The combination of quantitative faecal occult blood test and faecal calprotectin is a cost-effective strategy to avoid colonoscopies in symptomatic patients without relevant pathology

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Abstract

Background: Faecal occult blood test (FOBT) has demonstrated effectiveness in colorectal cancer (CRC) screening. Faecal calprotectin (FC) has proven efficient for evaluating activity in inflammatory bowel disease (IBD), but its value in CRC detection is less established. Most symptomatic patients have benign pathologies, but still undergo colonoscopy in many settings.
Aims: To evaluate the diagnostic accuracy and cost-effectiveness of the combination of FOBT plus FC in symptomatic patients.
Methods: Patients who completed colonic investigations and returned stool samples, on which FOBT and FC were performed, were recruited prospectively. CRC, advanced adenoma, IBD and angiodysplasia were considered as relevant pathologies.
Results: A total of 404 patients were included, of whom 87 (21.5%) had relevant pathologies. Sensitivity and specificity were 50.6% and 69.6% for FOBT, 78.2% and 54.4% for FC. Negative predictive value (NPV) was 90.1% for FC and 86.9% for FOBT. NPV for the combination of FOBT and FC was 94.1%, with a sensitivity and specificity of 88.5% and 50.3%. The area under ROC (receiver operator curve) (AUC) was 0.741 for FOBT, 0.736 for FC and 0.816 for the combination. The total cost for visits and procedures was €233,016 (€577/patient). Using a combination of FOBT and FC as pre-endoscopic tool allows colonoscopies to be reduced by 39.4%, reducing total costs by 20.5%.
Conclusion: The combination of FOBT and FC has a better diagnostic accuracy compared with each test alone. Performing both tests before colonoscopy is a less costly and more effective strategy, reducing unnecessary procedures and complications.

Keywords: faecal biomarkers, colonoscopy, colorectal cancer, inflammatory bowel disease, symptomatic patients, health economics

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Introduction

Colorectal cancer (CRC) is the third most common cancer in terms of incidence but second in terms of mortality worldwide.[1] The prognosis of CRC depends mainly on tumor stage at diagnosis[2]; several studies on the early identification of CRC-suspected patients have been published, and referral systems in symptomatic patients have been developed across European health systems to target early diagnosis.[3,4]

Gastrointestinal symptoms (i.e. abdominal pain, change in bowel habit, rectal bleeding), are common reasons for consultation in primary care. Most patients presenting with these symptoms have no relevant pathology[5]; however, in an effort

not to miss cancer or precancerous lesions, many of them undergo colonoscopy anyhow. As a consequence, a noteworthy proportion of colonoscopies result in benign pathologies or normal examinations[6]; still, they increase the already high burden on endoscopic units and expose patients without significant pathology to the non-negligible risk of endoscopy-related complications, estimated to be around 1.6% considering all the unplanned hospital visits within the 7 days following colonoscopy.[7] In addition, the implementation of national CRC screening programs has and will further increase the colonoscopy workload for hospital endoscopy units.[8] To counter this trend, new non-invasive strategies are urgently needed to determine which patients with gastrointestinal symptoms are more likely to present significant colorectal pathology, with the ultimate goal of minimizing the number of unnecessary colonoscopies. Some non-invasive faecal tests that are already used in clinical practice to answer other diagnostic questions, such as the faecal occult blood test (FOBT) and faecal calprotectin (FC), may be useful to reach this target.

It has already been demonstrated that the use of FOBT for CRC screening in an average risk population reduces both incidence and mortality of CRC.[9] In particular, screening for CRC also appears to be a cost-effective strategy,[10] and the reduction in mortality has been stable for over 30 years of follow up.[11,12]

FOBT has also been evaluated in symptomatic patients.[13–15] In their referral guidance for suspected cancer, the National Institute for Health and Care Excellence (NICE) lists those alarm symptoms that, if present, require the patient to be seen by a specialist within 2 weeks, with the purpose of reducing the interval between the initial consultation and diagnostic colonoscopy. In the 2015 update of this guidance, it is also recommended to perform FOBT to help referral decision in patients with unexplained symptoms not meeting the criteria for suspected cancer pathway referral.[16]

Prior to this update, in 2014, Cubiella *et al.* reported that the use of FOBT at a cut-off of 20 µg/g in a cohort of 787 symptomatic patients led to negative predictive values (NPV) equal to 97.8% and 90.8% for CRC and advanced neoplasia (CRC + advanced adenoma), respectively, FOBT being a more accurate tool for the detection of CRC than the NICE overall referral criteria in symptomatic patients.[14]

Calprotectin is a calcium- and zinc-binding protein present in the cytoplasm of neutrophil polymorphonuclear leukocytes, and also in monocytes and reactive macrophages.[17] It is eliminated intact in faeces, and it correlates with bowel inflammation; therefore, this marker has proved useful for the diagnosis and monitoring of inflammatory bowel disease (IBD) thanks to its high sensitivity and specificity, which can differentiate between IBD and functional gastrointestinal disorders.[18] The current NICE guidelines recommend FC testing for the differential diagnosis of IBS or irritable bowel syndrome in adults with recent onset lower gastrointestinal symptoms if cancer is not suspected (according to NICE guideline on IBD).[19] The value of FC for the diagnosis of CRC and adenoma in a symptomatic population is less established. In a study published in 2016, FC was analysed in 654 symptomatic patients with alarm symptoms referred because of suspected CRC (according to NICE criteria); results showed, at a cut-off of 50 µg/g, a NPV for CRC of 98.6%, and 97.2% when including polyps bigger than 10 mm.[20]

The diagnostic accuracy of the combination of both tests (FOBT+FC) has already been assessed in previous studies, where it appears that the combination does not offer better diagnostic accuracy than FOBT alone, which may depend on the population characteristics and the cut-offs chosen. Mowat *et al.* performed a study in a Scottish cohort of 755 symptomatic patients, using the combination of quantitative FOBT and FC.[21] In this latter study, the cut-off selected for FOBT was any detectable faecal hemoglobin, which maximized the NPV of FOBT for significant colonic pathology (100% for CRC, 97.8% for advanced adenoma), with a positive predictive value (PPV) for significant colonic pathology equal to 20.6%. FOBT used alone yielded superior results to both FC and the combination of the two tests in this setting. At a cut-off of 10 µg/g, three cases of CRC were undetected, but the cut-off of any detectable hemoglobin was intentionally chosen in this study in order to not miss any case of CRC. One year later, Widlak *et al.* reported that, in a cohort of 430 symptomatic patients referred with suspected CRC according to NICE criteria, when using a cut-off of any detectable faecal hemoglobin, FOBT was sufficiently sensitive to exclude CRC, and, when used in combination with FC, FC did not appear to provide any additional diagnostic information.[22]

These two studies were performed in patients referred to colonoscopy by primary care. No evidence is

available regarding the diagnostic accuracy of these biomarkers, either in patients from primary or secondary care, or in the Spanish population.

The aim of this study is to evaluate whether the combination of FOBT and FC can improve the overall diagnostic accuracy for the detection of significant colonic pathology in prospectively enrolled symptomatic patients referred to colonoscopy in the area of Zaragoza (Spain), compared with the use of each test individually; the secondary objective was to determine the potential health economic benefits associated with this strategy.

Methods

Study population and samples

This is a single-centre, prospective observational study enrolling symptomatic patients referred for diagnostic colonoscopy to the Endoscopic Unit of the Hospital Clinico Universitario Lozano Blesa (Zaragoza). Ethical approval was granted by the regional Ethics Committee – Comité de Ética de la Investigación de la Comunidad Autónoma de Aragón (CEICA) – 21/2014.

Patients aged 18 years or older, referred for colonoscopy between June 2015 and April 2017 from either primary or secondary care (gastroenterology clinic or other specialists) with a complete colonoscopy performed in the Endoscopic Unit of HCU Lozano Blesa (Zaragoza), and with a stool sample available were enrolled prospectively and consecutively into the study. Patients were contacted approximately 1 week before the colonoscopy was scheduled to be informed about the study and, if they agreed to participate, they were asked to bring a stool sample, to be collected before starting the colonic preparation. Patients were given instructions on how to collect the faecal sample in a universal faecal container and stored it refrigerated at 4°C. A written informed consent form was signed by every patient.

Patients were excluded from the study if the colonoscopy was requested for indications other than gastrointestinal symptoms (e.g. CRC screening, follow up of adenomas, polyposis, and previous diagnosed IBD), or if the stool sample returned was insufficient or unsuitable for the analysis (i.e. if the sample was stored without refrigeration or if it was collected during bowel preparation).

Endoscopy and laboratory methods

FOBT was performed using the SENTiFIT 270 FOB Gold® (Sysmex-Sentinel Ch SpA, Barcelona, Spain) test, and results were considered positive above 20 µg/g. This test, at the same cut-off, is the one currently used for the standard CRC screening program in our population. FC was analysed using the EliA™ Calprotectin 2 immunoassay (Thermo Fisher Scientific, Uppsala, Sweden), at a cut-off of 50 µg/g, which is the cut-off used in most studies conducted in symptomatic patients.[20–22] Regarding the endoscopic findings, the presence of either CRC, advanced adenoma (⩾3 adenomas, any adenoma ⩾10mm, villous component or high grade dysplasia), IBD, microscopic colitis and angiodysplasia was considered as 'relevant pathology'.[23] All diagnoses were confirmed histologically. Non-advanced adenomas were registered and included in the final analysis, but not considered as relevant pathology, as the associated risk of developing CRC is very low.[24]

Sensitivity, specificity, PPV and NPV for each faecal test and for its combination were calculated for detecting relevant pathology and each pathology separately. The area under ROC (receiver operator curve) (AUC) for relevant colonic pathology was calculated for FOBT, FC and its combination.

In the present study, all patients were tested with FOBT and FC, and also underwent a colonoscopy. However, with the goal of evaluating both diagnostic clinical effectiveness and potential cost savings, three possible non-invasive pre-endoscopic interventions were assessed: I_1, the use of FOBT alone; I_2, the use of FC alone; or I_3, the combination of both tests FOBT+FC). These interventions were compared with the 'gold standard', that is, the scenario in which all patients were diagnosed using colonoscopy alone. In the scenarios I_1–I_3, patients would undergo colonoscopy only if the pre-endoscopic test was positive; in scenario I_3 positivity in at least one of the two tests was considered as a 'positive' result.

Pharmacoeconomic analysis

A pharmacoeconomic analysis was performed, collecting prospective real-life data from every patient included in the study. These data include endoscopic diagnoses, costs of doctor visits, costs associated with colonoscopy (including sedation and procedures performed – biopsies, polypectomies, etc.), the cost of faecal non-invasive tests and costs due to
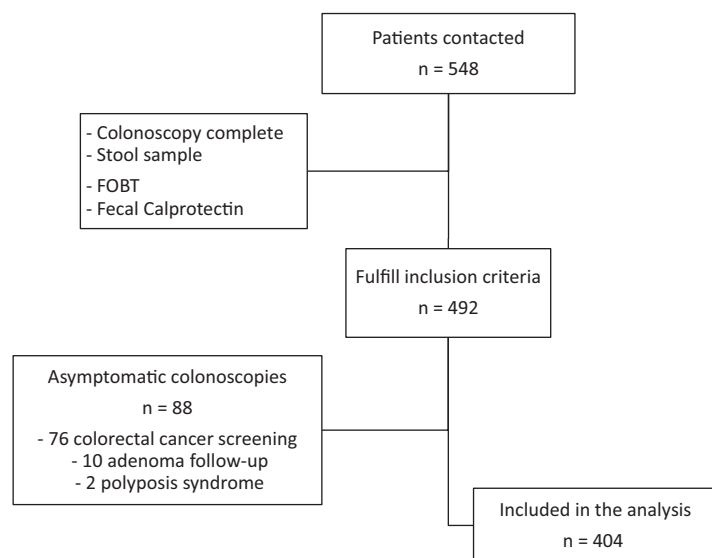
Figure 1. Flowchart of the inclusion process.
FOBT, faecal occult blood test.

colonoscopy-related complications and resource utilization (such as visits to the emergency department, days of hospitalization, visits to gastroenterology units or to primary care, eventual surgery performed)[25]; all the unit costs are summarized in Table S1 available in the supplementary material. It is worth noting here that the costs associated with the elective surgeries performed to treat the CRC cases identified in this study were not included in the economic calculations.

Both direct and indirect costs are considered in this economic assessment. The costs of clinical procedures (e.g. diagnostic tests, surgery and hospitalisation expenses, etc.) and of resource utilisation (such as doctor's visits) are direct costs, and reflect the healthcare perspective. Indirect costs refer to productivity loss and the time of sick leave from work brought about by the clinical procedures performed; the indirect cost analysis simulates the societal perspective. Table S1 lists the time of sick leave from work we assumed and used in the indirect cost analysis for the visits with healthcare practitioners, for the various diagnostic procedures and for the eventual colonoscopy-related complications.

Results

Study population and samples
A total of 548 patients were contacted, of whom 492 fulfilled the inclusion criteria. In all, 88

patients were excluded because of the indication of colonoscopy: 76 because of CRC screening, 10 for follow up of previously resected adenoma, and 2 for polyposis syndrome. This left 404 patients included in the final analysis (Figure 1).

Baseline characteristics
More than half of the patients were women (59%) with a median age of 59 years [interquartile range (IQR) 47–69 years]. 14.1% of patients were active nonsteroidal anti-inflammatory drugs (NSAIDs) users, while 9.1% of patients were taking aspirin at the time of colonoscopy. Almost half of the patients were referred for colonoscopy because of a recent history of rectal bleeding (41.2%), followed by a change in bowel habits, abdominal pain, diarrhoea and anaemia. Most colonoscopies were requested by general practitioners (60.2%). The baseline characteristics of the study population are summarized in Table 1.

Endoscopy and laboratory methods
Of the 404 colonoscopies performed, 87 (21.5%) detected significant colonic pathology, the most frequent significant colonic pathology being advanced adenoma, which occurred in 9.6% of all colonoscopies performed in this study. CCR was detected in 16 patients (3.9%).

When considered alone, FOBT (I_1) and FC (I_2) were positive in 77/404 (19%) and 213/404 (52.6%) of patients, respectively. Both tests (I_3) were negative in 169/404 (41.8%) of patients. Table 2 summarizes the results of colonoscopies and laboratory tests.

Diagnostic accuracy of faecal tests
For relevant colonic pathology, FOBT (I_1) returned a sensitivity of 50.6%, a specificity of 89.6%, a PPV of 57.1% and a NPV of 86.9%. FC (I_2) had a sensitivity of 78.2%, a specificity of 54.4%, with a PPV of 31.9% and a NPV of 90.1%. The combination of both tests (I_3), for example, positivity to at least one of the two tests, was associated with a sensitivity of 88.5%, a specificity of 50.3%, a PPV of 32.8% and a NPV of 94.1%. All these results (sensitivity, specificity, NPV and PPV) for FOBT, FC and the combination of both tests for relevant colonic pathology, as well as for each pathology

Table 1. Baseline characteristics of the study population.

Gender	Female	238 (59%)
	Male	166 (41%)
Age		59 (47–69)
Referred by	General practitioner	243 (60.2%)
	Gastroenterologist	106 (26.2%)
	General surgeon	32 (7.9%)
	Others	23 (5.7%)
Drugs	NSAIDs	57 (14.1%)
	ASA	37 (9.1%)
	Dicumarinic anticoagulant	7 (1.7%)
	Other anticoagulant	13 (3.2%)
	Other antiplatelet agent	12 (2.9%)
Indication	Rectal bleeding	166 (41.2%)
	Change in bowel habit	62 (15.3%)
	Abdominal pain	56 (13.8%)
	Chronic diarrhoea	50 (12.3%)
	Anaemia	47 (11.6%)
	Others	23 (5.7%)

ASA, acetylsalicylic acid; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2. Endoscopic findings and laboratory test results.

Endoscopic findings		Relevant colonic pathology	87 (21.5%)
		1. CRC	16 (3.9%)
		2. Advanced adenoma	39 (9.6%)
		3. IBD	23 (5.7%)
		4. Angiodysplasia	5 (1.2%)
		5. Microscopic colitis	4 (0.9%)
		No relevant colonic pathology	317 (78.4%)
		1. Non advanced adenoma	41 (10.1%)
		2. Other findings	276 (68.3%)
Laboratory tests	FOBT	Positive	77 (19%)
		Negative	327 (81%)
	FC	Positive	213 (52.6%)
		Negative	191 (47.4%)
	Combination	At least one positive	235 (58%)
		Both negatives	169 (42%)

CRC, colorectal cancer; FC, faecal calprotectin; FOBT, faecal occult blood test; IBD, inflammatory bowel disease.
Other findings: include normal colonoscopies, non-complicated diverticular diseases and haemorrhoids.

Table 3. Sensitivity, specificity, PPV and NPV of FOBT, FC and combination of both tests for relevant colonic pathology and for each pathology separately.

		FOBT	FC	Combination
Relevant colonic pathology ($n=87/404$)	Sensitivity	50.6%	78.2%	88.5%
	Specificity	89.6%	54.4%	50.3%
	PPV	57.1%	31.9%	32.8%
	NPV	86.9%	90.1%	94.1%
CRC ($n=16/404$)	Sensitivity	87.5%	75%	93.75%
	Specificity	83.7%	48.2%	43.3%
	PPV	18.2%	5.6%	6.4%
	NPV	99.4%	97.9%	99.4%
Advanced adenoma ($n=39/404$)	Sensitivity	46.15%	66.6%	82%
	Specificity	83.8%	48.8%	44.4%
	PPV	23.4%	12.2%	13.6%
	NPV	93.57%	93.2%	98.85%
Advanced neoplasia: CRC + advanced adenoma. ($n=55/404$)	Sensitivity	58.2%	69.1%	85.5%
	Specificity	87.1%	49.9%	46.1%
	PPV	41.55%	17.8%	20%
	NPV	92.9%	91.1%	95.3%
IBD ($n=23/404$)	Sensitivity	43.47%	100%	100%
	Specificity	82.41%	50.1%	44.3%
	PPV	13%	10.8%	9.8%
	NPV	96%	100%	100%
Advanced neoplasia + IBD ($n=78/404$)	Sensitivity	53.8%	78.2%	89.7%
	Specificity	89.3%	53.4%	49.4%
	PPV	54.5%	28.6%	29.8%
	NPV	89%	91.1%	95.3%
Microscopic colitis ($n=4/404$)	Sensitivity	25%	50%	50%
	Specificity	81%	47.25%	41.7%

(Continued)

Table 3. (Continued)

		FOBT	FC	Combination
	PPV	1.3%	0.9%	0.8%
	NPV	99%	98.9%	98.8%
Angiodysplasia (*n* = 5/404)	Sensitivity	20%	100%	100%
	Specificity	81%	47.8%	42.3%
	PPV	1.3%	2.3%	2.1%
	NPV	98.7%	100%	100%

CRC, colorectal cancer; FC, faecal calprotectin; FOBT, faecal occult blood test; IBD, inflammatory bowel disease; NPV, negative predictive value; PPV, positive predictive value.

separately, are summarized in Table 3, while Table 4 presents these results stratified by gender, symptoms and age.

ROC curve analysis

The AUC for relevant colonic pathology was 0.741 (95% CI 0.673–0.809) for FOBT; 0.735 (95% CI 0.677–0.794) for FC and 0.815 (95% CI 0.763–0.868) for the combination of both tests. The comparison of the AUC results showed that the combination of FOBT and FC (I_3) had a significant higher diagnostic accuracy compared with both tests separately ($p < 0.05$), while no difference was observed when the diagnostic accuracy of FOBT (I_1) and FC (I_2) were compared (Figure 2).

Pharmacoeconomic analysis

Direct costs analysis: healthcare perspective. In our cohort, the total cost for the realisation of 404 colonoscopies was €233,016, with an average of €577 per individual enrolled in the study. Figure 3a shows how the total costs are distributed; 84.4% of the cost is due to resource utilization and clinical procedures to diagnose patients, while the rest is ascribable to colonoscopy-related complications. Of the 10 patients (2.5% of the totality of individuals entering the study) who experienced colonoscopy-related complications, 5 (50.0%) had no relevant colonic pathology; hospitalisation was necessary in only 4 patients (0.99%), in 3 cases due to perforation and in the other because of abdominal pain in a patient who had been diagnosed with CRC. The other six cases reported acute abdominal pain within 7 days after colonoscopy, but did not require hospitalization or any specific treatment (four were managed in the emergency department and two in primary care settings). Surgical treatment due to colonoscopy-related complications was necessary in the three patients complicated by perforation, two of whom did not have relevant colonic pathology. We should note that these patients were older (73 and 79 years old) in comparison with the median age of our cohort, and with important comorbidities. The other case was a 24-year-old woman diagnosed with Crohn's disease colitis. These three complications accounted for €36,279 (15.6% of the total costs) because of the long hospitalisation necessary for these individuals (57 days in hospital in total). The average cost per correctly diagnosed patient is €2678.

In the simulated scenario I_1 (Table 5), the total costs associated with the use of the pre-endoscopic FOBT test alone would have been €110,078 (€273 on average per individual enrolled), colonoscopy-related complications accounting for 8.3% of the total costs (€9321, Figure 3b). In 43 patients (49.4%) with relevant colonic pathology (Figure 4a), FOBT was below the cut-off, which means that they would have remained undetected; the costs brought about by these missed patients account for 18.4% of the total FOBT costs. The average cost per patient with relevant colonic pathology correctly identified was €2502 (Figure 4). The total cost of FOBT testing was €735, which represents 0.7% of the total costs associated with this diagnostic strategy.

Table 4. Sensitivity, specificity, PPV and NPV of FOBT, FC and combination of both tests for any relevant colonic pathology (*n* = 87) stratified by symptoms, gender, and age.

			FOBT	FC	Combination
Indication	Rectal bleeding (*n* = 166)	Sensitivity	61.5%	79.5%	92.3%
		Specificity	90.5%	58.3%	54.3%
		PPV	66.7%	36.9%	38.3%
		NPV	88.5%	90.2%	95.8%
	Change in bowel habit (*n* = 62)	Sensitivity	54.5%	72.7%	90.1%
		Specificity	92.1%	49%	47.1%
		PPV	60%	23.5%	27%
		NPV	90.4%	89.3%	96%
	Abdominal pain (*n* = 56)	Sensitivity	20%	50%	60%
		Specificity	94.1%	68.6%	64.7%
		PPV	25%	11.1%	14.3%
		NPV	92.3%	94.6%	94.3%
	Chronic diarrhoea (*n* = 50)	Sensitivity	38.5%	76.9%	84.6%
		Specificity	91.9%	56.8%	54.1%
		PPV	62.5%	38.5%	39.3%
		NPV	81%	87.5%	90.1%
	Anemia (*n* = 47)	Sensitivity	41.7%	83.3%	91.7%
		Specificity	74.3%	20%	11.4%
		PPV	35.7%	26.3%	26.2%
		NPV	78.8%	77.8%	80%
	Other indications (*n* = 23)	Sensitivity	42.9%	85.7%	85.7%
		Specificity	87.5%	62.5%	56.2%
		PPV	60%	50%	46.2%
		NPV	77.8%	90.9%	90%
Gender	Female (*n* = 238)	Sensitivity	54.2%	79.2%	89.6%
		Specificity	90%	55.8%	52.1%
		PPV	57.8%	31.1%	32.1%
		NPV	88.6%	91.4%	95.2%
	Male (*n* = 166)	Sensitivity	46.2%	76.9%	87.2%
		Specificity	89%	52%	47.2%
		PPV	56.2%	33%	33.7%
		NPV	84.3%	88%	92.3%
Age	≥50 years old (*n* = 285)	Sensitivity	51.5%	75%	88.2%
		Specificity	88.5%	47.9%	44.2%

(Continued)

Table 4. (Continued)

		FOBT	FC	Combination
	PPV	58.3%	31.1%	33.1%
	NPV	85.3%	85.9%	92.3%
<50 years old (*n* = 119)	Sensitivity	47.4%	89.5%	89.5%
	Specificity	92%	68%	63%
	PPV	52.9%	34.7%	31.5%
	NPV	90.2%	97.1%	96.9%

CRC, colorectal cancer; FC, faecal calprotectin; FOBT, faecal occult blood test; IBD, inflammatory bowel disease; NPV, negative predictive value; PPV, positive predictive value.
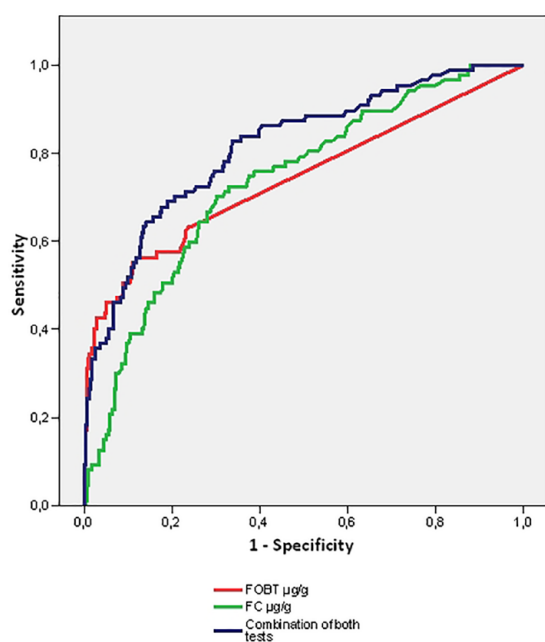
Figure 2. ROC for FOBT, FC and combination of both tests to predict relevant pathology observed during colonoscopy.
FC, faecal calprotectin; FOBT, faecal occult blood test; ROC, receiver operator curve.

The simulated use of FC alone (I_2, Figure 3c) would have cost in total €178,730 (€442 per individual entering the study, on average), €36,128 (20.2% of total costs) in complications that led to an emergency room (ER) visit, hospitalisation and, in some cases, surgery; at the threshold selected, 19 patients (21.8%) with relevant colonic pathology would have been missed, contributing to 6.6% of total costs. In I_2, the average cost per correctly identified patient is €2628. The total costs associated with the FC tests were €3030 (1.7% of total costs).

The combined simulated usage of both pre-endoscopic tests (I_3, Table 5 and Figure 3d) would have costed € 185,151 in total (€ 458 per person on average), complication costs being € 36,128 (19.5%); 10 patients (11.5%) with relevant colonic pathology would have been missed, accounting for 3.3% of total costs. The average cost per correctly diagnosed patient is €2404. The pre-endoscopic tests performed cost €3765 in total, that is 2.0% of the total costs of this diagnostic approach. Figure 4 shows that FOBT+FC is the most cost-effective pre-endoscopic intervention, as it allows for €254 savings, on average, per patient correctly identified.

Indirect costs analysis – societal perspective. Indirect costs were added to the direct costs only for the 211 individuals (52.2%) still actively working at the time they entered the study. In the simulations performed, 54 (13.4%) workers contributed to the indirect costs of the I_1 FOBT analysis, 101 (25.0%) to the I_2 FC analysis, while 110 (27.2%) I_3 to the FOBT+FC simulation. Table 5 shows that indirect costs increase the total costs by 10.7% in the colonoscopy setting, by 10.0% in the FOBT analysis, by 8.7% in the FC simulation and by 5.4% in FC+FOBT.

Discussion

Study population and samples
This study evaluates the diagnostic accuracy of two faecal non-invasive biomarkers (FOBT and FC), in symptomatic patients referred for
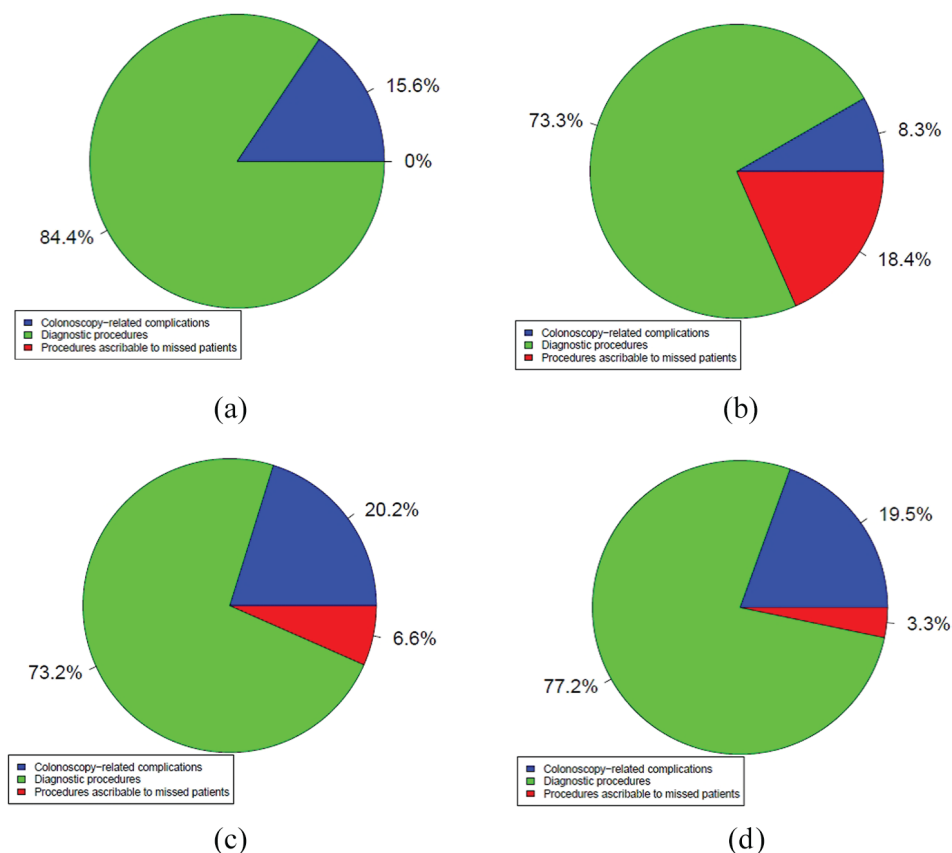
Figure 3. Total direct cost breakdown for each diagnostic strategy: in green, the costs of clinical procedures and resource utilisation needed to reach diagnosis, in blue the costs brought about by colonoscopy-related complications, and in red the costs ascribable to those patients with relevant colonic pathology that were missed in each diagnostic strategy. (a) Colonoscopy; (b) FOBT; (c) FC; (d) FOBT+FC.
FC, faecal calprotectin; FOBT, faecal occult blood test.

colonoscopy mostly from the primary care level (60.2%), but also from secondary care. This represents the major difference when comparing our results with those of other studies conducted with similar design,[21,22] in which only patients referred from primary care level were included.

Endoscopy and laboratory methods
In our study, the combination of FOBT and FC (I_3) showed better diagnostic accuracy performance compared with each test used alone (I_1–I_2). Our findings differ from the conclusions reached in other studies,[21,22] in which FOBT appeared to be superior to FC, and the combination of both tests did not appear to provide additional information. This difference can be ascribed either to differences in the origin of the population mentioned above, or, and most likely, to the cut-off values chosen (any

detectable faecal hemoglobin in the studies by Mowat *et al.*[21] and Widlak *et al.*[22] and 20 μg/g in our study).

A negative result of FOBT with the cut-off used in our study showed a NPV for CRC >99%, similar to the NPV obtained in these studies with lower cut-off, and also close to the NPV (97.9%) reported by Cubiella *et al.*,[14] using the same cut-off of 20 μg/g. It is important to highlight that, in our population, two CRC cases were not detected by FOBT used alone (I_1), and with the combination of both tests (I_3), one case still passed undetected.

The improvement in diagnostic accuracy reached with the combination of both tests lies not simply in the known capacity of FC in diagnosing inflammatory bowel disease (FOBT resulted negative in 13/23 patients, while FC
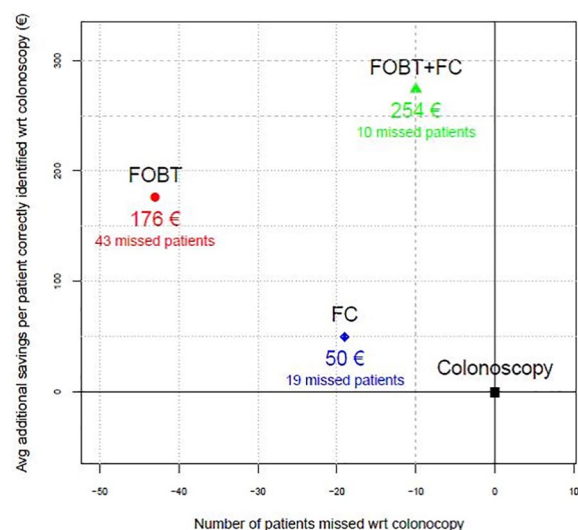
Figure 4. Cost-effectiveness results of each non-invasive diagnostic strategy compared with the direct colonoscopy approach obtained when exploring the cost per correctly identified patient with relevant colonic pathology. Thanks to its ability of correctly identifying 88.5% (77/87) of the patients with pathology, the FOBT+FC strategy (green) is associated with the highest average savings (€) per patient correctly identified (€254) compared with colonoscopy. The FOBT and FC approaches are depicted in red and in blue, respectively.
FC, faecal calprotectin; FOBT, faecal occult blood test.

correctly detected all the cases), but also in its ability to detect advanced adenomas (FOBT was negative in 21/39 patients with advanced adenoma, whereas with the combination of both tests only seven cases were not diagnosed).

The specificity of FC used alone for the diagnosis of IBD was 50.1%, which appears to be low when compared with other studies exclusively designed to differentiate between IBD and irritable bowel syndrome patients[18]; however, this figure is similar to that found in other studies conducted in non-selected symptomatic patients (the specificity was quantified as 39.3% in the study by Mowat *et al.*).[21]

However, despite the high NPV for the combination of both tests (94.1%), it should be noted that 10 patients with significant colon pathology had a negative result for both FC and FOBT. These 10 cases are summarized in Table 6. In particular, one case of CRC would potentially have been missed if relying only on the combination of the two pre-endoscopic tests. However, the patient was a woman of 55 years old who presented rectal bleeding, so colonoscopy would have been appropriately indicated according to

Table 5. Pharmacoeconomic results of the study, comparing the direct colonoscopy diagnostic strategy with the three different non-invasive pre-endoscopic interventions.

	Colonoscopy	I₁ – FOBT	I₂ – FC	I₃ – FC + FOBT
Total direct costs (% of the costs of the direct colonoscopy strategy)	€233,016	€110,078 (47.2%)	€178,730 (76.7%)	€185,151 (79.5%)
Total direct + indirect costs (% of the costs of the direct colonoscopy strategy)	€260,963	€122,391 (46.9%)	€195,720 (75.0%)	€195,720 (75.0%)
Average direct cost per patient correctly identified	€2678	€2502	€2628	€2404
Average direct + indirect cost per patient correctly identified	€3000	€2782	€2878	€2542
Number (%) of patients with relevant colonic pathology missed in each strategy	0 (0.0%)	43 (49.4%)	19 (21.8%)	10 (11.5%)
Number (%) of colonoscopies that can be avoided based on the pre-endoscopic test results	0 (0.0%)	284 (70.3%)	172 (42.6%)	159 (39.4%)
Total costs of non-invasive tests (FOBT and/or FC)	€0	€735	€3030	€3765

FC, faecal calprotectin; FOBT, faecal occult blood test.

Table 6. Patients with significant colonic pathology missed using FOBT + FC.

Patient ID	Gender	Age	Symptom	Pathology
156	Female	55	Rectal bleeding	Colorectal cancer
268	Male	57	Rectal bleeding	Advanced adenoma (villous component)
314	Female	66	Abdominal pain	Advanced adenoma (>3 adenomas)
333	Male	69	Change in bowel habit	Advanced adenoma (>3 adenomas)
372	Male	61	Rectal bleeding	Advanced adenoma (villous component)
385	Male	62	Weight loss	Advanced adenoma (>1 cm)
414	Female	72	Anemia	Advanced adenoma (>1 cm)
422	Male	80	Abdominal pain	Advanced adenoma (villous component)
453	Male	41	Diarrhoea	Microscopic colitis
477	Female	37	Diarrhoea	Microscopic colitis

FC, faecal calprotectin; FOBT, faecal occult blood test.
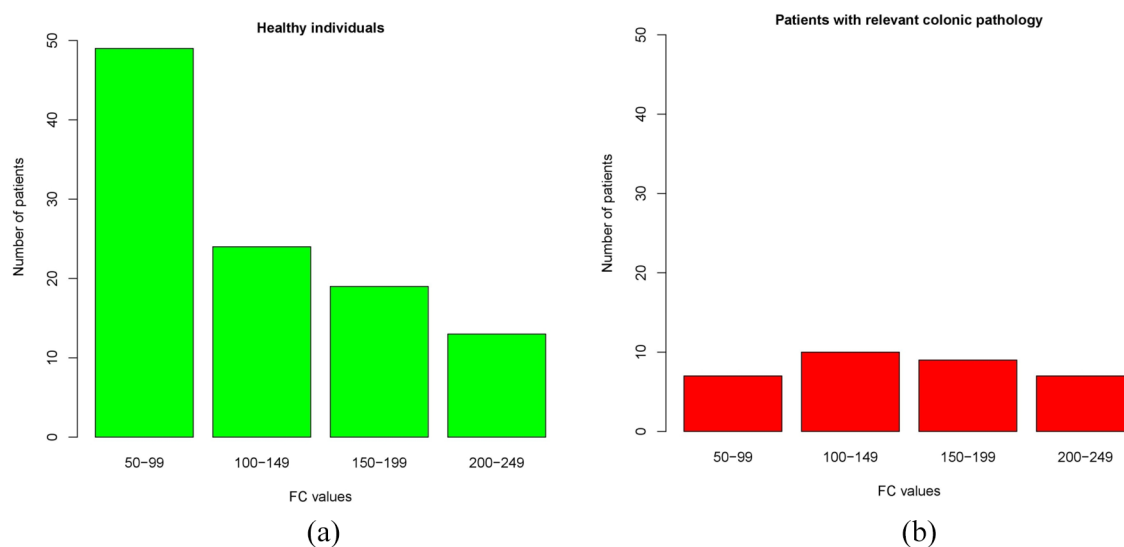
Figure 5. Distribution of patients in the different slightly positive FC ranges (50–250 µg/g). (a) Most healthy patients fall into the category 50–99 µg/g. (b) Distribution in patients with relevant pathology, with no predominance of any range.
FC, faecal calprotectin.

the NICE guidelines.[16] The NPV for the combination of both tests is higher in females (95.2%) and in younger patients (96.9% in patients younger than 50 years old, 100% when considering only advanced neoplasia + IBD).

Therefore, FOBT and FC used in combination appear to be useful markers to determine which symptomatic patients need further endoscopic examinations, but they cannot fully replace accurate clinical judgement, and colonoscopy may be

necessary even for patients in which both tests are negative. In the study reported by Widlack *et al.*,[22] 24 out of 799 patients were diagnosed with CRC (prevalence of 3%, comparable to the 3.9% prevalence found in this study), 3 were not detected by FOBT alone, and 1 case was both FOBT and FC negative; these results are similar to those found in our cohort.

The positivity rate of FOBT (19%), is lower than that found in similar studies (58.3% in the study by Mowat *et al.*). This is due mainly to the different cut-off value. However, when applying the same cut-off values, we found that the positivity rate of FC is comparable (52.6% in our study, 60% in the study by Mowat *et al.*).[21]

One might believe that performing FOBT in a patient presenting with rectal bleeding (41.2% in our population) makes no clinical sense. However, this indication is also frequent in other studies, where it is reported that, after an episode of transient rectal bleeding, FOBT can be negative in a considerable proportion of patients, due mostly to haemorrhoids. In our population, 166 patients presented with rectal bleeding, and in 127 of them no significant colonic pathology was found (76.5%, comparable to the figure reported by Mowat *et al.* – 79%).[21] Of patients presenting with rectal bleeding, 78.3% had negative FOBT, with a NPV for significant pathology in this subgroup of 88.5%. Therefore, performing FOBT in patients with previous episodes of rectal bleeding can be a useful strategy.

Another finding of this study is that nearly 80% of the colonoscopies showed no significant pathology, a result similar to that reported in most of the studies mentioned previously.[6,14,21,22] The prevalence of CRC was 3.9%, comparable to that reported in similar studies (3% reported by Widlack *et al.*, 3.7% by Mowat *et al.*).[21,22] These facts further highlight the need to find strategies to avoid these unnecessary colonoscopies. Regarding the endoscopy-related complications, 10 patients (2.5%) attended either primary care or the emergency department in the 7 days after colonoscopy due to symptoms related to this procedure; 4 required hospitalization and surgery was needed in 3 cases. These figures are comparable with those reported in other studies.[7,26]

Pharmacoeconomic analysis

Some pharmacoeconomic analyses are available in the literature on the use of FOBT for CRC screening, or on the use of FC to distinguish IBD from IBS. This is the first prospective economic analysis on the use of these markers in association to diagnose relevant colonic pathology, and this is a strength of this study.

The economic results show that the combined use of FOBT and FC is the most cost-effective of the three pre-endoscopic interventions considered, as it combined the highest savings with respect to the scenario 'direct colonoscopy' (Figure 4, €254 on average per correctly identified patient) with the lowest rate of missed patients (10). FOBT and FC used alone do not appear to be an optimal choice, as the first test misses almost half of the patients with relevant colonic pathology, while the second marker is associated with higher costs (comparing I_2 and I_3, Figure 3c). Moreover, it is worth noting here that the cost of the *in vitro* tests is negligible (2% at the most) compared with the total costs brought about by invasive methods.

Limitations

Regarding limitations, in our study, even people with a slightly positive FC test result are sent straight for colonoscopy; however, when used to rule out IBD, individuals with slightly positive FC test results (between 50 and 250 µg/g) are usually re-tested before being sent for colonoscopy, to increase cost-effectiveness.[27] In our cohort, out of the 136 individuals (33.7%) with a slightly positive result to FC, 103 did not have relevant colonic pathology, and most of them (70.9%) had a result lower than 150 µg/g (Figure 5). We could speculate that re-testing these patients with FC to decide the actual need for a colonoscopy, as has been recommended in several studies and guidelines,[28] could contribute to increasing cost-effectiveness, and that our cost savings associated with FOBT+FC may be actually underestimated. Further research is needed in this field.

Another limitation of our pharmacoeconomical analysis is that it is difficult to estimate the costs of delayed diagnosis in scenarios I_1–I_3, as in our cohort every patient underwent a colonoscopy. Most patients with both negative biomarkers and relevant pathology (Table 6) were diagnosed

with advanced adenomas. It has been reported that there is a discrepancy in the result between different FOBT samples from the same patient taken in different days, as high as 42% in patients with advanced adenoma and 25% with CRC, possibly due to the intermittent bleeding of these lesions.[29] Therefore, taking into account that the time for adenomas to progress into cancer is long, repeating both biomarkers, a procedure that is non-invasive and cheap, could be an effective strategy to avoid a delay in significant diagnosis. Prospective studies with this design are needed.

Conclusion

The use of FOBT combined with FC prior to endoscopic evaluation in symptomatic patients appears to be a useful strategy to select patients with lower risk of significant colonic pathology. As these are non-invasive tests that can be performed at the primary care level, this strategy could greatly reduce the number of unnecessary referrals to endoscopic units. According to the results of our pharmacoeconomic analysis, we can also conclude that the combination of both tests is less costly and more effective than the other diagnostic alternatives considered, allowing not only to simply avoid unneeded colonoscopies and to prioritise those with higher risk of pathology, but also to reduce the unwanted costs derived from these interventions and their potential complications.

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Conflict of interest statement

Barbara Mascialino and Carmen Andalucia are Thermo Fisher Scientific employees, manufacturer of EliA Calprotectin 2. Angel Lanas is Advisor to Sysmex Iberia (Barcelona, Spain), manufacturer of SENTiFIT 270 FOB Gold ®. The other authors have no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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