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Development and Validation of a Calculator to Predict the Pathological Nature of Colorectal Tumors

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ABSTRACT

Background and aims: No single endoscopic feature can reliably predict the pathological nature of Colorectal Tumors (CRTs). We aimed to establish and validate a simple online calculator to predict the pathological nature of CRTs based on white light endoscopy.

Methods: This is a single center study. During identification stage, 530 consecutive patients with CRTs were enrolled from January 2015 to December 2021 as the derivation group. Logistic regression analysis was performed. A novel online calculator to predict the pathological nature of CRTs based on white light image was established and verified internally. During validation stage, two series of 110 images obtained using white light endoscopy were distributed to 10 endoscopists (five Highly Experienced Endoscopists (HEEs) and five Less Experienced Endoscopists (LEEs) for external validation, before and after systematic training.

Results: A total of 750 patients were included, with an average age of 63.6 ± 10.4 year-old. Early Colorectal Cancer (ECRC) was detected in 351 (46.8%) patients. Tumor size, left semicolon, rectum, acanthosis, depression and an uneven surface were independent risk factors for ECRC. The C-index of ECRC calculator prediction model was 0.906 (p=0.225, Hosmer-Lemeshow test). For the LEEs, significant improvement was made in the sensitivity, specificity and accuracy (57.6% versus 75.5%; 72.3% versus 82.4%; 64.2% versus 80.2%; p<0.05), respectively, after the training with ECRC online calculator prediction model.

Conclusion: A novel online calculator including tumor size, location, acanthosis, depression and uneven surface can accurately predict the pathological nature of ECRC.

Keywords: Pathological nature; Colorectal tumors, White light endoscopy; Early Colorectal Cancer (ECRC); Magnification Endoscopy (ME)

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INTRODUCTION

According to the latest global cancer statistics, there were more than 1.9 million new cases of Colorectal Cancer (CRC) and more than 930,000 deaths worldwide in 2020 [1]. CRC ranks third in terms of incidence and second in terms of mortality among all malignancies. In China, the incidence of CRC has been increasing year by year partially attributed to life style changes and westernized dietary pattern [2]. CRC is generally defined as malignant progression from adenomas through an adenoma-carcinoma sequence [3,4]. Early detection and removal of adenomas shall provide an opportunity for screening and preventing the development of Early Colorectal Cancer (ECRC). This strategy can substantially reduce the incidence and mortality of CRC [5,6].

Colorectal Adenoma (CRA) and ECRC (including high-grade intraepithelial neoplasia and intramucosal cancer) are absolute indications for endoscopic treatment. SM1 (corresponding to submucosal invasion <1000 μm) stage CRC with superficial infiltration is a relative indication for endoscopic treatment. This approach requires strict pathological evaluation of resected specimens to determine the presence of lymphatic and vascular infiltration and the necessity for extensive surgery [7]. Therefore, it is important to differentiate colorectal neoplastic from non-neoplastic lesions and to determine the depth of invasion of colorectal neoplastic lesions based on endoscopic features. At present, Kudo's pit, capillary and surface vascular patterns are widely applied to assess the risk of CRC [8-10]. However, these staging systems require staining endoscopy, Magnification Endoscopy (ME), Narrow Band Imaging (NBI) and experienced endoscopists who can operate NBI and ME. However, ordinary hospitals are short of experienced endoscopists and top-tier endoscopic equipment, so the above staging systems are not applicable. In this study, we aimed to establish a simple, practical and stable online calculator to predict the nature of Colorectal Tumors (CRTs) based on White Light Image (WLI). This calculator can assist the endoscopists in diagnosing ECRC, improving the detection rate and selecting treatment protocols.

MATERIALS AND METHODS

Participants

We carefully reviewed two datasets; one for the development and internal validation of a calculator, another for the external validation of the calculator. Patients who met the following inclusion criteria were recruited: ECRC or CRA detected by colonoscopy; patients with accurate pathological diagnosis and with high-quality endoscopic images. The histological diagnosis was based on the World Health Organization criteria. Exclusion criteria included: ECRC or CRA not treated with endoscopy or surgery; patients with familial adenomatous polyposis, Lynch syndrome or Peutz-Jeghers syndrome, inflammatory bowel disease, intestinal tuberculosis; patients underwent colectomy for other diseases; poorly intestinal preparation and patients with incomplete medical records [11]. Patients' demographic (age and gender) and clinicopathological characteristics (tumor location, size, differentiation, gross type, depth of invasion), as well as endoscopic features (redness, erosion, expansion, depression, uneven surface, lobulation, acanthosis and nodules larger than 10 mm) were independently evaluated by three experienced endoscopists.

A total of 10 endoscopists with varying levels of experience participated in the present study. The endoscopists were divided into two groups a group of Less Experienced Endoscopists (LEEs) who had performed less than 1000 colonoscopies and a group of Highly Experienced Endoscopists (HEEs) who had performed more than 3000 colonoscopies [12].

Study Design

The present study consisted of two phases. During identification phase, we retrospectively reviewed 530 patients who underwent surgery or endoscopic treatment for ECRC or CRA between January 2015 and December 2021 at Beijing Shijitan hospital, capital medical university. Baseline information on demographic, clinicopathological and endoscopic characteristics of all patients were collected. Then, logistic regression analysis was performed and a novel online calculator to predict the pathological nature of CRTs based on WLI was developed and verified internally.

During validation phase, external validation of the calculator was performed. Ten endoscopists were required to independently evaluate a series of 110 images of CRTs according to WLI. Then, a systematic training program on this online calculator was conducted. During the training process, a schematic representation of the calculator was posted on the wall of each endoscopic room and the images used to educate the participants were presented in PowerPoint (Microsoft Corp.) by the leading investigator who was not involved in this study (**Figure 1**). Afterwards, the participants were immediately asked to score another series of 110 images of CRTs by using the calculator (post-test). These images had been retrospectively collected from 220 CRTs patients who had undergone colonoscopy between January 2015 and December 2021 by the leading investigator.

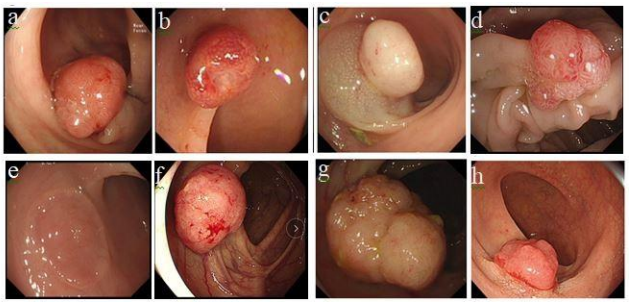

Figure 1: (a) Hyperemia, (b) Erosion, (c) Acanthosis, (d) Lobulation, (e) Depression, (f) Expansive appearance, (g) Larger nodule, (h) Uneven surface

Evaluation of Endoscopic Findings

All the endoscopic images were taken using an endoscope (PCF-H260, PCF-Q260, CF-H260, CF-HQ290 and PCF-H290; Olympus, Tokyo, Japan) during preoperative diagnosis based on WLI. Generally, NBI+ME, stained endoscopy and ultrasound endoscopic evaluation were performed when carcinoma or submucosal carcinoma were suspected. The location, diameter, color, substrate, surface and morphology of tumors were noted. Tumor location was divided into the right colon (including the cecum, ascending colon, transverse colon and splenic flexure), left colon (including the descending colon and sigmoid colon) and rectum. Lesion size was estimated using 7 mm diameter open biopsy forceps. The Paris staging 11 was used to classify and describe the morphology, while tumors larger than 10 mm growing superficially along the intestinal lumen were defined as Laterally Spreading Tumor (LST) type.

We investigated endoscopic findings of the CRTs, including lobulation, erosion, expansion, depression, acanthosis, lifting sign, stiffness and nodules larger than 10 mm. The definitions of the eight endoscopic findings were as follows:

- **Hyperemia:** Redness and hyperemia on the surface of a tumor;
- **Erosion:** Erosion and hyperemia on the surface of a tumor;
- **Acanthosis:** Chicken skin mucosa beside the tumor;
- **Lobulation:** Multiple nodules on the surface of a tumor;
- **Depression:** Depressed demarcation on the surface of a tumor;
- **Expansion:** A bursting appearance due to the expansive growth of a tumor;
- **Large nodule:** Nodules larger than 10 mm;
- **Uneven surface:** Surface with bulges and depressions.

Statistical Analysis

All statistical analysis was conducted using SPSS version 21.0 for Windows (SPSS, Chicago, IL, USA). Baseline information on demographic, endoscopic and clinicopathological characteristics were collected as candidate risk variables. The nature of CRTs was defined as a dependent variable. Continuous variables were presented as mean ± SD whereas categorical variables as percentages. For comparisons of categorical and continuous variables, *chi-square* tests or individual sample t-tests were applied, as appropriate. Univariate logistic regression analyses were performed on the derivation dataset to identify risk factors for ECRC. Multivariable logistic regression analyses were conducted on variables with a $p<0.05$ for univariate analysis. The multivariate logistic regression model was built up from the set of candidate variables by removing predictors based on P values, in a stepwise manner. Model discrimination was assessed by calculating the Area Under the Receiver Operator Characteristic (AUROC) curve (or C-index), whereas model calibration was determined by the Hosmer Lemeshow (H-L) test. The nomogram was formulated based on multivariate analysis by using the RMS package. The performance of the nomogram model was examined by calibration (calibration curves), discrimination (AUC) and clinical usefulness (decision curves), which was validated in the validation cohort. The "shiny: Web Application Framework for R" package was used to develop an online tool.

The performance of the calculator in the histological prediction of CRTs included sensitivity, specificity, predictive values and accuracy. All these indicators were calculated in 2-phases, with the histopathological diagnosis as the gold standard. Estimation of diagnostic accuracy was based on average values and 95% Confidence Intervals (CIs). Sensitivity, specificity and accuracy were compared between the two phases and between the two groups by using the paired samples student's t-test and independent samples student's test, respectively. A $p<0.05$ was considered statistically. significant.

RESULTS

Patient Characteristics

A total of 750 patients were enrolled in this study, 530 cases in the derivation group and 220 cases in the validation group. The mean age was 63.6 ± 10.4 years and 499 patients (66.5%) were male. ECRC was detected in 351 (46.8%) patients, including 243 (45.8%; 243/530) in the derivation group and 108 (49.1%; 108/220) in the validation group. The incidence of ECRC was not significantly different between the derivation group and the validation group ($P>0.05$). The mean size of the lesion was 15.32 ± 9.68 mm. Lesions were located in the right semicolon (n=358), left semicolon (n=266) and rectum (n=126). The size and location of the lesions were not significantly different between the derivation group and the validation group ($P>0.05$).

Risk Factors of ECRC

In univariate models, location, size, hyperemia, erosion, acanthosis, lobulation, depression, expansive appearance, a large nodule and an uneven surface were associated with the development of ECRC ($P<0.05$) (**Table 1**).

Table 1: Clinical and endoscopic characteristics of patients with CRA and ECRC in model cohorts.

Variables	CRA (n=287)	ECRC (n=243)	p-value
	Gender		
Male (n, %)	191 (66.6)	172 (70.8)	0.296

Female (n, %)	96 (33.4)	71 (29.2)	
Age (year) (x ± SD)	60.86 ± 10.37	64.65 ± 9.91	0.146
Type			
0-I (n, %)	210 (73.2)	180 (74.1)	0.086
0-II (n, %)	45 (15.7)	25 (10.3)	
LST (n, %)	32 (11.1)	38 (15.6)	
Location			
Rectum (n, %)	26 (9.1)	54 (22.2)	0
Left semicolon (n, %)	140 (48.8)	136 (56.0)	
Right semicolon (n, %)	121 (42.2)	53 (21.8)	
Size (mm,`x ± SD)	10.36 ± 5.61	19.28 ± 11.36	0
Size (mm)			
＜ 10 (n, %)	147 (51.2)	25 (10.3)	0
≥ 10 (n, %)	140 (48.8)	218 (89.7)	
Size (mm)			
≤ 20 (n, %)	257 (89.5)	129 (53.1)	0
＞ 20 (n, %)	30 (10.5)	114 (46.9)	
White-light endoscopy			
Hyperemia (n, %)	76 (26.5)	160 (65.8)	0
Erosion (n, %)	3 (1.0)	38 (15.6)	0
Acanthosis (n, %)	57 (19.9)	166 (68.3)	0
Lobulation (n, %)	66 (23.0)	100 (41.2)	0
Depression (n, %)	12 (4.2)	74 (30.5)	0
Expansive appearance (n, %)	37 (12.9)	63 (25.9)	0
Large nodule (n, %)	15 (5.2)	44 (18.1)	0
Uneven surface (n, %)	24 (8.4)	125 (51.4)	0

In multivariate models, size (OR, 5.233; 95% CI, 2.008-13.636), left semicolon (OR, 2.338; 95% CI, 1.329-4.111), rectum (OR, 3.715; 95% CI, 1.692-8.160), acanthosis (OR, 5.199; 95% CI, 3.057-8.842), depression (OR, 5.162; 95% CI, 2.216-12.021) and an uneven surface (OR, 5.583; 95% CI, 3.030-10.286) were independent risk factors for ECRC (**Table 2**).

Table 2: Risk factors for ECRC in multivariable logistic regression model.

Variable	Univariate model	Multivariate model		
	P-value	OR (95% CI)	β	P value
Size	＜ 0.001	5.233 (2.008-13.636)	1.655	0.001
Left semicolon	＜ 0.001	2.338 (1.329-4.111)	0.849	0.003

Rectum	< 0.001	3.715 (1.692-8.160)	1.312	0.001
Hyperemia	< 0.001	1.305 (0.756-2.251)	0.266	0.339
Erosion	< 0.001	3.848 (0.820-18.052)	1.348	0.088
Acanthosis	< 0.001	5.199 (3.057-8.842)	1.648	0
Lobulation	< 0.001	1.276 (0.729-2.233)	0.243	0.394
Depression	< 0.001	5.162 (2.216-12.021)	1.641	0
Expansive appearance	< 0.001	0.910 (0.471-1.756)	-0.095	0.778
Large nodule	< 0.001	1.146 (0.480-2.732)	0.136	0.759
Uneven surface	< 0.001	5.583 (3.030-10.286)	1.72	0

Development of the Nomogram and the Calculator

An online calculator to predict the pathological nature of CRTs was established according to the above six independent risk factors (size, left semicolon, rectum, acanthosis, depression and uneven surface). A nomogram was constructed with point scales of these variables (**Figure 2**).

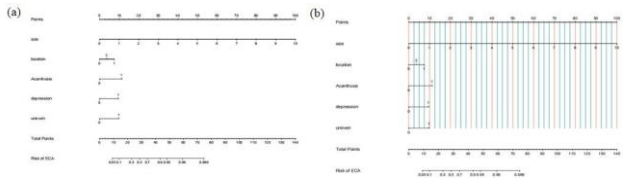

Figure 2: Nomogram for predicting the pathological nature of CRTs.

The sum of each variable point was plotted on the total point axis. The probability rate of ECRC was obtained by drawing a vertical line from the plotted total point axis straight down to the outcome axis. Based on these nomogram models, online web-based calculators were developed to assess the probability of ECRC among patients with CRTs (**Figure 3**). When users simply input the requested information, the probability of ECRC can be derived.

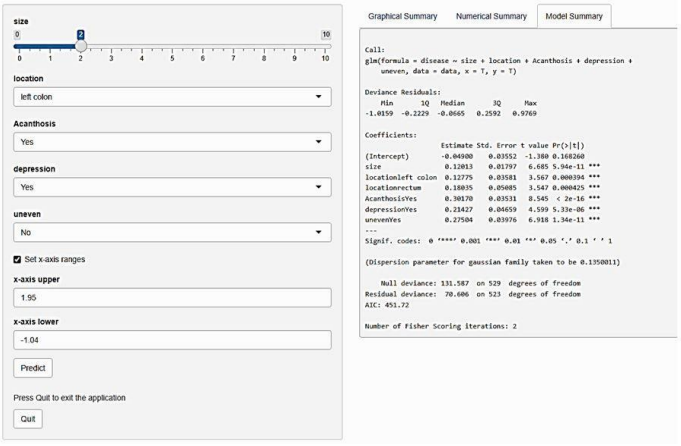

Figure 3: Internet browser-based online calculator.

Validation of the Prediction Calculator

After performing the internal validation by generating 1000 bootstrap replications, the calculator remained high accuracy, with a resulting AUROC (C-index) of 0.906 (95% CI, 0.880-0.932) (**Figure 4**).

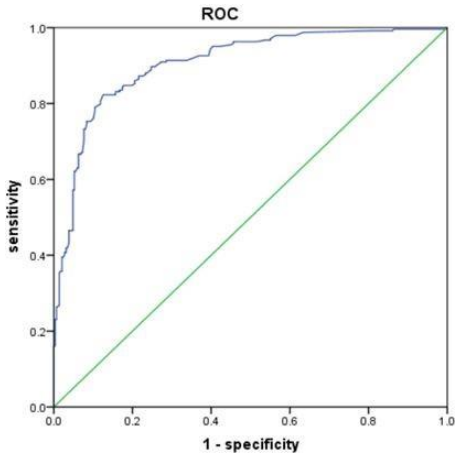

Figure 4: Receiver operator characteristic curve in the validation cohort.

Moreover, the calibration plot of the internal validation demonstrated good calibration ($\chi 2$=10.614; P=0.225) with the Hosmer-Lemeshow (H–L) test (**Figure 5**). DCA curve was performed to ascertain its clinical usefulness (**Figure 6**). These results indicated good clinical applicability of the calculator in predicting the pathological nature of CRT according to good net benefit with wide and practical ranges of threshold probabilities.

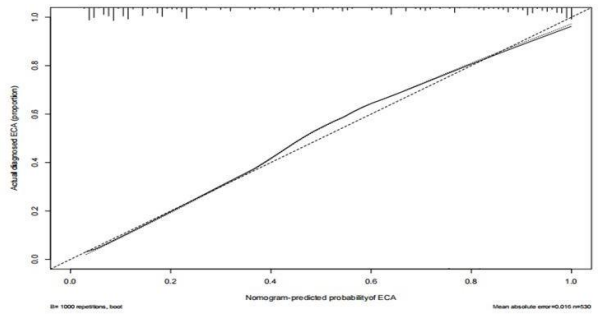

Figure 5: Calibration plot of the prediction model.

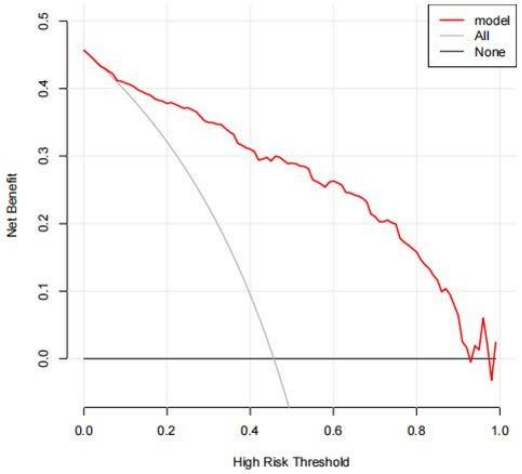

Figure 6: DCA curve for the prediction model.

To explore if the calculator would be applicable to endoscopists, we conducted an external validation study among 10 endoscopists with varying levels of experience. Comparisons of performance for diagnosing CRTs histology between pre-training test and post-training test (**Table 3**) were as follows: LEEs made significant improvement in the sensitivity, specificity and accuracy in the post-training test compared with the pre-training test. The LEEs' performance characteristics in the pre-training test versus post-training test were as follows: Sensitivity 57.6% versus 75.5% (p=0.004), speci icity 72.3% versus 82.4% (p=0.023) and accuracy 64.2% *vs.* 80.2% (p<0.001). The κ-value of the LEEs in the pre-training test and post-training test was 0.72 and 0.83, respectively, indicating good (>0.60) to excellent (>0.80) agreement. The HEEs made significant improvement in sensitivity in the post-training test compared with the pre-training test, but not in specificity or accuracy. The HEEs' performances in the pre-training test versus post-training test were as follows: sensitivity 71.2% versus 80.4% (p=0.043), specificity 82.1% versus 88.2% (p=0.223) and accuracy 76.5%versus 86.0% (p=0.071). The κ-value of the HEEs in pre-training test and post-training test was 0.81 and 0.89, respectively. The κ-values were improved in both groups, especially in the LEEs, suggesting that the LEEs bene ited more from this predicting calculator.

Table 3: Sensitivity, specificity and accuracy in histology prediction during pre-training test and post-training test.

Group	Pre-training test	Post-training test	p-value
	LEE		
Sensitivity	57.6 (48.5-66.4)	75.5 (67.0-82.4)	0.004
Specificity	72.3 (61.8-80.5)	82.4 (74.2-88.5)	0.032
Accuracy	64.2 (56.4-70.3)	80.2 (71.3-87.6)	< 0.001
	HEE		
Sensitivity	71.2 (60.4-80.1)	80.4 (71.6-88.1)	0.043
Specificity	82.1 (73.8-88.2)	88.2 (81.5-95.3)	0.223
Accuracy	76.5 (69.3-83.6)	86.0 (80.2-91.7)	0.071

DISCUSSION

The CRA is a precancerous lesion of CRC, since most of the CRCs develop from CRAs through adenoma carcinoma pathway. Without timely intervention, precancerous lesions will progress to CRC within 10 to 15 years [13]. Notably, if the lesions are detected in the early stages of CRC and treated timely, the 5 years survival rate of these patients can reach as high as 90% [14]. By contrast, if the lesions are detected in the late stages of CRC, the 5-year survival rate will be reduced to less than 10%. Colon endoscopy can directly observe intestinal lesions, which is irreplaceable in the examination of intestinal diseases, especially CRC. To improve the detection rate of precancerous lesions and early-stage CRC, assistive techniques have been introduced to clinical practice, such as chromoendoscopy, magnifying endoscopy, fluorescence endoscopy, confocal laser endoscopy and electronic staining endoscopy. However, the process of chromoendoscopy is complicated, time consuming, labor intensive and requiring magnification endoscopes. In addition, fluorescence endoscopy and confocal laser endoscopy are expensive. These disadvantages limit the application of the above techniques. Moreover, in clinical practice, the experience and the degree of image interpretation can be varied greatly between endoscopists, which results in different judgments being made for the same lesion and thus a decrease in the accuracy

of colonoscopy. To solve this problem, many endoscopists with extensive experience have defined and standardized the characteristics of CRTs and several staging systems have been established and promoted, in an attempt to improve the diagnostic accuracy and to reduce the possibility of missed diagnoses. With the advent of magnifying endoscopy, the resolution of imaging has been substantially improved. Now endoscopists can clearly observe the morphology of glandular duct openings and microvasculature on the mucosal surface of CRTs [15]. Kudo's pit pattern classification under magnifying chromoendoscopy was proposed in 1994. Later on, microvessel pattern under magnifying NBI was proposed by Sano et al. in 2006 [16]. These staging systems have been highly effective in predicting the histology of CRTs. Subsequently, JNET typing, Hiroshima typing18 and Jikei typing emerged based on mucosal microvascular morphology and surface structure. These typing systems have better performance in differentiating colorectal neoplastic and non-neoplastic lesions by combining the endoscopic features of lesions. Accordingly, the accuracy of differentiating benign from malignant lesions can be improved by providing appropriate training to primary endoscopists [17]. However, the above typing systems require time-consuming, labor-intensive and magnification endoscopes. Unfortunately, magnification endoscopes are not widely applied in the majority of primary-level hospitals and a LEE lacks experience in operating NBI+ME. These conditions limit the promotion of staging systems such as Kudo' pit pattern classification, NICE and JNET in primary-level hospitals. Therefore, in this study, we have established an online calculator to predict the pathological nature of CRTs based on white-light endoscopy. The model consists of five variables: Location of the lesion, size of the lesion, acanthosis, depression and an uneven surface. The AUC of the scoring system in our modeling cohort was 0.906 (>0.80), indicating a good degree of differentiation. Based on the Hosmer-Lemeshow goodness-of-fit test (p=0.225, >0.1), our prediction model has value for risk-stratification among patients with CRTs of unknown nature, which can provide a preliminary basis for the differential diagnosis of CRT. External verification identified significant improvement in the sensitivity and specificity in the post-training test compared with the pre-training test, especially in the LEEs. Thus, this calculator may be applicable in primary-level hospitals. Our model and its scoring system may have good clinical credibility. Firstly, the methods used for establishing and verifying the models are widely accepted, with external validation among endoscopists with different levels of experience. Secondly, all of the potential predictors were included and there were no obvious missing items [18]. Thirdly, five variables (location, size, acanthosis, depression and uneven surface) associated with CRC were obtained by logistic regression models.

The incidence of the Left Sided CRC (LCRC) has been higher than that of the Right Sided CRC (RCRC). The American Cancer Society confirms a higher proportion of LCRC (51%) than RCRC (42%) in the US [19]. The patients with RCRC present with more advanced tumor stages than those with LCRC. Furthermore, higher TNM stages, larger tumors, increased frequency of vascular invasion, mucinous type, high grade and invasive tumor border were more common in RCRC, whereas annular and polypoid tumors were more common in LCRC21 [20]. In our study, more patients were diagnosed with LCRC than RCRC, which was similar to previous studies.

The CRC is originated from a CRA, which slowly increases in size, followed by dysplasia and malignant transformation [21]. The size of a CRA is predictive for CRC diagnosis, which underscores the significance of this factor, especially considering its association to a less favorable histology and increased long-term risk of CRC [22]. The 10 mm cut-off represents a critical factor, since a small percentage of larger polyps contain cancerous cells [23-25]. Of the 530 lesions with CRTs, 243 were diagnosed as ECRC. The mean size of the lesions was 19.28 mm ± 11.36 mm, of which 89.7% were ≥ 10 mm, consistent with previous studies.

It was reported that demarcated depression, fullness and stalk swelling were typical findings of ECRC. Notably, 2.0% of the tumors were carcinoma, especially for depressed tumors, which had a significantly higher frequency of carcinoma and submucosal invasion regardless of tumor size [26]. The Japanese Guideline for CRC has listed the following endoscopic findings as diagnostic indicators of SM-Ca: Expansive appearance, erosion/ulceration, fold convergence and deformation/stiffness 28. In univariate models, most lesions of ECRC had the following characteristics based on WLI: hyperemia, erosion, acanthosis, lobulation, depression, expansive (sun-burst) appearance, larger nodules and an uneven surface. In multivariate models, five independent risk factors: size, location, acanthosis, depression and an uneven surface were predictive indicators of ECRC [27].

CONCLUSION

Thus, a simple online calculator to predict the pathological nature of CRTs based on WLI was established, with an AUC value of 90.6% and high diagnostic specificity and accuracy. Internal and external validation of this model indicated good consistency of CRC risk with postoperative pathology and good agreement in application between endoscopists with various levels of experiences. We present a novel online calculator to predict the pathological nature of CRTs. This calculator may play a practical and important role in reducing the cost and duration of colonoscopy. However, this was a single-center study, further high quality; multi-center clinical studies should be conducted to access the stability and generalizability of this scoring system.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by Ethics Committee of Beijing shijitan hospital, sjtkyll-lx-2020. All methods were carried out in accordance with relevant guidelines and regulations. This study was carried out in compliance with the ARRIVE guidelines. Informed consent was obtained from all subjects and/or their legal guardian.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available on request from the corresponding author.

COMPETING INTEREST

All authors declare no conflicts of interest.

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AUTHORS' CONTRIBUTIONS

Yadan Wang performed data analysis and interpretation and drafted the manuscript. Wu Jing performed experimental design and supervised the project. Boyang Huang, Chunmei Guo, Canghai Wang, Hui Su, Hong Liu, Miaomiao Wang, Jing Wang, Li Li, Pengpeng Ding and Mingming Meng performed experiments and edited the manuscript.

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