Answering to the reviewers

Reviewer #1:
The idea of this article is excellent, and the correlation between the colonic loop and ADR must be evaluated. I have three questions.

First, the authors said those with a history of colorectal surgery were excluded. How about women who had gynecologic surgery such as hysterectomy?[1]

ref) 1.Adams C, Cardwell C, Cook C, Edwards R, Atkin WS, Morton DG. Effect of hysterectomy status on polyp detection rates at screening flexible sigmoidoscopy. Gastrointest Endosc. 2003;57(7):848-853.

Thank you for reviewing our article and insightful comments. We excluded patients with a history of colorectal surgery, because colorectal surgery affected colorectal polyp detection.

Adams *et al*. reported that women with a history of hysterectomy had more incomplete examination and flexible sigmoidoscopy was more difficult, more painful, and less extensive in women with a history of hysterectomy. Lower polyp and adenoma detection rates were found in women who have underwent a hysterectomy.

As the reviewer noted, Adamas et al. have shown that gynecological surgery has impacts on the colorectal polyp detection. Gynecologic surgeries are not fully registered in our data. Therefore, we added a limitation as shown below.

Secondly, although patients' body mass index, family history of colorectal cancer, and gynecological surgery are associated with the presence of premalignant polyps and looping[25][Adamas et al.], they were not examined. Further verification will be required in the future.

Second, Since mucosal exposure can affect ADR[2], successful de-looping after cecal intubation should be evaluated, not only the degree of the loop during insertion. ref) 2.McGill SK, Rosenman J, Wang R, Ma R, Frahm JM, Pizer S. Artificial intelligence identifies and quantifies colonoscopy blind spots. Endoscopy. 2021;53(12):1284-1286.

Thank you for your suggestion. Successful de-looping after cecal intubation should be evaluated. Unfortunately, our database dose not separate the de-looping during and after cecal intubation. We added this point to the Limitations as a future issue.

Thirdly, since mucosal exposure can affect adenoma detection rate[McGill et al.], successful de-looping after cecal intubation, not only the degree of the looping during insertion, should be evaluated. However, our data do not have this information. Further verification will be required in the future.

Third, For the cases with a severe loop, which is difficult to insert, the possibility that it was performed by a more experienced endoscopist cannot be excluded. So it is necessary to check whether the experience of endoscopists and the degree of the loop is even distributed.

As you pointed out, the experience of endoscopists is an important point. We checked it out. We defined experienced endoscopists as endoscopists with more than 15 years of experience in endoscopy. The cases with severe looping were significantly more often performed by the experienced endoscopists (revised Tables 1 and 2).

Table 1. Characteristics of the study subjects.

N	12,259
Age, mean (SD), years	53.6 (12.2)
Male sex, %	50.7
Looping, none/mild/severe, n	5,532/4,399/2,253
Insertion time, mean (SD), min	4.57 (2.66)
Withdrawal time, mean (SD), min	13.87 (4.19)
Experienced endoscopist, %	70.4
Polyp detection	
Adenoma DR, %	44.7
Advanced adenoma DR, %	2.0
High-risk adenoma DR, %	9.9
CSSP DR, %	8.9
SSL DR, %	3.5
Number of adenomas, mean (SD), n	0.82 (1.25)
Number of SSLs, mean (SD), n	0.04 (0.24)

SD, standard deviation; DR, detection rate; CSSP, clinically significant serrated polyp; SSL, sessile serrated lesion.

Table 2. Subject characteristics based on severity of the looping.

	No looping	Mild looping	Severe looping	*P* value
N	5,532	4,399	2,253	
Age, mean (SD), years	51.5 (11.5)	54.2 (12.2)	56.7 (13.0)	< 0.001
Male sex, %	62.8	44.6	33.4	< 0.001
Insertion time, mean (SD), min	3.53 (1.89)	4.95 (2.41)	6.38 (3.44)	< 0.001
Withdrawal time, mean (SD), min	13.70 (4.30)	14.17 (4.29)	13.74 (3.66)	< 0.001*
Experienced endoscopist, %	61.1	73.7	87.6	< 0.001

Polyp detection				
Adenoma DR, %	42.2	45.0	50.2	< 0.001
Advanced adenoma DR, %	1.8	2.1	2.3	0.166
High-risk adenoma DR, %	8.4	9.8	13.5	< 0.001
CSSP DR, %	7.8	9.5	10.3	< 0.001
SSL DR, %	3.2	3.7	3.9	0.064
Number of adenomas, mean (SD), n	0.74 (1.16)	0.81 (1.25)	1.03 (1.44)	< 0.001
Number of SSLs, mean (SD), n	0.04 (0.22)	0.05 (0.26)	0.05 (0.26)	0.553

P values were calculated using the Cochran–Armitage trend test and Jonckheere-Terpstra test for categorical and continuous variables, respectively.

* There were 22,065,005 and 19,833,488 combinations of increasing and decreasing trends, respectively.

SD, standard deviation; DR, detection rate; CSSP, clinically significant serrated polyp; SSL, sessile serrated lesion.

The endoscopist experience was added to the multivariate analysis of the effect on polyp detections (revised Table 3). The multivariate analysis showed that high detection rates of premalignant polyps was associated with severe looping regardless of the endoscopist experience. We added this information to the Abstract, Introduction, Methods, and Results.

Table 3. Multivariate analysis of the effect on polyp detections.

	Odds ratio	**95% confidence interval**	**DOF**	***P* value**
Adenoma				
Looping*	1.13	1.06-1.20	1	< 0.001
Age	1.05	1.04-1.05	1	< 0.001
Male sex	1.39	1.28-1.50	1	< 0.001
Insertion time	0.94	0.92-0.96	1	< 0.001
Withdrawal time	1.14	1.13-1.15	1	< 0.001
Endoscopist's experience	1.68	1.53-1.85	1	< 0.001
High-risk adenoma				
Looping*	1.25	1.13-1.38	1	< 0.001
Age	1.05	1.05-1.06	1	< 0.001
Male sex	1.527	1.33-1.74	1	< 0.001
Insertion time	0.90	0.87-0.93	1	< 0.001
Withdrawal time	1.20	1.18-1.21	1	< 0.001

Endoscopist's experience	3.91	3.17-4.82	1	< 0.001
Clinically significant serrated polyp				
Looping*	1.14	1.04-1.26	1	0.007
Age	1.00	0.99-1.01	1	0.999
Male sex	0.60	0.52-0.68	1	< 0.001
Insertion time	0.92	0.88-0.95	1	< 0.001
Withdrawal time	1.16	1.14-1.17	1	< 0.001
Endoscopist's experience	2.04	1.71-2.43	1	< 0.001

P value was calculated using binomial logistic regression model.

* No, mild, and severe looping were scored as 0, 1, and 2, respectively.

DOF: degree of freedom.

Furthermore, we performed sub-group analysis limited to the experienced endoscopists. The sub-group analysis did not change the results. Looping severity was independently associated with high detection rates of premalignant polyps (Table 4). We added this information to the Methods and Results.

Table 4. Multivariate analysis of the effect on polyp detections in sub-analysis of the experienced endoscopists.

	Odds ratio	95% confidence interval	DOF	*P* value
Adenoma				
Looping*	1.14	1.07-1.23	1	< 0.001
Age	1.05	1.05-1.05	1	< 0.001
Male sex	1.42	1.29-1.56	1	< 0.001
Insertion time	0.93	0.91-0.95	1	< 0.001
Withdrawal time	1.13	1.11-1.14t	1	< 0.001
High-risk adenoma				
Looping*	1.27	1.14-1.41	1	< 0.001
Age	1.05	1.05-1.06	1	< 0.001
Male sex	1.56	1.35-1.81	1	< 0.001
Insertion time	0.89	0.85-0.92	1	< 0.001
Withdrawal time	1.18	1.16-1.20	1	< 0.001
Clinically significant serrated polyp				

Looping*	1.15	1.04-1.28	1	0.008
Age	1.00	1.00-1.01	1	0.627
Male sex	0.66	0.57-0.77	1	< 0.001
Insertion time	0.92	0.89-0.96	1	< 0.001
Withdrawal time	1.13	1.11-1.15	1	< 0.001

P value was calculated using binomial logistic regression model.

* No, mild, and severe looping were scored as 0, 1, and 2, respectively.

DOF: degree of freedom.

Reviewer #2:

This is an interesting article. I have some comments mentioned below: 1-This is a retrospective, single-center study.

Thank you for your review. As you pointed out, this study is a retrospective and single-center study. We described this limitation in the Discussion section as the following:

Firstly, this study was retrospectively conducted at a single institution; however, the medical data was well controlled.

2- can you please say the causes of incomplete cecal intubation and whether looping is a cause or not?

This study excluded 20 colonoscopies with incomplete cecal intubation. The main cause of incomplete intubation is stenosis due to colorectal tumor (N=8), followed by looping (N=6). We added this information to the Results section as the following:

We excluded 236 patients undergoing treatment such as polypectomy and hemostasis, 77 with poor bowel preparation, 217 with previous colorectal surgery, 20 with incomplete cecal insertion (including 8 with stenosis due to colorectal tumor and 6 with colonic looping), 22 with withdrawal time less than 6 min, and 484 who were examined using an ultrathin colonoscope.

3-in your opinion, what are the solutions to decrease the looping rate?

In our opinion, the looping is hard to solve because it's due to colonic redundancy, which is inherent.

4- please add a degree of freedom for each p-value.

We added a degree of freedom for each *p*-value in Tables 3 and 4.

Reviewer #3:

This article is a retrospective study to clarify the effect of looping on colorectal premalignant polyp detection. And it provides promising results for the independent association between looping severity and high detection rates of premalignant polyps. The study design and statistics analysis are rigorous and appropriate. However, the definitions of different looping severity classification are not rigorous enough. Also, there are several questions should be explained or solved. Suggestions are listed as below:

1. In the part of Introduction: "Factors related to premalignant polyp detection include patient characteristics, such as age and sex[8, 9], and endoscopic procedure-related factors, such as cecal intubation time[10] and withdrawal time[11-14]." It is not rigorous. Why not consider the influence factors of polyp itself, such as size and number.

As you pointed out, the factors of polyp itself such as size are important points. We added "advanced adenoma" as the analysis item. Advanced adenoma is defined as an adenoma with a villous component, with a size > 10 mm, or with high-grade dysplasia. Tables 1 and 2 were revised.

Table 1. Characteristics of the study subjects.

N	12,259
Age, mean (SD), years	53.6 (12.2)
Male sex, %	50.7
Looping, none/mild/severe, n	5,532/4,399/2,253
Insertion time, mean (SD), min	4.57 (2.66)
Withdrawal time, mean (SD), min	13.87 (4.19)
Experienced endoscopist, %	70.4
Polyp detection	
Adenoma DR, %	44.7
Advanced adenoma DR, %	2.0
High-risk adenoma DR, %	9.9
CSSP DR, %	8.9
SSL DR, %	3.5
Number of adenomas, mean (SD), n	0.82 (1.25)
Number of SSLs, mean (SD), n	0.04 (0.24)

SD, standard deviation; DR, detection rate; CSSP, clinically significant serrated polyp; SSL, sessile serrated lesion.

Table 2. Subject characteristics based on severity of the looping.

	No looping	Mild looping	Severe looping	P value
N	5,532	4,399	2,253	
Age, mean (SD), years	51.5 (11.5)	54.2 (12.2)	56.7 (13.0)	< 0.001
Male sex, %	62.8	44.6	33.4	< 0.001
Insertion time, mean (SD), min	3.53 (1.89)	4.95 (2.41)	6.38 (3.44)	< 0.001
Withdrawal time, mean (SD), min	13.70 (4.30)	14.17 (4.29)	13.74 (3.66)	< 0.001*
Experienced endoscopist, %	61.1	73.7	87.6	< 0.001
Polyp detection				
Adenoma DR, %	42.2	45.0	50.2	< 0.001
Advanced adenoma DR, %	1.8	2.1	2.3	0.166
High-risk adenoma DR, %	8.4	9.8	13.5	< 0.001
CSSP DR, %	7.8	9.5	10.3	< 0.001
SSL DR, %	3.2	3.7	3.9	0.064
Number of adenomas, mean (SD), n	0.74 (1.16)	0.81 (1.25)	1.03 (1.44)	< 0.001
Number of SSLs, mean (SD), n	0.04 (0.22)	0.05 (0.26)	0.05 (0.26)	0.553

P values were calculated using the Cochran–Armitage trend test and Jonckheere-Terpstra test for categorical and continuous variables, respectively.

* There were 22,065,005 and 19,833,488 combinations of increasing and decreasing trends, respectively.

SD, standard deviation; DR, detection rate; CSSP, clinically significant serrated polyp; SSL, sessile serrated lesion.

The detection rates of advanced adenoma tended to increase with the severity of looping, but it was not significant. On the other hand, high-risk adenoma is defined as at least one advanced adenoma and/or three or more adenomas. High-risk adenomas increased with the severity of looping (P<0.001). Furthermore, the number of adenomas increased with looping severity (P<0.001).

2. In the part of Definition of looping, the definitions of different looping severity classification are not rigorous enough. Authors only assess looping by number of straightening the colonic loop. From the references 19 and 24 you cited, loops occur in the transverse and sigmoid colons, and the sigmoid loops include alpha and N shapes. So, for the different shape loops, whether the ways of straightening the colonic loop are different. Does this reason affect the assessment of loop?

Magnetic endoscopic imaging showed that looping was the most common in the order of N-sigmoid, deep transverse, and alpha sigmoid[Shah, et al. Gastrointest Endosc. 2000. DOI. 10.1067/mge.2000.107296]. However, in this study, MEI was not used.

Therefore, the shape of the looping was not accurately investigated. We can not assess the effect of looping shape for de-looping method. This issue is important and should be solved in the future. We added this point to the limitations as the following:

The shape of looping, the de-looping method, and successful de-looping after cecal intubation should be evaluated, not only the degree of the looping during insertion. However, our data do not have this information. Further verification will be required in the future.

Although authors write a lot of methods in the part of Colonoscopy, I think they should reconsider this problem. If authors have their own considerations, please explain it. This problem is the most essential.

Thank you for your significant proposal. When looping was formed, we commonly controlled colonoscope using position change into supine or right lateral and manual abdominal compression by the assistant [Shah, et al. Gastrointest Endosc. 2000. DOI. 10.1067/mge.2000.107296]. We added this sentence to the Colonoscopy in the Methods section.

3. In the part of Colorectal polyp, the definitions of CSSPs and High-risk adenoma are out of sequence. Because whether preamble or postamble, their sequence is inappropriate.

Thank you for your appropriate instruction. We revised the sequence as the following:

Advanced adenomas comprised adenomas ≥ 10 mm in size, villous adenomas, and adenomas with high-grade dysplasia. High-risk adenoma was defined as the presence of advanced adenoma and/or three or more adenomas. CSSPs comprised all sessile serrated lesions (SSLs), all traditional serrated adenomas, hyperplastic polyps of size ≥ 10 mm anywhere in the colorectum, and hyperplastic polyps of size ≥ 5 mm located between the cecum and the descending colon[30-33].

4. In the part of Methods of Abstract, the data about the number of adenomas and SSLs were not investigated. However, in Table 1 and Table 2, they were included.

According to the reviewer, we changed Methods of Abstract from:

We extracted data from the clinic's endoscopy database on patient age, sex, endoscopist-assessed looping, colonoscopy duration, and premalignant polyp detection.

To:

We extracted data from the clinic's endoscopy database on patient age, sex, endoscopist-assessed looping, colonoscopy duration, and detection rate and number of premalignant polyp.

Reviewer #4:
Thank you for this interesting and valuable paper. I can only stand in respect for this professional work. This study will change our view to looping during colonoscopy. My comments: The title reflects the main purpose of this study. Abstract provides summarized data. Key words show the focus points of the paper. Background shows brief information about the known data and the significance of this study. According to the suitable study design, paper could achieve the main purpose of this study. The manuscript interprets the findings and discuss them logically. Tables were sufficient and clear.

Thank you for your review.