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Original Article

ORIGINAL ARTICLE

Risk factors for recurrence of colorectal conventional adenoma and serrated polyp

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Abstract

Background Removal of colorectal polyps during screening could reduce the incidence of colorectal cancer (CRC). However, there is a lack of data on risk factors associated with recurrence of polyps, including conventional adenomas and serrated polyps (SPs). This study aimed to determine risk factors for recurrence of colorectal polyps and their subtypes based on the characteristics of the patients and polyps.

Methods A total of 1,165 patients diagnosed with conventional adenoma or SP in the Sixth Affiliated Hospital of Sun Yat-sen University between January 2013 and December 2019 were enrolled in this study, including 668 cases with conventional adenomas, 385 with SPs, and 112 with coexistence of adenomas and SPs. Univariate analysis and multivariate logistic regression were used to identify potential risk factors for polyp recurrence. A nomogram was established according to risk factors and the performance was evaluated using calibration plots.

Results During a median follow-up of 24 months, recurrent polyps were observed in 531 (45.6%) cases. Male, age $\geq$50 years, body mass index (BMI) $\geq$24 kg/m^2, at least three polyps, smoking, alcohol consumption, family history of polyps, and family history of CRC were independent risk factors for polyp recurrence. The Harrell's C-index of the nomogram developed with these parameters was 0.69 and the calibration plots showed good agreement between actual polyp recurrence and nomogram-predicted recurrence probability. In the subtype analyses, conventional adenomas had the same risk factors for recurrence as all polyps, while smoking, alcohol consumption, family history of polyps, and family history of CRC were not risk factors for SP recurrence.

Conclusions We identified several risk factors for recurrence of colorectal polyps and found that some of them could increase the risk of adenoma recurrence but not SP recurrence, including smoking, alcohol consumption, and family history of polyps/CRC, which might help us to understand different etiology and biology between conventional adenomas and SPs.

Key words: colorectal polyps; recurrence; conventional adenomas; serrated polyps; risk factors

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Introduction

Colorectal cancer (CRC) ranks third in the incidence of cancer and is the second leading cause of cancer-related death in the world, accounting for 1.8 million new cases and 881,000 deaths in 2018 [1, 2]. As known, polyps are considered as precancerous lesions. Based on the World Health Organization (WHO) classification, polyps can be divided into four types: adenomas, serrated polyps (SPs), inflammatory polyps, and hamartomas [3]. Conventional adenomas (including tubular, tubulovillous, and villous adenomas) and SPs (including hyperplastic polyps [HPs], sessile serrated adenoma/polyps [SSA/Ps], and traditional serrated adenomas [TSAs]) are considered as two distinct etiologic pathways of carcinogenesis. About two-thirds of CRC cases have been believed to develop through the adenoma–carcinoma sequence for decades [4]. However, accumulated evidence supports that the remaining one-third of CRC cases can originate from the serrated pathway [5]. To be sure, both carcinogenic pathways indicate that the occurrence of CRC is a progressive process. Resection of the polyp in CRC screening is helpful to reduce the incidence and mortality of CRC [6]. Thus, colonoscopic polypectomy and surveillance are important for the prevention of CRC. Guidelines recommend various monitoring intervals after polyp resection according to polyp characteristics [7, 8].

It is worth noting that recurrence rate of polyp is as high as 20%–50% [9, 10]. Some previous studies had paid attention to the risk factors for polyp recurrence and showed that age and being male are risk factors for polyp recurrence [11, 12]. As for living habits, a study from China indicated that smoking status was related to the recurrence of adenomas in the elderly [13], while another study from the USA did not get similar results [14]. However, the sample size of these studies was small and they paid more attention to adenomas rather than SPs. Although some studies have been conducted on the influence of polyp characteristics on polyp recurrence, their conclusions are varied, which may be due to short follow-up time and small sample size [15–20]. Besides, it was reported that poor bowel preparation was associated with a lower polyp detection rate [21, 22]. However, it seems that the aforementioned studies rarely ruled out the influence of this factor on the polyp detection rate, which would confuse the influence of risk factors on polyp recurrence.

In general, although the carcinogenic factors of colorectal polyps have reached a consensus, the factors leading to the recurrence of polyps are still uncertain. Patient demographics (sex, age, lifestyle, etc.), polyp characteristics (growth site, number, size, pathological type, etc.), and procedural factors (follow-up time after polypectomy, quality of polypectomy, etc.) are potential risk factors for polyp recurrence. The purpose of this study was to investigate the risk factors for polyp recurrence and establish a nomogram to predict the risk of polyp recurrence. Besides, we performed a subgroup analysis to explore whether risk factors differed between conventional adenomas and SPs, because they might be genetically different.

Patients and methods

Study design and study subjects

All patients who were diagnosed with conventional adenomas or SPs based on pathology results in the index colonoscopy for any indication or screening purpose and underwent at least one surveillance colonoscopy more than 1 year after index colonoscopy in the Sixth Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between January 2013 and December 2019 were enrolled in this retrospective observational study. Exclusion criteria were as follows: (i) other pathological types of the polyp (e.g. inflammatory polyps and hamartomas) in the index colonoscopies; (ii) personal history of CRC based on International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes; (iii) other histories of colorectal diseases, such as inflammatory bowel disease, familial adenomatous polyposis, Peutz-Jeghers syndrome, or intestinal tuberculosis based on ICD-10 codes; (iv) patients with poor bowel preparation; (v) the polyps were not resected completely during the index colonoscopy.

Based on the results of surveillance colonoscopies, patients who were diagnosed with conventional adenomas or SPs were categorized into the recurrence group, while others were included in the non-recurrence group. The study protocol was approved by the Ethics Review Committee of the Sixth Affiliated Hospital of Sun Yat-sen University without informed consent because we retrieved data anonymously from the electronic databases (No.2021ZSLYEC-264).

Data collection and study definitions

We collected the following clinical data through telephone follow-up and the medical records of the Sixth Affiliated Hospital of Sun Yat-sen University: (i) patient information including sex, age, body mass index (BMI), personal history (e.g. hypertension or diabetes), living habits (e.g. smoking status or alcohol consumption), and family history of CRC or polyps; (ii) polyp characteristics including size, number, anatomical location, pathological diagnosis, and the interval between initial and surveillance colonoscopies. Cigarette-smoking status was defined as smoking at least one cigarette per day for >3 months. Alcohol consumption was defined as three or more drinks per week for 6 consecutive months. Family history of CRC or polyp was defined as positive when at least one relative of that disease was found. Besides, in our study, BMI was divided into <24 and $\geq 24\ kg/m^2$ according to Chinese classification [23].

All pathological diagnoses were performed by two experienced pathologists separately and only consistent results will be adopted. If there was a disagreement between pathologists, the specimen would be further reviewed by a third pathologist and the final diagnosis would be made by all pathologists together. For patients with multiple polyps, we selected the index polyp by the following standard: (i) for patients with SPs, the largest polyp in size was selected; (ii) for patients with at least one conventional adenoma of ≥ 10 mm, we selected the largest one; (iii) for patients with all conventional adenomas of <10 mm, the polyp with high-grade dysplasia or the most villous structure was selected. The anatomical location of the polyp was divided into the proximal colon (caecum to splenic flexure), distal colon (descending colon to sigmoid colon), and rectum. In the case of multiple polyps, polyp location was defined as that of the index polyp.

Index colonoscopy was defined as the colonoscopy with the polyp detected first, while surveillance colonoscopy was defined as the colonoscopy performed >1 year later. The guidelines for the intervals of colonoscopy surveillance vary widely. In our study, individuals with one or two small (<10 mm) tubular adenoma were advised to undergo repeated colonoscopy in 5–10 years and those with adenoma of ≥ 10 mm or more than three small tubular adenomas were advised 3–5 years. For individuals with SPs in our study, we recommend a 5-year surveillance interval for SPs of <10 mm and a 3-year interval for SPs of

≥10 mm. The individuals who suffered from polyps with high-grade dysplasia were advised to undergo repeated colonoscopy in 1 year.

Statistical analyses

A student's *t*-test or Mann–Whitney *U* test was used to compare continuous variables according to their respective applicable conditions. Chi-square test was used to compare categorical variables. Multivariate logistic regression was performed to identify risk factors for polyp recurrence. All variables that were predictive at the 0.05 level by using a univariate analysis fit into the multivariate logistic-regression model in an 'ENTER' way. We listed the odds ratio (OR) and 95% confidence interval (CI) for each variable. All statistical tests were on two sides and a *P*-value of <0.05 was considered significant. The statistical analyses mentioned above were performed using SPSS software (Version 22.0).

A nomogram for polyp recurrence was established based on the multivariate logistic-regression model. The performance of the nomogram was evaluated using Harrell's concordance index (Harrell's C-index) and calibration plots with bootstrap samples.

Table 1. Univariate and multivariate logistic-regression analysis on risk factors for polyp recurrence

Characteristic	No. of patients ($n = 1,165$)	Polyp recurrence ($n = 531$)	Univariate		Multivariate	
			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age						
<50 years	447	167 (37.4)	1		1	
≥50 years	718	364 (50.7)	1.72 (1.36–2.19)	<0.01	1.70 (1.31–2.20)	<0.01
Gender						
Female	426	149 (35.0)	1		1	
Male	739	382 (51.7)	1.99 (1.56–2.54)	<0.01	1.42 (1.07–1.90)	0.02
Body mass index						
<24 kg/m^2	668	264 (39.5)	1		1	
≥24 kg/m^2	497	267 (53.7)	1.78 (1.41–2.25)	<0.01	1.59 (1.23–2.04)	<0.01
Number of polyps						
<3	919	366 (39.8)	1		1	
≥3	246	165 (67.1)	3.08 (2.29–4.14)	<0.01	1.97 (1.34–2.90)	0.01
Anatomical location						
Proximal colon	369	177 (48.0)	1			
Distal colon	496	228 (46.0)	0.92 (0.70–1.21)	0.56		
Rectum	300	126 (42.0)	0.79 (0.58–1.07)	0.12		
Size						
<10 mm	907	415 (45.8)	1			
≥10 mm	258	116 (45.0)	0.97 (0.73–1.28)	0.97		
Pathological type						
Serrated polyps	385	177 (46.0)	1			
Conventional adenomas	780	354 (45.4)	0.98 (0.76–1.25)	0.98		
Coexistence of adenomas and serrated polyps						
No	1,053	461 (43.8)	1		1	
Yes	112	70 (62.5)	2.14 (1.43–3.20)	<0.01	1.28 (0.81–2.02)	0.28
High-grade dysplasia						
No	1,053	479 (45.5)	1			
Yes	112	52 (46.4)	1.04 (0.70–1.54)	0.85		
Smoker status						
Never	909	373 (41.0)	1		1	
Current	256	158 (61.7)	2.32 (1.74–3.08)	<0.01	1.52 (1.09–2.13)	0.01
Alcohol consumption						
Never	1,086	476 (43.8)	1		1	
Current	79	55 (69.6)	2.94 (1.79–4.81)	<0.01	1.84 (1.08–3.16)	0.03
History of hypertension						
No	916	393 (42.9)	1		1	
Yes	249	138 (55.4)	1.65 (1.25–2.19)	<0.01	1.20 (0.87–1.64)	0.26
History of diabetes						
No	1,105	493 (44.6)	1		1	
Yes	60	38 (63.3)	2.14 (1.25–3.67)	0.01	1.47 (0.83–2.63)	0.19
Family history of polyps						
No	1,068	476 (44.6)	1		1	
Yes	97	55 (56.7)	1.63 (1.07–2.48)	0.02	1.65 (1.06–2.59)	0.03
Family history of CRC						
No	1,095	486 (44.4)	1		1	
Yes	70	45 (64.3)	2.26 (1.36–3.73)	0.01	2.15 (1.26–3.67)	0.01

OR, odds ratio; CI, confidence interval; CRC, colorectal cancer.

Harrell's C-index was calculated using 1,000-fold bootstrap resampling iterations to an initial fitted model in the derivation set. Calibration plots are graphic evaluations of predictive ability that compare observed probabilities with nomogram-predicted probabilities. The same strategy was used for the subgroup analysis. The nomogram-associated statistical analyses were performed using R software (Version 4.0.0).

Results

A total of 1,165 eligible patients were included in the study. There were 739 males and 426 females with a median (interquartile range [IQR]) age of 53 (45, 62) years. The baseline characteristics of these patients are summarized in **Table 1**. Due to the low compliance, some patients did not strictly follow the above screening strategy. The median (IQR) interval between the index and surveillance colonoscopies was 24.2 (16.0, 35.9) months. Recurrent polyps were observed in 531 (45.6%) cases. The median (IQR) number and size of polyps were 1 (1, 2) and 5 (4, 8) mm, respectively.

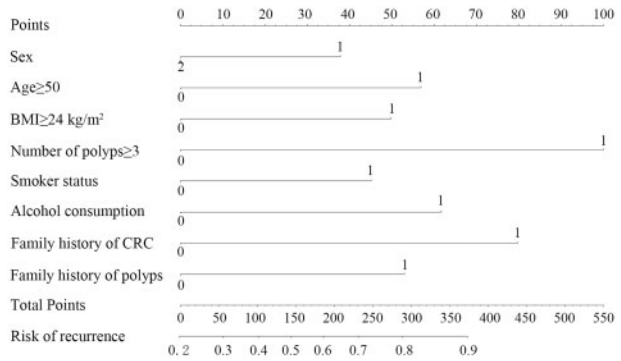

Figure 1. Nomogram for predicting polyp recurrence. For the variable 'Sex', 1 = 'Male', 2 = 'Female'. For other variables, 1 = 'Yes', 0 = 'No'. BMI, body mass index; CRC, colorectal cancer; SPs, serrated polyps.

Risk factors for recurrence of polyps

We analysed risk factors for recurrent polyps by univariate and multivariate logistic-regression analysis. Being male, age ≥50 years, BMI ≥24 kg/m^2, more than three polyps, smoking, alcohol consumption, family history of polyps, and family history of CRC were independent risk factors for polyp recurrence (Table 1). We established a nomogram for polyp recurrence based on the above independent risk factors (Figure 1). In this way, we can get the risk probability of polyp recurrence. Harrell's C-index for the derivation set was 0.69 and the nomogram was well calibrated (Figure 2).

Subgroup analyses based on conventional adenomas and SPs

Among the 1,165 patients in our study, 668 and 385 patients, respectively, were diagnosed as conventional adenomas or SPs only, while the remaining 112 patients suffered from both types of polyps and were excluded in the subgroup analyses. Of 668 patients in the conventional adenomas subgroup, 284 cases had polyp recurrence. Risk factors associated with conventional adenomas recurrence did not vary from those of all polyps (Table 2). Similarly, a nomogram for conventional adenoma recurrence was established using a Harrell's C-index of 0.68 (Supplementary Figure 1). The nomogram was well calibrated (Supplementary Figure 2).

Of 385 patients who suffered from SPs, 177 cases had polyp recurrence. It is worth noting that there were only six SSPs and no TSAs in 385 cases. The results of logistic-regression analysis showed that being male, age ≥50 years, BMI ≥24 kg/m^2, and more than three SPs were associated with a higher risk for SP recurrence. Differently from conventional adenomas, smoking, alcohol consumption, family history of polyps, and family history of CRC were not risk factors for SP recurrence (Table 2). The nomogram for the recurrence of SPs is shown in Supplementary Figure 3, with a Harrell's C-index of 0.69. The nomogram was well calibrated (Supplementary Figure 4).

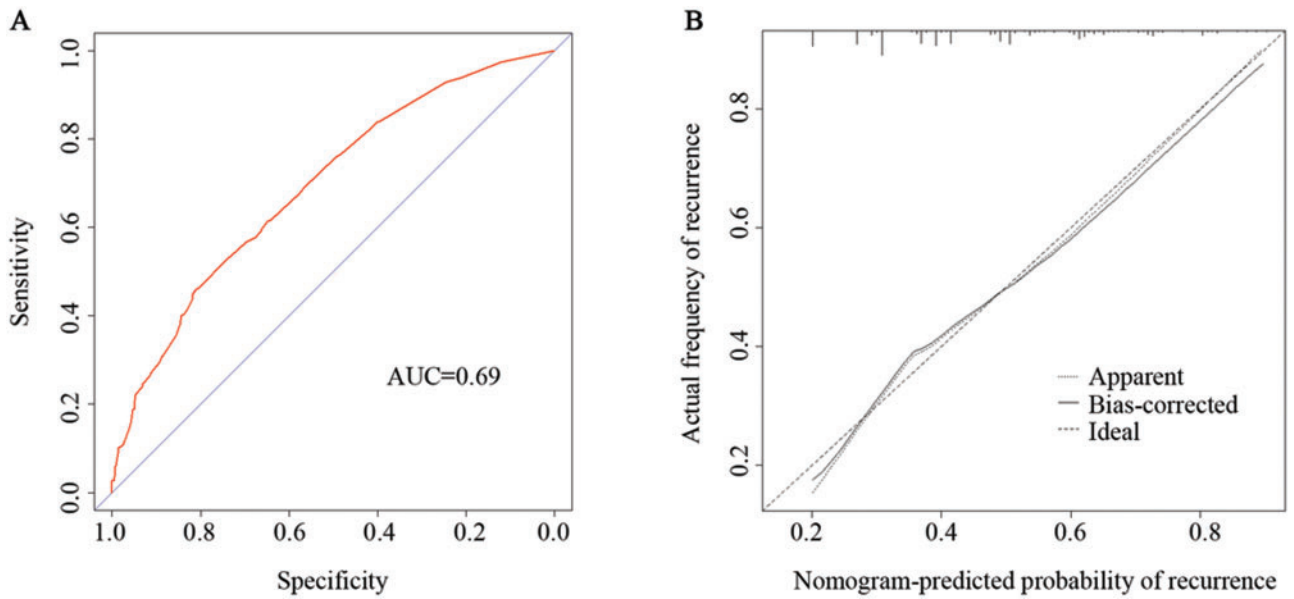

Figure 2. Receiver-operating characteristic curve (A) and calibration plots (B) of the prediction model for polyp recurrence

Table 2. Univariate and multivariate logistic-regression analysis on risk factors for recurrence of conventional adenomas and serrated polyps

Characteristic	Conventional adenomas						Serrated polyps					
	No. of patients ($n = 668$)	Recurrence ($n = 284$)	Univariate		Multivariate		No. of patients ($n = 385$)	Recurrence ($n = 177$)	Univariate		Multivariate	
			OR (95% CI)	P	OR (95% CI)	P			OR (95% CI)	P	OR (95% CI)	P
Age												
<50 years	233	79 (33.9)	1		1		179	67 (37.4)	1		1	
≥50 years	435	205 (47.1)	1.74 (1.25–2.42)	<0.01	1.64 (1.15–2.35)	<0.01	206	110 (53.4)	2.49 (1.62–3.84)	<0.01	2.06 (1.31–3.23)	<0.01
Gender												
Female	247	86 (34.8)	1		1		143	46 (32.2)	1		1	
Male	421	198 (47.0)	1.66 (1.20–2.30)	<0.01	1.33 (0.92–1.93)	0.13	242	131 (54.1)	1.92 (1.27–2.88)	<0.01	1.72 (1.02–2.89)	0.04
Body mass index												
<24 kg/m^2	380	147 (38.7)	1		1		236	88 (37.3)	1		1	
≥24 kg/m^2	288	137 (47.6)	1.44 (1.05–1.96)	0.02	1.36 (1.03–1.89)	0.03	149	89 (59.7)	2.55 (1.64–3.80)	<0.01	2.25 (1.43–3.55)	<0.01
Anatomical location												
Proximal colon	218	102 (46.8)	1				101	43 (42.6)	1			
Distal colon	320	130 (40.6)	0.78 (0.55–1.10)	0.16			130	68 (52.3)	1.48 (0.88–2.50)	0.14		
Rectum	130	52 (40.0)	0.76 (0.49–1.18)	0.22			154	66 (42.9)	1.01 (0.61–1.68)	0.96		
Number of polyps												
<3	604	244 (40.4)	1		1		336	145 (43.2)	1		1	
≥3	64	40 (62.5)	2.46 (1.45–4.18)	<0.01	1.98 (1.14–3.45)	0.02	49	32 (65.3)	2.48 (1.33–4.64)	<0.01	1.87 (1.11–3.69)	0.02
Size (mm)												
<10	469	202 (43.1)	1				358	165 (46.1)	1			
≥10	199	82 (41.2)	0.93 (0.66–1.30)	0.66			27	12 (44.4)	0.84 (0.43–2.06)	0.87		
High-grade dysplasia												
No	571	244 (42.7)	1				379	172 (45.4)	1			
Yes	97	40 (41.2)	0.94 (0.61–1.46)	0.78			6	5 (83.3)	6.02 (0.70–52.00)	0.10		
Smoker status												
Never	538	212 (39.4)	1		1		291	118 (40.6)	1		1	
Current	130	72 (55.4)	1.91 (1.30–2.81)	<0.01	1.38 (1.19–2.15)	0.02	94	59 (62.8)	2.47 (1.53–4.00)	<0.01	1.38 (0.76–2.49)	0.29
Alcohol consumption												
Never	625	256 (41.0)	1		1		357	157 (44.0)	1		1	
Current	43	28 (61.1)	2.69 (1.41–5.14)	<0.01	1.84 (1.01–3.67)	0.04	28	20 (71.4)	3.19 (1.37–7.42)	<0.01	1.73 (0.67–4.46)	0.26
History of hypertension												
No	534	216 (40.4)	1		1		308	135 (43.8)	1			
Yes	134	68 (50.7)	1.52 (1.04–2.22)	0.03	1.29 (0.85–1.94)	0.23	77	42 (54.5)	1.54 (0.93–2.54)	0.09		
History of diabetes												
No	638	270 (42.3)	1				364	161 (44.2)	1		1	
Yes	30	14 (46.7)	1.19 (0.57–2.49)	0.64			21	16 (76.2)	4.04 (1.45–11.25)	<0.01	2.17 (0.73–6.50)	0.17
Family history of polyps												
No	622	258 (41.5)	1		1		344	155 (45.1)	1			
Yes	46	26 (56.5)	1.83 (1.00–3.36)	0.04	2.81 (1.42–5.57)	<0.01	41	22 (53.7)	1.41 (0.74–2.70)	0.30		
Family history of CRC												
No	626	256 (40.9)	1		1		362	165 (45.6)	1			
Yes	42	28 (66.7)	2.89 (1.49–5.60)	<0.01	1.95 (1.04–3.67)	0.04	23	12 (52.2)	1.30 (0.56–3.03)	0.54		

OR, odds ratio; CI, confidence interval; BMI, body mass index; CRC, colorectal cancer.

Discussion

In the study, we explored the risk factors for polyp recurrence and performed a subgroup analysis based on the histopathological features of the polyps. We identified that patient characteristics such as being sex, age ≥50 years, BMI ≥24 kg/m^2, smoking, alcohol consumption, family history of polyps, and family history of CRC were associated with polyp recurrence. The most highlighted issue in this study was that we excluded participants with poor bowel preparation, as colonoscopy with poor bowel preparation might raise the missing rate of advanced neoplasia to 18%–27% [21, 22], which might make the results more solid.

Given that these precancerous lesions can develop into CRC successively, it is necessary to clarify the risk factors for polyp recurrence and help to adjust the monitoring strategies for CRC [24–26]. However, the risk factors for recurrence of conventional adenomas and SPs seemed to be different. Compared with conventional adenomas, we found that smoking, alcohol consumption, family history of polyps, and family history of CRC were irrelevant with SPs. Considering their carcinogenic mechanism [4, 5], this difference might be explained by distinct etiology and biology between these two types of polyp. Notably, we found that patients with both conventional adenomas and SPs had a significantly higher risk of recurrence than those with conventional adenomas or SPs only, which indicated that a stricter monitoring strategy should be scheduled for patients with coexistent conventional adenomas and SPs.

The current study found that smoking and alcohol consumption were risk factors for conventional adenoma recurrence [13, 27]. The carcinogenic components in cigarettes lead to oxidative stress and DNA damage, producing various carcinogens, which will interrupt cellular replication and inhibit the DNA-repair process [28, 29]. Differently from conventional adenomas, smoking or alcohol consumption did not affect the recurrence of SPs in our study, which was not in line with another study [30]. Since patients who smoke and drink in this study were relatively few, we could not draw a solid conclusion. The association between positive family history of CRC and colorectal neoplasms had been reported prior [31, 32] and we further found that positive family history of polyps or CRC was a risk factor for recurrence of conventional adenomas but not SPs. On the one hand, the rationale for this might be that the etiology was different between these two types of polyp [4, 5]. On the other hand, it was worth noting that limited reports of positive family history in this study would lead to imprecise results. In addition, the risk of polyp recurrence increased along with aging and BMI, which were also proved in previous studies [13, 33, 34]. Advanced age and obesity may be involved in the presence of chronic subclinical inflammatory conditions, which may contribute to polyp recurrence [35]. Also, obesity might elevate the expression level of insulin and insulin-like growth factor-1, which could stimulate the recurrence of polyps [36].

It seemed that the recurrence of polyps was affected by various factors. To assess the influence of risk factors on polyp recurrence more accurately, we put the potential risk factors into the nomogram and calibrated it using calibration plots. When patients with a higher probability of recurrence are identified using the nomogram, they should receive stricter monitoring. However, the power of the nomogram was not enough (AUC = 0.69), which suggested that the factors determined above might lack sufficient ability to predict the recurrence of polyps.

Several limitations need to be noted as well. First, selection bias and recall bias could not be ruled out since our study was a single-center retrospective study. Second, Chinese pathologists did not pay enough attention to the diagnosis of SSPs and TSAs in the past few decades because of the evolving nature and lack of consensus on the diagnostic criteria of SPs. Third, we did not analyse the impact of dietary factors and exercise-related data on polyp recurrence because the related information was hardly achieved in this retrospective study. Multicenter, large-scale, prospective research is needed in the future to solve these problems.

In conclusion, our study illustrated several risk factors for the recurrence of colorectal polyps. Being male, age ≥50 years, BMI ≥24 kg/m^2, smoking, alcohol consumption, family history of polyps, and family history of CRC are indicated as risk factors for polyp recurrence. We also found that some risk factors could increase the risk of adenoma recurrence, but not SP, including smoking, alcohol consumption, and positive family history of polyps or CRC.

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

Authors' Contributions

Conceptualization: Z.C., Y.L., and J.H. Methodology: Z.C. and Y.L. Software: J.C. and X.C. Validation: M.Y.L. and B.Z. Formal analysis: Z.C., Y.L., and J.H. Investigation: Z.C. and J.H. Resources: Y.C. and J.H. Data curation: Z.C. and Y.L. Writing—original draft preparation: Z.C. Writing—review and editing: X.H. and P.L. Visualization: M.Y.L. and X.C. Funding acquisition: X.H. and P.L. Supervision: P.L.

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None.

Conflict of Interest

None declared.

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