ORIGINAL ARTICLE

Journal of Digestive Diseases | WILEY

Effects of age, sex and pathological type on the risk of multiple polyps: A Chinese teaching hospital study

Xu Han[1] | Wei Qian[1] | Yu Liu[1] | Ting Zheng[2] | Xiao Ju Su[1,3] | Ping Ping Zhang[1,3] | Yan Chen[1,3] | Liang Hao Hu[1,3] | Zhao Shen Li[1,3]

[1]Department of Gastroenterology, Changhai Hospital, Second Military Medical University, Shanghai, China

[2]Department of Medicine, Michigan Medicine University of Michigan, Ann Arbor, Michigan

[3]Digestive Endoscopy Center, Changhai Hospital, Second Military Medical University, Shanghai, China

Correspondence
Zhao Shen Li, Department of Gastroenterology, Digestive Endoscopy Center, Changhai Hospital, Second Military Medical University, 168 Changhai Road, Shanghai 200433, China
Email: zhaoshen-li@hotmail.com

Objectives: The lack of risk profile data on changes in multiple polyps identified by a colonoscopy constrains the creation of evidence-based guidelines. Our study aimed to investigate the relationship between size, location and histology of multiple polyps and patients' characteristics in a large teaching hospital-based Chinese population.

Methods: We conducted a large, case-control, retrospective analysis on polyps obtained from 8308 patients who presented at the Digestive Endoscopy Center, Changhai Hospital (Shanghai, China) from January 2013 to August 2015. In total 10572 polyps were analyzed, with risk factors extrapolated through chart reviews of patients' electronic medical records.

Results: Single polyps were identified in 6843 (82.4%) patients while multiple polyps were found in 1465 (17.6%). A multivariate analysis indicated that men were more likely than women to have multiple polyps ($P < 0.001$). Compared with the single polyps group, the numbers of patients with multiple polyps increased significantly with age ($P < 0.001$). Multiple small (6-9 mm) non-advanced adenomas were more likely to be found than were diminutive (<5 mm) non-advanced adenomas ($P < 0.001$). While most advanced and non-advanced adenomas were diagnosed in patients with single adenomas (55.9% and 65.6%, respectively), advanced adenomas were more likely than non-advanced adenomas to be in multiples ($P < 0.001$).

Conclusions: Our data indicate that particular features of colorectal polyps, such as their large size, advanced histology, together with patients' characteristics, including their sex and age, are risk factors associated with multiple polyps during diagnosis, screening and surveillance.

KEYWORDS
colon polyp, multiplicity, risk factor

1 | INTRODUCTION

Colorectal cancer (CRC) is a common and lethal disease. In China the incidence of CRC has continued to increase since 1998. It is currently the sixth most common cancer and the fifth leading cause of cancer-related death in China, contributing to an estimated 132110 deaths in 2010.[1] CRC is therefore an important public health concern due to its rising incidence and prevalence, in addition to the accompanied burden of disease.

There is robust evidence that early detection of CRC by screening and removing cancer precursor lesions offers an effective method to reduce its morbidity and mortality.[2] However, clinically most colorectal polyps do not cause symptoms. A key method of determining the suitability of cancer surveillance is to perform a risk stratification of

the findings during colonoscopy screening and to apply updated guidelines for CRC surveillance.

Due to limited prospective studies, detailed subgroup analysis of follow-up surveillance data is lacking for patients with multiple polyps in Asian countries such as China. The currently available Asia-Pacific consensus recommendations on CRC screening were adapted from the US Multi-Society Task Force on CRC guidelines for colonoscopy surveillance. However, these guidelines cannot be applied worldwide due to different characteristics of various populations in Europe, America and Asia. For example, different strategies are used for follow-up surveillance in patients with more than one polyp in the US and UK risk-stratification guidelines.[3-5] A single examination after one year is recommended in the UK for patients with more than five small adenomas, or more than three if at least one is ≥1 cm in size. While the US guidelines recommend a shorter follow-up interval for those with more than 10 adenomas.

The primary aim of this study was to identify the high-risk features of multiple polyps including their size, location and histological type. Patients' age and sex were also characterized on the basis of a contingency analysis of a large series of Chinese patients with colorectal polyps.

2 | PATIENTS AND METHODS

2.1 | Study population and data sources

This study was designed as a retrospective case-control analysis of biopsy samples obtained from patients undergoing a screening colonoscopy at the Digestive Endoscopy Center, Changhai Hospital, Second Military Medical University (Shanghai, China) between January 2013 and August 2015. The procedures were performed by eight fully trained, experienced gastroenterologists.

All biopsy samples and resected polyps were submitted to Department of Pathology of Changhai Hospital for review. Exclusion criteria were: (i) patients with hereditary CRC syndromes, such as Lynch syndrome, familial adenomatous polyposis and Peutz-Jeghers syndrome; (ii) a history of inflammatory bowel disease; and (iii) missing pathologic report from the index colonoscopy, or an incomplete colonoscopic assessment as a result of inadequate bowel cleansing or lack of cecum intubation. This study was approved by the Ethics Committee of Shanghai Changhai Hospital. All procedures conformed to the principles outlined in the Declaration of Helsinki (2013). Written, informed consent was obtained from all participants before colonoscopy and biopsy.

2.2 | Measures and definitions

Patients' characteristics (age and sex) and their polyp features (size, multiplicity, location and pathological diagnosis) were collected from electronic medical record database. At the time of submission, gross descriptions of the biopsies were recorded in the database. All biopsies were fixed in formalin and systematically processed.

Colorectal polyps were histologically classified as either non-neoplastic, colorectal adenomas or serrated lesions by reference to a standard set of diagnostic terms used by pathologists.[6] Non-neoplastic polyps were classified as inflammatory, lymphoid or juvenile polyps. Juvenile polyps of the colon are benign and hamartomatous and are the most frequent gastrointestinal polyp observed in children.[7,8] They have a cystic appearance with spaces filled with mucous and prominent irregular cystically dilated glands with lymphoplasmacytic infiltration. Lymphoid polyps consist of well-differentiated lymphoid tissue, characterized by small, uniformly localized or generalized polypoid lesions. Colorectal adenomas include tubular, tubulovillous and villous adenomas, which are classified as either non-advanced or advanced adenomas based on their pathological characteristics.[9] Advanced adenomas are defined as those of ≥10 mm in diameter, polyps with high grade dysplasia, tubulovillous adenoma containing >25% villous architecture, or villous adenoma.[10,11] Advanced histopathological features of adenomas are defined as polyps with severe dysplasia and or a villous component, features predicting an increased likelihood of malignant transformation. Serrated lesions are identified by reference to the World Health Organization classification,[12] being slightly elevated lesions with irregular borders and possibly covered with mucus, as observed under endoscopy.[13] Serrated adenomas are typically distorted, with widened, boot-shaped crypt bases.[14] Polyps were categorized by diameter size into three groups: diminutive (≤5 mm), small (6-9 mm) or large (≥10 mm). The location of polyps is defined as proximal when located in the cecum, ascending colon or transverse colon, or distal for all polyps found in the descending colon to the rectum. In the present study, we defined multiple adenomas or polyps as the presence of two or more adenomas or polyps.

2.3 | Statistical analysis

Statistical analyses were performed by using SPSS software version 20.0 (IBM, Armonk, NY, USA). Pearson χ^2 test and the Cochran-Mantel-Haenszel general association statistical test were conducted for bidirectionally unordered contingency tables. Wilcoxon rank-sum and Cochrane-Mantel-Haenszel tests were used to calculate differences in scores for single ordinal contingency data. A Spearman's rank correlation analysis was performed and the Cochran-Mantel-Haenszel statistic was used to calculate bidirectionally ordinal contingency tables. Odds ratio (OR) and 95% confidence interval (CI) were calculated. Two-sided P values < 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics of the patients and the features of colorectal polyps

Of the 11 170 participants who underwent a colonoscopic biopsy between January 2013 and August 2015, a total of 2862 patients

were excluded either because they met at least one exclusion criterion or because their pathology or endoscopy reports were incomplete. The remaining 8308 patients were included in the study. The patients' baseline characteristics are shown in Table 1. Of these, 5260 (63.3%) were men and 3048 (36.7%) were women. A total of 10572 colonoscopically resected polyps were identified, including 961 (9.1%) non-neoplastic polyps, 3757 (35.5%) serrated lesions and 5854 (55.4%) colorectal adenomas. Among the colorectal adenomas, 4272 were tubular adenomas, 1133 were tubulovillous adenomas and 449 were villous adenomas. The percentage of all polyps detected in men was higher than that in women (7002 [66.2%] vs 3570 [33.8%]). Of the total patients enrolled in this study, most were at 51-60 years of age. Of the 961 non-neoplastic polyps, unlike juvenile polyps, of which nearly 76% were ≥10 mm in diameter, more than half of the lymphoid and inflammatory polyps were ≤5 mm in diameter, while fewer than 10% of them were ≥10 mm. A total of 3757 serrated lesions were identified, of which 2385 (63.5%) were ≤5 mm, 990 (26.3%) were 6-9 mm and 382 (10.2%) were ≥10 mm in diameter. Of the 5854 colorectal adenomas, 2158 (36.9%) were ≤5 mm, 1605 (27.4%) were 6-9 mm and 2091 (35.7%) were at least 10 mm in diameter. Among the 1582 tubulovillous and villous adenomas, 84.6% and 80.6%, respectively, were at least 10 mm in diameter, 11.2% and 15.8% were 6-9 mm, and only less than 5% were ≤5 mm. Tubular adenomas, on the other hand, showed an opposite trend; 18.0% were at least 10 mm in diameter and nearly half were ≤5 mm. Among all polyps, most were found in the distal colon compared with the proximal colon (57.3% vs 42.7%), especially juvenile polyps, of which more than 90% were in the distal colon. Moreover, as shown in Table 2, the proportion of patients with non-advanced adenomas decreased, while the percentage with advanced adenomas increased gradually with increasing age ($P < 0.001$). In the proximal colon, most colorectal adenomas were non-advanced (66.1%), whereas in the distal colon, the percentage of non-advanced and advanced adenomas was 57.6% and 42.4%, respectively (all $P < 0.001$).

3.2 | Distribution of polyps by sex, age and location

The differences in distributions of patients' sex, age and lesion location of the single and multiple polyps are shown in Table 3. Of 8308 patients 6843 (82.4%) had single polyp and 1465 (17.6%) had multiple polyps. Among male patients, 79.2% had single polyps, and the remaining 20.8% had multiple polyps (a 3.8-fold difference), compared with 87.8% of female patients with single polyps and 12.2% with multiple polyps (a 7.2-fold difference). Thus, male patients were more likely to develop multiple polyps than female patients ($P < 0.001$).

Patients younger than 40 years mostly had single polyps (single vs multiple: 712 [92.5%] vs 58 [7.5%]). The percentage of patients with single polyps decreased gradually with increasing age, while that with multiple polyps increased gradually. In patients aged over 70 years, the proportion with single polyps decreased to 76.2%, with 23.8% having multiple polyps ($P<0.001$).

Among all non-advanced colorectal adenomas, 2354 (65.6%) were single polyps, while 1234 (34.4%) were multiple polyps. While for advanced adenomas, 1266 (55.9%) were single polyps and 1000 (44.1%) were multiple polyps. In the non-advanced adenomas group, the number of single polyps was 1.9-fold as many as that of multiple polyps. While in the advanced adenomas group, single polyps were 1.3-fold as many as multiple polyps, as shown in Table 3 ($P < 0.001$).

The distribution of single and multiple polyps was as follows: 2894 single polyps in the proximal colon and 3949 in the distal side. A total of 1624 multiple polyps were identified in the proximal colon, while 2105 were distal ($P > 0.05$).

3.3 | Size distribution of neoplasia in the polyps

As shown in Table 4, according to the pathological classification, polyps were categorized as either non-neoplastic or colorectal adenomas or serrated lesions. Single colorectal adenomas were more than 2-fold more likely to be 6-9 mm in diameter and 6-fold more likely to be ≥10 mm than single non-neoplastic polyps (OR 2.483, 95% CI 1.997-3.088 for those of 6-9 mm in diameter; OR 6.156, 95% CI 4.625-8.194 for those ≥10 mm in diameter). Multiple colorectal adenomas were 1.5-fold more likely to be 6-9 mm and 1.3-fold more likely to be ≥10 mm in diameter than multiple non-neoplastic polyps (OR 1.486, 95% CI 1.163-1.898 for 6-9 mm; OR 1.308, 95% CI 1.052-1.627 for ≥10 mm in diameter).

3.4 | Size distribution of advanced neoplasia

There were even greater differences between non-advanced and advanced adenomas. Single advanced adenomas were more than 4-fold more likely to be 6-9 mm and 2174-fold more likely to be ≥10 mm in diameter than non-advanced adenomas (OR 4.29, 95% CI 2.79-6.58 for 6-9 mm; OR 2173.87, 95% CI 1278.44-3696.43 for ≥10 mm). Multiple advanced adenomas were 4.6-fold more likely to be 6-9 mm in diameter and 1865-fold more likely to be ≥10 mm than non-advanced adenomas (OR 4.62, 95% CI 2.50-8.56 for 6-9 mm; OR 1864.66, 95% CI 946.83-3672.21 for ≥10 mm in diameter) (Table 5).

Among single non-advanced adenomas, 1465 (62.2%) were ≤5 mm in diameter and 889 (37.8%) were 6-9 mm in diameter. There were nearly twice as many diminutive adenomas as small ones. The proportion of diminutive and small adenomas was similar for the multiple non-advanced adenomas. Multiple adenomas tend to be in larger size than single non-advanced adenomas ($P < 0.001$). However, no such difference was observed in the advanced adenoma group (Table 6).

4 | DISCUSSION

In this study, we demonstrated that in older individuals adenoma was an important predictor of advanced adenomas. Similar results were

TABLE 1 Baseline characteristics of patients and polyps (n, %)

Characteristics	All patients (N = 8308)	Non-neoplastic polyps (N = 961)			Colorectal adenomas (N = 5854)			Serrated lesions (N = 3757)	
		Lymphoid (n = 243)	Inflammatory (n = 676)	Juvenile (n = 42)	Tubular (n = 4272)	Tubulovillous (n = 1133)	Villous (n = 449)	Hyperplastic (n = 3484)	Serrated (n = 273)
Patients' sex									
Male	5260 (63.3)	148 (60.9)	473 (70.0)	28 (66.7)	2755 (64.5)	794 (70.1)	298 (66.4)	2316 (66.5)	190 (69.6)
Female	3048 (36.7)	95 (39.1)	203 (30.0)	14 (33.3)	1517 (35.5)	339 (29.9)	151 (33.6)	1168 (33.5)	83 (30.4)
Patients' age, y									
≤40	770 (9.3)	47 (19.4)	97 (14.4)	15 (35.7)	340 (8.0)	48 (4.2)	21 (4.7)	389 (11.2)	25 (9.1)
41-50	1810 (21.8)	52 (21.4)	179 (26.5)	15 (35.7)	863 (20.2)	183 (16.2)	80 (17.8)	871 (25.0)	57 (20.9)
51-60	2806 (33.8)	77 (31.7)	234 (34.6)	9 (21.4)	1396 (32.7)	383 (33.8)	142 (31.6)	1186 (34.0)	99 (36.3)
61-70	2127 (25.6)	56 (23.0)	128 (18.9)	3 (7.2)	1201 (28.1)	359 (31.7)	119 (26.5)	785 (22.5)	69 (25.3)
≥71	795 (9.5)	11 (4.5)	38 (5.6)	0 (0)	472 (11.0)	160 (14.1)	87 (19.4)	253 (7.3)	23 (8.4)
Polyp size									
≤5mm		173 (71.2)	495 (73.2)	1 (2.4)	2094 (49.0)	48 (4.2)	16 (3.6)	2245 (64.4)	140 (51.3)
6-9mm		52 (21.4)	150 (22.2)	9 (21.4)	1407 (32.9)	127 (11.2)	71 (15.8)	913 (26.2)	77 (28.2)
≥10mm		18 (7.4)	31 (4.6)	32 (76.2)	771 (18.0)	958 (84.6)	362 (80.6)	326 (9.4)	56 (20.5)
Polyp location									
Proximal colon		112 (46.1)	232 (34.3)	4 (9.5)	1975 (46.2)	388 (34.2)	180 (40.1)	1522 (43.7)	105 (38.5)
Distal colon		131 (53.9)	444 (65.7)	38 (90.5)	2297 (53.8)	745 (65.8)	269 (59.9)	1962 (56.3)	168 (61.5)

TABLE 2 Patients' sex, age, and adenomas features

Colorectal adenomas (n = 5854)			
n, %	Non-advanced adenomas (n = 3588)	Advanced adenomas (n = 2266)	P value
Sex			
Male	2342 (60.9)	1505 (39.1)	0.482
Female	1246 (62.1)	761 (37.9)	
Age, y			
≤40	321 (78.5)	88 (21.5)	<0.001
41-50	813 (72.2)	313 (27.8)	
51-60	1138 (59.2)	783 (40.8)	
61-70	967 (57.6)	712 (42.4)	
≥71	349 (48.5)	370 (51.5)	
Location			
Proximal colon	1680 (66.1)	863 (33.9)	<0.001
Distal colon	1908 (57.6)	1403 (42.4)	

TABLE 3 Patients' characteristics, polyp pathology and location of single and multiple polyps

n, %	Single	Multiple	P value
Sex			
Male	4168 (79.2)	1092 (20.8)	<0.001
Female	2675 (87.8)	373 (12.2)	
Age, y			
≤40	712 (92.5)	58 (7.5)	<0.001
41-50	1580 (87.3)	230 (12.7)	
51-60	2284 (81.4)	522 (18.6)	
61-70	1661 (78.1)	466 (21.9)	
≥71	606 (76.2)	189 (23.8)	
Colorectal adenomas			
Non-advanced	2354 (65.6)	1234 (34.4)	<0.001
Advanced	1266 (55.9)	1000 (44.1)	
Location			
Proximal colon	2894 (64.1)	1624 (35.9)	>0.05
Distal colon	3949 (65.2)	2105 (34.8)	

found in the group with multiple polyps. With increasing age, the proportion of patients with multiple polyps increased gradually. In the non-advanced adenoma group, patients with small (6-9 mm) adenomas were more likely to have multiple adenomas than those with diminutive (<5 mm) adenomas. More importantly, advanced adenomas were disproportionally more likely to arise from multiple adenomas than non-advanced adenomas.

In this study, we showed that advanced adenomas were more common than non-advanced adenomas in the distal colon and a biopsy of these lesions is recommended. Polyp multiplicity is one of the most important predictors both in US and European CRC screening guidelines that determine when to repeat a surveillance colonoscopy. By conducting univariate and multivariate analyses, a

retrospective study from Korea found that the number of adenomas was an independent high-risk factor for polyp recurrence.[15] An earlier study found that the number of advanced adenomas was directly related to the rate of metachronous CRC.[16] In the present study, the risk of advanced adenomas was found to increase progressively with the number of adenomas. This result was confirmed by another study, showing that patients with five or more adenomas had a 24% of risk of developing advanced adenomas; nearly 2.7-fold higher than patients with single adenoma.[17]

Colorectal advanced adenoma is the most frequent precancerous lesion among all potentially premalignant gastrointestinal conditions. A previous study found that the number of advanced adenomas was directly related to the rate of metachronous CRC.[16] Patients with multiple adenomas have a high risk of developing CRC. We have found a close correlation between advanced adenomas and multiple polyps. In addition to the results described above, for the first time an association has been found between increased rate of polyp multiplicity, male sex and older age. Multiple polyps were found to be more common in men than in women in the present study. More than 20% of male patients presented with multiple polyps, compared with only 10% of women. Patients' characteristics, such as sex, as a risk factor for colon cancer have been previously studied in a number of Western counties.[18,19] One group[18] used univariate analysis to demonstrate that the prevalence of advanced adenomas was higher in men than in women, suggesting that male sex was associated with increased odds of dysplasia. Such findings were confirmed in another group who concluded that male sex was a moderate risk factor for advanced adenomas.[20] In addition, a study from Japan also revealed that colorectal neoplasms were in general more likely to develop in men.[21] Despite large amounts of data and clinical research suggesting that male sex is an independent risk factor for CRC, the correlation between the male sex and polyp multiplicity is reported here for the first time.

Older age has been found to be associated with an increased risk of advanced adenomas in previous studies. This is confirmed in

TABLE 4 Odds ratio (OR) of non-neoplastic polyps and colorectal adenomas stratified by polyp size

	Non-neoplastic polyps (n)	Colorectal adenomas (n)	OR (95% CI)	AOR (95% CI)
Single				
≤5 mm	453	1495	Ref.	Ref.
6-9 mm	118	967	2.483 (1.997 - 3.088)	2.405 (1.932 - 2.995)
≥10 mm	57	1158	6.156 (4.625 - 8.194)	5.655 (4.240 - 7.543)
Multiple				
≤5 mm	216	663	Ref.	Ref.
6-9 mm	93	638	1.486 (1.163-1.898)	1.476 (1.154-1.888)
≥10 mm	24	933	1.308 (1.052-1.627)	1.359 (1.090-1.649)

Abbreviations: AOR, adjusted odd ratio; CI, confidence interval; Ref., reference.

TABLE 5 Odds ratio (OR) of advanced pathology stratified by adenoma size

	Non-advanced (n)	Advanced (n)	OR (95% CI)	AOR (95% CI)
Single				
≤5 mm	1465	30	Ref.	Ref.
6-9 mm	889	78	4.29 (2.79-6.58)	4.18 (2.71-6.42)
≥10 mm	0	1158	2173.87 (1278.44-3696.43)	2212.16 (1289.28-3795.66)
Multiple				
≤5 mm	650	13	Ref.	Ref.
6-9 mm	584	54	4.62 (2.50-8.56)	4.52 (2.43-8.39)
≥10 mm	0	933	1864.66 (946.83-3672.21)	1976.94 (992.17-3939.15)

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; Ref., reference.

TABLE 6 Difference in size distribution between single and multiple adenomas (n %)

	Single	Multiple	P value
Non-advanced adenomas	n = 2354	n = 1234	
≤5 mm	1465 (62.2)	650 (52.7)	
6-9 mm	889 (37.8)	584 (47.3)	0.000*
Advanced adenomas	n = 1266	n = 1000	
≤5 mm	30 (2.4)	13 (1.3)	
6-9 mm	78 (6.2)	54 (5.4)	0.102**
≥10 mm	1158 (91.5)	933 (93.3)	0.061***

*≤5 mm vs 6-9 mm for non-advanced adenomas.
**≤5 mm vs 6-9 mm for advanced adenomas.
***≤5 mm vs ≥10 mm for advanced adenomas.

our study. More importantly, we report that the proportion of multiple polyps increases with patients' age. A scientific team from Oakland estimated that the increase in number with age was similar for both men and women, with prevalence rising across all 5-year age categories, reaching a peak at 70-74 years of age. A 2011 study reported that the highest incidence of colorectal tumors in the age range of 75-80 years.[22] Our findings not only support the current Chinese consensus, but also suggest that colonoscopists should focus on elderly patients with multiple polyps who may be at risk of CRC.

Another interesting finding in this study was the relationship between the size and number of adenomas. We demonstrated that their increase in size was a risk factor for both single and multiple colorectal adenomas compared with those that were non-neoplastic. There was a strong correlation between the number and size of adenomas observed in this study for non-advanced adenomas. Multiple non-advanced adenomas were more likely to be larger in size. However, there was no such correlation between the number and size of advanced adenomas. The US Multi-Society Task Force guidelines [3] recommend 3-year intervals for CRC surveillance in patients with a history of 3-10 tubular adenomas of any size. This is aimed at minimizing the lesions or interval cancers that may be missed, while maintaining cost-effectiveness and patient adherence to colonoscopy screening. However, the present study suggests that in addition to the number of adenomas, the size of multiple non-advanced adenomas should also be considered in the colonoscopy screening guidelines. One study also questioned whether patients who had a medical history of 3-5 diminutive colorectal adenomas truly had an increased risk of advanced neoplasia compared with those who had fewer but larger adenomas during surveillance.[23] The authors found a strong association between the findings at baseline screening colonoscopy and rate of serious incident lesions; in that patients with 1 or 2 non-advanced neoplasia ≤10 mm in diameter were at low risk of serious lesions. Although the recommended surveillance interval for one or more tubular adenomas ≥10 mm in diameter is 3 years, the difference in incidence rate in single

and multiple non-advanced adenomas suggests that different surveillance and screening interval strategies should be implemented based on the number of polyps identified by colonoscopies.

It is generally believed that the malignant potential of adenomas correlates with their size and location. In the present study, large size was strongly associated with the development of advanced adenomas. In addition, a greater number of adenomas were found in the distal than the proximal colon, especially in advanced adenomas. This tendency was observed in patients with either single or multiple polyps.

One limitation of this study was that we did not sub-categorize multiple adenomas based on their number, or investigate the correlation between number and size in these subgroups. Second, the retrospective design of the study in a single referral center makes it prone to possible confounders, and thus it might have limited application in other regions. Third, the sample size was relatively small. Therefore, a large, multicenter, prospective study is needed to confirm risk factors for multiple polyps.

In conclusion, particular features of colorectal polyps such as being large in size and of an advanced neoplastic type in addition to patients' characteristics such as being male and middle-aged are among the associated risk factors of multiple polyps and thus should be incorporated into future guidelines for CRC surveillance in China.

CONFLICTS OF INTERESTS

The authors declare that they have no conflicting interests.

ORCID

Xu Han https://orcid.org/0000-0003-2407-7179

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