

Developing a Nomogram for Predicting Colorectal Cancer and Its Precancerous Lesions Based on Data from Three Non-Invasive Screening Tools, APCS, FIT, and sDNA

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Purpose: This study aimed to develop and validate a nomogram for predicting positive colonoscopy results using the data from non-invasive screening strategies.

Methods: The volunteers participated in primary colorectal cancer (CRC) screenings using Asia-Pacific colorectal screening (APCS) scoring, faecal immunochemical testing (FIT) and stool deoxyribonucleic acid (sDNA) testing and underwent a colonoscopy. The positive colonoscopy results included CRC, advanced adenoma (AA), high-grade intraepithelial neoplasia (HGIN), and low-grade intraepithelial neoplasia (LGIN). The enrolled participants were randomly selected for training and validation sets in a 7:3 ratio. A model for predicting positive colonoscopy results was virtualized by the nomogram using logistic regression analysis.

Results: Among the 179 enrolled participants, 125 were assigned to training set, while 54 were assigned to validation set. After multivariable logistic regression was done, APCS score, FIT result, and sDNA result were all identified as the predictors for positive colonoscopy results. A model that incorporated the above independent predictors was developed and presented as a nomogram. The C-index of the nomogram in the validation set was 0.768 (95% CI, 0.644–0.891). The calibration curve demonstrated a good agreement between prediction and observation. The decision curve analysis (DCA) curve showed that the model achieved a net benefit across all threshold probabilities. The AUC of the prediction model for predicting positive colonoscopy results was much higher than that of the FIT + sDNA test scheme.

Conclusion: The nomogram for predicting positive colonoscopy results was successfully developed based on 3 non-invasive screening tools (APCS scoring, FIT and sDNA test).

Keywords: nomogram, colorectal cancer, primary screening, faecal immunochemical testing, stool deoxyribonucleic acid

Introduction

Colorectal cancer (CRC) is the third most common cancer with about 1.8 million people affected globally in each year.¹ It remains the second leading cause of cancer worldwide, resulting in over 50,000 deaths annually.^{1,2} The increasing incidence and mortality of CRC worldwide bring many challenges for public health. Due to the much better prognosis of patients with CRC diagnosed at early stages, early detection using the screening strategies is a promising method to reduce the burden of CRC.³ Previous evidences have shown that screening significantly decrease CRC incidence and mortality.⁴

Currently, the CRC screening strategies differ worldwide based on population risk and resources.⁵ Colonoscopy is the golden diagnostic criteria for CRC with extremely high specificity. However, it also has many disadvantages, such as invasiveness, high cost and patient discomfort, which limit its clinical use.⁶ The non-invasive screening strategies, including Asia-Pacific colorectal screening (APCS) scoring, fecal immunochemical testing (FIT), stool deoxyribonucleic acid (sDNA) test, CT colonography and blood-based tests, are more convenient and available for CRC screening.⁵

APCS score is a well validated scoring system with an aim to assess the risk of CRC in Asian populations.⁷ Previous studies have shown that APCS score achieves optimal primary screening efficiency with low cost-effectiveness.⁸ However, the specificity of APCS score in CRC screening is very low; thus, other non-invasive strategies are suggested to combine with APCS score in order to improve the diagnostic accuracy.⁶ FIT is highly sensitive in detecting blood hemoglobin in the fecal lower digestive tract. It has become a preferred method for CRC screening.⁹ The detection of methylated and tumor DNA in stool (sDNA test) is a promising strategy to enhance the sensitivity of FIT especially for advanced precancerous lesions.⁵ Xu et al¹⁰ found that the APCS score combined with a sDNA test significantly improved the detection of colorectal advanced neoplasm. Aniwan et al¹¹ reported that high APCS scores with positive FIT results had a significantly higher detection rate of advanced neoplasia. Furthermore, our previous study⁶ found that the combined use of the 3 methods of APCS score, FIT and sDNA test demonstrated remarkable improvements in CRC screening efficiency and sensitivity for detecting positive lesions. Thus, the combination of APCS score, FIT and sDNA test is a potential non-invasive strategy for CRC and precancerous lesions screening.

However, how to combine these 3 non-invasive screening strategies for CRC and precancerous lesions screening has not been determined yet. Nomograms are commonly used tools to estimate prognosis in oncology and medicine.¹² Nomograms are widely used predictive models in oncology. They allow physicians and patients to quickly and intuitively assess an individual patient's prognosis or disease risk. Nomograms have been applied to a variety of tumors and precise predictions have been achieved in these tumors.¹³ We planned to use the tool of nomogram to construct a prediction model for CRC and precancerous lesions screening. Thus, this study aimed to develop and validate a nomogram for predicting positive colonoscopy results using the data from non-invasive screening strategies. It helps clinicians to identify colorectal cancer and its precancerous lesions earlier in clinical practice, thereby improving the early diagnosis rate and it is essential to improve patient survival and reduce cancer mortality.

Materials and Methods

Study Population

From September 2021 to April 2022, the Affiliated Hospital of Jiangnan University invited local permanent residents aged 45 to 75 years old to participate in CRC screening. This study was approved by the ethics committee of the Affiliated Hospital of Jiangnan University (approval number: LS2021013) in accordance with Declaration of Helsinki. Written informed consent was obtained from all participants. All laboratory examinations and consultations for screening were free of charge for the participants.

The inclusion criteria were showed as followed: (1) individuals with age between 45 and 75 years old; (2) individuals did not show any symptom or sign of CRC; (3) individuals willing to voluntarily participate.

The main exclusion criteria were as followed: (1) individuals with contraindication of intestinal preparation or colonoscopy; (2) individuals with known history of CRC or who had prior colorectal resections; (3) individuals who had high risk for CRC such as inflammatory bowel disease, Lynch syndrome and familial adenomatous polyposis; (4) individuals who have undergone a colonoscopy within the last five years; (5) individuals with organ dysfunction or severe systemic disease; (6) individuals with abnormal coagulability; (7) pregnant or lactating women.

Clinical Procedures

After the informed consent was signed, the trained study staff helped the participants complete the baseline information questionnaire and calculated the APCS scores. Subsequently, FIT and sDNA test sampling devices were provided to the participants and the fecal samples were collected. According to the results of non-invasive tools, all participants were suggested to perform a voluntary colonoscopy.

Stool Sample Collection

The participants were taught how to take feces samples before collection. Each participant was required to provide a 1.5 to 10 g (average 4.5 g) stool sample in a semiquantitative stool collection device. The stool samples were required to send to the hospital within 24 h. Then, the collecting staff strictly followed the product's instructions to check whether the quality was qualified. The samples were transported to the Creative Biosciences Co., Ltd. (Guangzhou, China) laboratory for analysis.

Screening Methods

APCS score: The questionnaire of APCS score included age (<50 years: 0; 50–69 years: 2; ≥70 years: 3), sex (female: 0; male: 1), family history of CRC (absent: 0; first-degree relative: 2), and smoking history (never: 0; current or past: 1). The patients were included in the 3 risk groups according to the total score: 0–1 = average risk, 2–3 = moderate risk and 4–7 = high risk.⁸

FIT: The OC-SENSOR Micro instrument and corresponding stool collection bottles and reagents (Eiken Chemical Co., Ltd., Tokyo, Japan) were used to process the samples and quantify the fecal hemoglobin by latex-enhanced immunoturbidimetry. According to the thresholds provided by the manufacturer, a result of ≥100 ng hemoglobin/mL was defined as positive.

sDNA test: The sDNA test kit (Lot#20160062) was based on the methylated human Syndecan-2 (SDC2) gene assay provided by Creative Biosciences Co., Ltd. (Guangzhou, China). DNA was isolated from stool samples, and the test was conducted according to the product's instructions. Results for the sDNA test were designated as “positive” or “negative” by the manufacturer based on the cycling threshold (CT) value. Positivity for SDC2 methylation was defined as a CT value less than or equal to 38, while negativity for SDC2 methylation was defined as a CT value greater than 38 or undetected Ct values.¹⁴

Colonoscopy and Histopathologic Examination

All colonoscopies were carried out in a designated endoscopy center by trained endoscopists with an operation experience ≥5 years. All participants were performed bowel preparation before colonoscopy in accordance with the guidelines of the Chinese Society of Digestive Endoscopy (2019).¹⁵ The participants without adequate bowel preparation were scheduled for another colonoscopy within 3 days. During colonoscopy, the camera was successfully inserted into the cecum of all participants and biopsies were taken for histologic examination observed by an experienced pathologist (experience ≥ 15 years).

In the study, the classification of colonoscopy pathological findings was as followed: positive results included CRC, advanced adenoma (AA), high-grade intraepithelial neoplasia (HGIN), and low-grade intraepithelial neoplasia (LGIN); negative results included inflammatory polyps, chronic colitis, proliferative polyps, and no abnormalities. Notably, AA was defined as the adenomas (including sessile serrated lesions) with diameters ≥10 mm, or adenomas with villous structures, or HGIN.¹⁶

Statistical Analysis

The enrolled participants were randomly selected for training and validation sets, and the split ratio was 7:3. The training set was used to train the prediction model. The validation data were used to validate the model.

The data analysis was performed using SPSS 25.0 software and R4.0.3 software. Continuous data were expressed as mean ± SD and compared by Student's *t*-test. The qualitative data were expressed as percentages and compared by Chi-square or Fisher's exact tests. A model for predicting the positive results of colonoscopy was virtualized by the nomogram based on the independent variables extracted from multivariable logistic regression using the training set. The validation set was used to confirm the newly established nomogram. The concordance index (c-index) was used to evaluate the predictive accuracy of the model. Sensitivity and specificity were evaluated by receiver operating characteristics curve (ROC). Furthermore, the clinical value of the model was evaluated by decision curve analysis (DCA). The DeLong test was used to compare the AUC of the ROC curves. A *p* value < 0.05 was considered as statistically significant.

On the basis of Harrell's guidelines,¹⁷ when the outcome is binary, the minimum value of the frequencies of the 2 response levels should be greater than 10 times the number of predictors. Our nomogram planned to include 3 predictors (APCS score, FIT result and sDNA result); thus, the limiting sample size for participants with positive colonoscopy results was 30.

Results

A total of 824 participants were recruited between September 2021 and April 2022. Of these, 90 participants met the exclusion criteria and 734 completed the primary screening. 555 of the 734 participants did not have colonoscopy outcomes. Finally, 179 (21.72%) participants with evaluative colonoscopy outcomes were included in the study analysis (Figure 1). Of the 179 participants enrolled, 88 (49.16%) were males and 91 (50.84%) were females, with an age of (57.36 ± 8.10) years old. There was a total of 92 (51.40%) participants with positive colonoscopy results, including 2 (2.17%) cases of CRC, 29 (31.52%) cases of AA/HGIN, and 61 (66.31%) cases of LGIN. Among the enrolled 179 participants, 125 were assigned to training set, while 54 were assigned to validation set. The comparative clinical characteristics among the training and validation sets are shown in Table 1.

After multivariable logistic regression was done, APCS score (moderate risk vs average risk: odds ratio [OR] = 11.032, 95% confidence interval [CI] = 1.155–105.403, $p = 0.037$; high risk vs average risk: OR = 38.262, 95% CI = 3.820–383.218, $p = 0.002$), FIT result (OR = 20.376, 95% CI = 2.037–203.820, $p = 0.010$), and sDNA result (OR = 8.521, 95% CI = 2.209–32.874; $p = 0.002$) were all identified as the predictors of positive results for colonoscopy. The results of the univariate and multivariate analyses are listed in Table 2. Then, a model that incorporated the above independent predictors was developed and presented as a nomogram (Figure 2).

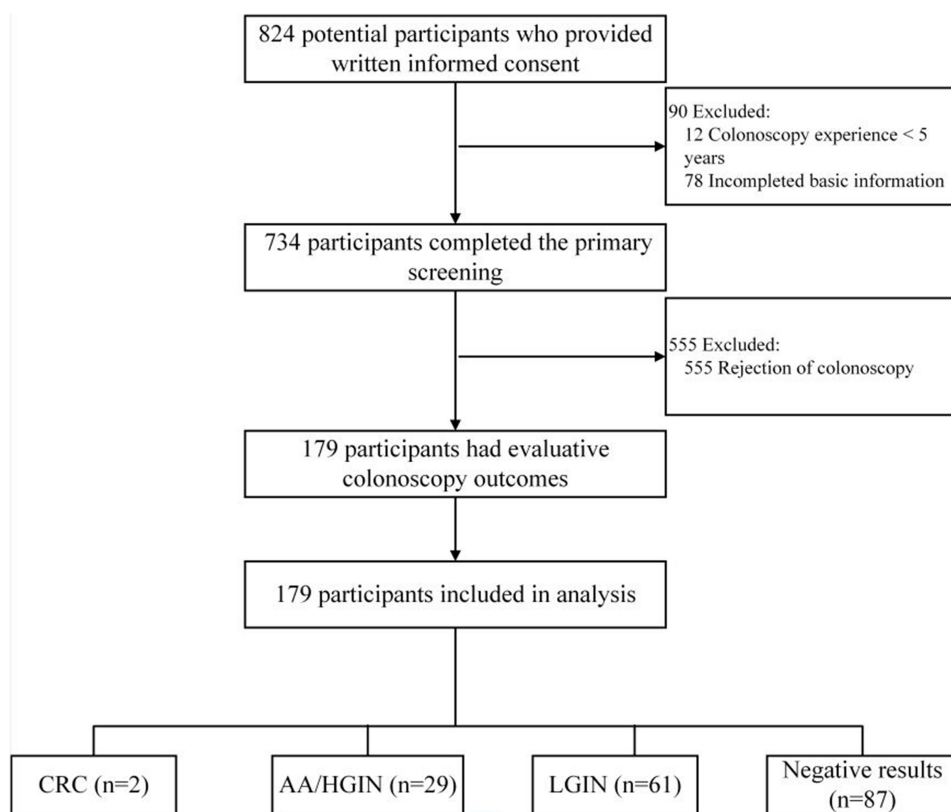


Figure 1 Flowchart of the participants.

Abbreviations: CRC, colorectal cancer; AA, advanced adenoma; HGIN, high-grade intraepithelial neoplasia; LGIN, low-grade intraepithelial neoplasia.

Table 1 The Demographic Data for the Enrolled Participants (n = 179)

Characteristics	Training Set (n=125)	Validation Set (n=54)	p value
Gender, n(%)			0.883
Male	61 (48.80)	27 (50.00)	
Female	64 (51.20)	27 (50.00)	
Age, mean \pm SD, years	57.36 \pm 8.21	57.37 \pm 7.92	0.994
Smoking, n (%)	36 (28.80)	18 (33.33)	0.544
Regular alcohol drinking, n (%)	27 (21.60)	8 (14.81)	0.293
Family history of CRC, n (%)	27 (21.60)	10 (18.52)	0.640
The results of colonoscopy, n (%)			0.624
CRC	1 (0.80)	1 (1.85)	
AA/HGIN	22 (17.60)	7 (12.96)	
LGIN	44 (35.20)	17 (31.48)	
Negative	58 (46.40)	29 (53.70)	
APCS scores, n (%)			0.779
Average risk	15 (12.00)	7 (12.96)	
Moderate risk	65 (52.00)	25 (46.30)	
High risk	45 (36.00)	22 (40.74)	
FIT results, n (%)			0.737
Negative	111 (88.80)	47 (87.04)	
Positive	14 (11.20)	7 (12.96)	
sDNA results, n (%)			0.915
Negative	101 (80.80)	44 (81.48)	
Positive	24 (19.20)	10 (18.52)	

Abbreviations: CRC, colorectal cancer; AA, advanced adenoma; HGIN, high-grade intraepithelial neoplasia; LGIN, low-grade intraepithelial neoplasia; APCS, Asia-Pacific colorectal screening; FIT, fecal immunochemical testing; sDNA, stool deoxyribonucleic acid; SD, standard deviation.

Table 2 Univariate and Multivariate Analysis of Predictors for Positive Colonoscopy Results in the Training Cohort

Tools	Univariate Analysis		Multivariate Logistic Regression	
	OR (95% CI)	p value	OR (95% CI)	p value
APCS score				
Average risk	Reference		Reference	
Moderate risk	6.703 (1.400–32.094)	0.017	11.032 (1.155–105.403)	0.037
High risk	16.000 (3.159–81.033)	0.001	38.262 (3.820–383.218)	0.002
FIT				
Negative	Reference		Reference	
Positive	6.109 (1.306–28.568)	0.021	20.376 (2.037–203.820)	0.010
sDNA				
Negative	Reference		Reference	
Positive	8.370 (2.347–29.848)	0.001	8.521 (2.209–32.874)	0.002

Abbreviations: CI, confidence interval; APCS, Asia-Pacific colorectal screening; FIT, fecal immunochemical testing; sDNA, stool deoxyribonucleic acid.

The C-index for the prediction nomogram was 0.799 (95% CI, 0.727–0.87) in the training set (Figure 3A) and 0.768 (95% CI, 0.644–0.891, Figure 3B) in the validation set. The Hosmer–Lemeshow test found no statistical significance in the validation set ($p = 0.432$), indicating that no departure from a perfect fit was found. The calibration curve demonstrated a good agreement between prediction and observation in the validation set (Figure 4). To evaluate the clinical usefulness of the model, we conducted DCA in the validation set. The DCA curve showed that the model achieved a net benefit across all threshold probabilities (Figure 5).

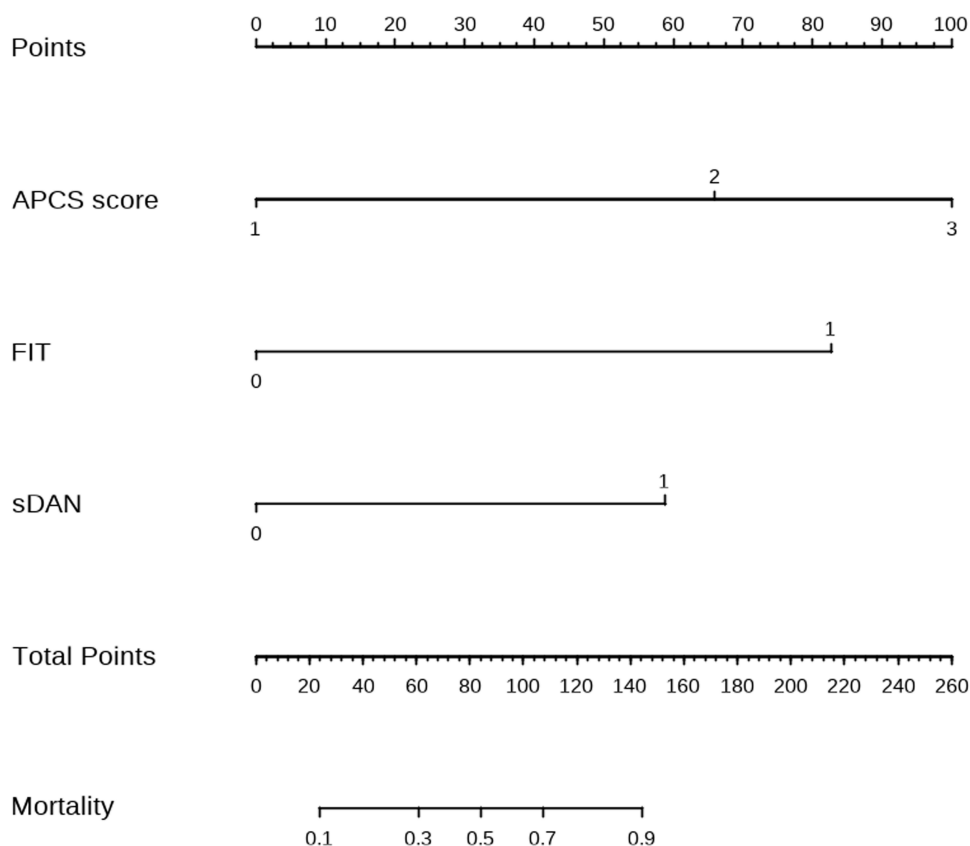


Figure 2 The nomograms for predicting positive colonoscopy results.

Abbreviations: APCS, Asia-Pacific colorectal screening; FIT, fecal immunochemical testing; sDNA, stool deoxyribonucleic acid.

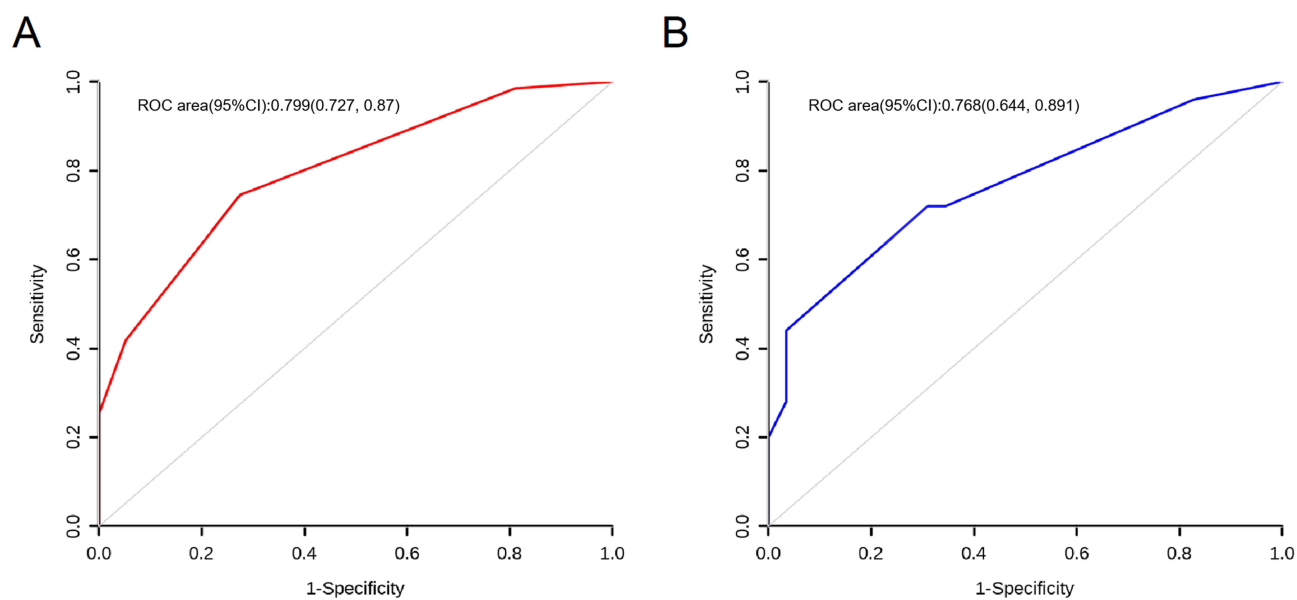


Figure 3 ROC curves of the established model in the training set (A) and validation set (B).

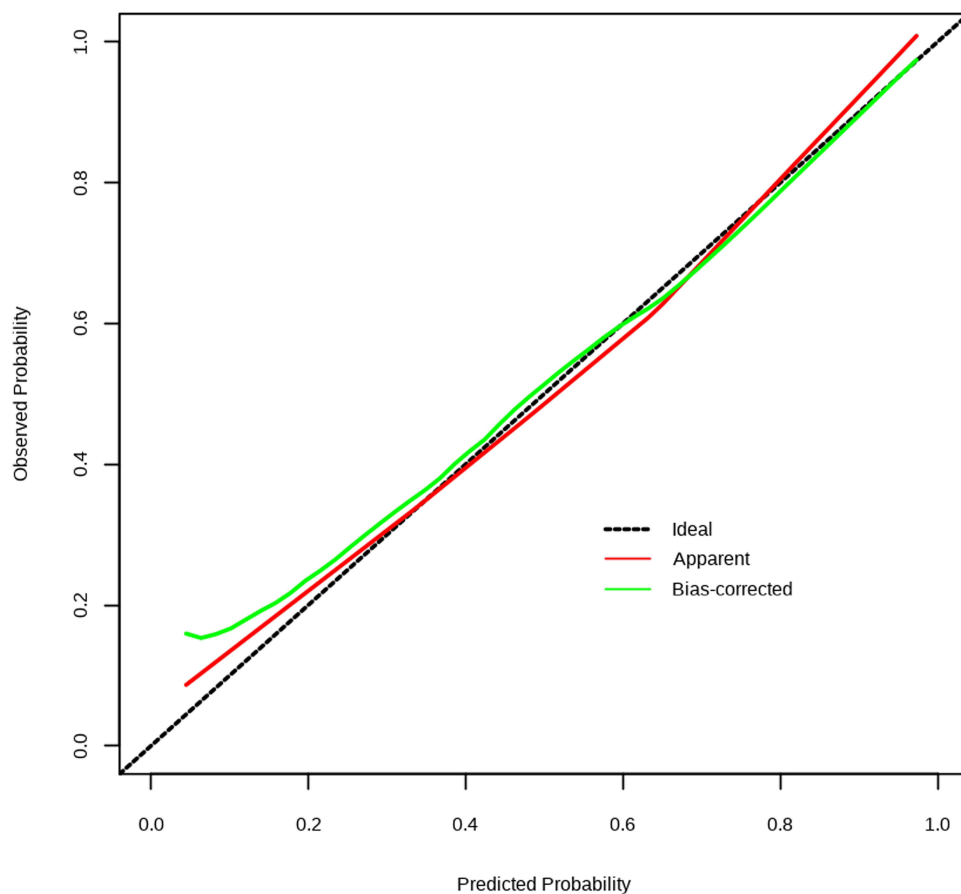


Figure 4 Calibration curve of the model in the validation set.

Then, we compared the diagnostic performance of our prediction model and combined FIT + sDNA test scheme in the validation set. The results showed that the AUC of our prediction model for predicting positive colonoscopy results was much higher than that of the FIT + sDNA test scheme (0.768 vs 0.580, $p = 0.002$, Figure 6). These results indicated that our prediction model had a good diagnostic value in predicting positive colonoscopy results.

Discussion

Comparing to colonoscopy, the non-invasive screening strategies, including APCS scoring, FIT, and sDNA test are more convenient and available for CRC screening.⁵ In the present study, an effective nomogram that used 3 non-invasive screening tools to predict positive colonoscopy results was developed and validated. Our results identified that our nomogram was a highly predictive tool that could be applied directly.

Nomograms are statistical predictive models that incorporate independent factors of prognosis to estimate prognosis for individual patients.¹⁸ Nomograms is a widely used predictive model in the medical field, particularly in oncology. They allow physicians and patients to quickly and intuitively assess the prognosis or disease risk of an individual patient by integrating multiple predictors into a graph.¹⁹ As a prediction tool, Nomograms have been applied in a variety of tumors, such as breast cancer, pancreatic ductal adenocarcinoma, bladder cancer, non-small cell lung cancer, and gastric cancer, etc, and have achieved precise prediction in these cancers.²⁰ To the best of our knowledge, there are few studies focusing on the development of nomograms for CRC screening using the existing non-invasive screening tools. In this study, 3 frequently used non-invasive screening tools (APCS score, FIT and sDNA) were included in our prediction nomogram.

FIT, which is enable detection of a tiny amount of blood by targeting haemoglobin, is the most common and low-cost non-invasive faecal tests for CRC screening.²¹ A systematic review and meta-analysis of 19 studies revealed that the

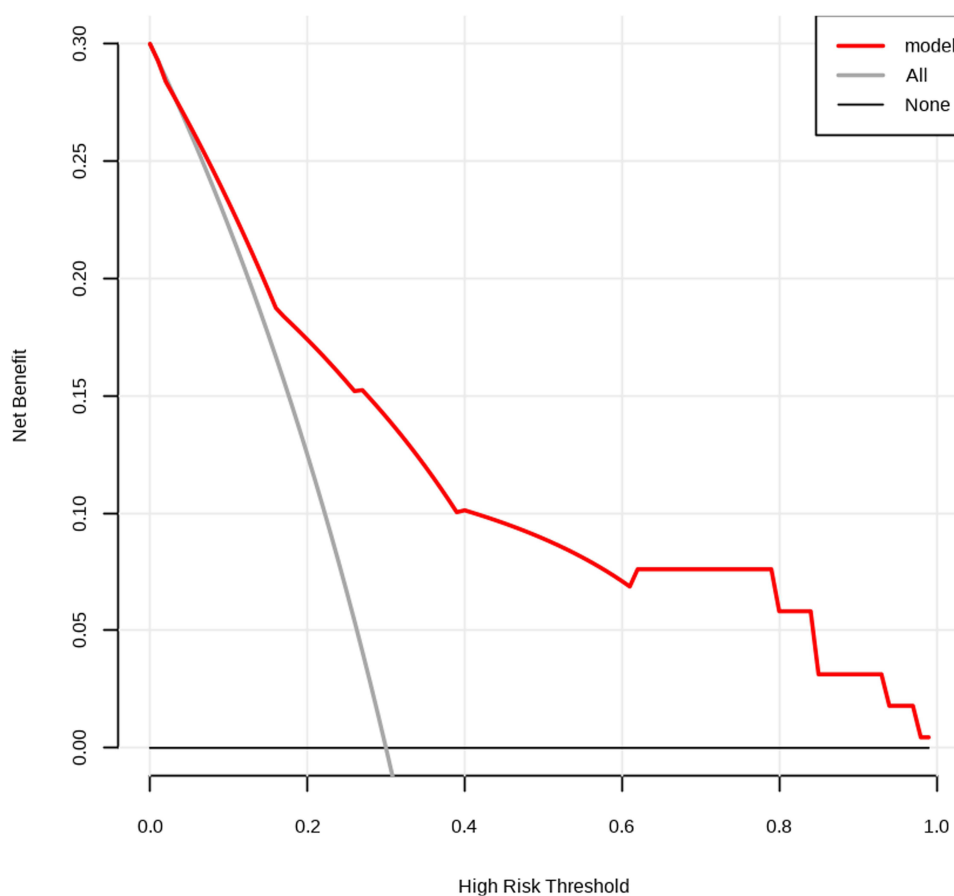


Figure 5 Decision curve analysis (DCA) for the predictive model. The net benefit was produced against the high-risk threshold.

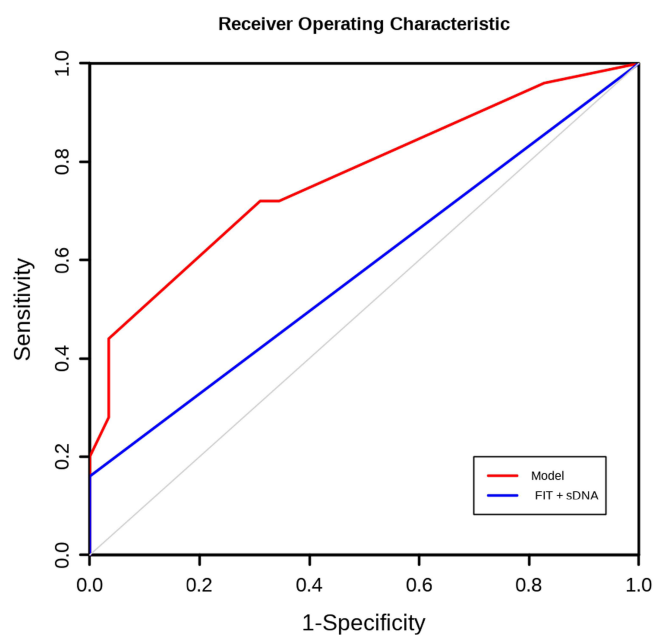


Figure 6 Comparison of ROC curves of the established model and FIT + sDNA.

Abbreviations: ROC, receiver operating characteristic; FIT, fecal immunochemical testing; sDNA, stool deoxyribonucleic acid.

pooled sensitivity and specificity of FIT for CRC were 0.79 (95% CI, 0.69 to 0.86) and 0.94 (CI, 0.92 to 0.95), with a high overall diagnostic accuracy.²² However, the sensitivity of FIT is not high enough, especially for advanced precancerous lesions. Bosch et al²³ reported that the sensitivity of FIT alone in detecting advanced precancerous lesions in the average-risk screening population was as low as 27%.

sDNA test is designed to detect faeces-based DNA biomarkers with occult haemoglobin.²¹ The aberrant methylations of certain genes including BMP3, NDRG4, and TFP12 have been used as molecular markers to develop user-friendly sDNA screening method for CRC.^{16,24} It has been reported that sDNA test was more likely to predict neoplasia than FIT.²⁵ SDC2 is a tumor suppressor, belonging to syndecan family. Hypermethylation of SDC2 promoter region is a frequent epigenetic change occurring during the development of colorectal neoplasms, which can be successfully detected in stool.²⁶ More importantly, a previous study found that positive stool SDC2 methylation could be observed in most of early stages CRC and advanced adenomas.²⁷ Thus, SDC2 methylation has been regarded as a potential diagnostic marker for early detection of CRC. In China, a sDNA test kit (Colosafe) using methylated SDC2 was approved by National Medical Products Administration (NMPA) in 2018, which is the first commercially available sDNA testing kit in China. Due to the accessibility of market in China, we chosen sDNA testing kit of SDC2 methylation in this study. Wang et al¹⁶ conducted a multicenter clinical trial included 1110 participants and found that sDNA test using methylated SDC2 is a clinically viable and accurate CRC detection method. In our previous study, sDNA test using methylated SDC2 exhibited better sensitivity than FIT for detecting LGIN, AA and advanced colorectal neoplasia.⁶

APCS score is a risk-stratification tool that helps predict the risk for advanced colorectal neoplasia in asymptomatic Asian populations.²⁸ Li et al²⁸ found that patients in high-risk tiers based on APCS scores had 6.1-fold increased risk of advanced colorectal neoplasia as compared with those in the average-risk tiers. Similarly, Luu et al⁷ revealed that high-risk group classified by APCS scores had a 3.1-fold higher risk of advanced colorectal neoplasia than the average-risk group. In our nomogram, APCS score owned the highest weight to predict positive colonoscopy results, further demonstrating its role in CRC screening.

After the nomogram was constructed, we validated the prediction model in the validation set. The AUC of the model was 0.768 in the validation set. Additionally, calibration curve analysis and Hosmer–Lemeshow test further showed good calibration of our model in the validation set. Finally, we evaluated the clinical usefulness of the model by DCA and found that the model achieved a net benefit across all threshold probabilities, indicating that the nomogram has high clinical usefulness in our studied population.

The study conducted by Mo et al²⁹ reported that the combination of FIT and sDNA tests had a sensitivity of 81.5% for CRC and was diagnostically superior to FIT or sDNA alone. But for precancerous lesions, the diagnostic value of FIT + sDNA was not as good as expected. In a previous study, the combination of FIT and sDNA tests obtained a sensitivity of about 50.00% for precancerous lesions.⁶ In the present study, most of the positive cases we enrolled were LGIN. We found that the AUC of our prediction model for predicting positive colonoscopy results was much higher than that of the FIT + sDNA test scheme. This result indicated that the prediction model we constructed might have a good diagnostic performance in predicting precancerous lesions.

The present study has several limitations. First, the nomogram was established based on data obtained from a single center in China. This may cause selection bias. The high prevalence of colorectal lesions (51%) in this study likely enhances the positive predictive value of the screening tests. This might limit the nomogram's applicability in general screening populations, necessitating further validation in broader settings with varying lesion prevalence rates. Second, the nomogram we developed did not be validated by external dataset. Further prospective studies are needed to validate our model. Third, the number of patients with CRC was much low. Forth, an important limitation of this study is the small sample size of the “average risk” reference group, which may impact the statistical power and generalizability of our findings to this population. Future research involving larger sample sizes, especially within the average risk category, is needed to validate and extend our findings. Fifth, the participant selection and gender distribution in our study indeed warrant careful interpretation of the findings. The reduced number of participants with evaluable colonoscopy outcomes may introduce selection bias, potentially impacting the generalizability of our nomogram. The higher proportion of females in the training set, despite a higher prevalence of colon polyps in males, further complicates this bias. These aspects highlight the need for broader, more inclusive studies to validate our findings across diverse populations and to

ensure the nomogram's applicability in clinical practice, accounting for variations in compliance and demographic characteristics. Finally, the sDNA kit we used in this study was one available in China, which only targeted for SDC2 methylation. The FDA-approved multitarget stool DNA (MT-sDNA) test and other non-invasive screening should be tested in the further studies to enhance the diagnostic performance of our nomogram in predicting CRC and precancerous lesions.

The nomogram developed in this study offers a strategic tool for optimizing colonoscopy resource allocation by prioritizing high-risk individuals for further diagnostic procedures. Although the frequency of CRC, HGIN, and LGIN in those with negative screenings remains unquantified, the nomogram's risk stratification could enhance screening efficiency by reducing unnecessary colonoscopies in low-risk populations. This approach aligns with personalized medicine principles, guiding clinicians in tailoring screening strategies to individual risk profiles. Future research should focus on validating the nomogram across diverse populations and investigating surveillance strategies for high-risk individuals with negative screening results. In addition, this study may require longer follow-up to assess outcomes such as morbidity and mortality to further validate the accuracy of the conclusions.

Conclusion

In the present study, we developed an effective nomogram that used 3 non-invasive screening tools (APCS scoring, FIT and sDNA test) to predict positive colonoscopy results. Our results identified that our nomogram was a highly predictive tool that could be applied directly. Compared with previous studies, our nomogram predicted positive colonoscopy results with better diagnostic value than the combined FIT + sDNA assay protocol and more accurate diagnostic results. Therefore, our nomogram may be a promising strategy for CRC and precancerous lesion screening. This nomogram can help physicians identify CRC and its precancerous lesions earlier, thereby improving the early diagnosis rate of CRC, which is essential to improve patient survival and reduce cancer mortality.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of the Affiliated Hospital of Jiangnan University (approval number: LS2021013) in accordance with Declaration of Helsinki. Written informed consent was obtained from all participants.

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Disclosure

The authors declare no conflict of interest.

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