Potential Modifiers and Different Cut-offs in Diagnostic Accuracy of Fecal Immunochemical Test in Detecting Advanced Colon Neoplasia: A Diagnostic Test Accuracy Meta-analysis

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Abstract

Background:
Fecal immunoglobulin test (FIT) has been advocated as the first line of screening for colorectal cancer (CRC) in several jurisdictions. Most studies have focused on CRC as the outcome of interest. Our goal was to quantify the diagnostic accuracy of different thresholds of FIT as compared with colonoscopy for detection of advanced colonic neoplasia and potential modifiers using proper Cochrane methodology.

Methods:
A comprehensive electronic search was performed for studies on FIT using colonoscopy as the reference standard to detect advanced neoplasia. Cochrane methodology was used to perform a diagnostic test accuracy (DTA) meta-analysis. Diagnostic accuracy of different cut-offs of FIT, including 25, 50, 75, 100, 150, and 200 ng/mL, were calculated separately. Meta-regression analysis was also performed to detect potential *a priori* modifiers, including age, location of the tumor, and time from FIT to colonoscopy.

Results:
Twenty-four studies were included with no evidence of publication bias. The sensitivity of FIT did not decrease with lowering the cut-off, although specificity increased in higher cut-offs. Commonly used cut-offs of 50 ng/mL, 75 ng/mL, and 100 ng/mL for FIT provided sensitivity of 39%, 36%, 27% and specificity of 92%, 94%, 96%, respectively. Diagnostic accuracy of FIT did not significantly differ in proximal versus distal lesions or in individuals below or over the age of 50 years. The results remained robust in a meta-regression of the location of the study, time from FIT to colonoscopy, and methodological quality.

Conclusion:
The sensitivity of FIT might have been overestimated in previous studies focusing on CRC, and it seems to be independent of age, location of neoplasia, or cut-offs, contrary to some previous studies. Lowering the cut-off will reduce the diagnostic odds ratio (DOR) by increasing specificity but without any effect on sensitivity.

Keywords:
Colon cancer screening, Fecal immunoglobulin test, Colonoscopy, Meta-analysis

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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 methods for CRC.[1] Apart from colonoscopy, fecal immunoglobulin test (FIT) has recently gained popularity, but colonoscopy remains the reference standard to detect CRC and colorectal precancerous polyps and is therefore used in most diagnostic accuracy studies.[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 30% diagnostic accuracy for CRC or advanced adenoma (diameter > 1cm or villous/advanced dysplasia).[9] However, FIT has been proved to miss a significant portion of early stage I or distal cancers and precancerous polyps, which could be easily removed in colonoscopy.[10] In 2017, the United States Multi-Society Task Force on Colorectal Cancer recommended colonoscopy every 10 years or annual FIT as first-tier options for screening the average-risk persons for colorectal neoplasia.[9] A few groups to date have attempted to perform diagnostic test accuracy (DTA) meta-analysis assessing various cut-offs of FIT using colonoscopy as the reference standard, but the effect of factors such as age, location of the tumor, and the time gap between the FIT and colonoscopy has not yet been defined.[10-12] Most studies have focused on colon cancer and not advanced neoplasia. The advantage of finding advanced adenomas as compared with cancer is a potentially better outcome and avoiding surgical resection and possibly chemotherapy or radiation. Individual studies have shown a lower sensitivity of FIT for proximal and compared to distal lesions and increased sensitivity but decreased specificity by decreasing the cut-off.[13,14] In this study, we aimed to investigate the role of cut-offs in the accuracy of FIT in detecting advanced neoplasia, including cancer and advanced adenomas, as well as factors that might affect this accuracy, including the location of the tumor and the age of patients.

Materials and Methods

Registration

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

Study Selection

We included all studies assessing the diagnostic accuracy of FIT using colonoscopy as the reference standard. 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 August 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 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/or colonoscopy when applicable. All reporting units were converted to ng/mL for consistency.

Assessment of Methodological Quality

Study quality and risk of bias were assessed by two

independent reviewers (MY and PM) using the Cochrane tool for assessment of the risk of bias according to the recommendation by the Cochrane Collaboration.[15] 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 low risk of bias. The quality of the body of evidence was assessed by two independent reviewers (MY and PM) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[15,16]

Outcome Measures

The main outcome of interest was the DTA of FIT in detecting advanced neoplasia, defined as advanced adenoma or cancer in different cut-offs. Secondary objectives were to identify the diagnostic accuracy of FIT in proximal versus distal lesions as well as in individuals under 50 as compared with those over 50 years old.

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 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. Model fit was assessed by examining goodness of fit, bivariate normality, and outlier effects using the *modchk* command. Publication bias was evaluated using Deek's funnel plot test (*pubbias* command). The proportion of heterogeneity likely due to cut-off effects was computed since the univariate tests for heterogeneity do not account for heterogeneity explained by positivity cut-off effects. Given that there were different thresholds in our variation, we visually inspected the degree to which the observed study results lied close to the summary ROC curve as depicted graphically.[15]

We conducted sensitivity analyses using univariable meta-regression approaches and the *reg* command. A random effect model was used in DTA meta.[10] GRADEpro guideline development tool by McMaster University was used to assess the level of evidence.

Results

Literature Search

A total of 24 out of a total of 1722 records were included in the DTA meta-analysis. These studies were published between 2005 and 2018. Eleven studies were from Asia and 13 from the rest of the world. All studies defined advanced neoplasia as the total number of advanced adenoma and cancer. Figure 1 depicts the PRISMA flowchart for the detail of study selection, and Table 1 shows the characteristics of included studies. The risk of bias using the Cochrane tool in included studies is represented in Figures 2 and 3.

Cut-off Effect on Diagnostic Accuracy of FIT

Table 2 depicts the detail of the analysis of diagnostic accuracy of different cut-offs of FIT by considering colonoscopy as the reference standard. Diagnostic accuracy and specificity numerically increased by increasing the cut-off for FIT positivity, but the sensitivity did not follow any pattern (Table 2). Figure 4 depicts the SROC across different thresholds of FIT. The Forest plot for sensitivity and specificity of FIT across different cut-offs is presented in Figure 5.

Test for Publication Bias

There was no prominent visual asymmetry in the Deek's funnel plot for DORs, and the Deek's Funnel plot asymmetry test showed no significant publication bias ($P=0.31$).

Subgroup and Sensitivity Analyses for Diagnostic Accuracy of FIT

Effect of Location of Neoplasia in Diagnostic Accuracy of FIT

The sensitivity and specificity of FIT were 31% (26-36%) and 95% (94-96%), respectively, for distal lesions and 20% (13-27%) and 95% (94-96%), respectively, for proximal lesions. The joint model did not show a significant difference in diagnostic accuracy of FIT in detecting proximal versus distal lesions ($P=0.16$) in three studies, including 47688 patients reporting extractable information for this analysis.

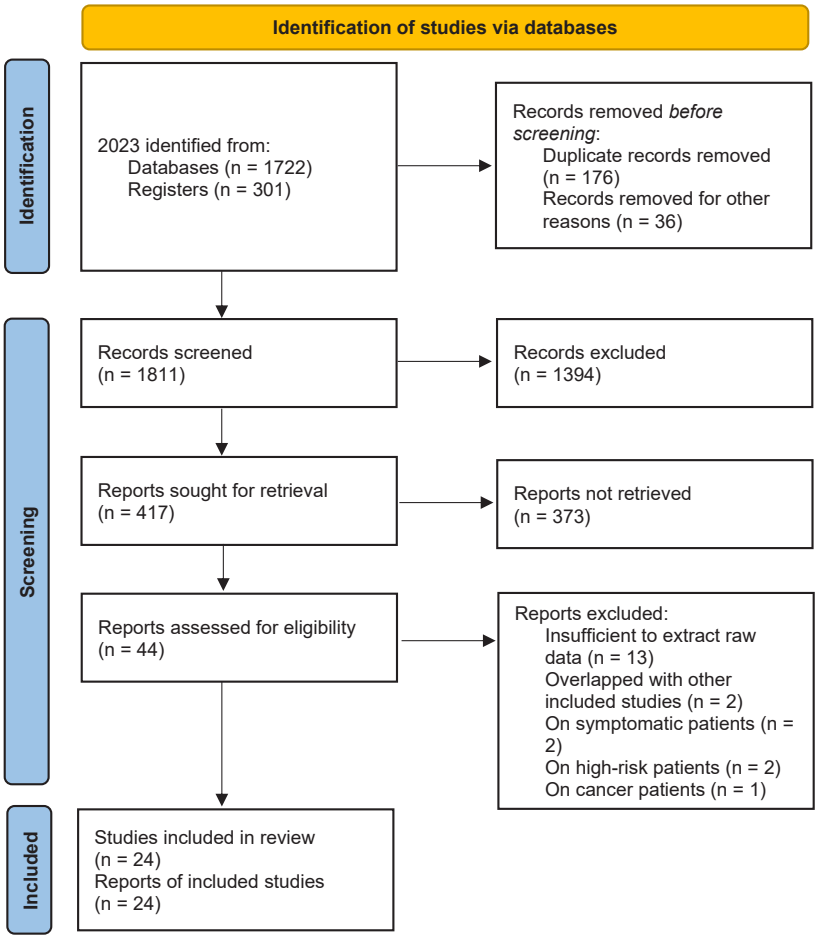

Figure 1. PRISMA study flow diagram for inclusion of eligible studies

Effect of Age on Diagnostic Accuracy of FIT

The sensitivity and specificity of FIT were 18% (3-33%) and 97% (96-98%), respectively in those older than 50 as compared to 10% (1-19) and 98% (97-99%), respectively, for those under 50. The joint model did not show a significant difference in diagnostic accuracy of FIT in patients over and under 50 ($P=0.47$) in four studies, including 36,755 patients reporting extractable information for this analysis.

Meta-regression Analysis

Meta-regression analysis did not show any significant predictability for the location of the study (Asian versus non-Asian, $P=0.06$), the inclusion of patients with unclear or high risk (P=0.14), time gap from FIT to colonoscopy ($P=0.09$) and risk of bias (high or unclear as compared to low) criteria in diagnostic accuracy of FIT ($P=0.82$)

Heterogeneity

The visual assessment showed a low to moderate amount of heterogeneity in SROC. Further analysis showed that studies avoiding inappropriate exclusion, as compared to those which did not, showed a numerically higher diagnostic accuracy in all cut-offs of FIT.

Assessment of Quality of Body of Evidence

The quality of evidence was evaluated as low to moderate due to imprecision and indirectness.

Discussion

In this study, we showed that higher cut-offs of FIT increased specificity and positive likelihood ratio while sensitivity and negative likelihood ratio did not show a predictable pattern. Furthermore, we demonstrated

Table 1. Characteristics of included studies (N=24)

Study	Design	Year of publication	Country of origin	Study population	Study objective	Time between FIT and colonoscopy (days)	Bowel preparation	Age range	Sample size	Number of adenoma	Number of advanced neoplasia	Advanced non-cancerous neoplasia	Cancer
Aniwan[17]	Multicenter cross-sectional	2017	Thailand	Average-risk	Optimal cut-off for FIT	3	Not available	50-75	1479	547	137	123	14
Chang[18]	Unicenter cross-sectional	2017	Taiwan	Average risk	FIT in Sessile lesions	2	Not available	50+	6198	Not available	339	NA	Not available
Chen[19]	Multicenter cross-sectional	2014	Taiwan	Average risk	Accuracy of FIT	Unclear	2-L Polyethylene glycol or Pico-Salax x2	40-87	6096	Not available	254	241	13
Chiu[20]	Multicenter cross sectional	2016	South-East Asia	Low and average risk had FIT	Accuracy of FIT	28	Split or same day prep	40+	3889	692	174	158	16
De Wijkerslooth[21]	Randomized sampling	2012	Netherlands	Average risk	Accuracy of FIT	2	Polyethylene glycol	50-75	1256	453	119	111	8
Graser[22]	Consecutive design	2009	Germany	FIT available	Accuracy of FIT, FOBT, CT-colonogram and colonoscopy	Unclear	Polyethylene glycol	50-81	269	NA	25	Not available	Not available
Hernandez[23]	Multicenter cross-sectional	2014	Spain	Average risk	Comparing 1 vs 2 sample FIT	7	Not available	50-69	779	202	97	92	5
Hundt[24]	Multicenter cross-sectional	2009	Germany	Average-risk	Accuracy of FIT	Unclear	Not available	55+	3211	405	130	130	0
Imperiale[25]	Multicenter cross-sectional	2014	North America	Average risk	Accuracy of FIT, fecal DNA and colonoscopy	Not available	Not available	50-84	9989	2893	822	757	65
Khalid-de Bakker[26]	Unicenter cross-sectional	2011	Netherlands	Employees of university medical ctr	FIT, sigmoidoscopy and colonoscopy	14	Polyethylene glycol 4L	50-65	447	86	38	38	0
Kim[27]	Multicenter cross-sectional	2016	Korea	Average risk	Accuracy of FIT in age<50	3	Polyethylene glycol 4L	30-50+	26316	Not available	464	454	10
Liles[28]	Multicenter cross-sectional perspective	2018	USA	Average-risk	Comparing 1 vs 2 sample FIT	270	2L Polyethylene glycol or Pico-Salax x2	49-75	2771	570	211	209	2
Morikawa[29]	Multicenter cross-sectional	2005	Japan	Average-risk	Accuracy of FIT	1	2L Polyethylene glycol	20-91	21805	Not available	727	648	79
Omata[30]	Retrospective	2011	Japan	All incomers but no genetic syndrome	Optimal FIT cut-off	7	Not available	64+/-11	1085	Not available	71	63	8
Oort[31]	Multicenter cross-sectional	2011	Netherlands		Accuracy of 1 vs 2 sample FIT	2	Not available	19-91	1096/15 were excluded for sn/sp calc	Not available	124	89	35

Table 1. Continued.

Study	Design	Year of publication	Country of origin	Study population	Study objective	Time between FIT and colonoscopy (days)	Bowel preparation	Age range	Sample size	Number of adenoma	Number of advanced neoplasia	Advanced non-cancerous neoplasia	Cancer
Ou[32]	Multicenter cross-sectional	2013	Taiwan	Average risk	Optimal FIT cut-off	Unclear	Not available	Median: 59.5	699	133	37	34	3
Park[33]	Multicenter cross-sectional	2010	South Korea	Average-risk	Accuracy of FOBT vs. FIT	7	Not available	50-75	770	Not available	72	59	13
Parra-Blanco[34]	Randomized sampling	2010	Spain	Average risk	Accuracy of FOBT vs. FIT	Unclear	Not available	50-79	1756	Not available	63	49	14
Rozen[35]	Multicenter cross-sectional	2009	Israel	Average and non-average	Accuracy of FOBT vs. FIT	Unclear	Not available	50-75	330	Not available	32	26	6
Shapiro[36]	Multicenter cross-sectional RCT	2018	USA	Average-risk	Accuracy of FOBT vs FIT	100	Not available	50-75	1095	Not available	55	53	2
Siripongpreda[37]	Unicenter cross-sectional	2016	Thailand	Average risk	Accuracy of FIT	Unclear	Pico-Salax	50-65	1404	277	116	98	18
Sohn[38]	Unicenter cross-sectional	2005	South Korea	Average risk versus CRC	Accuracy of FIT	Unclear	Not available	15-78	3794	613	79	67	12
Terhaar[39]	Multicenter cross-sectional	2011	The Netherlands	Average and non-average risk	Accuracy of FIT	1	Not available	40-89	2145	Not available	315	236	79
Wong[40]	Multicenter cross-sectional	2012	Canada	Average risk, including FH	Accuracy of FOBT versus FIT	10	Polyethylene glycol 4L	40-75	1075	252	69	67	2

that the sensitivity and specificity of FIT for advanced neoplasia were not significantly affected by age or location of the lesion, and they might be lower than presented in previous studies, given that most studies used CRC as the outcome of interest.

To our knowledge, there are a few ongoing RCTs comparing screening colonoscopy and FIT in longitudinal observational studies.[41-43] 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%).[41] Advanced neoplasia 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 higher participation with FIT (40.7% versus 24.6%) with no difference in cancer detection (0.4% vs. 0.4%) although advanced neoplasia detection was higher with colonoscopy (1.3%) as compared to FIT (0.8%).[44] One should note that diagnosis of advanced adenoma has potential advantages to the diagnosis of CRC in avoiding the need for an extensive colorectal resection and/or chemoradiation therapy.

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. Most of the guidelines have quoted sensitivity of around 60% for FIT as compared to 27-48% in the analysis of different cut-offs of FIT in our study.[45] This warrants a new cost-effectiveness 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.[46] Different estimates of sensitivity and specificity of FIT up to 0.79 and 0.94, respectively have been reported.[47] 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.[11] Therefore, FIT may not be a screening tool as desirable as it was previously assumed.

In our study, we did not find a significant difference in diagnostic accuracy of FIT above and under the age of 50. Previous studies reported a higher detection rate for

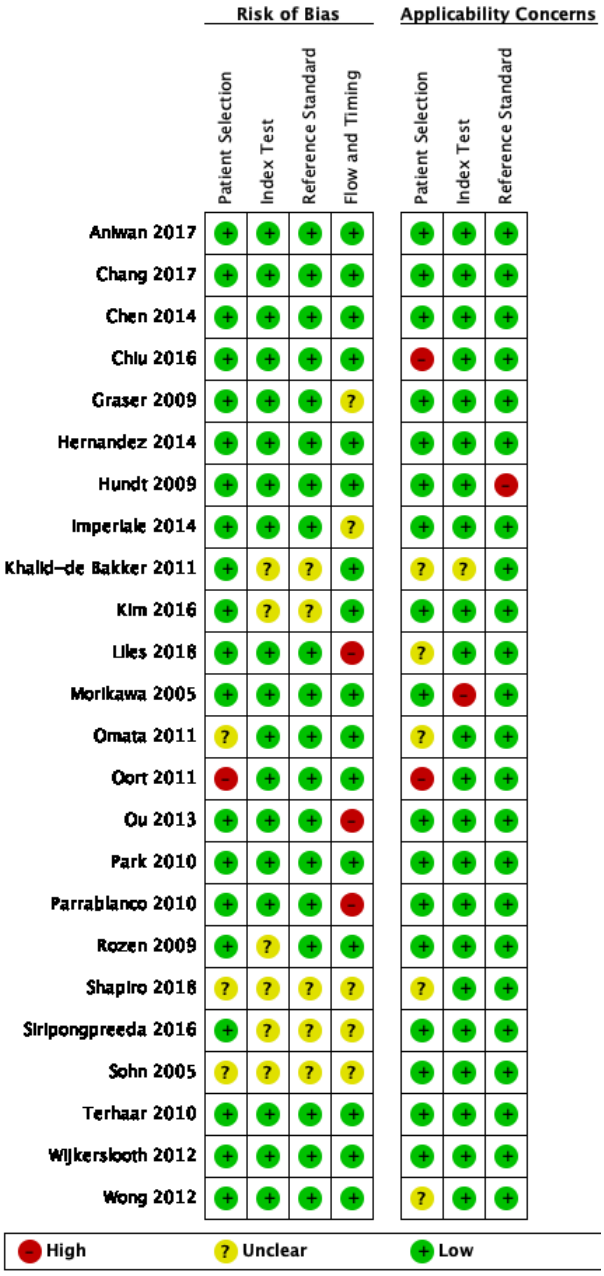

Figure 2. Cochrane risk of bias assessment of each included study

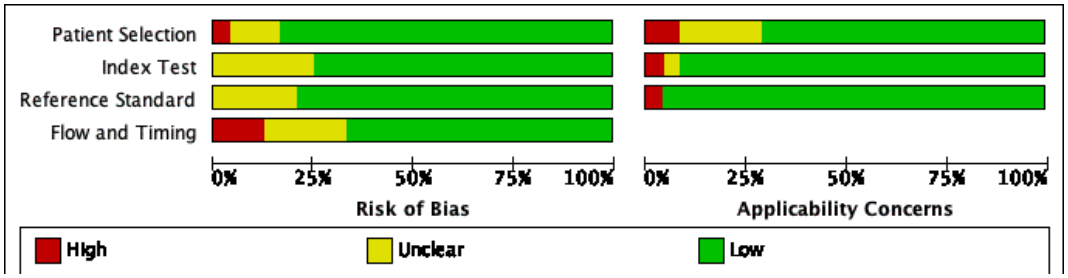

Figure 3. Cochrane risk of bias assessment presented as a percentage across all studies

Table 2. Diagnostic test accuracy of FIT for most used cut-off

Cut-off	Number of studies	Sensitivity	Specificity	Area under curve	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio
25 ng/mL	6	0.48 (0.37-0.59)	0.84 (0.73-0.91)	0.69 (0.65-0.73)	3.0 (2.1-4.3)	0.62 (0.54-0.71)	5 (4-7)
50 ng/mL	17	0.35 (0.30-0.42)	0.93 (0.91-0.94)	0.78 (0.74-0.81)	4.8 (3.8-6.0)	0.70 (0.64-0.76)	7 (5-9)
75 ng/mL	10	0.36 (0.29-0.43)	0.94 (0.92-0.96)	0.79 (0.75-0.82)	5.9 (4.5-7.8)	0.69 (0.62-0.76)	9 (6-12)
100 ng/mL	15	0.27 (0.20-0.34)	0.96 (0.95-0.97)	0.85 (0.82-0.88)	7.1 (6.0-8.5)	0.76 (0.70-0.83)	9 (8-12)
150 ng/mL	9	0.29 (0.21-0.39)	0.96 (0.96-0.97)	0.92 (0.89-0.94)	7.9 (6.7-9.4)	0.72 (0.65-0.82)	10.9 (8.3-14.2)
200 ng/mL	5	0.37 (0.30-0.46)	0.96 (0.95-0.97)	0.87 (0.84-0.90)	10.0 (7.8-12.9)	0.65 (0.58- 0.73)	15 (12-21)

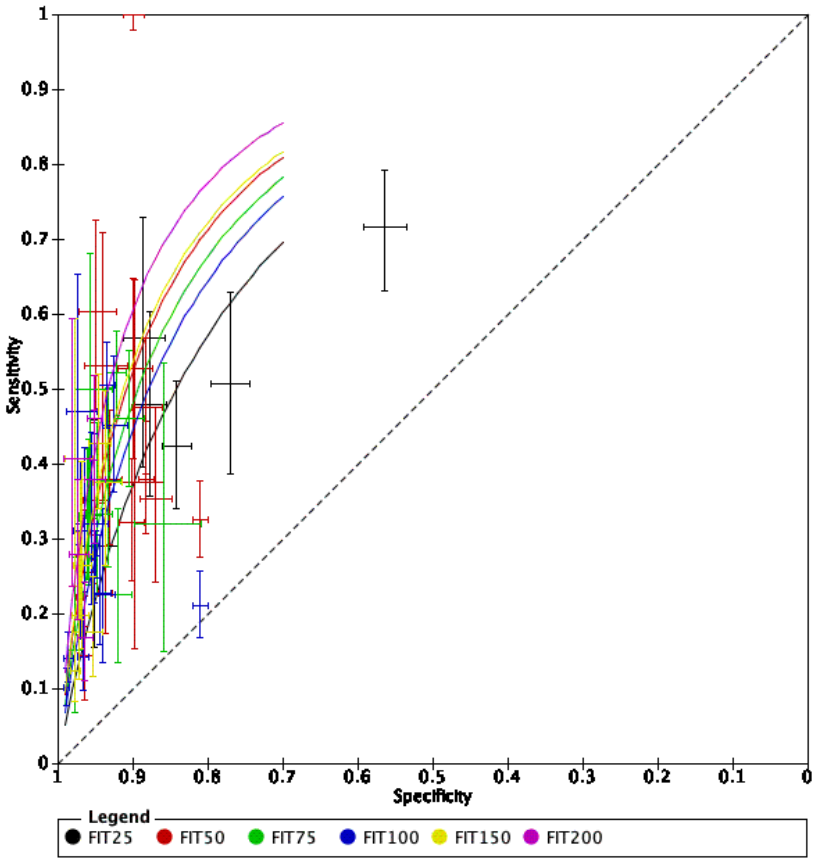

Figure 4. Summary receiver operating characteristic curve (SROC) of diagnostic accuracy of colonoscopy and different cut-offs of FIT

advanced adenoma or cancer in older individuals,[48] but one should note that the detection rate is independent of the diagnostic accuracy and is more a representation of prevalence, which is expectedly higher in the older individuals.

Our study showed that commonly used cut-offs of 50, 100, and 150 ng/mL for FIT provide very modest sensitivity for detecting advanced neoplasia of under 39%, 27%, and 29%, respectively, when providing an acceptable specificity, albeit still not as accurate as colonoscopy. A cost-effective analysis using this data will shed some light on whether using FIT is within the acceptable framework in each jurisdiction. Our results are also in accordance with the findings of a recent study which showed that reducing the cut-off of FIT will not improve the accuracy of the test.[45] This will also answer an important question on this topic since each jurisdiction chooses its own cut-off. Based

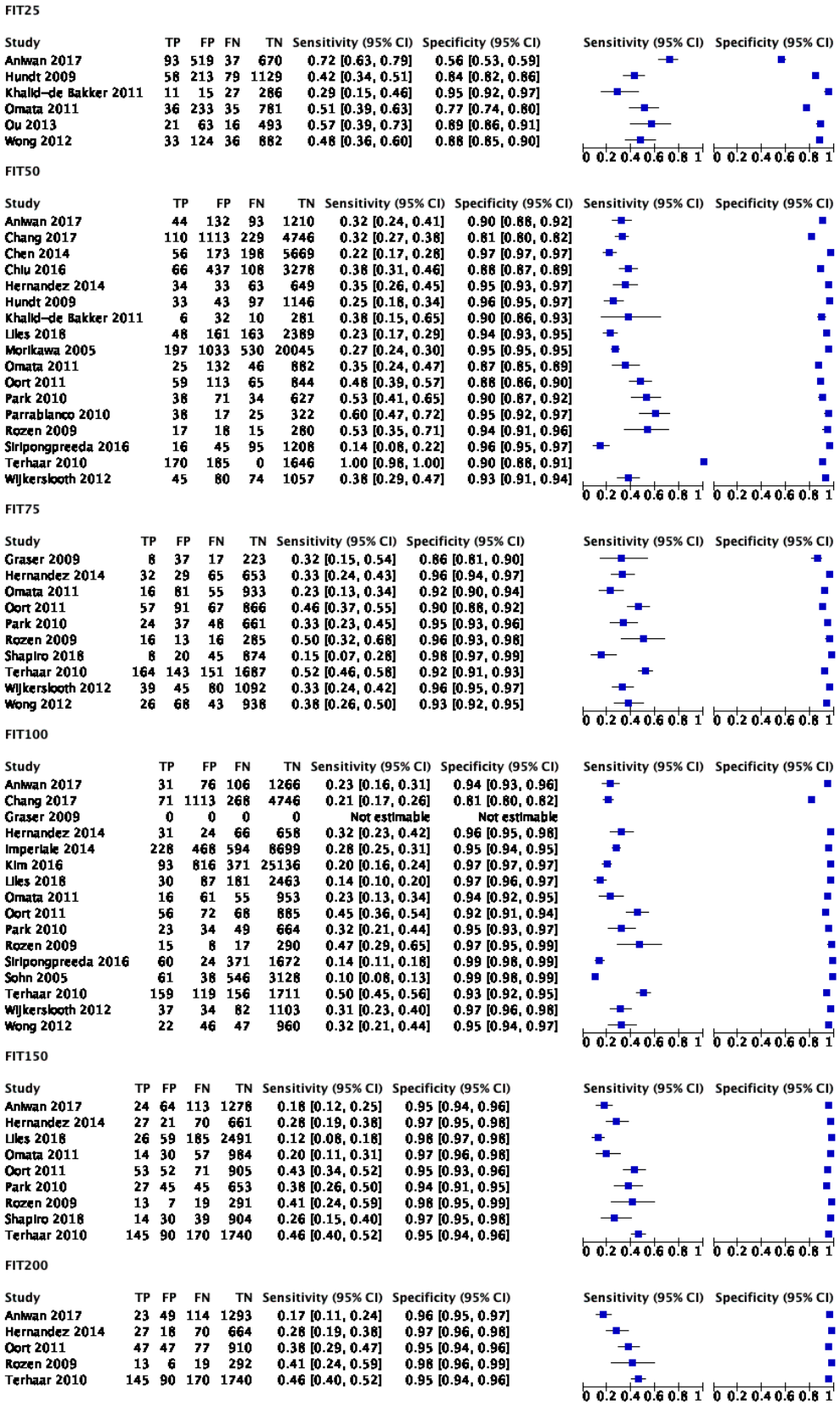

Figure 5. Forest plot for diagnostic accuracy of FIT at various cut-offs

on this data, it might be reasonable to increase the cut-off to achieve higher specificity without sacrificing sensitivity. Previous studies have shown that the diagnostic accuracy of FIT may not simply follow the common sense. For instance, one might expect higher sensitivity of FIT in more advanced stages of CRC; however, Niedermaier et al showed that the sensitivity of FIT is unrelated to the stage of cancer and may even decrease in higher stages, likely due to anemia caused by the tumor. They also showed that although sensitivity is decreasing by rising the cut-off in T1 tumors, such a relation was not true for higher-stage tumors.[10] This might support the overall lack of relationship between the cut-off and sensitivity of FIT in our study. Future studies may focus on the different diagnostic accuracy of FIT in different stages of a polyp or cancer and identify pitfalls where further optimization might be required.

One of the limitations of this study was the cross-sectional method in all included studies. Most authorities recommend biennial FIT screening as compared to one in ten years frequency of colonoscopy. One might expect higher overall diagnostic accuracy for FIT in 10 years as compared to what is shown in our study based on one test. Once again, it should be noted that the lesions which are missed in the initial test as false negative and are found in the subsequent screening will likely be of higher grade and require a more advanced therapeutic modality. Moreover, there is no evidence that adding more tests in upcoming years will necessarily 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 over time. As an example, if we consider the sensitivity and specificity of 0.35 and 0.93, respectively, for FIT50 achieved in our study, 24% of the average risk population screened by FIT, including all true and false positives, will require a colonoscopy in the first year. All other individuals with true and false negative results will have a FIT test in 2 years, and if the diagnostic accuracy of FIT50 remains the same, another 22% (previous false negatives and new true and false positives) will require colonoscopy. In this example, a total of 46% of the initial population required a colonoscopy just in 2 years, and this will incrementally increase up to 10 years. Therefore, 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.

One of the *a priori* sources of heterogeneity in our study was the variety of FIT tests across different trials, geographical and ethnic disparity, different demographics of included cases, and variation in methodology. A meta-regression analysis did not show any significant impact by location of the study, patient's risk of developing CRC, time gap from FIT to colonoscopy, and the quality of methodology, and the results remained robust after excluding the role of these potential factors. Furthermore, the possibility of publication bias was ruled out by using a proper statistical method. Lastly, our study was limited by the limited sample size due to the cost and complexity associated with performing a DTA study using additional reference standards to colonoscopy alone.

We found that the accuracy of FIT was not different in detecting proximal versus distal lesions. This has been a controversial topic, and although some studies showed less sensitivity for more proximal lesions, others failed to show so.[13,14] The study by Kim et al also showed that lowering the cut-off of FIT did not change the accuracy for proximal lesions.[13] One major reason might be that some studies looked at the sensitivity as compared to overall diagnostic accuracy.

Although screening colonoscopy has the potential to be a cost-effective form of CRC screening, although it requires a large number of precipitants, non-invasive screening strategies can also be cost-effective.[46] Studies on FIT which used almost similar sensitivity to our results, have shown colonoscopy to be more cost-effective than FIT in screening for CRCs.[47] However, another study assuming a sensitivity of 35% for FIT did show similar cost-effectiveness for the two strategies.[49] Another study reached the same conclusion using a sensitivity of 42% for detection of advanced adenoma for FIT.[50] Therefore, it seems that the relative cost-effectiveness of two tests can be changed based on which number 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 to 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 to 28.0% in the FIT outreach group ($P<0.001$).[51]

On the other hand, multiple studies have shown higher sensitivity of FIT for CRC and much lower sensitivity for the detection of advanced adenoma.[41-43] One should consider major comorbidities and mortality due to late or even early diagnosis of CRC as compared to adenoma since an adenoma is usually treated by an endoscopic resection without the need for surgical intervention and/or chemotherapy or radiation 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 requires 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, this study provided a more realistic estimation of the sensitivity and specificity of FIT as a screening modality to be used in new cost-effectiveness analyses to determine if current guidelines and policies by associations and health jurisdictions need to be revised accordingly.

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Author Contributions

Mohammad Yaghoobi: Conceptualization, data curation, formal analysis, supervision, verifying 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.

Conflict of Interest

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

Ethical Approval

There is nothing to be declared.

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