Original Article:

Title: Yield of colorectal cancer at colonoscopy according to faecal haemoglobin concentration in symptomatic patients referred from primary care

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Abstract

Background

Lower gastrointestinal (GI) symptoms are poor predictors of colorectal cancer (CRC). This study examined the diagnostic yield of colonoscopy by faecal haemoglobin concentration (f-Hb) in symptomatic patients assessed in primary care by faecal immunochemical testing (FIT).

Methods

In three Scottish NHS Boards, FIT kits (HM-JACKarc, Hitachi Chemical Diagnostics Systems Co., Ltd, Tokyo, Japan) were used by GPs to guide referrals for patients with lower GI symptoms (lab data studied for 12 months from December 2015 onward in Tayside, 18 months from June 2018 onward in Fife, and 5 months from September 2018 onward in Greater Glasgow and Clyde). CRC cases diagnosed at colonoscopy were ascertained from colonoscopy and pathology records.

Results

4841 symptomatic patients who underwent colonoscopy after FIT submission were included. Of 2166 patients (44.7%) with f-Hb <10 μg Hb/g faeces (μg/g), 14 (0.6%) were diagnosed with CRC, with a number needed to scope (NNS) of 155. Of 2675 patients (55.3%) with f-Hb ≥10 μg/g, 252 were diagnosed with CRC (9.4%) with a NNS of 11. Of 705 patients with f-Hb ≥400 μg/g, 158 (22.4%) were diagnosed with CRC with a NNS of 5. Over half of those diagnosed with CRC with f-Hb <10 μg/g had co-existing anaemia.

Conclusions

Symptomatic patients with f-Hb ≥10 μg/g should undergo further investigation for CRC, while higher f-Hb could be used to triage its urgency during the COVID-19 recovery phase. Patients with f-Hb <10 μg/g, without anaemia, are very unlikely to be diagnosed with CRC and the majority need no further investigation.

What does this add to the literature?

This study of 4841 patients undergoing colonoscopy across three Scottish NHS Boards, concludes that reliance should not be placed on symptoms when deciding who to refer for colonoscopy. Symptoms should be regarded as an entry point to the diagnostic pathway and decision making should be guided by faecal haemoglobin.

Introduction

Both NHS Scotland and National Institute for Health and Care Excellence (NICE) guidance to general practitioners (GPs) suggest a variety of lower GI symptoms which should prompt either an urgent referral for an appointment within two weeks, or consideration of such a referral, varying with age and the additional presence of iron deficiency anaemia [1-2].

Lower gastrointestinal (GI) symptoms are poor predictors of colorectal cancer (CRC) [3]. Indeed, most symptoms that can be present in patients with CRC and other significant bowel disease (SBD: higher-risk adenoma and inflammatory bowel disease), often reflect non-significant or functional bowel disorders [4-5]. Consequently, the introduction of the "urgent suspicion of cancer" (USC) referral and "two week wait (2ww)" pathways in Scotland and England respectively led to a large increase in referrals but no change in stage of diagnosis of patients with CRC [6].

NICE have also issued diagnostic guidance (DG30) regarding the use of faecal haemoglobin concentration (f-Hb) measured using a faecal immunochemical test (FIT) [7]. It is recommended that a f-Hb threshold of 10 μg Hb/g faeces (μg/g) be used to "guide" referral from primary care in patients without rectal bleeding, and who do not meet the criteria for a suspected cancer pathway per NICE (NG12) guidance.

Prior to the COVID-19 pandemic, pressure on existing referral pathways and endoscopy capacity had led NICE to develop the above guidance, in which f-Hb would be used to guide referral of patients with symptoms [8]. Such guidance was given further support by several observational studies on symptomatic patients in the United Kingdom (UK) [9-11]. However, the current climate has seen significant curtailment of endoscopy activity across the UK, with many NHS Boards and Trusts initially ceasing activity entirely, and most now entering a period of "recovery" of activity [12-13]. Despite this, ongoing requirements for

patient investigation, endoscopy suite decontamination and the existing backlog of participants with a positive screening test result, and symptomatic patients requiring colonoscopy, are likely to lead to greater pressures over the long term. Therefore, the need for useful triage of patients with lower GI symptoms is even greater, and f-Hb has already been reported to be effective in this respect [14-16].

**What is less clear is whether the symptomatic f-Hb threshold suggested in DG30 (10 μg/g) remains the most appropriate to guide referral for colonoscopy in symptomatic patients in the post-COVID-19 recovery phase, including in those patients meeting NG12 referral criteria. Furthermore, a key question of the moment relates to the yield of CRC at higher f-Hb thresholds in light of guidance being issued by the British Society of Gastrointestinal and Abdominal Radiology (BSGAR, with acknowledgement of British Society of Gastroenterology [BSG]), for example, advocating urgent investigation in those with NG12 specified symptoms only for those with f-Hb >100 μg/g [17]. In contrast, the Scottish Government recommendations are to investigate all symptomatic patients with f-Hb ≥10 μg/g during the COVID 19 recovery phase, using the f-Hb concentration to determine the modality and urgency of further investigation [12].

Therefore, the aim of the present study was to examine the yield of CRC in patients who had undergone colonoscopy across three Scottish NHS Boards, having been referred from primary care with lower GI symptoms and having submitted a FIT at the time of referral.

Patients and Methods

Patients:

In three Scottish NHS Boards (Tayside, Fife and Greater Glasgow and Clyde), a FIT kit with one specimen collection device (Hitachi Chemical Diagnostics Systems Co., Ltd, Tokyo, Japan), along with pictorial instructions for use and a return envelope, were made available to GP practices as an adjunct to clinical acumen and a full blood count to guide referral practice for all patients presenting with lower GI symptoms. The period of data collection was between December 2015 – December 2016 (12 months) in Tayside, June 2018 - December 2019 (18 months) in Fife, and September 2018 – January 2019 (5 months) in Greater Glasgow and Clyde.

In all three NHS Boards, patients were requested to collect a single faecal sample and to return the FIT kit as soon as possible to the GP surgery. The kits were transported to the local departments of laboratory medicine at ambient temperature by means of the routine specimen collection services and then stored at 4°C prior to analysis. Analyses were carried out from Monday to Friday, so that most samples were analysed on the day of receipt in the laboratory, and results were reported electronically to the requesting GP. Samples collected in Tayside and Fife were analysed at Ninewells Hospital, Dundee, while samples collected in Greater Glasgow and Clyde were analysed at Stobhill Hospital, Glasgow.

Only patients who had undergone colonoscopy as a result of a primary care referral with lower GI symptoms (including rectal bleeding), with an associated FIT result, were included. All categories of urgency of referral were included. Patients without a FIT result, who had undergone colonoscopy without submitting a previous FIT, had not undergone colonoscopy

following a FIT or had been investigated by other methods such as CT colonography, were not included in the analysis.

Methods:

Faecal haemoglobin concentration (f-Hb) was measured using the HM-JACKarc (Hitachi Chemical Diagnostics Systems) analytical system in the two laboratories serving the three NHS Boards. For f-Hb, this system has a limit of detection (LoD) of 2 μg/g, a limit of quantitation (LoQ) of 7 μg/g and an upper measurement limit of 400 μg/g. Samples with results above the upper measurement limit were therefore reported as ≥ 400 μg/g, and results with f-Hb ≥ 10 μg/g were defined as "positive", that is worthy of further investigation, as recommended in NICE DG30 [7]. The reports also sign-posted GPs to advice that f-Hb < 10 μg/g, in the absence of iron deficiency anaemia (IDA), rectal bleeding, persistent diarrhoea, or a mass, suggests that SBD was extremely unlikely.

In this observational study, data on all FIT specimens received from primary care were retrieved from the laboratory databases of each NHS Board and manually linked using the patient's unique identifier, the Community Health Index (CHI) number, with the NHS Boards' electronic patient record to access all correspondence, laboratory results, referrals to secondary care, colonoscopy findings, hospital admissions and any subsequent attendance at the primary care out-of-hours (OOH) service. Linkage was then performed with regional cancer registry and colorectal multi-disciplinary team data to confirm CRC diagnoses and flag any potentially missed cancers.

Caldicott Guardian and ethical approvals were in place from all three NHS Boards to safeguard the record linkage.

Analysis:

The diagnostic yield of colonoscopy with respect to CRC was calculated in terms of predetermined f-Hb ranges and thresholds and summarised in terms of the number of colonoscopies required to diagnose one CRC, that is, the number needed to scope (NNS). The details of patients diagnosed with CRC and f-Hb <10 μg/g were recorded and presented.

MedCalc statistical software (MedCalc Software, Mariakerke, Belgium) was used for all Tayside calculations, with Microsoft Excel (Microsoft, Microsoft Campus, Reading UK) for Fife calculations, and SPSS v25 (IBM, NY, USA) used for Greater Glasgow and Clyde calculations.

Results

Patients

In total, 4841 patients were included, (Table 1). Of these, 266 (5.5%) were diagnosed with CRC, giving a NNS of 19 for the entire cohort. Of the included patients, 2675 (55.3%) had a f-Hb ≥10 μg/g, and 705 (14.6%) patients had a f-Hb ≥400 μg/g.

NHS Tayside included 1447 patients, of whom 92 (6.4%) were diagnosed with CRC. There were 684 males (47.3%) and 763 females (52.7%) with a median age of 66 years(IQR 55-75). NHS Fife included 2082 patients, of whom 125 (6.0%) were diagnosed with CRC. There were 958 males (46.0%) and 1124 females (54.0%) with a median age of 65 years (IQR 54-75). NHS Greater Glasgow and Clyde included 1312 patients, of whom 49 (3.7%) were diagnosed with CRC. There were 567 males (43.2%) and 745 females (56.4%) with a median age of 60 years (IQR 49-70).

Yield of CRC according to faecal haemoglobin concentration (f-Hb)

As the ranges of f-Hb studied increased, there was a reduction in the within-range NNS to detect CRC (Table 2). Of the 2166 patient within the f-Hb range <10 μg/g, 14 (0.6%) were diagnosed with CRC, with a NNS of 155 within that f-Hb range. Of the 705 patients with f-Hb ≥400 μg/g, 158 (22.4%) were diagnosed with CRC with a NNS of 5 within that f-Hb range.

As the f-Hb thresholds related to the ranges studied increased, the trend was for a decrease in NNS to diagnose one CRC (Table 3). Above the NICE DG30 suggested f-Hb threshold of ≥10 μg/g, 2675 colonoscopies were performed, and CRC diagnosed in 252 (9.4%), accounting for 94.7% of all CRC and giving a NNS of 11.

Above a f-Hb threshold of ≥20 μg/g, 2135 colonoscopies were performed, and CRC diagnosed in 242 (11.3%), accounting for 91.0% of all CRC and giving a NNS of 9.

Above a f-Hb threshold of ≥100 μg/g, 1165 colonoscopies were performed, and CRC diagnosed in 205 (17.6%), accounting for 77.1% of all CRC and giving a NNS of 6.

Yield of CRC according to f-Hb concentration by NHS board

In NHS Tayside, at the NICE DG30 suggested f-Hb threshold of ≥10 μg/g, CRC was diagnosed in 84 patients, accounting for 91.3% of all CRC and giving a NNS of 9. In NHS Fife, at the NICE DG30 suggested f-Hb threshold of ≥10 μg/g, CRC was diagnosed in 122 patients, accounting for 97.6% of all CRC and giving a NNS of 10. In NHS GGC, at the NICE DG30 suggested f-Hb threshold of ≥10 μg/g, CRC was diagnosed in 46 patients, accounting for 93.9% of all CRC and giving a NNS of 15.

Characteristics of patients with f-Hb <10 μg/g diagnosed with CRC

Of the 14 patients diagnosed with CRC with a f-Hb <10 μg/g, nine were male and five were female (Table 4). Only one patient was aged younger than 50 years (the age of first invite to the Scottish Bowel Screening Programme). At the time of referral, 9 (64.3%) were found to be anaemic [18], of which 8 were iron deficient and the remaining patient had a pattern in keeping with anaemia of inflammation. Furthermore, 8 patients diagnosed with CRC with a f-Hb <10 μg/g had a primary tumour location proximal to the splenic flexure. Finally, three of these patients had polyp cancers.

Discussion

This multi-centre retrospective observational study conducted across three Scottish NHS Boards demonstrates that FIT used in primary care as part of symptomatic lower GI symptom referral pathways can be used to appropriately guide further investigation, regardless of the "urgency" of the referral.

Here, we report the colonoscopy findings in 4841 patients referred with "low" and "high risk" symptoms but who had all completed a FIT in primary care. Of 2166 patients with f-Hb <10 μg/g, only 14 were diagnosed with CRC (0.6%), requiring 155 colonoscopies to detect one CRC (a NNS of 155). In contrast, of the 2675 patients with f-Hb ≥10 μg/g, 252 (9.4%) had CRC, accounting for 94.7% of all CRC and giving an NNS of 11. Although 6.3% of CRC was diagnosed in those with f-Hb <10 μg/g, this compares favourably to colonoscopy alone, with 6.5% of all patients who had undergone colonoscopy in England in 2013 being diagnosed with CRC within three years of the index procedure [19].

Previous studies have reported using detectable f-Hb, usually 2 or 4 μg/g, as a threshold for further investigation [15-16]. Indeed, the LoD of the HM-JACKarc FIT system used in the present study is 2 μg/g. However, the NHS Tayside Department of Blood Science and NHS Greater Glasgow and Clyde Department of Clinical Biochemistry do not routinely quantitate f-Hb below the LoQ of 7 μg/g due to the associated measurement imprecision below this concentration. Additionally, values below 9 μg/g are not reported to clinicians in NHS GGC since they do not currently form part of any clinical guidance, pathway or framework.

It has also been proposed that, higher f-Hb thresholds be used to guide referral for investigation of symptomatic patients during the COVID pandemic and recovery phases. In the present study, however, a modest increase in the f-Hb threshold to 20 μg/g resulted in a

9% rate of undetected CRC. Alternatively, an additional higher threshold might be considered to allow triage of investigation urgency. The recent guidance issued by the Scottish Government recommends that whilst patients with f-Hb ≥10 μg/g are referred for further investigation, those with f-Hb ≥400 μg/g should undergo highest priority investigation, including colonoscopy and alternatives to colonoscopy such as computed tomography (CT) of abdomen and pelvis or colon capsule endoscopy (CCE) where available, during the COVID-19 pandemic and recovery periods [12]. This very high-risk subgroup of patients with f-Hb ≥400 μg/g (15.4% of patients in the presented data in this study) had a NNS of 5 to detect one CRC.

The diagnostic yield of colonoscopy for CRC in the present study at higher f-Hb thresholds (18.9% at f-Hb ≥150 μg/g) is lower than that reported in studies from Nottingham [14, 16] (30.9% CRC at f-Hb ≥150 μg/g) and in the upcoming NICE FIT study (unpublished data). However, those studies included a high proportion of patients with high risk symptoms or who were referred along "2 ww" pathways. In contrast the present study included patients referred from primary care at all levels of urgency.

This study has a number of limitations. The data were collected from three Scottish NHS Boards each with slight differences in their primary care referral pathways. The data do not capture those patients who submitted a FIT and then either were not referred from primary care or did not undergo colonoscopy. This could include patients who did attend secondary care and were discharged without colonoscopy, or those investigated via other modalities such as CT with or without osmotic bowel preparation and pneumocolon. Therefore, patients with f-Hb <10 μg/g in this study are likely to represent a higher-risk group than those patients with f-Hb <10 μg/g who were either not referred or did not undergo colonoscopy. Furthermore, due to the retrospective nature of the study, patient level symptom data were not available, and therefore no association can be drawn between these and f-Hb or the diagnostic

yield of CRC. In addition, other factors recognised to influence both f-Hb at the diagnostic likelihood of SBD, including age, sex, and deprivation were not considered in the analysis [21-23]. Finally, the study did not include patients with other SBD. This was in part due to the perceived prioritisation of CRC detection in the present COVID-19 pandemic and recovery phases, and also due to availability of more robust registration and data relating to CRC across all three NHS Boards.

However, the strengths of the presented data include large numbers of patients investigated by the "gold standard" investigation in the diagnosis of CRC. These data were collected by each NHS Board following the introduction of FIT into symptomatic referral pathways so can be regarded as "real world" data. In addition, this study is one of the few to include patients referred at all level of urgency. In this study, only the first submitted valid f-Hb result was recorded and therefore no comment can be made on the possible use of multiple simultaneous or time distanced repeated f-Hb estimations in patients with ongoing or recurrent symptoms. Limited evidence does exist in these areas in screening and symptomatic cohorts [24], but further work is required before the impact of changes in f-Hb on diagnostic likelihood can be described in CRC. Further, the FIT analytical systems used in the two laboratories were the same (HM-JACKarc), allowing pooling of data. This is an important consideration since different systems give different numerical estimates of f-Hb, and therefore data generated using the threshold of 10 μg/g as measured in this study may not be equivalent to that measured by other systems included in DG30 guidance, including OC Sensor and FOB Gold [25].

Finally, the presented characteristics of patients diagnosed with CRC with f-Hb <10 μg/g can be used to inform the very important issue of "safety netting", in other words how to identify patients with low f-Hb who should go on to further investigation. Anaemia and significant weight loss, both of which would often generate referral to secondary care even without the

presence of lower GI symptoms, were prevalent amongst those with CRC and f-Hb <10 μg/g; however, further studies are needed to confirm these associations and determine their clinical utility. In addition, symptomatic patients with low f-Hb should be kept under observation until their symptoms have abated and GP must not be discouraged from referring such patients if they have severe and/or persistent symptoms.

In summary, the results of this study add to the ample evidence in the literature that low f-Hb identifies a group of symptomatic patients at very low risk of CRC and SBD, and that high f-Hb identifies a high-risk group. Not only that, f-Hb estimation clearly outperforms symptoms as a predictor of CRC and SBD, even in those with "red flag" symptoms including rectal bleeding [26].

It can therefore be stated with confidence that reliance should not be placed on specific symptoms or symptom complexes when deciding who to refer for colonoscopy. Symptoms should be regarded as an entry point to the diagnostic pathway and decision making on investigations should be guided by f-Hb. Symptomatic patients with f-Hb <10 μg/g are very unlikely to be diagnosed with CRC and should not undergo investigation for this purpose without very good reason [12]. Furthermore, higher f-Hb should be used to triage the modality and urgency of investigation for possible CRC in symptomatic patients. Such an approach will be required during the COVID-19 recovery period, during which access to colonoscopy is likely to remain limited, but also should be considered for use in the longer term to reduce the burden of over-investigation for both patients, and for stretched endoscopy resources. Indeed, failure to implement this is likely to delay diagnosis of CRC due to dilution of the pool of referred patients who have CRC into a larger referral cohort that cannot be investigated in a timely fashion due to the capacity limitations of the NHS.

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Tables and footnotes

Table 1: Demographic characteristics of cohorts of patients undergoing colonoscopy after submitting a faecal immunochemical test (FIT) as part of symptomatic referral pathways in NHS Tayside, NHS Fife and NHS Greater Glasgow and Clyde (GGC),

Region		**NHS Tayside**	**NHS Fife**	**NHS GGC**
Total	n	1447	2082	1312
CRC	n (%)	92 (6.4)	125 (6.0)	49 (3.7)
Sex	Male, n (%)	684 (47.3)	958 (46.0)	567 (43.2)
	Female, n (%)	763 (52.7)	1124 (54.0)	745 (56.4)
Age	years, median (IQR)	66 (55-75)	65 (54-75)	60 (49-70)

CRC: colorectal cancer, GGC: Greater Glasgow and Clyde, IQR: interquartile range

Table 2: Colonoscopies and colorectal cancer (CRC) diagnoses made per given faecal haemoglobin concentration (f-Hb) ranges (µg/g)) in symptomatic patients using a faecal immunochemical test (FIT and number needed to scope (NNS) to detect one CRC in that range

f-Hb range (µg/g)	Colonoscopies performed within f-Hb range (n)	CRC diagnosed within f-Hb range (n)	NNS within f-Hb range (n)
All	4841	266	19
<10	2166	14	155
10-19	540	10	54
20-49	609	22	28
50-99	361	15	25
100-149	150	13	12
150-199	94	4	24
200-249	63	7	9
250-299	63	5	13
300-349	41	7	6
350-399	49	11	5
≥400	705	158	5

CRC: colorectal cancer, f-Hb: faecal haemoglobin concentration, NNS: number needed to scope to detect one CRC

Table 3: Diagnostic yield of faecal haemoglobin concentration (f-Hb, µg/g) above threshold values (µg/g) to diagnose colorectal cancer (CRC) in symptomatic patients using a faecal immunochemical test (FIT) and number needed to scope to detect one CRC (NNS)

f-Hb threshold (µg/g)	Proportion of colonoscopies required (%)	Proportion of CRC diagnosed (%)	NNS (n)
10	55.3	94.7	11
20	44.1	91.0	9
50	31.5	82.7	7
100	24.1	77.1	6
150	21.0	72.2	6
200	19.0	70.7	5
250	17.7	68.0	5
300	16.4	66.2	5
350	15.6	63.5	5
400	14.6	59.4	5

CRC colorectal cancer, f-Hb: faecal haemoglobin concentration, NNS: number needed to scope to detect one CRC

Table 4: Characteristics of symptomatic patients diagnosed with colorectal cancer (CRC) with faecal haemoglobin concentration <10 µg/g by a faecal immunochemical Test (FIT)

Age (years)	Sex	Symptoms	Blood Hb (mg/L)	CRC size (mm)	Primary CRC site	TNM stage
89	M	Anaemia Diarrhoea	71	17	Transverse colon	I
54	F	Diarrhoea	150	30	Rectum	I
78	M	Anaemia Change in bowel habit	120	26	Ascending colon	I
74	F	Anaemia Diarrhoea	102	60	Caecum	NA
58	M	Rectal bleeding	134	NA	NA	NA
87	F	Anaemia	108	28	Caecum	I
66	M	Anaemia Change in bowel habit	94	57	Transverse colon	II
67	M	Weight loss Change in bowel habit	162	32	Transverse colon	IV
85	M	Anaemia Rectal mass (palpable)	122	35	Rectum	I
68	F	Anaemia Change in bowel habit	95	NA	Transverse colon	IV
69	M	Anaemia Weight loss	94	120	Caecum	III
59	M	Anaemia	122	50	Descending colon	II
39	M	Change in bowel habit	152	25	Sigmoid colon	II
66	F	Change in bowel habit	144	14	Sigmoid colon	II

CRC: colorectal cancer, F female, Hb: haemoglobin, M: male, NA not available, TNM: tumour, node, metastases