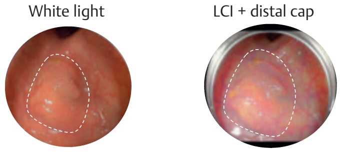
Sessile serrated lesion prevalence and factors associated with their detection: a post-hoc analysis of a multinational randomized controlled trial from Asia

GRAPHICAL ABSTRACT

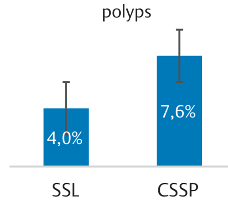
Prevalence of SSLs and endoscopic factors associated with their detection

→ Data on SSL and CSSP prevalence in Asia are limited

- Post-hoc analysis of a multicenter trial
- 4 countries/regions in Asia
- 2898 colonoscopies



Prevalence of serrated polyps



SSL, sessile serrated lesion
CSSP, clinically significant serrated polyp
LCI, linked-color imaging

Factors associated with SSL detection

	Adjusted risk ratio
Experienced endoscopists	1.9
Distal cap	1.7
LCI	1.6
Withdrawal time, per additional minute	1.1

Use of a distal cap attachment and LCI are associated with increased SSL detection

Endoscopy

Authors

Chin Kimg Tan[1,2], Sho Suzuki[3], Tiing Leong Ang[1,2], Xuan Han Koh[4], Lai Mun Wang[5,6], Satimai Aniwan[7], Han-Mo Chiu[8], Kannikar Laohavichitra[9], Sakkarin Chirapongsathorn[10], Takeshi Yamamura[11], Chen Ya Kuo[12], Naohisa Yoshida[13], Takahito Takezawa[14], Rungsun Rerknimitr[7], Hideki Ishikawa[15], Takuji Gotoda[16]

Institutions

1 Gastroenterology and Hepatology, Changi General Hospital, Singapore, Singapore
2 Medicine Academic Clinical Programme, SingHealth Duke-NUS Academic Medical Centre, Singapore, Singapore
3 Gastroenterology and Hepatology, International University of Health and Welfare School of Medicine, Narita, Japan
4 Health Services Research, Changi General Hospital, Singapore, Singapore
5 Laboratory Medicine, Changi General Hospital, Singapore, Singapore
6 Pathology Academic Clinical Programme, SingHealth Duke-NUS Academic Medical Centre, Singapore, Singapore
7 Center of Excellence in Endoscopy for Gastrointestinal Oncology, Chulalongkorn University Department of Internal Medicine, Bangkok, Thailand
8 Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
9 Rajavithi Digestive Endoscopy Center, Rajavithi Hospital, Bangkok, Thailand
10 Gastroenterology and Hepatology, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand
11 Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Nagoya, Japan
12 Gastroenterology, Fu Jen Catholic University Hospital, New Taipei City, Taiwan
13 Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto, Japan
14 Medicine, Division of Gastroenterology, Jichi Medical University, Shimotsuke, Japan
15 Molecular-Targeting Cancer Prevention, Kyoto Prefectural University of Medicine, Kyoto, Japan
16 Gastroenterology, Cancer Institute Hospital, Tokyo, Japan

received 15.10.2023
accepted after revision 18.4.2024
published online 10.6.2024

Bibliography
Endoscopy 2024; 56: 684–693
DOI 10.1055/a-2324-6262
ISSN 0013-726X

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Corresponding author
Sho Suzuki, MD, PhD, Department of Gastroenterology and Hepatology International University of Health and Welfare, School of Medicine, Kozunomori, Narita-City 4–3, 286-8686 Chiba, Japan
s.sho.salubriter.mail@gmail.com

Supplementary Material
Supplementary Material is available under
https://doi.org/10.1055/a-2324-6262

ABSTRACT

Background Sessile serrated lesions (SSLs) are associated with an increased risk of colorectal cancer. Data on the prevalence of SSLs in Asia are limited. We performed this study to estimate the prevalence of SSLs in Asia and to explore endoscopic factors that are associated with SSL detection.

Methods This is a post-hoc analysis of a multicenter randomized controlled trial from four Asian countries/regions that compared adenoma detection rates using linked-color imaging (LCI) and white-light imaging. Colonoscopies were performed in an average-risk population for screening, diagnostic examination, or polyp surveillance. Patients with SSLs were compared against those without SSLs to evaluate for possible predictors of SSL detection using Firth's logistic regression.

Results 2898 participants (mean age 64.5 years) were included in the analysis. The estimated prevalence of SSLs was 4.0% (95%CI 3.4%–4.8%), with no sex or age group differences. On multivariable analysis, use of LCI (adjusted odds ratio [aOR] 1.63, 95%CI 1.10–2.41), experienced endoscopists (aOR 1.94, 95%CI 1.25–3.00), use of transparent cap (aOR 1.75, 95%CI 1.09–2.81), and longer withdrawal time (aOR 1.06, 95%CI 1.03–1.10) were independently associated with SSL detection. Synchronous adenoma detection (aOR 1.89, 95%CI 1.20–2.99) was also predictive of SSL detection.

Conclusion The prevalence of SSLs in Asia is 4.0%. Use of LCI or a transparent cap, greater endoscopist experience, and longer withdrawal time were all associated with increased SSL detection.

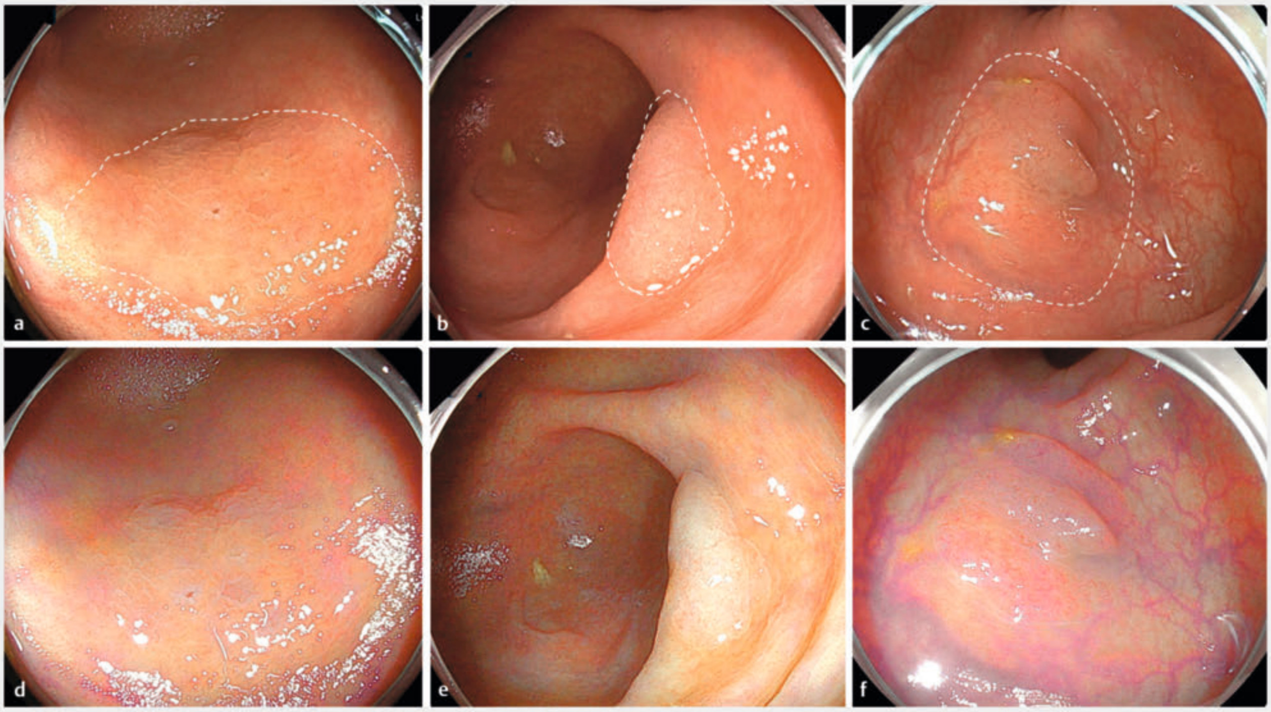
Introduction

The serrated pathway contributes to 15%–30% of colorectal cancer (CRC) and is an important cause of interval CRC [1]. The precursor lesion in the serrated pathway was previously termed a sessile serrated adenoma/polyp (SSA/P). The reported prevalence of SSA/Ps ranged from 5% to 15% [2], with regional differences and lower prevalence in Asia compared with other parts of the world [3]. This prevalence was derived from publications prior to 2018 and used varying terminology for SSA/Ps. Based on the most recent World Health Organization (WHO) 5th edition guideline published in 2019, the term sessile serrated lesion (SSL) is recommended instead of SSA/P, with updated histologic criteria [4]. While an SSA/P was formerly defined as having the presence of at least three abnormal crypts (boot-shaped or anchor-shaped base), the diagnosis of an SSL is made with the presence of only one abnormal crypt [4]. It remains unclear what the prevalence of SSLs is in Asia based on this updated definition. Understanding the prevalence of SSLs will help guide target setting and quality metrics for improving CRC screening.

The detection of SSLs is challenging owing to their subtle endoscopic appearance (pale in color and flat, with indistinct margins and the presence of a mucus cap) and location in the right colon (▶ **Fig. 1**). Whilst linked-color imaging (LCI) has been shown to improve SSL detection based on randomized controlled trials (RCTs) [5, 6], other endoscopic factors that have been associated with higher SSA/P detection include experienced endoscopists [6], endoscopist adenoma detection rate (ADR) [7, 8, 9], and withdrawal time [6, 10]. SSA/P detection has also been associated with synchronous adenoma detection [3, 6, 11, 12] and the presence of hyperplastic polyps (HPPs) [12, 13]. As these studies used the older definition of SSA/Ps and are based on retrospective review of cases, it is uncertain whether the same associations are applicable for SSLs.

Identifying possible endoscopy-related factors associated with increased SSL detection will guide future research to improve the SSL detection rate (SSLDR), as low serrated polyp detection has been shown to be predictive of post-colonoscopy CRC [8, 9, 13]. This is especially relevant in Asia, where the incidence and mortality of CRC is on the rise [14].

With the revised definition of SSLs, improved lesion detection using high definition endoscopes, and heightened awareness of SSLs amongst endoscopists and pathologists, we hypothesize that the true prevalence of SSLs is higher than has been previously reported. Therefore, this post-hoc analysis was performed with the objectives of estimating the prevalence of SSLs in Asia and evaluating the endoscopic factors that are associated with increased SSL detection.



▶ **Fig. 1** Three examples of sessile serrated lesions are shown: **a–c** on white-light endoscopy; **d–f** on linked-color imaging of the same lesions.

Methods

Study design and population

This is a post-hoc analysis of a large multinational RCT that compared the ADR using LCI versus conventional white-light imaging (WLI) [5]. The original study recruited a total of 3050 participants aged 40–89 years who were at average risk of CRC from November 2020 to January 2022. Participants underwent colonoscopy for indications including CRC screening (including fecal immunochemical test [FIT]-positive cases), symptom evaluation, or post-polypectomy surveillance. Those with a previous history of colorectal surgery (excluding appendicectomy), inflammatory bowel disease, or hereditary or nonhereditary polyposis syndrome, or known presence of a colorectal adenoma, polyps, or cancer at the beginning of the trial were excluded. The study involved 11 institutions from four countries in Asia (Japan, Thailand, Taiwan, and Singapore).

All participants who underwent complete colonoscopy, including where performed with the incorrect observation mode or with poor bowel preparation, were included in the study. Participants with missing data, incomplete colonoscopy, or who had their procedure cancelled were excluded from the final analysis.

Colonoscopy procedures

All participants received standard bowel preparation. Colonoscopies were performed by both experienced (≥5000 colonoscopies) and less experienced endoscopists (<5000 colonoscopies), using high definition colonoscopes with either the ELUXEO or LASEREO system. As part of the original trial protocol, half of the participants were randomized to observation by LCI and the other half by WLI. Use of a distal transparent cap or antispasmodic agents, and the choice of polyp removal technique were at the discretion of the endoscopists. The quality of bowel preparation was reported based on the Aronchick Bowel Preparation Scale [15].

Outcomes and definitions

The primary outcomes were the prevalence of SSLs and endoscopic factors associated with SSL detection. The secondary outcomes were the prevalence of clinically significant serrated polyps (CSSPs), HPPs, and proximal HPPs. We also reported on the prevalence of SSLs and CSSPs in patients who underwent index colonoscopy. All histopathologic slides were reviewed by experienced gastrointestinal (GI) pathologists from each institution and were reported according to the most up-to-date WHO 5th edition classification of GI tumors [4]. CSSPs were defined as SSLs, traditional serrated adenomas (TSAs), HPPs ≥10 mm, and HPPs >5 mm that were proximal to the sigmoid colon [16]. Advanced adenomas were defined as being adenomas of ≥10 mm or those with a villous component or high grade dysplasia.

Data source and management

Deidentified datasets were obtained from the University Hospital Medical Information Network Individual Case Data Repository after approval had been received from each participating institution.

The need for patient consent was waived as the analysis was performed on anonymized data that were previously collected as part of study protocol.

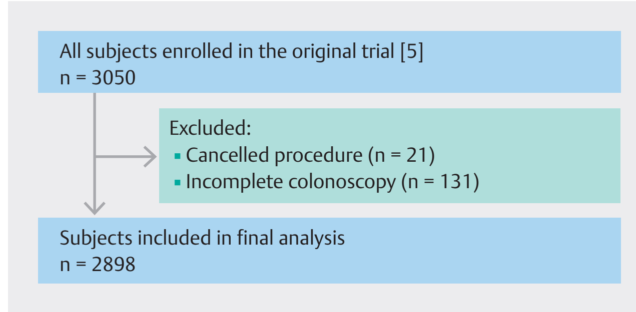
Statistical analysis

Descriptive analysis of baseline demographic and colonoscopy procedure-related characteristics were reported as number (%) for categorical data, mean (SD) for normally distributed data, and median and interquartile range (IQR) for non-normally distributed data. The prevalences of SSLs and other colorectal lesions in the overall study population, grouped by age and sex, were estimated as percentages with corresponding 95%CI. We divided the age groups into <65 and ≥65 years. The differences in prevalence of colorectal lesions between the sexes and the two age groups were assessed using the Pearson's chi-squared test.

Participants were divided into two groups for further analysis based on the detection or not of SSLs. Firth's penalized likelihood logistic regression was used to identify factors associated with the identification of SSLs [17]. We chose this method to avoid small-sample bias and the problem of separation as detecting an SSL is a rare event [18]. Multivariable Firth's logistic regression identified independent factors associated with SSL detection. These factors were determined a priori based on the existing literature for SSA/Ps as: use of LCI, experienced endoscopists, endoscopists' baseline ADR, withdrawal time, bowel preparation quality, and the presence of synchronous adenomas. We also explored possible factors that might increase SSL detection based on clinical expert opinion: use of a transparent cap and use of antispasmodic agents, which may enhance visualization of the colonic mucosa. Simultaneous forced entry of these variables into the multivariable model was performed.

Results were reported as unadjusted odds ratios (ORs) for univariable analysis and adjusted odds ratios (aORs) for multivariable analysis, with corresponding 95% CI. The aORs were converted to the corresponding adjusted risk ratios (aRRs) using the formula detailed by Zhang and Yu [19].

For potential explanatory variables in the multivariable analysis, we performed further analysis to look for evidence of multicollinearity that might induce bias in the analysis. To determine if the log-odds of SSL detection were linearly associated with continuous predictors, we performed a Box–Tidwell test. Where there was evidence of nonlinearity, we used a restricted cubic spline function with three knots at the 10th, 50th, and 90th percentiles to model the relationship between a continuous predictor and SSL detection [20]. To adjust for multiple comparisons, a Bonferroni correction was applied. Given that two novel factors were tested, the two-tailed significance level was adjusted from 0.05 to 0.025. All statistical analyses were conducted using Stata 17 (StataCorp LLC, College Station, Texas, USA).



▶ **Fig. 2** Study flow chart showing the participants excluded from the final analysis.

Results

After the exclusion of 21 participants who had their procedures cancelled and 131 participants with incomplete colonoscopy, a total of 2898 participants were included in the final analysis (▶ **Fig. 2**).

Baseline demographics and procedure-related characteristics

The mean (SD) age of the participants was 64.5 (11.3) years and 57.1% were men (▶ **Table 1**). More than half of the colonoscopies were performed in Japan (n = 1830; 63.1%). There were 1184 index colonoscopies (40.9%) performed, while for 30.6% (n = 888) there was a history of polypectomy. The most common indication for colonoscopy was screening colonoscopy following a positive FIT (n = 657; 22.7%), followed by polyp surveillance (n = 630; 21.7%).

Approximately 90% of patients had excellent or good bowel preparation, and the mean withdrawal time was 8.3 minutes. More than half of the colonoscopies (n = 1746; 60.2%) were performed by experienced endoscopists, with the median baseline ADR being 39% among all endoscopists. A transparent cap was used in more than half of the patients (n = 1766; 60.9%).

A total of 178 SSLs were detected in 117 participants. The clinical and pathologic features of the SSLs are shown in ▶ **Table 2**.

Prevalence of SSLs, CSSPs, HPPs, and proximal HPPs

The prevalence of SSLs in the entire cohort was 4.0% (95%CI 3.4%–4.8%). There were no differences in the prevalence of SSLs between the sexes: 4.1% (95%CI 3.2%–5.1%) in men and 4.0% (95%CI 3.0%–5.3%) in women (**Fig. 1s**, see online-only Supplementary material). The prevalence of SSLs was similar across the two age groups: <65 years (3.6%, 95%CI 2.7%–4.8%) and ≥65 years (4.4%, 95%CI 3.4%–5.6%).

The estimated prevalences of CSSPs, HPPs, and proximal HPPs were 7.6% (95%CI 6.7%–8.6%), 52.9% (95%CI 51.0%–54.7%), and 10.3% (95%CI 9.2%–11.5%), respectively. ▶ **Fig. 3** shows the prevalences of CSSPs, HPPs, and proximal HPPs by age group and sex. The estimated prevalences of SSLs and CSSPs in patients undergoing index colonoscopy were 3.6% (95%CI 2.6%–4.9%) and 7.1% (95%CI 5.7%–8.7%), respectively.

▶ **Table 1** Demographic and procedure-related characteristics of the participants, with comparison of those with and without a sessile serrated lesion (SSL) present.

	All patients (n = 2898)	SSL present (n = 117)	SSL absent (n = 2781)
Demographic characteristic			
Age, mean (SD), years	64.5 (11.3)	64.7 (11.3)	64.4 (11.3)
▪ <65, n (%)	1375 (47.4)	50 (42.7)	1325 (47.6)
Sex, male, n (%)	1655 (57.1)	67 (57.3)	1588 (57.1)
Institution country, n (%)			
▪ Japan (5 institutions)	1830 (63.1)	87 (74.4)	1743 (62.7)
▪ Thailand (3 institutions)	652 (22.5)	11 (9.4)	641 (23.0)
▪ Taiwan (2 institutions)	366 (12.6)	17 (14.5)	349 (12.5)
▪ Singapore (1 institution)	50 (1.7)	2 (1.7)	48 (1.7)
Previous history of colonoscopy, n (%)	1714 (59.1)	74 (63.2)	1640 (59.0)
Previous history of polypectomy, n (%)	888 (30.6)	49 (41.9)	839 (30.2)
Colonoscopy-related characteristics			
Indication for colonoscopy, n (%)			
▪ Positive FIT	657 (22.7)	28 (23.9)	629 (22.6)
▪ Surveillance after polypectomy	630 (21.7)	37 (31.6)	593 (21.3)
Experienced endoscopist, n (%)	1746 (60.2)	85 (72.6)	1661 (59.7)
Endoscopists' baseline ADR, median (IQR), %	39 (15)	40 (12)	39 (15)
Use of antispasmodic agents, n (%)	1809 (62.4)	86 (73.5)	1723 (62.0)
Endoscopy system, n (%)			
▪ ELUXEO	2615 (90.2)	89 (76.1)	2526 (90.8)
▪ LASEREO	283 (9.8)	28 (23.9)	255 (9.2)
LCI observation, n (%)	1451 (50.1)	74 (63.3)	1377 (49.5)
Use of transparent cap, n (%)	1766 (60.9)	86 (73.5)	1680 (60.4)
Withdrawal time, mean (SD), minutes	8.3 (4.4)	9.1 (5.2)	8.3 (4.3)
Bowel preparation, n (%)			
▪ Excellent (≥95% mucosa visible)	1793 (61.9)	61 (52.1)	1732 (62.3)
▪ Good (90%–95% mucosa visible)	804 (27.7)	43 (36.8)	761 (27.4)
▪ Fair (80%–90% mucosa visible)	244 (8.4)	11 (9.4)	233 (8.4)
▪ Poor (<80% mucosa visible)	57 (2.0)	2 (1.7)	55 (2.0)
Clinical findings			
Number of lesions detected at colonoscopy, mean (SD)	1.8 (2.4)	4.6 (4.3)	1.6 (2.2)
Synchronous adenoma detected, n (%)	1532 (52.9)	86 (73.5)	1446 (52.0)
Synchronous advanced adenoma detected, n (%)	347 (12.0)	26 (22.2)	321 (11.5)

FIT, fecal immunochemical test; ADR, adenoma detection rate, IQR, interquartile range; LCI, linked-color imaging.

Figs. 2s and **3s** show the prevalences of SSLs, CCSPs, HPPs, and proximal HPPs according to age in 10-year intervals.

Endoscopic factors associated with SSL detection

In univariable analysis, prior history of polypectomy, experienced endoscopists, endoscopists' baseline ADR, LCI observation, use of a transparent cap, use of antispasmodic agents,

▶ Table 2 Clinical and pathologic features of the 178 sessile serrated lesions (SSLs) detected.

Feature	n (%) unless otherwise stated
Size, median (IQR), mm	7 (4)
Morphology, n (%)	
▪ Nonpolypoid/flat type*	112 (62.9)
▪ Polypoid type†	65 (36.5)
▪ Mixed type‡	1 (0.6)
Location, n (%)	
▪ Ascending colon	49 (27.5)
▪ Sigmoid colon	38 (21.3)
▪ Transverse colon	32 (18.0)
▪ Cecum	24 (13.5)
▪ Rectum	20 (11.2)
▪ Descending colon	15 (8.4)
Type	
▪ SSL without dysplasia	174 (97.8)
▪ SSL with dysplasia	4 (2.2)

IQR, interquartile range.
* Defined as IIa, IIb, IIc, or a laterally spreading tumor.
† Defined as Is, Isp, or Ip.
‡ Defined as IIa + IIc, Is + IIc, or others.

the presence of adenomas, advanced adenomas, and HPPs were predictive of SSL detection (▶ **Table 3**).

In multivariable analysis, use of LCI (aRR 1.60, 95%CI 1.10–2.30), experienced endoscopists (aRR 1.89, 95%CI 1.24–2.84), and transparent cap use (aRR 1.72, 95%CI 1.09–2.68) were independently associated with increased SSL detection. An increase of 1 minute in withdrawal time was associated with 6% higher odds of SSL detection (aRR 1.06, 95%CI 1.03–1.10). The presence of synchronous adenoma (aRR 1.85, 95%CI 1.19–2.86) was also associated with SSL detection.

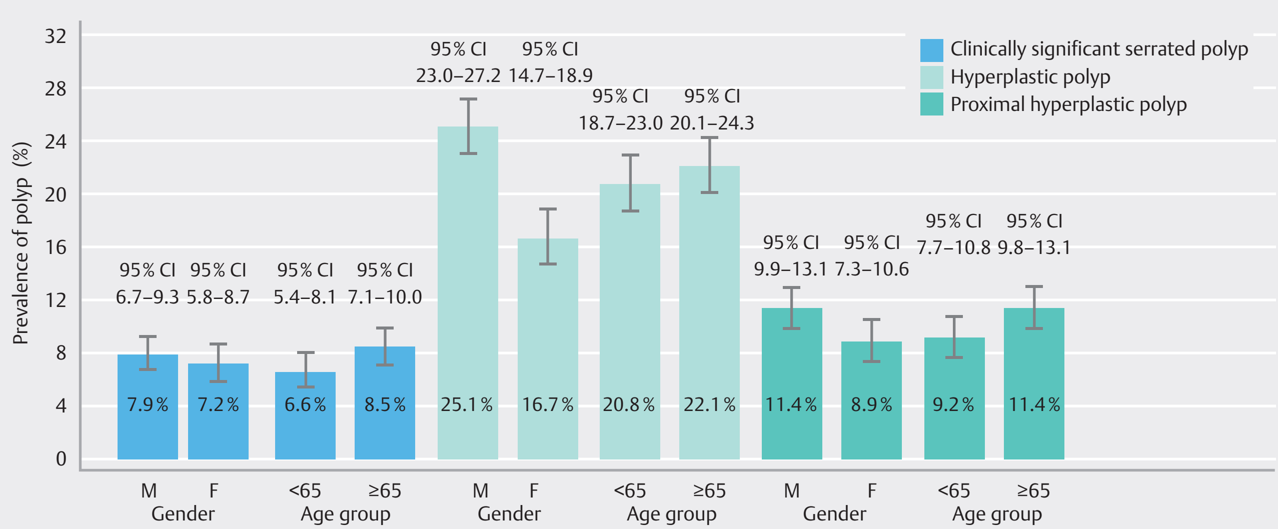
Age, sex, history of polypectomy, endoscopists' baseline ADR, bowel preparation, and the presence of HPPs were not associated with increased odds of SSL detection, after adjustment for the other potential explanatory variables in the model. When tested for multicollinearity, the variance inflation factor was <2 for all variables, suggesting that all included variables appear stable.

As there was evidence of nonlinearity for colonoscopy withdrawal time (Box–Tidwell test, $P = 0.005$), but not endoscopists' ADR before the trial ($P = 0.48$), we modelled the relationship between colonoscopy withdrawal time and SSL detection using restricted cubic splines. This showed an incremental increase in SSL detection with longer withdrawal time, with similar predictors of SSL on multivariable analysis (**Table 1s**, **Figs. 4s** and **5s**).

In the leave-one-out sensitivity analysis, most of the estimated coefficients in the main analysis were not sensitive to any particular endoscopist, except for sex, LCI group, and possibly endoscopists' baseline ADR, which were sensitive to an endoscopist who performed 18.5% of all colonoscopies (**Table 2s**).

Discussion

This is a multicenter study from Asia that reports on the estimated prevalence of SSLs and the endoscopic factors associated with SSL detection based on a post-hoc analysis of an RCT. This is the first large multinational study in Asia that has examined the prevalence of SSLs based on the most up-to-date WHO de-



▶ Fig. 3 Bar chart showing the prevalences of clinically significant serrated polyps, hyperplastic polyps, and proximal hyperplastic polyps by age group and sex. Error bars indicate 95%CI of the prevalence.
M, male; F, female.

▶ **Table 3** Firth's logistic regression of the potential endoscopic factors associated with the detection of sessile serrated lesions.

Variable	Univariable analysis		Multivariable analysis		
	Unadjusted odds ratio (95%CI)	P value	Adjusted odds ratio (95%CI)	P value	Adjusted risk ratio* (95%CI)
Patient demographics					
▪ Age, ≥65 (vs. <65)	1.22 (0.84–1.76)	0.30	0.94 (0.64–1.39)	0.77	0.94 (0.65–1.37)
▪ Sex, female	1.00 (0.69–1.44)	0.98	1.34 (0.91–1.98)	0.14	1.32 (0.91–1.90)
▪ History of polypectomy	1.67 (1.15–2.43)	0.007	1.28 (0.86–1.91)	0.22	1.27 (0.87–1.85)
Colonoscopy-related factors					
▪ Observation mode, LCI (vs. WLI)	1.75 (1.19–2.56)	0.004	1.63 (1.10–2.40)	0.01	1.60 (1.10–2.31)
▪ Endoscopist, experienced† (vs. less experienced)	1.77 (1.18–2.68)	0.006	1.93 (1.25–2.98)	0.003	1.89 (1.24–2.84)
▪ Pre-trial endoscopist ADR‡	1.03 (1.01–1.04)	0.002	1.02 (1.00–1.04)	0.02	1.02 (1.00–1.04)
▪ Antispasmodic agent use	1.69 (1.11–2.55)	0.01	1.23 (0.78–1.93)	0.37	1.22 (0.79–1.88)
▪ Use of transparent cap	1.80 (1.19–2.73)	0.005	1.78 (1.12–2.82)	0.02	1.72 (1.09–2.68)
▪ Colonoscopy withdrawal time§	1.03 (1.00–1.06)	0.03	1.06 (1.03–1.10)	<0.001	1.06 (1.03–1.10)
▪ BPS, good/excellent (vs. poor/fair)	0.90 (0.50–1.60)	0.71	1.06 (0.57–1.99)	0.85	1.06 (0.58–1.91)
Clinical factors					
▪ Synchronous adenoma	2.54 (1.67–3.84)	<0.001	1.89 (1.20–2.99)	0.006	1.85 (1.19–2.86)
▪ Synchronous advanced adenoma	2.22 (1.42–3.47)	<0.001	1.49 (0.91–2.44)	0.11	1.46 (0.91–2.31)
▪ Synchronous hyperplastic polyp	1.74 (1.17–2.60)	0.006	1.41 (0.93–2.12)	0.10	1.39 (0.94–2.04)

WLI, white-light imaging; LCI, linked-color imaging; ADR, adenoma detection rate; BPS, bowel preparation scale.
* Converted from adjusted odds ratios using the formula in Zhang and Yu [19].
† ≥5000 colonoscopy cases.
‡ Per additional 1% increase in ADR.
§ Per additional minute of withdrawal time.

finition of SSLs. This study included high quality colonoscopy that fulfilled the key colonoscopy quality indicators (split-dose bowel preparation, and only 2% of patients with poor bowel preparation) [21], with 60% of cases performed by experienced endoscopists and a high overall ADR of 52.9% among all participants in the RCT. In addition, the resected specimens were examined by specialized GI pathologists using uniform and the most up-to-date histologic criteria for SSLs. All of these factors allowed us to give a better estimate of the prevalence of SSLs.

Based on our study, the estimated prevalence of SSLs in Asia is 4.0% (95%CI 3.8%–4.6%), which is higher and more precise than what has been previously reported [3]. In the most recently published meta-analysis on SSLs, the prevalence of SSLs was 2.6% in Asia, with a wide confidence interval and poor precision [3]. There are multiple reasons that may account for this observation. High quality colonoscopy, dedicated GI histopathologists, and alternative definitions of more clinically relevant serrated polyps have been shown to detect a higher mean prevalence of SSLs [3, 12]. In addition, half of the patients underwent colonoscopy using LCI, which increases SSL detection up to 1.99-fold compared with WLI [5, 6].

A key finding from our study is the prevalence of CSSPs in Asia, which we estimate to be 7.6% (95%CI 6.7%–8.6%). A recent study showed that the CSSP detection rate is associated with post-colonoscopy CRC, with a rate of at least 7% being proposed as a quality measurement for endoscopy [8]. Data on CSSPs in Asia are lacking and more studies are needed to determine whether the same cutoff as used in the West is applicable in Asia.

We did not observe any differences in SSL prevalence relating to sex and age, which is in keeping with previous studies [3, 14]. We categorized patients into two age groups using a cutoff of 65 years because a recent territory-wide case–control study from Hong Kong showed that age ≥66 years and male sex were independent risk factors for the presence of SSLs [22].

Our findings of increased odds of SSL detection for experienced endoscopists (aRR 1.89, 95%CI 1.24%–2.84%) and for each minute increase in withdrawal time (aRR 1.06, 95%CI 1.03%–1.10%) concurred with a subgroup analysis from another recent RCT from China [6], albeit using a different definition of experienced endoscopists, with our study using a higher cutoff for experienced endoscopists (>5000 vs. >500 colonoscopies in the previous study). Although the currently recommended minimum withdrawal time is 6 minutes for negative-result screening colonoscopies [21], longer withdrawal times beyond 6 minutes have been shown to have incremental bene-

Tan ChinKimg et al. Sessile serrated lesion … Endoscopy 2024; 56: 684–693

fit on ADR [23, 24, 25], and are associated with reduced risk of interval CRC [23]. While a recent tandem RCT showed a higher ADR with a withdrawal time of 9 minutes versus 6 minutes, the study did not find a significant difference in terms of SSL detection between the two withdrawal times [24], although the study was limited by the small number of SSLs detected (only 11 among 733 participants).

While the impact of withdrawal time on ADR is well established, we have demonstrated a similar incremental benefit of longer withdrawal time on SSL detection (**Figs. 4s** and **5s**). Withdrawal time varies depending on bowel preparation and may be longer in the presence of SSLs, as SSLs may be masked by a mucus cap. Rather than adhering to minimum withdrawal times, clinicians should ensure adequate mucosal visualization and detection of SSLs, especially in the presence of synchronous adenomas, which increase the odds of SSL detection (aRR 1.85, 95%CI 1.19%–2.86%) [3, 11, 12].

We did not observe any clinically meaningful effect of endoscopists' baseline ADR on the SSL detection rate on multivariable analysis (aRR 1.02, 95%CI 1.00%–1.04%), which contrasts with earlier studies [7, 8, 9]. When we performed additional analysis for CSSPs (**Table 3s**), there was no change in our findings. The high baseline ADR of the endoscopists in our study (median ADR 39%; compared with a minimum recommended ADR of 30% in men [21]) may explain the lack of association between incremental ADR increase and SSL detection in our study.

In addition, we did not notice any significant difference in the SSL detection rate for patients with suboptimal bowel preparation (fair/poor bowel preparation), which is contrary to earlier study findings [26, 27]. There are two reasons that may account for this discrepancy. First, almost 90% of patients in our study had optimal bowel preparation (excellent/good), with the proportions of those with optimal bowel preparation being similar for both groups. Second, more than half of the colonoscopies were performed by experienced endoscopists who had a high baseline ADR.

This is the first study that supports the use of a transparent cap to increase SSL detection. Whilst a marginal improvement in ADR using a distal cap attachment has been reported [28], a similar effect was not shown for SSA/Ps based on meta-analysis of 1427 cases of cap-assisted colonoscopy (CAC) from three RCTs [29]. Our study included a large number of CACs (n = 1766), and after adjusting for other possible confounders of SSL detection, CAC was found to increase the odds of SSL detection by 72% (aRR 1.72, 95%CI 1.09%–2.68%).

Thus far, there has been no prospective study that is powered to detect a difference in the SSL detection rates for CAC and conventional colonoscopy. This is a potential area that could be explored as CAC may improve mucosal visualization and the benefits of CAC on polyp detection have predominantly been observed in Asia [24]. On further exploratory analysis, the effect of transparent cap use on SSL detection was found to be accentuated in the transverse, descending, and sigmoid colon, and the rectum (**Table 4s**). Furthermore, it remains unclear how CAC performs compared with second-generation distal assistive devices, which have shown conflicting data with regard to improving serrated polyp detection [30, 31].

There were some limitations to our study. We would like to stress that the measured prevalence is an estimate; the true prevalence of SSLs may have been underestimated as LCI was not used in all cases and there was no central reporting of SSLs. While we strived to have accurate histopathologic reporting by limiting the reporting to a specialized GI pathologist in each center, there is known variation in pathologist reporting of serrated polyps [32, 33]. We attempted to overcome this limitation by including the prevalence of CSSPs, which include proximal HPPs of 5–9 mm in size that may have been SSLs.

There is known regional and racial variation in SSL prevalence, with Asians often grouped under one umbrella [3, 6]. As the proportions of cases from each country were not equal, we were unable to obtain a good estimate of the prevalence in each country or to report the regional differences within Asia. A recent multicenter RCT from China reported an SSL detection rate of 11.3% in the LCI group versus 5.9% in the WLI group, with a hazard ratio of 1.99 (95%CI 1.20–3.29; $P = 0.007$) [13]. The overall SSL prevalence was approximately 8.6% in their cohort of patients who underwent index colonoscopy. The higher SSL prevalence in that study compared with our study population may be driven by geographic variation, race, or exposure to different risk factors for SSLs. This hypothesis is supported by the epidemiologic trend of increasing incidence of CRC in China, as opposed to in Japan [14]. In addition, our study also included patients with prior colonoscopy and polypectomy, which may have contributed to a lower prevalence rate compared with the Chinese study, although the SSL prevalence of those with index colonoscopy was similar to the overall cohort and, on multivariable analysis, previous polypectomy did not have any impact on SSL detection.

In our study population, SSLs remained rare, which might have led to small-sample bias. An attempt was made to overcome this bias using Firth's logistic regression and testing for multicollinearity, but we are unable to exclude this as a possibility. As we included colonoscopies performed for disparate indications (screening, polyp surveillance, and symptom evaluation), this may have a potential impact on the endoscopic factors associated with SSL detection. We attempted to address this concern by performing exploratory analysis based on the indication for colonoscopy; however, power is a challenge in these subgroup analyses, with greater risk for small-sample bias. Based on our subgroup analyses, some of the coefficients varied greatly depending on the aim of the colonoscopy (**Table 5s**). Furthermore, as this was a post-hoc analysis of an RCT, we were unable to evaluate the potential confounding effects of race [6, 11], smoking [11, 21], diabetes, and elevated body mass index [21], which have all been associated with an increased risk of SSL.

The beneficial effect of LCI may not be replicable without high quality colonoscopic examination, particularly adequate bowel preparation. Despite the lack of association between ADR and SSL detection in our study, this may not be generalizable to less experienced endoscopists and those with lower baseline ADRs. Similarly, although we did not note an association between bowel preparation and SSL detection, mucosal visibility is key to identifying SSLs. In addition, although we did not note any association between the use of antispasmodic agents and SSL detection, there was insufficient power to determine this conclusively owing to sample size limitation.

In conclusion, the prevalence of SSLs in Asia is 4%. Prospective studies evaluating the prevalence of SSLs based on the updated histologic definition and performing high quality colonoscopy are required to improve the estimates of SSL prevalence in different regions of the world. Use of a distal cap attachment and LCI improve SSL detection, but the key to improving SSL detection still remains careful examination of the colon, with adequate mucosal exposure and withdrawal time, and good bowel preparation.

Conflict of Interest

S. Suzuki, T.L. Ang, H.-M. Chiu, and C.-Y. Kuo have received lecture fees from Fujifilm Corporation. T. Gotoda has received lecture fees from Fujifilm Corporation and Fujifilm Medical Co. Ltd. N. Yoshida and T. Takezawa have received research grants from Fujifilm Corporation. C.K. Tan, X.H. Koh, L.M. Wang, S. Aniwan, K. Laohavichitra, S. Chirapongsathorn, T. Yamamura, R. Rerknimitr, and H. Ishikawa declare that they have no conflict of interest.

References

[1] East JE, Atkin WS, Bateman AC et al. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. Gut 2017; 66: 1181–1196 doi:10.1136/gutjnl-2017-314005

[2] Crockett SD, Nagtegaal ID. Terminology, molecular features, epidemiology, and management of serrated colorectal neoplasia. Gastroenterology 2019; 157: 949–966.e4 doi:10.1053/j.gastro.2019.06.041

[3] Meester RGS, van Herk MMAGC, Lansdorp-Vogelaar I et al. Prevalence and clinical features of sessile serrated polyps: a systematic review. Gastroenterology 2020; 159: 105–118.e25 doi:10.1053/j.gastro.2020.03.025

[4] Nagtegaal ID, Odze RD, Klimstra D et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020; 76: 182–188 doi:10.1111/his.13975

[5] Suzuki S, Aniwan S, Chiu HM et al. Linked-color imaging detects more colorectal adenoma and serrated lesions: an international randomized controlled trial. Clin Gastroenterol Hepatol 2023; 21: 1493–1502.e4

[6] Li J, Zhang D, Wei Y et al. Colorectal sessile serrated lesion detection using linked color imaging: a multicenter, parallel randomized controlled trial. Clin Gastroenterol Hepatol 2023; 21: 328–336.e2

[7] Kahi CJ, Hewett DG, Norton DL et al. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. Clin Gastroenterol Hepatol 2011; 9: 42–46

[8] Anderson JC, Hisey W, Mackenzie TA et al. Clinically significant serrated polyp detection rates and risk for postcolonoscopy colorectal cancer: data from the New Hampshire Colonoscopy Registry. Gastrointest Endosc 2022; 96: 310–317

[9] van Toledo DEFWM, IJspeert JEG, Bossuyt PMM et al. Serrated polyp detection and risk of interval post-colonoscopy colorectal cancer: a population-based study. Lancet Gastroenterol Hepatol 2022; 7: 747–754

[10] de Wijkerslooth TR, Stoop EM, Bossuyt PM et al. Differences in proximal serrated polyp detection among endoscopists are associated with variability in withdrawal time. Gastrointest Endosc 2013; 77: 617–623

[11] Li D, Woolfrey J, Jiang SF et al. Diagnosis and predictors of sessile serrated adenoma after educational training in a large, community-based, integrated healthcare setting. Gastrointest Endosc 2018; 87: 755–765.e1

[12] Crockett SD, Barry EL, Mott LA et al. Predictors of incident serrated polyps: results from a large multicenter clinical trial. Cancer Epidemiol Biomarkers Prev 2022; 31: 1058–1067

[13] Li D, Doherty AR, Raju M et al. Risk stratification for colorectal cancer in individuals with subtypes of serrated polyps. Gut 2022; 71: 2022–2029

[14] Onyoh EF, Hsu WF, Chang LC et al. The rise of colorectal cancer in Asia: epidemiology, screening, and management. Curr Gastroenterol Rep 2019; 21: 36 doi:10.1007/s11894-019-0703-8

[15] Aronchick CA, Lipshutz WH, Wright SH et al. Validation of an instrument to assess colon cleansing. Am J Gastroenterol 1999; 94: 2667

[16] Anderson JC, Butterly LF, Weiss JE et al. Providing data for serrated polyp detection rate benchmarks: an analysis of the New Hampshire Colonoscopy Registry. Gastrointest Endosc 2017; 85: 1188–1194 doi:10.1016/j.gie.2017.01.020

[17] Firth D. Bias reduction of maximum likelihood estimates. Biometrika 1993; 80: 27–38

[18] Heinze G, Schemper M. A solution to the problem of separation in logistic regression. Stat Med 2002; 21: 2409–2419 doi:10.1002/sim.1047

[19] Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes JAMA 1998; 280: 1690–1691 doi:10.1001/jama.280.19.1690

[20] Harrell FEJr. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. New York: Springer; 2001

[21] Rex DK, Schoenfeld PS, Cohen J et al. Quality indicators for colonoscopy. Gastrointest Endosc 2015; 81: 31–53 doi:10.1016/j.gie.2014.07.058

[22] Lui RN, Kyaw MH, Lam TYT et al. Prevalence and risk factors for sessile serrated lesions in an average risk colorectal cancer screening population. J Gastroenterol Hepatol 2021; 36: 1656–1662 doi:10.1111/jgh.15368

[23] Shaukat A, Rector TS, Church TR et al. Longer withdrawal time is associated with a reduced incidence of interval cancer after screening colonoscopy. Gastroenterology 2015; 149: 952–957

[24] Zhao S, Yang X, Wang S et al. Impact of 9-minute withdrawal time on the adenoma detection rate: a multicenter randomized controlled trial. Clin Gastroenterol Hepatol 2022; 20: e168–e181 doi:10.1016/j.cgh.2020.11.019

[25] Desai M, Rex DK, Bohm ME et al. Impact of withdrawal time on adenoma detection rate: results from a prospective multicenter trial. Gastrointest Endosc 2023; 97: 537–543.e2

[26] Zhou MJ, Lebwohl B, Krigel A. Patient and physician factors associated with adenoma and sessile serrated lesion detection rates. Dig Dis Sci 2020; 65: 3123–3131 doi:10.1007/s10620-020-06419-8

[27] Clark BT, Laine L. High-quality bowel preparation is required for detection of sessile serrated polyps. Clin Gastroenterol Hepatol 2016; 14: 1155–1162 doi:10.1016/j.cgh.2016.03.044

[28] Ng SC, Tsoi KK, Hirai HW et al. The efficacy of cap-assisted colonoscopy in polyp detection and cecal intubation: a meta-analysis of randomized controlled trials. Am J Gastroenterol 2012; 107: 1165–1173 doi:10.1038/ajg.2012.135

[29] Nutalapati V, Kanakadandi V, Desai M et al. Cap-assisted colonoscopy: a meta-analysis of high-quality randomized controlled trials. Endosc Int Open 2018; 6: E1214–E1223 doi:10.1055/a-0650-4258

[30] Patel HK, Chandrasekar VT, Srinivasan S et al. Second-generation distal attachment cuff improves adenoma detection rate: meta-analysis of randomized controlled trials. Gastrointest Endosc 2021; 93: 544–553.e7

[31] Verheyen E, Castaneda D, Gross SA et al. Increased sessile serrated adenoma detection rate with mechanical new technology devices: a systematic review and meta-analysis. J Clin Gastroenterol 2021; 55: 335–342 doi:10.1097/MCG.0000000000001363

[32] Gourevitch RA, Rose S, Crockett SD et al. Variation in pathologist classification of colorectal adenomas and serrated polyps. Am J Gastroenterol 2018; 113: 431–439 doi:10.1038/ajg.2017.496

[33] Keswani RN, Crockett SD, Calderwood AH. AGA clinical practice update on strategies to improve quality of screening and surveillance colonoscopy: expert review. Gastroenterology 2021; 161: 701–711 doi:10.1053/j.gastro.2021.05.041