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Symptom-Based Predictive Model for Colorectal Cancer Diagnosis: Optimization According to Chilean Public Health Policy Guidelines

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Modelo predictivo basado en síntomas para el diagnóstico de cáncer colorrectal: Optimización según las directrices de la política pública de salud chilena

ABSTRACT

In Chile, the public health policy known as "Explicit Health Guarantees" (GES) allows the referral of patients with suspected Colorectal Cancer (CRC) to a tertiary center for colonoscopy within 45 days of evaluation. The correlation of these symptoms with the diagnosis has not been analized. ***Aim:*** *This study aims to analyze variables linked to CRC diagnosis, those in GES guidelines and other clinically important, and to develop a symptom-based predictive model for CRC diagnosis.* ***Methods:*** *A retrospective analytical study was conducted from July 2016 to December 2021. Inclusion criteria were patients referred for colonoscopy as per GES guidelines. Colonoscopy variables were evaluated for test quality. Sixteen variables were included in the predictive model, ten from the GES guidelines and six of clinical interest. Statistical univariate analysis with SPSS 26® ($p<0.05$). Multivariate analysis used binary logistic regression with ROC analysis and 95% confidence intervals for comparison.* ***Results:*** *The cohort included 1099 patients with a mean age of 63.9±13.3 years; 61.1% were female. 148 patients (13%) were diagnosed with neoplasia with 66.9% stage III-IV. Significant variables in the predictive model included age, gender, diarrhea, lower gastrointestinal bleeding, compromised general condition, anemia, palpable rectal mass, suggestive ultrasound, and CT scan, with an AUC of 0.86 (95%CI 0.83-0.89). A model without imaging variables achieved an AUC of 0.81 (95%CI 0.78-0.85).* ***Conclusion:*** *The GES policy enabled a CRC detection rate of 13% in this cohort. Predictive models were developed to optimize referrals for colonoscopy*

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and enhance public health policy. The models require validation in an independent cohort to determine their real-world applicability.
Keywords: *Chile; Colorectal Neoplasms; Health policy; Symptom Assessment.*

RESUMEN
En Chile, la política pública de salud conocida como "Garantías Explícitas en Salud" (GES) permite la derivación de pacientes con sospecha de CRC a un centro terciario para realizar una colonoscopia dentro de los 45 días posteriores a la evaluación. Sin embargo, la correlación de estos síntomas con el diagnóstico no ha sido analizada. ***Objetivo:*** *Este estudio tiene como objetivo analizar las variables vinculadas al diagnóstico de CRC, tanto las establecidas en las guías del GES como otras de interés clínico, y desarrollar un modelo predictivo basado en síntomas para el diagnóstico de CRC.* ***Métodos:*** *Se realizó un estudio retrospectivo analitico desde julio de 2016 hasta diciembre de 2021. Los criterios de inclusión fueron pacientes derivados para colonoscopia según las guías del GES. Se evaluaron las variables de la colonoscopia para determinar la calidad de esta prueba diagnóstica. Se incluyeron dieciséis variables en el modelo predictivo, diez provenientes de las guías del GES y seis de interés clínico. Se realizó un análisis estadístico univariado con SPSS 26® (p<0.05). El análisis multivariado utilizó regresión logística binaria con análisis ROC y un intervalo de confianza del 95% para la comparación.* ***Resultados:*** *La cohorte incluyó a 1099 pacientes con una edad media de 63.9±13.3 años; el 61.1% eran mujeres. A 148 pacientes (13%) se les diagnosticó neoplasia, con el 66.9% en estadio III-IV. Las variables significativas en el modelo predictivo incluyeron edad, sexo, diarrea, sangrado gastrointestinal bajo, condición general comprometida, anemia, masa rectal palpable, ecografía sugestiva y tomografía computarizada, con un AUC de 0.86 (IC95% 0.83-0.89). Un modelo sin variables de imágenes alcanzó un AUC de 0.81 (IC95% 0.78-0.85).* ***Conclusión:*** *La política GES logró una tasa de detección de CRC del 13% en esta cohorte. Se desarrollaron modelos predictivos para disminuir las derivaciones a una colonoscopía, optimizando recursos. Estos modelos requieren ser validados en una cohorte independiente que permita determinar su aplicabilidad en la práctica clínica habitual.*
Palabras clave: *Chile; Evaluación de Síntomas; Neoplasias Colorrectales; Política de Salud.*

Colorectal cancer (CRC) poses a global health issue[1]. In Chile, the incidence, prevalence, and mortality rates increased by 40%, 57%, and 38% respectively from 2009 to 2018[2]. According to GLOBOCAN 2020, Chile reported an incidence of 19.9 per 100,000 inhabitants and a mortality rate of 9.4 per 100,000 inhabitants[3,4]. Mortality is influenced by the stage at diagnosis, whereas 65% of patients debut with an advanced stage[5]. Early detection is crucial for effective treatment[6].

Screening programs aim to detect premalignant lesions and early-stage CRC to reduce associated mortality[7]. American and European guidelines recommend screening for asymptomatic individuals over 50 years old[8,9,10]. These studies have shown a CRC detection rate of 0.1-1%[11,12]. A Population-based screening study in Chile, using Fecal Occult Blood Test (FOBT) and colonoscopy, detected CRC in 1.1% of patients, with 65.7% in early stages[13].

To optimize resources regarding diagnosis strategies, alternative detection methods target patients[14] with genetic CRC risk factors and those with clinical symptoms indicative of CRC[15,16]. The strategy for diagnosing CRC in symptomatic patients has been implemented in Chile since 2016 through the public health policy known as "Explicit Health Guarantees" (GES). These guidelines mandate that patients with suspected CRC be referred to a tertiary center for a colonoscopy within 45 days of evaluation[17]. While the GES guidelines primarily consider clinical variables for referral, they also allow suspicion based on laboratory and imaging tests[18,19].

Despite identification and referral, this guideline has not been analized in terms of CRC detection rate or stage of disease. Additionally, equally weights each symptom without discriminating patients at higher risk. Optimizing resources through predictive models could reduce the waiting list for colonoscopies, a resource expected to be increasingly required throughout the 21st century[20,21].

The objective of this study is to analyze variables associated to CRC diagnosis, the ones propose in the GES guidelines and others of clinical importance, and to develop a symptom-based predictive model for the diagnosis of this neoplasm.

Methods

This retrospective analytical study involved patients referred under the GES guidelines from July 2016 to December 2021 at the Hospital Regional de Concepción, Chile. Referrals were made via electronic interconsultation based on one or more criteria.

The referral criteria consider the following symptoms and signs: abdominal pain, change in bowel habits, rectal bleeding, hematochezia, anemia, compromised general condition, unintentional weight loss, palpable abdominal mass, palpable rectal mass, and low intestinal obstruction. Abdominal pain was characterized as chronic abdominal pain (localized or diffuse), change in bowel habits considered constipation or diarrhea in the last months of symptomatology, the variable lower gastrointestinal bleeding was composed of the presence of macroscopic bleeding - hematochezia and/or rectal bleeding - and microscopic bleeding - positive guaiac fecal occult blood test (gFOBT). Compromised general condition was characterized as asthenia or adynamia. Weight loss was defined, according to ESPEN 2017 guidelines, as more than 5% in 6 months or 10% in one year[22]. Additionally, other variables of interest were analyzed such as: age, sex, duration of symptoms, imaging suggestive of CRC - ultrasound or computed tomography - and family history of CRC.

Characterization of the sample was performed using endoscopic reports. Additionally, the rates of patients with polyps and other colonoscopy findings-such as hemorrhoids, diverticula, and angiodysplasia-are presented. Patients identified with CRC were staged using computed tomography and received appropriate oncological treatment.

Data were tabulated in Excel®. Statistical analysis was performed with SPSS 26® and sample size estimation with RStudio 2021.09.0. Univariate analysis with Chi-square association tests, then multivariate analysis was performed using binary logistic regression, A p-value < 0.05 was considered statistically significant. A comparison was made in terms of the area under the curve and respective 95% confidence interval (CI).

This study was approved by the ethics committee of our institution.

Results

Clinical Variables in Patients Referred for Colonoscopy

Evaluation for colonoscopy was requested for 1099 patients with an average age of 63.9±13.3 years (minimum 23 years and maximum 92 years) and 61.1% were female (Table 1). 154 (14%) patients were referred with only one criterion, 311

Table 1. Demographics and Referral Variables for Colonoscopy.

n= 1099		n (%)
Age (years) ± SD		63.9 ± 13.3
Gender (Female)		661 (60.1)
Symptoms duration (n= 1036)		
<3 months		266 (25.7)
3-6 months		127 (12.3)
>6 months		643 (62.1)
Change in bowel habits	(yes)	556 (50.6)
Lower gastrointestinal bleeding	(yes)	743 (67.6)
Abdominal Pain	(yes)	558 (50.8)
Compromised general condition	(yes)	155 (16,1)
Unintentional weight loss	(yes)	502 (45.7)
Anorexia	(yes)	130 (11.8)
Palpable abdominal mass	(yes)	16 (1.5)
Palpable rectal mass	(yes)	48 (4,4)
Family history of CRC (n= 557)	(yes)	144 (25.9)
Anemia	(yes)	311 (28.3)
Suggestive ultrasound	(yes)	24 (2.2)
Suggestive computed tomography	(yes)	118 (10.7)

(28.3%) patients with 2 criteria, and 279 (25.9%) patients with 3 criteria. 200 patients (18.1%) had positive fecal occult blood tests (FOBT) without presenting macroscopic gastrointestinal bleeding.

Analysis of the Performed Colonoscopies

A complete colonoscopy was achieved in 82.9% of patients, with 81.9% having satisfactory bowel preparation. Two patients experienced a medical complication during the procedure, one with a hematoma of the rectosigmoid junction and one with symptomatic bradycardia; no perforation was reported in this series (Table 2).

Table 2. Overview of Colonoscopy Variables.

n= 1099	n (%)	
Tolerance		
Excelent	113	(10.3)
Good	853	(77.6)
Regular	81	(7.4)
Bad	50	4.5)
End Point		
Ileum	257	(23.4)
Cecum	649	(59.1)
Transverse Colon	71	(6.4)
Descending Colon	21	(1.9)
Sigmoid Colon	65	(5.9)
Rectum	36	(3.3)
Boston (n= 816)		
>7	414	(50.7)
Bowel Preparation (n= 1097)		
Satisfactory	900	(82)
Colonoscopy		
Complete	911	(82.9)
Incomplete – tumoral stenosis	82	(7.5)
Incomplete – technical aspects	46	(4.2)
Incomplete – bad preparatio	31	(2.8)
Incomplete – bad tolerance	29	(2.6)
Presence of Polyps (yes)	375	(34.1)
Presence of Diverticula (yes)	348	(31.7)
Presence of Angiodysplasia (yes)	14	(1.3)
Internal Hemorrhoids (n= 274)		
Grade I-II	232	(83.5)
Grade III-IV	33	(11.9)
Non graded	9	(3.2)

CRC Diagnosis

A total of 148 patients (13%) with neoplasia were identified, with a mean age of 69.3±12 years (range 36-92 years). Among them, 141 (95.3%) had adenocarcinoma of the colon or rectum, and 7 had other neoplasms. Twelve patients (8.1%) were aged 50 years or younger.

For adenocarcinomas, 68 patients (45.9%) had rectal neoplasms, 40 (27%) had left colon neo-

plasms, 33 (22.3%) had right colon neoplasms, 5 had multiple tumors, and 2 had transverse colon neoplasms. Staging showed 11 patients (7.4%) at stage 0, 7 (4.7%) at stage I, 31 (20.9%) at stage II, 37 (25%) at stage III, and 62 (41.9%) at stage IV.

Additionally, four patients had neuroendocrine tumors of the rectum, two had undifferentiated carcinoma of the colon, and one had squamous cell carcinoma of the rectum.

Predictive Model of CRC

A total of 333 patients (30.3%) with polyps were excluded from the predictive model. Univariate and multivariate analyses are shown in table 3. Significant variables from multivariate analysis are presented with their Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value in table 4.

The initial model identified significant variables: age, male gender, diarrhea, lower gastrointestinal bleeding, compromised general condition, anemia, palpable rectal mass, suggestive ultrasound, and CT scan, with an AUC of 0.86 (95% CI 0.83-0.89).

The secondary model, excluding imaging variables, found significant variables: age, male gender, lower gastrointestinal bleeding, compromised general condition, anemia, anorexia, and palpable rectal mass, with an AUC of 0.81 (95% CI 0.78-0.85).

Applications of the Prediction Model

When applying Model 1 to our sample, we evaluated various cutoff points along the ROC curve, which allowed us to define different sensitivity levels and subsequently determine the numbers of true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN). These values indicate the potential number of colonoscopies required to detect colorectal cancer, depending on the chosen sensitivity threshold.False positives represent the number of potentially unnecessary colonoscopies that could be avoided, depending on the selected sensitivity threshold-at the expense of potentially missing patients with cancer, as reflected in the false negatives (FN) column (Table 5).

Discussion

In this cohort, the CRC detection rate was higher than in screening programs. Studies show colonoscopy detection rates in symptomatic patients ranging from 1% to 10%[23,24,25], including 4% in those under 40 years old[26]. Despite the high detection rate, two-thirds of patients were diagnosed at advanced stages, indicating that the GES protocol prioritizes colonoscopy but misses early-stage diagnoses. Early-stage cancers have significantly different treatments and costs compared to advanced stages, particularly stage IV, where curative treatment cannot always be offered.

The variables associated with CRC align with other studies[18,27]. Our symptom-based models highlight the importance of clinical evaluation, especially physical exam. Given the high negative predictive value for lower gastrointestinal bleeding[28], tests like FOBT should be considered and potentially added to the GES guidelines before endoscopy.

The predictive models developed, with and without imaging variables, allow their application in different settings. It should be noted that the variables such as presence of abdominal pain, significant weight loss, anorexia, or palpable abdominal mass were not associated with CRC detection in this study and perhaps should not be used as the sole criteria for referred as GES guidelines determines.

Identified biases include the lack of standardized referral for colonoscopy. The referral to our center is electronic, and only variables pertinent to the referral were reported. For example, only half of the patients were asked about their family history of CRC. Both a standardized referral form and a checklist[29] would allow for deeper inquiry. These checklists could include sedentary lifestyle, body mass index, smoking, diabetes mellitus, among others[30].

International experiences have evaluated the prioritization of symptomatic patients to optimize CRC detection and diagnosis. In the study by Fernández-Bañares, et al. in 2019[31], clinical variables and laboratory studies with FIT were used to generate a score and stratification of patients, prioritizing a colonoscopy in those at high risk.

Table 3. Univariate and Multivariate Analysis for CRC Predictive Model (n= 766).

Variables		No Cancer n= 618 n (%)	Cancer n= 148 n (%)	Univariate Analysis p-value	Multivariate Analysis OR [95% CI]	Multivariate Analysis p-value
Age (years) ± SD		62.2±13.6	69.3±12.1	<0.001	1.04[1.01-1.06]	<0.001
Gender (Male)		204 (33)	91 (61.5)	<0.001	2.49 [1.58-3.91]	<0.001
Symptoms duration (n=1036)						
<3 months		156 (27.1)	43 (30.1)	0.74		NS
3-6 months		59 (10.3)	23 (16.1)			
>6 months		360 (62.6)	77 (53.8)			
Constipation	(yes)	205 (33.2)	37 (25)	0.055		
Diarrhea	(yes)	160 (25.9)	51 (34.5)	0.036	1.77 [1.08-2.89]	0.022
Lower gastrointestinal bleeding	(yes)	405 (65.5)	120 (81.1)	<0.001	3.47 [1.91-6.28]	<0.001
Abdominal Pain	(yes)	317 (51.3)	82 (55.4)	0.369		
Compromised general condition	(yes)	80 (12.9)	59 (39.9)	<0.001	2.20 [1.31-3.69]	0.003
Unintentional weight loss	(yes)	275 (44.5)	90 (60.8)	<0.001		NS
Anemia	(yes)	168 (27.2)	78 (52.7)	<0.001	2.70 [1.67-4.38]	<0,001
Anorexia	(yes)	58 (9.4)	40 (27)	<0.001		NS
Palpable abdominal mass	(yes)	5 (0.8)	7 (4.7)	0.003		NS
Palpable rectal mass	(yes)	9 (1.5)	29 (19.6)	<0.001	22.98 [9.21-57.31]	<0.001
Suggestive ultrasound	(yes)	7 (1.1)	14 (9.5)	<0.001	5.62 [1.80-17.51]	0.003
Suggestive computed tomography	(yes)	51 (8.3)	44 (29.7)	<0.001	9.45 [5.01-17.81]	<0.001
Family history of CRC (n= 377)	(yes)	83 (26.6)	12 (18.5)	0.169		

Table 4. Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of Variables Identified in Multivariate Analysis.

	Sensitivity (IC 95%)	Specificity (IC 95%)	PPV (IC 95%)	NPV (IC 95%)
Diarrhea	0.345 (0.271-0.423)	0.741 (0.706-0.775)	0.242 (0.187-0.302)	0.825 (0.792-0.855)
Lower gastrointestinal bleeding	0.811 (0,743-0.868)	0,345 (0.308-0.383)	0.229 (0.194-0.266)	0,884 (0.839-0.920)
Anemia	0.527 (0.447-0.606)	0.728 (0.692-0.762)	0.310 (0.261-0.377)	0.865 (0.834-0.893)
Palpable abdominal mass	0.047 (0.021-0.089)	0.992 (0.983-0.997)	0.583 (0.309-0.825)	0.813 (0.784-0.840)
Palpable rectal mass	0.196 (0.138-0.265)	0.985 (0.974-0.993)	0.763 (0.614-0.878)	0.837 (0.809-0.862)
Suggestive ultrasound	0.095 (0.054-0.149)	0.989 (0.978-0.995)	0.667 (0.454-0.841)	0.820 (0.791-0.847)
Suggestive computed tomography	0.297 (0.228-0.374)	0.917 (0.894-0.937)	0.463 (0.365-0.563)	0.845 (0.816-0.871)

Table 5. Analysis of Predictive Model 1 at Different Sensitivity Levels.

Sensitivity	Specificity	True Positive	False Negative	True Negative	False Positive
100%	0.2%	148	0	2	949
96%	33.3%	142	6	317	634
89.50%	54.5%	132	16	518	433
85%	73.0%	126	22	694	257

The GES policy was assessed in clinical terms. Within this cohort, a 13% CRC detection rate was observed, primarily among patients with advanced-stage cancer. The proposed predictive models have the potential to reduce the number of colonoscopies needed to identify colorectal cancer patients. However, these models require validation in an independent cohort to determine their real-world applicability and to effectively optimize referrals and resource allocation within our public health policy.

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