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Effect of Real-Time Computer-Aided Polyp Detection System (ENDO-AID) on Adenoma Detection in Endoscopists-in-Training: A Randomized Trial

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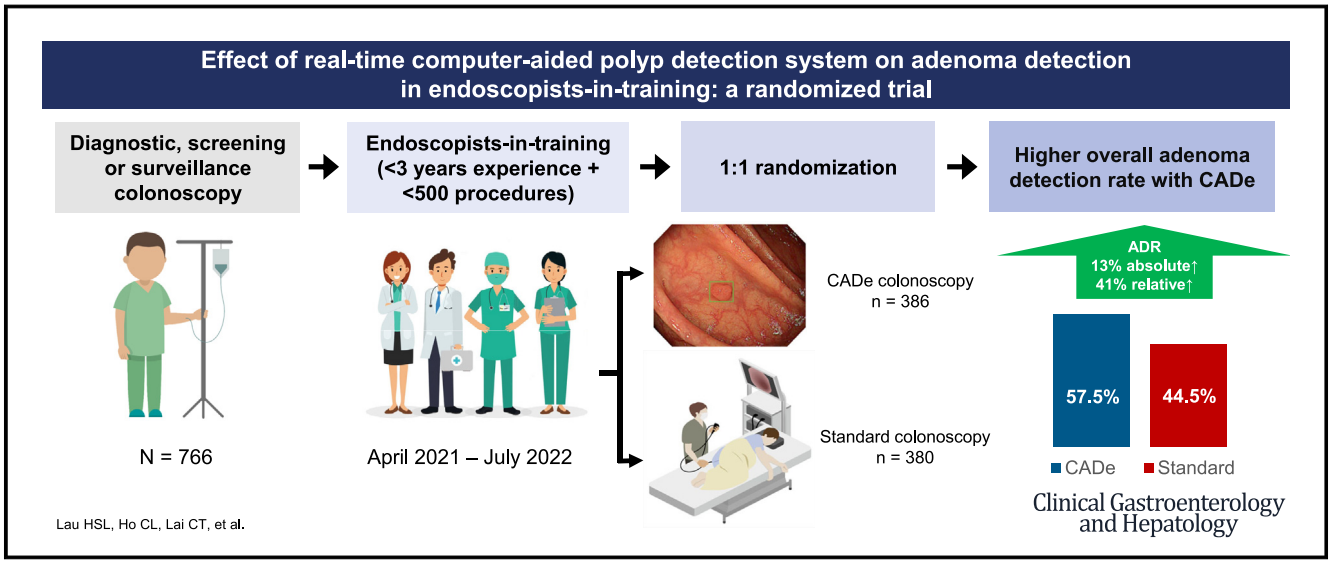

BACKGROUND: The effect of computer-aided polyp detection (CADe) on adenoma detection rate (ADR) among endoscopists-in-training remains unknown.

METHODS: We performed a single-blind, parallel-group, randomized controlled trial in Hong Kong between April 2021 and July 2022 (NCT04838951). Eligible subjects undergoing screening/surveillance/diagnostic colonoscopies were randomized 1:1 to receive colonoscopies with CADe (ENDO-AID [OIP-1]) or not (control) during withdrawal. Procedures were performed by endoscopists-in-

Abbreviations used in this paper: ADR, adenoma detection rate; APC, adenomas per colonoscopy; CADe, computer-aided polyp detection; CI, confidence interval; CRC, colorectal cancer; RR, relative risk; SSL, sessile serrated lesion.

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training with <500 procedures and <3 years' experience. Randomization was stratified by patient age, sex, and endoscopist experience (beginner vs intermediate level, <200 vs 200–500 procedures). Image enhancement and distal attachment devices were disallowed. Subjects with incomplete colonoscopies or inadequate bowel preparation were excluded. Treatment allocation was blinded to outcome assessors. The primary outcome was ADR. Secondary outcomes were ADR for different adenoma sizes and locations, mean number of adenomas, and non-neoplastic resection rate.

RESULTS: **A total of 386 and 380 subjects were randomized to CADe and control groups, respectively. The overall ADR was significantly higher in the CADe group than in the control group (57.5% vs 44.5%; adjusted relative risk, 1.41; 95% CI, 1.17–1.72; $P < .001$). The ADRs for <5 mm (40.4% vs 25.0%) and 5- to 10-mm adenomas (36.8% vs 29.2%) were higher in the CADe group. The ADRs were higher in the CADe group in both the right colon (42.0% vs 30.8%) and left colon (34.5% vs 27.6%), but there was no significant difference in advanced ADR. The ADRs were higher in the CADe group among beginner (60.0% vs 41.9%) and intermediate-level (56.5% vs 45.5%) endoscopists. Mean number of adenomas (1.48 vs 0.86) and non-neoplastic resection rate (52.1% vs 35.0%) were higher in the CADe group.**

CONCLUSIONS: **Among endoscopists-in-training, the use of CADe during colonoscopies was associated with increased overall ADR. (ClinicalTrials.gov, Number: NCT04838951).**

Keywords: Colonoscopy; Training; Computer-Aided Polyp Detection; CADe; Adenoma Detection Rate; ADR.

Colonoscopy reduces colorectal cancer (CRC)–related mortality by detecting and removing premalignant polyps or early CRC.[1] However, colonoscopy is imperfect, with miss rates of up to 26% for adenomas and 9% for advanced adenomas.[2] As a result, postcolonoscopy CRC can occur due to missed lesions during index colonoscopies, leading to adverse outcomes and mortality.[3] Risk factors for missed lesions include proximal location, flat morphology, poor bowel preparation, and short withdrawal time.[4,5] Notably, insufficient trainee experience is also associated with a higher adenoma miss rate.[6]

To overcome these pitfalls, methods have been developed to improve the adenoma detection rate (ADR), the colonoscopy quality indicator that has been shown to be inversely associated with risk of postcolonoscopy CRC.[7] Techniques including water exchange,[8] second examination of the right colon,[9] and distal attachment devices[10] have been shown to increase ADR. However, these techniques are operator-depedent with variable performance in different settings.

The advent of artificial intelligence enabling automatic, real-time computer-aided polyp detection (CADe) has the potential to revolutionize the field. Several randomized trials reported a significant benefit of CADe-assisted colonoscopy over standard colonoscopy.[11–19] The ADR was consistently higher regardless of polyp size, location, and morphology in meta-analyses.[20–22] Nonetheless, most published clinical trials involved senior endoscopists with extensive experience. To date, only 1 study investigated the effect of endoscopist experience on CADe with a cutoff at 2000 procedures.[23] Theoretically, senior endoscopists are more skillful in mucosal exposure and computer signal interpretation, leading to an enhanced CADe performance. The benefit of CADe among less experienced endoscopists-in-training remains largely unknown. A dedicated randomized trial to provide high-quality evidence would be necessary before incorporating CADe into real-world clinical use and endoscopy training.[24]

In this study, we aimed to evaluate the effect of a new CADe system (ENDO-AID[OIP-1]; Olympus, Tokyo, Japan) on ADR and colonoscopy quality in junior endoscopists-in-training.

Materials and Methods

Study Design

A single-blind, parallel-group, superiority randomized controlled trial was performed in the Prince of Wales Hospital in Hong Kong, China, between April 2021 and July 2022.

Participants

The study population included adult subjects ≥18 years of age undergoing elective colonoscopies for screening, surveillance, or diagnostic purposes. Subjects were excluded if they had contraindications to colonoscopy or polypectomy, known colorectal lesions for staged procedures, previous colonic resection, personal history of CRC/polyposis syndrome/inflammatory bowel disease, advanced comorbid conditions (American Society of Anesthesiologists grade ≥4), or pregnancy.

Randomization and Blinding

Consecutive eligible subjects were randomized in a 1:1 ratio to receive colonoscopies with (intervention) or

without (control) the CADe system (ENDO-AID[OIP-1]) during the withdrawal phase. Randomization was stratified by age (<65 years vs ≥65 years), sex, and endoscopist experience (beginner vs intermediate level) in variable block sizes of 2 and 4. Before the procedure, a research staff assigned the treatment arms in each stratum according to consecutive computer-generated study numbers. Treatment allocation was blinded to study subjects and outcome assessors (pathologists and data analysts), but not the endoscopists.

Procedures

Endoscopists and Training. All colonoscopies were performed by endoscopists-in-training, who were defined as gastroenterologists or surgeons-in-training with a personal experience of <500 procedures and <3 years of training. Based on a learning curve analysis,[25] junior endoscopists were further stratified into beginner (<200 procedures) and intermediate (200–500 procedures) groups. A total of 22 junior endoscopists (12 in the beginner and 10 in the intermediate group) were involved in this study. All junior endoscopists performed at least 20 colonoscopies under supervision and received training on the CADe system before study initiation.

Role of Supervisors. Supervisors were present to provide on-site or next-door supervision for safety reasons, with minimal interference in junior endoscopists' decisions whenever possible. When a junior endoscopist failed to achieve cecal intubation, the supervisor would help advance the colonoscope to the cecum, without any contribution to withdrawal or polyp detection. The entire withdrawal phase and polyp detection process were performed by the trainees. When a junior endoscopist failed to recognize a polyp and withdrew the colonoscope to next colonic segment, the on-site supervisor (if any) would alert them and record it as a missed polyp. When a junior endoscopist decided to resect a detected lesion, the supervisor would not intervene with the decision, but rather would offer suggestions and/or take over for the endoscopic resection.

Endoscopic Procedures. All procedures were performed under conscious sedation or monitored anesthesia with high-definition white light endoscopy. Subjects with Boston Bowel Preparation Scale 0 or 1 in any colonic segment were excluded from primary analysis. For details of the CADe device, equipment, and procedures, refer to the Supplementary Materials.

All resected polyps were fixed in formalin solution and sent for histopathology interpretation according to the Vienna classification.[26] Specimens were evaluated by independent pathologists, who were blinded to the randomization. An advanced adenoma was defined as an adenoma ≥10 mm, and/or with villous component ≥20%, and/or harboring high-grade dysplasia. A sessile serrated lesion (SSL) was defined as a serrated polyp with at least 1 unequivocal aberrant crypt.[27]

What You Need to Know

Background

There is increasing evidence that computer-aided polyp detection (CADe) systems can enhance adenoma detection during colonoscopies by expert endoscopists. However, the effect (or drawback) of CADe in less experienced junior endoscopists remains largely unknown.

Findings

In a randomized controlled trial, CADe increased the adenoma detection rate among endoscopists-in-training. This was particularly the case for smaller adenomas and irrespective of baseline experience levels.

Implications for patient care

Our study provides novel high-quality evidence on the clinical benefit of CADe in less experienced endoscopists-in-training. This could form the basis for future potential incorporation of artificial intelligence into endoscopy training curricula and quality initiatives.

Outcomes

The primary endpoint was ADR, which was defined as the proportion of subjects with at least 1 histologically confirmed adenoma (SSL were excluded from the ADR definition). Secondary endpoints included ADR for adenomas of different sizes (<5 mm, 5–10 mm, >10 mm) and locations, mean number of adenomas per colonoscopy (APC), advanced ADR, SSL detection rate, polyp detection rate, non-neoplastic resection rate, supervisor-reported missed polyp rate, endoscopist-reported false positive signal rate, cecal intubation time, withdrawal time excluding interventions, total procedure time, and change in ADR in relation to endoscopist experience. Additional details for endpoint definitions are in the Supplementary Materials.

Statistical Analysis

The sample size was calculated based on the primary outcome (ADR). Based on published local data, baseline ADR for nonscreening standard colonoscopies was estimated to be 40%.[28] The study was designed as a superiority study. To allow ≥80% power to detect a 10% difference in ADR (50% vs 40%), with a 1-sided significance level of .025, a sample size of 385 subjects per arm was required. Allowing a 10% potential exclusion, the target enrolment goal was set at 856 subjects. The modified intention-to-treat analysis was performed for all randomized subjects who received a complete colonoscopy with adequate bowel preparation. Additional data analysis details are in the Supplementary Materials.

Data Transparency Statement

De-identified individual data from this article will be made available on reasonable request to the corresponding author, with an approved study protocol and valid methodology. Access to the data of the CADe system (ENDO-AID[OIP-1]) should be obtained from Olympus Corporation.

Results

Study Flow and Baseline Parameters

From April 15, 2021, to July 22, 2022, 880 subjects were screened and 856 subjects were eligible. A total of 427 and 429 subjects were randomized to the intervention (CADe) and control arms, respectively. Subjects (n = 41 in the CADe group, n = 49 in the control group) were excluded from the primary analysis due to inadequate bowel preparation, incomplete colonoscopy or distal attachment device use. As a result, 386 and 380 subjects were analyzed in the CADe and control groups, respectively (Figure 1).

Baseline demographics and procedural data are shown in Table 1. No significant difference was detected between the 2 groups, except a longer mean withdrawal time (excluding intervention) in the CADe arm (14.9 minutes vs 13.7 minutes). Clinical indications and bowel preparation were comparable. A total of 110 (28.5%) and 105 (27.6%) colonoscopies were performed by endoscopists at beginner level (<200 procedures) in each group. The majority of junior endoscopists were gastroenterologists-in-training (78.8% vs 76.3%), and the remainder were surgeons.

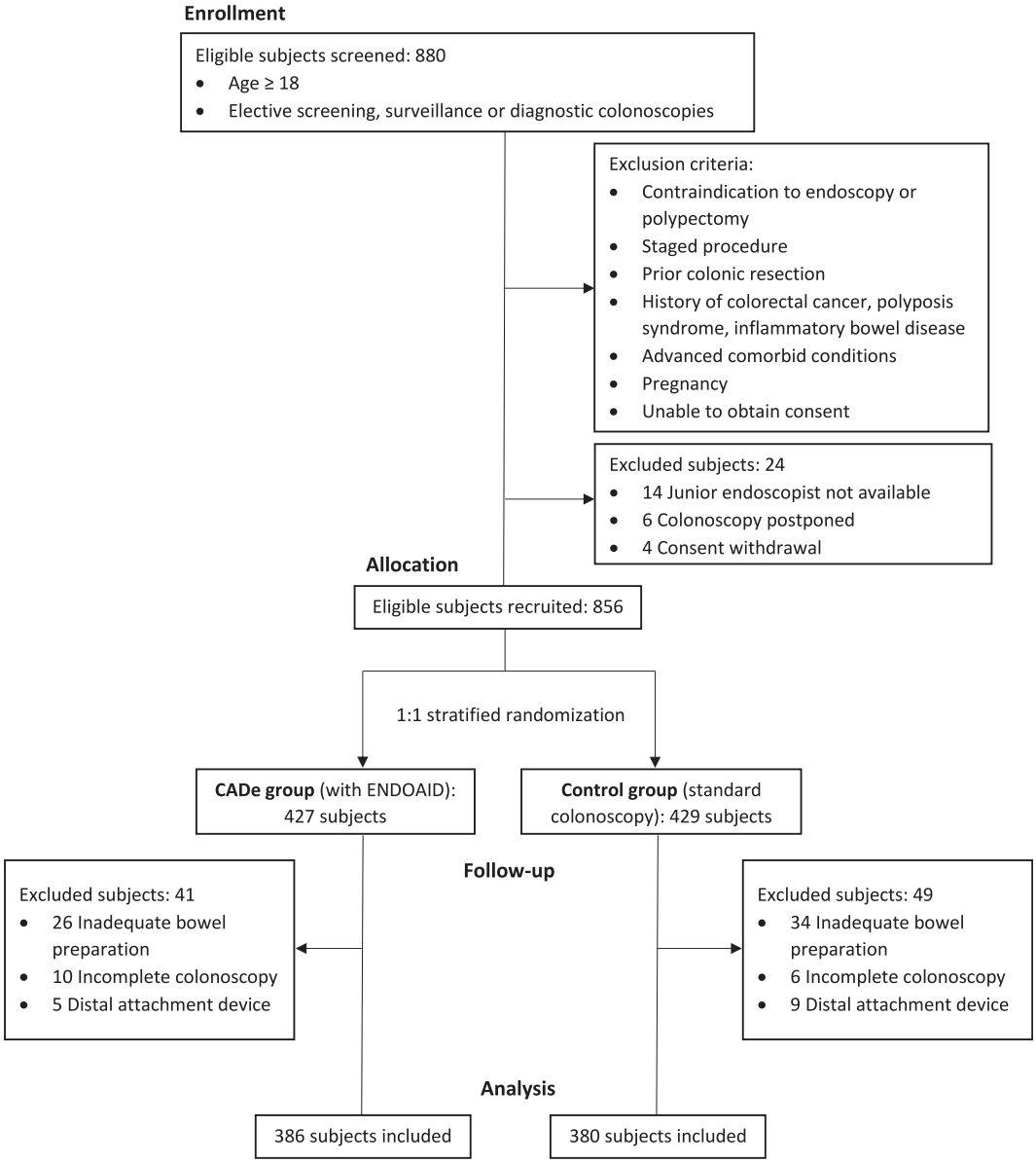

Figure 1. Study flow diagram (CONSORT).

Table 1. Baseline Demographic Data and Procedural Characteristics Between the CADe and Control Groups

	CADe Group (n = 386)	Control Group (n = 380)
Sex		
Male	205 (53.1)	211 (55.5)
Female	181 (46.9)	169 (44.5)
Age, y	66.00 ± 10.05	65.36 ± 11.33
Ethnicity		
Chinese	384 (99.5)	376 (98.9)
Others	2 (0.5)	4 (1.1)
Smoking[a]		
Current	42 (11.1)	38 (10.5)
Former	33 (8.7)	33 (9.1)
No	303 (80.2)	292 (80.4)
Alcohol use[b]		
Current	37 (9.8)	32 (8.8)
Former	19 (5.0)	20 (5.5)
No	323 (85.2)	311(85.7)
Family history of colorectal cancer[c]		
Yes	72 (19.5)	55 (15.6)
No	298 (80.5)	298 (84.4)
Colonoscopy indication		
Screening	28 (7.3)	23 (6.1)
Surveillance	126 (32.6)	121 (31.8)
Symptomatic	232 (60.1)	236 (62.1)
Experience of endoscopist		
Beginner (<200 procedures)	110 (28.5)	105 (27.6)
Intermediate (200–500 procedures)	276 (71.5)	275 (72.4)
Specialty of endoscopist		
Gastroenterologist	304 (78.8)	290 (76.3)
Surgeon	82 (21.2)	90 (23.7)
Endoscope model		
HQ290 series	376 (97.4)	374 (98.4)
EZ1500/XZ1200-series	10 (2.6)	6 (1.6)
Boston Bowel Preparation Scale[d]		
Total	7.85 ± 1.17	7.84 ± 1.21
Right	2.43 ± 0.50	2.45 ± 0.50
Transverse	2.69 ± 0.46	2.69 ± 0.46
Left	2.72 ± 0.45	2.70 ± 0.46
Cecal intubation by junior endoscopists	365 (94.6)	362 (95.3)
Cecal intubation time[e]	9.84 ± 7.71	9.82 ± 8.17
Withdrawal time excluding intervention[f]	14.94 ± 8.08	13.74 ± 8.66

Values are n (%) or mean ± SD.
CADe, computer-aided polyp detection system.
[a]Missing information in 8 and 17 cases in CADe and control arms, respectively.
[b]Missing information in 7 and 17 cases in CADe and control arms, respectively.
[c]Missing information in 16 and 27 cases in CADe and control arms, respectively.
[d]Missing information in 1 and 1 cases in CADe and control arms, respectively.
[e]Missing information in 1 and 4 cases in CADe and control arms, respectively.
[f]Baseline *P* values were evaluated by Pearson chi-square test, Fisher's exact test, Wilcoxon rank sum test, and *t* tests when appropriate. The *P* values for all parameters were >.05 (except withdrawal time exclude intervention, $P = .048$).

Primary and Secondary Outcomes: Adenoma and Polyp Detection

The overall ADR was significantly higher in the CADe group (57.5% [n = 222 of 386]) than the control group (44.5% [n = 169 of 380]) (adjusted relative risk [RR], 1.41; 95% confidence interval [CI], 1.17–1.72; $P < .001$) (Figure 2*A*). Among different sizes, the ADRs were significantly higher in the CADe group for <5-mm adenomas (40.4% vs 25.0%; adjusted RR, 1.79; 95% CI, 1.38–2.30; $P < .001$) and 5- to 10-mm adenomas (36.8% vs 29.2%; adjusted RR, 1.31; 95% CI, 1.03–1.68; $P = .030$) but not for >10 mm adenomas (1.8% vs 4.2%; $P = .060$). At different locations, the ADRs were significantly

higher in the CADe group at both right-sided colon (42.0% vs 30.8%; adjusted RR, 1.45; 95% CI, 1.15–1.84; $P = .002$) and left-sided colon (34.5% vs 27.6%; adjusted RR, 1.31; 95% CI, 1.01–1.68; $P = .041$). For different morphologies, the CADe group had a higher ADR for nonpedunculated adenomas (56.5% vs 39.5%; adjusted RR, 1.63; 95% CI, 1.33–1.99; $P < .001$) but not pedunculated lesions (Figure 2*B*). A total of 571 and 328 adenomas were found in the CADe group and control group, with 7 (1.8%) and 9 (2.4%) adenomas with high-grade dysplasia, respectively. The mean APC was significantly higher in the CADe group (1.48 vs 0.86; adjusted fold change, 1.78; 95% CI, 1.46–2.18; $P < .001$). There was no significant difference in advanced ADR (8.3% vs 10.0%; adjusted RR, 0.82; 95% CI, 0.51–1.31; $P = .397$) and SSL detection rate (2.1% vs 1.8%; adjusted RR, 1.14; 95% CI, 0.42-3.11; $P = .801$) between the CADe and control groups. The overall polyp detection rate was higher in the CADe group (75.9% vs 61.8%; adjusted RR, 1.42; 95% CI, 1.21–1.66; $P < .001$). There was only 1 supervisor-reported missed polyp in each group (0.26% vs 0.26%).

Secondary Outcome: Non-Neoplastic Resection

The non-neoplastic resection rate was higher in the CADe group (52.1% vs 35.0%; adjusted RR, 1.70; 95% CI, 1.37–2.11; $P < .001$), with a higher mean number of non-neoplastic resections (1.17 vs 0.61; adjusted fold change, 1.92; 95% CI, 1.54–2.41; $P < .001$) (Table 2). The proportion of subjects who only had non-neoplastic resection was similar between 2 groups (17.9% vs 16.8%). In fact, there were more subjects in the CADe group (34.2% [n = 132 of 386]) than the control group (18.2% [n = 69 of 380]) who had both adenomas and non-neoplastic lesions resected.

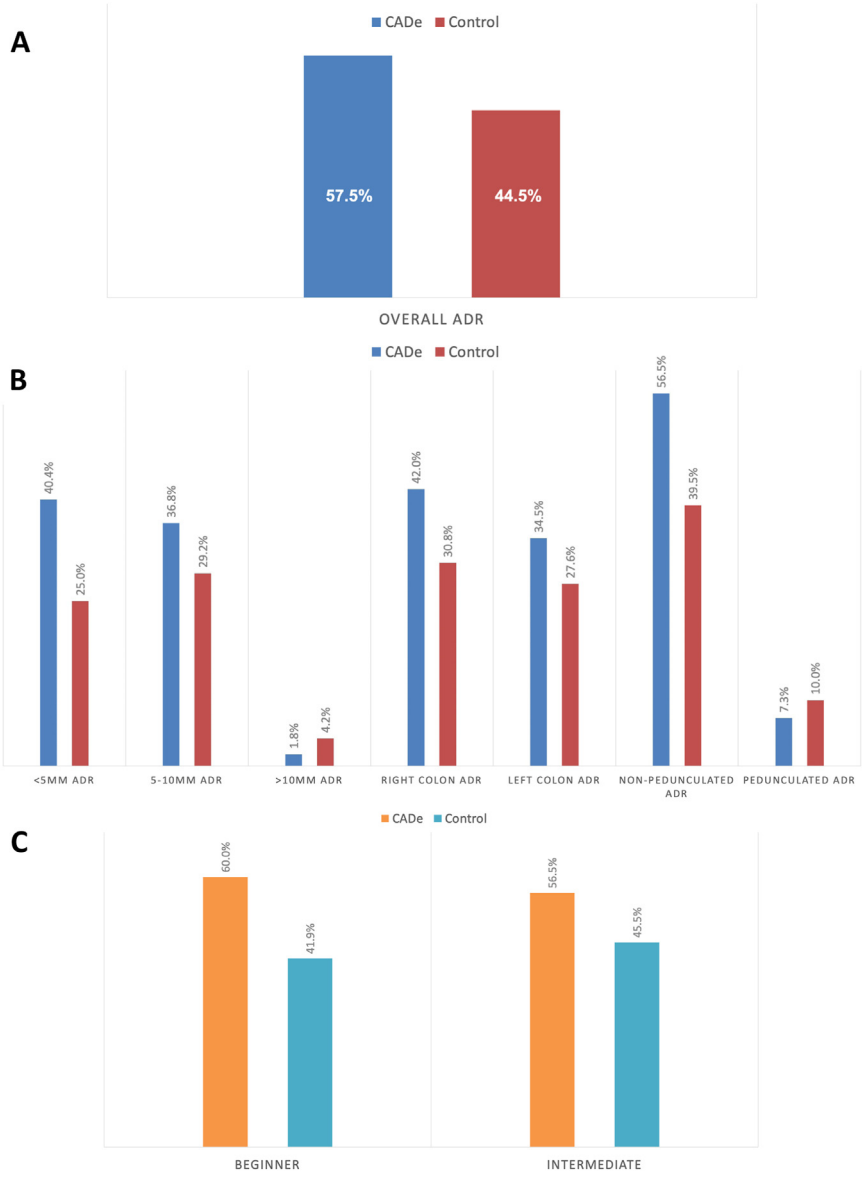

Figure 2. (*A*) Overall ADRs; (*B*) ADRs by different sizes, locations and morphologies between the CADe and control groups; (*C*) ADRs in different levels of endoscopist experience (beginner vs intermediate).

Table 2. Modified Intention-to-Treat Analysis of the Primary Endpoint (ADR) and Secondary Endpoints (ADR by Size/Location/Morphology, APC, Advanced ADR, SSL Detection Rate, PDR, Non-Neoplastic Resection Rate)

	CADe Group (n = 386)	Control Group (n = 380)	RR/FC (95% CI)	*P* Value
Overall ADR	222 (57.5)	169 (44.5)	1.41 (1.17–1.72)	<.001
ADR by size				
<5 mm	156 (40.4)	95 (25.0)	1.79 (1.38–2.30)	<.001
5–10 mm	142 (36.8)	111(29.2)	1.31 (1.03–1.68)	0.030
>10 mm	7 (1.8)	16 (4.2)	0.43 (0.17–1.04)	0.060
ADR by location				
Right colon[a]	162 (42.0)	117 (30.8)	1.45 (1.15–1.84)	0.002
Cecum	27 (7.0)	19 (5.0)	1.41 (0.78–2.54)	0.253
Ascending colon	83 (21.5)	54 (14.2)	1.57 (1.12–2.21)	0.010
Hepatic flexure	31 (8.0)	15 (3.9)	2.05 (1.11–3.80)	0.022
Transverse colon	92 (23.8)	55 (14.5)	1.73 (1.24–2.41)	0.001
Left colon[a]	133 (34.5)	105 (27.6)	1.31 (1.01–1.68)	0.041
Splenic flexure	5 (1.3)	3 (0.8)	1.69 (0.41–7.04)	0.472
Descending colon	64 (16.6)	43 (11.3)	1.50 (1.02–2.22)	0.041
Sigmoid colon	76 (19.7)	63 (16.6)	1.22 (0.87–1.70)	0.251
Rectum	26 (6.7)	13 (3.4)	2.07 (1.06–4.06)	0.033
ADR by morphology				
Nonpedunculated[b]	218 (56.5)	150 (39.5)	1.63 (1.33–1.99)	<.001
Pedunculated[b]	28 (7.3)	38 (10.0)	0.72 (0.44–1.17)	0.181
Overall APC	1.48 ± 2.06	0.86 ± 1.53	1.78 (1.46–2.18)	<.001
APC by size				
<5 mm	0.77 ± 1.34	0.37 ± 0.83	2.09 (1.61–2.73)	<.001
5–10 mm	0.69 ± 1.31	0.45 ± 0.94	1.60 (1.23–2.07)	<.001
>10 mm	0.02 ± 0.13	0.05 ± 0.24	0.39 (0.15–0.92)	0.040
APC by location				
Right colon[a]	0.90 ± 1.44	0.48 ± 1.05	1.89 (1.48–2.43)	<.001
Left colon[a]	0.58 ± 1.11	0.38 ± 0.79	1.59 (1.23–2.08)	<.001
APC by morphology				
Nonpedunculated[b]	1.38 ± 1.91	0.71 ± 1.20	2.00 (1.63–2.46)	<.001
Pedunculated[b]	0.10 ± 0.40	0.15 ± 0.63	0.71 (0.41–1.22)	0.216
Advanced ADR[c]	32 (8.3)	38 (10.0)	0.82 (0.51–1.31)	0.397
SSL detection rate	8 (2.1)	7 (1.8)	1.14 (0.42–3.11)	0.801
Polyp detection rate	293 (75.9)	235 (61.8)	1.42 (1.21–1.66)	<.001
Non-neoplastic resection rate[d]	201 (52.1)	133 (35.0)	1.70 (1.37–2.11)	<.001
Non-neoplastic resection per colonoscopy[d]	1.17 ± 1.65	0.61 ± 1.13	1.92 (1.54–2.41)	<.001

Values are n (%) or mean ± SD. RR and FC were estimated by a Cox regression model with constant time at risk and robust variance and a negative binomial regression model, respectively.

ADR, adenoma detection rate; APC, adenomas per colonoscopy; CADe, computer-aided polyp detection system; FC, fold change; PDR, polyp detection rate; RR, relative risk; SSL, sessile serrated lesion.

[a]Right colon refers to cecum, ascending colon, hepatic flexure, and transverse colon. Left colon refers to splenic flexure, descending colon, sigmoid colon, and rectum.

[b]Nonpedunculated morphology refers to sessile (Is), slightly elevated (IIa), flat (IIb), slightly depressed (IIc), and excavated (III) types according to Paris classification. Pedunculated morphology refers to pedunculated (Ip) type according to Paris classification.

[c]Advanced adenoma refers to an adenoma larger than 10 mm, and/or with villous component ≥20%, and/or harboring high grade dysplasia.

[d]Non-neoplastic resection refers to a resected specimen without adenoma or SSL component.

Subgroup Analysis: Endoscopists and Colonoscopy Indications

In a priori subgroup analysis for different endoscopist experience levels, 215 colonoscopies were performed by beginners and 551 colonoscopies were performed by intermediate-level endoscopists. The relative increment in ADR by CADe was significantly higher among beginners (60.0% vs 41.9%; adjusted RR, 1.58; $P = .015$) than intermediate-level endoscopists (56.5% vs 45.5%; adjusted RR, 1.36; $P = .009$) (Figure 2*C*, Table 3). The ADRs with regard to individual endoscopists are shown in Supplementary Figure 2. All junior endoscopists except 1 had at least 10% ADR gain by using CADe

Table 3. Subgroup Analysis at Different Levels of Endoscopist Experience (Beginner vs Intermediate)

	Beginner (<200 Procedure)				Intermediate (200–500 Procedures)			
	CADe (n = 110)	Control (n = 105)	RR/FC	*P* Value	CADe (n = 276)	Control (n = 275)	RR/FC	*P* Value
Overall ADR	66 (60.0)	44 (41.9)	1.58	.015	156 (56.5)	125 (45.5)	1.36	.009
ADR by size								
<5 mm	55 (50.0)	29 (27.6)	2.08	.001	101 (36.6)	66 (24.0)	1.66	.001
5∼10 mm	31 (28.2)	21 (20.0)	1.42	.218	111 (40.2)	90 (32.7)	1.29	.071
>10 mm	1 (0.9)	5 (4.8)	0.19	.127	6 (2.2)	11 (4.0)	0.54	.224
ADR by location								
Right colon[a]	47 (42.7)	30 (28.6)	1.59	.044	115 (41.7)	87 (31.6)	1.41	.015
Left colon[a]	40 (36.4)	24 (22.9)	1.76	.028	93 (33.7)	81 (29.5)	1.17	.291
ADR by morphology								
Nonpedunculated[b]	65 (59.1)	38 (36.2)	1.91	.001	153 (55.4)	112 (40.7)	1.53	<.001
Pedunculated[b]	6 (5.5)	14 (13.3)	0.37	.045	22 (8.0)	24 (8.7)	0.93	.805
APC	1.52 ± 2.26	0.79 ± 1.49	1.91	.001	1.46 ± 1.98	0.89 ± 1.55	1.73	<.001
PDR	79 (71.8)	63 (60.0)	1.31	.079	214 (77.5)	172 (62.5)	1.46	<.001
Non-neoplastic resection rate	52 (47.3)	37 (35.2)	1.44	.082	149 (54.0)	96 (34.9)	1.80	<.001
Non-neoplastic resection per colonoscopy	1.19 ± 1.71	0.68 ± 1.27	1.69	.023	1.16 ± 1.63	0.58 ± 1.07	2.00	<.001

Values are n (%) or mean ± SD. RR and FC were estimated by a Cox regression model with constant time at risk and robust variance and a negative binomial regression model, respectively.
ADR, adenoma detection rate; APC, adenomas per colonoscopy; CADe, computer-aided polyp detection system; FC, fold change; PDR, polyp detection rate; RR, relative risk.
[a]Right colon refers to cecum, ascending colon, hepatic flexure, and transverse colon. Left colon refers to splenic flexure, descending colon, sigmoid colon, and rectum.
[b]Nonpedunculated morphology refers to sessile (Is), slightly elevated (IIa), flat (IIb), slightly depressed (IIc), and excavated (III) types according to Paris classification. Pedunculated morphology refers to pedunculated (Ip) type according to Paris classification.

during colonoscopies. In subgroup analysis across different specialties, there were more significant benefits from CADe among gastroenterologists than surgeons, with a higher overall ADR and other outcome measures (Supplementary Table 1). In subgroup analysis across different colonoscopy indications, the CADe group demonstrated a consistent result with the main analysis in both diagnostic and surveillance cases (Supplementary Table 2).

Predictors for ADR

Considering a longer mean withdrawal time in the CADe arm and other potential confounding factors (age, sex, colonoscopy indications, bowel preparation, and endoscopist experience/specialty), a prespecified multivariable analysis by Cox regression model with constant time at risk and robust variance was developed. It demonstrated that age ≥65 years, male sex, longer withdrawal time, gastrointestinal endoscopists, and the use of CADe were significant factors for higher ADR. The use of CADe remained an independent factor for higher ADR after adjustment (adjusted RR, 1.40; 95% CI, 1.16–1.69; $P < .001$) (Table 4).

False Positives and Adverse Events

The false positive signal rate reported by endoscopists was 23.8% in the CADe group. Most were due to wrinkled colonic mucosa (18.9%), stool debris (7.0%), and air bubbles (6.5%). The mean number of false positive signals per colonoscopy was 1.1 (Supplementary Table 3). Only 3 procedure-related serious adverse events were noted. One subject in the CADe group had postpolypectomy coagulation syndrome, and 2 subjects in the control group had delayed postpolypectomy bleeding.

Discussion

To the best of our knowledge, this is the first randomized trial evaluating the clinical benefit of CADe-assisted colonoscopy among less experienced junior endoscopists-in-training. Our study demonstrated a 13% absolute increase and a 41% relative increase in ADR with the additional use of CADe. The ADR increment was particularly higher in small-to-medium-sized (up to 79% relative increase) and nonpedunculated (63% relative increase) adenomas, in both right-sided and left-sided

Table 4. Covariate-Adjusted Cox Regression Model With Constant Time at Risk and Robust Variance, Adjusted With Age, Sex, Colonoscopy Indications, BPPS, Withdrawal Time (Excluding Intervention), and Endoscopist Experience

	Relative Risk (95% CI)	*P* Value
CADe	1.40 (1.16–1.69)	<.001
Age		
<65 y	1	NA
≥65 y	1.80 (1.42–2.27)	<.001
Sex		
Female	1	NA
Male	1.47 (1.20–1.80)	<.001
Colonoscopy Indication		
Screening	1	NA
Surveillance	0.88 (0.60–1.28)	.503
Symptomatic	0.73 (0.51–1.05)	.094
BBPS (overall)[a]	0.99 (0.91–1.07)	.734
Withdrawal time (exclude intervention)	1.03 (1.02–1.05)	<.001
Experience of endoscopist		
Beginner (<200 procedures)	1	NA
Intermediate (200–500 procedures)	1.19 (0.94–1.51)	.156
Specialty of endoscopist		
Surgeons	1	NA
Gastroenterologists	1.39 (1.04–1.87)	.028

BPPS, Boston Bowel Preparation Scale; NA, not applicable.
[a]2 missing values in BBPS are replaced by the integer closest to the mean of remaining BBPS values.

colon. In addition, there was a relatively larger ADR gain among novice and less experienced endoscopists (58% in the beginner group vs 36% in the intermediate-level group). Considering a longer withdrawal time of 1.2 minutes, the use of CADe remained an independent factor for ADR increment after adjustment. Despite a higher chance of concurrent adenomas being detected and resected, CADe resulted in a higher non-neoplastic resection rate by 17% and an average of 0.6 unnecessary resections per colonoscopy.

The current evidence of CADe-assisted colonoscopy was strong among experienced and expert endoscopists in a number of clinical trials, showing a higher ADR and APC.[11–17,20,21] Despite the wider acceptance in clinical practice and position statements from professional societies,[24,29] there are ongoing debates and unsolved problems before the universal implementation of CADe, including a failure to improve advanced neoplasia detection,[30] overall cost-effectiveness,[31] and the impact on surveillance intervals.[32] Importantly, the effect of CADe on low detectors and novice and inexperienced trainees remains largely unknown. Junior endoscopists are generally less skilful and require a higher level of assistance during their initial learning phases. The use of CADe may provide benefit and standardization in terms of colonoscopy quality, but could also hamper overall performance due to the continuous distractions during the procedures.

Our study confirmed the clinical benefit of CADe to enhance adenoma detection ability among endoscopists with different levels of experience. Compared with CADe, the water exchange method and second forward-view examination are generally more time consuming, and distal attachment devices are not as eco-friendly as disposables. On the contrary, CADe systems are reusable, automated, and directly linked to the real-time display monitors, which in practice allow endoscopists to have extra eyes for simutaneous inspection and to avoid missing subtle lesions during colonoscopies. This benefit is particularly relevant for inexperienced endoscopists, when hands-on training opportunities and on-site supervisors are limited in many low- and middle-income countries. It also sheds light on the potential of incorporating CADe into future endoscopy training curricula.

Despite these promising results, the current performance of CADe is not perfect. In the intervention arm, we observed a longer withdrawal time, a higher non-neoplastic resection rate and a relatively high endoscopist-reported false positive rate. These findings were consistent with meta-analyses showing a longer inspection time and more unnecessary removal of non-neoplastic polyps.[22] These phenomena inevitably lead to a lower efficiency of colonoscopy procedures. We believe that this could be attributed to both endoscopist and system factors. For junior endoscopists, the lack of experience can lead to a lower confidence in accurately classifying non-neoplastic and neoplastic lesions, resulting in more unnecessary polypectomies. Even in a Japanese referral center, the sensitivity was reported to be only 67% in differentiating non-neoplastic lesions by optical diagnosis among nonexpert endoscopists.[33] The rapid development of artificial intelligence in assisting polyp diagnosis (computer-aided polyp diagnosis) may potentially address this unmet clinical need by allowing a diagnose-and-leave strategy.[34] For the current CADe system, the relatively high rate of false positive signals can create unnecessary distractions for junior endoscopists, who are less experienced in differentiating true and false positive lesions, resulting in a longer withdrawal time. This problem can be rectified by introducing an open source database and optimizing the deep learning algorithms. In addition, it remains questionable whether the increased detection and removal of small-to-medium-sized adenomas can be translated into long-term clinical benefit. It will also result in a temporary surge of surveillance colonoscopies. A prosepctive longitudinal study would be necessary to provide the long-term data and confirm its cost-effectiveness.[31] Nevertheless, we believe that the clear benefits of CADe in CRC prevention and its potential role in endoscopy training still outweigh the previous minor drawbacks.

Our results have successfully bridged the current knowledge gap using a robust study design and a unique study population. First, this was a parallel-group randomized control study with a lower likelihood of bias than tandem studies.[35] Second, unlike other studies, only inexperienced endoscopists were involved throughout the study to reflect the true effect on trainees. Nevertheless, there are limitations to our study. First, we could not exclude operational bias and a Hawthorne effect due to the single-blind design, as endoscopists were aware of the randomization groups. However, the ADR in our control group was even higher than the reported ADR from a previous study in our facility, suggesting a true incremental gain in ADR by CADe.[28] Second, our study was performed in a single-center setting, and in a nonscreening population including different age groups and indications, leading to a higher ADR at baseline, which may limit the generalizability of results. However, recent studies have shown that overall ADR across different indications is comparable to the conventional screening ADR in reflecting colonoscopy quality.[36,37] Third, our study was not powered to detect differences in advanced adenoma and SSL detection rates. Finally, the missed polyp and false positive rates were reported by operators only. Another large-scale clinical trial will be warranted to address the previous questions.

In conclusion, among junior endoscopists-in-training, a novel real-time CADe system (ENDO-AID) during colonoscopies could increase the overall ADR, especially for small-to-medium-sized and nonpedunculated adenomas, in different locations of the colon and different levels of experience. This was paralleled by an acceptable increase in the withdrawal time and a higher nonneoplastic resection rate. However, the benefit of CADe for large and advanced adenomas remains unclear. The performance optimization of CADe devices, concurrent development of computer-aided polyp diagnosis systems, and incorporation of artificial intelligence into endoscopy training curricula should be the focus of future efforts.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.10.019.

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Conflicts of interest
These authors disclose the following: Louis H.S. Lau has received research grant support from GenieBiome; and served as lecture speaker for Olympus, Boston Scientific, and GenieBiome. Vincent W.S. Wong is a cofounder of

Illuminatio Medical Technology Limited; has received research grant support from Gilead Sciences; has served as a consultant for AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Inventiva, Novo Nordisk, Pfizer, Sagimet Biosciences, and TARGET PharmaSolutions; and has served as a lecture speaker for Abbott, AbbVie, Gilead Sciences, Novo Nordisk, and Unilab. Francis K.L. Chan is the Senior Associate Editor of *Gastroenterology*; is the scientific cofounder of GenieBiome; and has served as an advisor and lecture speaker for Eisai, AstraZeneca, Pfizer, Takeda Pharmaceutical, and Takeda (China) Holdings. Philip W.Y. Chiu has served in a research collaboration with Boston Scientific; and as an advisor for EndoVision and EndoMaster; and as a lecture speaker for Olympus. The remaining authors disclose no conflicts.

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Supplementary Materials and Methods

Study Design

The study protocol was approved by the Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee (CREC Reference Number: 2021.141). The study is reported according to the CONSORT guidelines and registered at ClinicalTrial.gov (NCT04838951). All authors had access to the study data and approved the final manuscript.

Computer-Aided Polyp Detection System

ENDO-AID was a preinstalled computer-aided polyp detection system (CADe) device linked to the Olympus' EVIS X1 CV-1500 endoscopy processor and compatible with existing colonoscopes (1500, 1200, 290, and 190 series). The application was developed based on a deep learning architecture using about 12 million images and videos from Japan and other countries. In a performance evaluation conducted in Japan by 185 videos, the sensitivity per lesion was reported to be 97.5%. It could provide real-time automatic detection with prompting on the main screen by toggling between normal mode and target mode (Supplementary Figure 1). In normal mode, when a suspicious lesion was detected, the alert flag would be activated and a picture in picture would be displayed on the screen. In target mode, suspicious areas were marked with green borders and displayed on the procedural image simultaneously. During this study, target mode was used in all procedures, and it was activated during colonoscope withdrawal in intervention arm only.

Equipment

High-definition white light endoscopy was performed by EVIS X1 system (Olympus CV-1500; Olympus Co., Tokyo, Japan), together with EVIS LUCERA ELITE colonoscopes (CF-HQ290L/I series; Olympus Co.) or EVIS X1 colonoscopes (CF-EZ1500DL/I series; Olympus Co.). The use of light-modification technologies such as narrow-band imaging or texture and color enhancement imaging were restricted only for polyp characterization. No magnification or chromoendoscopy was allowed. Use of distal attachment devices (eg, transparent cap, Endocuff Vision) was prohibited.

Endoscopic Procedures

The cecal intubation time, withdrawal time (excluding interventions), and total procedure time were recorded by stopwatch in the computer system. During the procedure, the location, size, and morphology of each colonic polyp was recorded. All polyps were removed, with the exception of diminutive, non-neoplastic, hyperplastic polyps judged by operators. The endoscopic resection technique and use of prophylactic clipping were selected at the discretion of endoscopists. Staged procedures were arranged for large polyps that were detected during index colonoscopies but were not amenable to conventional polypectomy. The final histopathology after endoscopic resection in staged procedures was used for outcome measurement.

Endpoint Definitions

Polyp location was classified as right-sided (from cecum to transverse colon) and left-sided (from splenic flexure to rectum). Mean adenoma per colonoscopy referred to the total number of adenomas divided by the number of colonoscopies. Non-neoplastic resection was defined as the absence of adenoma or sessile serrated lesion within resected specimen. Missed polyps were defined as polyps detected by the supervisor but not recognied by the junior endoscopist who withdrew the endoscope to the next colonic segment, and did not contribute to the adenoma detection rate. False positive signals referred to incorrect alerts from computer artifacts due to various reasons, which lasted for $\geq$2 seconds, and reported by operators. Procedure-related adverse events were recorded.

Data Analysis

Categorical variables were expressed as number and percentage. Continuous and count variables were expressed as mean $\pm$ SD. Due to the stratified randomization design, a Cox regression model with constant time at risk and robust variance was used to estimate the relative risk for all binary endpoints after adjustment of stratification factors (age, sex, endoscopist experience). A negative binomial regression model was applied to estimate the fold change for count variables after adjusting stratification factors. A prespecified multivariable analysis on adenoma detection rate using Cox regression model with constant time at risk and robust variance was performed to adjust for unbalanced baseline variables and other potential confounding factors. A priori subgroup analyses based on endoscopist experience and colonoscopy indications were conducted. A P value of $<.05$ was regarded as statistically significant. Data were analyzed by R software (4.3.0; R Foundation for Statistical Computing, Vienna, Austria).

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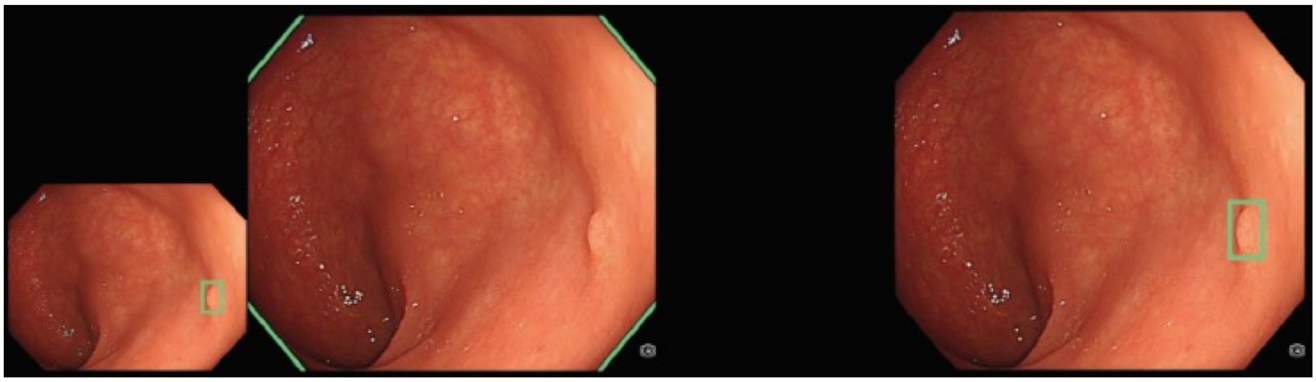
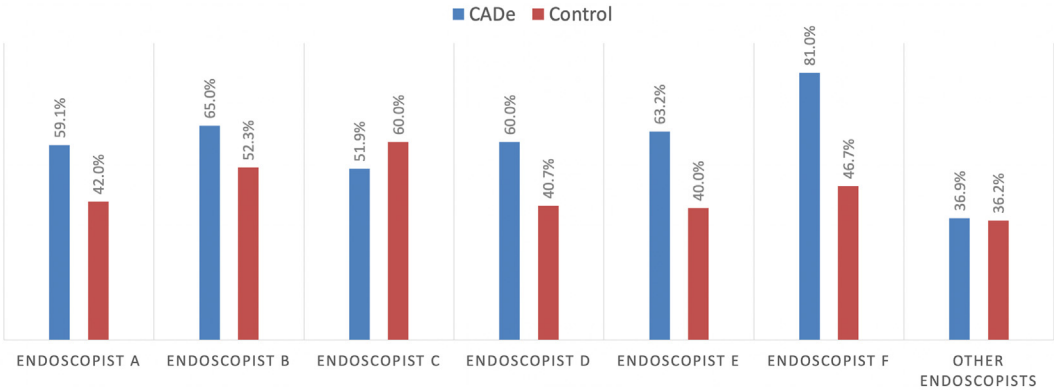


Supplementary Figure 1. Normal mode (left) and target mode (right) of computer-aided polyp detection system (ENDO-AID [OIP-1]).



Supplementary Figure 2. Adenoma detection rates at individual endoscopist level between computer-aided polyp detection system (CADe) and control groups. Endoscopists A–F refer to junior endoscopists who performed >20 colonoscopies throughout the study period. Number of colonoscopies performed by endoscopists A–F were 287, 166, 52, 52, 39, and 36, respectively.

Supplementary Table 1. Subgroup Analysis Between Different Endoscopist Specialties (Gastroenterologists and Surgeons)

	Gastroenterologist (n = 594)				Surgeon (n = 172)			
	CADe (n = 304)	Control (n = 290)	RR/FC	*P* Value	CADe (n = 82)	Control (n = 90)	RR/FC	*P* Value
Overall ADR	191 (62.8)	133 (45.9)	1.53	<.001	31 (37.8)	36 (40.0)	1.01	.958
ADR by Size								
<5 mm	130 (42.8)	70 (24.1)	1.97	<.001	26 (31.7)	25 (27.8)	1.31	.340
5–10 mm	130 (42.8)	90 (31.0)	1.47	.005	12 (14.6)	21 (23.3)	0.65	.233
>10 mm	6 (2.0)	11 (3.8)	0.50	.169	1 (1.2)	5 (5.6)	0.23	.162
ADR by location								
Right colon[a]	140 (46.1)	93 (32.1)	1.53	.001	22 (26.8)	24 (26.7)	1.14	.648
Left colon[a]	118 (38.8)	83 (28.6)	1.43	.012	15 (18.3)	22 (24.4)	0.76	.416
ADR by morphology								
Nonpedunculated[b]	190 (62.5)	120 (41.4)	1.75	<.001	28 (34.1)	30 (33.3)	1.16	.573
Pedunculated[b]	19 (6.3)	25 (8.6)	0.69	.233	9 (11.0)	13 (14.4)	0.84	.690
APC	1.65 ± 2.17	0.86 ± 1.31	1.95	<.001	0.83 ± 1.46	0.89 ± 2.10	1.11	.705
PDR	247 (81.3)	181 (62.4)	1.56	<.001	46 (56.1)	54 (60.0)	1.01	.964
Non-neoplastic resection rate[c]	171 (56.3)	103 (35.5)	1.84	<.001	30 (36.6)	30 (33.3)	1.21	.462
Non-neoplastic resection per colonoscopy	1.29 ± 1.71	0.59 ± 1.06	2.15	<.001	0.73 ± 1.33	0.66 ± 1.34	1.07	.806

Values are n (%) or mean ± SD. RR and FC were estimated by a Cox regression model with constant time at risk and robust variance and a negative binomial regression model, respectively.
ADR, adenoma detection rate; APC, adenoma per colonoscopy; CADe, computer-aided polyp detection system; FC, fold change; PDR, polyp detection rate; RR, relative risk.
[a]Right colon refers to cecum, ascending colon, hepatic flexure and transverse colon. Left colon refers to splenic flexure, descending colon, sigmoid colon, and rectum.
[b]Nonpedunculated morphology refers to sessile (Is), slightly elevated (IIa), flat (IIb), slightly depressed (IIc), and excavated (III) types according to Paris classification. Pedunculated morphology refers to pedunculated (Ip) type according to Paris classification.
[c]Non-neoplastic resection refers to a resected specimen without adenoma or SSL component.

Supplementary Table 2. Subgroup Analysis in Different Colonoscopy Indications (Symptomatic, Surveillance, Screening)

	Symptomatic			Surveillance			Screening		
	CADe (n = 232)	Control (n = 236)	RR/FC	CADe (n = 126)	Control (n = 121)	RR/FC	CADe (n = 28)	Control (n = 23)	RR/FC
Overall ADR	118 (50.9)	94 (39.8)	1.31	88 (69.8)	64 (52.9)	1.63	16 (57.1)	11 (47.8)	1.38
ADR by Size									
<5 mm	83 (35.8)	49 (20.8)	1.79	62 (49.2)	39 (32.2)	1.85	11 (39.3)	7 (30.4)	1.36
5–10 mm	74 (31.9)	60 (25.4)	1.27	56 (44.4)	45 (37.2)	1.28	12 (42.9)	6 (26.1)	1.80
>10 mm	4 (1.7)	13 (5.5)	0.27	3 (2.4)	1 (0.8)	2.90	0 (0)	2 (8.7)	0
ADR by location									
Right colon[a]	79 (34.1)	56 (23.7)	1.47	70 (55.6)	52 (43.0)	1.51	13 (46.4)	9 (39.1)	1.51
Left colon[a]	73 (31.5)	62 (26.3)	1.17	50 (39.7)	37 (30.6)	1.43	10 (35.7)	6 (26.1)	1.29
ADR by morphology									
Nonpedunculated[b]	114 (49.1)	82 (34.7)	1.50	88 (69.8)	61 (50.4)	1.74	16 (57.1)	7 (30.4)	2.39
Pedunculated[b]	20 (8.6)	27 (11.4)	0.70	5 (4.0)	5 (4.1)	1.09	3 (10.7)	6 (26.1)	0.54
APC	1.32 ± 2.07	0.76 ± 1.56	1.71	1.84 ± 2.17	1.02 ± 1.38	1.88	1.14 ± 1.18	1.09 ± 1.88	1.25
PDR	161 (69.4)	133 (56.4)	1.36	112 (88.9)	86 (71.1)	1.61	20 (71.4)	16 (69.6)	1.20
Non-neoplastic resection rate[c]	113 (48.7)	74 (31.4)	1.74	75 (59.5)	49 (40.5)	1.70	13 (46.4)	10 (43.5)	1.02
Non-neoplastic resection per colonoscopy	1.04 ± 1.51	0.51 ± 1.03	2.00	1.44 ± 1.85	0.78 ± 1.32	1.87	0.96 ± 1.69	0.70 ± 0.97	1.44

Valuesa re n (%) or mean ± SD. RR and FC were estimated by a Cox regression model with constant time at risk and robust variance and a negative binomial regression model, respectively.
ADR, adenoma detection rate; APC, adenoma per colonoscopy; CADe, computer-aided polyp detection system; FC, fold change; PDR, polyp detection rate; RR, relative risk.
[a]Right colon refers to cecum, ascending colon, hepatic flexure, and transverse colon. Left colon refers to splenic flexure, descending colon, sigmoid colon, and rectum.
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[c]Non-neoplastic resection refers to a resected specimen without adenoma or SSL component.

Supplementary Table 3. Endoscopist-Reported False Positive Signal Rate and Mean Number of False Positive Signals per Colonoscopy (Computer-Aided Polyp Detection Group)

Endoscopist-Reported False Positive Signal	False Positive Rate (%)	Mean Number of False Positives per Colonoscopy
Overall	23.83	1.085
Air bubbles	6.48	0.218
Stool or undigested debris	6.99	0.223
Wrinkled colonic mucosa	18.91	0.544
Diverticulum	0.78	0.008
Local inflammation or bleeding	3.63	0.039
Drug pills	0.26	0.003
Others	3.89	0.052

False positive signals refer to incorrect alerts from computer artifacts due to various reasons, which lasted for longer than 2 seconds.