Prevalence and predictive factors of colorectal sessile serrated lesions in younger individuals

OPEN ACCESS

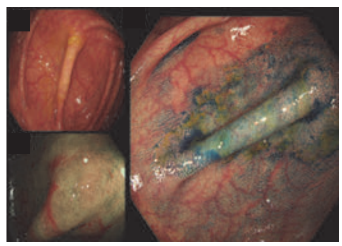
GRAPHICAL ABSTRACT

Colorectal sessile serrated lesions (SSLs) in patients under 50

Retrospective study
- Index colonoscopy
- 2018–2022
- E-Da DaChang Hospital, Taiwan

9854 individuals

Younger (20–49 years) n = 4712	**Older** (≥50 years) n = 5142



	<50	≥50	*P* value
Adenoma	23%	46%	<0.001
SSL	7.2%	6.5%	0.16

Predictive factors for SSLs in <50s
- **Age 40–49** (OR 1.81)
- **Withdrawal time** (OR 1.17, per minute)
- **Endoscopist** (OR 3.35, high vs. average performer)

SSLs are NOT uncommon in people aged under 50

Endoscopy

Authors

Jen-Hao Yeh[1,2], Chih-Wen Lin[3], Po-Jen Hsiao[2], Daw-Shyong Perng[3], Jen-Chieh Chen[4], Kuo-Tung Hung[2], Chia-Chang Hsu[4], Chia-Chi Chen[5], Yu-Peng Liu[1,6], Yi-Chia Lee[7], Jaw-Yuan Wang[1,8,9]

Institutions

1 Graduate Institute of Clinical Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
2 Division of Gastroenterology and Hepatology, Department of Internal Medicine, E-Da DaChang Hospital, I-Shou University, Kaohsiung, Taiwan
3 Division of Gastroenterology and Hepatology, Department of Internal Medicine, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan
4 Department of Health Examination, E-Da Hospital, I-Shou University, Kaohsiung , Taiwan
5 Department of Pathology, E-Da Hospital, I-Shou University, Kaohsiung , Taiwan
6 Research Center for Environmental Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
7 Division of Gastroenterology and Hepatology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
8 Department of Surgery , Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
9 Center for Cancer Research, Kaohsiung Medical University, Kaohsiung, Taiwan

received 15.10.2023
accepted after revision 16.2.2024
accepted manuscript online 20.2.2024
published online 4.4.2024

Bibliography
Endoscopy 2024; 56: 494–502
DOI 10.1055/a-2272-1911
ISSN 0013-726X

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

Supplementary Material
Supplementary Material is available under https://doi.org/10.1055/a-2272-1911

Scan this QR-Code for the author commentary.

Corresponding author
Jaw-Yuan Wang, MD, PhD, Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, No. 100 Tzyou 1st Road, Kaohsiung 807, Taiwan
jawyuanwang@gmail.com

ABSTRACT

Background Sessile serrated lesions (SSLs) are obscured lesions predominantly in the right-sided colon and associated with interval colorectal cancer; however, their prevalence and risk factors among younger individuals remain unclear.

Methods This retrospective study enrolled individuals who underwent index colonoscopy. The primary outcome was the SSL prevalence in the younger (<50 years) and older (≥50 years) age groups, while the secondary outcomes included clinically significant serrated polyps (CSSPs). Multivariable logistic regression was employed to identify predictors.

Results Of the 9854 eligible individuals, 4712 (47.8%) were categorized into the younger age group. Individuals in the younger age group exhibited lower prevalences of adenomas (22.6% vs. 46.2%; P<0.001) and right-sided adenomas (11.2% vs. 27.2%; P<0.001) compared with their older counterparts. However, both groups exhibited a similar prevalence of SSLs (7.2% vs. 6.5%; P = 0.16) and CSSPs (10.3% vs. 10.3%; P = 0.96). Multivariable analysis revealed that age 40–49 years (odds ratio [OR] 1.81, 95%CI 1.01–3.23), longer withdrawal time (OR 1.17, 95%CI 1.14–1.20, per minute increment), and endoscopist performance (OR 3.35, 95%CI 2.44–4.58) were independent predictors of SSL detection in the younger age group. No significant correlation was observed between adenoma and SSL detection rates among endoscopists.

Conclusion SSLs are not uncommon among younger individuals. Moreover, diligent effort and expertise are of paramount importance in SSL detection. Future studies should explore the clinical significance of SSLs in individuals of younger age.

Introduction

Colorectal cancer (CRC) consistently ranks as a prominent malignancy in developed countries [1, 2, 3]. The majority of CRC cases originate from adenomatous polyps; however, nearly 10%–15% of CRC cases have a different origin, stemming from a distinct premalignant lesion known as a sessile serrated lesion (SSL) [4, 5]. Unlike conventional adenomas, SSLs tend to be located in the right-sided colon, exhibit a flat and obscure appearance, and are often covered by mucus (▶ **Fig. 1**) [6, 7, 8]. These characteristics can pose challenges in their detection through the current screening tools, potentially leading to screening failure [9, 10, 11]. Moreover, under-detection of SSLs may be associated with the development of subsequent interval CRCs [12, 13].

The natural progression of SSLs is characterized by an indolent course, often taking more than 10–15 years to advance to cytologic dysplasia and ultimately malignant transformation [14, 15, 16]. Progressive promoter hypermethylation, a prerequisite for SSL carcinogenesis, becomes more pronounced with advanced age [17]. Interestingly, research has indicated that serrated CRCs are relatively rare in younger patients [18, 19]. Nevertheless, whether this rarity in younger age groups is attributable to the infrequency of SSLs in this population or is a consequence of the gradual and indolent nature of the carcinogenesis process remains an unresolved question.

A systematic review indicated that the combined overall prevalence of SSLs was 4.6%, with only a modest increase with advancing age compared with conventional adenomas [6]; however, this review did not include individuals aged under 50 owing to the lack of available data. Until recently, most CRC screening programs and databases have focused on the “average risk population,” typically aged ≥50 years. Therefore, it is imperative to determine the true prevalence of SSLs and the proportion of cases with cytologic dysplasia among younger individuals to gain a more comprehensive understanding of SSLs in early onset CRC.

▶ **Fig. 1** Endoscopic images of a large sessile serrated lesion at the hepatic flexure showing on: **a** white-light imaging, a thick fold covered by mucus; **b** narrow-band imaging, a cloudy surface pattern with lacy vessels; **c** chromoendoscopy with indigo carmine spray, the border of the whole lesion now clearly visualized.

At present, only a few studies have explored the prevalence of SSLs in this younger age group [20, 21]; however, in their results, SSLs were mixed with other types of lesions such as hyperplastic polyps (HPPs), and neither of the studies identified clinical risk factors in this population. Therefore, our study aimed to address this research gap by examining the prevalence of SSLs and identifying any potential clinical risk factors associated with SSLs in younger individuals. During 2018–2022, our institute achieved a noteworthy SSL detection rate of 7.1% through index colonoscopies, which is higher than that achieved in historically pooled data [6] and meets the conventionally stipulated detection benchmark [22]. The present study aimed to explore the prevalence of SSLs and determine the potential clinical risk factors for SSLs in younger individuals.

Methods

Study design

This retrospective single-center study analyzed colonoscopy records obtained from outpatient services and health check-up services at E-Da Dachang Hospital. The data were collected between June 2018 and June 2022. E-Da Dachang Hospital, established in 2016 in downtown Kaohsiung, served as the primary source of these records. The study protocol was approved by the institutional review board of our institute (No. EMRP111149).

The study included individuals aged ≥20 years who underwent a complete index colonoscopy. Individuals who visited outpatient services were mostly symptomatic, eligible for screening colonoscopy, or had had abnormal fecal/tumor marker test results. Additionally, asymptomatic individuals who underwent health check-ups at their own expense or who adhered to national labor law requirements were included. The exclusion criteria were as follows: (i) duplicated cases owing to prior colonoscopy examinations; (ii) inadequate bowel preparation; (iii) history of hospitalization or colonoscopy as part of an emergency room visit; (iv) unsuccessful cecal intubation or flexible sigmoidoscopy; (v) suspicion of or confirmed inflammatory bowel disease. Notably, individuals who had previously undergone colonoscopy at other hospitals, as confirmed by their electronic medical records or chart review, were also excluded.

Eligible individuals were subsequently classified into two groups: a younger age group (20–49 years) and an older age group (>50 years).

Colonoscopy procedures and histologic evaluation

All colonoscopies in this study were performed by experienced endoscopists who had conducted >500 colonoscopy procedures annually, with ≥300 diagnostic or therapeutic procedures. The EvisLucera CV-290 colonoscope (Olympus Medical Systems, Tokyo, Japan) was used. Patients received bowel preparation regimens that included split-dose sodium phosphate, sodium picosulfate/magnesium citrate, or same-day polyethylene glycol solution. During the examinations, the decision to perform a biopsy, snare polypectomy, or endoscopic mucosal resection for a colorectal neoplasm was made at the discretion of the endoscopist. In cases involving difficult-to-treat polyps, subsequent endoscopic or surgical resection was performed within 6 months following the index colonoscopy.

The final histologic diagnosis was based on the results from both the index colonoscopy and the subsequent analysis; however, polyps and lesions that were not removed within 6 months of the index colonoscopy were excluded from the analysis, regardless of the initial endoscopic diagnosis. A total of 10 pathologists involved in the histologic evaluation in the study period. All of the lesions included in this study were confirmed through histologic evaluation by the on-duty pathologist in our hospital.

Outcome assessment

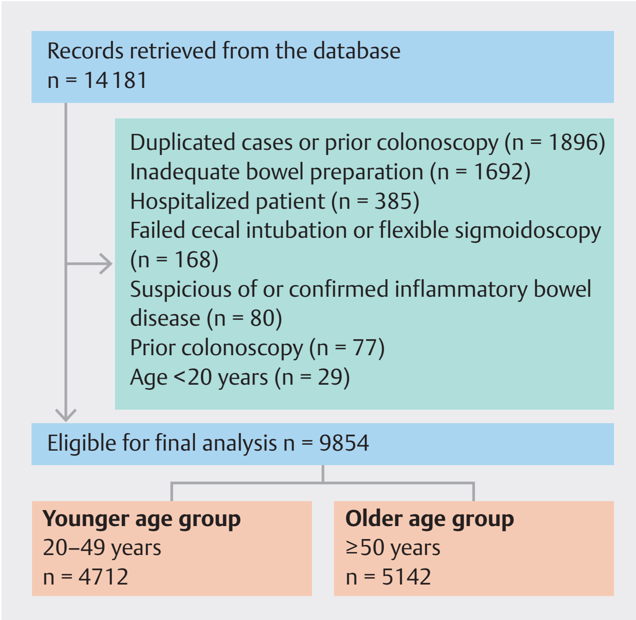
The primary outcome of this study was SSL prevalence. The secondary outcomes were the prevalences of SSLs with cytologic dysplasia, clinically significant serrated polyps (CSSPs), and the detection rate of right-sided HPPs. CSSPs were defined as the combination of: (i) SSLs; (ii) traditional serrated adenomas; and (iii) any HPP ≥1 cm in the left-sided colon or ≥0.5 cm in the right-sided colon [22]. Additional auxiliary outcomes included the prevalences of adenomas, advanced adenomas, and CRC. Advanced adenomas were characterized by polyps meeting one of the following criteria: (i) high grade dysplasia, carcinoma in situ, or intramucosal carcinoma; (ii) a size of ≥1 cm; or (iii) containing >25% villous component. The right-sided colon refers to the cecum, ascending colon, and transverse colon.

Various baseline and endoscopic characteristics, including age, sex, use of intravenous anesthesia, withdrawal time, bowel preparation status, and any family history of CRC, were recorded for predictive factor analysis. Adequate bowel preparation was defined as excellent or good based on the Aronchick scale [23]. The definitions of metabolic disease including obesity, metabolic syndrome, hypertension, diabetes mellitus, and fatty liver disease were described according to our previous article [24] (**Appendix 1s**, see online-only Supplementary material).

Statistical analysis

In this study, continuous variables were compared using Student's *t* test and are presented as mean (SD). Categorical variables were compared using the chi-squared test and are presented as frequency (percentage). $P < 0.05$ indicated statistical significance. To compare the primary outcomes, odds ratios (ORs) and their corresponding 95%CIs were calculated. All statistical analyses were conducted using SPSS version 22.0 (IBM, Armonk, New York, USA).

To evaluate the predictors of SSLs in the younger age group, we considered several variables, including age, sex, any family history of CRC, presence of symptoms (abdominal pain, bowel habit changes, or hematochezia), the proportion of positive fecal immunochemical tests, the use of intravenous anesthesia, colonoscopy withdrawal time, and the presence of relevant neoplasms. Significant variables in the univariable analyses were included in the multivariable binary logistic regression model using the enter method. Subsequently, the significant variables were subjected to validation and sensitivity analysis using data from the older age group. To further examine the



▶ **Fig. 2** Flowchart of participant inclusion and exclusion in the study.

potential correlation between variables, we employed a two-sided partial correlation analysis using SPSS software.

Results

Study participants and baseline characteristics

In all, 14 181 records were initially retrieved from the database. A flowchart of the participant selection process is presented in ▶ **Fig. 2**. Following the application of the exclusion criteria, a final cohort of 9854 individuals (51.5% women) was eligible for the analysis. Within this cohort, 4712 and 5142 individuals belonged to the younger and older age groups, respectively.

The baseline characteristics of each group are summarized in ▶ **Table 1**. The younger and older age groups had mean ages of 39.7 and 61.3 years, respectively. A larger proportion of individuals in the younger age group underwent colonoscopy as part of a health check-up compared with the older age group (47.6% vs. 24.3%; P < 0.001). Compared with those in the younger age group, a significantly higher proportion of individuals in the older age group had adenomas (46.2% vs. 22.6%; P <0.001), advanced adenomas (14.2% vs. 4.0%; P <0.001), and CRC (1.4% vs. 0.4%; P <0.001). A significantly longer mean (SD) withdrawal time (9.4 [5.3] vs. 7.5 [3.5] minutes; P <0.001) and mean (SD) number of adenomas (0.7 [1.0] vs. 0.3 [0.6]; P <0.001) were also found in the older age group. The detection rate of SSLs however was similar in the two groups (6.5% vs. 7.2%; P=0.16). Furthermore, the older age group exhibited a nearly twofold higher occurrence of cytologic dysplasia, although this difference did not reach statistical significance (5.1% vs. 2.6%; P=0.10). Similarly, the prevalence of CSSPs was comparable between the two groups (10.3% vs. 10.3%; P= 0.96).

▶ **Table 1** Baseline demographic and endoscopic characteristics of the two age cohorts.

	Younger age group (<50 years)	Older age group (≥50 years)	*P* value
Cases, n (%)	4712 (47.8)	5142 (52.1)	–
Cases from health check-up, n (%)	2242 (47.6)	1248 (24.3)	**<0.001**
Symptomatic cases, n (%)	1985 (42.1)	2763 (53.7)	**<0.001**
Age, mean (SD)	39.7 (6.4)	61.3 (8.0)	**<0.001**
Sex, female, n (%)	2425 (51.5)	2649 (51.5)	0.96
Family history of CRC, n (%)	318 (6.7)	164 (3.2)	**<0.001**
Intravenous anesthesia used, n (%)	3875 (82.2)	3579 (69.6)	**<0.001**
Withdrawal time, mean (SD), minutes	7.5 (3.5)	9.4 (5.3)	**<0.001**
Adenomas, n (%)	1063 (22.6)	2375 (46.2)	**<0.001**
Advanced adenomas, n (%)	188 (4.0)	728 (14.2)	**<0.001**
Right-sided adenomas, n (%)	526 (11.2)	1399 (27.2)	**<0.001**
Right-sided advanced adenoma, n (%)	63 (1.3)	336 (6.5)	**<0.001**
Adenoma numbers, mean (SD)	0.3 (0.6)	0.7 (1.0)	**<0.001**
CRCs, n (%)	19 (0.4)	72 (1.4)	**<0.001**
SSLs, n (%)	341 (7.2)	335 (6.5)	0.16
SSLDs, n (%)	9 (0.2)	17 (0.3)	0.18
SSLD among SSLs, n (%)	9 (2.6)	17 (5.1)	0.10
Right-sided HPPs, n (%)	181 (3.8)	243 (4.7)	**0.03**
Traditional serrated adenomas, n (%)	8 (0.2)	21 (0.4)	**0.03**
CSSPs, n (%)	485 (10.3)	531 (10.3)	0.96
CSSP numbers, mean (SD)	0.1 (0.4)	0.1 (0.4)	0.55

CRC, colorectal cancer; SSL, sessile serrated lesion; SSLD, SSL with dysplasia; HPP, hyperplastic polyp; CSSP, clinically significant serrated polyp.

Clinical features of outpatient versus health check-up cases in the younger age group

Nearly half (47.6%) of the younger individuals underwent colonoscopy as part of a health check-up service, and their clinical characteristics are further detailed in ▶ **Table 2**. Compared with those who underwent health check-ups, younger individuals who visited the outpatient service were less likely to have had intravenous anesthesia used (69.0% vs. 96.8%; *P*<0.001) and a positive fecal occult blood test (0.5% vs. 7.2%; *P*<0.001). No significant differences in age and sex were observed between the two subgroups.

Younger individuals who visited the outpatient service had lower risks of overall adenomas (20.7% vs. 24.6%; *P* = 0.001) and right-sided adenomas (8.8% vs. 13.8%; *P*<0.001), but greater risks of advanced adenomas (4.7% vs. 3.2%; *P* = 0.009) and CRC (0.6% vs. 0.1%; *P* = 0.005). The younger outpatients also had a lower rate of SSLs (5.4% vs. 9.3%; *P*<0.001), right-sided HPPs (2.8% vs. 5.0%; *P* < 0.001), and CSSPs (7.8% vs. 13.1%; *P* <0.001), and a slightly longer mean (SD) withdrawal time (7.7 [3.8] vs. 7.4 [3.0] minutes; *P*<0.001) compared with those who underwent health check-ups. The proportion of SSLs with cytologic dysplasia was similar in the two subgroups (3.8% vs. 1.9%; *P* = 0.30).

Correlation between adenoma and SSL detection rates among endoscopists

This study involved seven endoscopists (endoscopists A–G). Their adenoma detection rates ranged from 17.1% to 43.8%, while their SSL detection rates ranged from 2.0% to 11.0%. The corresponding data are presented in **Fig. 1s**. Two endoscopists (endoscopists E and G) had the highest SSL detection rates (7.7% and 11.0%, respectively). These two endoscopists were responsible for conducting 90.7% of the health check-up colonoscopy examinations and 44.5% of outpatient colonoscopy examinations, which may explain the better performance observed in the health check-up subgroup. Interestingly, our analysis did not reveal a significant correlation between the prevalence of adenomas and SSL detection rate (*P* = 0.08).

Predictors of SSL detection in the younger age group

In our analysis, we investigated the associations with the presence of SSLs during colonoscopy among younger individuals. The results of the univariable analysis for predefined clinical factors are presented in ▶ **Table 3**. Younger individuals with SSLs tended be older (41.6 [SD 5.2] vs. 39.6 [SD 6.4] years; *P*<0.001), male (55.1% vs. 48.0%; *P* = 0.003), and have longer mean (SD) withdrawal times (10.6 [4.3] vs. 7.3 [3.3] minutes; *P*<0.001). They were also more likely to be asymptomatic (72.7% vs. 56.7%; *P*<0.001) and have undergone colonoscopy during a health check-up (61.0% vs. 46.5%; *P*<0.001). Because the latter two variables seemed to be highly correlated, and the two higher performers were responsible for the majority of the health check-up examinations, we finally took age, sex, withdrawal time, and endoscopist performance into the multivariable analysis.

▶ **Table 2** Baseline characteristics of younger individuals (aged <50 years) from outpatient services and younger individuals from health check-up services.

	Outpatient	Health check-up	*P* value
Cases, n (%)	2470 (52.4)	2242 (47.6)	–
Age, mean (SD)	39.7 (6.6)	39.6 (6.1)	0.58
Sex, female, n (%)	1293 (52.3)	1132 (50.5)	0.20
Intravenous anesthesia used, n (%)	1704 (69.0)	2171 (96.8)	**<0.001**
Family history of CRC, n (%)	182 (7.4)	136 (6.1)	0.08
Positive fecal occult blood test, n (%)	179 (7.2)	11 (0.5)	**<0.001**
Withdrawal time, mean (SD), minutes	7.7 (3.8)	7.4 (3.0)	**0.001**
Adenomas, n (%)	511 (20.7)	552 (24.6)	**0.001**
Advanced adenomas, n (%)	116 (4.7)	80 (3.2)	**0.009**
Right-sided adenomas, n (%)	217 (8.8)	309 (13.8)	**<0.001**
Right-sided advanced adenoma, n (%)	30 (1.2)	33 (1.5)	0.44
Adenoma numbers, mean (SD)	0.2 (0.6)	0.3 (0.6)	**0.014**
CRCs, n (%)	16 (0.6)	3 (0.1)	**0.005**
SSLs, n (%)	133 (5.4)	208 (9.3)	**<0.001**
SSLDs, n (%)	5 (0.2)	4 (0.2)	0.85
SSLD among SSLs, n (%)	5 (3.8)	4 (1.9)	0.30
Right-sided HPPs, n (%)	69 (2.8)	112 (5.0)	**<0.001**
Traditional serrated adenomas, n (%)	3 (0.1)	5 (0.2)	0.40
CSSPs, n (%)	192 (7.8)	293 (13.1)	**<0.001**
CSSP numbers, mean (SD)	0.1 (0.3)	0.1 (0.4)	**<0.001**

CRC, colorectal cancer; SSL, sessile serrated lesion; SSLD, SSL with dysplasia; HPP, hyperplastic polyp; CSSP, clinically significant serrated polyp.

In the multivariable analysis, we divided the individuals in the younger age group into three subgroups (20–29, 30–39, and 40–49 years) for finer grained results on age. The benchmark SSL detection rate was set at 7% to define high performers and average performers [22]. Consequently, binary logistic regression results (▶ **Table 4**) revealed that increased age (40–49 years, OR 1.81, 95%CI 1.01–3.23; *P* = 0.04), longer withdrawal

▶ **Table 3** Baseline characteristics of younger individuals with and without a sessile serrated lesion (SSL).

	With SSL (n = 341)	Without SSL (n = 4371)	P value
Age, mean (SD), years	41.6 (5.2)	39.6 (6.4)	**<0.001**
20–29, n (%)	13 (3.8)	363 (8.3)	
30–39, n (%)	87 (25.5)	1551 (35.5)	
40–49, n (%)	241 (70.7)	2457 (56.2)	
Sex, female, n (%)	153 (44.9)	2272 (52.0)	**0.011**
From outpatient service, n (%)	133 (39.0)	2337 (53.5)	**<0.001**
Symptomatic cases, n (%)	93 (27.3)	1892 (43.3)	**<0.001**
Family history of CRC, n (%)	26 (7.0)	294 (6.7)	0.83
Positive fecal occult blood test, n (%)	14 (4.1)	176 (4.0)	0.94
Intravenous anesthesia used, n (%)	278 (81.5)	3597 (82.3)	0.72
Withdrawal time, mean (SD), minutes	10.6 (4.3	7.3 (3.3	**<0.001**
Adenomas, n (%)	84 (24.6)	979 (22.4)	0.34
Advanced adenomas, n (%)	14 (4.1)	174 (4.0)	0.91
Right-sided adenomas, n (%)	49 (14.4)	477 (10.9)	0.05
Right-sided advanced adenoma, n (%)	4 (1.2)	59 (1.3)	0.78
CRCs, n (%)	1 (0.3)	18 (0.4)	0.74
Right-sided HPPs, n (%)	9 (2.6)	172 (3.9)	0.23
Traditional serrated adenomas, n (%)	0	8 (0.2)	0.43

CRC, colorectal cancer; HPP, hyperplastic polyp.

time (OR 1.17, 95%CI 1.14–1.20, per minute increment; *P*<0.001), and endoscopist performance (high vs. average performers, OR 3.35, 95%CI 2.44–4.58, per minute increment; *P*<0.001) were independent predictors of SSLs among the younger individuals.

Sensitivity analysis and subgroup analysis

The effects of withdrawal time, endoscopist performance, and age were further examined using the data from the older age group. Longer withdrawal time (OR 1.07, 95%CI 1.05–1.09, per minute increment; *P*<0.001) and endoscopist performance (high performers, OR 2.41, 95%CI 1.89–3.07; *P*<0.001) remained significant predictive factors for SSL detection in this group. However, individuals aged 50–59 years exhibited SSL detection rates similar to those in the group aged 40–49 years (OR 0.91, 95%CI 0.75–1.11; *P* = 0.91). All other older age subgroups exhibited lower SSL detection rates, implying a potential peak at the age range of 40–49 years in this cohort (**Table 1s**). Age-based analysis suggested that, although adenoma detection was strongly correlated with advanced age, the detection rates of SSLs, SSLs with cytologic dysplasia, and CSSPs exhibited flatter trends with age increment (**Fig. 2s**). Notably, significant correlation was observed between SSLs and cytologic dysplasia per 10-year age increment (partial correlation 0.19; *P*<0.001).

Finally, we analyzed the data of individuals who had their SSLs detected in a health check-up; we did so to identify additional predictors of SSLs at a younger age (**Table 2s**). In this subgroup, younger individuals with SSLs tended to have a slightly higher mean (SD) age (41.4 [5.2] vs. 39.5 [6.4] years; *P*<0.001). They were also more likely to be obese (24.5% vs. 17.7%; *P* = 0.02), have metabolic syndrome (16.8% vs. 11.9%; *P*<0.001), and have diabetes mellitus (7.2% vs. 2.8%; *P*<0.001). Additionally, current tobacco use (22.1% vs. 15.4%; *P* = 0.01) was more prevalent among individuals with SSLs, and they had longer mean (SD) colonoscopy withdrawal times (9.7 [3.5] vs. 7.1 [2.8] minutes; *P*< 0.001); however, the multivariable logistic regression revealed that only colonoscopy withdrawal time was a significant factor (**Table 3s**).

Discussion

Currently, the recommended starting age for CRC screening is set at 45 years in response to the increasing incidence of early onset CRC, which occurs before the age of 50 [25, 26]. Although SSLs are less likely to be associated with early onset CRC, effective screening for SSLs may lead to further cancer prevention given their long indwelling time.

This study explored SSL prevalence among younger adults using a cohort with a high detection rate. The findings highlight that SSL prevalence is not negligible among individuals aged <50 years. Moreover, by the age of 40, the prevalence becomes comparable with that observed in older individuals. The association between age and SSLs in younger people has been explored by only a few studies [20, 21].

Our findings were in line with the current literature, in that SSLs exhibit a steadier prevalence with age in comparison with adenomas. There are however several differences between the current and previous studies. The primary outcome in Kim et al. [21] was serrated lesions, which were predominantly HPPs, so the SSL prevalence was quite low (0.5%) in their cohort. In contrast, the design of the study of Lall et al. [20] is more similar to our study, and the non-differing SSL detection rates between the younger and older age groups was concordant with our study. They did not however exclude patients with prior colonoscopies; as it would be suggested that patients with prior lesions undergo follow-up, the detection rate might be cofoun-

▶ **Table 4** Results of logistic regression analysis of predictive factors for the presence of sessile serrated lesions in the younger age group.

	Univariable analysis		Multivariable analysis	
	Odds ratio (95%CI)	***P* value**	**Odds ratio (95%CI)**	***P* value**
Age, vs. 20–29 years				
30–39 years	1.56 (0.86–2.83)	0.14	1.22 (0.67–2.24)	0.51
40–49 years	2.73 (1.55–4.83)	**0.001**	1.81 (1.01–3.23)	**0.04**
Withdrawal time, per 1-minute increment	1.18 (1.15–1.21)	**<0.001**	1.17 (1.14–1.20)	**<0.001**
Sex, male	1.33 (1.06–1.66)	**0.01**	1.09 (0.87–1.38)	0.43
Endoscopist, vs. average performers (SSLDR <7%)				
High performers (SSLDR ≥ 7%)	3.01 (2.24–4.05)	**<0.001**	3.35 (2.44–4.58)	**<0.001**

SSLDR, sessile serrated lesion detection rate.

ded by metachronous lesions, which could consequently affect the analysis of results. Moreover, some technical issues, such as withdrawal time and the variation in endoscopist expertise, were less explored in the previous study. Lastly, cytologic dysplasia, which is considered a critical step in SSL transformation, was not analyzed. While these two studies were important foundations for the current study, we also look forward to further validation studies regarding SSLs in younger people.

Because a substantial proportion of SSLs may develop in younger adults, effective detection and management of SSLs among younger individuals may be beneficial in preventing future serrated CRCs; however, detecting and completely resecting SSLs may be challenging owing to their obscured appearance and indistinct borders [8, 11, 27]. Although the SSL detection rate has been shown to be correlated with adenoma detection rates, endoscopists may differ considerably in their clinical performance [28, 29], as also demonstrated in the present study. In the present study, no significant correlation was noted between adenoma detection and SSL detection, which may be attributed to the relatively small number of endoscopists involved, leading to statistically underpowered results. Our findings did however reveal that longer withdrawal times were associated with higher SSL detection rates, which is consistent with the findings of prior studies [30, 31].

Endoscopist performance independent of withdrawal time was also highlighted in our study. Although the exact factors affecting detection performance remain to be investigated, expertise may be attributed to the recognition of lesion characteristics, examination technique, and the use of image-enhanced endoscopy. Inspiringly, detection ability may be improved by active training [32]. Furthermore, the assistance of attachment devices and artificial intelligence may also aid better detection of SSLs [33, 34]. Overall, detecting SSLs requires a considerable level of expertise and meticulous effort, and strategies to improve outcomes should be formulated.

This study is one of the few to have explored the prevalence of SSLs in younger adults and has several strengths, including a large cohort and a high detection rate. Additionally, we employed a strict definition of SSLs based on histologic diagnosis, and considered CSSPs and right-sided HPPs, which are highly correlated with SSLs in clinical practice. Moreover, the study population consisted mainly of relatively healthy individuals undergoing an index colonoscopy, which may reflect a scenario similar to ordinary screening practice. We also undertook meticulous analysis in order to reduce potential cofounding, such as discrepancy in endoscopist performance in subsets of the cohorts.

Nevertheless, this study has some limitations. First, although we tried our best to include only index examinations, individuals who underwent prior colonoscopies may not have been reported. That said, given the slow growth of SSLs, intervention bias may be extremely low for younger individuals, as indicated by the age-specific prevalence analysis. Second, some key factors, such as smoking, obesity, and diabetes mellitus, were only available for a subset of study participants, which may lead to underpowering for these factors. Diabetes mellitus has been reported to be a well-known risk factor of CRC by mechanisms that include enhanced DNA methylation, which is also an important carcinogenesis pathway for serrated CRCs [35]. Therefore, further analysis with a larger patient database in the future may provide more insights into these factors. Third, the withdrawal time in our study consisted of both observation and intervention; however, the association is even more prominent in cases that had a withdrawal time ≤9 minutes (OR 1.85, 95%CI 1.68–2.04), suggesting minimal intervention bias. Fourth, we did not report the prevalence of serrated polyposis syndrome among younger people. Finally, interobserver variation among pathologists may not be completely ruled out. Future large-scale studies with expert pathologists are warranted to investigate the role of SSLs in early and late onset CRC in the younger population.

In summary, our study demonstrated that SSLs are not uncommon in younger individuals, with a significant increase in prevalence starting at the age of 40. Longer withdrawal times during colonoscopy and endoscopist expertise appear to be associated with improved SSL detection. Further research is required to assess the clinical significance of SSLs in younger people and their potential implications for future screening practices.

Acknowledgement

The authors appreciate the assistance of Ms. Tzu-Shan Chen for advice on statistical analysis, and Ms. Pin-Yu Haung for clinical data collection. We also thank the Division of Medical Statistics and Bioinformatics, Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung Medical University for help provided. This manuscript was edited by Wallace Academic Editing.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding Information

National Science and Technology Council
http://dx.doi.org/10.13039/501100020950
MOST 111-2314-B-037-070-MY3,NSTC 112-2314-B-037-050-MY3, NSTC 112-2314-B-037-090
Ministry of Health and Welfare
http://dx.doi.org/10.13039/501100003625
12D1-IVMOHW02
Kaohsiung Medical University
http://dx.doi.org/10.13039/501100004694
KMU-TC112A04,KMUH-SH11207,KMUH112-2M27,KMUH112-2M28, KMUH112-2M29,KMUH112-2R37,KMUH112-2R38,KMUH112-2R39E-Da Hospital
http://dx.doi.org/10.13039/501100004738
EDAHS112014,EDAHS112029,EDDHP112001

References

[1] Arnold M, Sierra MS, Laversanne M et al. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017; 66: 683–691 doi:10.1136/gutjnl-2015-310912

[2] Cardoso R, Guo F, Heisser T et al. Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. Lancet Oncol 2021; 22: 1002–1013 doi:10.1016/S1470-2045(21)00199-6

[3] Wong MC, Huang J, Lok V et al. Differences in incidence and mortality trends of colorectal cancer worldwide based on sex, age, and anatomic location. Clin Gastroenterol Hepatol 2021; 19: 955–966.e961

[4] Murcia O, Juárez M, Hernández-Illán E et al. Serrated colorectal cancer: Molecular classification, prognosis, and response to chemotherapy. World J Gastroenterol 2016; 22: 3516–3530 doi:10.3748/wjg.v22.i13.3516

[5] Nakanishi Y, Diaz-Meco MT, Moscat J. Serrated colorectal cancer: the road less travelled? Trends Cancer 2019; 5: 742–754 doi:10.1016/j.trecan.2019.09.004

[6] Meester RG, van Herk MM, Lansdorp-Vogelaar I et al. Prevalence and clinical features of sessile serrated polyps: a systematic review. Gastroenterology 2020; 159: 105–118.e125

[7] Murakami T, Kurosawa T, Fukushima H et al. Sessile serrated lesions: Clinicopathological characteristics, endoscopic diagnosis, and management. Dig Endosc 2022; 34: 1096–1109 doi:10.1111/den.14273

[8] Nishizawa T, Yoshida S, Toyoshima A et al. Endoscopic diagnosis for colorectal sessile serrated lesions. World J Gastroenterol 2021; 27: 1321 doi:10.3748/wjg.v27.i13.1321

[9] Burnett-Hartman AN, Newcomb PA, Phipps AI et al. Colorectal endoscopy, advanced adenomas, and sessile serrated polyps: implications for proximal colon cancer. Am J Gastroenterol 2012; 107: 1213–1219 doi:10.1038/ajg.2012.167

[10] Chang L-C, Shun C-T, Hsu W-F et al. Fecal immunochemical test detects sessile serrated adenomas and polyps with a low level of sensitivity. Clin Gastroenterol Hepatol 2017; 15: 872–879.e871

[11] Zorzi M, Senore C, Da Re F et al. Detection rate and predictive factors of sessile serrated polyps in an organised colorectal cancer screening programme with immunochemical faecal occult blood test: the EQuIPE study (Evaluating Quality Indicators of the Performance of Endoscopy). Gut 2017; 66: 1233–1240

[12] 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

[13] 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

[14] Bettington M, Walker N, Rosty C et al. Clinicopathological and molecular features of sessile serrated adenomas with dysplasia or carcinoma. Gut 2017; 66: 97–106 doi:10.1038/nrgastro.2017.119

[15] Bouwens MWE, Riedl RG, Bosman FT et al. Large proximal serrated polyps: natural history and colorectal cancer risk in a retrospective series. J Clin Gastroenterol 2013; 47: 734–735 doi:10.1097/MCG.0b013e318293a656

[16] Holme Ø, Bretthauer M, Eide TJ et al. Long-term risk of colorectal cancer in individuals with serrated polyps. Gut 2015; 64: 929–936

[17] Liu C, Bettington ML, Walker NI et al. CpG island methylation in sessile serrated adenomas increases with age, indicating lower risk of malignancy in young patients. Gastroenterology 2018; 155: 1362–1365.e1362

[18] Lieu CH, Golemis EA, Serebriiskii IG et al. Comprehensive genomic landscapes in early and later onset colorectal cancer. Clin Cancer Res 2019; 25: 5852–5858 doi:10.1158/1078-0432.CCR-19-0899

[19] Perea J, Rueda D, Canal A et al. Age at onset should be a major criterion for subclassification of colorectal cancer. J Mol Diagn 2014; 16: 116–126

[20] Lall V, Ismail AGM, Ayonrinde OT. Disparate age and sex distribution of sessile serrated lesions and conventional adenomas in an outpatient colonoscopy population–implications for colorectal cancer screening? Int J Colorectal Dis 2022; 37: 1569–1579 doi:10.1007/s00384-022-04191-x

[21] Kim HY, Kim SM, Seo J-H et al. Age-specific prevalence of serrated lesions and their subtypes by screening colonoscopy: a retrospective study. BMC Gastroenterol 2014; 14: 82

[22] 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

[23] Aronchick CA, Lipshutz WH, Wright SH et al. A novel tableted purgative for colonoscopic preparation: efficacy and safety comparisons with Colyte and Fleet Phospho-Soda. Gastrointest Endosc 2000; 52: 346–352

[24] Yeh JH, Lin CW, Wang WL et al. Positive fecal immunochemical test strongly predicts adenomas in younger adults with fatty liver and metabolic syndrome. Clin Transl Gastroenterol 2021; 12: e00305

[25] US Preventive Services Task Force. Davidson KW, Barry MJ et al. Screening for colorectal cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2021; 325: 1965–1977 doi:10.1001/jama.2022.13044

[26] Patel SG, May FP, Anderson JC et al. Updates on age to start and stop colorectal cancer screening: recommendations from the U.S. Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2022; 162: 285–299

[27] Pohl H, Srivastava A, Bensen SP et al. Incomplete polyp resection during colonoscopy—results of the Complete Adenoma Resection (CARE) study. Gastroenterology 2013; 144: 74–80.e71

[28] 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

[29] Payne SR, Church TR, Wandell M et al. Endoscopic detection of proximal serrated lesions and pathologic identification of sessile serrated adenomas/polyps vary on the basis of center. Clin Gastroenterol Hepatol 2014; 12: 1119–1126 doi:10.1016/j.cgh.2013.11.034

[30] Butterly L, Robinson CM, Anderson J et al. Serrated and adenomatous polyp detection increases with longer withdrawal time: results from the New Hampshire Colonoscopy Registry. Am J Gastroenterol 2014; 109: 417

[31] 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

[32] Jennifer T, Lovedeep G, Steven P et al. Higher adenoma detection, sessile serrated lesion detection and proximal sessile serrated lesion detection are associated with physician specialty and performance on Direct Observation of Procedural Skills. BMJ Open Gastroenterol 2021; 8: e000677

[33] 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

[34] Wu Z, Yao L, Liu W et al. Development and validation of a deep learning–based histologic diagnosis system for diagnosing colorectal sessile serrated lesions. Am J Clin Pathol 2023; 160: 394–403 doi:10.1093/ajcp/aqad058

[35] Cheng H-C, Chang T-K, Su W-C et al. Narrative review of the influence of diabetes mellitus and hyperglycemia on colorectal cancer risk and oncological outcomes. Transl Oncol 2021; 14: 101089 doi:10.1016/j.tranon.2021.101089