Lorena Rodriguez-Alonso, Francisco Rodriguez-Moranta, Alexandra Ruiz-Cerulla, Claudia Arajol, Katja Serra, Pau Gilabert, Gemma Ibañez-Sanz, Blau Camps and Jordi Guardiola*

The use of faecal immunochemical testing in the decision-making process for the endoscopic investigation of iron deficiency anaemia

https://doi.org/10.1515/cclm-2019-0203
Received February 21, 2019; accepted July 17, 2019; previously published online November 30, 2019

Abstract

Background: Blood loss from the gastrointestinal (GI) tract is the most common cause of iron deficiency anaemia (IDA) in adult men and postmenopausal women. Gastroduodenal endoscopy (GDE) and colonoscopy are frequently recommended, despite uncertainty regarding the coexistence of lesions in the upper and lower GI tract. The faecal immunochemical test (FIT) measures the concentration of faecal haemoglobin (f-Hb) originating only from the colon or rectum. We aimed to assess whether the FIT was able to select the best endoscopic procedure for detecting the cause of IDA.

Methods: A prospective study of 120 men and postmenopausal women referred for a diagnostic study of IDA were evaluated with an FIT, GDE and colonoscopy. The endoscopic finding of a significant upper lesion (SUL) or a significant bowel lesion (SBL) was considered to be the cause of the IDA.

Results: The diagnoses were 35.0% SUL and 20.0% SBL, including 13.3% GI cancer. In the multivariate analysis, the concentration of blood haemoglobin (b-Hb) <9 g/dL (OR: 2.60; 95% CI 1.13–6.00; p = 0.025) and non-steroidal anti-inflammatory drugs NSAIDs (2.56; 1.13–5.88; p = 0.024) were associated with an SUL. Age (0.93; 0.88–0.99; p = 0.042) and f-Hb ≥ 15 μg Hb/g faeces (38.53; 8.60–172.50; p < 0.001) were associated with an SBL. A "FIT plus gastroscopy" strategy, in which colonoscopy is performed only when f-Hb ≥15 μg Hb/g faeces, would be able to detect 92.4% of lesions and be 100% accurate in the detection of cancer while avoiding 71.6% of colonoscopies.

Conclusions: The FIT is an accurate method for selecting the best endoscopy study for the evaluation of IDA. An FIT-based strategy is more cost-effective than the current bidirectional endoscopy-based strategy and could improve endoscopic resource allocation.

Keywords: accuracy; endoscopy; faecal immunochemical test; iron deficiency anaemia.

Introduction

Iron deficiency anaemia (IDA) is the most common form of anaemia in the developed world and its prevalence in adult men and postmenopausal women is approximately 2%–5% [1, 2]. The main cause of IDA in this subgroup of patients is blood loss from the gastrointestinal (GI) tract [3, 4] and is due to malignant lesions in 10%–17% of cases [5–7]. The National Institute for Health and Care Excellence (NICE) updated colorectal cancer (CRC) guidelines consider the presence of significant IDA to be a relevant symptom for the selection of individuals for urgent referral [8–10]. Accordingly, IDA is a common cause for referral to a gastroenterologist in order to proceed to endoscopic studies [3, 11].

There are no consistent data about dual pathology in IDA patients [3, 11] nor criteria for selecting the preferential study of the upper or lower GI tract. Guidelines for the management of IDA establish that bidirectional endoscopy, including gastroduodenal endoscopy (GDE) and colonoscopy, should be considered in adult men and postmenopausal women with confirmed IDA [3].

The faecal immunochemical test (FIT) has largely replaced biochemical tests as a method for CRC population screening. Furthermore, the FIT is also an objective

***Corresponding author: Jordi Guardiola,** Department of Gastroenterology and Hepatology, University Hospital of Bellvitge-IDIBELL, Feixa Llarga S/N, 08907, L'Hospitalet de Llobregat, Barcelona, Spain; and Universidad de Barcelona, Barcelona, Spain, Phone: +34 932 607 500x2692/2826, Fax: +34 93 2607883, E-mail: jguardiola@bellvitgehospital.cat
Lorena Rodriguez-Alonso, Francisco Rodriguez-Moranta, Alexandra Ruiz-Cerulla, Claudia Arajol, Katja Serra, Pau Gilabert and Blau Camps: Department of Gastroenterology and Hepatology, University Hospital of Bellvitge-IDIBELL, Barcelona, Spain
Gemma Ibañez-Sanz: Department of Gastroenterology and Hepatology, University Hospital of Bellvitge-IDIBELL, Barcelona, Spain; and Catalan Institute of Oncology, Cancer Prevention and Control Programme, IDIBELL, Barcelona, Spain

and accurate method for detecting advanced adenoma and CRC in symptomatic patients [10, 12]. The FIT has shown a better discriminatory ability than lower abdominal symptoms for this purpose [10, 12, 13].

The FIT selectively detects human globin-protein in faeces. This globin is prone to degradation from GI proteases in the upper GI tract and this property confers on the FIT the specificity required to detect exclusively colorectal blood loss [14–17]. With that in mind, the FIT could potentially be used to estimate the risk of significant colonic lesions in IDA patients and may help the physician in the decision-making process when selecting the most appropriate form of endoscopic exploration (GDE or colonoscopy).

The objective of this study was therefore to evaluate the effectiveness of different FIT-based endoscopic strategies for the diagnosis of IDA and to establish whether any of these strategies is more efficient than the standard bidirectional endoscopic study.

Materials and methods

Study design and patients

This prospective study included men and postmenopausal women over 18 years of age with IDA referred to the Endoscopy Unit of the Bellvitge University Hospital for bidirectional endoscopy (GDE and colonoscopy) between September 2011 and October 2012. The study was carried out following the Standards for Reporting Diagnostic accuracy studies (STARD) guidelines (Supplementary Table S1). All patients were studied with an FIT and a bidirectional study (GDE and colonoscopy). Follow-up data based on health care facility medical records and death certificates were collected at 12 months to investigate undiagnosed causes of IDA.

IDA is defined by the World Health Organization as a blood-haemoglobin (b-Hb) of <12 g/dL in men and <13 g/dL in postmenopausal women and the presence of iron deficiency (ferritin concentrations <15 μg/L or microcytosis (mean corpuscular volume ≤80 fL).

We excluded premenopausal women, hospitalised patients, those with a personal history of haematological disorders and patients with symptoms of any other source of blood loss (epistaxis, haematuria and haemoptysis). Patients with a family history of IDA (which may indicate inherited iron absorption disorders) were also excluded. Patients with incomplete colonoscopies were included only if the cause was a stenosing neoplasm. Upper GI bleeding was not evaluated as this diagnosis triggers a situation of emergency. Referrals were both outpatient requests from general practitioners and community gastroenterologists and in-hospital requests.

An exhaustive questionnaire was administered by a gastroenterologist in a face-to-face interview. The following variables were evaluated for their potential association with significant upper lesions (SULs), significant bowel lesions (SBLs) and GI cancer: gender, age, body mass index, diabetes mellitus, dyslipidaemia, anti-platelet therapy, anticoagulant therapy or non-steroidal anti-inflammatory drug (NSAID) use, tobacco or alcohol use including current exposure or risk exposure in the past, family history of GI cancer and severity of IDA. Average alcohol consumption (in standard units of alcohol, SUA), was categorized into low-risk and high-risk consumption (>4 SUA/day in men and >2 SUA/day in women) [18].

On the day of the consultation, the patient was given a specimen collection device (OC Sensor® Eiken Chemical Co., Ltd., Tokyo, Japan) and instructions were given on how to complete the test at home. Patients were instructed to store the sample in the refrigerator at <4 °C and submit it within 7 days. If the test was done incorrectly or there was a storage error, the test was repeated or the patient was excluded from the study. One experienced technician performed the analyses of quantitative FIT. All tests were analysed using the OC sensor MICRO desktop analyser (Eiken Chemical Co., Ltd., Tokyo, Japan). In our study, faecal haemoglobin concentration (f-Hb) ≥15 μg Hb/g faeces was taken as a cut-off value. The test was identified with a barcode and patient data remained under the exclusive control of the investigators in order to preserve patient privacy and colonoscopies were performed by experienced endoscopists.

Conscious sedation was administered using intravenous propofol. The dose of medication was titrated according to patient needs and the duration of the procedure. The colonoscopy was considered complete if caecal intubation was achieved as demonstrated by the visualisation of the ileocecal valve or the appendiceal orifice. Bowel preparation was evaluated using the validated Boston bowel preparation scale. The study protocol was approved by the ethics committee of our institution and written informed consent was obtained from all patients.

Outcome measures

All patients underwent GDE and colonoscopy. The endoscopic finding of an SUL, an SBL or a GI cancer was considered as the cause of the IDA.

SUL was defined by endoscopic and histological criteria as the presence of disruption of the mucosa (ulcer, erosive gastritis), vascular lesion (angiodysplasia, portal hypertensive gastropathy) or neoplastic lesions (cancer or polyps >10 mm) detected by GDE.

SBL was defined by endoscopic and histological criteria as the presence of disruption of the mucosa (ulcer, erosions, any kind of colitis, including inflammatory bowel disease), vascular (angiodysplasia) or neoplastic lesions (advanced adenoma or invasive carcinoma) detected by colonoscopy. Advanced adenoma was defined as adenoma ≥10 mm, villous component or high-grade dysplasia.

Theoretical FIT-based strategies

All patients were studied with a quantitative FIT and a bidirectional study (GDE and colonoscopy). In order to evaluate the effectiveness of different FIT-based endoscopic strategies for the diagnosis of IDA we compared three theoretical FIT based-strategies (see Figure 1).

- "FIT plus gastroscopy" involved performing an FIT and GDE on all patients. Colonoscopy was added only in case of f-Hb ≥15 μg Hb/g faeces.
- "FIT guided endoscopy" involved the initial performance of an FIT. If f-Hb ≤15 μg Hb/g faeces the only examination considered was a GDE. If f-Hb ≥15 μg Hb/g faeces the only examination considered was a colonoscopy.

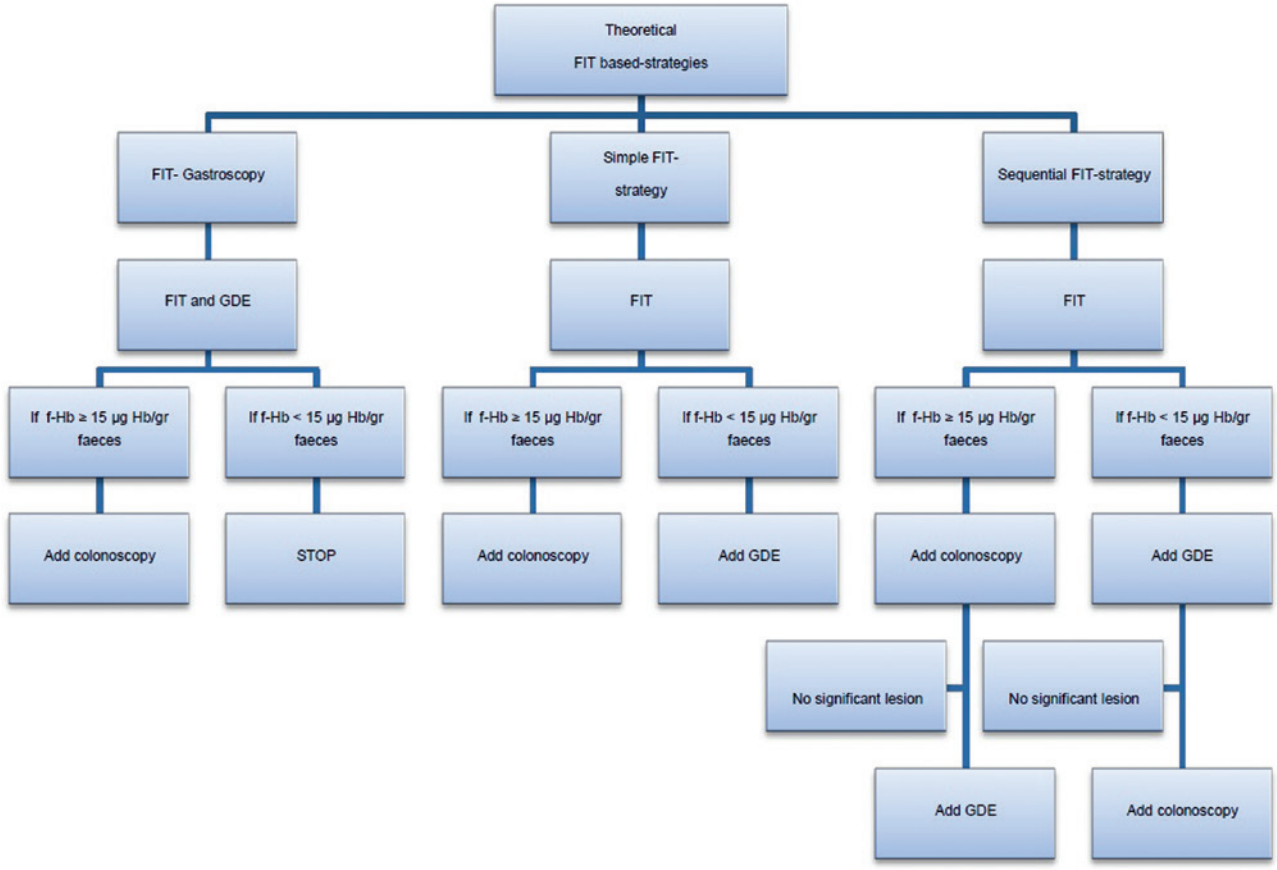

Figure 1: Theoretical FIT based-strategies for study of IDA.

– "Sequential FIT guided endoscopy" strategy involved the initial performance of the FIT. If f-Hb ≤15 µg Hb/g faeces, GDE was the first examination considered. If an SUL was not detected, colonoscopy was subsequently considered. If f-Hb ≥15 µg Hb/g faeces, colonoscopy was the first examination considered. If an SBL was not detected, GDE was subsequently considered.

Statistical analysis

Categorical variables are presented as number and proportion (%). We used Chi square (χ^2) and Fisher's exact test to compare categorical variables and Student's t analysis to compare quantitative variables. A multivariate analysis based on a logistic regression procedure was performed in order to identify the independent predictive factors of SUL, SBL and GI cancer. Factors were included in the multivariable model based on their univariate association with SUL, SBL and GI cancer ($p < 0.05$). Factors not reaching statistical significance were also included if they were considered to be clinically relevant. The results of the model are reported as adjusted odds ratios (OR) and their 95% confidence intervals (CI).

We performed a cost analysis of FIT-based strategies. The reference standard test was bidirectional endoscopy study (GDE and colonoscopy). Costs were expressed in Euros according to the prices applied at Bellvitge University Hospital in the years 2011 and 2012. In this case: FIT €2.45, GDE with sedation: €244, colonoscopy with sedation: €367. We compared global costs and the cost per significant lesion and per cancer of the different theoretical strategies in comparison with the standard study (upper and lower endoscopy). The statistical analysis was carried out using SPSS, Version 17 (SPSS Inc, Chicago, IL, USA).

Results

Descriptive findings

During the study period, 1054 patients were referred for endoscopy as part of the study of abdominal symptoms and were potentially eligible for the study. Anaemia was the cause of referral in 230 patients, among whom 120 patients fulfilled the inclusion criteria and were enrolled in the study (Supplementary Figure S1). The prevalence of SUL, esophagogastroduodenal cancer (EGDC), SBL and CRC in our population was 35.0%, 5.8%, 20.0% and 7.5%, respectively. The coexistence of significant lesions in the upper and lower GI tract was detected in five out of 120 patients (4.1%). Table 1 shows the lesions detected by endoscopic study.

Table 1: Potential causes of IDA in the study population.

Lesions	n, %
SUL	
Neoplasic (cancer or polyps >10 mm)	13 (10.8)
EGD cancer	7 (5.8)
EGD vascular lesion	5 (4.2)
EGD disruption of the mucosa	24 (20.0)
No SUL	78 (65.0)
SBL	
Neoplasic (CRC or advanced adenoma)	16 (13.3)
CRC	9 (7.5)
Colorectal vascular lesion	3 (2.5)
Colorectal disruption of the mucosa	5 (4.2)
No SBL	96 (80.0)
No SUL nor SBL[a]	59 (49.1)
Total	120 (100)

[a]No upper nor significant bowel lesion were detected.
EGD,esophagogastroduodenal; SUL, significant upper lesion; CRC, colorectal cancer; SBL, significant bowel lesion.

Evaluation of significant lesions at baseline

In the univariate analysis, exposure to alcohol, NSAID treatment and severe IDA (b-Hb < 9 g/dL) were associated with SUL, whereas, male gender, exposure to tobacco and alcohol and f-Hb measured by the FIT ≥ 10, ≥ 15 and ≥ 20 μg Hb/g faeces were associated with SBL (Table 2).

In the multivariate analysis, the severity of IDA (OR: 2.60; 95% CI 1.13–6.00; p = 0.025) and NSAIDs therapy (2.56; 95% CI 1.13–5.88; p = 0.024) were independent risk factors for SUL (Table 3). Age (0.93; 95% CI 0.88–0.99; p = 0.042) and f-Hb ≥15 μg Hb/g faeces (38.53; 95% CI 8.60–170.50; p < 0.001) were identified as independent risk factors for SBL (Table 3).

The areas under the receiver operating characteristic (ROC) curve for FIT in the detection of an SBL was 0.84 (95% CI 0.73–0.94). After ROC curve analysis, the optimal cut-off points of the f-Hb for SBL was ≥15 μg Hb/g faeces.

Cost analysis of FIT-based strategies

Table 4 shows the proportion of significant lesions detected by applying the different strategies, together with the associated cost per significant lesion detected. FIT plus gastroscopy and sequential FIT guided endoscopy detected more than 90% of significant lesions and did not miss any diagnoses of cancer, though the former saved €31,564 whereas the latter saved €15,790 compared to bidirectional endoscopy.

Follow-up of patients at 12 months

Four new relevant diagnoses were detected at 1 year of follow-up. One was a patient with coeliac disease who had been diagnosed with an SUL (hiatal hernia with Cameron ulcers) and not SBL at baseline and another was a patient with gastric cancer. This patient was diagnosed with an SBL (colonic ulcers) and normal GDE at baseline. Another

Table 2: Prevalence of SULs and SBLs by risk factors.

	All subjects' prevalence, n = 120, %	SUL		SBL	
		Prevalence, %	p-Value	Prevalence, %	p-Value
Age, ≥60 years	93 (77.5)	33 (34.0)	0.837	19 (20.4)	0.514
Gender, male	58 (48.3)	18 (31.0)	0.378	17 (29.3)	0.006
Exposure to tobacco	56 (46.6)	15 (26.8)	0.078	16 (28.5)	0.014
Exposure to alcohol	21 (16.9)	3 (14.3)	0.028	8 (38.1)	0.015
NSAID	51 (42.5)	12 (23.5)	0.024	13 (25.5)	0.130
PPIs	83 (69.2)	31 (37.3)	0.476	15 (18.1)	0.598
b-Hb					
< 8 g/dL	24 (20.0)	10 (41.6)	0.444	6 (25.0)	0.417
< 9 g/dL	36 (30.0)	18 (50.0)	0.024	9 (25.0)	0.288
< 10 g/dL	65 (54.2)	24 (36.9)	0.631	15 (23.1)	0.237
< 11 g/dL	94 (78.3)	36 (38.3)	0.150	18 (19.1)	0.991
Weight loss	37 (30.8)	17 (45.9)	0.093	4 (10.8)	0.121
f-Hb ≥ 10 μg Hb/g faeces	35 (29.1)	10 (28.5)	0.343	19 (54.3)	<0.001
f-Hb ≥ 15 μg Hb/g faeces	34 (28.3)	10 (29.4)	0.420	19 (55.8)	<0.001
f-Hb ≥ 20 μg Hb/g faeces	26 (21.6)	9 (34.6)	0.963	16 (61.5)	<0.001

SUL, significant upper lesion; SBL, significant bowel lesion; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; b-Hb, blood haemoglobin concentration; f-Hb, faecal haemoglobin concentration.

Table 3: Multivariate predictors of SUL and SBL.

Risk factors	SUL			SBL		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Age	1.01	0.97–1.04	0.653	0.93	0.88–0.99	0.042
Male gender	0.72	0.34–1.55	0.406	2.74	0.66–10.88	0.166
NSAIDs therapy	2.56	1.13–5.88	0.024	1.83	0.60–5.43	0.291
PPIs treatment	1.43	0.59–3.43	0.422	1.46	0.46–4.60	0.518
Severe IDA[a]	2.60	1.13–6.00	0.025	1.93	0.70–5.63	0.196
f-Hb ≥ 15 μg Hb/g faeces	1.07	0.67–3.03	0.464	38.53	8.60–172.50	<0.001

[a]Severe IDA, b-Hb concentration <9 g/dL. NSAIDs, non-steroidal anti-inflammatory drugs; CI, confidence interval; PPIs, proton pump inhibitors; IDA, iron deficiency anaemia; f-Hb, faecal haemoglobin concentration; OR, odds ratio; SUL, significant upper lesion; SBL, significant bowel lesion.

Table 4: Cost analysis according to FIT-based strategies.

	SL detected, n (%)	Cancer detected, n (%)	Cost analysis		
			Cost per SL, €	Cost per cancer, €	Overall cost, €
Bidirectional study	66 (100)	16 (100)	1116	4601	73,614
FIT plus gastroscopy	61 (92.4)	16 (100)	689	2628	42,050
FIT guided endoscopy	51 (77.3)	16 (100)	663	2112	33,799
Sequential FIT guided endoscopy	61 (92.4)	16 (100)	948	3580	57,824

Bidirectional study: gastroduodenal endoscopy and colonoscopy; FIT-gastroscopy strategy: GDE and FIT, colonoscopy if f-Hb ≥ 15 μg Hb/g faeces; Simple FIT-strategy: GDE if f-Hb < 15 μg Hb/g faeces, colonoscopy if f-Hb ≥ 15 μg Hb/g faeces; Sequential FIT-strategy: GDE if f-Hb < 15 μg Hb/g faeces, if not lesion detected colonoscopy; colonoscopy if f-Hb ≥ 15 μg Hb/g faeces, if not lesion detected gastroduodenal endoscopy. FIT, faecal immunochemical test; SL, significant lesion; f-Hb, faecal haemoglobin concentration.

patient with duodenal cancer was diagnosed with an SUL (duodenal ulcer without histology) and had presented a normal colonoscopy result at baseline. The last patient was diagnosed with lung cancer during follow-up. This patient was diagnosed with an SBL (colonic angiodysplasia) and not an SUL at the beginning of the study. No CRC was detected at 12 months of follow-up. Among the 120 individuals diagnosed with IDA, there were nine deaths over follow-up, representing a mortality rate of 8.3%. The causes of death were CRC in one patient, a gastroduodenal cancer in five others, lung cancer in two individuals and cardiogenic shock in one case.

Discussion

Our study shows that the FIT can be a useful tool in the diagnostic work-up of IDA by helping physicians to select the most appropriate exploration procedure (GDE or colonoscopy). This approach may be more efficient that the standard bidirectional endoscopic study proposed by clinical guidelines for diagnosing IDA with a high suspicion of a GI cause (men and postmenopausal women).

There are many studies addressing the use of the FIT in the assessment of symptomatic patients. The recently updated NICE CRC guidelines considered a positive FIT as a criterion for urgent referral in adult patients and recommends tests for occult blood in faeces for cases without rectal bleeding but with unexplained symptoms that do not meet the criteria for a suspected cancer pathway referral in the recommendations [8].

To the best of our knowledge, there are no studies that evaluate the role of FIT in the study of IDA. FIT measures the concentration of f-Hb originating from the colon or rectum but not blood loss from upper GI lesions [15–17]. Accordingly, a diagnostic strategy based on the FIT in IDA patients can identify the most likely localization of blood loss (upper GI tract or colon and rectum) and select the most adequate endoscopic study.

For our research study, an FIT, a GDE and a colonoscopy were performed on all patients in order to detect an SUL, an SBL and GI cancer. We detected an SUL and an SBL in 35.0% and 26.7% of patients, respectively. Regarding cancer diagnoses, we identified EGDC and CRC in 5.8% and 7.5% of patients, respectively, which is in line with previous studies [5, 19, 20]. Information

on the coexistence of lesions in the upper and lower GI tract in patients with IDA is scant. In our population this occurred in 3.3% of patients, which is in line with the previous findings [3]. During the 12-month follow-up, two additional cases of upper GI cancers were detected, a gastric adenocarcinoma and a duodenal carcinoma, but no further CRCs.

The first theoretical evaluated strategy was the FIT plus gastroscopy strategy which involves performing a GDE and an FIT. In this approach, colonoscopy is only considered when f-Hb is ≥15 μg Hb/g faeces. This approach detected 92.4% of the significant lesions and 100% of GI cancers while avoiding 71.6% of the colonoscopies that would have been performed following the conventional approach. Furthermore, this strategy results in a cost per significant lesion (including cancer) detected of approximately half that of a conventional bidirectional endoscopy (Table 4). In our series, the undetected lesions with this strategy would have been three patients with advanced adenoma and two patients with NSAID-induced colitis (Table 5).

The next evaluated strategy was the FIT guided strategy which involves the initial performance of an FIT. With this approach, if f-Hb ≥ 15 μg Hb/g faeces, colonoscopy is considered as the only examination. If f-Hb ≤ 15 μg Hb/g faeces, gastroscopy is considered as the only procedure. This strategy provides the highest savings in relation to a bidirectional endoscopic study while detecting 100% of individuals with cancer. Nevertheless, 23.8% of significant lesions would be missed. The undetected lesions would be three patients with advanced adenoma, two patients with NSAID-induced colitis, five patients with vascular lesions and five patients with erosive mucosal disease.

The final evaluated strategy was a sequential FIT guided strategy. This approach involves the initial performance of an FIT. If f-Hb ≥ 15 μg Hb/g faeces, colonoscopy is considered as the first examination. If SBL is not detected, GDE is subsequently performed. If f-Hb ≤ 15 μg Hb/g faeces, GDE is considered as the first examination. If SUL is not detected, colonoscopy is subsequently performed. The sequential FIT guided strategy detects 92.4% of the significant lesions, which is similar to the FIT plus gastroscopy strategy, but at the expense of a higher number of explorations. The undetected lesions would be in two patients with upper vascular lesions and in two patients with upper erosive mucosal disease. An argument in favour of this strategy is the detection of all cases of colonic advanced adenoma while avoiding 26.6% of colonoscopies.

It is important to point out that all of the possible evaluated strategies detected 100% of the individuals with cancer. Given our results, we consider that a cost-efficient strategy for the study of IDA is the FIT plus gastroscopy strategy. This approach detects most of the lesions and all the GI cancers at half the cost of a conventional bidirectional endoscopy by preventing the performance of two-thirds of colonoscopies. However, the risk of the non-detection of a colonic adenoma must be taken into account. This risk can be minimized by adopting a low threshold for the FIT. Furthermore, patients who avoid colonoscopy can be encouraged to participate in CRC screening programmes when available. On the other hand, the sequential FIT guided endoscopy detects 92.4% of the significant lesions, including all cases of adenoma advanced while saving the 21.4% of the cost in comparison with bidirectional endoscopy study.

The strengths of this study include its prospective design, which allowed for the inclusion of a "real life" homogenous population of patients with IDA referred to an endoscopy unit for a complete and rigorous endoscopic

Table 5: Diagnose of causes of IDA according to FIT based strategies.

	SUL detected, n (%)	Upper GI cancer, n (%)	SBL detected, n (%)	CRC, n (%)	Undiagnosed lesion, n (%)	Type undiagnosed lesion, n
Number of lesions	42 (100)	7 (100)	23 (100)	9 (100)	–	
FIT gastroscopy	42 (100)	7 (100)	19 (82.6)	9 (100)	4 (6.1)	Colonic advanced adenoma, 3 Colitis induced by NSAIDs, 1
Simple FIT	32 (76.2)	7 (100)	19 (82.6)	9 (100)	14 (21.5)	EGD vascular lesion, 5 EGD disruption of the mucosa, 5 Colonic advanced adenoma, 3 Colitis induced by NSAIDs, 1
Sequential FIT	38 (90.4)	7 (100)	23 (100)	9 (100)	4 (6.1)	EGD vascular lesion, 2 EGD disruption of the mucosa, 2

SUL, significant upper lesion; GI, gastrointestinal lesion; SBL, significant bowel lesion; CRC, colorectal cancer; FIT, faecal immunochemical tests; NSAIDs, non-steroidal anti-inflammatory drugs; EGD, esophagogastroduodenal.

evaluation. The vast majority of previous IDA studies were retrospective and included premenopausal women for whom the main cause of IDA was gynaecological. In addition, in these studies the endoscopic information was often partial and not available for all patients. To the best of our knowledge, this is the first study that evaluates the role of the FIT in the assessment of IDA patients. The FIT is reproducible, easily available, affordable, user friendly and the result can be obtained in 24 h and can therefore be implemented easily in clinical practice and prevent unnecessary endoscopies. Furthermore, the design of the study with a 1-year follow-up period allowed for the identification of lesions that would be potentially missed in an initial endoscopic study and to assess the possible limitations of strategies other than a bidirectional endoscopic study.

Our study presents several limitations. Firstly, the patients were evaluated in a tertiary hospital, which may result in a selection bias. Secondly, no standardized definition of a significant lesion exists when evaluating IDA patients. We decided to define significant lesions as those that, in our opinion, were likely to be the source of IDA. Thirdly, coeliac disease was not properly evaluated. However, this limitation has no impact on the potential avoidance of colonoscopies when using an FIT-based strategy in the evaluation of IDA.

In conclusion, the quantitative FIT is an objective and accurate method for selecting the endoscopic studies to be performed in an IDA work-up. An FIT-based strategy can accurately estimate the localisation of significant lesions in patients with IDA and help the physician in the decision-making process. Furthermore, an FIT-based strategy has a higher cost-effective ratio than a bidirectional endoscopic study.

Acknowledgments: We would like to thank Esther Quilez for her administrative support, Natividad Valera for her technical support and David Bridgewater for his helpful advice and manuscript corrections.

Author contributions: LRA: study design, enrolment of patients, acquisition of data, analysis and interpretation of data, statistical analysis, drafting and revision of the manuscript; FRM: study design, enrolment of patients, analysis and interpretation of data, statistical analysis, drafting and revision of the manuscript; ARC: acquisition of data and revision of the manuscript; CA: acquisition of data and revision of the manuscript; KS: acquisition of data and revision of the manuscript; PG: acquisition of data and revision of the manuscript; GI: revision of the manuscript; BC: acquisition of data and revision of the manuscript; JG: study design, analysis and interpretation of data, statistical analysis, drafting and revision of the manuscript, and corresponding author. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: This work was supported by a grant from the Societat Catalana de Digestolologia (SCD), Catalonia, Spain and by the Instituto de Salud Carlos III, co-founded by FEDER funds – a way to build Europa – (grants PI11/01439 and PI11/01593). The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Mclean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993–2005. Public Health Nutr 2009;12:444–54.
2. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anaemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anaemia. Blood 2004;104:2263–8.
3. Goddard AF, James MW, McIntyre AS, Scott BB, British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia. Gut 2011;60:1309–16.
4. Bouri S, Martin J. Investigation of iron deficiency anaemia. Clin Med (London) 2018;18:242–44.
5. Rockey DC, Cello JP. Evaluation of the gastro-intestinal tract in patients with iron deficiency anaemia. N Engl J Med 1993;329:1691–95.
6. Coban E, Timuragaoglu A, Meriç M. Iron deficiency anaemia in the elderly: prevalence and endoscopic evaluation of the gastrointestinal tract in outpatients. Acta Haematol 2003;110:25–8.
7. Annibale B, Capurso G, Chistolini A, D'Ambra G, DiGiulio E, Monarca B, et al. Gastrointestinal causes of refractory iron deficiency anaemia in patients without gastrointestinal symptoms. Am J Med 2001;111:439–45.
8. National Institute for Health and Care Excellence. The diagnosis and management of colorectal cancer. https://www.nice.org.uk/guidance/ng12.
9. Mashlab S, Large P, Laing W, Ng O, D'Auria M, Thurston D, et al. Anaemia as a risk stratification tool for symptomatic patients referred via the two-week wait pathway for colorectal cancer. Ann R Coll Surg Engl 2018;100:350–56.
10. Rodríguez-Alonso L, Rodríguez-Moranta F, Ruiz-Cerulla A, Lobatón T, Arajol C, Binefa G, et al. An urgent referral strategy for symptomatic patients with suspected colorectal cancer based on a quantitative immunochemical fecal occult blood test. Dig Liver Dis 2015;47:797–804.

11. James MW, Chen CM, Goddard WP, Scott BB, Goddard AF. Risk factors for gastrointestinal malignancy in patients with iron-deficiency anaemia. Eur J Gastroenterol Hepatol 2005;17:1197–203.
12. Godber IM, Todd LM, Fraser CG, MacDonald LR, Younes HB. Use of a faecal immunochemical test for haemoglobin can aid in the investigation of patients with lower abdominal symptoms. Clin Chem Lab Med 2016;54:595–602.
13. Fraser CG. Faecal immunochemical tests for haemoglobin (FIT) in the assessment of patients with lower abdominal symptoms: current controversies. Gastroenterol Hepatol 2019;42:263–70.
14. Allison JE, Fraser CG, Halloran SP, Young GP. Population screening for colorectal cancer means getting FIT: the past, present, and future of colorectal cancer screening using the fecal immunochemical test for haemoglobin (FIT). Gut Liver 2014;8:117–30.
15. Telford JJ. Effectively using the fecal immunochemical test. BC Med J 2013;55:334–5.
16. Levi Z, Vilkin A, Niv Y. Esophago-gastro-duodenoscopy is not indicated in patients with positive immunochemical test and nonexplanatory colonoscopy. Eur J Gastroenterol Hepatol 2010;22:1431–34.
17. Chiang TH, Lee YC, Tu CH, Chiu HM, Wu MS. Performance of the immunochemical fecal occult blood test in predicting lesions in the lower gastrointestinal tract. Can Med Assoc J 2011;183:1474–81.
18. Cordoba R. Recomendaciones sobre el estilo de vida. Aten Primaria 2014;46(Suppl 4):16–23.
19. Ho CH, Chau WK, Hsu HC, Gau JP, You JY, Chen CC. Predictive risk factors and prevalence of malignancy in patients with iron deficiency anaemia in Taiwan. Am J Hematol 2005;78:108–12.
20. Kawasaki K, Hamamoto Y, Horibe M, Shimura K, Nakamura A, Kanai T, et al. Curative resectability of gastrointestinal cancer identified from iron deficiency anaemia. Oncol Lett 2017;14:4301–04.

Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/cclm-2019-0203).