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The ColonView (CV) Quick Test for Fecal Occult Blood Shows Significantly Higher Diagnostic Accuracy in Detecting Distal than Proximal Colorectal Cancer

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Abstract. *Aim: The present study compared the accuracy of ColonView (CV) quick test in detecting proximal versus distal colorectal cancer (CRC). A traditional guaiac-based fecal occult blood test (gFOBT) (Hemoccult SENSA) was used as a reference. Patients and Methods: A cohort of 368 colonoscopy-referral patients were asked to collect 3 consecutive fecal samples, to be analyzed by both assays (CV, SENSA). Receiver operating characteristic (ROC) analysis was used to find the optimal cut-off values for both Hb and Hb/Hp of the CV test. Summary hierarchical ROC (HSROC) curves were used to visualize the pooled overall accuracy of visually analysed (VA) and automatically analyzed (AA) reading modes in proximal and distal CRC detection. Results: The overall specificity (Sp) of the AA reading mode for the proximal CRC and distal CRC endpoint was 73% and 76%, respectively. For proximal CRC, the two most sensitive AA tests showed 90% sensitivity (Se), while for distal CRC, the two most sensitive AA tests showed 100% Se. In the HSROC analysis, the AUC values were as follows: i) VA in proximal CRC: 0.765, ii) AA in proximal CRC: 0.878, iii) VA in distal CRC: 0.955 and iv) AA in distal CRC: 0.961. In roccomp analysis, AUC values were significantly different in: VA vs. AA in proximal CRC p=0.009; VA in proximal vs. VA in distal CRC p<0.0001; VA in proximal vs. AA in distal CRC p<0.0001; AA in proximal vs. VA in distal CRC p=0.021; AA in proximal CRC vs. AA in distal CRC p=0.006. Conclusion: The applicability of the CV test (a new-generation FIT) in CRC screening was confirmed. The AA reading was superior to VA (or SENSA) in its diagnostic accuracy in detecting proximal CRC patients. Distal CRCs were more accurately detected than proximal CRCs by both reading modes.*

Colorectal cancer (CRC) is the third common cancer and fourth common cause of cancer-related death worldwide with 1,850 000 new cases and 880,000 deaths occurring in 2018 (1). European Guidelines (2) based on previous randomized trials suggest that annual or biennial fecal occult blood (FOB) screening associated with a 15-33% decrease in CRC mortality rates (2-4).

Bleeding in colorectal neoplasms (CRN) is usually intermittent with varying in degree and therefore FOB and Hb is measured using either simple guaiac-based fecal occult blood tests (gFOBTs) or more recently introduced fecal immunochemical tests (FITs) (2-4). A significant technical enhancement is achieved by using an antibody specific to human globin, the protein component of Hb. Immunochemical test technology (FITs) enables detection of bleeding and Hb at lower concentrations than gFOBTs and therefore have several advantages, including improved clinical performance and higher efficiency by detecting smaller CRN with intermittent bleeding (2-4). In several modern FITs the cut-off concentrations are adjusted with a reader device and such

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Key Words: Fecal immunochemical test, FIT, colorectal cancer screening, ROC, proximal colon, distal colon.

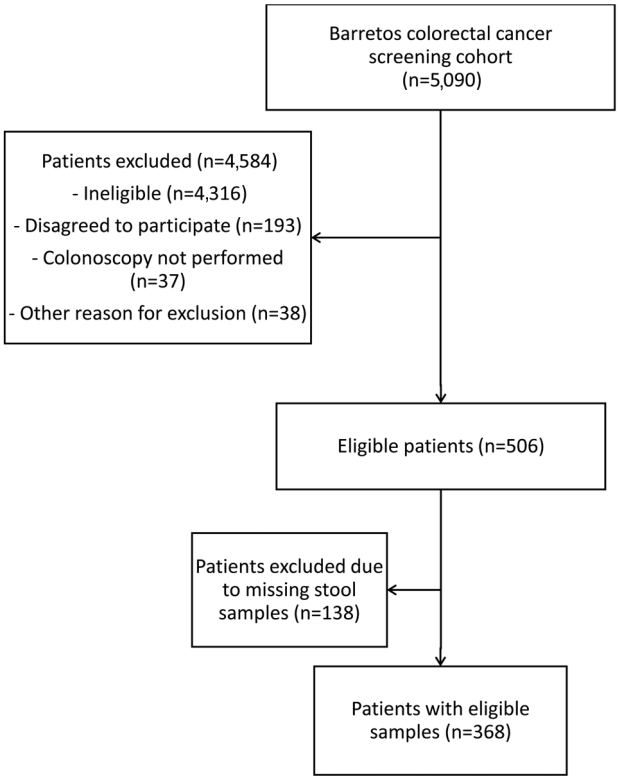

Figure 1. *Flow-chart of the study.*

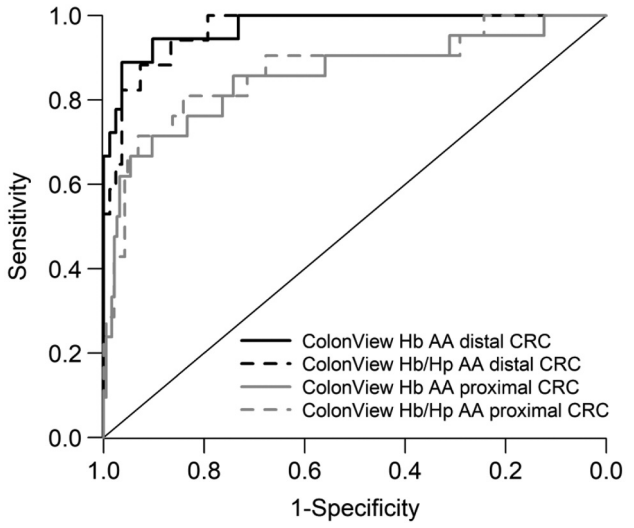

Figure 2. *Receiver operating characteristic (ROC) curve for test optimization and finding optimal cut-off point for automatically analyzed (AA) ColonView (CV) Hb and Hb/Hp tests in proximal and distal colorectal cancer (CRC) endpoints.*

device can provide possibility to automate the test process (2). The latest development in this field represents a second-generation FIT test (ColonView® quick test) (CV), having the advantage of measuring two components of FOB; Hb and Hb/Hp complex (3-4).

There is increasing evidence suggesting that the diagnostic performance of FOBTs may depend on the anatomical site of CRC, as discussed in three recent reviews (6-8). Unfortunately, the CV test was not included in these analyses; however, the present study is the first where the diagnostic accuracy of the CV test was compared in detection of the proximal and distal CRCs. This analysis was extended by applying hierarchical summary receiver operating characteristic (HSROC) analysis to test the different cut-offs and to assess the diagnostic performance of the CV test in colonoscopy-referral screening patients.

Patients and Methods

The Barretos Cancer Hospital (BCH) colorectal neoplasia (CRN) screening cohort included 5,090 individuals (Figure 1). Detailed description of all detected lesions was provided, including their number, size and exact locations: *proximal* (from cecum to splenic flexure) or distal (descending colon to rectum). The study protocol and inclusion/exclusion criteria of study patients were detailed in a previous report by Guimaraes *et al*. (9).

Sample collection, processing, and interpretation of results. A new-generation FIT, ColonView® quick test (CV) (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 traditional FOBT (Hemoccult SENSA, Beckman Coulter Inc., Pasadena, CA, USA) was used as the reference in this study. The sample collection protocol of both tests was described in more detail recently (9).

For the CV test, two optional reading modes are available: visual analysis (VA) and automatic analysis (AA). The latter is performed by using opTrilyzer Lateral flow reader (Chembio Diagnostics GmbH, Berlin, Germany), as described before (9-10). The analytical sensitivity for CV Hb is 15 ng/ml, and for CV Hb/Hp complex, 4 ng/ml (11, 12).

Statistical analysis. STATA/SE version 17.0 (StataCorp, College Station, TX, USA) and MetaDiSc software 1.4 (Meta Analysis of Diagnostic and Screening Test; Unit of Clinical Biostatistics team of the Ramón y Cajal Hospital, Madrid, Spain) were used for analysis. The statistical tests performed were two-sided, and p-values <0.05 were considered statistically significant. Using 2×2 tables, sensitivity (Se) and specificity (Sp) with 95% confidence intervals (95% CI) for each FOB test was determined. Conventional receiver operating characteristic (ROC) analysis was used to graph for Se and Sp and to find the optimal cut-off values for both Hb and Hb/Hp of the CV test (Figure 2). Meta-analytical technique (metaprop; Stata) was used to create separate forest plots for Se and Sp, with each set of data included (*i.e.*, test components Hb, Hb/Hp, cut-offs). We also calculated the summary estimates of Se and Sp, positive (LR+) and negative likelihood ratio (LR-) as well as diagnostic odds ratio, using a random effects bivariate model and fitted the summary hierarchical ROC (HSROC; MetaDiSc) curves for the CRC as the endpoint. Roccomp test (Stata) was used to compare the statistical significance between the area under the curve (AUC) values of AA and VA modes for proximal and distal CRC endpoint.

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

Test number	Fecal occult blood tests	Positive endpoint (colorectal cancer)	Negative endpoint (no colorectal cancer)	TP	FN	FP	TN
VA 1	HemoccultSENSA	Test positive	Test negative	12	9	42	151
VA 2	ColonView Hb VA	Test positive	Test negative	18	3	91	93
VA 3	ColonView Hb/Hp VA	Test positive	Test negative	18	3	83	105
VA 4	ColonView Hb + Hb/Hp VA	One or more sample positive	All samples negative	18	3	97	91

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

Results

Proximal CRC endpoint with VA tests. The Se, Sp and efficiency of the SENSA test for CRC were as follows: 57.0%, 78.0% and 76.2% (Table I, Figure 3 and Figure 4). The Se, Sp and efficiency of the visually analysed CV Hb and CV Hb/Hp tests for CRC were as follows: 86.0/86.0%, 51.0/56.0% and 54.1/58.9% (Table I, Figure 3 and Figure 4). The positive predictive value (PV+) of the CV Hb/Hp VA test was slightly higher than that of the CV Hb VA test (17.8% *vs*. 16.5%; Table I). When CV Hb + Hb/Hp VA were used as a combined test panel for the CRC endpoint, the panel had 86% Se, 48% Sp and 52.2% efficiency (Table I, Figure 3 and Figure 4).

Proximal CRC endpoint with AA tests. The overall Se of the AA reading mode for proximal CRC was 84.0% (95% CI=75-92%) (Table II, Figure 5 and Figure 6). The two most sensitive AA tests (CV Hb AA at cut-off ≥11.61 reader units (RU) and CV Hb/Hp AA at cut off ≥7.48 RU) showed 90% Se (Table II, Figure 5). The overall Sp of the AA reading mode for the proximal CRC endpoint was 73% (95% CI=52-89%; Figure 6). The two most specific AA tests (CV Hb AA at cut-off ≥158.8 RU, CV Hb/Hp AA at cut-off ≥54.62 RU) in proximal CRC diagnosis showed Sp range of 84-90% (Figure 6).

Distal CRC endpoint with VA tests. The Se, Sp and efficiency of the SENSA test for distal CRC were as follows: 95%, 87% and 88.2% (Table III, Figure 7 and Figure 8). The Se, Sp and efficiency of the visually analysed CV Hb and CV Hb/Hp tests for distal CRC were as follows: 100%/100%, 70%/58% and 75.0%/65.3% (Table III, Figure 7 and Figure 8). The PV+ of the CV Hb VA test was slightly higher than that of the CV Hb/Hp VA test (41.9% *vs*. 33.3%; Table III). When CV Hb + Hb/Hp VA were used as a combined test panel for the CRC endpoint, the panel had 100% Se, 56% Sp and 64.0% efficiency (Table III, Figure 7 and Figure 8).

Distal CRC endpoint with AA tests. The overall Se of the AA reading mode for distal CRC was 98% (95% CI=92-100%) (Table III, Figure 9). The two most sensitive AA tests (CV Hb AA at cut-off ≥9.13 RU and CV Hb/Hp AA at cut off ≥10.78 RU) showed 100% Se (Figure 9). The overall Sp of the AA reading mode for the distal CRC endpoint was 76% (95% CI=58-90%; Figure 10). The two most specific AA tests (CV Hb AA at cut-off ≥43.83 RU, CV Hb/Hp AA at cut-off ≥47.65 RU) in distal CRC diagnosis showed Sp range of 87-90% (Figure 10).

ROC analysis and optimal cut-off values of the CV for proximal CRC endpoint. The ROC analysis (Figure 2) for proximal CRC endpoint showed the optimal cut-off value of ≥158.80 RU for CV Hb AA (Table II) and ≥54.62 RU for CV Hb/Hp AA (Table II). Using these cut-offs, the Se, Sp and efficiency of the CV Hb AA (Table II) and CV Hb/Hp AA (Table II) tests for CRC were as follows: 71.4/81.0%, 90.3/83.9% and 88.4/83.8%. The PV+ of CV Hb AA (Table II) was significantly higher than that of test CV Hb/Hp AA (Table II); 45.5% *vs*. 36.2%.

ROC analysis and optimal cut-off values of the CV for distal CRC endpoint. The ROC analysis (Figure 2) for distal CRC endpoint showed the optimal cut-off value of ≥43.83 RU for CV Hb AA (Table IV) and ≥47.65 RU for CV Hb/Hp AA (Table IV). Using these cut-offs, the Se, Sp and efficiency of the CV Hb AA (Table IV) and CV Hb/Hp AA (Table IV) tests for CRC were as follows: 94.4%/94.1%, 90.2/86.6% and 91.0/87.9%. The PV+ of CV Hb AA (Table IV) was significantly higher than that of test CV Hb/Hp AA (Table IV); 68.0% *vs*. 59.3%.

HSROC and AUC values. HSROC curves were used to visualize the pooled overall accuracy of VA and AA reading modes in proximal and distal CRC detection. In the HSROC analysis, the AUC values were as follows: i) VA in proximal CRC: AUC=0.765 (95% CI=0.680-0.845) (Figure 11), ii) AA in proximal CRC: AUC=0.878 (95% CI=0.808-0.948) (Figure 12), iii) VA in distal CRC: AUC=0.955 (95% CI=0.901-0.999) (Figure 13) and iv) AA in distal CRC: AUC=0.961 (95% CI=0.904-1.000) (Figure 14). In roccomp

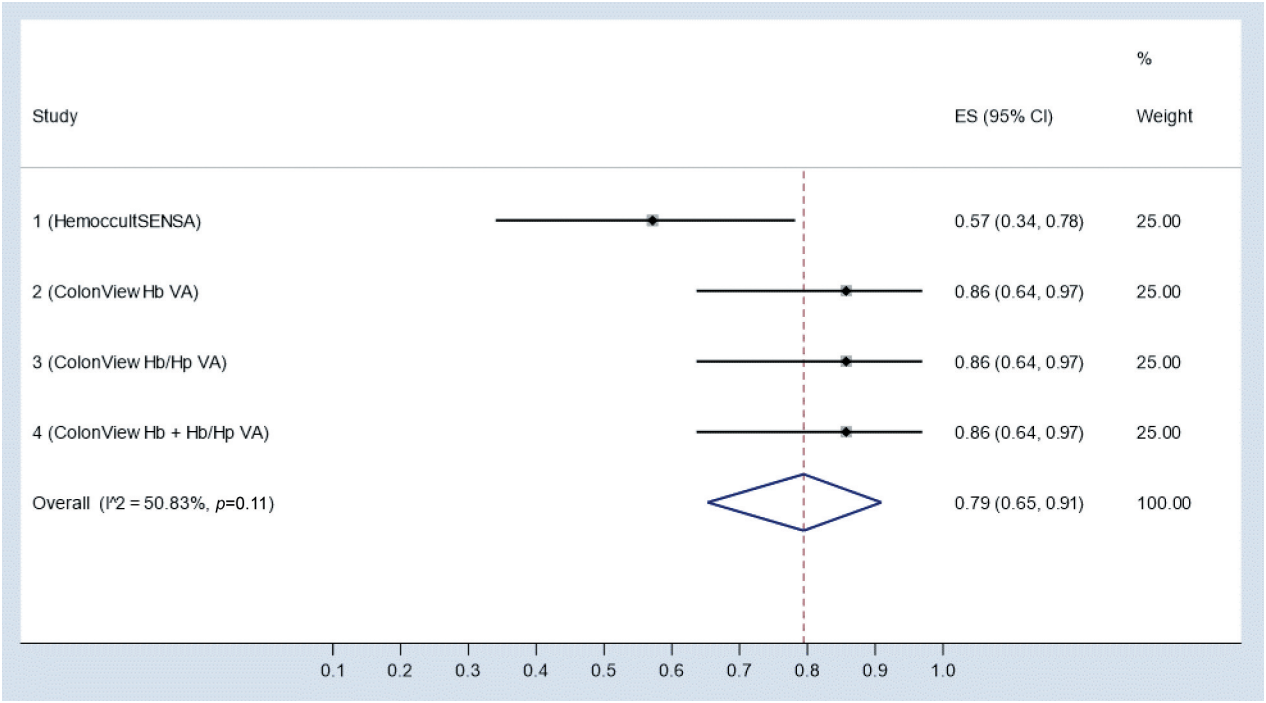

Figure 3. *Sensitivity values of visually analyzed (VA) screening tests for proximal colorectal cancer endpoint. ES: Estimated sensitivity; CI: confidence interval.*

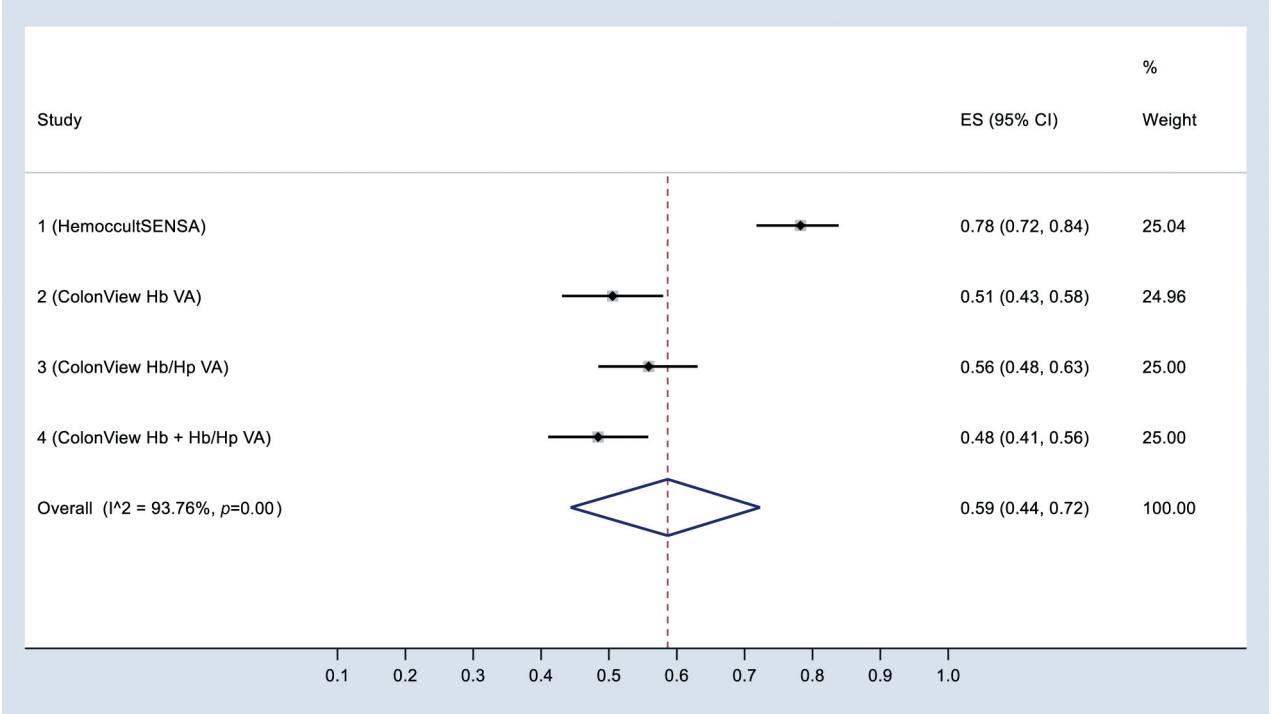

Figure 4. *Specificity values of visually analyzed (VA) screening tests for proximal colorectal cancer endpoint. ES: Estimated specificity; CI: confidence interval.*

Table II. *Automatically analyzed screening tests for proximal colorectal cancer 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	≥11.61 (median)	<11.61 (median)	19	2	84	102
AA 2	ColonView Hb/Hp AA	≥7.48 (median)	<7.48 (median)	19	2	86	103
AA 3	ColonView Hb AA	≥158.80 (ROC)	<158.80 (ROC)	15	6	18	168
AA 4	ColonView Hb/Hp AA	≥54.62 (ROC)	<54.62 (ROC)	17	4	30	159

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

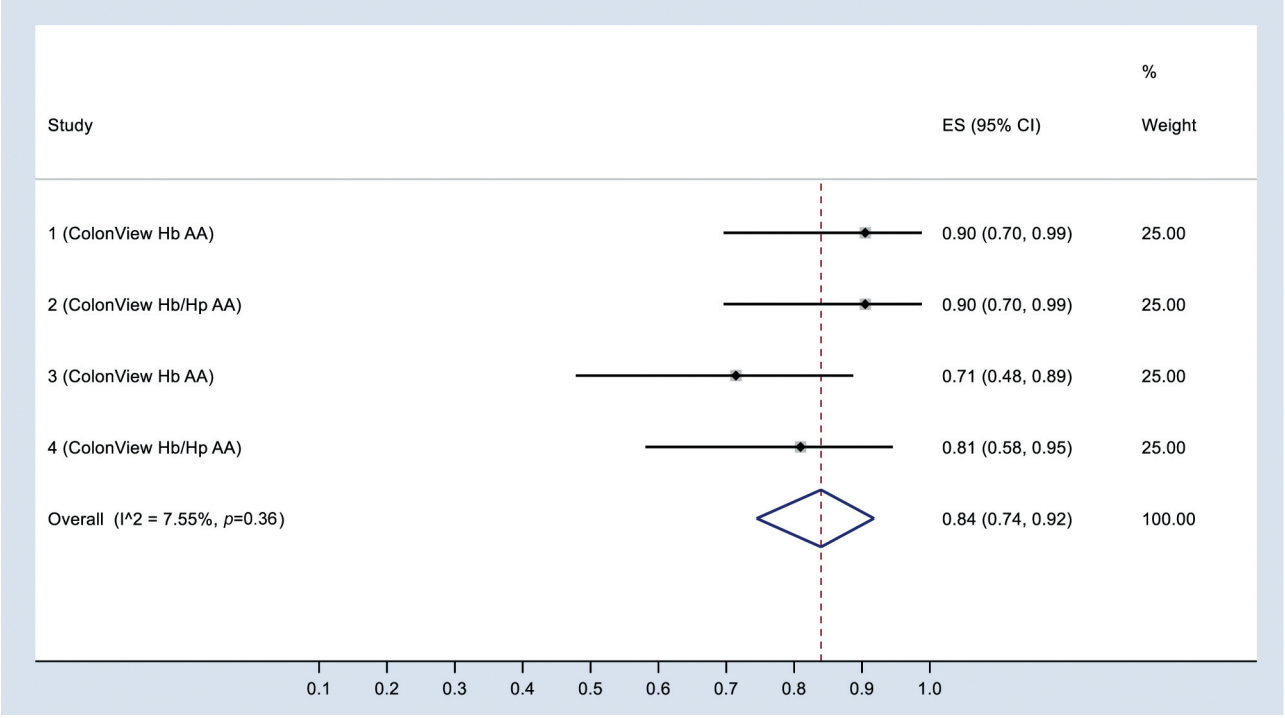

Figure 5. *Sensitivity values of automatically analyzed (AA) screening tests for proximal colorectal cancer endpoint. ES: Estimated sensitivity; CI: confidence interval.*

analysis, statistical significance of the differences in AUC values was: VA *vs*. AA in proximal CRC $p=0.009$; VA in proximal *vs*. VA in distal CRC $p<0.0001$; VA in proximal *vs*. AA in distal CRC $p<0.0001$; AA in proximal *vs*. VA in distal CRC $p=0.021$; AA in proximal CRC *vs*. AA in distal CRC $p=0.006$; and VA *vs*. AA in distal CRC $p=0.809$.

Discussion

Relatively few FITs have been tested for clinical Se and Sp in CRC screening settings (3, 4). In addition, most FITs on the market are based on the detection of the globin moiety of human Hb, and few detect, in addition, the Hb/Hp complex. The advantages of testing both Hb and Hb/Hp complex are obvious, and have been discussed in detail in two recent communications (9, 10) as well as in our previous meta-analysis (3, 4). In the previous studies for Hb and Hb/Hp (CV), VA and AA reading modes were reported separately (9, 10). For the AA mode, the Quick Test Reader (QTR) is needed. QTR is a mobile device for quantitative evaluation of Lateral Flow Assays and the protocol of this instrument has been previously described in detail (9, 12).

Vasilyev *et al*. (10) and Guimaraes *et al*. (9) have performed a head-to-head comparison study with SENSA and CV in two independent CRC screening settings. Both studies were concordant in that the characteristics of the FIT (CV)

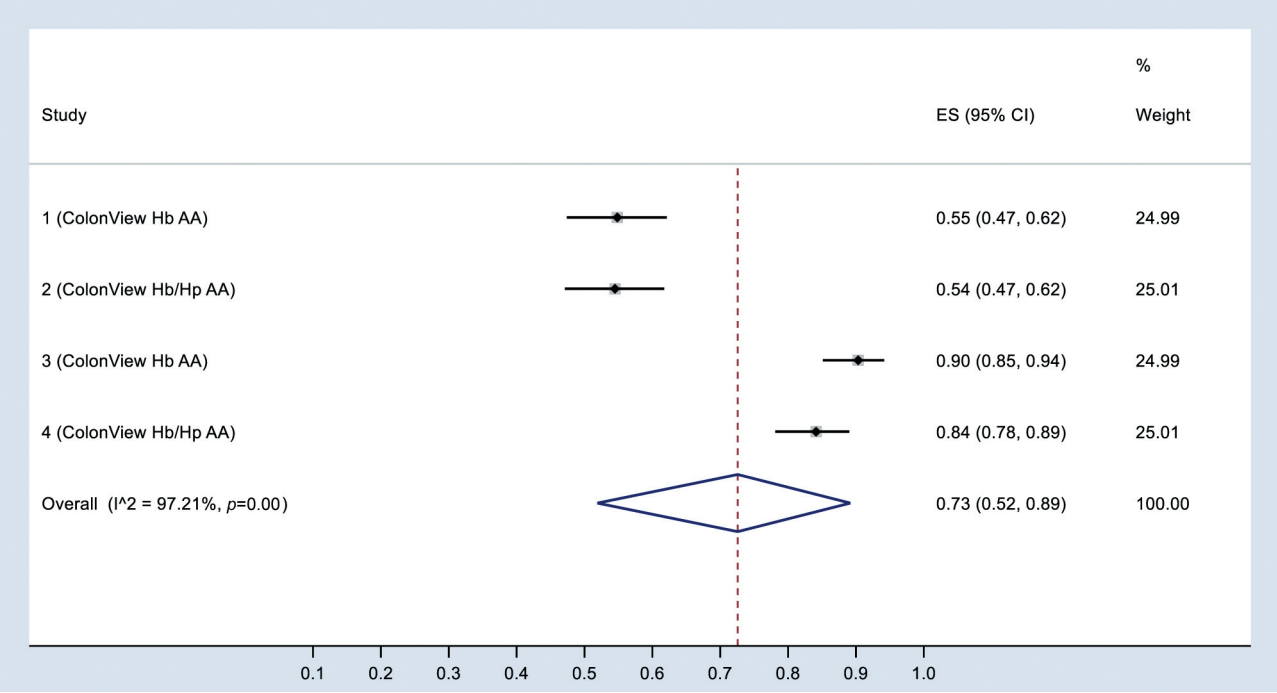

Figure 6. *Specificity values of automatically analyzed (AA) screening tests for proximal colorectal cancer endpoint. ES: Estimated specificity; CI: confidence interval.*

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

Test number	Fecal occult blood tests	Positive endpoint (colorectal cancer)	Negative endpoint (no colorectal cancer)	TP	FN	FP	TN
VA 1	HemoccultSENSA	Test positive	Test negative	18	1	11	72
VA 2	ColonView Hb VA	Test positive	Test negative	18	0	25	57
VA 3	ColonView Hb/Hp VA	Test positive	Test negative	17	0	34	47
VA 4	ColonView Hb + Hb/Hp VA	One or more sample positive	All samples negative	18	0	36	46

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

are superior to those of gFOBT (SENSA) as a screening tool for CRC (9, 10). In the present study, we compared the diagnostic accuracy of the two reading modes, using proximal *versus* distal CRC endpoint in a screening setting. In proximal CRC endpoint, the overall Se of the VA reading was only slightly inferior to that of the AA reading mode. However, the pooled Sp of the AA reading in proximal CRC endpoint, was significantly higher than that of the VA reading mode. Until present, three comprehensive reviews and meta-analyses have been published, where the accuracy of FOBTs was compared in diagnosis of proximal and distal CRCs (6-8). Unfortunately, however, the new-generation ColonView® quick test was not included in these analyses, in part due to the more recent launch of the CV test. Thus, in 2011, Haug *et al*. (6) reviewed the published screening studies conducted by FOBTs (both FIT and/or guaiac-based) in average-risk adult colonoscopy patients, comparing the test Se for proximal *versus* distal colorectal neoplasia. Altogether, 7 studies were found eligible. In most of these studies, Se of FOBTs for advanced neoplasia was higher in the distal than in the proximal colon (6). The authors, concluded, however, that the available literature is scarce and not entirely consistent. This review did not include HSROC analysis of the diagnostic performance of the FOBTs (6).

In 2016, Hirai *et al*. (7) reported a meta-analysis assessing the diagnostic accuracy of FOBTs stratified by the

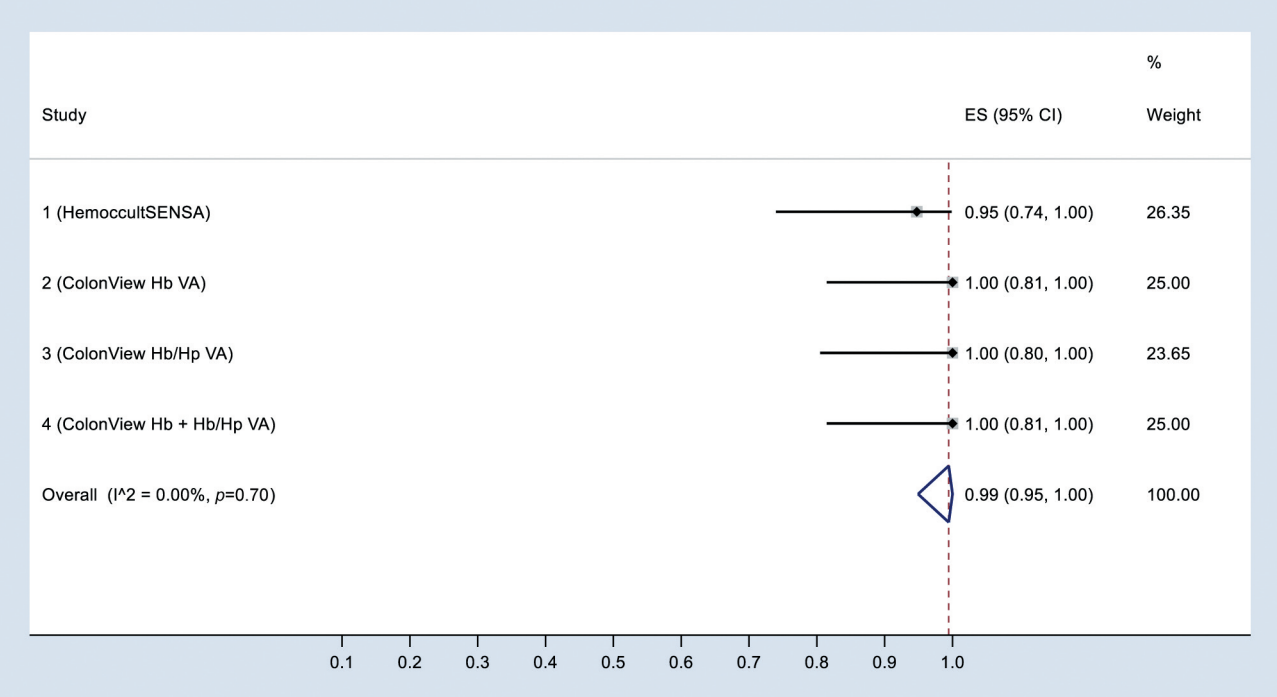

Figure 7. *Sensitivity values of visually analyzed (VA) screening tests for distal colorectal cancer endpoint. ES: Estimated sensitivity; CI: confidence interval.*

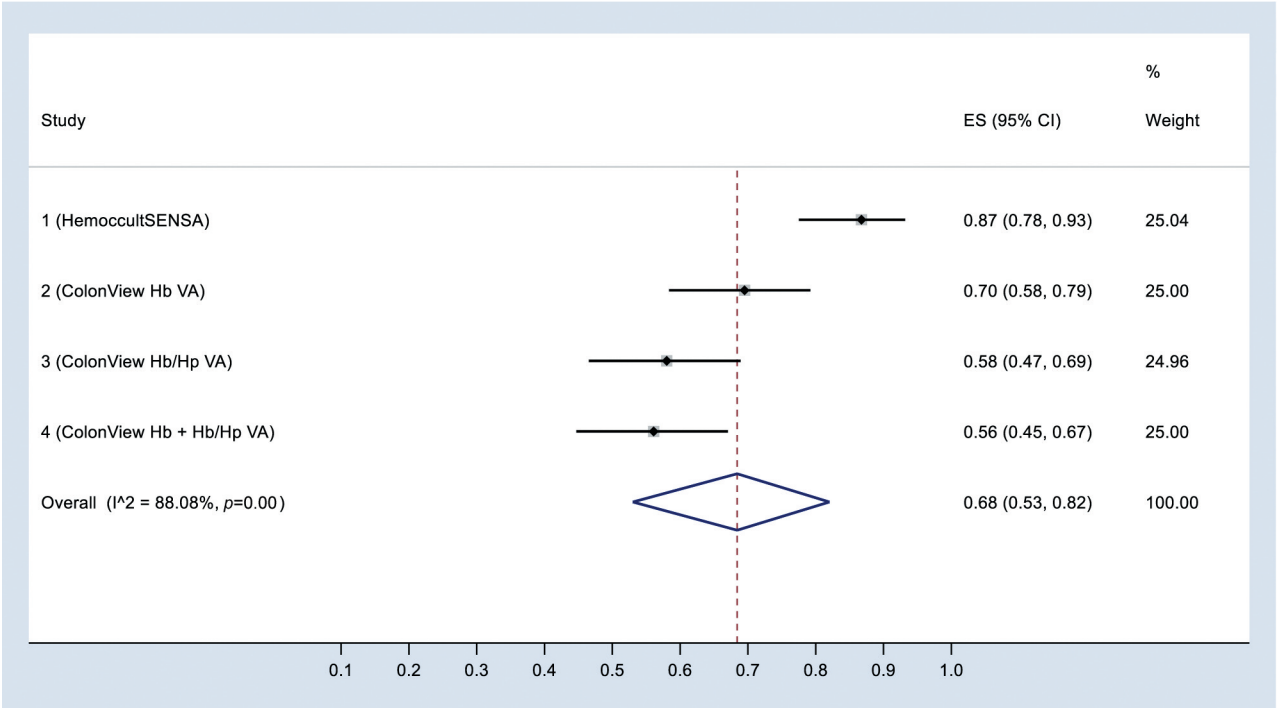

Figure 8. *Specificity values of visually analyzed (VA) screening tests for distal colorectal cancer endpoint. ES: Estimated specificity; CI: confidence interval.*

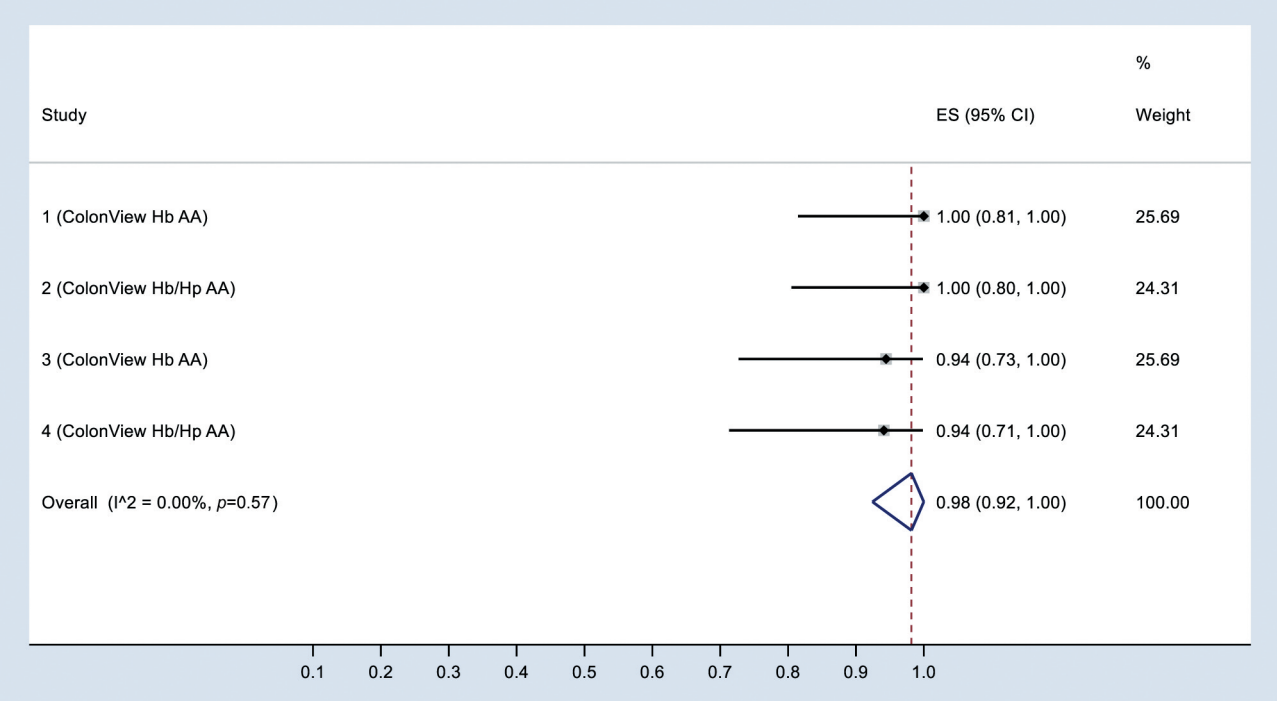

Figure 9. *Sensitivity values of automatically analyzed (AA) screening tests for distal colorectal cancer endpoint. ES: Estimated sensitivity; CI: confidence interval.*

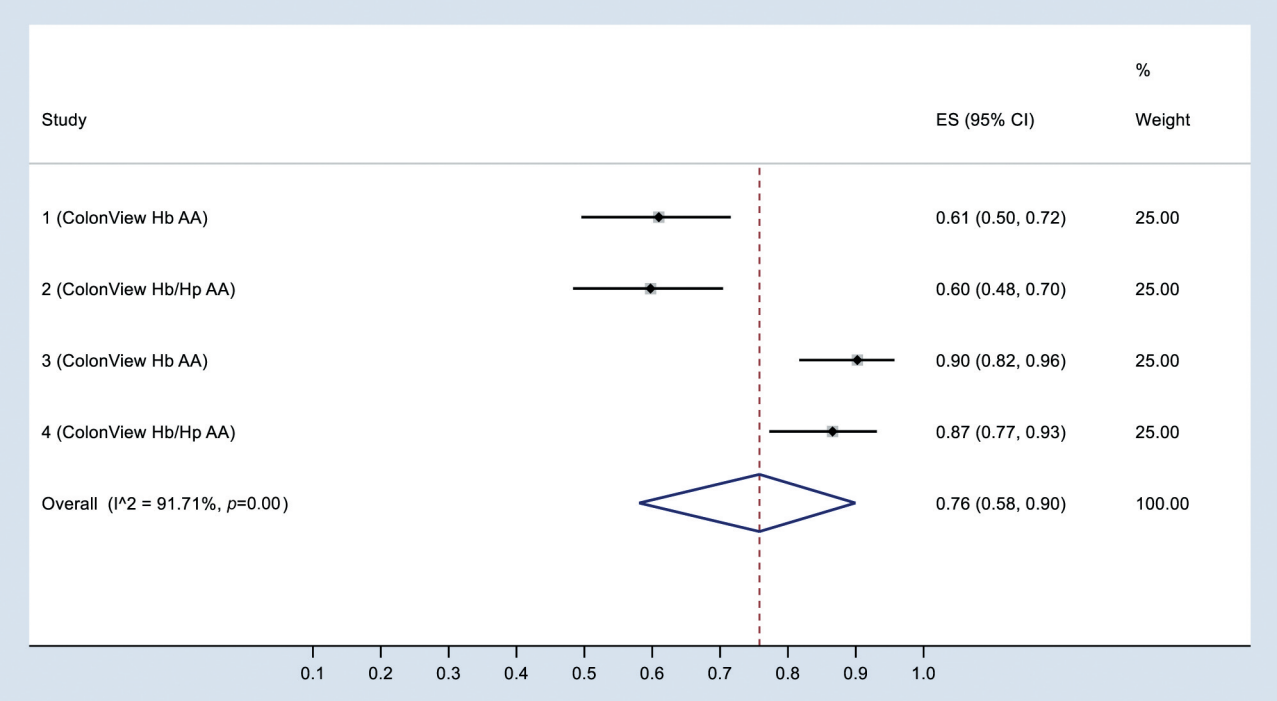

Figure 10. *Specificity values of automatically analyzed (AA) screening tests for distal colorectal cancer endpoint. ES: Estimated specificity; CI: confidence interval.*

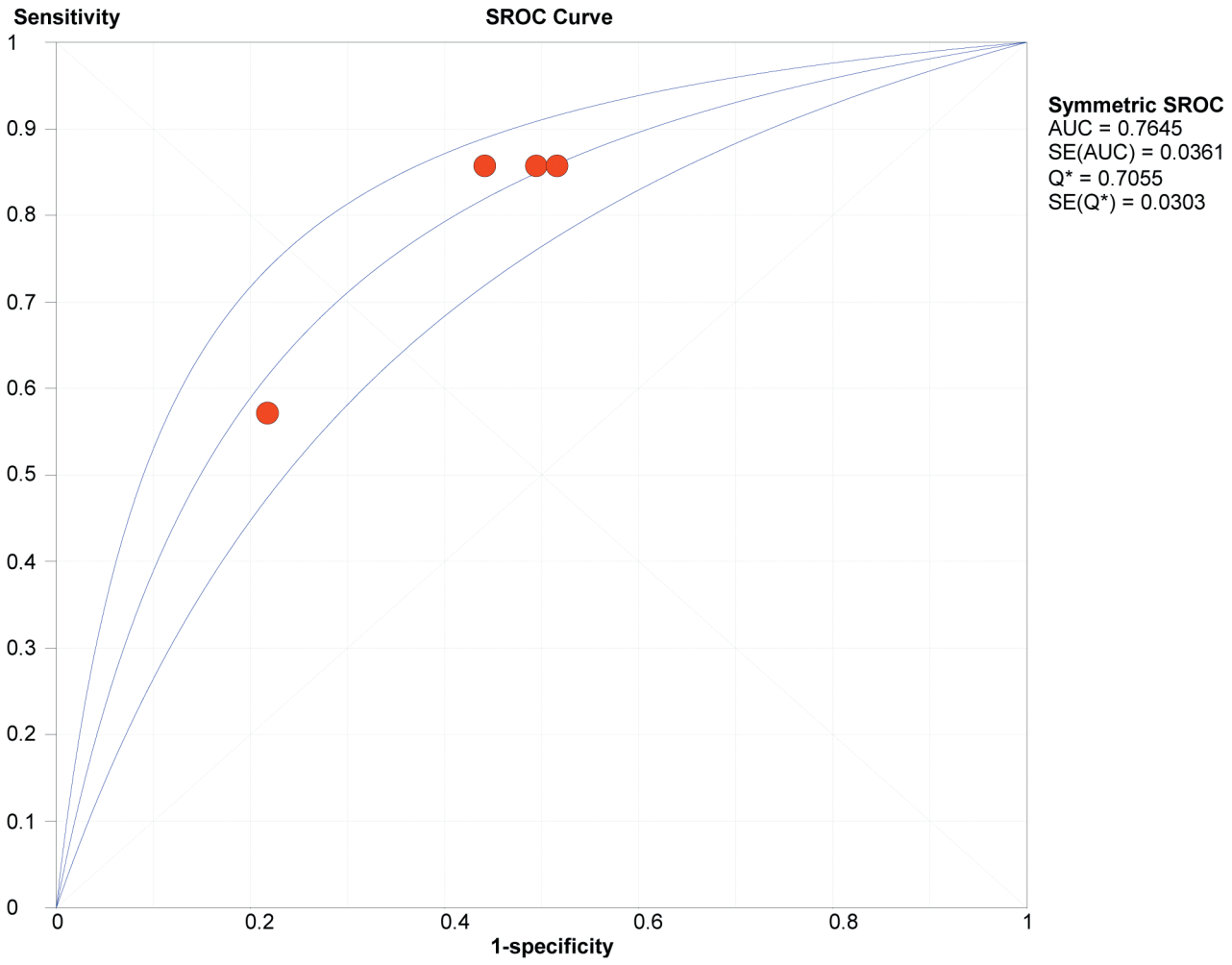

Figure 11. *Hierarchical summary receiver operating characteristic (HSROC) curve of the visually analyzed (VA) screening tests for proximal colorectal cancer endpoint. The upper and lower lines represent the 95% confidence interval (CI) of the summary ROC curve. The red dots represent the combinations of the ColonView/SENSA tests as shown in the Tables. SE(Q*), standard error of the Q* index.*

Table IV. *Automatically analyzed screening tests for distal colorectal cancer 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	≥9.13 (median)	<9.13 (median)	18	0	32	50
AA 2	ColonView Hb/Hp AA	≥10.78 (median)	<10.78 (median)	17	0	33	49
AA 3	ColonView Hb AA	≥43.83 (ROC)	<43.83 (ROC)	17	1	8	74
AA 4	ColonView Hb/Hp AA	≥47.65 (ROC)	<47.65 (ROC)	16	1	11	71

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

anatomical location of CRC. In their meta-analysis, 13 eligible studies reported the diagnostic performance of FOBTs (with the AUC values) in diagnosis of proximal and distal CRC (7). The pooled Se was 90% for proximal and 94% for the distal CRC (p=0.014). The results of these two meta-analyses (6, 7) are fully consonant with the results of the present analysis, where the CV test proved to be more accurate in detecting distal than proximal CRC. This is

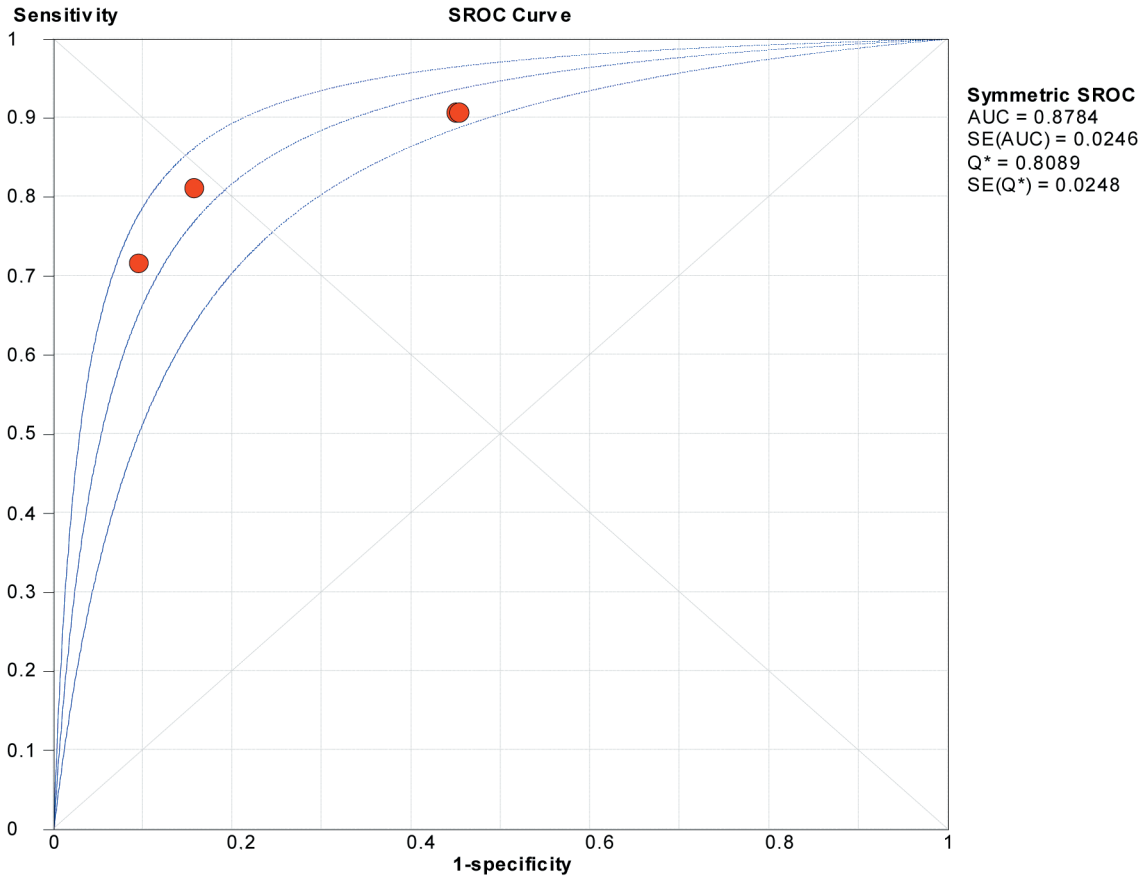

Figure 12. *Hierarchical summary receiver operating characteristic (HSROC) curve of the automatically analyzed (AA) screening tests for proximal colorectal cancer endpoint. The upper and lower lines represent the 95% confidence interval (CI) of the summary ROC curve. The red dots represent the combinations of the ColonView tests as shown in the Tables. SE(Q*), standard error of the Q* index.*

despite the fact that the CV test includes the Hb/Hp complex, which has been previously shown to be highly accurate in detection of proximal CRC, far exceeding the accuracy of the Hb component (9, 10). The most recent (in 2019) of the three meta-analysis by Lu *et al.* (8) reviewed available FOBT studies; however, failed to disclose any significant difference in the diagnostic accuracy of the FOBTs for CRC located in the distal *versus* proximal colon.

Irrespective of the reading mode of the CV test used (AA or VA) or whether Hb or Hb/Hp complex was analyzed, the diagnostic accuracy of the CV test in the detection of CRC in the proximal colon was inferior to that of the CRC in the distal colon. This observation has important implications in the practice of organized CRC screening. In reality, fecal occult blood derived from the tumors located in the proximal colon, might be missed more easily than the blood from distal CRC lesions. The CV test including the Hb/Hp complex seems to increase the likelihood of detecting FOB from the proximal lesions (9, 10). Another issue is to increase the number of samples. Because of the intermittent bleeding (and its longer passage) from the proximal CRC, multiple samples collected on several consecutive days could probably increase the likelihood of detecting the bleeding, thus increasing the diagnostic performance of the FOBT. This is, indeed, the case with the CV test, as shown by the post-hoc analysis of the data of the recently published study (10); increasing the number of samples from 1 to 3 led to parallel increase in test sensitivity (for all endpoints), reaching 100% for the CRC endpoint (unpublished).

These data are consistent with the results reported by van Roon *et al.* (2011) (13), who conducted a population-based trial to determine attendance and diagnostic performance of 1- and 2-sample FIT screening in CRC. The detection rates for advanced neoplasia were 3.1% in the 1-sample group and 4.1% in the 2-sample group (at least 1 positive test) implicating that two-sample FIT screening was associated with a higher detection rate of advanced neoplasia compared to 1-sample iFOBT screening (13). However, concerns might arise of the

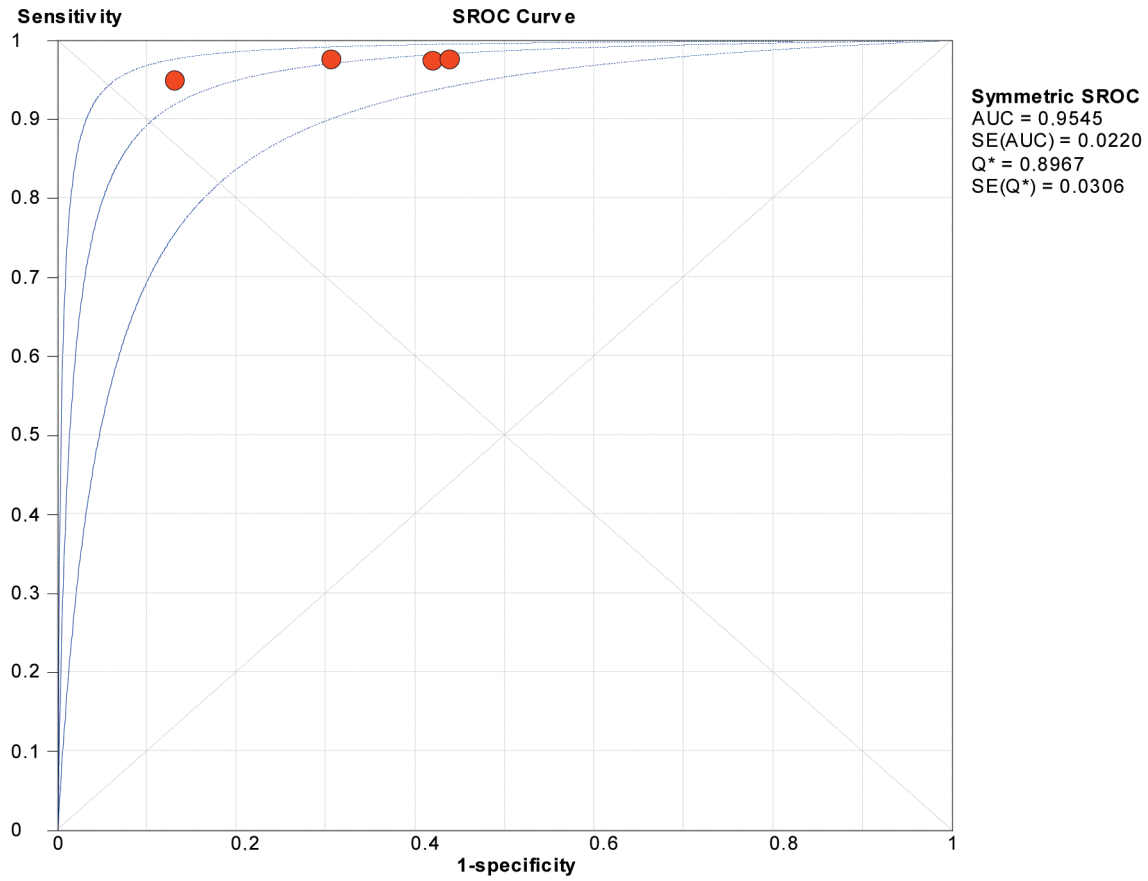

Figure 13. *Hierarchical summary receiver operating characteristic (HSROC) curve of the visually analyzed (VA) screening tests for distal colorectal cancer endpoint. The upper and lower lines represent the 95% confidence interval (CI) of the summary ROC curve. The red dots represent the combinations of the ColonView/SENSA tests as shown in the Tables. SE(Q*), standard error of the Q* index.*

endoscopy resources and screening compliance, and therefore, further studies on cost-effectiveness need to be performed (13).

HSROC analysis has become a convenient approach to evaluate the diagnostic performance of various diagnostic tests (14-22). When applied to the present setting, HSROC curve for the AA reading mode in proximal CRC diagnosis shows a reasonably high AUC value, which is significantly higher than that for VA reading in diagnosis of proximal CRC. However, for the distal CRC endpoint, the diagnostic accuracy of both AA and VA reading is clearly superior to the diagnostic accuracy for the proximal CRC endpoint. As confirmed in a recent meta-analysis, these outstanding performance indicators of the CV favourably compete with the other FIT tests on the market (4).

Conclusion

The present study confirms the applicability of the ColonView quick test (a new-generation FIT) in CRC screening. The AA reading mode showed significantly better diagnostic accuracy as compared to the VA reading (or SENSA), in detecting proximal CRC. When stratified by the cancer site (proximal *vs.* distal), the diagnostic performance of both the AA and VA reading modes is clearly superior for cancers in the distal site as compared with the proximal cancers. As determined from the results of a recent meta-analysis (4), these performance indicators of the CV test (both VA and AA) favourably compete with the most advanced FIT tests on the market.

Conflicts of Interest

Tapani Tiusanen, Ph.D., is employee of Biohit Oyj, Helsinki, Finland. The other Authors report 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, read and approved the final article.

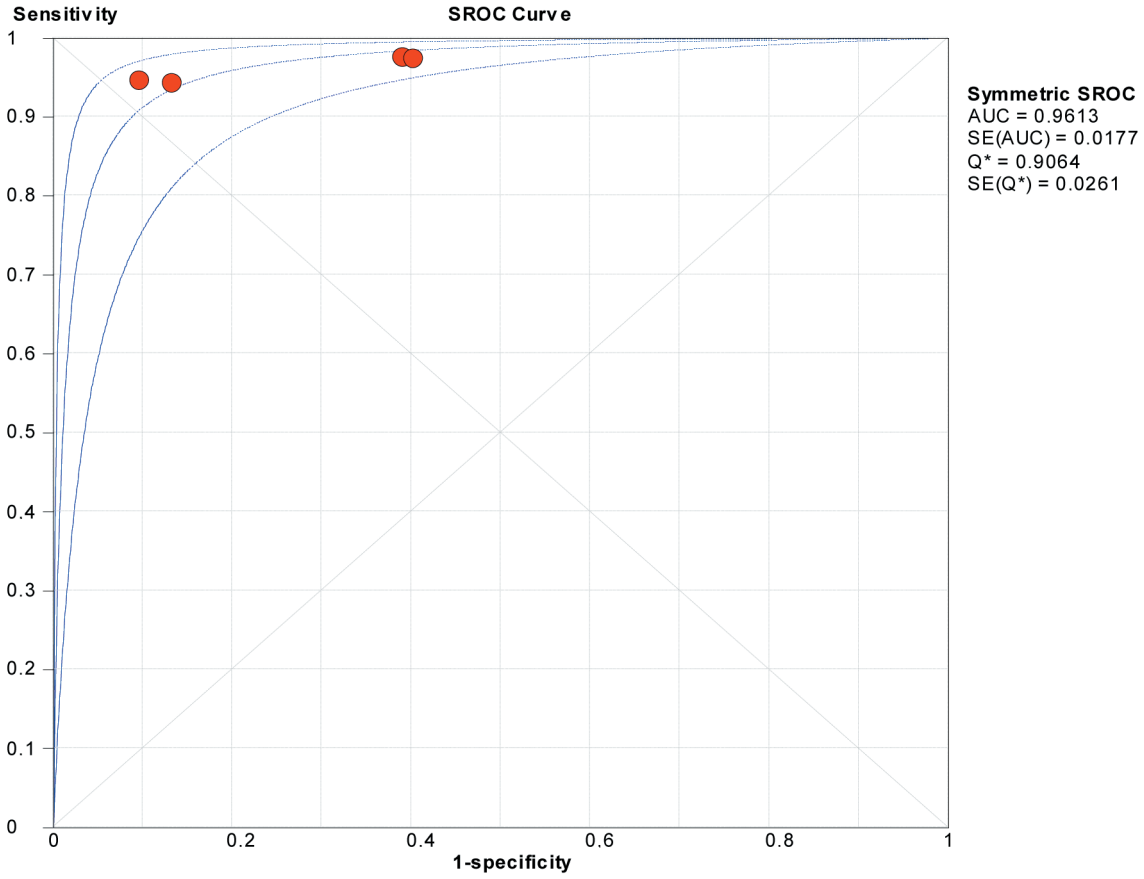

Figure 14. *Hierarchical summary receiver operating characteristic (HSROC) curve of the automatically analyzed (AA) screening tests for distal colorectal cancer endpoint. The upper and lower lines represent the 95% confidence interval (CI) of the summary ROC curve. The red dots represent the combinations of the ColonView tests as shown in the Tables. SE(Q*), standard error of the Q* index.*

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