

# Role of immune- based faecal occult blood test for screening of colonic pathologies

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## ABSTRACT

**Introduction:** The Identification of colonic pathologies at their early stages is of paramount if the good outcome and prognosis is sought. Additionally, early diagnosis is associated with lower burden on the health service resources. Immune-based Faecal Occult Blood Test (IFOBT) is one of the measures that is implemented in some countries for early identification of colonic cancer. However, to our best knowledge no study was done, so far, to examine the applicability of IFOBT to identify other colonic pathologies at different age groups. Furthermore, no research was performed to examine IFOBT clinical value in our demographic and health service setting. **Aim:** To examine the usefulness of IFOBT for screening of colonic pathologies in different age groups by comparing it with the gold standard approach, colonoscopy with biopsy and identification the role of IFOBT in promoting adherence to colonoscopy. **Material and method:** In this prospective study, we included 238 patients who are expected, due to clinical suspicion, to have colonic pathologies of various types. All of them were examined for faecal occult blood using immune based method kits (IFOBT) from two commercial suppliers; Plasmatic (UK) and AllTest (China). Colonoscopy was done for patients who agreed on at the Gastrointestinal and Hepatology centre at Azadi Teaching Hospital, Kirkuk and appropriate cases were sent for histopathology. **Results:** Of the 238 patients, 142 were males and 96 females, 109 (46%) had positive IFOBT while in the remaining 129 cases (54%) the test was negative. Reproducible results using two commercially available kits showed that the test is robust and reliable. 150 (63%) patients agreed for colonoscopy. Most patient with positive IFOBT (82%, no: 90/109) agreed for colonoscopy, this percentage was significantly higher ( $P < 0.001$ ) compared to the colonoscopy performer with negative IFOBT (46%, no: 60/129). Considering colonoscopy as gold standard method, IFOBT would have the sensitivity of 95.9% and specificity of 98.3%. Accordingly, IFOBT has positive and negative predictive values (98.9%-99%, CI 94.2% to 99.97%) and (93.44%-95%, CI 84.05% to 98.18%) respectively. **Conclusion:** IFOB is a cost effective and a versatile method for screening of colonic abnormalities, that is very specific with a relatively high sensitivity. Presence of faecal occult blood increases adherence to colonoscopy. Additionally, it is simple method that can be implanted in almost all clinical setting.

**Keywords:** Colonic pathologies, Faecal occult blood, Colonoscopy, Screening.

## Introduction:

Colonic pathologies are not uncommon in all age groups, especially the elderly (1, 2). The range of the colonic lesions is wide, it might be simple polyp, vascular abnormalities, diverticulosis, and inflammatory bowel diseases or more serious pathology such as malignancy with metastasis (1, 3). It is estimated that lesions in the colon and rectum are present in about one quarter of the general population with huge burden on the sufferer and on the health services (2). For example, colon cancer incidence increases with age, and at the age of 70 years, it is estimated that 5% of this age group will ultimately develop cancer (4). Fortunately, colon cancer is almost always preceded by long standing adenomas in paradigm known as the adenoma-carcinoma sequence (5).

Additionally, the overall prevalence of diverticulosis in western countries increases with age. Approximately 50% of individuals aged 60 years and over will have diverticulosis and by the age of 80 years approximately 70% of them will develop it (6). It is well recognised that colo-rectal pathologies that are picked while in their infancy are associated with lower mortality and morbidity rates with a fair chance of cure (7). For instance, removal of colonic adenomas is associated with near abolishment of cancer occurrence (7).

Accordingly, there was exponential increase in the development of tests that can identify colo-rectal lesions as early as possible, each method has advantages and disadvantages.

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The gold standard method for screening and diagnosis is colonoscopy with biopsy (8). However, this technique has a great deal of inconvenience for the patient with possible serious complications, it is resource demanding and requires expert endoscopist (9). Imaging investigations such as; computed tomographic colonography (CT), magnetic resonance colonography, capsule endoscopy and double contrast barium enema are costly, equipment demanding, not easy to perform and not readily understood (10).

Another newly developed method is molecularly dependent approach which relies on the mutation pattern of colo-rectal tumour cells that are exfoliated with stool (11). It can only identify pathologies that are caused by tumours whether benign or malignant (11). In addition to its limited list of target diseases, it is complicated with unsatisfactory level of sensitivity (11).

Interestingly, most of the colo-rectal pathologies are associated with bleeding of tiny amount of blood (occult) during their early hidden stages. Occult Gastrointestinal Tract (GIT) bleeding is defined as bleeding that is unnoticed by the patient, it is more common than overt bleeding of the lower GIT lesions (12).

Faecal occult blood test has emerged as promising approach for screening of colonic pathologies. Faecal occult bleeding is usually associated with anaemia, weakness and other non-specific signs and symptoms (12).

Initial methods to test for hidden blood exploits the reductive ability of the haemoglobin, the test gained the name guaiac faecal occult blood test (gFOBT) (13, 14). Since many drugs and food share this reductive activity, intense patient preparation was required for three days prior to test with eventual poor sensitivity (13, 14).

Immune-based Faecal Occult Blood Test (IFOBT) for haemoglobin is another modality to test for faecal occult blood, it uses antibodies specific for the globin moiety of human haemoglobin (15). Unlike gFOBT, it is specific for human blood and does not require dietary restriction neither react to blood from upper GIT (15). These qualities attracted many researchers to examine the feasibility of IFOBT to detect occult blood from lower GIT, with variable result from different setting. Most of the previous studies shed light on the clinical utility of faecal occult blood to detect pre-malignant and malignant colonic pathologies of a defined age range, with other lesions and age groups were marginalised with no significant attention (16).

#### **Aim of the study:**

In this study, we tried to expand the value of IFOBT for the screening of various colo-rectal pathologies at different age groups.

#### **Material, methods and subjects:**

This prospective observational study included 238 patients (called Initial study population) and was conducted from 1 st January 2015 to 1st May 2016.

The clinical indications for lower GIT endoscopy were; unexplained anaemia, abdominal pain (suggestive of colonic origin), weight loss, altered bowel motion (diarrhoea or constipation) and stool colour change (black color).

We excluded patients who were unable to give informed consent or had a history of; colorectal cancer, adenomatous polyp, or inflammatory bowel disease; or, if they had severe or terminal illness. Those with frank rectal bleeding or physically unfit were also exempted. Clinicopathological characteristics of the study population were obtained including: age, sex, weight and haemoglobin concentration.

Ethical approval was obtained from the Ethical committee of Kirkuk Medical College. The patients were informed about the procedures and their possible risks, written consent was obtained from each patient. Immunochemical faecal occult blood test (IFOBT; qualitative, results reported as 'positive' or 'negative') was done once on a single stool sample using two commercially available Point-of-Care Testing kits (PLASMATEC™, Plasmatec Laboratory Products, UK and ALL TEST™, Hangzhou AllTest Biotech Co., Ltd, China) at a private laboratory in Kirkuk without prior dietary restriction.

One hundred fifty patients agreed on, and underwent colonoscopy (Olympus colonoscope, Japan) at the Gastrointestinal and Hepatology Centre at Azadi Teaching Hospital, Kirkuk, Biopsy was taken from lesion when appropriate and sent to the Histopathology Unit at Azadi Teaching Hospital. Stringent preparation for colonoscopy was implemented by a low fibre diet, 2 L of hypertonic polyethylene glycol solution (Moviprep; Netherlands) and 2 L of fluids.

SPSS software version 17 was used to calculate sensitivity, specificity, and positive and negative predictive values of the cases who underwent colonoscopy and tested by IFOBT. The statistical significance of difference was set at  $< 0.05$ .

#### **Results:**

Our studied population (called Initial study population, table 1) encompassed 238 patients with clear male dominance (Male: 142, 60%, female: 96, 40%), with age range of 20-80 years, the statistical mode of age group was 40-70 years, which accounted for almost 70% of the study population. The most common reason for referral for endoscopy was abdominal pain suggestive of large bowel origin (42%), followed by altered bowel motion (20%). Other indications were anaemia, weight loss and

black coloured stool at rates of 18%, 13% and 7% respectively (as shown in Table 1).

Of the 238 patients (Initial study population, IFOBT only population), 109 (46%) had positive IFOBT while in 129 (54%) cases the test was negative.

We tested each stool sample once with two different kits (PLASMATEC™ and ALL TEST™), the results of both IFOBT kits were 100% identical (the results of each sample tested were the same by both kits) proving the reliable and robust nature of the IFOBT (Figure 1). Almost two- third (63%, no:150) of the initial study population underwent

colonoscopy ( this group called : Final study colonoscopy, Table 1&2), the remaining patients (37%, no:88) refused colonoscopy. The reasons of colonoscopy rejection in this study were as follow: inconvenience of the procedure (shyness, pain, self-esteem concern) accounts for almost half of those who did not agreed to perform colonoscopy (40%, no:35) that is far followed by the phobia of the procedure as a cause of rejection (20%, no:18). Financial reasons, preparation steps and fear of the results of colonoscopy accounted for 18%, 13% and 9% respectively as shown in Table 2

**Table 1. Demographic and clinicopathological characteristics of the Initial study population (IFOBT only) and causes of referral. Male patients make almost two-third of the study subjects. The 40-70 age group represented the statistical mode of the cases. Abdominal pain was the main concern that is followed by altered bowel motion. The IFOBT was positive in more than half of the cases.**

Clinicopathological characteristics	Number	%
<b>Gender</b>		
Male	142	60
Female	96	40
<b>Age / year</b>		
20 -40	51	21.5
41 -50	65	27.4
51 - 60	47	20
61 - 70	53	22
≥ 70	22	9.1
<b>Reason for referral</b>		
Abdominal pain	100	42
Altered bowel motion	47	20
Iron deficiency anaemia	43	18
Weight loss	31	13
Stool colour	17	7
<b>Immune-faecal occult blood test result</b>		
Positive	109	46
Negative	129	54
<b>Performance of colonoscopy /total</b>		
Yes	150	63
No	88	37

The demographic characteristics (age and sex) of the final study population (IFOBT and colonoscopy) were similar to those of the initial population, Table 2. Table 2 shows that 60% of those who underwent colonoscopy (150 patients) were IFOBT positive (90/150), the vast majority 82% (90/109) of IFOBT positive cases underwent colonoscopy. A smaller fraction of patients with IFOBT negative result underwent colonoscopy (46.5%, 60/129). The percentage difference between the two groups (IFOBT positive and IFOBT negative) with regard to their involvement in endoscopy was statistically significant ( $P < 0.001$ ).

Colonoscopy identified lesions in 93 patients, pathologies in the ascending colon made up nearly one-third of the identified lesions, the remaining were almost equally distributed among transverse colon, hepatic flexure and caecum (Table 2).

The most common identified pathology was polyp which makes up more than half of the 93 seen lesions (~56%, 52/93). The next common lesion was cancer which was confirmed by histopathology (27%, 25/93). Diverticular diseases were identified in 8 patients (8%, 8/93).

lesions such lipoma was identified in three patients (two of them were ulcerated) and angiodysplasia was seen in two cases.

Example of the lesions are shown in Figure 1 and numerically are illustrated in Table 3. Nearly all the patients who had negative faecal occult blood and colonoscopy (no.60) had no pathology seen by the last procedure. The exception was in four patients who were IFOBT negative but lesions were seen by colonoscopy: two cases of adenomatous polyp and one patient had diverticular disease, with one case of non-ulcerated lipoma and can be called false negative cases as illustrated in Table 3. One case which was found to have positive IFOBT failed to show any lesion by colonoscopy, making this case a false positive case (Table 3).

Considering colonoscopy as the gold standard for detection of colonic lesions, IFOBT would have sensitivity (calculated only for the cases who underwent colonoscopy and IFOBT) of 95.9% and specificity of 98.3%. Accordingly, IFOBT has positive and negative predictive values of (98.9% - 99.9%-, CI 94.2% to 99.97%) and (93.44%-95%, CI 84.05% to 98.18%) respectively.

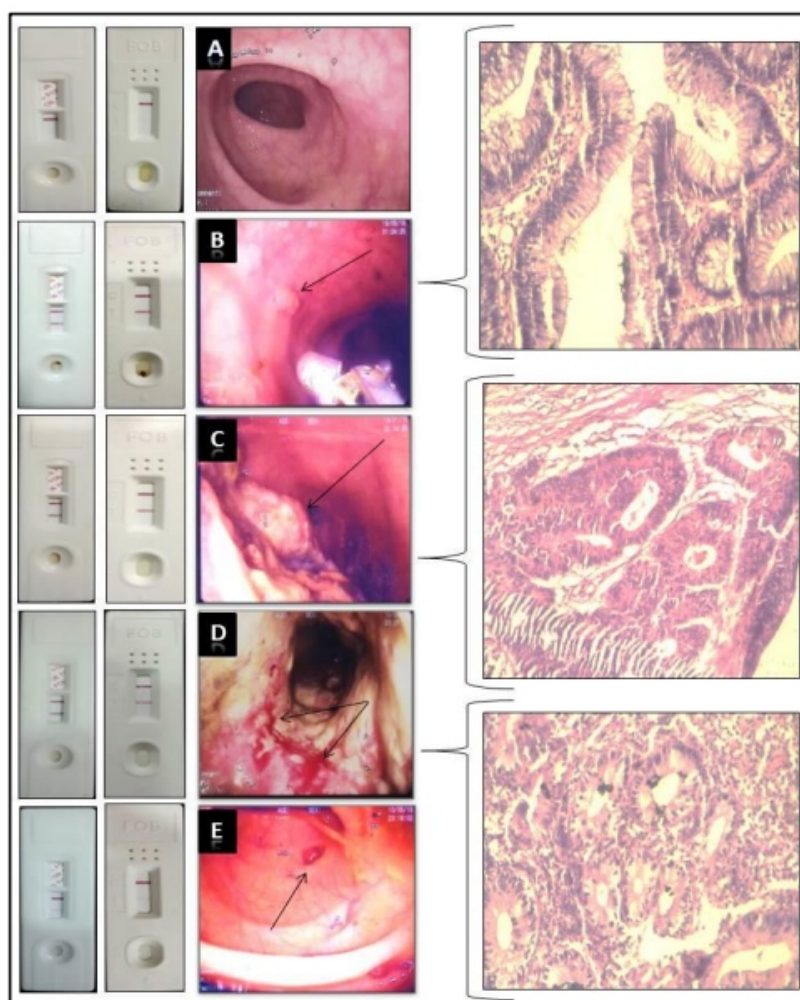
**Table 2 . Demographic and clinicopathological characteristics of the Final Study Population (IFOBT and Colonoscopy). Most of the patients were male with the age group 40-70 years being the mode age. The majority of the patients who agreed to undertake colonoscopy had positive occult blood.**

Clinicopathological characteristics	Number	%
<b>Gender</b>		
Male	95	63.3
Female	55	36.7
<b>Age, year</b>		
20 - 40	32	21.3
41 - 50	41	27.3
51 - 60	30	20
61 - 70	33	22
≥ 70	14	9.4
<b>IFOBT</b>		
Positive	90	60
Negative	60	40
<b>Reason for rejection of colonoscopy</b>		
Non-convent	35	40
Procedure phobia	18	20
Cost	16	18
Preparation	11	13
Result phobia	8	9
<b>Performance of colonoscopy / According to IFOBT</b>		
Positive (109)	90 / 109	82.3
Negative (129)	60 / 129	46.5
<b>Location of the lesion by colonoscopy (number 93)</b>		
Ascending colon	30	32.2
Transverse colon	23	24.8
Hepatic flexure	21	22.5
Caecum	19	20.5



**Table 3: Results of the colonoscopy. The most common lesion is polyp that is followed by colon cancer and diverticular diseases. The sensitivity and specificity of IFOBT was done for cases who underwent, both, colonoscopy and IFOBT**

I ĬČĎŮ	HŇŇŮPŮŇŇ NŘ colonoscopy	GŤNŇŮČŇŇ-Ů ŇŇŇŮŇ test positive	Ī ŇŮČŮPŮR	Ī ŇŇŇŮŇŮR
Ī ŐŖŮCE	DČ	DĆ	EDĚĂ	EDĚCĂ
FŇŇŇŮ	ČD	ČĎ		
GŇŮPŮŇ ar diseases	Đ	Đ		
HĚG	Ç	Ç		
Ŧpoma	Ć	Č		
É ŐŇŇŇŮŇŮŮŮ	Ê	Ĉ		
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İ ŐŮŮŮŮ ŇŇŮ	EĆ	EĆ		



**Figure 1. Faecal occult blood testing, colonoscopy results and histopathological outcome of some of the study cases. (A) a Patient has negative IFOBT(using two test kits) and normal colon as seen by colonoscopy, no biopsy was done.(B) is a case of positive IFOBT which was found to be caused by colonic inflammatory polyp which was confirmed by histopathological examination. The third case (C) had positive IFOBT and adeno-carcinoma features by colonoscopy with verification by biopsy with histopathological examination. (D) is a case of ulcerative colitis with all the FOBT, colonoscopy and histopathology were observed. The last patient (E) had positive IFOBT with colonoscopy identifying inflamed diverticulum, no biopsy was taken.**

## Discussion:

The modern health systems focus on disease prevention and early detection through screening programmes. It is generally accepted that most of the diseases that are identified early in their natural course would have better prognosis and even cure with lower burden on the health system.

Colonic pathologies, mainly tumours, were on top of the list of the diseases that are considered as classic example of usefulness of screening programme. Data from the United Kingdom, bowel cancer screening programme showed that large number of the cancer precursor, polyps, were identified and most of the cancer observed where at their early stages, which means better chance of prevention and cure (17).

Most of the studies focused on the use of IFOBT for screening of malignant and premalignant lesions at old age group. No study was done so far to examine the usefulness of IFOBT for screening of other colon-rectal pathologies at different age group in Iraq. We selected IFOBT as the screening tool as it is simple, inexpensive, and easily diffused through the population and the act of screening is safe and acceptable. Additionally, globin is degraded by upper GIT enzymes and thus IFOBT does not detect blood from upper gastrointestinal tract which, ultimately, shorten the list of possible diagnoses (18). The IFOBT in this study had high sensitivity compared to other's works such as the American screening study which had a sensitivity of ~ 11%, 28% and 78% for adenoma, advanced adenoma and carcinoma respectively (19).

An Asian study reported IFOBT to have a sensitivity and specificity of 95.4% 44.4 % sequentially, with nearly similar frequency for the types of the identified lesions (20).

Other studies showed that almost half of the cases of the positive faecal occult blood test had no abnormality detected by colonoscopy (21).

The design of these study is to use three samples collected on three different occasions and the population age group was old with higher possibility of microscopical lesions, bleeding (regular NSAID user and smoking) being the cause of IFOBT (21).

To explain false negative cases in IFOBT, some lesions ooze blood to a level that is below the kit detection limit. It is estimated that commercial kits have sensitivity for the presence of haemoglobin down to 75 ng/ml of stool (22-24).

Above facts give a clue to why we missed four cases by IFOBT (False negative), two cases were polyp, one diverticular diseases and one lipoma (not ulcerated).

Additionally, it is well recognised that bleeding from the colonic lesions is intermittent and this might further justify the above false negative cases (25).

One sample that was IFOBT positive but colonoscopy negative (false positive) might be too small to be seen by colonoscopy or it was a lesion that healed after IFOBT and before colonoscopy (26, 27).

In this study, pre-malignant lesions, polyps, were the most common cause of positive faecal occult blood followed by colon cancer. This finding emphasises the importance of the IFOBT screening for early identification of these curable lesions (polyp) if recognised very early in their course and localisation.

The rate of non-neoplastic findings (NNF) was 21% in the English Bowel Cancer Screening Programme (28). This percentage is higher in the this study. Diverticulosis is common especially in old age group and it is associated with serious complications if left untreated (29). In our research, other pathologies with passage of blood or inflammation such as inflammatory bowel disease, ulcerated lipoma and angiodysplasia were also identified by IFOBT showing the ability of the test to identify different colonic pathologies.

Two-third of our initial study population agreed on doing colonoscopy, most of them had positive IFOBT which is similar to the 75% seen in the American population with positive faecal occult blood (30). This indicates that IFOBT increases adherence to colonoscopy.

Positive occult blood test will encourage patients to perform colonoscopy, and negative cases would not be in desperate urge for colonoscopy and be classified as low risk.

## Conclusion:

It is safe to say that IFOBT is a good and versatile screening test to examine the presence of various colonic lesions regardless of the population age. This will reduce the number of patients who are exposed to unnecessary colonoscopy with its known burden on the patient and health system.

Being a point of care test, IFOBT is highly recommended to use in primary care health centres to categories patients, to high and low risk patients for colonoscopy referral purposes.

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