

Are Hemorrhoids Associated with False-Positive Fecal Immunochemical Test Results?

Nam Hee Kim, Jung Ho Park, Dong Il Park, Chong Il Sohn, Kyuyong Choi, and Yoon Suk Jung

Division of Gastroenterology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea.

Purpose: False-positive (FP) results of fecal immunochemical tests (FITs) conducted in colorectal cancer (CRC) screening could lead to performing unnecessary colonoscopies. Hemorrhoids are a possible cause of FP FIT results; however, studies on this topic are extremely rare. We investigated whether hemorrhoids are associated with FP FIT results.

Materials and Methods: A retrospective study was conducted at a university hospital in Korea from June 2013 to May 2015. Of the 34547 individuals who underwent FITs, 3946 aged ≥ 50 years who underwent colonoscopies were analyzed. Logistic regression analysis was performed to determine factors associated with FP FIT results.

Results: Among 3946 participants, 704 (17.8%) showed positive FIT results and 1303 (33.0%) had hemorrhoids. Of the 704 participants with positive FIT results, 165 had advanced colorectal neoplasia (ACRN) and 539 had no ACRN (FP results). Of the 1303 participants with hemorrhoids, 291 showed FP results, of whom 81 showed FP results because of hemorrhoids only. Participants with hemorrhoids had a higher rate of FP results than those without hemorrhoids (291/1176, 24.7% vs. 248/2361, 10.5%; $p < 0.001$). Additionally, the participants with hemorrhoids as the only abnormality had a higher rate of FP results than those experiencing no such abnormalities (81/531, 15.3% vs. 38/1173, 3.2%; $p < 0.001$). In multivariate analysis, the presence of hemorrhoids was identified as an independent predictor of FP results (adjusted odds ratio, 2.76; 95% confidence interval, 2.24–3.40; $p < 0.001$).

Conclusion: Hemorrhoids are significantly associated with FP FIT results. Their presence seemed to be a non-negligible contributor of FP results in FIT-based CRC screening programs.

Key Words: Hemorrhoids, false-positive, fecal immunochemical test

INTRODUCTION

Colorectal cancer (CRC)-associated mortality has been effectively reduced by removing precursor lesions.^{1,2} However, CRC remains the third most common cancer in Western countries, and its incidence is rapidly increasing, especially in Asia.³⁻⁵ Therefore, prevention and early detection of CRC has emerged

as an important global issue, and many countries are conducting population-based CRC screening programs by means of fecal immunochemical tests (FITs). FITs are currently recognized as the best available non-invasive means of investigation in CRC screening programs.⁶

After screening by FITs, participants with positive FIT results are required to undergo colonoscopic examinations. However, FITs have been reported to show low positive predictive values for advanced colorectal neoplasm (ACRN) (about 39–52%).⁷⁻¹⁰ In other words, in almost half of all individuals showing positive FIT results, no ACRN is detected on performing colonoscopy.⁷⁻¹¹ These false-positive (FP) results could cause psychological stress and anxiety because of the possibility of cancer, and could also lead to unnecessary colonoscopies that increase costs and adverse event risks during the diagnostic procedure. Data on risk factors of FP FIT results are clinically important for the individualization of CRC screening programs.

Hemorrhoids are major sources of rectal bleeding, and their

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Corresponding author: Dr. Yoon Suk Jung, Division of Gastroenterology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 03181, Korea.
Tel: 82-2-2001-8577, Fax: 82-2-2001-8360, E-mail: ys810.jung@samsung.com

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presence may be a possible cause of FP FIT results. Nevertheless, studies evaluating the association between hemorrhoids and FP FIT results are extremely rare. To date, only a few studies have investigated this topic.^{8,12,13} Two previous studies showed a lack of association between FP FIT results and the presence of hemorrhoids.^{8,13} Another recent study also showed that hemorrhoids could only infrequently be designated as the solitary cause of FP FIT results.¹² However, these previous results were contrary to our expectations. Hemorrhoids are a plausible explanation for occult bleeding, and in fact, clinicians do not infrequently experience cases that have positive FIT results caused by hemorrhoids. We speculated that hemorrhoids could cause FP FIT results, and the results of the previous studies led us to question whether hemorrhoids are indeed unrelated with FP results. Moreover, the previous studies included a rel-

atively small number of subjects. Therefore, the present study was conducted to evaluate the association between the presence of hemorrhoids and FP FIT results in a large sample of subjects attending a health-screening program.

MATERIALS AND METHODS

Study population

The National Cancer Screening Program (NCSP) of Korea provides a single annual FIT for adults aged 50 years or older for initial CRC screening and a confirmatory colonoscopy as a second test for those with a positive FIT. This retrospective study consisted of participants who underwent a single FIT for CRC screening through the NCSP at Kangbuk Samsung Hospital in

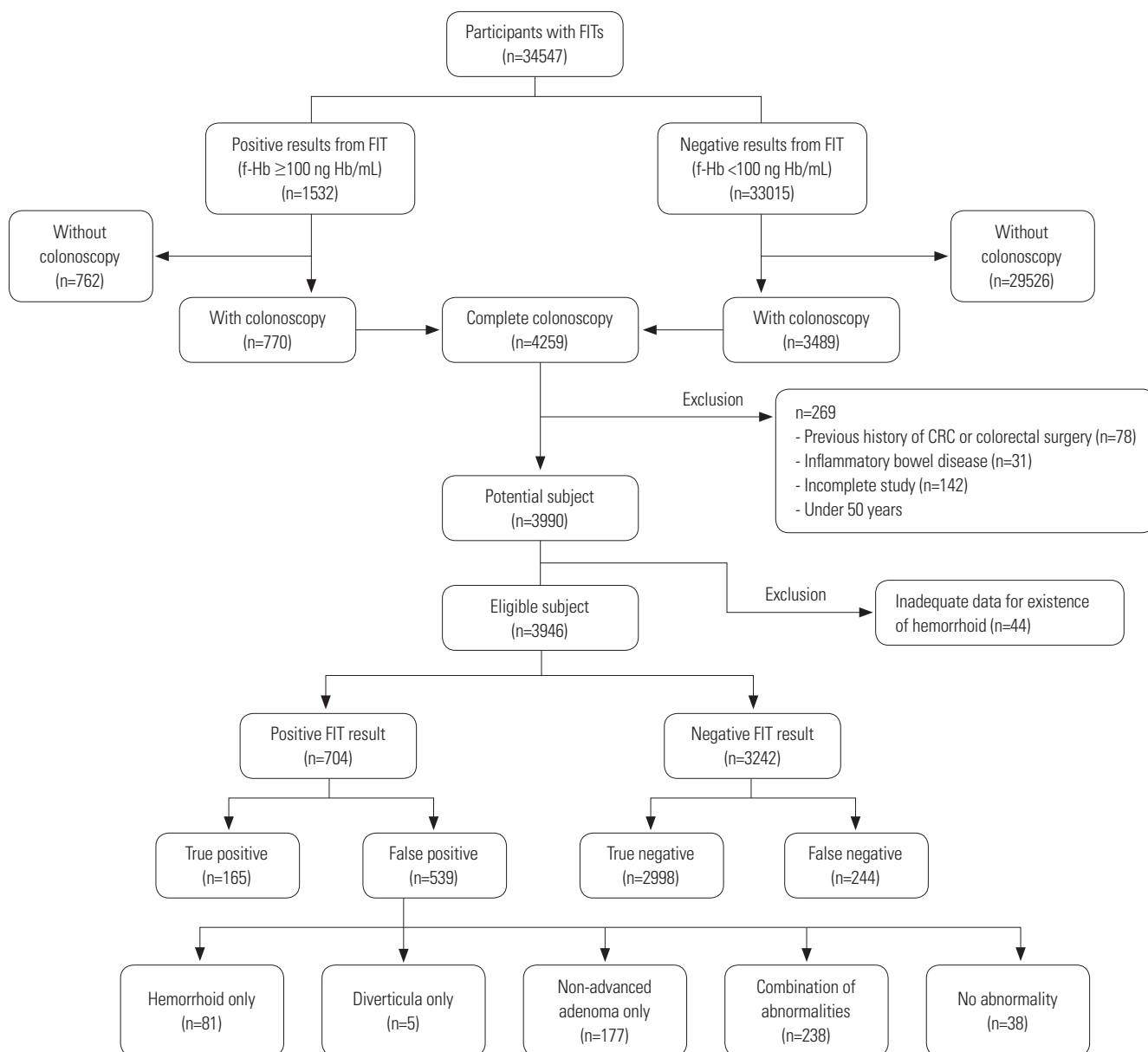


Fig. 1. Flow diagram illustrating the selection of study subjects. FIT, fecal immunochemical test; F-Hb, fecal hemoglobin; CRC, colorectal cancer.

Korea, from June 2013 to May 2015. Of the 34547 participants who underwent FITs, 1532 (4.4%) showed positive results and 33015 (95.6%) showed negative results. Of these participants, 770 with positive FIT results and 3489 with negative FIT results underwent colonoscopy.

The exclusion criteria were set as follows: history of CRC or colorectal surgery (n=78), history of inflammatory bowel disease (n=31), incomplete colonoscopy (n=142) such as that in which the cecum was not reached (n=3), inadequate bowel preparation (n=131), lack of adequate biopsy (n=8), age less than 50 years (n=18), and inadequate data on the presence of hemorrhoids (patients who had no picture of endoscopic retroflexion, n=44). Finally, the total number of eligible subjects for the study was 3946 (Fig. 1).

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, which exempted the requirement for informed consent because we only assessed non-identifiable data.

Measurements and definitions

Data on medical history and health-related behavior were collected through a self-administered questionnaire, whereas physical measurements and laboratory tests were performed by trained staff. Blood samples were collected from the antecubital vein after at least a 10-hour fast. Serum levels of total cholesterol and triglycerides were determined using an enzymatic colorimetric assay. Fasting blood glucose (FBG) levels were measured using the hexokinase method. For blood pressure (BP) measurements, the average of two measurements was used for the data analysis.

Body mass index (BMI) was calculated by dividing measured weight (kg) by height squared (m^2). Obesity was defined as BMI $\geq 25 \text{ kg}\cdot\text{m}^{-2}$, which is the proposed cut-off for the diagnosis of obesity in Asians.¹⁴ Metabolic syndrome (MetS) was diagnosed when three or more of the following criteria were satisfied: abdominal obesity ($\geq 90 \text{ cm}$ and $\geq 80 \text{ cm}$ in Asian men and women, respectively), elevated FBG levels ($\geq 100 \text{ mg/dL}$ or use of

glucose-lowering medications), elevated BP ($\geq 130 \text{ mm Hg}$ systolic, $\geq 85 \text{ mm Hg}$ diastolic, or intake of antihypertensive drugs), elevated triglyceride levels ($\geq 150 \text{ mg/dL}$), and reduced high-density lipoprotein cholesterol levels ($< 40 \text{ mg/dL}$ and $< 50 \text{ mg/dL}$ in men and women, respectively).¹⁵ The FIT positivity cut-off value was designated as 100 ng hemoglobin (Hb)/mL.

Fecal immunochemical test

All the participants were instructed on how to collect their fecal samples at the screening center, and no dietary- or medication-related restrictions were advised. For each participant, the collected fecal material was placed in a sampling tube (Eiken Chemical Company, Tokyo, Japan) containing 2.0 mL of buffer designed to minimize the degradation of Hb and sent to the laboratory sealed in a plastic bag. Quantitation of the fecal Hb was performed using OC-SENSOR DIANA (Eiken Chemical Company), an immunoassay-based test that uses rabbit polyclonal antibodies to detect Hb in the feces. This test is a turbidimetric latex agglutination test in which the Hb present in the patient sample combines with latex-coated antibodies to cause a change in the absorbance. A light beam is passed through the reaction cells, and changes in the intensity of the light beam are measured. The test is performed using an automated analyzer, and qualitative results are generated. The results of FIT are expressed in nanograms of Hb per milliliter of buffer, and OC-SENSOR, most widely used for conducting quantitative FIT, commonly applies a cut-off of 100 nanograms of Hb per mL buffer (100 ng Hb/mL, equivalent to 20 micrograms of Hb per gram of the feces).¹⁶ We performed a regular calibration analysis once a month, and the regular quality control analysis was done with two levels of control materials every working day using materials provided by the manufacturer.

Colonoscopy and histologic examination

Colonoscopy was performed by experienced gastroenterologists using an EVIS LUCERA CV-260 colonoscope (Olympus,

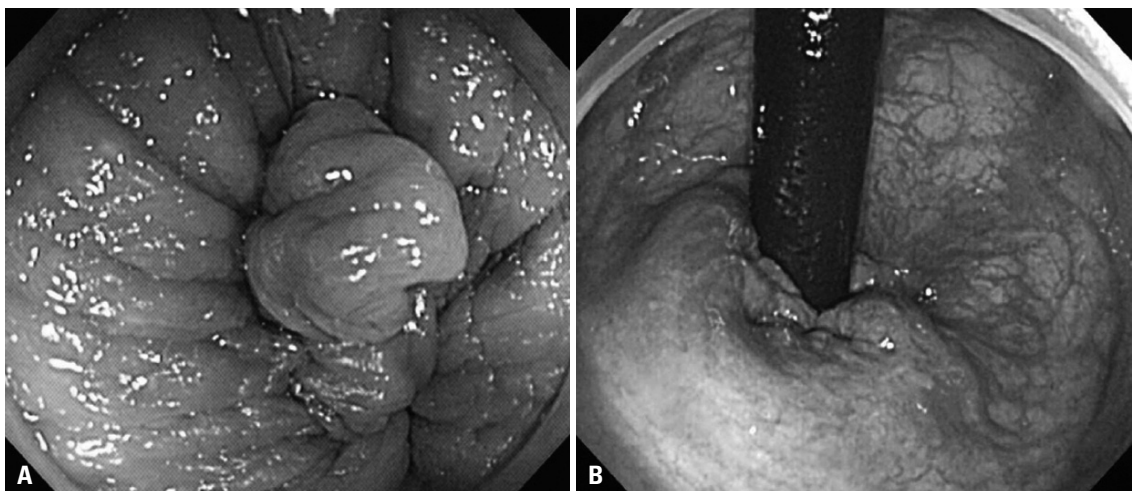


Fig. 2. (A) External hemorrhoid. (B) Internal hemorrhoid.

Tokyo, Japan). All the participants took 4 L of polyethylene glycol solution for bowel preparation. Colonoscopy was considered complete when the cecum was intubated. The bowel cleansing adequacy was assessed using the Boston Bowel Preparation Scale.¹⁷ Based on this scale, we defined inadequate bowel preparation as a score of 0 or 1 on any colon segment, and adequate preparation as a score of ≥ 2 for all locations.

The presence of hemorrhoids included external or internal hemorrhoid. An external hemorrhoid was defined as when an enlarged vein was located at or below the dentate line (Fig. 2A), while an internal hemorrhoid was defined as when an enlarged vein originating above the dentate line was found at retroflexion of colonoscope (Fig. 2B).¹⁸ In order to eliminate risks of underreporting or overreporting hemorrhoids between endoscopists (inter-observer variability), two endoscopists (N. H. K.

and Y. S. J.) independently evaluated the presence of hemorrhoids by reviewing colonoscopic pictures for all study participants. If there were any disagreements, a third endoscopist (J. H. P.) determined the presence of hemorrhoids. Additionally, to evaluate the presence of hemorrhoids more accurately, we excluded 44 patients who had no pictures of endoscopic retroflexion, because it was difficult to judge whether they had hemorrhoids or not. The grade of hemorrhoids could not be evaluated by endoscopic pictures, because it could be judged by spontaneous or manual reduction.¹⁸ The presence of diverticula was classified retrospectively as reported in the endoscopy report.

All detected polypoid lesions were biopsied or removed and histologically assessed by experienced pathologists. Polyps were classified by number, size, and histologic characteristics

Table 1. Baseline Characteristics of Participants with and without Hemorrhoids

	Total (n=3946)	Hemorrhoids (n=1303)	No hemorrhoid (n=2643)	p value
Age, yrs (mean)	64.3±7.8	64.9±7.8	64.0±7.8	0.678
Male sex	2136 (54.1)	716 (55.0)	1420 (53.7)	0.468
Current or ex-smoker*	1474/3603 (40.9)	480/1186 (40.5)	994/2417 (41.1)	0.708
BMI (kg/m ²) [†]	23.9±2.9	23.9±2.9	24.0±2.9	0.477
Obesity (BMI ≥ 25.0 kg/m ²) [†]	1100/3210 (34.3)	368/1045 (35.2)	732/2165 (33.8)	0.432
MetS [†]	918/3210 (28.6)	289/1045 (27.7)	629/2165 (29.1)	0.412
Abdominal obesity [‡]	1279/3210 (39.8)	410/1045 (39.2)	869/2165 (40.1)	0.624
Elevated FBG [§]	1234/3210 (38.4)	392/1045 (37.5)	842/2165 (38.9)	0.452
Elevated BP [¶]	1790/3210 (55.8)	590/1045 (56.5)	1200/2165 (55.4)	0.581
Elevated TG [¶]	834/3210 (26.0)	261/1045 (25.0)	573/2165 (26.5)	0.367
Reduced HDL-C ^{**}	631/3210 (19.7)	203/1045 (19.4)	428/2165 (19.8)	0.819
F-Hb concentration, ng Hb/mL	81.8±213.7	135.1±271.6	55.4±172.4	<0.001
Any adenoma	2065 (52.3)	696 (53.4)	1369 (51.8)	0.339
LGD	2053 (52.0)	693 (53.2)	1360 (51.5)	0.307
HGD	54 (1.4)	20 (1.5)	34 (1.3)	0.527
TVA or VA	20 (0.5)	8 (0.6)	12 (0.5)	0.506
Size ≥ 10 mm	357 (9.0)	110 (8.4)	247 (9.3)	0.352
3 or more adenomas	632 (16.0)	220 (16.9)	412 (15.6)	0.297
Advanced adenoma	372 (9.4)	117 (9.0)	255 (9.6)	0.499
High risk adenoma	774 (19.6)	253 (19.4)	521 (19.7)	0.826
Cancer	72 (1.8)	26 (2.0)	46 (1.7)	0.574
Intramucosal cancer	23 (0.6)	6 (0.5)	17 (0.6)	0.478
Stage I–II	28 (0.7)	11 (0.8)	17 (0.6)	0.479
Stage III–IV	21 (0.5)	9 (0.7)	12 (0.5)	0.337
ACRN	409 (10.4)	127 (9.7)	282 (10.7)	0.371
Overall CRN	2082 (52.8)	702 (53.9)	1380 (52.2)	0.314
Proximal ACRN	171 (4.3)	51 (3.9)	120 (4.5)	0.364
Distal ACRN	206 (5.2)	67 (5.1)	139 (5.3)	0.876
Diverticula	414 (10.5)	204 (15.7)	210 (7.9)	<0.001

FIT, fecal immunochemical test; BMI, body mass index; MetS, Metabolic syndrome; FBG, fasting blood glucose; BP, blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; F-Hb, fecal hemoglobin; LGD, low grade dysplasia; HGD, high grade dysplasia; TVA, tubulovillous adenoma; VA, villous adenoma; ACRN, advanced colorectal neoplasia; CRN, colorectal neoplasia.

Values are presented as mean±standard deviation or number (%).

*Data for smoking status were available for 3603 participants, [†]Data for BMI, obesity, and MetS were available for 3210 participants, [‡]Abdominal circumference ≥ 90 cm and ≥ 80 cm in Asian men and women, respectively, [§]FBG ≥ 100 mg/dL or use of glucose-lowering medications, [¶]BP $\geq 130/85$ mm Hg or use of antihypertensive drugs, ^{**}HDL-C < 40 mg/dL in men or < 50 mg/dL in women.

(tubular, tubulovillous, or villous adenoma; hyperplastic polyp; inflammatory polyp; sessile serrated adenoma or traditional serrated adenoma). Pathologic results of hyperplastic polyps or inflammatory polyps were considered normal findings. Dysplasia was classified as low or high. Advanced adenoma was defined as the presence of one of the following features: >10 mm diameter, tubulovillous or villous structure, and high-grade dysplasia.¹⁹ High-risk adenoma was defined as advanced adenoma or three or more adenomas.¹⁹ ACRN was defined as a cancer or advanced adenoma, and overall CRN was defined as a cancer or any adenoma.

Statistical analysis

Data are expressed as a mean±standard deviation or frequency (%). Baseline characteristics and colorectal lesions in the participants with and without hemorrhoids were compared by the chi-square analysis or Fisher’s exact test for categorical variables and by Student’s t-test for continuous variables. FP FIT results were defined as positive FIT results in participants who were identified with no ACRN on subsequent colonoscopies. We compared the frequency of FP FIT results in the participants with hemorrhoids with that in the participants without hemorrhoids using chi-square analysis. Additionally, the frequency of FP results in the participants with hemorrhoids as the only abnormality was compared with that in participants without any abnormalities. Logistic regression analysis was performed to determine factors associated with FP FIT results. In multivariate analysis, age, sex, smoking status, and colonic abnormalities that were significant in univariate analysis were adjusted. For each variable, the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were reported. All *p* values <0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS statistics 18.0 (IBM, Armonk, NY, USA).

RESULTS

Baseline characteristics of study population

A total of 3946 participants who underwent FIT and a complete colonoscopy for CRC screening were eligible for the analysis (Fig. 1). Among the 3946 participants, 704 (17.8%) showed positive FIT results and 1303 (33.0%) had hemorrhoids. Of the 1303 participants with hemorrhoids, 291 showed FP results. Further, of these 291 participants, 81 showed FP results because of hemorrhoids only.

Baseline characteristics and colorectal lesions of the participants with and without hemorrhoids are compared in Table 1. Mean age of the study population was 64.3 years and the proportion of men was 54.1%. Age and sex differences were not observed in the two groups. Data for BMI, obesity, and MetS were available for 3210 participants, and data for smoking status were available for 3603 participants. There were no significant differences in the proportion of current or ex-smokers, obesity, and MetS between the two groups. Fecal Hb concentrations were significantly higher in the subjects with hemorrhoids (135.1 vs. 55.4 ng Hb/mL, *p*<0.001).

A total of 372 advanced adenoma cases (9.4%), 72 CRC cases (1.8%), and 409 ACRN cases (10.4%) were detected among the study population. There were no significant differences in the prevalences of advanced adenoma (9.0% vs. 9.6%, *p*=0.499), CRC (2.0% vs. 1.7%, *p*=0.574), and ACRN (9.7% vs. 10.7%, *p*=0.371) between subjects with hemorrhoids and those without hemorrhoids. The proportion of diverticula was higher in the subjects with hemorrhoids (15.7% vs. 7.9%, *p*<0.001).

In addition, we compared baseline characteristics between patients who did and did not undergo a colonoscopy among patients with positive FIT results and among patients with negative FIT results, respectively, because the differences among the groups might cause selection bias. As a result, among patients with positive FIT results, the proportion of male sex was higher in patients who underwent a colonoscopy than in those who did not (57.0% vs. 47.5%, *p*<0.001), although other baseline characteristics did not differ between the two groups. Among patients with negative FIT results, the mean age was higher in patients who underwent a colonoscopy than in those who did not (64.0±7.8 vs. 63.2±8.4, *p*<0.001), and other baseline characteristics did not differ between the two groups (data not shown).

False-positive FIT results and hemorrhoids

Of the 704 participants who showed positive FIT results, 165 (23.4%) had ACRN and 539 (76.6%) had no ACRN (FP results). In 81 individuals (15.0%) who showed FP results, the presence of hemorrhoids was the only abnormality, while in 38 other individuals (7.1%) showing FP results, normal findings without any abnormalities were observed on colonoscopy (Fig. 1).

Among the 3537 subjects without ACRN, hemorrhoids were detected in 1176 (33.2%) subjects. We compared the frequency of FP FIT results in subjects with hemorrhoids versus those without hemorrhoids among the 3537 subjects without ACRN (Table 2). The frequency of FP FIT results in the subjects with

Table 2. Frequency of False-Positive FIT Results in Subjects with Versus without Hemorrhoids among 3537 Subjects without Advanced Neoplasia

	Total	Hemorrhoids, n (%)	No hemorrhoid, n (%)*	<i>p</i> value
Positive FIT results (≥100 ng Hb/mL)	539	291 (24.7)	248 (10.5)	<0.001
Negative FIT results (<100 ng Hb/mL)	2998	885 (75.3)	2113 (89.5)	
Total	3537	1176 (100.0)	2361 (100.0)	

FIT, fecal immunochemical test; Hb, hemoglobin.

*Other colonic abnormalities may be present in both the groups.

hemorrhoids was significantly higher than that in the subjects without hemorrhoids (291/1176, 24.7% vs. 248/2361, 10.5%; $p < 0.001$). To exclude the potential confounding influences of other colonic abnormalities, such as diverticula or non-advanced adenoma, the frequency of FP FIT results in the subjects without any abnormalities were compared to that in the subjects with hemorrhoids as their only abnormality (Table 3). The subjects with hemorrhoids as the only abnormality had a higher rate of FP results than those without any abnormalities (81/531, 15.3% vs. 38/1173, 3.2%; $p < 0.001$).

Risk factors for false-positive FIT results

A logistic regression analysis was performed to determine which abnormalities significantly attribute to FP FIT results. Table 4 presents the risk factors for FP FIT results according to age, sex, smoking status, and colonic abnormalities, including hemorrhoids, diverticula, and non-advanced adenoma. In the univariate analysis, older age (OR, 1.02; 95% CI, 1.01–1.03; $p = 0.001$), the presence of hemorrhoids (OR, 2.78; 95% CI, 2.31–3.34; $p < 0.001$), diverticula (OR, 1.69; 95% CI, 1.30–2.19, $p < 0.001$), and non-advanced adenoma (OR, 5.09; 95% CI, 4.14–6.27; $p < 0.001$) were significantly associated with FP FIT results.

In the multivariate analysis, adjusted for age, sex, and smoking status, presence of diverticula, and presence of non-advanced adenomas, the presence of hemorrhoids was identified as an independent risk factor of FP results [adjusted OR (AOR), 2.76; 95% CI, 2.24–3.40; $p < 0.001$]. In addition, diverticula (AOR, 1.43; 95% CI, 1.06–1.93; $p = 0.019$) and non-advanced adenoma (AOR, 5.15; 95% CI, 4.10–6.47; $p < 0.001$) were identified as independent risk factors of FP results.

DISCUSSION

This large-scale study of 3946 asymptomatic participants evaluated the association between the presence of hemorrhoids and FP FIT results. In our study, hemorrhoids were the only abnormality detected in 15.0% of all FP results. We found that the frequency of FP FIT results in the subjects with hemorrhoids was significantly higher than that in the subjects without hemorrhoids. Additionally, the subjects with hemorrhoids as the only abnormality had a significantly higher rate of FP results than those without any abnormalities. Furthermore, in multivariate analysis adjusted for age, sex, smoking status, and other colonic abnormalities, the presence of hemorrhoids was identified as an independent risk factor for FP results.

FITs use specific antibodies that selectively react with the globin moiety of the human Hb, and detect colonic blood with great sensitivity (at a level of as little as 0.3 mL of blood added to stool).^{20,21} Because globin is rapidly degraded by proteases during its passage through the gastrointestinal tract, FIT does not detect small amounts of blood in the upper GI tract, and selectively recognizes occult bleeding of colorectal origin.^{20,22} Because of these characteristics, FIT has been widely adopted as a CRC screening tool.⁶ However, about 40–60% of the subjects with positive FIT results are found to have no ACRN.^{7–11} These FP results could lead to unnecessary colonoscopies, which increase costs and adverse event risks during the procedure, and also cause psychological stress and anxiety associated with the possibility of having cancer. A recent study showed that a person with FP FIT results recalled for further diagnostic tests could experience a high level of anxiety and a lower quality of life, and this psychological distress can last until 6 weeks after a normal colonoscopy.²³ Meanwhile, re-attendance in screening rounds was reported to be lower in individuals who had previ-

Table 3. Frequency of False-Positive FIT Results in Subjects with Hemorrhoids Only Versus in Subjects without Any Abnormalities

	Total	Hemorrhoids only, n (%)	No abnormalities, n (%)	p value
Positive FIT results (≥ 100 ng Hb/mL)	119	81 (15.3)	38 (3.2)	<0.001
Negative FIT results (<100 ng Hb/mL)	1585	450 (84.7)	1135 (96.8)	
Total	1704	531 (100.0)	1173 (100.0)	

FIT, fecal immunochemical test; Hb, hemoglobin.

Table 4. Univariate and Multivariate Analyses for Factors Associated with False-Positive FIT Results (n=539)

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	AOR	95% CI	p value
Age	1.02	1.01–1.03	0.001	1.01	0.99–1.02	0.304
Male sex	0.93	0.77–1.11	0.415	0.80	0.60–1.06	0.112
Current or ex-smoker	0.92	0.75–1.12	0.383	0.92	0.69–1.22	0.549
Colonic abnormalities						
Hemorrhoids	2.78	2.31–3.34	<0.001	2.76	2.24–3.40	<0.001
Diverticula	1.69	1.30–2.19	<0.001	1.43	1.06–1.93	0.019
Non-advanced adenomas	5.09	4.14–6.27	<0.001	5.15	4.10–6.47	<0.001

FIT, fecal immunochemical test; OR, odds ratios; AOR, adjusted odds ratios; CI, confidence intervals.

Multivariate analysis was adjusted for age, sex, smoking status, presence of diverticula, and presence of non-advanced adenomas.

ously undergone FP screening tests.²⁴ Therefore, it is clinically important to reveal the risk factors of FP FIT results to ensure individualization of the CRC screening programs.

Hemorrhoids are one of the major sources of rectal bleeding, and hemorrhoidal bleeding is likely to be a cause of FP FIT results. As expected, our study showed that hemorrhoids are significantly associated with FP FIT results. To date, only a few studies have evaluated the influence of hemorrhoids on the effectiveness of FIT-based screening programs.^{8,12,13,25} However, these previous studies have showed conflicting results. In a case-control study of 82 subjects with hemorrhoids, 82 subjects with CRC, and 82 healthy subjects, FIT positive rates in the subjects with and without hemorrhoids were found to be similar (6.9% vs. 6.5%).²⁵ The study indicated that FIT is unsuitable for the diagnosis of hemorrhoids, and colonoscopy is necessary in the cases where the FIT results are positive but there is a sign of hemorrhoids.²⁵ However, they did not compare the positive rates of FIT among the subjects with hemorrhoids as the only abnormality at colonoscopy and those without any abnormalities. Additionally, they did not evaluate whether hemorrhoids are associated with FP FIT results. One population-based study conducted in the Netherlands included 1112 asymptomatic individuals and investigated risk factors for false FIT results. They reported that the presence of hemorrhoids is not associated with FP FIT results.¹³ In another Taiwanese study involving 2796 asymptomatic participants, the prevalence of hemorrhoids was similar among those with positive FIT results (15.4%) and those with negative FIT results (13.3%). The study also showed a lack of association between positivity of FIT and the presence of hemorrhoids among the participants with negative findings after undergoing colonoscopy, and suggested that hemorrhoids should not be used to explain a positive FIT result or hamper the indication for colonoscopy.⁸ Similar to our study, a recent study focused on the contribution of hemorrhoids to the frequency of FP FIT results. The study demonstrated that the subjects with hemorrhoids as the only abnormality did not have more positive results, compared with the subjects without any abnormalities (9/134, 6.7% vs. 43/886, 4.9%; $p=0.396$). Further, the authors concluded that the number of FP FIT results that can be attributed to hemorrhoids only is small; therefore, hemorrhoids should not be used as a reason to determine whether any patient with a positive FIT result should be referred for colonoscopy.¹² The reasons for this disparity in the influence of hemorrhoids on FP FIT results between our study and the previous studies are not clear; however, some plausible explanations may be differences in the cut-off values for positivity, the characteristics of the participants, the study design, or the number of subjects under study. Further large-scale prospective studies are required to clarify the impact of hemorrhoids on the FIT results in FIT-based CRC screening programs.

The presence of hemorrhoids is a common condition in the target age range for CRC screening.²⁶ Additionally, a substan-

tial proportion of the subjects with prior FP FIT results are more likely to have second positive results during the repeated testing as compared to those without any prior FP results; this is possibly because of a persistent source of intestinal bleeding.²⁷ Hemorrhoids may also give rise to repeated FP results. Actually, not uncommonly, clinicians encounter cases in which positive FIT results are caused by hemorrhoids. When patients who are found with no abnormalities on undergoing recent colonoscopies (e.g., within 1 or 2 years) show positive FIT results, it may often be caused by hemorrhoids. Based on our results, before referring for colonoscopy, it is important to confirm whether hemorrhoids are known or expected to be present in a patient showing positive FIT results. We suggest that when patients who are found with no abnormalities except for hemorrhoids on undergoing recent colonoscopies under adequate bowel preparation show positive FIT results, physicians need to consider observation carefully rather than recommend colonoscopy immediately in young patients or patients without risk factors for CRN. Our study supports that hemorrhoids may be a clinically important condition affecting quality and effectiveness of FIT-based CRC screening programs.

The strength of our study was that our study included a large number of subjects, compared to the related studies, and we investigated the influence of hemorrhoids on the FP FIT results systematically and in detail. However, our study has several limitations. First, this was a retrospective study with a corresponding potential bias in design. About half of the participants with positive FIT results did not undergo colonoscopy. In addition, a large proportion of participants with negative FIT results were excluded. These excluded participants might cause selection bias. However, we confirmed that baseline characteristics between patients who had a positive FIT results that did and did not undergo a colonoscopy did not differ significantly, except for sex, and also, baseline characteristics between those who had negative FIT results that did and did not undergo a colonoscopy did not differ significantly, except for age. Second, our study was not population-based but rather hospital-based. As a result, there is likely some degree of selection bias. However, because our study consisted of asymptomatic participants who underwent FITs and colonoscopies as part of a health screening, a referral bias is unlikely. Finally, data on medication use, such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and anticoagulant, which could be possible confounders, were not available. These drugs could increase the risk of bleeding from non-neoplastic lesions and cause FP FIT results.^{8,28} In addition, the use of aspirin or NSAID could be related with the risk of CRN development.

In conclusion, a significant number of subjects with hemorrhoids had FP FIT results. Moreover, the presence of hemorrhoids was found to be an independent risk factor for FP results. The impact of hemorrhoids on the effectiveness of FIT-based CRC screening programs appears to be non-negligible.

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