RESEARCH ARTICLE

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The Performance of Modified Swede Colposcopic Index to Predict High Grade Cervical Intraepithelial Neoplasia and Cervical Cancer in the Real Clinical Practice, an External Validation Study

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Abstract

Objective: The primary objective is to examine the external validity of the modified Swede colposcopic index (MSCI) for predicting cervical intraepithelial neoplasia grade 2-3, including cancer (CIN2+), and to evaluate inter-rater and intra-rater reliability as a secondary objective in women with abnormal cervical cancer screening. **Methods:** We conducted a prospective study to predict CIN2+ in women aged 25-65 years with abnormal cervical cancer screening results (atypical squamous cells of undetermined significance (ASC-US) or higher and/or high-risk HPV infection). All participants were previously undiagnosed with CIN2+. We evaluated the effectiveness of MSCI in detecting CIN2+ using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). **Results:** A total of 118 women were included in this study. Gynecologic oncologists using the MSCI achieved a sensitivity of 46.9%, specificity of 87.2%, PPV of 57.7%, NPV of 81.5%, and accuracy of 76.27%. Inter-rater reliability for the MSCI was good (ICC=0.77, 95%confidence interval=0.67-0.84), and intra-rater reliability was excellent (ICC=0.98, 95%confidence interval =0.97-0.99). **Conclusion:** In a real-world clinical setting, studies have demonstrated that MSCI exhibits high specificity while maintaining acceptable sensitivity.

Keywords: Colposcopy- Modified Swede colposcopic index- Cervical cancer- Cervical intraepithelial neoplasia

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Introduction

Cervical cancer is the 2rd most common type of cancer in Thai women and the 4th most common type of cancer worldwide [1, 2]. Cervical cancer is a cancer that can be prevented and precancerous lesions can be detected and treated [3]. Therefore, it is considered a cancer that can be completely eradicated. Currently, the World Health Organization has set a goal to hasten the eradication of cervical cancer by setting a goal such that the incidence of new cancers will not exceed 4 in every 100,000 women per year, to be achieved by 2030 and 90% of the patients get treatment if precancerous and cancerous lesions are found [4].

Colposcopy is an important tool for diagnosis after abnormal cervical cancer screening is found. Its purpose is to detect lesions in the cervix and guide the location for biopsy to lead to diagnosis and treatment [5, 6]. Currently, common colposcopic grading systems used is the Swede Colposcopic index (SCI), with cutoff 8 has sensitivity and specificity equal to 42.42% and 100% to detecting CIN2-3 and cancer (CIN2+), respectively. If the cutoff is 5, sensitivity and specificity are found to be equal to 100% and 88.37%, respectively [7]. The development of the scoring system aims to make colposcopic findings more accurate and objective, independent of the colposcopist's experience [3]. Therefore, the scoring system should be simple to assess and still have good diagnostic accuracy. In real practice, it has been found that there are limitations in measuring the size of the lesion and interpreting the iodine staining results in SCI. The study of the Modified Swede Colposcopic index (MSCI) has adjusted the evaluating criteria to be simpler to assess than the original SCI, including aceto-uptake, margin and surface, vessels, lesion size, and location of the lesion. A full score of 15 points and a cut-off of 11 points were used and found to be accurate in diagnosing CIN 2-3 and cancer, with sensitivity and specificity found to be 84.21% and 96.2%, without missing cancerous lesions [8]. When compared to the Reid Colposcopic Index (RCI), a traditional and widely used colposcopic index, the RCI had a sensitivity of 83.7% and a specificity of 89.7%, results comparable

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to the MSCI [9]. However, the effectiveness of MSCI in real world clinical setting has never been studied.

The primary objective of this study was to examine the external validity of the MSCI. The correlation of the MSCI between experienced and less experienced colposcopists has not been previously evaluated. This evaluation could indicate whether less experienced colposcopists are equally adept at using the MSCI to predict precancerous lesions or cervical cancer compared to experienced colposcopists. Therefore, the study of inter-rater and intra-rater reliability was included as a secondary objective.

Materials and Methods

A prospective descriptive study was conducted at the colposcopic clinic, HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC), Srinakharinwirot University Hospital, during the period between February 2023 and February 2024. The study received an appropriate approval from the institutional review board (IRB) (SWUEC/E/M-094/2565).

The participants were non-pregnant females aged 25-65 years, with abnormal cervical cancer screening results either from cytology of ASC-US or higher cytology or/and high-risk HPV infection and had never received a previous diagnosis of CIN2+. For the exclusion criteria, If the participants had an obvious cervical mass or lesion, a colposcopic direct biopsy was not done, a colposcopic examination did not reveal any cervical lesion, inadequate colposcopy or a transformation zone type 3 and the patient who refused treatment was excluded from the study. The informed consent was obtained from all participants during their colposcopic examination visit.

Study protocol

The participants who meet the inclusion criteria will be invited to join in the study and will be informed about the diagnostic methods through colposcopy, including taking biopsies from the ectocervix and endocervix in an abnormal area for diagnosis. When colposcopic findings reveal multiple lesions, we assess the MSCI score for each lesion and also perform a colposcopic directed biopsy on each. Consequently, the number of participants depended on the number of lesions, rather than the number of patients.

During the same colposcopic examination visit, a gynecologic oncologist and gynecologic oncologic fellow assessed the modified Swede colposcopic index (MSCI) as Table 1. To reduce bias, the colposcopists were blinded to the abnormal cervical cancer screening results beforehand. Separate data recording forms were used and linked using the research participant number. General information about the participants, cervical cancer screening results, colposcopic impression, cervicographic findings, MSCI scores, and pathological report collected and recorded for statistical analysis. The fellow (N.K.) and the gynecologic oncologist (N.R.), both single individuals, participated in the study. During the colposcopic exam, the fellow was under the supervision of the gynecologic oncologist, and the treatment plan was decided by the gynecologic oncologist.

The tissue obtained from colposcopic directed biopsies was evaluated by a total of three general pathologists. They were all qualified staff members of the university hospital and had at least 10 years of experience in the field of gynecologic pathology. The pathological reports adhered to the 5th Edition of the WHO classification of tumours of female genital tumours, identified as the most recent and standard reference [10]. The grade of the lesion was defined by both MSCI scoring and histopathology. An MSCI score of less than 11 was defined as low grade, and a score of 11 or greater was defined as high grade. Low grade pathology included benign findings, cervicitis, koilocytosis, and CIN1, while high grade pathology included CIN2, CIN3, and cancer. The low and high grade MSCI scores correlated with the respective low and high grade pathology.

The cervicographic finding was recorded in at least four images, both before and after applying 3% acetic acid. Magnification of 15x was used for the first set of images, and 7.5x for the second set. Additional recordings may be made as needed to ensure visualization of all lesions. (colposcopy using Leisegang Model 3ML illumination LED, magnification 7.5X, 15X, 30X working distance 300 mm, eyepiece straight insight). The cervicographic finding will be reevaluated with the modified SCI again after 2 weeks by a fellow who will be blinded to the patient's abnormal cervical cancer screening results, previously assessed MSCI scores, and pathological biopsy results. This is to assess intra-ratter reliability. All participants had a follow-up visit in 3 weeks and received standard treatment based on their pathology reports. The study diagram showed as Figure 1.

Sample size calculation and statistical analysis

The sample size was calculated from the Area under ROC curve (AUC) using the MedCalc version 20 by setting the alpha value to 5% and the power to 80%. The AUC value of the Modified Swede colposcopic index from a previous study was 0.95. In real clinical practice, it will have an estimated AUC value of not less than 0.88. Therefore, the sample size will be 112 cases and add 5% to prevent data loss. Therefore, a total sample size of 118 cases was required.

This study will utilize Stata version 13 (StataCorp, College Station, TX, USA) for statistical analysis of the data. Patient demographics will be presented using appropriate descriptive statistics based on the underlying data distribution (e.g., mean ± standard deviation, median, interquartile range, or percentages). The diagnostic performance of the MSCI will be evaluated by calculating its sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Additionally, the area under the receiver operating characteristic curve (AUC) of the index will be compared between gynecological oncologists and fellows using a chi-square test to assess potential differences in their colposcopists. Inter- and intra-ratter reliability will be assessed using the intraclass correlation coefficient (ICC) with a two-way random-effects model for inter-rater reliability and a two-way mixed-effects model for intra-rater reliability, with absolute agreement as the criterion.

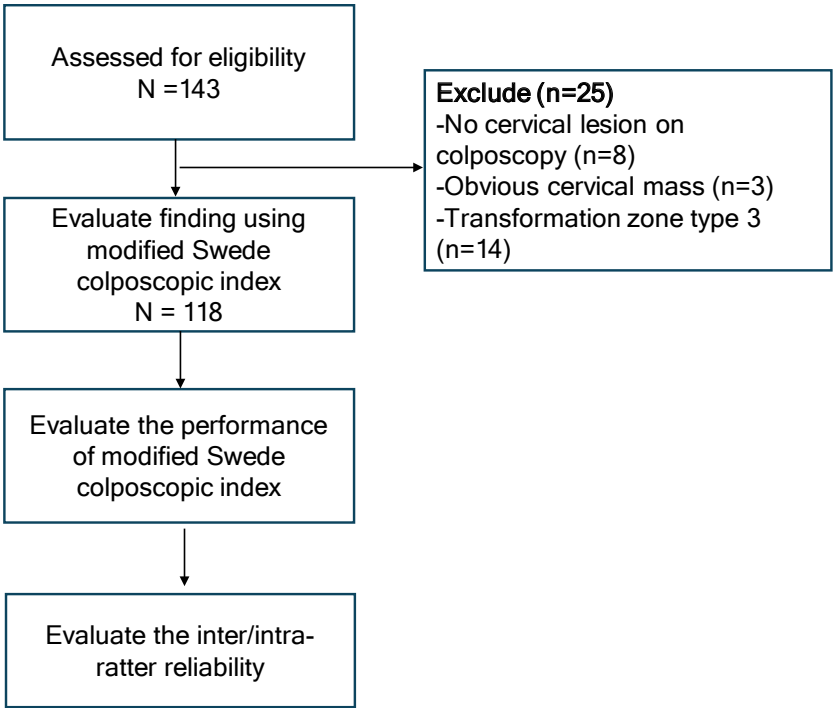

Figure 1. The Research Diagram

Results

Among the 143 participants who met the inclusion criteria for the study, 8 had no lesion on colposcopy, 3 had an obvious cervical mass, and 14 had transformation zone type 3. Consequently, 25 participants were excluded from the study. Therefore, a total of 118 patients were included, and each of these patients had a single lesion on colposcopic exam. The average participant age was 41.3 years (standard deviation ± 8 years). The majority (87.3%) of participants were premenopausal, and 82.2% were multiparous. Regarding cervical cancer screening results, 21.2% of patients fell into the high-grade cytology group (ASC-H, HSIL, AGC-FN, AIS, and cancer), 56.9% into the low-grade cytology group (NILM with HPV, ASC-US, LSIL, AGC-NOS, AEC-NOS), and 22% into the high-risk HPV group (HPV 16 or 18). Pathology results revealed that 72.9% of patients had low-grade histology, while 27.1% had high-grade histology. Notably, 3.4% of patients received a diagnosis of cervical cancer and none of the patients had received the HPV vaccine. Further details on patient demographics are presented in Table 2.

Based on the main objective of the study, the diagnostic performance of the MSCI for identifying high-grade cervical lesions as shown on Table 3. Gynecologic oncologists using the MSCI achieved a sensitivity of 46.9%, specificity of 87.2%, PPV of 57.7%, NPV of 81.5%, and accuracy of 76.27%. Fellows using the MSCI demonstrated a sensitivity of 53.13%, specificity of 93.02%, PPV of 73.91%, NPV of 84.21%, and accuracy of 82.2%. While the AUC was higher for fellows (0.73) compared to oncologists (0.67), however, this difference was not statistically significant by DeLong's test (p=0.25). Inter-rater reliability for the MSCI was good (ICC=0.77, 95% confidence interval=0.67-0.84), while intra-rater reliability was excellent (ICC=0.98, 95% confidence interval =0.97-0.99).

Discussion

Colposcopy is a tool for diagnosing precancerous and cancerous lesions of cervix. The development of the colposcopic grading system has made the assessment of these lesions more objective, helping differentiate CIN2+

Table 1. Modified Swede Colposcopic Index Scoring System

Features	Score 1	Score 2	Score 3
Acetouptake	None or transparent	Shady, milky neither transparent nor opaque	Distinct, opaque white
Margin and surface	Diffuse	Sharp but irregular, jagged, geographic satellites	Sharp and even, difference in surface level includes cuffing
Vessels	Fine, regular	Absent	Coarse or atypical
Lesion size	Involve 1/4 of transformation zone area in single lesion	Involve 2/4 of transformation zone area in single lesion or involve 2 quadrants in multiple lesion	Involve ≥3/4 of transformation zone area in single lesion or involve 3–4 quadrants in multiple lesion or undefined endocervically
Location of lesion	Only outer one-half of transformation zone	Both inner and/or outer one half of transformation zone	Invade endocervical canal

Table 2. Demographic Data of the Patients (118 Patients).

Patient characteristic	Case, n (%)
Age, Mean±SD (year-old)	41.3±8
Menopausal status	
Pre-menopause	103 (87.3)
Post-menopause	15 (12.7)
Parity	
Nulliparous	21 (17.8)
Multiparous	97 (82.2)
History HPV vaccine	
Yes	0 (0)
No	118 (100)
Cervical cancer screening	
NILM, HPV HR positive	2 (1.7)
HPV 16 positive	21 (17.8)
HPV 18 positive	5 (4.2)
ASC-US, unknow HPV	15 (12.7)
ASC-US, HPV high risk positive	2 (1.7)
ASC-US, HPV other high risk positive	14 (11.9)
LSIL	28 (23.8)
ASC-H	10 (8.5)
HSIL	12 (10.2)
AEC-NOS	2 (1.7)
AGC-NOS	4 (3.4)
AGC-FN	1 (0.8)
AIS	1 (0.8)
Adenocarcinoma	1 (0.8)
Histology	
Low grade pathology	
Benign	26 (22.0)
Cervicitis	2 (1.7)
Koilocytosis	6 (5.1)
CIN 1	52 (44.1)
High grade pathology	
CIN 2	14 (11.9)
CIN 3	14 (11.9)
Cancer	4 (3.4)

SD, standard deviation; NILM, negative for intraepithelial lesion or malignancy; ASC-US, Atypical squamous cells of undetermined significance; LSIL, Low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells, cannot rule out HSIL; HSIL, High-grade squamous intraepithelial lesion; AGC-NOS, atypical glandular cell not otherwise specified; AEC-NOS, atypical endocervical cell not otherwise specified; AGC-FN, atypical glandular cell favor neoplasia; CIN, cervical intraepithelial neoplasia; AIS, Adenocarcinoma in situ

Table 3. The Diagnostic Performance of MSI

Performance	Gynecologic oncologist assessment	Fallow assessment
Sensitivity	46.90%	53.13%
Specificity	87.20%	93.02%
Positive predictive value	57.70%	73.91%
Negative predictive value	81.50%	84.21%
Accuracy	76.27%	82.20%
AUC	0.67*	0.73*

from low-grade lesions, and facilitate use in real-world clinical practice. According to this study, the assessment of cervical lesions under colposcopy using MSCI showed a sensitivity of 46.9%, specificity of 87.2%, PPV of 57.7%, NPV of 81.5%, and an AUC of 0.67. There was no significant difference in performance between assessments by gynecological oncologists and gynecological fellows. Inter-rater reliability was assessed using the ICC, which was 0.76. Intra-rater reliability was also high, with an ICC of 0.97. The prevalence of CIN 2+, including cancer, was 27.12% in this study. Additionally, 3.4% of patients were diagnosed with cervical cancer.

A previous study by Rodpenpear et al. [8], a developmental model study, found that using the MSCI with a cut-off of 11 points resulted in high performance (84.21% sensitivity and 96.2% specificity) for diagnosing CIN2+, with no missed cancerous lesions. However, the original study only included patients with abnormal cervical cytology and did not include abnormal HPV DNA testing, which is a standard component of cervical cancer screening today. Furthermore, a study by Murat Alan et al. found the Swede Colposcopic Index to be effective in detecting high-grade lesions in patients with HPV-positive (non-16, 18) genotypes, demonstrating a sensitivity of 92% and a specificity of 98% [11]. These findings suggest that the colposcopic index may still perform well in the presence of abnormal HPV DNA testing, indicating that HPV does not significantly interfere with the index's assessment.

The external validation study demonstrated lower diagnostic performance than the development model study due to differences in the study populations. The external validation population had a higher proportion of low-grade pathology (CIN1 and lower) compared to high-grade pathology (CIN2+); low grade and high grade pathology was 72.88%and 27.12%, respectively, whereas the original study included groups with relatively equal proportions of low-grade and high-grade pathology (low grade and high grade pathology was 48.2% and 51.8%, respectively). To address this discrepancy, new cut-off points for the MSCI score were identified. A score of 10 yielded the following diagnostic performance: sensitivity, 53.1%; specificity, 84.9%; PPV, 56.7%; NPV, 83.0%; accuracy, 76.3%; and AUC, 0.69. The diagnostic performance for CIN2+ was slightly better at a score of 10 compared to a cut-off point of 11 (The detail of result showed in supplementary materials: Table S1, S2 and Figure S1). Notably, both cut-off points (10 and 11) demonstrate high specificity with acceptable sensitivity, which is a desirable characteristic for a diagnostic test.

Therefore, before implementing any diagnostic test in the real-world clinical practice, it is crucial to consider the prevalence of the disease the test is designed to detect. The performance of a diagnostic test can vary significantly depending on the prevalence of the disease

in the population being tested. Studies that develop diagnostic models may be influenced by differences in population characteristics, and their findings may not translate directly to real-world scenarios with different disease prevalence. However, from Nutacha et al. [12] study found the prevalence of low grade pathology and high grade pathology of cervix in a suburban Thai population was 82.53% and 17.47%, respectively. The prevalence was concordance with this study. Therefore, the performance of MSCI from this study was mimic in the real-world clinical practice.

The performance of the MSCI in predicting CIN2+ observed by fellows was slightly higher than that of gynecologic oncologists. This finding may be due to the fellows' recent training and adherence to study protocols. However, this difference in performance was not statistically significant. Therefore, even inexperienced colposcopists can utilize the MSCI as effectively as experienced colposcopists. Furthermore, acceptable inter- and intra-rater reliability (ICC=0.77 and 0.98, respectively) demonstrates the reproducibility of the MSCI as a diagnostic tool for CIN2+ prediction. Additionally, Bland-Altman plots, shown in the supplementary appendix (Figure S3), also confirm good agreement for both inter-rater and intra-rater reliability.

While MSCI cannot yet fully replace standard colposcopic grading due to limitations in detecting advanced precancerous lesions, it has the advantage of not missing cancerous lesions. However, integration with biopsy results remains essential for treatment planning of both low-grade and high-grade lesions. Given the practical challenge of differentiating between high-grade and low-grade lesions, a low MSCI score can be particularly beneficial for less experienced colposcopists. This has the potential to provide early reassurance regarding the possibility of a low-grade lesion, even before final pathology reports are available.

This study presents several strengths. First, it utilizes a prospective design, which mimics real-world clinical practice and minimizes recall bias. Second, it evaluates the MSCI effectiveness among both experienced and less experienced colposcopists and assesses both inter-rater and intra-rater reliability. Third, the result of cervical cancer screening was blinded to colposcopists to reduce bias in assessing MSCI. This study had two main limitations. First, the prevalence of high-grade lesions might differ in other populations, potentially impacting MSCI's effectiveness. Second, the study did not encompass the population receiving primary HPV vaccination. Future studies should address this gap to broaden the real-world applicability of MSCI in clinical practice.

In conclusion, the MSCI demonstrated high specificity with acceptable sensitivity and reproducibility, effectively minimizing the likelihood of missing cancerous lesions. The new cut-off point of 10 offers improved performance and facilitates its ready applicability in real-world practice.

Author Contribution Statement

N Klangprapan (N.K.): Data curation, Formal analysis, Investigation, Methodology, Writing – first draft. N Rodpenpear (N.R.): Conceptualization, Data curation, Formal analysis, Investigation, Methodology Funding acquisition, Writing – review and editing.

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General

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Declaration

Approval was obtained from the ethics committee of Srinakharinwirot University. The procedure used in this study adheres to the tenets of the Declaration of Helsinki.

Availability of data

The datasets used and analyzed during the present study are available from the corresponding author upon reasonable request.

Study Registration

The study protocol was registered in the Thai Clinical Trial Registry (https://www.thaiclinicaltrial.org) (TCTR20240331002).

Declaration of generative AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Google Gemini AI (https://gemini.google.com/app) in order to grammar checking and correction purposes. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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