Simple clinical risk score identifies patients with serrated polyps in routine practice

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- Silvia Sanduleanu: study concept and design; acquisition of data; analysis and interpretation of data; statistical analysis; drafting the manuscript; critical revision of the manuscript; study supervision; final approval of the article.

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- Ad A.M. Masclee: acquisition of data; drafting the manuscript; critical revision of the manuscript; final approval of the article.
ABSTRACT

Large, proximal or dysplastic (LPD) serrated polyps (SPs) need accurate endoscopic recognition and removal as these might progress to colorectal cancer. Herewith, we examined the risk factors for having ≥1 LPD SP. We developed and validated a simple SP risk score as a potential tool for improving their detection.

We reviewed clinical, endoscopic and histologic features of SPs in a study of patients undergoing elective colonoscopy (derivation cohort). A self-administered questionnaire was obtained. We conducted logistic regression analyses to identify independent risk factors for having ≥1 LPD SP and incorporated significant variables into a clinical score. We subsequently tested the performance of the SP score in a validation cohort.

We examined 2244 patients in the derivation and 2402 patients in the validation cohort; 6.3% and 8.2% had ≥1 LPD SP, respectively. Independent risk factors for LPD SPs were age >50 years (OR 2.2, 95% CI 1.3 – 3.8, p=0.004), personal history of SPs (OR 2.6, 95% CI 1.3 – 4.9, p=0.005), current smoking (OR 2.2, 95% CI 1.4 – 3.6, p=0.001) and non-daily/no aspirin use (OR 1.8, 95% CI 1.1 – 3.0, p=0.016). In the validation cohort, a SP score ≥5 points was associated with a 3.0 fold increased odds for LPD SPs, compared to patients with a score <5 points.

In the present study, age >50 years, a personal history of SPs, current smoking and non-daily/no aspirin use were independent risk factors for having LPD SPs. The SP score might aid the endoscopist in the detection of such lesions.
INTRODUCTION

As colonoscopy with the removal of precancerous lesions is considered the gold standard modality in the prevention of colorectal cancer (CRC) (1), concerns were raised by studies showing limited effectiveness of colonoscopy in the proximal colon (2-4). The serrated neoplastic pathway may contribute to the occurrence of some post-colonoscopy cancers, as some precursor lesions, especially sessile serrated adenomas/polyps (SSA/Ps), are easily overlooked during colonoscopy (5, 6) and are more challenging to remove endoscopically (7). It is generally accepted that large, proximal or dysplastic (LPD) serrated polyps (SPs) portend significant risk for malignant transformation, whereas non-dysplastic small distal SPs do not (8-11). Some studies indicate that 31% of hyperplastic polyps and 27% of non-adenomatous polyps are missed during colonoscopy (12, 13), which is consistent with a high variability in SP detection among endoscopists (i.e. ranging from 8% to 32% for all SPs, and from 1% to 18% for proximal SPs) (14, 15). Taken together these findings highlight the need for improving detection of these lesions. To this end, Kahi et al. (16) recently proposed a minimal detection target of 5% for proximal SPs.

Previous studies identified risk factors associated with an increased risk of having SPs, such as smoking (17-22), alcohol consumption (20) and obesity (17, 19, 20, 22), while daily aspirin and NSAID use seem to be protective (19-23). Nevertheless, data on risk factors for SPs are still controversial, probably due to large variation between endoscopists in SP detection (14, 15), relatively small number of patients with SPs examined (19, 20), inclusion of patients with distal SPs only (18, 23) or a predominant male population (21).

In an attempt to clarify the risk profile associated with having ≥1 LPD SP, we firstly trained the endoscopists in the detection of non-polypoid colorectal lesions (24, 25), with focus on quality indicators (26), and subsequently examined these risk factors in a derivation cohort. We assumed that a priori estimation of the risk for having LPD SPs may heighten the vigilance of trainees and less experienced endoscopists in detecting such lesions, thereby reducing the high variability in SP detection. We finally developed and validated a simple risk score, i.e. the SP risk score, as a potential tool for improving the recognition of these lesions in routine practice.
METHODS

Derivation cohort en data collection

In an ongoing initiative, aiming to improve the quality of colonoscopic cancer prevention in South Limburg, The Netherlands, we familiarized our endoscopists on the recognition, classification and management of non-polypoid colorectal lesions, as described previously (24, 25), with focus on quality indicators (26). Subsequently, we included all patients undergoing elective colonoscopy at our university hospital, from February 2008 to February 2010, in a cross-sectional study (i.e. derivation cohort). We excluded patients aged <18 years, those with hereditary CRC syndromes (i.e. known gene mutations or fulfilling the WHO criteria for serrated polyposis syndrome), inflammatory bowel disease, a personal history of CRC or prior colonic surgery. We also excluded patients in whom CRC was detected at the time of colonoscopy, to prevent potential bias from underestimating the SP rates in this situation. As we reported on the individual detection rates of ≥1 LPD SP among the endoscopists, we excluded data from endoscopists performing <50 colonoscopies during the study period, to attenuate the effects of random error by stratification. In patients who underwent multiple colonoscopies during the study period, data from one colonoscopy only were evaluated: index colonoscopy data were used when a second colonoscopy was performed due to onset of new symptoms, polypectomy or post-polypectomy surveillance, while data from the second colonoscopy were used in cases of poor bowel preparation or incomplete first colonoscopy. The study was approved by the local Institutional Review Board (MEC 10-4-020) and registered in the Dutch Trial Register (NTR 1891).

According to routine clinical care, patients received 2 to 4 L polyethylene glycol solution for bowel preparation. Colonoscopies were performed by 8 gastroenterologists and 6 trainees, using conventional white-light colonoscopy. The endoscopists were familiarized with the detection of non-polypoid lesions (24, 25), but unaware of the main study hypothesis and clinical risk profiling associated with having SPs. Complete clinical, endoscopy and pathology data were collected and registered into a standardized database. Proximal SPs were defined as SPs located proximal to the splenic flexure. Size of polyps was visually assessed using a biopsy forceps or mini-snare; large SPs were defined as sized ≥6 mm. We used a cut-off of 6 mm for large SPs for the following reasons: SPs are usually smaller than adenomas, less than 6 mm in size (10, 27), approximately 30% to 50% of all SSA/Ps are sized 6 to 9 mm (5, 10, 28) and experts recently recommended removal of all SPs,
excepting distal SPs <6 mm in size (11). Histopathologic classification of all polyps was performed by 2 experienced GI pathologists (A.D, R.R), according to the WHO classification (29). SPs comprised hyperplastic polyps, SSA/Ps without dysplasia and dysplastic SPs (i.e. SSA/Ps with dysplasia and traditional serrated adenomas; TSAs). Advanced adenomas were defined as adenomas sized \( \geq 10 \) mm, containing high-grade dysplasia or any villous components. The pathologists were unaware of the study hypothesis.

A questionnaire including demographics, smoking, body mass index (BMI), medication (i.e. use of aspirin / NSAIDs) and alcohol consumption, was administered to all eligible patients shortly after the colonoscopy. Inconsistent or missing data were verified through medical records and recorded as missing in case this information could not be retrieved. Patients who completed the questionnaire and provided informed consent were included in the final analyses. Smoking status was categorized into current, former or never and BMI classified in normal (i.e. <25 kg/m\(^2\)), overweight (i.e. \( \geq 25 \) kg/m\(^2\) - <30 kg/m\(^2\)) and obesity (i.e. \( \geq 30 \) kg/m\(^2\)). Medication use was categorized as daily versus non-daily/no use and alcohol consumption was divided into very low/no alcohol consumption (\( \leq 1 \) glass per day) and alcohol use (\( >1 \) glass per day). Indications for aspirin use were primary or secondary prevention of cardiovascular events, for which standard daily doses of 100 mg were used. Personal history of adenomatous or SPs was retrieved from medical records.

**Development of the SP risk score from the derivation cohort**

The primary outcome measure of this study was the risk profile associated with having \( \geq 1 \) large, proximal or dysplastic (LPD) SP. Although the majority of SSA/Ps are featured by a large size and/or proximal location (11), recent studies suggest that a subset of SSA/Ps, in particular those harboring dysplasia, may be smaller in size and more distally located in the colon (25, 30). Thus, to ensure capturing of all SSA/Ps, we specifically examined the group of LPD SPs (8-11, 25, 30-32). Unadjusted logistic regression analyses were conducted using a total of 12 clinically relevant parameters. As a minimum of 10 events are recommended per independent variable (33), we estimated \( \geq 120 \) events will be needed. Based on previous data (5), we estimated that the prevalence of \( \geq 1 \) LPD SP in our cohort will be at least 4%. Assuming a questionnaire response rate of 60% (34) and inclusion of on average 200 patients undergoing colonoscopy each month, we expected 24 months will be needed to accomplish data collection. Adjusted logistic regression analyses were performed to identify
independent risk factors for having ≥1 LPD SP, using variables selected from the unadjusted logistic regression analyses (only variables with p-value ≤0.20 were included). The Hosmer-Lemeshow goodness-of-fit statistic was used to test reliability of the model.

Secondary aim of this study was to develop a SP risk score. Independent risk factors were incorporated into the risk score and for each risk factor, we assigned weight in the risk score by using the odds ratios from the adjusted logistic regression analyses and rounded it to the nearest whole number. Total scores were obtained by summing up the individual scores and the risks for having ≥1 LPD SP were calculated. Patients were subdivided into an average risk group (i.e. a priori defined as having a lower cumulative prevalence of LPD SPs than the previously proposed minimum detection target of 5% (16), and corresponding to a total score <5 points) and a high risk group (i.e. a priori defined as having a higher cumulative prevalence of LPD SPs than the suggested reference standard (16), and corresponding to a total score ≥5 points). In addition, the sensitivity and specificity of the risk score to identify patients with ≥1 LPD SP were calculated.

Validation of the SP risk score
For this purpose, a second cohort was prospectively accrued at our institution, comprising all consecutive patients undergoing colonoscopy from February 2010 to February 2012. In assembling this cohort we used a similar methodology (i.e. inclusion and exclusion criteria) as in the derivation cohort. Based on their total score, patients in the validation cohort were subdivided into the average risk group (i.e. corresponding to a total score <5 points) and high risk group (i.e. corresponding to a total score ≥5 points). Subsequently, the sensitivity and specificity of our risk score were calculated.

Statistical analysis
Means (standard deviations) and numbers (percentages) were used to describe continuous and categorical variables, respectively. Differences in continuous variables were analysed using the independent samples t-test and differences in categorical values using the Chi-square test and Fisher exact test, when appropriate. Two-sided p values ≤0.05 were considered statistically significant and all odds ratios are presented with 95% confidence intervals (CI). Statistical analyses were conducted using the Statistical Package for the Social Sciences version 19.0.
RESULTS

In the derivation cohort, a total of 5246 colonoscopies were performed in 4753 patients. Of these, 1100 patients were excluded (<18 years, n=18; hereditary CRC syndrome, n=39; inflammatory bowel disease, n=356; personal history of CRC, n=172; prior colonic surgery n=81; unattainable for questionnaire, n=290; or newly diagnosed CRC at colonoscopy, n=144). Figure 1A illustrates the study diagram for the derivation cohort. A total of 3653 patients received the questionnaire, of whom 994 (27.2%) patients did not respond to the request (i.e. non-responders) and the remaining 2659 (72.8%) patients returned the questionnaire (i.e. responders). Responders were older (mean age [SD] 60 [14] years vs. 52 [18] years, p<.001) and more often had ≥1 colorectal polyp (37.7% vs. 30.8%, p<.001), ≥1 adenoma (29.8% vs. 23.4%, p<.001) and ≥1 LPD SP (5.8% vs. 2.2%, p<.001) compared to non-responders. No significant differences were found between responders and non-responders regarding gender (males, 45.2% vs. 42.7%, p=0.174), personal history of ≥1 adenoma (9.5% vs. 8.8%, p=0.510) or personal history of ≥1 SP (4.6% vs. 4.4%, p=0.765). A total of 316 (8.7%) non-participants (providing no informed consent, n=201; or returning a blank questionnaire, n=115) and patients receiving an examination by an endoscopist performing <50 colonoscopies (n=99) were also excluded resulting in a total of 2244 (61.4%) patients finally analyzed.

In the validation cohort, a total of 5883 colonoscopies were performed in 5266 patients. After exclusion, data from 2402 patients were finally examined. Figure 1B illustrates the study diagram of the validation cohort.

Quality indicators

Cecal intubation rates were 90.2% in symptomatic patients and 95.7% in asymptomatic patients, 30.6% had ≥1 adenoma and 15.9% ≥1 SP. As shown in Supplementary Table S1, in the derivation cohort, individual detection rates of ≥1 LPD SP ranged from 2.9% to 7.8% among gastroenterologists and from 2.3% to 12.1% among trainees.

Characteristics of patients in the derivation and validation cohort

Data from 2244 patients in the derivation cohort were finally analyzed. The mean (SD) age of the study population was 60 (14) years and 46.1% were males. In 80.3%, colonoscopy was performed for symptoms, whereas 10.1% underwent colonoscopy for surveillance (i.e. previous adenoma/CRC) and
9.6% for screening indications. **Table 1** depicts the baseline characteristics of the study population in the derivation and validation cohort subdivided according to presence of ≥1 LPD SP. In the derivation cohort, the prevalence of ≥1 LPD SP was higher in patients referred for surveillance versus symptoms or screening (13.3% vs. 5.3%, p<.001, 13.3% vs. 7.4%, p=0.045, respectively). No significant differences were found in prevalences of ≥1 LPD SP between patients referred for symptoms versus screening (5.3% vs. 7.4%, p=0.187). Patients with ≥1 LPD SP had significantly more adenomas and advanced adenomas compared to patients with non-dysplastic small distal or no SPs. Baseline characteristics regarding risk factors and the presence of ≥1 LPD SP in the derivation and validation cohort are presented in **Table 2**.

**Risk factors for the presence of ≥1 LPD SP and ≥1 adenoma in the derivation cohort**

With regard to LPD SPs, results from the unadjusted and adjusted logistic regression analyses for the presence of ≥1 LPD SP are summarized in **Table 3**. Variables associated with the presence of ≥1 LPD SP (i.e. p-value ≤0.20) in the unadjusted logistic regression analyses were incorporated into the adjusted logistic regression analyses. Adjusted logistic regression analyses showed that age >50 years (OR 2.2, 95% CI 1.3 – 3.8, p=0.004), a personal history of ≥1 SP (OR 2.6, 95% CI 1.3 – 4.9, p=0.005), current smoking (OR 2.2, 95% CI 1.4 – 3.6, p=0.001) and non-daily or no aspirin use (OR 1.8, 95% CI 1.1 – 3.0, p=0.016) were independent risk factors for the presence of ≥1 LPD SP. Separate logistic regression analysis were performed using a cut-off value of ≥10 mm for large SPs, which did not significantly change the results.

With regard to adenomas, results from the unadjusted and adjusted logistic regression analysis for the presence of ≥1 adenoma are summarized in **Supplementary Table S2**. Adjusted logistic regression analyses showed that age >50 years (OR 3.8, 95% CI 2.8 – 5.2, p<.001), male gender (OR 1.8, 95% CI 1.5 – 2.2, p<.001), a personal history of ≥1 adenoma (OR 2.8, 95% CI 2.0 – 3.9, p<.001) and current smoking (OR 2.0, 95% CI 1.5 – 2.7, p<.001) were all independent risk factors for the presence of ≥1 adenoma.

**Development of the clinical SP risk score in the derivation cohort**

Independent risk factors were incorporated into the SP risk score (**Table 3**). The Hosmer-Lemeshow goodness-of-fit statistic was p=0.279 for our model. **Figure 2A** depicts the percentage of patients with...
≥1 LPD SP per score category and corresponding 95% CI in the derivation cohort. Based on their total score, patients were subdivided into an **average risk group** (i.e. total score <5 points, n=1950) and a **high risk group** (i.e. total score ≥5 points, n=294). Prevalence of ≥1 LPD SP was 5.0% in the average risk group versus 14.6% in the high risk group (**Table 4A**). Patients in the high risk group had a 3.2 fold increased odds of having ≥1 LPD SP than those in the average risk group. The sensitivity and specificity of our SP risk score to identify patients with ≥1 LPD SP were 30.5% (95% CI, 23.5% – 38.5%) and 88.1% (95% CI, 86.6% – 89.4%), respectively. Additional logistic regression analyses including different cut-off levels for age (i.e. ≥55 years; ≥60 years; ≥65 years, as well as age in decades) did not improve the sensitivity and specificity of our risk score.

**Validation of the SP risk score**

**Figure 2B** depicts the percentage of patients with ≥1 LPD SP per score category and corresponding 95% CI in the validation cohort. The prevalence of ≥1 LPD SP was 6.5% in the **average risk group** and 17.2% in the **high risk group** (**Table 4B**). As compared to the average risk group, patients in the high risk group had a 3.0 fold increased odds of having ≥1 LPD SP. The sensitivity and specificity of the SP risk score were 33.2% (95% CI, 27.0% – 40.0%) and 93.5% (95% CI, 92.4% – 94.5%), respectively.
DISCUSSION

In this study, we found that 6.3% of all patients undergoing colonoscopy had ≥1 large, proximal or dysplastic SP. Age >50 years, a personal history of SPs, current smoking and non-daily/no aspirin use were independent risk factors for having LPD SPs. According to our SP score, patients in the high risk group had a 3.0 fold increased odds of having ≥1 LPD SP as compared to those in the average risk group. We suggest that pre-assessment of the clinical risk for having LPD SPs may heighten the vigilance of endoscopists in recognizing such lesions, and might reduce the observed variability in detection.

Several studies suggest that LPD SPs, in particular SSA/Ps, might contribute to the occurrence of post-colonoscopy cancers through a serrated neoplastic pathway (10, 35). It became clear that SPs often have a subtle endoscopic appearance, thereby explaining the operator-dependent variation in their detection, ranging from 8% to 32% (14, 15). This high variability in detection highlights the need for education and training, for which a systematic approach is needed, i.e. by means of video-training, computer-aided programs and learning from experts (14, 15). In this context, the simple clinical score described in our study, might be a useful tool as we assume that a priori estimation of the risk for having LPD SPs may increase the awareness of the endoscopist to detect such lesions, through careful examination of the proximal colon (i.e. longer withdrawal time, twice examination or retroflexion, use of selective dye-based or digital chromoendoscopy or, perhaps additional tools, such as caps or endocuffs) (36).

Several studies have demonstrated that increasing age is associated with the presence of both adenomas and synchronous SPs (19, 21, 37, 38), whereas the association between age and SPs only remains controversial (19-21, 37, 38). In the current study, 51.1% of all patients with ≥1 LPD SP had ≥1 synchronous adenoma, at a mean (SD) age of 63 (11) years, suggesting that aging may increase the risk for having both LPD SPs and adenomas (19-21, 23). Some previous studies found an association between female gender and presence of SPs (9, 39) whereas others, including the current study, did not (40, 41). Most of these studies observing gender differences were retrospective in nature and based on histopathology data only. As the current study was prospective and based on standardized data registration, we assume that this setting might provide more accurate estimates of the prevalence of SPs in relation to gender. Our data are also in line with studies showing no association between obesity and presence of SPs (37, 38) but at odds with others (19, 20, 22). These
discrepancies might possibly be explained by the wide variations in the composition of populations examined. Moreover, we found that daily aspirin use has a protective effect against LPD SPs, in line with earlier studies (19-21, 23). The strong association between current smoking and presence of ≥1 LPD SP is in agreement with existing literature data (18-21, 37, 38, 42). Of note, (current) smoking has been also associated with proximal CRCs, showing extensive DNA methylation, BRAF mutation and microsatellite instability (43, 44). These shared molecular features in SPs and CRCs arising through the serrated neoplastic pathway (39, 45-47) may imply smoking has an important role in the serrated carcinogenesis.

Some studies suggested that the risk factors for having SPs might differ from those associated with adenomas (19, 38). In our study, current smoking and increasing age were associated with both the presence of adenomas and SPs, whereas male gender was an independent risk factor for the presence of ≥1 adenoma only. An interesting finding of this study was that a personal history of ≥1 adenoma was associated with the presence of ≥1 adenoma, while a personal history of ≥1 SP was associated with the presence of ≥1 SP.

In the present study we found that patients with ≥1 LPD SP significantly more frequently had adenomas and advanced adenomas compared to patients with non-dysplastic small distal or no SPs, which is in line with previous data by us (5) and others (31, 32). Taken together, these data suggest that older age, prior history of SPs, current smoking and non-daily/no aspirin use, as well as presence of adenomas, may define a risk phenotype which is associated with synchronous LPD SPs. This observation is of relevance as it may highlight a subgroup of patients in whom multiplicity of lesions may require personalized surveillance, with regard to the frequency of examination or technique used (i.e. chromoendoscopy, either dye-based or digital-based techniques). In a previous study by our group, we found that presence of (advanced) adenomas during colonoscopic examination might be considered a ‘red flag’ for synchronous SPs (5). The SP risk score proposed in the current study extends these observations, by identifying an a priori risk profile for having ≥1 LPD SP.

Some methodological issues of this study need to be further addressed. As a strength, all endoscopists were familiarized with the recognition of non-polypoid colorectal lesions before commencing this study. This was essential, as nearly half of the SPs have a non-polypoid appearance (5, 6). We used a standardized endoscopic reporting system, including quality benchmarking, and applied the WHO histologic classification of SPs. As a potential limitation, in our
study, questionnaire responders were older than non-responders, in line with other Dutch surveys (34), and had more often colorectal lesions. As responders did not differ from non-responders with regard to gender, personal history of adenomas or SPs, we assume the differences found in prevalence of colorectal polyps may rather reflect the effect of aging than differences in response. To mitigate this source of bias logistic regression analyses were conducted adjusting for age. Second, as the questionnaire was distributed to the patients shortly after the colonoscopy, the possibility of a recall bias cannot be excluded. Nevertheless, other studies, employing a similar methodology as our study, found no differences in the reported risk factors among patients receiving the questionnaires before versus shortly after the colonoscopy (48). Third, the SP risk score proposed in our study was developed in a real-life cohort, including symptomatic and asymptomatic patients, and hence generalizability to a screening population needs to be further examined. Fourth, the ability of identifying patients with \( \geq 1 \) LPD SP, using the clinical SP risk score proposed in our study is only moderate with a sensitivity of 33% and specificity of 94%, albeit comparable with other clinical scores (49, 50). Finally, not unexpected, prevalences of \( \geq 1 \) LPD SP and SSA/Ps without dysplasia were higher in the validation cohort than the derivation cohort. As the endoscopists and pathologists were unaware of the study hypothesis, we believe these findings rather reflect improvements in their learning curves through performance.

In conclusion, the present study indicates that age \( \geq 50 \) years, a personal history of \( \geq 1 \) SP, current smoking and non-daily/no aspirin use are all independent risk factors for having \( \geq 1 \) LPD SP. Risk pre-assessment of patients undergoing colonoscopy, using the simple clinical SP risk score proposed in our study, might enable identification of patients at higher risk of having \( \geq 1 \) LPD SP. Careful colonoscopic inspection in these patients, especially of the proximal colon, may reduce the currently observed variation among endoscopists in the detection of these lesions and finally improve the quality of examination.
REFERENCES


Table 1. Baseline characteristics derivation (A) and validation (B) cohort subdivided according to presence of ≥1 large, proximal or dysplastic (LPD) serrated polyp (SP).

<table>
<thead>
<tr>
<th></th>
<th>A. DERIVATION COHORT</th>
<th>B. VALIDATION COHORT</th>
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<tbody>
<tr>
<td></td>
<td>Total population</td>
<td>Patients with ≥1 LPD SP</td>
</tr>
<tr>
<td>Number of patients (%)</td>
<td>2244</td>
<td>141 (6.3)</td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>60 (14)</td>
<td>63 (11)</td>
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<tr>
<td>Male gender (%)</td>
<td>1034 (46.1)</td>
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<td>Indication for colonoscopy</td>
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<tr>
<td>Symptoms (%)</td>
<td>1803 (80.3)</td>
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<tr>
<td>Screening (%)</td>
<td>215 (9.6)</td>
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<td>Surveillance (%)</td>
<td>226 (10.1)</td>
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<tr>
<td>≥1 proximal SP (%)</td>
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<tr>
<td>≥1 distal SP (%)</td>
<td>283a (12.6)</td>
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<td>≥1 SSA/P with dysplasia (%)</td>
<td>24 (1.1)</td>
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<td>≥1 SSA/P without dysplasia (%)</td>
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<td>≥1 TSA (%)</td>
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<td>Category</td>
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<td>Group 2</td>
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<td>≥1 hyperplastic polyp (%)</td>
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<td>≥1 adenomatous polyp (%)</td>
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<td>≥1 advanced adenoma&lt;sup&gt;b&lt;/sup&gt; (%)</td>
<td>317 (14.1)</td>
<td>42 (29.8)</td>
</tr>
</tbody>
</table>

**Legend**

- <sup>a</sup> Information on polyp location could not be obtained from the endoscopy report in 1 case
- <sup>b</sup> Advanced adenoma was defined as size ≥10 mm, containing villous component or with high-grade dysplasia
- <sup>c</sup> Patients with ≥1 large, proximal or dysplastic serrated polyp versus patients with non-dysplastic small distal or no serrated polyps
- <sup>d</sup> Fisher exact test

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Table 2. Baseline characteristics regarding risk factors in the derivation (A) and validation (B) cohort subdivided according to presence of ≥1 large, proximal or dysplastic (LPD) serrated polyp (SP).

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<td>2244</td>
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<tr>
<td>History of ≥1 adenoma (%)</td>
<td>212 (9.4)</td>
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<td>History of ≥1 SP (%)</td>
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<td>Smoking</td>
<td>a0.002</td>
<td></td>
</tr>
<tr>
<td>Current (%)</td>
<td>407 (18.1)</td>
<td>40 (28.4)</td>
</tr>
<tr>
<td>Former (%)</td>
<td>1034 (46.1)</td>
<td>64 (45.4)</td>
</tr>
<tr>
<td>Never (%)</td>
<td>803 (35.8)</td>
<td>37 (26.2)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>a0.356</td>
<td></td>
</tr>
<tr>
<td>Normal (%)</td>
<td>1022 (45.5)</td>
<td>61 (43.3)</td>
</tr>
<tr>
<td>Overweight (%)</td>
<td>843 (37.6)</td>
<td>50 (35.5)</td>
</tr>
<tr>
<td>Obese (%)</td>
<td>379 (16.9)</td>
<td>30 (21.3)</td>
</tr>
<tr>
<td>Non-daily/no NSAID use (%)</td>
<td>2027 (90.3)</td>
<td>128 (90.8)</td>
</tr>
<tr>
<td>Non-daily/no aspirin use (%)</td>
<td>1782 (79.4)</td>
<td>120 (85.1)</td>
</tr>
<tr>
<td>Legend</td>
<td>Alcohol use (%)</td>
<td>Diabetes mellitus (%)</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Patients with ≥1 large, proximal or dysplastic serrated polyp versus patients with non-dysplastic small distal or no serrated polyps</td>
<td>a0.457</td>
<td>a0.681</td>
</tr>
<tr>
<td>878 (39.1)</td>
<td>919 (38.3)</td>
<td></td>
</tr>
<tr>
<td>51 (36.2)</td>
<td>29 (40.0)</td>
<td></td>
</tr>
<tr>
<td>827 (39.3)</td>
<td>823 (37.3)</td>
<td></td>
</tr>
<tr>
<td>12 (8.5)</td>
<td>29 (14.8)</td>
<td></td>
</tr>
<tr>
<td>201 (9.6)</td>
<td>244 (11.1)</td>
<td></td>
</tr>
<tr>
<td>213 (9.5)</td>
<td>273 (11.1)</td>
<td></td>
</tr>
</tbody>
</table>

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Table 3. Risk factors associated with the presence of ≥1 large, proximal or dysplastic serrated polyp (SP) in unadjusted and adjusted logistic regression analyses

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Unadjusted analysis</th>
<th>Adjusted analysis</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI p-value</td>
<td>OR 95% CI p-value</td>
<td></td>
</tr>
<tr>
<td>Age &gt;50 years (vs. ≤50 years)</td>
<td>2.1 1.3 – 3.6 0.004</td>
<td>2.2 1.3 – 3.8 0.004</td>
<td>2</td>
</tr>
<tr>
<td>Male gender (vs. female gender)</td>
<td>0.9 0.6 – 1.2 0.386</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>History of ≥1 adenoma (vs. none)</td>
<td>2.5 1.6 – 3.8 &lt;.001</td>
<td>1.4 0.8 – 2.5 0.193</td>
<td>-</td>
</tr>
<tr>
<td>History of ≥1 serrated polyp (vs. none)</td>
<td>3.8 2.3 – 6.5 &lt;.001</td>
<td>2.6 1.3 – 4.9 0.005</td>
<td>3</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current (vs. never)</td>
<td>2.3 1.4 – 3.6 0.001</td>
<td>2.2 1.4 – 3.6 0.001</td>
<td>2</td>
</tr>
<tr>
<td>Former (vs. never)</td>
<td>1.4 0.9 – 2.1 0.141</td>
<td>1.2 0.8 – 1.9 0.310</td>
<td>-</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight (vs. normal)</td>
<td>1.0 0.7 – 1.5 0.973</td>
<td>1.0 0.6 – 1.4 0.818</td>
<td>-</td>
</tr>
<tr>
<td>Obesity (vs. normal)</td>
<td>1.4 0.9 – 2.1 0.190</td>
<td>1.4 0.9 – 2.3 0.123</td>
<td>-</td>
</tr>
<tr>
<td>Non-daily or no NSAID use (vs. daily)</td>
<td>1.1 0.6 – 1.9 0.852</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Non-daily or no aspirin use (vs. daily)</td>
<td>1.5 0.9 – 2.4 0.086</td>
<td>1.8 1.1 – 3.0 0.016</td>
<td>2</td>
</tr>
<tr>
<td>Alcohol use (vs. very low/no alcohol use)</td>
<td>0.9 0.6 – 1.2 0.458</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes mellitus (vs. no diabetes)</td>
<td>0.9 0.5 – 1.6 0.682</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 4. Prevalence of ≥1 large, proximal or dysplastic (LPD) serrated polyp (SP) and risk for ≥1 LPD SP according to risk group in the derivation (A) and validation (B) cohort.

<table>
<thead>
<tr>
<th>A. DERIVATION COHORT</th>
<th>B. VALIDATION COHORT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk group</strong></td>
<td><strong>Number of total population (%)</strong></td>
</tr>
<tr>
<td>Average</td>
<td>1950 (86.9)</td>
</tr>
<tr>
<td>High</td>
<td>294 (13.1)</td>
</tr>
</tbody>
</table>
FIGURE LEGENDS

**Figure 1.** Study diagram derivation cohort (A) and validation cohort (B). CRC; colorectal cancer

**Figure 2.** Percentage of patients with ≥1 large, proximal or dysplastic (LPD) serrated polyp (SP) per score category and corresponding 95% confidence intervals (CI) in the derivation cohort (A) and validation cohort (B).
A. Derivation cohort

5246 colonoscopies in 4753 consecutive patients
February 2008 – February 2010

Exclusion (n=1100):
- <18 years of age (n=18)
- hereditary CRC syndromes (n=39)
- inflammatory bowel disease (n=356)
- personal history of CRC (n=172)
- colonic resection (n=81)
- unattainable for questionnaire (n=290)
- CRC detected at colonoscopy (n=144)

3653 patients received questionnaire

994 (27.2%) non-responders

2659 (72.8%) responders

316 (8.7%) non-participants
  (no informed consent / blank questionnaire)

2343 (64.1%) participants

99 (2.7%) colonoscopies performed by endoscopists with <50 colonoscopies

2244 patients final study population

B. Validation cohort

5883 colonoscopies in 5266 consecutive patients
February 2010 – February 2012

Exclusion (n=1216):
- <18 years of age (n=20)
- hereditary CRC syndromes (n=68)
- inflammatory bowel disease (n=495)
- personal history of CRC (n=205)
- colonic resection (n=80)
- unattainable for questionnaire (n=190)
- CRC detected at colonoscopy (n=158)

4050 patients received questionnaire

1208 (29.8%) non-responders

2842 (70.2%) responders

368 (9.1%) non-participants
  (no informed consent / blank questionnaire)

2474 (61.1%) participants

72 (1.8%) colonoscopies performed by endoscopists with <50 colonoscopies

2402 patients final study population

Figure 1A and 1B

Figure 1. Study diagram derivation cohort (A) and validation cohort (B). CRC, colorectal cancer.
Figure 2A and 2B

A. Derivation cohort

B. Validation cohort

Prevalence of 21 LPD SP with corresponding 95% CI

Total points vs. Prevalence of 21 LPD SP

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Simple clinical risk score identifies patients with serrated polyps in routine practice


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