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ORIGINAL ARTICLE

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Fecal occult blood and calprotectin testing to prioritize primary care patients for colonoscopy referral: The advantage study

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Abstract

Background: Colonoscopy is the gold standard for colorectal cancer (CRC) diagnosis and screening, but endoscopy services are usually overburdened. This study aims to investigate the usefulness of fecal hemoglobin (fHb) and calprotectin (FC) for the identification of patients with high probability of CRC who need urgent referral.

Methods: In a multicenter prospective study, we enrolled symptomatic patients referred from primary care for colonoscopy. Prior to bowel preparation, fHb and FC quantitative tests were performed. The diagnostic performance was estimated for each biomarker/combination. We built a multivariable predictive model based on

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logistic regression, translated to a nomogram and a risk calculator to assist clinicians in the decision-making process.

Results: The study included 1224 patients, of whom 69 (5.6%) had CRC. At the fHb cut-offs of >0 and 10 μg/g, the negative predictive values for CRC were 98.8% (95% confidence interval 97.8%–99.3%) and 98.6% (95%CI 97.7%–99.1%), and the sensitivities were 85.5% (95%CI 75.0%–92.8%) and 79.7% (95%CI 68.3%–88.4%), respectively. When we added the cut-off of 150 μg/g of FC to both fHb thresholds, the sensitivity of fecal tests improved. In the multivariate logistic regression model, the concentration of fHb was an independent predictor for CRC; age and gender were also independently associated with CRC.

Conclusions: fHb and FC are useful as part of a triage tool to identify those symptomatic patients with high probability of CRC. This can be easily applied by physicians to prioritize high-risk patients for urgent colonoscopy.

KEYWORDS
colon cancer, colonoscopy, fecal calprotectin, fecal hemoglobin, fecal occult blood

INTRODUCTION

During the last decade, health care systems have experienced a progressive increase in the demand for diagnostic endoscopy, and colonoscopy is currently the most requested endoscopic test, which has created significant waiting lists in many endoscopy services.[1,2] One reason for this increasing demand, apart from colorectal cancer (CRC) screening programs, is the direct access to the test from Primary Care (PC), being able to refer symptomatic patients to an endoscopic examination.[3] The over-burdening of endoscopy services is a very serious problem, especially for tax-financed health systems. Several guidelines recommend preferential diagnostic colonoscopy for patients with rectal bleeding, recent bowel habit changes, iron deficiency anemia, abdominal pain associated with unexplained weight loss, or the presence of a rectal mass,[4,5] but many of these patients will not present a significant colorectal lesion because symptoms alone are poor predictors of severe underlying pathology.[6,7]

Various studies have suggested the utility of quantitative fecal immunochemical tests (FIT) for hemoglobin (Hb) to guide PC referral to colonoscopy.[8–11] Moreover, two predictive models for CRC that included FIT determination (COLONPREDICT and FAST) have been developed, demonstrating a higher diagnostic accuracy than the referral criteria from the National Institute for Health and Care Excellence (NICE) based on symptoms and signs suggestive of cancer.[12,13] An important finding derived from these studies is the negative predictive value (NPV) of FIT for detecting significant colorectal lesions, so that an NPV near to 100% practically rules out the presence of CRC.

Fecal calprotectin (FC) is the gold-standard measure of intestinal inflammation[14] and plays an important role in the diagnosis and monitoring of patients with inflammatory bowel disease.[15] Several studies have shown that patients with CRC also have a high concentration of FC.[11,16] These data suggest that FIT, together with the FC test, could be of great utility as a filter (triage) prior to diagnostic colonoscopy in patients from PC with digestive symptoms suggestive of CRC. However, well-designed prospective studies are necessary to verify whether a positive FIT and/or a positive calprotectin test is a good predictor of colorectal neoplasia and therefore an indication for preferential colonoscopy, while negative results can avoid the colonoscopy and the associated risks to the patient. Thus, the main objective of this study was to investigate the usefulness of the FIT test together with the calprotectin test, using the Sentifit® 270 analyser, to create a new PC algorithm for the identification of patients with high probability of CRC.

Key summary

Summarize the established knowledge on this subject

- Colonoscopy is the gold standard for colorectal cancer diagnosis and screening, but endoscopy services are usually overburdened.

What are the significant and/or new findings of this study?

- Fecal concentrations of hemoglobin and calprotectin, together with age and sex, may serve as part of a triage tool to identify symptomatic patients with high probability of colorectal cancer.
- This tool can be useful to prioritize high-risk patients for urgent colonoscopy and to prevent unnecessary referrals and the corresponding burden for patients and health care systems

PATIENTS AND METHODS

Study design and patients

This was a multicenter, prospective study conducted in 10 centers from Spain and Portugal. Study period was between June 2018 and March 2019. Adult patients referred from PC for colonoscopy were assessed for eligibility and included if they initially presented one or a combination of the following symptoms/signs for more than 6 weeks: rectal bleeding, bowel habit changes, iron deficiency anemia (Hb < 13 g/dl in men or < 12 g/dl in post-menopausal women or in women of childbearing age in whom gynecological causes had been ruled out, in both cases with serum ferritin <30 ng/dl), and abdominal pain associated with unexplained weight loss (considering weight loss to be >5% weight loss in 6–12 months). Patients with rectal or abdominal masses, previous colectomy, or relevant comorbidity that prevented the colonoscopy were excluded. The study was approved by the Ethical Committee of HCU Lozano Blesa and was conducted in accordance with the principles of the Declaration of Helsinki. All included participants received oral and written information and provided signed informed consent before their inclusion.

Procedures

Participants were evaluated by a nurse practitioner to verify the eligibility criteria. Once included, they were given the SENTiFIT pierce tube for sample collection, that should be collected 24–48 h before starting the bowel preparation for the colonoscopy. Each patient delivered the sample to the laboratory or Endoscopy Unit on the day of the colonoscopy. Samples were stored at 4°C (fHb) or −20°C (FC) prior to analysis to ensure stability. Fecal occult blood (FOB) and calprotectin were determined using the Sentifit® 270 Analyser. The conduction of the study did not alter the diagnosis, treatment, and follow-up of the patients, which were performed according to the usual clinical practice of each hospital. Patients with incomplete colonoscopy due to poor preparation (Boston scale less than two in any colorectal segment) repeated the procedure. Patients with incomplete colonoscopy due to any technical difficulty that impeded the exploration of the caecum were evaluated by another imaging technique (CT colonography, colonic capsule, or opaque enema).

Diagnostic devices

The SENTiFIT 270® system (Sentinel CH. SpA, Milan, Italy) is a specific automatic analyser to identify occult blood in feces with the quantitative immunological analytical method Sentifit FOB Gold Latex. The performance characteristics of this device are as follows: measurement range, 15–1000 ng/ml (2.55–170 μg/g); limit of blank, 6.0 ng/ml (1.0 μg/g); limit of detection, 10.4 ng/ml (1.8 μg/g). The sample collection device, SENTiFIT® pierceTube, only opens at one end, minimizing possible sampling errors. In turn, this device has a barcode for reading and a pierceable end for automatic analysis. The CALiaGold test is a particle-enhanced turbidimetric immunoassay for automatic quantification of fecal calprotectin in SENTiFIT 270.

Outcomes

The main diagnostic outcome was the presence of CRC. Endoscopists were blinded to the fecal test results and other diagnostic information. The diagnoses were confirmed by a gastrointestinal pathologist at each participating center.

Statistical analysis

Quantitative variables are expressed as mean ± standard deviation (SD) or as medians with interquartile range (IQR), whereas qualitative variables are described with frequencies and percentages. Comparison of characteristics between participants with and without CRC was done using student's *t* test, Fisher's exact test and Mantel-Haenszel test, as appropriate. Negative predictive value, positive predictive value, sensitivity, and specificity were estimated with their corresponding confidence intervals (95%) for the selected cut-off values of >0 and 10 μg/g for fHb and 150 μg/g for FC. We calculated the colonoscopies that could be avoided or delayed using these thresholds. We used odds ratio analysis and logistic regression method for multivariate modeling of the probability of CRC. The model was then used to make a nomogram to improve decision making and a derived risk calculator. All statistical tests were performed with two-sided 95% CI (95% CI) and 5% significance level. Statistical analyses were performed using the R version 4.0.1 and SAS version 9.4 statistical software.

RESULTS

Study population and colonoscopy findings

A total of 1224 patients referred for colonoscopy consented to participate and were included in the study. Women were predominant ($n = 685$, 55.9%) and the mean age of the cohort was 61.3 years (range, 18–92). Nearly all patients ($n = 1161$, 94.9%) got the complete exploration of the colon. The results of the colonoscopy are shown in Supplementary Table S1. A total of 69 (5.6%) patients had CRC, of whom 6 had synchronic malignancy; advanced adenomas were found in 143 patients (11.7%) and inflammatory bowel diseases in 34 patients (2.8%). As shown in Table 1, CRC was most frequent in older patients, in men, and in those with shorter duration of symptoms. None of the symptoms by itself associated with the diagnosis of CRC. Patients with CRC had a median (IQR) fHb concentration of 285.4 (20.6–942.9) μg/g versus 0.0 (0.0–3.6) μg/g in those without CRC ($p < 0.001$). FC values were 513.7 (283.0–1220.8) and 117.3 (26.5–390.8) μg/g, respectively ($p = 0.001$).

TABLE 1 Characteristics of patients with and without CRC detected during the colonoscopy.

Variable	CRC: No N = 1155	CRC: Yes N = 69	p value
Sex, males (*n*, %)	495 (42.9%)	44 (63.8%)	= 0.001
Age, years (mean, SD)	60.7 (15.2)	71.6 (12.1)	<0.001
Familial history of CRC[a] (*n*, %)			
No	981 (84.9%)	64 (92.8%)	= 0.080
Yes	174 (15.1%)	5 (7.2%)	
Number of symptoms (*n*, %)			
=1	279 (24.1%)	14 (20.3%)	= 0.562
>1	876 (75.8%)	55 (79.7%)	
History of rectal bleeding (*n*, %)			
No	700 (60.6%)	35 (50.7%)	= 0.128
Yes	455 (39.4%)	34 (49.3%)	
Bowel habit changes (*n*, %)			
No	471 (40.8%)	32 (46.4%)	= 0.379
Yes	684 (59.2%)	37 (53.6%)	
Iron deficiency anemia (*n*, %)			
No	747 (73.4%)	45 (66.2%)	= 0.205
Yes	270 (26.5%)	23 (33.8%)	
Abdominal pain (n, %)			
No	737 (63.8%)	45 (65.2%)	= 0.897
Yes	418 (36.2%)	24 (34.8%)	
Weight loss (n, %)			
No	978 (84.7%)	55 (79.7%)	= 0.304
Yes	177 (15.3%)	14 (20.3%)	
Symptom duration, weeks (median, IQR)	12.0 (8.0–24.0)	9.0 (8.0–16.0)	<0.001
fHb concentration, μg/g (median, IQR)	0.0 (0.0–3.6)	285.4 (20.6–942.9)	<0.001
fHb (μg/g)			
=0	799 (69.2%)	10 (14.5%)	<0.001
>0	356 (30.8%)	59 (85.5%)	
≤10	973 (84.2%)	14 (20.3%)	<0.001
>10	182 (15.8%)	55 (79.7%)	
FC concentration, μg/g (median, IQR)	117.3 (26.5–390.8)	513.7 (283.0–1220.8)	= 0.001
FC (μg/g)			
=0	252 (21.8%)	1 (1.4%)	<0.001
>0	903 (78.2%)	68 (98.6%)	
≤150	641 (55.5%)	9 (13.0%)	<0.001
>150	514 (44.5%)	60 (87.0%)	

Abbreviations: CRC, colorectal cancer; FC, fecal calprotectin; fHb, fecal hemoglobin; IQR, interquartile range.

[a]Family history refers to any relative with CRC.

Performance of fHb with or without FC in CRC prediction

The diagnostic accuracy of FIT for CRC at fHb cut-offs of >0 μg/g and 10 μg/g are shown in Table 2. The proportion of patients with positive FIT results at fHb cut-offs of >0 and 10 μg/g were 33.9% and 19.4%, respectively. At these cut-offs, the NPVs for CRC were 98.8% (95% CI, 97.8%–99.3%) and 98.6% (95% CI 97.7%–99.1%), and the sensitivities for CRC were 85.5% (95% CI, 75.0%–92.8%) and 79.7% (95% CI, 68.3%–88.4%), respectively. When we added the cut-off of 150 μg/g of FC to both fHb thresholds, the sensitivity of fecal tests improved, with the highest sensitivity for the cut-offs of fHb >0 μg/g or FC > 150 μg/g (Table 2). Patients with fHb or FC below these values could delay or avoid the colonoscopy, totaling almost 40% of the procedures.

Factors associated with CRC and nomogram to predict CRC probability

The variables showing significant differences in the univariate analysis were included in the multivariate logistic regression model, except for symptom duration that has a subjective component and is dependent on patients' recall (Table 3). Concentration of fHb (odds ratio per μg/g, 1.002; 95% CI, 1.001–1.002); $p < 0.001$) was an independent predictor for CRC, whereas FC did not reach significance. Age and gender were also independently associated with CRC. For a predicted probability of the event of 0.02, the sensitivity and specificity of the model were 95.7% and 37.1%, respectively (Table S2). The area under Receive operating characteristic curve (AUC) value was 0.855 (Figure 1). The nomogram derived from the model allows for CRC prediction according to fHb and FC as continuous variables (Figure S1). Based on this nomogram, we developed a freely available risk calculator which allows the users entering patients' data to predict the probability of CRC (see excel calculator in Supplemental material).

DISCUSSION

Colonoscopy remains the gold standard technique for the detection of CRC and represents the most requested endoscopic procedure, which generates significant waiting lists in endoscopy services and subsequent delays in diagnosis and treatment. Thus, there is a need to improve the suitability of referrals from PC for the investigation of symptoms suggestive of CRC, which have very low positive predictive values.[7,17] In this prospective study, we attempted to find a simplified approach to identify symptomatic patients needing immediate colonoscopy based on fecal concentrations of Hb (by FIT) and calprotectin, determined by the automatic Sentifit® 270 analyser. The utility of FIT for this purpose has already been investigated using different fHb cut-off values,[18–20] and it has demonstrated fairly good accuracy for identifying CRC. However, for the use of FIT as a rule-out test in PC, it is important to find the optimal cut-off level so as to prevent unnecessary referrals while avoiding missing cases of CRC, and the combination with other lab tests may increase the predictive power of FIT. Here, we found that adding the cut-off of 150 μg/g of FC to the fHb determination (either fHb >0 or ≥10 μg/g) improved the diagnostic accuracy and reduced the number of false negative cases (NPV 99.6% and 99.5%, respectively). This FC concentration is somewhat high compared with the cut-off of >50 μg FC/g feces used in previous studies,[11,16] but the high NPV achieved combining the two biomarkers provides reassurance, and the clinician can be confident that the patient is very unlikely to have CRC if fHb and FC are below the thresholds. Even more, only one of the 69 patients with confirmed CRC in our study had no FC detected (Table 1), which may suggest that the absence of FC in stool is incompatible with the presence of CRC.

Apart from fHb and FC concentrations, the logistic regression method identified male gender and increasing age to be independent predictors of CRC. These risk factors are consistent with the findings of other multivariate analyses in symptomatic and asymptomatic populations.[13,21,22] These variables can be combined in a score that could help the physician in the decision-making process when evaluating patients with lower bowel symptoms.[10,13,23] Thus, we

TABLE 3 Multiple logistic regression predicting the probability of CRC.

Variable	Odds ratio (CI 95%)	*p* value
fHb (μg/g)	1.002 (1.001–1.002)	<0.001
FC (μg/g)	1.000 (1.000–1.000)	=0.292
Age (year)	1.065 (1.040–1.091	<0.001
Sex (female: Male)	0.523 (0.303–0.904)	=0.020

Abbreviations: CI, confidence interval; CRC, colorectal cancer; FC, fecal calprotectin; fHb, fecal hemoglobin.

TABLE 2 Diagnostic accuracy of the selected cut-offs of fHb and FC for CRC.

Cut-off	Positivity, n/N (%)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV	NPV	Saving in colonoscopies (%)
fHb > 0 μg/g	415/1224 (33.9)	85.5 (75.0–92.8)	69.2 (66–71.8)	14.2	98.8	66.1
fHb ≥ 10 μg/g	237/1224 (19.4)	79.7 (68.3–88.4)	84.2 (82.0–86.3)	23.2	98.6	80.6
fHb > 0 or FC > 150 μg/g	735/1224 (60.0)	97.1 (89.9–99.6)	41.7 (38.8–44.6)	9.1	99.6	39.9
fHb ≥ 10 or FC > 150 μg/g	652/1224 (53.3)	95.6 (87.8–99.1)	49.3 (46.3–52.2)	10.1	99.5	47.7

Abbreviations: CRC, colorectal cancer; FC, fecal calprotectin; fHb, fecal hemoglobin; NPV, negative predictive value; PPV, positive predictive value.

generated a simple nomogram and the corresponding Excel, Microsoft calculator, which allow the stratification of patients according to their foreseeable risk of CRC. This approach is thought to have better accuracy than both risk grouping systems and physician judgment when facing a diagnostic clinical problem.[24] In our population, using this decision tool to prioritize the colonoscopy for patients with high probability of CRC, a substantial proportion of the procedures would be delayed or avoided. With less referrals to colonoscopy, fast-track referrals may be seen more quickly, and the waiting list could be reduced. Apart from the significant cost savings that this strategy would produce, many patients could avoid the inconvenience and discomfort of bowel preparation and the non-negligible potential complications associated with colonoscopy, such as bleeding and bowel perforation.[25,26]

Although many patients considered to have high probabilities of CRC according to the nomogram did not have cancer (the overall CRC rate was 5.6%), many of them had another significant bowel disease, such as precancerous polyps and advanced adenomas. Although these were not included in the outcome of the study, the detection of these lesions would confer an additional benefit because their removal alters the natural history of the neoplasm and may hamper cancer development.[27,28] Additionally, it is possible that a patient with low likelihood of CRC (according to the nomogram) still had CRC or other significant bowel disease, so vigilance at the PC setting is crucial for patients with high and low probability of CRC with persisting symptoms, and a new stool test could be done for reassurance. We interpret the results of the current study as favoring the nomogram as an integral part of the colorectal referral pathway. The need to prioritize the high-risk patients for colonoscopy is justified because delays in reaching a CRC diagnosis is associated with worse prognosis.[29,30]

One strength of the current study is the use of the same method for collecting and quantifying fHb and FC, which minimizes the effect of post-collection variables and diverse detection thresholds and analytic sensitivities of different brands of FIT. However, this strength is also a limitation because our ruling out cut-offs and nomogram are based on the fecal testing derived from the Sentifit® 270 analyser; therefore, in clinical settings where other assays are used, these thresholds may change. Another strength is the large number of patients enrolled, and the elevated proportion of them with the complete exploration of the colon achieved, which determines confidence in the results of the study.

In conclusion, the proposed nomogram and the easy-to-use calculator show great promise as a triage tool to identify those zsymptomatic patients with high probability of CRC diagnosis. If further validated, it can be easily applied by PC physicians to prioritize high-risk patients for urgent colonoscopy, who will benefit most from limited endoscopy services. Moreover, the ruling out strategy

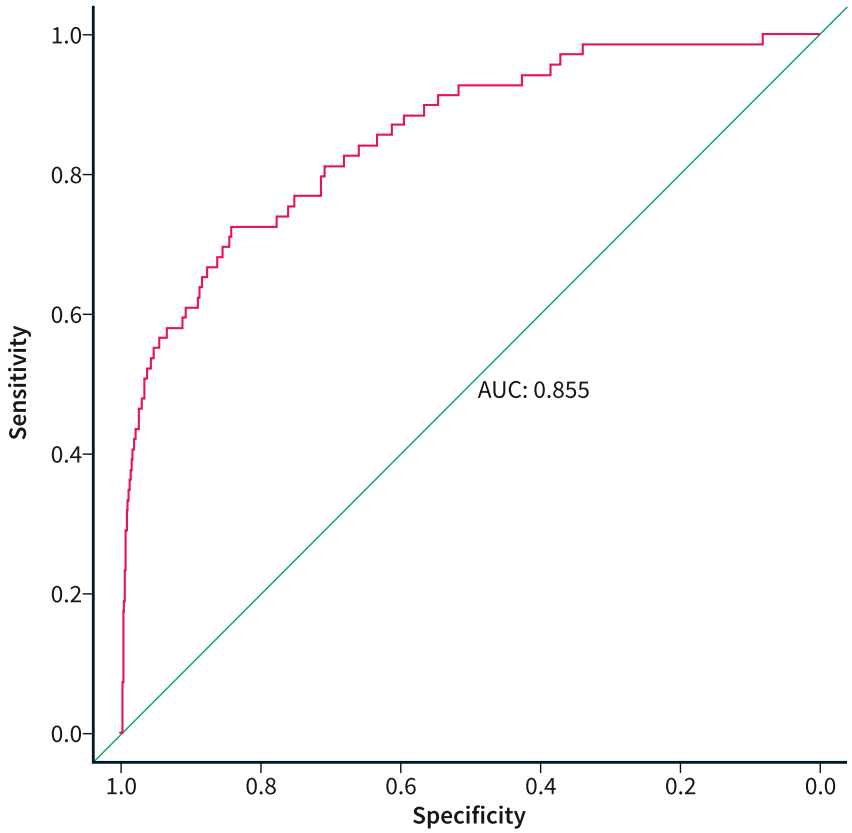

FIGURE 1 Receive operating characteristic (ROC) plot for the formulated nomogram predicting CRC. CRC, colorectal cancer.

could prevent unnecessary referrals and the corresponding burden for patients and health care systems.

AUTHOR CONTRIBUTIONS

This study was designed, provided conceptually, directed, and coordinated by Balaguer F, Lanas A and Quintero E. The data were collected and analyzed by all authors. The manuscript was commented on by all authors.

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CONFLICT OF INTEREST STATEMENT

FB received endoscopic equipment on loan of Fujifilm, received an honorarium for consultancy from Sysmex (2017–2020) and CPP-FAP (2018), speaker's fee from Norgine Iberia, and editorial fee from Elsevier as editor of Gastroenterologia y Hepatologia. EQ and AL received an honorarium for consultancy from Sysmex (2017–2020). The other authors declare no conflict of interest regarding this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

ETHICS APPROVAL

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethical Committee of HCU Lozano Blesa. All patients provided signed informed consent for the study.

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