Fecal occult blood testing for the prediction of small-bowel pathology detected by capsule endoscopy: a systematic review and meta-analysis

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Abstract	
	Background Fecal occult blood testing (FOBT) has been suggested as a potential screening tool for small-bowel capsule endoscopy (CE). We conducted a meta-analysis of studies correlating FOBT and CE findings to examine the predictive value of positive FOBT for CE findings.
	Methods PubMed and Embase search. Sensitivity, specificity and diagnostic odds ratios (DORs) were calculated.
	Results Six studies were identified. Four used fecal immunochemical testing (FIT), one used FIT and guaiac FOBT, one used hemoglobin/haptoglobin complex testing (Hb/Hpt). Five of the 6 studies were suitable for statistical analysis. For all positive FOBT, sensitivity for small-bowel findings was 0.60 (95%CI 0.50-0.69), specificity was 0.72 (95%CI 0.52-0.86), and DOR was 3.96 (95%CI 1.50-10.4). For the 4 studies using only FIT, sensitivity was 0.48 (95%CI 0.36-0.61), specificity was 0.60 (95%CI 0.42-0.76), and DOR was 1.41 (95%CI 0.72-2.75).
	Conclusions Although a number of modalities have been suggested for screening small-bowel CE referrals, none of them, including FOBT, offer a comprehensive solution. Further work is required to refine screening methods for small-bowel CE referrals.
	Keywords Capsule endoscopy, fecal occult blood test, fecal immunochemical test, small bowel, meta-analysis, systematic review
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Introduction

Capsule endoscopy (CE) has become a prime mode of investigating the small bowel (SB), because of its high diagnostic yield (DY), minimal invasiveness and ease of use [1-3]. The DY of CE has been consistent across studies at about 60% [1]; this could be partially due to the widespread, and occasionally injudicious, use of CE [4], leading to several ultimately normal SBCE examinations [5]. Therefore, as the demand for CE increases, there is a need to develop screening pathways in order to prioritize SBCE referrals [3]. For example, a recent meta-analysis has found that fecal calprotectin has a high negative predictive value in patients undergoing CE for SB Crohn's disease (CD) [6].

Because of their simplicity and user-friendliness, and despite their low sensitivity, guaiac-based fecal occult blood testing (gFOBT) and fecal immunochemical testing (FIT) have found widespread use in colorectal cancer screening [7,8]. However, 40-60% individuals with positive FIT (cutoff values 75 and 100 ng/mL, similar to the gFOBT threshold)

have no colorectal lesions [9], raising the possibility of SB bleeding. Overall, data on the predictive value of FOBT for SB pathology are scarce.

This study aimed to investigate the usefulness of gFOBT or FIT as a screening tool for CE, by examining the predictive value of positive gFOBT and FIT for SB lesions detected on CE.

Materials and methods

A comprehensive literature search was conducted using the PubMed and Embase databases (January 2000 to June 2016). The search was performed in July 2016. In order to capture as many articles as possible, a broad search strategy was employed by combining the terms "capsule endoscopy" and "f(a)ecal occult blood", as detailed below. The search was performed with no limitations.

A further keyword search for "capsule endoscopy" AND "fecal occult blood" was conducted in Google Scholar, turning up one more article [10], available online whilst awaiting print publication. A flowchart detailing the search and selection process is presented in Fig. 1.

For a study to be included in this meta-analysis, the following predefined inclusion criteria were applied: observational and case-control studies or series of FOB/FIT and CE in patients (both prospective and retrospective), articles published in English. Exclusion criteria were: systematic reviews and/or meta-analyses, editorials, opinion papers, studies published as abstracts only, studies involving the use of CE to visualize areas of the GI tract other than SB (e.g. colon CE).

Data extraction and quality control were performed independently by 2 reviewers (SV, DY). A third reviewer (AK), an expert in the content material, was involved if any conflict occurred. When additional data were required, primary (first and/or senior) authors of the corresponding manuscript(s) were contacted by email with relevant questions.

Outcome measures

The diagnostic accuracy (sensitivity, specificity, diagnostic odds ratio) of gFOBT/FIT in the diagnosis of SB pathology was evaluated. For the purposes of analysis, we used the diagnoses reported in each included publication, without adjusting for any structured terminology or scoring system in CE.
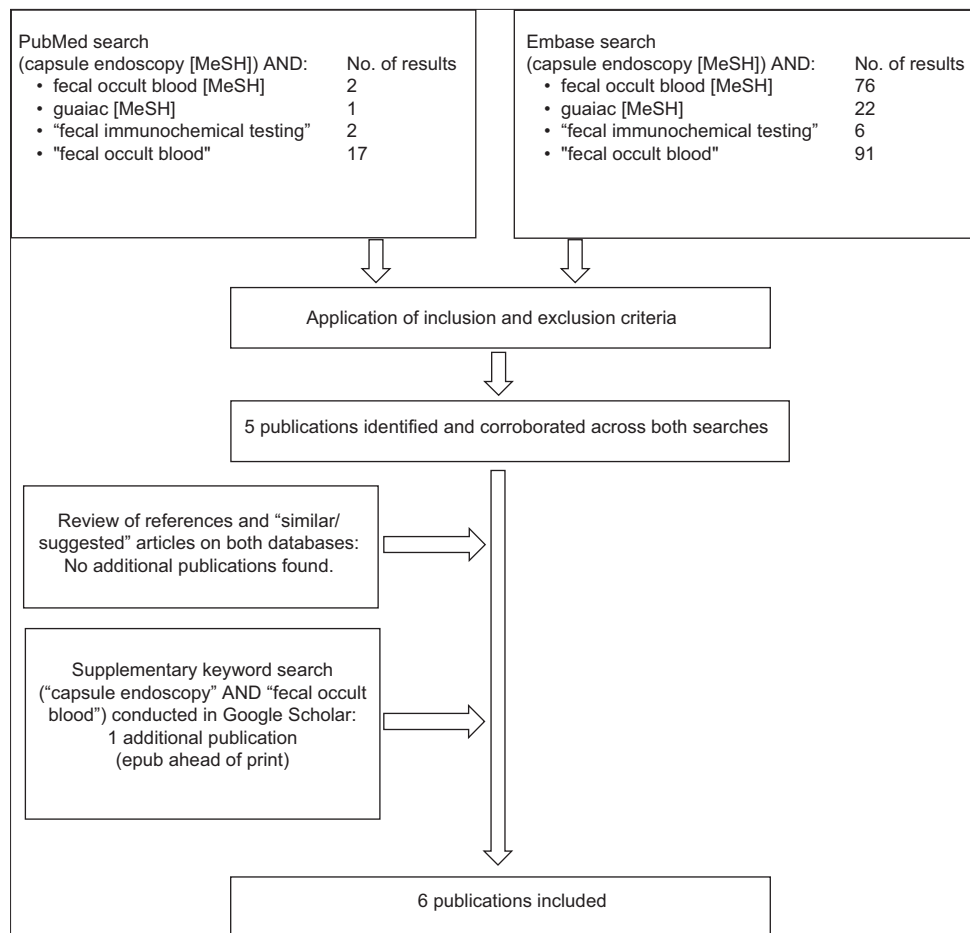

PubMed search (capsule endoscopy [MeSH]) AND:	No. of results
• fecal occult blood [MeSH]	2
• guaiac [MeSH]	1
• "fecal immunochemical testing"	2
• "fecal occult blood"	17

Embase search (capsule endoscopy [MeSH]) AND:	No. of results
• fecal occult blood [MeSH]	76
• guaiac [MeSH]	22
• "fecal immunochemical testing"	6
• "fecal occult blood"	91

Application of inclusion and exclusion criteria

5 publications identified and corroborated across both searches

Review of references and "similar/suggested" articles on both databases: No additional publications found.

Supplementary keyword search ("capsule endoscopy" AND "fecal occult blood") conducted in Google Scholar: 1 additional publication (epub ahead of print)

6 publications included

Figure 1 Flowchart for selection of studies in this meta-analysis

Statistical analysis

We listed the number of true positive, true negative, false positive and false negative results per study, with the hemoglobin (Hb) cutoff. We then calculated the sensitivity, specificity and diagnostic odds ratio (DOR). We used the bivariate model for data summary. Parameter estimates from the model were used to obtain hierarchical summary receiver operating curves, with 95% confidence intervals (CI), and a 95% prediction region defining the sensitivity and specificity values within which we could expect the results of a future study to lie. Only direct test comparisons were performed. Because of the statistical heterogeneity, the DerSimonian–Laird random effects model was applied. The methodological quality of the included studies was evaluated using the quality assessment of diagnostic accuracy studies (*QUADAS*) 2 scale [11]. Analyses were conducted using the STATA 12 (StataCorp, College Station, Texas, USA) and RevMan 5.3 (Cochrane Corporation, London, UK) software packages.

Results

Six studies [5,10,12-15] were included for review, with a total of 607 patients (380 male/227 female). Four [10,12-14] used FIT (Eiken Chem, Tokyo, Japan), with an Hb cutoff of 100 ng/mL; one [5] used both FIT (Onsight, Laboratory diagnostics; cutoff 100 ng/mL) and gFOBT (Stanbio, Laboratory diagnostics); and one [15] used the Hb/haptoglobin (Hpt) complex test (Eiken Chem, Tokyo, Japan) with a cutoff of 0.1 ng/mL. All studies were published between 2011 and 2016. Four [10,12,13,15] were carried out in Japan, one [5] in Australia and one [14] in Israel; all were single-center studies. Moreover, all but one [13] of the studies were prospective. All studies used capsule endoscopes from Medtronic: one study [5] used the M2A® capsule and all others used various versions of PillCam®, i.e. SB/SB2/SB3. The number of CE readers ranged from 1 to 3. The time between FOBT and CE ranged from 3 days to 4 months; in most studies the time lag was in the range of 1-2 weeks. All studies were designed so that the higher/highest FOBT result was considered; most studies used 1 of 2 samples, whilst one study used 1 of 3 [14]. The majority of the indications for CE referral were obscure gastrointestinal (GI) bleeding (both occult and overt), following negative bidirectional GI endoscopy. Table 1 details the included studies.

Overall, 5/6 studies were suitable for statistical analysis; one study was excluded from the analysis [12] as it included only patients with positive FIT and was therefore unsuitable for this meta-analysis. When all positive FOBT results regardless of type of test were analyzed (Fig. 2), the sensitivity for SB findings was 0.60 (95%CI 0.50-0.69), specificity was 0.72 (95%CI 0.52-0.86), and the DOR of any positive FOBT was 3.96 (95%CI 1.50-10.4).

Four studies [5,10,13,14] dealing only with FIT were analyzed (Fig. 3). The sensitivity of FIT for SB findings on CE was 0.48 (95%CI 0.36-0.61), specificity was 0.60 (95%CI 0.42-0.76), and the DOR of positive FIT was 1.41 (95%CI 0.72-2.75).
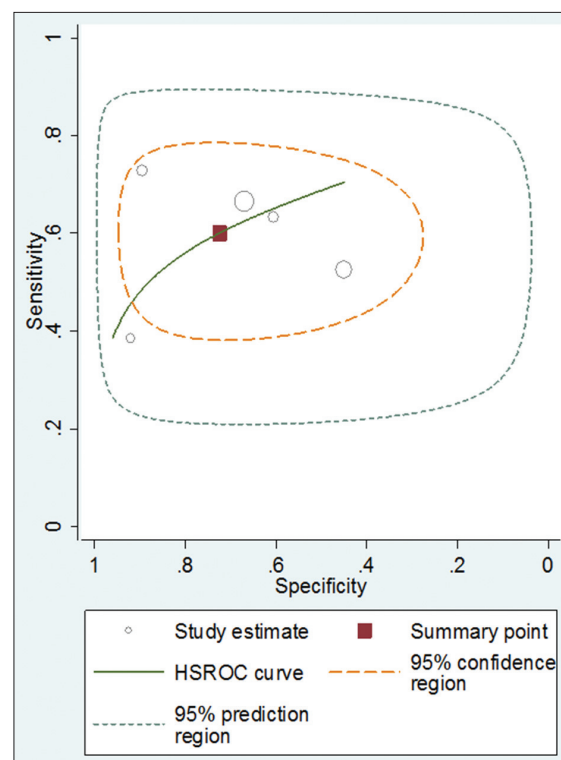

Figure 2 Hierarchical summary receiver operating characteristic (HSROC) curve of all fecal occult blood tests for prediction of small-bowel pathology on capsule endoscopy
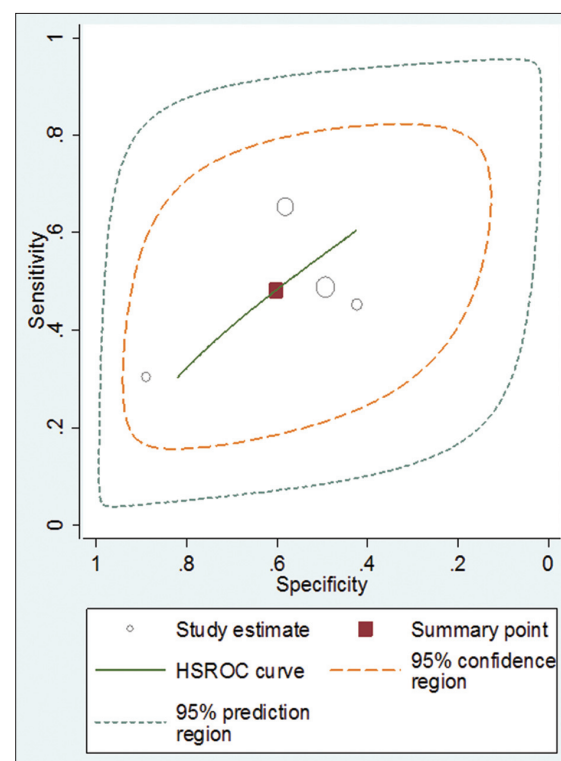

Figure 3 Hierarchical summary receiver operating characteristic (HSROC) curve of all fecal immunochemical tests for prediction of small-bowel pathology on capsule endoscopy

Table 1 Summary of included studies

Authors, Year[ref]	Country	Prospective/ Retrospective	No. of patients	Mean age of patients (yrs) ± SD	Gender of patients	Reason for CE referral (n)	CE model	No. of CE reviewers	Type of FOBT	FOBT threshold	No. of FOBTs	Time between FOBT and CE	TP	FP	TN	FN
Chiba, 2011 [12]	Japan	Prospective	53	52.1±12	37M/16F	Positive FIT, asymptomatic	PillCam SB2	2	FIT (Eiken Chem)	100 ng/mL	2	4 months	28 pts had CE findings; 25 normal CE. No patients with negative FOBT.			
Efthymiou, 2011 [5]	Australia	Prospective	68	69 (median); range 58-75	33M/35F	Overt OGIB (28), occult OGIB/recurrent IDA (40)	M2A	2 (3 if discrepancies)	FIT (Onsight laboratory diagnostics); gFOBT (Stanbio laboratory diagnostics)	Not specified	1 FIT and 1 gFOBT	2 weeks	19	15	23	11
Levi, 2011 [14]	Israel	Prospective	51	63.3±15	30M/21F	Occult OGIB/IDA (all)	PillCam SB	1	FIT (Eiken Chem)	Both 75 and 100 ng/mL examined	3	1 week	10	2	23	16
Shiotani, 2014 [15]	Japan	Prospective	76	66.1±14.77	39M/37F	OGIB (43), IDA (8), suspected SB disease (25)	PillCam SB2	2	Hb/Hpt complex test (Eiken Chem)	0.1 ng/mL of Hb/Hpt complex	2	3 days	35	2	17	13
Kobayashi, 2015 [13]	Japan	Retrospective	202	63.6±14	118M/84F	Previous overt OGIB (96), occult OGIB (102)	PillCam SB/SB2	3	FIT (Eiken Chem)	100 ng/mL	2	Mean 8 days (range 0-156)	66	34	69	33
Endo, 2016 [10]	Japan	Prospective	157	72.2±9.2	123M/34F	Not specified	PillCam SB2/SB3	3	FIT (Eiken Chem)	100 ng/mL	2	2 weeks	51	33	27	46

FOBTs were compared using CE as the standard, therefore the breakdown of patients is as follows: True positive (TP) – positive FOBT and CE; False positive (FP) – positive FOBT but no significant findings on CE; True negative (TN) – negative FOBT and CE; False negative (FN) – negative FOBT but positive CE findings

CE, capsule endoscopy; FIT, faecal immunochemical test; FOBT, faecal occult blood test (referring to all types); FP, false positive; gFOBT guaiac faecal occult blood test; Hb/Hpt, hemoglobin/haptoglobin complex test; IDA, iron deficiency anemia; OGIB, obscure gastrointestinal bleeding; TN, true negative; TP, true positive; SD, standard deviation

Subgroup analyses

When we examined studies where only FIT produced by Eiken Chem was used [10,13-15], we obtained a sensitivity of 0.59 (95%CI 0.47-0.70), a specificity of 0.76 (95%CI 0.51-0.91) and a DOR of 4.51 (95%CI 1.36-15.7). When only prospective studies were included [5,10,14,15], the sensitivity was 0.58 (95%CI 0.46-0.69), specificity was 0.75 (95%CI 0.49-0.90), and DOR was 4.10 (95%CI 1.14-14.8).

QUADAS-2

The included studies had a low risk of bias, except for one study [12] that examined FOBT positive patients only. The results of the quality analysis are summarized in Table 2.

Discussion

FOBT detects the presence of traces of blood in stool [7]. Conventional gFOBT is based on guaiac, which detects pseudoperoxidase activity and is therefore not specific for human blood [8]. Conversely, FIT specifically detects human blood by antibody reaction to human globin. Moreover, it is thought to be more specific for distal GI blood loss and also has the advantage of providing quantitative results [16,17]. Hb/Hpt complex testing is a variant of FIT that uses an immunoradiometric assay for the Hb/Hpt complex. Hpt forms a soluble complex with Hb, which remains stable even following incubation with gastric juice and fecal extracts [15].

Our results show the low sensitivity and specificity of FOBT, and specifically of FIT, for SB findings on CE. Overall, the attempted use of FIT as a selection tool for SBCE showed a sensitivity of 0.48 and specificity of 0.60; i.e. neither positive nor negative FIT results are good predictors of SB findings on CE. However, when all positive FOBT methods (i.e. gFOBT, FIT

and Hb/Hpt testing) were combined, although the sensitivity remained low (0.60), specificity increased to 0.72 and the DOR was also improved. Nevertheless, none of the aforementioned meta-analysis parameters are sufficiently significant to support the use of FOBT as a screening tool for SBCE.

CE is currently the third-line test following negative bidirectional GI endoscopy. There is good supporting evidence for its use in obscure GI bleeding [18]. However, the DY of CE (although superior to other modalities [3]), remains less than ideal. This could be due to the inherent limitations of commercially available capsules [19], but may also be due to pressures on CE services nationwide and/or inappropriate referrals being made [4]. CE remains a labor-intensive investigative modality; therefore, despite increasing use and demand, there is the need to rationalize SBCE referrals [1,4].

There are currently no validated selection tools for CE referral, while the most recent European Society of Gastrointestinal Endoscopy guidelines state that there is insufficient evidence concerning the use of FOBT as a CE screening tool [1]. Referring to our previous work on young patients with iron deficiency anemia [20], the available data on the use of CE in specific subgroups of patients with SB bleeding [21] are minimal and present future research opportunities. A recent meta-analysis from our group examined the use of fecal calprotectin as a selection tool for CE, finding that it displayed good sensitivity and specificity at a cutoff of 50 μg/g [6].

FOBT is currently in nationwide use for colorectal cancer screening. There is a good amount of evidence regarding the usefulness of FIT in colon cancer, especially as it is more specific to lower GI tract blood loss [7,17,22]. Current national threshold levels for FIT are 100 ng/mL and there was only one study included here which investigated a lower threshold of 75 ng/mL. Although in a study by Levi *et al* [14] both thresholds corresponded well with significant SB lesions, our meta-analysis has shown that FIT has not performed well overall.

Limitations of this meta-analysis include the small number of included articles, emphasizing the paucity of literature on this topic. There was also a lack of standardization between the included studies in lesion classification. Therefore, the definition of a positive SBCE examination may have differed between studies, with some studies reporting all SB findings while others may have considered only clinically significant findings. Furthermore, what is clinically significant or positive may vary with the indication for SBCE and with the SBCE reader's opinion and/or expertise. This limitation is highlighted by an American Gastroenterological Association technical review on occult and obscure GI bleeding, which suggested that the criteria used to determine the source of positive FOBT or iron deficiency anemia are not standardized, as GI mucosal lesions are rarely actively bleeding or showing stigmata of recent bleeding at the time of endoscopy [18].

In conclusion, although a number of modalities, including FOBT, have been suggested for screening SBCE referrals, this meta-analysis shows that FOBT does not offer a comprehensive solution. Further work is required to refine screening methods, such as combining other fecal or serum markers, for the selection of patients for SBCE. This would help rationalize the use of valuable resources.

Table 2 Quality assessment of diagnostic accuracy studies (QUADAS) 2 results for the included studies, "+" denotes low risk of bias, "-" high risk of bias, and "?" unclear risk.

Author, year [ref]	Item 1: Risk of bias in patient selection?	Item 2: Representative patient spectrum?	Item 3: Risk of bias in conduct or interpretation of index test?	Item 4: Applicability of index test to review question?	Item 5: Risk of bias from conduct or interpretation of reference standard?	Item 6: Does the target condition match the review question?	Item 7: Acceptable delay between tests?
Chiba, 2011 [12]	−	+	+	+	−	+	+
Efthymiou, 2011 [5]	+	+	?	+	+	+	+
Levi, 2011 [14]	+	+	+	+	+	+	+
Shiotani, 2014 [15]	+	+	+	+	+	+	+
Kobayashi, 2015 [13]	?	+	+	+	+	+	?
Endo, 2016 [10]	+	+	+	+	+	+	+

Summary Box

What is already known:

- Small-bowel capsule endoscopy (SBCE) is invaluable for minimally-invasive SB examination
- The accuracy of SBCE could be improved by more judicious patient selection
- Selection pathways using easily obtained and measured biomarkers are desirable to rationalize the use of scarce resources

What the new findings are:

- Fecal occult blood testing (FOBT) has limited predictive value for SB findings overall
- The overall specificity (72%) of FOBT for SB findings is superior to its sensitivity (60%)
- Other fecal or serum markers could be used in conjunction with FOBT to improve the selection of patients prior to SBCE

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