Hemorrhoids as a risk factor for colorectal adenomas on colonoscopy

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ABSTRACT

Background and study aims Colorectal premalignant polyps and hemorrhoids are important findings in colonoscopy; however, the association between them is unclear. Therefore, we investigated the association between the presence and severity of hemorrhoids and the detection of precancerous colorectal polyps on colonoscopy.

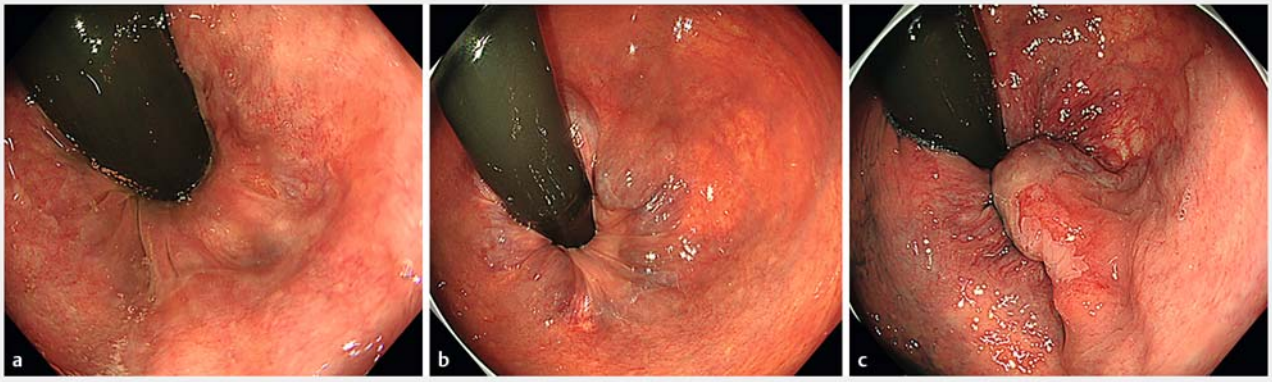
Patients and methods This retrospective, single-center, cross-sectional study enrolled patients who underwent colonoscopy at Toyoshima Endoscopy Clinic between May 2017 and October 2020. The association between hemorrhoids and other outcomes (patient age, sex, withdrawal time for colonoscopy, expert endoscopist, number of adenomas per colonoscopy, detection rates of adenoma, advanced neoplasia, clinically significant serrated polyp, and sessile serrated lesion) was assessed using a binomial logistic regression model.

Results A total of 12,408 patients were enrolled in this study. Hemorrhoids were identified in 1,863 patients. Univariable analysis showed that patients with hemorrhoids were older (61.0 vs. 52.5 years, $P<0.001$), had a higher number of adenomas per colonoscopy (1.16 vs. 0.756, $P<0.001$) than those without hemorrhoids. Multivariable analyses also demonstrated that hemorrhoids were associated with a higher number of adenomas per colonoscopy (odds ratio [OR]: 1.061; $P=0.002$), regardless of patient age, sex, and expert endoscopist. Among patients with hemorrhoids, severe hemorrhoids with a mucosal elevation ≥ 10 mm were associated with a higher number of adenomas per colonoscopy than mild hemorrhoids (OR: 1.112, $P=0.044$), regardless of patient age, sex, and expert endoscopist.

Conclusions Hemorrhoids, especially severe ones, are associated with a high number of adenomas. Complete colonoscopy should be performed in patients with hemorrhoids.

Introduction

Colorectal adenomas (CRAs) and serrated polyps are precancerous lesions [1, 2]. The endoscopic removal of precancerous colorectal polyps can prevent colorectal cancer [3]. Hemorrhoids are common outpatient gastrointestinal disorders [4] in the United States and can be accurately diagnosed in retroflexed view colonoscopy [5, 6]. The classification of hemorrhoids based on colonoscopy findings reflects the severity of symptoms, such as hematochezia and anal prolapse [7, 8]. Al-



▶ **Fig. 1** Representative colonoscopic images of hemorrhoids on retroflexed view. **a** No hemorrhoid. **b** Mild hemorrhoids. **c** Severe hemorrhoids.

though both premalignant colorectal polyps and hemorrhoids are important findings in colonoscopy, their association is unclear. Therefore, we investigated the association between the presence and severity of hemorrhoids and the detection of precancerous colorectal polyps on colonoscopy. This study aimed to determine the clinical significance of hemorrhoids.

Patients and methods

Study design and patients

This retrospective, single-center, cross-sectional study was conducted at Toyoshima Endoscopy Clinic, a representative outpatient clinic specializing in endoscopy in Japan [9, 10]. Patients who underwent colonoscopy at the clinic between May 2017 and October 2020 were enrolled in this study. The indications for colonoscopy included screening, family history of colorectal cancer, examination for symptoms (e. g., hematochezia, abnormal bowel habits, and abdominal pain), abnormal test results (e. g., fecal immunochemical test), and surveillance (e. g., colorectal polyp). Patients who underwent colonoscopy for surveillance of colorectal cancer or inflammatory bowel disease, and treatment (e. g., planned polypectomy and emergency hematemesis) were excluded [11, 12].

Ethics

The study was based on a protocol prepared by the Toyoshima Endoscopy Clinic and approved by the Certified Institutional Review Board of Yoyogi Mental Clinic on July 16, 2021 (approval no. RKK227). We published the study protocol on our clinic's website (www.ichou.com); thus, patients could opt out of the study if they desired. Written informed consent for the use of clinical information was obtained before the colonoscopy.

Hemorrhoids

Anorectal mucosal elevations with dilated veins were defined as hemorrhoids. Hemorrhoids were examined in the retroflexed view during colonoscopy because internal hemorrhoids are best visible in this view [5]. Patients with internal and mixed (intron–external) hemorrhoids were included in the analysis; however, patients with only external hemorrhoids were excluded because of the difficulty in evaluating the severity of hemorrhoids during colonoscopy. Hemorrhoids with mucosal elevation ≥ 10 mm were diagnosed as severe hemorrhoids. The diameter of the colonoscope was used as the reference [7]. Representative images of the hemorrhoids are shown in ▶ **Fig. 1**.

Colorectal polyps

All polyps suspected to be cancers, adenomas, or clinically significant serrated polyps were excised or biopsied during colonoscopy. Colorectal polyps were diagnosed based on histological examination of the resected or biopsied specimens. An advanced neoplasia was defined as an adenoma measuring ≥ 10 mm in diameter, villous adenoma, adenoma with high-grade dysplasia, or invasive cancer [13]. Clinically significant serrated polyps comprised all traditional serrated adenomas, sessile serrated lesions, hyperplastic polyps measuring ≥ 10 mm, and hyperplastic polyps measuring ≥ 5 mm proximal to the sigmoid colon [14].

Colonoscopy

Thirty endoscopists with various levels of experience performed the colonoscopies. Endoscopists with adenoma detection rates ≥ 40 % were defined expert endoscopists [15]. A combination of the Elite system and CF-HQ290ZI, CF-HQ290I, PCF-H290ZI, or PCF-PQ260 L colonoscopes (Olympus Corporation) was used [16]. Withdrawal time was defined as the time required to examine the colorectal mucosa and remove the polyps [11, 12].

Outcomes

The following data were extracted from the endoscopy database of the Toyoshima Endoscopy Clinic: patient age, sex, withdrawal time for colonoscopy, endoscopists, severity of hemorrhoids, number of adenomas per colonoscopy, detection rates of adenoma, advanced neoplasia, clinically significant serrated polyp, and sessile serrated lesion [17].

Statistical analysis

The effect of premalignant polyp detection and other outcomes on presence and severity of hemorrhoids was estimated using a binomial logistic regression model. Multivariable analysis was performed using possible clinically significant variables. The causal graph is shown in ▶ **Supplementary Fig. 1**. A subgroup analysis, limited to the expert endoscopists, was performed, following which the association between the severity of hemorrhoids and detection of colorectal polyps were estimated among patients with hemorrhoids. Complete case analysis was performed for missing data. $P<0.05$ was considered statistically significant. Calculations were performed using BellCurve for Excel version 3.22 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

Baseline characteristics of patients

Among the 13,314 patients, we excluded 436 who underwent colonoscopy for the surveillance of colorectal cancer, 236 who underwent colonoscopy for the surveillance of inflammatory bowel disease, and 234 who underwent colonoscopy for treatment. Finally, 12,408 patients were enrolled in this study. The mean age was 53.9 years, and 49.5% of the patients were men. Expert endoscopists performed 68.3% of the colonoscopies. Hemorrhoids were identified in 1,863 (15.2%) patients. Mild and severe hemorrhoids were found in 1,735 and 128 patients, respectively. The mean number of adenomas detected per colonoscopy was 0.821. The detection rates of adenoma, advanced neoplasia, clinically significant serrated polyp, and sessile serrated lesion were 44.9%, 2.68%, 8.89%, and 3.47%, respectively (▶ **Table 1**).

▶ **Table 1** Baseline characteristics of study patients.

N	12,408
Age, years (SD)	53.9 (12.3)
Male sex, %	49.5
Withdrawal time, min (SD)	13.9 (4.13)
Expert endoscopist, %	68.3
Hemorrhoids, n (%)	1,863 (15.2)
Mild/severe hemorrhoids, n	1,735/128
Number of adenomas per colonoscopy, n (SD)	0.821 (1.25)
Adenoma detection rate, %	44.9
Advanced neoplasia detection rate, %	2.68
Clinically significant serrated polyp detection rate, %	8.89
Sessile serrated lesion detection rate, %	3.47

SD, standard deviation.

Association between presence of hemorrhoids and detection of colorectal polyp

On univariable analysis, patients with hemorrhoids were older (61.0 vs. 52.5 years, odds ratio [OR]: 1.059, 95% confidence interval [CI]: 1.055–1.064, $P<0.001$), had a higher number of adenomas per colonoscopy (1.16 vs. 0.756, OR: 1.243, 95% CI: 1.201–1.286, $P<0.001$), and had a higher adenoma detection rate (56.4% vs. 42.7%, OR: 1.735, 95% CI: 1.571–1.916, $P<0.001$) than those without hemorrhoids. Expert endoscopists performed cases with hemorrhoids more often (▶ **Table 2** and ▶ **Supplementary Table1**).

Multivariable analyses showed that hemorrhoids were associated with a high number of adenomas per colonoscopy (OR: 1.061, 95% CI: 1.022–1.101, $P=0.002$) regardless of patient age, sex, and expert endoscopist (▶ **Table 3**).

▶ **Table 2** Univariable analysis of effects on hemorrhoids.

	No hemorrhoid	Hemorrhoids	Odds ratio	95% CI
N	10,434	1,863		
Age, years (SD)	52.5 (11.7)	61.0 (12.6)	1.059	1.055–1.064
Male sex, %	49.2	51.3	1.089	0.987–1.202
Withdrawal time, min (SD)	13.9 (4.20)	13.9 (3.72)	0.999	0.987–1.011
Expert endoscopist, %	66.3	79.6	1.983	1.759–2.235
Number of adenomas per colonoscopy, n (SD)	0.756 (1.19)	1.16 (1.48)	1.243	1.201–1.286
Adenoma detection rate, %	42.7	56.4	1.735	1.571–1.916
Advanced neoplasia detection rate, %	2.42	2.84	1.183	0.876–1.598
Clinically significant serrated polyp detection rate, %	8.84	9.34	1.063	0.897–1.260
Sessile serrated lesion detection rate, %	3.54	3.22	0.908	0.688–1.198

CI, confidence interval; SD, standard deviation.

▶ **Table 3** Multivariable analysis of effects on hemorrhoids.

	Odds ratio	95 % CI	*P* value
Age	1.055	1.050–1.059	<0.001
Male sex	1.106	0.998–1.226	0.055
Expert endoscopist	1.542	1.360–1.747	<0.001
Number of adenomas per colonoscopy	1.061	1.022–1.101	0.002

CI, confidence interval.

▶ **Table 4** Multivariable analysis of effects on hemorrhoids in the sub-analysis of expert endoscopists.

	Odds ratio	95 % CI	*P* value
Age	1.059	1.054–1.065	<0.001
Male sex	1.061	0.943–1.194	0.327
Number of adenomas per colonoscopy	1.066	1.024–1.109	0.002

CI, confidence interval.

Subgroup analysis limited to expert endoscopists

We performed a subgroup analysis that was limited to the expert endoscopists. Multivariable analysis showed similar results to the all-case analyses; in other words, the presence of hemorrhoids was independently associated with a high number of adenomas per colonoscopy (OR: 1.066, 95 % CI: 1.024–1.109, $P = 0.002$) regardless of patient age and sex (▶ **Table 4**).

Association between the severity of hemorrhoids and detection of colorectal polyp

We performed a sub-analysis of the association between the severity of hemorrhoids and the detection of colorectal polyps among patients with hemorrhoids (▶ **Table 5** and ▶ **Supplementary Table 2**). Multivariable analysis showed that severe hemorrhoids were associated with a higher number of adenomas per colonoscopy than mild hemorrhoids (OR: 1.120, 95 % CI: 1.003–1.250, $P = 0.044$), regardless of patient age, sex, and expert endoscopist (▶ **Table 6**).

Discussion

This study found that hemorrhoids were associated with a high number of CRAs on colonoscopy regardless of patient age, sex, and expert endoscopist. Additionally, hemorrhoid severity was independently associated with the number of CRAs. In some studies, patients with hemorrhoids had a high incidence of colorectal cancer, especially in the sigmoid colon and rectum [18, 19]. Our results are in line with those of previous studies since colorectal cancer mainly occurs from adenomas, known as the adenoma-carcinoma sequence [20]. If hemorrhoids are found on rectal retroflection during flexible sigmoidoscopy, a full colonic examination may be considered because of the likelihood of a high number of CRAs. More CRAs may be detected in patients previously diagnosed with hemorrhoids on endoscopy; thus, a more careful inspection is warranted.

The pathology of hemorrhoids includes abnormal distal displacement of the anal cushions caused by degeneration of the collagen fibers and fibroelastic tissue, along with venous dilation and distortion of the vascular channel [21, 22]. Previous studies had demonstrated the inconsistent association between benign anal diseases and anal cancer or colorectal cancer. Several possible biological behaviors of hemorrhoids may explain their association with CRAs. The levels of matrix metalloproteinases (MMPs), which degrade extracellular proteins such as elastin, fibronectin, and collagen, are increased in pa-

▶ **Table 5** Univariable analysis of effects on severity of hemorrhoids.

	Mild hemorrhoids	Severe hemorrhoids	Odds ratio	95 % CI
N	1,735	128		
Age, years (SD)	60.7 (12.6)	64.3 (12.8)	1.024	1.009–1.039
Male sex, %	51.1	53.9	1.118	0.780–1.603
Withdrawal time, min (SD)	13.9 (3.75)	13.7 (3.34)	0.987	0.938–1.038
Expert endoscopist, %	79.2	85.2	1.507	0.913–2.487
Number of adenomas per colonoscopy, n (SD)	1.13 (1.46)	1.56 (1.76)	1.177	1.063–1.304
Adenoma detection rate, %	55.6	67.2	1.634	1.116–2.391
Advanced neoplasia detection rate, %	2.71	4.69	1.766	0.740–4.213
Clinically significant serrated polyp detection rate, %	9.22	10.9	1.209	0.678–2.156
Sessile serrated lesion detection rate, %	3.17	3.91	1.242	0.488–3.158

CI, confidence interval; SD, standard deviation.

▶ **Table 6** Multivariable analysis of effects on severity of hemorrhoids.

	Odds ratio	95 % CI	*P* value
Age, years	1.018	1.002–1.034	0.032
Male sex	1.095	0.761–1.575	0.624
Expert endoscopist	1.197	0.709–2.022	0.502
Number of adenomas per colonoscopy	1.120	1.003–1.250	0.044

CI, confidence interval.

tients with hemorrhoids [23, 24]. MMPs are also associated with the colorectal adenoma-carcinoma sequence [20, 25]. Endoglin (CD105), a binding site of transforming growth factor-beta and a proliferative marker for neovascularization, was expressed in > 50 % of the hemorrhoidal tissue specimens, but not in normal anorectal mucosa specimens [26]. Endoglin expression was increased in tissues with CRA and carcinoma compared to that in normal tissues, and the expression levels were related to the degree of dysplasia [27].

A previous report showed that patients with a positive fecal immunochemical test result had a significantly higher number of adenomas per colonoscopy and a higher adenoma detection rate [28]. Moreover, hemorrhoids are a major cause of positive fecal immunochemical test results [29]. The fact that both CRA detection and the presence of hemorrhoids were associated with a positive fecal immunochemical test result is consistent with our findings. Although several studies show common situations between these pathologies, such as the levels of MMPs, Endoglin, and positive fecal immunochemical test, there may be some other factors that have not yet been demonstrated.

Hemorrhoids, CRA, and cancer share several risk factors such as obesity [30], smoking [31], low fiber intake [32], and low physical activity [33–36]. These commonalities may explain why patients with hemorrhoids have a higher adenoma rate.

Retroflexion of the colonoscope in the rectum allows for close inspection of the anal canal through a frontal view. However, observation was incomplete in 20 % of the male patients and 6 % of the female patients, possibly as pelvic capacity is narrower in men than in women. In the patients with anal sphincter failure, the observation was not complete because of inadequate rectal distension caused by leakage of insufflated air [7]. A new classification which best evaluates hemorrhoidal disease is BPRST, an acronym in which each letter corresponds to an important aspect of hemorrhoidal disease that interferes with clinical reasoning: bleeding, prolapse, reducibility, skin tags, and thrombosis [37]. Verification with BPRST is needed in the future.

This study has several limitations. First, as described above, hemorrhoids and CRAs have some risk factors, such as body mass index, smoking, red meat consumption [38], and physical activity, that could have been confounding factors in this analysis. However, we did not evaluate these confounding factors in this retrospective study. A prospective analysis that includes these confounding factors is warranted in future studies. Second, although Goligher's classification is commonly used as a criterion for the degree of hemorrhoids, this study adopted the endoscopic classification described by Sadahiro et al [7]. Although hematochezia is the main symptom of hemorrhoids, the Goligher's classification is mainly based on the degree of anal prolapse. The endoscopic standard proposed by Sadahiro et al. is preferable because it reflects the severity of rectal bleeding and anal prolapse [8, 22, 39]. However, Sadahiro's classification does not correctly assess prolapse or external hemorrhoids. The degree of hemorrhoids is best assessed by an anoscopy. Retroflexion is not an adequate method for assessing the degree or severity of hemorrhoids, but it is an accurate method for assessing signs of bleeding. To perform rectal retroflexion through the colonoscope, it is necessary to hyperinflate the rectum, which leads to partial collapse of the hemorrhoids, impairing evaluation. New studies with more appropriate methodologies will be needed to confirm our hypothesis. Third, this study only included Japanese patients. The prevalence of hemorrhoids varies according to race and socioeconomic status of individuals [21]. Hemorrhoids affect 13 % to 39 % of the general population [40–43]. Our study detected hemorrhoids in 15.2 % of patients. This prevalence was consistent with that reported in previous studies. However, future research that incorporates patient backgrounds into the analysis is desirable.

Conclusions

In conclusion, CRAs are frequently diagnosed in patients with hemorrhoids, especially in those with severe hemorrhoids. Therefore, a complete colonoscopy should be performed in patients with hemorrhoids.

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Competing interests

Dr. Fujishiro received research grants and honoraria from Olympus Corporation.

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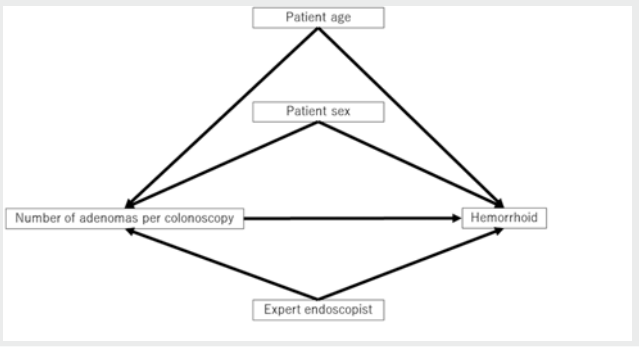

▶ **Supplementary Fig. 1** Causal graph.

▶ **Supplementary Table 1** Univariable analysis of effects on hemorrhoids with relative risk.

	No hemorrhoid	Hemorrhoids	Relative risk	Odds ratio	95% CI
N	10,434	1,863			
Age, years (SD)	52.5 (11.7)	61.0 (12.6)		1.059	1.055–1.064
Male sex, %	49.2	51.3	1.075	1.089	0.987–1.202
Withdrawal time, min (SD)	13.9 (4.20)	13.9 (3.72)		0.999	0.987–1.011
Expert endoscopist, %	66.3	79.6	2.248	1.983	1.759–2.235
Number of adenomas per colonoscopy, n (SD)	0.756 (1.19)	1.16 (1.48)		1.243	1.201–1.286
Adenoma detection rate, %	42.7	56.4	1.595	1.735	1.571–1.916
Advanced neoplasia detection rate, %	2.42	2.84	1.151	1.183	0.876–1.598
Clinically significant serrated polyp detection rate, %	8.84	9.34	1.053	1.063	0.897–1.260
Sessile serrated lesion detection rate, %	3.54	3.22	0.921	0.908	0.688–1.198

CI, confidence interval; SD, standard deviation.

▶ **Supplementary Table 2** Univariable analysis of effects on severity of hemorrhoids with relative risk.

	Mild hemorrhoids	Severe hemorrhoids	Relative risk	Odds ratio	95% CI
N	1,735	128			
Age, years (SD)	60.7 (12.6)	64.3 (12.8)		1.024	1.009–1.039
Male sex, %	51.1	53.9	1.110	1.118	0.780–1.603
Withdrawal time, min (SD)	13.9 (3.75)	13.7 (3.34)		0.987	0.938–1.038
Expert endoscopist, %	79.2	85.2	1.470	1.507	0.913–2.487
Number of adenomas per colonoscopy, n (SD)	1.13 (1.46)	1.56 (1.76)		1.177	1.063–1.304
Adenoma detection rate, %	55.6	67.2	1.582	1.634	1.116–2.391
Advanced neoplasia detection rate, %	2.71	4.69	1.680	1.766	0.740–4.213
Clinically significant serrated polyp detection rate, %	9.22	10.9	1.192	1.209	0.678–2.156
Sessile serrated lesion detection rate, %	3.17	3.91	1.222	1.242	0.488–3.158

CI, confidence interval; SD, standard deviation.