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Sessile serrated lesions in focus: Examining temporal trends, patient risk factors, and the role of the endoscopist in lesion detection

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Sessile serrated lesions in focus: Examining temporal trends, patient risk factors, and the
role of the endoscopist in lesion detection

by

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A THESIS

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Abstract

Serrated polyps of the colorectum have become increasingly recognized as an important clinical entity, as these precursor lesions are hypothesized to be responsible for up to 25% of sporadic cases of colorectal cancer. Much confusion exists regarding these polyps; particularly, their classification and associated malignant risk due to varied nomenclature, evolving pathological criteria, and ongoing research in prognostication. A specific subtype, sessile serrated lesions (SSLs), are of particular interest, as they are the most prevalent premalignant subtype and are over-represented in cases of interval cancers. Accurate identification and risk assessment remains a challenge owing to variable detection of clinically relevant serrated lesions by endoscopists, high inter-observer variability in diagnosis by pathologists, and an incomplete understanding of risk of future neoplasia.

In this thesis, we analyze over 75,000 screening colonoscopies performed over a five-year period at a dedicated, large volume, high-efficiency screening centre to identify trends in the endoscopic detection of SSLs. The intent of this work is to better understand the temporal factors influencing SSL detection prevalence, the patient risk factors that are associated with these lesions, and how detection is related to procedural and endoscopist factors. The analysis includes consideration of traditional statistical methods as well as novel machine learning algorithms.

We demonstrated a positive temporal trend in SSL detection over study period and identified several patient, procedural, and endoscopist factors associated with SSL detection. Machine learning models improved upon the predictive capabilities of traditional statistical models, yet a

significant proportion of variability in risk remained unexplained, underscoring the complexity of accurately predicting SSLs. Endoscopic detection of SSLs demonstrates strong correlation with other detection metrics, notably adenoma detection rate, implying a shared underlying skillset requisite for the identification of these distinct polyp types. This connection highlights opportunities for enhancing detection through benchmarking and established quality improvement strategies.

Preface

This thesis is original, unpublished, independent work by the author, Matthew Mazurek.

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Contributions

Matthew Mazurek was involved in conception of the study, design, data cleaning, modelling, analysis, and writing of the manuscripts. Darren Brenner and Robert Hilsden were involved in the conception of the study. Robert Hilsden is the curator of the CCSC Quality Assurance Database and graciously provided access to this data. Joon Lee provided guidance and assistance with machine learning model design. All authors participated in the final development of the manuscript and approved its content.

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List of symbols, abbreviations, and nomenclature

AA	Advanced adenoma
ADR	Adenoma detection rate
AU(RO)C	Area under the (receiver operating characteristic) curve
CCSC	Colon Cancer Screening Centre
CI	Confidence interval
CIMP	CpG island methylator phenotype
CRC	Colorectal cancer
CSSP	Clinically significant serrated polyp
FIT	Fecal immunohistochemical test
IQR	Interquartile range
ML	Machine learning
MLP	Multilayer perceptron
MSI	Microsatellite instability
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PDR	Polyp detection rate
PSPDR	Proximal serrated polyp detection rate
SSL	Sessile serrated lesion
SSLDR	Sessile serrated lesion detection rate
TSA	Traditional serrated adenoma
TSADR	Traditional serrated adenoma detection rate
WHO	World Health Organization
XGB	Extreme gradient boosting

Chapter 1. Introduction

1.1. Background

Colorectal cancer (CRC) represents a leading cause in cancer-related mortality and is projected to account for approximately 12% of all cancer-related deaths in 2020.¹ Serrated polyps of the colorectum have become increasingly recognized as an important clinical entity, as they are hypothesized to be responsible for up to 25% of sporadic cases of colorectal cancer²⁻⁵ and a disproportionate number of “interval” cancers following an index colonoscopy.⁶

1.1.1. *Classification of serrated polyps*

Serrated polyps comprise a heterogeneous group of colonic neoplasia characterized by a “saw-toothed” appearance of the crypt epithelium. Prior to 2010, these lesions were underrecognized by endoscopists and, when resected, were broadly considered by pathologists to be harmless “hyperplastic” polyps without malignant potential. However, careful analysis of the morphological and molecular profiles of these lesions has since permitted an accurate subclassification, stratified by risk of malignant transformation.⁷ There are now three well-described serrated polyp entities, which include hyperplastic polyps, sessile serrated lesions (SSL)—previously referred to as sessile serrated adenomas or sessile serrated polyps—and traditional serrated adenomas.⁸

Hyperplastic polyps are the most common, comprising approximately 75% of all serrated polyps.⁵ They are benign lesions that are distinguished by serrations present near the luminal aspect of the crypts with straight, elongated crypts, and are preferentially located in the rectosigmoid

colon. These polyps are diagnosed by excluding cellular atypia or architectural distortion characteristic of SSLs or TSAs in a well oriented tissue section.⁸

Contrastingly, SSLs account for approximately 25% of serrated polyps. These are pre-malignant lesions that are distinguished by the variable presence of serrations throughout the crypt length, architectural disturbances at the crypt base (“boot-shaped” crypts), dilated crypts with basal goblet cells, variable cellular atypia, and are commonly located in the proximal colon. Using modern classification criteria, SSLs have an estimated detection prevalence of 9–12% at all indication colonoscopy when performed by high-detecting endoscopists.^{9, 10} The progression to serrated adenocarcinoma occurs via a dysplastic intermediate, the so-called sessile serrated lesion with dysplasia (SSL-D). Transition from SSL to SSL-D is not believed to occur with high frequency as only 4-8% of SSLs contain dysplasia.^{11, 12} Dysplastic patterns can be characterized into intestinal dysplasia (similar to that observed in conventional adenomas), serrated dysplasia (indicative of progression to TSA), and minimal deviation dysplasia, although most SSL-Ds will have an undefined pattern of dysplasia.^{13, 14} While these different classifications of dysplasia have limited diagnostic value, clinically important dysplasia can be identified by immunohistochemical analysis for loss of MLH1 expression, which occurs in up to 80% of cases of SSL-D.¹³

Traditional serrated adenomas also possess malignant potential but are far less common. They are villous polyps with prominent eosinophilic cytoplasm and penicillate nuclei with a distinct pattern of narrow-slit serration throughout the length of the crypt.⁸ These polyps may also feature ectopic crypt formation and variable cellular atypia, and are typically located in the distal colon.¹⁵

1.1.2. *Evolution of the histopathologic diagnostic criteria of SSLs*

One of the main challenges in studying serrated polyps is the recent evolution of their diagnostic criteria, resulting in high inter-observer variation and misclassification—particularly of hyperplastic polyps and SSLs—when comparing older studies with more modern ones.¹⁶⁻¹⁸ In 2010, SSLs were included in the World Health Organization (WHO) classification (at that time as sessile serrated adenomas or sessile serrated polyps) as an entity distinct from hyperplastic polyps by the presence of at least one or two dilated crypts.¹⁹ After this change in definition, an estimated 8–19% of all hyperplastic polyps diagnosed between 2000-2010 were reclassified as SSLs, with estimates as high as 28% when considering only large hyperplastic polyps.²⁰⁻²⁴ The 4th edition WHO classification later relaxed this criteria in 2019 to allow for a diagnosis of an SSL with the presence of a single dilated crypt.⁸ These more sensitive criteria have led to an estimated 7% additional increase in the proportion of serrated polyps being diagnosed as SSLs.²⁵ While there are some reports of reduced inter-observer variability after implantation of the one crypt rule,²⁶ the distinction between a hyperplastic polyp and an SSL now rests on the identification of a single dilated crypt, which is highly dependent on adequate specimen orientation. When the diagnosis is unclear, a pathologist may use a common “rule of thumb,” classifying serrated polyps greater than 5 mm in size and/or located in the right colon as an SSL.

1.1.3. *Serrated adenocarcinoma and the serrated pathway*

Now recognized as a distinct CRC subtype, serrated adenocarcinoma arises independently of the traditional adenoma-to-carcinoma sequence via the serrated pathway from a serrated precursor lesion. This pathway is associated with activating mutations in *BRAF* or *KRAS*, widespread

methylation of CpG islands in promoter regions of tumor suppressors, and aberrant Wnt signaling. An estimated 10-15% of colorectal tumours are classified as serrated adenocarcinoma based on histological features, while up to 25% can be similarly classified by pathognomonic molecular features, as not all will maintain their serrated morphology.^{5, 27}

The serrated pathway describes a series of genetic and epigenetic changes during polyp formation that can be tracked with characteristic histologic features evolving from hyperplastic mucosal tissue to dysplasia to carcinoma.⁵ The initial sequence is believed to begin with an activating mutation in the mitogen-activated protein kinase pathway, typically affecting either *BRAF* or, less frequently, *KRAS*.^{28, 29} Activating mutations in *BRAF* are associated with the CpG island methylator phenotype (CIMP), which results in the silencing of a number of genes, including tumour suppressors.^{30, 31} *BRAF*-associated hypermethylation of the *MLH1* promotor results in a specific polymorphism of this DNA mismatch repair enzyme with reduced activity, which in turn, leads to microsatellite instability (MSI).³² This *MLH1* polymorphism is responsible for the MSI observed in approximately 75% of SSLs-D¹⁵ and its immunostaining can therefore be used as a marker of dysplasia.^{13, 15} TSAs, on the other hand, commonly exhibit *BRAS*-associated hypermethylation of the *CDKN2A* promoter, which encodes the tumour suppressor, P16.³³ In both SSLs and traditional serrated adenomas, further progression along the serrated pathway involves activation of the Wnt signaling pathway. Whereas the majority of conventional adenomas will exhibit truncating *APC* mutations leading to instability of the β -catenin destruction complex and resulting Wnt activation, β -catenin persistence is instead mediated by upstream effects via mutations either in the RNF43–ZNRF3 complex, (common in SSLs) or those resulting in fusions of genes in the R-spondin family (more typical of traditional serrated adenomas).³⁴

It is generally accepted that CRC with *BRAF* somatic mutations and resulting high levels of CIMP and MSI are of serrated origin and, in particular, are derived from SSLs.⁵ While, in epidemiologic studies, only a minority of SSLs exhibit dysplasia, those that do are believed to rapidly evolve toward carcinoma.³⁵ These aggressive molecular features are clinically associated with older age, female sex, and proximal colonic location.³⁶

1.1.4. *Epidemiology of SSLs*

Using data from a recently published colonoscopy series, detection prevalence is estimated to be 9–12% at all indication colonoscopy.^{9, 10} When considering only high-detecting endoscopists and centers, reported prevalence values increase to 13–20%.^{29, 37} Age does not appear to play the same role in conferring risk in SSLs as it does in conventional adenomas. While those patients who are younger than 50 years of age have a lower risk of SSLs than those older than 50, the risk has not been shown to increase significantly beyond age 50.³⁸⁻⁴⁰ Sex distribution of SSLs appears to be equivalent between males and females,⁴¹⁻⁴³ although there are conflicting reports in the literature with some studies demonstrating higher rates among men^{44, 45} and others reporting higher rates among women.^{46, 47}

Several additional epidemiologic risk factors for SSLs have been identified.^{40, 48} Cigarette smoking is associated with an overall higher risk of SSLs and large SSLs, as well as a higher risk of both distal and proximal serrated polyps in general. Inconsistent associations have been demonstrated with alcohol, fiber, and calcium intake, as well as non-steroidal anti-inflammatory drug (NSAID) use, family history of colorectal cancer, and high body mass index. Contrastingly, physical activity and folate intake have been demonstrated to be protective.

1.1.5. Challenges in the detection of SSLs

Accurate detection of SSLs poses several difficulties. Screening for these lesions with either fecal immunochemical testing or computed tomography has low sensitivity^{49, 50} and endoscopic recognition is often challenging.^{9, 42, 51} Myriad features of these lesions can impede endoscopic detection. These include (1) a tendency to be located in the proximal colon, where visualization may suffer from inadequate bowel preparation, (2) a subtle endoscopic appearance, including flat morphology with smooth mucosal surface, and (3) a propensity to be obscured by a mucous cap.⁴⁸ Additionally, the histologic diagnosis of SSLs is not always clear. Low inter-rater concordance among pathologists has been observed with serrated polyp detection rates varying absolutely by as much as 10%.⁵²

1.1.6. Variability in SSL detection among endoscopists

Highly variable rates of serrated polyp detection have been reported in the literature, which range from 0.1%–20%.^{51, 53-58} In a recent systematic review and meta-analysis looking at procedures performed for average-risk screening, pooled sessile serrated lesion detection rate (SSLDR) was found to be low at 2.5% (95 % CI [1.8%–3.4%]), with significant heterogeneity in prevalence reporting.⁵⁶ Some of the variability in detection prevalence is likely accounted for by the variable adoption of standardized diagnostic criteria. Other potential contributors include advancements in endoscopic technology^{59, 60} and heightened endoscopist awareness of and vigilance for SSLs.⁶¹

Hetzel and colleagues performed a retrospective review of screening colonoscopies performed over a 3-year time period between 2006–2008 and found that endoscopists' serrated polyp

detection rates were positively correlated with their adenoma detection rates ($r = 0.84$, $p < 0.001$ for hyperplastic polyps; $r = 0.64$, $p = 0.019$ for SSLs).⁴² More recently, Crockett *et al.* examined endoscopist factors that influence detection of serrated polyps in general.⁹ They demonstrated that gastroenterologist specialty (OR 1.89, 95% CI [1.33–2.70]), fewer years in practice (≤ 9 years vs. ≥ 27 years, OR 1.52, 95% CI [1.14–2.04]), and higher procedural volumes (highest vs. lowest quartile, OR 1.77, 95% CI [1.27–2.46]) were associated with enhanced serrated polyp detection.

Considering the variability of SSL detection that exists among endoscopists, serrated polyp detection benchmarks could be used to motivate endoscopists and screening centres to ensure their practices are meeting quality standards.

1.1.7. *Defining serrated polyp-specific detection benchmarks*

The establishment of appropriate benchmarks promotes high-quality screening practices among endoscopists, thereby optimizing the detection of pre-malignant lesions. Previous work has established the association between lower adenoma detection rate (ADR) and interval colorectal cancer.⁶² Acknowledging the importance of ADR as a quality indicator for screening colonoscopy, the American College of Gastroenterology/American Society for Gastrointestinal Endoscopy (ACG/ASGE) recommends a minimum adenoma detection rate of 25% in a mixed-sex screening population.⁶³ Within the recent past, ADR targets have been raised, with a clinical practice update from the American Gastroenterological Association now recommending goal and aspirational detection rates of $\geq 30\%$ and $\geq 35\%$, respectively, on a per endoscopist basis.⁶⁴ This recommendation is made based on evidence demonstrating an apparent linear relationship

between ADR and risk of interval CRC.^{65, 66} Endoscopists who are not meeting these thresholds are encouraged to extend withdrawal times and/or participate in educational interventions.

Serrated polyp-specific detection benchmarks are a novel addition to practice guidelines, reflecting the recent evolution of our understanding of these lesions as important, independent drivers of CRC. Multiple studies have proposed specific serrated polyp detection targets. Anderson *et al.*, using data from 29,960 screening colonoscopies, proposed detection benchmarks of 7% and 11% for clinically significant and proximal serrated polyps, respectively.⁶⁷ These figures were arrived at by calculating the average detection rates for those endoscopists with ADR $\geq 25\%$. In their study, clinically significant polyps were defined as any SSL or traditional serrated adenoma, or hyperplastic polyp >1 cm anywhere in the colon or hyperplastic polyp >5 mm in the proximal colon; proximal serrated polyps were defined as those of any size proximal to the sigmoid colon. In a review on the management of serrated polyps, Fan *et al.* echoed these proposed targets by suggesting reasonable benchmarks be 5–7% and 10–12% for SSLDR and proximal serrated polyp detection rate (PSPDR), respectively.⁶⁸ Another study analyzing data from multiple screening centres across Europe, identified a median SSLDR of 3.3% and a median clinically relevant serrated polyp detection rate of 4.6%.³⁸ The authors suggest that these values could define minimum targets among European countries, irrespective of colonoscopy indication. Leveraging data from Anderson *et al.*,⁶⁷ the American Gastroenterological Association recommends that SSLDR should be measured and reported both at the endoscopist and unit level, with specific goal and aspirational targets of $\geq 7\%$ and $\geq 10\%$, respectively.⁶⁴ Considerable heterogeneity among these proposed targets highlights the challenge of developing a one-size-

fits-all benchmark for screening centres with varying case-mix and histopathological diagnostic capabilities.

1.2. Aims and objectives

In this thesis, we aim to conduct a comprehensive analysis on SSLs, including temporal trends in detection prevalence, predisposing patient characteristics, and associated endoscopist factors, using data from a high-volume, dedicated colonoscopy screening center over a five-year period from 2013–2017. To this end, this work will focus on the following primary objectives:

- (1) We posit that the considerable variability in reported SSLDR in the literature stems from an evolving understanding of these lesions and staggered integration of various cognitive and technological advancements at various sites. To better understand the component factors determining serrated polyp detection and how changes in these elements may have impacted detection rates, we conduct a temporal analysis of serrated polyp detection at our institution. We analyze various patient, endoscopist, and procedural factors while considering how changes in histologic definitions may have influenced SSL detection prevalence.
- (2) Accurately predicting SSL risk presents a significant challenge, yet it is a critical factor in establishing screening and surveillance intervals. To improve upon our ability to predict SSL risk, we aim to develop novel risk prediction models, integrating key determinants identified in traditional statistical models, and leverage machine learning algorithms to account for possibly non-linear associations and interactions among temporal, patient, endoscopist and procedural determinants of SSLs. In so doing, we hope to advance the development of individualized screening strategies and improve our understanding of the multifaceted factors influencing SSL occurrence.

(3) A high degree of variability in SSLDR exists among endoscopists. Understanding the driving factors behind this disparity is critical to improve overall detection rates. Variations in endoscopist performance may stem from numerous factors, including procedural volumes, specialty, experience, and overall procedural completion rate. Motivated by this insight, we aim to evaluate these endoscopist-related characteristics in relation to SSL detection. Further, we will assess the appropriateness of using ADR, an established benchmark of quality colonoscopy, as a predictor of SSLDR. Finally, we investigate the feasibility of using the more accessible metric, PSPDR, as a surrogate of the more clinically relevant SSLDR. Overall, this analysis will enhance our understanding of the factors that contribute to endoscopists' proficiency in SSL detection and inform strategies for decreasing SSLDR variability through enhanced lesion detection.

This manuscript-based thesis is comprised of two original research articles. The first of these, titled "Temporal trends and risk prediction of sessile serrated lesions: Results from a high-volume dedicated public screening centre" addresses Objectives (1) and (2), while the second, "Association between endoscopist factors and sessile serrated lesion detection" explores Objective (3). These manuscripts follow from the natural progression of our research aims, which initially sought to describe the temporal trends of SSL detection rates, but, noting heterogeneity in SSL detection prevalence, our attention turned to identifying either patient- or endoscopist-level determinants of SSL detection, while accounting for these previously identified temporal differences.

Chapter 2. Temporal trends and risk prediction of sessile serrated lesions: Results from a high-volume dedicated public screening centre

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2.1. Abstract

2.1.1. *Background*

Sessile serrated lesions (SSL) are pre-malignant polyps that are responsible for a disproportionate number of interval colorectal cancers following screening or surveillance colonoscopy. Despite growing recognition and reporting of these lesions, SSL detection rate (SSLDR) estimates are highly variable, reflecting differences in patient populations and inconsistencies in both histopathologic diagnosis and endoscopic detection. In this study, we attempt to explain the variation in SSLDR by examining temporal trends in polyp detection and modeling SSL risk based on patient, procedural, and temporal factors.

2.1.2. *Methods*

We conducted a retrospective analysis on screening and surveillance colonoscopies performed at a high-volume public screening centre between 2013–2017. Univariable logistic regression was used to identify relevant patient, procedural, and endoscopist factors that were associated with SSLs, which were then used to derive a multivariable logistic regression and a mixed effects logistic regression model of SSLDR over time. The temporal analysis informed the selection of relevant predictors that were then used to train several supervised machine learning models to estimate individualized SSL risk.

2.1.3. *Results*

74,283 unique patient procedures were performed by 57 endoscopists during the study period. SSLDR was shown to increase from 8.1% in 2013 to 12.2% in 2017. Unlike adenoma detection,

the temporal trend in SSLDR persisted after controlling for relevant patient-, procedure-, and endoscopist-level variables. Several patient factors were identified as being weakly predictive of SSL detection, while the performing endoscopist, adenoma detection rate, withdrawal time, and year of procedure, were found to be much stronger predictors of SSLs. All predictive models exhibited relatively poor performance metrics.

2.1.4. *Conclusions*

SSLDR has increased over time, independent of known patient-, procedure-, and provider-level factors. Accurately estimating individual SSL risk remains a challenge, even when accounting for temporal factors. Further work is required to elucidate important predictors to help enhance risk prediction and endoscopic detection.

2.2. Introduction

Colorectal cancer (CRC) represents a leading cause of cancer-related mortality, estimated to account for approximately 12% of all cancer-related deaths.¹ As premalignant polyps of the colorectum, sessile serrated lesions (SSLs) are becoming increasingly recognized as an important clinical entity. They are hypothesized to give rise to 10–25% of sporadic cases of CRC²⁻⁵ and account for a disproportionate number of interval cancers following screening or surveillance colonoscopy.^{6, 11, 69, 70} These recent insights have challenged the current CRC screening paradigm and called into question the adequacy of SSL diagnostic criteria and endoscopic detection. Indeed, despite these lesions accounting for a large proportion of CRC, at all indication colonoscopy, detection prevalence is estimated to only be 4.6%.⁵⁸ As our understanding of these lesions has evolved over time, so too have best care practices, which now reflect the importance

of optimizing the detection, removal, and surveillance of any serrated polyp with risk of malignant potential.^{48, 61}

2.2.1. Evolution of the diagnostic criteria of sessile serrated lesions

One of the main challenges in studying serrated polyps is the recent evolution of their diagnostic criteria, resulting in high inter-observer variation and misclassification when comparing older studies with more modern ones.¹⁶⁻¹⁸ In 2010, SSLs were included in the World Health Organization (WHO) classification as an entity distinct from hyperplastic polyps by the presence of at least one or two dilated crypts.¹⁹ The 4th edition WHO classification later relaxed this criteria in 2019 to allow for a diagnosis of an SSL with the presence of a single dilated crypt.⁸ The distinction between hyperplastic polyps and SSLs now rests on the identification of a single dilated crypt, which is highly dependent on adequate specimen orientation. When the diagnosis is unclear, a pathologist may use a common “rule of thumb,” classifying serrated polyps greater than 5 mm in size and/or located in the right colon as SSL.

Beyond the difficulties that inter-pathologist variability poses in the study of SSLs, endoscopic detection rates are inconsistently reported⁵⁵ and, when they are, estimates of detection prevalence are highly variable, ranging from 0.1%–20%.^{51, 53-58} It has been suggested that this variability can be explained by differences in the performing endoscopist,^{42, 51, 71} as detection of the subtle morphological features of SSLs is highly dependent on the adequacy of mucosal examination and vigilance exercised by the provider.

2.2.2. *Aims and objectives*

Despite several studies attempting to explain the observed variation in SSL detection by examining static patient-, procedure-, and provider-level factors, little work has yet been done to investigate the trend of SSLDR over time. Such an analysis would admit the possibility of dynamic factors in SSL detection—i.e., the evolution of histopathologic diagnosis with adoption of newer diagnostic criteria and the change in endoscopic practices, reflecting greater provider recognition of these lesions and integration of technological advancements in endoscopy. In service of Objective (1), we attempt to explain the variation in SSLDR in the literature by examining temporal trends in polyp detection in a large cohort of healthy individuals undergoing CRC screening. Accounting for these temporal factors would allow for more accurate prediction models of SSL risk, which could be used to provide tailored screening and surveillance recommendations. Accordingly, and in service of Objective (2), we then integrate the temporal data and use traditional statistical techniques to identify relevant epidemiological risk factors associated with SSLs and employ machine learning (ML) algorithms to develop risk prediction models that account for possibly non-linear associations among SSL determinants.

2.3. **Methods**

2.3.1. *Study design*

We performed a large, single-centre retrospective study using clinical and administrative data prospectively collected on individuals undergoing screening or surveillance colonoscopy at the Colon Cancer Screening Centre (CCSC) in Calgary, Alberta, Canada (CCSC Quality Assurance Database). The CCSC is a high-volume, publicly funded screening centre with a case load of 17,500

colonoscopies annually. Referrals are accepted from the City of Calgary and surrounding areas for individuals aged 50–75 years who are asymptomatic and in good general health (typically American Society of Anesthesiologists [ASA] classification 1 or 2). Referral indications include average-risk screening, personal or family history of CRC or adenomatous polyps, or investigation of a positive fecal immunohistochemical test. Endoscopists include both gastroenterologists and colorectal surgeons.

2.3.2. Cohort selection

The CCSC Quality Assurance Database contains 132,131 screening or surveillance colonoscopies performed on 111,392 patients between the years 2008–2017. Individuals were included in our study if they were > 18 years of age at time of colonoscopy and were undergoing colonoscopy for the purposes of CRC screening, surveillance, or to investigate a positive screening testing, such as the guaiac-based fecal occult blood test or fecal immunohistochemical test (FIT). Data for which SSLs are reliably reported are available in the interval between 2013–2017; we have thus limited our attention to these years. Cases were excluded if the patient had a known genetic syndrome, mutation, or occupational exposure predisposing them to colonic neoplasia or if their exam was incomplete. Analysis was performed on a per-patient basis, using only the index procedure to avoid confounding by short-interval surveillance examinations and correlations between procedures performed on the same patient. The only exception to this being in cases where the index procedure was incomplete due to poor bowel preparation, then the second complete exam was included instead. 74,283 unique patient procedures comprised the final study cohort (**Figure 1**).

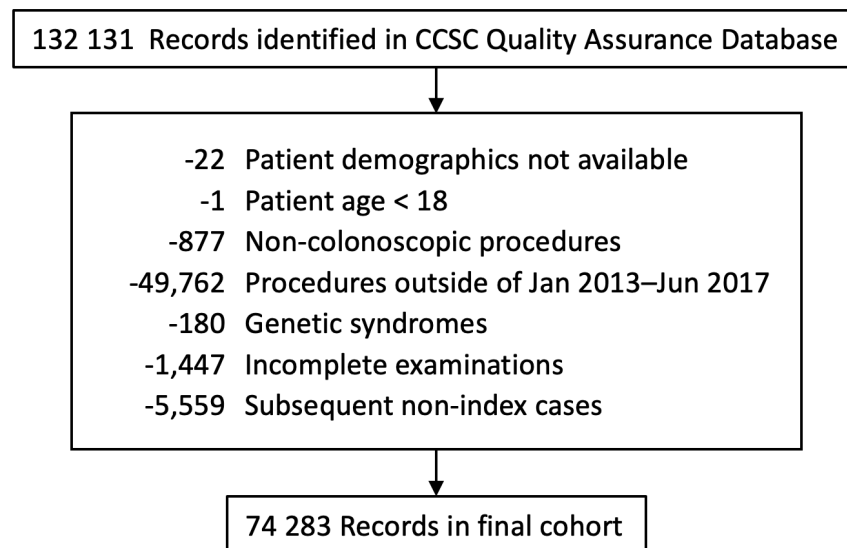


Figure 1. Cohort selection. CCSC, Colon Cancer Screening Centre.

2.3.3. Data sources and variables

Data is routinely collected on all patients undergoing procedures at the CCSC. These include patient demographics, diabetic status, FIT status, as well as post-colonoscopy outcomes, including polyp number, size, morphology, and histology. Colonoscopy report data was obtained from data linkage with the endoscopy reporting program endoPRO (Pentax Medical). Captured data elements included procedure date, indication (average-risk screening, family history of CRC or advanced adenoma, positive FIT, or surveillance), depth of colonoscope insertion (terminal ileum, cecum, or incomplete exam), bowel preparation quality (optimal, sub-optimal, inadequate), whether a polypectomy was performed, and withdrawal time in minutes. Withdrawal time, in this study, is defined as post-cecal intubation procedure time and does not exclude the time required for therapeutic intervention, such as polypectomy. As programmatic FIT screening was introduced in Alberta in October 2013, univariable analysis involving FIT was

limited to 2014 and onwards. Withdrawal time was dichotomized to ≥ 6 minutes in this analysis, as this is the minimum amount of time required for adequate mucosal inspection according to experts in screening colonoscopy.⁷² A cut-point between optimal and sub-optimal was used to dichotomize bowel preparation into high and poor quality. Pathology data were obtained from linkage with the CCSC Pathology Database, which includes a structured summary of the pathology report, including the histologic diagnosis. Histological variables include the presence or absence of any polyp, as well as adenomatous, advanced adenomatous, sessile serrated, traditional serrated, and hyperplastic polyps. The endoscopist performing each procedure is identified with a unique code and their specialty, either gastroenterologist or colorectal surgeon, is known. To maintain confidentiality, all patient and endoscopist data were de-identified prior to its release to the researchers. In addition to the target variable—sessile serrated lesion pathology—a total of eight patient predictors, two endoscopist predictors, four procedural predictors, and four histopathologic predictors were deemed relevant to the research question and were selected from the linked dataset (**Table 1**). Variable selection was guided by previous epidemiologic research^{40, 43, 48, 73-78} and expert opinion from practicing clinicians. Additional feature engineering was performed to allow for generalizability of certain predictive models; in particular, endoscopist adenoma detection rate (ADR)—defined as the proportion of procedures during which at least one adenomatous polyp was found—was calculated for each endoscopist over the study period.

Table 1. List of variables used in the current study. A single target variable—sessile serrated lesion pathology—is modeled by a total of eight patient predictors, two endoscopist predictors, four procedural predictors, and four histopathologic predictors. Endoscopist adenoma detection rate is an engineered variable used to improve generalizability of selected predictive models.

Feature	Description	Type
pt_sex	Male sex	dichotomous
pt_age	Patient age	continuous
pt_diabetic	Diabetic status	dichotomous
pt_fit	Stool screening test status	dichotomous
risk_avg	Procedure performed for average-risk screening	dichotomous
risk_fhx	Procedure performed for family history of advanced adenoma or CRC	dichotomous
risk_polyp	Procedure performed for personal history of polyps	dichotomous
risk_ca	Procedure performed for personal history of colorectal cancer	dichotomous
doc_id	Anonymized unique endoscopist identifier	categorical
doc_adr	Endoscopist adenoma detection rate	continuous
doc_spec	Endoscopist specialty (gastroenterology or colorectal surgeon)	dichotomous
proc_year	Year in which procedure was performed (from 2013–2017)	categorical
proc_wt6	Colonoscopy withdrawal time ≥ 6 minutes	dichotomous
proc_diff	Difficult procedure, as rated by the endoscopist	dichotomous
prep_poor	Poor bowel preparation, as rated by the endoscopist	dichotomous
path_adenoma	Any adenomatous polyp found during the procedure	dichotomous
path_adv_ad	Advanced adenomatous polyp found during the procedure	dichotomous
path_hp	Hyperplastic polyp found during the procedure	dichotomous
path_ssl	Sessile serrated lesion found during the procedure	dichotomous
path_tsa	Traditional serrated adenoma found during the procedure	dichotomous

2.3.4. SSL outcome definitions

The clinicopathologic definition of SSLs has evolved over time to reflect advancements in the understanding of this neoplastic lesion (**Figure 2**). To reduce inconsistency arising from inter-pathologist variation in reporting of SSLs, the CCSC adopted an internal policy in 2016 of

reclassifying all hyperplastic polyps > 5 mm in size and proximal to the sigmoid colon as SSLs. The rationale of this decision was to capture more polyps that were truly SSLs but had been misclassified as hyperplastic. The potential loss in specificity of the SSL diagnosis was felt to be minimal, as large, proximal hyperplastic lesions are rare. For these reasons, examinations were considered positive for an SSL if either (1) SSL histology was identified on the pathology report or (2) if a hyperplastic polyp met the above institutional criteria and was later re-classified by our pathology nurse. Where a discrepancy existed between these two sources in distinguishing hyperplastic polyps from SSLs, the source making an SSL diagnosis was favored.

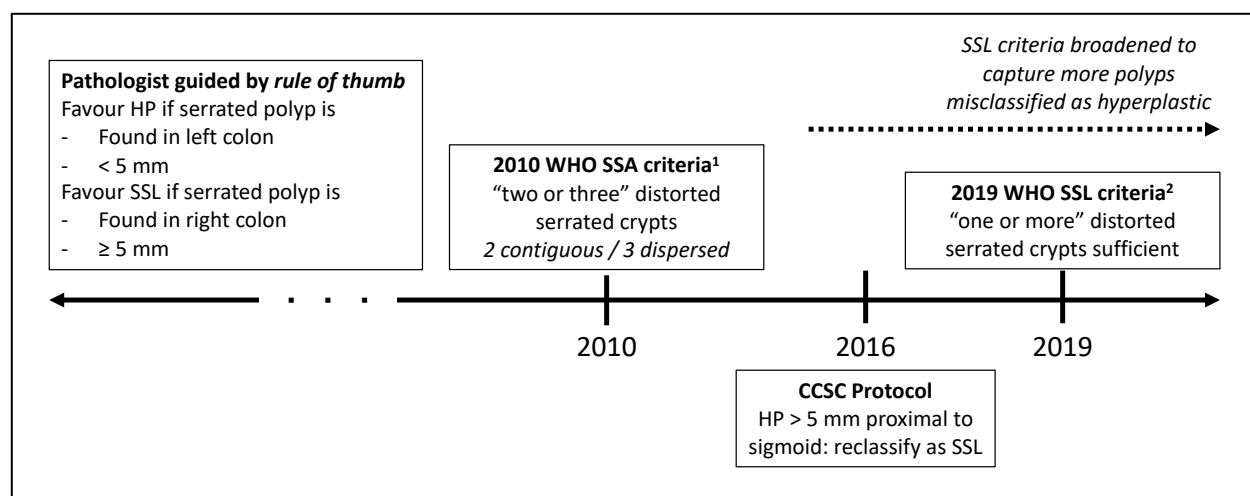


Figure 2. Evolution of SSL criteria. Classically, serrated polyps found in the left colon and/or < 5 mm in size were favored to represent hyperplastic polyps, while those found in the right colon and/or ≥ 5 mm in size were favored to be SSLs. The World Health Organization (WHO) published criteria in 2010 for SSLs requiring "two or three" distorted serrated crypts¹⁹ and then later expanded this criteria to include all serrated polyps with "one or more" distorted crypts.⁸ During the interval in which these criteria were being relaxed, our institution adopted an internal policy in 2016 of reclassifying all hyperplastic polyps > 5 mm in size that were proximal to the sigmoid colon as SSLs.

This choice was made to increase SSL diagnostic sensitivity, while only incurring a minimal loss in specificity, as large, proximal hyperplastic lesions are relatively rare.

2.3.5. *Statistical analyses*

Significant trends in SSLDR were assessed using the non-parametric Jonckheere–Terpstra test for trend. Logistic regression modelling was used to assess for potential effect modifiers and confounders of the relationship between SSL detection rate and year of procedure, treated as a categorical variable. Model fit was assessed by the Pearson chi-squared goodness-of-fit test. Subsequently, multivariable logistic regression analysis was conducted using the statistically significant or clinically relevant variables identified in the univariable analysis. Missing data was addressed using listwise deletion. Model fit was assessed quantitatively with Hosmer–Lemeshow chi-squared goodness-of-fit test and qualitatively via calibration plots comparing deciles of observed and predicted proportions. Model accuracy was evaluated with 200-fold bootstrap optimism-corrected area under the receiver operating characteristic curve (AUC). To account for the random effect of the performing endoscopist, we modeled the relationship between SSLDR and procedure year using a mixed effects multiple logistic regression with 1000-fold clustered bootstrapping. Model fit was assessed similarly to the multiple logistic regression model.

Finally, several common supervised ML models were considered to investigate for potential non-linear, complex relationships among covariates. Selected learning algorithms included the ensemble classification models—random forest and extreme gradient boosting—as well as feed-forward neural networks. These models were chosen for their relative simplicity in implementation and high performance in complex-relation ML tasks using a dataset of this size.

All relevant predictive features were made available during model training. Data was partitioned into 80-20 train-test sets to permit internal validation. A preprocessing pipeline included simple imputation, one-hot encoding of categorical features, and standard scaling of continuous features to zero mean and unit variance. Model hyperparameters were selected using a grid search strategy with 3-fold cross-validation and evaluated by AUC. This threshold agnostic metric was used to counter issues with class imbalance. Confusion matrices for the various ML models were calculated using a detection threshold set equal to the SSL prevalence in the training dataset and used to generate model sensitivity, specificity, accuracy, balanced accuracy, and F1 score. Models were further evaluated by constructing receiver operating characteristic and precision-recall curves. In the case of the decision-tree models, feature importance was calculated using mean decrease in impurity, and, for all models, feature permutation importance was calculated as the mean decrease in AUC during 10-fold shuffling of predictor variables. Calibration plots were constructed to interrogate model reliability using deciles of model predictions plotted against the true SSL detection prevalence, evaluated over the test dataset. Code for model architecture, training, evaluation, and interpretability analysis has been made available online along with the final model parameters (**Appendix A**).

Statistical analysis was conducted using Stata version 17.0.⁷⁹ ML models were trained and evaluated in Python using scikit-learn version 1.1.2⁸⁰ with the extreme gradient boosting algorithm provided by the XGBoost library.⁸¹

2.3.6. *Ethical Considerations*

Appropriate ethical review and approval of consent procedures, data collection, and data storage has been obtained through the Health Research Ethics Board of Alberta (HREBA.CC-21-0329).

2.4. Results

2.4.1. *Study cohort*

A total of 74,283 unique patient procedures performed by 57 endoscopists comprised the final study cohort. Patient and procedure characteristics are reported in **Table 2**. There were 7,573 procedures during which one or more SSLs were detected, corresponding to an average SSLDR of 10.2% (95% CI [10.0%–10.4%]) over the study period.

SSLDR was seen to increase over time from an initial rate of 8.1% (95% CI [7.7%–8.5%]) in 2013 to a rate of 12.2% (95% CI [11.5%–13.0%]) in 2017. The trend over time was significant (Jonckheere–Terpstra test for trend, $z = 13.9$, $p < 0.001$). The increase in SSLDR was mirrored by a similar increase in ADR over the same time period, from a rate of 32.6% (95% CI [31.9%–33.3%]) in 2013 to a maximum of 43.5% (95% CI [42.3%–44.7%]) in 2017. However, the increase seen in ADR was largely driven by an increase in the proportion of FIT positive procedures being performed. When stratifying by FIT status, the trend of increasing polyp detection is well preserved for SSLs but is attenuated for adenomas (**Figure 3**).

Table 2. Patient and procedure characteristics stratified by SSL status. Patient age in years is given as average \pm standard deviation. *p*-values are shown for tests of equal proportions or two-sample *t*-test between those procedures with and without SSL, where appropriate. CRC/AA, colorectal cancer or advanced adenoma; FIT+, positive fecal immunohistochemical test; OR, odds ratio; SSL, sessile serrated lesion.

	Overall (n = 74,283)	No SSL detected (n = 66,710)	SSL detected (n = 7,573)	<i>p</i> -value
Sex				
Male	37,623 (50.6%)	33,894 (50.8%)	3,729 (49.2%)	0.010
Female	36,660 (49.4%)	32,816 (49.2%)	3,844 (50.8%)	
Age, years	57.9 (± 7.6)	57.8 (± 7.6)	58.3 (± 7.7)	< 0.001
Diabetic	4,799 (6.5%)	4,402 (6.6%)	397 (5.2%)	< 0.001
FIT+	13,410 (23.9%)	11,988 (18.0%)	1,428 (18.9%)	0.058
Risk				
Average risk	31,873 (42.9%)	29,133 (43.7%)	2,740 (36.2%)	< 0.001
Family history CRC/AA	18,476 (24.9%)	16,516 (24.8%)	1,960 (25.9%)	0.032
Personal history polyps	11,192 (15.1%)	9,649 (14.5%)	1,543 (20.4%)	< 0.001
Personal history CRC	345 (0.5%)	309 (0.5%)	36 (0.5%)	0.883
Procedure year				
2013	18,109	16,648	1,461	< 0.001
2014	18,521	16,764	1,757	
2015	16,322	14,562	1,760	
2016	14,534	12,769	1,765	
2017	6,797	5,967	830	
Withdrawal time ≥ 6 min	58,069 (81.1%)	51,054 (79.3%)	7,015 (96.3%)	< 0.001
Poor bowel preparation	19,815 (26.8%)	17,553 (26.4%)	2,262 (30.0%)	< 0.001
Difficult procedure	9,608 (13.2%)	8,640 (13.2%)	968 (13.0%)	0.637

2.4.2. Sessile serrated lesion detection over time

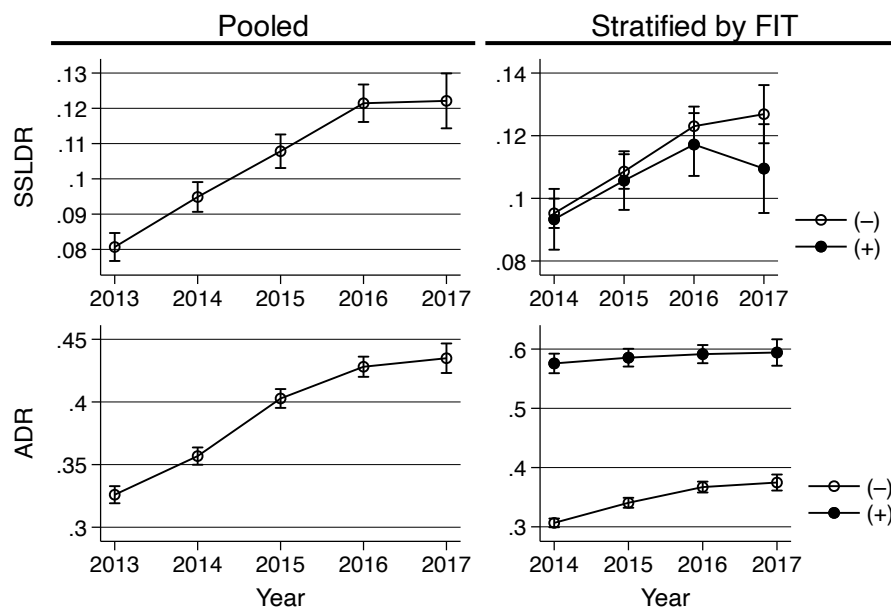


Figure 3. Sessile serrated lesion and adenoma detection prevalence over time. Crude detection rates are presented as either pooled proportions or stratified by fecal immunohistochemical test status. Error bars represent 95% confidence intervals. ADR, adenoma detection rate; FIT, fecal immunohistochemical test; SSLDR, sessile serrated lesion detection rate.

Multivariable logistic regression modeling was used to model SSLDR over time while adjusting for relevant covariates identified in the univariable analysis (**Table 3**).

Table 3. Patient and procedural factors influencing sessile serrated lesion detection. Estimates are shown for the multivariable logistic regression model and the mixed effects logistic regression model, accounting for the random assignment of the endoscopist. Confidence intervals for the mixed effect model were derived from 1,000-fold normal-based bootstrap estimations. CI confidence interval; CRC/AA, colorectal cancer or advanced adenoma; FIT+, positive fecal immunohistochemical test; OR, odds ratio; SSL, sessile serrated lesion.

	Logistic regression model, SSL OR (95% CI)	Mixed effects logistic regression model, SSL OR (95% CI)
Procedure year (vs 2013)		
2014	1.15 (1.06–1.24)*	1.13 (1.03–1.25)*
2015	1.23 (1.14–1.33)*	1.16 (1.03–1.30)*
2016	1.29 (1.19–1.40)*	1.20 (1.05–1.38)*
2017	1.28 (1.16–1.40)*	1.20 (1.06–1.35)*
Patient age (per decade)	1.01 (1.00–1.01)*	1.01 (1.00–1.01)*
Patient sex (female vs male)	1.17 (1.11–1.23)*	1.16 (1.09–1.24)*
Diabetic	0.72 (0.64–0.80)*	0.73 (0.67–0.80)*
FIT+	0.99 (0.92–1.06)	0.98 (0.91–1.05)
Family history CRC/AA	1.17 (1.10–1.25)*	1.13 (1.08–1.19)*
Personal history of polyps	1.43 (1.33–1.53)*	1.40 (1.30–1.51)*
Poor bowel preparation	1.12 (1.06–1.18)*	1.10 (1.02–1.18)*
Withdrawal time	6.66 (5.87–7.54)*	6.26 (4.39–8.92)*

* Denotes statistical significance at the $\alpha = 0.05$ level

SSLDR continued to increase over time after adjusting for relevant covariates (**Figure 4**). While SSLDR was seen to increase over the entire study period (2017 vs 2013, OR 1.28, 95% CI [1.16–1.40]), detection rates began to stabilize towards the end of the study (2017 vs 2016, OR 0.987, 95% CI [0.901–1.08]). Withdrawal time ≥ 6 minutes was the strongest predictor of SSL detection over time (OR 6.66, 95% CI [5.87–7.54]), while female sex (OR 1.17 95% CI [1.11–1.23]), personal

history of polyps (OR 1.43, 95% CI [1.33–1.53]), family history of advanced adenoma or CRC (OR 1.17, 95% CI [1.10–1.25]) and poor bowel preparation (OR 1.12, 95% CI [1.06–1.18]) remained weakly associated with SSL detection. Advancing patient age was also weakly associated with SSL detection, with each decade increasing odds of SSL detection by a factor of 1.06 (95% CI [1.02–1.10]). Positive diabetic status was observed to be a protective factor (OR 0.72, 95% CI [0.64–0.80]). FIT positivity (OR 0.99, 95% CI [0.92–1.06]) was not associated with SSL detection.

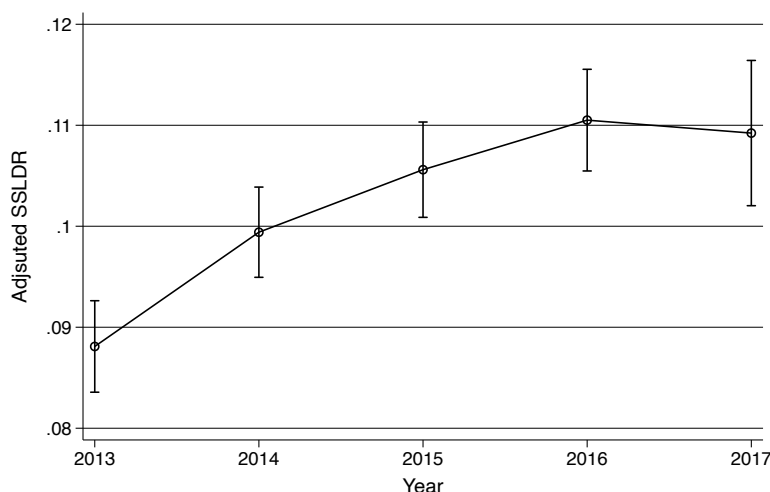


Figure 4. Adjusted sessile serrated lesion detection prevalence over time. Data points represent the marginal proportion of procedures in which a sessile serrated lesion was detected in each year, adjusted for relevant confounders in the multivariate logistic regression model. Error bars represent 95% confidence intervals. SSLDR, sessile serrated lesion detection rate.

Model diagnostics for the multivariable logistic regression analysis demonstrated a reasonable fit to the observed data by both goodness-of-fit testing (Hosmer–Lemeshow χ^2 , $p = 0.179$) and visual inspection of the calibration plot (**Figure 5**). Model accuracy was low, however, with optimism-corrected AUC of 0.631 (95% CI [0.625–0.637]).

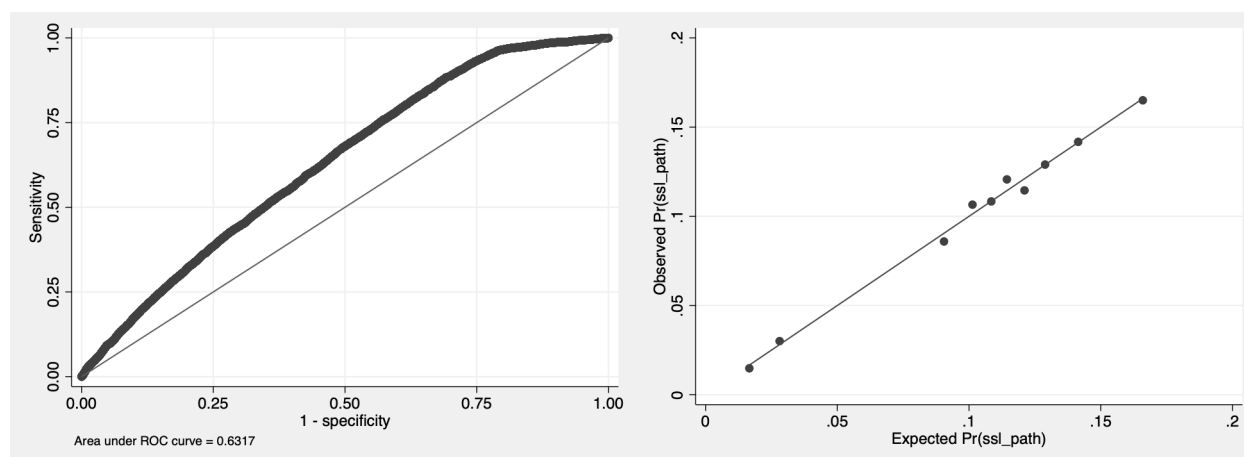


Figure 5. Model performance and diagnostics for the multivariable logistic regression model predicting sessile serrated lesion based on year of procedure, and relevant patient and procedural factors. Plots show ROC curve (optimism-corrected AUC 0.631, 95% CI [0.625–0.637]) and calibration curve. Goodness of fit Pearson chi-square p -value 0.067. Hosmer–Lemeshow chi-square p -value 0.179.

Similar results were obtained when accounting for the random assignment of the endoscopist using a mixed effects multiple logistic regression model (**Table 3, Figure 6**). The trend of increasing SSL detection over time persisted (e.g., 2017 vs 2013, OR 1.19, 95% CI [1.06–1.35]). Detection rates were again demonstrated to stabilize over the last two years in the dataset (2017 vs 2016, OR 0.995, 95% CI [0.920–1.08]). Withdrawal time ≥ 6 min remained the strongest predictor of SSL detection (OR 6.26, 95% CI [4.39–8.92]). The endoscopist accounted for only a relatively small proportion of the variability in SSL detection (intra-class correlation 4.56%, 95% CI [2.58%–7.74%]). Model predictions that considered the random effects of the endoscopist were more accurate than those considering fixed effects only (AUC 0.673, 95% CI [0.667–0.679] vs 0.631, 95% CI [0.625–0.637]). Overall, however, accuracy remained low.

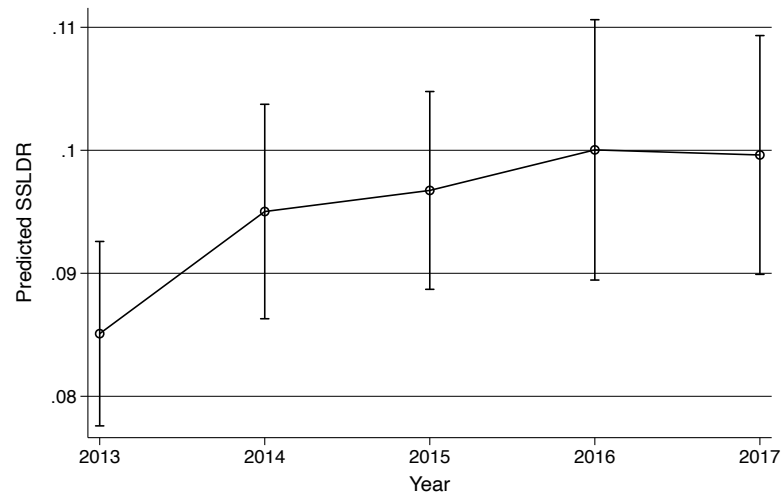


Figure 6. Marginal predictions for sessile serrated lesion detection prevalence over time accounting for clustering by performing endoscopist. Data points represent the marginal predictions of sessile serrated lesion detection prevalence in each year, adjusted for fixed relevant confounders and random effects of the performing endoscopist under the mixed effects multiple logistic regression model. Error bars represent 95% prediction intervals estimated with 1,000 bootstrap replications. SSLDR, sessile serrated lesion detection rate.

The mixed effects model fit the observed data reasonably well by goodness-of-fit testing (Hosmer–Lemeshow χ^2 , $p = 0.429$) and by visual inspection of the calibration plot (**Figure 7**). Model fit was superior to the simpler ordinary logistic regression model that did not account for the endoscopist ($\bar{\chi}_{01}^2 = 601.25$, $p < 0.001$).

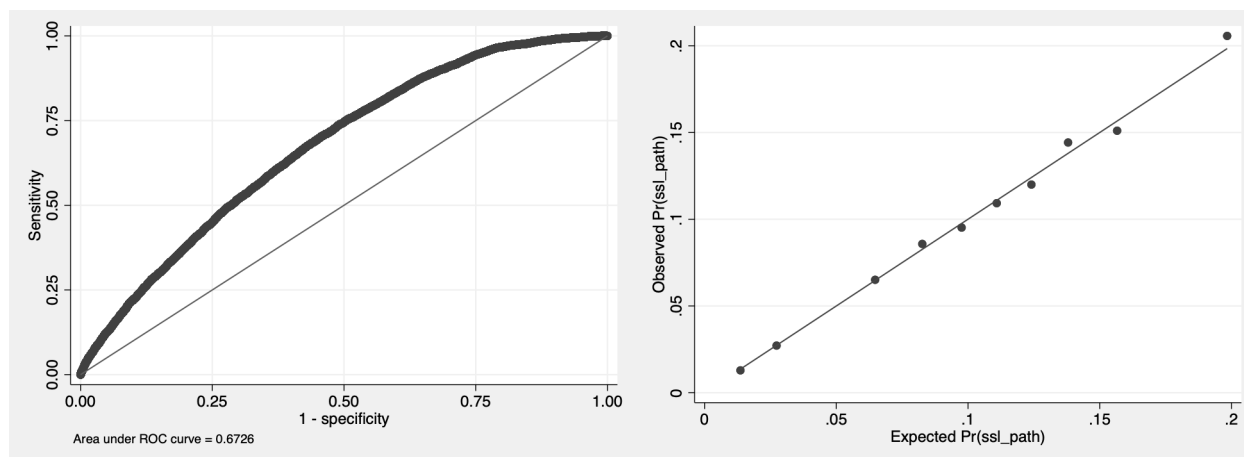


Figure 7. Model performance and diagnostics for the mixed effects multivariable logistic regression model predicting sessile serrated lesion based on year of procedure, relevant patient and procedural factors, and random effects of the performing endoscopist. Plots show ROC curve using predictions incorporating the random effect of the endoscopist (AUROC 0.673, 95% CI [0.667–0.679]) and calibration plot. Hosmer–Lemeshow chi-squared p -value 0.429.

2.4.3. Predicting risk of sessile serrated lesions

We trained several ML models to develop clinical risk prediction tools of SSLs within our cohort. The hyperparameter search space and final model hyperparameters have been made available in **Table 4**. Model parameters are available in an online repository (**Appendix A**). All models performed better than the naïve classifier when comparing balanced classification metrics (*i.e.*, balanced accuracy, F1 score), but exhibited relatively low prediction accuracy when evaluated with AUC (**Table 5**). Under this metric, the model trained with extreme gradient boosting performed better (AUC 0.667, 95% CI [0.655–0.681]) than the random forest classifier or the feed forward neural network (AUC 0.660, 95% CI [0.649, 0.676] and 0.628, 95% CI [0.613–0.639], respectively), which were both superior to the baseline naïve classifier (AUC 0.500, 95% CI [0.492–0.505]).

Table 4. Model hyperparameters for machine learning models. Model hyperparameters were selected from a reasonable range of values using a grid search strategy with 3-fold cross-validation and evaluated by AUROC.

Hyperparameter	Search space	Grid search-optimized hyperparameters	
		Endoscopist-specific	Endoscopist-agnostic
Random forest			
n_estimators	[10, 50, 100, 250, 500]	100	250
min_samples_split	[2, 5, 10]	2	5
min_samples_leaf	[2, 4, 8]	8	8
max_features	['auto']	'auto'	'auto'
max_depth	[5, 10, 15]	10	15
bootstrap	[True]	True	True
Extreme gradient boosting			
max_depth	[3, 5, 7, 9]	5	5
min_child_weight	[1, 3, 5]	1	3
subsample	[0.6, 0.7, 0.8, 0.9]	0.8	0.6
colsample_bytree	[0.6, 0.7, 0.8, 0.9]	0.8	0.6
gamma	[0.0, 0.1, 0.2, 0.3, 0.4]	0.1	0.0
learning_rate	[0.1, 0.3, 0.5, 1]	0.1	0.1
n_estimators	[50, 100, 250, 500, 1000]	50	100
Neural network			
hidden_layer_sizes	[(25, 10, 10),(50, 25, 25),(100, 50, 25)]	(25, 10, 10)	(25, 10, 10)
activation	['tanh', 'relu']	'tanh'	'relu'
solver	['adam']	'adam'	'adam'
alpha	[1e-4]	1e-4	1e-4
learning_rate	['adaptive']	'adaptive'	'adaptive'

Table 5. Classification metrics of machine learning models predicting SSL status. Models were trained with either knowledge of the specific performing endoscopist or with an engineered feature containing the endoscopist adenoma detection rate (endoscopist-agnostic models). Models were evaluated using test data not seen during training. Classification threshold was set equal to the SSL prevalence in the training dataset (0.102). 95% confidence intervals were calculated using decile-based 100-fold bootstrap estimates. AUC, area under the receiver operating characteristic curve; XGB, extreme gradient boosting.

	Sensitivity	Specificity	Balanced accuracy	F1 score	AUC
<i>Endoscopist-specific models</i>					
Random forest	0.694 (0.671–0.716)	0.527 (0.519–0.533)	0.610 (0.598–0.623)	0.238 (0.227–0.249)	0.660 (0.645–0.676)
XGB	0.669 (0.645–0.689)	0.559 (0.550–0.566)	0.614 (0.599–0.624)	0.242 (0.232–0.253)	0.667 (0.655–0.679)
Neural network	0.565 (0.539–0.587)	0.614 (0.605–0.621)	0.590 (0.576–0.601)	0.228 (0.217–0.239)	0.628 (0.612–0.641)
<i>Endoscopist-agnostic models</i>					
Random forest	0.684 (0.665–0.706)	0.533 (0.526–0.541)	0.609 (0.599–0.621)	0.237 (0.227–0.250)	0.658 (0.646–0.672)
XGB	0.700 (0.675–0.721)	0.522 (0.514–0.532)	0.611 (0.599–0.625)	0.238 (0.227–0.248)	0.660 (0.650–0.673)
Neural network	0.665 (0.641–0.688)	0.548 (0.540–0.556)	0.607 (0.596–0.619)	0.237 (0.227–0.250)	0.658 (0.644–0.668)
Naïve classifier	0.110 (0.094–0.126)	0.902 (0.897–0.906)	0.506 (0.498–0.514)	0.111 (0.097–0.127)	0.506 (0.498–0.512)

Using feature permutation importance to identify salient predictors, the performing endoscopist was uniformly selected as the most important factor in predicting SSL status across all models. Other important factors common to all models were the procedure year, patient age and sex, and if an adenomatous polyp was also found during the procedure (**Figure 8**). Model reliability was assessed visually with calibration plots (**Figure 9**). All models were better calibrated than the naïve classifier when comparing predicted probabilities with observed SSLDR. Models were only reliable within a small range of probabilities close to the average detection prevalence and tended to overestimate true SSL risk at higher predictions.

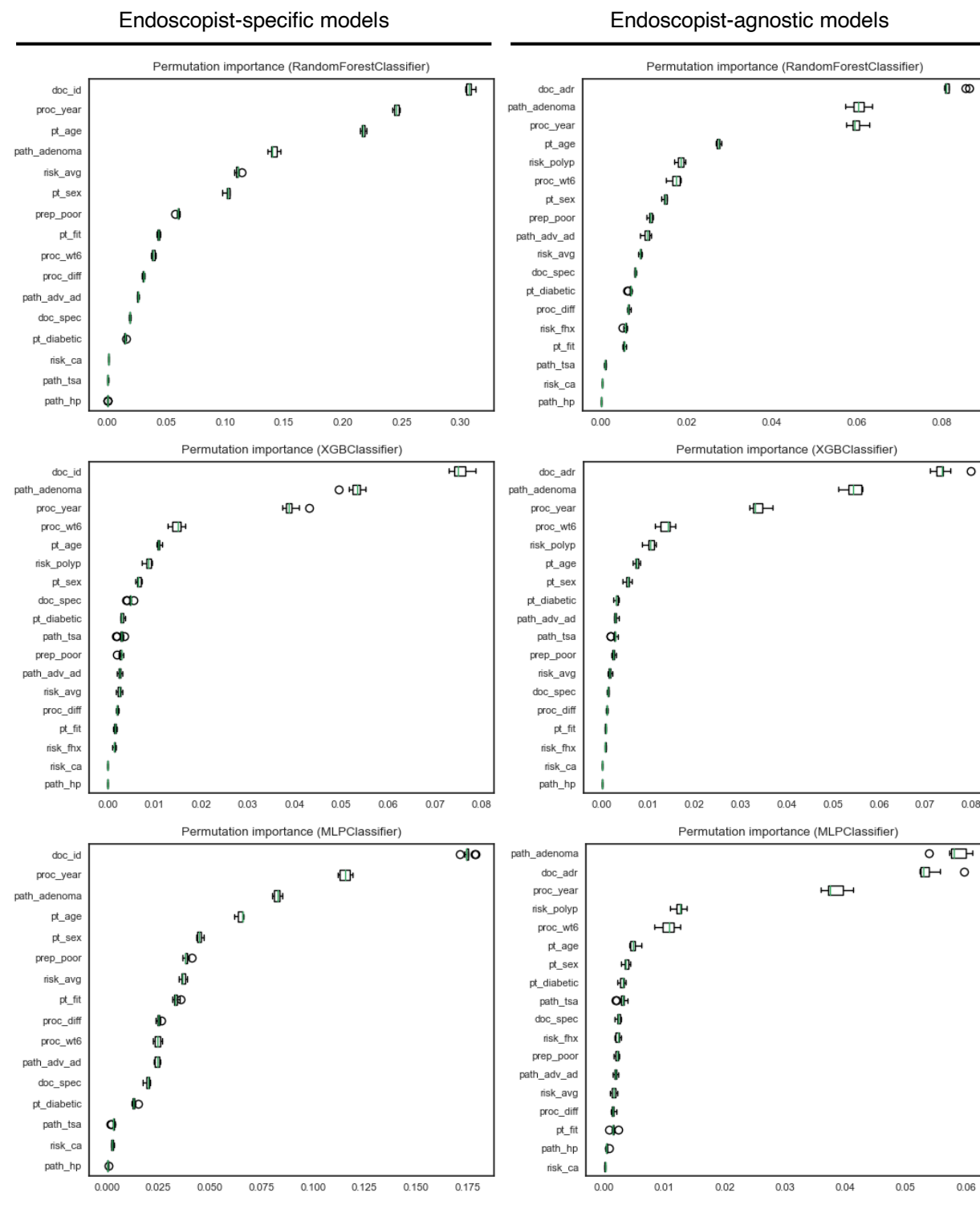


Figure 8. Feature permutation importance in predicting SSL probability in endoscopist-specific and -agnostic machine learning models. Machine learning models, trained on datasets using either a unique endoscopist identifier

(endoscopist-specific) or their adenoma detection rate (endoscopist-agnostic), were interrogated for interpretability by feature importance. This was calculated as the mean decrease in AUC during 10-fold shuffling of rows within a specified predictor variable. RandomForestClassifier, random forest model; XGBClassifier, extreme gradient boosting model; MLPClassifier, feed-forward neural network.

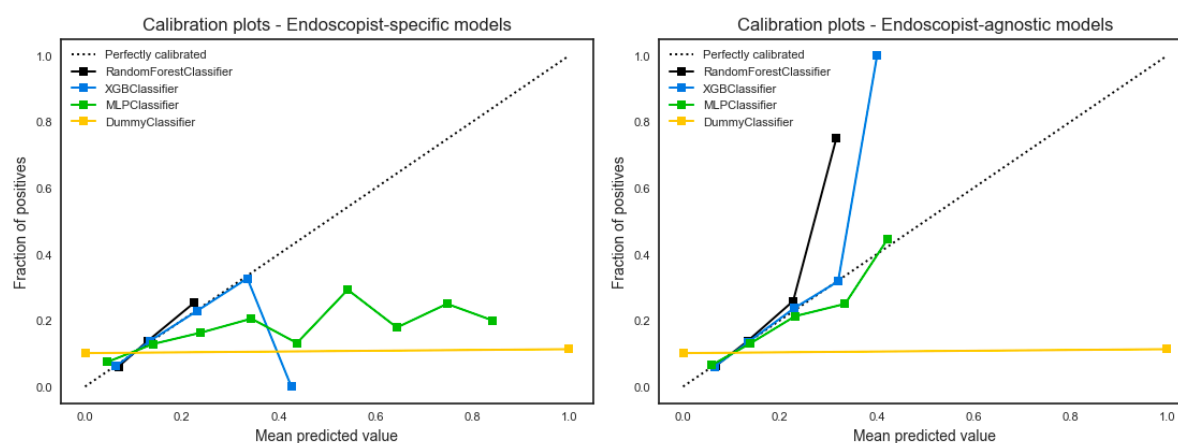


Figure 9. Calibration plots for machine learning models trained on datasets using either a unique endoscopist identifier (endoscopist-specific) or their adenoma detection rate (endoscopist-agnostic). Plots were constructed using deciles of model predictions plotted against the true SSL detection prevalence, evaluated over the test dataset. MLPClassifier, feed-forward neural network; RandomForestClassifier, random forest model; XGBClassifier, extreme gradient boosting model.

Because the key factor in predicting SSL status in these ML models was the specific performing endoscopist, the utility of these model predictions is inherently limited to our specific cohort. Therefore, to improve the generalizability of these predictions outside of our cohort, the models were retrained after substituting each performing endoscopist for their ADR over the study period, which is a well-accepted marker of quality in screening colonoscopy. These endoscopist-agnostic models were demonstrated to have no meaningfully different performance in SSL prediction (**Table 5, Figure 10**).

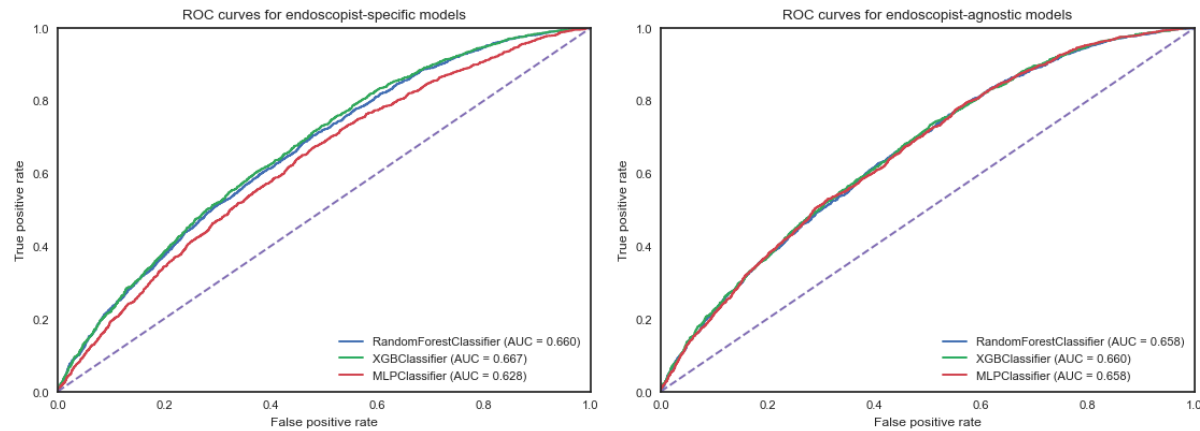


Figure 10. Receiver operating characteristic curves for machine learning models trained on datasets using either a unique endoscopist identifier (endoscopist-specific) or their adenoma detection rate (endoscopist-agnostic) and evaluated on the test dataset. AUC, area under the receiver operating characteristic curve; MLPClassifier, feed-forward neural network; RandomForestClassifier, random forest model; XGBClassifier, extreme gradient boosting model.

The model trained with extreme gradient boosting again performed better than the other classifiers, when comparing AUC (0.660, 95% CI [0.648–0.673]; $p < 0.001$), while the feed-forward neural network performed similarly to the random forest classifier (AUC 0.658, 95% CI [0.641–0.670] vs 0.658, 95% CI [0.643–0.672], respectively; $p = 0.374$). Feature permutation importance analysis revealed ADR and synchronous adenoma to be the most important factors influencing model accuracy across all models, when evaluated with AUC (**Figure 8**). Other important factors common to all models were the year in which the procedure was performed, withdrawal time ≥ 6 minutes, patient age and sex, and prior personal history of polyps. Calibration plots demonstrated reasonable reliability when predictions were close to the mean detection prevalence, but ensemble models tended to underestimate SSL risk at higher levels of predicted

risk (**Figure 9**). The neural network model, however, appeared well-calibrated throughout its range of predicted risk.

2.5. Discussion

In this 5-year study at a high-volume, dedicated colonoscopy screening centre, we demonstrated a mean SSLDR of 10.2% and a recent positive temporal trend in SSL detection, with SSLDR having increased from an initial rate of 8.1% in 2013 before appearing to plateau at 12.2% by 2017. This pattern of enhanced SSL detection during recent years may explain some of the variability in SSLDR reported in the literature.^{51, 53-58}

2.5.1. Temporal trends of SSLDR in the literature

Positive trends in SSLDR have been demonstrated by other groups as well. In an audit of pathologic SSL reporting over the years 2009–2012, there was an exponential growth in the absolute number of SSLs reported during this period, even when using the relatively restrictive 2010 WHO SSL diagnostic criteria.⁸² More recently, a study examining over 10,000 colonoscopies between 2012–2018 found that procedures performed in later years were associated with higher SSLDR; though, overall SSLD was low at 2.2%.⁸³ Data from a large quality improvement registry examining over 5 million procedures across the United States showed a significant increase in SSLDR from 5.0% in 2014 to 7.1% in 2017.⁸⁴ Taken together with our own results, these data provide convincing evidence for a positive trend in SSLRD, even if considerable variability between centres exists. Indeed, it is well known that SSL detection is highly dependent on the endoscopy centre, likely reflecting differences in the ability of pathologists to correctly identify and diagnose SSLs.⁵⁴

2.5.2. *Hypothesizing mechanisms to explain the observed trend of increasing SSLDR over time*

We posit several reasons to account for this trend of increasing SSL detection. First, the adoption of standardized diagnostic criteria for SSLs has likely led to enhanced pathologic detection and fewer lesions being misclassified as hyperplastic polyps. Over the past several years, the WHO classification of SSLs has undergone two main revisions. After 2010, when diagnostic criteria were updated to distinguish SSLs from hyperplastic polyps by the presence of at least one or two dilated crypts,¹⁹ an estimated 8–19% of all hyperplastic polyps diagnosed between 2000-2010 were reclassified as SSLs.²⁰⁻²⁴ When considering only large hyperplastic polyps, the estimated increase in SSL diagnosis grew to 28%. When classification criteria were relaxed in 2019 to only require the presence of a single dilated crypt,⁸ a further 7% increase was seen in the proportion of serrated polyps diagnosed as SSLs.²⁵ This streamlining of classification criteria has been demonstrated to reduce inter-observer variability among pathologists.²⁶ Screening centres that have access to specialized gastrointestinal pathologists who are familiar with these criteria tend to report higher SSLDRs, after adjusting for patient case-mix.⁸⁴

Second, as we developed a better understanding of SSLs, their role as a precursor of serrated adenocarcinoma, and their association with interval cancer, endoscopist awareness and vigilance for these polyps has increased. Indeed, expert opinion and practice guidelines from the early part of the last decade have already been advocating for the optimization of detection, removal, and surveillance of clinically significant serrated polyps.^{48, 61} With the growing recognition of SSLs as being important targets of screening and surveillance colonoscopy, their specific detection benchmarks are now being published in practice guidelines.^{64, 67, 85} While the publication of these

benchmarks comes too late to influence SSLDR in our study, other centres with lower detection rates may soon see similar improvements in SSL detection with enhanced endoscopist awareness and/or through quality improvement initiatives aimed at meeting detection targets.

Finally, recent years have seen a panoply of technological advancements and adjunctive techniques to enhance polyp detection at endoscopy.^{59, 60} Optical enhancements, wide-angle or full-spectrum colonoscopy, distal attachment devices, and colonoscopy in retroflexion have seen variable adoption at screening centres, but studies investigating SSL prevalence do not routinely report or stratify by adjunctive technology. Therefore, while such advances are anticipated to have improved SSL detection over the last decade, little is known of their true effect on SSLDR. Within the last few years, real-time computer-assisted polyp detection systems have been demonstrated to enhance detection of colonic neoplasia, including SSLs.⁸⁶ This technology is still in its early stages, however, and further work is still required to see how artificial intelligence systems will affect SSL detection in the future.

2.5.3. Patient, procedural, and endoscopist factors influencing SSLDR

To demonstrate that the observed trend in SSLDR was not an artifact of shifting case-mix within our centre, we analyzed several potential patient confounders, including FIT status. In response to increasing screening demands, our centre prioritized FIT positive patients in later years. Consequently, as FIT is known to correlate well with adenomas,⁸⁷ there was an observed increase in ADR over the study period. As expected, this trend was attenuated after adjusting for FIT status. SSLDR, however, was not dependent on FIT and the trend in SSL detection persisted in these adjusted models. This finding is consistent with the results from a large case-series of

72,000 colonoscopies from an Italian CRC screening program that demonstrated a lack of association between FIT and SSL detection.⁵⁷

At the patient level, advancing age, female sex, non-diabetic status, a personal history of polyps, or a family history of advanced adenoma or CRC was associated with SSL detection, while FIT status was not. Age does not appear to play the same role in conferring risk in SSLs as it does in conventional adenomas. While those patients who are younger than 50 years of age have a lower risk of SSLs than those older than 50, the risk has not been shown to increase significantly beyond age 50.³⁸⁻⁴⁰ In other studies, sex distribution of SSLs appears to be equivalent between males and females,⁴¹⁻⁴³ although there are conflicting reports in the literature with some studies demonstrating higher rates among men^{44, 45} and others reporting higher rates among women.^{46,}⁴⁷ Type 2 diabetes is known to be associated with both overall and proximal CRC.⁸⁸ However, this risk is specific to men and was further increased by a present or past history of smoking. There is some evidence that diabetes may be associated with SSL detection,⁸⁹ but in this retrospective case-controlled study, the authors note that diabetes was closely linked with obesity, and diabetic status was omitted from final multivariable models. It remains unclear if diabetes plays a role in the serrated adenocarcinoma pathway. Unlike ADR, which is known to be significantly higher among those undergoing surveillance versus screening colonoscopy, SSLDR has been demonstrated to be only weakly associated with a personal history of polyps.⁹⁰ Our findings support this conclusion with only a modest increase in odds of SSL detection observed among those with previous polyps.

Out of all procedural factors considered, withdrawal time was the strongest predictor of SSL detection. In procedures where the withdrawal times was at least 6 minutes, the odds of SSL detection were more than six times those with shorter withdrawal times, after accounting for variation in the performing endoscopist. It is important to note that our analysis could not differentiate between withdrawal time and post-cecal intubation procedure time on a per-procedure basis. Therefore, the association between SSL detection and longer withdrawal time is most likely reflective of the additional time required to perform polypectomy. However, we also hypothesize that additional factors contribute to this association. Specifically, longer withdrawal time allows for more meticulous cleansing and inspection of the mucosal surface. Such scrupulousness is particularly important for the detection of SSLs, which often have subtle features and are more often located in the proximal colon, where bowel preparation tends to be poorer. Similar associations of SSLs and withdrawal time have been previously demonstrated.^{71,}

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Somewhat counterintuitively, we demonstrated a weak association between SSL detection and less than optimal bowel preparation. The idea that residual stool may obscure sessile polyps is supported by evidence from a Veterans Affairs study examining 749 males undergoing screening or surveillance colonoscopy.⁹² The authors showed a significantly lower SSLDR in those with intermediate- vs high-quality bowel preparation (4.6% vs 12.0%) and the effect was even stronger for proximal SSLs. Other groups,^{53, 71} however, have not demonstrated a significant association between bowel preparation quality and SSL detection. These authors hypothesize that small amounts of residual stool/mucous may be beneficial in localizing SSLs by enhancing the visual contrast between clean mucosa and the mucous cap of an SSL. Alternatively, the additional

washing required in poorer bowel preparations may help focus the attention of the endoscopist to these polyps. The findings of our study lend credence to these later hypotheses.

2.5.4. *SSL risk prediction with ML models*

Prediction accuracy of all ML models was superior to the ordinary logistic regression model (comparing test-set AUC to optimism-corrected AUC), but no better than the mixed effects logistic regression model that accounted for clustering by the performing endoscopist. The best-performing algorithm only achieved an accuracy of 66.7%, as assessed by AUC. Taken together, these findings suggest that while the relationship between SSL risk and various patient, procedural, and endoscopist factors may be complex, much of the variability in SSL risk is still likely accounted for by unmeasured variables.

Several additional epidemiologic risk factors for SSLs not included in our study have been identified in the literature. Cigarette smoking is associated with an overall higher risk of SSLs and large SSLs, as well as a higher risk of both distal and proximal serrated polyps in general.^{40, 43, 48, 75, 77, 89} Higher body mass index^{75, 89} and higher education⁴³ have been correlated with SSLs. Inconsistent associations have been demonstrated with alcohol, fiber, and calcium intake, as well as NSAID use.⁴⁸ Contrastingly, physical activity and intake of vitamin D, folate, and omega-3 fatty acid have been demonstrated to be protective.^{48, 75} Predictive models that incorporate these epidemiologic factors are likely to exhibit better performance metrics.

Our ML analysis underscores the association between the performing endoscopist and SSL detection. The endoscopist-specific models uniformly identified the provider as the single most

important factor in predicting SSL risk. When the identity of the provider was hidden from the models, colonoscopy quality metrics, including ADR and longer withdrawal time, became important factors in predicting SSL risk. This finding suggests that high quality examination technique, and its proxy measure, ADR, are good surrogates for the performing endoscopist in predicting SSL detection. Moreover, this lends support for the hypothesis that endoscopist performance in SSL detection is not just reflective of innate technical qualities, but instead, can be influenced by modifiable characteristics. Thus, quality improvement initiatives, including program audits and physician feedback may have an important role to play in determining future trends of SSLDR. While the utility of these interventions in enhancing ADR has been previously demonstrated,⁹³ further work is still needed to determine if the benefits of such interventions are transferable to SSL detection.

2.5.5. Study strengths and limitations

Our study has several strengths. This was a large study spanning five years, which included prospectively collected data from an administrative database on all patients undergoing colonoscopies at a dedicated screening and surveillance centre. As such, deficiencies in data were minimal and both the study target population and the outcome measure of SSL were well defined. As we were strictly investigating only screening and surveillance procedures, our results are directly applicable to other high-quality screening programs. Our institution has access to a dedicated gastrointestinal-specialized pathology group, providing additional confidence and consistency in SSL diagnosis, as per latest WHO diagnostic criteria. Further, our study captured a particularly relevant five-year period that was able to demonstrate significant growth in SSLDR

before appearing to reach a plateau. Finally, to our knowledge, this is the first use of ML algorithms to predict SSL risk in a screening-eligible population.

Limitations of this work that should also be considered. First, while our data were prospectively collected, the study design is inherently retrospective. We were thus limited in the variables available to assess for SSL risk. For example, while we were able to determine if an SSL was detected during a procedure, we did not know if or how many other SSLs were synchronously detected. Patients with multiple concurrent SSLs may be used to highlight important determinants of SSL risk. Further, our dataset did not include additional patient-level factors that have been previously shown to be associated with SSLs, such as diet, medications, and supplements. This likely contributed to lower model accuracy in predicting SSL risk. With respect to procedure-level factors, withdrawal time and endoscopic adjuncts were not accurately captured. While withdrawal time typically refers to the time spent washing and inspecting the mucosal surface and excludes therapeutic interventions, our data did not distinguish between withdrawal time and post-cecal intubation procedural time, and therefore, on a per-procedure basis, we were unable to control for this confounding factor. We explore the effect of withdrawal time on a per-endoscopist basis in a future analysis. We were also unable to account for potential technological advances in endoscope technology or for the use of endoscopic adjuncts that may have enhanced SSL detection. Secondly, this was a single centre study, and, while we used internal validation to evaluate the accuracy of our models, a lack of external validation that data from other sites would afford limits the generalizability of our findings.

2.5.6. *Concluding remarks and future directions*

In this study, we observed an increase in SSLDR over time, which was independent of known patient-, procedure-, and provider-level factors. We speculate that the cause of this trend is multifactorial and includes the adoption of a standardized diagnostic criteria for SSLs, enhanced awareness and recognition of SSLs by endoscopists, and technological advancements in endoscopy that improve lesion detection. Despite accounting for these temporal trends, accurately modeling SSL risk at a patient level remains a challenge, as much of the variability in SSL risk is likely attributable to either unknown or unmeasured patient factors. Further work is still required to elucidate other relevant patient risk factors to enhance the predictive capabilities of models that could then be used to inform individualized screening and surveillance intervals. Another key finding of this work is that procedural and endoscopist factors, including withdrawal time and ADR, are important predictors of SSL risk. This observation highlights important opportunities for SSL detection benchmarking and quality improvement, which we intend to explore in future work.

Chapter 3. Association between endoscopist factors and sessile serrated lesion detection

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None

Word Count

5761

3.1. Abstract

3.1.1. *Background*

Sessile serrated lesions (SSLs) are responsible for a disproportionate number of interval colorectal cancers following high-quality screening colonoscopy. While clinical practice guidelines promote minimum SSL detection benchmarks, considerable variation in SSL detection still exists. The endoscopist factors driving suboptimal performance remain largely unknown. In this large, cross-sectional study at a dedicated screening centre, we report detection rates of serrated polyps and construct statistical models to analyze key endoscopist factors influencing SSL detection.

3.1.2. *Methods*

Screening and surveillance colonoscopies performed between 2013–2017 were analyzed, with relevant patient, procedural, and endoscopist characteristics being abstracted. Each provider's number of years since graduation and specialty were available, while their procedural volumes, cecal intubation rate, and polyp detection rates were calculated. Adenoma detection rate (ADR), SSL detection rates (SSLDR), and proximal serrated polyp detection rate (PSPDR) were calculated as the proportion of procedures during which one or more polyps of a specified type was identified. Linear regression was used to model SSL detection rate at the endoscopist level, and logistic regression was used to analyze the relationship between polyp detection rates and various endoscopist factors at the procedural level.

3.1.3. Results

75,079 unique patient procedures were performed by 53 endoscopists. Overall SSLDR was 10.1%, (95% CI [9.9%–10.3%]) and PSPDR was 9.88% (95% CI [9.63%–10.12%]) with considerable variability demonstrated between endoscopists. PSPDR was a reliable surrogate marker of SSLDR ($r=0.93$, 95% CI [0.90–0.97]) and ADR was predictive of SSLDR ($r=0.84$, 95% CI [0.75–0.92]). Higher annual procedure volumes (≥ 500 vs < 250 , OR 1.23, 95% CI [1.12–1.34]), fewer years since graduation (< 10 vs ≥ 20 , OR 1.97, 95% CI [1.81–2.14]) and gastroenterology specialty (gastroenterology vs colorectal surgery, OR 1.52, 95% CI [1.40–1.65]) were associated with enhanced SSL detection.

3.1.4. Conclusion

SSLs are variably detected by endoscopists, with endoscopist performance being linked to both modifiable and unmodifiable characteristics. Because SSLDR correlates with ADR, targeted quality improvement interventions that are known to increase ADR might also be leveraged to improve SSL detection.

3.2. Introduction

Sessile serrated lesions (SSLs) have become increasingly recognized as an important clinical entity, as these polyps represent a disproportionate number of interval cancers at screening and surveillance colonoscopies.^{6, 11, 69, 70} Low SSL detection prevalence coupled with a relatively high incidence of serrated adenocarcinoma raises concerns about the current screening paradigm of colorectal cancer (CRC) and questions the adequacy of SSL detection. To address this deficiency

in care, practice guidelines now reflect the importance of optimizing detection, removal, and surveillance of all serrated polyps with malignant potential.^{61, 68, 85}

Several reasons have been posited as to why serrated adenocarcinomas—*i.e.*, those cancers that arise from SSL precursors—are overrepresented among all interval CRCs. SSLs tend to have subtle morphological features, making endoscopist detection more challenging; they are typically flat or sessile and are often obscured by a mucous cap.⁴⁸ Moreover, SSLs have a higher prevalence in the proximal colon,⁹⁴ where accurate detection is more sensitive to the quality of bowel preparation. When SSLs are identified, resection rates are more often incomplete compared with other polyps, owing to their often-ill-defined borders and the difficulty associated with resection of flat lesions.⁹⁵ All these features are hypothesized to reduce the effectiveness of colonoscopy screening by increasing the probability of dysplastic lesions left *in situ*. While only a minority of SSLs exhibit dysplasia, those that do are believed to exhibit aggressive molecular features and evolve rapidly toward carcinoma.³⁵

To reduce CRC-related deaths, colonoscopy quality benchmarks have been established, setting minimum standards for screening colonoscopy. Common quality metrics include adenoma detection rate (ADR), the proportion of colonoscopies performed in which one or more adenomas were detected; cecal intubation rate (CIR), a proxy of the completeness of mucosal examination; and withdrawal time, a surrogate marker of the thoroughness of inspection.^{63, 72, 96} These benchmarks correlate well with important patient outcomes. For example, ADR has been shown to be inversely associated with the risk of interval CRC and cancer-related death.^{65, 66} Mirroring the recent recognition of SSLs as clinically relevant lesions, clinical practice guidelines

have begun to include suggested detection rates for SSLs alongside other colonoscopy quality benchmarks.^{64, 85} Experts generally recommend a minimum SSL detection rate (SSLDR) target of $\geq 7\%$ at screening colonoscopy.^{64, 67} PSPDR has been proposed as a more practical metric and surrogate marker of SSLDR. It includes all serrated polyps proximal to the splenic flexure and is insensitive to inter-pathologist variability in distinguishing large hyperplastic polyps from SSLs. Published PSPDR benchmarks range between 4.5–11%.^{67, 85, 97}

Endoscopist-level factors, including procedural volumes and specialty training, have been previously demonstrated to be associated with key colonoscopy quality indicators and relevant clinical outcomes.^{98, 99} More recently, endoscopist factors have also been examined as potential determinants of the variation seen specifically in serrated polyp detection. For example, those endoscopists with lower ADRs have been shown to also have lower SSLDRs (fourth vs. first quartile ADR, OR 1.89, 95% CI [1.24–2.90]).⁵⁷ Moreover, in a large multi-centre cross-sectional study examining more than 100,000 procedures, gastroenterologist specialty (OR 1.89, 95% CI [1.33–2.70]) fewer years in practice (≤ 9 years vs. ≥ 27 years, OR 1.52, 95% CI [1.14–2.04]), and higher procedural volumes (highest vs. lowest quartile, OR 1.77, 95% CI [1.27–2.46]) were associated with enhanced serrated polyp detection.⁹ These findings have been subsequently replicated in a separate cohort, strengthening the evidence of these associations.¹⁰⁰

3.2.1. *Aims and objectives*

While these studies provide some initial insight into current SSL detection prevalence and some of the determinants of SSLDR, the considerable variation in reporting of serrated polyp detection has limited the consistent messaging and practicable implementation of SSL detection

benchmarks that could be used to ensure quality standards among endoscopists. In this study, in fulfillment of Objective (3), we share our experience at a dedicated, large volume, high-efficiency screening centre, with the aim of reporting detection rates of serrated polyps and elucidating the key drivers of enhanced SSL detection, both at the procedural level and with respect to the performing endoscopist. Further, we aim to assess the accuracy of using ADR or PSPDR as a predictor of, and surrogate marker for, SSLDR, respectively. This work may serve to inform detection benchmarks, provide a basis for targeted quality improvement initiatives, and advance future work in understanding the impact of SSL detection on interval CRC. This work constitutes a novel addition to current literature, given our focus exclusively on screening colonoscopies conducted within a dedicated screening center. Such a setting inherently fosters a high standard of quality, further enhancing the validity and impact of our findings.

3.3. Methods

3.3.1. *Study design and setting*

This was a large single-centre retrospective cross-sectional study using prospectively collected administrative data available within the Colon Cancer Screening Centre (CCSC) Quality Assurance Database. The CCSC is a high-volume, publicly funded screening centre, performing approximately 17,500 screening or surveillance colonoscopies each year. Referrals are accepted from the Calgary Health Zone for asymptomatic individuals aged 50–75 years who are in good general health (American Society of Anesthesiologists classification 1 or 2). Referral indications include average-risk screening, personal or family history of CRC or adenomatous polyps, or

investigation of a positive fecal immunohistochemical test (FIT). Procedures are performed by a mix of board-certified gastroenterologists and colorectal surgeons.

3.3.2. Cohort selection

The CCSC Quality Assurance Database was reviewed for records appropriate for inclusion in our study (**Figure 11**).

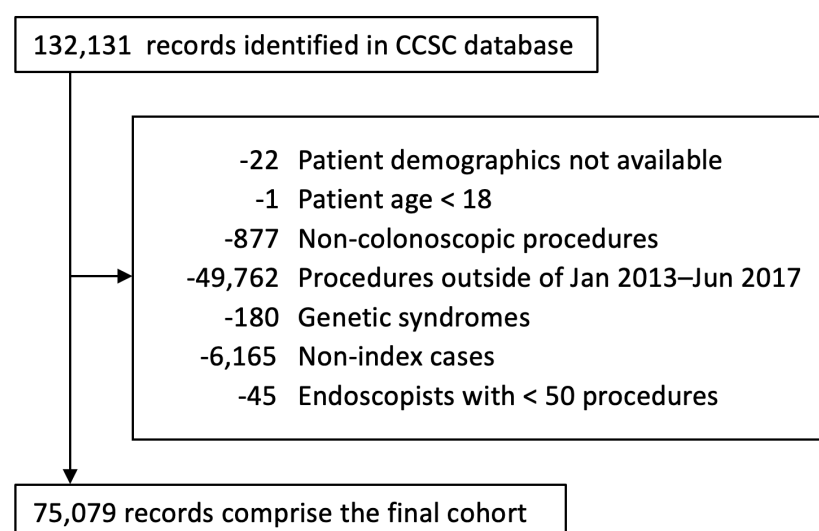


Figure 11. Cohort selection. 132,131 endoscopic procedures were performed at the CCSC between the years 2008–2017. Only colonoscopies performed on adults for the purposes of colorectal cancer screening, surveillance, or to investigate a positive fecal immunohistochemical test were included. Records were excluded if the patient had a known genetic syndrome, mutation, or occupational exposure predisposing them to colonic neoplasia. Only index procedures were considered. Four endoscopists, representing a total of 45 procedures, performed fewer than 50 procedures each during the study period and were excluded. 75,079 unique patient procedures comprised the final study cohort. CCSC, Colon Cancer Screening Centre.

All individuals > 18 years of age undergoing colonoscopy for screening or surveillance, or for the purposes of investigating a positive FIT, between the years of 2013–2017 were considered for inclusion. We limited the scope of our analysis to these years, as SSLs only began to be reliably reported at the start of this interval. Cases were excluded if the patient had a known genetic syndrome, mutation, or occupational exposure predisposing them to colonic neoplasia. Analysis was performed using the index procedure only (i.e., on a per-patient basis) to avoid confounding by short-interval surveillance examinations and correlations between procedures performed on the same patient. Procedures were also excluded if they were performed by an endoscopist whose total case volume was < 50 procedures during the interval to prevent our results from being skewed by potential outliers. This resulted in the exclusion of an additional 45 cases performed by four low-volume endoscopists.

3.3.3. *Data sources and variables*

The CCSC Quality Assurance Database contains several datapoints routinely collected on all patients undergoing procedures at the facility. These include patient demographics, diabetic status, FIT status, as well as post-colonoscopy outcomes, including polyp number, size, morphology, and histology. This administrative dataset was supplemented using data linkage with the endoscopy reporting program, endoPRO (Pentax Medical). Captured variables included procedure date, indication (average-risk screening, family history of CRC or advanced adenoma, positive FIT, or surveillance), depth of colonoscope insertion (terminal ileum, cecum, or incomplete exam), bowel preparation quality (clean, residual stool, inadequate), whether a polypectomy was performed, and withdrawal time in minutes. Here, we use post-cecal

intubation procedure time as a surrogate for withdrawal time. Additional data linkage with the CCSC Pathology Database provided details regarding the presence or absence of adenomatous, sessile serrated, traditional serrated, and hyperplastic polyps. The performing endoscopist as well as details regarding the provider specialty (either gastroenterology or colorectal surgery) and year of graduation from medical school were known. Both patient and provider confidentiality were assured using a deidentified dataset.

3.3.4. *Definitions*

An exam was considered complete if the depth of insertion was to the cecum or beyond. Bowel preparation was dichotomized into poor (residual stool or inadequate) and optimal (clean). Overall and endoscopist-specific mean withdrawal time was determined by using the post-cecal intubation procedure time during procedures in which no polyps were removed. This was then dichotomized using ≥ 6 minutes as a cut-point, which experts agree is the minimum amount of time required for adequate mucosal inspection.⁷² To mitigate inconsistency arising from inter-pathologist variation in reporting of SSLs during the evolution of SSL pathologic criteria, all hyperplastic polyps > 5 mm in size that were proximal to the sigmoid colon were re-classified as SSLs in the original dataset. This decision allowed for greater sensitivity for SSLs that may have been misclassified as HPs. The potential loss in specificity, however, is felt to be minimal, as large, proximal hyperplastic lesions are rare. Accordingly, examinations were considered positive for an SSL if either (1) SSL histology was identified on the pathology report or (2) if a hyperplastic polyp was later re-classified using the above institutional criteria. Polyp detection rates were calculated as the proportion of procedures during which at least one polyp of the specified pathology was

identified. PSPDR was calculated similarly for any serrated polyp (SSL, TSA, or HP) found proximal to the splenic flexure. As serrated polyp location data were only reliably available for those procedures performed after 2014, PSPDR was calculated based on this subset of procedures. An endoscopist's annual procedure volume was calculated as the total number of procedures they contributed to the dataset divided by the difference in time between their first and last procedure in the dataset, expressed as years. Procedural volume calculations do not include colonoscopies that were performed by the endoscopist at other centres. Endoscopist experience was calculated as the mean number of years between their year of graduation from medical school and the date of the procedure.

3.3.5. *Statistical analyses*

Descriptive statistics were calculated at both the procedure and endoscopist levels. Univariable logistic regression analysis was performed to identify both patient and endoscopist factors affecting SSL detection. Patient factors of interest included age, sex, diabetic status, FIT status, personal history of polyps, family history of advanced adenoma or CRC, the year of the procedure, and the quality of the bowel preparation. Endoscopist factors of interest included annual procedure volumes, years after graduation from medical school, specialty, and cecal intubation rate. Multivariable logistic regression models were then constructed to evaluate the relationship between polyp detection rates and the specific performing endoscopist, adjusting for relevant confounders identified in the univariable analysis. Missing data were addressed using listwise deletion. Endoscopist-specific adjusted polyp detection metrics for each polyp type were calculated as the marginal detection rate, holding the endoscopist fixed and averaging over

patient covariates. Model fits were assessed with the Hosmer-Lemeshow goodness-of-fit test grouping by deciles of predicted probabilities. At the endoscopist level, the relationship between SSLDR and proxy measures, ADR and PSPDR, was assessed qualitatively with scatter plots and quantitatively with linear regression. Both crude and adjusted detection rates were analyzed in this way. The strengths of associations were estimated using correlation coefficients and normal-based 1000-fold bootstrap confidence intervals (CI). Finally, multiple univariable and multivariable logistic regression models were fit to assess the relationship between either SSLDR or PSPDR and various endoscopist factors, with or without controlling for relevant patient and procedural factors. Crude and adjusted detection rates were calculated for each stratum and odds ratios between strata levels are reported. All statistical analysis was conducted using Stata version 17.0.⁷⁹

3.3.6. *Ethical Considerations*

Ethical review and approval of consent procedures, data collection, and data storage was obtained via the Health Research Ethics Board of Alberta (HREBA.CC-21-0329).

3.4. Results

The final study cohort was comprised of 75,079 unique patient procedures performed by 53 endoscopists. **Table 6** summarizes relevant patient and procedural characteristics. 7,556 cases had at least one SSL detected (SSLDR 10.1%, 95% CI [9.9%–10.3%]), while 6,232 cases performed after 2014 had at least one serrated polyp of any subtype detected proximal to the splenic flexure (PSPDR 8.3%, 95% CI [8.1%–8.5%]). Provider characteristics are summarized in **Table 7**. Most of the endoscopists were gastroenterologists. Median years after graduation from medical school

was 11.0 (IQR [5.55–18.7]), while median annual procedural volume was 318 (IQR [154–539]). All but one endoscopist had a mean withdrawal of 6 minutes or more.

Table 6. Patient and procedure characteristics. 75,079 unique patient procedures comprised our study cohort. Age is reported as mean (\pm standard deviation). Detection rate is the proportion of procedures during which one or more polyps of the indicated type was identified. PSPDR was calculated for procedures occurring in 2014 and beyond (n=56,727). AA, advanced adenoma; ADR, adenoma detection rate; CRC, colorectal cancer; PDR, polyp detection rate; PSPDR, proximal serrated polyp detection rate; SSLDR, sessile serrated lesion detection rate; TSADR, traditional serrated adenoma detection rate.

	n (%)
Total	75,079
Sex	
Male	37,918 (50.5%)
Female	37,161 (49.5%)
Age, years	57.9 (\pm 7.6)
Diabetic	4,875 (6.5%)
FIT+	13,588 (18.1%)
Risk	
Average-risk	32,221 (42.9%)
Family history AA/CRC	18,683 (24.9%)
Personal history of polyp	11,280 (15.0%)
Personal history of CRC	344 (0.5%)
Quality indicators	
Cecal intubation rate	73,940 (98.5%)
Withdrawal time \geq 6 min	19,205 (63.7%)
Difficult procedure	10,287 (14.0%)
Poor bowel preparation	20,170 (27.0%)
Year of procedure	
2013	18,373 (24.5%)
2014	18,754 (25.0%)
2015	16,473 (21.9%)
2016	14,663 (19.5%)
2017	6,861 (9.1%)
Polyp detection rate	
Any polyp (PDR)	43,180 (57.5%)
Adenoma (ADR)	28,306 (37.7%)
Sessile serrated lesion (SSLDR)	7,556 (10.1%)
Traditional serrated adenoma (TSADR)	266 (0.4%)
Proximal serrated polyp (PSPDR)	5,601 (9.9%)

Table 7. Endoscopist characteristics. Polyp detection statistics are reported as the unweighted mean of endoscopist polyp detection with 95% confidence intervals. Detection rate is the proportion of procedures during which one or more polyps of the indicated type was identified. PSPDR was calculated based on procedures occurring in 2014 and beyond (n=49). Adjusted detection metrics were derived using multiple logistic regression modeling to adjust for salient patient and procedural factors.

	n (%)
Total	53
Annual procedural volumes	
0–250	19 (35.8%)
250–500	18 (34.0%)
≥ 500	16 (30.2%)
Years after graduation	
0–10	10 (38.5%)
10–20	11 (42.3%)
≥ 20	5 (19.2%)
Specialty	
Gastroenterology	45 (84.9%)
Colorectal surgery	8 (15.1%)
Cecal intubation rate	
< 95%	2 (3.8%)
≥ 95%	51 (96.2%)
Withdrawal time	52 (98.1%)
< 6 minutes	1 (1.9%)
≥ 6 minutes	51 (98.1%)
Polyp detection	
ADR	36.8% (34.9%–38.8%)
SSLDR	9.5% (8.4%–10.5%)
PSPDR	8.8% (2.9%–15.1%)
Adjusted polyp detection	
aADR	37.5% (35.7%–39.7%)
aSSLDR	9.7% (8.6%–10.7%)
aPSPDR	8.8% (3.0%–15.0%)

3.4.1. Endoscopist detection metrics

Both crude and adjusted polyp detection metrics were calculated for each provider. At the endoscopist level, mean adjusted SSLDR was 9.7% (95% CI [8.6%–10.7%]), while mean adjusted PSPDR was 8.8% (95% CI [7.7%–9.9%]). Both SSLDR and PSPDR were approximately normally distributed (**Figure 12**), with considerable variation being demonstrated among endoscopists; adjusted detection rates ranged between 0.7%–18.2% and 1.1%–18.4%, respectively.

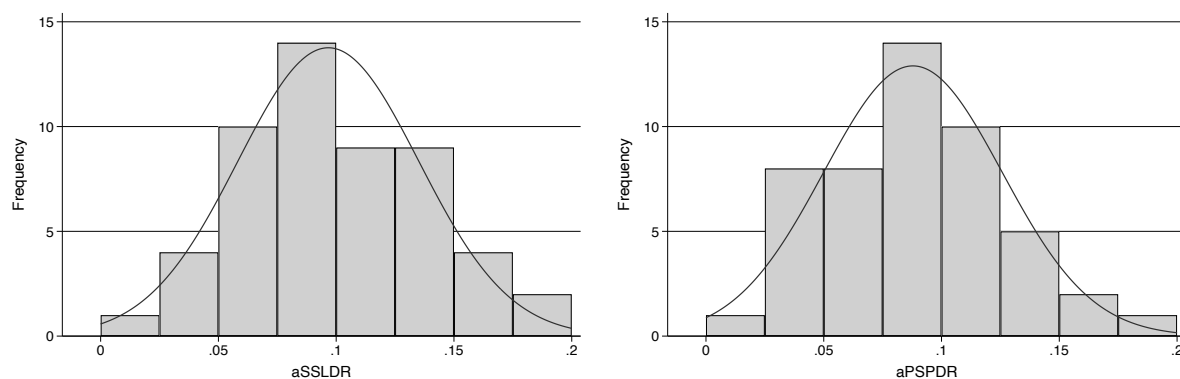


Figure 12. Distribution of endoscopists detection metrics for sessile serrated lesions and their proxy measure, proximal serrated polyps. Detection metrics are adjusted for salient patient and procedural factors. Mean aSSLDR was 9.67% (95% CI [8.63%–10.7%]), while mean aPSPDR was 8.79% (95% CI [3.03%–15.01%]). aSSLDR, adjusted sessile serrated lesion detection rate; aPSPDR, adjusted proximal serrated polyp detection rate. Detection rates are the unweighted mean and 95% confidence interval for each stratum.

Endoscopist SSLDR was highly correlated with PSPDR ($r=0.93$, 95% CI [0.90–0.97], $p < 0.0001$) and was predicted reasonably well by ADR ($r=0.84$, 95% CI [0.75–0.92], $p < 0.0001$), after controlling for salient patient and procedural factors (**Figure 13**). Within the domain of the model inputs,

every percentage point increase in endoscopist ADR resulted in an additional 0.47% (95% CI [0.38%–0.56%]) absolute increase in SSLDR. Whereas endoscopists with lower ADRs tended to have lower SSLDRs, those with ADRs above the mean detection rate had more variable SSLDRs, with a few endoscopists performing below the mean SSLDR and several detecting at much higher than predicted levels.

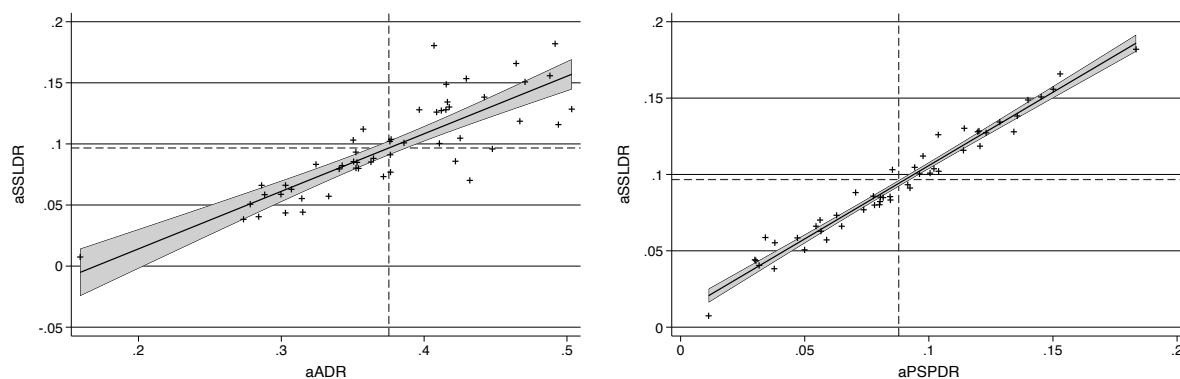


Figure 13. SSLDR is positively correlated with ADR and PSPDR. At the endoscopist level, sessile serrated polyp detection is predicted by adenoma detection rate ($r = 0.840$, 95% CI [0.750–0.920], $p < 0.0001$) and is closely correlated with proximal serrated polyp detection rate ($r = 0.931$, 95% CI [0.897–0.966], $p < 0.0001$) after adjusting for relevant patient and procedural factors. Every percentage point increase in ADR results in an additional 0.47% (95% CI [0.38%–0.56%]) increase in SSLDR. Dotted lines denote mean detection rates. aADR, adjusted adenoma detection rate; aPSPDR, adjusted proximal serrated polyp detection rate; aSSLDR, adjusted sessile serrated lesion detection rate.

3.4.2. Endoscopist factors associated with SSLDR and PSPDR

Crude and adjusted marginal detection rates on a per-procedure basis at various levels of endoscopist factors are made available in **Table 8**. Model coefficients are summarized as odds

ratios in **Table 9**. Only one endoscopist had a mean withdrawal time of less than six minutes. When withdrawal time was recorded for this endoscopist, no serrated polyps were detected. Thus, withdrawal time was not included in the final analysis.

Table 8. Crude and adjusted marginal endoscopist serrated polyp detection rates. Logistic regression was used to model the relationship between sessile serrated lesion detection and various endoscopist factors independently on a per-procedure basis. Marginal estimates are reported as either crude or adjusted for relevant patient and procedural factors. SSLDR, sessile serrated lesion detection rate; PSPDR, proximal serrated polyp detection rate.

	SSLDR, % (95% CI)				PSPDR, % (95% CI)			
	Crude	<i>p</i>	Adjusted	<i>p</i>	Crude	<i>p</i>	Adjusted	<i>p</i>
Annual procedural volume								
0–250	8.7% (8.1%–9.4%)		8.7% (8.0%–9.3%)		7.7% (7.0%–8.4%)		7.6% (6.9%–8.3%)	
250–500	9.9% (9.5%–10.3%)	*	9.7% (9.3%–10.1%)	*	9.9% (9.4%–10.3%)	*	9.7% (9.3%–10.2%)	*
≥ 500	10.3% (10.1%–10.6%)	*	10.4% (10.2%–10.7%)	*‡	10.2% (9.9%–10.5%)	*	10.3% (10.0%–10.6%)	*
Years in practice								
0–10	12.8% (12.3%–13.2%)		12.5% (12.0%–12.9%)		12.5% (11.9%–13.0%)		12.3% (11.7%–12.8%)	
10–20	9.7% (9.3%–10.1%)	*	9.7% (9.3%–10.2%)	*	9.7% (9.2%–10.1%)	*	9.7% (9.3%–10.2%)	*
≥ 20	6.5% (6.1%–7.0%)	*‡	6.8% (6.3%–7.2%)	*‡	5.6% (5.1%–6.1%)	*‡	5.7% (5.2%–6.2%)	*‡
Specialty								
Gastroenterology	10.5% (10.3%–10.7%)		10.5% (10.2%–10.7%)		10.4% (10.1%–10.7%)		10.4% (10.1%–10.6%)	
Colorectal surgery	7.1% (6.5%–7.6%)	*	7.2% (6.6%–7.7%)	*	6.3% (5.7%–6.8%)	*	6.3% (5.7%–6.9%)	*
Cecal intubation rate								
< 95%	9.4% (5.6%–13.3%)		10.9% (6.5%–15.2%)		11.0% (4.2%–17.7%)		11.7% (4.6%–18.8%)	
≥ 95%	10.1% (9.9%–10.3%)		10.1% (9.8%–10.3%)		9.9% (9.6%–10.1%)		9.9% (9.6%–10.1%)	

* $p < 0.05$ when compared with first level in the specified stratum

‡ $p < 0.05$ when compared with second level in the specified stratum

Table 9. Endoscopist factors predicting sessile serrated lesion detection. Logistic regression was used to model the relationship between sessile serrated lesion detection and various endoscopist factors independently. Estimates are reported as either crude or adjusted for relevant patient and procedural factors. OR, odds ratio; Ref, reference stratum; SSL, sessile serrated lesion.

	SSL Detection			
	Crude OR (95% CI)	<i>p</i>	Adjusted OR (95% CI)	<i>p</i>
Annual procedural volume				
0–250	1 (Ref.)		1 (Ref.)	
250–500	1.15 (1.05–1.27)	*	1.13 (1.03–1.24)	*
≥ 500	1.21 (1.10–1.32)	*	1.23 (1.12–1.34)	*‡
Years after graduation				
0–10	1 (Ref.)		1 (Ref.)	
10–20	0.74 (0.69–0.78)	*	0.76 (0.71–0.81)	*
≥ 20	0.48 (0.44–0.52)	*‡	0.51 (0.47–0.55)	*‡
Specialty				
Gastroenterology	1 (Ref.)		1 (Ref.)	
Colorectal surgery	0.65 (0.60–0.70)	*	0.66 (0.60–0.71)	*
Cecal intubation rate				
< 95 %	1 (Ref.)		1 (Ref.)	
≥ 95 %	1.08 (0.69–1.69)		0.91 (0.58–1.44)	

* $p < 0.05$ when compared with first level in the specified stratum

‡ $p < 0.05$ when compared with second level in the specified stratum

Higher annual procedural volumes were associated with higher SSLDR. Specifically, the adjusted odds of SSL detection were 1.23 (95% CI [1.12–1.34]) times greater in procedures performed by endoscopists with annual case volumes of ≥ 500 vs < 250 procedures. A smaller, but still significant effect was observed when comparing those endoscopists with case volumes of 250–500 vs < 250 procedures (OR 1.13, 95% CI [1.03–1.24]). SSL detection was highest among those endoscopists who most recently completed their medical training, with SSLDR decreasing for each additional interval of time after graduation. (≥ 20 vs < 10 years since graduation, adjusted

OR 0.51, 95% CI [0.47–0.55]). When examining provider specialty, colorectal surgeons exhibited lower SSL detection compared to gastroenterologists (adjusted OR 0.66, 95% CI [0.60–0.71]). Cecal intubation rate did not affect SSL detection ($\geq 95\%$ vs $< 95\%$, adjusted OR 0.91, 95% CI [0.58–1.44]). Annual procedural volumes, years since graduation, provider specialty, and cecal intubation rate were found to have similar effects on PSPDR as well.

3.5. Discussion

In this study performed at a dedicated, high-volume screening centre, we estimated the overall ADR to be 37.7% and SSLDR to be 10.1%. These detection rates are in keeping with proposed aspirational targets of $\geq 35\%$ and $\geq 10\%$ for ADR and SSLDR, respectively.⁶⁴

3.5.1. ADR as a predictor of SSLDR

SSLDR benchmarks have been informed by examining the SSL detection rates of high-performing endoscopists, as determined by their ADR. Yet, whether endoscopists who are skilled at detecting adenomas are also proficient at detecting SSLs remains an open question. Many of the technical and cognitive skills that are required for adenoma detection are reasonably predicted to be transferable to SSL detection, such as colonoscope insertion, adequacy of mucosal exposure, and diligence in mucosal inspection.⁵¹ However, whereas adenomas tend to be polypoid and have distinct borders, SSLs are flat or sessile lesions with indistinct margins and often obscured by mucous. These morphological differences may render SSL detection more challenging than adenoma detection in a way that is dependent on the performing endoscopist.¹⁰¹ To address these assumptions, several studies have looked at the appropriateness of using ADR as a surrogate marker of SSLDR. While some research points to a weak association between SSSLDR

and ADR,⁴⁴ there is greater evidence to suggest that ADR is a significant predictor of SSLDR at the per-endoscopist level,^{57, 102} and that even advanced ADR is weakly associated with SSLDR.⁹ Our findings provide further evidence for the correlation between ADR and SSLDR, suggesting that skilled endoscopists tend to be adept at detecting both adenomas and SSLs. As a result, these findings strengthen the versatility of skills assumption upon which the SSLDR benchmarks were established. While this association appears to hold in general, it is important to note that, in our analysis, there were a few endoscopists who had above-average ADRs but below-average SSLDRs. Given the potential for discrepancy in detection metrics for a particular endoscopist, we support the measurement, reporting, and benchmarking of SSLDR targets, separate from ADR targets, for the purposes of quality assurance. If serrated polyp detection rates are not available, ADR may be used as a predictor of SSLDR to identify those endoscopists who may most benefit from targeted quality improvement initiatives.

3.5.2. *PSPDR as a surrogate marker of SSLDR*

Some studies suggest the use of PSPDR as a practical surrogate marker of SSLDR.^{56, 103} PSPDR includes all serrated polyps proximal to the splenic flexure and is therefore not reliant on the histopathological discrimination between serrated polyp subtypes nor on accurate polyp size estimation. Detractors of this metric argue that it conflates benign hyperplastic polyps with clinically relevant lesions and is unable to account for distal SSLs. Despite these flaws, one study analyzing prospectively collected data on more than 2000 screening colonoscopies found that PSPDR was an adequate proxy measure for clinically relevant serrated polyp detection rate with a high degree of correlation ($r=0.94$).¹⁰⁴ While our definition of SSL and these author's definition

of clinically relevant serrated polyp differed slightly (we excluded those hyperplastic polyps 5–9 mm in size proximal to the splenic flexure and all TSAs), we also demonstrated a strong correlation with PSPDR ($r=0.931$). In a study by Crocket *et al.*—a large multicentre study that included over 100,000 outpatient colonoscopies performed by over 200 endoscopists on patients without inflammatory bowel disease—the detection rate of non-HP serrated polyps was also closely correlated with the detection of proximal non-HP serrated polyps ($r=0.96$).⁹ A caveat, however, is that in contrast to the typical definition of PSPDR, HPs were specifically excluded in the calculation of proximal serrated polyps, making this comparison less applicable. However, taken together, these results suggest that PSPDR may be an acceptable surrogate marker of the more clinically meaningful SSLDR, particularly in centres lacking a dedicated gastrointestinal pathology group. As such, guidelines may consider publishing PSPDR targets alongside SSLDR to provide accessible quality assurance targets to all endoscopy centres.

3.5.3. *Endoscopist factors associated with SSL detection*

We demonstrated that endoscopist-specific SSLDR and PSPDR are highly variable, with several endoscopist factors predicting higher detection rates, including gastroenterology specialty, fewer years since graduation, and higher annual procedural volumes. Similar endoscopist factor associations were demonstrated in the multicentre study by Crocket *et al.*;⁹ gastroenterologist specialty, fewer years in practice, and higher procedural volumes were associated with enhanced serrated polyp detection. These findings have been subsequently replicated in a separate cohort, strengthening the evidence of these associations.¹⁰⁰

Several studies have looked specifically at the association between endoscopist specialty and serrated polyp detection.^{9, 57, 100, 105, 106} One analysis involving 104,326 colonoscopies performed by 261 physicians to investigate FIT positive stool found that SSLDR was higher among gastroenterologists than surgeons (OR 0.89, 95% CI [0.81–0.97]) or primary care physicians/internists (OR 0.67, 95% CI [0.49–0.92]).¹⁰⁵ In a multicentre Italian study examining 72,021 colonoscopies performed on FIT-positive patients, SSLDR was higher among gastroenterologists (2.1%, 95% CI [2.0%–2.2%]) compared to surgeons (1.0%, 95% CI [0.8%–1.2%]).⁵⁷ Two smaller studies examined the association between endoscopist specialty and PSPDR,^{100, 106} with both finding higher detection rates among gastroenterologists. However, in the study by Sarvepalli et al.,¹⁰⁰ after adjusting for the endoscopists using a mixed effects model, the association between PSPDR and specialty was no longer significant, suggesting that differences between endoscopists other than specialty may be responsible for the variation observed in PSPDR. Specialty-specific differences in serrated polyp detection may arise due to differences in training programs with variable levels of exposure to cases and whether this exposure is longitudinal or occurring at a discrete point in time. As training paradigms shift to adopt a competency-based learning model rather than requiring a minimum volume of procedures, differences serrated polyp detection between specialties are anticipated to diminish.¹⁰⁷

Endoscopist experience has also been assessed as a putative predictive factor of SSLDR. In a smaller study involving 7,192 average-risk colonoscopies, the number of years since graduation from fellowship was not associated with the detection of SSLs ($r=0.39$ $p=0.185$).⁴² Another study examining 28,544 screening colonoscopies found that there was greater variability in SSLDR

among non-expert versus expert gastroenterologists, although the data were produced by only five endoscopists.¹⁰⁸ Contrastingly, when using a much larger dataset, Telford *et al.* did demonstrate an association between fewer years since graduation and higher SSLDR (graduation after 2000 vs before 1980, OR 1.48, 95% CI [1.30–1.69]).¹⁰⁵ A similar trend was observed by Zorzi *et al.*, with SSLDR of 3.0% (95% CI [2.5%–3.5%]) and 1.6% (95% CI [1.5%–1.7%]) for those with ≤ 5 and ≥ 10 years of experience, respectively.⁵⁷ The phenomenon of enhanced polyp detection among endoscopists with fewer years since graduation has been previously established for adenomatous polyps.¹⁰⁹ This trend may reflect improvements to endoscopy training programs that provide instruction on enhanced SSL detection or perhaps reflect a decay in endoscopy skills over time. The later possibility suggests a potential role for longitudinal competency assessment in determining maintenance of certification and informing targeted quality improvement interventions.

Consistent with previous research, we demonstrated that procedural volumes are associated with SSLDR.^{9, 100} Sarvepalli *et al.* showed that the odds of SSL detection increased by a factor of 1.05 (95% CI, [1.01–1.11]) per additional 50 colonoscopies. In the study by Zorzi *et al.*, the highest SSLDR occurred among those endoscopists performing between 300–600 all-indication colonoscopies per year and decreased for those with either lower or higher procedural volumes.⁵⁷ The study by Telford *et al.*, however, did not demonstrate a relationship between procedural volumes and SSLDR (OR 1.00, 95% CI [0.96–1.06]).¹⁰⁵ This may be because the procedural volumes in this study were comparatively lower (median 70, IRQ [17–159]). It is interesting to note that unlike SSLDR, ADR has not been shown to be associated with procedural volumes.⁹⁸ One hypothesis to explain this disparity is that because SSLs are less common than

adenomas, higher procedural volumes are required for an endoscopist to attain the same exposure and become adept at detecting these lesions. Similarly, the absence of association between adenomas and procedural volumes may reflect a threshold effect, where inadequate exposure to adenomas among endoscopists is quite rare. The association between higher procedural volumes and enhanced SSL detection suggests that endoscopic skill enhancement through practiced repetition may be warranted for those with suboptimal SSLDR and low annual procedural volumes.

3.5.4. Study strengths and limitations

There are several strengths of our study. Our dataset included over 75,000 colonoscopies performed at a dedicated screening and surveillance centre. The large dataset size is particularly important given the relative rarity of SSLs compared with conventional adenomas. As data were collected prospectively, data deficiencies were minimal. Histologic analysis was performed with access to a dedicated gastrointestinal-specialized pathology group, providing confidence and consistency in SSL diagnosis. Our focus on screening and surveillance procedures makes our results directly applicable to other high-quality screening programs.

We also consider a few of the limitations of this study. The retrospective study design limits our ability to control for potential confounding factors and prevents the analysis of unmeasured variables. However, the selection and recall bias typical of retrospective studies were mitigated by the prospective collection of data in our administrative dataset. Variables of interest that were not available in this analysis include endoscopist age and sex, which have demonstrated to be variably association with polyp detection.^{9, 57, 100} Only a fraction of the endoscopists had reported

experience (years since graduation), resulting in less precise estimates for how experience relates to SSLDR. While we were able to calculate procedural volumes for screening/surveillance colonoscopies performed at our screening centre, total procedural volumes including hospital-performed screening/surveillance colonoscopies and all-indication colonoscopies were not available. While this limits our ability to estimate the effect of procedural volumes on SSLDR, we would argue that the number of screening/surveillance procedures are more relevant than the number of all-indication colonoscopies, as the former relates directly to the detection of screening-relevant lesions, including SSLs. Moreover, hospital-performed screening/surveillance procedures are anticipated to be relatively rare, due to the prioritization of diagnostic/therapeutic procedures at acute care sites. Finally, use of endoscopic adjuncts such as optical enhancements or distal attachment devices,^{59, 60} both of which are available at our institution, was not recorded. Thus, their effect on SSL detection and their correlation with other endoscopist factors remain unknown.

3.5.5. Conclusions and future work

In conclusion, considerable variability in SSL detection exists between endoscopists. Certain endoscopist factors including higher annual procedure volumes, fewer years since graduation, and gastroenterology specialty were associated with enhanced SSL detection, even after adjusting for relevant patient and procedural factors. PSPDR was shown to be a reliable surrogate marker of SSLDR, permitting assessment of endoscopist performance independent of institutional capabilities of rendering an accurate histopathologic diagnosis. We also demonstrated ADR to be predictive of SSLDR, suggesting that endoscopists who are proficient in

detecting conventional adenomas are also skilled in detecting SSLs. Taken together, our work suggests a need to improve the consistency of SSL detection among endoscopists. The broader reporting of SSLDR and/or PSPDR in the literature and benchmarking of these metrics in society guidelines could help endoscopists ensure they are meeting minimum detection targets. Moreover, targeted and evidence-based quality improvement initiatives aimed at improving endoscopist ADR might also be beneficial for improving SSL detection.

Future work is still required to identify other relevant endoscopist factors associated with SSL detection and to establish the validity of serrated polyp detection benchmarks. The association between SSLs and serrated adenocarcinoma has been previously established.⁴⁸ While guidelines publishing SSLDR benchmarks have been reasonably motivated by previous literature demonstrating an association between higher endoscopist ADR and reduction in post-colonoscopy colorectal cancer,^{65, 66} a similar association for SSLDR and serrated adenocarcinoma has yet to be clearly demonstrated. Future work should be directed at providing measurable outcomes (interval serrated adenocarcinoma and death) for SSLDR and PSPDR quality benchmarks.

Chapter 4. Discussion

4.1. Integration and synthesis of key findings

In this thesis, we conducted a comprehensive analysis on sessile serrated lesions, including temporal trends in detection prevalence, predisposing patient characteristics, and associated endoscopist factors, using data from a high-volume, dedicated colonoscopy screening center over a five-year period from 2013–2017.

4.1.1. *Temporal trends in SSL detection*

The first study of this thesis focused on temporal trends and risk factors in predicting SSLs. During the study period, we demonstrated a mean SSLDR of 10.2%. Stratifying by year of procedure, we observed a positive temporal trend in SSL detection, with SSLDR increasing from 8.1% in 2013 before appearing to plateau at 12.2% by 2017. Moreover, this trend was maintained even after adjusting for relevant patient factors to account for the shifting case-mix observed at our centre. These years marked a significant shift in detection prevalence at our institution, highlighting the evolving understanding of SSLs, the recognition of these polyps as screening-relevant lesions, and their improved histopathologic and endoscopic detection. Our work adds to a growing body of literature that similarly demonstrates a positive trend in detection prevalence, although significant variability in absolute detection rates exists between reporting centres.

We posit several reasons for the observed increase in SSLs detection independent of patient risk factors. These include (1) the relaxing of histopathologic diagnostic criteria to ameliorate inter-observer variability among pathologists in distinguishing between serrated polyp subtypes, (2) a heightened endoscopist awareness and vigilance for these polyps that mirrors the publication of detection benchmarks in society guidelines, and (3) the advent of technological advancements and adjunctive techniques to augment endoscopic polyp detection. It is important to note that updates in histologic criteria and advancements in endoscopic technology are not anticipated to be uniformly adopted across all healthcare facilities. Further, the implementation timeline of these factors and the evolution of endoscopists understanding and recognition of SSLs are going to occur at different paces. This staggered integration may contribute to the variability observed in detection rates of SSLs across institutions.

4.1.2. Patient risk factors associated with SSLs

In an analysis of patient factors associated with SSLs, we found that advancing age, female sex, non-diabetic status, a personal history of polyps, or a family history of advanced adenoma or CRC was associated with SSL detection, while FIT status was not. These findings are largely compatible with previously published risk factors. A personal history of polyps—irrespective of polyp subtype—was the largest personal risk factor for SSL presence. Notably, age does not appear to be as important in conferring risk in SSLs as it does in conventional adenomas, likely reflecting distinct pathophysiologic mechanisms at play in the classical adenoma-to-carcinoma sequence compared to the serrated adenocarcinoma pathway.

4.1.3. Procedural factors influencing SSL detection

Our analysis identified withdrawal time as the primary procedural determinant of SSL detection. Withdrawals exceeding six minutes yielded a six-fold increase in SSL detection odds, independent of endoscopist variability. This aligns with the understanding that extended withdrawal facilitates meticulous mucosal inspection, which is crucial for detecting subtly presenting SSLs. These findings corroborate previous studies linking SSL detection with longer withdrawal times. Interestingly, suboptimal bowel preparation showed a weak correlation with SSL detection. This could be attributed to residual stool enhancing visual contrast via adherence to the mucous cap, or the increased washings necessitated by poor preparations directing endoscopist focus towards these polyps.

4.1.4. Leveraging machine learning models to enhance SSL risk prediction

To enhance the predictive capabilities of our traditional statistical models, we applied machine learning algorithms to consider potentially non-linear and interdependent relationships among patient, procedural, and endoscopist variables. While these models were generally superior in terms of prediction accuracy, overall performance as measured by AUC was only 66.7%, suggesting that a substantial amount of variability in SSL risk may stem from unmeasured factors. Despite the performing endoscopist accounting for only 5% of the variability in SSL detection in the mixed effects model, the machine learning models identified the endoscopist (or their ADR in endoscopist-agnostic models) as the single most important factor in predicting SSL risk. This finding again highlights the inadequacy of currently available data in accurately predicting SSL

risk, but also underscores the importance of high-quality examination technique, by way of its proxy measure, ADR, in SSL detection.

4.1.5. Endoscopist characteristics predictive of SSL detection

Given the crucial role of the endoscopist in SSL detection, as revealed by both mixed effects regression and machine learning models, we evaluated multiple endoscopist-related factors in the second study of this thesis to identify specific endoscopist characteristics predictive of SSLs. Several factors, including gastroenterology specialty, fewer years since graduation, and higher annual procedural volumes were predictive of higher SSLDR. These findings suggest that differences in specialty-specific training, recent changes to endoscopic curricula incorporating instruction on SSL recognition, endoscopic skill decay over time, and skill enhancement through repetition, may be important factors contributing to endoscopist SSL detection ability. This work aligns with the findings reported by other researchers.

4.1.6. ADR and PSPDR as a predictor and surrogate marker of SSLDR, respectively

Unlike SSLDR, ADR is a commonly measured and reported metric, with established benchmarks tied to clinically significant outcomes. Given its widespread use and recognition, being able to leverage ADR as a predictor of SSLDR would be advantageous in indirectly assessing endoscopist skill in SSL detection. In this study, we demonstrated a close positive correlation between ADR and SSLDR, suggesting that skilled endoscopists tend to be adept at detecting both adenomas and SSLs. Indeed, variations in the endoscopic appearance of adenomas and serrated lesions are likely to influence their detectability in a way that is dependent on the performing endoscopist. Nonetheless, other technical and cognitive skills requisite for adenoma detection, such as

colonoscope insertion, sufficient mucosal exposure, and meticulous mucosal inspection, are reasonably expected to be transferable to SSL detection. Therefore, ADR serves as a logical and, as our findings illustrate, dependable predictor of SSLDR.

PSPDR, which includes all serrated polyps proximal to the splenic flexure, is an attractive surrogate of the more clinically relevant SSLDR, as it is not reliant on the histopathological discrimination between serrated polyp subtypes nor on accurate polyp size estimation. Our findings reveal a strong positive correlation between PSPDR and SSLDR, thereby validating its potential as a credible surrogate of SSLDR.

4.2. Implications and recommendations for clinical practice

SSLs, which are responsible for a significant proportion of sporadic colorectal cancer cases and are overrepresented in interval colorectal cancer, are of particular importance in colorectal cancer screening. This thesis delivers a comprehensive exploration of these lesions, encompassing temporal trends in detection, patient risk factors, and relevant endoscopist characteristics. Our findings, as outlined above, suggest several potential interventions and implications for clinical practice aimed at improving screening and surveillance of these premalignant lesions.

There is a high degree of variability in SSL detection reported in the literature. Viewed in the context of our study demonstrating an escalating trend in SSL detection rates over time at a single institution, implies that the reported variability could be attributable to disparate timelines in adopting SSL detection-enhancing practices across different institutions. Efforts should therefore

be directed at minimizing the variability in screening practices by improving overall detection rates.

4.2.1. Routine monitoring and reporting of serrated polyp detection rates

A prerequisite for implementing quality improvement initiatives is to first identify and quantify present discrepancies in clinical care. While we have demonstrated that other indirect measures, including ADR and PSPDR, have high correlation with SSLDR, these proxies necessarily lack the specificity and accuracy inherent in direct measurements of SSLDR. We therefore propose the systematic tracking and reporting of SSLDR, analogous to current ADR practices. Such data would yield actionable insights at both the endoscopist and institutional levels to rectify any identified deficiencies.

4.2.2. Multifaceted approach to improving SSL detection.

SSL detection prevalence is a complex measure with many inputs. The formation of an SSL is determined by the interplay between patient characteristics and environmental influences. The detection of these lesions hinges on endoscopist characteristics interacting with procedural factors. Finally, the diagnosis of an SSL is determined by classification criteria and the interpreting pathologist. Each of these components can dynamically evolve affecting the detection prevalence of SSLs in a time-dependent manner. We propose the following multifactorial model to understand the key determinants of SSL detection prevalence (**Figure 14**).

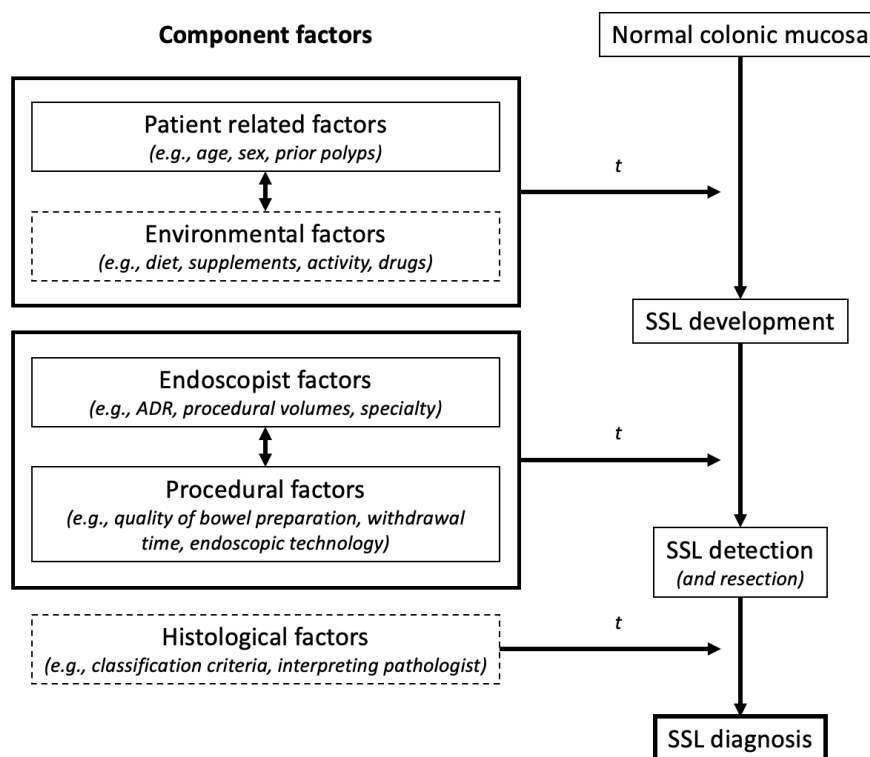


Figure 14. Multifactorial Influences on SSL detection prevalence. SSL detection prevalence is determined by a multifaceted interplay of patient, environmental, endoscopist, procedural, and histological factors, as illustrated. The double-headed arrows signify the interaction between these variables. These components, subject to temporal evolution (denoted by t in the diagram), collectively determine the ability to diagnose an SSL, thereby influencing detection prevalence. Dotted lines indicate unmeasured factors in this thesis.

Endoscopists identified with suboptimal SSLDR could be the focus of quality improvement efforts. Although our study identified some immutable endoscopist characteristics associated with lower SSLDR (non-gastroenterologist specialty and greater number of years since graduation), we propose that these factors are associative, and not causative. Hence, targeted interventions could potentially enhance SSL detection, regardless of these characteristics.

Specific interventions may include education and training focused on the recognition of SSLs, providing endoscopists with regular feedback on their detection rates compared to their peers and/or established benchmarks, encouraging practices that allow for the meticulous inspection of colonic mucosa such as longer withdrawal times, and providing opportunities to meet procedural volume thresholds for skill maintenance.

Several institutional strategies can be implemented to bolster SSL detection:

- (1) Equipment should be regularly maintained and, where feasible, upgraded to leverage advances in endoscopic technology, including high definition endoscopy, optical enhancement, and computer assisted detection systems. The provision of endoscopic adjuncts, including distal attachment devices, may also enhance detection.
- (2) Protocols to ensure optimal bowel preparation should be instituted to increase the visibility of polyps during colonoscopy.
- (3) Systematic quality improvement initiatives, such as regular audits of SSL detection rates and feedback mechanisms, should be implemented to augment endoscopist detection rates.
- (4) Regular training via accredited educational programs should be provided to endoscopists to increase awareness and knowledge about SSLs, or opportunities to attend such programs should be facilitated.
- (5) Polyp histology should ideally be assessed by a gastroenterology-specialized pathology group, or, at a minimum, by pathologists utilizing the latest SSL classification guidelines.

Finally, we would advocate for the incorporation of serrated polyp detection benchmarks, both minimum and aspirational, in societal guidelines. While the primary emphasis should be placed on SSLDR targets, the inclusion of PSPDR as a surrogate for SSLDR could provide attainable quality assurance goals for all endoscopy centers. This is particularly pertinent for facilities without a dedicated pathology group, where the precision of SSL diagnosis may vary.

4.3. Future directions

This thesis lays the groundwork for several avenues for future investigation.

4.3.1. *Addressing variability in SSL detection across institutions*

Given the observed variability in SSL detection across different healthcare institutions, an investigation into the distinct institutional and endoscopist factors at specific sites could illuminate key determinants of SSL detection prevalence. While we posited several potential reasons responsible for the trend of increased SSL detection over time, measuring these institutional- and endoscopist-specific factors would lend credence to (or refute) this hypothesis. Further research should delve into these disparities, examining the potential variations in endoscopist training protocols, the pace of technology adoption, and the influence of institutional policies on endoscopic practice. By delineating these contributing factors, we can devise universal strategies to enhance SSL detection, ultimately improving the efficacy of colorectal cancer prevention.

4.3.2. *Improving predictive models for SSL risk*

Work in this thesis developed machine learning models to augment SSL risk prediction. However, the best-performing models achieved an AUC of only 66.7%, signifying potential for improvement. Future research should focus on identifying and incorporating novel patient predictors to bolster performance. Some potential factors to consider, as identified in existing literature, include cigarette smoking and alcohol usage, intake of fibre, folate, vitamin D, calcium, and omega-3 fatty acids, non-steroidal anti-inflammatory usage, body mass index, levels of physical activity, and level of education attained. Enhanced predictive models could expand our understanding of SSL pathogenesis and facilitate the identification of patients at high risk for SSLs, thereby informing screening and surveillance strategies.

4.3.3. *Establishing the clinical significance of SSLDR*

Previous studies have demonstrated a clear relationship between higher ADR and reduced incidence of interval colorectal cancer, firmly asserting ADR as a clinically relevant metric. However, a parallel connection for SSLDR has yet to be established. While it may be reasonable to extrapolate from ADR data and speculate that higher SSLDR should be associated with lower rates of interval serrated adenocarcinoma, this hypothesis still requires empirical substantiation. Validating SSLDR should be the focus of subsequent studies to provide a firm foundation for SSLDR benchmarks and quality improvement strategies.

Chapter 5. Conclusion

An increase in SSL detection prevalence was observed over time at our centre, with SSLDR increasing from 8.1% in 2013 to 12.2% by 2017 and appearing to plateau at this level. This work strengthens a growing body of literature that similarly demonstrates increases in detection prevalence over time. We provide and explore several potential explanations for this trend, including evolving histopathologic diagnostic criteria, a greater recognition of these lesions among endoscopists, and advances in endoscopic technology.

SSL risk is predicted by various ML models with an accuracy of 67%, suggesting that a substantial amount of variability in SSL risk is likely accounted for by unmeasured factors. The performing endoscopist, or their ADR, was consistently identified in these models as the single most important factor in predicting SSL risk, emphasizing the critical role that skillful perception plays in successful lesion detection. Analysis of endoscopist characteristics revealed that gastroenterology specialty, fewer years since graduation, and higher annual procedural volumes were associated with enhanced SSL detection. Moreover, we observed a close positive correlation between endoscopist ADR and SSLDR, implying a shared set of skills is required for detecting polyp of different types and that SSL detection may be improved via methods that enhance ADR. Further, a strong correlation between PSPDR and SSLDR suggests that PSPDR could serve as a surrogate of SSLDR in research or quality improvement and assurance efforts.

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Appendices

Appendix A. ML model source code and parameters

The source code for machine learning models and model parameters have been made available at the following GitHub repository:

<https://github.com/matthewmazurek/msc-ssl>