ABSTRACT

Background: The COVID-19 pandemic is an evolving healthcare challenge causing secondary disruption of cancer services. Quantitative Faecal Immunochemical Testing (qFIT) has been established as a screening method in asymptomatic patients. We aim to assess its utility as a triage tool to prioritise investigations in symptomatic patients with suspected colorectal cancer.

Methods: At the commencement of the COVID-19 pandemic a database was established to include patients awaiting red flag outpatient consultation or colonic investigations and new red flag referrals from March to June 2020. Patients were supplied with qFIT kits and returned results categorised into 3 priority groups according to the qFIT value. Group 1 >150µg Hb/g, Group 2 ≥10 to ≤150µg Hb/g and Group 3 <10µg Hb/g. Subsequent colonic evaluation was offered by colonoscopy or cross-sectional imaging with urgency determined by qFIT priority group. When identified colorectal cancer, inflammatory bowel disease or high-risk polyps were recorded as “significant colorectal pathology.”

Findings: Three hundred and seventeen patients were identified with data analysed on 290 patients. Colorectal malignancy was identified in 17 patients; 94% of these patients were in Group 1. A qFIT result >150 µg Hb/g had a sensitivity and specificity for colorectal cancer of 94.12% (95% CI 71.31-99.85) and 91.21% (95% CI 87.20-94.29) respectively. No malignancy was detected in Priority Group 3; negative predictive value of 100% (95% CI 98.06-100).

Conclusions: In symptomatic, suspect lower GI cancer patients qFIT is a useful adjunct for prioritising patients and can be used to determine the urgency of colorectal investigations.

Key words: Quantitative Faecal immunochemical testing, qFIT, Colorectal cancer, symptomatic, COVID-19

INTRODUCTION

Cessation of services and disruption of established cancer pathways are secondary healthcare implications of the COVID-19 pandemic. This has resulted in a greater burden on existing healthcare waiting lists which already have limited resources. Faecal immunochemical testing (FIT) has been integrated as a colorectal cancer (CRC) screening method since 2017 across parts of the UK. It has been used for screening asymptomatic patients to detect early colorectal malignancy. In the current COVID-19 climate, this technique has been used as a triaging adjunct with symptomatic colorectal patients, identifying those at greatest risk of significant colorectal pathology, ultimately allowing prioritisation of endoscopic and radiological investigation.

As the 4th most prevalent malignancy in the UK, colorectal cancer represents 10% of all cancer deaths in the UK, with 42,300 new cases per annum. When detected at an early stage, colorectal cancer is associated with significantly better outcomes reflected by its recognised screening programme. Colonoscopy remains the gold standard of colorectal investigation, with CT Colonography a suitable alternative in the appropriate patient.

Research to date has focused on the use of Quantitative Faecal Immunochemical Testing (qFIT) in the asymptomatic patient and comparing use of faeces analysis - FIT vs guiacl-based faecal occult blood (FOB) testing. There is a paucity of evidence of the use of qFIT to triage referrals in the symptomatic colorectal patient.

Aim

We aim to evaluate the quantitative relationship between qFIT value and the detection of significant colorectal pathology, determining its utility as a triage tool to prioritise investigations in patients with red flag colorectal symptoms.

METHODS AND MATERIALS

At the commencement of the COVID-19 pandemic (March 2020), a prospective database was established of all patients awaiting a colorectal red flag outpatient appointment, or colonic investigations, either endoscopically or via cross-sectional imaging. In addition, all new consecutive referrals triaged as red flag or urgent with symptoms concerning for gastrointestinal pathology were included from March...
2020 to July 2020. Referrals were inclusive of those from primary care, specialty referral, and inpatient follow-up to the General Surgery or Gastroenterology services. Four hundred and fifty-six patients were supplied with qFIT kits via the post. A database of 317 patients who returned qFIT kits was created with those excluded following consultant led discharge and non-responders. Quantitative analysis was carried out via automated standardised analysers and all returned results were categorised by qFIT value. Patients who did not respond were given further opportunity to return via written communication.

All 317 patients were offered colonic evaluation either by colonoscopy or cross-sectional imaging. The priority of this investigation during the pandemic was determined by their quantitative FIT result: Priority Group 1: qFIT >150mg Hb/g, Priority Group 2: qFIT ≥10 to ≤150µg Hb/g, and Priority Group 3: qFIT <10mg Hb/g.

Outcome data was collected prospectively throughout the evolving pandemic with the introduction of qFIT over the four month period. Further exclusion criteria were determined: asymptomatic patients undergoing investigation as part of screening; patients within their 5-year cancer post-op surveillance period; declining investigation through the patient’s own choice.

Analysis

A comprehensive review of each patient’s electronic care record and medical notes were completed. Patient demographics, qFIT value, referral information, serum haemoglobin (Hb), investigation modality, and diagnosis were recorded. Significant colorectal pathology was defined as colorectal cancer, inflammatory bowel disease, or high-risk polyps when diagnosed at time of colonoscopy or cross-sectional imaging. British Society of Gastroenterology define high-risk polyps as 2 or more premalignant polyps including at least one advanced colorectal polyp (defined as a serrated polyp of at least 10mm in size or containing any grade of dysplasia, or an adenoma of at least 10mm in size of containing high-grade dysplasia); or 5 or more premalignant polyps.13 When significant pathology was identified, these patients were categorised according to qFIT value and stage and treatment of disease were recorded. Statistical analysis was performed with IBM SPSS using Chi-Square and ANOVA techniques.14 Significance was defined as a p value of less than 0.05. Diagnostic test evaluation was performed using MedCalc statistical software.15

RESULTS

A total of 317 patients were identified; 290 of which were analysed following application of exclusion criteria. These 290 patients were categorised into three priority groups based on their qFIT value; Priority Group 1 >150mg Hb/g, Priority Group 2 ≥10 to ≤150µg Hb/g and Priority Group 3 <10mg Hb/g. The characteristics of red flag symptomatic patients are categorised by qFIT value outlined in Table 1.

Pathology identified across the population group included GI malignancy, inflammatory bowel disease, high and low risk polyps, inflammatory (diverticulitis, infective, and microscopic colitis), and proctology. Distribution of pathology characterised by priority group is demonstrated in Table 2. Colorectal investigation yielded pathology in 181 (65%) patients with no pathology identified in the remaining 109 (37%) patients.

Malignancy was detected in 18 patients across the 290 patients; CRC identified in 17 patients and an upper GI cancer in 1 patient. 16 of 17 CRC were identified in priority group 1 (>150mg Hb/g). No malignancy was detected in priority group 3 (≤10mg Hb/g). Figure 1 outlines graphical depiction of colorectal cancer by qFIT group; 77% of CRC detected was advanced stage (T3 and T4).

Priority group 1 contained 40 patients (21 male (53%)), with a median age of 64 years (range 36 – 88 years). 38 patients underwent endoscopy and 2 CT imaging. Colorectal malignancy was diagnosed in 16 patients (40%). Significant pathology was identified in 23 patients (58%), of which 16 (40%) were diagnosed with Colorectal malignancy.

Priority group 2 had 62 patients (27 male (44%)), with median age of 68 years (range 29 – 90 years). 58 patients underwent endoscopy and 4 CT imaging. Colorectal malignancy was diagnosed in 1 patient (2%). Significant pathology was identified in 6 patients (10%).

Priority group 3 contained 188 patients (83 male (44%)), with median age of 64 years (range 26 – 92 years). 182 patients underwent endoscopy and 6 CT imaging. No malignancy was detected in Priority Group 3. Significant pathology was identified in 6 patients (3%).

Two hundred and seventy-eight patients underwent endoscopic evaluation (98% colonoscopy; 2% flexible sigmoidoscopy) and 12 patients underwent cross sectional CT imaging (67% CT Colonogram; 33% CT abdomen, pelvis).
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The age distribution between the three priority groups did not differ significantly (ANOVA f-ratio value 2.81; p>0.05). A Chi-squared test of independence showed that there was no significant association between gender and qFIT value, $X^2 (1, N=290) = 1.0127, p = 0.602$.

Patients’ blood test results at time of referral were assessed in 248 cases. Median serum Hb 135 (75 – 165 g/dL) in priority group 1, 128 (70 - 160 g/dL) for priority group 2, and Hb 136 (75 – 165 g/dL) for priority group 3. At time of referral amongst the cancer population diagnosed, 47% were anaemic.

Priority group 1 had a sensitivity and specificity for colorectal cancer of 94.12% (95% CI 71.3-99.85) and 91.21% (95% CI 87.20-94.29) respectively. In addition, carried a positive predictive value (PPV) of 40% (95% CI 30.88-49.87), and negative predictive value (NPV) 99.6% (95% CI 97.38-99.94), respectively. Priority group 1 had a sensitivity and specificity for significant colorectal pathology of 65.71%.

Table 1: Characteristics of red flag symptomatic patients categorised by qFIT value.

| Characteristic | Priority Group 1 >150µg Hb/g | Priority Group 2 ≥10 to ≤150µg Hb/g | Priority Group 3 <10µg Hb/g |
|---------------|-------------------------------|-----------------------------------|-----------------------------|
| Number        | %                             | Number                            | %                           | Number                      | %                           |
| Age, years    |                               |                                   |                             |                             |
| Median (IQR)  | 64 (52-76)                    | 68 (58-77)                        | 64 (54-72)                  |
| <50           | 6                             | 15                                | 6                            | 10                           | 33                           | 18                           |
| 50-59         | 8                             | 20                                | 14                           | 23                           | 42                           | 22                           |
| 60-69         | 11                            | 28                                | 13                           | 21                           | 54                           | 29                           |
| 70-79         | 6                             | 15                                | 16                           | 26                           | 50                           | 27                           |
| ≥80           | 9                             | 23                                | 13                           | 21                           | 9                             | 5                            |
| Gender        |                               |                                   |                             |                             |
| Men           | 21                            | 53                                | 27                           | 44                           | 83                           | 44                           |
| Women         | 19                            | 48                                | 35                           | 56                           | 105                          | 56                           |
| Hb            |                               |                                   |                             |                             |
| Median        | 135                           | 128                               | 136                         |
| Unknown       | 5                             | 13                                | 7                            | 11                           | 30                           | 16                           |
| Imaging       |                               |                                   |                             |                             |
| Endoscopy     | 38                            | 95                                | 58                           | 94                           | 182                          | 97                           |
| CT            | 2                             | 5                                 | 4                            | 6                            | 6                            | 3                            |

Table 2: Distribution of pathology categorised by priority group.

Pathology | Priority Group 1 >150µg Hb/g | Priority Group 2 ≥10 to ≤150µg Hb/g | Priority Group 3 <10µg Hb/g |
|-----------|-------------------------------|-----------------------------------|-----------------------------|
| Number    | %                             | Number                            | %                           | Number                      | %                           |
| Lower GI Cancer | 16                           | 40                                | 1                            | 2                           | 0                            | 0                            |
| Other     | 0                             | 0                                 | 1                            | 2                           | 0                            | 0                            |
| IBD       | 3                             | 8                                 | 2                            | 3                           | 0                            | 0                            |
| All Polyps | 13                            | 33                                | 19                           | 31                          | 43                           | 23                           |
| *High Risk Polyp | 4                            | 2                                 | 2                            | 6                           |                             |                              |
| Inflammatory | 3                             | 8                                 | 16                           | 8                           | 44                           | 23                           |
| Proctology | 0                             | 0                                 | 6                            | 0                           | 14                           | 7                            |
| NAD       | 5                             | 13                                | 17                           | 13                          | 87                           | 46                           |
| Total     | 40                            | 62                                | 188                          |

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The negative predictive value of priority group 2 associated with any significant colorectal pathology was 96.81% (95% CI 94.49-98.17). Within this group the NPV of colorectal cancer was 96.81% (95% CI 95.69-97.64) with a sensitivity and specificity of 14.29% (95% CI 0.36-57.87) and 74.9% (95% CI 68.96-80.22), respectively.

No cancer was identified in priority group 3 with a specificity of 100% (95% CI 98.06-100) and NPV for cancer of 100%. Figure 2 displays distribution of pathology by qFIT priority group.

Sixteen percent of polyps identified were high-risk polyps. 33% of the high-risk polyps were in priority group 1. 50% were in priority group 3.

DISCUSSION

Analysis of the quantitative relationship between qFIT value and the detection of significant colorectal pathology in symptomatic patients has been demonstrated. Additionally, it was illustrated that a higher qFIT value correlates to increased incidence of colorectal cancer detection. Investigation in this patient group should be triaged with greatest urgency and a lower qFIT value can be down triaged.

Allison et al has demonstrated the use of qFIT in the asymptomatic patient.\(^\text{16}\) We report the first use of qFIT in symptomatic patients in Northern Ireland during the COVID-19 pandemic. A well-established screening programme and red flag cancer service for suspected lower gastrointestinal pathology exists.\(^\text{5,6}\) However, prior to March 2020, qFIT was not included in Northern Ireland screening or red flag referral pathways. The focus of research to date has centred around the use of qFIT in the asymptomatic patient and its use in screening.\(^\text{17,18,19}\) Studies have reported the challenges in accordance with 2017 DG30 NICE guidance of integration of qFIT into primary care pathways.\(^\text{4}\) Lack of guidance awareness and limited access to qFIT testing have been highlighted as contributing to these challenges.\(^\text{20}\)

Supporting evidence as early as 2015 has demonstrated the use of faecal Hb as an exclusion test with high NPV for significant colorectal disease.\(^\text{12}\) qFIT in the symptomatic patient has been assessed with overall diagnostic accuracy for CRC in patients with red flag symptoms and has been shown to be useful beyond NICE referral criteria alone.\(^\text{21,22}\) Evidence to date has also explored that a single FIT sample is suffice to obtain a reliable result.\(^\text{23,24}\)

Direct visualisation via colonoscopy remains the gold standard test for colorectal cancer diagnosis.\(^\text{3,6}\) Common presenting symptoms of rectal bleeding, altered bowel habit, and anaemia constitute signs necessitating referral for clinical assessment and possible investigation.\(^\text{25}\) This adheres to the recognised benefit of early colorectal cancer detection and correlates to reduced mortality than late detection of advanced stage of pathology.\(^\text{7,9}\)

During this unpredicted time, national guidance limited endoscopy allocation to emergent and essential only.\(^\text{1}\) A strategy for healthcare provision within these restrictions had to be developed. In symptomatic patients, qFIT was used as a method of stratification and distribution of resources to identify significant colorectal pathology at an early stage and prioritise those at greatest need. Our results have demonstrated a quantitative relationship between qFIT value and the detection of significant pathology on investigation.

We have demonstrated across our patient population that the detection of colorectal cancer was associated with a higher qFIT score. A lower value conferred a more unremarkable investigation and therefore a low risk of cancer pathology. Endoscopic colonic evaluation was carried out in the majority of cases, as remains the gold standard investigation in the appropriate patient. A higher qFIT value categorised as priority 1 patients were offered investigation more promptly compared to the other priority groups. The results from this priority group 1 yielded a greater number of cases of colorectal cancer detection as well as further significant pathology in over half the patients in this group. Amongst this group, 47% of patients were anaemic which is reflected in the need for haematological work-up and primary care evaluation.\(^\text{20}\) The median age between priority groups did not differ significantly and a male preponderance was seen in priority group 1, compared to priority groups 2 and 3.

The challenge moving through this pandemic for both surgeons and gastroenterologists is navigating the imbalance between growing referral and waiting lists with restricted investigation and surgical provision. Our suggestion from our evaluation is that a high qFIT value should result in expedient investigation and true red flag assessment. Those that fall within the middle priority group 2, cancer pathology may be present but carries a negative predictive value of 96.81%. However, significant colorectal pathology has been demonstrated on investigation. These conditions may be readily treatable and also pre-cancerous so should be investigated in an urgent manner.\(^\text{26}\) In priority group 3,
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a negative predictive value for colorectal cancer detection of 100% was established but high-risk polyps were still a significant finding amongst this group. In practice, these symptomatic priority 3 patients with low qFIT results should still undergo appropriate investigation, but the other symptomatic groups should be prioritised. This approach demonstrates a strategy of resource allocation using qFIT value distributing resources to those in greatest need.

Limitations

Our study size is not sufficient to definitively show that no further investigation is required in symptomatic patients with a low qFIT. A return rate of 70% qFIT tests within this study is favourable when compared with other studies in this area.12 All initial non-responders were followed up with further written communication to ensure the highest possible response rate. The COVID-19 pandemic has created a challenging environment for research with rapid and dynamic guidance development but also the opportunity for transformation of practice.

Clinical implication and future research

We have demonstrated a quantitative relationship between qFIT value and colorectal cancer which highlights its utility as a triage tool for resources. Therefore, its role should be considered as an integral constituent of the primary care red flag referral pathway for symptomatic patients. Future research should focus on larger population studies to determine if it is possible to risk stratify further the low priority qFIT group to safely eliminate unnecessary investigations.

CONCLUSION

As we meet the challenges of the immediate and longer-term impact of the COVID-19 pandemic on healthcare, a consolidated approach to resource allocation is required. qFIT enables prioritisation of the patient pathway of those with suspected significant colorectal pathology and allows most effective use of resources based on the appropriate risk stratification.

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