ANTICANCER RESEARCH *42*: 3557-3567 (2022)
doi:10.21873/anticanres.15842

Site-specific Performance of ColonView (CV) Fecal Immunochemical Test (FIT) With Differences Between Proximal and Distal Colorectal Adenoma

MAARET ESKELINEN[1*], JANNICA MEKLIN[1*], DENISE PEIXOTO GUIMARAES[2], TUOMAS SELANDER[3], TAPANI TIUSANEN[4], KARI SYRJÄNEN[2,5] and MATTI ESKELINEN[1]

[1]*Department of Surgery, Kuopio University Hospital and School of Medicine, University of Eastern Finland, Kuopio, Finland;*
[2]*Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, Brazil;*
[3]*Science Service Center, Kuopio University Hospital, Kuopio, Finland;*
[4]*Department of Clinical Research, Biohit Oyj, Helsinki, Finland;*
[5]*SMW Consultants, Ltd., Kaarina, Finland*

Abstract. *Background/Aim: The aim of this study was to assess the diagnostic accuracy (DA) of a ColonView (CV) test in proximal versus distal colorectal adenoma (pCRA versus dCRA). Patients and Methods: The colorectal neoplasia (CRN) screening cohort included 5,090 individuals and 506/5,090 (10%) were eligible for the study. Finally, only 127/506 were included in the CRA analysis and hierarchical summary ROC (HSROC) curves were used to show the pooled overall DA of visually analyzed (VA) and automatically analyzed (AA) techniques in pCRA and dCRA detection. Results: The overall specificity (Sp) of the AA technique for the pCRA and dCRA endpoint was 46% and 43%, respectively. The most sensitive AA test in pCRA patients showed 76% sensitivity (Se) versus 58% Se in dCRA patients. In the HSROC analysis, area under the curve (AUC) values were as follows: i) VA in pCRA: AUC=0.503, ii) AA in pCRA: AUC=0.560, iii) VA in dCRA: AUC=0.552 and iv) AA in dCRA: AUC=0.486. In Roccomp analysis, the statistically significant AUC values were available between VA and AA reading modes in pCRA (p=0.044) and in AA reading between pCRA and dCRA (p=0.024). Conclusion: As compared with the CRC endpoint, the DA value of the CV test is far inferior for the CRA endpoint, as determined by the AUC values.*

Colorectal cancer (CRC) is the second most common cause of cancer death in Western countries, although, many of these cancer deaths could be avoided by effective early diagnosis by programmed colorectal neoplasia (CRN) screening. Therefore, European Commission guidelines recommend CRN screening for every European citizen from 50 years of age (1). In order to make CRN screening as efficient as possible, European Guidelines recommend tireless efforts on appropriate quality assurance at all levels (1). The ideal test for CRN screening would be a biochemical test sensitive and specific for both colorectal adenoma (CRA) and CRC, which could be easily collected and transported to the laboratory for accurate automated analysis. Because none of the currently available tests fully meet all these criteria in programmed CRN screening, we have here analyzed the diagnostic accuracy (DA) of a new-generation fecal immunochemical test (FIT), ColonView® (CV) quick test (2-4).

There is recently published evidence that the DA of fecal occult blood tests (FOBTs) could be site-specific depending on the location of colorectal neoplasia (CRN) (5-8). Although, the CV test was included in one of these analyses (8), it is yet unclear how the site-specificity of CRAs would influence the DA of the CV test in CRN screening. In addition, several studies have shown that proximal CRAs significantly enhance the risk of CRC by 2-fold (9-11). The present study is the first to analyze the DA of the two reading techniques of the CV test: Visual analysis (VA) and automatic analysis (AA) using

*These Authors contributed equally to this study.

Correspondence to: Matti Eskelinen, MD, Ph.D., School of Medicine, University of Eastern Finland, P.O. Box 100, FI-70029 KYS, Finland. Tel: +358 17173311, Fax: +358 17172611, GSM: +358 400969444, e-mail: matti.eskelinen@kuh.fi

Key Words: Fecal occult blood, fecal immunochemical test, FIT, colorectal adenoma screening, sensitivity, specificity, false negative, false positive, ROC, HSROC.

proximal and distal CRAs (pCRA and dCRA) were used as the endpoint in colonoscopy-referral patients for detection of CRN.

Patients and Methods

Flow-chart of the study shows the trial protocol and number of patients included in the study (Figure 1). The CRN screening cohort included 5,090 individuals and 506/5,090 (10%) were eligible for the study. Finally, only 127/506 were included in the CRA analysis. Detailed description of the study design and protocol was provided in previous reports by Meklin *et al*. (3, 4).

Sample collection, processing, and interpretation of results. A new-generation FIT, CV test (Biohit Oyj, Helsinki, Finland) does not necessitate any preparatory steps of the patient or compliance with any restrictions in the daily diet or medication. The guaiac-based FOBT (Hemoccult SENSA, Beckman Coulter Inc., Pasadena, CA, USA) was used as the reference test in this study. The sample collection protocols of both tests were described in more detail recently (2).

For the CV, two optional reading techniques are available: VA and AA. The latter is performed by using opTrilyzer Lateral flow reader (Chembio Diagnostics GmbH, Berlin, Germany), as described before (2). In fully compliant patients, three stool samples were tested by CV and the result was interpreted positive if any of the three samples tested positive for either haemoglobin (Hb) or Haemoglobin/Haptoglobin (Hb/Hp) complex. The analytical sensitivity for CV Hb is 15 ng/ml, and for CV Hb/Hp complex, 4 ng/ml (2). Normal colonoscopy was used as the gold standard indicating a negative result regarding the study endpoints, as described before (2).

Statistical analysis. STATA/SE version 17.0 (StataCorp, College Station, TX, USA) was used for analysis. The statistical tests presented were two-sided, and p-value <0.05 was considered statistically significant. Using 2×2 tables, sensitivity (Se) and specificity (Sp) with 95% confidence intervals (95%CI) for each test was determined. The study protocols of receiver operating characteristic (ROC) analysis and meta-analytical technique (metaprop; STATA) used in this study were detailed in previous reports by Meklin *et al*. (3, 4).

Results

The pCRA endpoint with VA tests (Table I, Figure 2 and Figure 3). The Se, Sp, and efficiency of the SENSA test for CRA were 22.8%, 81.3%, and 37.3%, respectively. The Se, Sp, and efficiency of the VA CV Hb and CV Hb/Hp tests for CRA were 50.7/42.9%, 54.2/52.1%, and 51.6/45.2%, respectively. The positive predictive value (PV+) of the CV Hb/Hp VA test was slightly higher than that of the CV Hb VA test (75.8% *vs*. 72.3%). When CV Hb + Hb/Hp VA were used as a test panel for the CRA endpoint, the panel had 50.7% Se, 45.8% Sp, and 49.5% efficiency.

The pCRA endpoint with AA tests (Table II, Figure 4 and Figure 5). The overall Se of the AA reading for pCRA was 63% (95%CI=53-72%) The most sensitive AA test [CV Hb/Hp AA at cut off ≥1.06 reading unit (RU)] showed 76% Se. The overall Sp of the AA reading technique for the pCRA endpoint was 46% (95%CI=36-56%). The two most specific AA tests (CV Hb AA at cut-off ≥10.23 RU, CV Hb AA at cut-off ≥8.44 RU) in pCRA diagnosis showed an Sp range of 51-55%.

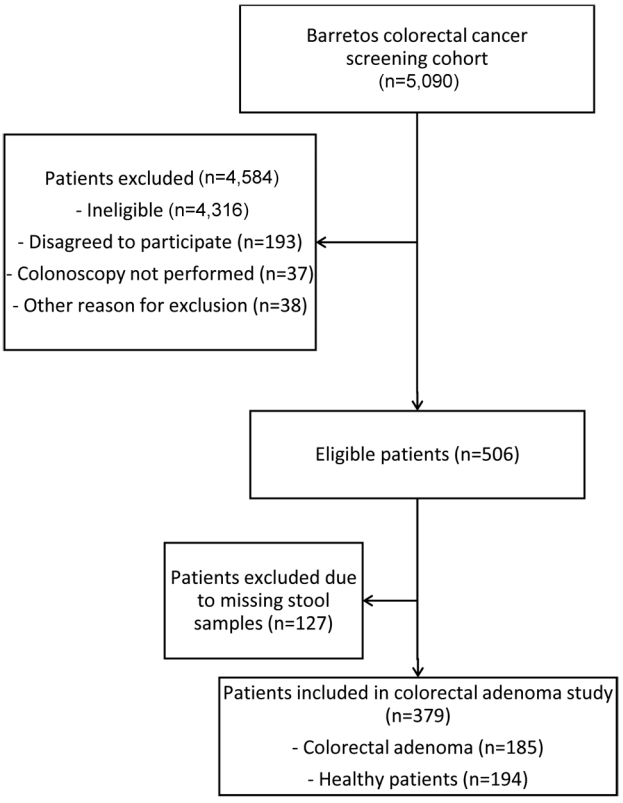

Figure 1. *Flow-chart of the study.*

The dCRA endpoint with VA tests (Table III, Figure 6 and Figure 7). The Se, Sp, and efficiency of the SENSA test for dCRA were 15.4%, 88.6%, and 54.2%, respectively. The Se, Sp, and efficiency of the VA CV Hb and CV Hb/Hp tests for dCRA were 32.5%/45.0%, 71.4%/61.0%, and 52.4%/53.1%, respectively. When CV Hb + Hb/Hp VA were used as a test panel for the CRA endpoint, the panel had 50.0% Se, 61.9% Sp, and 56.1% efficiency. The PV+ of the CV Hb VA test was slightly higher than that of the CV Hb/Hp VA test (52.0% *vs*. 52.9%). The PV+ of the VA reading modes in dCRA patients ranged between 52.0-55.5%.

The dCRA endpoint with AA test (Table III, Figure 8 and Figure 9). The overall Se of the AA reading for dCRA was 55% (95%CI=47-62%). The combination of the two sensitive AA tests (CV Hb AA at cut off ≥6.23 RU) showed 58% Se. The overall Sp of the AA reading technique for the distal CRA endpoint was 43% (95%CI=37-50%). The most specific AA test (CV Hb/Hp AA at cut-off ≥11.83 RU) in distal CRA

Table I. *Visually analyzed screening tests for proximal colorectal adenoma endpoint.*

Test number	Fecal occult blood tests	Positive endpoint (colorectal adenoma)	Negative endpoint (no colorectal adenoma)	TP	FN	FP	TN
VA 1	HemoccultSENSA	Test positive	Test negative	33	112	9	39
VA 2	ColonView Hb VA	Test positive	Test negative	69	67	22	26
VA 3	ColonView Hb/Hp VA	Test positive	Test negative	60	80	23	25
VA 4	ColonView Hb + Hb/Hp VA	One or more sample positive	All samples negative	71	69	26	22

FN: False-negative; FP: false-positive; TN: true negative; TP: true positive; VA: visually analyzed.

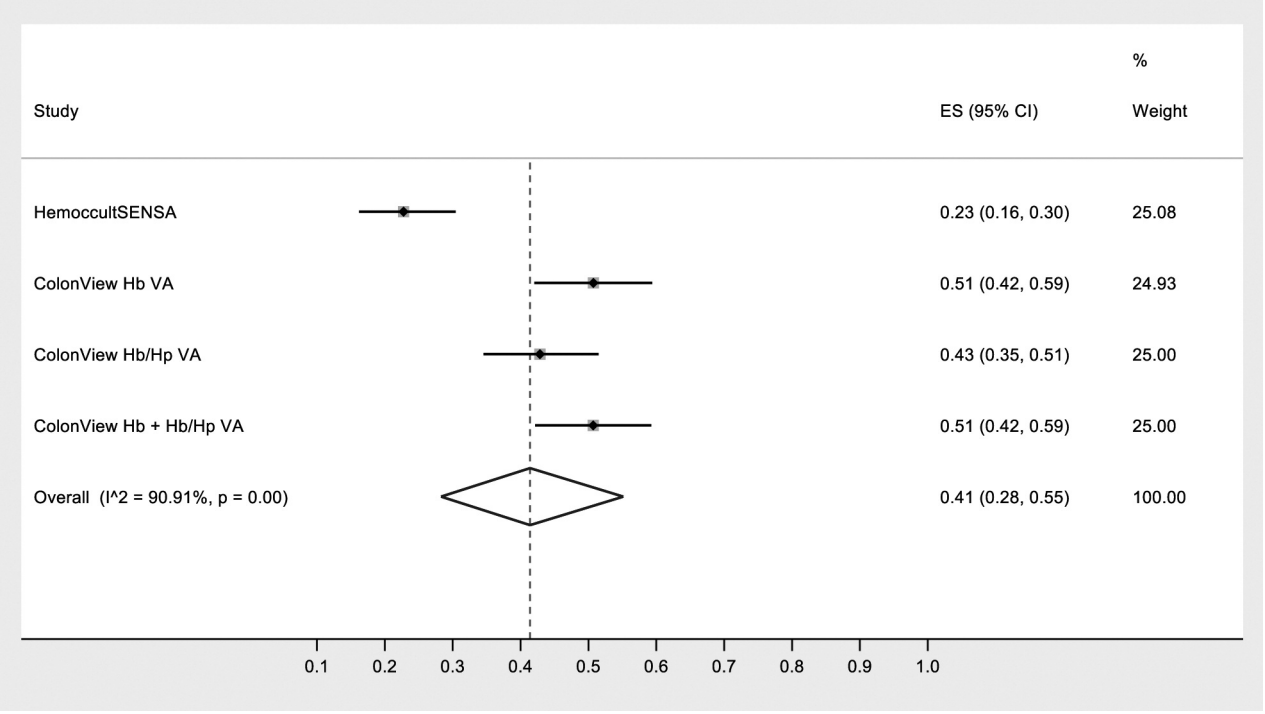

Figure 2. *Sensitivity values of visually analyzed (VA) screening tests for proximal colorectal adenoma endpoint. ES: Estimated sensitivity; CI: confidence interval.*

diagnosis showed 54% Sp. The PV+ of the AA reading techniques in distal CRA patients ranged between 41.4-43.5%.

ROC analysis for pCRA endpoint (Table II). The ROC analysis for pCRA endpoint showed the optimal cut-off value of ≥8.44 RU for CV Hb AA and ≥1.06 RU for CV Hb/Hp AA. Using these cut-offs, the Se, Sp, and efficiency of the CV Hb AA and CV Hb/Hp AA tests for CRA were 61.7/75.8%, 50.9/32.1%, and 58.9/64.8%, respectively. The PV+ of CV Hb AA was similar than that of test CV Hb/Hp AA; 78.5% *vs*. 76.8%.

ROC analysis for dCRA endpoint (Table IV). The ROC analysis for the dCRA endpoint showed the optimal cut-off value of ≥6.23 RU for CV Hb AA and ≥11.83 RU for CV Hb/Hp AA. Using these cut-offs, the Se, Sp, and efficiency of the CV Hb AA and CV Hb/Hp AA tests for CRA were 58.1/46.5%, 40.4/53.6%, and 48.0/50.5%, respectively. The PV+ of CV Hb AA was similar to that of test CV Hb/Hp AA; 42.4% *vs*. 43.5%.

HSROC and area under the curve (AUC) values. HSROC curves were used to visualize the pooled DA of VA and AA techniques in pCRA and dCRA. In the HSROC analysis, the AUC values were as follows: i) VA in pCRA: AUC=0.503 (95%CI=0.450-0.550) (Figure 10), ii) AA in pCRA: AUC=0.560 (95%CI=0.0512-0.614) (Figure 11), iii) VA in dCRA: AUC=0.552 (95%CI=0.480-0.623) (Figure 12) and

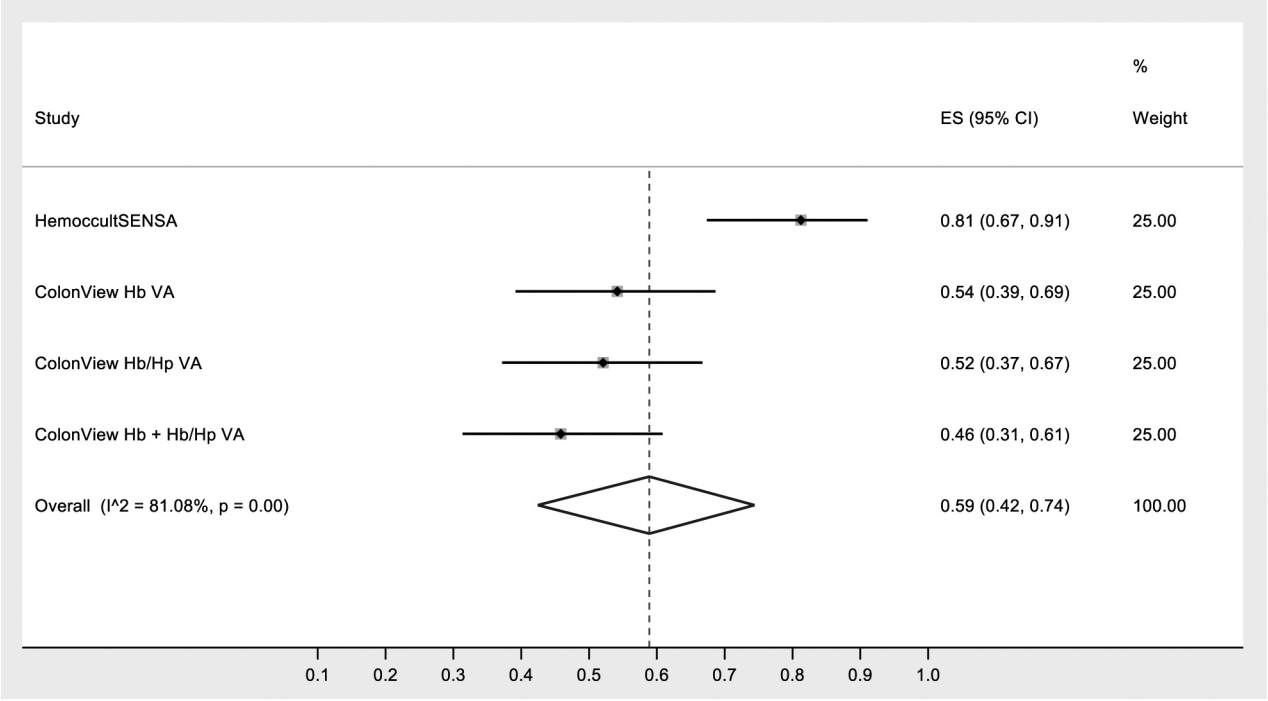

Figure 3. *Specificity values of visually analyzed (VA) screening tests for proximal colorectal adenoma endpoint. ES: Estimated specificity; CI: confidence interval.*

Table II. *Automatically analyzed screening tests for proximal colorectal adenoma endpoint.*

Test number	Fecal occult blood tests	Positive endpoint (colorectal adenoma)	Negative endpoint (no colorectal adenoma)	TP	FN	FP	TN
AA 1	ColonView Hb AA	≥10.23 (median)	<10.23 (median)	88	66	24	29
AA 2	ColonView Hb/Hp AA	≥5.96 (median)	<5.96 (median)	86	71	28	25
AA 3	ColonView Hb AA	≥8.44 (ROC)	<8.44 (ROC)	95	59	26	27
AA 4	ColonView Hb/Hp AA	≥1.06 (ROC)	<1.06 (ROC)	119	38	36	17

FN: False-negative; FP: false-positive; TN: true negative; TP; true positive; AA: automatically analyzed.

iv) AA in dCRA: AUC=0.486 (95%CI=0.410-0.562) (Figure 13). In Roccomp analysis, statistical significance of the differences in AUC values was: VA *vs*. AA in pCRA p=0.044; VA in pCRA *vs*. VA in dCRA p=0.166; VA in pCRA *vs*. AA in dCRA p=0.679; AA in pCRA *vs*. VA in dCRA p=0.882; AA in pCRA *vs*. AA in dCRA p=0.024; and VA *vs*. AA in dCRA p=0.098.

Discussion

The present investigation is the first where the DA of the two reading techniques of the CV test: VA and AA for proximal and distal CRA were used as the endpoint in colonoscopy-referral patients for detection of CRN. This study was also extended by applying HSROC analysis to test the different cut-offs and to assess the DA of the CV test. Despite the large cohort (n=5,090) of subjects originally screened, 90% of the study patients (n=4,584) were excluded, and only 506/5,090 (10%) were eligible for the study. Finally, only 127/506 were included in the present CRA analysis.

The vast literature on FOB tests was recently subjected to review by Meklin *et al*. (12, 13). In total, 33 studies fulfilled all the inclusion criteria and were eligible for this meta-analysis. Meklin *et al*. (12, 13) decided to conduct their meta-analysis using CRC as the only study endpoint, because the reporting practices of CRAs in different studies were heterogeneous (12, 13). The Hb/Hp complex plays an important role in the retrieval of Hb from the lysed

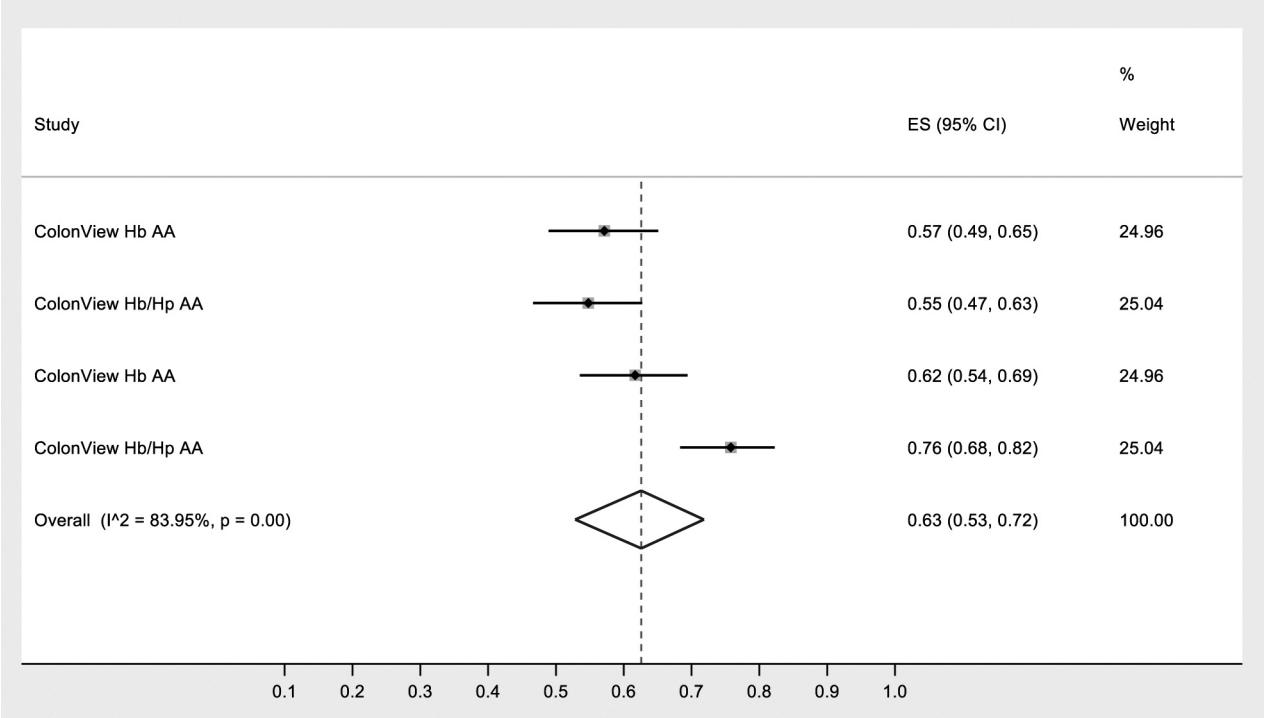

Figure 4. *Sensitivity values of automatically analyzed (AA) screening tests for proximal colorectal adenoma endpoint. ES: Estimated sensitivity; CI: confidence interval.*

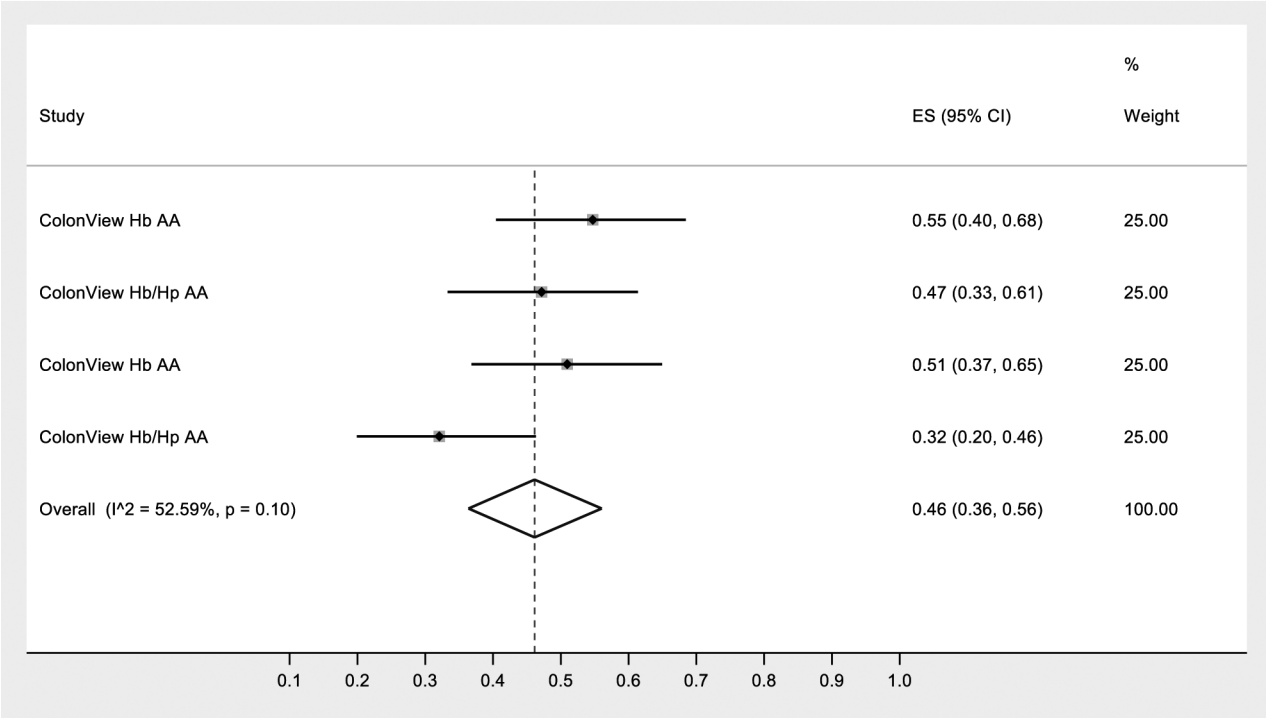

Figure 5. *Specificity values of automatically analyzed (AA) screening tests for proximal colorectal adenoma endpoint. ES: Estimated specificity; CI: confidence interval.*

Table III. *Visually analyzed screening tests for distal colorectal adenoma endpoint.*

Test number	Fecal occult blood tests	Positive endpoint (colorectal adenoma)	Negative endpoint (no colorectal adenoma)	TP	FN	FP	TN
VA 1	HemoccultSENSA	Test positive	Test negative	6	33	5	39
VA 2	ColonView Hb VA	Test positive	Test negative	13	27	12	30
VA 3	ColonView Hb/Hp VA	Test positive	Test negative	18	22	16	25
VA 4	ColonView Hb + Hb/Hp VA	One or more sample positive	All samples negative	20	20	16	26

FN: False-negative; FP: false-positive; TN: true negative; TP; true positive; VA: visually analyzed.

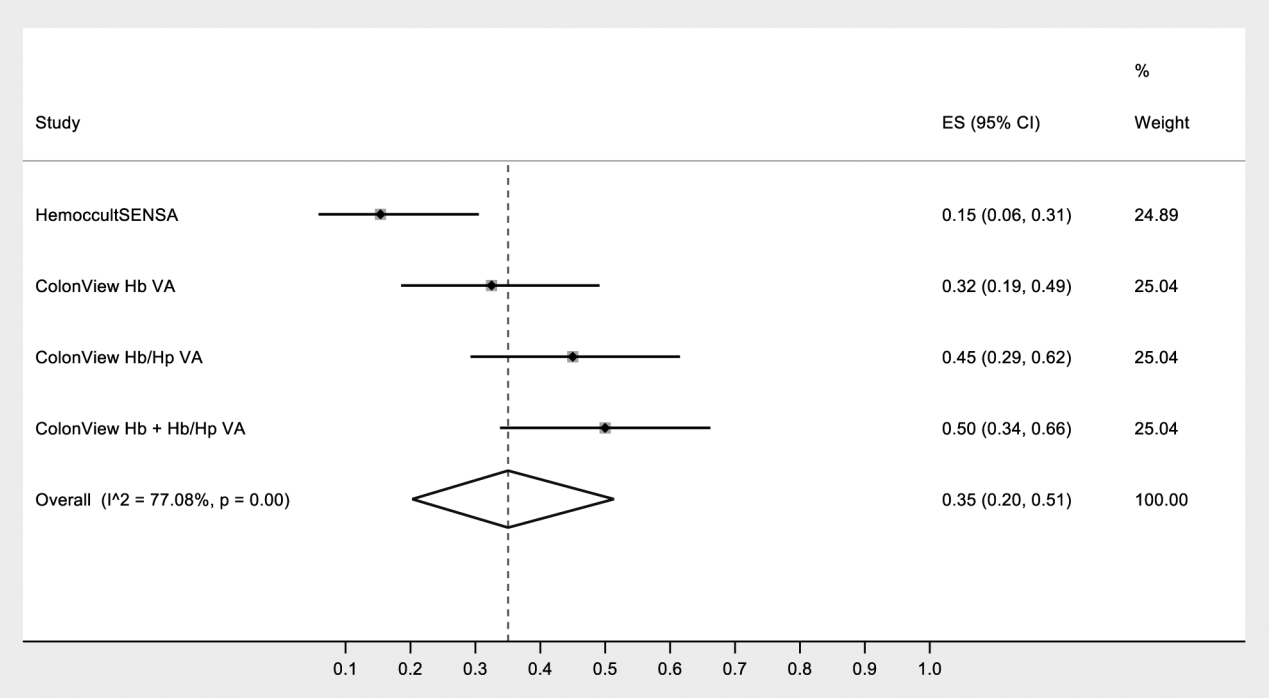

Figure 6. *Sensitivity values of visually analyzed (VA) screening tests for distal colorectal adenoma endpoint. ES: Estimated sensitivity; CI: confidence interval.*

erythrocytes and, importantly, this complex is stable resisting acid and proteolytic degradation. This means that the Hb/Hp complex can be detected even at longer time points in the bowel, thus increasing the chance that blood derived from pCRAs to be detected in the stool sample (14, 15). Among the CRC patients, changes in the bowel habits, rectal bleeding, and iron deficiency anemia have been shown to have a PV+ of about 3% (16). In addition, Holtedahl *et al.* (16) found that none of the CRC patients with a proximal tumor had rectal bleeding at initial doctor's consultation, but 3/18 (17%) did show this symptom at a later consultation. The National Institute of Health (NIH) guidelines for suspected CRC recognition and referral recommend 3% PV+ cut-off for diagnosing cancer (17).

Of the two tests used in the present study, HemoccultSENSA is based on Hb detection alone, while the CV test detects both Hb and the Hb/Hp complex. Thus, the demonstration of a significantly higher Se of the CV test provides indirect confirmatory evidence to substantiate the observations of Sieg *et al.* (14, 15). To provide direct evidence that detection of the Hb/Hp complex is superior to Hb alone, the performance indicators of the CV test were analyzed here separately for its Hb and Hb/Hp components. In proximal CRA patients, the VA and AA reading modes showed quite similar PV+ values of 72.3-78.6% *versus* 75.4-78.6%, respectively. When the AUC values were compared (roccomp analysis), the AA reading mode showed significantly higher DA in proximal CRA patients (p=0.044), whereas in distal CRA patients, there was no

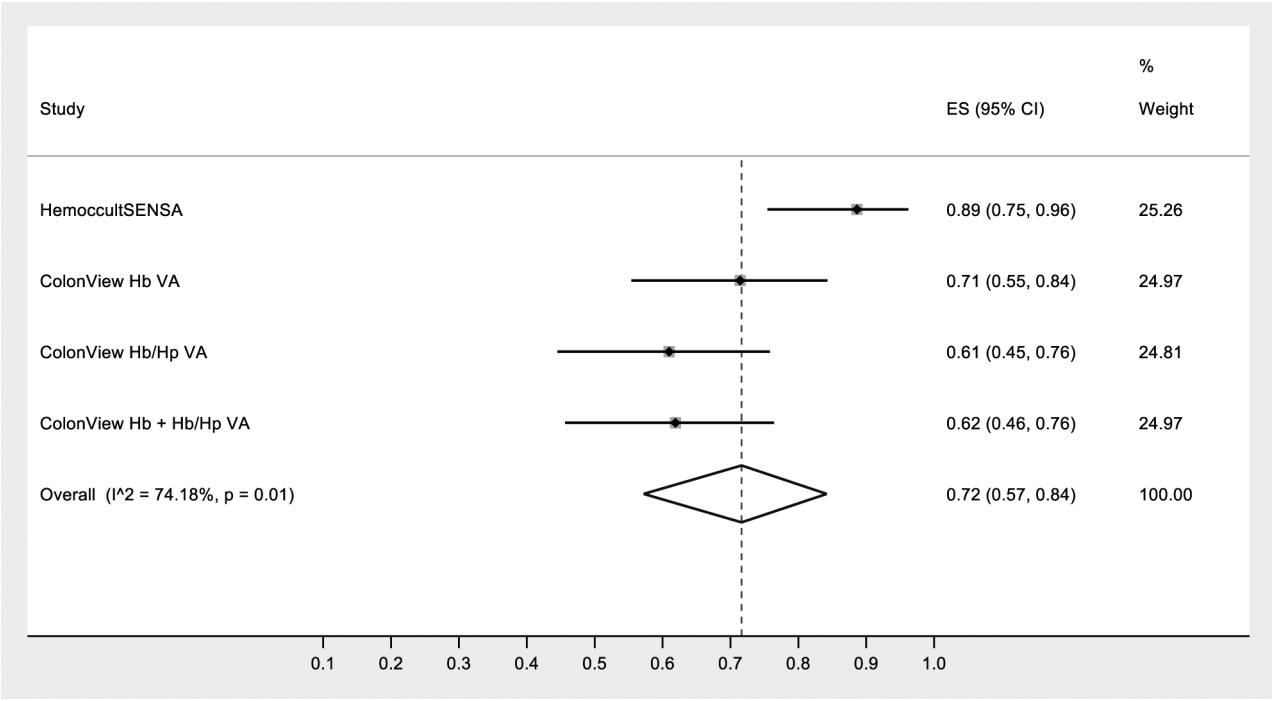

Figure 7. *Specificity values of visually analyzed (VA) screening tests for distal colorectal adenoma endpoint. ES: Estimated specificity; CI: confidence interval.*

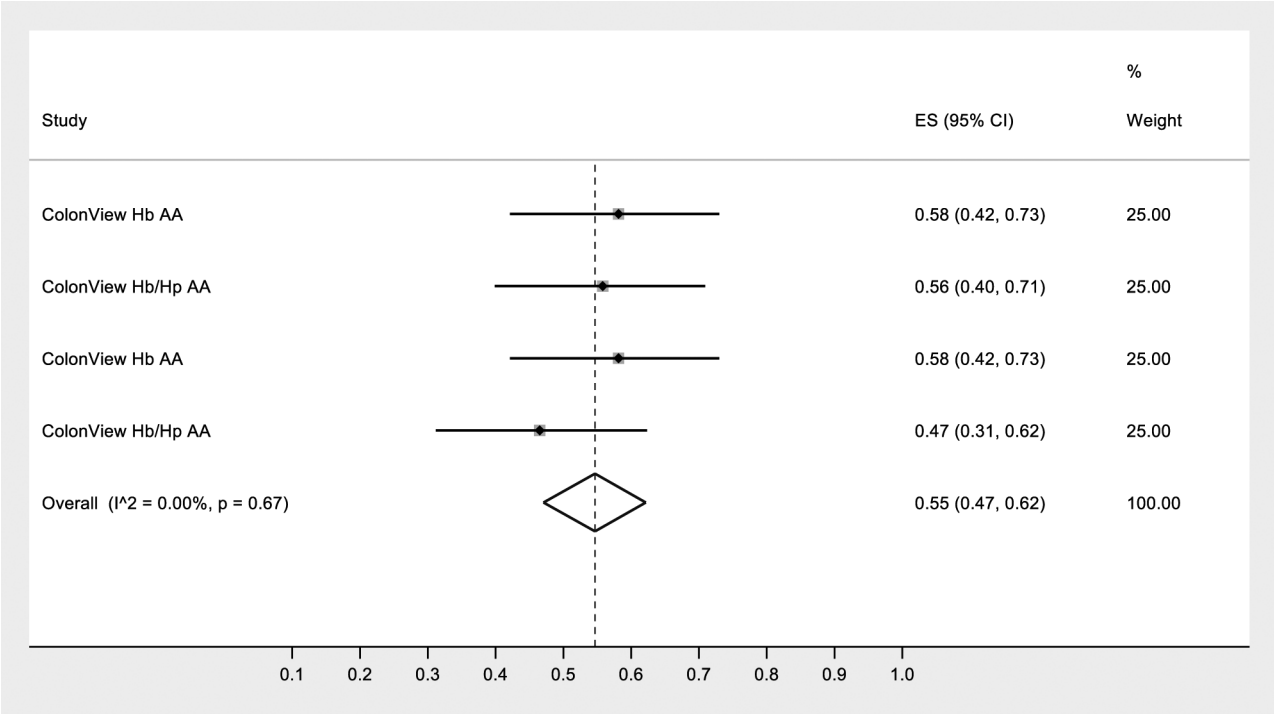

Figure 8. *Sensitivity values of automatically analyzed (AA) screening tests for distal colorectal adenoma endpoint. ES: Estimated sensitivity; CI: confidence interval.*

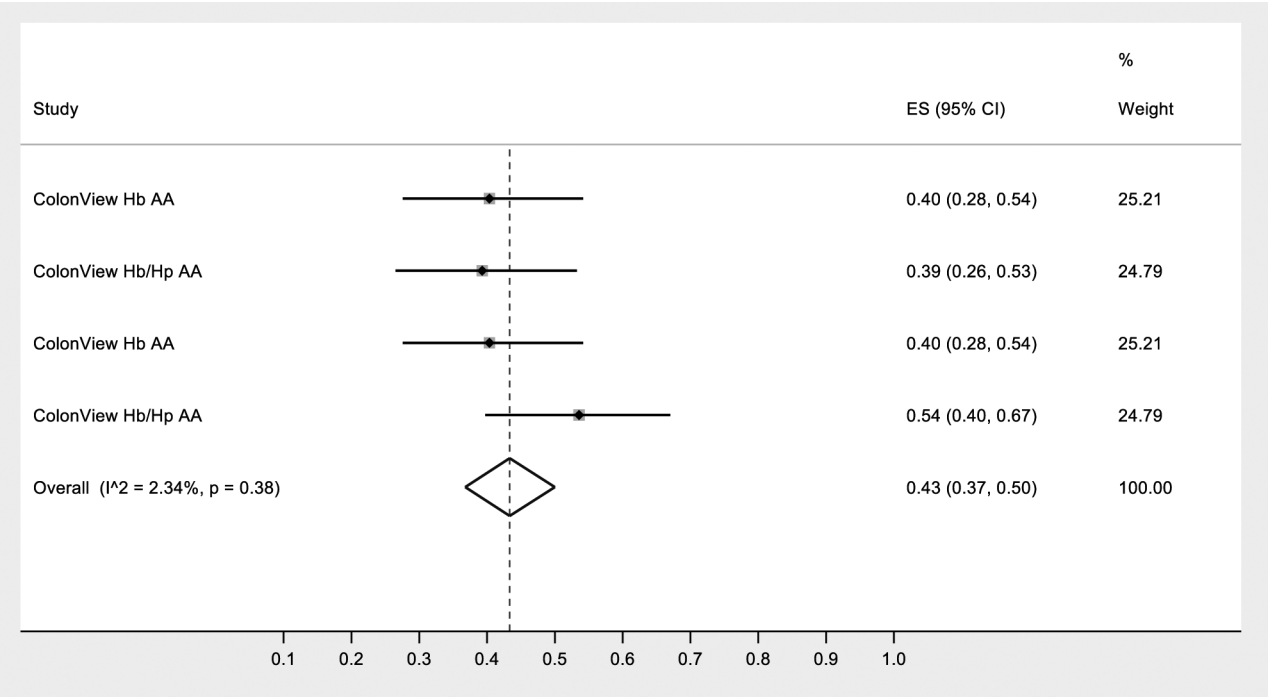

Figure 9. *Specificity values of automatically analyzed (AA) screening tests for distal colorectal adenoma endpoint. ES: Estimated specificity; CI: confidence interval.*

Table IV. *Automatically analyzed screening tests for distal colorectal adenoma endpoint.*

Test number	Fecal occult blood tests	Positive endpoint (colorectal cancer)	Negative endpoint (no colorectal cancer)	TP	FN	FP	TN
AA 1	ColonView Hb AA	≥6.23 (median)	<6.23 (median)	25	18	34	23
AA 2	ColonView Hb/Hp AA	≥7.27 (median)	<7.27 (median)	24	19	34	22
AA 3	ColonView Hb AA	≥6.23 (ROC)	<6.23 (ROC)	25	18	34	23
AA 4	ColonView Hb/Hp AA	≥11.83 (ROC)	<11.83 (ROC)	20	23	26	30

FN: False-negative; FP: false-positive; TN: true negative; TP; true positive; AA: automatically analyzed.

statistically significant difference in AUC values between the VA and AA reading modes (p=0.098). When stratified by the CRA site (proximal *versus* distal), AUC values of the AA reading mode in proximal (AUC=0.560) were significantly higher than those (AUC=0.486) in distal CRA patients (p=0.024). The difference between Hb and Hb/Hp complex was less dramatic for the proximal and distal CRAs. Even if the AA reading mode performs markedly better in proximal than in distal CRAs, the difference between Hb and Hb/Hp complex is less significant. This applies to the comparison between VA reading and AA reading in proximal and distal CRA patients.

Data are unanimous in that CRA significantly increases the risk for subsequent CRC. The risk for CRC among patients with proximal CRA is 1.5-2.5-fold higher compared with the patients having CRA only in the distal colon (8-10). However, it is not yet clear, whether all CRAs and early-stage CRCs bleed and whether they bleed intermittently, depending on the mechanics of the alimentary tract and the passage of the digested food. The variable bleeding may partially explain why the gFOBTs do not show consistently positive test results in CRC patients. Fraser *et al.* (18) used the FOB Gold FIT to show a relationship between increasing FOB concentration and histopathological findings in 375 samples from participants of the Scottish screening population. Similarly, Ciatto *et al.* (19) demonstrated using the OC-SENSOR FIT, that adenomas detected at colonoscopy showed increasing fecal Hb concentration with increasing lesion severity and size.

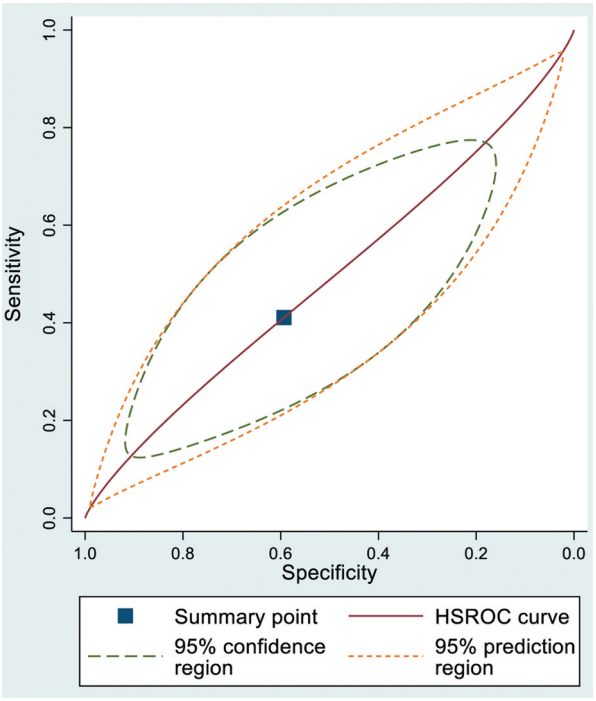

Figure 10. *Hierarchical summary receiver operating characteristic (HSROC) curve of the visually analyzed (VA) screening tests for proximal colorectal adenoma endpoint.*

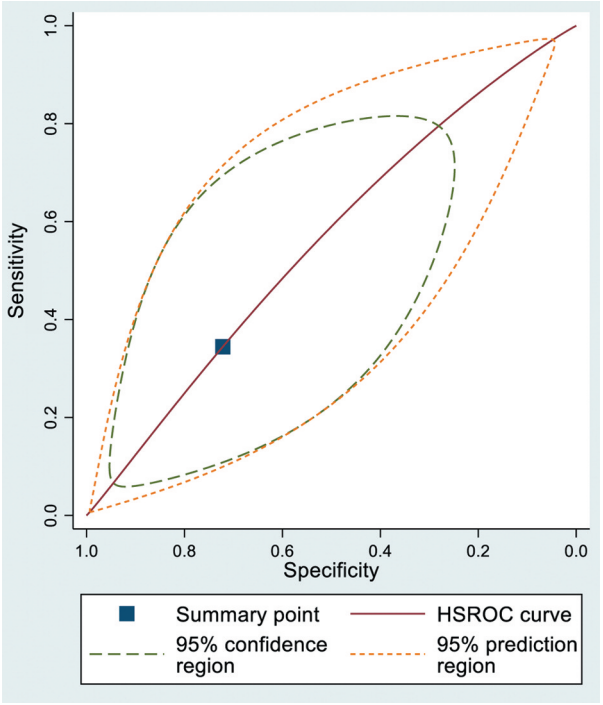

Figure 12. *Hierarchical summary receiver operating characteristic (HSROC) curve of the visually analyzed (VA) screening tests for distal colorectal adenoma endpoint.*

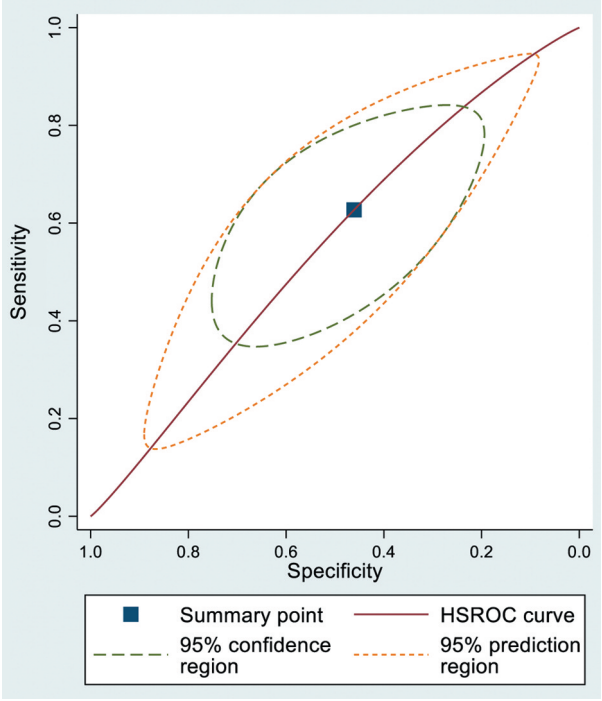

Figure 11. *Hierarchical summary receiver operating characteristic (HSROC) curve of the automatically analyzed (AA) screening tests for proximal colorectal adenoma endpoint.*

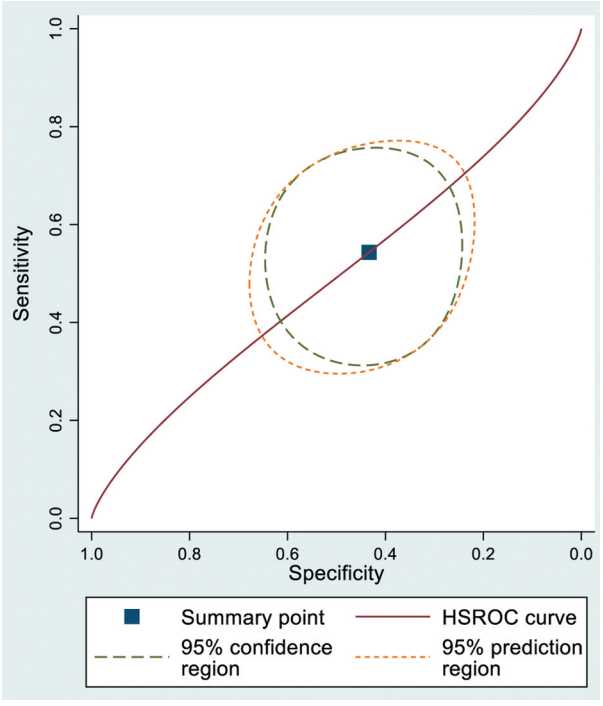

Figure 13. *Hierarchical summary receiver operating characteristic (HSROC) curve of the automatically analyzed (AA) screening tests for distal colorectal adenoma endpoint.*

The stool sample collection process for FOBT procedure should be as simple as possible to encourage screening participation, and the collection instructions need to be clear and practical. Current FOBTs use cardboard and spatulas or plastic probes. Many test devices even accept stool samples taken from toilet tissue paper. Cole *et al*. (20) demonstrated that different stool sampling procedures can change FOBT screening compliance. Similarly, Greenwald *et al*. (21) and Ellis *et al*. (22), in two cross-sectional studies, showed results on the preference among different stool collection devices and the difficulties in collecting stool samples when the sampling instructions are complex.

There is published evidence to suggest that the screening performance of FOBTs depends on the location of CRN (5-8). Haug *et al*. (5) is the only previous study where both Hb and Hb/Hp complex are available. They recruited 1,319 participants of screening colonoscopy (mean age 63 years). Fecal Hb and Hb/Hp levels were measured using an automated RIDASCREEN ELISA test. A total of 130 participants (10%) had an advanced adenoma with AUC of 0.68 for Hb and 0.64 for Hb/Hp (p=0.034). At 95% Sp level, the Se for advanced adenoma was 33% for the Hb test and 24% for the Hb/Hp test. According to the study design, the screening participants collected stool samples into one container and did not use the collection device associated with each test, which may limit the analysis of the participants' ability to use various collection procedures.

Wong *et al*. (23) analyzed a CRC screening program in Canada and used FITs in proximal (n=184) and distal (n=230) CRAs. A limitation of the study is that it does not predict HSROC-based AUC values for the FOBTs. Interestingly, Wong *et al*. (23) concluded that the automated FITs offer advantages to programmed CRC screening such as integration into laboratory information system, high volume capacity analysis, and opportunity for quality control. Hirai *et al*. (6) performed a meta-analysis assessing a DA of FOBTs by the anatomical location of CRC. The AUC values for proximal CRC were 90% (95%CI=87-92%) and for distal CRC 94% (95%CI=92-96%), respectively. This study is limited by the fact that CRAs were not included in the analysis. Lu *et al*. (7) reviewed available CRA studies and found that FITs showed significantly higher AUC values for distal CRA (AUC=0.822) than for the proximal CRA (AUC=0.760) (p=0.023).

Conclusion

HSROC analysis has gained increasing popularity in evaluating the diagnostic performance of diagnostic tests (13). As more than 80% CRCs arise from adenomas, screening for CRAs is effective for both early detection and prevention. Diagnosis of CRCs through screening tends to occur 2-3 years before detection of clinical symptoms. Any CRAs that are detected can be removed, and thus prevent CRAs from turning into CRC. As compared with the CRC endpoint (8), the DA value of the CV test is far inferior for the CRA endpoint, as determined by the AUC values.

Conflicts of Interest

Tapani Tiusanen, PhD, is an employee of Biohit Company, Helsinki, Finland. The other Authors have no conflicts of interest or financial ties to disclose.

Authors' Contributions

All Authors contributed to the collection and analysis of data, drafting, and revising the manuscript, and read and approved the final article.

Acknowledgements

The study was funded by the Päivikki and Sakari Sohlberg Foundation, Helsinki, Finland.

References

1 Minozzi S, Armaroli P and Segnan N: Principles of evidence assessment and methods for reaching recommendations. *In*: European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis. Segnan N, Patrick J and von Karsa L (eds.). Luxemburg, Publications Office of the European Union, 2010.

2 Guimarães DP, Fregnani JH, Reis RM, Taveira LN, Scapulatempo-Neto C, Matsushita M, Silva SRM, Oliveira CZ, Longatto-Filho A, Eklund C, Paloheimo L, Mauad E, Suovaniemi O and Syrjänen K: Comparison of a new-generation fecal immunochemical test (FIT) with guaiac fecal occult blood test (gFOBT) in detecting colorectal neoplasia among colonoscopy-referral patients. Anticancer Res *39(1)*: 261-269, 2019. PMID: 30591467. DOI: 10.21873/anticanres.13106

3 Meklin J, Eskelinen M, Guimaraes DP, Selander T, Inkinen J, Tiusanen T, Syrjänen K and Eskelinen M: The new generation immunochemical test for fecal occult blood (ColonView Quick Test) shows a high diagnostic accuracy in colorectal cancer detection. Anticancer Res *41(10)*: 5071-5079, 2021. PMID: 34593457. DOI: 10.21873/anticanres.15323

4 Meklin J, Eskelinen M, Guimaraes DP, Selander T, Tiusanen T, Syrjänen K and Eskelinen M: The Automatically Analyzed (AA) ColonView (CV) quick test for fecal occult blood shows higher diagnostic accuracy in detection of colorectal adenoma than visually analyzed tests. Anticancer Res *41(11)*: 5517-5525, 2021. PMID: 34732422. DOI: 10.21873/anticanres.15365

5 Haug U, Hundt S and Brenner H: Quantitative immunochemical fecal occult blood testing for colorectal adenoma detection: evaluation in the target population of screening and comparison with qualitative tests. Am J Gastroenterol *105(3)*: 682-690, 2010. PMID: 19953091. DOI: 10.1038/ajg.2009.668

6 Hirai HW, Tsoi KK, Chan JY, Wong SH, Ching JY, Wong MC, Wu JC, Chan FK, Sung JJ and Ng SC: Systematic review with meta-analysis: faecal occult blood tests show lower colorectal

cancer detection rates in the proximal colon in colonoscopy-verified diagnostic studies. Aliment Pharmacol Ther *43(7)*: 755-764, 2016. PMID: 26858128. DOI: 10.1111/apt.13556

7 Lu M, Luo X, Li N, Chen H and Dai M: Diagnostic accuracy of fecal occult blood tests for detecting proximal *versus* distal colorectal neoplasia: a systematic review and meta-analysis. Clin Epidemiol *11*: 943-954, 2019. PMID: 31695506. DOI: 10.2147/CLEP.S213677

8 Eskelinen M, Meklin J, Guimarães DP, Selander T, Tiusanen T, Syrjänen K and Eskelinen M: The ColonView (CV) quick test for fecal occult blood shows significantly higher diagnostic accuracy in detecting distal than proximal colorectal cancer. Anticancer Res *42(4)*: 1879-1891, 2022. PMID: 35347006. DOI: 10.21873/anticanres.15664

9 Alberts DS, Martínez ME, Roe DJ, Guillén-Rodríguez JM, Marshall JR, van Leeuwen JB, Reid ME, Ritenbaugh C, Vargas PA, Bhattacharyya AB, Earnest DL and Sampliner RE: Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network. N Engl J Med *342(16)*: 1156-1162, 2000. PMID: 10770980. DOI: 10.1056/NEJM200004203421602

10 Laiyemo AO, Pinsky PF, Marcus PM, Lanza E, Cross AJ, Schatzkin A and Schoen RE: Utilization and yield of surveillance colonoscopy in the continued follow-up study of the polyp prevention trial. Clin Gastroenterol Hepatol *7(5)*: 562-7; quiz 497, 2009. PMID: 19138760. DOI: 10.1016/j.cgh.2008.12.009

11 Martínez ME, Baron JA, Lieberman DA, Schatzkin A, Lanza E, Winawer SJ, Zauber AG, Jiang R, Ahnen DJ, Bond JH, Church TR, Robertson DJ, Smith-Warner SA, Jacobs ET, Alberts DS and Greenberg ER: A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. Gastroenterology *136(3)*: 832-841, 2009. PMID: 19171141. DOI:10.1053/j.gastro.2008.12.007

12 Meklin J, Syrjänen K and Eskelinen M: Colorectal cancer screening with traditional and new-generation fecal immunochemical tests: a critical review of fecal occult blood tests. Anticancer Res *40(2)*: 575-581, 2020. PMID: 32014898. DOI: 10.21873/anticanres.13987

13 Meklin J, Syrjänen K and Eskelinen M: Fecal occult blood tests in colorectal cancer screening: systematic review and meta-analysis of traditional and new-generation fecal immunochemical tests. Anticancer Res *40(7)*: 3591-3604, 2020. PMID: 32620599. DOI: 10.21873/anticanres.14349

14 Sieg A, Scheida M, John MR, Hertel A, Schröter M, Lüthgens K and Schmidt-Gayk H: Validity of new immunological human fecal hemoglobin and albumin tests in detecting colorectal neoplasms – an endoscopy-controlled study. Z Gastroenterol *36(6)*: 485-490, 1998. PMID: 9675833.

15 Sieg A, Thoms C, Lüthgens K, John MR and Schmidt-Gayk H: Detection of colorectal neoplasms by the highly sensitive hemoglobin-haptoglobin complex in feces. Int J Colorectal Dis *14(6)*: 267-271, 1999. PMID: 10663892. DOI: 10.1007/s00384 0050226

16 Holtedahl K, Borgquist L, Donker GA, Buntinx F, Weller D, Campbell C, Månsson J, Hammersley V, Braaten T and Parajuli R: Symptoms and signs of colorectal cancer, with differences between proximal and distal colon cancer: a prospective cohort study of diagnostic accuracy in primary care. BMC Fam Pract *22(1)*: 148, 2021. PMID: 34238248. DOI: 10.1186/s12875-021-01452-6

17 Suspected cancer: recognition and referral. London, National Institute for Health and Care Excellence (NICE), 2021. Available at: https://www.ncbi.nlm.nih.gov/books/NBK555330 [Last accessed on June 13, 2022]

18 Fraser CG, Mathew CM, McKay K, Carey FA and Steele RJ: Automated immunochemical quantitation of haemoglobin in faeces collected on cards for screening for colorectal cancer. Gut *57(9)*: 1256-1260, 2008. PMID: 18467371. DOI: 10.1136/gut.2008.153494

19 Ciatto S, Martinelli F, Castiglione G, Mantellini P, Rubeca T, Grazzini G, Bonanomi AG, Confortini M and Zappa M: Association of FOBT-assessed faecal Hb content with colonic lesions detected in the Florence screening programme. Br J Cancer *96(2)*: 218-221, 2007. PMID: 17211476. DOI: 10.1038/sj.bjc.6603534

20 Cole SR, Young GP, Esterman A, Cadd B and Morcom J: A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. J Med Screen *10(3)*: 117-122, 2003. PMID: 14561262. DOI: 10.1177/096914130301000304

21 Greenwald B: A pilot study evaluating two alternate methods of stool collection for the fecal occult blood test. Medsurg Nurs *15(2)*: 89-94, 2006. PMID: 16700247.

22 Ellis RJ, Wilson S, Holder RL and McManus RJ: Different faecal sampling methods alter the acceptability of faecal occult blood testing: a cross sectional community survey. Eur J Cancer *43(9)*: 1437-1444, 2007. PMID: 17475476. DOI: 10.1016/j.ejca.2007.03.019

23 Wong CK, Fedorak RN, Prosser CI, Stewart ME, van Zanten SV and Sadowski DC: The sensitivity and specificity of guaiac and immunochemical fecal occult blood tests for the detection of advanced colonic adenomas and cancer. Int J Colorectal Dis *27(12)*: 1657-1664, 2012. PMID: 22696204. DOI: 10.1007/s00384-012-1518-3

Received April 4, 2022
Revised June 12, 2022
Accepted June 14, 2022