Multivariable Models for Advanced Colorectal Neoplasms in Screen-Eligible Individuals at Low-to-Moderate Risk of Colorectal Cancer: Towards Improving Colonoscopy Prioritization

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Research Article

Keywords: Colorectal cancer, colonoscopy, clinical prediction rule, multivariable prediction model

Posted Date: May 5th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-471644/v1

Abstract

Background

Advanced colorectal neoplasms (ACNs), including colorectal cancers (CRC) and high-risk adenomas (HRA), are detected in less than 20% of persons aged 50 years or older who undergo colonoscopy. We sought to derive predictive models that identify persons at high risk of harbouring ACNs to improve the rational allocation of colonoscopy resources.

Methods

We characterized neoplastic findings through chart review for consecutive individuals aged 50 years or older who underwent outpatient colonoscopy at The Ottawa Hospital (Ottawa, Canada) between April 1, 2008 and March 31, 2012 for low-to-moderate risk indications. We collected candidate predictors from chart review and population-level health administrative datasets to derive multivariable logistic regression models for risk of harboring ACNs at colonoscopy. We assessed model discriminatory capacity and calibration and ability of the models to improve colonoscopy specificity while maintaining excellent sensitivity for ACN capture.

Results

We modelled 17 candidate predictors in 11,724 individuals. The final CRC model comprised 8 variables and had a c-statistic value of 0.957 and a goodness-of-fit p-value of 0.527. Application of the models to our cohort permitted 100% sensitivity for identifying persons with CRC and > 90% sensitivity for identifying persons with HRA, while improving colonoscopy specificity for ACNs by 23.8%.

Conclusions

Our multivariable models show excellent discriminatory capacity for persons with ACNs and can significantly increase colonoscopy specificity. If validated, these models could allow more efficient allocation of colonoscopy resources, potentially reducing wait times for those at higher risk while deferring unnecessary colonoscopies in low-risk individuals.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related death, accounting for 3 to 4% of all deaths in Canada and other developed nations.[1,2] Moreover, the burden of CRC continues to rise due to an aging population that is living longer.[1] Therefore, reducing CRC incidence and related mortality have become major public health goals.

By virtue of its ability to accurately diagnose and treat colorectal neoplasms, colonoscopy is considered the gold standard test to evaluate individuals with signs or symptoms or other risk factors for CRC, and is often preferred to fecal occult blood testing (FOBT) for asymptomatic average-risk screening.[3] Colonoscopy has been shown to reduce the incidence of colorectal cancer (CRC) and CRC-related death.[4,5] However, colonoscopy is also an invasive test that carries potential serious risks for patients and significant costs for society.[6,7] Colonoscopy demands are also increasing in the context of an aging population and the expansion of population-based FOBT screening programs in persons over age 50, prolonging wait times for individuals at high risk of harboring CRC.[8] Therefore, it is imperative to develop effective ways to target colonoscopy resources to those that would obtain the greatest benefit.

The greatest protective effect of colonoscopy is derived from its ability to detect and remove high-risk adenomas (HRA) and to diagnose early stage CRC (at an curable stage), as these lesions have the greatest potential to progress to advanced incurable CRC.[9,10] Conversely, low-risk adenomas often do not progress to CRC or do so over a long time (typically more than 10 years).[11] Studies have shown that persons with HRA have a higher CRC-related mortality risk while those with LRA alone have a lower CRC-related mortality risk than members of the general population.[12,13] Therefore, colonoscopy would ideally be targeted to individuals with CRC or HRA, collectively termed advanced colorectal neoplasms (ACNs). However, ACNs are presently detected in less than 20% of persons over age 50 undergoing either screening or diagnostic colonoscopy,[14,15] and less than 6% of those undergoing average-risk screening.[16] Therefore, most individuals are unnecessarily exposed to the risks and costs of colonoscopy, and these individuals further increase wait times for individuals who are potentially at higher risk.

Current risk stratification methods for colonoscopy consider a limited number of factors applied in isolation, guided by expert opinion.[3,17] However, the predictive value of any single factor is low, leading to misallocation of resources. Algorithms that consider the collective contribution of multiple risk factors and protective factors are not currently in widespread use in clinical practice. Earlier efforts at developing such models by different groups have been hampered by either poor performance, model complexity, difficult to ascertain or overly complex variables or inappropriate patient selection, limiting their utility.[18–26] An important shortcoming of most models is the absence of prior colonoscopy or polypectomy as model variables,[22–26] despite their significant influence on future CRC risk.[4,5,12,13,27,28]

Therefore, we sought to derive prediction models that could be easily applied in clinical practice to better discriminate which individuals over age 50 could stand to benefit from colonoscopy based on the likelihood of harbouring ACNs.

Methods

Patients and Setting

This study was approved by the Ottawa Health Science Network Research Ethics Board. We studied consecutive individuals aged 50 years or older who underwent outpatient colonoscopy for perceived low-to-moderate risk indications at The Ottawa Hospital (Ottawa, Canada) between April 1, 2008 and March 31, 2012. The Ottawa Hospital is a tertiary care facility that provides inpatient and ambulatory endoscopy services to a catchment area of more than 1.2 million individuals in Eastern Ontario. Only the first complete colonoscopy for each person was included.

We conducted an initial chart review for 16,441 potentially eligible individuals, identified through The Ottawa Hospital's archived medical records, to identify persons who underwent a high-quality colonoscopy and to exclude individuals who underwent colonoscopy for the following high-risk indications: (i) inflammatory bowel diseases (IBD); (ii) recognized hereditary CRC syndrome (i.e. Lynch syndrome, familial adenomatous polyposis, etc.); (iii) personal history of CRC; (iv) prior incomplete polypectomy; (v) colorectal polyp or mass identified by diagnostic imaging or sigmoidoscopy; (vi) positive FOBT; (vii) unexplained venous thromboembolism; and (viii) cancer of unknown origin. We further excluded individuals who had an incomplete colonoscopy, due to failure to intubate the cecum or poor bowel preparation, and those with inadequate documentation to allow accurate ascertainment of colonoscopy indications or procedural findings.

We linked these individuals deterministically to province-wide health administrative datasets for Ontario, Canada, held at IC/ES, to ascertain additional variables that could not be determined through chart review, such as historical sociodemographic or health care utilization variables. IC/ES is a not-for-profit research institute encompassing a community of research, data and clinical experts, and a secure and accessible array of Ontario's health-related data.[29] The administrative datasets and variable coding definitions used in this study are provided in Supplemental Table 1. The accuracy of capture of colonoscopy procedures in the Ontario Health Insurance Plan (OHIP) database,[30] of primary discharge diagnoses and procedures in the hospital discharge abstract database,[31] and of cancer diagnoses in the Ontario Cancer Registry[32] have been shown to be high.

Following linkage to IC/ES datasets, we excluded persons who did not have valid and continuous health care registration in Ontario for at least ten years preceding the index colonoscopy or whose primary residence was in a small geographic region in south-eastern Ontario where physicians do not routinely submit billing claims (necessary to determine historical colonoscopy exposure in the OHIP database) or who had undergone colonoscopy or sigmoidoscopy at any facility in the province within the preceding year (as these individuals may have had high risk indications for repeat colonoscopy). Additionally, we linked patients to the Ontario Crohn's and Colitis Cohort[33] and the Ontario Cancer Registry to definitively exclude individuals with a history of IBD or CRC prior to index colonoscopy.

Variable Selection And Operationalization For Model Building

Three of the study investigators who are practicing adult gastroenterologists (SM, CD, AR) convened to develop an evidence-based list of variables that could potentially impact an individual's risk of developing

ACNs. From this list, we retained variables that could be accurately determined through retrospective review of patients' medical records and would also be easy to apply in an office setting as part of a clinical prediction model. We identified key variables encompassing colonoscopy indication, age, sex, comorbidity burden, cancer history, colonoscopy history and polypectomy history. Environmental factors, such as diet and smoking history, body mass index, physical activity and NSAIDs use, were not included due to incomplete and varied reporting in patients' records and perceived difficulty with quantifying an individual's lifetime exposure for future application in a predictive model. Candidate predictors tested in the multivariable models are provided in Table 1.

Table 1
Distribution of Candidate Predictors and Outcomes in Study Cohort (N = 11,724)

Variable	Distribution
Major Colonoscopy Indication: Signs/symptoms	39.6%
Major Colonoscopy Indication: First-degree relative with CRC	24.9%
Major Colonoscopy Indication: Surveillance (history of polyps)	14.3%
Major Colonoscopy Indication: Asymptomatic screening*	28.2%
Symptom Indication: Rectal bleeding	19.7%
Symptom Indication: Anemia	7.4%
Symptom Indication: Unintentional weight loss	1.6%
Symptom Indication: Other gastrointestinal symptoms (abdominal or rectal pain, new diarrhea or constipation, rectal urgency, fecal incontinence)	20.3%
Age in years (median (IQR))	61 (55–68)
Male sex	46%
Charlson-Deyo co-morbidity score 0–1 2+	93.2% 6.8%
History of Diabetes Mellitus	17.6%
Prior gastrointestinal malignancy (excluding CRC)	0.5%
Any prior malignancy (excluding CRC)	11.1%
Lower endoscopy within past 10 Years	42.3%

* Default indication if the three other major colonoscopy indications (signs or symptoms, family history or surveillance) were negative

** ≥ 3 adenomas, adenoma ≥ 1 cm or adenoma with villous/serrated/high-grade dysplastic features

Variable	Distribution
# Years since most recent lower endoscopy	4.9%
< 2	9.6%
2–4	18.0%
4–6	6.7%
6–8	3.1%
8–10	57.7%
> 10 (or none)	
Complete colonoscopy (to cecum) within past 10 years	37.9%
Polypectomy or polyp fulguration within past 10 years	15.6%
Highest neoplasia grade at colonoscopy	1.5%
Invasive cancer	11.5%
High-risk adenoma**	87%
Low-risk adenoma or normal	
* Default indication if the three other major colonoscopy indications (signs or symptoms, family history or surveillance) were negative	
** ≥ 3 adenomas, adenoma ≥ 1 cm or adenoma with villous/serrated/high-grade dysplastic features	

We conducted a detailed chart review of the endoscopy and pathology records of eligible persons following initial screening for procedure indications, neoplastic findings, patient age and sex. We stratified colonoscopy indications into four major categories: (i) non-life-threatening signs or symptoms (ii) a personal history of colorectal polyps; (iii) family history of CRC in a first-degree relative; and (iv) asymptomatic average-risk screening. During model building, asymptomatic average-risk screening was considered the default indication if the other three major indications were negative. We further stratified non-life-threatening signs or symptoms into the following categories: (i) rectal bleeding; (ii) anemia; (iii) weight loss; and (iv) other gastrointestinal (GI) symptoms (i.e. abdominal or rectal pain, altered bowel habits, rectal urgency and fecal incontinence). An individual could have had more than one procedural indication.

We classified neoplastic findings into the following three mutually exclusive categories: cancer (n = 173), HRA (n = 1,349) and insignificant (LRA or normal) (n = 10,202). HRA was defined as any of large adenoma (> 1 cm), multiple (≥ 3) adenomas or adenoma with any of villous, serrated or high-grade dysplastic features, as per current guidelines.[17] LRA was defined as 1–2 sub-centimeter tubular adenomas without high grade dysplasia.

Following cohort linkage to provincial administrative datasets we obtained information on co-morbidity burden (based on the Charlson-Deyo index,[34] using an ICES macro of documented diagnoses from health care encounters in the preceding two years), lower endoscopy exposure (either partial or complete colonoscopy) within the preceding ten years, polyp treatment within the preceding ten years and cancer history (both gastrointestinal and non-gastrointestinal cancers).

Model Building And Interpretation

We performed a complete case analysis for model building, given the large sample size of our study and absence of any reason to suspect that excluding persons with missing data would bias the cohort. We performed stepwise multivariable logistic regression modelling to arrive at our final models. All variables were tested for multicollinearity prior to inclusion. A candidate predictor could enter the model if its univariate association with the outcome was significant at a p-value of 0.2 and it was eliminated from the model if its independent association with the outcome was non-significant at a p-value of 0.1. Age was tested as a continuous variable; other variables were tested as categorical variables. We tested interaction terms between age, sex and prior colonoscopy exposure in the final models and retained any terms that were significant.

We first modelled CRC alone to ensure a high sensitivity of CRC capture (Model #1). We applied different sensitivity thresholds for CRC detection to determine probability cut-offs above which persons would be deemed to benefit from colonoscopy. Many individuals with HRA would also be captured among those who fell above this pre-specified threshold. For individuals who fell below the pre-specified threshold in the CRC model, we derived a second model (Model #2) for residual ACNs (CRC or HRA not captured in the first model). We again applied various sensitivity thresholds for detection of ACNs to determine probability cut-offs for each person. We then evaluated different probability cut-off pairs for the two models to determine the overall sensitivity and specificity for predicting CRC and HRA. We tested the robustness of our modelling strategy in the following subgroups of individuals: (i) those with signs/symptoms or other risk factors for CRC (all persons not undergoing asymptomatic average-risk screening); (ii) those with signs or symptoms (irrespective of other risk factors); (iii) those aged 50–74; and (iv) those aged 75 or older.

We assessed individual model performance by its discriminatory capacity (using the c-statistic value, equivalent to the area under the receiver operating curve) and calibration (using the Hosmer-Lemeshow goodness-of-fit test).[35] We further assessed the ability of our model pair to increase the specificity of colonoscopy without overly sacrificing sensitivity for detecting ACNs at different probability cut points for the two models. We prioritized detection of CRC over detection of HRA in choosing optimal probability cut-offs, as the latter are benign lesions that could theoretically be captured in a future screening exam before progressing to advanced CRC. We also tested different sensitivity thresholds for CRC and HRA detection, thereby allowing for flexible application of the models based on physician and patient preference as well as institutional/jurisdictional resources and priorities.

Results

Study Cohort

A total of 11,724 individuals met eligibility criteria. Of these, 71.8% had one or more major indications for colonoscopy and 13% had one or more advanced neoplasms identified during colonoscopy. From the initial cohort, 15% of persons were excluded from model building due to missing or uncertain data in one or more variables. The distribution of patient characteristics across candidate predictors and outcomes is provided in Table 2.

Table 2
Final Model Variables and Model Performance Characteristics in Complete Study Cohort

CRC Model (Model #1)		
Variable	**Estimate (SE)**	**Odds Ratio (95% CI)**
Colonoscopy indication – signs/symptoms (y/n)	0.665 (0.286)	1.94 (1.11–3.40)
Colonoscopy indication – history of polyps (y/n)	0.687 (0.277)	1.99 (1.16–3.42)
Colonoscopy indication – rectal bleeding (y/n)	0.773 (0.232)	2.17 (1.38–3.41)
Colonoscopy indication – anemia (y/n)	0.578 (0.257)	1.78 (1.08–2.95)
Age (years)	0.0432 (0.00926)	1.04 (1.03–1.06)
Charlson-Deyo co-morbidity score (0–1 vs. 2+)	2.33 (0.224)	10.3 (6.65–16.0)
History of non-CRC malignancy (y/n)	2.73 (0.245)	15.3 (9.45–24.7)
Complete colonoscopy within past 10 years (y/n)	-1.66 (0.256)	0.191 (0.116–0.315)
c-statistic **0.957**		
Goodness of fit p-value **0.527**		
Residual CRC or HRA Model (Model #2)*		
Variable	**Estimate (SE)**	**Odds Ratio (95% CI)**
Colonoscopy indication – CRC in FDR (y/n)	0.325 (0.114)	1.38 (1.11–1.73)
Colonoscopy Indication – history of polyps (y/n)	0.311 (0.158)	1.36 (1.001–1.86)
Age (years)	0.0384 (0.00783)	1.04 (1.02–1.06)
Sex (M/F)	-0.470 (0.105)	0.625 (0.509–0.767)

* Based on model of persons who fell below lowest probability cut point associated with 100% CRC sensitivity in Model #1

CRC Model (Model #1)		
# Years since any lower endoscopy	-0.0762 (0.219)	0.927 (0.604–1.42)
1–2	-1.09 (0.216)	0.336 (0.22–0.513)
2–4	-0.766 (0.168)	0.465 (0.334–0.646)
4–6	-0.541 (0.207)	0.582 (0.388–0.873)
6–8	-0.0903 (0.258)	0.914 (0.552–1.51)
8–10	Ref	Ref
> 10 or none		
Polyp treatment within past 10 years (y/n)	0.794 (0.157)	2.21 (1.63–3.01)
c-statistic **0.662**		
Goodness of fit p-value **0.792**		
* Based on model of persons who fell below lowest probability cut point associated with 100% CRC sensitivity in Model #1		

SE = standard error; CI = confidence interval

Regression Models And Performance

The final variables retained in the CRC model (Model #1) and the residual ACNs model (Model #2), along with model performance characteristics (c-statistic and goodness-of-fit p-value), parameter estimates and odds ratios are provided in Table 2. Receiver operating curves for each of these models is provided in Fig. 1. Cancer history, co-morbidity burden, colonoscopy history and age contributed substantially to overall model fit for Model #1, while colonoscopy indications contributed to a lesser degree (Table 2). Prior colonoscopy or polyp treatment, as well as age and sex, contributed substantially to overall model fit for Model #2, while colonoscopy indications contributed to a lesser degree (Table 2).

The calibration was good for both models in the overall cohort and in all subgroups (p-value > 0.5 for Hosmer-Lemeshow Goodness of Fit Test). The regression model for CRC demonstrated excellent discriminatory capacity in the overall cohort and in all subgroups (c-statistic 0.95–0.96). The regression model for residual ACNs displayed more modest discrimination (c-statistic 0.66–0.68 for all models).

The effects of application of the models to our reference cohort on colonoscopy specificity at various pre-determined sensitivity thresholds for CRC and HRA capture, are provided in Tables 3 and 4 for the complete cohort and in Supplemental Tables 2 to 9 for designated subgroups. Applying both models in

sequence to our reference cohort, the specificity of colonoscopy could be substantially improved with little loss in sensitivity for CRC and HRA detection (relative to performing colonoscopy in all individuals). For example, applying a probability cut point associated with 100% sensitivity for CRC detection in Model #1 permitted up to a 44% reduction in colonoscopy volume in our cohort (Table 3).

Table 3. Performance of Logistic Regression Model of CRC at Different Sensitivity Thresholds for CRC Detection

Performance Characteristic	Sensitivity of CRC Detection		
	100%	99%	95%
% missed CRC	0	0.58	5.2
% missed HRA	31.5	35.7	68.2
% colonoscopies avoided	44.1	50.0	79.1

Interpretation (100% Column): At the minimum probability cut point to permit 100% CRC detection, the model predicts a miss rate of 0% for CRC and 31.5% for HRA and reduces colonoscopy burden by 44.1%

Similarly, applying probability cut points in the sequential models (Models #1 and 2) to permit 100% sensitivity for CRC capture and greater than 90% sensitivity for HRA capture, allowed near 25% reduction in colonoscopy volume in our cohort (Table 4).

Table 4
Performance of Sequential Modelling Strategy at Different Sensitivity Thresholds for CRC and HRA Detection

Performance Characteristic	Sensitivity of CRC Detection in Complete Cohort (Model #1)			Sensitivity of CRC or HRA Detection in Residual Cohort (Model #2)
	100%	**99%**	**95%**	
% missed CRC	0	0	0.58	**80%**
% missed HRA	6.2	7.2	13.7	
% colonoscopies avoided	16.4	18.7	31.3	
% missed CRC	0	0.58	0.58	**70%**
% missed HRA	9.5	10.5	20.7	
% colonoscopies avoided	23.8	25.5	40.9	
% missed CRC	0	0.58	0.58	**60%**
% missed HRA	12.7	14.4	27.6	
% colonoscopies avoided	27.5	30.5	48.7	
Interpretation (100% Column, 80% row): At minimum probability cut points to permit 100% CRC detection in Model #1 and 80 CRC/HRA detection in Model #2, application of the sequential modelling strategy predicts a miss rate of 0% for CRC and 6.2% for HRA and reduces colonoscopy burden by 16.4%				

These findings were consistent across all subgroups, with application of the sequential models producing a minimum 20% reduction in colonoscopy volume with a miss rate of less than 1% for CRC and less than 10% for HRA (Supplemental Tables 2 to 9).

Discussion

In this retrospective study of 11,724 consecutive individuals, 50 or older, who underwent colonoscopy for indications associated with a low-to-moderate risk of CRC, we derived multivariable prediction models comprising eight easily ascertainable variables. The modes demonstrated excellent discriminatory capacity for CRC and good calibration for CRC and HRA, allowing for significant improvement in colonoscopy specificity in exchange for a small decrease in sensitivity of HRA capture. These findings were consistent across all designated subgroups of individuals. Application of the models to our full reference cohort would have permitted close to a 25% reduction in colonoscopy volume with no reduction in CRC detection and less than 10% reduction in HRA detection. Repeated application of the models at

regular intervals (i.e. annually) could allow future capture of these missed HRA prior to their progression to advanced CRC. Notably, as large or advanced HRA will often give rise to symptoms that would increase an individuals' predicted probability of having CRC or HRA in our models, and thus prompt colonoscopy, many of the HRA missed in applying our models are likely early HRA, such as 1–2 cm adenomas without high-grade dysplasia.

In return for a modest reduction in HRA capture, application of our models could permit re-allocation of many colonoscopy procedures from low-risk persons to those with higher risk indications, thereby reducing wait times and potential risk of advanced CRC in high-risk individuals, while also reducing unnecessary risks and costs of colonoscopy in low-risk individuals. As judgements regarding an acceptable trade-off between missed advanced neoplasms and colonoscopy resource optimization will vary across patients, practitioners and settings, we have provided estimates for colonoscopy specificity at different sensitivity thresholds for CRC and HRA capture. Nonetheless, if successfully validated, our models have the potential to substantially improve colonoscopy prioritization over what is currently being offered.

The contributions of less well-established risk factors, such as cancer history, comorbidity burden and patient sex, as well as of prior colonoscopy and polyp treatment in our models provide a more complete picture of an individual's current need for colonoscopy in the context of new signs or symptoms or family history of CRC. The ability to quantify an individual's risk of harbouring CRC or HRA would enhance the process of patient-practitioner shared decision-making regarding the value and urgency of colonoscopy. We feel that our models would likely perform better than expert opinion and clinician judgment alone in persons with signs, symptoms or other risk factors for CRC (i.e. family history, previous polyps), who are currently referred directly for colonoscopy without undergoing FOBT screening. Importantly, such individuals comprise more than 70% of those over age 50 undergoing colonoscopy for low-to-moderate risk indications in Canada.[8] However, the impact of our models on colonoscopy resource optimization ultimately depends on the frequency with which our models are applied in practice and with which the results are used to guide management.

It is to be noted that the purpose of our models differs from many prediction models, in that we were not interested in finding a probability cut point that optimizes sensitivity and specificity. With respect to diagnosing ACNs, sensitivity is more important than specificity, and so we pre-defined sensitivity thresholds to determine how much specificity of colonoscopy could be improved at these thresholds over current methods. The relevant outcome in our evaluation is thus the proportion of colonoscopies that could be reasonably deferred or avoided without overly sacrificing sensitivity, particularly for CRC. For this reason, we used a "two-model" strategy that allowed independent control of CRC ascertainment.

Given the low prevalence of ACNs in our cohort (and society), the predictive capacity of our models for these outcomes (i.e. positive predictive value (PPV) and positive likelihood ratio (PLR)) is expected to be very low when using probability cut points associated with high sensitivity for CRC and HRA detection. Even at a specificity of 99% (sensitivity of 54%) for CRC in Model #1, the PPV is only 44%, whereas the

PPV is just 2.6% at 100% sensitivity for CRC capture (PLR 1.81). However, the latter still represents a considerable improvement over the probability of CRC in the absence of our models, which was 1.5% in our cohort, allowing for improvement in the specificity of CRC capture when our models are applied. Conversely, at our chosen high sensitivity thresholds, the negative predictive value approaches 100% while the negative likelihood ratio approaches 0. Therefore, in practice, our models should not be used to define predicted probability of individuals harbouring ACNs, but rather to “rule out” the possibility of an individual having CRC or HRA if they fall below a predetermined probability threshold associated with a high sensitivity of CRC and HRA capture. The models would ultimately guide who could safely defer or avoid colonoscopy in this population.

Multiple groups have attempted to develop prediction models of ACNs, both in screening[18–21] and symptomatic[22–26] cohorts. However, shortcomings in model development have limited uptake of these models into clinical practice. Models that have been developed in asymptomatic average-risk screening cohorts have generally performed poorly. Models that have incorporated symptoms and other CRC risk factors have fared better, but have either not performed well enough for adoption to clinical practice practice,[23,24] have included too many variables to allow for easy application in clinical practice,[23,24,26] have included variables that are challenging to ascertain and/or quantify in an office setting,[23,25] have included high-risk patient groups that would not be appropriate to risk stratify using such a tool,[25,26] or have focused on CRC prediction and ignored HRA.[23–25] In addition to overcoming most of these shortcomings, our models incorporated additional variables that have not been tested in most other models, including prior colonoscopy exposure and polyp treatment, as well as cancer history, all of which strongly influenced CRC and HRA risk prediction in our study.

Our study has several limitations. The reference cohort used to derive the models was ascertained retrospectively, which could have resulted in missing or inaccurate data for one or more variables, particularly colonoscopy indication. Due to our study population being restricted to the screen eligible people, our models cannot be extrapolated to persons under age 50. Moreover, our models did not test environmental risk factors for CRC, such as smoking, diet or NSAIDs because of the difficulty in ascertaining and quantifying the lifetime contribution of such factors. Finally, as these models have not been externally validated, they are not yet suitable for translation to clinical practice.

Conclusions

In conclusion, we have been able to produce multivariable models with overall good calibration, high discriminatory capacity for CRC and modest discriminatory capacity for HRA. These models would enhance shared decision-making regarding the utility of colonoscopy as well as afford a reduction in colonoscopy burden among persons aged 50 or older without high-risk indications for colonoscopy. Our models would be easy to apply in an office setting could serve general practitioners, endoscopists and patients to make decisions regarding the urgency and potential benefit of undergoing colonoscopy and

reduce the number of unnecessary colonoscopies performed. Future work will consist of a prospective study to validate these models and to determine their suitability for clinical practice.

Abbreviations

CRC – Colorectal Cancer

FOBT – Fecal Occult Blood Test

HRA – High-Risk Adenomas

LRA – Low-Risk Adenomas

ACN – Advanced Colorectal Neoplasms

IBD – Inflammatory Bowel Disease

OHIP – Ontario Health Insurance Plan

PPV – Positive Predictive Value

PLR – Positive Likelihood Ratio

Declarations

Ethics approval and consent to participate

This study was approved by the Ottawa Health Science Network Research Ethics Board. Informed consent was waived by the Ottawa Health Science Network Research Ethics Board, as per Health Canada guidelines for retrospective studies. The protocol involving human data was in **accordance with national and institutional guidelines and the Declaration of Helsinki.**

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no completing interests.

Funding

This study was funded by The Ottawa Hospital Academic Medical Organization through an Academic Health Sciences Center Alternate Funding Plan Innovation Fund Grant.

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

Eric Benchimol was supported by a New Investigator Award from the Canadian Institutes of Health Research, Canadian Association of Gastroenterology and Crohn's and Colitis Canada. Eric Benchimol was also supported by the Career Enhancement Program of the Canadian Child Health Clinician Scientist Program.

Authors' contributions

All co-authors made substantial contributions to this manuscript. Specifically: SM was most responsible for concept and design, analysis and interpretation of the data and drafting of the article; RH and SB were responsible for data collection; LA, CD, EIB, GLG, TR and AR were responsible for interpretation of the data and critical revision of the article for important intellectual content; all authors were responsible for final approval of the article.

Acknowledgements

Not applicable.

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Supplemental Files

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Figures

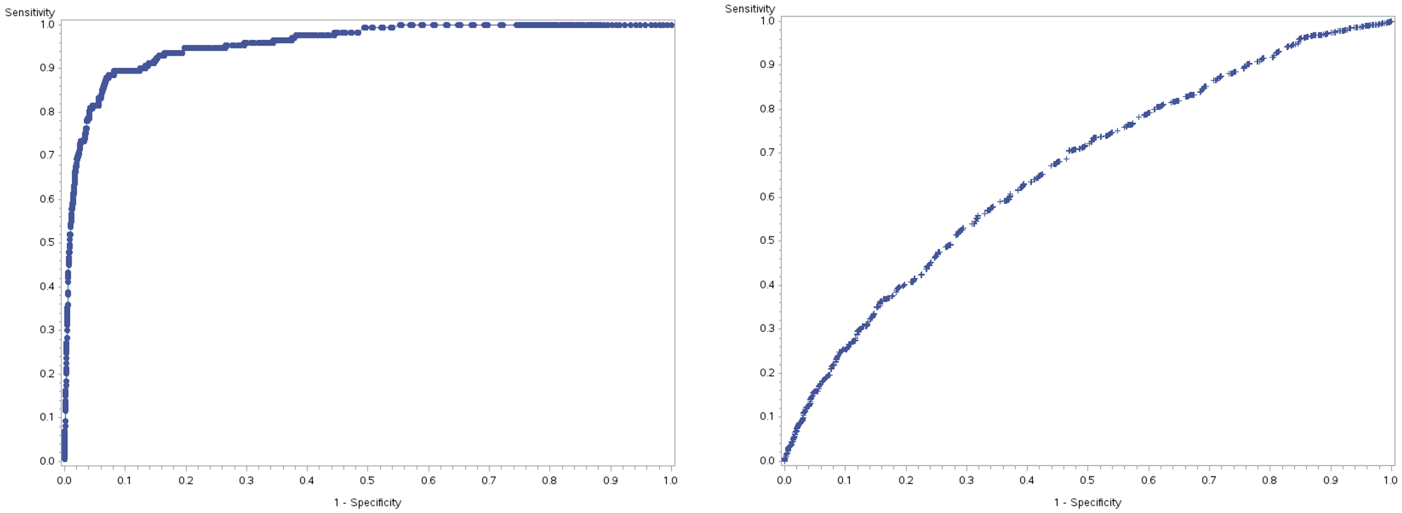

Figure 1

Receiver operating curves (ROC) for logistic regression models. Left Panel – Model for CRC in complete cohort (AUROC 0.96). Right Panel – Model for CRC/HRA among individuals falling below the minimum probability cut-off to permit > 99% CRC capture in Model #1 (AUROC 0.66).

Supplementary Files

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