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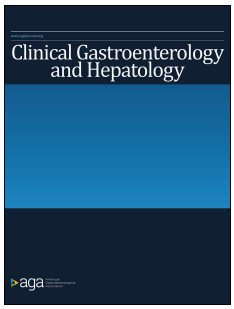

Effect of real-time computer-aided polyp detection system (ENDO-AID) on adenoma detection in endoscopists-in-training: a randomized trial

Louis H.S. Lau, Jacky C.L. Ho, Jimmy C.T. Lai, Agnes H.Y. Ho, Claudia W.K. Wu, Vincent W.H. Lo, Carol M.S. Lai, Markus W. Scheppach, Felix Sia, Kyle H.K. Ho, Xiang Xiao, Terry C.F. Yip, Thomas Y.T. Lam, Hanson Y.H. Kwok, Heyson C.H. Chan, Rashid N. Lui, Ting-Ting Chan, Marc T.L. Wong, Man-Fung Ho, Rachel C.W. Ko, Sok-Fei Hon, Simon Chu, Koari Futaba, Simon S.M. Ng, Hon-Chi Yip, Raymond S.Y. Tang, Vincent W.S. Wong, Francis K.L. Chan, Philip W.Y. Chiu, (ENDOAID-TRAIN study group)

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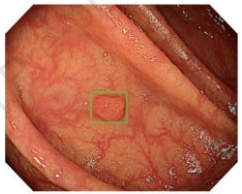
Effect of real-time computer-aided polyp detection system on adenoma detection in endoscopists-in-training: a randomized trial

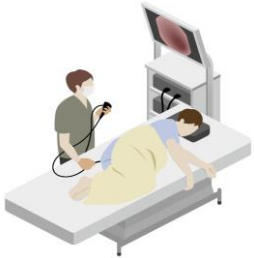
Diagnostic, screening or surveillance colonoscopy → **Endoscopists-in-training (<3 years experience + <500 procedures)** → **1:1 randomization** → **Higher overall adenoma detection rate with CADe**

N = 766

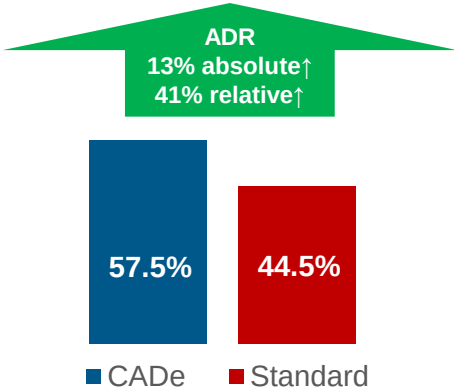
April 2021 – July 2022



CADe colonoscopy
n = 386



Standard colonoscopy
n = 380



Lau HSL, Ho CL, Lai CT, et al.

Clinical Gastroenterology and Hepatology

Effect of real-time computer-aided polyp detection system (ENDO-AID) on adenoma detection in endoscopists-in-training: a randomized trial

Short Title: ENDOAID-TRAIN study

Louis H.S. Lau[1,2,3], Jacky C.L. Ho[1], Jimmy C.T. Lai[1], Agnes H.Y. Ho[1], Claudia W.K. Wu[1], Vincent W.H. Lo[1], Carol M.S. Lai[4], Markus W. Scheppach[2,5], Felix Sia[2], Kyle H.K. Ho[2], Xiang Xiao[2,6], Terry C.F. Yip[6], Thomas Y.T. Lam[7], Hanson Y.H. Kwok[1], Heyson C.H. Chan[1], Rashid N. Lui[1], Ting-Ting Chan[1], Marc T.L. Wong[1], Man-Fung Ho[4], Rachel C.W. Ko[4], Sok-Fei Hon[4], Simon Chu[4], Koari Futaba[4], Simon S.M. Ng[2,4], Hon-Chi Yip[2,4], Raymond S.Y. Tang[1,2,3], Vincent W.S. Wong[1,2,3], Francis K.L. Chan[1,2,3], Philip W.Y. Chiu*[2,4] (ENDOAID-TRAIN study group)

1. Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong
2. Institute of Digestive Disease, The Chinese University of Hong Kong
3. State Key Laboratory of Digestive Disease, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong
4. Department of Surgery, Faculty of Medicine, The Chinese University of Hong Kong
5. Gastroenterology, Faculty of Medicine, University of Augsburg - Germany
6. Medical Data Analytic Centre, The Chinese University of Hong Kong
7. Stanley Ho Big Data Decision Analytics Research Centre, The Chinese University of Hong Kong

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Abbreviations: ADR: adenoma detection rate; APC: adenomas per colonoscopy; BPPS: Boston Bowel Preparation Scale; CADe: computer-aided polyp detection; CRC: colorectal cancer; FC: fold change; PCCRC: post-colonoscopy CRC; PDR: polyp detection rate; RR: relative risk; SSL: sessile serrated lesion

Correspondence:
Philip W.Y Chiu, MD
Department of Surgery, Faculty of Medicine, The Chinese University of Hong Kong
30-32 Ngan Shing Street, Prince of Wales Hospital, Hong Kong SAR
Email: philipchiu@surgery.cuhk.edu.hk

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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), Olympus Co., Tokyo, Japan) should be obtained from Olympus Corporation, Japan.

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Abstract

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), Olympus Co., Japan) or not (control) during withdrawal. Procedures were performed by endoscopists-in-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

386 and 380 subjects were randomized to CADe and control groups, respectively. The overall ADR was significantly higher in CADe than control group (57.5% vs 44.5%, adjusted relative risk 1.41, 95%CI 1.17-1.72, p<0.001). The ADRs for <5mm (40.4% vs 25.0%) and 5-10mm adenomas (36.8% vs 29.2%) were higher in CADe group. The ADRs were higher in CADe group in both right (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 CADe group among beginners (60.0% vs 41.9%) and intermediate-level endoscopists (56.5% vs 45.5%). Mean number of adenomas (1.48 vs 0.86) and non-neoplastic resection rate were higher in CADe group (52.1% vs 35.0%).

Conclusions

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

Keywords: colonoscopy; training; computer-aided polyp detection; CADe; adenoma detection rate; ADR

Introduction

Colonoscopy reduces colorectal cancer (CRC)-related mortality, by detecting and removing pre-malignant 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, post-colonoscopy CRC (PCCRC) 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 PCCRC . (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 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 one study investigated the effect of endoscopist experience on CADe with a cut-off at 2,000 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 Co., Tokyo, Japan) on ADR and colonoscopy quality in junior endoscopists-in-training.

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 aged ≥18 years old 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 Anaesthesiologists 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), Olympus Co., Tokyo, Japan) during the withdrawal phase. Randomization was stratified by age (<65 vs ≥65), 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 groups (200-500 procedures). A total of 22 junior endoscopists (12 in beginner and 10 in intermediate groups) 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 caecal intubation, the supervisor

would help advance the colonoscope to the caecum, 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 would offer suggestions and/or take over for the endoscopic resection.

Endoscopic Procedures

All procedures were performed under conscious sedation or monitored anaesthesia 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 **Supplementary Materials**.

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

Outcomes

The primary endpoint was ADR, which was defined as the proportion of subjects with at least one histologically-confirmed adenoma (SSL were excluded from the ADR definition). Secondary endpoints included ADR for adenomas of different sizes (<5mm, 5-10mm, >10mm) and locations, mean number of adenomas per colonoscopy (APC), advanced adenoma detection rate, SSL detection rate, polyp detection rate (PDR), non-neoplastic resection rate, supervisor-reported missed polyp rate, endoscopist-reported false positive signal rate, caecal 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 **Supplementary Materials**.

Statistical Analysis

The sample size was calculated based on the primary outcome (ADR). Based on published local data, baseline ADR for non-screening 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 one-sided significance level of 0.025, 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**.

Results

Study Flow and Baseline Parameters

From 15 April 2021 to 22 July 2022, 880 subjects were screened and 856 subjects were eligible. 427 and 429 subjects were randomized to the intervention (CADe) and control arms respectively. Subjects (n=41 in CADe, n=49 in control) 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 analysed in the CADe and control groups respectively. (**Figure 1**)

Baseline demographics and procedural data were shown in **Table 1**. No significant difference was detected between the two groups, except a longer mean withdrawal time (excluding intervention) in the CADe arm (14.9 vs 13.7 minutes). Clinical indications and bowel preparation were comparable. 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%), the remainder were surgeons.

Primary and Secondary Outcomes – Adenoma and Polyp Detection

The overall ADR was significantly higher in the CADe group (57.5%, 222/386) than the control group (44.5%, 169/380) (adjusted RR 1.41, 95% confidence interval (CI) 1.17-1.72, p<0.001). (**Figure 2a**) Among different sizes, the ADRs were significantly higher in the CADe group for <5mm adenomas (40.4% vs 25.0%, adjusted RR 1.79, 95%CI 1.38-2.30, p<0.001) and 5-10mm adenomas (36.8% vs 29.2%, adjusted RR 1.31, 95%CI 1.03-1.68, p=0.030), but not for >10mm adenomas (1.8% vs 4.2%, p=0.060). 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=0.002) and left-sided colon (34.5% vs 27.6%, adjusted RR 1.31, 95%CI 1.01-1.68, p=0.041). For different morphologies, the CADe group had a higher ADR for non-pedunculated adenomas (56.5% vs 39.5%, adjusted RR 1.63, 95%CI 1.33-1.99, p<0.001), but not pedunculated lesions. (**Figure 2b**) 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 HGD

respectively. The mean APC was significantly higher in the CADe group (1.48 vs 0.86, adjusted fold change (FC) 1.78, 95%CI 1.46-2.18, p<0.001). There was no significant difference in advanced ADR (8.3% vs 10.0%, adjusted RR 0.82, 95%CI 0.51-1.31, p=0.397) and SSL detection rate (2.1% vs 1.8%, adjusted RR 1.14, 95%CI 0.42-3.11, p=0.801) between CADe and control groups. 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<0.001). There was only one supervisor-reported missed polyp in each group (0.26% vs 0.26%).

Secondary Outcome – Non-neoplastic Resection

Non-neoplastic resection rate was higher in CADe group (52.1% vs 35.0%, adjusted RR 1.70, 95%CI 1.37-2.11, p<0.001) with a higher mean number of non-neoplastic resection (1.17 vs 0.61, adjusted FC 1.92, 95%CI 1.54-2.41, p<0.001). (**Table 2**) The proportion of subjects who only had non-neoplastic resection was similar between two groups (17.9% vs 16.8%). In fact, there were more subjects in CADe group (34.2%, 132/386) than control group (18.2%, 69/380) who had both adenomas and non-neoplastic lesions resected.

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=0.015) than intermediate level endoscopists (56.5% vs 45.5%, adjusted RR 1.36, p=0.009). (**Figure 2c, Table 3**) The ADRs with regard to individual endoscopists were shown in **Supplementary Figure 2**. All junior endoscopists except one had at least 10% ADR gain by using CADe during colonoscopies. In subgroup analysis across different specialties, there were more significant benefits from CADe among gastroenterologists (GI) 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, gender, colonoscopy indications, bowel preparation and endoscopist experience/specialty), a pre-specified multivariable analysis by Cox regression model with constant time at risk and robust variance was developed. It demonstrated that age ≥65 years old, male gender, longer withdrawal time, GI

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 to 1.69, p<0.001). (**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 three procedure-related serious adverse events were noted. One subject in the CADe group had post-polypectomy coagulation syndrome, and two subjects in the control group had delayed post-polypectomy 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 size (up to 79% relative increase) and non-pedundulated adenomas (63% relative increase), in both right-sided and left-sided colon. In addition, there was a relatively larger ADR gain among novice and less experienced endoscopists (58% in beginners vs 36% in 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, 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 to CADe, water exchange method and second forward-view examination are generally more time consuming, and distal attachment devices are not 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 non-expert endoscopists. (33) The rapid development of artificial intelligence in assisting polyp diagnosis (CADx) 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 size adenomas can be translated into longterm clinical benefit. It will also result in a temporary surge of surveillance colonoscopies. A prosepctive longitudinal study would be necessary to provide the longterm 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 above 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 controlled 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 a non-screening 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 above 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 size and non-pedunculated 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 non-neoplastic resection rate. However, the benefit of CADe for large and advanced adenomas remains unclear. The performance optimization of CADe devices, concurrent development of CADx systems, and incorporation of artificial intelligence into endoscopy training curricula should be the focus of future efforts.

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Supplementary Materials

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ENDO-AID was a pre-installed 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.

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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., Tokyo, Japan) or EVIS X1 colonoscopes (CF-EZ1500DL/I series; Olympus Co., Tokyo, Japan). The use of light-modification technologies such as Narrow Band Imaging (NBI) or Texture and Color Enhancement Imaging (TXI) were restricted only for polyp characterization. No magnification or chromoendoscopy was allowed. Use of distal attachment devices (e.g. transparent cap, Endocuff Vision®) was prohibited.

Endoscopic Procedures

The caecal 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 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 caecum to transverse colon) and left-sided (from splenic flexure to rectum). Mean APC referred to the total number of adenomas divided by the number of colonoscopies. Non-neoplastic resection was defined as the absence of adenoma or SSL within resected specimen. Missed polyps were defined as polyps detected by the supervisor, but not recognised by the junior endoscopist who withdrew the endoscope to the next colonic segment, and did not contribute to the ADR. False positive signals referred to incorrect alerts from computer artifacts due to various reasons, which lasted for ≥2 seconds and reported by operators. Procedure-related adverse events were recorded.

Data Analysis

Categorical variables were expressed in number (percentage). Continuous and count variables were expressed in mean (standard deviation). 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 (RR) for all binary endpoints after adjustment of stratification factors (age, gender, endoscopist experience). A negative binomial regression model was applied to estimate the fold change (FC) for count variables after adjusting stratification factors. A pre-specified multivariable analysis on ADR 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 less than 0.05 was regarded as statistically significant. Data were analysed by R software (4.3.0; R Foundation for Statistical Computing, Vienna, Austria).

Role of Funding Source

This study was supported by a research grant from the Asian Endoscopy Research Forum (AERF), which is a non-profit academic organisation. The funder of this study had no role in study design, data collection, data analysis, data interpretation, or

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Figure Legends

Figure 1. Study Flow Diagram (CONSORT)

Figure 2. (a) Overall adenoma detection rates; **(b)** adenoma detection rates by different sizes, locations and morphologies between computer-aided polyp detection system (CADe) and control groups; **(c)** adenoma detection rates in different levels of endoscopist experience (beginner vs intermediate)

Table 1. Baseline demographic data and procedural characteristics between computer-aided polyp de

	CADe group (n=386)	**Control group** (n=380)
Sex [n (%)]		
Male	205 (53.1)	211 (55.5)
Female	181 (46.9)	169 (44.5)
Age [mean (SD)]	66.00 (10.05)	65.36 (11.33)
Ethnicity [n (%)]		
Chinese	384 (99.5)	376 (98.9)
Others	2 (0.5)	4 (1.1)
Smoking [n (%)] *		
Current	42 (11.1)	38 (10.5)
Former	33 (8.7)	33 (9.1)
No	303 (80.2)	292 (80.4)
Alcohol use [n (%)] **		
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 [n (%)] #		
Yes	72 (19.5)	55 (15.6)
No	298 (80.5)	298 (84.4)
Colonoscopy Indication [n (%)]		
Screening	28 (7.3)	23 (6.1)
Surveillance	126 (32.6)	121 (31.8)
Symptomatic	232 (60.1)	236 (62.1)
Experience of endoscopist [n (%)]		
Beginner (<200)	110 (28.5)	105 (27.6)
Intermediate (200-500)	276 (71.5)	275 (72.4)
Specialty of endoscopist [n (%)]		
Gastroenterologist	304 (78.8)	290 (76.3)
Surgeon	82 (21.2)	90 (23.7)
Endoscope model [n (%)]		
HQ290-series	376 (97.4)	374 (98.4)
EZ1500/XZ1200-series	10 (2.6)	6 (1.6)
Boston Bowel Preparation Scale [mean (SD)] ##		
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)

Caecal intubation by junior endoscopists [n (%)]	365 (94.6)	362 (95.3)
Withdrawal time excluding intervention [mean (SD)]^^	14.94 (8.08)	13.74 (8.66)

*Missing information in 8 and 17 cases in CADe and control arm, respectively.

**Missing information in 7 and 17 cases in CADe and control arm, respectively.

#Missing information in 16 and 27 cases in CADe and control arm, respectively.

##Missing information in 1 and 1 cases in CADe and control arm, respectively.

^Missing information in 1 and 4 cases in CADe and control arm, respectively.

^^Baseline *p* values were evaluated by Pearson Chi-squared, Fisher's Exact, Wilcoxon rank-sum and t-tests when appropriate. The *p* values for all parameters were >0.05 (except withdrawal time exclude intervention, $p = 0.048$).

Table 2. Modified intention-to-treat analysis of primary endpoint (adenoma detection rate, ADR) and se

ADR, sessile serrated lesion (SSL) detection rate, polyp detection rate (PDR), non-neoplastic resection rate). Relative risk (RR) and fold change (FC) were estimated by Cox regression model with constant time at risk and robust variance and negative binomial regression model respectively.

	CADe group (n=386)	**Control group** (n=380)	**Relative Risk (RR) Or Fold Change (FC) (95% C.I.)**	***p* value**
Overall ADR [n (%)]	222 (57.5)	169 (44.5)	1.41 (1.17 to 1.72)	<0.001
ADR by Size [n (%)]				
<5mm	156 (40.4)	95 (25.0)	1.79 (1.38 to 2.30)	<0.001
5-10mm	142 (36.8)	111(29.2)	1.31 (1.03 to 1.68)	0.030
>10mm	7 (1.8)	16 (4.2)	0.43 (0.17 to 1.04)	0.060
ADR by Location [n (%)]				
Right Colon*	162 (42.0)	117 (30.8)	1.45 (1.15 to 1.84)	0.002
Caecum	27 (7.0)	19 (5.0)	1.41 (0.78 to 2.54)	0.253
Ascending Colon	83 (21.5)	54 (14.2)	1.57 (1.12 to 2.21)	0.010
Hepatic Flexure	31 (8.0)	15 (3.9)	2.05 (1.11 to 3.80)	0.022
Transverse Colon	92 (23.8)	55 (14.5)	1.73 (1.24 to 2.41)	0.001
Left Colon*	133 (34.5)	105 (27.6)	1.31 (1.01 to 1.68)	0.041
Splenic Flexure	5 (1.3)	3 (0.8)	1.69 (0.41 to 7.04)	0.472
Descending Colon	64 (16.6)	43 (11.3)	1.50 (1.02 to 2.22)	0.041
Sigmoid Colon	76 (19.7)	63 (16.6)	1.22 (0.87 to 1.70)	0.251
Rectum	26 (6.7)	13 (3.4)	2.07 (1.06 to 4.06)	0.033
ADR by Morphology [n (%)]				
Non-pedunculated^	218 (56.5)	150 (39.5)	1.63 (1.33 to 1.99)	<0.001
Pedunculated^	28 (7.3)	38 (10.0)	0.72 (0.44 to 1.17)	0.181
Overall APC [mean (SD)]	1.48 (2.06)	0.86 (1.53)	1.78 (1.46 to 2.18)	<0.001
APC by Size [mean (SD)]				
<5mm	0.77 (1.34)	0.37 (0.83)	2.09 (1.61 to 2.73)	<0.001
5-10mm	0.69 (1.31)	0.45 (0.94)	1.60 (1.23 to 2.07)	<0.001
>10mm	0.02 (0.13)	0.05 (0.24)	0.39 (0.15 to 0.92)	0.040
APC by Location [mean (SD)]				
Right Colon*	0.90 (1.44)	0.48 (1.05)	1.89 (1.48 to 2.43)	<0.001
Left Colon*	0.58 (1.11)	0.38 (0.79)	1.59 (1.23 to 2.08)	<0.001
APC by Morphology [n (%)]				
Non-pedunculated^	1.38 (1.91)	0.71 (1.20)	2.00 (1.63 to 2.46)	<0.001
Pedunculated^	0.10 (0.40)	0.15 (0.63)	0.71 (0.41 to 1.22)	0.216
Advanced ADR[#] [n (%)]	32 (8.3)	38 (10.0)	0.82 (0.51 to 1.31)	0.397
SSL detection rate [n (%)]	8 (2.1)	7 (1.8)	1.14 (0.42 to 3.11)	0.801

Polyp detection rate [n (%)]	293 (75.9)	235 (61.8)	1.42 (1.21 to 1.66)	<0.001
Non-neoplastic resection per colonoscopy## [mean (sd)]	1.17 (1.65)	0.61 (1.13)	1.92 (1.54 to 2.41)	<0.001

*Right colon refers to caecum, ascending colon, hepatic flexure and transverse colon. Left colon refers to splenic flexure, descending colon, sigmoid colon and rectum.

^Non-pedunculated 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.

#Advanced adenoma refers to an adenoma larger than 10mm, and/or with villous component ≥20%, and/or harbouring high grade dysplasia.

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

Table 3. Subgroup analysis at different levels of endoscopist experience (beginner vs intermediate). CA

detection rate; APC: adenoma per colonoscopy; PDR: polyp detection rate. Relative risk (RR) and fold change (FC) were estimated by Cox regression model with constant time at risk and robust variance and negative binomial regression model respectively.

	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 [n (%)]	66 (60.0)	44 (41.9)	1.58	0.015	156 (56.5)	125 (45.5)	1.36	0.009
ADR by Size [n (%)]								
<5mm	55 (50.0)	29 (27.6)	2.08	0.001	101 (36.6)	66 (24.0)	1.66	0.001
5~10mm	31 (28.2)	21 (20.0)	1.42	0.218	111 (40.2)	90 (32.7)	1.29	0.071
>10mm	1 (0.9)	5 (4.8)	0.19	0.127	6 (2.2)	11 (4.0)	0.54	0.224
ADR by Location [n (%)]								
Right Colon*	47 (42.7)	30 (28.6)	1.59	0.044	115 (41.7)	87 (31.6)	1.41	0.015
Left Colon*	40 (36.4)	24 (22.9)	1.76	0.028	93 (33.7)	81 (29.5)	1.17	0.291
ADR by Morphology [n (%)]								
Non-pedunculated^	65 (59.1)	38 (36.2)	1.91	0.001	153 (55.4)	112 (40.7)	1.53	<0.001
Pedunculated^	6 (5.5)	14 (13.3)	0.37	0.045	22 (8.0)	24 (8.7)	0.93	0.805
APC [mean (SD)]	1.52 (2.26)	0.79 (1.49)	1.91	0.001	1.46 (1.98)	0.89 (1.55)	1.73	<0.001
PDR [n (%)]	79 (71.8)	63 (60.0)	1.31	0.079	214 (77.5)	172 (62.5)	1.46	<0.001
Non-neoplastic resection rate [n (%)]	52 (47.3)	37 (35.2)	1.44	0.082	149 (54.0)	96 (34.9)	1.80	<0.001
Non-neoplastic resection per colonoscopy [mean (SD)]	1.19 (1.71)	0.68 (1.27)	1.69	0.023	1.16 (1.63)	0.58 (1.07)	2.00	<0.001

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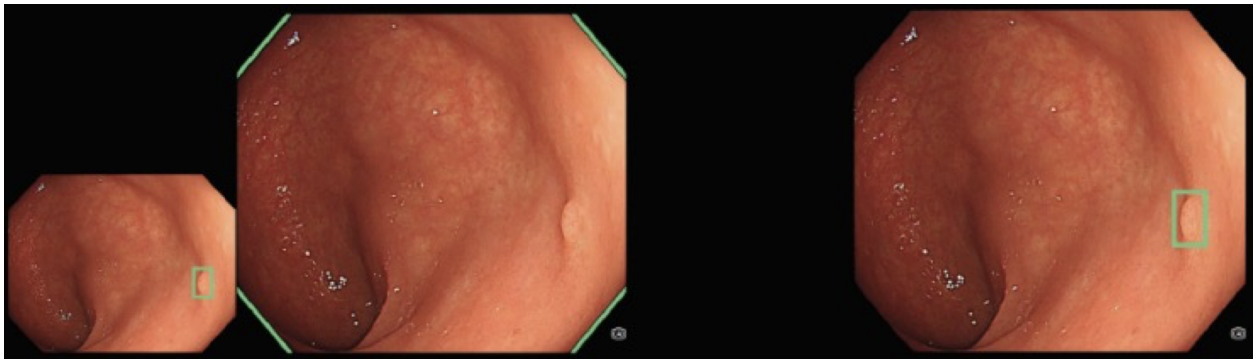
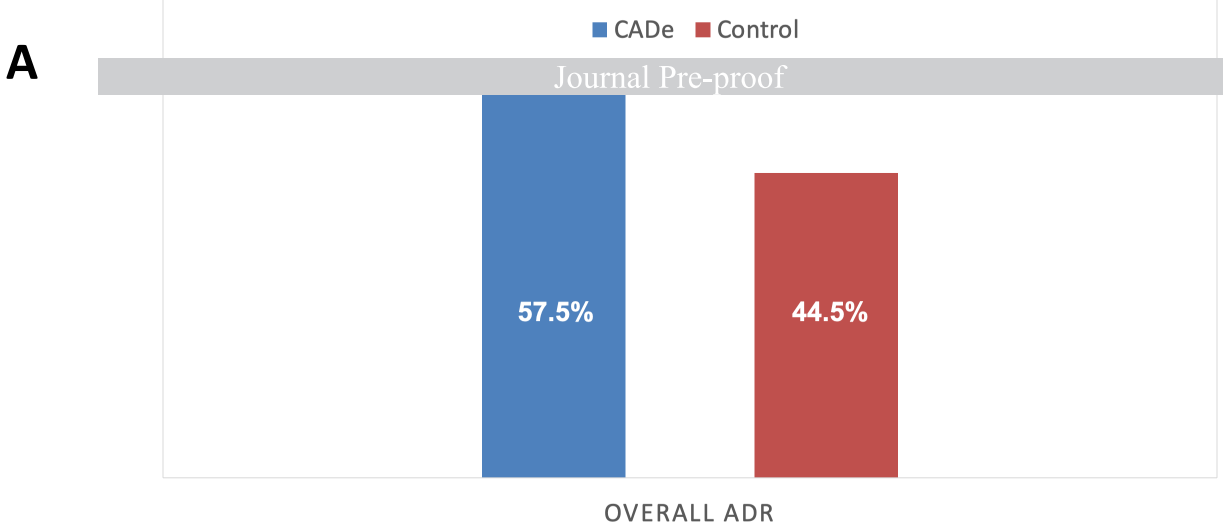
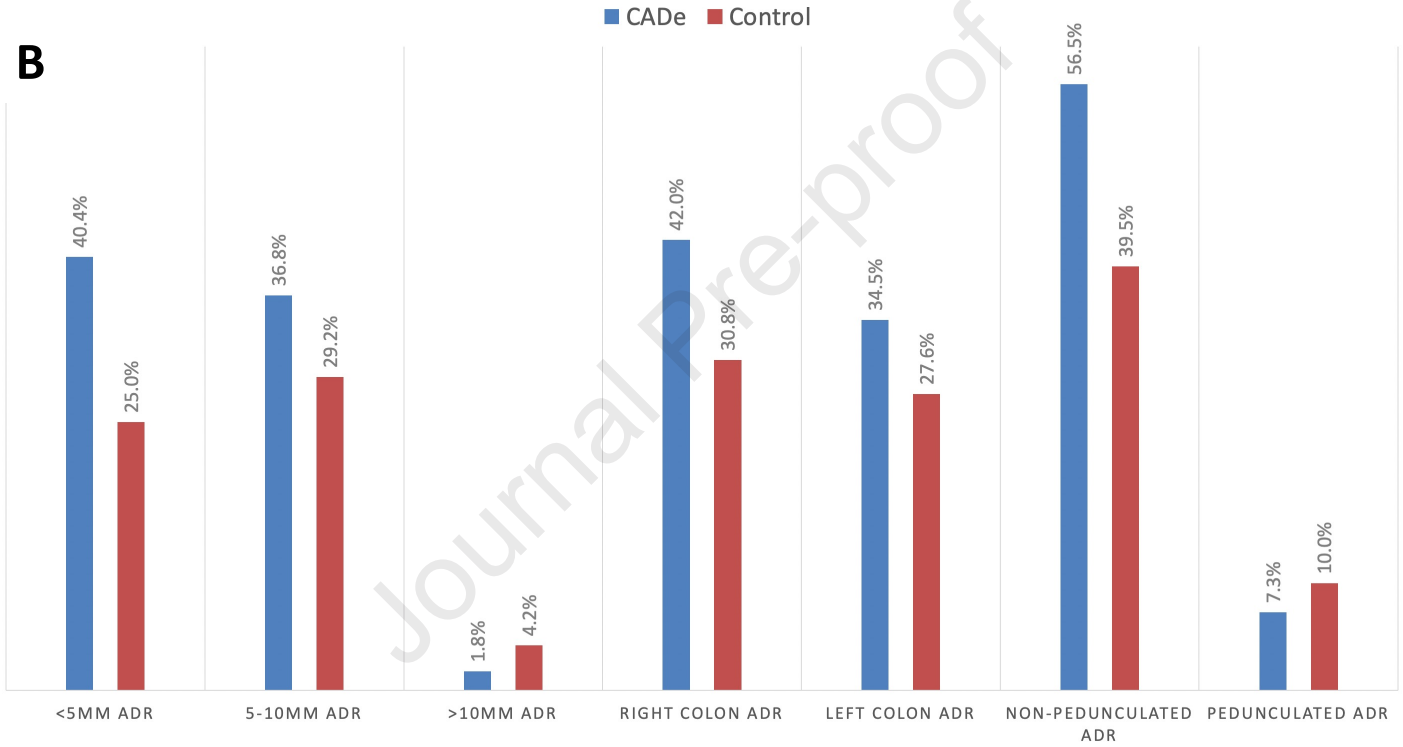
Table 4. Covariate-adjusted Cox regression model with constant time at risk and robust variance, adal time (excluding intervention), endoscopist experience. NA: not applicable.

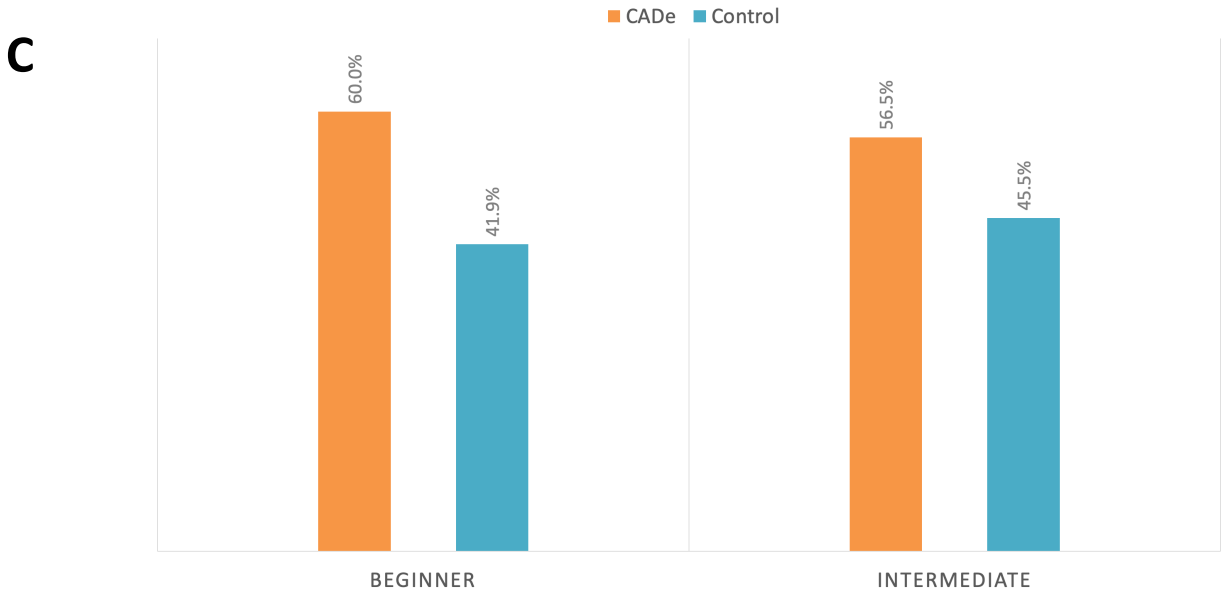
	Relative Risk (95% C.I.)	***p* value**
Computer-aided polyp detection system (CADe)	1.40 (1.16 – 1.69)	<0.001
Age		
<65	1	NA
≥65	1.80 (1.42 – 2.27)	<0.001
Sex		
Female	1	NA
Male	1.47 (1.20 – 1.80)	<0.001
Colonoscopy Indication		
Screening	1	NA
Surveillance	0.88 (0.60 – 1.28)	0.503
Symptomatic	0.73 (0.51 – 1.05)	0.094
BBPS (Overall)*	0.99 (0.91 – 1.07)	0.734
Withdrawal Time (exclude intervention)	1.03 (1.02 – 1.05)	<0.001
Experience of Endoscopist		
Beginner (<200)	1	NA
Intermediate (200-500)	1.19 (0.94 – 1.51)	0.156
Specialty of Endoscopist		
Surgeons	1	NA
Gastroenterologists	1.39 (1.04 – 1.87)	0.028

*2 missing values in BBPS are replaced by the integer closest to the mean of remaining BBPS values.









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The caecal 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 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 caecum to transverse colon) and left-sided (from splenic flexure to rectum). Mean APC referred to the total number of adenomas divided by the number of colonoscopies. Non-neoplastic resection was defined as the absence of adenoma or SSL within resected specimen. Missed polyps were defined as polyps detected by the supervisor, but not recognised by the junior endoscopist who withdrew the endoscope to the next colonic segment, and did not contribute to the ADR. False positive signals referred to incorrect alerts from computer artifacts due to various reasons, which lasted for ≥2 seconds and reported by operators. Procedure-related adverse events were recorded.

Data Analysis

Categorical variables were expressed in number (percentage). Continuous and count variables were expressed in mean (standard deviation). 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 (RR) for all binary endpoints after adjustment of stratification factors (age, gender, endoscopist experience). A negative binomial regression model was applied to estimate the fold change (FC) for count variables after adjusting stratification factors. A pre-specified multivariable analysis on ADR 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 less than 0.05 was regarded as statistically significant. Data were analysed by R software (4.3.0; R Foundation for Statistical Computing, Vienna, Austria).

Role of Funding Source

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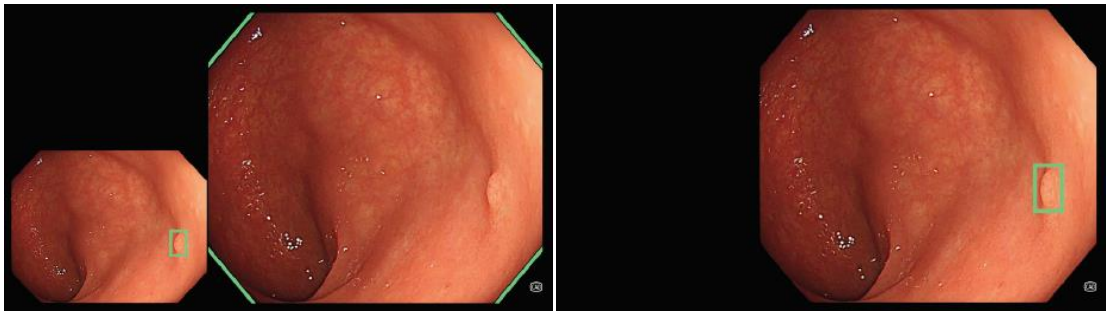
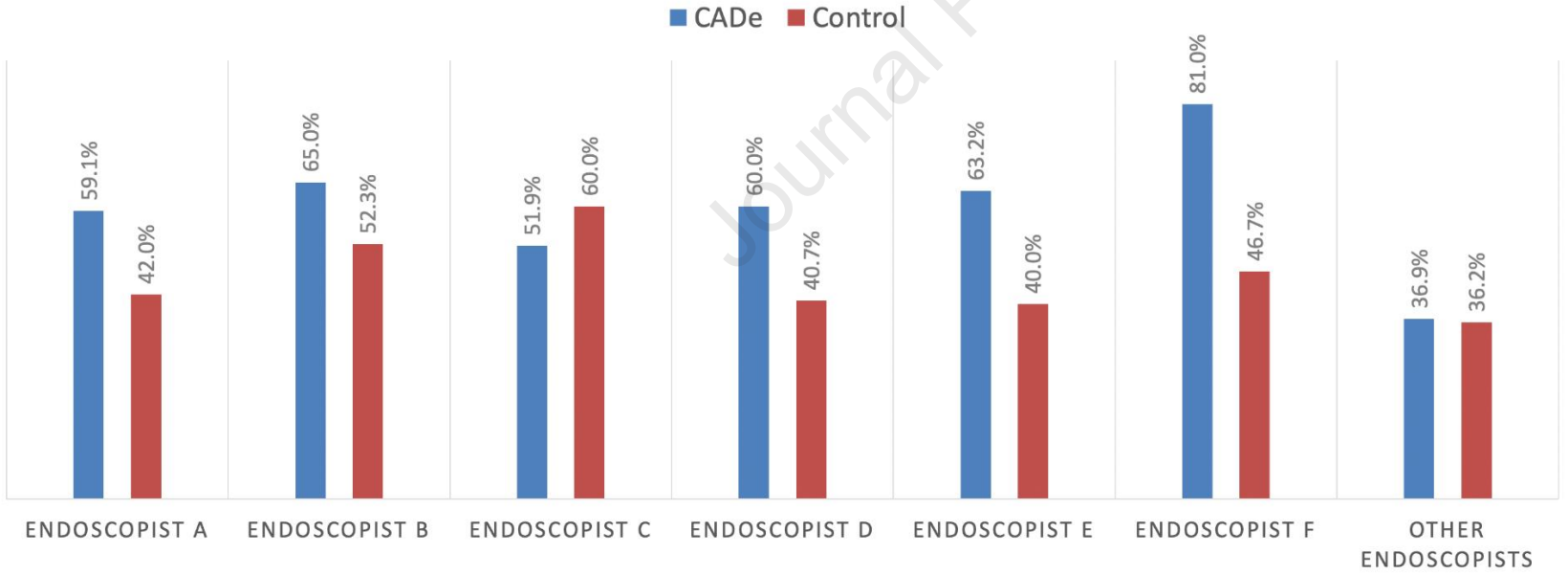
Supplementary Figure 1. Normal Mode (left) and Target Mode (right) of computer-aided polyp detection system (ENDO-AID(OIP-1), Olympus Co., Tokyo, Japan)



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). CADe: computer-aided polyp detection system; ADR: adenoma detection rate; APC: adenoma per colonoscopy; PDR: polyp detection rate. Relative risk (RR) and fold change (FC) were estimated by Cox regression model with constant time at risk and robust variance and negative binomial regression model respectively.

	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 [n (%)]	191 (62.8)	133 (45.9)	1.53	<0.001	31 (37.8)	36 (40.0)	1.01	0.958
ADR by Size [n (%)]								
<5mm	130 (42.8)	70 (24.1)	1.97	<0.001	26 (31.7)	25 (27.8)	1.31	0.340
5-10mm	130 (42.8)	90 (31.0)	1.47	0.005	12 (14.6)	21 (23.3)	0.65	0.233
>10mm	6 (2.0)	11 (3.8)	0.50	0.169	1 (1.2)	5 (5.6)	0.23	0.162
ADR by Location [n (%)]								
Right Colon*	140 (46.1)	93 (32.1)	1.53	0.001	22 (26.8)	24 (26.7)	1.14	0.648
Left Colon*	118 (38.8)	83 (28.6)	1.43	0.012	15 (18.3)	22 (24.4)	0.76	0.416
ADR by Morphology [n (%)]								
Non-pedunculated^	190 (62.5)	120 (41.4)	1.75	<0.001	28 (34.1)	30 (33.3)	1.16	0.573
Pedunculated^	19 (6.3)	25 (8.6)	0.69	0.233	9 (11.0)	13 (14.4)	0.84	0.690
APC [mean (SD)]	1.65 (2.17)	0.86 (1.31)	1.95	<0.001	0.83 (1.46)	0.89 (2.10)	1.11	0.705
PDR [n (%)]	247 (81.3)	181 (62.4)	1.56	<0.001	46 (56.1)	54 (60.0)	1.01	0.964
Non-neoplastic resection rate## [n (%)]	171 (56.3)	103 (35.5)	1.84	<0.001	30 (36.6)	30 (33.3)	1.21	0.462
Non-neoplastic resection per colonoscopy	1.29 (1.71)	0.59 (1.06)	2.15	<0.001	0.73 (1.33)	0.66 (1.34)	1.07	0.806

*Right colon refers to caecum, ascending colon, hepatic flexure and transverse colon. Left colon refers to splenic flexure, descending colon, sigmoid colon and rectum.

^Non-pedunculated 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.

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). CADe: computer-aided polyp detection system; ADR: adenoma detection rate; APC: adenoma per colonoscopy; PDR: polyp detection rate. Relative risk (RR) and fold change (FC) were estimated by Cox regression model with constant time at risk and robust variance and negative binomial regression model respectively.

	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 [n (%)]	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 [n (%)]									
<5mm	83 (35.8)	49 (20.8)	1.79	62 (49.2)	39 (32.2)	1.85	11 (39.3)	7 (30.4)	1.36
5-10mm	74 (31.9)	60 (25.4)	1.27	56 (44.4)	45 (37.2)	1.28	12 (42.9)	6 (26.1)	1.80
>10mm	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 [n (%)]									
Right Colon*	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*	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 [n (%)]									
Non-pedunculated^	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^	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 [mean (SD)]	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 [n (%)]	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## [n (%)]	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 [mean (SD)]	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

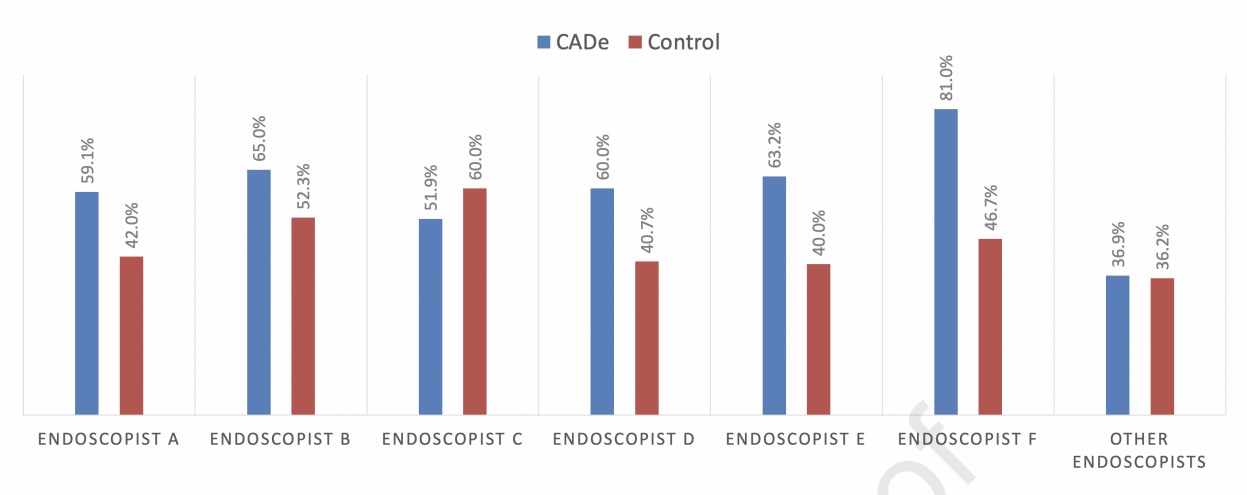
*Right colon refers to caecum, ascending colon, hepatic flexure and transverse colon. Left colon refers to splenic flexure, descending colon, sigmoid colon and rectum.

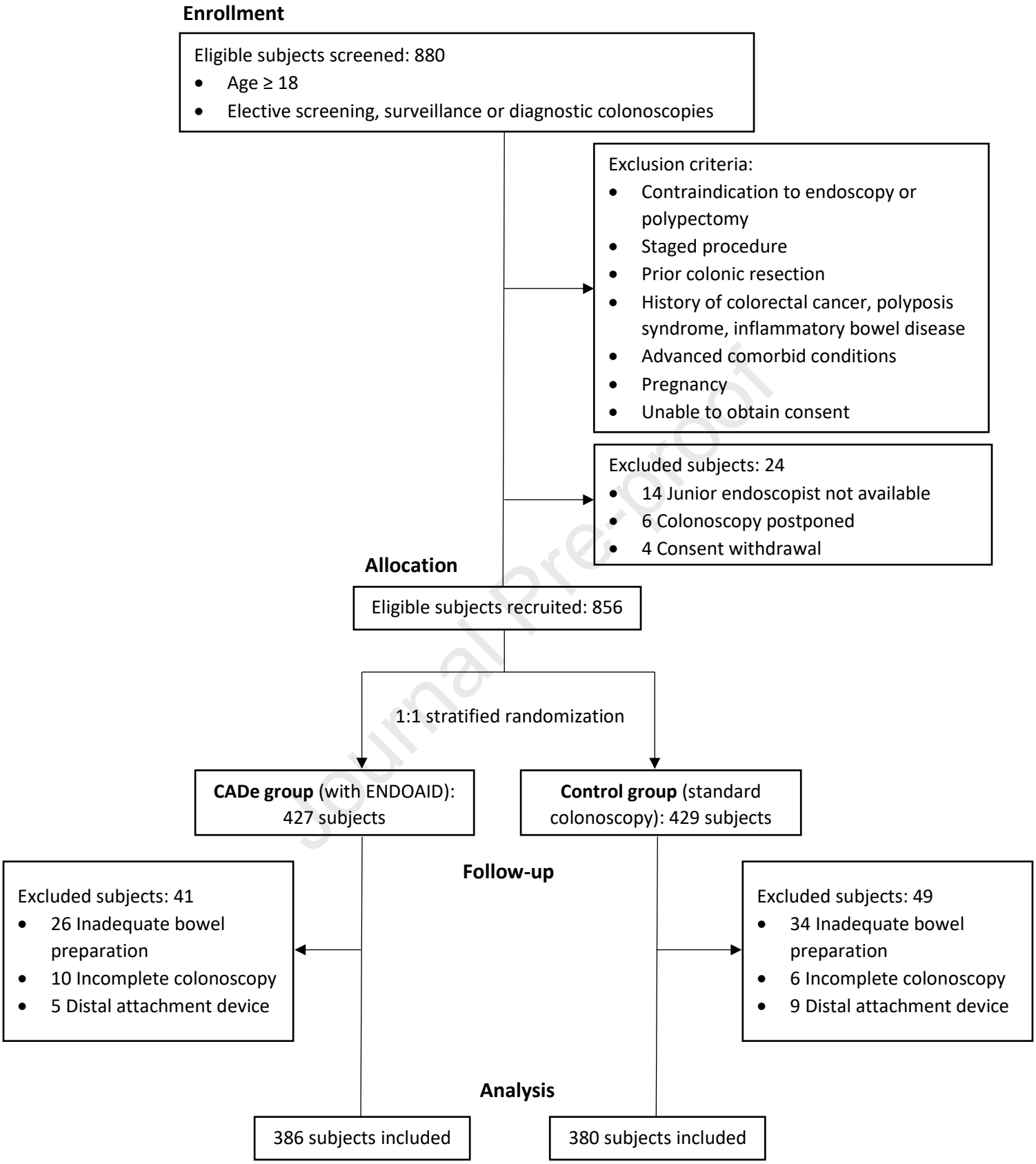
^Non-pedunculated morphology refers to sessile (Is), slightly elevated (IIa), flat (IIb), slightly depressed (IIc) and excavated (III) types according to Paris classification. Pedunculated morphology refers to pedunculated (Ip) type according to Paris classification.

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 signal per colonoscopy (computer-aided polyp detection group). False positive signals refer to incorrect alerts from computer artifacts due to various reasons, which lasted for longer than 2 seconds.

Endoscopist-Reported False Positive Signal	**False Positive Rate (FPR)**	**Mean Number of False Positive 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





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.