ORIGINAL ARTICLE

# COLORECTAL CANCER SCREENING USING IMMUNOCHEMICAL FECAL OCCULT BLOOD TEST

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## ABSTRACT

*Fecal occult blood test (FOBT) screening has been shown to decrease the incidence and mortality of colorectal cancer (CRC). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the immunochemical fecal occult blood test (i-FOBT) in diagnosing CRC were assessed among the patients in a tertiary referral hospital in Malaysia. A total sample of 814 patients aged 16 to 85 years old who performed i-FOBT and endoscopic screenings was obtained. The patients were recruited for a retrospective investigation. Sensitivity, specificity, PPV, and NPV were derived for the CRC screenees. Out of the 814 patients screened using i-FOBT, half of them were above 59 years old (49.6%), and 36% had positive i-FOBT. Gender distribution was almost equal, where 53.4% of the patients were female, and 46.6% were male. Majority of the patients were Malays (56.6%), followed by Chinese (24.0%), Indians (16.5%), and others (2.9%). Among the 71 patients referred for colonoscopy, 57.7% and 42.3% corresponded to positive and negative i-FOBT cases, respectively. Polyps were found to be most common among the patients (25.6%), 7.0% were found positive for invasive CRC, and 35.2% had normal colonoscopic findings. There was a significant association between colonoscopic finding and positive i-FOBT (p=0.001). The sensitivity, specificity, PPV, and NPV for CRC detection were 66.7%, 43.0%, 9.8%, and 93.3%, respectively. The results indicate that i-FOBT is a useful tool in the detection of abnormalities in the lower gastrointestinal tract and therefore serves as a cornerstone for potential large-scale screening programmes.*

***Keywords:*** *Colorectal cancer, screening, immunochemical fecal occult blood test*

## INTRODUCTION

Colorectal cancer (CRC) is one of the leading causes of cancer-related death in the world[1]. With more than 1.2 million new cases and over 600,000 deaths annually, CRC is ranked the third most common cancer and the fourth most common cause of mortality globally[2]. In Malaysia, this disease is the second most predominant cancer after breast cancer[3]. In view of its high incidence, mortality and morbidity rates, and the high socio-economic burden associated with CRC, it has become a paramount and challenging public health problem.

Primary prevention of CRC which based principally on the adoption of healthy lifestyle measures including alterations in dietary habits has not been proven effective, and hence CRC screening turns to be visible in improving prognosis and reducing mortality by the detection of cancer at its early stages[4]. Colorectum, similarly to those of the breast and uterine cervix, is a good target for early diagnosis because it is often preceded by preneoplastic lesion that typically has a long natural history. A considerable amount of research has been undertaken over the last 20 years to evaluate the ability of several screening tests to decrease CRC mortality and incidence[5-12]. The widely-accepted screening methods currently include fecal occult blood test (FOBT), sigmoidoscopy and colonoscopy. According to the World Gastroenterology Organisation[13], although these techniques are cost-effective apart from requiring different amounts of resources in terms of financial, professional, facilities and patient effort, they also differ in what stage of the disease detection is possible. Colonoscopy may be better at detecting pre-malignant conditions which offer CRC prevention. Notwithstanding its reliability, colonoscopy is not practicable in a developing country like Malaysia, being expensive and qualified manpower dependent. FOBT is relatively cheaper and more practical for population screening.

Immunochemical fecal occult blood test (i-FOBT) is known to be a newer, simpler, more sensitive, less expensive and non-invasive approach to CRC screening available[11-12]. The most prominent advantage is that i-FOBT makes quality control possible. It holds considerable promise in diagnostic performance over the traditional guaiac-fecal occult blood test (g-FOBT). Furthermore, evidence suggests that i-FOBT, using one or two samples of feces, has better clinical

sensitivity than g-FOBT does. It detects the presence of haemoglobin, a protein found in blood, which exhibits improved sensitivity and specificity that are higher among those of FOBTs. It also involves no dietary restriction because i-FOBT is specific for human haemoglobin, resulting in fewer abnormalities due to interfering substances[14].

Despite widespread of i-FOBT usage, less is understood about the application of i-FOBT for CRC detection in Malaysia. Hence, the present study aimed to investigate the use of i-FOBT in detecting CRC in a tertiary referral setting in Malaysia, in order to obtain a more detailed explanation on i-FOBT and its clinical significance towards CRC. We also performed method analyses for the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of i-FOBT in CRC screening. It is postulated that by using i-FOBT for initial screening of CRC, it might be useful as a tool to reduce the incidence of the CRC mortality rate and improves human health[15].

## MATERIALS/PATIENTS AND METHODS

A retrospective study was carried out in a tertiary referral setting, Serdang Hospital, using a case-control study design. From January 2012 to June 2013, the subjects were accrued from an existing large linked database. All the medical records of patients that registered for i-FOBT screening at the Department of Pathology, Serdang Hospital, Selangor Darul Ehsan, Malaysia, were recruited. The medical record consists of a chart note, procedural note and laboratory report. The data accessed included socio-demographic backgrounds (age, gender and ethnicity), indication of i-FOBT test, and medication history [specifically non-steroidal anti-inflammatory drugs (NSAIDs) and anticoagulants]. Subsequently, all the data obtained was compiled and reviewed by gastroenterologists under strict quality control.

An immunologic test that is rapid, convenient, and non-offensive (Hema-Screen, Immunostics Inc., New Jersey, USA) was used to detect fecal occult blood (FOB). The test was performed on a single stool sample of the screenees and did not require them to adhere to any drug and dietary restriction or modification. Further investigation was performed for the patients with either positive or negative result. A patient with a positive i-FOBT result required clinical examination for benign causes of bleeding and was likely to require referral for an endoscopy. A negative result does not guarantee that an adenoma or cancer is absent because the lesions may not be bleeding, or the bleeding may be intermittent. Hence, the patients with negative test results, but with other clinical findings or history that are suggestive of cancer, such as loss of weight, strong family history of CRC or abdominal/per rectal mass, were offered an appointment for an endoscopy. The endoscopy that constitutes oesophagogastroduodenoscopy (OGDS) and colonoscopy was performed by two certified gastroenterologists privileged by the well-equipped tertiary setting. Subsequently, information on the endoscopic procedure, date, and lesions detected including the number, location, depth, size and histopathology, was abstracted from the clinical records, coded and entered into a separate database. The patients with CRC detected during endoscopic screening were also identified by a computerized search of the data.

The detection rate was calculated as the number of screenees with a positive i-FOBT relative to the total number of participants in the study. Sensitivity, or true positive rate (TPR), measures the probability of detecting an adenocarcinoma or CRC correctly. Although i-FOBT does not have direct toxic consequences, the risk is associated with false-positive results, which may provoke unnecessary potentially harmful diagnostic endoscopic examinations[16]. Specificity, or true negative rate (TNR), refers to the test's ability to exclude a condition correctly. Specificity in the screened population was estimated according to rare disease assumption as the ratio of the number of all participants with a negative screening test to the total number of participants, reduced by the number of true positives with CRC. The positive predictive value (PPV) or precision, is one of the most crucial markers in the screening programme, where high rates of false-positives yield large numbers of unnecessary investigations being undertaken. PPV was calculated as the number of true CRC-positive patients relative to the total number of CRC-positive patients who followed up with colonoscopy. The negative predictive value (NPV) relates to the proportion of negative results that is true negative.

### Statistical Analysis

Our analysis included i-FOBT-screenees who had a valid test result, whether positive or negative. All the data was analysed using IBM SPSS Statistics software version 21.0 (IBM Corp, Armonk, New York, USA). Descriptive statistics were presented as percentages. The differences in the frequency of the distribution between patients with positive and negative i-FOBT results were compared using chi-squared test. The confidence interval was set as 95%, and a $p$ value of less than 0.05 was considered statistically significant.

## RESULTS

Of the 1064 patients recruited, 814 patients (76.5%) were included in the statistical analysis due to the completeness of data, while 250 (23.5%) of them with insufficient information were excluded. Table 1 demonstrates the distribution of socio-demographic characteristics, clinical i-FOBT result, and endoscopic findings of the 814 patients aged 16 to 85 years old. Overall, most of the patients were from the age group of older than 59 years old (49.6%). In terms of gender, 53.4% were female, and 46.6% were male. The majority of the patients were Malay (56.6%), followed by Chinese (24.0%), Indian (16.5%), and others (2.9%), which comprised of Sikhs, Ibans, and foreigners ($p$=0.002). Among the patients who underwent i-FOBT, 17.0% of them were prescribed NSAIDs and 4.1% consumed anticoagulants, while 77.6% were not prescribed with both NSAIDs and anticoagulant. Only 1.4% of patients consumed both drugs.

The results show that among the 814 patients who had undergone the i-FOBT, 36% of them were positive while 64% were negative. Out of the positive result cases, over 60% were screenees aged above 59 years old, followed by 24.1% screenees aged 40 to 50 years old, 8.5% aged 20 to 39 years old and 6.1% aged below 20 years old ($p$<0.001). A comparable trend applied to the negative i-FOBT screened patients. There was no significant association observed between drug history and i-FOBT results. The majority of the patients did the i-FOBT on the basis of anemia (83.8%), followed by malaena (8.2%), altered bowel habit (5.5%), loss of weight and appetite (1.2%), surveillance (0.2%), and others (1.1%).
We discovered that majority of the patients did not undergo endoscopy (69.4%), whereas 21.9% of the patients had undergone OGDS only, and 2.7% were referred for colonoscopy only. There was 6.0% of them underwent both procedures. Among the 71 patients screened by colonoscopy, including the patients who underwent colonoscopy only, and those who done both types of scopes, 25 of them (35.2%) had normal colonoscopic findings. A colonic neoplasm was detected in 14 cases (19.7%); five patients (7.0%) were found to have invasive CRC using colonoscopy, four (5.6%) had colonic diverticular only, followed by two (2.8%) with colitis. Three cases (4.2%) presented with polyps and haemorrhoids, one (1.4%) was diagnosed with both colitis and polyps, while fistula, intussusception, or volvulus were diagnosed in four of the patients (5.6%) using colonoscopic screening. Seven of the patients (9.9%) had abandoned colonoscopy due to incomplete bowel preparation, poor scope view, or failure of scope owing to severe looping, of whom they were offered either CT colonography or less-invasive barium enema.

The colonoscopic findings associated with the i-FOBT results are indicated in Table 2. Colonoscopy was performed on 71 patients, where 41 (57.7%) and 30 (42.3%) corresponded to positive and negative i-FOBT cases, respectively. There were significantly more cases of CRC detected among the screenees aged above 59 years old compared to the screenees aged below 59 years of age ($p$<0.001). Six patients with positive i-FOBT were diagnosed with CRC through histopathological examination (HPE) after colonoscopy (five patients) and exploratory laparotomy (one patient). The prevalence of CRC for the positive i-FOBT patients in this study was 9.8%. The sensitivity, specificity, PPV, and NPV for i-FOBT in detecting CRC was 66.7%, 43.0%, 9.8%, and 93.3%, respectively.

**Table 1: Patient demographic, clinical, i-FOBT, and endoscopic findings (N=814)**

| | N | Percentage (%) |
|---|---|---|
| Socio-demographic data | | |
| Age | | |
| <20 | 52 | 6.4 |
| 20-39 | 113 | 13.9 |
| 40-59 | 245 | 30.1 |
| >59 | 404 | 49.6 |
| Sex | | |
| Male | 379 | 46.6 |
| Female | 435 | 53.4 |
| Race/Ethnicity | | |
| Malay | 461 | 56.6 |
| Chinese | 195 | 24.0 |
| Indian | 134 | 16.5 |
| Others | 24 | 2.9 |
| i-FOBT | | |
| Positive result | 295 | 36.0 |
| Negative result | 519 | 64.0 |
| NSAIDs/anticoagulant medication | | |
| Not on medication | 632 | 77.6 |
| NSAIDs only | 138 | 17.0 |
| Anticoagulant only | 33 | 4.1 |
| NSAIDs and anticoagulant | 11 | 1.4 |
| Indication of i-FOBT | | |
| Anemia | 682 | 83.8 |
| Malaena | 67 | 8.2 |
| Altered bowel habit | 45 | 5.5 |
| Loss of weight and appetite | 10 | 1.2 |
| Surveillance | 1 | 0.2 |
| Others | 9 | 1.1 |
| Endoscopic findings | | |
| None | 565 | 69.4 |
| *OGDS* | 178 | 21.9 |
| Colonoscopy | 22 | 2.7 |
| OGDS and colonoscopy | 49 | 6.0 |
| Colonoscopic findings (N=71) | | |
| Normal colonoscopy | 25 | 35.2 |
| Polyps only | 14 | 19.7 |
| Adenocarcinoma | 5 | 7.0 |
| Haemorrhoids only | 4 | 5.6 |
| Colonic diverticular only | 6 | 8.5 |
| Colitis only | 2 | 2.8 |
| Polyps and haemorrhoids | 3 | 4.2 |
| Colitis and polyps | 1 | 1.4 |
| Others[†] | 4 | 5.6 |
| Abandoned colonoscopy[Ψ] | 7 | 9.9 |

*NSAIDs: non-steroidal anti-inflammatory drugs; i-FOBT: immunochemical fecal occult blood test; OGDS: oesophagogastroduodenoscopy, [†]fistula, intussusception, or volvulus,*
*[Ψ]because of incomplete bowel preparation, poor scope view, or failure of scope due to severe looping*

## DISCUSSIONS

The remarkable increasing incidence of CRC warrants its consideration as a major healthcare problem worldwide. Early detection of CRC has been shown to improve outcomes through the detection of early-stage cancers and precursor lesions[17]. On the basis of the typically slow development of CRC, the disease is frequently asymptomatic. CRC screening for the general population could decrease CRC incidence and mortality. As a consequence of the characteristics of CRC, where a major effect on prognosis that depending on the stages of diagnosis and a long pre-clinical phase with frequent pre-cancerous lesions, substantial effort has been focused on devising an effective screening programme. Up to date, colonoscopy is the most accurate "gold standard" for detecting early cancers, and the detection and removal of advanced adenomas. However, due to its potential limitations, mainly being the discomfort of colonoscopy, higher cost and strategies[18], resulting it not routinely recommended as a screening tool. The use of the FOBT has been proposed for large-scale population screening programmes throughout the world. FOB may be a sign of cancer in the colon or rectum, or other conditions, such as large polyps, hemorrhoids, unexpected anemia, anal fissures, inflammatory bowel disease or stomach ulcers that cause the digestive tract to bleed.

Initially, g-FOBT that detects the peroxidase-like activity of haemoglobin was introduced. However, this traditional method has been criticized due to several drawbacks[7]. The g-FOBT has lower clinical sensitivity and specificity[12,20-22] for they react with peroxidase activity in some fresh fruits and vegetables and non-human haem in red meat.[6] Additionally, bleeding from upper intestinal tract lesions, including erosions, ulcers, and hemorrhagic gastritis from *Helicobacter pylori*-associated infection[23] or nonsteroidal anti-inflammatory medications may contribute to g-FOBT false-positive results, whereas ingestion of vitamin C may cause false-negative tests. In addition, independent assessment of a pilot study highlighted that the most positive g-FOBT results arose from repeat testing of initially weak positive tests, which increased the screening period for a number of participants, and may be overly burdensome of use in a national screening programme. Some other benefits of i-FOBT over g-FOBT include fewer stool samples needed, and no diet or medication restrictions are required. The quantitative nature of the new generation i-FOBT may also allow for an optimal cut-off point to be chosen, and the i-FOBT testing samples can be analyzed automatically, offering the best balance between effectiveness and cost[7]. For all these reasons, CRC screening using g-FOBT is less encouraged, particularly on the Malaysian market where it is virtually unavailable in the local health settings, and attention has been transited to the alternative, i-FOBT[24].

**Table 2: Results of i-FOBT and colonoscopic findings**

| | i-FOBT | | Total | p |
|---|---|---|---|---|
| | Positive | Negative | | |
| Colonoscopy | | | | |
| Polyps only | 9 (64.3) | 5(35.7) | 14 (19.7) | 0.001 |
| Adenocarcinoma | 3 (60.0) | 2 (40.0) | 5 (7.0) | |
| Haemorrhoids only | 3 (75.0) | 1 (25.0) | 4 (5.6) | |
| Colonic diverticular only | 4 (66.7) | 2 (33.3) | 6 (8.5) | |
| Colitis only | 2 (100) | 0 (0.0) | 2 (2.8) | |
| Polyps and haemorrhoids | 2 (66.7) | 1 (33.3) | 3 (4.2) | |
| Colitis and polyps | 1 (100) | 0 (0.0) | 1 (1.4) | |
| Normal colonoscopy | 8 (32.0) | 17 (68.0) | 25 (35.2) | |
| Others | 3 (75.0) | 1 (25.0) | 4 (5.6) | |
| Abandoned colonoscopy | 6 (85.7) | 1 (14.3) | 7 (9.9) | |
| Total | 41(57.7) | 30 (42.3) | 71 (100.0) | |

Values in paren

In the present study, the number of patients who had undergone i-FOBT had increased risk of CRC as their age elevated. The finding is in line with the Guidelines of the Malaysian Society of Gastroenterology and Hepatology, which recommended routine screening for CRC in

average-risk individuals over 50 years old[25]. Significantly more CRC was detected in the screenees aged above 59 years old than in those aged below 59 years old. The observation is in agreement with the studies that reported an increased prevalence of CRC at an older age[26-29].

We also determined the association between both NSAIDs and anticoagulant medication with the result of i-FOBT. It is crucial to examine the drug-use history of the patients, especially for NSAIDs and warfarin. This is because NSAIDs have been pointed out to be associated with an increased risk of major and minor upper gastrointestinal bleeding[25] that may produce a false positive result. Patients may be advised to discontinue blood thinners, such as warfarin, prior to undergoing i-FOBT. It is supported by a meta-analysis that there were no statistically significant differences between FOBT, with or without warfarin for colonoscopy findings (OR=0.88, $p$=0.67), or detection of neoplasia (OR=0.88, $p$=0.57), any adenomas (OR=1.08, $p$=0.71), advanced adenomas (OR=1.07, $p$=0.78), and CRC (OR=0.69, $p$=0.21)[30]. Conversely, another study by Bujanda et al. reported that those who had undergone dual antiplatelet therapy have an increased rate of positive i-FOBT[31]. Furthermore, the use of aspirin, non-aspirin anti-platelet agents, or both, did not modify the PPV for advanced neoplasia among the patients.

In screening using colonoscopy, the most common finding was colonic polyps. The result is consistent the finding reported by Ramirez and co-authors[32] that colonic polyps was the major finding during colonoscopy. There were only five cases of diagnosed CRC using colonoscopy, while another case was diagnosed by exploratory laparotomy. However, other abnormalities in their gastrointestinal tracts were revealed, such as haemorrhoids, diverticulosis and colitis. All these abnormalities could be contributing factors for positive i-FOBT results.

The prevalence of positive i-FOBT, and its sensitivity, specificity, PPV and NPV in detecting CRC did not yield consistent results with the literature. We found the sensitivities of i-FOBT for detecting neoplasia and carcinoma respectively are in agreement with a smaller study in Malaysia (N=103)[6] (neoplasia 53% and carcinoma 77.8%) whereas the specificities reported (neoplasia 91.7% and carcinoma 84%) were in conflict, which was seen nearly two folds of the specificity in this study. Similar patterns observed from a work by Chen et al. (2012) where the iFOBT led to 69.4% sensitivity and 75.5% specificity for detecting combined CRC and cancerous lesions[8]. A part of our results was contradictory to the study conducted by Levi et al., where the sensitivity, specificity and PPV 100%, 85.9% and 9.1%, respectively (except prevalence of i-FOBT 32% and its NPV 99.8% which are paralleled to our findings)[33]. While we deem it unlikely, the variation of sensitivity and specificity detections compared to other studies might have arisen from plausible factors related to cut-off value for the detection of CRC[11], haemoglobin degradation, sampling, laboratory handling, reagent quality and equipment performance. Moreover, some of the patients with positive i-FOBT results in this setting did not perform colonoscopy, which might affect the number of patients diagnosed with CRC. In other words, some CRC cases might be missed. The selection criteria of our study protocol investigated a screened population of subjects that may exhibit a high pre-test probability of presenting pathology. This limits the conclusion that may be drawn about PPV; a measure more accurately drawn by large cohort prospective studies that track subjects longitudinally. Further local studies comparing the screening accuracy and number of errors of the i-FOBT-based CRC screening among Malaysians are recommended to be carried out.

The purpose of this retrospective study is weighed toward elucidating the specificity and sensitivity in detecting CRC among the Malaysian population with positive i-FOBT results, as well as concordance of the method to clinical findings. It is beneficial in the aspect of knowing the practicality of i-FOBT in detecting CRC at an earlier stage than the symptomatic presentation and its clinical significance in decreasing CRC mortality, in particular among the Asian populations.

Some limitations of this study deserve careful consideration. Firstly, we had to rely on retrospective secondary data, and thus screenees without complete data had to be excluded. Another limitation of the present study was that only a small number of subjects who had either a positive or a negative i-FOBT result underwent colonoscopy on the ground of aforementioned reasons, which possibly resulted in some missed CRC cases. Besides, we only obtained data for a single sample of the i-FOBT, nevertheless, it is worth taking note of the contentious suggestions on the number of i-FOBT sample used in CRC screening. On one hand, a previous study by Levi and co-authors[28] reported that 1000 symptomatic and other high-risk Israeli patients underwent three separate sample tests. The authors observed an elevated sensitivity for more than one sample, although the difference between two and three samples was not significant. The specificity decreased when more samples were used. It is

conceivable that a screening strategy with two samples results in a different optimal cut-off value when compared with a one-sample screening. However, it could be foreseen for an increase in sensitivity, therefore detection rate by two tests could be matched by a decrease in the participation rate that resulting in a decrease in the detection rate. On the other hand, according to the results of Guittet et al.[9] and Park et al.[10], one-sample iFOBT could provide similar performances to two-sample iFOBT in average-risk population provided that a different cut-off is chosen, and one-sample iFOBT is of importance because using only one sampling could improve participation and reduce costs.

## CONCLUSION

In summary, i-FOBT appears to be a useful tool in the detection of abnormalities in the lower gastrointestinal tract. We suggest implementation of large-scale screening programs through the detection of FOB using i-FOBT as the screening method and colonoscopy as a confirmation test.

## AUTHOR CONTRIBUTORS

Concept – J Y Chieng; Design - J Y Chieng; Supervision – J Y Chieng; Resource – J Y Chieng; Data collection and/or Processing – J Y Chieng, O C Ng, R Y Paul Yap, Y Pan; Analysis and/or Interpretation – M C Tan; Literature Search – M C Tan; Writing – M C Tan; Critical Reviews – J Y Chieng, M C Tan, O C Ng, R Y Paul Yap, Y Pan.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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