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Original Article

Head-to-Head Diagnostic Test Accuracy Meta-analysis of Colonoscopy and Fecal Immunochemical Test in Detecting Advanced Colon Neoplasia

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Abstract

Background: Studies on the use of fecal immunochemical test (FIT) in colorectal screening have long assumed perfect accuracy for colonoscopy. No study to date has directly compared the diagnostic accuracy of colonoscopy and FIT to detect advanced neoplasia (AN) in a head-to-head diagnostic accuracy meta-analysis.

Methods: A comprehensive electronic search was performed for a head-to-head comparison of FIT and colonoscopy using a third acceptable reference standard in asymptomatic adults. Cochrane methodology was used to perform a head-to-head diagnostic test accuracy (DTA) meta-analysis. Quality assessment tool for diagnostic accuracy studies-2 (QUADAS-2) was used to assess the risk of bias in included studies.

Results: Two studies met the eligibility criteria. Overall sensitivity and specificity were 98.5 (95% CI 96.3-100%) and 100% (99.9-100%) for colonoscopy and 16.4% (10.3-22.6%) and 95.4% (94.3-96.4%) for FIT. Colonoscopy was significantly better than FIT ($P<0.0001$). The positive and negative likelihood ratios (LRs) were 1.75 (1.57-1.96) and 0.03 (0.01-0.08) for colonoscopy and 3.02 (2.01-4.55) and 0.88 (0.82-0.95) for FIT, respectively.

Conclusion: Colonoscopy provides significantly better diagnostic accuracy to detect AN compared with FIT (GRADE: ⊕⊕◯◯). Our study provided precise sensitivity and specificity of both colonoscopy and FIT and a revision in screening policies based on an updated cost-effectiveness analysis considering the results of the head-to-head analysis.

Keywords: Fecal immunochemical test, Colonoscopy, Diagnostic accuracy

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and colonoscopy is one of the most accurate and commonly performed screening and preventive method for CRC.[1] Fecal immunochemical test (FIT) is also a popular screening method, although colonoscopy remains the reference standard to detect CRC and colorectal precancerous polyps.[2,3] Despite its widespread use, the utility of colonoscopy is hindered by a sub-optimal participation rate due to the semi-invasive nature of the procedure, risk of potential complications, and higher costs.[4,5]

In contrast to colonoscopy, FIT is less expensive, non-invasive, and does not require bowel preparation, resulting in improved participation.[6-8] In addition, FIT has shown a promising diagnostic accuracy for CRC or advanced adenoma (diameter > 1 cm or villous/advanced dysplasia).[9] To date, a few groups have attempted to perform a diagnostic test accuracy (DTA) meta-analysis on the accuracy of FIT using colonoscopy as the reference standard but all failed to compare FIT and colonoscopy in head-to-head analysis using a third acceptable reference standard.[10-12] This is mainly due to the absence of an optimal reference standard and the assumption of colonoscopy as a gold standard, as opposed to the reference standard, with a sensitivity and specificity of 100%, which is not supported by evidence and may result in the overestimation of the diagnostic accuracy of FIT. To address these deficiencies in the previous meta-analyses, in this report, we aimed to quantify the specificity and sensitivity of FIT and colonoscopy for advanced neoplasia (AN) using a third acceptable reference standard by only

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considering head-to-head comparison.

Materials and Methods

Registration

The study protocol was registered (CRD42020177526) with the International prospective register of systematic reviews (PROSPERO).

Study Selection

We included the head-to-head comparison of FIT and colonoscopy using an acceptable reference standard including the combination of long-term follow-up, surveillance colonoscopy, or computed tomography (CT) colonography in the average-risk population. Studies with insufficient data, abstracts, pediatric studies, duplicate publications, lack of DTA data, and studies with no reference standards were excluded. No restriction was applied in terms of language, location, or quality of the studies. Two authors (MY and PM) independently screened references and selected studies for inclusion. A third author (YY) assisted with decision-making if there was a conflict.

Search Methods for Identification of Studies

Two individual investigators completed a comprehensive literature search using MEDLINE (Ovid), EMBASE (Ovid), Web of Science, Cochrane Library, and Google Scholar databases up to June 2020. The following search terms were used: colorectal or rectal-neoplasm, cancer, adenocarcinoma, malignancy or tumor, fecal immunochemistry test, FIT, diagnostic accuracy, sensitivity, and specificity. MeSH terms as well as free text words were searched, and variations of root words were searched. No restriction was applied in terms of language, and publication year during the literature search. Recursive searching and cross-referencing were carried out by using a "similar articles" function. References of articles identified after the initial search were manually reviewed.

Data Extraction and Management

Two authors (MY and PM) independently extracted data from each included study. A third author (YY) was involved in the event of a conflict. True positive, true negative, false negative, and false positive values were determined for FIT and colonoscopy when applicable.

Assessment of Methodological Quality

Study quality and risk of bias were assessed by two independent reviewers (MY and PM) using the quality assessment tool for diagnostic accuracy studies-2 (QUADAS-2) tool for assessment of the risk of bias according to the recommendation by the Cochrane Collaboration.[10] There are two main categories: risk of bias and applicability. Each category has its own set of assessment domains. Studies without "high risk of bias" in all domains were considered to have a low risk of bias. The quality of the body of evidence was assessed by two independent reviewers (MY and PM) using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[13,14]

Outcome Measures

The main outcome of interest was the DTA of FIT and colonoscopy in detecting AN defined as an advanced adenoma (diameter > 1cm or villous/advanced dysplasia in pathology) or cancer.

Statistical Analysis and Data Synthesis

We reported pooled sensitivities and specificities, diagnostic odds ratio (DOR) and area under the curve (AUC), 95% confidence intervals where appropriate, alongside positive and negative likelihood ratio (LR) forest plots and receiver operating characteristic (ROC) curves. We used RevMan version 5.4 to create forest plots and risk of bias graphs. We computed the pooled diagnostic accuracy (sensitivity, specificity, DOR) using the *midas* command in STATA version 16.0 using a bivariate mixed-effects regression framework. To conduct head-to-head comparisons of FIT versus colonoscopy, we computed the pooled sensitivity, specificity, and DOR for both tests from the same studies, and estimated the chance of corrected absolute difference between two sensitivities and specificities. The DORs were compared using the approach recommended by Altman and Bland.[15] Head-to-head comparisons were conducted using WINPEPI.[16] Random effect model was used in DTA meta.[11] Youden's index was calculated separately for colonoscopy and FIT in comparison studies.[17] Comparisons are reported with 95% confidence intervals and *P* values.

Results

Literature Search

A total of two out of a total of 1811 records including 1673 individuals were included in the DTA meta-analysis. Figure 1 depicts the PRISMA flowchart for the detail of study selection, and Table 1 the characteristics of included studies. The risk of bias using the QUADAS-2 tool in included studies is represented in Figure 2 and Figure 3. In summary, both studies provided a low to moderate risk of bias.

FIT versus Colonoscopy

Studies were done in patients 50-81 years old. The reference standard was the combination of CT colonography and surveillance colonoscopy in one study to provide an enhanced diagnostic tool, and clinical follow-up combined with surveillance colonoscopy in the other. One study used a cut-off of 14 ng/mL and the other used both 50 and 100 ng/mL. The diagnostic accuracy of FIT and colonoscopy in head-to-head studies as well as a direct comparison of the two modalities are depicted below:

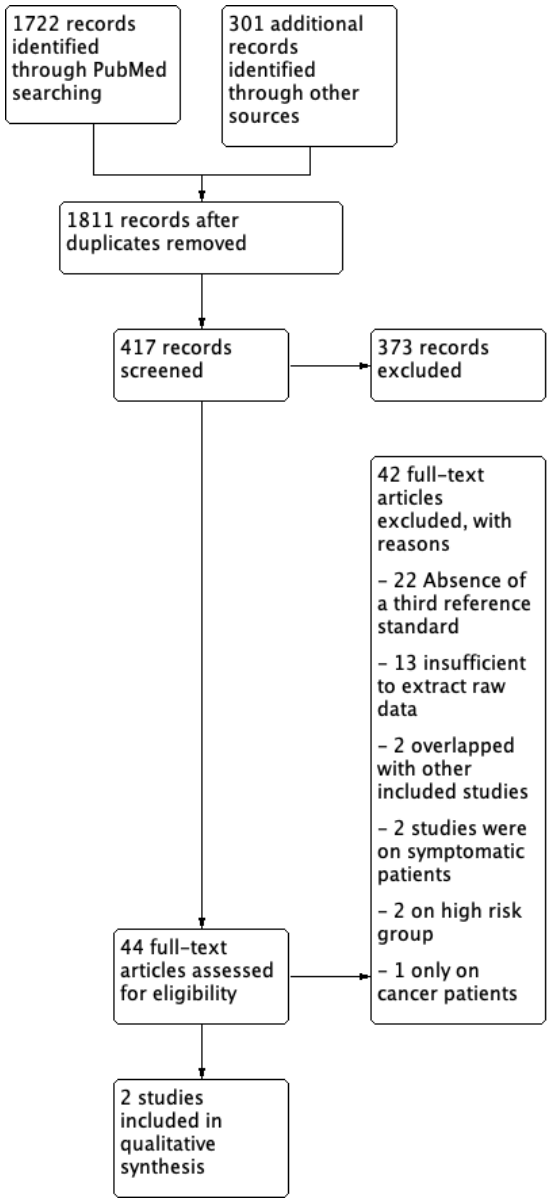

Figure 1. PRISMA study flow diagram for inclusion of eligible studies

Colonoscopy

Overall pooled sensitivity and specificity of colonoscopy to detect AN was 98.5% (96.3-100%) and 100% (99.9-100%). The DOR was 377.38 (137.95-1032.38) and Youden's index for this analysis was 0.88 (0.85-0.91). The positive LR was 1.75 (1.57-1.96) and the negative LR was 0.03 (0.01-0.08).

FIT

Overall weighted sensitivity and specificity of FIT to detect AN in head-to-head studies were 16.4% (10.3-22.6%) and 95.4% (94.3-96.4%), respectively. The pooled DOR was 3.56 (2.17-5.81) and Youden's index for this analysis was 0.12 (0.05-0.18). The positive LR was 3.02 (2.01-4.55) and the negative LR was 0.88 (0.82-0.95).

Head-to-Head Comparison

Figure 4 depicts the Forest plot and Figure 5 shows the summary receiver operating characteristic (SROC) corresponding to the head-to-head comparison of FIT to colonoscopy. The DOR of colonoscopy (377.38) to FIT (3.56) was 106.01 (34.57-325.02) significantly higher for colonoscopy as compared with FIT ($P<0.0001$) in comparative studies. The Youden's index was also significantly better for colonoscopy as compared with FIT (98.7 versus 11.5%; $P<0.001$).

Heterogeneity

There was no heterogeneity in the analysis of sensitivity with Higgins & Thompson's H of 1.2 for colonoscopy ($P=0.21$) and 1.0 for FIT ($P=0.38$). There was significant heterogeneity in the analysis of specificity with Higgins & Thompson's H of 28.5 for colonoscopy ($P<0.001$) and 6.2 for FIT ($P<0.001$). There was significant heterogeneity in the analysis of DOR with Higgins & Thompson's H of 3.3 for colonoscopy ($P<0.001$) but not for FIT with an H of 1.0 for FIT ($P=0.55$). The proportion of heterogeneity likely due to the cut-off effect was calculated at 0.25 but it was not possible to delve into the causes of heterogeneity due to the limited number of studies in this analysis.

Assessment of Quality of Body of Evidence

The quality of evidence was evaluated as low to moderate due to imprecision and indirectness (Table S1 of Supplementary file 1).

Discussion

This is the first DTA meta-analysis using appropriate methodology including the head-to-head comparison of FIT and colonoscopy using a third enhanced reference standard that was a combination of long-term follow-up, surveillance colonoscopy, and/or CT-colonography. We showed that colonoscopy provides significantly higher diagnostic accuracy, by a large margin, with overall weighted sensitivity and specificity of 98.5% and 100% as compared with 16.4% and 95.4% for FIT to detect AN.

Studies have long used colonoscopy alone as the reference standard for detecting AN. However, colonoscopy is not a perfect test and a recent meta-analysis of 43 studies showed that the miss rate was up to 9% for advanced adenomas.[20,21] Our study is likely the first to provide evidence-based meta-analytic data for the expected accuracy of colonoscopy as well as supporting its reliable role as probably the most appropriate reference standard.

To our knowledge, there are a few ongoing RCTs comparing screening colonoscopy and FIT in longitudinal observational studies.[22-24] The interim result of one study on 26 703 individuals who were invited to have a screening colonoscopy and 26 599 to have biennial FIT showed that participation was higher in the FIT arm (34.2% vs 24.6%).[22] AN detection was higher in individuals randomized to colonoscopy (1.9% vs 0.9%). Another US study compared participation with a no-cost FIT and no-cost screening colonoscopy in an uninsured US population and showed

Table 1. Characteristics of included studies

Study		Graser et al[18]	Siripongpreeda et al[19]
Year of publication		2009	2016
Country of origin		Germany	Thailand
Design		Consecutive enrollment	Single center cross-sectional
Population		Asymptomatic population	Asymptomatic population
Age range		50-81 years old	50-65 years old
Objective		Accuracy of FIT, FOBT, CTC, and colonoscopy	Accuracy of FIT
FIT cut-off		14 ng/mL	50 ng/mL
Time between FIT and colonoscopy		Unclear	Unclear
Duration of follow-up			5 years
Additional tests		CT-colonography on the same day and FOBT	Clinical follow-up and surveillance FIT and colonoscopy at 1, 3 and 5 years as appropriate CT-colonography in 5 incomplete colonoscopies
Bowel preparation		polyethylene glycol (PEG)	Picosalax® (magnesium oxide, citric acid, sodium picosulphate)
Sample size		269	1404
Male/female ratio		171/140	429/975
Outcome		Advanced neoplasia	All adenomas and advanced neoplasia
Number of adenomas		NA	277
Number of advanced neoplasias		25	116
Number of advanced non-cancerous neoplasias		NA	98
Number of cancers		NA	18
FIT	**Sensitivity**	%32	%14
	Specificity	%86	%96
Colonoscopy	**Sensitivity**	%100	%97
	Specificity	%43	%100

NA: Not available; FIT, fecal immunochemical test.

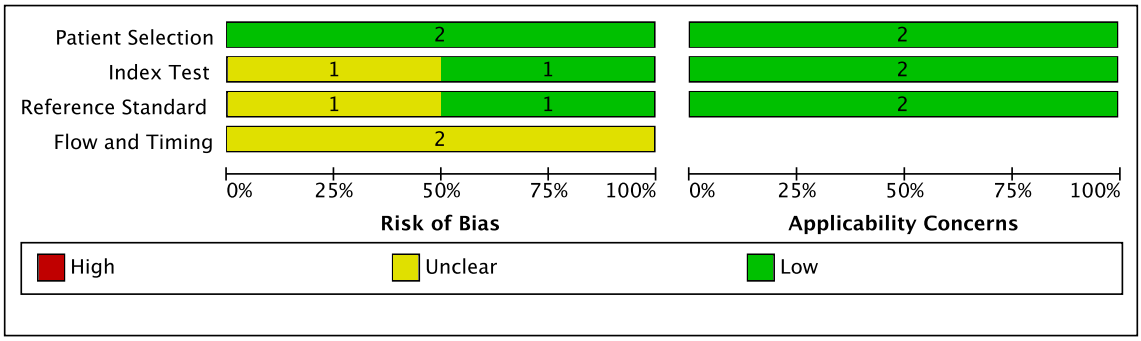

Figure 2. Cochrane risk of bias assessment presented as a percentage across all studies

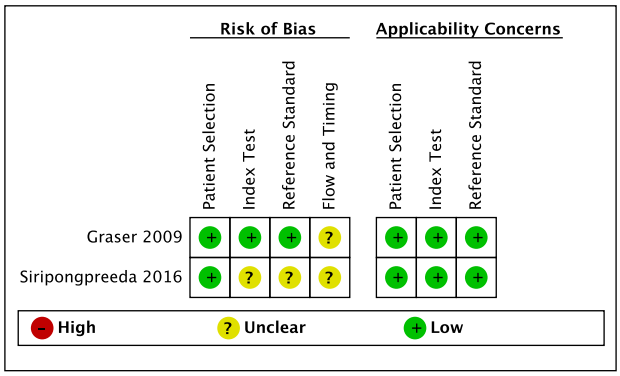

Figure 3. Cochrane risk of bias assessment of each included study

higher participation with FIT (40.7% versus 24.6%) with no difference in cancer detection (0.4% vs 0.4%) although AN detection was higher with colonoscopy (1.3%) as compared with FIT (0.8%).[25]

Recommendations on using FIT as the first option for screening for CRC for the average-risk population are mainly based on financial advantage and ease of access rather than robust diagnostic accuracy, which can be used as a triaging tool for a more invasive screening test. Most of the guidelines have quoted a sensitivity of around 60% for FIT as compared with 16% shown in our head-to-head comparison or 27% to 48% in the analysis of different cut-offs of FIT.[26] This warrants a new cost-effectiveness

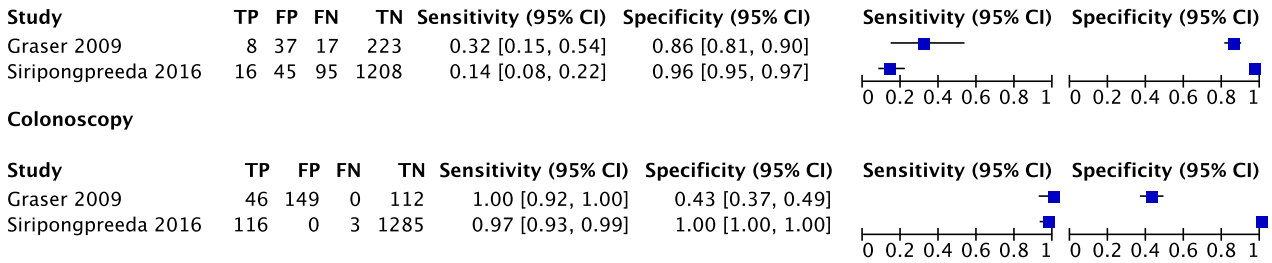

Figure 4. Forest plot for diagnostic accuracy of FIT at various cut-offs

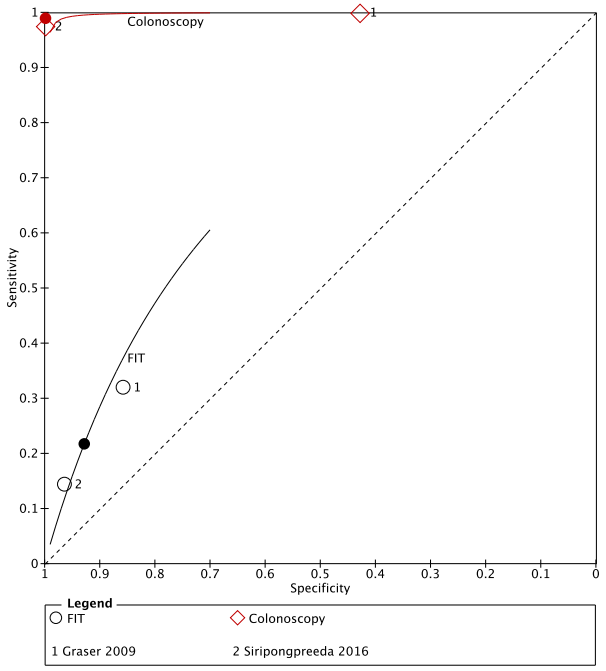

Figure 5. SROC of diagnostic accuracy of colonoscopy as compared with FIT

analysis to see if the policies need to be revised.

Currently, most people undergo colonoscopy as the screening method of choice in the United States.[27] Different estimates of sensitivity and specificity of FIT up to 0.79 and 0.94, respectively have been reported.[28] Based on these values many jurisdictions, employed FIT as the preferred screening method as its cost was significantly lower than colonoscopy, however, later studies showed lower values of 0.40 to 0.95.[11] In our study when compared directly to colonoscopy, we showed even a lower sensitivity for FIT with a comparable specificity for detecting AN. This may partly be due to the fact that some studies only focus on detecting cancer which precludes the screening purpose of the test to detect advanced adenoma, which could be easily treated.

Our study was limited by the limited number of included studies due to the cost and complexity associated with performing a DTA study using additional reference standards to colonoscopy alone. It is possible that the concept of our study lead to the emergence of properly done large randomized trials directly comparing FIT and colonoscopy using acceptable third reference standards such as long-term follow-up and multiple surveillance colonoscopy. Another limitation of this study was the cross-sectional method in all included studies. Most authorities recommend biennial FIT screening as compared with one in 10 years frequency of colonoscopy. One might expect higher overall diagnostic accuracy for FIT in 10 years as compared with what is shown in our study based on one test, although this conclusion is not necessarily true since there is no evidence that adding more tests in upcoming years will increase diagnostic accuracy given the absence of long-term studies and the fact that the number of false positives and false negative results will also increase by time. It should be noted that FIT is only cost-effective and ethically permitted if provided a certain level of diagnostic accuracy and therefore more accurate modeling and prediction will shed more light on this aspect of the applicability of FIT.

Screening colonoscopy has the potential to be the most effective form of CRC screening, although it requires a large number of precipitants and one should note the semi-invasive nature of the procedure. However, if non-invasive tests are preferred by a recipient, other screening strategies, particularly those using the risk score, can be more effective and cost-effective.[27] Studies that used almost similar sensitivity of around 23%, to our results, for FIT have shown colonoscopy to be more cost-effective than FIT in screening for CRCs.[28] However, another study assuming a sensitivity of 35% for FIT did show similar cost-effectiveness for the two strategies.[29] Another study reached the same conclusion using a sensitivity of 42% for the detection of advanced adenoma for FIT.[30] Therefore it seems that the relative cost-effectiveness of two tests can be changed based on which study is quoted and this may have led to different jurisdictions recommending different screening modalities.

Some investigators have described better compliance with FIT as an advantage, as compared with colonoscopy, although this remains controversial. A recent large randomized controlled trial in the United States comparing FIT versus colonoscopy outreach invited 2400 individuals aged 50-64 years in each group to attend the screening program and they showed that 38.4% of the target population completed screening in the colonoscopy outreach group as compared with 28.0% in the FIT outreach group ($P<0.001$).[31]

On the other hand, multiple studies have shown higher sensitivity of FIT for CRC and much lower sensitivity for the detection of advanced adenoma.[22-24] One should consider major comorbidities and mortality due to late or even early diagnosis of CRC as compared with adenoma since an adenoma is usually treated by an endoscopic resection without the need for surgical intervention and/or chemotherapy and basically replaces a preventive measure by a therapeutic measure. Also, it is likely less complicated to remove a small polyp at an earlier age rather than waiting till a polyp is advanced enough to be detected by FIT and likely requiring more advanced endoscopic techniques such as endoscopic mucosal resection and endoscopic submucosal dissection or a full thickness resection such as hemicolectomy. So far, no study has compared the long-term effectiveness of FIT and colonoscopy by considering all these factors.

In conclusion, we showed colonoscopy was a reliable reference standard for research purposes as well as the most accurate screening modality for CRC. The conventional diagnostic accuracy studies may have overestimated the sensitivity and specificity of FIT and therefore it might be prudent to take another look at the cost-effectiveness of this approach by using new data.

Authors' Contribution

Mohammad Yaghoobi: Conceptualization, data curation, formal analysis, supervision, verified the underlying data. Parsa Mehraban Far: Data curation, verified the underlying data. Lawrence Mbuagbaw: Formal analysis, supervision, verified the underlying data. Yuhong Yuan: Review and editing. David Armstrong: Review and editing, supervision. Lehana Thabane: Review and editing, formal analysis. Paul Moayyedi: Supervision, review, and editing.

Competing Interests

The authors declare no conflict of interest related to this work.

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Supplementary Files

Supplementary file 1 contains Table S1.

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