ORIGINAL ARTICLE

MAYO CLINIC PROCEEDINGS:
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MAYO CLINIC

Stool-Based Colorectal Cancer Screening Test Performance Characteristics in Those With and Without Hemorrhoids

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Abstract

Objective: To evaluate the effect of hemorrhoids on noninvasive stool test performance for colorectal cancer (CRC) screening.

Patients and Methods: We conducted a retrospective cohort study of test characteristics for the fecal immunochemical test (FIT) and the multitarget stool DNA (mt-sDNA) test, on the basis of hemorrhoid status, recorded at the time of colonoscopy, among patients enrolled in the pivotal prospective study for mt-sDNA that was conducted from June 2011, to May 2013. Test characteristics (sensitivity, specificity, positive, and negative predictive values) for FIT and mt-sDNA (performed < 90 days before colonoscopy) were stratified by the presence of hemorrhoids and compared.

Results: Hemorrhoids were found in 51.7% (5163 of 9989) of the study cohort. Across all test characteristics, there were no statistically significant differences for FIT or mt-sDNA when stratified by hemorrhoid status. Analysis revealed mt-sDNA sensitivity of 44% and 41% for advanced precancerous lesions in nonhemorrhoidal and hemorrhoid patients, respectively (P=.41). The FIT sensitivity among the same lesion category was 24.9% in patients without hemorrhoids and 22.8% in those with hemorrhoids (P=.48). The mt-sDNA specificity was 86.4% in patients without hemorrhoids vs 87.7% in those with hemorrhoids (P=.67), although FIT specificity was 95.0% among patients without hemorrhoids vs 94.7% in those with hemorrhoids (P=.44).

Conclusion: The presence of asymptomatic hemorrhoids did not adversely affect test performance in this large clinical study. These findings suggest that in the absence of overt gastrointestinal bleeding, FIT and mt-sDNA are options for CRC screening, irrespective of hemorrhoid status.

Trial Registration: clinicaltrials.gov Identifier: NCT01397747

 ■ Mayo Clin Proc Inn Qual Out 2023;7(4):320-326

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Despite effective preventive strategies, colorectal cancer (CRC) remains a leading cause of cancer incidence and mortality in the United States.[1] Although the overall mortality of CRC has declined,[1,2] population-level CRC screening has yet to reach the public health goal of 80% adherence as set forth by the National Colorectal Cancer Roundtable.[3,4] Several strategies may be used for CRC screening, and these strategies differ in effectiveness, safety, cost, and guideline-recommended frequency; thus, the patients' likelihood of completing the recommended screening may differ by screening method.

Clinicians have raised concerns regarding false-positive stool-based tests, as these result in unnecessary colonoscopies, with the potential to strain local access to endoscopy and place patients at procedure-associated risk. Furthermore, discordant outcomes (positive stool test and a negative colonoscopy) can lead to lingering psychologic distress[5] and could lead to rescreening sooner than the recommended 10-year interval.[6] Considering the effect of nonneoplastic stool blood on test accuracy,

Mayo Clin Proc Inn Qual Out ■ August 2023;7(4):320-326 ■ https://doi.org/10.1016/j.mayocpiqo.2023.06.003
www.mcpiqojournal.org ■

clinicians may also advise against stool-based CRC screening in persons with hemorrhoids given concern for a false-positive test.

Hemorrhoids that are common and can occasionally bleed, may call into question the use of stool-based CRC screening tests that target hemoglobin as a marker of colorectal neoplasia. Furthermore, patients or clinicians may also defer follow-up colonoscopy by erroneously attributing a positive stool-based test to hemorrhoid-associated hemoglobin from presumed rectal outlet bleeding.

Despite these concerns, very few studies have evaluated the potential influence of hemorrhoids on stool-based test results. Results of a meta-analysis of studies conducted outside the United States found that hemorrhoids did not significantly increase the number of false-positive fecal immunochemical tests (FIT).[7] By contrast, a more recent study found that hemorrhoids were associated with higher odds of a false-positive FIT.[8]

Moreover, the relationship between hemorrhoids and multitarget stool DNA (mt-sDNA) test performance has not been well described. Similar to FIT, the mt-sDNA test has a fecal hemoglobin immunoassay but also evaluates *KRAS* mutations, aberrant *NDRG4*, *BMP3* methylation, and β-actin followed by a logistic-regression algorithm whose sum translates to a positive or negative result.[9] In the study by Johnson et al[10] evaluating the influence of mt-sDNA test result knowledge on follow-up colonoscopy findings, hemorrhoids were reported as incidental nonneoplastic findings and not part of the primary analysis.[10] The pivotal study comparing mt-sDNA and FIT with colonoscopy as the reference standard[9] provides an accessible cohort for retrospective evaluation of the association between hemorrhoids identified at the time of colonoscopy and both mt-sDNA and FIT screening performance. Herein, we describe screening performance characteristics among trial participants on the basis of hemorrhoid status—ie, the anatomic presence or absence of hemorrhoids. All trial participants were at average risk for CRC and found no symptoms (gastrointestinal bleeding or pain) that would have otherwise warranted a diagnostic evaluation. Whether the hemorrhoids observed during colonoscopy were new or historically present is unknown.

MATERIALS AND METHODS

Study Population and Design

In this retrospective cross-sectional analysis, participants from the prospectively enrolled pivotal trial DeeP-C[9] served as the sole data source. The DeeP-C[9] was a blinded prospective, cross-sectional study that enrolled over 12,000 participants at average risk for CRC across 90 sites throughout the United States and Canada to assess mt-sDNA and FIT performance characteristics in CRC and advanced precancerous lesion (APL) detection. DeeP-C[9] was an IRB-approved study, and informed consent was provided by each study participant.

As with DeeP-C[9], this analysis was limited to participants with completed and valid results for mt-sDNA, FIT, and colonoscopy; thus, patients with missing or invalid mt-sDNA or FIT results, or missing or incomplete colonoscopy were excluded. Participants were divided into 2 groups: those with and those without hemorrhoids detected at the time of colonoscopy; the presence of hemorrhoids was a predefined category on the trial colonoscopy case report form reflecting the presence of hemorrhoids during the preprocedural perianal examination or during rectal retroflexion. The DeeP-C[9] trial participants were excluded for any of the following: personal history of colorectal neoplasia, digestive cancer, or inflammatory bowel disease; colonoscopy within the previous 9 years or a barium enema, computed tomographic colonography, or sigmoidoscopy within the previous 5 years; positive results on fecal blood testing within the previous 6 months; a colorectal resection for any reason other than sigmoid diverticula; overt rectal bleeding within the previous 30 days (eg hematochezia or melena); personal or family history of CRC; participation in any interventional clinical study within the previous 30 days; or unwilling to provide written informed consent. Blood seen only on toilet paper did not constitute rectal bleeding.

Statistical Analyses

The study cohort analyzed was equivalent to the primary analysis population in DeeP-C[9]. Patient characteristics and the most advanced histopathological findings were summarized overall and by presence or absence of

hemorrhoids. Group differences were compared using χ^2 tests for categorical variables and *t* tests for continuous variables, after assessing normality. Levels of most advanced colonoscopy finding that differed significantly by hemorrhoid status were then assessed, with adjustment for covariates (age, sex, ethnicity, race, smoking history, and body mass index (BMI)) using logistic regression. Sensitivity and specificity were reported by hemorrhoid status with 95% CI calculated using the Wilson score method and compared using χ^2 tests. Positive and negative predictive values were secondarily calculated.

RESULTS

Demographics and Baseline Characteristics by Hemorrhoid Status

There were 9989 patients included in the analysis, 5163 (51.7%) of whom had hemorrhoids detected at the time of colonoscopy. Compared with those without hemorrhoids, participants with hemorrhoids were more frequently Hispanic or Latino (11.1% vs 8.6%), non-White (17.9% vs 13.9%), and current smokers (9.9% vs 8.1%). Those with hemorrhoids also found a higher mean BMI (29.0 kg/m^2 vs 28.7 kg/m^2) (Table 1).[11] Because of the large sample size, some of the differences that were statistically significant have uncertain or no clinical significance.

Participants with hemorrhoids more frequently reported nonadvanced neoplasia (30.4% vs 27.4%; *P*=.001), and nonneoplastic findings (hyperplastic polyps or "polyps" without precancerous features on histopathologic review, 19.0% vs 17.4%; *P*=.04), and a lower rate of no findings on colonoscopy (42.4% vs 47.0%; *P*=<.001), respectively. After controlling for age, sex, ethnicity, race, smoking history, and BMI, observed differences remained statistically significant for nonadvanced neoplasia (*P*=.002) and no findings (*P*=<.001), but not for nonneoplastic findings (*P*=.08).

Test Characteristics of Mt-sDNA and FIT by Hemorrhoid Status

None of the test characteristics differed significantly on the basis of hemorrhoid status for either mt-sDNA or FIT (Table 2). Test specificity (and therefore false-positive rates) did not differ significantly by hemorrhoid status. The mt-sDNA assay found a specificity of 86.7% in those with hemorrhoids vs 86.4% for those without hemorrhoids, resulting in corresponding false-positive rates of 13.3% and 13.6%, respectively. The FIT specificity in the absence of advanced neoplasia was 94.7% with hemorrhoids vs 95.0% without hemorrhoids. A comparison of negative results on colonoscopy (no findings and clean colon) was 90.3% vs 89.3% for mt-sDNA, and 96.3% vs 96.4% for FIT − with and without hemorrhoids, respectively.

Colorectal cancer and APL sensitivity did not differ by hemorrhoid status. The CRC sensitivity was 92.9% vs 91.9% for mt-sDNA, and 78.6% vs 70.3% for FIT—with and without hemorrhoids, respectively. The APL sensitivity was 41.0% vs 44.0% for mt-sDNA, and 22.8% vs 24.9% for FIT—with and without hemorrhoids, respectively.

Positive and Negative Predictive Values

Positive predictive values (95% CI) for mt-sDNA and FIT for CRC were 4.3% (3.1%-5.9%), and 7.8% (5.4%-11.1%), respectively, in the absence of hemorrhoids and were 3.2% (2.2%-4.6%) and 6.0% (4.0%-9.0%), respective in the presence of hemorrhoids, with no statistical differences on the basis of hemorrhoid status. For advanced neoplasia, positive predictive values for mt-sDNA and FIT in the absence of hemorrhoids were 24.1% (21.2%-27.2%) and 34.3% (29.4%-39.6%), respectively, and were 23.2% (20.4%-26.2%) and 31.0% (26.4%-35.9%), respectively, with hemorrhoids present. For both CRC and advanced neoplasia, the numerically higher positive predictive values for FIT reflect the higher specificity of FIT. Given the expected low prevalence of CRC, negative predictive values for (absence of) CRC for both mt-sDNA and FIT fell between 99.8% and 100%, with no differences on the basis of hemorrhoid status. Negative predictive values for (absence of) advanced neoplasia were 95.0% (94.2%-95.6%) for mt-sDNA and 93.8% (93.0%-94.5%) for FIT in the absence of hemorrhoids and 94.5% (93.8%-95.2%) for mt-sDNA and 93.4% (92.7%-94.1%) for FIT in the presence of hemorrhoids, with no statistical differences on the basis of hemorrhoid status. The numerically higher negative

TABLE 1. Patient Characteristics Overall and by Hemorrhoid Status

Characteristic	Total (N=9989)	No Hemorrhoids (n=4826)	Hemorrhoids (n=5163)	*P*
Age (y), mean ± SD	64.2±8.4	64.1±8.3	64.3±8.5	0.22
44-49, n (%)	3 (0.0)	2 (0.0)	1 (0.0)	—
50-59, n (%)	2858 (28.6)	1377 (28.5)	1481 (28.7)	—
60-64, n (%)	819 (8.2)	422 (8.7)	397 (7.7)	—
65-69, n (%)	3670 (36.7)	1788 (37.0)	1882 (36.5)	—
70-74, n (%)	1735 (17.4)	828 (17.2)	907 (17.6)	—
≥75, n (%)	904 (9.0)	409 (8.5)	495 (9.6)	—
Sex, n (%)	—	—	—	0.21
Female	5364 (53.7)	2560 (53.0)	2804 (54.3)	—
Male	4625 (46.3)	2266 (47.0)	2359 (45.7)	—
Ethnicity, n (%)	—	—	—	<0.0001
Hispanic or Latino origin	987 (9.9)	415 (8.6)	572 (11.1)	—
Not Hispanic or Latino origin	8998 (90.1)	4407 (91.3)	4591 (88.9)	—
Unknown	4 (0.0)	4 (0.1)	0 (0.0)	
Race, n (%)				<0.0001
White	8392 (84.0)	4154 (86.1)	4238 (82.1)	—
Black or African American	1068 (10.7)	443 (9.2)	625 (12.1)	—
Asian	259 (2.6)	106 (2.2)	153 (3.0)	—
Other	264 (2.6)	117 (2.4)	147 (2.8)	—
Missing	6 (0.1)	6 (0.1)	0 (0.0)	—
Smoking History, n (%)				0.01
Never Smoked	5510 (55.2)	2693 (55.8)	2817 (54.6)	—
Former Smoker	3580 (35.8)	1743 (36.1)	1837 (35.6)	—
Current Smoker	899 (9.0)	390 (8.1)	509 (9.9)	—
BMI (kg/m^2), mean ± SD	28.8±5.8, n=9981	28.7±5.8, n=4825	29.0±5.9, n=5156	0.01
Most advanced finding				
Colorectal cancer				
Any	65 (0.7)	37 (0.8)	28 (0.5)	0.16
Stage I-III[a]	60 (0.6)	33 (0.7)	27 (0.5)	0.30
Advanced precancerous lesion[b]	757 (7.6)	357 (7.4)	400 (7.7)	0.51
Nonadvanced adenoma	2,893 (29.0)	1,324 (27.4)	1,569 (30.4)	0.001
Negative colonoscopy				
Nonneoplastic finding	1,817 (18.2)	838 (17.4)	979 (19.0)	0.04
No findings	4,457 (44.6)	2,270 (47.0)	2,187 (42.4)	<0.0001

[a]Staging per American joint committee on cancer.[11]
[b]Includes advanced adenomas and sessile serrated polyps measuring 1 cm or more.
Note: Advanced finding categories and definitions taken from DeeP-C[9] clinical trial

predictive values for mt-sDNA for advanced neoplasia reflect the higher sensitivity of mt-sDNA for this finding.

DISCUSSION

As the largest analysis addressing the association of hemorrhoids and stool-based test performance, this study provides support for average-risk, stool-based CRC screening regardless of hemorrhoid status, in the absence of overt or visible rectal bleeding. Among participants enrolled in the prospective DeeP-C[9] study, the presence of hemorrhoids noted at index colonoscopy was not associated with an increased false-positive rate. However, the frequency of no findings at colonoscopy was greatest among those without hemorrhoids, whereas for patients

TABLE 2. Test Performance Characteristics of mt-sDNA and FIT by Hemorrhoid Status

Test Characteristic	No Hemorrhoids			Hemorrhoids			
Mt-sDNA	n	%	95% CI	n	%	95% CI	*P*
Sensitivity for colorectal cancer (CRC[a])	37	91.9	78.7-97.2	28	92.9	77.4-98.0	0.89
Sensitivity for APL[a]	357	44.0	38.9-49.2	400	41.0	36.3-45.9	0.41
Specificity for advanced neoplasia[b]	4432	86.4	85.4-87.4	4735	86.7	85.7-87.7	0.67
Specificity: negative results on colonoscopy (no findings, clean colon)	2270	89.3	88.0-90.5	2187	90.3	88.9-91.4	0.31
FIT[a]							
Sensitivity for colorectal cancer (CRC[a])	37	70.3	54.2-82.5	28	78.6	60.5-89.8	0.45
Sensitivity for APL[a]	357	24.9	20.7-29.7	400	22.8	18.9-27.1	0.48
Specificity for advanced neoplasia[b]	4432	95.0	94.4-95.6	4735	94.7	94.0-95.3	0.44
Specificity: negative results on colonoscopy (no findings, clean colon)	2270	96.4	95.6-97.1	2187	96.3	95.4-97.0	0.81

[a]Abbreviations: APL, advanced precancerous lesions; CRC, colorectal cancer; mt-sDNA, multitarget stool DNA; FIT, fecal immunochemical test.
[b]Advanced neoplasia=CRC or APL. Specificity calculation includes all nonadvanced adenomas, nonneoplastic findings, and negative results on colonoscopy.

with hemorrhoids, there was a higher rate of neoplasia. This trend is not due to older age in those with hemorrhoids because the finding persisted despite age adjustment. The significant difference in neoplasia yield among those with hemorrhoids was primarily driven by an increased frequency of nonadvanced neoplasia. Our study design did not permit sufficient data to fully explore the increased rate of neoplasia among those with hemorrhoids, but this perhaps reflects a shared dietary risk factor. Although high fiber diets are thought to confer a protective effect against CRC, presumably low fiber diets increase the risk for hemorrhoid development by straining from constipation. When test performance for mt-sDNA and FIT was stratified by the presence of hemorrhoids, there were no differences in test characteristics for CRC and APLs. Hemorrhoids were not associated with an increased false-positive rate, suggesting the presence of hemorrhoids should not preclude the utilization of a stool-based test for CRC screening (given a theoretical concern for false-positive tests).

This study has important implications when placed in a clinical context. When counseling a patient on CRC screening strategies, it is still imperative to review signs and symptoms that are associated with CRC. Unintentional weight loss, abdominal pain, changes in bowel characteristics, and blood per rectum should signal a recommendation for diagnostic colonoscopy because a stool-based test would be both inadequate and inappropriate for evaluation. Although the detection of hemorrhoids may be influenced by technique (such as adequacy of perianal or digital rectal examination, degree of colonoscope torsion, and insufflation during rectal retroflexion), gastroenterologists have shown a high degree of accuracy in diagnosing hemorrhoids relative to other providers.[12]

We acknowledge that there is a distinction between the anatomic presence of hemorrhoids (dilated venous channels proximal to the dentate line) and a disease state for hemorrhoids that renders clinical symptoms (bleeding or pain). However, endoscopists performing colonoscopy for the purpose of CRC screening may not routinely conduct a detailed review of systems to delineate a disease state associated with the anatomic detection of hemorrhoids. However, the identification of hemorrhoids is typically noted to inform subsequent management by the referring provider. In our study, patients were asymptomatic with respect to hemorrhoid status, supporting the use of stool-based CRC screening in the absence of overt rectal bleeding during sample collection.

The study of hemorrhoids and noninvasive stool-based CRC screening has historically been challenged by study design and sample size. Before our evaluation, the work from Kim et al[13] had been the largest series

Mayo Clin Proc Inn Qual Out ■ August 2023;7(4):320-326 ■ https://doi.org/10.1016/j.mayocpiqo.2023.06.003
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evaluating false-positive FIT tests. In the study conducted by Kim et al,[13] among 704 patients with a positive FIT, 539 were considered falsely positive given the absence of advanced neoplasia. Among this group, only 15% (81 of the 539) presented with hemorrhoids at the time of colonoscopy, compared with 7% (38 of the 539) with no abnormality ($P<.001$). This observation was then used to suggest that the presence of hemorrhoids was an independent risk factor for a false-positive FIT result. Although the analysis plan was done to exclude potential confounders (such as the effect of diverticula), this markedly decreased the sample size. Kim et al[13] suspected that hemorrhoids may contribute to false-positive test results by occult bleeding; however, there was no report of excluding individuals with overt visible rectal bleeding at the time of FIT collection. Given the retrospective design of their study,[13] it is plausible that this variable was inadequately controlled for in the data analyses.

Similarly, a retrospective study by Law et al[8] supported increased odds of a false-positive FIT given the presence of hemorrhoids on the basis of multiple logistic regression, although a history of hemorrhoid-associated bleeding was unknown.[8] Lack of firm awareness of hemorrhoid-associated bleeding may be more typical of the real-world, but this does not lend greater strength to study conclusions if known or measured. By contrast, an earlier prospective population-based pilot by Stegeman et al[14] among asymptomatic adults evaluated risk factors that could influence FIT and found no association with hemorrhoids; however, the sample size was small.[14] Moreover, these findings were consistent with another comparative prospective study by Chiang et al[15]

The rigorous study exclusions for the DeeP-C[9] study provide a unique opportunity to evaluate the influence of hemorrhoids on stool-based screening results. Although retrospective studies can confirm the absence or presence of hemorrhoids from procedure documentation or photos, the ability to accurately examine a history of rectal outlet bleeding associated with hemorrhoids is limited. We were able to overcome this limitation because our retrospective analysis is on the basis of the prospective study design of the DeeP-C[9] trial and its exclusion of patients with overt gastrointestinal bleeding before testing. Had hemorrhoids been associated with an increased false-positive rate, test specificity and positive predictive value would have been significantly reduced. There were no significant differences observed when test performance was stratified by the presence of hemorrhoids, as outlined in Table 2. Although not significant, the rates of no neoplasia were lowest among those with hemorrhoids for both positive and negative stool-based tests.

Strengths, Limitations, and Bias Considerations

Although the sample size and study design of the original DeeP-C clinical trial provided precision and power for our evaluation, this cohort was not initially designed to evaluate the influence of hemorrhoids. In addition, mis-categorization of patients with hemorrhoids into the nonhemorrhoid cohort could lead to a type II error. We did not validate the reporting of hemorrhoids because such validation would have been impractical given the multisite participation. We do note that there were strict requirements for colonoscopy reporting, and most of the patients were found to have hemorrhoids (Table 1). Although study enrollment is historic -spanning from 2011 to 2013, subsequent advancements in endoscopic technique, technology, and widespread use of performance metrics would likely nondifferentially increase the detection of neoplasia universally and not significantly affect the study findings. Our analysis focused on neoplasia diagnosis and was stratified by hemorrhoid status. Additionally, other nonneoplastic factors such as angioectasias or diverticulum were not controlled for; thus, the potential influence of these factors on test results is unknown and rightfully deserves additional evaluation. Nonneoplastic findings (nondysplastic or hyperplastic polyps) were significantly higher among those with hemorrhoids, and assuming they would introduce risk for a false-positive test, the present analysis would have overestimated the likelihood that hemorrhoids are associated with a false-positive test. Finally, the inclusion of participants with asymptomatic hemorrhoids was on the basis of their self-reported absence of rectal outlet bleeding. Thus, the exclusion of

people with visible bleeding likely accounts for the comparable test characteristics between hemorrhoid and nonhemorrhoid groups.

CONCLUSION

Among CRC screen-eligible adults, hemorrhoids are common and have a potential to introduce visible rectal outlet bleeding that may affect stool-based test performance. Inherently, chances of a false-positive stool-based test exist for patients with hemorrhoids. However, among patients at average risk for CRC with hemorrhoids and no evidence of overt rectal bleeding leading up to the time of stool sample collection, stool-based test (mt-sDNA and FIT) performance was no different compared with patients without hemorrhoids.

To our knowledge, this evaluation of the association between hemorrhoids and stool-based test performance is the largest performed to date and provides convincing evidence that, in the absence of overt gastrointestinal bleeding, stool-based CRC screening can be used with confidence in patients with hemorrhoids. The findings herein suggest enhanced confidence in stool-based screening among the asymptomatic hemorrhoidal cohort.

POTENTIAL COMPETING INTERESTS

The authors have no additional relevant financial or non-financial interests to disclose.

ACKNOWLEDGMENTS

With his permission, we acknowledge the medical writing and editorial support provided by William K Johnson, PhD, an employee of Exact Sciences. This work was funded and supported by Exact Sciences Corporation, LLC (Madison, WI).

Abbreviations and Acronyms: **APL**, advanced precancerous lesion; **BMI**, body mass index; **CRC**, colorectal cancer; **FIT**, fecal immunochemical test; **mt-sDNA**, multitarget stool DNA

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