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FIT-based risk-stratification model effectively screens colorectal neoplasia and early-onset colorectal cancer in Chinese population: a nationwide multicenter prospective study

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Abstract

No fully validated risk-stratification strategies have been established in China where colonoscopies resources are limited. We aimed to develop and validate a fecal immunochemical test (FIT)-based risk-stratification model for colorectal neoplasia (CN); 10,164 individuals were recruited from 175 centers nationwide and were randomly allocated to the derivation ($n = 6776$) or validation cohort ($n = 3388$). Multivariate logistic analyses were performed to develop the National Colorectal Polyp Care (NCPC) score, which formed the risk-stratification model along with FIT. The NCPC score was developed from eight independent predicting factors and divided into three levels: low risk (LR 0–14), intermediate risk (IR 15–17), and high risk (HR 18–28). Individuals with IR or HR of NCPC score or FIT+ were classified as increased-risk individuals in the risk-stratification model and were recommended for colonoscopy. The IR/HR of NCPC score showed a higher prevalence of CNs (21.8%/32.8% vs. 11.0%, $P < 0.001$) and ACNs (4.3%/9.2% vs. 2.0%, $P < 0.001$) than LR, which was also confirmed in the validation cohort. Similar relative risks and predictive performances were demonstrated between non-specific gastrointestinal symptoms (NSGS) and asymptomatic cohort. The risk-stratification model identified 73.5% CN, 82.6% ACN, and 93.6% CRC when guiding 52.7% individuals to receive colonoscopy and identified 55.8% early-onset ACNs and 72.7% early-onset CRCs with only 25.6% young individuals receiving colonoscopy. The risk-stratification model showed a good risk-stratification ability for CN and early-onset CRCs in Chinese population, including individuals with NSGS and young age.

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To the Editor,

Risk-stratification screening efficiently reduces the incidence and mortality rate of colorectal cancer (CRC) [1], but no risk-stratification model has been extensively validated in China where the limited colonoscopy resources are mainly occupied by low-risk individuals with non-specific gastrointestinal symptoms (NSGS) [2, 3], who are considered equivalent to average-risk population for the risk of advanced colorectal neoplasia (ACN) [4, 5]. Current guidelines struggle to recommend to start colonoscopy screening at the age of 45 or 50 [6, 7]. However, any "one-size-fits-all" standard for age may prevent the detection of many early-onset CRCs [8, 9]. Herein, under the dilemma of inefficient detection, limited resources, and increasing early-onset CRC screening faced by colonoscopy practice, we developed and validated a risk-stratification model for colorectal neoplasia (CN).

From 2018 to 2020, the National Colorectal Polyp Care (NCPC) program was implemented in 175 centers nationwide (Fig. 1A), where consecutive adult individuals who had no alarming symptoms or signs of CRC were enrolled, regardless of NSGS [4]. All participants completed questionnaires regarding baseline information and life risk factors and received fecal immunochemical tests (FITs) and colonoscopies. A central database was established to manage the uploaded data from all centers (accessed at www.ncrcgastro.org). The primary outcome was the CN [10]. The details of methods, including exclusion criteria, outcome measures, sample size calculation, and statistical analysis, are illustrated in Additional file 1: Supplementary Methods.

A total of 10,164 participants were enrolled (Fig. 1B), whose clinical characteristics were comparable between the derivation and validation cohort (Additional file 2: Tables S1–2). The univariate analysis identified 11 potential risk factors, and eight variables (sex, age, body mass index, smoking, drinking, diabetes, first-degree relative of CRC, history of previous negative colonoscopy) were identified as independent predicting factors for developing NCPC score (Additional file 2: Table S3, Fig. 1C), while the other variables were excluded (Additional file 2: Table S4). The NCPC score was divided into three levels according to the mean CN prevalence: low risk (LR 0–14, 0–17.4%), intermediate risk (IR 15–17, 18.8–24.0%), and high risk (HR 18–28, ≥ 25.9%) (Additional file 2: Table S5). Compared with FIT- individuals, FIT+ individuals showed higher risks for CN, ACN, and CRC in all subgroups of NCPC score (all $P < 0.001$) (Additional file 2: Table S6). Therefore, the risk-stratification model (Changhai Li's Model) triaged individuals with IR or HR NCPC scores or FIT+ as increased-risk individuals to receive colonoscopy.

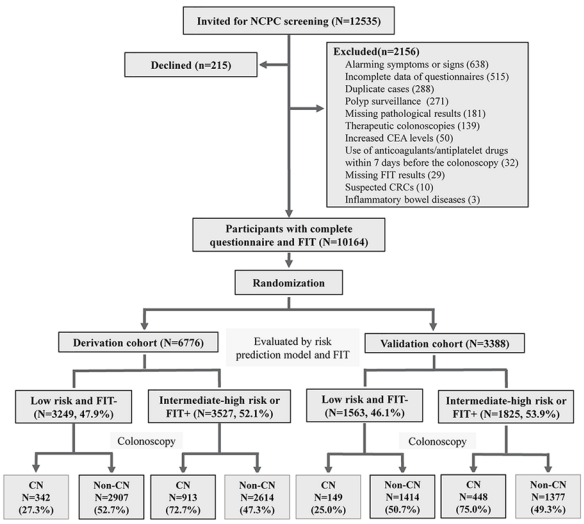
The model showed good calibrations no significant difference of area under curve (AUC) between the derivation and validation cohort (0.68 vs. 0.68, $P = 0.80$); consistent predicting performance in risk-stratification ability and individuals' distribution were confirmed in the deviation and validation cohort (Figs. 1D, 2A). No significant difference of AUC was also found between NSGS and asymptomatic population (0.68 vs. 0.67, $P = 0.31$), where the predicting performances were demonstrated to be similar; individuals' distribution and prevalence of CN and ACN were also found to be consistent between NSGS and asymptomatic individuals (Figs. 1D, 2B).

Compared with FIT or other Asian models, the NCPC score showed the best discriminative ability for CN [0.67, $P < 0.001$] and ACN [0.70, $P < 0.001$ or $= 0.002$] [1, 11, 12] (Fig. 2C-E). The NCPC score could identify 70.7% CN, 77.7% ACN, and 78.7% CRC when reducing 29.2%, 35.5%, and 36.4% number needed for screening colonoscopies to detect one lesion (NNS), respectively (Fig. 2F). The risk-stratification model could identify 73.5% CN, 82.6% ACN, and 93.6% CRC when recommending 52.7% individuals to receive colonoscopy (Fig. 2F). By using risk-stratification model, only 25.6% young individuals will be recommended for colonoscopy, and 55.8% ACN and 72.7% CRC of young population could be identified when reducing 54.2% and 64.8% corresponding NNS, respectively (Fig. 2F).

In summary, a risk-stratification model (Changhai Li's Model) for CN, consisting of FIT and NCPC score, was developed and validated to improve the efficiency of CRC screening. The model was able to save almost a half colonoscopy resources when maintaining a high sensitivity for CN, ACN, and CRC. Notably, 55.8% early-onset ACN and 72.7% early-onset CRC were identified with only 25.6% young individuals receiving colonoscopy. Consistent risk-stratifying performance was demonstrated between NSGS and asymptomatic population, which could rationally promote scope of CRC screening to cover the previously "ignored" NSGS population and avoid "indication gaming." This model holds the promise as a feasible risk-stratification approach to improve the colonoscopy efficiency and CRC-screening scope in China and other countries with limited resources.

A

B



C

Variable	Adjusted OR (95% CI)	P value	Log-Odds Coefficients	Points assigned*
Sex		<0.001		
Female	Reference			0
Male	1.45 (1.24-1.69)	<0.001	0.370	2
Age, year		<0.001		
<35	Reference			0
35-45	2.93 (2.10-4.09)	<0.001	1.075	7
45-50	4.47 (3.20-6.25)	<0.001	1.498	9
50-60	6.12 (4.48-8.37)	<0.001	1.811	11
60-70	7.68 (5.55-10.63)	<0.001	2.039	13
≥70	8.05 (5.25-12.36)	<0.001	2.086	13
BMI, kg/m²		0.01		
< 24	Reference			0
≥ 24	1.18 (1.03-1.34)	0.01	0.163	1
Smoking		0.003		
No	Reference			0
Current	1.38 (1.14-1.66)	0.001	0.321	2
Past	1.30 (0.94-1.80)	0.12	0.260	2
Drinking		0.003		
No	Reference			0
Current	1.36 (1.13-1.63)	0.001	0.304	2
Past	0.96 (0.63-1.45)	0.84	-0.044	0
Diabetes		0.002		
No	Reference			0
Yes	1.53 (1.17-1.99)	0.002	0.424	3
FDR of CRC		0.04		
No	Reference			0
Yes	1.42 (1.01-1.99)	0.04	0.351	2
History of PNC		<0.001		
Yes	Reference			0
No	1.63 (1.29-2.07)	<0.001	0.490	3

D

Variables	Derivation cohort (n=6776)	Validation cohort (n=3388)	NSGS cohort (n=6026)	Asymptomatic cohort (n=4138)
Discrimination, AUC (95% CI) *	0.68 (0.66-0.70)	0.68 (0.65-0.70)	0.68 (0.67-0.70)	0.67 (0.65-0.69)
Calibration (P value)	0.91	0.13	0.47	0.39
Selecting 15 as cut-off value				
Sensitivity, % (95% CI)	70.0 (67.2-72.4)	72.4 (68.6-75.9)	70.0 (67.1-72.7)	71.6 (68.3-74.7)
Specificity, % (95% CI)	55.2 (53.8-56.5)	53.2 (51.3-55.1)	55.6 (54.2-57.0)	52.9 (51.2-54.6)
Positive predictive value, % (95% CI)	26.2 (24.7 -27.7)	24.9 (22.9-27.0)	25.1 (23.5-26.7)	26.6 (24.7-28.5)
Negative predictive value, % (95% CI)	89.0 (87.8-90.0)	90.0 (88.4-91.4)	89.7 (88.6-90.7)	88.7 (87.2-90.0)
Positive likelihood ratio, 95% CI	1.56 (1.49-1.63)	1.55 (1.45-1.65)	1.58 (1.50-1.66)	1.52 (1.44-1.61)
Negative likelihood ratio, 95% CI	0.55 (0.50-0.59)	0.52 (0.46-0.59)	0.54 (0.49-0.59)	0.54 (0.48-0.60)

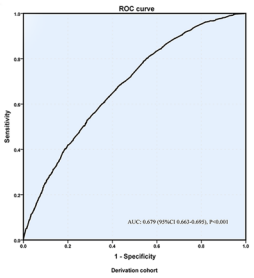
Fig. 1 **A** The distribution of 175 participating centers in the provincial-level administrative regions of China. **B** Flowchart of enrollment, allocation, and study design. **C** Independent risk factors for colorectal neoplasia in the multivariate logistic regression model and points assigned to the NCPC score. * Points were assigned by dividing the Log-Odds coefficients by the absolute value of the smallest coefficient (BMI 0.163) and rounding up to the nearest integer. **D** Predicting performance of NCPC score in the derivation cohort, validation cohort, NSGS cohort, and asymptomatic cohort. * No significant differences were found for AUC between derivation and validation cohort ($P = 0.80$) or between NSGS and asymptomatic cohort ($P = 0.31$). NCPC, national colorectal polyp care; CEA, carcinoembryonic antigen; FIT, fecal immunochemical test; CRC, colorectal cancer; CN, colorectal neoplasia; OR, odds ratio; CI, confidence interval; BMI, body mass index; FDR, first-degree relative; PNC, previous negative colonoscopy; NSGS, non-specific gastrointestinal symptom; and AUC, area under the receiver operating characteristic curve

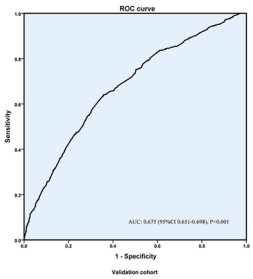
(See figure on next page.)

Fig. 2 **A–B** Risk-stratification based comparisons of CN, ACN, and CRC prevalence between derivation and validation cohort or between NSGS and asymptomatic cohort. [&] Low risk represents participants with FIT- and low-risk score, and high risk represents participants with FIT+ or intermediate/high-risk score; * *P* value for intermediate risk vs. low risk; [#] *P* value for high risk vs. low risk. **C–E** Comparison of AUCs for CN, ACN, and CRC between the NCPC score and selected risk models or FIT for overall cohort. **F** Performance of NCPC score or risk-stratification model guided colonoscopy and estimated reduction of colonoscopy burden. [&] Low risk represents participants with FIT- and low-risk score, and high risk represents participants with FIT + or intermediate/high-risk score; reduction of NNS = (NNS by primary colonoscopy – NNS by NCPC (+FIT)-based algorithm)/(NNS by primary colonoscopy). AUC, area under the receiver operating characteristic curve; CN, colorectal neoplasia; CI, confidence interval; ACN, advanced colorectal neoplasia; CRC, colorectal cancer; NCPC, National Colorectal Polyp Care; BMI, body mass index; FDR, first-degree relative; PNC, previous negative colonoscopy; APCS, Asia–Pacific Colorectal Screening score; FIT, fecal immunochemical test; RR, relative risk. NNS, number needed for screening colonoscopy to detect one lesion; and ROC, receiver operating characteristic

A

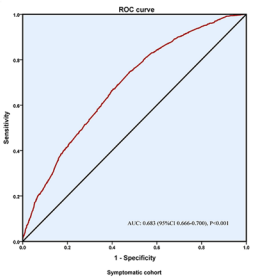
	Derivation cohort				Validation cohort			
	Low risk	Intermediate risk	High risk	P value	Low risk	Intermediate risk	High risk	P value
NCPC score								
Subjects (%)	3423 (50.5)	2026 (29.9)	1327 (19.6)		1650 (48.7)	1041 (30.7)	697 (20.6)	
CN (%)	378 (11.0)	442 (21.8)	435 (32.8)	<0.001*	165 (10.0)	223 (21.4)	209 (30.0)	<0.001*
RR (95% CI)	Reference	2.25 (1.93-2.61)	3.93 (3.36-4.60)	<0.001#	Reference	2.45 (1.97-3.05)	3.86 (3.07-4.84)	<0.001#
ACN (%)	69 (2.0)	88 (4.3)	122 (9.2)	<0.001*	21 (1.3)	46 (4.4)	57 (8.2)	<0.001*
RR (95% CI)	Reference	2.21 (1.60-3.04)	4.92 (3.64-6.66)	<0.001#	Reference	3.59 (2.13-6.05)	6.91 (4.15-11.19)	<0.001#
CRC (%)	9 (0.3)	9 (0.4)	17 (1.3)	0.27*	1 (0.1)	6 (0.6)	5 (0.7)	0.04*
RR (95% CI)	Reference	1.69 (0.67-4.27)	4.92 (2.19-11.07)	0.001#	Reference	9.56 (1.15-79.52)	11.92 (1.39-102.17)	0.02#
Risk-stratification model &								
Subjects (%)	3249 (47.9)	-	3527 (52.1)		1563 (46.1)	-	1825 (53.9)	
CN (%)	342 (10.5)	-	913 (25.9)	<0.001	149 (9.5)	-	448 (24.5)	<0.001
RR (95% CI)	Reference	-	2.46 (2.19-2.76)		Reference	-	2.58 (2.17-3.06)	
ACN (%)	54 (1.7)	-	225 (6.4)	<0.001	16 (1.0)	-	108 (5.9)	<0.001
RR (95% CI)	Reference	-	3.84 (2.86-5.15)		Reference	-	5.78 (3.44-9.73)	
CRC (%)	3 (0.1)	-	32 (0.9)	<0.001	0 (0.0)	-	12 (0.7)	0.001
RR (95% CI)	Reference	-	9.83 (3.01-32.06)		Reference	-	(-)	

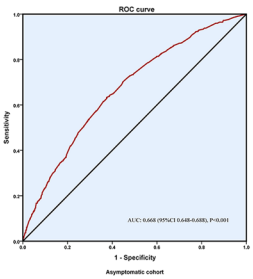


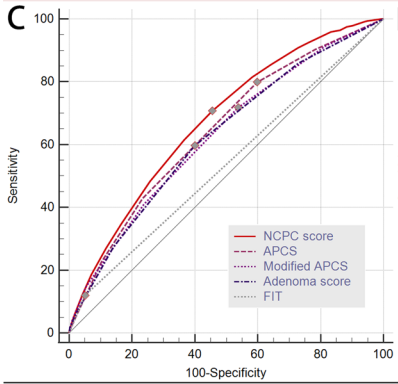


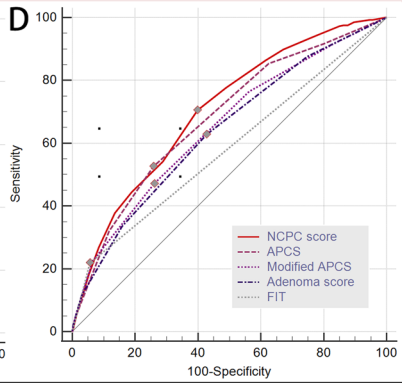
B

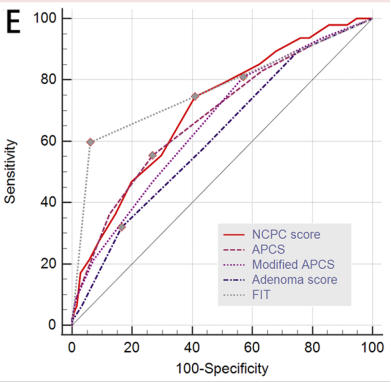
	NSGS cohort				Asymptomatic cohort			
	Low risk	Intermediate risk	High risk	P value	Low risk	Intermediate risk	High risk	P value
NCPC score								
Subjects (%)	3080 (51.1)	1806 (30.0)	1140 (18.9)		1993 (48.2)	1261 (30.5)	884 (21.4)	
CN (%)	317 (10.3)	382 (21.2)	357 (31.3)	<0.001*	226 (11.3)	283 (22.4)	287 (32.5)	<0.001*
RR (95% CI)	Reference	2.34 (1.99-2.75)	3.97 (3.35-4.71)	<0.001#	Reference	2.26 (1.87-2.74)	3.76 (3.09-4.58)	<0.001#
ACN (%)	52 (1.7)	80 (4.4)	100 (8.8)	<0.001*	38 (1.9)	54 (4.3)	79 (8.9)	<0.001*
RR (95% CI)	Reference	2.70 (1.89-3.85)	5.60 (3.98-7.89)	<0.001#	Reference	2.30 (1.51-3.51)	5.05 (3.40-7.50)	<0.001#
CRC (%)	7 (0.2)	13 (0.7)	20 (1.8)	0.01*	3 (0.2)	2 (0.2)	2 (0.2)	0.95*
RR (95% CI)	Reference	3.18 (1.27-7.99)	7.84 (3.31-18.59)	<0.001#	Reference	1.05 (0.18-6.32)	1.50 (0.25-9.02)	0.65#
Risk-stratification model &								
Subjects (%)	2949 (48.9)	-	3077 (51.1)		1863 (45.0)	-	2275 (55.0)	
CN (%)	292 (9.9)	-	764 (24.8)	<0.001	199 (10.7)	-	597 (26.2)	<0.001
RR (95% CI)	Reference	-	2.51 (2.21-2.84)		Reference	-	2.46 (2.12-2.85)	
ACN (%)	41 (1.4)	-	191 (6.2)	<0.001	29 (1.6)	-	142 (6.2)	<0.001
RR (95% CI)	Reference	-	4.47 (3.20-6.23)		Reference	-	4.01 (2.70-5.95)	
CRC (%)	2 (0.1)	-	38 (1.2)	<0.001	1 (0.1)	-	6 (0.3)	0.14
RR (95% CI)	Reference	-	18.21 (4.40-75.41)		Reference	-	4.91 (0.59-40.78)	











Risk-stratification score	Predictors	Score range or risk groups	AUC for CN (95% CI)	P value	AUC for ACN (95% CI)	P value	AUC for CRC (95% CI)	P value
NCPC score	Sex, age, BMI, smoking, drinking, diabetes, FDR of CRC, history of PNC	0-28	0.67 (0.66-0.69)	Reference	0.70 (0.68-0.73)	Reference	0.71 (0.63-0.78)	Reference
APCS	Age, sex, FDR of CRC, smoking	0-7	0.64 (0.63-0.66)	<0.001	0.68 (0.65-0.71)	0.002	0.68 (0.60-0.76)	0.19
Modified APCS	Age, sex, FDR of CRC, smoking, BMI	0-6	0.63 (0.62-0.64)	<0.001	0.65 (0.62-0.68)	<0.001	0.66 (0.58-0.74)	0.03
Adenoma score	Age, gender, FDR of CRC, smoking, BMI, diabetes	0-6	0.63 (0.61-0.64)	<0.001	0.64 (0.61-0.67)	<0.001	0.62 (0.54-0.70)	<0.001
FIT	FIT	Negative or positive	0.54 (0.52-0.55)	<0.001	0.58 (0.55-0.62)	<0.001	0.77 (0.68-0.85)	0.08

F

	Overall cohort					Young cohort				
	Low-risk group	High-risk group	Sensitivity (95% CI)	Specificity (95% CI)	Reduction of NNS (95% CI)	Low-risk group	High-risk group	Sensitivity (95% CI)	Specificity (95% CI)	Reduction of NNS (95% CI)
NCPC score Subjects (%)	5073 (49.9)	5091 (50.1)				3838 (78.4)	1059 (21.6)			
CN (%)	543 (10.7)	1309 (25.7)	70.7 (68.5-72.7)	54.5 (53.4-55.6)	29.2 (25.4-32.4)	347 (9.0)	236 (22.3)	40.5 (36.5-44.6)	80.9 (79.7-82.1)	46.6 (37.5-54.1)
ACN (%)	90 (1.8)	313 (6.1)	77.7 (73.2-81.6)	51.1 (50.1-52.1)	35.5 (30.2-39.8)	52 (1.4)	34 (3.2)	39.5 (29.3-50.7)	78.8 (0.78-0.80)	45.2 (22.1-59.6)
CRC (%)	10 (0.2)	37 (0.7)	78.7 (63.9-88.8)	50.0 (49.1-51.0)	36.4 (20.1-44.7)	7 (0.2)	4 (0.4)	36.4 (12.4-68.4)	78.4 (77.2-79.6)	40.6 (0-70.0)
Risk-stratification model & Subjects (%)	4812 (47.3)	5352 (52.7)				3645 (74.4)	1252 (25.6)			
CN (%)	491 (10.2)	1361 (25.4)	73.5 (71.4-75.5)	52.0 (50.9-53.1)	28.4 (24.9-31.5)	314 (8.6)	269 (21.5)	46.1 (42.1-50.3)	77.2 (75.9-78.5)	44.5 (36.3-51.6)
ACN (%)	70 (1.5)	333 (6.2)	82.6 (78.5-86.1)	48.6 (47.6-49.6)	36.2 (31.7-40.0)	38 (1.0)	48 (3.8)	55.8 (44.7-66.4)	75.0 (73.7-76.2)	54.2 (40.0-63.3)
CRC (%)	3 (0.1)	44 (0.8)	93.6 (81.4-98.3)	47.5 (46.6-48.5)	43.7 (34.1-47.4)	3 (0.1)	8 (0.6)	72.7 (39.3-92.7)	74.5 (73.3-75.8)	64.8 (31.8-73.7)

Fig. 2 (See legend on previous page.)

Abbreviations
ACN: Advanced colorectal neoplasia; AUC: Area under curve; CI: Confidence interval; CN: Colorectal neoplasia; CRC: Colorectal cancer; FIT: Fecal immunochemical test; HR: High risk; IR: Intermediate risk; LR: Low risk; NCPC: National Colorectal Polyp Care; NNS: Number needed for screening colonoscopy to detect one lesion; NSGS: Non-specific gastrointestinal symptom.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-022-01378-1.

Additional file 1. Supplementary methods

Additional file 2. Table S1. Clinical characteristics of participants and colonoscopy findings between the derivation and validation cohort; **Table S2**. Indications and quality indicators of colonoscopy between the derivation and validation cohort; **Table S3**. Univariate and multivariable analyses of variables included in the NCPC score based on the derivation cohort; **Table S4**. Univariate and multivariable analyses of variables excluded by the NCPC score based on derivation cohort; **Table S5**. Distribution of subjects, CN and ACN for each score category in the derivation and validation cohort; **Table S6**. CN risk stratified by NCPC score and FIT in the derivation and validation cohort.

Additional file 3. Supplementary lists

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Author contributions
LZS, BY, and ZSB contributed to study concept and design; ZSB, PP, WSL, XT, WRD, CX, YF, GL, HZX, WJY, MQQ, WTC, FQW, MXM, YHG, ZJH, BC, CDF, ZXP, RX, XLM, YP, XGS, SX, DT, WLX, WW, DSX, CHF, GAX, LJ, and ZH were involved in acquisition of data; ZSB, WSL, CQC, DYQ, HZX, and YF contributed to analysis and interpretation of data; ZSB was involved in drafting of the manuscript; ZSB, BY, LZS, PP, WSL, CQC, and DYQ contributed to critical revision of the manuscript; ZSB, CQC, HZX, WSL, CX, and XT were involved in statistical analysis; BY, LZS, and DYQ contributed to administrative, technical, or material support; and BY and LZS were involved in study supervision. All authors read and approved the final manuscript.

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Availability of data and materials
All data related to the study are included in the paper and its supplementary materials.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of the National Clinical Research Center for Digestive Disease (Shanghai, China). All participants provided signed informed consent. The NCPC program was registered in the ClinicalTrials.gov (NCT03712059).

Consent for publication
Not applicable.

Competing interests
There is no conflict of interests for each author.

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