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Melanosis coli: A factor not associated with histological progression of colorectal polyps

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Objective: In this study we aimed to investigate the association of melanosis coli (MC) and the colorectal polyp detection rate (PDR).

Methods: In all, 1104 MC patients and 62 181 non-MC participants were enrolled. And 2208 controls were matched by participants' age and gender, and quality of bowel preparation using the propensity score matching (PSM) method. Additionally, 490 polyps in MC and 980 in controls matched by age and gender, and size and location of polyps were analyzed. The association of PDR and pathological features of polyps with MC were also analyzed.

Results: MC patients showed a higher PDR (44.3% vs 39.3%, $P = 0.006$) and detection rate of low-grade adenoma (45.4% vs 36.7%, $P = 0.002$) but fewer large polyps (≥10 mm) (18.8% vs 26.9%, $P = 0.001$), fewer polyps in the left colon (33.5% vs 40.0%, $P = 0.018$), and a lower detection rate of advanced adenoma/adenocarcinoma (17.4% vs 24.3%, $P = 0.003$) than the matched controls. On multivariate logistic regression analysis, MC was independently associated with an increased PDR (odds ratio 1.184, 95% confidence interval 1.045–1.343, $P = 0.008$). Analysis targeting polyps showed that there were significant differences in age, gender, location, and pathology ($P < 0.001$) between polyps with and without MC. However, after adjusting for participants' age and gender, size and location of polyps, there was no difference between the two groups in pathology ($P = 0.635$).

Conclusion: MC is independently associated with increased colorectal PDR, but not with histological progression of polyps.

KEYWORDS
colonoscopy, colorectal adenoma, colorectal neoplasms, melanosis coli, polyp detection rate

1 | INTRODUCTION

Melanosis coli (MC) refers to brownish or black pigmentation of the colonic mucosa, which results from excessive deposits of lipofuscin in the macrophages within the colonic lamina propria. The etiology of MC

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is complex and diverse, including the abuse of laxatives (anthraquinone laxatives in particular), chronic constipation, inflammatory bowel disease, and chronic diarrhea.[1–4] MC more frequently affects women and the elderly.[5] In recent years, due to aging of the population, change in dietary habits and lifestyle, as well as the advances in colonoscopic techniques, the detection rate of MC has been increasing.[5]

The relationship between MC and colorectal polyps, colorectal adenomas in particular, has been widely investigated. Two case–control retrospective studies in China have reported that MC was independently associated with increased low-grade adenomas.[6,7] Another study and meta-analysis in Japan has also demonstrated the association between MC and an increased detection rate of adenoma.[8] The adenoma–carcinoma pathway is an oncogenic pathway involved in the development of colorectal cancer (CRC). Moreover, adenomas are recognized as precursor lesions for CRC. Although MC is a benign and reversible disorder, its close relationship with colorectal adenoma has aroused attention. However, whether this relationship is causal or simply due to an increased detection of adenomas in MC remains to be investigated. Use of laxatives, as one of the main etiologies of MC, may cause the development of adenomas by damaging epithelial cells.[9] Additionally, apparent contrast of polyps and the dark background mucosa is a likely explanation for their increased detection. Elucidation of the relationship between MC and colonic polyps may help guide the clinical management of MC.

In the present study we aimed to clarify the association of MC and colorectal polyps and that between histological progression of polyps and MC by analyzing the clinicopathological data of the patients with MC through a multivariate logistic regression model and the propensity score matching (PSM) method.

2 | PARTICIPANTS AND METHODS

2.1 | Participants

Adult participants who underwent colonoscopy at Tongji Hospital, School of Medicine, Tongji University (Shanghai, China) from March 2012 to June 2019 were retrospectively recruited. Their medical records including a total of 63285 colonoscopic procedures and 24577 complete pathological reports of colorectal polyps were procured from the digital endoscopic and pathological databases, respectively, and were reviewed. Age and gender of the participants, use of sedation during the procedure, experiences of the endoscopists, and endoscopic and histological findings, etc, were collected. This study was approved by the Institutional Ethics Committee of the hospital (no. K-W-2021-014). Written informed consent was waived due to the retrospective study design.

2.2 | Study design

This study was divided into two parts (Figure 1). In the first part, a multivariate logistic regression model for all the enrolled participants and comparison of the differences between MC patients and controls matched by using the PSM method were conducted to determine the relationship between MC and the polyp detection rate (PDR) when adjusting for other potential confounders. The PSM method was conducted by using the R software (R Foundation for Statistical Computing, Vienna, Austria) with a ratio of 1:2, whereby each patient with MC was matched with two non-MC participants on a caliper distance of 0.01 and priority given to exact matches. In the second part, the pathology of polyps was analyzed and compared between these two groups after adjusting for other confounding factors to clarify whether MC increased the risk of polyp progression or provided a dark background to make polyps easier to be detected.

2.3 | Definitions

MC was diagnosed clinically according to the gross appearance of brownish or black colonic mucosa during the colonoscopy. The quality of bowel preparation was evaluated by the Boston bowel preparation scale (BBPS).[10] A good bowel preparation was defined as a total BBPS ≥6 and a partial BBPS ≥2 in each segment (right, transverse and left colon). The location of the polyps was divided into the right and left colon, in which the transverse colon was included in the right colon. Experienced endoscopists were defined as those having over 10 years of experiences for colonoscopy or had performed over 3000 colonoscopic procedures. Polyps were classified as inflammatory or hyperplastic polyp, low-grade adenoma (tubular adenoma with or without mild-to-moderate dysplasia), advanced adenoma (adenomas >10 mm in diameter, villous or tubulovillous adenomas, those with high-grade dysplasia), or adenocarcinoma, respectively.[11]

2.4 | Statistical analysis

All the statistical analyses were carried out by using the SPSS software version 26.0 (IBM, Armonk, NY, USA). By using the PSM method, 1104 MC patients with 2208 controls (matched by age, gender, quality of bowel preparation) and 490 polyps in the MC patients with 980 in the controls (matched by age, gender, size, and location of polyps) were enrolled for analysis. Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were expressed as numbers and percentages or frequencies. An unpaired *t*-test and Chi-square test were used to analyze the differences in continuous and categorical variables, respectively, between the MC patients and the matched controls. A two-sided *P* value of less than 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Study part 1: based on the presence and absence of MC

3.1.1 | Baseline characteristics of the participants

Altogether 1104 MC patients (the MC group) and 62 181 participants without MC (the non-MC group) were enrolled. Their baseline

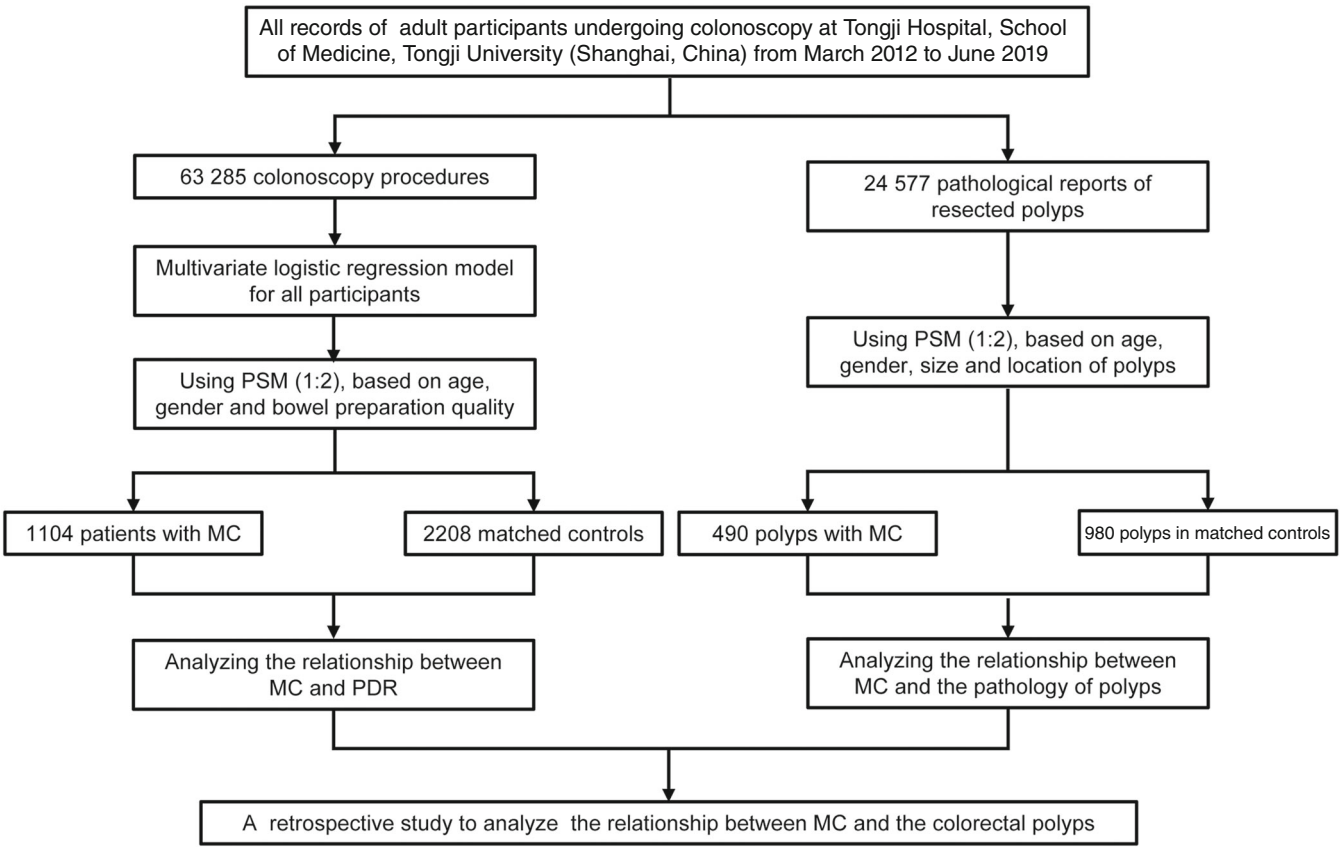

FIGURE 1 Schematic diagram of study design. Abbreviation: MC, melanosis coli; PDR, polyp detection rate

characteristics are shown in Table 1. Compared with the non-MC group, the MC patients were elder (65.28 ± 12.39 y vs 55.60 ± 13.91 y, $P < 0.001$) with a female predominance (60.0% vs 49.2%, $P < 0.001$). Moreover, a higher rate of poor quality of bowel preparation was also noted in the MC group (8.8% vs 3.6%, $P < 0.001$). There were no significant differences in the rate of sedation during the endoscopic procedure (82.6% vs 82.0%, $P = 0.594$) or the experience of endoscopists (81.3% vs 82.3%, $P = 0.344$) between the MC and the non-MC groups. Notably, the PDR was significantly higher in the MC group (44.3% vs 36.6%, $P < 0.001$).

3.1.2 | Association between MC and an increased PDR

By using the PSM method, the 1104 MC patients were matched with those without MC by age, gender, and the quality of bowel preparation in a ratio of 1:2. After adjusting for the aforementioned confounders, PDR of the MC group was significantly higher than that of the matched controls (44.3% vs 39.3%, $P = 0.006$; Table 1).

The multivariate logistic regression analysis showed that after adjusting for age and gender of the participants, quality of bowel preparation, experience of endoscopists, and sedation, MC was found to be independently associated with an increased PDR (odds ratio [OR] 1.184, 95% confidence interval [CI] 1.045–1.343, $P = 0.008$; Table 2).

3.1.3 | Association between MC and the features of polyps

The endoscopic and pathological features of polyps detected in MC patients and the matched controls are shown in Table 3. The polyps of the MC patients were less detected in the left colon than in the matched controls (33.5% vs 40.0%, $P = 0.018$). In terms of the number of polyps, significantly more MC patients had 6–10 polyps (25.6% vs 18.2%, $P = 0.001$) or over 10 polyps (8.0% vs 4.8%, $P = 0.019$). Regarding the size of the largest polyp, the detection rate of polyps of 1-5 mm (37.8% vs 34.9%, $P = 0.288$) and 6–9 mm (43.4% vs 38.2%, $P = 0.062$) seemed to be higher in the MC group than in the matched controls, although the differences were not statistically significant; while polyps ≥10 mm were less frequently detected in the MC group (18.8% vs 26.9%, $P = 0.001$). Additionally, compared with the matched controls, patients with MC had a significantly higher rate of low-grade adenoma (45.4% vs 36.7%, $P = 0.002$) but a lower rate of advanced adenomas or adenocarcinoma (17.4% vs 24.3%, $P = 0.003$), while that of inflammatory or hyperplastic polyps did not differ between the two groups (37.2% vs 39.0%, $P = 0.521$).

TABLE 1 Baseline characteristics of melanosis coli (MC) patients compared with non-MC participants and matched controls (n, %)

	MC (n = 1104)	Non-MC (n = 62 181)	Matched controls (n = 2 208)	*P* value*	*P* value#
Age (y)					
Mean ± SD	65.28 ± 12.39	55.60 ± 13.91	65.26 ± 12.361	<0.001	0.951
18–40	44 (4.0)	10 275 (16.5)	88 (4.0)	<0.001	1.000
41–50	73 (6.6)	8941 (14.4)	146 (6.6)		
51–60	234 (21.2)	17 579 (28.3)	468 (21.2)		
61–70	377 (34.1)	18 159 (29.2)	754 (34.1)		
>70	376 (34.1)	7 227 (11.6)	752 (34.1)		
Gender (n, %)					
Male	442 (40.0)	31 582 (50.8)	885 (40.1)	<0.001	0.980
Female	662 (60.0)	30 599 (49.2)	1 323 (59.9)		
Bowel preparation (n, %)					
Poor	97 (8.8)	2 215 (3.6)	197 (8.9)	<0.001	0.897
Good	1 007 (91.2)	59 966 (96.4)	2 011 (91.1)		
Sedation for procedures (n, %)					
No sedation	192 (17.4)	11 201 (18.0)	396 (17.9)	0.594	0.700
Sedation	912 (82.6)	50 980 (82.0)	1 812 (82.1)		
Endoscopists (n, %)					
Less experienced	207 (18.8)	10 977 (17.7)	403 (18.3)	0.344	0.727
Experienced	897 (81.2)	51 204 (82.3)	1 805 (81.7)		
Polyp detection (n, %)	489 (44.3)	22 754 (36.6)	867 (39.3)	<0.001	0.006

*MC vs non-MC. #MC vs matched controls.
Abbreviation: SD, standard deviation.

TABLE 2 Multivariate analysis of independent parameters associated with polyp detection rate

	Polyp detection, n/N (%)	OR (95% CI)	*P* value
Age (y)			
18–40	1 550/10 319 (15.0)	Reference	
41–50	2 484/9 014 (27.6)	2.303 (2.143–2.476)	<0.001
51–60	7 096/17 813 (39.8)	4.307 (4.043–4.587)	<0.001
61–70	8 613/18 536 (46.5)	5.565 (5.227–5.924)	<0.001
>70	3 500/7 603 (46.0)	5.486 (5.104–5.896)	<0.001
Gender			
Female	9 134/31 261 (29.2)	Reference	
Male	14 109/32 024 (44.1)	2.206 (2.131–2.284)	<0.001
Bowel preparation			
Good	22 468/60 973 (36.8)	Reference	
Poor	775/2 312 (33.5)	0.728 (0.664–0.798)	<0.001
Sedation for procedure			
No sedation	3 340/11 393 (29.3)	Reference	
Sedation	19 903/51 892 (38.4)	1.602 (1.530–1.678)	<0.001
Melanosis coli			
Absent	22 754/62 181 (36.6)	Reference	
Present	489/1 104 (44.3)	1.184 (1.045–1.343)	0.008
Endoscopists			
Less experienced	3 778/11 184 (33.8)	Reference	
Experienced	19 465/52 101 (37.4)	1.198 (1.145–1.254)	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 3 Features of polyps in patients with melanosis coli (MC) and matched controls (n, %)

	MC (n = 1 104)	Matched controls (n = 2 208)	*P* value
Polyps	489 (44.3)	867 (39.3)	0.006
Location			
Left colon	164 (33.5)	347 (40.0)	0.018
Right colon	160 (32.7)	265 (30.6)	0.411
Total colon	165 (33.7)	255 (29.4)	0.098
Number			
1–5	325 (66.5)	667 (76.9)	<0.001
6–10	125 (25.6)	158 (18.2)	0.001
>10	39 (8.0)	42 (4.8)	0.019
Size of the largest polyp (mm)			
1–5	185 (37.8)	303 (34.9)	0.288
6–9	212 (43.4)	331 (38.2)	0.062
≥10	92 (18.8)	233 (26.9)	0.001
Pathology			
Inflammatory/hyperplastic polyp	182 (37.2)	338 (39.0)	0.521
Low-grade adenoma	222 (45.4)	318 (36.7)	0.002
Advanced adenoma/adenocarcinomas	85 (17.4)	211 (24.3)	0.003

TABLE 4 Baseline characteristics of all resected polyps (n, %)

	All polyps (n = 24 577)	Polyps in MC (n = 493)	Polyps in non-MC (n = 24 084)	*P* value
Age (y)				
Mean ± SD	60.95 ± 11.331	68.67 ± 10.47	60.79 ± 11.29	<0.001
18–40	1 405 (5.7)	4 (0.8)	1 401 (5.8)	<0.001
41–50	2 376 (9.7)	14 (2.8)	2 362 (9.8)	
51–60	7 013 (28.5)	92 (18.7)	6 921 (28.7)	
61–70	9 540 (38.8)	161 (32.7)	9 379 (38.9)	
>70	4 243 (17.3)	222 (45.0)	4 021 (16.7)	
Gender				
Male	12 141 (49.4)	197 (40.0)	11 944 (49.6)	<0.001
Female	12 436 (50.6)	296 (60.0)	12 140 (50.4)	
Location of the polyps				
Cecum	1 094 (4.5)	29 (5.9)	1 065 (4.4)	<0.001
Ascending colon	3 093 (12.6)	84 (17.0)	3 009 (12.5)	
Transversal colon	7 575 (30.8)	182 (36.9)	7 393 (30.7)	
Descending or sigmoid colon	7 846 (31.9)	133 (27.0)	7 713 (32.0)	
Rectum	4 969 (20.2)	65 (13.2)	4 904 (20.4)	
Size of the largest polyp (mm)				
1–5	9 659 (39.3)	200 (40.6)	9 459 (39.3)	0.133
6–9	9 530 (38.8)	203 (41.2)	9 327 (38.7)	
≥10	5 388 (21.9)	90 (18.2)	5 298 (22.0)	
Pathology of the polyps				
Inflammatory/hyperplastic polyp	8 123 (33.0)	129 (26.2)	7 994 (33.2)	<0.001
Low-grade adenoma	11 519 (46.9)	278 (56.4)	11 241 (46.7)	
Advanced adenoma/adenocarcinomas	4 935 (20.1)	86 (17.4)	4 849 (20.1)	

Abbreviation: MC, melanosis coli; SD, standard deviation.

TABLE 5 Characteristics of polyps in melanosis coli (MC) and matched controls (n, %)

	Polyps with MC (n = 490)	Polyps in matched controls (n = 980)	*P* value
Age (y)			
18–40	4 (0.8)	8 (0.8)	1.000
41–50	14 (2.9)	28 (2.9)	
51–60	92 (18.8)	184 (18.8)	
61–70	161 (32.9)	327 (33.4)	
>70	219 (44.7)	433 (44.2)	
Gender			
Male	197 (40.2)	392 (40.0)	0.940
Female	293 (59.8)	588 (60.0)	
Location of the polyps			
Cecum	29 (5.9)	64 (6.5)	0.988
Ascending colon	83 (16.9)	165 (16.8)	
Transversal colon	180 (36.7)	365 (37.2)	
Descending or sigmoid colon	133 (27.1)	257 (26.2)	
Rectum	65 (13.3)	129 (13.2)	
Size of the largest polyp (mm)			
1–5	197 (40.2)	395 (40.3)	0.990
6–9	203 (41.4)	408 (41.6)	
≥10	90 (18.4)	177 (18.1)	
Pathology of the polyps			
Inflammatory/hyperplastic polyp	127 (25.9)	265 (27.0)	0.635
Low-grade adenoma	277 (56.5)	527 (53.8)	
Advanced adenoma/adenocarcinomas	86 (17.6)	188 (19.2)	

3.2 | Study part 2: based on the presence or absence of polyps in MC

3.2.1 | Baseline characteristics of all resected polyps

The baseline characteristics of 493 polyps resected from 489 MC patients and 24 084 polyps from 22 754 participants without MC are shown in Table 4. Consistent with the results in the study part 1, there were more females (60.0% vs 50.4%, $P < 0.001$) and the participants were elder (68.67 ± 10.47 y vs 60.79 ± 11.29 y, $P < 0.001$) in the MC with polyps group than in the non-MC with polyps group. Meanwhile, there was a significant difference between the two groups regarding the location and pathology of the polyps (both $P < 0.001$), but not regarding their size ($P = 0.133$).

3.2.2 | Association between MC and the pathology of polyps

There were 490 successful matching sets by using the PSM method at a ratio of 1:2 based on patients' age and gender, and the location and size of the polyps. The pathology of 490 colorectal polyps with MC and that of the 980 polyps in matched controls are shown in Table 5. There was no difference between the two groups in the detection rates of inflammatory or hyperplastic polyp, low-grade adenoma, and advanced adenoma or adenocarcinoma ($P = 0.635$).

4 | DISCUSSION

Previous studies have reported more colorectal polyps in MC patients than control subjects matched by age and gender.[6,7] In addition, the number of polyps of ≤5 and 6–9 mm in diameter was significantly higher in MC patients.[6] Consistently, we found in the current study that the polyps were more commonly found and that the polyps were smaller in MC. One possible explanation might be the "enhance effect." The dark background mucosa in MC is beneficial for the detection of non-pigmented polyps, especially tiny polyps. A meta-analysis showed that compared with control subjects, the OR for colorectal neoplasms in MC was approximately 1.5, which was similar to that for colorectal polyps under chromoscopy when comparing with white-color imaging),[8] suggesting that MC and color enhancement by chromoscopy contribute similarly to a higher PDR.

The relationship between MC and the CRC is controversial. Previous studies have reported an increased detection rate of adenomas in

MC patients.[6–8,12] At the same time, MC is an independent risk factor for an increased detection rate of low-grade adenomas after adjusting for confounders such as age, gender, and lifestyle of the individuals.[7] Furthermore, a prospective study of patients undergoing endoscopy reported a clear-cut correlation between MC and CRC in male and those aged under 70 years.[13] However, some other clinical studies found that MC was irrelevant to CRC.[6–8,12,14] A recent meta-analysis including 1619 individuals with MC and 3953 controls revealed that MC was not significantly associated with an elevated risk of colorectal adenocarcinoma.[8] The first part of this study showed a higher detection rate of low-grade adenoma and a lower detection rate of advanced adenoma or adenocarcinoma in MC patients than in the matched controls. It is noteworthy that the polyps in the controls were larger in size and mostly distributed in the left colon. It has been demonstrated that large polyps show higher rates of high-grade dysplasia and invasive cancer than subcentimeter colorectal polyps.[15] In addition, advanced adenomas and CRC are more commonly distributed in the left colon.[16,17] Therefore, the pathological differences between the two groups may be due to various sizes and locations of the polyps.

To clarify whether MC increases the risk of histological progression of polyps or simply provides a dark background to make polyps easier to be detected, thus leading to a higher detection rate of adenomas, the focus shifts from the presence or absence of MC to polyps in the presence or absence of MC. The age and gender of the patients, location and pathological features of the polyps significantly differ between the polyps with and without MC groups. Considering the association between certain characteristics of colorectal polyps and predisposition to CRC, further analysis was conducted after confounders were adjusted through the PSM method to investigate the relationship between MC and colorectal polyps. The results showed no significant difference between the MC patients and the matched controls in hyperplastic or inflammatory polyp, low-grade adenoma, and advanced adenoma or adenocarcinoma, suggesting that the risk of histological progression of polyps may be similar between MC patients and those without MC.

MC is closely related to chronic constipation and the abuse of anthraquinone laxatives. Despite controversy, many studies have demonstrated that increased constipation was positively associated with CRC.[18–22] A meta-analysis of 14 case–control studies revealed a statistically significant association of CRC with constipation and laxative use.[18] Also, a prospective study suggested that the use of non-fiber laxative increased the risk of CRC.[23] Animal studies also revealed that repeated administration of anthraquinone laxatives impaired intestinal peristalsis and promoted adenomatous hyperplasia of the colon.[24,25] In this study, we found that MC was not significantly associated with the histological progression of polyps. The association of constipation, anthraquinone laxatives, and CRC should be noted. Chronic constipation and overuse of anthraquinone laxatives, but not MC, may be involved in the histological progression of polyps, which requires further investigation.

In the present study we combined a multivariate logistic regression model with the PSM method to analyze the relationship between MC and the histological progression of polyps, and focused on both the patients and the polyps. These findings suggest that MC may not be associated with the risk of histological progression of the polyps, and a higher PDR in MC could be due to the optical enhanced effect of dark background mucosa. It implies that physicians may not need to take too many therapeutic interventions for MC, while patients may not need to worry too much about MC. On the other hand, chromoscopy could be used to increase the PDR.

There were some limitations to this study. This was a single-center retrospective study, which might have caused bias. In addition, confounders such as smoking and alcohol consumption could have affected the results were not taken into account in this study. Further studies are needed to elucidate the impact of these factors.

In conclusion, in this retrospective study we found that MC was independently associated with an increased colorectal PDR, but not with histological progression of polyps. A higher PDR in MC patients may be due to the optical enhanced effect of the dark background mucosa.

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CONFLICT OF INTEREST

None.

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