

Factors Associated with False Positive Fecal Immunochemical Tests in Trang Colorectal Cancer Screening Program Population

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Abstract

Background and Objective: Early detection of colorectal cancer (CRC) has emerged as an important global issue. Since 2018, fecal immunochemical tests (FITs) have been offered as a primary screening test for CRC by the Thai National Health Service plan despite their varied accuracy according to various factors. The primary aim of this study was to identify demographic factors associated with false-positive (FP) FIT results in CRC screening in the Trang population. The secondary aim was to report the outcomes of the screening program in Trang Province.

Methods: The data of all 542 participants in Trang with positive FIT tests from the CRC screening program conducted at Trang Hospital between 1 October 2021 and 28 February 2023 were retrospectively reviewed. Of these, 347 with complete colonoscopy studies were analyzed. Patients' characteristics, colonoscopy findings, and pathologic data were recorded. Univariable and multivariable logistic regression analysis was performed to determine factors associated with FP FIT results.

Results: Among 347 participants who showed positive FIT with complete colonoscopy for CRC screening, 33 participants (9.5%) had advanced colorectal neoplasia (ACRN), and 314 participants (90.5%) had FP FIT results (no ACRN). The participants aged under 65 had a higher rate of FP results than the older age group. Female gender and aged under 65 were two factors associated with false positivity. Multivariable logistic regression showed that age < 65 was the only independent risk factor associated with FP FIT results in multivariate analysis (OR = 2.81; 95% CI 1.24-6.35; $p = 0.013$).

Conclusion: FP FIT results in the Trang population were relatively high. The age < 65 is a significant factor associated with FP FIT results. This result can be used as a piece of evidence to optimize CRC screening strategies.

Keywords: Fecal immunochemical tests, Colorectal cancer, Screening, False positive

INTRODUCTION

Colorectal cancer (CRC) is the third most common cause of death from cancer in Thailand and worldwide.^{1,2} Early detection of CRC has emerged as an important global issue. CRC screening programs have been conducted in many countries. In particular, non-invasive screening by Fecal Immunochemical Tests (FITs) has been offered as a primary screening test.^{3,4} The par-

ticipants with positive FIT results are further referred to undergo colonoscopy examinations.

Since 2018, FIT has been offered as a primary screening test for CRC in the Thai National Health Service plan but its accuracy varies due to differences in participant-related factors such as sex, age, metabolic diseases, and the presence of hemorrhoids, etc.⁵⁻¹⁰

Received for publication 13 June 2023; Revised 22 September 2023; Accepted 23 September 2023

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Previous studies have reported false positive (FP) FIT rates of 4.3 - 70%.^{5,6} In CRC screening in Trang, more than half of all participants showed positive FIT results with no advanced colorectal neoplasm (ACRN) detected on colonoscopy examinations. False positive results caused psychological stress to the patients,¹¹ unnecessary colonoscopies, risk of adverse events during the procedures, extra costs, and increased healthcare workloads.

However, the studies of risk factors for FP FIT results remain unclear. Many studies from different populations have conflicts in associated factors with FP FIT results.⁵⁻¹⁰ The knowledge about associated factors for FP FIT results will improve the efficiency of the screening program. Therefore, this study aims to identify demographic factors associated with FP FIT results and report the colorectal cancer screening program outcomes in Trang Province.

MATERIALS AND METHODS

The data of all 542 participants with positive FIT tests of the Trang CRC screening program were reviewed between 1 October 2020 and 28 February 2023. All positive FIT participants were referred to perform colonoscopy examinations by general surgeons at Trang Hospital (a province hospital). The cut-off threshold for a positive FIT was ≥ 100 ng Hb/ml buffer. The exclusion criteria were set as follows: denied colonoscopy (33.2%, $n = 180$), incomplete colonoscopy (1.47%, $n = 8$), inadequate bowel preparation (1.1%, $n = 6$), and perforation during the procedure (0.18%, $n = 1$). As a result, the total number of eligible subjects for the study was 347. The characteristic data, colonoscopy findings, and pathologic data were recorded. An FP FIT result was defined as positive FIT results in participants who were identified with no advanced colorectal neoplasm (ACRN) detected.⁸ ACRN was defined as cancer or advanced adenoma.^{8,12} Advanced adenoma was defined as the presence of one of the following features: > 10 mm diameter, tubulovillous or villous structure, high-grade dysplasia, and three or more adenomas.^{8,9,12}

The data were summarized as counts, frequency (%), and mean $\pm$ standard deviation (SD). The population characteristics were compared using the chi-square, Fisher's exact test, or t-test as appropriate. Univariate and

multivariate logistic regression analysis was performed to determine factors associated with FP FIT results. For each variable, the adjusted odd ratio (OR) and 95% confidence interval (CI) were reported. A p -value < 0.05 was determined to be significant. All statistical analyses were performed using the statistical package SPSS v.26.0 (IBM, New York, USA). Institutional Review Board approval was obtained for this study.

RESULTS

A total of 347 participants who showed positive FIT and completed colonoscopy for CRC screening were eligible for the analysis. The main characteristics of the study population and colonoscopy findings are shown in Table 1. The mean age of the overall participant was 59.1 ± 6.6 years (range 43 to 83 years; mode 56). The majority of the participant was female (70%, $n = 243$). The mean BMI was 25.3 ± 4.1 kg/m². More than half of the participants had metabolic syndrome (74.6%, $n = 259$). The female participants were found to have more BMI and metabolic syndrome than the male. From the colonoscopy findings, 162 participants (46.7%) were normal, 33 participants (9.5%) had ACRN, and 314 participants (90.5%) had FP FIT results. Common non-neoplastic findings were hemorrhoids (12.1%) and diverticulosis (10.4%). Other non-neoplastic findings included colitis, proctitis, ulcer, and parasitic worm infections.

Additionally, comparing between genders, there were no significant differences in colonoscopy findings between males and females, but a significant difference in FP FIT results between genders was found ($p = 0.026$).

Table 2 shows the frequencies of FP FITs in the study population, using cut-offs ≥ 100 ng Hb/ml in variables associated with FP FITs. In the univariate analysis, female gender (OR = 2.42; 95% CI 1.17 - 4.99; $p = 0.026$), age < 65 years old (OR = 2.28; 95% CI 1.06 - 4.87; $p = 0.043$), non-advanced adenoma (OR = 0; 95% CI 0; $p = < 0.001$), and hemorrhoids (OR = 0; 95% CI 0; $p = 0.022$) were significantly associated with FP FIT results.

In multivariable logistic regression (Table 3), the age < 65 was the only independent risk factor for FP FIT results (OR = 2.81; 95% CI 1.24 - 6.35; $p = 0.013$), whereas apparent associations of gender, non-advanced adenoma, and hemorrhoids with FP FIT results in univariate analyses were not statistically significant.

Table 1 Population characteristics

Characteristic	Total population (%) N = 347	Male (%) N = 104	Female (%) N = 243	p-value
Age: years, mean $\pm$ SD	59.1 $\pm$ 6.6	59.9 $\pm$ 5.9	58.8 $\pm$ 6.8	0.132
Age range: number (%)				0.322
Age < 65	272 (78.4)	78 (75.0)	194 (79.8)	
Age $\geq$ 65	75 (21.6)	26 (25.0)	49 (20.2)	
BMI (kg/m²): mean $\pm$ SD	25.3 $\pm$ 4.1	24.4 $\pm$ 3.6	25.7 $\pm$ 4.3	0.002
BMI (kg/m ²) range: number (%)				0.036
< 25	170 (49)	60 (57.7)	110 (45.3)	
$\geq$ 25	177 (51)	44 (42.3)	133 (54.7)	
Underlying diseases: number (%)				
Diabetes	34 (9.8)	9 (8.7)	25 (10.3)	0.698
Hypertension	112 (32.3)	31 (29.8)	81 (33.3)	0.534
Dyslipidemia	113 (32.6)	22 (21.2)	91 (37.4)	0.003
Other underlying diseases	53 (15.3)	25 (24.0)	28 (11.5)	0.005
Colonoscopy findings: number (%)				
Normal	162 (46.7)	49 (47.1)	113 (46.5)	0.916
Cancer	6 (1.7)	3 (2.9)	3 (1.2)	0.370
Colonic polyps	113 (32.6)	36 (34.6)	77 (31.7)	0.618
Advanced adenoma	29 (8.4)	14 (13.5)	15 (6.2)	
Non-advanced adenoma	84 (24.2)	22 (21.2)	62 (25.5)	
Diverticulosis	37 (10.7)	12 (11.5)	25 (10.3)	0.708
Hemorrhoids	42 (12.1)	9 (8.7)	34 (14.0)	0.213
Other non-neoplastic findings	9 (2.6)	2 (1.9)	7 (2.9)	0.730
False Positive FIT result: number (%)	314 (90.5)	88 (84.6)	226 (93.0)	0.026

Table 2 Univariate logistic regression analysis for Factors Associated with False-Positive FIT Results (N = 314)

Variable	False positive, n (%)	Univariate analysis	
		OR (95% CI)	p-value
Female Gender: n (%)	226 (72.0)	2.42 (1.17 - 4.99)	0.026
Age < 65 years old: n (%)	251 (79.9)	2.28 (1.06 - 4.87)	0.043
BMI < 25 kg/m ² : n (%)	157 (50.0)	1.54 (0.74 - 3.20)	0.276
Diabetes: n (%)	29 (9.2)	0.57 (0.20 - 1.59)	0.349
Hypertension: n (%)	102 (32.5)	1.11 (0.51 - 2.41)	0.848
Dyslipidemia: n (%)	103 (32.8)	1.12 (0.52 - 2.45)	0.847
Other underlying diseases: n (%)	47 (15.0)	0.79 (0.31 - 2.02)	0.613
Non-advanced Adenomas: n (%)	84 (26.8)	0 (0)	< 0.001
Diverticulosis: n (%)	36 (11.5)	4.14 (0.55 - 31.25)	0.230
Hemorrhoids: n (%)	43 (13.7)	0 (0)	0.022

Table 3 Multivariate logistic regression analysis for Factors Associated with False-Positive FIT Results

Variable	Multivariate analysis	
	OR (95% CI)	p-value
Female Gender	2.04 (0.95 - 4.36)	0.067
Age < 65 years old	2.81 (1.24 - 6.35)	0.013
Non-advanced Adenomas	0 (0)	0.996
Hemorrhoids	0 (0)	0.997

DISCUSSION

CRC screening program based on fecal immunochemical tests (FITs) has been offered as a primary screening test worldwide as well as in Thailand. Its positive rates marked differences across different programs and countries: Australia, 4.6 - 9.0%, Korea, 7.3 - 11.2%, Netherlands, 5.5 - 8.8%, Italy, 3.7%, Germany, 5.0%, and the USA, 2.6%.⁷ In Trang, the CRC screening program as a part of the Thai national health service plan began in 2018. The Trang Health Data Center (THDC) data showed the FIT-positive rates from 2018 to 2022 in Trang's population between 3.8 - 8.9% and FP FIT rates between 84.8 - 90.6%.¹³ Due to the COVID-19 pandemic, the colonoscopy program was paused, causing some participants to drop out of the program. This study collected the data from the point program resumed on 1 October 2020 until 28 February 2023. Although the target participants of the Thai National Health Service Plan CRC screening were people aged 50 - 70, this study covered participants aged between 43 and 83.

Of all the positive FIT participants in the study, 10.5% had ACRN, and 90.5% had FP FIT results. This data was similar to the data of THDC.¹³ Although the specificity of FIT is relatively high, up to 25% of patients are shown to have the FP results.¹⁴ In a study from Australia, the colonoscopy revealed neoplasia to be absent in 54.5% of those with positive FIT results.⁷ The rates of FP FIT results in the Trang screening program are higher than all of the previous studies reporting false positive (FP) FIT rates of 4.3 - 70%.^{5,6,8,10,15}

The higher FP FIT rates led to psychological stress for the patients worrying about their chance of having cancer,¹¹ unnecessary colonoscopies, and increased procedural risks, costs, and healthcare workload. It is, therefore, important to understand the factors associated

with FP FIT results. Several studies and meta-analyses have demonstrated that different populations showed different conflicts of participant-related factors associated with FP FIT results. According to the meta-analyses, the most frequently studied risk factors for FP FIT results are the use of anticoagulants and antithrombotic drugs, sex, and age.⁶

Among FP FIT participants, most of them had normal results on colonoscopy examination. Colonic polyps, which were non-advanced adenomas, diverticula, and hemorrhoids, were the most 3 abnormal findings detected in 45.5% of all FP results. Of these factors, this study focused on the most controversial factors associated with FP FITs results, including sex, age, obesity (BMI $\geq$ 25 kg/m²), DM/hyperglycemia, dyslipidemia, high blood pressure, hemorrhoids, added-on diverticula, and non-advanced adenomas.

In a systematic review and meta-analysis of Klerk et al., no significant associations were found for the use of anticoagulants or antithrombotic drugs. Many factors also appeared not to affect FP results: family history of CRC, socioeconomic status, obesity, diverticula, high blood pressure, hyperglycemia, low high-density lipoprotein, metabolic syndrome, anemia, use of combined medication, smoking, alcohol drinking and participation in prior screening rounds.⁶

A study in Hong Kong reported that polypoid adenomas were associated with FP results.¹⁰ The result of hemorrhoids, a commonly suspected source of lower gastrointestinal bleeding, showed only a weak, statistically nonsignificant association with FP FIT results in the same way as a German study⁵ and meta-analyses⁶ in contrast to the Korean study.⁸

A large German CRC screening study conducted by Amitay et al. found that male gender, older age ($\geq$ 65 years), obesity, smoking, and use of aspirin were associated with increased FP FIT.⁵ Similarly, the meta-analysis showed that risk factors associated with a lower risk of FP results were male sex and age higher than 65.⁶ In contrast, Symonds et al. reported FP was associated with female gender and younger age.⁷ This study observed significant differences in FP results between genders, but there was no significant association in multivariate analysis. However, this study found that age < 65 was the only statistically significant independent risk factor for FP FIT results.

In Trang's population, participants below 65 years old might be screened by combining blood-based biomarker tests (CEA, Ferritin) and FIT results required to reduce unnecessary colonoscopy. In a recent study by Peterson et al.,¹⁵ based on 4,048 FIT-positive (cut off ≥ 100 ng Hb/ml) subjects from the Danish National Colorectal Cancer Screening Program. The authors proposed a 2-step screening approach with an initial FIT test followed up by a blood test if the FIT was positive. The combined result of the blood test, FIT result, and demographics (age and sex) decided whether a colonoscopy was required. They tested 2 algorithm models, and the first was a predefined model including FIT result, age, and 3 biomarkers of CEA, Ferritin, and CRP. The second was the exploratory model, which added other 6 biomarkers and sex as potential predictors. Both approaches were significantly better than using FIT alone in the discrimination of cases with CRC vs. cases with no CRC. Overall reduction in colonoscopy requirements by 4 - 11% without reducing detection of colorectal cancer.¹⁵

Environmental factors may also influence FIT positivity. There were still conflicting findings. Some studies showed the detection of advanced neoplasia in different seasons, while others reported no seasonal effect.⁷

There is currently insufficient evidence to recommend the use of repeat/second FIT to guide colonoscopy.^{4,7} Repeat FIT testing may enhance sensitivity after the first negative test (increased sensitivity and decreased specificity), or identify people who may not need colonoscopy unless both tests are positive (decreased sensitivity and increased specificity). Further studies are required.⁴

Though the evidence from Rerknimit et al.,¹⁶ suggests that the optimal cutoff threshold in advanced neoplasia and CRC screening in Thailand is 150 ng/ml, the threshold for FIT positive in this study was set at ≥ 100 ng Hb/ml according to Thai Guidelines for CRC screening program¹⁷ and other foreign studies.^{5,18} Some European countries used higher cutoff thresholds ranging between 150 to 750 ng/ml.¹⁵ The FIT threshold used in true screening practice should be chosen based on a balance of reducing the total number of required colonoscopies, procedural complications, and stress of participants without compromising CRC detection.

This study was based on data from 347 participants with a positive FIT result in the Trang Province CRC screening program, a true screening setting consisting of asymptomatic participants; a referral bias was unlikely.

Although this was not a large number of subjects studied, it was not small compared to other studies in the meta-analysis.⁶ There were several limitations in the current study. First, this was a retrospective study with potential bias in design. Second, data on using anticoagulants or antithrombotic drugs, using NSAIDs, smoking, and alcohol drinking, which could be possible confounders, were unavailable. These factors could increase the risk of FP FIT results.^{9,10,19} Future studies on these factors should be done. Lastly, no further examinations were conducted to elucidate reasons for FP FIT results.

CONCLUSION

The variable positive rates in FIT-based CRC screening suggested differences in results between programs. FP FIT results in the Trang population were relatively high. The knowledge about risk factors associated with FP FIT results could improve the effectiveness and efficiency of the screening program. Therefore, the screening strategy should be adjusted, especially among people aged under 65, which was a significant factor associated with FP FIT results in Trang.

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