ORIGINAL ARTICLE

Identifying the best cutoff value of the fecal occult blood immunochemical test in the detection of advanced and neoplastic colorectal lesions

Identificación del mejor punto de corte de la prueba inmunoquímica de sangre oculta en heces en la detección de lesiones colorrectales avanzadas y neoplásicas

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Abstract

Objective: *Screening is an effective tool for detecting colorectal lesions in asymptomatic subjects. There is a positive correlation between fecal immunochemical test (FIT) values and the size of tumors. Despite the efficacy of screening, the detection of colorectal cancer (CRC) remains low. The primary objective was to evaluate the best FIT cutoff value for detecting advanced adenomas and CRC among individuals at average risk in a country with a high incidence and morbidity from CRC.* **Methods:** *This observational and prospective study analyzed consecutive cases in 1461 asymptomatic subjects with a positive FIT (≥ 100 ng hemoglobin [Hb]/mL) referred for colonoscopy (2012-2015) at a tertiary center in Uruguay.* **Results:** *Colorectal lesions were detected in 35.3% (516/1461) of cases, with a mean age of 62.8 ± 8.3 years. About 53.2% were men and 65.1% of the tumors were located in the left side of the colon. The size of the lesion and FIT values (p = 0.001) were positively correlated. Laterally spreading tumors predominated in the right colon (586 ng Hb/mL; 95% Confidence interval [CI] 443.4-760). One hundred and thirty-five (26%) lesions were advanced adenomas (15 ± 6.7 mm); 694.6 ng/mL; 95% CI 632.4-756.9). The highest diagnostic yield (0.5112) for advanced adenomas was at a FIT level of 400 ng Hb/mL (accuracy 88.6%). There were significant differences in FIT values early and advanced CRC (927 ng/mL; [95% CI: 637-1082] vs. 1453 [95% CI: 1352-1594; p = 0.001]).* **Conclusions:** *A FIT value of 400 ng Hb/mL was the best diagnostic yield to detect advanced adenomas and CRC. This value is useful during the COVID-19 pandemic as it allows prioritization of colonoscopy to those most at risk of significant disease, thus reducing risks to both patients and healthcare workers.*

Keywords: *FIT. Fecal occult blood immunochemical test. Advanced adenomas. Colorectal cancer.*

Resumen

Objetivo: *El cribado es una herramienta eficaz para detectar lesiones colorrectales en sujetos asintomáticos. Existe una correlación positiva entre los valores de la prueba inmunoquímica fecal (FIT) y el tamaño de los tumores. A pesar de la eficacia del cribado, la detección del cáncer colorrectal (CCR) sigue siendo baja. El objetivo principal fue evaluar el mejor valor de corte FIT para detectar adenomas avanzados y CCR entre personas con riesgo promedio en un país con alta incidencia y morbilidad por CCR.* **Métodos:** *Este estudio observacional y prospectivo analizó 1461 sujetos asintomáticos con FIT positivo (≥ 100 ng de hemoglobina [Hb]/mL) remitidos para colonoscopia (2012-2015) en un centro terciario en Uruguay.* **Resultados:** *Se detec-*

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taron lesiones colorrectales en el 35.3% (516/1461) de los casos, con una edad media de 62.8 ± 8.3 años. Alrededor del 53.2% eran hombres y el 65.1% de los tumores estaban ubicados en el lado izquierdo del colon. El tamaño de la lesión y los valores FIT (p = 0.001) se correlacionaron positivamente. Los tumores con extensión lateral predominaron en el colon derecho (586 ng Hb/mL; intervalo de confianza [IC] del 95%: 443.4-760). Ciento treinta y cinco (26%) lesiones fueron adenomas avanzados (15 ± 6.7 mm); 694.6 ng/ml; IC 95% 632.4-756.9). El rendimiento diagnóstico más alto (0.5112) para los adenomas avanzados se obtuvo con un nivel FIT de 400 ng Hb/ml (precisión del 88.6%). Hubo diferencias significativas en los valores de FIT de CCR temprano y avanzado (927 ng/mL; [IC 95%: 637-1082] vs. 1453 [IC 95%: 1352-1594; p = 0.001]). **Conclusiones:** *Un valor FIT de 400 ng Hb/mL fue el mejor rendimiento diagnóstico para detectar adenomas avanzados y CCR. Este valor es útil durante la pandemia de COVID-19, ya que permite priorizar la colonoscopia a aquellos con mayor riesgo de padecer una enfermedad importante, reduciendo así los riesgos tanto para los pacientes como para los trabajadores de la salud.*

Palabras clave**:** *Prueba inmunoquímica de sangre oculta en heces. Adenomas avanzados. Cáncer colorrectal.*

Introduction

The incidence and mortality of cancer have increased in lower-income countries. This is likely due to epidemiological and demographic transition (aging and population growth) as well as exposure to risk factors such (alcohol and smoking).[1] In 2018, the number of new cases detected was 18.1 million with, 9.6 million cancer-related deaths. The incidence in the United States of America (USA) was 21% with a mortality of 14.4%.[2-4] The organs most commonly involved in Central and South America were as follows: prostate, lung, colon, and rectum colorectal cancer (CRC) and stomach in men, and breast, cervix/uterus, CRC, and lung in women. In 2018, the overall incidence and mortality reported were 10.2% and 9.2%, respectively, for both men and women.[2]

Cancer incidence has increased in Central/South America and Eastern Europe but is decreasing in developed countries such as the USA, Canada, Australia, New Zealand, and the rest of Europe).[2] The incidence rates among men and women in Latin America were 10.3 and 16.8, respectively. Incidence in the countries with the highest rates was as follows: Uruguay (34.2 men and 24.7 women), Brazil (27.7 and 21.5), and Argentina (25.2 in men).

Mortality is extremely high in Central (8-9 fold) and South America (3-5 fold) when compared to Europe and USA[5]. Although it has generally been reported as being < 10, mortality is high in Uruguay (17.7 among men and 12.0 among women), Cuba (11.3 women), and Argentina (14.6 men).[6,7]

Uruguay and Argentina have implemented national programs for the early detection of CRC.[7-10] Detailed knowledge of the natural history of cancer development (the adenoma-carcinoma sequence) allows for early detection at the subclinical stage and appropriate therapeutic intervention.[11]

In sporadic CRC, the tiered non-linear accumulation of genetic and chromosomal alterations occurs in approximately 7-10 years;[11,12], but this time period is shorter for hereditary CRC.

CRC is a common public health problem (5% incidence). Screening is effective when the appropriate population is targeted. Endoscopic removal of adenomas reduces the incidence of CRC (76%) and its mortality (53%).[13-15] Although colonoscopy is the most commonly used method for detecting adenomas and CRC, it is not the most cost-effective tool.[16,17] Screening programs have been implemented in the WHO population programs.[18,19]

The fecal occult blood (FOB) or fecal immunochemical test (FIT) is currently the best screening method[20]. FIT accurately detects globin component of hemoglobin (Hb) to the nearest nanogram (ng) per milliliter (mL) of feces using immunoassay. Colonoscopy is indicated when the patients' FIT values are ≥ 100 ng Hb/mL, due to the high sensitivity of detecting disease.[16,21,22]

For adequate population screening, FIT positivity rates should range around 3-6%.[21-25] In the case of CRC, sensitivity (Sn), specificity (Sp), positive predictive values, and negative predictive values (NPV) of FIT were reported as 100%, 90%, 16%, and 100%, respectively; and 74%, 93%, 45%, and 98%, respectively, for all neoplasms. FIT detects virtually all CRCs and 74% of significant colorectal lesions.[26]

Screening should be started at the age of 50 and be suspended either at 75 years of age or when the patient is expected to live < 10 years. Between 75 and 85 years, the risk to benefit ratio should be individualized. There is no benefit beyond the age of 85.[11] In the US, screening is opportunistic, unlike other

countries where it is more systematic and organized to cover more of the population.

The primary objective was to evaluate the best FIT cutoff value for detecting advanced adenomas and malignancies among individuals at average risk in a country with a high incidence and morbidity from CRC.

Methods

Consecutive patients with an average risk of CRC and a positive FIT (> 100 ng Hb/mL) scheduled for a colonoscopy at the Centre for Digestive Cancer of the National Cancer Institute of Montevideo, Uruguay, were recruited. All individuals provided written consent and this study followed the standards for reporting diagnostic accuracy. This cross-sectional, prospective, observational, and single-center study was carried out between 2012 and 2015. The study is part of the systematic program for the prevention and early detection of CRC under the Ministry of Health of Uruguay.

Selection criteria

- Inclusion: asymptomatic individuals, over 50 years of age, positive FIT (> 100 ngHb/mL), and informed written consent.
- Exclusion: personal or family history of CRC, digestive bleeding, colorectal resective surgery, inflammatory bowel disease and/or red flag signs (weight loss, anemia, and abdominal masses), and incomplete examination due to poor bowel cleansing.

Mass media campaign (television, radio, and press) were used to invite the population to participate in the national CRC screening program. The process for collecting samples, storing at –10°C, and returning it within 5 days was explained to each patient. There were no restrictions on diet or medication.

Patients with positive FIT results were scheduled for a colonoscopy within 8 weeks, which was performed after informed consent and after bowel preparation. The quality of FIT measurements was ensured through daily calibration and external validation using samples supplied by the manufacturer every 6 months. The colonoscopies were performed by three experienced endoscopists with a minimal total experience of 3000 colonoscopies. The cold technique was typically used to remove lesions < 5 mm and endoscopic mucosal resection to remove larger ones.

Clinical and demographic data were recorded, including age, sex, FIT values (ng Hb/mL), presence of colorectal lesions (type – Paris classification –, size and location; in addition to laterally spreading tumors (LST) > 10 mm), and histological types (subtypes and degree of dysplasia/differentiation).

The adenomas were classified as advanced or not advanced. Early CRC did not extend beyond the submucosa (Tis-T1); for invasive, CRC malignant cells were observed in the *muscularis propria* or beyond. The size of the polyps was defined *ex vivo* after resection and before fixation with 10% formaldehyde.

Definition of variables

- Subjects at average risk of CRC: Asymptomatic adult individuals over 50 years of age, with no personal/family history of CRC and/or adenomas or inflammatory bowel disease[7].
- Advanced adenomas: Adenomas ≥ 10 mm and/or with villous component ≥ 25% and/or high-grade dysplasia. Non-advanced adenoma: 1-2 adenomas each < 10 mm in size.[7]
- (FIT-OC-Eiken [Eiken Chemical Co., Eiken, Japan]) was used during this study. The reported sensitivity and specificity was 96-98% and 91-95%, respectively.[27,28] The detection range was between 0 and 2000 ng Hb/mL of buffer, which enabled the cutoff point to be set for a positive result. The cutoff point was 100 ng Hb/mL as recommended by the manufacturers.[14]

Statistical analysis

The data were captured in a Lotus Approach v. 9.7 Windows database and included age, sex, topography, size, histopathological diagnosis, and FIT quantification. To evaluate the differences between independent samples, Chi-squared tests and the exact Fisher's test were used for categorical variables and Student's t-test was applied for quantitative variables, with a significance level of 0.05. One-way analyses of variance and covariance were used to adjust the contrast between lesions in terms of age, sex, and positive findings of colorectal lesions. A hyperbolic function was calculated for two parameters.

The Sn, Sp, PPV, NPV, and accuracy of different FIT cutoff points were calculated, and the ROC curve plotted ($y = 0.5 \text{ Ln } (x) + 1$ Area Under the Curve × 0.5112) for the best FIT cutoff point in the detection of advanced adenoma. SPSS v. 17.0 and Epi Info v. 3.3.2.0 as statistical software were used.

Table 1. Type of colorectal lesions detected through colonoscopy in asymptomatic individuals

Paris classification	Type of colorectal polyps detected in 516 colonoscopies				
	A Pedunculated Polyp (Ip)	B Semi-pedunculated polyp (Isp)	C Sessile Polyp (Is)	D Lateral spreading tumor	p
Number of lesions	142	114	248	12	-
Age (years)					
Average	62.1	62,8	62.4	65.5	0.5
SD	88	8.2	8.1	8.3	
95% CI	60.6-63.6	61.1-64.5	61.3-63.5	60.8-70.3	
Size (mm)					0.001
Average	12.9	8.6	5.6	14.8	
SD	6.2	5.4	4.3	9.5	
IC95%	11.9-13.1	7.4-9.7	5.0-6.3	12.1-17.5	
FIT (ng Hb/mL)					0.001
Average	631.3[a]	452.1[b]	401.4[c]	779.2[d]	
SD	484	407	368	525	
IC95%	537.6-705	366.2-558	348.7-454.5	544-1614	

The letters (a, b, c or d) show the statistically significant differences between the groups, where the letter a differs from the other groups (b, c or d). Example: a = a, but a ≠ b or c or d.
FIT: fecal occult blood immunochemical test; SD: standard deviation; 95% CI: confidence interval 95%.

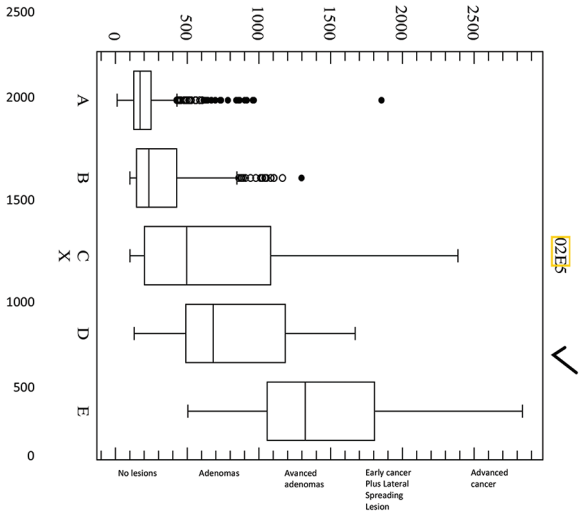

Figure 1. *Differences between FIT levels and the type of colorectal lesion.*

Results

The study included 1461 colonoscopies of subjects with average cancer risk and with FIT values ≥ 100 ng. Complete FIT and colonoscopy outcomes were available for 1461 patients who met the inclusion criteria for the final analysis.

No colorectal lesions (advanced adenomas/adenomas/early CRC or advanced CRC) were detected in 945 cases (64.6%). The average age of those subjects was 61 ± 9 years (55% men) and their average FIT was 317 ± 180 (95% CI 295.9-338.5). No visible lesions were found in 485 (237 ± 140 ng; 95% CI 21.3-270.7). Median FITs were 237, 370, 382, and 188 for diverticulitis (n = 396), angiodysplasias (n = 36), non-specific rectocolitis (n = 10), and colonic ulcers (n = 7), respectively. Other findings included three cases of pinworm (*Enterobius vermicularis*), two submucosal lesions, and two cases of chronic idiopathic ulcerative colitis.

Colorectal lesions were detected in 516 cases (35.3%). About 25.7% of the patients presented with > 2 lesions. For the purpose of FIT value analysis, the largest lesion was used. The average age was 62.8 ± 8.3 years and 53.2% were male. Majority of lesions were located in the left colon (336, 65.1%)) and with 180 (34.9%) in the right colon. The morphological Paris classification of lesions is described in table 1. There was a statistical difference between lesion types and FIT levels (p = 0.0001) and also size (p = 0.001). Figure 1 demonstrates differences between FIT levels and lesion type.

The most common lesions confirmed by histology were tubular adenoma (n = 167), tubulovillous adenoma (n = 104), hyperplastic (n = 63), advanced CRC (n = 54) villous adenoma (n = 38), early CRC (n = 17), and serrated adenomas.[12] Lesion size and FIT levels were positively correlated (p = 0.001), see table 2. Patient's age did not correlate with FIT levels. There was no significant difference between FIT value and LST or early CRC size.

Table 2. Colorectal lesions and FIT levels

Lesions	FIT Levels (ng Hb/mL)								
	100-200	201-300	301-400	401-500	501-600	601-700	701-800	> 801	p
Number	169	62	45	24	18	21	28	149	
Average size (mm) (SD)	6.37 (3.3)	7.1 (4.1)	7.5 (5.3)	10.8 (8.5)	12.6 (7.8)	12.6 (7.9)	14.2 (8)	22 (13.1)	0.001
95% CI	4.8-7.8	4.7-9.6	4.7-10.4	6.9-14.7	8-17.1	8.4-16.8	10.6-17.9	20.5.23.6	

FIT: fecal occult blood immunochemical test; SD: standard deviation; 95% CI: confidence interval 95%.

Table 3. Diagnostic accuracy to correctly diagnose colorectal lesions based on the 400 ng/mL FIT cutoff value

Tumor	ROC Curve (AUC)	IC 95%
Adenoma	0.691	0.656, 0.724
Advanced adenoma	0.831	0.798, 0.861
Laterally Spreading Tumors	0.907	0.878, 0.933
Early CRC	0.996	0.985, 0.999
Advanced CRC	1.0	0.993, 1.0
Laterally Spreading Tumors + early CRC	1.0	0.992, 1.0
All the lesions	0.777	0.749, 0.802

AUC: area under the curve; 95% CI: 95% confidence interval; CRC: colorectal cancer.

LST lesions predominated in the right colon (n = 12; 66.6%) and early CRC in the left (n = 17; 88%). There were no significant differences between size (17.5 vs. 15, p = 0.1) and FIT values (average 626 vs. 927 ng/mL, p = 0.1).

There were 135 cases of advanced adenomas, with an average size of 15 ± 6.7 mm (95% CI 13.6-16.3) and FIT levels of 694.6 ng (95% CI 632.4-756.9). There was no correlation between advanced adenoma size and FIT levels (R = 0.22). The best cutoff value for detecting significant pathology was 400 ng/mL (Sn 0.59, Sp 0.84) with false-negative rates of 0.16. The positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were 3.81 and 0.48, respectively. Table 3 and figure 2 illustrate the diagnostic accuracy for a 400 ng/mL cutoff and ROC curves. Diagnostic accuracy for different FIT levels is demonstrated in table 4.

There were 71 cases of CRC (17 early and 54 advanced) with an average age of 65.8 ± 8 years (1:1 male-female ratio) predominating in the left colon (88% early and 80% advanced). There were significant differences between FIT values for early and advanced CRC (average 927 ng; [95% CI: 637-1082] vs. 1453 [95% CI: 1352-1594; p = 0.001]). The degree of tumor differentiation was well differentiated (n = 31), moderately differentiated (n = 34), and poorly differentiated (n = 6).

11/12 LST were treated endoscopically and one was surgically resected. 14/17 early CRC were treated by endoscopic resection and the remainder required surgery. All advanced CRCs were referred to the oncology team.

Discussion

A FIT cutoff value of 100 ng Hb/mL is highly sensitive for detecting CRC and advanced adenomas. The Sn, Sp, PPV, and NPV to detect CRC were 100%, 90%, 16%, and 100%, respectively, and for advanced neoplasms 74%, 93%, 45%, and 98%, respectively. A FIT detects 100% of CRC and 74% of colorectal lesions.[29]

Although the frequency of advanced adenomas and malignant lesions was higher in our studied population, there was not a correlation between the size (average 15 ± 6.7 mm) and the FIT level of 694.6 ng (R = 0.22). However, the most significant accuracy was seen with a value of 400 ng Hb/mL (Sn 0.59, Sp 0.84) with a 0.16 false-negative rate, a positive likelihood ratio (LR+) and negative likelihood ratio (LR-) of 3.81 and 0.48, respectively.

Nagorni et al.[30] reported a higher detection rate of advanced adenoma among individuals with a positive FIT than in symptomatic subjects undergoing colonoscopy (11.6% vs. 5.1%).[30] Similarly, our group reported a higher detection rate in colonoscopy in asymptomatic subjects (positive FIT) compared with symptomatic patients without FIT testing (8.9 vs. 4.35%) in 3234 consecutive cases at the Cancer Detection Center in Montevideo, Uruguay.[31] qFIT (quantitative)

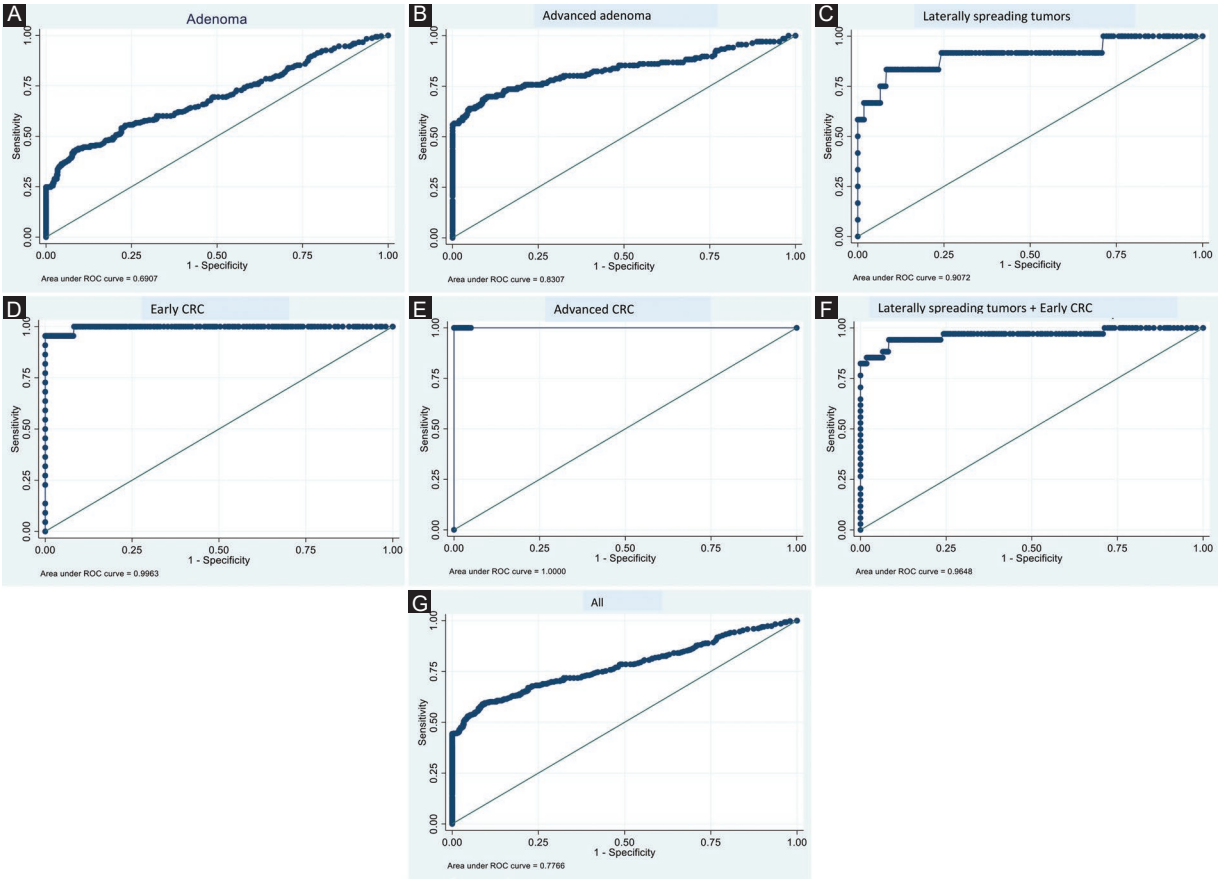

Figure 2. *ROC curve for the detection of colorectal lesions using FIT.* **A:** *simple adenomas,* **B:** *advanced adenomas,* **C:** *laterally spreading tumors,* **D:** *early CRC,* **E:** *advanced CCR,* **F:** *laterally spreading tumors plus early CRC, and* **G:** *all.*

showed a directly proportional relationship between the size of the lesion and the amount of bleeding. For each mm increase, the value of Hb in FIT increased by 35 ± 9 ng ($p < 0.001$) with the best diagnostic yield of 15 mm, where the values stabilized and the curve almost flattened between 1100 and 1900 ng/Hb.

The frequency of advanced adenomas/CRC was high (13.7%) in our study when compared to previous studies. Van Rossum et al.[29] reported a CRC detection rate of 0.45, 0.44, 0.39, 0.39, 0.39, 0.39, 0.39, and 0.37% using values of 50, 75, 100, 125, 150, 175, 200, and 225 ng Hb/mL, respectively. However, the number of colonoscopies required to detect one case was 15.3 (50 ng Hb/mL), 12.4 (75 ng Hb/mL), 11.7 (100 ng Hb/mL), 10.3 (125 ng Hb/mL), 9.8 (150 ng Hb/mL), 9.0 (175 ng Hb/mL), 8.3 (200 ng Hb/mL), and 8.1 (225 ng Hb/mL) with very wide 95% confidence intervals (95% CI). In this study, the Sp to detect advanced adenoma using a value of 400 ng Hb/ml was over 96% (96-98.7%).

Hernandez et al.[32] reported that the FIT cutoff points with the highest yield for advanced neoplasm and CRC were 272.57 ± 597.28 (ROC Curve 0.97) and 998.00 ± 1,075.44 (ROC Curve 0.72), respectively. In our study, the cutoff points with the highest yield (the highest true-positive rate together with the lowest false-positive rate) for predicting advanced adenoma were 395 ng Hb/mL, 927 Hb/mL ng for early CRC, and 1453 ng Hb/mL for advanced CRC.

The assessment of FIT cutoff values and advanced adenomas is often limited in studies due to the number of colonoscopies performed, type of FIT immunoassay used, and the inclusion of both the high-risk screening population and symptomatic patients. These cofounders limit the applicability of findings to screening populations.

Yuan et al. reported that different cutoff values were associated with the performance of qFIT (quantitative). The sensitivity and specificity of qFIT for advanced neoplasia (AN) was 51.3% and 86.4%, respectively, with the best cutoff level of 400 ng/mL. The sensitivity and specificity for CRC were 61.0% and 89.1%, with the best cutoff level of 500 ng/mL.[33]

Table 4. Diagnostic accuracy of FIT for lesions at different cutoff values

Diagnosis	200	300	400	500	600	700	800	900	1000
Adenoma									
Sensitivity	58.0	43.0	29.0	21.0	17.0	13.4	9.4	6.4	5.0
Specificity	70-0	91.2	97.0	100	100	100	100	100	100
Accuracy	65.1	71.8	69.7	68.2	66.6	65.2	63.6	62.5	62.0
Advanced adenoma									
Sensitivity	78.6	67.0	59.5	51.5	48.5	46.3	38.2	33.1	29.4
Specificity	70.0	91.2	100	100	100	100	100	100	100
Accuracy	72.0	85.5	88.3	88.6	88.0	87.4	85.5	84.3	83.5
Laterally spreading									
tumors	91.7	88.3	-	66.7	41.7	-	-	-	33.3
Sensitivity	70.0	91.2	-	97.0	100	-	-	-	100
Specificity	74.0	91.0	-	96.2	98.5	-	-	-	98.2
Accuracy									
Early CRC									
Sensitivity	100	100	95.4	-	81.8	60.0	50	-	31.8
Specificity	70.0	91.2	97.0	-	100	100	100	-	100
Accuracy	71.3	91.6	97	-	99.1	98.0	97.6	-	96.5
Advanced CRC									
Sensitivity	100	100	100	100	94.3	92.4	88.7	79.2	70.770.3
Specificity	70.3	91.2	97.0	100	100	100	100	100	100
Accuracy	73.3	92.1	97.4	100	95.4	99.2	98.8	97.8	97.0
CRC + Lateral Spreading									
Sensitivity	97.0	94.1	94.1	85.2	-	64.7	47.0	35.3	32.3
Specificity	70.7	91.2	92.0	97.0	-	100	100	100	100
Accuracy	72.0	91.4	91.8	96.2	-	97.5	96.2	95.4	95.2
All lesions									
Sensitivity	70.0	58.3	47.8	39.7	-	36.2	33.4	23.0	20.5
Specificity	70.2	91.2	97.0	100	-	100	100	100	100
Accuracy	70.0	73.5	70.0	67.5	65.3	63.5	61.0	48.5	57.1

Shahidi and Cheung[34] evaluated FIT performance in an average risk Canadian population; using cutoff values of > 100 ng Hb/mL, this increased the PPV for advanced adenoma by 6.5% and CRC by 1.5% but the main trade-off was the potential for missed lesions. A 50 ng Hb/mL cutoff value has been shown to be most cost-effective value.

These findings could be highly important in the decision-making process during the SARS-COV-2 (COVID-19) pandemic, helping clinicians to risk stratify which invasive aerosol generating procedures are need to be undertaken in timely manner and which can be safely postponed to a later date. During the most difficult times in the COVID-19, pandemic screening programs, elective colonoscopies in patients with positive FITS were postponed and only emergency procedures undertaken.[35]

Unfortunately, it is still too early to know the impact on the subsequent health, quality of life, and endoscopic lesion detection of the postponed individuals with positive FIT who were scheduled for colonoscopy.

In our study, the detection rate of colorectal lesions was 35% (post-test likelihood) using a non-invasive test (FIT) in subjects at average risk. We observed significant differences in location (left colon), FIT values (p = 0.0001), and lesion size (p = 0.001), but not for age or gender.

Nationwide policies have implemented CRC screening programs in many countries[11]. CRC along with breast cancer screening is the only malignancies where screening is effective in the prevention or progression of disease. In 90% of cases, colorectal lesions are in the pre-cancerous (adenomatous) phase when patients are usually asymptomatic; therefore, screening can be highly effective.[21]

Screening in asymptomatic subjects reduces the incidence and mortality of CRC. Colonoscopy is the most commonly used method following a positive FIT for lesion detection and removal.[13] However, it is not a cost-effective tool for screening as over 75% of the detected lesions are not CRC.[29]

Uruguay and Argentina have implemented screening programs for CRC. Uruguay initiated a study to promote screening and healthy behavior in the general population and those most at risk (14,000 people)[9] Uruguay has had a National Policy for the Detection of (CRC Program) since 1998. It includes the annual screening of asymptomatic individuals with ages ranging from 50 to 70 years using an immunochemical test (iFOBT). This recently changed to FIT as this more specific to the lower GI tract. Colonoscopy is then recommended for positive cases.[9,10] The widespread use of FIT is vitally important in countries where cancer poses a major health problem.[13]

The compliance rates for FIT and colonoscopy in a feasibility study involving 11,734 asymptomatic individuals over the age of 50 were 90.1% and 75.1%, respectively. FIT was positive in 1170 (11.1%) responders and colonoscopy was performed in 879 (75.1%), revealing 330 (38%) lesions, including 54 advanced cancers, 47 early cancers, 131 advanced adenomas, and 98 low-risk non-advanced adenomas. Predictive values for cancer were 0.95 and 8.6% and for advanced adenomas 1.24 and 11.2%.[14]

In one Dutch study, 8806 (3.3%) of 265 881 participants had a positive FIT. Three thousand two hundred and fifty-four (1.2%) AN and 557 (0.2%) CRC were reported in colonoscopy. Prognostic models for detecting AN and CRC in round 3 were performed. The predicted risk ranged from 0.4% to 36.7% for AN and from 0.0% to 5.5% for CRC. In external validation, the model retained similar discrimination accuracy for AN (C-statistic 0.77, 95% CI 0.66 to 0.87) and CRC (C-statistic 0.78, 95% CI 0.66 to 0.91). The models accurately predict the risk of subsequent AN and CRC, discriminate those outcomes with a high degree of concordance, and allow for clinically meaningful risk stratification.[36]

FIT and colonoscopy have been shown in randomized trials to reduce the incidence of CRC and its associated mortality. The incidence of advanced adenoma and CRC in preventive screening (Positive Fecal Tests) is depending on the number of people who undergo endoscopy. Even though, they have been showed to decrease CRC mortality but overestimate the rate of adenomas and cancer.[37]

Our study has also shown that the population most at risk of malignancies is an economically active population (> 60 years) who are also more likely to have comorbidity. Thus, we must consider this in addition to the patient's individual risk and the odds based on FIT values.

Future risk stratification will require evaluating the current cutoff point (FIT > 100 ng) to enhance the performance of the test, while not overwhelming the health-care system. The likelihood of detecting colorectal neoplasms was 25% before the test and 37.7% after the test (LR+ 5.7) in 63,393 subjects with average risk in Uruguay[10] suggesting that deferring the colonoscopy would not be the most appropriate strategy. It is important to consider that the age group in which colonoscopy is indicated matches the age group with a higher potential risk of complications from COVID-19.

There are, however, some limitations of this study, with the main one being that the short and long-term patient outcomes are unknown for those who did not proceed to colonoscopy with a positive FIT. Furthermore, the results from this tertiary center may not be generalizable to smaller hospitals with different patient demographics as other risks influence mortality such as associated diseases such as cardiovascular disease or infection, population pyramid, and the prevalence of overweight or obese individuals.[37-39]

The main findings of the study are well-timed to guide service delivery during the COVID-19 pandemic, with a diagnostic yield of 400 ng Hb/mL demonstrating likely advanced adenomas or CRC. The indirect benefit of implementing such a cutoff is that it would reduce the burden of care and the risk of transmission of the virus during the epidemic in subjects at higher risk of comorbidity. Although lower cutoff levels would increase the detection rate of lesions, this would be at the expense of a higher number of colonoscopies. Prioritization of patients based on this cut-off point (400 ngHb/mL) in the challenging new setting for endoscopy in the fight against CRC, appears to be a feasible strategy that can lower the risks to both patients and healthcare workers.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely

collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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