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ORIGINAL ARTICLE

Prospective Study

Serum homocysteine-based traffic light triage colonoscopy screening in colorectal cancer at-risk patients: A prospective cohort study

Francisco Xavier Cano, José María Duque, Lucia Seoane, Miguel Puga-Tejada, Alejandra Espinoza de los Monteros, Pablo Bermeo, Eduardo Junquera, Daniel Pérez, Jimmy Martin-Delgado, Monica Santelli, Carla Pérez, Francisco Javier Pérez Rivera

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Francisco Xavier Cano, Alejandra Espinoza de los Monteros, Pablo Bermeo, Jimmy Martin-Delgado, Monica Santelli, Instituto de Investigación e Innovación en Salud Integral, Universidad Católica de Santiago de Guayaquil, Guayaquil 090615, Guayas, Ecuador

Francisco Xavier Cano, Department of Gastroenterology, Hospital de Especialidades Alfredo G. Paulson, Guayaquil 090514, Guayas, Ecuador

José María Duque, Eduardo Junquera, Daniel Pérez, Department of Digestive Service, Hospital Universitario San Agustín de Aviles, Aviles 33401, Asturias, Spain

Lucia Seoane, Department of Digestive Service, Hospital Universitario Lucus Augusti, Lugo 27003, Galicia, Spain

Miguel Puga-Tejada, Department of Clinical Research & Biostatistics, Instituto Ecuatoriano de Enfermedades Digestivas, Guayaquil 090505, Guayas, Ecuador

Alejandra Espinoza de los Monteros, Jimmy Martin-Delgado, Department of Clinical Research, Hospital de Especialidades Alfredo G. Paulson, Guayaquil 090514, Guayas, Ecuador

Carla Pérez, Department of Biochemistry Service, Hospital Público de Verín, Ourense 32600, Galicia, Spain

Francisco Javier Pérez Rivera, Doctoral Department, Universidad de Leon, Leon 24004, Castille-Leon, Spain

Corresponding author: Francisco Xavier Cano, MD, PhD, Professor, Researcher, Instituto de Investigación e Innovación en Salud Integral, Universidad Católica de Santiago de Guayaquil, Av. Pdte. Carlos Julio Arosemena Tola, Guayaquil 090615, Guayas, Ecuador.
francisco.cano@cu.ucsg.edu.ec

Abstract

BACKGROUND

Elevated plasma homocysteine (Hcy) levels are associated with increased risk of colorectal cancer (CRC), particularly in patients with systemic inflammation or

Hours



chronic conditions.

AIM

To evaluate serum Hcy levels as a predictive marker of lesion risk and CRC to prioritize patients undergoing diagnostic colonoscopy.

METHODS

We conducted a prospective cohort study of 301 fecal occult blood test-positive patients at San Agustín University Hospital in Asturias, Spain. Plasma Hcy levels were measured prior to the colonoscopy and classified into three thresholds: ≤ 12, 12-15, and > 15 μmol/L. Colonoscopy and histopathology determined the presence of low-risk, high-risk polyps or adenocarcinoma. Predictive performance of serum Hcy to detect lesions was assessed using logistic regression and diagnostic accuracy measures, including models adjusted for age and sex.

RESULTS

Median Hcy levels rose progressively with lesion severity, reaching 15.3 μmol/L in adenocarcinoma ($P < 0.001$). Higher levels were also observed in men and individuals aged 65 or older. A threshold above 15 μmol/L showed good sensitivity (76.6%) and positive predictive value (87.2%) for detecting adenocarcinoma. When combined with age and sex, predictive accuracy improved (area under the receiver operating characteristic curve = 0.706). Based on these findings, we propose a three-tier triage system: Green (≤ 12 μmol/L in both sexes, colonoscopy within three months), Yellow (> 12-15 μmol/L in men, intervention within one month and red (≥ 15 in either sex or > 12 μmol/L in women, immediate colonoscopy).

CONCLUSION

Serum Hcy is a clinically useful biomarker for identifying high-risk colorectal lesions and cancer, particularly when interpreted in combination with age and sex. This composite model improves predictive accuracy and enables a structured three-tiered triage system that supports faster colonoscopy scheduling for at-risk groups. The traffic light approach offers a low cost, scalable strategy to reduce delays and optimize resource use in CRC screening, especially in public health systems with limited endoscopic capacity.

Key Words: Homocysteine; Predictive value of a test; Colonoscopy; Colorectal cancer; Cancer screening

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Core Tip: In this study, we propose a traffic-light triage model based on serum homocysteine levels, sex, and age to prioritize colonoscopy after a positive fecal occult blood test. A green light (≤ 12 micromoles per liter in both sexes) indicates low risk and allows colonoscopy within three months. A yellow light (12-15 micromoles) in men suggests high-risk polyps and requires colonoscopy within one month. In women, the same range is already associated with adenocarcinoma and warrants immediate intervention. A red light (> 15 micromoles) in either sex is strongly associated with cancer and indicates the need for urgent colonoscopy.

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INTRODUCTION

Colorectal cancer (CRC) is a major cause of mortality worldwide, and hyperhomocysteinemia has been identified as a part of CRC oncogenic pathways[1-3]. Homocysteine (Hcy) is a sulfur-containing amino acid generated from methionine metabolism through the S-adenosylmethionine-dependent transmethylation pathway[4]. Preliminary research has established a correlation between elevated serum Hcy levels and an increased probability of developing high-risk polyps in the colon, which can be identified as precursors of CRC[2,3,5]. Furthermore, low blood levels of folate and vitamin B12 are associated with elevated Hcy levels, which are implicated in the occurrence of DNA hypomethylation and therefore induce oxidative stress and chromosomal instability, favoring carcinogenesis[3,6,7].

Early detection through screening programs, including fecal occult blood test (FOBT) followed by colonoscopy, has been shown to decrease both the incidence and mortality[1,8,9]. However, delays in performing diagnostic colonoscopies in FOBT-positive patients, often due to resource limitations and extensive waiting lists, may lead to the progression of neoplastic lesions to adenocarcinoma, compromising patient outcomes and decreasing the probability[1,10]. Therefore, given its wide availability and low cost, Hcy holds promise for addressing this gap[11,12], as Hcy strongly interacts with comorbid conditions such as renal dysfunction, cardiovascular disease, and metabolic syndrome, rendering it a relevant marker for identifying and stratifying risk in a diverse patient population and serving as a potential aid in triaging and prioritizing patients for timely diagnostic interventions[4,13,14]. The present study aimed to evaluate the role of serum Hcy levels for triaging of patients undergoing colonoscopy for the early detection of CRC.

MATERIALS AND METHODS

Study design

This prospective, analytical, monocentric, endoscopist-blind cohort study sought to determine the utility of serum Hcy as a predictive marker of lesion risk for prioritizing patients waitlisted for diagnostic colonoscopies in the Spanish Colon and Rectal Cancer Screening Program (CCCR). All participants were informed in advance of the research objectives and signed informed consent forms prior to sample collection or colonoscopy. This study was approved by the Hospital Ethics Committee of Asturias (official letter No. 244-18) in addition to the Heads of the Digestive and Clinical Biochemistry Service of San Agustín University Hospital. This manuscript was written according to the 2010 CONSORT checklist to improve reporting quality and accuracy.

Setting

The study was conducted in the Endoscopy Unit of the San Agustín University Hospital, located in in the city of Avilés, autonomous community of Asturias, Spain. In this unit, endoscopic assessments of patients recruited within the CCCR program were conducted.

Patient selection

Inclusion criteria: First-time patients recruited to the CCCR were invited to participate. Additionally, we also invited patients from the general population to whom a colonoscopy was requested cause of presumptive CRC diagnosis based on computed tomography (CT).

Exclusion criteria: Subjects who, due to clinical or technical circumstances, could not meet the endoscopic quality criteria established by the Spanish guidelines for CRC screening[10,15], subjects with a previous diagnosis of inflammatory bowel disease (IBD), non-IBD colitis (*e.g.* microscopic or eosinophilic colitis), active colonic inflammatory pathology of the ischemic type or associated with diverticula, familial polyposis, active extracolonic neoplastic pathology or under treatment at the time of the test, or any patient with criteria for colonoscopy surveillance cause to preexistences were excluded. Systemic autoimmune diseases, chronic kidney disease ≥ stage III, chronic infections known to be treated or not (human immunodeficiency virus, tuberculosis, hepatitis C virus, hepatitis B virus), or any patient with criteria for colonoscopy surveillance due to preexistences were also excluded.

Study endpoints

Stratification of CRC risk: The samples obtained were categorized according to colonoscopy findings as the diagnostic reference standard, defined by the quality and surveillance criteria of the Spanish Guide for Colon and Rectal Cancer Screening, which are detailed in Table 1.

Hcy cut-off values: The cohort classification in this study was defined by the three Hcy cut-off levels validated by receiver operating curves (ROC) analysis, and further detailed in the statistical analysis section. Hcy values ≥ 15 μmol/L are consistent with the validation study by Chen *et al*[2] as a reference standard.

Procedure

CCCR: The CCCR program is a nationwide preventive intervention that aims at performing periodical screenings for people at risk of CRC. The program identifies and invites all men and women between 50 and 69 years old for FOBT by mail. Individuals who accepted participation were mailed with a fecal occult immunochemical test kit that must be returned to the health system. If the result was negative, the patient was informed by confidential mail that they should test again in two years. If a patient's result was positive, the patient was called for an appointment to be enrolled in the

Table 1 Group stratification criteria

Group number	Criteria
Absence of lesion/no polyps	No pathological findings in the diagnostic colonoscopy
Low-risk lesion	Classified as low risk are those subjects who present the finding of polyps with low-risk endoscopic characteristics according to number (< 3), size (< 1 cm), endoscopic criteria of the Paris staging, and results of the pathological anatomy of the piece(s) obtained classified as adenoma
High-risk lesion	Polyps with high-risk endoscopic characteristics according to number (> 3), size (> 1 cm), endoscopic criteria of Paris staging, and pathological anatomy results of the piece(s) obtained compatible with a villous component, high-grade dysplasia, or intramucosal adenocarcinoma
Adenocarcinoma	Local and/or distant invasive adenocarcinoma

screening colonoscopy waiting list. Figure 1 summarizes the procedure used in this study.

Blood sample analysis: Before the colonoscopy procedure, a sample of 10 cc of peripheral venous blood was extracted. This extraction was performed at a puncture site different from the venous route used for sedation administration. Plasma samples were collected in tubes with ethylenediaminetetraacetic acid and immediately cold-centrifuged using the Allegra™ 6R centrifuge. The plasma was then stored in aliquots of 0.5 mL at -80 °C.

Sample processing

The blood samples were transferred and processed at the clinical analysis service of the Central University Hospital of Asturias in isothermal containers, strictly maintaining the cold chain at -80 °C. Plasma Hcy levels were determined by reversed-phase high-performance liquid chromatography using the breeze waters chromatograph equipment. The determination included derivatization with 7-fluorobenzene-2-oxa-1,3-diazol-4-ammonium sulfonate, and detection was performed by fluorescence, guaranteeing accuracy in the analysis.

Statistical analysis

Technical considerations: Statistically significant results were considered in those with a P value less than 0.05. The data analysis was carried out using R v4.0 (R Foundation for Statistical Computing; Vienna, Austria).

Sample size: Calculation was based on the need to compare two means, with a 95% confidence interval (95%CI) and a statistical power of 90%, resulting in a minimum sample of 258 cases. The population (n) was defined based on CRC incidence data from the Spanish Network of Cancer Registries (REDECAN), which reported 44231 cases in 2020.

Descriptive statistics: Continuous variables were described by means (SD) or median (IQR), in agreement to their statistical distribution according to the Kolmogorov-Smirnov normality test. Categorical variables were described by frequencies (%).

Inferential statistics: The Pearson's χ^2 or exact Fisher's test was applied to evaluate associations for categorical variables. For quantitative variables, Mann-Whitney and Kruskal-Wallis U tests were applied for two or more group comparisons, respectively, including *ad hoc* Bonferroni correction to adjust for multiplicity and type I errors. Diagnostic accuracy of Hcy was calculated in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and observed agreement. Hcy Optimal cut-off points were obtained through ROC analysis and Youden's index.

RESULTS

Recruitment

In 2018, the Asturias principality invited 20719 individuals by mail to participate in the program *via* mail. A total of 13515 participants did not respond, leaving 8495 participants who submitted fecal samples for FOBT. Among them, 629 were eligible for colonoscopy; however, 328 could not be enrolled because of non-attendance or inconclusive FOBT results. A total of 270 patients who underwent diagnostic colonoscopy as part of the screening program at San Agustín de Avilés University Hospital between November 2018 and June 2019 were included in this study. Furthermore, 31 patients diagnosed with CRC based on CT findings and requiring colonoscopy confirmation were enrolled. Figure 2 summarizes patient enrollment and cohort classification.

Patient demographics and clinical background

Table 2 shows the baseline and clinical characteristics of 301 patients. The median age of those who had no polyps or low-risk differed significantly from that of those with adenocarcinoma, and the highest proportion of cases was < 65 years old. Similarly, males dominated the sample (56.1%) and had higher proportions of high-risk polyps (70.1%) and adenocarcinoma (62.3%) than females. Analysis of the patients' clinical histories revealed that smoking was significantly associated with low- and high-risk polyps.

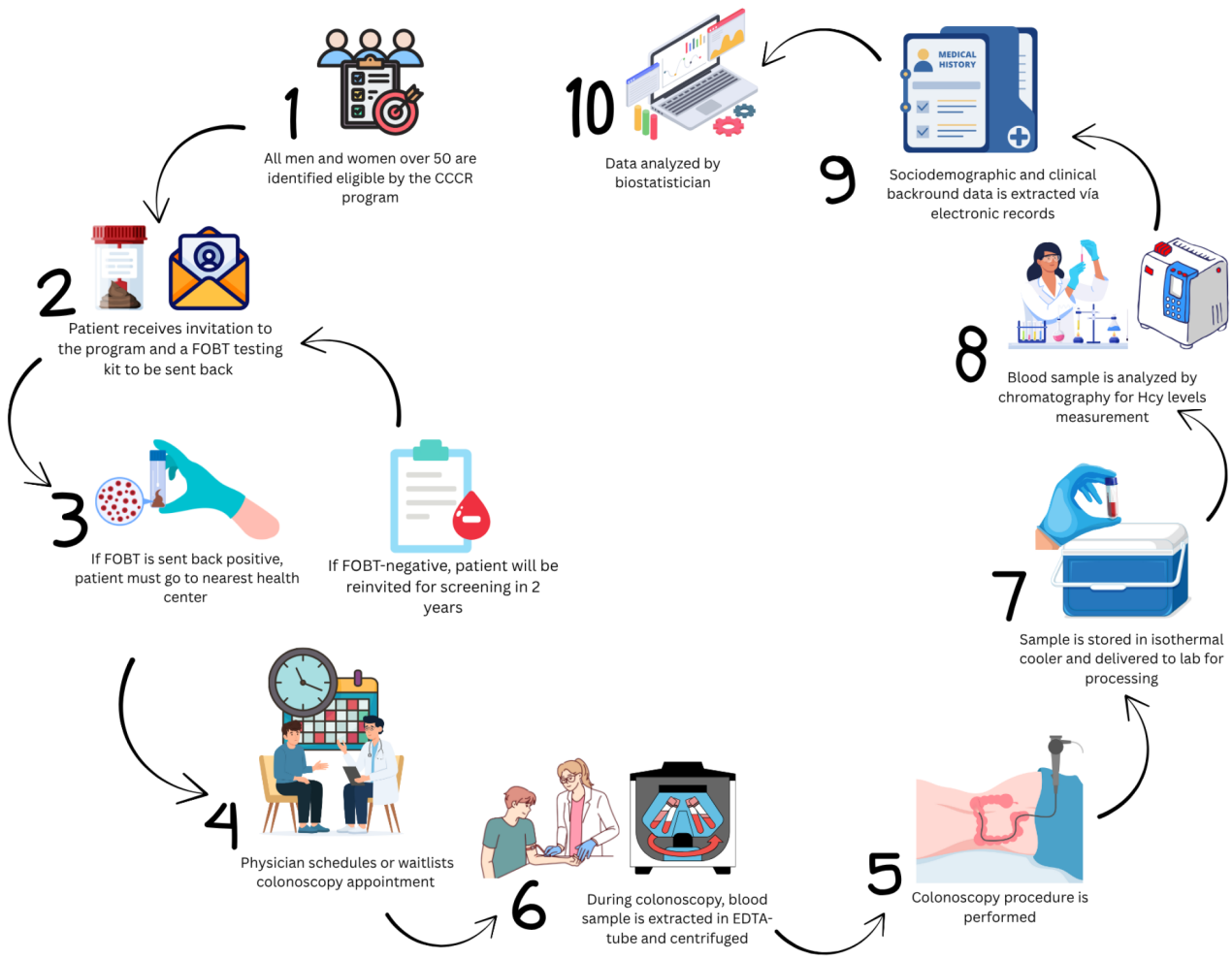


Figure 1 Visual summary of the study's procedures. FOBT: Fecal occult blood test.

As for Hcy levels, Table 2 shows how the median increases in accordance with the severity of lesions, with the group with adenocarcinoma showing the highest levels ($P < 0.0001$). In connection, patients who had no polyps or low-risk lesions were associated with Hcy < 15 μmol/L. Differences were also found according to sex, where females had Hcy levels < 15 μmol/L (50.7%) as compared to males who predominantly had Hcy > 15 μmol/L (72.7%; $P < 0.0003$). A small proportion (8%) of cases with CKD were found to have Hcy levels > 15 μmol/L ($P < 0.0168$), and most presented with risk lesions or adenocarcinoma. Similarly, the proportion of patients who took medication related to decreased Hcy levels was significantly associated with Hcy > 15 μmol/L.

Colonoscopy findings according to location, histology and Paris classification

Table 3 presents the characteristics of the 873 colorectal samples collected, of which 84 samples presented with no polyps. Most lesions were found in the left colon (69.3%), where high-risk polyps (88.6%) and adenocarcinomas (98.4%) tended to be larger (≥ 10 mm). Regarding morphology, 479 Low-risk polyps presented an Is pattern, whereas adenocarcinomas were predominant in the lateral spread tumor (LST) group (64.5%). As for histology, 74.9% of low-risk polyps were identified as tubular adenomas in similar fashion to high-risk polyps (51.9%).

Hcy levels according to lesion type, sex, and age.

In Figure 3, red dashed lines represent Hcy cut-off values at 12 μmol/L and 15 μmol/L, respectively. Figure 3A shows the differences in Hcy levels. For low-risk and high-risk polyps, the median of Hcy was close to the established cut-off of 12 μmol/L; nonetheless, greater variability in IQR and outliers were more frequent in high-risk lesions, particularly for patients < 65. In stark contrast, for adenocarcinoma lesions, Hcy levels surpassed the lowest cut-off, and it was noted that, particularly, serum Hcy rose significantly for people > 65 years old.

Similar to age, Figure 3B reveals that Hcy levels by sex increase as lesions evolve, with males exhibiting higher serum Hcy levels than females across all groups. It was also noted that females have similar Hcy levels for low- and high-risk lesions, with little variability compared to that of the males; however, for adenocarcinomas, most male and female cases were well above the 12 μmol/L cut-off, but male Hcy levels had a higher median and variability in comparison.

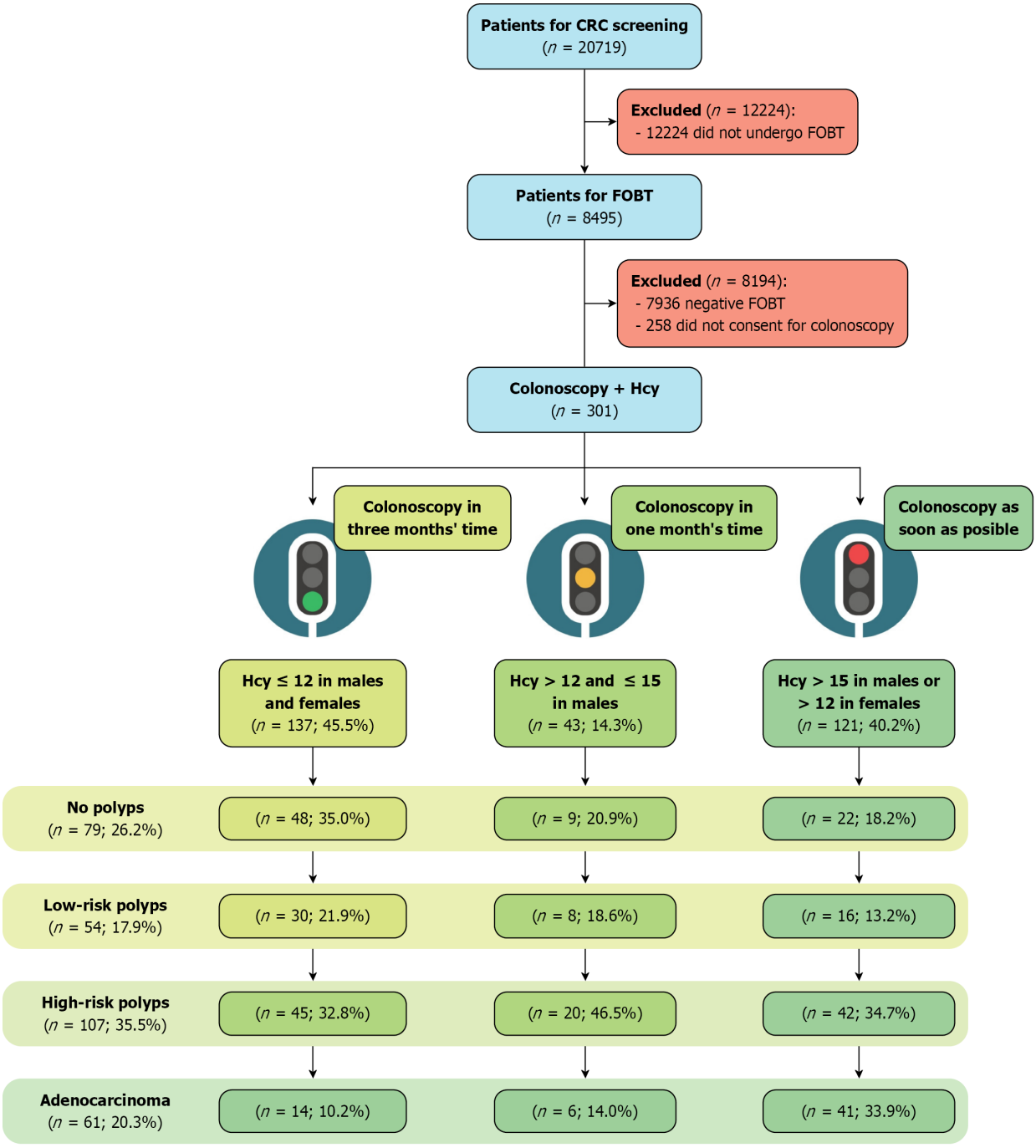


Figure 2 STARD flowchart of patient enrollment and cohort classification.

Demographic and clinical predictors of risk lesions or adenocarcinoma

In our multivariate model (Table 4), age [OR: 1.12 (95%CI: 1.06-1.17)], male sex [OR: 4.03 (95%CI: 1.48-11.1)], and higher serum Hcy [OR: 1.12 (95%CI: 1.06-1.19)], were independently associated with increased odds of presence of risk-lesions or adenocarcinoma. Similarly, an interaction was observed between male sex [OR: 1.12 (95%CI: 1.06-1.17)] and Hcy levels, indicating a strong relationship between these. No other clinical variables or medication interactions were significant.

Predictive accuracy of Hcy for precancerous lesions and CRC

Table 5 illustrates the diagnostic performance of serum Hcy levels at two different cut-off points, adjusted for age and sex, to identify adenocarcinoma alone or in combination with high-risk lesions. Hcy was higher for males (15 μmol/L) than for females (12 μmol/L). Analysis of Hcy ≥ 15 μmol/L revealed overall good sensitivity (79.58%) in identifying adenocarcinoma, with a PPV of 87.21%. A higher sensitivity was observed in male patients (71.76%) than in female patients (68.81%). Figure 4 shows the area under the receiver operating characteristic curve (AUROC) for adenocarcinoma (0.706), indicating fair discrimination. Hcy improved the predictive power, reaching 82.14% sensitivity, for cases ≥ 65 years old.

Table 2 Baseline and clinical data, *n* (%)

	Total (*n* = 301)	Colonoscopy findings				*P* value	Homocysteine		*P* value
		No polyps (*n* = 79)	Low-risk polyps (*n* = 54)	High-risk polyps (*n* = 107)	Adenocarcinoma (*n* = 61)		≤ 15 (*n* = 213)	> 15 (*n* = 88)	
Age (years), median (IQR)	63.0 (57.0-67.0)	61.0 (55.0-65.0)	61.0 (57.0-65.0)	62.0 (58.5-67.0)	69.0 (63.0-79.0)	< 0.0001	62.0 (57.0-67.0)	64.0 (60.0-70.0)	0.0046
< 65	177 (58.8)	55 (69.6)	36 (66.7)	65 (60.7)	21 (34.4)	0.0001	131 (61.5)	46 (52.3)	0.1767
≥ 65	124 (41.2)	24 (30.4)	18 (33.3)	42 (39.3)	40 (65.6)		82 (38.5)	42 (47.7)	
Sex						0.0001			0.0003
Female	132 (43.9)	48 (60.8)	29 (53.7)	32 (29.9)	23 (37.7)		108 (50.7)	24 (27.3)	
Male	169 (56.1)	31 (39.2)	25 (46.3)	75 (70.1)	38 (62.3)		105 (49.3)	64 (72.7)	
Alcohol intaking	73 (24.3)	14 (17.7)	16 (29.6)	24 (22.4)	19 (31.1)	0.2162	49 (23.0)	24 (27.3)	0.5235
Smoking	63 (20.9)	11 (13.9)	14 (25.9)	31 (29.0)	7 (11.5)	0.0139	40 (18.8)	23 (26.1)	0.2036
Diabetes	45 (15.0)	12 (15.2)	4 (7.4)	15 (14.0)	14 (23.0)	0.1349	29 (13.6)	16 (18.2)	0.4049
Hypertension	118 (39.2)	28 (35.4)	17 (31.5)	47 (43.9)	26 (42.6)	0.3735	80 (37.6)	38 (43.2)	0.4359
Obesity	95 (31.6)	26 (32.9)	19 (35.2)	33 (30.8)	17 (27.9)	0.8481	67 (31.5)	28 (31.8)	1.0000
Dyslipidemia	139 (46.2)	40 (50.6)	28 (51.9)	47 (43.9)	24 (39.3)	0.4411	104 (48.8)	35 (39.8)	0.1916
Coronaropathy	23 (7.6)	5 (6.3)	3 (5.6)	8 (7.5)	7 (11.5)	0.6598	14 (6.6)	9 (10.2)	0.3970
Chronic kidney injury	11 (3.7)	2 (2.5)	1 (1.9)	4 (3.7)	4 (6.6)	0.5979	4 (1.9)	7 (8.0)	0.0168
Family history of CRC	13 (4.3)	4 (5.1)	3 (5.6)	5 (4.7)	1 (1.6)	0.7309	9 (4.2)	4 (4.5)	1.0000
Colonoscopy findings						No significant connection			< 0.0001
No polyps	79 (26.2)	79 (100.0)	-	-	-		66 (31.0)	13 (14.8)	
Low-risk polyps	54 (17.9)	-	54 (100.0)	-	-		46 (21.6)	8 (9.1)	
High-risk polyps	107 (35.5)	-	-	107 (100.0)	-		73 (34.3)	34 (38.6)	
Adenocarcinoma	61 (20.3)	-	-	-	61 (100.0)		28 (13.1)	33 (37.5)	
Medication associated with increased Hcy	118 (39.2)	35 (44.3)	19 (35.2)	40 (37.4)	24 (39.3)	0.7109	81 (38.0)	37 (42.0)	0.6034
Medication associated with decreased Hcy	15 (5.0)	4 (5.1)	-	6 (5.6)	5 (8.2)	0.1920	5 (2.3)	10 (11.4)	0.0023
Homocysteine (μmol/L), median (IQR)	12.5 (10.8-15.5)	11.5 (9.74-13.5)	11.8 (10.8-13.3)	12.5 (10.9-16.0)	15.3 (12.4-19.3)	< 0.0001	11.3 (10.1-12.6)	17.7 (16.1-21.8)	n/c
Homocysteine						< 0.0001			n/c
≤ 15	213 (70.8)	66 (83.5)	46 (85.2)	73 (68.2)	28 (45.9)		213 (100.0)	-	
> 15	88 (29.2)	13 (16.5)	8 (14.8)	34 (31.8)	33 (54.1)		-	88 (100.0)	

Hcy: Homocysteine.

Table 3 Description of colorectal lesions found during colonoscopy, *n* (%)

	Total (*n* = 873)	No polyps (*n* = 84)	Low-risk polyps (*n* = 542)	High-risk polyps (*n* = 185)	Adenocarcinoma (*n* = 62)
Location					
Left colon	552 (69.3)	5 (62.5)	353 (65.1)	146 (78.9)	48 (77.4)
Right colon	245 (30.7)	3 (37.5)	189 (34.9)	39 (21.1)	14 (22.6)
Size (mm)					
< 10	570 (71.5)	6 (75.0)	542 (100.0)	21 (11.4)	1 (1.6)
≥ 10	227 (28.5)	2 (25.0)	-	164 (88.6)	61 (98.4)
Paris classification					
Is	554 (69.5)	7 (87.5)	479 (88.4)	65 (35.1)	3 (4.8)
Ip	82 (10.3)	1 (12.5)	20 (3.7)	59 (31.9)	2 (3.2)
Isp	48 (6.0)	-	20 (3.7)	26 (14.1)	2 (3.2)
IIa	36 (4.5)	-	16 (3.0)	20 (10.8)	-
IIb	17 (2.1)	-	7 (1.3)	10 (5.4)	-
IIc	8 (1.0)	-	-	2 (1.1)	6 (9.7)
IIa + IIc	7 (0.9)	-	-	3 (1.6)	4 (6.5)
IIc + IIa	5 (0.6)	-	-	-	5 (8.1)
Lateral spread tumor	40 (5.0)	-	-	-	40 (64.5)
Histology					
Adenocarcinoma	62 (7.8)	-	-	-	62 (100.0)
Tubulovillous adenoma	77 (9.7)	-	-	77 (41.6)	-
Tubular adenoma	502 (63.0)	-	406 (74.9)	96 (51.9)	-
Serrated adenoma	3 (0.4)	-	2 (0.4)	1 (0.5)	-
Hyperplastic	90 (11.3)	-	86 (15.9)	4 (2.2)	-
Non-retrieved specimen	44 (5.5)	-	41 (7.6)	3 (1.6)	-
Non-resected specimen	11 (1.4)	-	7 (1.3)	4 (2.2)	-
Inflammatory polyp	5 (0.6)	5 (62.5)	-	-	-
Lipoma	1 (0.1)	1 (12.5)	-	-	-
Normal colonic tissue	2 (0.3)	2 (25.0)	-	-	-
Colonoscopy without findings	76 (8.7)	76 (90.5)	-	-	-

LST: Lateral spread tumor.

Serum Hcy at ≥ 12 μmol/L moderately detected both high-risk lesions and adenocarcinoma, with an overall sensitivity of 63.16% and the AUROC slightly lower (0.670), with a modest improvement in patients > 65 (0.706). Mild differences in performance capability were also observed between males (AUROC: 0.642; sensitivity: 78.57%) and females (AUROC: 0.654; sensitivity: 71.43%). In terms of predictive value, the overall PPV for these groups was 57.93%, reflecting a better reliability in females (69.62%) than in males (44.4%). The overall specificity for adenocarcinoma alone was moderate (54.1%), and the NPV was 40.24%, indicating a moderate likelihood of false negatives at this threshold.

Hcy-age-sex traffic light system for FOBT-positive patients requiring screening colonoscopy

Figure 5 shows an effective visual representation that simplifies risk stratification and conveys the urgency levels for faster colonoscopy scheduling based on plasma Hcy levels, age, and sex. This approach facilitates clinical decision-making and helps clinicians prioritize patients who require immediate intervention and those who can wait without compromising their health. Traffic light levels are described as follows.

Red level (> 15.1 μmol/L in males and > 12 μmol/L in females): This level reflects a high urgency for immediate

Table 4 Explanatory variables for logistic regression model of associations with risk lesions or adenocarcinoma

	OR	95%CI	*P* value
Age (years)	1.120	1.06-1.17	< 0.001
Sex (male)	4.030	1.48-11.1	0.007
Alcohol intaking	1.060	0.74-1.52	0.7
Smoking	1.210	0.83-1.76	0.3
Diabetes	1.170	0.73-1.88	0.5
Hypertension	0.950	0.68-1.33	0.8
Obesity	0.960	0.69-1.34	0.8
Dyslipidemia	0.760	0.54-1.05	0.1
Coronaropathy	0.940	0.52-1.73	0.8
Homocysteine (μmol/L)	1.120	1.06-1.19	< 0.001
Age (≥ 65 years old) × Hcy	0.980	0.94-1.03	0.5
Sex (male) × Hcy	0.920	0.86-0.99	0.035
Medication associated with increased Hcy × Hcy	1.000	0.97-1.02	0.7
Medication associated with decreased Hcy × Hcy	0.990	0.95-1.03	0.7

95%CI: 95% confidence interval; Hcy: Homocysteine.

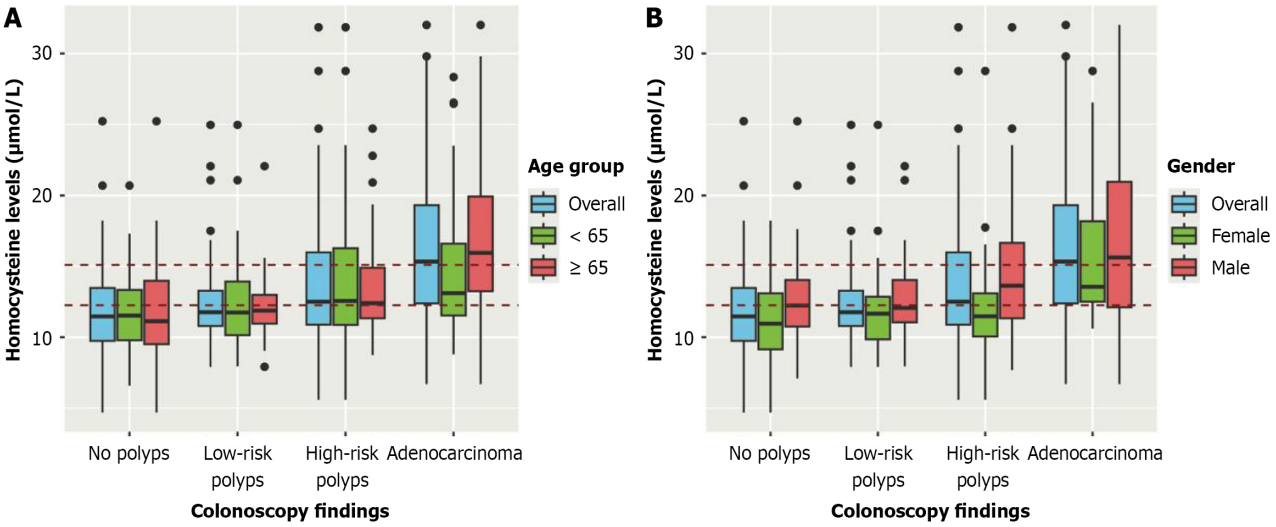


Figure 3 Homocysteine levels according to age and sex. A: Per-age sub-analysis; B: Per-gender sub-analysis.

scheduling of a colonoscopy intervention in both sexed. But higher priority should be provided if the patient is female and > 65.

Yellow level (> 12 μmol/L and ≤ 15 μmol/L in males): Although the risk is lower than in the red level, there is still a considerable likelihood of risk-lesions or adenocarcinoma, which warrant a colonoscopy in the short term, in which males ≤ 65 with Hyc < 15 μmol/L have a better NPV (82.86%) than females, warranting the former to be scheduled within a month for intervention and the latter for urgent colonoscopy.

Green level (≤ 12 μmol/L in males and females): Over 83% of samples with low-risk polyps or no polyps at all were stratified at this Hcy level, reflecting a low probability of injury, and allowing the colonoscopy to be scheduled up to three months in both sexes without compromising the patient's health.

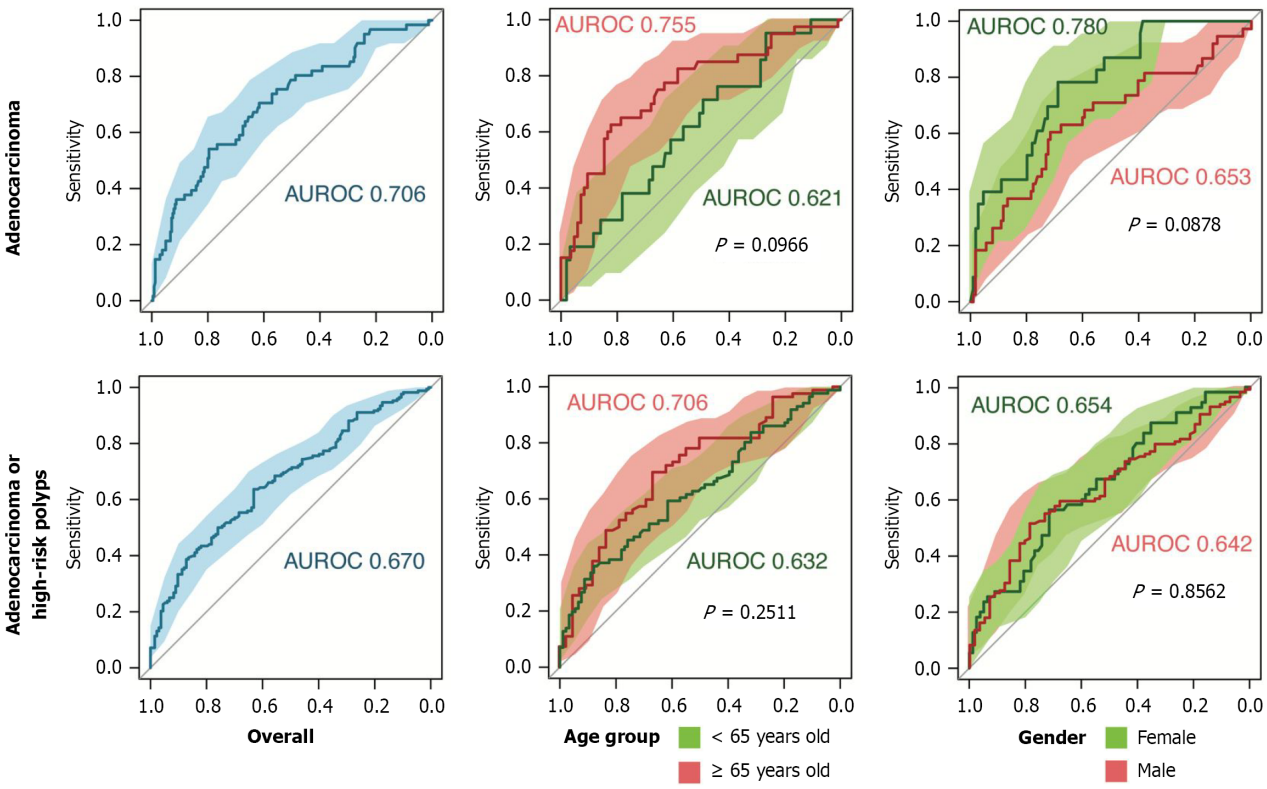


Figure 4 Receiver operating curves for precision identification of risk lesions or adenocarcinoma. AUROC: Area under the receiver operating characteristic curve.

DISCUSSION

The findings of this study introduce and validate the potential of Hcy as a triage instrument to be considered in the nationwide Spanish CCCR program for FOBT-positive patients, to prioritize faster scheduling of colonoscopy screening for those at the highest risk. Thus, the innovative traffic light triage system proposed in this study uses a composite triad of Hcy, age, and sex to provide a robust risk profile. This system could be useful in improving waiting times and response capacity by the health system, as Spanish guidelines reinforce that a 6-week delay of colonoscopy intervention in FOBT-positive patients is harmful[10,16], this recommendation is supported by Forbes *et al*'s systematic review[17] which analyzed a significant increase in CRC incidence in patients who underwent colonoscopy 6 months, 9 months, 10 months or 12 months after the FOBT-positive test. Furthermore, our findings are consistent with evidence linking elevated Hcy with the presence of risk lesions and adenocarcinoma, highlighting how pathological increase in free serum Hcy plays a mechanistic role in cellular dysregulation and carcinogenesis[2,3,5,18].

Previous studies have analyzed alterations in Hcy levels due to multimorbidity and medication, in which metabolic pathways can be disrupted due to chronic inflammatory states, vitamin deficiencies or decreased dietary intake of methionine that increase metabolic demands and biochemical processes[6,7,13,19]. In this study, most at-risk patients had over three chronic conditions, as well as polypharmacy, compounded by the current inflammatory state. Among these, CKD patients were more likely to have homocysteinemia, of which 7/11 stage II cases had serum Hcy > 15 μmol/L; in these cases, the reduced renal clearance compounded by deficiencies in vitamins B6, B9 and B2 could have led to Hcy accumulation, promoting endothelial dysfunction, oxidative stress and heightened cardiovascular risk[13,19]. These potential confounders were included in the logistic regression model, justifying age and sex as the only significant characteristics in the composite diagnostic accuracy AUROC model.

Variability was observed in homocysteinemia according to age, with higher levels detected in patients ≥ 65 years. This observation aligned with anticipated physiological changes in renal clearance associated with advancing age. These patients typically present with vitamin deficiencies and chronic conditions that can further increase serum Hcy levels[13,14]. Sex differences in Hcy levels were also observed, an observation consistent with existing literature[20,21]. Males exhibited higher levels of Hcy across all lesion types as compared to females. Logistic regression revealed that men had more than four times the odds for presence of risk-lesions or adenocarcinoma, independent of age and Hcy levels. However, while Hcy concentrations were higher in men, the clinical meaning of elevated Hcy is more pronounced in women. In particular, Hcy levels 12-15 were already associated with substantially increased likelihood of adenocarcinoma in females, while in males this range more often corresponded to high-risk polyps. This sex-dependent pattern reflects known differences in responses to oxidative stress and methylation efficiency, partially mediated by estrogen's effect on Hcy remethylation and clearance[13,18,22,23].

Table 5 Diagnostic accuracy of homocysteine

	Hcy cut-off value	Sensitivity	Specificity	PPV	NPV	Observed agreement	AUROC
Adenocarcinoma							
Overall	≥ 15.1	191/240; 79.58 (73.92-84.5)	33/61; 54.1 (40.85-66.94)	191/219; 87.21 (82.05-91.33)	33/82; 40.24 (29.56-51.66)	224/301; 74.42 (69.1-79.25)	0.706 (0.631-0.781)
< 65 years	≥ 15.1	122/156; 78.21 (70.9-84.41)	8/21; 38.1 (18.11-61.56)	122/135; 90.37 (84.1-94.77)	8/42; 19.05 (8.6-34.12)	130/177; 73.45 (66.3-79.79)	0.621 (0.496-0.747)
≥ 65 years	≥ 15.18	69/84; 82.14 (72.26-89.65)	25/40; 62.5 (45.8-77.27)	69/84; 82.14 (72.26-89.65)	25/40; 62.5 (45.8-77.27)	94/124; 75.81 (67.3-83.04)	0.755 (0.660-0.850)
Females	≥ 12.5	75/109; 68.81 (59.22-77.34)	18/23; 78.26 (56.3-92.54)	75/80; 93.75 (86.01-97.94)	18/52; 34.62 (21.97-49.09)	93/132; 70.45 (61.89-78.07)	0.780 (0.683-0.877)
Males	≥ 15.1	94/131; 71.76 (63.23-79.27)	23/38; 60.53 (43.39-75.96)	94/109; 86.24 (78.32-92.09)	23/60; 38.33 (26.07-51.79)	117/169; 69.23 (61.68-76.09)	0.653 (0.546-0.761)
Adenocarcinoma or high-risk polyps							
Overall	≥ 12.26	84/133; 63.16 (54.36-71.35)	107/168; 63.69 (55.93-70.96)	84/145; 57.93 (49.46-66.07)	107/156; 68.59 (60.68-75.78)	191/301; 63.46 (57.74-68.91)	0.670 (0.609-0.730)
< 65 years	≥ 15.1	80/91; 87.91 (79.4-93.81)	31/86; 36.05 (25.97-47.12)	80/135; 59.26 (50.47-67.63)	31/42; 73.81 (57.96-86.14)	111/177; 62.71 (55.14-69.85)	0.632 (0.551-0.714)
≥ 65 years	≥ 12.16	28/42; 66.67 (50.45-80.43)	57/82; 69.51 (58.36-79.2)	28/53; 52.83 (38.64-66.7)	57/71; 80.28 (69.14-88.78)	85/124; 68.55 (59.6-76.59)	0.706 (0.610-0.802)
Females	≥ 12.46	55/77; 71.43 (60-81.15)	31/55; 56.36 (42.32-69.7)	55/79; 69.62 (58.25-79.47)	31/53; 58.49 (44.13-71.86)	86/132; 65.15 (56.37-73.23)	0.654 (0.559-0.748)
Males	≥ 14.48	44/56; 78.57 (65.56-88.41)	58/113; 51.33 (41.74-60.84)	44/99; 44.44 (34.45-54.78)	58/70; 82.86 (71.97-90.82)	102/169; 60.36 (52.56-67.78)	0.642 (0.557-0.727)

Hcy: Homocysteine; PPV: Positive predictive value; NPV: Negative predictive value; AUROC: Area under the receiver operating characteristic curve.

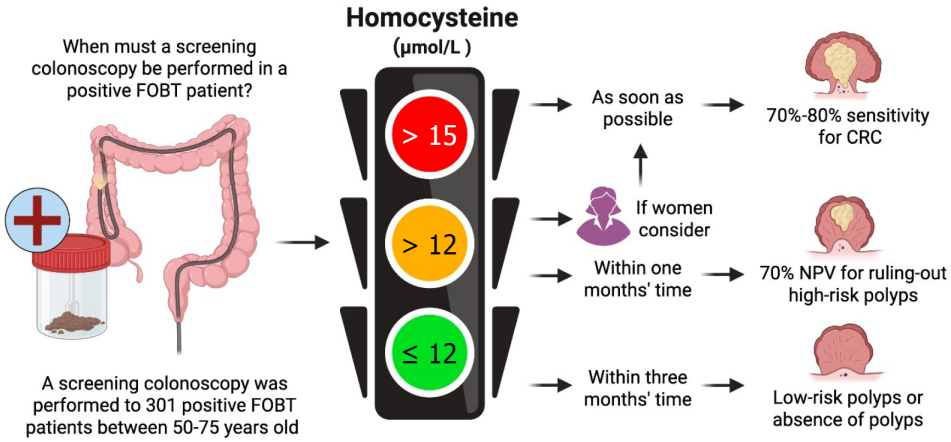


Figure 5 Serum homocysteine traffic light triage system for prioritizing colonoscopy in fecal occult blood test-positive patients. FOBT: Fecal occult blood test; CRC: Colorectal cancer; NPV: Negative predictive value.

A predominance of high-risk polyps and adenocarcinoma were found in the left colon, consistent with prior associations between left-sided lesions and adenocarcinoma[24]. However, over 40% of right-sided lesions in the sample were also classified as high-risk, as reported in a similar Spanish study by Álvarez-Delgado *et al*[8], highlighting the importance of evaluating the entire colon as also supported by colonoscopy quality guidelines[15]. Regarding lesion size, our findings align with previous evidence that smaller lesions (97.7%) are typically indicators of no or low risk, with only one adenocarcinoma and 21 at-risk polyps identified, whereas larger polyps were mostly high-risk, with 87.9% classified as precancerous and 98.4% as adenocarcinomas. In terms of morphology based on the Paris classification, Is-type lesions were most common in low-risk cases (33.9%), while Ip (32.8%) and LST (64.5%) patterns were associated with high-risk lesions and adenocarcinomas, consistent with similar studies and warrant prompt intervention according to Spanish guidelines[3,10]. Though less frequent overall, IIc and IIa/IIc morphologies were mostly observed in risk lesions and adenocarcinomas. Histologically, findings aligned with previous investigations[5,10,25]. In our sample, tubular adenomas

represented the most frequent subtype (63.9%) and were mainly found in low-risk lesions (55.2%). None of the adenocarcinomas showed tubular adenoma histology, while tubulovillous adenomas were more common in high-risk lesions (44.3%).

While our model shows strong internal validity within the Spanish CRC screening context, its generalizability to other populations should be interpreted with caution. Future research is warranted in neighboring European countries that implement similar FOBT-to-colonoscopy screening programs to stablish contextual Hcy thresholds[1,26]. Examples include the United Kingdom, Ireland, and Italy as sites that could potentially benefit from this tool in prioritizing patients and improving resource allocation, as these national programs do not account for clinical or demographic risk stratification. Although earlier investigations combined Hcy with folate and vitamins B6/B12[27-30], we selected Hcy alone, because the marker already captures the combined metabolic, nutritional, and inflammatory variables that would otherwise require multiple testing. Adding micronutrient testing to a population-level programme would raise costs and logistical complexity, whereas Hcy provides an integrated signal of dysregulation and oxidative stress[6,31-33]. Its robustness was evident in our cohort, where elevated levels of Hcy persisted even among patients receiving medication that ordinarily would lower it. We therefore reinforce that Hcy combined with age and sex offers a biologically grounded, cost-conscious triage tool for public health systems in which simplicity and feasibility are paramount. Nonetheless, we recognize that future multicenter work should explore whether adding micronutrient markers yields increased benefit in diverse screening settings.

CONCLUSION

This study demonstrated that elevated serum Hcy levels are significantly associated with the presence of high-risk colorectal lesions and adenocarcinoma in FOBT-positive patients. When combined with age and sex, Hcy level improved the accuracy of risk stratification, supporting its use as a practical adjunct in CRC screening programs. Notably, moderate elevations 12-15 were already linked to malignancy in women, while men exhibited a more linear Hcy-risk gradient, and older adults showed higher predictive sensitivity. Based on these findings, we propose a clinically actionable three-tiered traffic light triage system that integrates age and sex to prioritize colonoscopy scheduling. This system offers a low cost biologically grounded tool for improving risk-stratification and resource allocation in CRC screening. Its simplicity and scalability make it particularly suited for public health programs facing endoscopic capacity constraint. Future validation across broader populations is warranted to support its integration into routine screening protocols.

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FOOTNOTES

Author contributions: Cano FX designed and conducted the study; Seoane L, Junquera E, Pérez D, Santelli M, and Pérez D conducted the data collection and preliminary data review; Martin-Delgado J and Puga-Tejada M contributed to the statistical analysis; Pérez Rivera FJ and Duque JM supervised the study; Espinoza de los Monteros A and Bermeo P wrote and edited the manuscript.

Institutional review board statement: This study was approved by the Hospital Ethics Committee of Asturias (official letter No. 244-18) in addition to the Heads of the Digestive and Clinical Biochemistry Service of the San Agustín University Hospital.

Clinical trial registration statement: This study is a prospective observational cohort and was not registered as a clinical trial, as it did not involve assignment of interventions to human participants.

Informed consent statement: Patients were required to sign their informed consent prior to the endoscopic procedure according to the Organic Law on the Protection of Personal Data art. 15, 1999.

Conflict-of-interest statement: The authors report no relevant conflicts of interest.

Data sharing statement: sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author at francisco.cano@cu.ucsg.edu.ec.

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised accordingly.

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Country of origin: Ecuador

ORCID number: Francisco Xavier Cano 0000-0003-0745-8308; Lucia Seoane 0009-0007-5388-8604; Miguel Puga-Tejada 0000-0001-8853-0847; Alejandra Espinoza de los Monteros 0000-0002-9624-5824; Pablo Bermeo 0009-0004-7066-423X; Eduardo Junquera 0000-0001-5554-7626; Jimmy Martin-Delgado 0000-0003-4384-9197; Monica Santelli 0009-0000-8331-7254; Francisco Javier Pérez Rivera 0000-0003-1709-0439.

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