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Original Article

The factors associated with negative colonoscopy in screening subjects with positive immunochemical stool occult blood test outcomes

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Abstract

Background: The immunochemical fecal occult blood test (iFOBT) is an alternative method to colonoscopy that can be used for colorectal cancer (CRC) screening. If the iFOBT result is positive, a colonoscopy is recommended. In this retrospective study, we identify factors associated with negative colonoscopy and positive iFOBT results obtained during CRC screening.
Methods: We collected data for subjects who received a colonoscopy at Taipei Veterans General Hospital after receiving a positive iFOBT result during CRC screening from January 2015 to December 2015. Subjects' baseline data, medications, and co-morbidities as well as colonoscopy and histological findings were recorded. A negative colonoscopy result was defined as no detection of any colorectal neoplasia including non-advanced adenoma, advanced adenoma, and adenocarciona. Multivariate logistic regression analysis was conducted to identify the associated factors in screening subjects with positive iFOBT but negative colonoscopy results.
Results: 559 (46.3%) out of 1207 eligible study subjects received a colonoscopy with a negative result. Multivariate logistic regression analysis revealed that the use of antiplatelets [odds ratio (OR) = 0.654; 95% confidence interval (CI), 0.434−0.986], occurrence of hemorrhoid (OR = 0.595; 95% CI, 0.460−0.768), and the existence of colitis/ulcer (OR = 0.358; 95% CI, 0.162−0.789) were independent factors associated with negative colonoscopy but positive iFOBT results during CRC screening. The colon clean level, underlying diseases of gastrointestinal bleeding tendency (e.g., chronic kidney disease, cirrhosis), and the use of anticoagulant or nonsteroidal anti-inflammatory agents were not associated with negative colonoscopy and positive iFOBT results.
Conclusion: The use of antiplatelet agents and the presence of hemorrhoids and colitis/ulcers were factors associated with negative colonoscopy and positive iFOBT results.

Keywords: Antiplatelet agents; Colonoscopy; Colorectal neoplasia; Hemorrhoid; Immunochemical fecal occult blood test

1. Introduction

The incidence and mortality related to colorectal cancer (CRC) is rising in Asia.[1] The detection and removal of pre-cancerous lesions through CRC screening with colonoscopy can reduce CRC incidence and mortality.[2] However, previous

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studies showed significantly lower adherence to colonoscopy compared with the fecal occult blood test (FOBT) during CRC screening.[3] The immunochemical fecal occult blood test (iFOBT), which is differentiated from the guaiac FOBT (gFOBT), is a valid and alternative method to colonoscopy in CRC screening.[4,5] If the iFOBT result is positive, a colonoscopy is recommended.[6] Though a meta-analysis study showed that iFOBTs are moderately sensitive, highly specific, and have high overall diagnostic accuracy for detecting CRC,[7] some false-positive results exist. Therefore, some risk factors and scoring systems − with or without iFOBT − have been established to increase the accuracy of advanced neoplasia detection during screening.[8−10] Age, personal history of colon adenomatous polyp and inflammatory bowel disease, family history of CRC, smoking, lack of physical activity, and obesity are all risk factors for CRC.[11] Previous studies have also shown that age, male gender, current or past smoking status, personal history of colon adenoma, and metabolic syndrome (MS) were associated with colorectal neoplasia.[12−14] However, only some studies have evaluated the predictors of negative colorectal neoplasia by colonoscopy in screening subjects with positive iFOBT results,[15] and few studies considered whether hemorrhoid or underlying co-morbidities comprise a confounding factor for positive iFOBT results.

In this study, we tried to identify the factors associated with negative colonoscopy results after positive iFOBT outcomes during CRC screening.

2. Methods

The iFOBT test has been used for CRC screening in Taiwan since 2003. Most of the screening subjects in this study who were 50−75 years old were included in the national CRC screening program. The program was directed by the Health Promotion Administration, Ministry of Health and Welfare of Taiwan. Some of the screening subjects in this study received their CRC screening from their physician's clinical practice at outpatient clinics. No specific diets or medications were restricted in screening subjects. All fecal samples were analyzed at a single central laboratory (Taipei Veterans General Hospital, Taipei, Taiwan), and the iFOBT was processed without rehydration using an automated reading technique (HM-Jack, Kyowa, Japan). The positivity cut-off value was set at $\geq$ 12 ng Hb/mL buffer according to the results of a pilot trial in a CRC screening setting.[16] A colonoscopy was recommended to subjects with positive iFOBT results.

We retrospectively collected the data of subjects who were given a colonoscopy at the Endoscopy Center for Diagnosis and Treatment of Taipei Veterans General Hospital due to a positive iFOBT result during CRC screening from January 2015 to December 2015. This study has been approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital (No: 2016-08-020BC), a tertiary medical center that provides medical services for part of the million habitants living in northern Taiwan. The following information were gathered for all of the subjects: age; gender; smoking behavior (current, past, ever smoking, or non); alcohol drinking (80 g or more weekly)[17]; family history of CRC defined as having one or more first-degree relatives with a previous diagnosis of CRC[8]; current medications (taking them regularly within 2 weeks before iFOBT) including antiplatelets (aspirin, clopidogrel, ticlopidine), nonsteroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 inhibitors, anticoagulants (warfarin, dabigatran, and rivaroxaban), steroids, selective serotonin reuptake inhibitors (SSRIs), dipyridamole, and bisphosphonates; underlying co-morbidities including hypertension, diabetes mellitus (DM), cirrhosis, chronic kidney disease (CKD) (baseline serum creatinine >1.5 mg/dL or estimated glomerular filtration rate <60 ml/min/1.73 m^2),[18] coronary artery disease, heart failure, peptic ulcer disease, and chronic obstructive pulmonary disease (COPD). Subjects who had past history of colorectal polyps after polypectomy, history of CRC, clinical symptoms of gastrointestinal (GI) bleeding, and with a known pre-existing pathology that could account for a positive FOBT result—for example, underlying colorectal neoplasia, inflammatory bowel disease, hematuria, and menstruation at the time of stool sample collection for the iFOBT and who had incomplete data collection including regarding the colonoscopy were excluded.

The laxative Klean-Prep® (containing polyethylene glycol 59.0 g, sodium sulphate 5.68 g, sodium bicarbonate 1.68 g, NaCl 1.46 g, potassium chloride 0.74 g and aspartame 0.04 g) was used for bowel preparation before colonoscopy.[19,20] Colonoscopy (CF-H260 AZI and CF-H290 AZI; Olympus, Tokyo, Japan) was performed by experienced gastroenterologists and colorectal surgeons. The withdrawal time was at least 6 min to minimize any chance of missing lesions. Detailed colonoscopic findings including angiodysplasia, diverticula, hemorrhoid, inflammation/ulcer, size and morphology of the neoplastic lesions (polypoid and non-polypoid, Paris classification), their numbers and location as well as cecal or terminal ileal intubation and colon clean level were recorded.[20] Experienced pathologists confirmed the diagnosis of hyperplastic polyp, adenomatous polyp (tubular, tubulovillous, villous, sessile adenoma), advanced adenoma, or adenocarcinoma after reviewing the histologic examination. Advanced adenoma was defined as adenoma size >10 mm, with villous or tubule-villus architecture, or with high-grade dysplasia.[19] Advanced neoplasia included advanced adenoma and adenocarcinoma.The location of the adenoma/neoplasia was regarded as distal if a single lesion (non-advanced adenoma, advanced adenoma, or adenocarcinoma) or the major lesion (in the case of multiple lesions) was found from the rectum to the splenic flexure. The location was regarded as proximal if the single lesion or the major lesion (in the case of multiple lesions) was found proximal from the splenic flexure. If subjects exhibited non-advanced adenoma at both sides without advanced neoplasia or advanced adenoma at both sides without adenocarcinoma, we defined that they had both side lesions. Colon preparation was scored by the Boston bowel preparation scale (BBPS) ranging from 0 to 9; good clean was defined as BBPS score $\geq$ 5 and poor clean was defined as BBPS score < 5.[20] A negative colonoscopy result was defined as no detection of any colorectal neoplasia including non-advanced adenoma,

advanced adenoma, or adenocarciona. A positive colonoscopy result was defined as detection of any colorectal neoplasia.

2.1. Statistical analysis

We compared the parameters of the patients with colorectal neoplasia (positive colonoscopy) and without colorectal neoplasia (negative colonscopy) that both received positive iFOBT results. Our primary endpoint was to identify the factors associated with negative colonoscopy results after receiving positive iFOBT results. Our secondary endpoint was to identify the predictors of positive colonoscopy after a positive iFOBT result.

All statistical analyses were performed using the SPSS software (Version 17.0, SPSS Inc., Chicago, Illinois, USA). Demographic data were expressed as frequency (percentage) or as mean ± standard deviation. Continuous variables were compared using Student's t-test, while categorical data were compared using the Chi-square test and Yates' correction or Fisher's exact test, as appropriate. Multivariate logistic regression analysis was conducted to identify the predictors of negative and positive colonoscopy in screening subjects with positive iFOBT outcomes. A two-sided $p < 0.05$ was considered statistically significant.

3. Results

During the one-year period, there were 1422 out of 8505 subjects with positive iFOBT results that had received a colonoscopy during CRC screening at Taipei Veterans General Hospital. After excluding 96 subjects with past history of colon polyps with polypectomy, 8 subjects with past history of colon cancer post-surgical intervention, 33 subjects with known pre-existing underlying colorectal lesions and inflammatory bowel disease, 6 subjects with concomitant hematuria and menstruation, 34 subjects with incomplete colonoscopy, 38 subjects without histological examination, a total of 1207 eligible subjects were enrolled for analysis (Fig. 1). After reviewing histological and colonoscopic reports, 408 cases had non-advanced adenoma, 180 cases had advanced adenoma, and 60 cases had colorectal adenocarcinoma. The positive colonoscopy group (i.e., the colorectal neoplasia group including non-advanced adenoma, advanced adenoma, and adenocarcinoma contained 648 cases (53.7%). Regarding lesion location, there were 202 subjects with a proximal site lesion, 334 subjects with a distal lesion, and 112 subjects with lesions at both sides. The negative colonoscopy group was comprised of 559 subjects.

When the baseline characteristics between the subjects with colorectal neoplasia (positive colonoscopy group) and subjects without any adenoma (negative colonoscopy group) were compared, the positive colonoscopy group were significantly older and had a higher rate of male gender, smoking (current or past smoking), and DM ($p < 0.05$) (Table 1) than those in the negative colonoscopy group. Interestingly and reasonably, the negative colonoscopy group had a significantly higher rate of hemorrhoid, colitis/ulcer, and hyperplastic polyp than those in the positive colonoscopy group ($p < 0.05$) (Table 1).

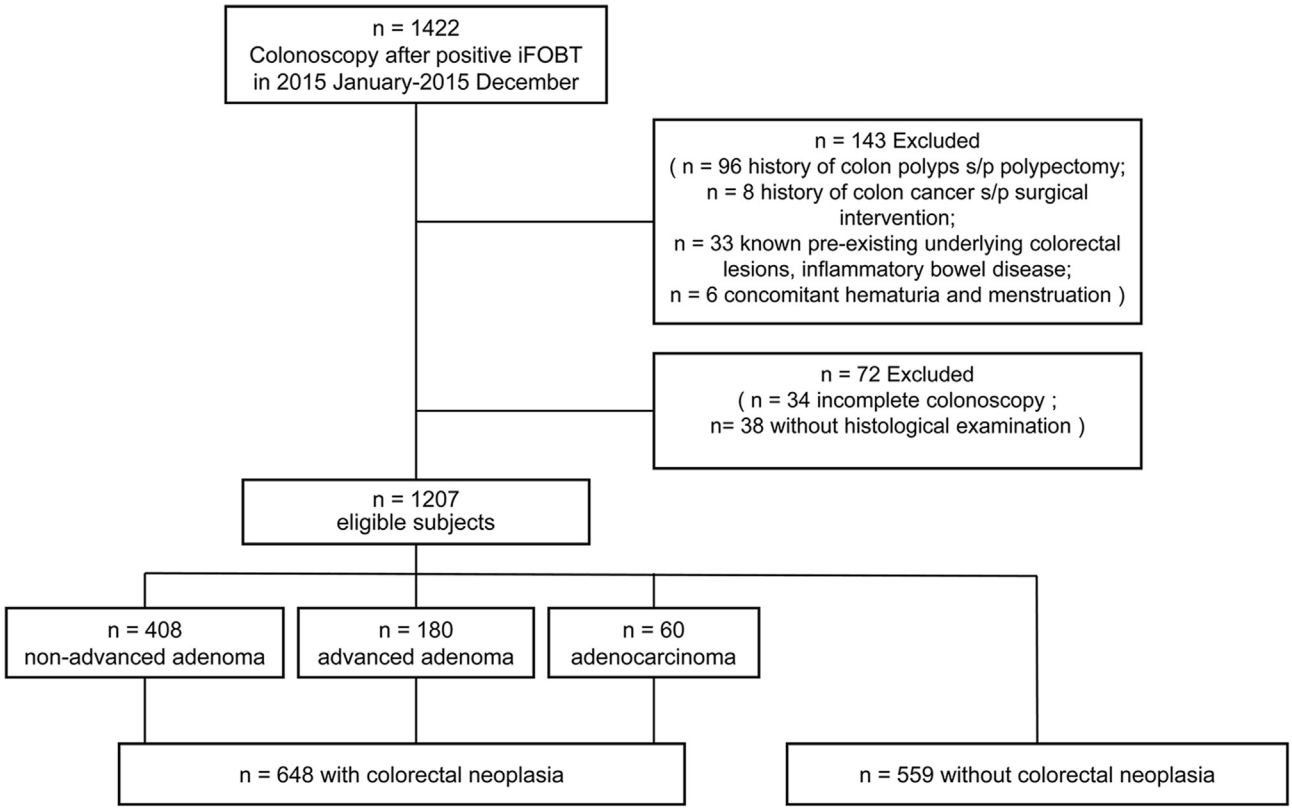

Fig. 1. The flowchart of enrolled subjects with colonoscopy after positive immunochemical fecal occult blood test.

Table 1
Baseline characteristics of colorectal cancer (CRC) screening subjects with positive immunochemical fecal occult blood test (iFOBT).

	Positive iFOBT with colorectal neoplasia n = 648	Positive iFOBT without colorectal neoplasia n = 559	*p*
Age	66.9 ± 10.6	62.7 ± 12.5	<0.001
Male, n (%)	381 (58.8)	300 (53.7)	0.041
Alcohol, n (%)	19 (2.9)	9 (1.6)	0.091
Current smoking, n	31 (4.8)	17 (3.0)	0.072
Past smoking, n	55 (8.5)	34 (6.1)	0.063
Ever smoking, n	86 (13.3)	51 (9.1)	0.014
Aspirin, n (%)	54 (8.3)	55 (9.8)	0.209
Clopidogrel, n (%)	12 (1.9)	9 (1.6)	0.463
Ticlopidine, n (%)	10 (1.6)	9 (1.6)	0.553
All antiplatelets, n	72 (11.1)	71 (12.7)	0.223
Dipyridamole, n	10 (1.5)	4 (0.7)	0.142
Warfarin, n (%)	6 (0.9)	11 (1.9)	0.107
Dabigatran, n (%)	7 (1.1)	4 (0.7)	0.350
Rivaroxaban, n (%)	6 (0.9)	3 (0.5)	0.350
All anticoagulants	21 (3.2)	16 (2.9)	0.417
NSAIDs, n (%)	43 (6.6)	46 (8.2)	0.172
Steroids, n (%)	22 (3.4)	24 (4.3)	0.254
SSRI, n (%)	9 (1.4)	8 (1.4)	0.570
Bisphosphonate, n	0 (0.0)	2 (0.4)	0.214
Cirrhosis, n (%)	11 (1.7)	16 (2.9)	0.121
CKD, n (%)	63 (9.7)	43 (7.7)	0.127
Heart failure, n (%)	16 (2.5)	13 (2.5)	0.512
Peptic ulcer, n (%)	70 (10.8)	78 (13.8)	0.058
COPD, n (%)	17 (2.6)	12 (2.1)	0.365
Hypertension, n (%)	274 (42.3)	222 (39.7)	0.199
CAD, n (%)	83 (12.8)	66 (11.8)	0.331
DM, n (%)	145 (22.4)	87 (15.6)	0.002
FH of CRC, n	24 (3.7)	25 (4.5)	0.298
Hemorrhoid, n (%)	249 (38.4)	281 (50.3)	<0.001
Diverticula, n (%)	127 (19.6)	106 (19.0)	0.419
Colitis/ulcer, n (%)	10 (1.5)	23 (4.1)	0.005
Angiodysplasia, n	2 (0.3)	0 (0.0)	0.288
Hyperplastic polyp	55 (8.5)	65 (11.6)	0.043
Good cleaning, n	518 (80.0)	434 (77.6)	0.154

Colorectal neoplasia included non-advanced adenoma, advanced adenoma, and adenocarcinoma.
iFOBT = immunochemical fecal occult blood test; CRC = colorectal cancer; NSAIDs = nonsteroidal anti-inflammatory drugs; SSRI = selective serotonine reuptake inhibitor; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease; DM = diabetes mellitus; FM = family history.

Multivariate logistic regression analysis revealed that the use of antiplatelets, occurrence of hemorrhoid, and colitis/ulcer were factors associated with negative colonoscopy results in subjects with positive iFOBT outcomes (odd ratio [OR] and 95% confidence interval < 1) (Table 2); also, age, smoking, and DM were all independent factors associated with positive colonoscopy after positive iFOBT outcomes (OR and 95% CI > 1) (Table 2). The colon clean level, use of NSAIDs and anti-coagulants, and underlying diseases of GI bleeding tendency like CKD and cirrhosis were not associated with negative colonoscopy results in subjects with positive iFOBT outcomes.

In the subgroup analysis for lesion sites, age and smoking were associated with proximal colorectal neoplasia after positive iFOBT results. However, hemorrhoid, colitis/ulcer, and hyperplastic polyp were factors associated with negative proximal colonoscopy results after positive iFOBT outcomes (Table 3). For detection of distal colorectal neoplasia, age, smoking, and DM were factors associated with distal colorectal neoplasia after positive iFOBT results (Table 4). However, hemorrhoid and antiplatelet usage were factors of negative distal colonoscopy after positive iFOBT outcomes.

4. Discussion

This study identified the factors associated with negative colonoscopy results (defined as no colorectal neoplasia) after positive iFOBT CRC screening outcomes and found that the use of antiplatelets, hemorrhoid, and colitis/ulcer, rather than the colon clean level, use of NSAIDs or anti-coagulants, and underlying diseases of GI bleeding tendency (CKD and cirrhosis) were the factors associated with negative colonoscopy in subjects with positive iFOBT CRC screening outcomes. In contrast, age, smoking, and DM were factors associated with positive colorectal neoplasia (non-advanced adenoma, advanced adenoma or adenocarcinoma) after colonoscopy in subjects with positive iFOBT screening results.

Age, smoking, family history of CRC, inflammatory bowel disease, increased body mass index (BMI), red meat intake, low physical activity, and less vegetable/fruit consumption

Table 2
Factors associated with colorectal neoplasia in positive iFOBT patients by multiple logistic regression analysis.

	Adjusted OR[a]	95% CI	*p*
Age	1.037	1.025–1.049	<0.001
Male	1.235	0.959–1.591	0.102
Alcohol	2.017	0.840–4.838	0.116
Smoking	1.658	1.093–2.516	0.017
Medication			
All antiplatelets	0.654	0.434–0.986	0.042
Dipyridamole	1.528	0.443–5.268	0.502
All anticoagulants	0.879	0.432–1.786	0.721
NSAIDs	0.804	0.506–1.280	0.359
Steroids	0.680	0.358–1.291	0.238
SSRI	0.897	0.330–2.434	0.830
Bisphosphonate			0.999
Co-morbidity			
Cirrhosis	0.696	0.300–1.617	0.400
CKD	1.120	0.703–1.783	0.633
Heart failure	0.786	0.339–1.821	0.574
Peptic ulcer	0.795	0.549–1.151	0.225
COPD	0.849	0.374–1.930	0.696
Hypertension	0.800	0.609–1.052	0.111
CAD	0.916	0.604–1.388	0.678
DM	1.573	1.130–2.189	0.007
Family history of CRC	0.875	0.479–1.598	0.664
Hemorrhoid	0.595	0.460–0.768	<0.001
Diverticula	0.920	0.677–1.250	0.593
Colitis/ulcer	0.358	0.162–0.789	0.011
Angiodysplasia	1.201	0.801–1.453	0.599
Hyperplastic polyp	0.698	0.468–1.041	0.078
Good cleaning	1.160	1.083–1.254	0.166

NSAIDs = nonsteroidal anti-inflammatory drugs; SSRI = selective serotonine reuptake inhibitor; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease; DM = diabetes mellitus; FM = family history; CRC = colorectal cancer.
[a] Each variable was adjusted for every other variable listed.

Table 3
Factors associated with proximal colorectal neoplasia in positive iFOBT patients by multiple logistic regression analysis.

	Adjusted OR	95% CI	*p*
Age	1.037	1.020–1.055	<0.001
Smoking	1.491	1.073–2.049	0.035
Hemorrhoid	0.545	0.382–0.776	0.001
Colitis/ulcer	0.202	0.046–0.888	0.034
Hyperplastic polyp	0.469	0.247–0.891	0.021

Table 4
Factors associated with distal colorectal neoplasia in positive iFOBT patients by multiple logistic regression analysis.

	Adjusted OR	95% CI	*p*
Age	1.029	1.015–1.043	<0.001
Smoking	1.771	1.092–2.873	0.020
Diabetes mellitus	1.517	1.025–2.244	0.037
Antiplatelets	0.493	0.292–0.832	0.008
Hemorrhoid	0.635	0.471–0.857	0.003

have all been identified as risks for CRC in epidemiologic studies.[11,21] Age, male, smoking, family history of CRC, and increased BMI were predictors of colorectal advanced adenoma and CRC in subjects receiving a colonoscopy as a primary screening method.[22–24] After obtaining positive results from the iFOBT screening method, our study showed that age, smoking (current or past), and DM were factors associated with any colorectal neoplasia after colonoscopy, which was consistent with Botteri's study showing that age, male gender, higher BMI, alcohol drinking, smoking, and less physical activity were predictors of advanced colorectal neoplasia after positive iFOBT outcomes.[15] It is also consistent with Lin and Krämer's studies showing that MS and DM were associated with colorectal neoplasia.[12,25] Interestingly, we further found that DM was associated with distal but not proximal colorectal neoplasia in patients with positive iFOBT results, which was consistent with Marchand's study showing increased odds ratios (OR) for distal colorectal cancer among patients with diabetes.[26] A possible explanation may be attributed to the fact that ELISA-based immunochemical FOBT is more sensitive for detecting left-sided advanced neoplasia than right-sided advanced neoplasia; therefore, further research on the differences in the pathophysiologic mechanisms of the relationship of DM and site-specific colorectal neoplasia is needed.[27]

Regarding the issue of obtaining negative colonoscopy results after obtaining positive iFOBT results during CRC screening, occult bleeding from hemorrhoids may be one of the commonly speculated causes of a false occult blood test. Variable prevalence of hemorrhoids ranging from 4 to 86% was noted during colonoscopy in previous studies.[28,29] One study showed 15.4% subjects with hemorrhoids based on positive iFOBT results at a health check-up.[30] In our study, a 50% detection rate of hemorrhoid existence may be the possible important reason for obtaining negative colonoscopy in subjects with positive iFOBT outcomes during CRC screening, which is inconsistent with a previous study that suggests that hemorrhoid existence is an infrequent cause of false-positive iFOBT outcomes.[28] Further studies and reviews of published articles are needed to clarify whether hemorrhoid existence is a negative factor of positive iFOBT outcomes during CRC screening. In our study, it is reasonable to suggest that colitis/ulcer is also a reason for false-positive iFOBT outcomes for colorectal neoplasia. Subtle colitis/ulcer may be not exhibit clinical symptoms such as abdominal pain and bloody stool. However, underlying co-morbidities like cirrhosis and CKD, which are risk factors for upper or lower GI bleeding, did not influence iFOBT outcomes.[31–33]

Concerning the interaction between antiplatelets or anti-coagulants and FOBT results, a meta-analysis study showed that there was no significant difference in the positive predictive value of iFOBT in patients taking aspirin when compared with control subjects for detecting significant colorectal neoplasia, whereas the positive predictive value of FOBT was increased in patients taking warfarin for CRC detection compared with control subjects.[34] Our study showed that antiplatelets rather than anti-coagulants or NSAIDs may cause false-positive iFOBT results, which coincided with Chiang's study showing that the use of antiplatelets increased the false-positive rate of iFOBT outcomes.[30] A possible reason was the mild bleeding effect of antiplatelets and impaired

mucosal healing of antiplatelets throughout the GI tract, which further resulted in occult blood loss and false-positive iFOBT outcomes.[35−37]

This study has several strengths. First, all colonoscopies and pathological diagnoses were performed in a single medical center in a limited time span with homogenous diagnostic tools and modalities. Second, some underlying co-morbidities including hypertension and DM were found to be associated with colorectal adenoma,[12,19] and cirrhosis, CKD, peptic ulcer disease, COPD, and DM were found to be associated with obscure or occult GI bleeding; they were therefore enrolled as confounding factors for analysis.[31−33,38]

Nonetheless, this study also has several limitations. First, nearly one ethnic group was enrolled in the study population because aborigine or foreigners are relatively rare in Taiwan. However, the risk factors of CRC or colorectal neoplasia were similar in different countries and areas. Second, some risk factors of CRC were not included for analysis in our study, such as life modification, body mass index (BMI), physical activities, and MS.[12] However, we included the parameters of hypertension, DM, and CAD as associated factors of negative colonoscopy. Third, all of the enrolled subjects obtained positive iFOBT results; we did not have data regarding colonoscopy and iFOBT results simultaneously, so the sensitivity, specificity, and negative predictive values were not available. The positive predictive value of iFOBT for colorectal neoplasia in this study was 53.7%.

In conclusion, the use of antiplatelets and presence of hemorrhoid or colitis/ulcer but not the colon clean level, use of NSAIDs and anti-coagulants, or underlying diseases of GI bleeding tendency such as CKD and cirrhosis were associated with negative colonoscopy results in subjects with positive iFOBT screen outcomes. Antiplatelet agents might be stopped if clinically feasible prior to stool collection for colorectal cancer screening.

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