

Appropriateness of the Indication for Colonoscopy: Systematic Review and Meta-analysis

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Abstract

Background & Aims: Application of appropriate indications for colonoscopy (OC) should conserve limited endoscopic resources. To perform a systematic review and meta-analysis to assess the accuracy of ASGE and EPAGE guidelines in selecting patients referred for OC, relative to the detection of neoplastic and non-neoplastic relevant endoscopic findings. **Methods:** Studies comparing the appropriateness of OC indication according to ASGE or EPAGE guidelines and the detection of cancer, adenomas, and benign relevant endoscopic findings were identified by searching MEDLINE (1982 – June 2009). Predefined outputs of the meta-analysis were sensitivity, specificity, positive and negative likelihood ratios (LR+, LR-), and the diagnostic odds ratio (DOR). **Results:** We included twelve cohort studies comprising 14,160 patients; 10,056 OC indications were categorized as appropriate, and 3,522 (26%) as inappropriate. For cancer detection, the weighted sensitivity, specificity, LR+, LR- and DOR were 89% (95% CI, 82-93%), 26% (95% CI, 21-31%), 1.2 (95% CI, 1.1-1.3), 0.45 (95% CI, 0.3-0.7), and 3 (95% CI, 1-5), respectively. For adenomas, the adjusted sensitivity, specificity, LR+, LR- and DOR were 85% (95% CI, 77-91%), 27% (95% CI, 22-32%), 1.14 (95% CI, 1-1.2), 0.6 (95% CI, 0.4-0.9), and 1.9 (95% CI, 1.2, 2.9), being for relevant findings equal to 89% (95% CI, 82-93%), 26% (95% CI, 21-31%), 1.16 (95% CI, 1-1.3), 0.44 (95% CI, 0.25-0.8), and 2.6 (95% CI, 1.2-5.6). **Conclusions:** Appropriateness guidelines appeared to have a suboptimal sensitivity and a poor specificity for colorectal cancer, being also characterized by a similar accuracy for the diagnosis of benign relevant endoscopic findings. Better strategies are required to select patients with significant pathology for OC.

Key words

Colonoscopy – appropriateness – colorectal cancer – adenoma – meta-analysis.

Introduction

Colonoscopy (OC) is the most accurate technique for the diagnosis, surveillance, or exclusion of important colorectal diseases, such as adenomatous polyps or cancer (CRC) [1,2]. Moreover, OC is among the recommended options for CRC screening in average-risk subjects, also representing the only available choice for subjects at increased risk, such as those with a family or personal history of neoplasia [2]. Open-access endoscopy allows physicians to directly schedule elective, common endoscopic procedures for their patients without prior consultation [3]. However, the increasing reliance by physicians on OC and the appreciation by their patients that OC is a relatively safe procedure have led to an increasing demand for open-access OC. Unfortunately, this has also resulted in a considerable increase in both overall cost and waiting lists for OC.

In order to optimize the use of finite resources in an open-access system, official guidelines for the appropriate use of OC have been proposed by the American Society for Gastrointestinal Endoscopy (ASGE) and by the European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE) [4,5]. The validity of these expert-derived guidelines has never been tested in a randomized study, generating some uncertainty on their efficacy. However, following the introduction of these guidelines in the clinical practice, some observational studies were aimed at relating the appropriateness of the indication with the endoscopic detection of relevant findings. Such studies have generally shown a substantial rate of inappropriate indications for OC, which in turn has been associated with a lower diagnostic yield for relevant findings as compared to appropriate procedures [6]. Most of these studies were based on single centres in different countries, with some of them including only a relatively small number of patients. For this reason, the real strength of the association between the appropriateness of the indication and the detection of relevant endoscopic findings is unclear.

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In particular, the association between the endoscopic prevalence of adenomatous polyps and CRC, on the one hand, and the appropriateness of the indication, on the other, is still controversial, because of unexpected colorectal neoplasia detected at OC performed for indications considered inappropriate in some series. Fear of missing a neoplastic lesion when not referring a patient with an inappropriate examination to endoscopy or not performing the procedure (i.e. the endoscopist refusing to perform it) presumably underlines one of the main reasons that prevents a widespread implementation of appropriateness guidelines [6], as shown by the similar rate of inappropriateness among studies performed in different periods. Such uncertainty may be related, at least in part, with the small sample size and the monocentric setting of most of these studies, unable to meaningfully represent the relatively low prevalence of CRC. As a result, large cohorts need to be studied, which often is not feasible. These problems may be overcome by performing a meta-analysis.

The aim of this meta-analysis was to assess the accuracy of ASGE and EPAGE guidelines in selecting patients referred for OC relative to the detection of relevant endoscopic findings, and, in particular, of adenomatous polyps and CRC.

Methods

Identification and selection of publications

A literature search was performed on December 2009. Relevant publications were identified by Medline for the period 1992-2009 (i.e. after the publication of ASGE guidelines in 1992). Medical subject heading (MeSH) terms “Endoscopy, Gastrointestinal” were utilized and the non-MeSH terms “colonoscopy”, “appropriateness”, “indication”, “ASGE”, and “EPAGE” were used in the search. Furthermore, additional publications were retrieved by reviewing references of selected studies. We did not include review articles, position papers, editorials, commentaries, and book chapters. The selection criteria for inclusion in the meta-analysis were: (a) adoption of ASGE and/or EPAGE guidelines to assess the appropriateness of the OC indication prior to endoscopy; (b) definition of relevant endoscopic findings; (c) prevalence of relevant endoscopic findings and cancer reported according to the appropriateness of the indication, so that it was possible to reconstruct 2 × 2 tables expressing endoscopic findings by appropriateness status. Prevalence of adenomatous polyps was also recorded when available. However, its presence was not required for a study to be included in the meta-analysis. Two investigators (CH and AZ) separately performed the search, selected the studies, and jointly performed data extraction using pre-defined data extraction forms. A third investigator (RM) arbitrated in the event of a lack of agreement.

Outcome measure and statistical methods

Two types of studies were eligible for inclusion: those based on ASGE and those based on EPAGE guidelines. The ASGE consensus statement on the “Appropriate use of Gastrointestinal

Endoscopy” classifies indications for OC as “generally indicated” or “generally not indicated”. In comparison, the EPAGE criteria categorizes indications as “appropriate”, “uncertain”, or “inappropriate”. For the purpose of this analysis, “appropriate” and “uncertain” indications are considered together [7], whereas “inappropriate” and “generally not indicated” categories were also grouped together.

Meta-analysis was performed according to QUORUM guidelines. The pre-defined outcome measures were sensitivity, specificity, diagnostic odds ratio (DOR), and positive and negative likelihood ratios (LP+, LP-) of appropriateness guidelines in identifying those patients with either a relevant endoscopic finding, an adenomatous polyp or a cancer (random effect model used if heterogeneity was present) [6]. We also calculated 95% confidence intervals (95% CI) using the method recommended by Newcombe and Altman [8]. From each report, reviewers independently abstracted the year of publication, institution, whether it was a single- or multi-center study, number of patients, types of guidelines adopted, appropriateness rate, definition of relevant endoscopic findings, and the rate of relevant findings, adenomatous polyps (when available) and cancer according to the appropriateness of the indication. We summarized the study results in a quantitative receiver-operating characteristic (SROC) curve, which shows the possible correlation between the sensitivity and specificity of diagnostic tests. Areas under the summary ROC curves were used as a measure of the diagnostic performance of the tests [9]. The Galbraith plot was used as a method to investigate heterogeneity in the meta-analysis. Multivariate meta regression analysis was used to determine the study characteristics that influenced the heterogeneity. We considered the following variables to be of potential importance for explaining heterogeneity and interstudy variability (i.e. potentially confounding variables): 1) type of guidelines adopted (ASGE/EPAGE); 2) number of patients included (more/less than 1,000); 3) number of centres included (mono-/multi-centric); 4) male/female sex; 5) mean age; 6) year of publication; 7) geographical localization of the study (Europe/non-Europe). Egger’s test was used to investigate whether publication bias or other small study effects may have adversely affected the results [10]. All the calculations were performed with STATA software, including a dedicated integration (StataCorp, Houston, TX, USA; Dwamena, Ben A. 2007. midas: Stata module for Meta-analytical Integration of Diagnostic Accuracy Studies, University of Michigan Medical School, Michigan, USA).

Risk of bias in individual studies

To assess the methodological quality of the included studies and detect potential bias, the 14 relevant items of the Quality Assessment of Diagnostic Accuracy in Systematic Reviews (QUADAS) were used [11]. The list of QUADAS items has been included in the Appendix.

Results

Our initial search yielded 85 literature citations. After

the initial review, 29 papers were retrieved to be studied in detail. Of these, 15 were excluded because they did not either report the endoscopic findings or report them in relation to the appropriateness of the indication, and an additional two because they did not include ASGE or EPAGE guidelines.

Therefore, 12 studies were included in the meta-analysis with a total of 14,160 patients (Fig. 1) [5, 12-22]. According to the design of these observational studies, appropriateness of the indication was pre-endoscopically assessed by endoscopists, and thereafter compared with the relevant findings at endoscopy (i.e. the gold-standard). In eight series ASGE guidelines were adopted, whilst in the remaining four EPAGE guidelines were used. Relevant endoscopic findings were defined homogeneously across the selected studies, including colorectal neoplasia (either adenoma or cancer), inflammatory bowel diseases, and colonic strictures. Overall, six studies were multi-centre, the remaining being performed in only one endoscopic unit. Regarding the geographical distribution of the studies, four were performed in Switzerland, three in Italy, and the remaining five in other countries. The characteristics of the studies included in the meta-analysis are shown in Table I.

Accuracy of appropriateness guidelines for cancer

According to appropriateness guidelines, 10,056 OC indications were categorized as appropriate, and 3,522 (26%) as inappropriate, the remaining 582 being excluded from the present analysis because they were not included in the current guidelines. As shown in Table II, 598 carcinomas were detected in the selected studies, corresponding to an endoscopic prevalence of 4.4%. Considering appropriateness as a diagnostic test (Fig. 2a), the overall adjusted sensitivity was 89% (95% CI, 82-93%) and the overall adjusted specificity 26% (95% CI, 21-31%). LP+, LP- and DOR were 1.2 (95% CI, 1.1-1.3), 0.45 (95% CI, 0.3-0.7), and 3 (95% CI, 1-5), respectively. There was heterogeneity in the analysis of accuracy for cancer (heterogeneity chi-squared = 99; degree of freedom = 11; p = 0.01; I2= 89%). None of the potentially confounding variables appeared to explain the heterogeneity at meta-regression analysis. Egger's

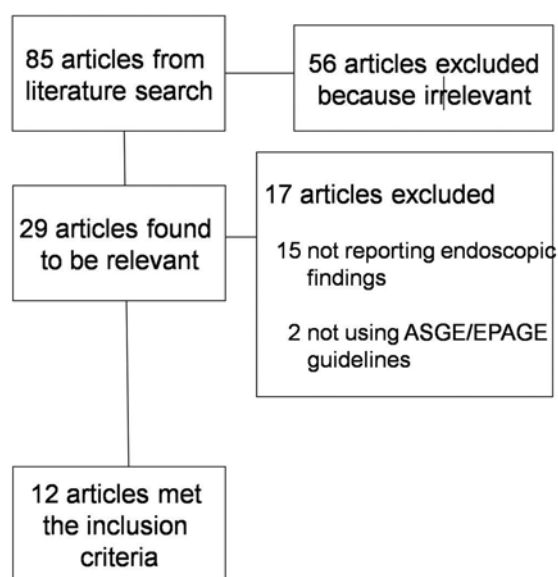


Fig 1. Flow-chart of the meta-analysis.

test (coefficient = 3.9; 95% CI: -14 to 21; p = 0.6) was not significant. Quantitative SROC analysis revealed area under the ROC curve to be 0.74 (Fig. 2b).

Accuracy of appropriateness guidelines for adenomas

Prevalence of adenomatous polyps was available in 8 series. Of the 11,886 included patients, the indication was inappropriate in 3,265 (27.5%) cases. Overall, 1,742 adenomatous lesions were detected, corresponding to a prevalence of 14.7% (Table II). Considering appropriateness as a diagnostic test (Fig. 3a), the overall adjusted sensitivity was 85% (95% CI, 77-91%) and the overall adjusted specificity 27% (95% CI, 22-32%). LP+ , LP- and DOR were 1.14 (95% CI, 1-1.2), 0.6 (95% CI, 0.4-0.9), and 1.9 (95% CI, 1.2, 2.9), respectively. There was heterogeneity in the analysis of accuracy for adenomas (heterogeneity chi-squared = 31; degree of freedom = 7; p < 0.01; I2= 77%). None of the potentially confounding variables appeared to explain the heterogeneity at meta-regression analysis. The Egger's test was significant (coefficient = 12; 95% CI: 1 to

Table I. Characteristics of the included studies.

Author	Year of Publication	Nation of the study	Centers	Guidelines	N° patients	Male sex %	Mean age Years	Inappropriateness rate, %
Froelich et al [5]	1998	Swiss	Multicentric	ASGE	553	55%	58	28
Morini et al [12]	2001	Italy	Multicentric	ASGE	1123	53%	56	29
Siddique et al [13]	2005	Kuwait	Monocentric	ASGE	736	56%	43	24
Burnand et al [14]	2006	Swiss	Multicentric	EPAGE	561	47%	53	14
Balaguer et al [15]	2005	Spain	Monocentric	EPAGE	350	45%	60	23
Jabar et al [16]	2004	Malaysia	Monocentric	ASGE	257	50%	56	16
Bersani et al [17]	2005	Italy	Monocentric	ASGE	2221	52%	57	37
De Bosset et al [18]	2001	Swiss	Multicentric	EPAGE	1144	48%	58	23
Adler et al [19]	2007	Germany	Multicentric	ASGE	605	39%	57	14
Grassini et al [20]	2007	Italy	Monocentric	ASGE	1017	55%	64	15
Chan et al [21]	2006	Malaysia	Monocentric	ASGE	380	63%	-	18
Gonvers et al [22]	2007	Swiss	Multicentric	EPAGE	5213	48%	57	27

Table II. Distribution of cancer, adenoma, and relevant findings according to the appropriateness of the indication in the selected studies.

Author	Cancer in appropriate colonoscopies	Cancer in inappropriate colonoscopies	Adenomas in appropriate colonoscopies	Adenomas in inappropriate colonoscopies	Relevant findings in appropriate colonoscopies	Relevant findings in inappropriate colonoscopies
	N (%)					
Froelich et al [5]	19 (7)	0 (0)	77 (27)	20 (18)	132 (46)	6 (5)
Morini et al [12]	48 (7)	1 (0)	189 (28)	34 (12)	295 (43)	45 (16)
Siddique et al [13]	21 (4)	0 (0)	54 (12)	1 (1)	177 (38)	7 (5)
Burnand et al [14]	4 (1)	0 (0)	-	-	81 (17)	4 (5)
Balaguer et al [15]	12 (5)	0 (0)	66 (28)	11 (15)	100 (42)	15 (21)
Jabar et al [16]	18 (8)	0 (0)	-	-	103 (48)	8 (20)
Bersani et al [17]	84 (6)	12 (1)	201 (14)	122 (15)	401 (29)	168 (20)
De Bosset et al [18]	50 (6)	1 (0)	90 (10)	14 (5)	227 (26)	45 (17)
Adler et al [19]	10 (2)	0 (0)	-	-	130 (25)	12 (14)
Grassini et al [20]	71 (8)	0 (0)	117 (14)	11 (7)	233 (27)	16 (11)
Chan et al [21]	24 (11)	5 (10)	-	-	80 (36)	17 (35)
Gonvers et al [22]	199 (5)	19 (1)	573 (15)	162 (11)	654 (17)	573 (41)

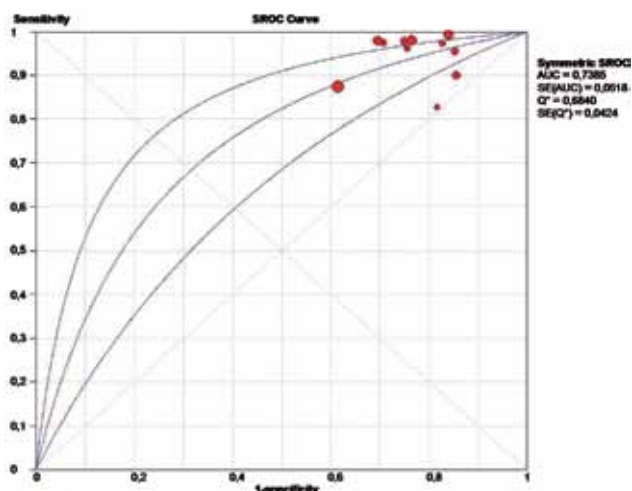
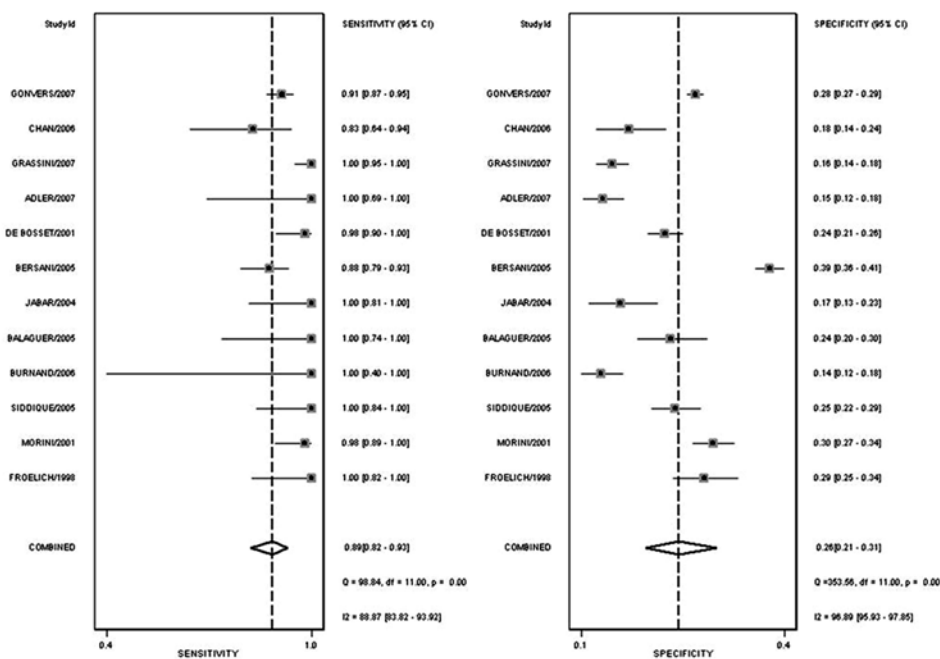


Fig. 2. a) Sensitivity and specificity meta-analysis plot of the appropriateness guidelines for cancer detection. b) Summary Receiver Operating Curve (SROC) of the appropriateness guidelines for cancer. The ROC represents the relationship between sensitivity and specificity. The dimension of the squares, each representing 1 study, is related to the sample size of the different studies.

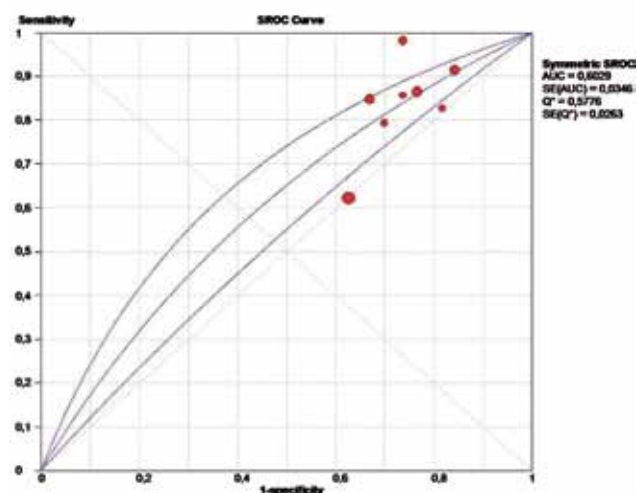
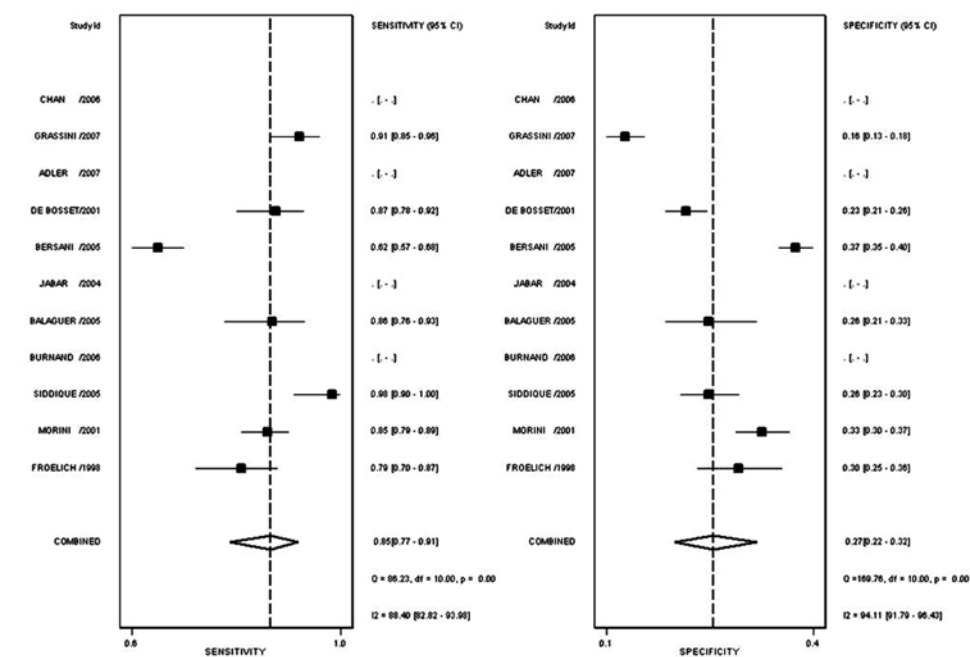


Fig 3. a) Sensitivity and specificity meta-analysis plot of the appropriateness guidelines for adenoma detection. b) Summary Receiver Operating Curve (SROC) of the appropriateness guidelines for adenoma. The ROC represents the relationship between sensitivity and specificity. The dimension of the squares, each representing 1 study, is related to the sample size of the different studies.

22; $p = 0.04$). Quantitative SROC analysis revealed the area under the ROC curve to be 0.6 (Fig. 3b).

Accuracy of appropriateness guidelines for relevant endoscopic findings

Pooled crude rate of relevant endoscopic findings was 26% (Table II). Considering appropriateness as a diagnostic test (Fig. 4a), the overall adjusted sensitivity was 89% (95% CI, 82-93%) and the overall adjusted specificity 26% (95% CI, 21-31%). LP+, LP- and DOR were 1.16 (95% CI, 1-1.3), 0.44 (95% CI, 0.25-0.8), and 2.6 (95% CI, 1.2-5.6), respectively. There was heterogeneity in the analysis of accuracy for relevant findings (heterogeneity chi-squared = 25; degree of freedom = 11; $p = 0.01$; $I^2 = 55\%$). None of the potentially confounding variables appeared to explain the heterogeneity at meta-regression analysis. The Egger’s test was significant (coefficient = 16.5; 95% CI: 5 to 27; $p = 0.01$). Quantitative SROC analysis revealed the area under the ROC curve to be 0.66 (Fig. 4b).

Risk of bias within studies

All the studies complied with the list of QUADAS items shown in the Appendix. The main bias appeared to be related to the fact that the endoscopist performing the OC (i.e. the gold-standard) was aware of the appropriateness of the examination, before undertaking the procedure. However, it is unlikely that such awareness could influence the detection rate of neoplastic or other relevant findings.

Discussion

Appropriateness guidelines appeared to have a suboptimal sensitivity for selecting patients affected by CRC for OC. When considering the 4.4% pooled prevalence of CRC and the 26% rate of inappropriate indications, this corresponds to a 1.9% CRC prevalence in patients with inappropriate indications; this means a 1:54 chance of overlooking malignancy in patients with an inappropriate indication. Of note, such estimate is substantially higher than the

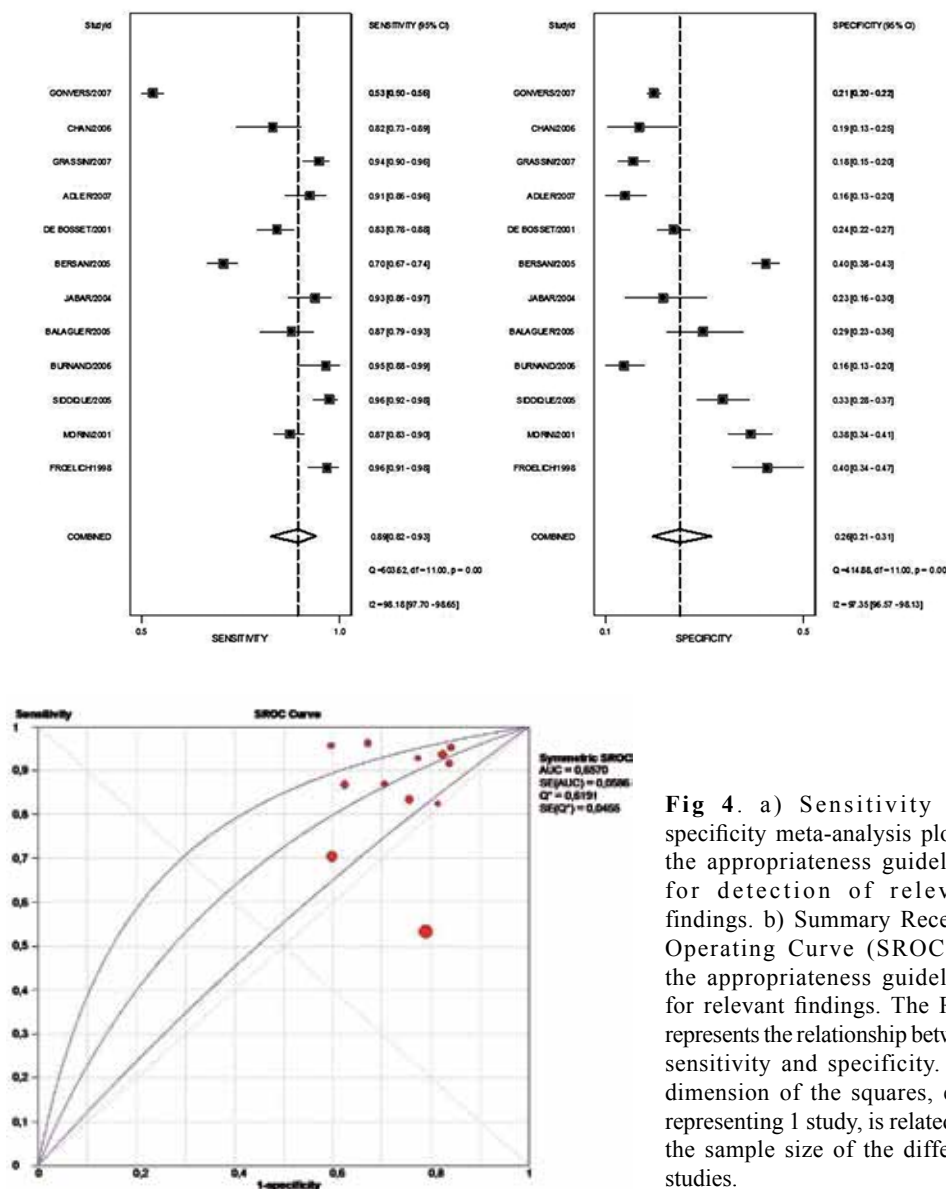


Fig 4. a) Sensitivity and specificity meta-analysis plot of the appropriateness guidelines for detection of relevant findings. b) Summary Receiver Operating Curve (SROC) of the appropriateness guidelines for relevant findings. The ROC represents the relationship between sensitivity and specificity. The dimension of the squares, each representing 1 study, is related to the sample size of the different studies.

1:175 chance of overlooking gastric cancer in patients without alarm symptoms at upper endoscopy, despite a 75% sensitivity of alarm symptoms for gastric cancer estimated in a dedicated meta-analysis [23]. This discrepancy appears to be mainly related with the higher prevalence of CRC as compared to gastric cancer at upper endoscopy (4.4% vs. 2.8%), and to the much higher probability of having an appropriate indication at OC as compared to that of having alarm symptoms at upper endoscopy (74% vs. 13%) [23, 24]. The suboptimal sensitivity of appropriateness guidelines for CRC may be related to two main reasons; that is a poor association between alarm symptoms and CRC, and/or a higher than expected CRC risk in patients in the follow up for colorectal neoplasia. Regarding the former, a recent meta-analysis has shown a poor sensitivity of alarm features, 5-64% for the diagnosis of CRC [25]. Regarding the latter, a higher than expected rate of CRC within 1 year – when

endoscopic surveillance is still not recommended by current guidelines – has been described in the follow up of both adenomas and CRC [26, 28].

Sensitivity of the appropriateness guidelines for adenomas was quite similar to that shown for CRC (85% vs. 89%). This was quite an unexpected finding, since, unlike CRC, adenomas tend to be asymptomatic. However, most of the adenomas identified in asymptomatic patients are detected either in the screening or follow up of colorectal neoplasia, which, when correctly scheduled, represent appropriate indications according to ASGE/EPAGE guidelines. Different from CRC, the false negative results for adenomatous polyps appear to affect only marginally the validity of the appropriateness guidelines, since these benign lesions do not represent an immediate threat to symptomatic patients, because of their very long dwelling-time [1]. On the other hand, the potential impact of the suboptimal sensitivity

for the other benign findings, such as inflammatory bowel diseases or diverticular strictures, on the quality of life of symptomatic patients is currently unknown, and it should be explored in future studies.

Our analysis also showed that the appropriate guidelines are hampered by a low specificity, so that the positive likelihood ratio was modest – ranging between 1.1 and 1.2 – irrespective of the selected finding. This poor specificity is due to the evidence that a substantial proportion of patients with either a symptom suggestive of organic disease – such as rectal bleeding or anaemia – or with a correctly scheduled follow up do not present with any relevant finding at endoscopy, representing false positive results. Interestingly, the same limit has also been observed when similar guidelines were implemented in order to select the access for upper endoscopy, mainly because of the poor specificity of alarm symptoms for malignancy [23,24]. The most important consequence of such a low specificity is represented by the fact that, even when widely implementing the appropriateness guidelines for OC, only a minority of the examinations would appear to be inappropriate, preventing a more substantial reduction of the long-lasting waiting list for OC. Future studies should address the possibility of improving the specificity of appropriateness guidelines, identifying stronger predictors of the presence of CRC or other relevant findings.

Our study also showed a considerable degree of variability among the different studies. For instance, sensitivity for relevant findings ranged between 53% and 96% among the included series. This finding is not surprising when considering that the application of the same guidelines in different linguistic, cultural, and clinical settings may be biased by subjective interpretation, leading to different accuracy profiles. Moreover, a substantial degree of variability in the adenoma detection rate among different endoscopists has been clearly shown [29]. Although dedicated studies are not available, it cannot be excluded that a similar degree of inter-observer variability is also present for other endoscopic findings, such as angiodysplasia or diverticular strictures. It should be noticed, however, that the inter-study variation of the sensitivity for CRC – the most crucial variable – was restricted in a quite narrow range (83-100%), being also unaffected by publication bias.

Conclusion

Appropriateness guidelines represent the only clinical means to rationalize the access to OC, especially when performed in an open-access setting. Although never tested in randomized trials, their accuracy has been assessed in several cohort studies based on analogous methodology. The meta-analysis of these studies showed that the diagnostic value of the appropriateness guidelines for OC is not optimal, raising an important question whether these guidelines should be used for deciding who to select for OC. To improve the identification of CRC and other relevant endoscopic findings, more effective strategies are needed.

Conflicts of interest

Nothing to declare.

Appendix

The 14 items of QUADAS tool

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
2. Were selection criteria clearly described?
3. Is the reference standard likely to correctly classify the target condition?
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
6. Did patients receive the same reference standard regardless of the index test result?
7. Was the reference standard independent of the index test i.e. the index test did not form part of the reference standard?
8. Was the execution of the index test described in sufficient detail to permit replication of the test?
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
10. Were the index test results interpreted without knowledge of the results of the reference standard?
11. Were the reference standard results interpreted without knowledge of the results of the index test?
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
13. Were uninterpretable/ intermediate test results reported?
14. Were withdrawals from the study explained?

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