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SHORT COMMUNICATION

Quantitative FIT stratification is superior to NICE referral criteria NG12 in a high-risk colorectal cancer population

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Abstract

Background Guidelines for urgent investigation of colorectal cancer (CRC) are based on age and symptom-based criteria. This study aims to compare the diagnostic value of clinical features and faecal immunochemical test (FIT) results to identify those at a higher risk of CRC, thereby facilitating effective triage of patients.

Methods We undertook a review of all patients referred for investigation of CRC at our centre between September 2016 and June 2018. Patients were identified using a prospectively recorded local database. We performed a logistic regression analysis of factors associated with a diagnosis of CRC.

Results One-thousand-and-seven-hundred-eighty-four patients with FIT results were included in the study. Change in bowel habit (CIBH) was the most common referring clinical feature (38.3%). Patients diagnosed with CRC were significantly older than those without malignancy (74.0 years vs 68.9 years, $p=0.0007$). Male patients were more likely to be diagnosed with CRC than females (6.5% vs 2.5%, Chi-squared 16.93, $p<0.0001$). CRC was diagnosed in 3.5% (24/684) with CIBH compared to 8.1% (6/74) with both CIBH and iron deficiency anaemia. No individual or combination of referring clinical features was associated with an increased diagnosis of CRC (Chi-squared, 8.03, $p=0.155$). Three patients with negative FIT results (< 4 µg Hb/g faeces) were diagnosed with CRC (3/1027, 0.3%). The highest proportion of cancers detected was in the ≥ 100 µg Hb/g faeces group (55/181, 30.4%).

Conclusion In a multivariate model, FIT outperforms age, sex and all symptoms prompting referral. FIT has greater stratification value than any referral symptoms. FIT does have value in patients with iron deficiency anaemia.

Keywords Colorectal cancer · Colorectal cancer risk · Symptomatic · Faecal immunochemical test · NG12

Introduction

Colorectal cancer (CRC) is a leading cause of cancer death in the UK and worldwide; the stage of disease at the time of treatment remains the most significant predictor of survival [1]. Whilst asymptomatic population-based screening programmes have been shown to identify a higher proportion of CRC at an earlier stage, advancement in the diagnosis of symptomatic patients has remained elusive despite concerted efforts over the past 20 years [2].

The Two-Week-Wait (2WW) referral pathway was introduced to decrease cancer-related mortality as part of the National Health Service (NHS) Cancer Plan in the UK in 2000. Publication of subsequent national guidelines has typically focused on optimising age and symptom-based criteria to identify patients requiring definitive investigation [3]. Owing to the variable and non-specific symptoms which are

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typical of CRC (if any symptoms are present at all), challenges remain triaging patients correctly and mitigating the risk of iatrogenic harm during investigations [1].

Recently, faecal immunochemical tests (FITs) have been nationally endorsed to guide secondary care referral in patients with low-risk symptoms [4]. We have previously discussed the safe incorporation of FIT, alongside common blood test parameters, into "high-risk" urgent symptomatic pathways in Nottingham [5, 6]. The publication of multicentre studies confirming the diagnostic accuracy of FIT in the UK may precipitate more widespread use of the test [7].

The COVID-19 pandemic is certain to burden diagnostic services in the immediate and medium-term future—with increasing referrals post lockdown likely to be met with limited colonoscopy and computed tomography (CT) colonogram capacity. A guidance document for the second phase of the NHS response to COVID-19 recommends the use of FIT to help prioritise 2WW referrals, but omits use of established risk factors like iron-deficiency anaemia (IDA) [8, 9]. The aim of this study was to compare the diagnostic value of clinical features and FIT results to identify those at a higher or lower risk of CRC, thereby facilitating effective triage of patients.

Materials and methods

Patients were identified using a prospectively collected local database of 2WW referrals, with outcomes identified from a retrospective review of electronic hospital databases from September 2016 to June 2018. An independent provider (Circle Health, London, UK) at a neighbouring treatment centre (TC) received 2WW referrals during this period which were not included in this study. CRC diagnosis following 2WW referral to TC and routine referral to Nottingham University Hospitals NHS Trust are discussed elsewhere [6]. All patients returned a self-collected FIT sample (OC-Sensor™; Eiken Chemical Company, Tokyo, Japan) via a postal service as part of their clinical investigation, as described previously [5].

Clinical features were recorded at the time of referral based on national 2WW referral guidelines. Abdominal pain, weight loss, abdominal mass, rectal mass, rectal bleeding, and referral prompted by FIT result were classified as "other symptoms" to facilitate comparison. Change in bowel habit (CIBH) was the most common clinical feature, and closest to the 3% risk-threshold recommended in the National Institute for Health and Care Excellence (NICE) guidelines (2015) (NG12); thus, it was used as the reference for comparison of other clinical features prompting referral.

FIT results were categorised as "Negative" if < 4 µg Hb/g faeces was detected, the limit of reliable detectability on the analyser platform. This group was used as the reference for comparison of the other FIT categories: 4–9.9 µg Hb/g faeces, 10–99.9 µg Hb/g faeces and ≥ 100 µg Hb/g faeces. The NICE DG30 guidelines recommend a threshold of 10 µg Hb/g faeces in symptomatic patients. Our local pathway utilises a threshold of 4 µg Hb/g faeces where other risk factors are present (anaemia, thrombocytosis, and abnormal ferritin). Where there were more than one FIT/referral, only the first FIT was included.

Statistical analysis

Data were assessed for normality using histograms and a Shapiro–Wilk test. Levene's test was used to confirm equal variance. The predictive value of age, gender, clinical features, and FIT categorisation was assessed by Pearson's chi-squared test/Fisher's exact test and calculating the positive predictive value (PPV), odds ratio (OR) and 95% confidence intervals (CI) as appropriate. Logistic regression models were used to assess the combination of all factors as predictors of CRC. Age was treated as a categorical variable (< 60 years/ ≥ 60 years) in univariate and multivariate logistic regression models. All statistics were performed using STATA v16 (Stata Corp, College Station, TX, USA). Tests of significance were considered significant if a p value of less than 0.05 was obtained.

Results

In total, 1784 patients investigated via the 2WW pathway during the study period were included with 76 (4.3%) colorectal cancers diagnosed. One-thousand-and-seven-hundred-twenty-seven patients (96.8%) had Haemoglobin and 1419 (79.5%) had ferritin/iron studies as part of their investigation. The median age was 71 years (range 18–96 years, interquartile range 61–79 years). The patients diagnosed with CRC were significantly older than those without (74.0 years vs 68.9 years, $p = 0.0007$). Male patients were more likely to be diagnosed with CRC than females (6.5% vs 2.5%, Chi-squared 16.93, $p < 0.0001$).

The most common referring clinical feature was CIBH alone with 684 patients (38.3% of referrals) with 24 CRCs detected (3.5%) (Table 1). The greatest proportion of colorectal cancers diagnosed by referring clinical feature was in the CIBH and IDA group with 74 referrals with six colorectal cancers diagnosed (8.1%). No single referring clinical feature or combination of clinical features was significantly associated with CRC diagnosis (Chi-squared, 8.03, $p = 0.155$). Patients with right-sided CRC were significantly more likely to be anaemia than those diagnosed with left-sided CRC (92.6% vs 30.6%, $p = < 0.0001$).

Table 1 Univariate and multivariate logistic regressions of CRC diagnosis accounting for age, sex, clinical features and FIT-based categorisation

Parameter	Total (%)	CRC (%)	Univariate analysis		Multivariate analysis	
			OR (CI)	*p* value	OR (CI)	*p* value
Total patients	1784	76 (4.3)				
< 60 years	402 (22.5)	10 (2.5)	Reference			
≥ 60 years	1382 (77.5)	66 (4.8)	1.96 (1.00–3.86)	0.050	1.56 (0.71–3.44)	0.267
Sex						
Female	996 (55.8)	25 (2.5)	Reference			
Male	788 (44.2)	51 (6.5)	2.69 (1.65–4.38)	< 0.001	2.30 (1.33–4.00)	0.003
Clinical features						
CIBH	684 (38.3)	24 (3.5)	Reference			
IDA	342 (19.2)	20 (5.8)	1.62 (0.87–3.00)	0.126	1.02 (0.50–2.07)	0.953
Other	362(20.2)	10 (2.8)	0.78 (0.37–1.66)	0.523	0.69 (0.30–1.58)	0.375
CIBH + IDA	74 (4.1)	6 (8.1)	2.43 (0.96–6.14)	0.061	2.79 (0.90–8.62)	0.075
CIBH + Other	260 (14.6)	13 (5)	1.45 (0.73–2.89)	0.294	1.37 (0.61–3.06)	0.449
IDA + Other	63 (3.5)	4 (6.3)	1.86 (0.63–5.55)	0.263	1.60 (0.46–5.53)	0.456
FIT result (μg Hb/g faeces)						
< 4	1027 (57.5)	3 (0.3)	Reference			
4–9.9	211 (11.8)	4 (1.9)	6.60 (1.47–29.69)	0.014	6.75 (1.49–30.59)	0.013
10–99.9	365 (20.4)	14 (3.8)	13.61 (3.89–47.65)	< 0.0001	12.75 (3.62–44.92)	< 0.0001
≥ 100	181 (10.1)	55 (30.4)	148.99 (45.94–483.28)	< 0.0001	139.73 (42.77–456.50)	< 0.0001

CRC colorectal cancer; *FIT* faecal immunochemical test; *CIBH* change in bowel habit; *IDA* iron-deficiency anaemia

A negative FIT result (< 4 μg Hb/g faeces) was found in 1027 (57.5%) patients, with three CRCs diagnosed (0.3%). Those found to have a malignancy from this subset returned a single FIT sample—two were referred with a change in bowel habit and one with IDA. The proportion of CRC detected increased with increasing FIT level from 0.3% (3/1027) in the < 4 μg Hb/g faeces group to 30.4% (55/181) in the > 100 μg Hb/g faeces group (Chi-squared 345.62, $p = < 0.0001$) (Table 1).

In the univariate analysis, age over 60 years and male sex were associated with a 2- and 2.7-fold increased risk of diagnosis of CRC, respectively (Table 1). The only symptoms associated with an increased risk of CRC compared to CIBH were CIBH *and* IDA which were associated with a 2.5-fold increased risk (OR 2.43, 95% CI 0.96–6.14). Each increasing stratum of FIT was associated with an increased risk of CRC compared to the baseline of < 4 μg Hb/g faeces (Table 1).

Multivariate logistic regression showed that only increasing FIT level and male sex were associated with increased risk of CRC; accounting for age and referring clinical features. Males in the cohort were more than twice as likely to be diagnosed with CRC compared to females (adjusted OR 2.30, 95% CI 1.33–4.00), whilst those with a FIT of 10–99.9 μg Hb/g faeces were more than 12 times more likely to be diagnosed with a CRC compared to those with a FIT of < 4 μg Hb/g faeces (adjusted OR 12.75, 95% CI 3.62–44).

Discussion

In this study, we aimed to identify patients at increased risk of CRC within a 2WW population. We previously published our experiences incorporating FIT in a 2WW pathway, discussing its discriminatory value across both "high-risk" and "low-risk" patients [6, 10]. Here, we confirm superiority of FIT stratification over clinical feature-based triage in a multivariate model accounting for age and sex. Although the overall detection of CRC in this cohort (4.3%) satisfies the 3% risk-threshold stipulated in NG12, further stratification of risk based on clinical features is of limited value, with no individual symptom or combination of clinical features conferring a significantly higher risk than CIBH on multivariate logistic regression.

The significant risk of CRC associated with a high FIT demonstrates the value of FIT for stratifying patients that need urgent investigation wherever diagnostic capacity is constrained, as well as in the challenging environment brought on by COVID-19. Conversely, a negative FIT corresponds with a 0.3% risk of CRC in this cohort which is consistent with previous service evaluation as well as emerging data from multicentre research studies [7, 11]. FIT appears safe for "rule out" and our data confirm its utility across all groups including IDA.

The CRC detection rates between 4 and 99.9 μg Hb/g faeces show that improvements in the PPV of FIT might be desirable. At these levels, the risk of CRC is closer to the

NG12 risk-threshold, and whilst further segmentation is possible, other stratification tools may be required to optimise diagnostic strategies. Our local pathway mandates an FBC for referral, informing whether risk factors like anaemia, thrombocytosis and abnormal ferritin are present. CRC-scoring systems which promise increased accuracy have been created [12], although their widespread applicability remains unproven [13] and blood parameters were not included.

The relatively small cohort size is a limitation of our study. Furthermore, we were unable to analyse the value of thrombocytosis of abnormal ferritin as these results were not available for some of the cohort, as highlighted above. However, we continue to use different FIT cut-offs for those with normal and abnormal blood test results. The increased frequency of anaemia in right-sided CRC patients who may theoretically have lower FIT results highlights the importance of blood tests in any risk stratification system. Whilst we offer further evidence of FITs value over symptoms in a clinical setting, we feel further improvements in stratification may arise if all these factors could be combined. Age, sex and blood test results might be used to define a pre-test probability that adjusts the FIT threshold for urgent investigation and further work in this area would represent a significant development in diagnostic pathways.

Conclusion

In a multivariate model, FIT outperforms age, sex and all symptoms prompting referral. FIT has greater stratification value than any referral symptoms. FIT does have value in patients with IDA iron deficiency anaemia.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The manuscript does not contain patient data. This research study was conducted retrospectively from data obtained for clinical purposes. We consulted with our institutional Research and Innovation (R&I) department and the local Research Ethics Committee who determined that our study did not need ethical approval.

Informed consent For this type of study, formal consent is not required.

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