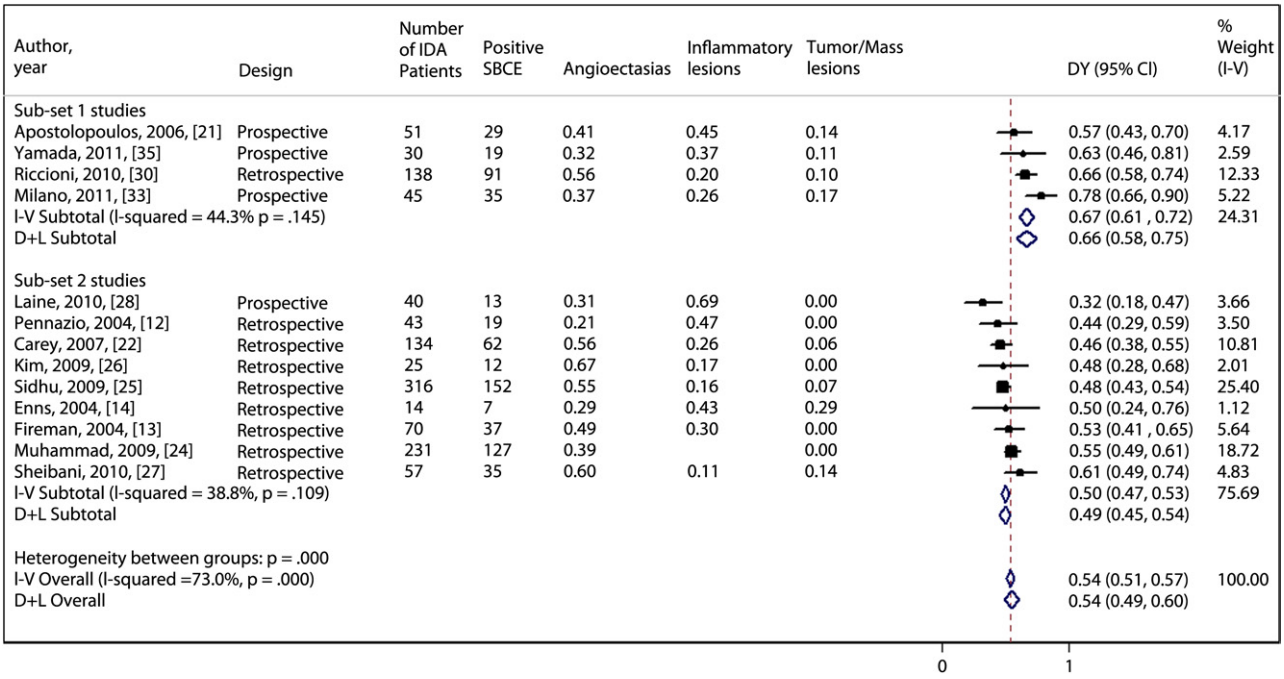

Figure 5. Forest plot of diagnostic yield (DY) given as separate study subsets (subset 1, studies focusing solely on IDA patients in the first part of the figure) and cumulative (at the bottom of the figure); subgroup analysis per findings category. D+L, random-effects meta-analysis estimate; DY, diagnostic yield; IDA, iron-deficiency anemia; I-V, fixed-effects meta-analysis estimate.

able (ie, P2) angioectasias (293; 45.9% of positive DY), inflammatory lesions (126; 19.7% of positive DY) and tumor/mass-type lesions (42; 6.6% of positive DY) (Table 3).

Moreover, only 3 studies reported data on the use of medication,[18,25,35] such as aspirin, clopidogrel, and warfarin, which have been shown able to have an impact on the DY of SBCE. Furthermore, 3 of 4 studies in subset 1[21,30,33] used the ingestion of the aforementioned medications as an exclusion criterion. Therefore, we believe that a formal subanalysis is not possible. Of note, many of the included studies are retrospective, lacking a clear picture of the severity of IDA (in fact, only 9 studies provided the Hb level at the time of SBCE).[12,13,17,20,21,27,30,33,35] Moreover, most investigators did not use a validated or widely accepted classification of small-bowel lesions[9,43] and do not report the location/topography of small-bowel lesions. Last, but not least, limited information on follow-up data may affect results.

In view of these limitations and to reduce doubt in terms of diagnosis, analysis was performed only on vascular lesions defined as clinically significant (or P2), irrespective of their number. Likewise, we decided to include all significant (as defined by studies' authors) small-bowel inflammatory lesions. Furthermore, our definition of DY did not include a further diagnostic/therapeutic workup or the impact of the procedure on long-term outcomes of patients (ie, mortality, anemia recurrence, and need for further transfusions or hospitalization). Finally, although we used a modified version of QUADAS as an assessment tool of study quality, we accept that it has been structured as a tool for diagnostic accuracy studies; despite that, we believe that it has provided relevant information for this review.

In conclusion, this analysis confirms the validity of SBCE in detecting pathology in patients with IDA (pooled DY of SBCE, evaluated by a random-effects model [48%]), when a previous diagnostic workup is negative. Careful patient selection leads, as expected, to a higher DY. In particular, more vascular (31% vs 22.6%, $P = .007$), inflammatory (17.8% vs 11.3%, $P = .009$), and mass/tumor (7.95% vs 2.25%, $P < .0001$) lesions were detected with SBCE in patients participating in studies including solely IDA patients.

Overall, clinically significant small-bowel angioectasias account for almost 50% of the SBCE DY. In an era of increasing use of antiplatelets/anticoagulants and expanding cardiology interventions, this information has potential clinical implications. At present, there is enough evidence to suggest that small-bowel angioectasias are more common with increasing age.[3,24,25]

Overall, only 6.6% of small-bowel lesions are caused by mass/tumor (hence, sinister). Furthermore, although sinister pathology in the colon is more common with increasing age,[6,40] this does not hold true for the small-bowel, where cancerous lesions are much less common with increased age In contrast, there is emerging evidence that sinister pathology such as Crohn's disease and masses/tumors appear to be more common in the younger age group; hence, the presence of IDA in that group should not be ignored as recent data suggest.[3,43]

However, this analysis cannot address this issue, and further large, high-quality studies with appropriately selected IDA patients (following clearly predefined criteria and specific diagnostic workup) that take into account long-term outcomes are still needed to firmly establish risk factors for the detection of sinister pathology with SBCE in this group and ultimately the exact role of SBCE in the diagnostic algorithm of patients with IDA.

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REFERENCES

1. Raju GS, Gerson L, Das A, et al; American Gastroenterological Association. American Gastroenterological Association (AGA) Institute technical review on obscure gastrointestinal bleeding. Gastroenterology 2007;133:1697-717.
2. Iddan G, Meron G, Glukhovsky A, et al. Wireless capsule endoscopy. Nature 2000;405:417.
3. Rondonotti E, Soncini M, Girelli C, et al; AIGO, SIED and SIGE Lombardia. Small bowel capsule endoscopy in clinical practice: a multicenter 7-year survey. Eur J Gastroenterol Hepatol 2010;22:1380-6.
4. Marmo R, Rotondano G, Rondonotti E, et al; Club Italiano Capsula Endoscopica-CICE. Capsule enteroscopy vs. other diagnostic procedures in diagnosing obscure gastrointestinal bleeding: a cost-effectiveness study. Eur J Gastroenterol Hepatol 2007;19:535-42.
5. Triester SL, Leighton JA, Leontiadis GI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. Am J Gastroenterol 2005; 100:2407-18.
6. Goddard AF, James MW, McIntyre AS, et al. Guidelines for the management of iron deficiency anaemia. Gut 2011;60:1309-16.
7. Ioannou GN, Rockey DC, Bryson CL, et al. Iron deficiency and gastrointestinal malignancy: a population-based cohort study. Am J Med 2002; 113:276-80.
8. Stroup DF, Berlin JA, Morton SC, et al; Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000; 283:2008-12.
9. Saurin JC, Delvaux M, Gaudin JL, et al. Diagnostic value of endoscopic capsule in patients with obscure digestive bleeding: blinded comparison with video push-enteroscopy. Endoscopy 2003;35:576-84.
10. Sterne JAC, Bradburn MJ, Egger M. Meta-analysis in Stata. In: Egger M, Smith GD, Altman DG, editors. Systematic reviews in health care: meta-analysis in context, 2nd ed.London (UK): BMJ Publishing Group; 2008. p. 347-69.
11. Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003;3:25.
12. Pennazio M, Santucci R, Rondonotti E, et al. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. Gastroenterology 2004;126:643-53.
13. Fireman Z, Eliakim R, Adler S, et al. Capsule endoscopy in real life: a four-centre experience of 160 consecutive patients in Israel. Eur J Gastroenterol Hepatol 2004;16:927-31.

14. Enns R, Go K, Chang H, et al. Capsule endoscopy: a single-centre experience with the first 226 capsules. Can J Gastroenterol 2004;18:555-8.
15. Ben Soussan E, Antonietti M, Hervé S, et al. Diagnostic yield and therapeutic implications of capsule endoscopy in obscure gastrointestinal bleeding. Gastroenterol Clin Biol 2004;28:1068-73.
16. De Leusse A, Landi B, Edery J, et al. Video capsule endoscopy for investigation of obscure gastrointestinal bleeding: feasibility, results, and interobserver agreement. Endoscopy 2005;37:617-21.
17. Kalantzis N, Papanikolaou IS, Giannakoulopoulou E, et al. Capsule endoscopy; the cumulative experience from its use in 193 patients with suspected small bowel disease. Hepatogastroenterology 2005;52: 414-9.
18. Qvigstaad G, Hatlen-Rebhan P, Brenna E, et al. Capsule endoscopy in clinical routine in patients with suspected disease of the small intestine: a 2-year prospective study. Scand J Gastroenterol 2006;41:614-8.
19. Van Tuyl SA, Van Noorden JT, Kuipers EJ, et al. Results of videocapsule endoscopy in 250 patients with suspected small bowel pathology. Dig Dis Sci 2006;51:900-5.
20. Estévez E, González-Conde B, Vázquez-Iglesias JL, et al. Diagnostic yield and clinical outcomes after capsule endoscopy in 100 consecutive patients with obscure gastrointestinal bleeding. Eur J Gastroenterol Hepatol 2006;18:881-8.
21. Apostolopoulos P, Liatsos C, Gralnek IM, et al. The role of wireless capsule endoscopy in investigating unexplained iron deficiency anemia after negative endoscopic evaluation of the upper and lower gastrointestinal tract. Endoscopy 2006;38:1127-32.
22. Carey EJ, Leighton JA, Heigh RI, et al. A single-center experience of 260 consecutive patients undergoing capsule endoscopy for obscure gastrointestinal bleeding. Am J Gastroenterol 2007;102:89-95.
23. Chami G, Raza M, Bernstein CN. Usefulness and impact on management of positive and negative capsule endoscopy. Can J Gastroenterol 2007; 21:577-81.
24. Muhammad A, Pitchumoni CS. Evaluation of iron deficiency anemia in older adults: the role of wireless capsule endoscopy. J Clin Gastroenterol 2009;43:627-31.
25. Sidhu R, Sanders DS, Kapur K, et al. Factors predicting the diagnostic yield and intervention in obscure gastrointestinal bleeding investigated using capsule endoscopy. J Gastrointest Liver Dis 2009;18: 273-8.
26. Kim S, Kedia PS, Jaffe DL, et al. Impact of capsule endoscopy findings on patient outcomes. Dig Dis Sci 2009;54:2441-8.
27. Sheibani S, Levesque BG, Friedland S, et al. Long-term impact of capsule endoscopy in patients referred for iron-deficiency anemia. Dig Dis Sci 2010;55:703-8.
28. Laine L, Sahota A, Shah A. Does capsule endoscopy improve outcomes in obscure gastrointestinal bleeding? Randomized trial versus dedicated small bowel radiography. Gastroenterology 2010; 138:1673-80.
29. van Turenhout ST, Jacobs MA, van Weyenberg SJ, et al. Diagnostic yield of capsule endoscopy in a tertiary hospital in patients with obscure gastrointestinal bleeding. J Gastrointest Liver Dis 2010;19:141-5.
30. Riccioni ME, Urgesi R, Spada C, et al. Unexplained iron deficiency anaemia: is it worthwhile to perform capsule endoscopy? Dig Liver Dis 2010; 42:560-6.
31. Katsinelos P, Chatzimavroudis G, Terzoudis S, et al. Diagnostic yield and clinical impact of capsule endoscopy in obscure gastrointestinal bleeding during routine clinical practice: a single-center experience. Med Princ Pract 2011;20:60-5.
32. Goenka MK, Majumder S, Kumar S, et al. Single center experience of capsule endoscopy in patients with obscure gastrointestinal bleeding. World J Gastroenterol 2011;17:774-8.
33. Milano A, Balatsinou C, Filippone A, et al. A prospective evaluation of iron deficiency anemia in the GI endoscopy setting: role of standard endoscopy, videocapsule endoscopy, and CT-enteroclysis. Gastrointest Endosc 2011;73:1002-8.
34. Efthymiou M, Allen PB, Jayasekera C, et al. Value of fecal occult blood test as a screening test before capsule endoscopy. Eur J Gastroenterol Hepatol 2011;23:690-4.
35. Yamada A, Watabe H, Yamaji Y, et al. Incidence of small intestinal lesions in patients with iron deficiency anemia. Hepatogastroenterology 2011; 58:1240-3.
36. Harbord RM. Meta-regression in Stata. Stata J 2008;8:493-519.
37. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
38. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
39. Harris R, Bradburn M, Deeks J, et al. Metan: fixed– and random– effects meta–analysis. Stata J 2008;8:3-28.
40. James MW, Chen CM, Goddard WP, et al. Risk factors for gastrointestinal malignancy in patients with iron-deficiency anaemia. Eur J Gastroenterol Hepatol 2005;17:1197-203.
41. Nahon S, Lahmek P, Lesgourgues B, et al. Predictive factors of GI lesions in 241 women with iron deficiency anemia. Am J Gastroenterol 2002;97: 590-3.
42. Leighton JA, Triester SL, Sharma VK. Capsule endoscopy: a meta-analysis for use with obscure gastrointestinal bleeding and Crohn's disease. Gastrointest Endosc Clin N Am 2006;16:229-50.
43. Gralnek IM, Defranchis R, Seidman E, et al. Development of a capsule endoscopy scoring index for small bowel mucosal inflammatory change. Aliment Pharmacol Ther 2008;27:146-54.