DOI: 10.4274/tjcd.galenos.2022.2021-11-5
Turk J Colorectal Dis 2022;32:178-185

RESEARCH ARTICLE

The Yield of Faecal Immunochemical Test in the Detection of Colorectal Cancer within a Fast-track Pathway at York, United Kingdom

Ahmed Elbeltagi, Mohamed Salama, Peter Boxall, Jesper Roos, Michael Lim

NHS York Scarborough Teaching Hospital, Department of General Surgery, York, United Kingdom

ABSTRACT

Aim: Access to colonoscopy was limited during the Coronavirus disease-2019 (COVID-19) pandemic peak. It was, therefore, of great importance that a tool such as faecal immunochemical test (FIT) be used to identify patients with a greater likelihood of colorectal cancer (CRC).

Method: A prospective cohort of patients referred through the fast-track pathway was sent a FIT test. A cut-off of 7 µgHb/g was used as the threshold for a positive result. A receiver operating curve (ROC) was subsequently constructed to identify the ideal threshold for detecting cancer.

Results: In total, there were 1,068 patients referred to the fast-track clinic. A greater proportion of patients who were FIT positive had CRC (17.4% vs. 0.4%, p=0.001) when compared with FIT negative patients. ROC curve analysis revealed an optimum sensitivity/specificity for detecting CRC using a FIT threshold of 19 µgHb/g.

Conclusion: The yield for CRC is minimal in a FIT negative patient - such patients may be safely discharged, as long as a clinical safety net is in place. Using sensitivity and specificity analysis, patients with a FIT above 19 µgHb/g should be investigated urgently to exclude cancer.

Keywords: Faecal immunochemical test, colorectal cancer, fast track, FIT

Introduction

Colorectal cancer (CRC) is the fourth most common cancer and the second most common cause of cancer death in the UK.[1] CRC can present with one or multiple symptoms to primary care. Symptoms include a change in bowel habits in the form of diarrhoea or constipation, both in terms of frequency and stool consistency, which is the most common CRC presentation in primary care.

Colonoscopy is the gold standard investigation to detect significant bowel disease (SBP). Significant bowel pathology encompasses a spectrum of conditions, including CRC, higher risk adenoma [(HRA), defined as three or more adenomas or any adenoma >1 cm], and inflammatory bowel disease (IBD) with high sensitivity and specificity.[2] A two-week pathway was initially introduced to help patients be seen sooner. The aim was to diagnose CRC early enough to minimise CRC mortality. This pathway has led to a massive increase in the number of referrals through primary care.[3] As a consequence of the need to investigate patients quicker and better, much pressure was placed on outpatient clinics and diagnostic services, such as endoscopy units and radiology departments, to increase capacity for these patients. Traditionally, CRC yield from the two-week pathway has been low, ranging between 3-7% at best.[3] Over the last five years, fast-track referrals have increased by 90%, leaving 45% of endoscopy units failing to meet their colorectal waiting list targets.[4,5] Therefore, prompt actions were needed to deal with these problems, with the aim of reducing unnecessary colonoscopies and mitigating the associated risks and costs of inappropriate tests.

In 2017, the National Institute for Health and Care Excellence (NICE) (DG30) introduced the faecal immunochemical test (FIT) to help with the referrals of patients with low-risk symptoms that did not meet the criteria for the two-week wait (2WW) pathway.[6] Currently, a positive FIT result

Address for Correspondence: Ahmed Elbeltagi, MD,
NHS York Scarborough Teaching Hospital, Department of General Surgery, York, United Kingdom
E-mail: Ahmed.elbeltagi@nhs.net **ORCID ID:** orcid.org/0000-0002-7369-7772
Received: 18.11.2021 **Accepted:** 05.02.2022

detected in a low-risk patient automatically upgrades them into a 2WW pathway. A 2WW referral is a referral from general practitioners (GPs) to provide patients with an urgent appointment when they have suspicious symptoms of cancer. However, currently, FIT has not been approved by NICE for routine use in these high-risk patients.

FIT detects the remote globin part of hemoglobin (Hb) by immunoassay in stool and can measure the faecal Hb concentration (f-Hb) to the nearest microgram of Hb per gram of faeces (µgHb/g).[7] NICE has recommended a threshold of 10 µgHb/g for a positive result. NHS England has also recently suggested that patients with a negative FIT test may be removed from the fast-track pathway and tracking list to ease pressure within the system.

A review of the published literature on FIT within a two-week pathway revealed six main projects that were done within the UK. The Nottingham series has the largest number of patients on FIT with 14,788 patients. This group published the only paper that followed the impact of FIT on yield longitudinally for two years. Access to the FIT test was via primary care. Unlike most other studies, the threshold for a positive FIT was set at >4 µgHb/g. Similarly, in Scotland, FIT was provided to primary care. The studied population was half the size of that in Nottingham, but a positive threshold was set at a higher cut-off of >10 µgHb/g. Another large national study was done recently, centered in Croydon Hospital, across 50 NHS hospitals with 9,822 patients being included with a very low threshold (>2 µgHb/g). Table 1 summarises the six main published papers.

To date, there has been little data looking at FIT in the Yorkshire region as a tool to maximise cancer detection. During the Coronavirus disease-2019 pandemic, the need for another test to aid the cancer diagnosis process has increased. As a result, York Teaching Hospital Foundation Trust adopted FIT as a diagnostic adjunct.

As seen from the published literature, there is variation in the positive FIT threshold between studies. Thresholds of 2, 4 and 10 µgHb/g have been used, and this will have an impact on reported yields within individual publications. NICE has recommended that the positive threshold for FIT be set at 10 µgHb/g. As FIT is a quantitative test, threshold values can be modified to improve the test's sensitivity or specificity. It is essential to determine the optimum cut-off value for patients with significant bowel pathology, including that of CRC, because it allows a service to define the patient group that is most at risk and prioritise them for investigations accordingly. Increasing the sensitivity of the test by reducing the threshold allows maximum detection of patients with pathology but results in a lot of negative colonoscopies and wasted capacity. Reducing the sensitivity optimises the yield for colonoscopy when it is performed but may result in some patients with significant pathology not being investigated. As there is a need to determine the optimum threshold for detection of bowel pathology in our local cohort of patients, we chose to study this in greater detail.

Table 1. Summary of studies which have examined the role of FIT in colorectal cancer pathways

Paper title	Location	Positive FIT threshold	Primary or secondary care	Population size	Year
Faecal immunochemical test (FIT) is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2WW pathway: A diagnostic accuracy study[7]	Croydon University Hospital	f-Hb >2 µgHb/g	Secondary care	9,822	October, 2020
Impact of introducing a FIT for haemoglobin into primary care on the outcome of patients with new bowel symptoms: A prospective cohort study[8]	Tayside Scotland	f-Hb >10 µgHb/g	Primary care	5,422	May, 2019
Early clinical outcomes of a rapid colorectal cancer diagnosis pathway using FIT in Nottingham[9]	Nottingham	f-Hb >4 µgHb/g	Primary care	1,947	December, 2019
Adoption of FIT for 2-week-wait colorectal patients during the COVID-19 pandemic: An observational cohort study reporting a new service at a regional centre[10]	Royal Surrey NHS Foundation Trust	f-Hb >10 µgHb/g	Primary care	391	October, 2020
FIT s in the COVID-19 pandemic; safety-netting of patients with symptoms and low faecal haemoglobin concentration - can a repeat test be used?[11]	Royal Surrey NHS Foundation Trust and University of Dundee	f-Hb >10 µgHb/g	Not applicable	Not applicable	October, 2020

2WW: Two-week wait, COVID-19: Coronavirus disease-2019

Materials and Methods

Patient Population, FIT and Processing of Results

A consecutive series of patients in North Yorkshire (including the towns of York, Scarborough, Whitby, Bridlington, Selby, and Malton), referred through the fast-track pathway, were sent a FIT test as part of their diagnostic work-up. Informed consent was obtained from those patients. All patients were asked to perform a FIT test before they were assessed in the clinic regardless of their symptoms. Patients received a FIT kit via the post. This kit includes a specimen collection device and instructions leaflet on collecting the sample and how to send it back to the laboratory. The department of Clinical Biochemistry at York Hospital analyses the FIT assay twice a week. Allocations of patients were made to appropriate telephone clinic slots with a FIT result at hand. Patients were assessed at the telephone clinic within the two-week timeframe, and a FIT result would be incorporated into the investigative algorithm when it subsequently became available on the Core Patient Database (CPD).

Triage of Patients

A measured FIT of >7 µgHb/g was regarded as positive, which was determined by our local laboratory. Given the published literature, which had both thresholds that were higher and lower for a similar cohort of patients, this positive threshold was deemed reasonable. Yield for CRC and significant bowel pathology was noted. The definition of a CRC is that of a lesion situated within the colon and rectum that has a confirmed biopsy of an adenocarcinoma. Although lesions of the anus that are squamous cell in origin are regarded as clinically significant they were, strictly speaking, not included as part of the definition of CRC within this study. The definition of significant bowel pathology included CRC, HRA and IBD, as reported by previous publications. HRA was defined as three or more adenomas or any adenoma >1 cm in size.

Inclusion and Exclusion Criteria

All patients referred from primary care with symptoms that met NICE referral criteria to fast-track clinics from March to October 2020 were included. Patients were excluded if they chose not to have any investigations after clinic consultation. Similarly, patients were excluded if they were deemed too frail for investigations by clinicians. A proportion of patients were also awaiting investigations at the time of collection of data.

Data Collection

All data was secured on a password-protected Excel spreadsheet within the trust. Clinic letters, investigations, results, and demographics were obtained from the interrogation of clinical information via CPD. Demographics (NHS number, age, and gender), presenting symptoms and signs, such as the presence of rectal bleeding, presence of mass/lump, and iron deficiency anaemia, were collected. Results from the test of choice (either colonoscopy, cross-sectional imaging, or both) were collected to determine the yield from these diagnostic tests. Other findings such as diverticulosis, haemorrhoids, solitary rectal ulcers, colitis, and low-grade adenomas were also recorded.

Statistical Analysis

Categorical and continuous variables were compared using the chi-square test or Mann-Whitney U test, respectively.

A receiver operating curve (ROC) was calculated to study the sensitivity and specificity of FIT thresholds for CRC and significant bowel pathology. The optimum threshold was determined by the calculation of the Youden index.

A p-value of less than 0.05 was deemed significant.

Results

Study Population

From March to October 2020, there were 1,068 patients referred to the fast-track clinic. Sixty-five patients declined investigations and 11 were pending, leaving 992 patients for analysis. There were 527 (53%) females and 465 (47%) males. The median age was 72 (interquartile range: 63-78) years. Fifty-two (5.2%) CRCs were detected in the study population of 992 patients. The proportion of CRC cases among women and men was not statistically different (28/527 vs 24/465, p-value=0.915).

FIT Test as a Diagnostic Tool

Among the 992 patients who had FIT, 282 patients were positive (>7 µgHb/g). In total, among 282 positive patients, there were fifty-two CRC cases (17.8%) and nineteen patients (6.7%) who had significant bowel pathology. Figure 1, 2 highlight this graphically.

Sensitivity, Specificity, and ROC Analysis of FIT Testing

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value of FIT using the initial threshold of 7 µgHb/g was 94.2%, 75.3%, 17.4% and 99.6%, respectively. To optimise the threshold of detection of CRC in our study population, we decided to perform a ROC analysis. The ROC analysis revealed an area under the curve of 0.89 [95% confidence interval (CI) 0.85-0.93]. This curve is illustrated and detailed further in Figure 3.

To determine the optimum sensitivity/specificity for detecting CRC, the Youden index was calculated. The Youden index was determined using the formula: sensitivity + specificity-1 for each data point on the ROC curve. The data points are highlighted in Table 2. The best Youden index was noted at FIT threshold between 10 and 19 µgHb/g.

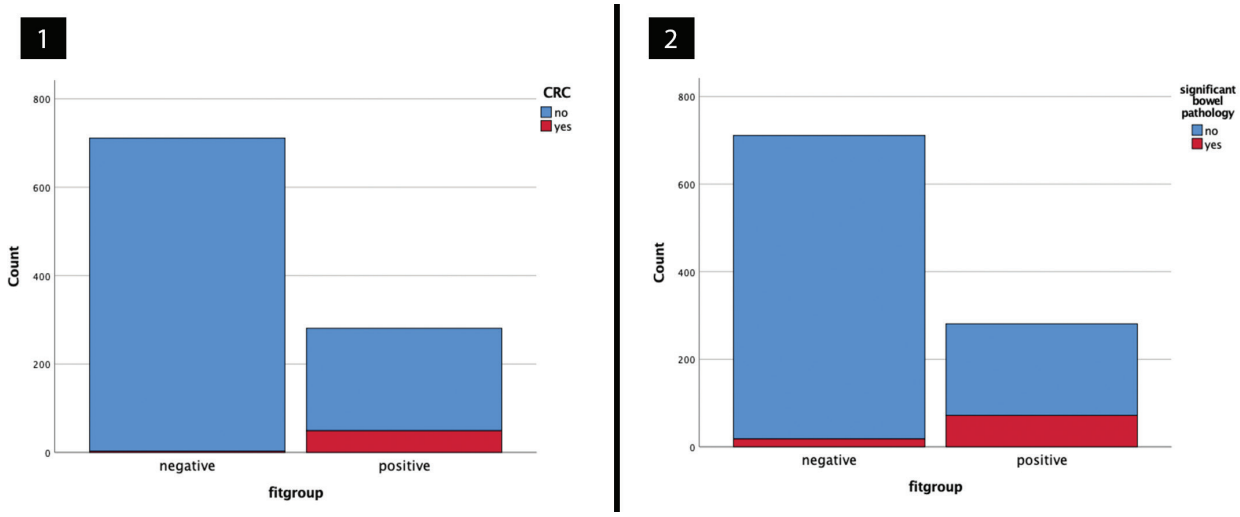

Figure 1, 2. FIT as a diagnostic tool for CRC and SBP

FIT: Faecal immunochemical test, CRC: Colorectal cancer, SBP: Significant bowel disease

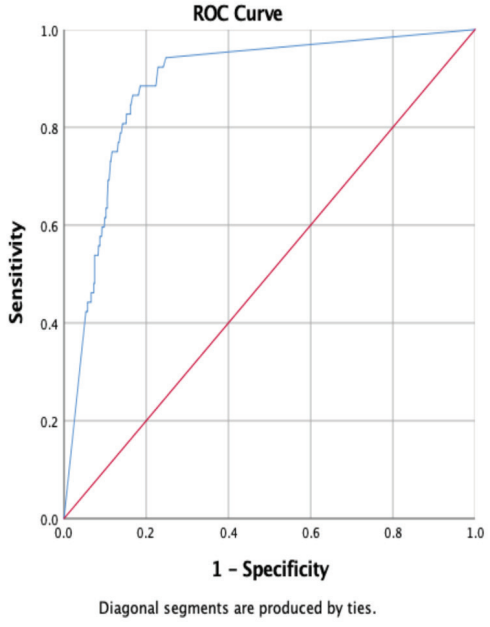

Figure 3. ROC curve

ROC: Receiver operating curve

Discussion

FIT as a Diagnostic Adjunct

The 2WW pathway has a yield of 3-4% but accounts for the detection of 30% of all CRC cases.[12-14] A longitudinal study conducted between 2009 and 2018 showed that the number of fast-track referrals for suspected CRC has doubled in the intervening period, and yet the overall yield for cancer has reduced by half because a large number of procedures need to be performed to detect occasional cancer.[14] Work from other centres also showed a similar trend - a consistent reduction in diagnostic yield with an increase in colonoscopy referrals.[15-18] The volume of endoscopy cases in the UK has nearly doubled in the last five years.[18] Each colonoscopy costs the NHS £372-£419, with an overall cost of £260 million per annum.[8,19] In contrast, NICE guidelines reported the cost of the FIT test to about £5-£6 according to the type of analyser used.[6] This would mean a saving of around £400 per patient. Therefore, better use of endoscopy and careful selection of patients who truly require the test via the 2WW pathway could potentially improve the yield for cancer and help the NHS fiscally.

It has always been a strategy to use FIT as a means to improve the 2WW pathway. This strategy aims to improve overall patient care by targeting the use of colonoscopy in the right group of patients and increasing the rates of detection of cancer and other significant bowel pathology. In our study, of the 992 patients, 282 (28%) patients were FIT positive (above 7 µgHb/g). There were 52 (5%) CRC cases. Therefore, overall cancer yield was 17%.

There were some similarities in the yield of SBP or CRC in the main projects we looked at. Some did not look at the yield of CRC separately but looked at the SBP yield as one. In Scotland, the yield for SBP in patients who had positive and negative test was 25% vs 1%, respectively, while the yield for CRC only was 8%. The projects with a FIT test threshold at 10 µgHb/g had quite a similar yield for CRC. Bailey et al.[11] in a two-year follow-up evaluation (with the largest population) had a CRC yield of 5.5%, while in Surrey, the yield was 3.7%. The previous three projects shared a positive FIT test threshold of 10 µgHb/g. In contrast, the multi-site study done in London using a threshold of 2 µgHb/g in 9,822 patients revealed a CRC yield of 17.4%,

Table 2. Sensitivity and specificity data points for each FIT threshold

Positive if greater than or equal to[a]	Sensitivity	1-specificity	Specificity	Youden index
6	1	1	0	0.00
7.5	0.942	0.248	0.752	0.69
8.5	0.923	0.241	0.759	0.68
9.5	0.923	0.237	0.763	0.69
10.5	0.923	0.229	0.771	0.69
11.5	0.885	0.223	0.777	0.66
12.5	0.885	0.218	0.782	0.67
13.5	0.885	0.206	0.794	0.68
14.5	0.885	0.205	0.795	0.68
15.5	0.885	0.202	0.798	0.68
16.5	0.885	0.195	0.805	0.69
17.5	0.885	0.191	0.809	0.69
18.5	0.885	0.189	0.811	0.70
19.5	0.885	0.185	0.815	0.70
20.5	0.865	0.181	0.819	0.68
21.5	0.865	0.178	0.822	0.69
22.5	0.865	0.174	0.826	0.69
23.5	0.865	0.173	0.827	0.69
24.5	0.865	0.172	0.828	0.69
25.5	0.865	0.169	0.831	0.70
26.5	0.865	0.167	0.833	0.70
27.5	0.846	0.163	0.837	0.68
28.5	0.846	0.162	0.838	0.68
29.5	0.827	0.162	0.838	0.67
30.5	0.827	0.16	0.84	0.67
31.5	0.827	0.156	0.844	0.67
32.5	0.827	0.154	0.846	0.67
33.5	0.827	0.152	0.848	0.68
34.5	0.808	0.151	0.849	0.66
35.5	0.808	0.149	0.851	0.66
36.5	0.808	0.145	0.855	0.66
38.5	0.808	0.143	0.857	0.67
40.5	0.788	0.139	0.861	0.65
41.5	0.788	0.137	0.863	0.65
42.5	0.769	0.134	0.866	0.64
44	0.769	0.133	0.867	0.64

Table 2. Continued

Positive if greater than or equal to[a]	Sensitivity	1-specificity	Specificity	Youden index
46	0.769	0.132	0.868	0.64
47.5	0.75	0.13	0.87	0.62
48.5	0.75	0.129	0.871	0.62
50	0.75	0.126	0.874	0.62
51.5	0.75	0.123	0.877	0.63
52.5	0.75	0.118	0.882	0.63
53.5	0.75	0.117	0.883	0.63
54.5	0.731	0.114	0.886	0.62
55.5	0.731	0.113	0.887	0.62
56.5	0.712	0.112	0.888	0.60
57.5	0.692	0.11	0.89	0.58
58.5	0.692	0.107	0.893	0.59
59.5	0.673	0.106	0.894	0.57
60.5	0.654	0.105	0.895	0.55
61.5	0.635	0.105	0.895	0.53
62.5	0.635	0.104	0.896	0.53
63.5	0.635	0.103	0.897	0.53
65	0.635	0.102	0.898	0.53
66.5	0.615	0.102	0.898	0.51
67.5	0.615	0.101	0.899	0.51
68.5	0.615	0.1	0.9	0.52
69.5	0.615	0.099	0.901	0.52
71	0.596	0.098	0.902	0.50
74	0.596	0.097	0.903	0.50
76.5	0.596	0.096	0.904	0.50
78.5	0.596	0.095	0.905	0.50
81	0.596	0.093	0.907	0.50
83	0.577	0.091	0.909	0.49
85	0.577	0.09	0.91	0.49
87	0.577	0.088	0.912	0.49
89	0.577	0.087	0.913	0.49
92.5	0.558	0.087	0.913	0.47
96.5	0.558	0.086	0.914	0.47
100	0.558	0.085	0.915	0.47
106	0.558	0.084	0.916	0.47
110.5	0.538	0.083	0.917	0.46
111.5	0.538	0.081	0.919	0.46

Table 2. Continued

Positive if greater than or equal to[a]	Sensitivity	1-specificity	Specificity	Youden index
114	0.538	0.08	0.92	0.46
116.5	0.538	0.078	0.922	0.46
118	0.538	0.077	0.923	0.46
120.5	0.538	0.076	0.924	0.46
123.5	0.538	0.074	0.926	0.46
126.5	0.519	0.074	0.926	0.45
132.5	0.5	0.074	0.926	0.43
139	0.481	0.074	0.926	0.41
150.5	0.481	0.073	0.927	0.41
162	0.481	0.072	0.928	0.41
165	0.462	0.072	0.928	0.39
167.5	0.462	0.071	0.929	0.39
195.5	0.462	0.069	0.931	0.39
222.5	0.462	0.068	0.932	0.39
227	0.462	0.067	0.933	0.40
241.5	0.462	0.066	0.934	0.40
260.5	0.442	0.066	0.934	0.38
276	0.442	0.065	0.935	0.38
285	0.442	0.064	0.936	0.38
292	0.442	0.063	0.937	0.38
297.5	0.442	0.062	0.938	0.38
303	0.442	0.061	0.939	0.38
308.5	0.442	0.059	0.941	0.38
322	0.442	0.057	0.943	0.39
348.5	0.423	0.057	0.943	0.37
373	0.423	0.056	0.944	0.37
387.5	0.423	0.055	0.945	0.37
395	0.423	0.054	0.946	0.37
399.5	0.423	0.053	0.947	0.37
401	0	0	1	0.00

which was close to our CRC yield (18.4%) using a higher threshold of 7 µgHb/g. It would seem that our CRC yield was indeed higher than those obtained from the other studies. It is difficult to explain the exact reasons for this observation when we control the variation seen in thresholds. However, it is possible that our patient population has a high incidence of cancer when compared with those from the other studies. What is clear from the data published at the time of writing is that FIT thresholds are inversely proportional to cancer yield.

In a recent two-year evaluation study performed in Nottingham, the authors retrospectively examined the stratification of FIT in conjunction with blood results to help to prioritise and detect CRC in more than 14,000 symptomatic patients. Only six CRC cases were detected in 11,194 patients who had FIT under 20 µg/g with normal blood tests and normal clinical examinations. Furthermore, it also showed that 5,588 patients (over 60 years) with FIT <4 µgHb/g were investigated by GPs after applying FIT results. With the implementation of FIT testing, the Nottingham group predicted that more than 230 additional referrals per month over two years had been avoided.[11]

In our series, there were only 52 cancers in 992 patients, which means that 95% of patients referred on a fast-track pathway did not have cancer. Three patients who were negative on FIT testing (<7 µgHb/g) had CRC. On closer examination, one patient had cancer in the rectosigmoid region, one in the distal transverse colon and one in the anal region. The presence of cancers in a FIT negative cohort is a little concerning. From a population perspective, patients who have a negative FIT result rarely have cancer, as this was only observed in 3 out of 711 (0.4%) patients. However, if one were to examine this from a cancer perspective, 3 out of 52 (6%) cancers were FIT negative. If one in every 20 cancers is not detected by a FIT test, then a serious question is raised. Although the risk of CRC is low in a FIT negative patient, is it low enough to justify the discharge of patients without any investigations at all? For this reason, guidelines in England contain a caveat. The guidelines stipulate that patients referred with NG12 symptoms who have negative FIT results (<10 µgHb/g) should be given a safety net appointment a few weeks later to ensure resolution and/or improvement of symptoms. Similar recommendations exist in Scotland. Patients who are negative on FIT testing should be re-assessed in six weeks to ensure the resolution of symptoms. If symptoms persist in these patients, then they should be re-referred to secondary care or be considered for a repeat FIT test.[20,21] Despite the above recommendation, there is insufficient evidence at this juncture to support serial FIT testing in patients with persistent symptoms who were negative at their index FIT.

The Optimum FIT Threshold

Using the initial threshold of 7 µgHb/g for FIT, we found that our sensitivity, specificity, PPV, and negative predictive value for the detection of CRC was 94.2%, 75.4%, 17.4% and 99.6%, respectively. Our results largely mirror the findings that were reported from previous publications. As mentioned, a few centres have been at the forefront

of employing FIT to assess high-risk symptoms, such as the group in Nottingham, Dundee, and London.[8,9,22] In Nottingham, Chapman et al.[22] looked at 1,106 patients with NICE NG12 symptoms. Rectal bleeding was excluded from this study. Sensitivity of FIT in CRC detection was 97.5%, 87.5% and 60% at cut-offs of 4 µgHb/g, 10 µgHb/g and 150 µgHb/g, respectively; the PPV for CRC at the same cut-offs were 12.5%, 14.6% and 35.8%, respectively. The Dundee authors studied 1,447 patients who had a FIT before colonoscopy. FIT sensitivity was 90.5%, and PPV was 11% at a cut-off of 10 µg/g. The largest multicentre London-based study conducted on 9,822 patients in 50 NHS hospitals from October 2017 to December 2019, revealed that sensitivity could be further improved to 97% if the threshold was reduced to 2 µgHb/g[23]. Last but not least, NICE as a governing body suggested that the threshold of a positive FIT be set at 10 µgHb/g for assessment of DG30 patients. This seems a reasonable compromise, but it does reduce the sensitivity slightly to 94%.

FIT has a high sensitivity of 94% but a lower specificity of 75% at a cut-off of 7 µgHb/g. A reduction of the threshold below 7 µgHb/g will increase the sensitivity marginally, but this translates to a larger number of unnecessary colonoscopies, the majority of which will be falsely positive. As the 3 FIT negative CRCs were not detected below the cut-off of 7 µgHb/g, it is intuitive to increase the threshold further in our study population to increase the specificity of the test and reduce the need for unnecessary colonoscopy.

As such, a ROC curve was performed in our study cohort to determine the ideal threshold of FIT so that both sensitivity and specificity could be maximised. Our ROC curve had an area under the curve of 0.89 (95% CI: 0.85-0.93) and confirmed that an increase of the FIT threshold to 19 µgHb/g optimised the utility of FIT in our study population to detect cancer. Our findings are mirrored by the Nottingham study, which showed that at a threshold of 20 µgHb/g, only one CRC case would have been missed in patients with normal blood results and rectal examination.[11] Therefore, we believe that patients with a FIT threshold of less than 19 µgHb/g should be safely reassured that their symptoms are unlikely to be due to CRC and their symptoms are most likely due to other pathology. At this cut-off, sensitivity was 89%, specificity was 81%, and the negative predictive value remained very high. In other words, patients referred through NICE guidelines and who have a FIT under 19 µgHb/g have a risk of less than 1% of CRC. Persistent symptoms may reflect other non-malignant pathology, which requires investigation, but this could be done via routine referrals rather than current fast-track pathways, which we know are increasingly overwhelmed. Although we have a decent sample size, we would have preferred to study a greater number of patients. This would have allowed us to identify more cancer patients who were FIT negative and determine the factors that may have led to this observation. We recognise that our study does not contain an original hypothesis or design but repeats studies in the published literature using a different cohort of patients. Moreover, the findings from this study cannot be generalized globally and is valid only within the UK. Patients that are eligible for the two-week pathway may create a selection bias and therefore thresholds values for FIT sensitivity and specificity in this study are applicable only for this particular population.

Conclusion

Patients who test positive on FIT are more likely to have CRC or other significant bowel pathology. The yield for CRC and significant pathology is minimal in a FIT negative patient - such patients may be safely discharged with appropriate safety-netting in place, either at the primary or secondary care level. A FIT threshold of 19 µgHb/g had the optimum sensitivity and specificity using ROC analysis in the tested population. Those patients with a FIT above 19 µgHb/g should be investigated urgently to exclude cancer. There remains an absence of national guidance on FIT stratification within the two-week pathway for patients with CRC. However, many trusts have begun incorporating FIT into their local pathway to circumvent the problems associated with capacity and access to colonoscopy. Further studies with large patient numbers are needed to address some of the unanswered questions regarding FIT.

Acknowledgment: Authors would like to thank Mr. Salama and Dr. Boxall for their contributions in the data collections, and Mr. Roos for supervision. Finally great thanks to Mr. Lim for leading this project.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Informed consent was obtained from those patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Supervision: J.R., M.L., Data Collection or Processing: A.E., M.S., P.B., Analysis or Interpretation: A.E., Writing: A.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Cancer Research UK. Bowel cancer statistics, 2017.
2. Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992;326:658-662.
3. Mozdiak E, Weldeselassie Y, McFarlane M, Tabuso M, Widlak MM, Dunlop A, Tsertsvadze A, Arasaradnam RP. Systematic review with meta-analysis of over 90 000 patients. Does fast-track review diagnose colorectal cancer earlier? Aliment Pharmacol Ther 2019;50:348-372.
4. NHS England. Cancer waiting times annual reports. NHS England and NHS Improvement, 2019.
5. Shenbagaraj L, Thomas-Gibson S, Stebbing J, Broughton R, Dron M, Johnston D, Shaw T, Haboubi HN, Green JT. Endoscopy in 2017: a national survey of practice in the UK. Frontline Gastroenterol 2019;10:7-15.
6. NICE. Diagnostics guidance [DG30]. Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care. National Institute for Health and Care Excellence, 2017.
7. D'Souza N, Georgiou Delisle T, Chen M, Benton S, Abulafi M; NICE FIT Steering Group. Faecal immunochemical test is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2WW pathway: a diagnostic accuracy study. Gut 2021;70:1130-1138.
8. Mowat C, Digby J, Strachan JA, McCann R, Hall C, Heather D, Carey F, Fraser CG, Steele RJC. Impact of introducing a faecal immunochemical test (FIT) for haemoglobin into primary care on the outcome of patients with new bowel symptoms: a prospective cohort study. BMJ Open Gastroenterol 2019;6:e000293.
9. Chapman C, Thomas C, Morling J, Tangri A, Oliver S, Simpson JA, Humes DJ, Banerjea A. Early clinical outcomes of a rapid colorectal cancer diagnosis pathway using faecal immunochemical testing in Nottingham. Colorectal Dis 2020;22:679-688.
10. Maclean W, Limb C, Mackenzie P, Whyte MB, Benton SC, Rockall T, Jourdan I. Adoption of faecal immunochemical testing for 2-week-wait colorectal patients during the COVID-19 pandemic: an observational cohort study reporting a new service at a regional centre. Colorectal Dis 2021;23:1622-1629.
11. Bailey JA, Weller J, Chapman CJ, Ford A, Hardy K, Oliver S, Morling JR, Simpson JA, Humes DJ, Banerjea A. Faecal immunochemical testing and blood tests for prioritization of urgent colorectal cancer referrals in symptomatic patients: a 2-year evaluation. BJS Open 2021;5:zraa056.
12. National Institute for Health and Care Excellence. Suspected cancer: recognition and referral NICE. guidelinehttps://www.nice.org.uk/guidance/ng12https://www.nice.org.uk/guidance/ng12/resources/suspected-cancer-recognition-and-referral-pdf-1837268071621. Accessed June 2020.
13. Fraser CG. Faecal immunochemical tests (FIT) in the assessment of patients presenting with lower bowel symptoms: concepts and challenges. Surgeon 2018;16:302-308.
14. Maclean W, Singh R, Mackenzie P, White D, Benton S, Stebbing J, Rockall T, Jourdan I. The two-week rule colorectal cancer pathway: an update on recent practice, the unsustainable burden on diagnostics and the role of faecal immunochemical testing. Ann R Coll Surg Engl 2020;102:308-311.
15. Patel RK, Sayers AE, Seedat S, Altayeb T, Hunter IA. The 2-week wait service: a UK tertiary colorectal centre's experience in the early identification of colorectal cancer. Eur J Gastroenterol Hepatol 2014;26:1408-1414.
16. Flashman K, O'Leary DP, Senapati A, Thompson MR. The Department of Health's "two week standard" for bowel cancer: is it working? Gut 2004;53:387-391.
17. Shenbagaraj L, Thomas-Gibson S, Stebbing J, Broughton R, Dron M, Johnston D, Shaw T, Haboubi HN, Green JT. Endoscopy in 2017: a national survey of practice in the UK. Frontline Gastroenterol 2019;10:7-15.
18. Aslam MI, Chaudhri S, Singh B, Jameson JS. The "two-week wait" referral pathway is not associated with improved survival for patients with colorectal cancer. Int J Surg 2017;43:181-185.
19. Westwood M, Corro Ramos I, Lang S, Luyendijk M, Zaim R, Stirk L, Al M, Armstrong N, Kleijnen J. Faecal immunochemical tests to triage patients with lower abdominal symptoms for suspected colorectal cancer referrals in primary care: a systematic review and cost-effectiveness analysis. Health Technol Assess 2017;21:1-234.
20. Benton SC, Fraser CG. Faecal immunochemical tests in the COVID-19 pandemic; safety-netting of patients with symptoms and low faecal haemoglobin concentration - can a repeat test be used? Ann Clin Biochem 2021;58:163-165.
21. Cancer Research UK. Early diagnosis of cancer how do we make sure patients don't slip through the net? Oxford: Cancer Research UK 2016; www.cancerresearchuk.org/sites/default/files/safety_nettingengland_201607.pdf (accessed: 1 August 2020).
22. Chapman C, Bunce J, Oliver S, Ng O, Tangri A, Rogers R, Logan RF, Humes DJ, Banerjea A. Service evaluation of faecal immunochemical testing and anaemia for risk stratification in the 2-week-wait pathway for colorectal cancer. BJS Open 2019;3:395-402.
23. D'Souza N, Delisle TG, Chen M, Benton SC, Abulafi M; NICE FIT Steering Committee. Faecal immunochemical testing in symptomatic patients to prioritize investigation: diagnostic accuracy from NICE FIT Study. Br J Surg 2021;108:804-810.