Cancer Screening and Prevention **2025** vol. 4(4) | 175–185
DOI: 10.14218/CSP.2025.00025

Original Article

Performance of the APCS-*SDC2* Score Based on a Fecal *SDC2* Methylation Assay for the Detection of Colorectal Polyps: A Multicenter Diagnostic Study

Xiaoliang Jin[1], Jing Zhao[1], Yuenian Chen[2], Li Xu[1], Ming Cheng[3], Ting Ye[4], Haifeng Jin[1], Liang Huang[1], Yue Hu[1], Haibiao Bao[1] and Bin Lyu[1*]

[1]*The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, Zhejiang, China;* [2]*Anji County Hospital of Traditional Chinese Medicine, Huzhou, Zhejiang, China;* [3]*Zhejiang Jin Hua Guang Fu Tumor Hospital, Jinhua, Zhejiang, China;* [4]*Hengdian Wenrong Hospital, Jinhua, Zhejiang, China*

Received: November 09, 2025 | **Revised:** November 18, 2025 | **Accepted:** December 10, 2025 | **Published online:** December 19, 2025

Abstract

Background and objectives: Accumulating evidence indicates that fecal syndecan-2 (*SDC2*) methylation is a promising biomarker for early detection of colorectal cancer. This study aimed to investigate the diagnostic efficacy of fecal *SDC2* methylation testing for adenomas and evaluate the risk stratification efficacy of the Asia-Pacific Colorectal Screening Scoring (APCS) combined with *SDC2* methylation status.

Methods: This was a prospective, multicenter diagnostic study. Adult participants with no history of colonoscopy within the past three years were enrolled. Demographic data were collected, and APCS scores were evaluated. All participants underwent fecal *SDC2* methylation testing and colonoscopy. Colonoscopy outcomes and pathological results of any polyps served as reference standards. The fecal *SDC2* methylation test and reference standard assessments were conducted in a blinded manner. The APCS-*SDC2* scoring system was developed by integrating fecal *SDC2* methylation results with APCS scores, and its efficacy was assessed.

Results: In total, 985 participants were enrolled, among whom 62 (6.3%) tested positive for fecal *SDC2* methylation. The sensitivity and specificity of fecal *SDC2* methylation in detecting advanced adenomas were 31.3% (95% confidence interval (CI): 21.6–42.7%) and 96.1% (95% CI: 94.6–97.2%), respectively. The APCS-*SDC2* scoring system demonstrated superior discriminatory performance for advanced adenomas (area under the curve: 0.7032; 95% CI: 0.5869–0.8195). For advanced adenoma screening, the specificity of the APCS-*SDC2* score was higher than that of the APCS score (86.7% vs. 66.7%; $P < 0.001$).

Conclusions: A positive fecal *SDC2* methylation test indicated a higher risk of advanced adenoma, and colonoscopy should be prioritized. The APCS-*SDC2* scoring system demonstrated superior risk stratification performance for advanced adenomas.

Introduction

Colorectal cancer (CRC) is a major threat to human health. According to the 2020 Global Cancer Statistics, the incidence of CRC ranks fifth globally.[1] Current investigations show that 70–90% of CRCs originate from adenomas and 10–20% evolve from serrated polyps.[2] Therefore, the early detection of colorectal adenomas is important for CRC screening. Colonoscopy is an effective method of screening for colorectal adenomas. Studies have shown that colonoscopy screening reduces the incidence of CRC by 18–26% and the mortality rate by 22–31%[3–7]; however, the acceptance of endoscopy by patients affects the screening effect to some extent.

A 10-year population-based multicenter study showed that the acceptance rate of the fecal occult blood test (FOBT) was significantly higher than that of colonoscopy among the population (34.25% vs. 25.38%, $P < 0.001$), and the acceptance rate of colon-

Keywords: Colorectal cancer; Adenoma; Diagnostic study; Asia-Pacific Colorectal Screening Scoring System; APCS-*SDC2* score; Cancer screening.

***Correspondence to:** Bin Lyu, Department of Gastroenterology, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, Zhejiang 310006, China. ORCID: https://orcid.org/0000-0002-6247-571X. Tel: +86-0571-8662-0286, Fax: +86-0571-8662-0286, E-mail: lvbin@medmail.com.cn

How to cite this article: Jin X, Zhao J, Chen Y, Xu L, Cheng M, Ye T, *et al*. Performance of the APCS-*SDC2* Score Based on a Fecal *SDC2* Methylation Assay for the Detection of Colorectal Polyps: A Multicenter Diagnostic Study. *Cancer Screen Prev* 2025;4(4):175–185. doi: 10.14218/CSP.2025.00025.

oscopy was even lower among older individuals with a high risk of colon cancer.[8] Many regions have established a two-step screening method, a screening strategy for selecting high-risk groups for CRC through the establishment of a risk model and then performing colonoscopy. Two-step risk models usually include demographic risk factors such as the Asia-Pacific Colorectal Screening Scoring System (APCS).[9,10] In addition, risk stratification models include FOBT and fecal DNA testing[11–13]; however, no study has provided clinical data for risk models that combine fecal syndecan-2 (*SDC2*) methylation testing.

SDC2 is located on human chromosome 8 (chr8:96,493,813–96,611,790) and encodes syndecan-2. It affects the proliferation and invasion of colon cancer cells by regulating their adhesion.[14,15] Research has shown that, compared with normal tissues, the *SDC2* gene exhibits higher levels of methylation at different stages of CRC and some adenoma tissues, and its expression in CRC and some adenoma tissues is also significantly higher than that in normal tissues, demonstrating its high diagnostic value.[16] Therefore, detecting the methylation level of *SDC2* in feces theoretically helps to diagnose colonic adenomas and colon cancer. Previous studies have confirmed that *SDC2* methylation has good sensitivity and specificity for detecting CRC or advanced adenomas.[17,18]

This study employed colonoscopy and histopathological examination as reference standards to conduct a multicenter diagnostic trial across six medical institutions, aiming to evaluate the sensitivity and specificity of the fecal double-fragment *SDC2* methylation test for CRC screening, refine the existing risk stratification scoring system, and validate its clinical utility.

Materials and methods

Study design

This study employed a prospective multicenter diagnostic research design and was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University (approval number: 2023-KLS-128-02); this approval covered all participating sites. This study adhered to the Declaration of Helsinki (as revised in 2024). Written informed consent was obtained from all participants. From August 2023 to February 2024, participants who met the inclusion criteria initially underwent fecal double-fragment *SDC2* methylation testing, followed by colonoscopy. During the colonoscopic procedure, polyps were removed upon obtaining written informed consent from the participants or their legally authorized representatives and were subsequently subjected to histopathological examination. Colonoscopy findings, combined with histopathological results, were used as reference standards to evaluate the performance of fecal double-fragment *SDC2* methylation testing. A novel risk stratification scoring system was developed by integrating the results of fecal double-fragment *SDC2* methylation testing with the APCS, and discriminatory and stratification efficacies were assessed.

Participants

Participants were enrolled consecutively and simultaneously from six medical institutions in Zhejiang Province, China, between August 2023 and February 2024. The participating institutions included the First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Anji County Hospital of Traditional Chinese Medicine, Quzhou Hospital of Traditional Chinese Medicine, Zhejiang Jin Hua Guang Fu Tumor Hospital, Hengdian Wenrong Hospital, and Jiaxing Xiuzhou District People's Hospital.

The participants were screened according to the following eligibility criteria. Inclusion criteria included: (1) age ≥ 18 years; (2) ability to provide a fresh fecal sample weighing > 2.5 g; and (3) no history of colonoscopy within the past three years. Exclusion criteria were as follows: (1) severe hepatic or cardiopulmonary dysfunction, coagulation or bleeding disorders, or recent use (within one week) of medications affecting the coagulation system that would contraindicate colonoscopy; (2) presence of watery stools; (3) confirmed diagnosis of Crohn's disease or ulcerative colitis with routine surveillance colonoscopies for inflammatory bowel disease; and (4) prior surgical intervention or other treatments for CRC.

Test methods

Prior to colonoscopy, participants collected fresh stool samples using the provided stool sampling kit, recorded demographic information (including patient ID, sex, and age) on the designated sampling card, and completed a case report form to document their medical history, including diabetes status, smoking and alcohol consumption, and family history of CRC.

The *SDC2* methylation test was performed by a certified third-party medical laboratory, and the laboratory personnel for *SDC2* were blinded to the colonoscopy and histology results. The fecal sampling kit with sample preservation solution (stored at room temperature and stable for up to seven days) and the human *SDC2* methylation detection kit were supplied by AI WEI KE BIOTECH Co., Ltd. In accordance with the testing protocol provided by the laboratory, the *SDC2* methylation assay consisted of the following four steps (for more details, please refer to the supplement file "Laboratory SOP"): (1) extraction of DNA from fecal samples, (2) bisulfite conversion of DNA, (3) polymerase chain reaction-based detection, and (4) result interpretation. A test result was considered negative if the ΔCt value in reaction solution A was ≥10.0 and the ΔCt value in reaction solution B was ≥10.5; otherwise, the result was considered positive.

Following the collection of fecal samples, the participants underwent bowel preparation prior to colonoscopy. Bowel cleansing was performed using 3,000 mL of isotonic full-bowel irrigation solution. The efficacy of bowel preparation was assessed during colonoscopy using the Boston Bowel Preparation Scale. The scores for the right, transverse, and left colons were all above 2 points, indicating adequate bowel preparation. The procedures were conducted using an Olympus HQ290AZI colonoscope, with a minimum withdrawal time of at least 6 m, a cecal intubation rate of at least 90%, and an adenoma detection rate of at least 20% (25% for men and 15% for women) set as quality metrics.[19] If colonoscopy findings indicated the presence of polyps, the endoscopists removed the polyps after obtaining written consent from the patient or their legally authorized representative. Histopathological evaluations were independently conducted by the Pathology Department of each participating institution. Throughout this process, both endoscopists and pathologists were blinded to the *SDC2* methylation test results.

Classification criteria

Based on the test results, samples were classified as negative or positive for *SDC2* methylation. According to the colonoscopic findings, individuals were categorized as having polyps (polyp-positive) or without polyps (polyp-negative). Polyps were further classified into hyperplastic polyps, adenomas, advanced adenomas, and carcinomas, based on histopathological evaluation. Adenomas meeting at least one of the following criteria were defined as advanced adenomas, which was pre-specified in the protocol[20]: (1) size ≥ 1 cm; (2) presence of high-grade intraepithelial neoplasia; (3) villous or tubulovillous architectural components.

Statistical analysis

Sample size estimation

The sample size was determined using the following formula:

$$n(\text{base on sensibility}) = \frac{Z_{1-\alpha/2} \times S_N \times (1 - S_N)}{L^2 \times \text{Prevalence}}$$

According to clinical research of the Human Fecal Double Fragment *SDC2* Gene Methylation Detection Kit (fluorescence polymerase chain reaction method), the assay demonstrated a sensitivity (S_N) of 66.1% for detecting advanced adenomas and CRC in asymptomatic individuals, with a specificity (S_P) of 90.1%. Based on previous data from our medical center,[21] the prevalence of colorectal adenomas among individuals undergoing colonoscopy was 25.8%, with advanced adenoma accounting for 8.3% and CRC detected in 0.6% of cases. The allowable margin of error (L) was set at 0.1, and the significance level (α) was established at 0.05. Based on sensitivity and specificity calculations, the required sample size was no less than 746 cases.

Risk factors and kappa analysis

Data were analyzed using SPSS version 25.0. Normally distributed measurement data are presented as mean ± standard deviation and were compared using the independent samples t-test. Non-normally distributed measurement data are expressed as medians (interquartile ranges) and were analyzed using the Mann–Whitney U test. Categorical variables, including rates and constituent ratios, are expressed as N (%) and were compared using the chi-square test or Fisher's exact test, as appropriate. The Kappa statistic was used to assess the agreement between the *SDC2* methylation detection results and colonoscopic findings. Concurrently, the sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

Model establishment and validation

This study employed a development-validation research design. During the model development phase, 632 participants were included, and data from an independent, randomly selected sample of 316 participants were used in the external validation set.

The RAND function in Excel was used to randomly select samples for model development. Ordered logistic regression was used to assess the effects of the predictor variables and assign the corresponding scores. Bootstrap optimism correction (n = 200) was used to evaluate model performance using the receiver operating characteristic curve and area under the curve (AUC). The Youden index and corresponding optimal cutoff values were determined.[22] The statistical significance of the differences in AUC values was assessed using the DeLong test. The calibration performance of the development set (n = 632) was evaluated via bootstrap optimism correction (B = 200) using the "rms" package in R 4.5.2. The calibration performance of the validation set was evaluated by directly applying the coefficients of the development set model to the validation set data (n = 316) and generating a scatter plot of the predicted versus observed probabilities. The calibration intercept represents the overall accuracy of the predicted risk, and the calibration slope represents the appropriateness of the predicted risk range.

Results

Patient characteristics

A total of 985 participants were recruited who underwent both fecal *SDC2* methylation kit testing. All *SDC2* test results were valid, with all participants demonstrating adequate bowel preparation and undergoing complete colonoscopy. During the period between fecal collection and colonoscopy, no new medical treatments were initiated for the participants, and patients with diabetes continued their original blood sugar management regimens. Polyps were detected in 462 individuals, among whom 37 did not undergo polypectomy or pathological examination at the medical centers involved in this study. These participants were included in the polyp detection rate; however, they were not included in the estimated risk factors and the APCS-*SDC2* scoring system. A total of 425 patients underwent endoscopic polypectomy and pathological examinations. The pathological types of the polyps are shown in Figure 1. There were 204 cases of adenomas, with a detection rate of 20.7%, and 80 cases of advanced adenomas, with a detection rate of 8.1%.

The risk factors for polyps, adenomas, and advanced adenomas were analyzed individually. The results of the univariate and multivariate logistic regression analyses are presented in Table 1. Age, male sex, and smoking history were identified as independent risk factors for polyps. Independent risk factors for adenomas included age, male sex, smoking history, and family history of CRC. Age, male sex, and a family history of CRC were identified as independent predictors of advanced adenomas.

Diagnostic effect

Pathological examination served as the reference standard for evaluating the diagnostic sensitivity and specificity of fecal *SDC2* methylation for the identification of colon polyps, adenomas, and advanced adenomas. The results demonstrated that the sensitivity of fecal double-fragment *SDC2* methylation detection for advanced adenomas was 31.3%, with a specificity of 96.1%, a positive predictive value of 42.4%, and a negative predictive value of 93.8%. Kappa consistency analysis indicated a statistically significant agreement between fecal *SDC2* methylation testing and the reference standard for the detection of polyps, adenomas, and advanced adenomas ($P < 0.001$), as detailed in Table 2.

APCS-SDC2 scoring system

By integrating the *SDC2* test results with the APCS score, we developed a novel scoring system, termed APCS-*SDC2*, which incorporates age, sex, smoking status, family history, and *SDC2* test results, as presented in Table 3. A total of 632 samples were randomly selected to develop the scoring system, and 316 samples were used to validate the performance of the model.

Receiver operating characteristic curves were used to assess the risk prediction performance of the APCS-*SDC2* system. First, in the development set: (1) for adenomas, the apparent AUC of the APCS-*SDC2* score was 0.6899 (95% confidence interval (CI): 0.644–0.7358), and the corrected AUC was 0.6879 after bootstrap optimism correction (mean optimism = 0.002). The apparent AUC of the APCS score was 0.682 (95% CI: 0.6365–0.7275, DeLong $P = 0.2016$). (2) For advanced adenomas, the apparent AUC of the APCS-*SDC2* score was 0.7917 (95% CI: 0.7311–0.8523), and the corrected AUC was 0.7915 after bootstrap optimism correction (mean optimism = 0.0002). The apparent AUC of the APCS was 0.7523 (95% CI: 0.6971–0.8074, DeLong $P = 0.0047$). Second, in the independent validation set: (1) for adenomas, the apparent AUC of the APCS-*SDC2* score was 0.6099 (95% CI: 0.5429–0.6769), and the apparent AUC of the APCS score was 0.5888 (95% CI: 0.5224–0.6553, DeLong $P = 0.0676$). (2) For advanced adenomas, the apparent AUC of the APCS-*SDC2* score was 0.7032 (95% CI:

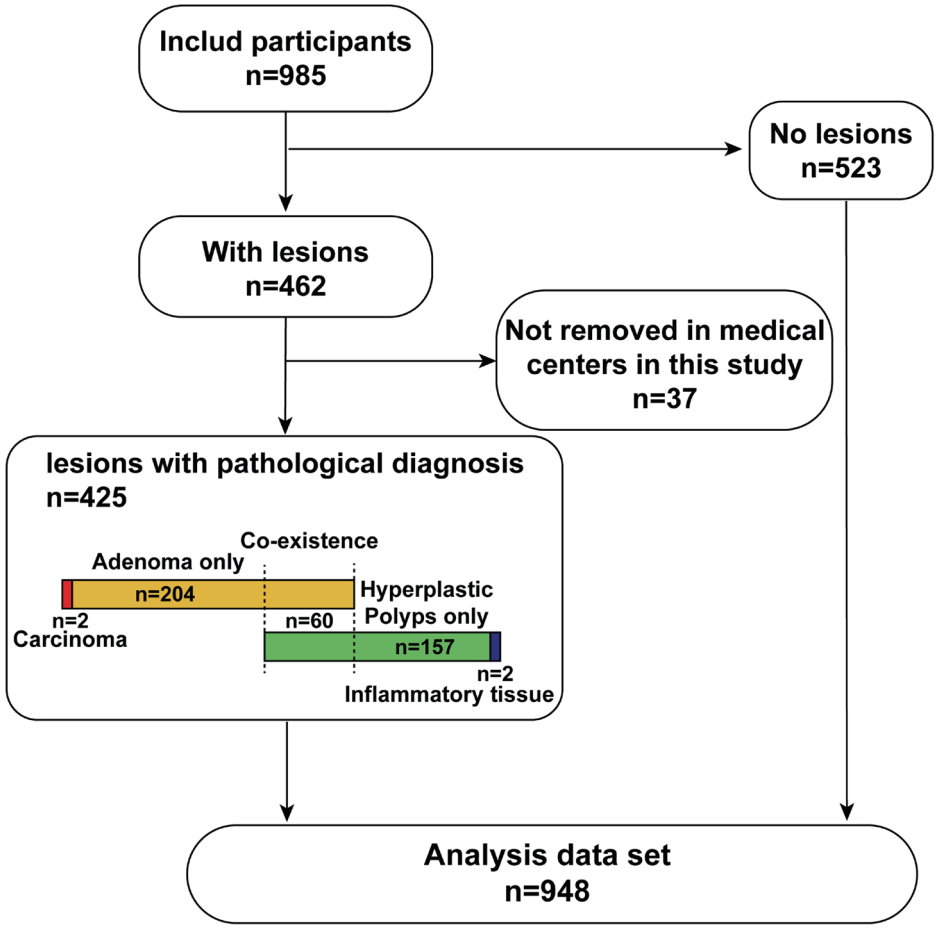

Fig. 1. The participants included in this study.

Table 1. Risk factors for polyp, adenoma, and advanced adenoma

Polyps	Univariate analysis			Multivariate analysis	
	Positive (n = 462)	Negative (n = 523)	*P*	OR (95% CI)	*P*
APCS score	2.43 ± 1.23	1.79 ± 1.18	<0.001		
Age	57.9 ± 9.6	53.1 ± 10.5	<0.001	1.046 (1.032–1.060)	<0.001
Sex			<0.001	1.684 (1.274–2.225)	<0.001
Female	212 (39.3%)	328 (60.7%)			
Male	250 (56.2%)	195 (43.8%)			
Smoke			<0.001	2.067 (1.105–3.865)	0.023
Yes	71 (74.1%)	24 (25.3%)			
No	391 (43.9%)	499 (56.1%)			
Drink			<0.001	1.486 (0.775–2.852)	0.233
Yes	59 (72.8%)	22 (27.2%)			
No	403 (44.6%)	501 (55.4%)			
Diabetes			0.072		
Yes	20 (62.5%)	12 (37.5%)			
No	442 (46.4%)	511 (53.6%)			

(continued)

Table 1. *(continued)*

Polyps	Univariate analysis			Multivariate analysis	
	Positive (n = 462)	Negative (n = 523)	*P*	OR (95% CI)	*P*
Family history of CRC			0.005	1667743611 (0-/)	0.999
Yes	7 (100%%)	0 (0%)			
No	455 (46.5%)	523 (53.5%)			
Boston score	7.46 ± 0.86	7.51 ± 0.82	0.195		
Right colon	2.48 ± 0.50	2.47 ± 0.50	0.615		
Transverse colon	2.47 ± 0.50	2.54 ± 0.50	0.665		
Left colon	2.51 ± 0.50	2.50 ± 0.50	0.829		

Adenoma	Univariate analysis			Multivariate analysis	
	Positive (n = 264)	Negative (n = 684)	*P*	OR (95% CI)	*P*
APCS score	2.56 ± 1.20	1.91 ± 1.21	<0.001		
Age	58.7 ± 9.5	54.0 ± 10.4	<0.001	1.045 (1.029–1.061)	<0.001
Gender			<0.001	1.578 (1.147–2.172)	0.005
Female	116 (22.2%)	407 (77.8%)			
Male	148 (34.8%)	277 (65.2%)			
Smoke			<0.001	2.036 (1.118–3.707)	0.020
Yes	49 (52.7%)	44 (47.3%)			
No	215 (25.1%)	640 (74.9%)			
Drink			<0.001	1.283 (0.683–2.411)	0.438
Yes	39 (49.4%)	40 (50.6%)			
No	225 (25.9%)	644 (74.1%)			
Diabetes			0.015	1.629 (0.768–3.453)	0.203
Yes	15 (46.9%)	17 (53.1%)			
No	249 (27.2%)	667 (72.8%)			
Family history of CRC			0.008	13.637 (1.554–119.682)	0.018
Yes	5 (83.3%)	1 (16.7%)			
No	259 (27.5%)	683 (72.5%)			
Boston score	7.44 ± 0.85	7.49 ± 0.84	0.782		
Right colon	2.48 ± 0.50	2.7 ± 0.50	0.564		
Transverse colon	2.46 ± 0.50	2.53 ± 0.50	0.358		
Left colon	2.50 ± 0.50	2.49 ± 0.50	0.812		

Advanced adenoma	Univariate analysis			Multivariate analysis	
	Positive (n = 80)	Negative (n = 868)	*P*	OR (95% CI)	*P*
APCS score	2.95 ± 0.99	2.01 ± 1.23	<0.001		
Age	61.4 ± 9.2	54.8 ± 10.3	<0.001	1.068 (1.041–1.095)	<0.001
Gender			<0.001	2.165 (1.269–3.693)	0.005
Female	29 (5.5%)	494 (94.5%)			
Male	51 (12.0%)	374 (88.0%)			
Smoke			<0.001	1.646 (0.725–3.737)	0.234

(continued)

Table 1. *(continued)*

Advanced adenoma	Univariate analysis			Multivariate analysis	
	Positive (n = 80)	Negative (n = 868)	*P*	OR (95% CI)	*P*
Yes	17 (18.3%)	76 (81.7%)			
No	63 (7.4%)	792 (92.6%)			
Drink			0.007	1.097 (0.453–2.656)	0.837
Yes	13 (16.5%)	66 (83.5%)			
No	67 (7.7%)	802 (92.3%)			
Diabetes			0.137	-	-
Yes	5 (15.6%)	27 (84.4%)			
No	75 (8.2%)	841 (91.8%)			
Family history of CRC			<0.001	16.531 (3.027–90.288)	0.001
Yes	3 (50%)	3 (50%)			
No	77 (8.2%)	865 (91.8%)			
Boston score	7.54 ± 0.83	7.47 ± 0.84	0.703		
Right colon	2.56 ± 0.50	2.46 ± 0.50	0.244		
Transverse colon	2.46 ± 0.50	2.51 ± 0.50	0.160		
Left colon	2.51 ± 0.50	2.49 ± 0.50	0.806		

APCS, Asia-Pacific Colorectal Screening Scoring; CI, confidence interval; CRC, colorectal cancer; OR, odds ratio.

0.5869–0.8195), and the apparent AUC of the APCS score was 0.6228 (95% CI: 0.5113–0.7343, DeLong $P = 0.0583$), as shown in Figure 2.

In the model developed to identify individuals at risk of adenomas, the calibration plot of the development set displayed favorable calibration characteristics (calibration slope = 1.0), and the calibration performance remained stable in the external validation set (calibration intercept = 0.021, calibration slope = 0.591). Similarly, after calibrating the model to identify individuals at high risk for advanced adenomas, the calibration plot of the development set

Table 2. The diagnostic performance of the fecal *SDC2* Methylation test

Polyps		Colonoscopy combined with pathology			Kappa value (95% CI)	*P*
		Positive	Negative			
SDC2	Positive	49	13	79.0% (66.5–87.9%)[c]	0.086 (0.05, 0.12)	<0.001
	Negative	413	510	55.3% (52.0–58.5%)[d]		
		10.6% (8.0–13.9%)[a]	97.5% (95.7–98.6%)[b]			

Adenoma		Colonoscopy combined with pathology			Kappa value (95% CI)	*P*
		Positive	Negative			
SDC2	Positive	32	27	54.2% (40.8–67.1%)[c]	0.107 (0.05, 0.16)	<0.001
	Negative	232	657	73.9% (70.9–76.7%)[d]		
		12.1% (8.6–16.8%)[a]	96.1% (94.2–97.3%)[b]			

Advanced adenoma		Colonoscopy combined with pathology			Kappa value (95% CI)	*P*
		Positive	Negative			
SDC2	Positive	25	34	42.4% (29.8–55.9%)[c]	0.310 (0.20, 0.42)	<0.001
	Negative	55	834	93.8% (92.0–95.3%)[d]		
		31.3% (21.6–42.7%)[a]	96.1% (94.6–97.2%)[b]			

[a]Sensitivity (95% confidence interval); [b]Specificity (95% confidence interval); [c]positive predictive value (95% confidence interval); [d]negative predictive value (95% confidence interval). CI, confidence interval; *SDC2*, syndecan-2.

Table 3. APCS-*SDC2* scoring system

Risk factor	Categories	Points
Age	<50	0
	50–69	2
	≥70	3
Gender	Female	0
	Male	1
Smoke	No	0
	Yes	1
Family history	No	0
	Yes	2
Fecal *SDC2* test	Negative	0
	Positive	2 or 3*

In the logistic regression model for adenoma, the intercept was −2.287 (SE: 0.229), the coefficient of the APCS score was 0.542 (SE: 0.085), and the coefficient of the fecal *SDC2* test was 0.889 (SE: 0.343). In the logistic regression model for advanced adenoma, the intercept was −4.768 (SE: 0.488), the coefficient of the APCS score was 0.831 (SE: 0.153), and the coefficient of the fecal *SDC2* test was 2.207 (SE: 0.378). The cut-off points of APCS-*SDC2* for adenoma and advanced adenoma were 4 and 5 points. *2 points for adenoma and 3 points for advanced adenoma in the APCS-*SDC2* scoring system. APCS, Asia-Pacific Colorectal Screening Scoring; *SDC2*, syndecan-2; SE, standard error.

demonstrated good calibration characteristics (calibration slope = 1.0), and the calibration performance remained stable in the external validation set (calibration intercept = −0.014, calibration slope = 0.695). This indicated that the predicted probabilities of the model exhibited good consistency across different populations, as shown in Figure 3.

The optimal cutoff value for the APCS score in adenoma screening was determined to be 2 points, yielding a sensitivity of 80% and a specificity of 31.9%. For the APCS-*SDC2* score, the corresponding cutoff value was 4 points, with a significantly lower sensitivity of 36.4% ($P < 0.001$) and a higher specificity of 76.3% ($P < 0.001$). In the detection of advanced adenomas, the APCS score demonstrated an optimal cutoff of 3 points, achieving a sensitivity of 50% and a specificity of 66.7%. For the APCS-*SDC2* score, the cutoff value was set at 5 points, resulting in a sensitivity of 36.4% ($P = 0.361$) and a significantly higher specificity of 86.7% ($P < 0.001$), as shown in Table 4. The clinical reclassification tables versus APCS showed that when the APCS score was 2, a positive *SDC2* indicated a transition from low risk to high risk of advanced adenomas (Table 5). No adverse events were observed during the study period.

Discussion

The prognosis of CRC is influenced by tumor stage, with the five-year survival rate decreasing as the tumor progresses. Early diagnosis and treatment are key to the management of colon cancer.[23] Research has shown that most CRCs originate from adenomas, and adenoma screening is an important means of reducing the incidence of colon cancer.[4] Significant changes in gene expression occur during the occurrence and development of CRC, such as the overactivation of proto-oncogenes and the inactivation of tumor suppressor genes.[24,25] Fecal DNA testing is a new detection method that combines gene sequencing technology.[26,27] Detection of specific gene fragments may improve the specificity of screening for colon adenomas and colon cancer and is a promising noninvasive method for screening CRC and adenomas.

Previous studies have shown significant differences in the methylation levels of *SDC2* between colon cancer tissues and adjacent tissues.[16] A detection kit developed based on this method has achieved positive results in previous clinical diagnostic studies.[17,28] A 2022 study indicated that the sensitivity of fecal *SDC2* and SFRP2 gene detection in CRC was 92.9%.[29] Many studies have demonstrated the screening role of noninvasive tests, such as the FOBT and fecal immunochemical test (FIT), in CRC. Some studies have also established a modified APCS combined with noninvasive tests to enhance stratification ability.[30–32] Subsequent studies have shown that the combination of fecal DNA testing (*SDC2* and *SFRP2*), FOBT, FIT, and APCS scores increases the detection rate of advanced adenomas (95.2% of CRC and 73.5% of advanced adenomas).[13] A meta-analysis demonstrated that the true positive rate of advanced adenomas detected through FIT screening was 6.6% (5.2–7.7%),[33] which was lower than the outcome of fecal *SDC2* detection (42.4%, 95% CI: 29.8–55.9%). Moreover, research has revealed that the sensitivity of the APCS score in combination with FIT for advanced adenoma was 28% (7/25),[34] which was also lower than that of the APCS-*SDC2* scoring system (31.3%, 95% CI: 21.6–42.7%).

Our results showed that the independent risk factors for colonic polyps, adenomas, and advanced adenomas were similar. In this study, the adenoma detection rate was 20.7%, which met the quality assessment criteria,[35] and the endoscopic results were reliable. The population with positive fecal *SDC2* methylation had a higher detection rate of polyps (odds ratio (OR) = 4.014, 95% CI: 2.091–7.707, $P < 0.001$), adenomas (OR = 2.806, 95% CI: 1.601–4.918, $P < 0.001$), and advanced adenomas (OR = 9.554, 95% CI: 5.137–17.770, $P < 0.001$). We further investigated the role of the fecal double-fragment *SDC2* test in population screening and established an APCS-*SDC2* scoring system by combining the results of the fecal *SDC2* methylation detection. The internal validation results showed that the modified APCS scoring system based on the *SDC2* test results had better discrimination of colon polyps, adenomas, and advanced adenomas than the original APCS scoring system. Therefore, the introduction of *SDC2* test results as a risk factor improved the ability of the model to distinguish high-risk populations for intestinal polyps, adenomas, and advanced adenomas. In addition, the APCS-*SDC2* scoring system significantly increased the specificity for advanced adenomas, and the sensitivity was not significantly different from that of the APCS scoring system and was consistent with colonoscopic results combined with pathological detection.

Limitations

This study has some limitations. Screening cost is a factor that must be considered in screening strategies. The trade-off between the cost of fecal *SDC2* methylation testing and patient willingness to accept invasive examinations is key to determining whether this technology has economic benefits.[36] Economic benefit analysis was not included in this study.

Conclusions

Among individuals with positive fecal *SDC2* methylation test results, the detection rates of advanced adenomas were significantly elevated, and colonoscopy should be prioritized. The APCS-*SDC2*

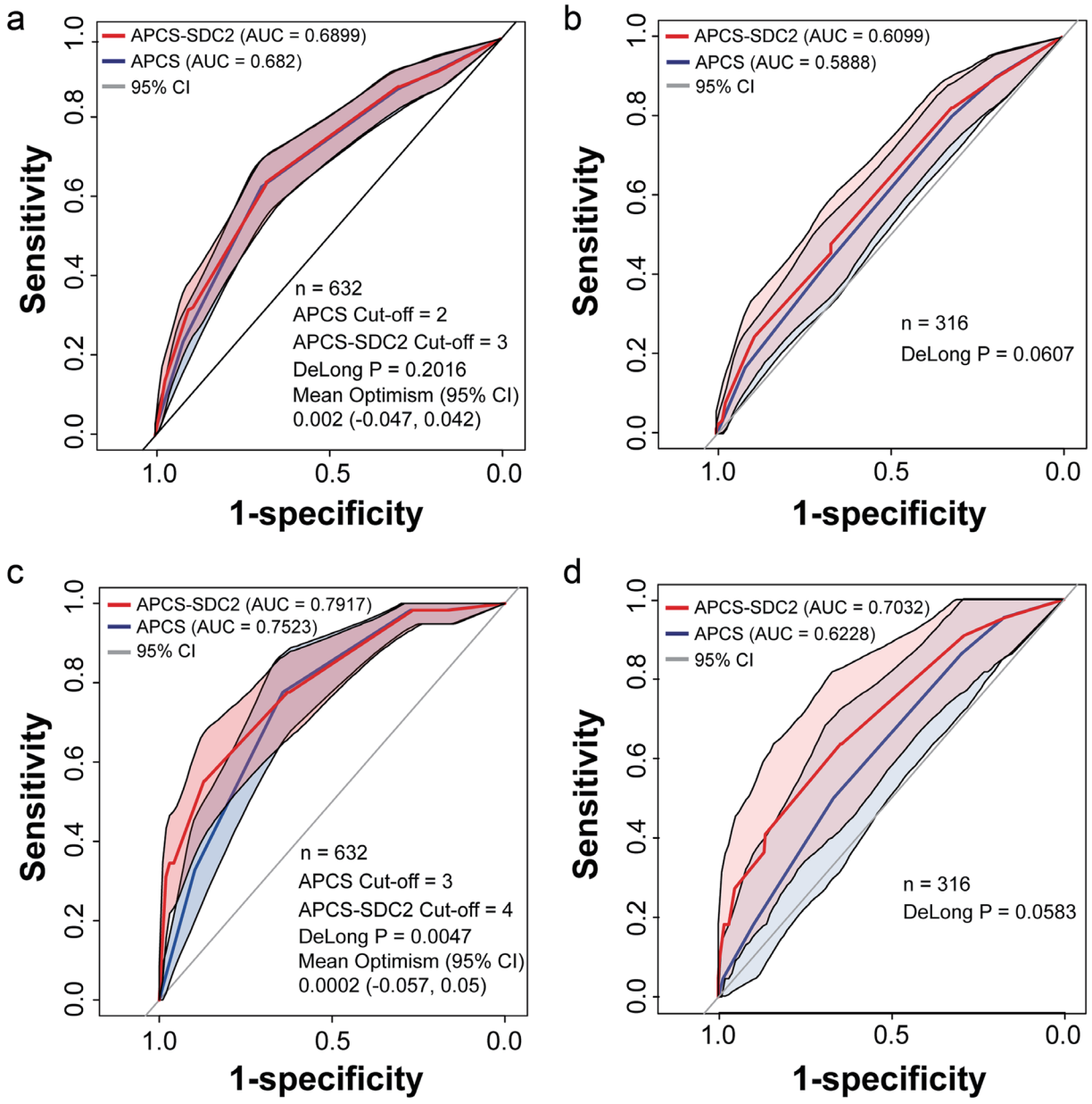

Fig. 2. ROC curves of the scoring system for adenomas and advanced adenomas. The comparison of the ROC curves of the APCS-*SDC2* score and APCS score in the diagnosis of adenomas (a: development set, b: validation set) and advanced adenomas (c: development set, d: validation set). The APCS-*SDC2* scoring system was developed using 632 samples selected randomly. Ordered logistic regression and bootstrap optimism correction were applied to assess the effects of predictor variables and assign corresponding scores. The validation cohort, including 316 samples, was used to validate the model's performance. The shaded area represents the 95% confidence interval. APCS, Asia-Pacific Colorectal Screening Scoring; AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic curve; *SDC2*, syndecan-2.

scoring system, which integrates fecal *SDC2* methylation testing, demonstrated superior risk stratification performance for advanced adenomas compared with the APCS scoring system, along with higher specificity.

Acknowledgments

The authors gratefully acknowledge Hangzhou AI WEI KE BIOTECH Co., Ltd. for providing fecal sampling kits, sample preservation solution, and human *SDC2* gene methylation detection kits.

Funding

This study received no funding support.

Conflict of interest

Prof. Bin Lyu has been an editorial board member of *Cancer*

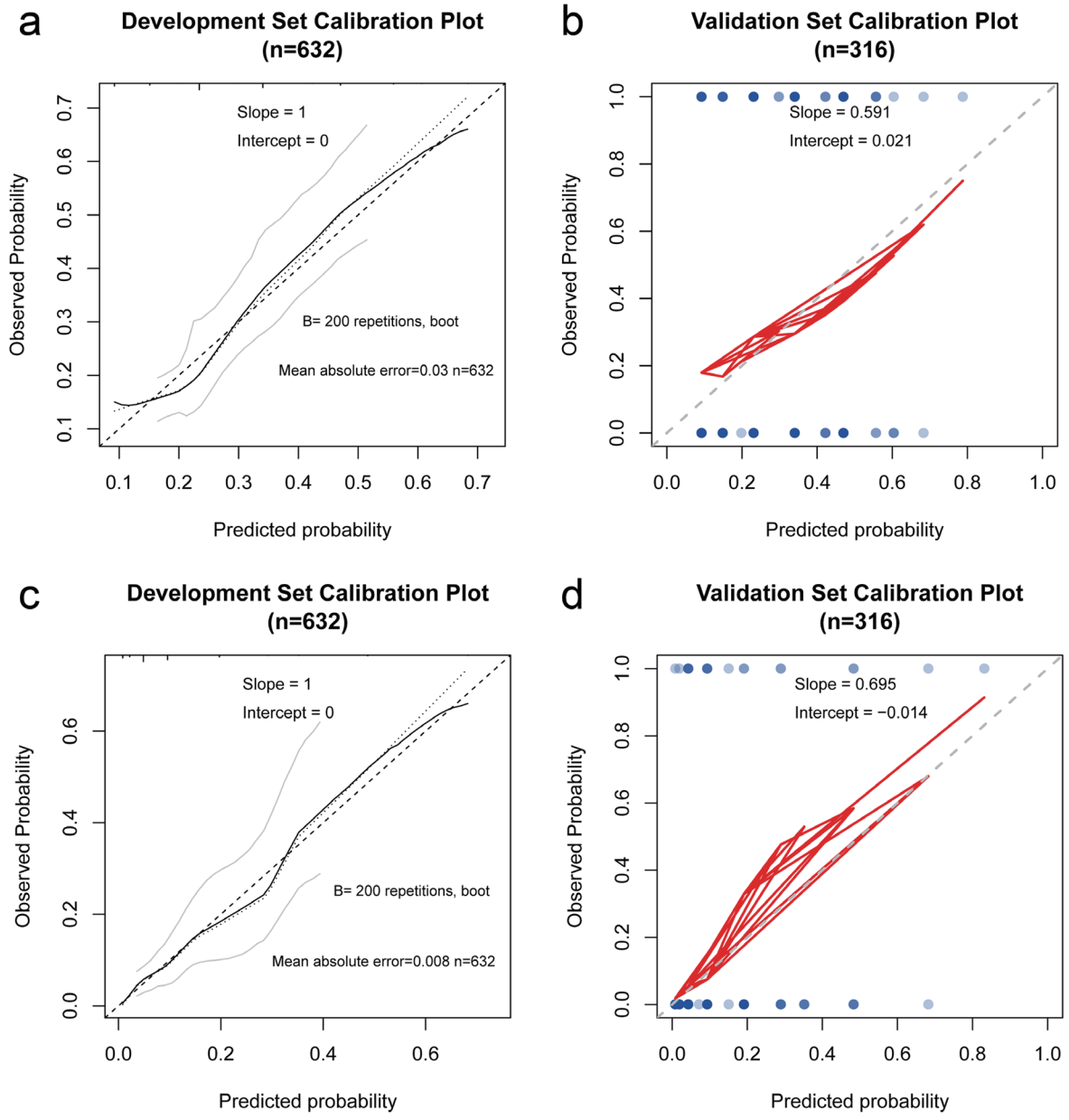

Fig. 3. The calibration plot of the development set and external validation set. Calibration plots for the development set (n = 632) targeting adenoma (a) and advanced adenoma (c). The solid line represents the observed calibration curve, the dashed line represents the ideal calibration (slope = 1, intercept = 0), and the histogram shows the distribution of predicted probabilities. The model was internally validated using bootstrap resampling (B = 200 repetitions), and the mean absolute error in the development set was 0.03. Calibration plots for the external validation set (n = 316). The calibration performance decreased in the validation set, with a calibration slope of 0.591 and an intercept of 0.021 for adenoma (b), and a slope of 0.695 and an intercept of −0.014 for advanced adenoma (d).

Screening and Prevention since February 2022. The authors have no other conflicts of interest related to this publication.

Author contributions

Writing - original draft, data curation, formal analysis, methodology, visualization (XJ), validation (XJ, JZ, YC, LX, MC, TY, HJ, HB), conceptualization (XJ, JZ, BL), project administration (JZ), investigation (YC, LX, MC, TY, HJ, HB, LH, YH), writing - review & editing, supervision, and funding acquisition (BL). All authors have approved the final version and publication of the manuscript.

Ethical statement

This study adhered to the Declaration of Helsinki (as revised in 2024) and was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University (approval number: 2023-KLS-128-02). Written informed consent was ob-

Table 4. Consistency test based on the scoring system

Adenoma		Colonoscopy combined with pathology			Kappa value (95% CI)	*P*
		Positive	Negative			
APCS	Positive	72	154	31.9% (25.8–38.4%)[c]	0.082 (0.009, 0.155)	0.035
	Negative	18	72	80% (70.2–87.7%)[d]		
		80% (70.2–87.7%)[a]	31.9% (25.8–38.4%)[b]			
APCS_*SDC2*	Positive	43	47	47.8% (37.1–58.6%)[c]	0.133 (0.023, 0.243)	0.016
	Negative	75	151	66.8% (60.3–72.9%)[d]		
		36.4% (27.8–45.8%)[a]	76.3% (69.7–82%)[b]			

Advanced adenoma		Colonoscopy combined with pathology			Kappa value (95% CI)	*P*
		Positive	Negative			
APCS	Positive	11	98	10.1% (5.1–17.3%)[c]	0.059 (−0.019, 0.137)	0.113
	Negative	11	196	94.7% (90.7–97.3%)[d]		
		50% (28.2–71.8%)[a]	66.7% (61–72%)[b]			
APCS_*SDC2*	Positive	8	39	17% (7.6–30.8%)[c]	0.151 (0.014, 2.88)	0.003
	Negative	14	255	94.8% (91.4–97.1%)[d]		
		36.4% (17.2–59.3%)[a]	86.7% (82.3–90.4%)[b]			

[a]Sensitivity (95% confidence interval); [b]Specificity (95% confidence interval); [c]positive predictive value (95% confidence interval); [d]negative predictive value (95% confidence interval). APCS, Asia-Pacific Colorectal Screening Scoring; CI, confidence interval; *SDC2*, syndecan-2.

Table 5. Clinical reclassification tables versus APCS

APCS Point	Adenoma		Advanced adenoma	
	APCS	Plus *SDC2*	APCS	Plus *SDC2*
1	low risk	low risk	low risk	low risk
2	high risk	high risk	low risk	high risk
≥3	high risk	high risk	high risk	high risk

APCS, Asia-Pacific Colorectal Screening Scoring; *SDC2*, syndecan-2.

tained from all participants.

Data sharing statement

The datasets analyzed during this study are available from the corresponding author upon reasonable request.

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