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Lower gastrointestinal symptoms and symptoms-based triaging systems are poor predictors of clinical significant disease on colonoscopy

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ABSTRACT

Introduction Lower gastrointestinal symptoms (LGS) are a common cause of referral to the gastroenterology service. International guidelines are available to prioritise referrals. Some studies have reported that symptoms alone are a poor marker of clinically significant disease (CSD) but symptoms remain the main way to prioritise referrals in routine clinical practice.

Aims/background To correlate LGS with colonoscopy findings in an unselected patient cohort and to investigate whether using National Institute for Health and Care Excellence (NICE) guidelines improve risk stratification.

Method Colonoscopy data over a 2-year period were obtained from our endoscopy database. Only patients with assessment of symptoms as their primary indication for colonoscopy were included. Patient records were retrospectively reviewed. Exclusion criteria: known inflammatory bowel disease (IBD), familial cancer syndromes, polyp and colorectal cancer (CRC) surveillance, and prior colonoscopy within 5 years. Demographics, symptoms and colonoscopy findings were recorded and analysed.

Results 1116 cases were reviewed; 493 (44%) males, age 54.3 years (16–91). CSD occurred in only 162 (14.5%); CRC 19 (1.7%), high-risk adenoma 40 (3.6%), inflammation 97 (8.7%) (IBD 65 (5.8%), microscopic colitis 9 (0.8%) and indeterminate-inflammation 23 (2%)), angiodysplasia 6 (0.5%). Diarrhoea gave the highest diagnostic yield for CSD of 5.3% (OR 3.15, 95% CI 2.2 to 4.7, p<0.001), followed by PR bleeding, 2.9% (OR 1.9, 95% CI 1.24 to 2.9, p=0.003). Weight loss gave the lowest diagnostic yield of 0.4%; (OR 0.79, 95% CI 0.28 to 2.24, p=0.65). 592 (53%) and 517 (46%) fitted the NICE guidelines for CRC and IBD, respectively. Using NICE positivity improved detection but overall yield remained low 3% vs 0.4% (OR 7.71, 95% CI 1.77 to 33.56, p=0.0064) for CRC, and 9% vs 2.8% (OR 3.5, 95% CI 1.99 to 6.17, p<0.0001) for IBD.

Conclusions The overall prevalence of CSD in our unselected symptomatic patients is low (14.5%). A holistic approach including combining symptoms and demographics with novel tools including stool biomarkers and minimally invasive colonoscopy alternatives should be applied to avoid unnecessary colonoscopy.

Summary box

What is already known about this subject?

- Symptoms-based triaging systems are the main way of prioritising referral for colonoscopy. Some studies have found that symptoms are poor at predicting clinically significant disease (CSD) on colonoscopy. Symptoms-based triaging systems exist including National Institute for Health and Care Excellence (NICE) guidelines to help identify high-risk patients and priorities referrals.

What are the new findings?

- Application of a high-risk triaging criteria (NICE guidelines for inflammatory bowel disease (IBD) and colorectal cancer (CRC)) does increase diagnosis of CRC and IBD but overall diagnostic yield remains low. NICE positivity does not significantly increase diagnostic yield.
- Symptoms in our cohort remain poor at predicting CSD.

How might it impact on clinical practice in the foreseeable future?

- A holistic approach including combining symptoms, demographics with novel tools including biomarkers (faecal calprotectin and faecal immunochemical test) and CT and/or PillCam Colon should be applied to avoid unnecessary colonoscopy.

INTRODUCTION

Over 10% of presentations to general practitioners (GP) are for gastrointestinal (GI) complaints; while most of these are dealt with by GPs many would require a referral to gastroenterology services.[1] Traditionally when patients present with lower GI symptoms, including change in bowel habit (diarrhoea, constipation or alternating symptoms), bloating, abdominal pain, bleeding per rectum (PR) or anaemia) they are seen by a gastroenterologist in an

outpatient clinic, where a clinical history, physical examination and routine blood tests are often performed. For a majority of patients as part of the subsequent workup, based on initial assessment, they are then triaged to either a routine or urgent appointment for a colonoscopy before arriving at a specific diagnosis. More recently, a significant proportion of patients referred by their GPs are sent directly for endoscopy procedures.[2] Patients on this open/direct access endoscopy pathway are also normally triaged based on their symptomology and demographics.

Previous studies have suggested that a combined clinical history and physical exam is a poor tool to predict clinically significant disease (CSD), defined as colorectal cancer (CRC), high-risk adenoma (HRA) and inflammatory bowel disease (IBD).[3] More recently, systems have been developed to improve patient triage, thereby identifying patients for early investigations and minimising unnecessary procedures. Including the National Institute for Health and Care Excellence (NICE) guidelines, which triaging patients based on symptoms and age for a diagnosis of CRC and IBD.[4 5] Although some symptoms employed are specific, unprovoked PR bleeding in someone over 50 years of age and the presence of a mass on examination for the diagnosis of CRC, others are more vague, a change in bowel habit in patients above 60 years old and CRC and ongoing symptoms of bloating over 6 weeks and a potential diagnosis of IBD.

The use of serum and stool biomarkers have been increasing in the past number of years to assess a wide variety of GI diseases. Ranging from the use of faecal immunochemical test (FIT) in population screening for bowel cancer to the use of faecal calprotectin (FC) to help assess disease activity in patients with IBD.[6–8] Data on their efficacy in symptomatic patient stratification are limited with only one large UK study published to date.[9] Further studies are required to set a universal cut-off for CSD. As such, symptom-based triaging remains the standard of care in clinical practice.

Colonoscopy is considered the gold-standard test to assess for bowel disease. It is performed in a dedicated fully-staffed endoscopy unit. Even though colonoscopy is usually well tolerated, it does come with its own limitations including potential complications which include bleeding and bowel perforation, and patients perceived inconvenience, discomfort or embarrassment.[10 11] Currently the need for colonoscopy far exceeds our ability to perform them, resulting in prolonged waiting lists and unfortunately in some cases delays in diagnosis and treatment. Based on national waiting-list data, there are a total of 54 625 patients awaiting endoscopy in Ireland by end of February 2018 and specifically in our hospital, 4591 patients are on a waiting list.[12] Similar problems have been encountered nationally and internationally in other centres. Due to limited resources, better means of patient selection and triage are badly needed, as current symptoms-based recommendation is unsustainable.

AIM

The aim of our study was to assess within an unselected group of patients how symptoms correlate with findings of CSD on colonoscopy and to evaluate whether using a high-risk triaging system (NICE guidelines) improves prediction and detection of CRC and IBD in our cohort of patients.

METHOD

Study design

A retrospective observational study based on our endoscopy records of an unselected symptomatic cohort referred for colonoscopy, over a 2-year period (2015–2016). Endoscopy reports were obtained from Unisoft Endoscopy reporting database. We recorded patients' symptoms prompting the colonoscopy and also the findings of the colonoscopy. We excluded patients with known IBD (either disease surveillance or assessment), patients for polyp surveillance, CRC surveillance, screening colonoscopy for a family history of CRC and a prior colonoscopy within 5 years. We also documented patients' demographic details. We defined CSD as CRC, inflammation (either IBD, microscopic colitis or indeterminate inflammation), (HRA—where one adenoma is larger than 10 mm, the presence of more than three adenomas or adenomas with high-grade dysplasia[13]) and presence of angiodysplasia.

Based on patients symptomology and demographic details, patients were then categorised into high-risk and low-risk groups based on the NICE guidelines for CRC and IBD.[4 5]

We did not discriminate based on source of referral, either from primary or secondary care. All referrals to our endoscopy service are triaged by consultant gastroenterologists using appropriate guidelines. The criteria used by our gastroenterologists are widely available and are already in use in general practice. Our study included all patients irrespective of urgency of referral.

Analysis

Data analysis was performed using MedCalc. We calculated the overall diagnostic yield and OR of all symptoms. We also calculated the diagnostic yield and OR based on NICE guideline positivity in terms of diagnosing IBD and CRC. A $p<0.05$ was considered to be statistically significant.

RESULTS

Study population

In total, 1116 patients were identified who underwent a colonoscopy for symptomatic assessment during our study period. Of this, 493 (44%) were male and mean age is 54.3 years (range 16–91). Indications included were abdominal pain in 104 (9.3%) patients, diarrhoea in 188 (16.8%), weight loss in 37 (3.3%), constipation in 57 (5.1%), anaemia in 212 (19%), alternating constipation with diarrhoea in 79 (7%), PR bleeding in 148

(13.3%) and others 291 (26%). In terms of quality indicators for colonoscopy, based on our local data and audit, the caecal intubation rate in our centre is 95.3% and adenoma detection rate is 12% in the symptomatic cohort over this time period.

CSD occurred in only 162 (14.5%) of our cohort; CRC in 19 (1.7%), HRA in 40 (3.6%), inflammation in 97 (8.7%) (IBD in 65 (5.8%), microscopic colitis in 9 (0.8%) and indeterminate inflammation in 23 (2%)), and angiodysplasia in 6 (0.5%).

Diagnostic yield and symptoms

With regard to the predictive value of symptoms for CSD, diarrhoea gave the highest diagnostic yield of 5.3% (n=59/1116); (OR 3.15, 95% CI 2.2 to 4.47, p<0.001), similarly PR bleeding also had a reasonable diagnostic yield of 2.9% (n=32/1116); (OR 1.9, 95% CI 1.24 to 2.9, p=0.003). Conversely weight loss and constipation gave the lowest diagnostic yields overall of 0.4% (n=4/1116); (OR 0.79, 95% CI 0.28 to 2.24, p=0.65) and 0.4% (n=5/1116); (OR 0.57, 95% CI 0.22 to 1.44, p=0.12), respectively, and did not correlate with significant disease. The breakdown of diagnostic yield by symptom are given in table 1.

In all, when looking at the break down of individual symptoms and the risk of CSD, of all patients with diarrhoea as their predominant symptom CRC occurred in 5 (3%) cases, inflammation in 45 (38%) cases (IBD in 31 (16%), microscopic colitis in 7 (4%), indeterminate inflammation in 7 (4%)), HRA in 6 (3%) angiodysplasia in 2 (1%) and 144 (78%) patients had a normal colonoscopy. For PR bleeding as the predominant symptom, CRC was diagnosed in 9 (6%) cases, HRA in 10 (7%), IBD in 10 (7%), microscopic colitis in 1 (1%), angiodysplasia in 1 (1%), indeterminate inflammation in 3 (2%) and 114 (79%) patients had a normal colonoscopy. While in anaemic patients, CRC was diagnosed in 4 (2%) cases, HRA in 12 (6%), IBD in 5 (2%), angiodysplasia in 2 (1%), indeterminate inflammation in 2 (1%) and negative in 187 (88%). Further breakdown is given in table 1.

When looking at the likelihood of finding CSD based on each symptom, as expected, the symptom of diarrhoea was strongly associated with a diagnosis of IBD compared with other symptoms (diarrhoea alone—OR 2.22, 95% CI 1.25 to 4.4, p=0.007 and any diarrhoea (including symptom of alternating diarrhoea with constipation) OR 2.08, 95% CI 1.14 to 3.84, p=0.01). Meanwhile the symptom of PR bleeding was strongly associated with a diagnosis of CRC compared with other symptoms (OR 3.9, 95% CI 1.54 to 9.7, p=0.005). The symptom of anaemia was not statistically associate with a diagnosis of CRC or IBD compared with other symptoms (OR 1.17, p=0.49 and OR 0.33, p=0.02).

For the cohort with CSD, a similar pattern was identified. In addition, anaemia was the most common indication in patients with HRA (30%). Further breakdown can be seen in table 2.

Impact of NICE guidelines

Based on patients' symptoms and demographics, 592 (53%) patients fitted the criteria for urgent referral for CRC and 517 (46%) for IBD based on the NICE guidelines. Only 19% (217) of our total patient cohort fitted neither criteria and would not have needed an urgent colonoscopy.

For patients meeting NICE criteria for CRC, the diagnostic yield for CRC was 3% (n=17/592) and the diagnostic yield for those not meeting the criteria was 0.4% (n=2/524). Fitting the criteria for CRC statistically increased the diagnostic yield compared with not fitting the criteria (OR 7.71, 95% CI 1.77 to 33.56, p=0.0064). For patients meeting the NICE criteria for IBD, the diagnostic yield was 9% (n=48/517) and the diagnostic yield for those not meeting the criteria was 2.8% (n=17/599). Fitting the criteria for IBD also statically increased the diagnostic yield compared with not using the criteria (OR 3.5, 95% CI 1.99 to 6.17, p<0.0001).

Although the diagnostic yield remained low, applying NICE criteria did increase the diagnostic yield from baseline; 1.7% (n=19/1116) to 3% (n=17/592) for CRC and from 5.8% (n=65/1116) to 9% (n=48/517) for IBD.

Being any NICE criteria positive versus any NICE negative gave an overall diagnostic yield for any CSD of 15% (n=133/889) vs 13% (n=28/217). If we were to consider being NICE positive as high risk, having a high-risk criteria does not statistically correlate with CSD (OR 1.44, 95% CI 0.919 to 2.278, p=0.11) (table 3).

DISCUSSION

The results of our study suggest that symptoms remain a poor determinant of significant bowel disease on colonoscopy. The diagnostic yield for CSD was only 14.5% in our symptomatic patient cohort. While there are established optimum detection rates for screening colonoscopies, the same cannot be said for the symptomatic cohort. More studies are needed to establish an optimum detection rate. Diarrhoea was the best indication for colonoscopy with a diagnostic yield of 5.3% (n=59/1116) and an OR of 3.15 followed closely by PR bleeding with a diagnostic yield of 2.9% (n=32/1116) and OR of 1.9. While using NICE guidelines for CRC and IBD improved diagnosis for each disease, overall diagnostic yield remained low, 3% vs 0.4% in CRC with (OR 7.71) and 9% vs 2.8% in IBD (OR 3.5). In agreement with our findings, NICE reported a PPV of 3% for CRC criteria positive patients.[5]

While most physicians agree, that a 'negative test' is often helpful to exclude CSD, the purpose of this study was not to prevent patients having a procedure but to better identify at risk patients requiring urgent referrals. We do not feel that colonoscopy is the most ideal negative test for reassurance based on its restrictions. Other potential candidates include faecal biomarkers (FIT and FC), CT Colon and Colon capsule endoscopy, all of which are considered minimally-invasive compared with colonoscopy and maybe

Table 1 Clinically significant disease frequency based on predominant symptom/indications

Symptoms (total)	Findings	No (%)	Diagnostic yield	OR (95% CI, p value)
Diarrhoea (total=188)	CRC	5 (3)	5.3% (n=59/1116)	3.15 (2.22 to 4.47, p<0.0001)
	HRA	7 (4)		
	Angiodysplasia	2 (1)		
	Inflammation—IBD	31 (16)		
	Inflammation—Microscopic Colitis	7 (4)		
	Inflammation—non-specific	7 (4)		
	Negative	129 (69)		
PR bleeding (total=148)	CRC	9 (6)	2.9% (n=32/1116)	1.9 (1.24 to 2.9, p=0.003)
	HRA	12 (8)		
	Inflammation—IBD	6 (4)		
	Inflammation—microscopic colitis	1 (1)		
	Inflammation—non-specific	3 (2)		
	Angiodysplasia	1 (1)		
	Negative	116(79)		
Anaemia (total=212)	CRC	4 (2)	2.2% (n=25/1116)	0.83 (0.53 to 1.29, p=0.4)
	HRA	12 (6)		
	Inflammation—IBD	5 (2)		
	Inflammation—non-specific	2 (1)		
	Angiodysplasia	2 (1)		
	Negative	187 (88)		
Weight loss (total=37)	HRA	3 (8)	0.4% (n=4/1116)	0.79 (0.28 to 2.24, p= 0.65)
	Inflammation—IBD	1 (3)		
	Negative	35 (94)		
Constipation (total=57)	HRA	2 (4)	0.4% (n=5/1116)	0.57 (0.22 to 1.45, p=0.12)
	Inflammation—IBD	1 (2)		
	Angiodysplasia	1 (2)		
	Negative	53 (93)		
Alternating constipation and diarrhoea (total=79)	CRC	1 (1)	1% (n= 12/1116)	1.23 (0.65 to 2.33, p=0.52)
	HRA	2 (3)		
	Inflammation—IBD	6 (8)		
	Inflammation—microscopic colitis	1 (1)		
	Inflammation—non-specific	2 (3)		
	Negative	67 (85)		
Abdominal pain (total=104)	CRC	1 (1)	0.8% (n=9/1116)	0.7 (0.37 to 1.33, p=0.28)
	HRA	1 (1)		
	Inflammation—IBD	4 (4)		
	Inflammation—non-specific	3 (3)		
	Negative	95 (91)		

CRC, colorectal cancer; HRA, high-risk adenoma; IBD, inflammatory bowel disease; PR, per rectum.

a better means for excluding CSD. While there are clear guidelines from the European Society of Gastrointestinal Endoscopy on the use of colon capsule endoscopy[14] as a diagnostic test for bowel disease, the role of biomarkers are less clear and warrants further investigations.

Our findings are similar to previous papers published by Selinger *et al*[15] who found that colonic investigations will not explain isolated abdominal pain in 92% of patients. In addition Mowat *et al*,[9] used a combination of symptoms and stool biomarkers to detect CSD. The diagnostic yield of symptoms in Mowat's cohort is quite similar to ours at 14%. In addition, their biomarker results would indicate that the absence of occult blood in the stool could potentially exclude significant disease. The use of FIT as a population

Table 2 Symptoms frequency according to CSD

CSD	Indications (%)	Total (%)
CRC	PR bleeding – 9 (47) Diarrhoea— 5 (26) Anaemia—4 (21) Abdominal pain—1 (5)	19 (1.7)
HRA	Anaemia—12 (30) PR bleeding—12 (30) Diarrhoea—7 (18) Weight loss—3 (8) Constipation—2 (5) Alt. constipation w diarrhoea—2 (5) Abdominal pain—1 (3) Others—1 (3)	40 (3.6)
Inflammation—IBD	Diarrhoea—31 (48) PR bleeding—6 (9) Alt constipation and diarrhoea—6 (9) Anaemia—5 (8) Abdominal pain—4 (6) Weight loss—1 (2) Constipation—1 (2) Other—11 (17)	65 (5.8)
Inflammation—microscopic colitis	Diarrhoea—7 PR bleeding—1 Alt. constipation with diarrhoea—1	9 (0.8)
Vascular—angiodysplasia	Diarrhoea—2 Anaemia—2 PR bleeding—1 Constipation—1	6 (0.5)

CRC, colorectal cancer; CSD, clinically significant disease; HRA, high-risk adenoma; IBD, inflammatory bowel disease; PR, per rectum.

screening for bowel cancer has been widely adopted internationally.[6] Different FIT cut-off's have been suggested for cancer screening, in some countries going as high as 250 µg/g.[16–19] It is interesting that in Mowat's study, they identified three patients with a FIT of less than 10 µg/g who had CRC, suggesting further studies are needed to set a cut-off point in the symptomatic patients.

While there is evidence that FC is helpful to asses for IBD activity,[7] its use for the screening of symptomatic patients for IBD is less clear and the limited data available suggests that it is less effective especially for borderline results (50–150 µg/g).[20] Mowat *et al* found, using a cut-off of 50 µg/g, the PPV for any CSD was only 16.9% and 6.4%

Table 3 Impact of NICE guidelines

	Diagnostic yield of CRC	Diagnostic yield of IBD	Overall diagnostic yield	OR
CRC NICE criteria positive (n=592)	3% (n=17)	n/a	n/a	7.71 (95% CI 1.77 to 33.56, p=0.0064)
CRC NICE criteria negative (n=524)	0.4% (n=2)	n/a	n/a	
IBD NICE criteria positive (n=517)	n/a	9% (n=48)	n/a	3.5 (95% CI 1.99 to 6.17, p<0.0001)
IBD NICE criteria negative	n/a	2.8% (n=17)	n/a	
CRC +IBD NICE criteria positive (n=899)	n/a	n/a	15% (n=133)	1.44 (95% CI 0.919 to 2.278, p=0.11)
CRC +IBD NICE criteria negative (n=217)	n/a	n/a	13% (n=28)	

CRC, colorectal cancer; IBD, inflammatory bowel disease; n/a, not applicable; NICE, National Institute for Health and Care Excellence.

for IBD.[9] However, the role of combined biomarkers may be an effective approach in the future.

While our study is based in secondary care, all referrals were vetted by a consultant gastroenterologist using standard criteria. In addition, all referrals to the gastroenterology OPD are also vetted and referred directly to colonoscopy if needed. These criteria are employed widely in primary care as well and currently remain the best way to triage patients. Based on the evidence to date, we feel that there is a clear need for a more holistic method of predicting which patients presenting with lower GI symptoms would require further investigation by means of a colonoscopy. We have clearly demonstrated in our large retrospective study that symptoms alone are poor at doing this. Despite using high-risk criteria such as the NICE guidelines, the diagnostic yield remains low. In the future, a combination of all traditional tools, that is, symptomology, physical examination and blood parameters with more novel methods of diagnosis including stool biomarkers (FIT and FC) and minimally invasive endoscopy (Colon capsule endoscopy or CT Colonoscopy) may be used to improve patient selection; improving access to colonoscopy while avoiding adverse events and warrants further investigations.

CONCLUSION

Our study clearly shows that symptoms alone remain a poor predictor of CSD on colonoscopy, although it still remains the most common method to triage referrals. A more holistic and novel approach needs to be studied and formulated using a combination of symptoms, blood and stool biomarkers and potentially minimally invasive colonoscopy in order to reduce the need for a 'negative' colonoscopy which would hopefully improve access, reduce waiting times and avoid unnecessary adverse events.

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